Universidade do Minho
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Nadine Castelhano Santos

Mining quorum sensing in pathogenic P. aeruginosa and C. albicans

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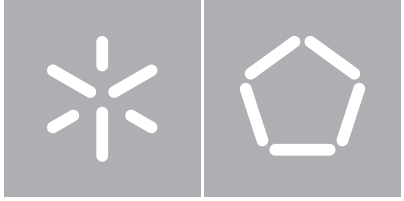

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Mining quorum sensing in pathogenic P. aeruginosa and C. albicans

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O estudo do fenómeno de cross-talking entre *P. aeruginosa* e *C. albicans* tem sido focado essencialmente nos processos de quorum sensing e formação de biofilmes, identificando-se os genes e proteínas envolvidas. Contudo, mesmo já existindo um grande conhecimento dos genes e proteínas envolvidas, ainda existe uma lacuna na integração dos mesmos nas redes biológicas dos respectivos microorganismos. O número e qualidade das redes biológicas existentes (Transcriptional Regulatory Network - TRN and Protein-protein Interactions - PPI) para os fenómenos chave tais como, quorum sensing, formação de biofilmes, resistência a antibióticos e patogenecidade, não evidenciam a importância de alguns destes genes no fenómeno de cross-talking. Esta tese apresenta-se como a primeira tentativa de colocar em evidência os genes e proteínas envolvidos em cross-talking, associando-os aos parceiros de interacção nas respectivas redes biológicas de cada microorganismo. Primeiramente, utilizou-se um processo de integração de redes para os dois microrganismos, levando ao aumento do conhecimento geral sobre os processos de patogenecidade dos dois microorganismos, e por fim os genes envolvidos em cross-talking, identificados na literatura, foram evidenciados nestas redes integradas. Com esta tese pretende-se dar algumas pistas sobre como é que estes genes de cross-talking estão envolvidos em importantes processos biológicos e também de algum modo apontar novos potenciais drug targets.

Palavras-chave: quorum sensing, formação de biofilms, TRN, PPI, integração

The study of the cross-talking phenomenon between *P. aeruginosa* and *C. albicans* has been focus on the processes of quorum sensing and biofilm formation, identifying the genes and proteins involved in this relationship. Although, there is a present knowledge on the genes and proteins involved, there is still a lack in the understanding on how these genes are integrated into biological regulatory networks of the respective microorganisms. The number and quality of the existing biological networks (i.e. Transcriptional Regulatory Network - TRN and Protein-protein Interactions - PPI) for key phenomena, such as quorum sensing, biofilm formation, antibiotic resistance and pathogenesis does not highlights the importance of some genes and proteins in the cross-talking phenomenon. In this thesis, constitutes the first attempt to put in evidence the genes involved in cross-talking, associating them to the interacting partners within the biological networks of the two microorganisms. First, the two microorganisms passed through a process of network integration, leading to an augmentation in the general knowledge on pathogenic processes, and then over those networks the cross-talking genes identified in literature were highlighted. With this thesis we expect to give some new perspectives on how these cross-talking genes are interconnected to important biological processes of the two microorganisms and to point some new potential drug targets.

Key-words: cross-talking, quorum sensing, biofilm formation, TRN, PPI, integration

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Chapter I – Introduction

I.1 Motivation

Therapeutics against the multitude of pathogenic species has been traditionally associated with antimicrobials. However, the antimicrobial resistance has been growing over the past decades, and the demand for new therapeutic strategies and drugs is becoming urgent [1]. Virulence can be defined as the ability of a pathogen to cause disease. Therefore, by targeting virulence one could address the development of new antibacterial drugs, namely by acting on the virulence factors, through the inhibition of the toxin function, the toxin delivery, the regulation of virulence expression (quorum sensing (QS) and two-component systems) or the blockade of adhesion [2].

Microorganisms can communicate through a phenomenon termed QS, which is based on the production of diffusible signal molecules called autoinducers (AI). Nowadays, it is well established that QS integrates the regulatory machinery of several bacterial species and has a major role in the control of virulence traits [3,4]. Indeed, AIs are able to activate or repress genes, as soon as the threshold concentration has been reached, according to population density and characteristics of the environment. The best described and studied AIs are the peptides of Gram-positive bacteria, such as *Staphylococcus aureus*, and the N-acylhomoserine lactones (AHLs) of Gram-negative bacteria, namely *Pseudomonas aeruginosa*. The QS phenomenon in *P. aeruginosa* possesses at least three tightly connected QS systems and one orphan AI receptor. The three QS systems are the *las*, *rhl* and *psq* systems and the orphan receptor protein is QscR [5].

The QS phenomenon is not exclusive of bacteria and more recently it has also been described in fungi. For instance, the polymorphic fungus *Candida albicans* regulates virulence through at least two QS signal molecules: farnesol and tyrosol. *C. albicans* is an opportunist human pathogen that is known for its ability to form biofilms on implanted devices such as indwelling catheters or prostetic heart valves, and also for its substantial morphotypic flexibility. This flexibility allows the existence of *C. albicans* in the form of budding yeast, filamenting hyphae or pseudohyphae, and hyphae formation. It has been suggested that morphological switching to filamentous growth is associated to virulence [6].

Regardless the particularities of each species, the level of complexity underlying QS phenomena requires integrated understanding of the perturbations occurring in the regulatory machinery of

the organisms in response to different environmental stimuli. In this regard, network analysis can be quite useful to integrate the data being generated on QS, analyse the interrelation of such data, and compare information within and across species [7–10]. Generally speaking, networks represent biological information in the form of a graph, i.e. by taking different kinds of biological entities as nodes and modelling the relationships of interest as edges linking the nodes. Specifically, the metabolic, adaptive and pathogenic capabilities of an organism are somewhat reflected in the fine-tuned performance of its regulatory system [11]. As basic representation, the transcriptional regulatory network (TRN) can be obtained through the collection of known regulatory network interactions connecting transcription factors (TFs), sigma factors, and anti-sigma factors to their target genes [12]. Then, hypotheses may be generated computationally by means of topological inspection (e.g. determining metrics of centrality, and finding clusters and motifs) and network simulation, and further validated experimentally [13–15].

Some TRNs for biofilm-forming organisms have already been presented. Galán-Vásquez and co-workers have put together a TRN of *P. aeruginosa*, which comprises processes such as biofilm formation, production of exopolysaccharide alginate, several virulence factors and quorum sensing regulons [16]. More recently, Nobile and co-workers (2012) have described and analysed the TRN controlling biofilm formation in the pathogenic *C. albicans*, identifying six master transcription regulators (Efg1, Tec1, Bcr1, Ndt80, Rob1 and Brg1) and approximately 1000 target genes regulated by those regulators [17].

I.2 Thesis contribution

The overall goal of this project is to bring forward new insights into the cross-talking phenomenon, taking advantage of recent existing regulatory networks and literature. Focus is set on the characterization of the biological network control of quorum sensing and biofilm formation in *P. aeruginosa* and *C. albicans*, respectively. Moreover, some recent biological networks were chosen to construct integrated networks to increase our knowledge in the important pathogenesis phenomena. Network topological analysis addressed the analysis of the regulatory mechanics intra-species, identifying the major regulatory players and network robustness, namely network hubs and bottlenecks, and identify QS and biofilm related regulatory clusters. This thesis, contributed to shed light into a network visualisation on important processes, described in literature for the cross-talking phenomenon between *P. aeruginosa* and *C. albicans*.

I.3 Dissertation outline

Chapter II presents the state of the art for the present subject of this thesis, namely pathogenesis phenomena description, such as virulence factors, cell-to-cell communication systems, antimicrobial resistance and applied systems biology (i.e. biological networks) for the two pathogen study, *P. aeruginosa* and *C. albicans*.

Chapter III describes the network mining part of this thesis, in which the several methods, such as the Cytoscape tools and plugins used to obtained and explore the integrated networks are described. All of the faced problems and strategies implemented found during network integration are described. The results obtained are plotted and illustrated and a brief discussion is made for each section since the individual study of the two microorganisms and the combine study reflecting the cross-talking phenomenon.

Chapter IV presents the conclusions obtained with this thesis, where some future lines of research are pointed.

Chapter II - Understanding microbial pathogenicity

II.1 Basic concepts

Pathogenicity has been a controversial concept over the years lacking a consensual definition. Pathogenicity is defined as the quality or state of a microorganism that confers it the ability to cause disease in a host [18]. Noteworthy, virulence and resistance are tightly intertwined to this latter definition, which are responsible for the ability of a microorganism to cause damage in the host extending or sustaining damage after antimicrobial treatment exposure [19]. Virulence, quantifies pathogenicity through some observable measure of disease severity [20]. Otherwise, resistance refers to the ability of the microorganism to resist or become tolerant to antimicrobial products [21].

II.1.1 Virulence factors

Pathogenicity, as being the capability of causing disease in a host is fully accomplished by a myriad of virulence factors (VFs) that can act individually or connected depending of the stage of infection and also the species and kingdoms involved [22].

P. aeruginosa

Pseudomonas aeruginosa is an opportunist Gram-negative bacterium known to colonise and persist in acute and chronic infections, mainly in immunocompromised patients. The capability of infecting a wide range of niches, such as burns, wounds, eyes, ears and indwelling medical devices is characteristic of this pathogen [23]. However, lung infection is the most relevant niche of colonisation being commonly found in polymicrobial biofilms, associated with *S. aureus* (e.g. cystic fibrosis) or *C. albicans* (ventilator-associated pneumonia-VAP) [24]. Cystic fibrosis is a manifestation of a lung chronic infection where *P. aeruginosa* undergoes a switching from a non-mucoid to an alginate overproducing mucoid phenotype. The exopolysaccharide alginate simulates the production of IgG and IgA antibodies, conferring a survival advantage since it protects the bacteria from phagocytosis and antibodies [25]. VAP is an example of an acute infection in which the principal determinant for development is the presence of the endotracheal tube, which enables the leakage of contaminated oropharyngeal secretions down to the lungs, and is vulnerable to colonisation by biofilm producing microorganisms [26].

Commonly, one can say that VFs in bacteria are associated with: motility (flagella, pili), production of toxins and proteases, invasion, adhesion to host (e.g. cell, tissues, and medical implants), pathogen persistence (e.g. switching from planktonic state to biofilms), formation of polysaccharide capsules and production of molecules for iron uptake (siderophores) [19]. In turn, acute and chronic traits of *P. aeruginosa* have distinct VFs associated. The pathogenesis of acute infections relies upon type II secretion system (T2SS) associated to the secretion of toxins and proteases, type IV pili (Tfp), flagella and type II secretion systems (T3SS). Also QS-regulated virulence factors (proteases, elastases, pyocyanin), which lead to tissue damage, sepsis and contribute to bacterial dissemination [3]. Further, the transition to a chronic virulence phenotype is hypothesized to occur via a continuum transition of signalling pathways, in which the bacterial population transits from cAMP/Vfr (initial attachment) and QS-dominated phenotypes to c-di-GMP and Gac/Rsm (pathway leading to a sessile phenotype) dominated phenotypes. Indeed, on the establishment of a chronic infection there exists an overproduction of extracellular polysaccharides, formation of biofilms and small colony variants (SCV) and up-regulation of the type VI secretion system (T6SS) [27]. The switching from acute to chronic infection is characterized by biofilm formation being typically associated to poor patient prognosis. Biofilm formation is under the control of the QS system that aids to coordinate genes expression, regulating cell lysis within biofilm, thus controlling the release of extracellular DNA (which is one of the key components of biofilms), as well as Pel and Psl polysaccharides, and alginate [27]. Often, the appearance of SCV phenotypes in clinical isolates of CF patients is correlated with poor lung function and enhanced antibiotic resistance and biofilm formation [25].

Nowadays, it is possible to have access to a full list of the VFs present in *P. aeruginosa* in public databases, such as Pseudomonas Genome Database [28] and Virulence Factors of Pathogenic Bacteria Database [29].

C. albicans

Candida albicans is a polymorphic fungus which can have a dual mode of life, normally being commensal and then in some situations turn into an opportunistic pathogen. Thus in is commensal form is known to colonise the mucosal membranes in the oral cavity, the gastrointestinal tract, the urogenital mucosa and the vagina [30]. Despite being a commensal organism in certain host conditions it may result into a transition to a pathogenic phase, responsible for clinical manifestations ranging from muco-cutaneous overgrowth to bloodstream

infections [31]. The infection caused by Candida species is generally termed candidiasis or candidosis [32]. Its transmission mechanisms are two-fold: endogenous candidaemia, in which Candida species develops an opportunist pathogenic behavior under host weakness conditions and exogenous candidaemia, which occurs mainly due to the hands of the health professionals, and health-care materials, such as contaminated catheters and intravenous solutions [33].

During infection, *Candida albicans* pathogenicity manifests through a number of VFs, such as morphological polymorphism (i.e. transition from yeast-to-hyphal form), expression of adhesins and invasins on the cell surface, thigmotropism, phenotypic switching, secretion of hydrolytic enzymes (e.g. proteases, phospholipases, lipases, and haemolysins) and biofilm formation [34]. Among all of the aforementioned VFs, filamentation (i.e. transition from yeast-to-hyphal form) and biofilm formation assume the most relevant space during the development of a virulent phenotype. Moreover, hyphal growth, as a virulence mechanism, plays an important role in tissue invasion and resistance to phagocytosis in host. Biofilm formation plays a pivotal role in virulence allowing the dissemination of infection through pseudomembranous biofilms constituting reservoirs for seeding further infection and antimicrobial resistance as well as obstructions in medical devices [6,35]. Furthermore, mature biofilms are more resistant to antifungal agents than planktonic cells and the dispersion of yeast cells is intimately related to virulence phenotypes [36]. Firstly, the phenomenon of adhesion, prior to biofilm implementation, is mediated by a specialized set of proteins (called adhesins) that enable adherence to other *C. albicans* cells, other microorganisms, to abiotic components and to host cells. The best studied adhesins are the agglutinin-like sequence (ALS) proteins, comprising a family of eight members (Als1-7 and Als9) encoded by glycosylphosphatidylinositol (GPI)-linked cell surface glycoproteins. The most important protein in adhesion, from the eight, is the hypha associated Als3 protein [34]. Proteases, phospholipases and lipases, constitute important hydrolytic enzymes, which enable the active penetration into the host cells and enhance extracellular acquisition of nutrients. The family of secreted aspartic proteases (Saps) isoenzymes comprises ten members, Sap1-10. SAP1-6 genes are related to tissue damage and immune response, and are comprised in the group of Sap1-8 as being in the surrounding medium, whereas Sap9 and Sap10 remain bound to the cell-surface. Nevertheless, the contribution of Saps for *C. albicans* virulence remains controversial. The family of phospholipases comprises four distinct classes (A, B, C and D). However, only the five members of class B (PBL1-5) are extracellular and active in pathogenicity, through disruption of host membranes [30,34].The lipase family consists of ten members (LIP1-

10) and there are experimental evidences that lip8Δ/Δ might be involved *C. albicans* pathogenicity [37]. Finally, the production of haemolysin plays an important role in virulence, since as being a protein that destroys red blood cells it can acquire the iron necessary for fungi survival and establishment of a proper host infection in human cells [34].

In contrast to *P. aeruginosa*, currently there is no public database giving a detail list of VFs of *C. albicans*.

II.1.2 Cell-to-cell communication

Quorum sensing can be described as a phenomenon of cell-cell communication that involves the production, detection, and response to extracellular signalling molecules called autoinducers (AIs). Once the AIs concentration reaches a threshold level (at which the population is considered to be "quorated"), a cascade of signal transduction is activated that, in turn, will activate or repress target genes in order to instigate a collective behavioural change to environmental challenges (e.g. antimicrobial treatments) [39,40]. Noteworthy, there are several phenomena that are controlled by QS systems, including bioluminescence, sporulation, competence, antimicrobial resistance, biofilm formation, and VF secretion [5]. The interface between QS and bacterial virulence represents a promising area of investigation in the battle to find new anti-virulence drugs [41,42].

P. aeruginosa

Quorum sensing systems are intertwined in the regulation of key processes, such as the production of VFs (i.e. extracellular proteases, iron chelators, among others), efflux pump expression, biofilm formation, motility and host-immune response [3]. In turn, this regulation is only achieved by three different QS systems; two N-acyl-homoserine lactone (AHL) mediated signalling systems (*las* and *rhl*) and a 2-alkyl-4-quinolone (AQ) mediated signalling system (Figure 1) [27].

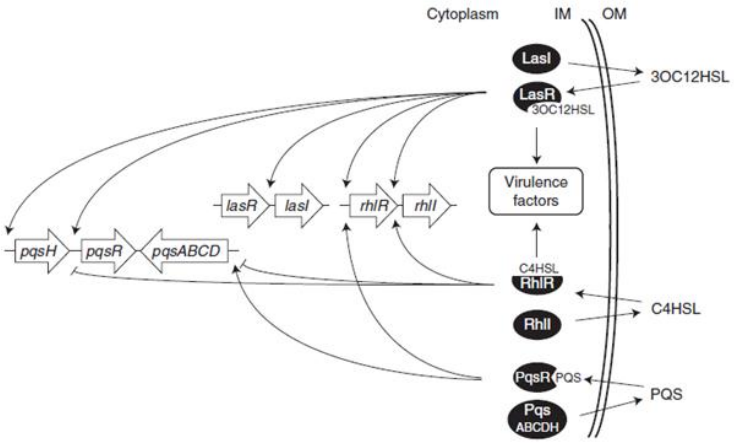

Figure 1: *P. aeruginosa* QS systems.

The three AI synthases, LasI, RhlI, and pqsABCDE, produce the AIs 3OC12HSL, C4HSL and PQS, respectively [40].

- AHL-mediated QS systems

P. aeruginosa has two canonical AHL QS signalling pathways, the *las* and *rhl* systems, encoding molecules 3-oxo-C12-homoserine lactone (3OC12HSL), butanoyl homoserine lactone (C4HSL), respectively (Figure 1) [40]. Surprisingly, these two QS systems affect directly or indirectly 10% of the *P. aeruginosa* transcriptome. When a certain threshold of AIs is achieved, the molecules bind and activate their cognate LuxR family regulators, LasR and RhlR (Figure 1) [3,43].

- AQ-mediated QS systems

P. aeruginosa QS system comprises two AQ signaling molecules, Pseudomonas Quinolone Signal (PQS - 2-heptyl-3-hydroxy-4-quinolone) and its precursor, 2-heptyl-4-quinolone (HHQ). The LysR-type transcription regulator, MvfR (also known as PqsR) appears to have both PQS and HHQ molecules enhancing the *in vitro* biding to the promoter of the *pqsABCDE* operon, suggesting an effector role for MvfR (Figure 1) [3]. PQS binds to its cognate LysR-type receptor MvfR (PqsR) controlling approximately 140 genes, most of which are co-regulated by *rhl* system [44].

- QS regulation

The three encoded QS systems of *P. aeruginosa* exhibit positive feed-forward autoregulation. Additionally, the 3OC12HSL-LasR complex positively regulates *lasI*, *rhlI*, *rhR* and *mvfR* accounting for a hierarchical relationship between the two QS systems (AHL and AQ) [45]. There are many global regulators that have been proved to modulate QS-dependent genes. For example, the

sigma factor RpoS, has been shown to modulate 40% of the QS regulon. The regulatory protein RsaL affects expression of 130 genes, through *las* system, including genes whose products are involved in antibiotic resistance and biofilm formation [27]. The transcription factor MvaT, as a member of the histone-like nucleoid structuring protein family involved in transcription silencing controls the expression of almost 150 genes. In fact, MvaT/U seems to establish the connection between the three QS systems through direct regulation of *lasR*, *lasI*, *rsaL*, *mvfR* and RpoS [46]. The virulence and quorum sensing regulator - VqsR, which belongs to the LuxR-type family of transcriptional regulators and is under LasR regulation, regulates QS through the blockage of QscR (LuxR-type regulator). The transcriptional regulator VqsM - AraC regulates VqsR in addition to numerous genes involved in QS, such as RsaL, PprB, MvfR, RpoS, AlgT/U (alginate master regulator) and MexR. Among others regulatory processes, RsmA negatively regulate *rhl* and *las* signalling, resulting in reduced AHL levels [3].

C. albicans

In the scope of QS systems for *C. albicans* two molecules, farnesol and tyrosol has been identified [47]. Farnesol is a sesquiterpene alcohol, which is produced from farnesyl pyrophosphate, an intermediate in the ergosterol biosynthesis. In fact, the molecule farnesol is only formed after a consecutive step of conversion during its biosynthesis (Figure 2) [48].

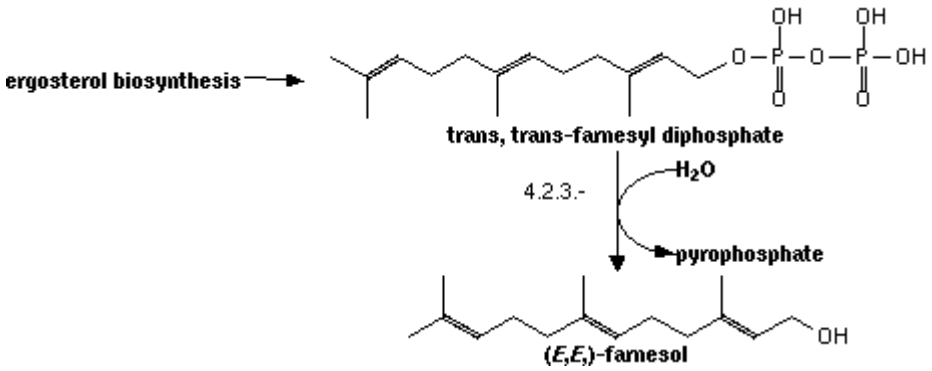

Figure 2: Farnesol biosynthesis pathway.
This scheme was constructed based on [38].

The other QS molecule, tyrosol (2,4-(hydroxyphenyl)-ethanol) requires an intact aromatic amino acid biosynthesis pathway to be synthetized (Figure 3) [49,50].

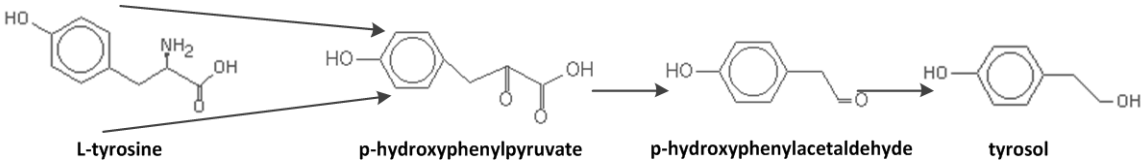

Figure 3: Tyrosol biosynthesis pathway.

This scheme was constructed based on [38].

- Antagonist relation – farnesol versus tyrosol

The two QS systems have antagonistic effects, tyrosol stimulates growth under dilute conditions ("lag phase" growth) and also stimulates germ tube formation. Moreover, tyrosol boots the formation of germ tubes in yeast cells and the development of hyphae in the early stage of biofilm formation [49]. However, when both tyrosol and farnesol are present, farnesol has a dominant effect, thus morphogenesis is repressed even in the presence of filamenting inducing conditions (**Erro! Fonte de referência não encontrada.**) [47,51]. Moreover, it has been proved that farnesol reversibly inhibits biofilm formation but not the elongation of pre-existing hyphae [51]. Furthermore, farnesol has also other roles in *C. albicans* physiology, related to increased expression of drug resistance genes and involvement in oxidative stress resistance response [6]. Décanis and co-workers (2011) investigated the effect of exogenous farnesol on yeast to hypha morphogenesis and Saps gene expression. This investigation revealed for the first time that, exogenous farnesol modulates the behaviour of *C. albicans*, shedding light into a possible role in pathogenesis modulation. Further conclusions on how farnesol modulate fungus growth were also achieved in this study, being related to a cell wall and/or membrane reorganization, at the level of cytoplasm integrity. Finally, the benefit of using farnesol as a potential molecule for pathogenesis fungus control has been elucidated, pointing Sap4-6 (Secreted aspartyl proteases) as possible targets for gene inhibition [4].

Cross-talking

Since the beginning of life on Earth, bacteria represents the most adaptable and abundant form of life. Therefore, coevolution of prokaryotes and eukaryotes has led to the widespread of phenomena such as quorum sensing (QS) cross-talk, biofilm formation and adhesion to host across kingdoms. In fact, cross-talking could be seen as an adaptive survival strategy of bacteria and eukaryotes to monitor their surroundings adjusting behaviour and

responses to conquer a challenging and mutational environment (e.g. contact with antimicrobial products) [39].

Both *C. albicans* and *P. aeruginosa* can be frequently found in cases of hospital-acquired infections in polymicrobial biofilms colonising medical devices and tissues. A classic example of this interaction could be seen in VAP, where endotracheal colonisation by *C. albicans* plays a pivot role in lung infection by *P. aeruginosa* [24]. The microbial coexistence in a polymicrobial biofilm is translated into the following scenario: *P. aeruginosa* adherence to *C. albicans* is only mediated during filamentation. In fact, fungus filaments are used by the bacteria as a source of nutrients, leaving filamentation as susceptible process of killing by *P. aeruginosa* [52]. The intracellular process of cross-talking uses 3OC12HSL molecule to block the yeast to-hypha transition or activates the genes promoting the hypha-to-yeast reversion. *C. albicans* reacts with the secretion of farnesol, which at low cell density inhibits PQS production responsible for the expression of several virulence factors [6,53].

II.1.3 Antimicrobial resistance

Since the early times of medical history until now antimicrobial therapy has been taken as a granted solution for every kind of infections. However, the intensive use of antimicrobial agents for medical and non-medical purposes revealed the greatest issue of concern nowadays - antimicrobial resistance. Furthermore, several pathogenic strains have acquired resistance to multiple drugs (e.g. antibiotics, antifungals and chemotherapeutics agents) leading to the emergence of a new and more threatening phenomenon called multidrug resistance [54,55].

Multidrug resistance in bacteria is often associated with (i) the accumulation of plasmids or transposons of genes, each coding for resistance of a specific agent, and (ii) the action of multidrug efflux pumps, which can pump more than one drug type [54,56]. For instance, regarding common features of multidrug resistance between bacteria and fungus one can enumerate: the existence of persister cells within biofilms and the biofilm formation by itself since, the matrix presence seems to restrict the penetration of drugs leaving only the superficial layers in contact with lethal doses of antimicrobial agents [54,57,58].

During the establishment of an infection, adhesion of the pathogen cells to host tissue is a crucial step. Nevertheless, human body had evolved several lines of defence against cell adhesion, such as continual exudation of epithelial cell surfaces, mucus coating of respiratory,

intestinal and reproductive tracts [2]. Blocking the initial attachment during biofilm formation is a possible strategy to prevent the colonisation of the epithelia cell surface of the human host [59]. The QS phenomenon is believed to be a central key to the disruption of virulence regulatory systems, constituting a valid target for antimicrobial targeting [30,42].

Nowadays, the urgent need for new drugs leads to growing mutation on how antimicrobial drugs are discovered. Thus, drug target discovery is still essential [42] [60,61], but other approaches are being used, such as the use of combination agents that are effective against more than one target in the cell [62], the repurposing of antimicrobial agents [63], and the design of antimicrobial agents with alternative modes of action [64–66].

II.2 Systems biology new perspectives

Network reconstruction from the genome sequence of the species it is getting a growing relevance into the identification of potential drug targets aiding wet lab researchers [61]. The Genome-scale computational models of metabolism, considered simulation frameworks of intracellular or intercellular behaviour are being currently built using data from several sources, such as high-throughput experiments, "Omics" and public databases [31,67–72]. In fact, regarding the current public databases used for collection data for network reconstruction one could indicate a fully updated review [73].

Generally speaking, networks represent biological information in the form of a graph, i.e. by taking different kinds of biological entities as nodes and modeling the relationships of interest as edges linking the nodes [74]. Specifically, the metabolic, adaptive and pathogenic capabilities of an organism are somewhat reflected in the fine-tuned performance of its regulatory system [11,75]. As basic representation, the transcriptional regulatory network (TRN) can be obtained through the collection of known regulatory network interactions connecting transcription factors (TFs), sigma factors, and anti-sigma factors to their target genes [12]. Protein-protein interaction network (PPI) is another type of network representation, in which only the relation among proteins is described lacking the regulatory information [76]. Then, considering both representations, hypotheses may be generated computationally by means of topological inspection (e.g. determining metrics of centrality, finding clusters and motifs) and network simulation, being further experimentally validated [13–15,77].

Regardless the particularities of each species, the level of complexity underlying QS phenomena requires integrated understanding of the perturbations occurring in the regulatory machinery of the organisms in response to different environmental stimuli. In this regard, network analysis can be quite useful to integrate the data being generated on QS, analysing the interrelation of such data, and compare information within and across species [8–10]. The intertwined QS related phenomena of virulence and resistance also require an integrated and systematic study of the regulatory machinery in microbial consortia and host-interaction. Regarding this subject, it is important to focus the adhesion mechanisms and infection signalling systems concerning several VFs [78–81].

Notably, network reconstructions of pathogenic species are being conducted focusing in the understanding of this pathogenicity issues, such as QS, biofilm formation, adhesion,

antimicrobial resistance and host-pathogen relationship. The following sections were obtained after an intense and careful scavenge of the present published network reconstructions regarding the present pathogens in analysis as well as *S. aureus* (not relevant for the present thesis) [73].

II.2.1 *P. aeruginosa* network reconstructions

P. aeruginosa regulatory machinery is being depicted in several different types of network reconstructions ranging from the well-kwon metabolic models to TRN and PPI networks. These reconstructions are centred in two main strains, the laboratory strain *P. aeruginosa* PAO1 [82] and the human clinical isolate *P. aeruginosa* PA14 [83].

In the scope of, metabolic modelling regarding *in silico* simulation there has been described two models, iMO1056 [84] and iMO1086 [85] for *P. aeruginosa*. The model iMO1056 comprises the description of pathways related to VFs production, such as alginate, rhamnolipids, phenazines, and QS molecules. Furthermore, this model used enzyme essentiality to compare results against a human metabolic model EHMN [86], proposing a list of 41 potential drug targets [84]. A comparative analysis of the virulence features of *P. aeruginosa* and *P. putida* (non-pathogenic strain) give rise to the second model, iMO1086. In fact, this study revealed significant differences between the two species in terms of pathway flexibility for VF production, confirming the speculation of higher flexibility in the pathogenic form (i.e. *P. aeruginosa*) [85].

Galán et al have reconstructed a TRN with a network dimension of 690 genes and 1020 regulatory interactions comprising 76 TFs, 14 sigma factors and 593 target genes. Important pathogenicity phenomena, such as alginate biosynthesis, antibiotic resistance and Qs systems are acknowledge in this network. Additionally, the topological analysis revealed the top ten global regulators (such as *lasR*, *rhlR*, *fur*, *mexT*, *vfr*, *algR*, *anr*, *lhf*, *ptxR*, *algw*) related to QS systems and VF regulation [16].

The protein interactome of *P. aeruginosa* proposed by Zhang et al discloses different aspects of network modelling, such as a main global network, a host-pathogen network, and also two case studies related to cystic fibrosis and QS [87]. The main network has 3343 proteins and 19416 potential interactions, and using Pseudomonas Genome Database one could distinguish 294 TFs, 66 pathogenic associated genes, 172 VF, 45 antibiotic resistance genes and 21 antibiotic drug targets [28]. The topological importance of a protein in a network using hubness and bottleneck topological analysis, and essentiality information enables the proposal of 28 new

potential drug targets. The two interactions maps were additionally originated from the main network: one describes the action of the anti-sigma factor MucA and the negative regulator MucB, involved in alginate regulation and mucoid phenotype on cystic fibrosis disease, and the other describes the interacting partners of the TF RhlR (*rhl* QS system). The human-*Pseudomonas* network constitutes an extension of the main network which was further enriched with human proteins retrieved from specific databases. This network allowed the discovery of three other potential drug targets, also by the same method previously applied [87].

Drug interaction network obtained through computational screening, can be used to discover drug repurposing opportunities, i.e. using existing drugs for new indications (e.g. as anti-virulence drug targets) [88]. Specifically, the study of raloxifene, a drug which is used in the prevention of osteoporosis and invasive breast cancer in post-menopausal women, has supported this drug interaction network study [63]. Thus, this drug has been predicted to bind to the protein PhzB2, which is involved in production of the QS signalling molecule pyocyanin via phenazine biosynthesis [63].

II.2.2 *C. albicans* network reconstructions

The existing *C. albicans* network reconstructions, in contrast to *P. aeruginosa* are mainly focused in host-pathogen networks. Likewise, TRNs and PPIs are depicted for this microorganism, while metabolic models are still not available yet. The main strain of network reconstruction for this fungus is the strain *C. albicans* SC5314 [89].

A computational screening of biofilm related TFs has exposed differences between biofilm and planktonic cells of *C. albicans* [90]. In turn, two TRNs have been reconstructed translating these differences, one for planktonic cells and another for biofilm communities. The network dimensions are of 421 genes and 2211 interactions and of 438 genes and 2149 interactions, respectively. Additionally, two other TRNs were extended after network comparison in terms of loss-of-function and gain-of-function (i.e. interaction detected in the planktonic network but not in the biofilm network and vice-versa). As a result from this study, 23 TFs presented differences in function being ten already well-known to be involved in biofilm formation, leaving 13 (namely, the TFs Ino4, Rpn4 and Met28) in which this role is still unclear. Still in the biofilm formation subject, Nobile et al proposed a TRN which described the master circuit of regulation for the most significant TFs behind biofilm formation [17]. The network composition of this TRN comprises 1061 genes and 2048 interactions having 284 TFs, counting with six biofilm-related

TFs. Therefore, the six TFs, namely Ndt80, Tec1, Brg1, Bcr1, Rob1 and Efg1, are all of them regulated by each other and most of the target genes are controlled by more than one TF [17]. Adhesion also plays a pivot role in the initial establishment of biofilm formation. In fact, *C. albicans* adherence regulators have also been characterized in terms of the regulatory relationships [91]. Moreover, according to this study, 30 TFs are required for adhesion in which twelve of those govern the expression of more than a quarter of the *C. albicans* cell surface proteins. The central role in adherence of the biofilm regulator Bcr1 is disclosed. Furthermore, another biofilm regulator, Ace2, revealed to be the major functional target of chromatin remodelling factor Snf5, which in its mutant form generates defects in silicone adherence. Still, there is other study regarding the regulation of *C. albicans* iron uptake genes in human oral epithelial cells during biofilm adhesion and invasion [92]. As result, this study revealed that the TFs Rim101, Hap3, Sef1 and Tup1 present a differential expression in experimental infection of human oral epithelial cells. Additionally, it supported the prediction of four new target genes for Rim101, eleven new target genes for Hap3, and the attribution of the first target gene (FRE7) to Sef1. In fact, even some potential new regulations of TFs are proposed, such as Hap3 involvement in the regulation of the gene coding for Rim101 and Tup1 [92].

Commensalism is a convertible phenomenon in *C. albicans* since depending on the host conditions the transition to systemic infection might occur. This subject is translated into a TRN comprising 814 genes and 1036 interactions, in which the relation between gastrointestinal colonisation and systemic infection was evaluated in animal models [93]. Indeed, it is possible to distinguish some TFs that act predominantly during intestinal colonisation (namely, the TFs TYE7, orf19.3625, and LYS144) and those acting during the establishment of a systemic infection (namely, the TFs ZCF21 and LYS14). There are also some genes acting in both scenarios (namely, the TFs RTG1/3 and HMS1). Some insights into relevant biological functions for *C. albicans* host proliferation are advanced, such as cell surface remodelling and the acquisition of carbon and nitrogen sources.

Host-pathogen network interactions, among *C. albicans* and other animal models, is disclosed in a TRN and in a PPI network. A TRN network comprising eleven genes and 21 interactions, including four interspecies (i.e. with *Mus musculus*) is considered as an interspecies example, disclosing phagocytosis in dendritic cells [94]. The interaction between the fungal TF Hap3 and the murine pattern recognition receptor Ptx3 is evaluated. In fact, it is proposed a mechanism by

which Ptx3 binds to *C. albicans* leading to cell wall reorganisation via Hap3 target genes and thus, changing the ability of the fungi to be recognised by immune cells. On the other hand, other animal model *Danio rerio* (zebrafish) constituting a model of infectious disease [95] is used for a PPI network reconstruction [96]. The intracellular interactions among this interspecies and the influence of fungus morphology on infectious of host tissues are the focus of this study. Time profile microarray data of *C. albicans* and zebrafish during infection allowed the reconstruction of three PPI networks: one for the hyphal growth (*C. albicans*), other for zebrafish and an integrated network resulting from the intracellular interaction between host and pathogen (i.e. reflecting intracellular invasion and cellular defence during infection). The later networks have different dimensions comprising: 557 proteins and 3452 interactions; 1282 proteins and 2501 interactions and 2577 proteins and 6880 interactions, respectively. The integrated PPI network is divided in eight levels according to the location of protein action (i.e. nucleus, intracellular, cell surface or extracellular). This network can be viewed by layers, at the top it is the dynamic hyphal PPI network of *C. albicans*, at the middle the host-pathogen intercellular interaction network and at the bottom, the defensive protein interaction network of zebrafish. As a result from this interspecies study, important and distinct biological functions were revealed during infection, for each species. Thus, for *C. albicans* hyphal growth, cell wall adhesion and remodelling, biofilm formation and iron homeostasis are the key functions while for zebrafish, the one involved into host-response during infection, those functions are the apoptosis and the innate immune responses [96].

Chapter III – Network mining

III.1 *P. aeruginosa* network mining – quorum sensing systems

Nowadays, the number of networks proposed for *P. aeruginosa* is already of considerable size and quality [73]. Regarding this scenario, network integration appeared as a possible strategy to enlarge our knowledge into important biological processes for this pathogen. The selection of the two networks for the integration was done according to the following criteria; network dimension and relevance of the biological processes described, such as pathogenesis related, quorum sensing and antimicrobial resistance. As a result, the chosen networks meeting the previous criteria were the TRN of Galán et al and the PPI network of Zhang et al [16,87]. The integration of these two networks presented some issues and challenges to implementation. The following section will described the several strategies used to overcome the inherent problems associated to the different nature of the two networks, in order to meet the final goal of having a general integrated network for *P. aeruginosa*.

III.1.1 Methods and Results

Networks pre-processing and integration

Previosly to this procedure of integration the two networks were subject of a detail analysis revealing some important issues that needed further attention. Thus, Gálan et al contrary to what was expected, has four different types of interactions - i.e. ?, d (presumably dual, but not specified) and the two common interactions, activation (+) and inhibition (-). Therefore, the suspicious interactions (? and d) were excluded from this network, leaving the network for integration with 672 nodes and 987 interactions (Figure 4).

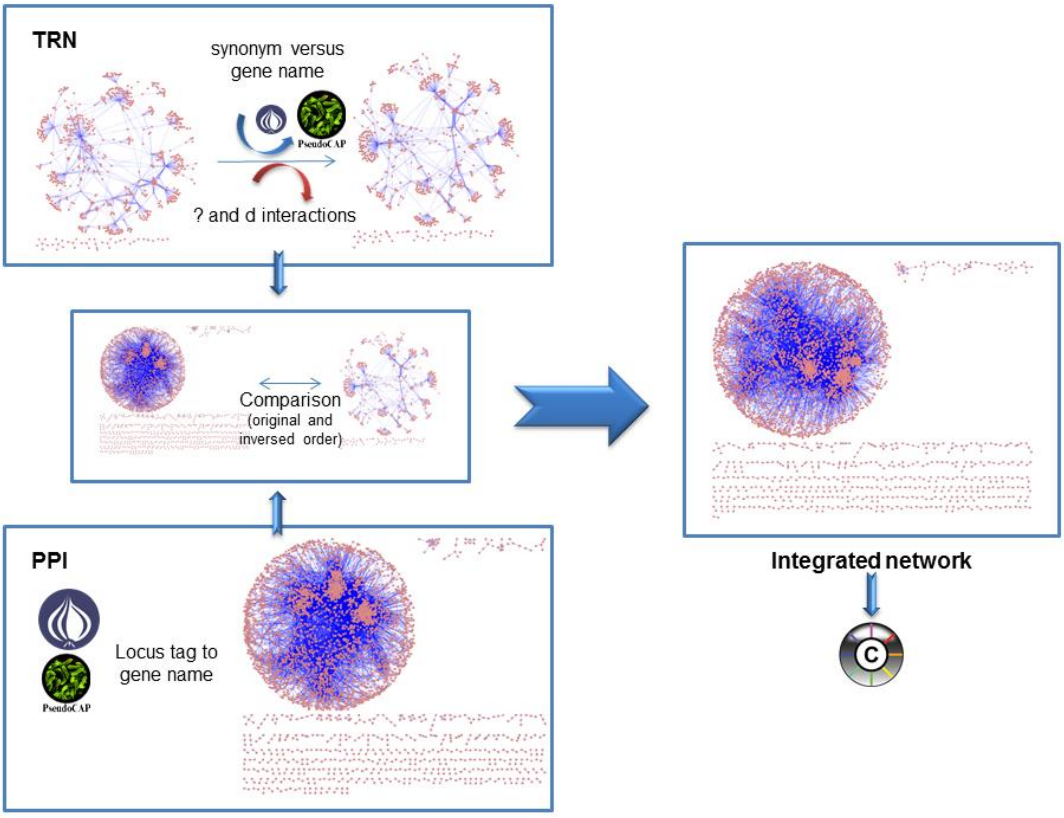

Figure 4: Description of the pre-processing treatment performed to each network and posterior network integration.

In fact, a more important challenge was presented in this integration; reach to a common representation of the nodes among the two types of networks TRN and PPI and also the choice of the type of interaction used. For this first challenge of representation, several rules were created according to the objective of having only the gene name or in cases of absence the protein name. The major transformation was performed in the PPI network of Zhang et al, since the node representation is entirely made with proteins (i.e. locus tag). Proteins were compared using a perl script, against a reference excel file from Pseudomonas Genome Database (Figure 4) [98]. Locus tag, was the reference used for comparison, retrieving from the database the respective gene name and synonym if present. The rules used for protein to gene name conversion were clear; first if there exist a corresponding gene name that is the one used even if exist a synonym, therefore the synonym is never used and the last rule, if there is no gene name the locus tag (protein name) remains the same. After this step, there were some first attempts of comparison among the two networks in order to see which duplicated interactions should be excluded. Surprisingly, it revealed an interesting scenario for the TRN of Galán et al, which it was supposed to be entirely corrected in terms of gene name or protein, according to what is currently allocated

in Pseudomonas Genome Database. The following problems were discovered; use of the synonym instead of gene name when there is one and use of synonym when there is no gene name but a locus tag. In fact, these issues needed to be resolved in order to obtain a better matching between the two networks. The solution found was to localize and substitute these nodes using other perl script and applying the same rules used for Zhang et al. Then, having the two networks entirely in the same type of representation it was applied the "Advanced Network Merge" tool from Cytoscape to merge the two networks. Surprisingly, the expected results were not achieved, since the integrated network obtained had 3586 nodes and 20374 interactions, but a careful analysis, with some excel tools, revealed that there were some problems. First, there were repeated interactions, which lead to repeated nodes and then the number of interactions does not reflect the complete match between the two networks, since the lack of direction of the PPI network was not considered. So, this approach was abandoned for this integration and a different strategy was adopted. First it was kept the order of the PPI network and then it was inversed, since a PPI network is undirected, but to better found the matches between the two networks, this strategy had to be implemented. At the end, after removing the duplicated edges leaving only one, an integrated network was obtained for *P. aeruginosa*. Although, having the networks integrated only the nodes were taken into consideration, and the interaction among nodes was kept as it was of the type protein-protein, meaning that the direction of the interaction was not important. This decision was made since there was a relevant variance among the network dimension of the two networks, one with 987 interactions (TRN) and the other with 19416 interactions (PPI). Analysing this integrated network as a PPI network was considered more advantageous for a preliminary study. Thus, this integrated network has the final network dimensions of 3585 nodes and 20348 interactions and it was further analysed using the Cytoscape version v2.8.3 (Figure 4)[97].

Topological analysis – hubs and bottlenecks

The topological analysis of this integrated network starts from the most basic statistics to a detail analysis for the presence of hubs and bottlenecks. The network statistics of the integrated network, given by the plugin Network analysis are depicted in Figure 5 and Figure 6.

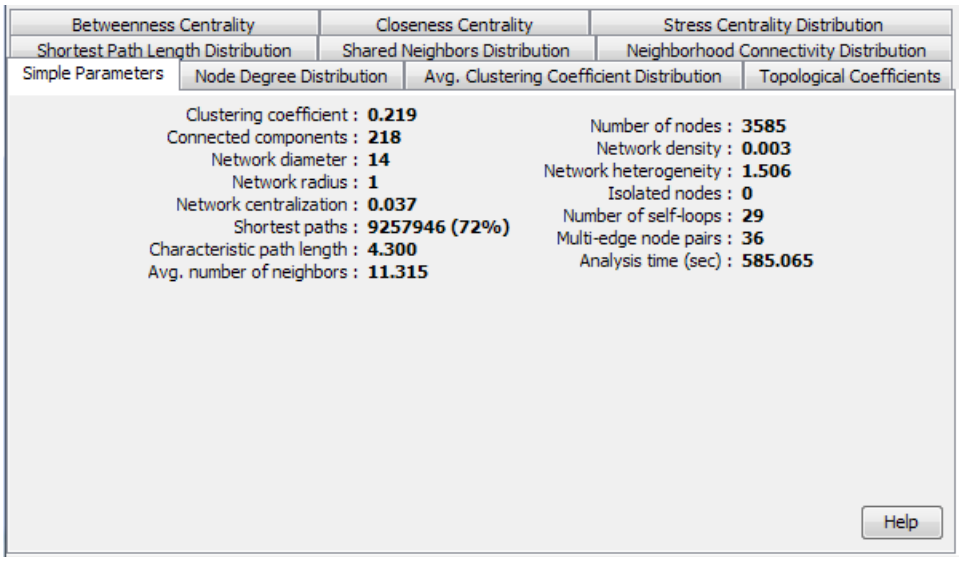

Figure 5: Network statistics of the new integrated network for *P. aeruginosa*, obtained with Network analysis tool.

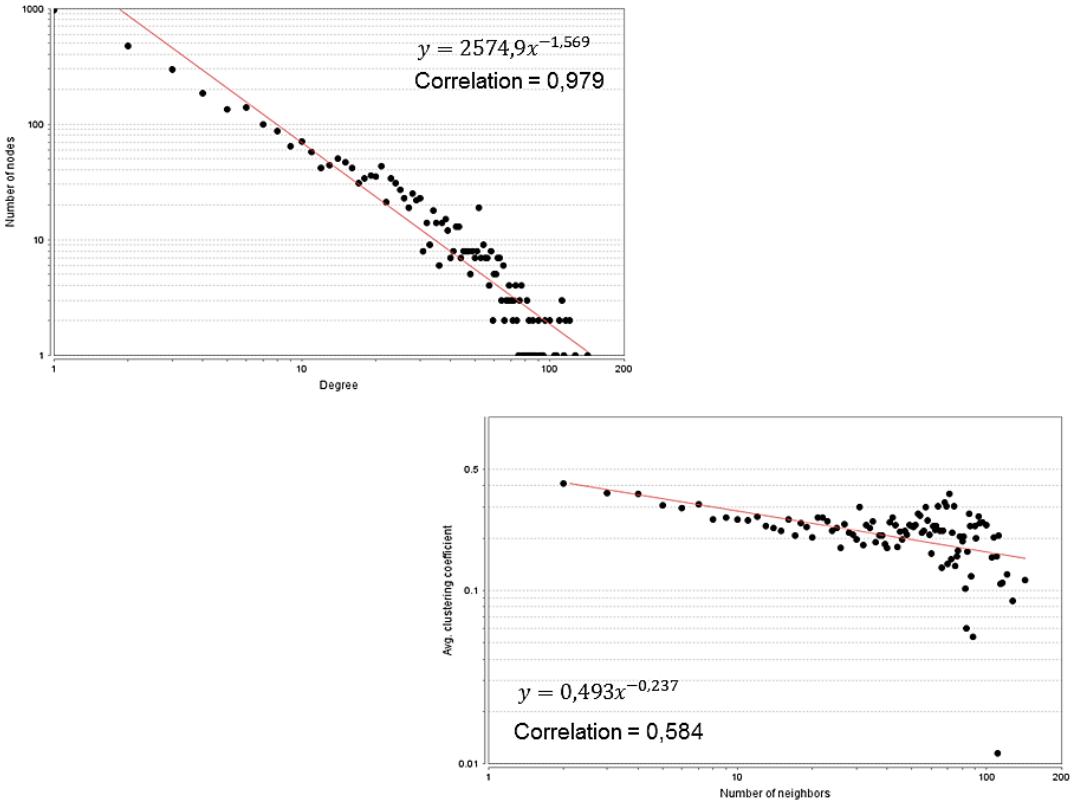

Figure 6: Degree distribution and clustering coefficient distribution of the integrated network.

It display scale-free topology with the exponent degree (γ) of 1,57 indicating the importance of the hubs in this network and also that since it ranges between 2 > γ > 3, there is hierarchy of the hubs, being the most connected hub in contact with a small fraction of all nodes (Figure 6) [97]. Then it has 11,32, 0,22 and 4,30 as its average degree, clustering coefficient, and shortest path

length, respectively (Figure 5 and Figure 6). Moreover, as expected, the topological behaviour of this network is similar to the PPI network of Zhang et al, constituing the most influence network in this integration. In terms of connectivity, this network presents 218 connected components, with one giant component of 3043 genes (85% genes).

Degree distribution is considered an important topological feature, which allow the detection of highly connected nodes known as *hubs* [74,99]. Hubs tend to be essential genes, actulally through degree distribution one can identified potential hubs which can also be considered potentail drug targets [100]. The discovery of important hubs was done using the Cytoscape plugin cyto-Hubba (v. 1.6) [101] which provide several topological analysis algorithms including Degree, Edge Percolated Component (EPC), Maximum Neighborhood Component (MNC), Density of Maximum Neighborhood Component (DMNC), Maximal Clique Centrality (MCC) and centralities based on shortest paths, such as Bottleneck (BN), EcCentricity, Closeness, Radiality, Betweenness, and Stress. First, Hubba results were computed for the entire network and then in the Hubba separator the first ranking method chosen was Degree and the top ten group with higher degree was obtained. The top ten hubs (pdxB, lpdG, hemA, rpsB, aceE, lipB, folD, lasR, rplA, and gshB) obtained, are depicted in Figure 7A, color intensity translates the ranking method based on the degree. Other display options were explored, such as the first-stage nodes (i.e. the first nodes and respective edges connected to the top ten group), the shortest path between the nodes and the extended subnetwork obtained from the shortest paths (Figure 7B and D).

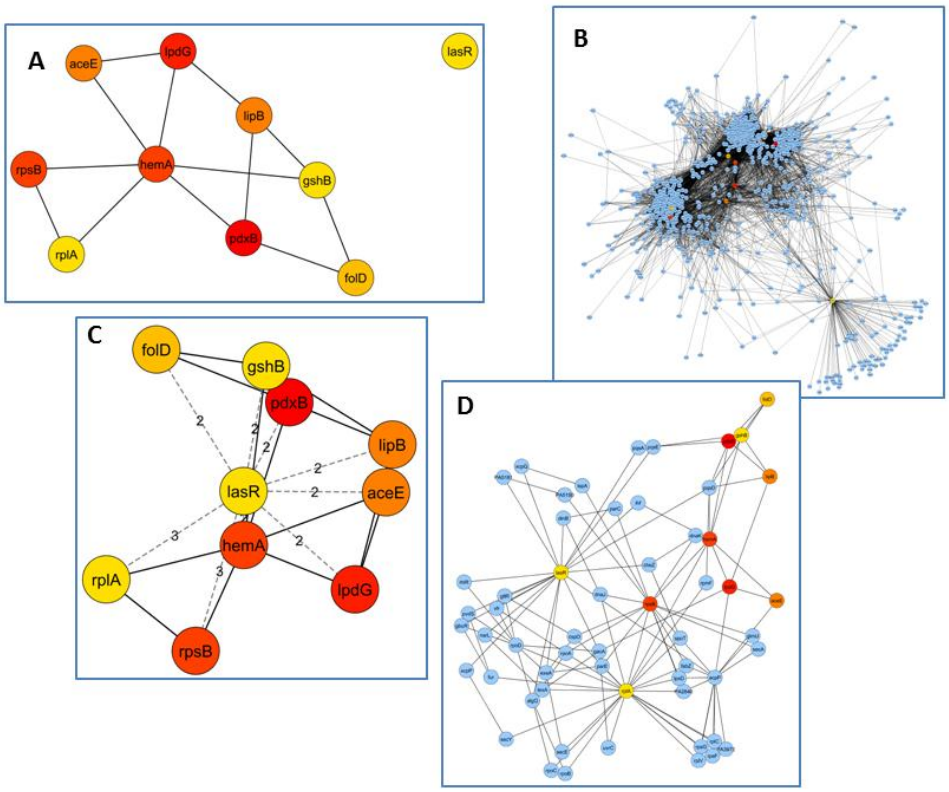

Figure 7: Cyto-Hubba results for the integrated network of *P. aeruginosa* for the ranking method – Degree. Top ten hubs (A), first-stage nodes (B), shortest path of the top ten hubs (C) and the expanded subnetwork (D).
The nodes of the expanded subnetwork are described in the Appendix (Table A 1).

Topological analysis of the nodes based on the degree value offered the opportunity to clarify the hypothesis which point topological importance and essentiality as key factors for drug target discovery. The top ten group of hubs and the expanded subnetwork (Figure 7 – A-D) were checked for essentiality and drug target (Table 1), based in the AEROPATH Target Database [102].

Table 1: Top ten hubs description including the information on the biological processes, gene essentiality and drug targets.

ID	Degree	Object_name	GO_Biological process	Essential	Drug target
pdxB	143.0	erythronate-4-phosphate dehydrogenase	[cellular amino acid metabolic process, cellular catabolic process, cofactor biosynthetic process]	Y	N
lpdG	127.0	lipoamide dehydrogenase-glc	[cellular amino acid metabolic process, generation of precursor metabolites and energy]	N	N
hemA	121.0	glutamyl-tRNA reductase	[cellular amino acid metabolic process, cellular protein metabolic process, cofactor biosynthetic process, porphyrin-containing compound biosynthetic process]	Y	N
rpsB	121.0	30S ribosomal protein S2	[cellular protein metabolic process]	Y	Y

ID	Degree	Object_name	GO_Biological process	Essential	Drug target
aceE	116.0	pyruvate dehydrogenase	[acetyl-CoA biosynthetic process from pyruvate, cellular amino acid metabolic process, generation of precursor metabolites and energy]	N	N
lipB	116.0	lipoate-protein ligase B	[cellular amino acid metabolic process, cofactor biosynthetic process, folic acid biosynthetic process, lipoate biosynthetic process, lysine catabolic process, ubiquinone biosynthetic process]	Y	N
folD	114.0	5,10-methylene-tetrahydrofolate dehydrogenase / cyclohydrolase	[10-formyltetrahydrofolate biosynthetic process, cellular protein metabolic process, cofactor biosynthetic process, histidine biosynthetic process, methionine biosynthetic process, nucleotide metabolic process, pantothenate biosynthetic process, purine nucleobase biosynthetic process]	Y	N
lasR	112.0	transcriptional regulator LasR	[regulation of transcription, DNA-dependent, response to stimulus]	N	N
rplA	112.0	50S ribosomal protein L1	[cellular protein metabolic process]	Y	Y
gshB	112.0	glutathione synthetase	[cellular amino acid metabolic process, cofactor biosynthetic process, glutathione biosynthetic process]	Y	N

The number of essential genes present in the top ten group of hubs is six (*pdxB*, *rpsB*, *hemA*, *lipB*, *folD*, *gshB*, and *rplA*) in which, two (*rpsB* and *rplA*) of those are also drug targets according to the reference database used (Table 1). The main function, according to Pseudomonas Genome Database, represented in the abovementioned essential genes is the amino acid biosynthesis and metabolism (*pdxB*, *hemA*, *lipB*, and *gshB*). The second function represented is related to translation and post-translation modifications, being part of this group two ribosomal proteins (*rpsB* and *rplA*) and the gene *folD* [28]. In the case of the expanded subnetwork, comprising 57 nodes and 118 interactions, the number of essential genes is 23 in which, seven of those are also drug targets and five are only classified as drug targets.

Another important topology feature for the drug target discovery is the bottlenecks [87], representing nodes with a high betweenness centrality (i.e. network nodes that have many shortest paths going through them) which, are considered key connector nodes important in network dynamics and with tendency to be essential [100]. The Hubba results for the bottleneck feature were displayed and a top ten group (*lasR*, *metK*, *fur*, *lpdG*, *mexT*, *gabT*, *exsA*, *gabD*, *argR*, *rpoN*) was obtained (Figure 8A). The first-stage nodes, the shortest path between the nodes and the extended subnetwork obtained from the shortest paths are display in Figure 8C to D.

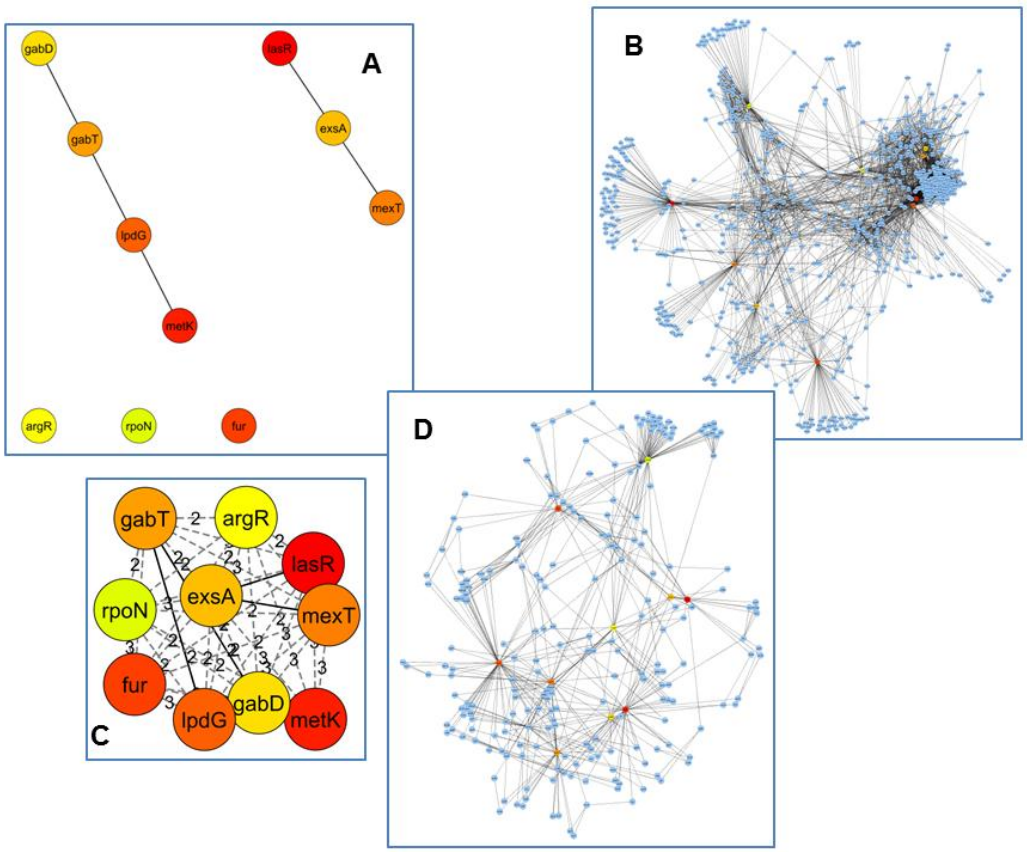

Figure 8: Cyto-Hubba results for the integrated network of *P. aeruginosa* for the ranking method – Bottleneck. Top ten bottlenecks (A), first-stage nodes (B), shortest path of the top ten hubs (C) and the expanded subnetwork (D). The nodes of the expanded subnetwork are described in the Appendix (Table A 2).

The same procedure of enrichment, in terms of gene essentiality and drug targets of the top ten group and the extended subnetwork was done for this new topological measure (Table 2). The number of essential genes present in the top ten group is two (*mexT* and *exsA*). Additionally, none of these four genes is considered a drug target and there is only a drug target (*rpoN*) that is non-essential gene. Thus, TF MexT is involved in multidrug resistance, namely to β-lactamases [103] and the TF ExsA is responsible for the control of secretion systems [104]. The expanded subnetwork, comprising 232 genes and 513 interactions, has 59 essential genes, 9 of them are drug targets and 5 are only classified as drug targets.

Table 2: Top ten bottlenecks description including the information on the biological processes, gene essentiality and drug targets.

ID	Bottleneck	Object_name	GO_Biological process	Essential	Drug target
lasR	163.0	transcriptional regulator LasR	[regulation of transcription, DNA-dependent, response to stimulus]	N	N
metK	114.0	methionine adenosyltransferase	[S-adenosylmethionine biosynthetic process, cellular amino acid metabolic process, metabolic process]	N	N
fur	79.0	ferric uptake regulation protein	[regulation of transcription, DNA-dependent]	N	N
lpdG	67.0	lipoamide dehydrogenase-glc	[cellular amino acid metabolic process, generation of precursor metabolites and energy]	N	N
mexT	66.0	transcriptional regulator MexT	[regulation of transcription, DNA-dependent]	Y	N
gabT	63.0	4-aminobutyrate aminotransferase	[cellular amino acid metabolic process, cellular catabolic process, gamma-aminobutyric acid catabolic process, metabolic process]	N	N
exsA	61.0	transcriptional regulator ExsA	[regulation of transcription, DNA-dependent, secretion]	Y	N
gabD	59.0	succinate-semialdehyde dehydrogenase	[cellular amino acid metabolic process, cellular catabolic process, gamma-aminobutyric acid catabolic process, metabolic process]	N	N
argR	79.0	ferric uptake regulation protein	[regulation of transcription, DNA-dependent]	N	N
rpoN	54.0	RNA polymerase sigma-54 factor	[regulation of transcription, DNA-dependent]	N	Y

Gene Ontology enrichment analysis

Functional enrichment of the integrated network was performed using the import Ontology data and annotation tool of the Cytoscape after choosing the reference organism *P. aeruginosa* PAO1. From this enrichment, one could have the following statistics, 1423 nodes (40% genes) out of 3585 nodes of the integrated network have GO annotation from the existing 3023 ontology annotations for *P. aeruginosa* PAO1.

Degree distribution was illustrated over the integrated network using the visualisation parameters tool with to criteria for visual style; node size, low values to small sizes and node color with low values to bright colours (i.e. from green to red) (Figure 9). This step was made to highlight the connection between the biological processes represented in the integrated network and the topological importance of the nodes involved.

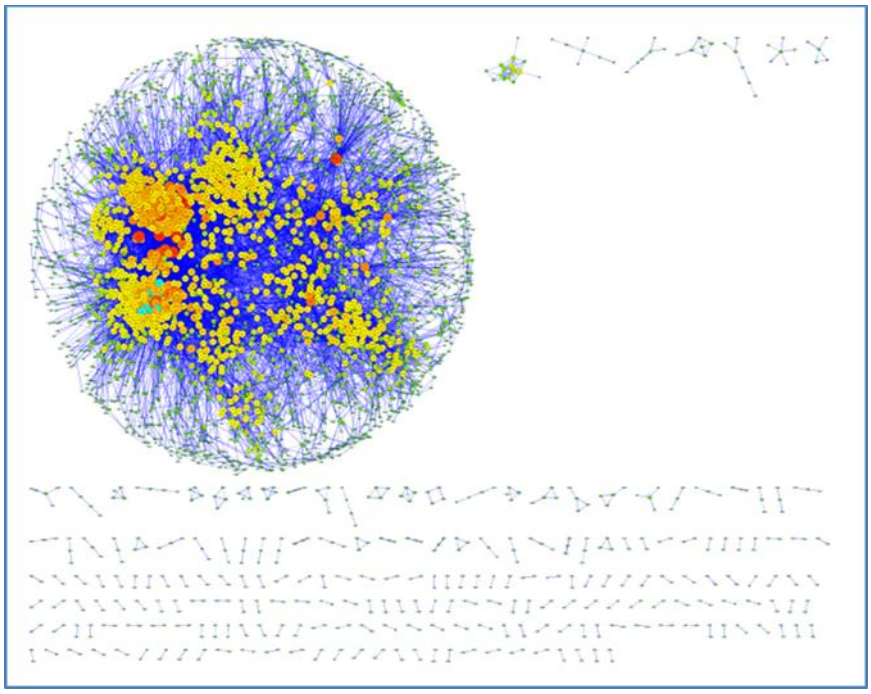

Figure 9: Degree parameter visualisation of the *P. aeruginosa* integrated network.

Thus, having the integrated network highlighted according to the topological feature degree distribution, other steps were made in order to filter the most relevant biological process annotated. First, the annotated nodes with the intended biological process were checked after using the filters separator of Cytoscape, in which the attribute GO_Biological process, imported for the annotation enrichment, was chosen. In this attribute it is possible to find all of the existing annotated processes and the corresponding nodes in the integrated network. This procure allowed the identification of the principal biological processes represented in the integrated network, which are *cellular amino acid metabolic process* (GO:0006520) with 195 nodes and the *cellular protein metabolic process* (GO:0044267) with 167 nodes. However, one could turn our attention in this filter for the scavenging of processes more related to pathogenesis and virulence, such as quorum sensing, response to stimulus, among others. The possibility of going beyond the simple detection of how many nodes existed in the integrated network, for a certain biological process, give rise to some additional steps. The objective was to create subnetworks, translating the biological process within the main network. Therefore, after applying the filter for a specific process, the nodes annotated appeared highlighted then, the adjacent edges were selected revealing the subnetwork within the integrated network. The three subnetworks depicted in Figure 10 were obtained based on the aforementioned steps. In subnetwork A the biological process represented is the *generation of precursor metabolites and energy* (GO:0006091) having 155

nodes and 1159 interactions, the subnetwork B represents the biological process *response to stimulus* (GO:0050896) with 110 nodes and 275 interactions and the last representation, subnetwork C depict the *quorum sensing* (GO:0009372) process, with only 24 nodes and 43 interactions.

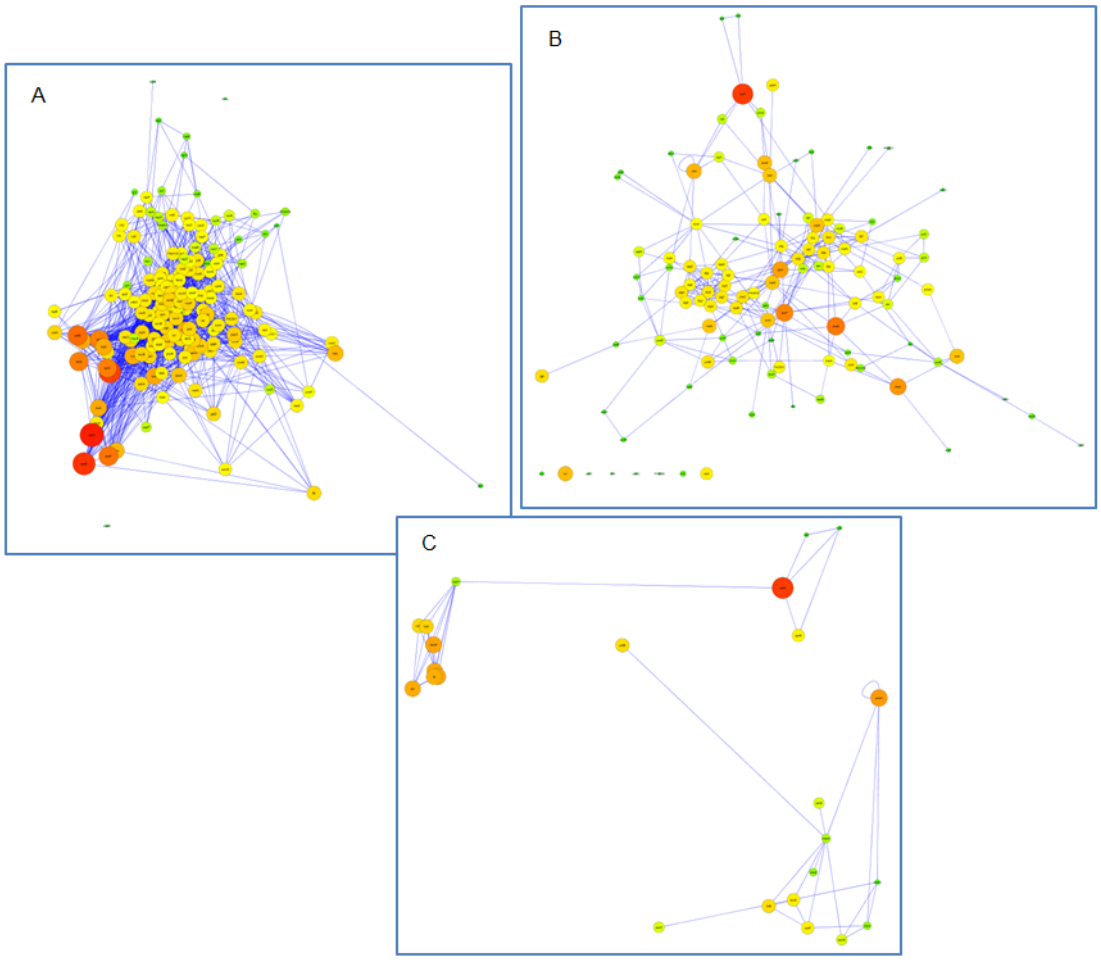

Figure 10: Gene Ontology enrichment analysis the colors of the nodes are the result of the degree visualisation parameter. A - *generation of precursor metabolites and energy* (GO:0006091), B - *response to stimulus* (GO:0050896) and C - quorum sensing (GO:0009372).

Taking advantage of the mask of degree distribution previously applied in the integrated network, the top values of degree (potentially hubs) were checked for each subnetwork. In subnetwork A the top values are assigned to the genes *lpdG*, ace and *sucA*, being only the succinate producer *sucA* considered as an essential gene. The subnetwork C has *lasR*, *dnaK* and *spoT* as the top values of degree, being only the gene *spoT*, responsible for nucleotide biosynthesis, assigned as essential gene. Finally, subnetwork C has also the gene *lasR*, and the bottleneck *pmrA*, which is essential as well as the *hemF* gene, involved in porphyrin and chlorophyll metabolism [28].

Close neighbours in protein interaction networks are commonly involved in similar processes and it has been shown that proteins in a cluster share at least one function [105]. In order, to identify the most represented functional modules in the integrated network, the molecular complex detection method, MCODE, a Cytoscape plugin, was applied [106]. This method allows the selection of densely connected subnetworks regions ignoring the rest of the network. In Figure 11 are illustrated the top three clusters (i.e. with a higher ranking score) of the total 122 clusters yielded by this plugin. These five clusters comprise 1153 nodes and 2709 interactions from the integrated network.

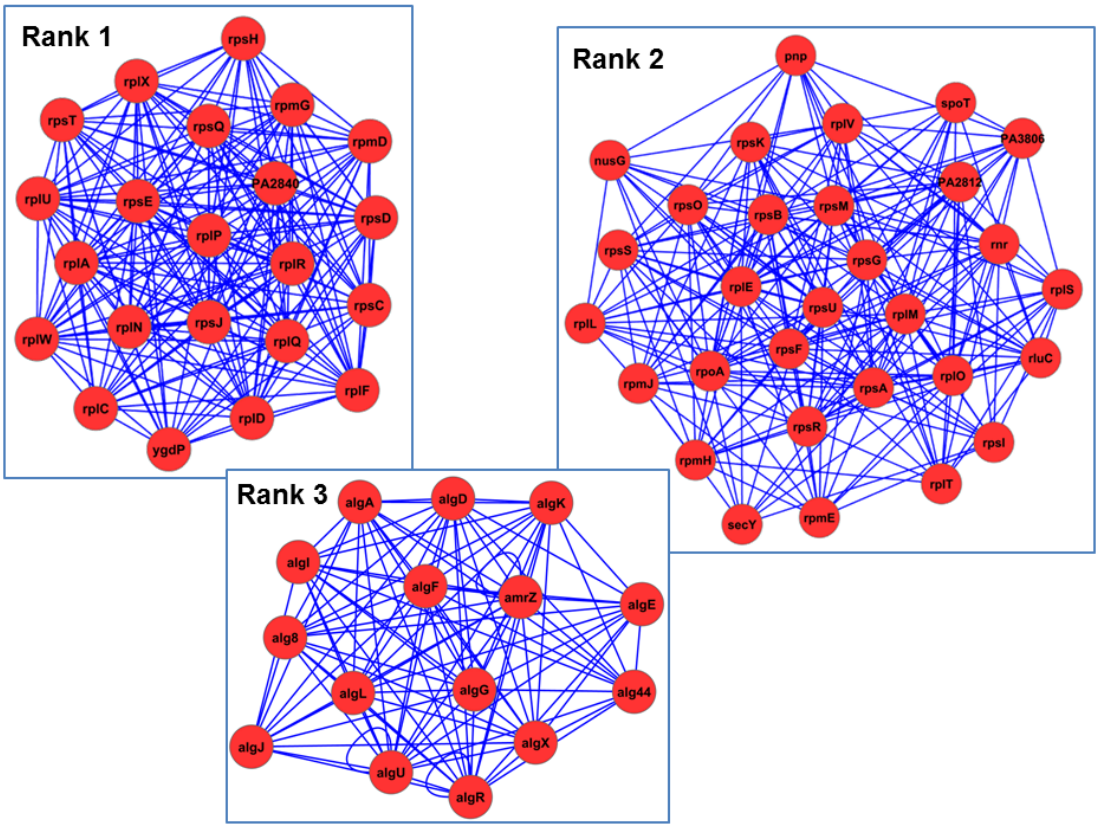

Figure 11: The top three higher ranked clusters afte MCODE application. The details of the 122 clusters obtained by this method are described in Appendix (Table A 3).

In this regard of MCODE clustering, different aspects were explored for the yielded clusters, such as the main biological process represented within the cluster, gene essentiality and topological importance (i.e. highly connected nodes - hubs). Thus the two clusters with higher rank, are mainly composed by ribosomal proteins, being highly enriched in the biological process, *cellular protein metabolic process* (GO:0044267) with the second cluster additionally enriched in *RNA metabolic process* (GO:0016070). The first clusters, in terms of top degree values have the

ribosomal proteins *rplA*, *rplC* and *rpsC*, in which only the *rplC* is non-essential. The second cluster has as top degree values the ribosomal proteins *rpsB*, *rplV*, *rpsG* which are all essential. At last the third cluster is enriched in the following biological processes *response to stimulus* (GO:0050896) and *alginic acid biosynthetic process* (GO:0042121), with the *algR* and *algU* assigned to the top degree values being *algU* an essential gene.

III.1.2 Discussion

In conclusion, this integrated network of *P. aeruginosa* is mainly affected by the PPI network of Zhang et al due to its size compared to the TRN of Galán et al. In fact, the influence is mainly reflected in the top ten hubs, which are exactly the same as the PPI network. In terms of network dynamics, namely the top ten bottlenecks, that influence is not reflected, but still there are some similarities against the two origin networks (*fur*, *mexT*, *lasR* and *rpoN*). Even the most represented biological processes (*cellular amino acid metabolic process* (GO:0006520) and the *cellular protein metabolic process* (GO:0044267)) are strongly associated to the PPI network. Although, the biological processes *generation of precursor metabolites and energy* (GO:0006091), and the *response to stimulus* (GO:0050896), the next most represented processes, are somehow related to the TRN of Galán et al. Therefore, this integrated network is enriched in metabolic processes and in some pathogenic processes, related to alginate biosynthesis, quorum sensing, iron metabolism, antibiotic resistance and production of virulence factors. Gene essentiality studies are public available in different sources for *P. aeruginosa*, and that information along with some important topological features (hubs and bottlenecks) could aid drug target discovery. During the study of this integrated network some essential genes and drug targets are pointed, and deserve further attention, namely the hubs *rpsB* and *rplA* and the bottlenecks *mexT* and *exsA*. The MCODE plugin application also revealed 37 essential genes from which only three of those were not consider drug targets. In fact in the first three higher ranked clusters the top degree values also follow this tendency.

III.2 *C. albicans* network mining – biofilm formation

As it was reviewed elsewhere [73] by our group and also in chapter 2, as result of the investigation process for the state of the art of this thesis, several biological networks of great quality and size have been described for *C. albicans*. However, only two networks were chosen to create an integrated network related to the main phenomenon of virulence for *C. albicans* – biofilm formation. Network dimension as well as biofilm formation as the main biological processes represented in the network were the key aspects for this choice. Therefore, only two TRN meet the previous criteria, the Nobile et al network, and the Wang et al network [17,90]. During this process of integration yet some issues appeared which had to be resolved being described in the following section of networks preparation.

III.2.1 Methods and Results

Networks pre-processing and integration

In order to obtain the TRN of Nobile et al, it was necessary to reconstruct the network based in the information provided in the supplementary material, more exactly the microarray data. Actually, this network has an image representation [17] but in the supplementary material there is not a file with all of the TF and target genes as well as the interactions of the network. In fact, only microarray and ChiP-chip data are available for a network reconstruction. Therefore, the microarray data was used to identify the target genes for each of the six TFs (Ndt80, Tec1, Brg1, Bcr1, Rob1 and Efg1), checking levels of expression different form zero. Thus, with all of the nodes of the TRN means the TF and the target genes the only part missing was the regulation. However, in theory the ChiP-chip data could give that information but an important value was missing in the description of this data, the cut-off value. Consequently, the establishment of a true TRN was not possible, since the information relative to the nature of the regulation (activation or inhibition) was not possible to ascertain. Another, issue emerged during this process, network reconstruction was made using the systematic name (i.e. orf19.2119) instead of the standard name (i.e. Ndt80), yet it was necessary to convert to the standard version, since the other network [90] was in that form (Figure 12). This conversion was done using a small script in perl, which compared each systematic name with an excel file from Candida Genome Database (CGD) [38], and if there was a standard name it made the conversion but if there was none it kept the systematic name.

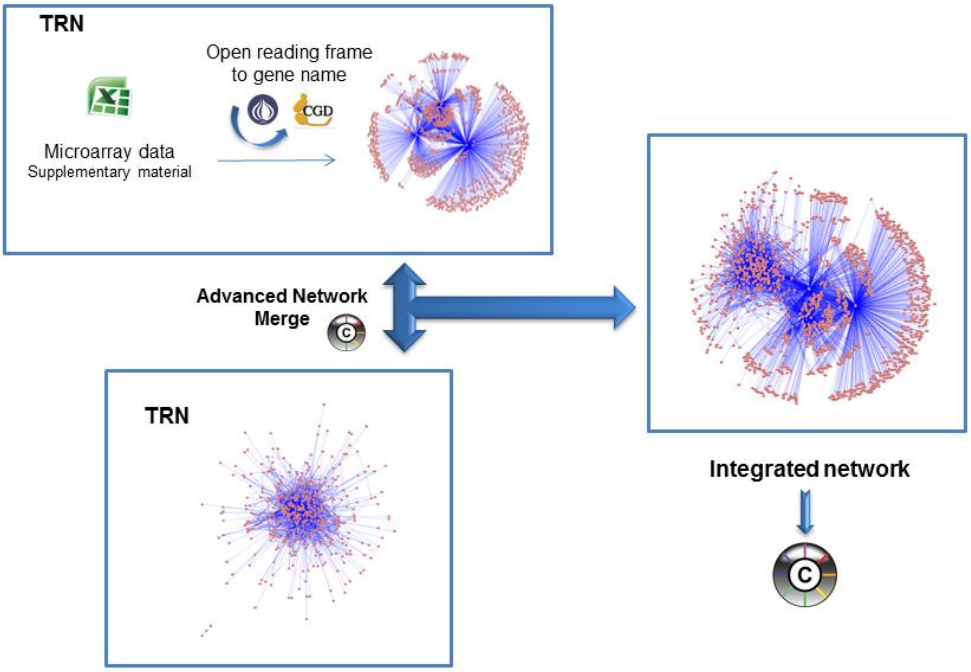

Figure 12: Description of the pre-processing treatment performed to each network and posterior network integration.

The network of Wang et al did not suffer any kind of intervention and since the two networks in its root are both TRN the comparison and integration was important for the augmentation on the knowledge on biofilm formation (Figure 12). In contrast, to the previous section of *P. aeruginosa* network mining, the Cytoscape tool "Advanced Network Merge" was used to merge the two networks, since in this case both networks are TRN. Thus, having one network with 1060 nodes and 2048 interactions [17] and the other with 438 nodes and 2149 interactions the final network obtained after merge has 1353 nodes and 4176 interactions. Still, this integrated network was constructed based in a PPI model, even though having both of the origin networks has TRN, since has it was explained before the Nobile et al network was not possible to be entirely reconstructed. Therefore one could say that the final integrated network is not a true PPI network, since it does not have the structure of protein-protein and only having the absence of interaction, which is not the same has having an interaction from the type protein-protein. This final integrated network was further analysed using the Cytoscape version v2.8.3 (Figure 12) [97].

Topological analysis – hubs and bottlenecks

The topological analysis of this integrated network starts from the most basic statistics to a detail analysis for the presence of hubs and bottlenecks. The network statistics, obtained by the Network analysis plugin are depicted in Figure 13 and Figure 14.

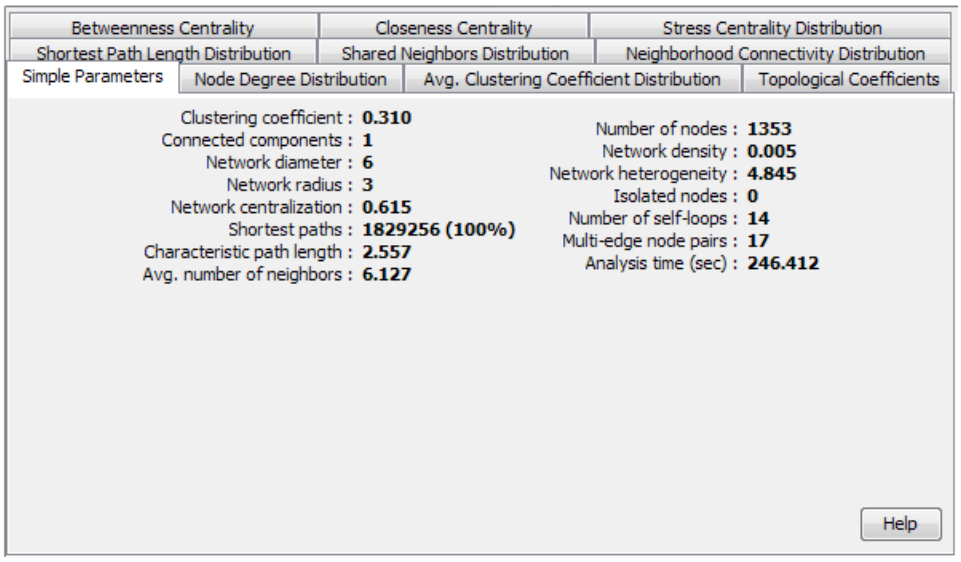

Figure 13: Network statistics of the new integrated network for C. albicans, obtained with Network analysis tool.

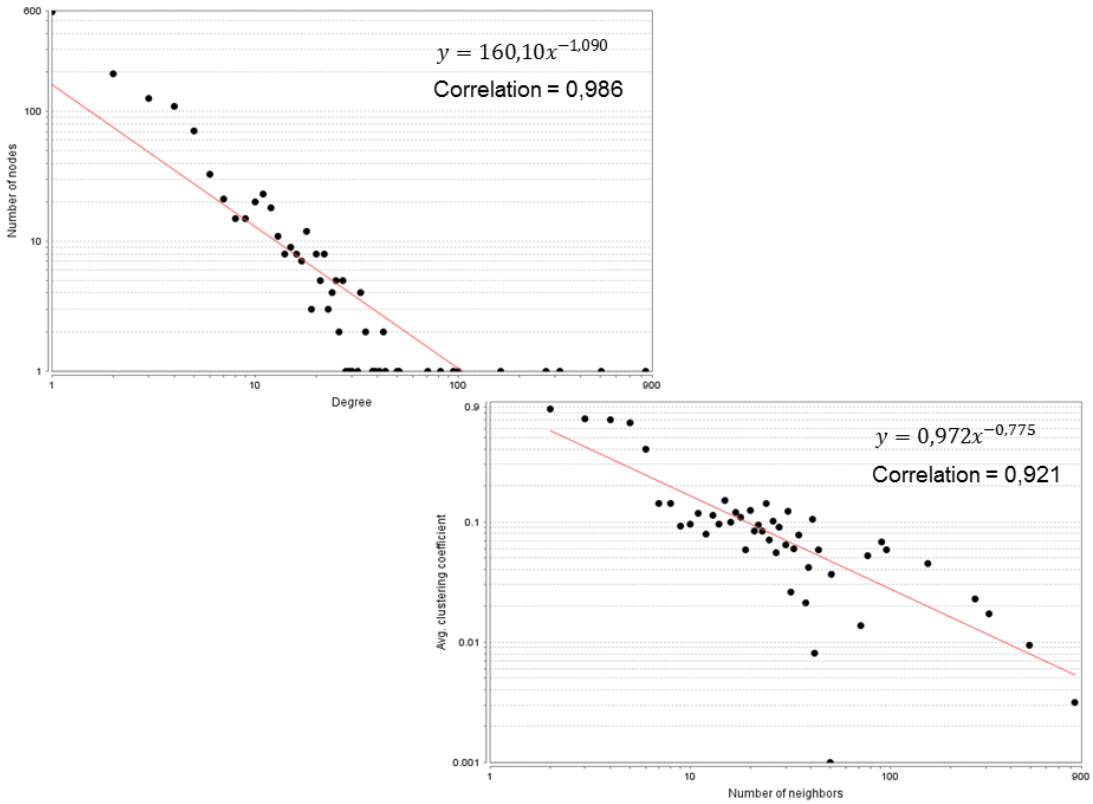

Figure 14: Degree distribution and clustering coefficient distribution of the integrated network.

This network displays a scale-free topology with an exponent degree (γ) of 1,09 which indicates the importance of the hubs in this network and also that since it ranges between 2 > γ > 3, there

is hierarchy of the hubs, being the most connected hub in contact with a small fraction of all nodes (Figure 14) [99]. Besides this property it presents the following values; 6,13, 0,31, 2,56 for average degree, clustering coefficient, and shortest path, respectively (Figure 13 and Figure 14). This network is comprised of a single principal component, it does not presents any connected components when checked by Network modifications plugin.

The degree distribution of the integrated network was computed with the Cyto-Hubba plugin, and the top ten group of genes with higher degree was obtained. The top ten hubs (Ndt80, Efg1, Brg1, Bcr1, Tec1, Rob1, Efh1, Cph1, orf19.5953 and Rap1) are depicted in Figure 15A and the annotated biological process is described in Table 3. Color intensity of the nodes translates the ranking score considering the degree feature.

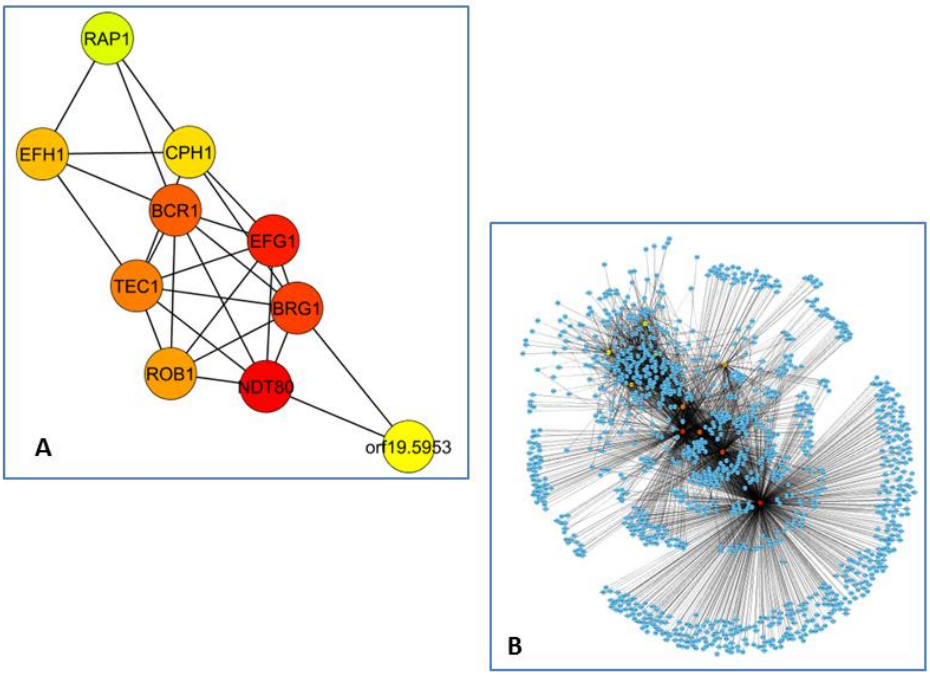

Figure 15: Cyto-Hubba results for the integrated network of C.albicans for the ranking method – Degree. Top ten hubs (A), first-stage nodes (B), shortest path of the top ten hubs (C) and the expanded subnetwork (D).

In this case there is no shortest path network, so only the first-stage nodes of the top ten with neighbours is represented in Figure 15B, in a network of 1186 nodes and 3285 interactions. Gene essentiality has been described elsewhere with a final number of 567 essential genes for *C. albicans* [107]. Although, these results are not publicly available since they were obtained inside a company project. Therefore, gene essentiality was checked in other sources, such as CGD [38],

with 296 essential genes and the Online Gene Essentiality database [108] in homology with *Saccharomyces cerevisiae*, with 350 essential genes (Table 3).

Table 3: Top ten hubs description including the information on the biological processes and gene essentiality.

ID	Degree	GO_Biological process	Essential
NDT80	839.0	[cellular response to N-acetyl-D-glucosamine, cellular response to biotic stimulus, cellular response to copper ion, cellular response to drug, cellular response to lithium ion, cellular response to oxidative stress, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to chemical stimulus, filamentous growth of a population of unicellular organisms in response to pH, hyphal growth, meiosis, pathogenesis, positive regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, positive regulation of filamentous growth of a population of unicellular organisms in response to chemical stimulus, positive regulation of filamentous growth of a population of unicellular organisms in response to pH, positive regulation of transcription from RNA polymerase II promoter, positive regulation of transcription from RNA polymerase II promoter in response to stress, regulation of single-species biofilm formation on inanimate substrate, regulation of transcription from RNA polymerase II promoter, single-species biofilm formation on inanimate substrate, transcription, DNA-dependent]	N
EFG1	507.0	[adhesion to host, cell adhesion, cell growth mode switching, budding to filamentous, cell migration, cell morphogenesis, cell-cell adhesion involved in flocculation, cell-substrate adhesion, cellular developmental process, cellular response to N-acetyl-D-glucosamine, cellular response to biotic stimulus, cellular response to chemical stimulus, cellular response to drug, cellular response to neutral pH, cellular response to starvation, chlamydospore formation, development of symbiont in host, entry into host, evasion or tolerance of host immune response, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to chemical stimulus, filamentous growth of a population of unicellular organisms in response to neutral pH, filamentous growth of a population of unicellular organisms in response to starvation, fungal-type cell wall organization or biogenesis, hyphal growth, negative regulation of transcription from RNA polymerase II promoter, pathogenesis, phenotypic switching, positive regulation of cell-substrate adhesion, positive regulation of filamentous growth of a population of unicellular organisms, positive regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, positive regulation of filamentous growth of a population of unicellular organisms in response to chemical stimulus, positive regulation of filamentous growth of a population of unicellular organisms in response to neutral pH, positive regulation of filamentous growth of a population of unicellular organisms in response to starvation, positive regulation of phenotypic switching, positive regulation of pseudohyphal growth, positive regulation of pseudohyphal growth by positive regulation of transcription from RNA polymerase II promoter, positive regulation of transcription from RNA polymerase II promoter, pseudohyphal growth, regulation of cell differentiation, regulation of phenotypic switching, regulation of pseudohyphal growth, regulation of single-species biofilm formation on inanimate substrate, regulation of transcription from RNA polymerase II promoter, regulation of transcription, DNA-dependent, single-species biofilm formation on inanimate substrate]	N
BRG1	317.0	[cellular response to biotic stimulus, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, pathogenesis, positive regulation of filamentous growth of a population of unicellular organisms, positive regulation of single-species biofilm formation on inanimate substrate, regulation of transcription from RNA polymerase II promoter, single-species biofilm formation on inanimate substrate]	

ID	Degree	GO_Biological process	Essential
BCR1	271.0	[carbon catabolite activation of transcription from RNA polymerase II promoter, cell-abiotic substrate adhesion, filamentous growth, growth of symbiont in host, positive regulation of cell adhesion involved in single-species biofilm formation, positive regulation of cell-substrate adhesion, positive regulation of growth of symbiont in host, positive regulation of transcription from RNA polymerase II promoter, regulation of single-species biofilm formation in or on host organism, regulation of single-species biofilm formation on inanimate substrate, regulation of transcription from RNA polymerase II promoter, regulation of transcription from RNA polymerase II promoter in response to salt stress, regulation of transcription, DNA-dependent, single-species biofilm formation in or on host organism, single-species biofilm formation on inanimate substrate]	
TEC1	162.0	[adhesion to host, cell adhesion, cellular response to biotic stimulus, chronological cell aging, development of symbiont in host, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to biotic stimulus, invasive growth in response to glucose limitation, pathogenesis, positive regulation of filamentous growth of a population of unicellular organisms, positive regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, positive regulation of pseudohyphal growth by positive regulation of transcription from RNA polymerase II promoter, positive regulation of transcription from RNA polymerase II promoter, positive regulation of transcription from RNA polymerase II promoter by pheromones, positive regulation of transcription from RNA polymerase II promoter in response to stress, positive regulation of transposition, RNA-mediated, pseudohyphal growth, regulation of pseudohyphal growth, regulation of single-species biofilm formation on inanimate substrate, regulation of transcription from RNA polymerase II promoter, regulation of transcription, DNA-dependent, single-species biofilm formation on inanimate substrate]	N
ROB1	100.0	[cellular response to biotic stimulus, chromatin remodeling, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, nucleosome positioning, positive regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, regulation of nitrogen utilization, regulation of single-species biofilm formation on inanimate substrate, regulation of transcription from RNA polymerase II promoter, single-species biofilm formation on inanimate substrate, transcription, DNA-dependent]	
EFH1	95.0	[growth of symbiont in host, negative regulation of transcription from RNA polymerase II promoter, phenotypic switching, positive regulation of phenotypic switching, positive regulation of transcription from RNA polymerase II promoter, pseudohyphal growth, regulation of cell differentiation, regulation of transcription from RNA polymerase II promoter]	
CPH1	82.0	[cellular response to biotic stimulus, cellular response to starvation, conjugation with cellular fusion, development of symbiont in host, evasion or tolerance of host immune response, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, fungal-type cell wall organization, galactose metabolic process, growth of unicellular organism as a thread of attached cells, invasive growth in response to glucose limitation, negative regulation of transcription from RNA polymerase II promoter by pheromones, pathogenesis, positive regulation of filamentous growth of a population of unicellular organisms, positive regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, positive regulation of filamentous growth of a population of unicellular organisms in response to starvation, positive regulation of growth of unicellular organism as a thread of attached cells, positive regulation of pseudohyphal growth by positive regulation of transcription from RNA polymerase II promoter, positive regulation of transcription from RNA polymerase II promoter by pheromones, pseudohyphal growth, regulation of filamentous growth of a population of unicellular organisms, regulation of pseudohyphal growth, regulation of single-species biofilm formation on inanimate substrate, regulation of transcription, DNA-dependent, signal transduction, single-species biofilm formation on inanimate substrate]	N
orf19.5953	71.0	[positive regulation of ribosomal protein gene transcription from RNA polymerase II promoter, regulation of cell size]	Y (CGD)

ID	Degree	GO_Biological process	Essential
RAP1	51.0	[chromatin silencing at silent mating-type cassette, establishment of chromatin silencing at telomere, establishment of protein localization to chromatin, establishment of protein localization to telomere, filamentous growth, filamentous growth of a population of unicellular organisms, negative regulation of chromatin silencing, negative regulation of pseudohyphal growth, negative regulation of transcription from RNA polymerase II promoter, protection from non-homologous end joining at telomere, pseudohyphal growth, regulation of glycolysis by positive regulation of transcription from RNA polymerase II promoter, regulation of transcription by chromatin organization, regulation of transcription, DNA-dependent, telomere capping, telomere maintenance, telomere maintenance via telomere lengthening]	Y (OGEE)

Gene essentiality and topological importance are pointed as important clues for potential drug targets discovery [87]. However, in this group of hubs there is only two genes pointed as essential, orf19.5953 and Rap1. These two hubs are both considering TFs, being orf19.5953 predicted to regulate ribosomal protein and biogenesis and Rap1 to be involved in telomere maintenance and hyphal growth repression under yeast favouring conditions [109,110].

The presence of bottlenecks was also checked to confirm is importance in network dynamics and integrity, as well as potential drug targets. Likewise, Cyto-Hubba plugin was used to compute the bottleneck results for the integrated network, the top ten group (Ndt80, Efg1, Tec1, Cph1, Brg1, Cph2, orf19.5953, Rfg1 and Fgr15) is depicted in Figure 16A and detail description with the annotated biological process is described in Table 4. Color intensity of the nodes translates the ranking score considering the bottleneck feature. Similarly, there is no shortest path network, so only the first-stage nodes of the top ten with neighbours is represented in Figure 16B, in a network of 1182 nodes and 3373 interactions.

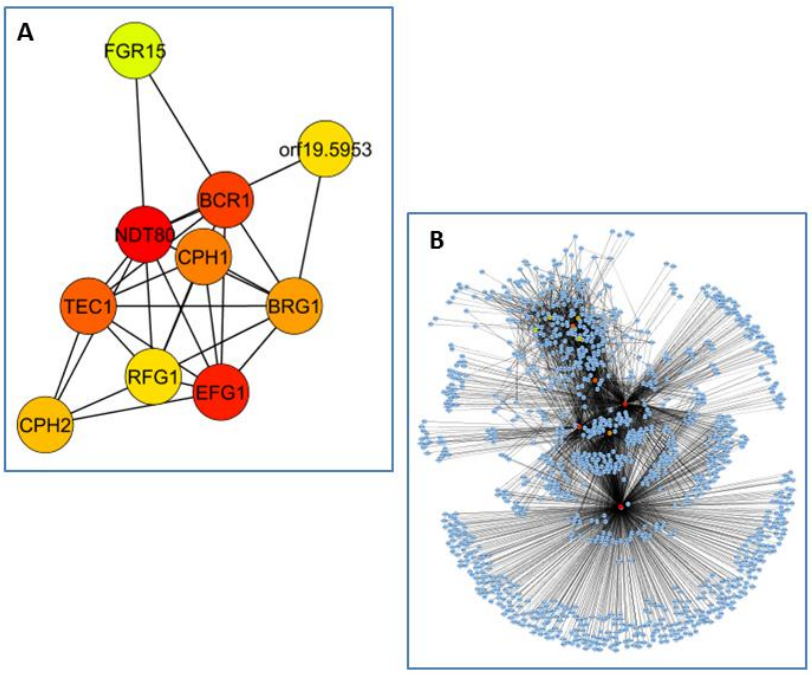

Figure 16: Cyto-Hubba results for the integrated network of P. aeruginosa for the ranking method – Bottleneck. Top ten bottlenecks (A), first-stage nodes (B), shortest path of the top ten hubs (C) and the expanded subnetwork (D).

Table 4: Top ten bottlenecks description including the information on the biological processes and gene essentiality.

ID	Bottleneck	GO_Biological process	Essential
NDT80	1353.0	[cellular response to N-acetyl-D-glucosamine, cellular response to biotic stimulus, cellular response to copper ion, cellular response to drug, cellular response to lithium ion, cellular response to oxidative stress, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to chemical stimulus, filamentous growth of a population of unicellular organisms in response to pH, hyphal growth, meiosis, pathogenesis, positive regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, positive regulation of filamentous growth of a population of unicellular organisms in response to chemical stimulus, positive regulation of filamentous growth of a population of unicellular organisms in response to pH, positive regulation of transcription from RNA polymerase II promoter, positive regulation of transcription from RNA polymerase II promoter in response to stress, regulation of single-species biofilm formation on inanimate substrate, regulation of transcription from RNA polymerase II promoter, single-species biofilm formation on inanimate substrate, transcription, DNA-dependent]	N

ID	Bottleneck	GO_Biological process	Essential
EFG1	526.0	[adhesion to host, cell adhesion, cell growth mode switching, budding to filamentous, cell migration, cell morphogenesis, cell-cell adhesion involved in flocculation, cell-substrate adhesion, cellular developmental process, cellular response to N-acetyl-D-glucosamine, cellular response to biotic stimulus, cellular response to chemical stimulus, cellular response to drug, cellular response to neutral pH, cellular response to starvation, chlamydospore formation, development of symbiont in host, entry into host, evasion or tolerance of host immune response, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to chemical stimulus, filamentous growth of a population of unicellular organisms in response to neutral pH, filamentous growth of a population of unicellular organisms in response to starvation, fungal-type cell wall organization or biogenesis, hyphal growth, negative regulation of transcription from RNA polymerase II promoter, pathogenesis, phenotypic switching, positive regulation of cell-substrate adhesion, positive regulation of filamentous growth of a population of unicellular organisms, positive regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, positive regulation of filamentous growth of a population of unicellular organisms in response to chemical stimulus, positive regulation of filamentous growth of a population of unicellular organisms in response to neutral pH, positive regulation of filamentous growth of a population of unicellular organisms in response to starvation, positive regulation of phenotypic switching, positive regulation of pseudohyphal growth, positive regulation of pseudohyphal growth by positive regulation of transcription from RNA polymerase II promoter, positive regulation of transcription from RNA polymerase II promoter, pseudohyphal growth, regulation of cell differentiation, regulation of phenotypic switching, regulation of pseudohyphal growth, regulation of single-species biofilm formation on inanimate substrate, regulation of transcription from RNA polymerase II promoter, regulation of transcription, DNA-dependent, single-species biofilm formation on inanimate substrate]	N
BCR1	254.0	[carbon catabolite activation of transcription from RNA polymerase II promoter, cell-abiotic substrate adhesion, filamentous growth, growth of symbiont in host, positive regulation of cell adhesion involved in single-species biofilm formation, positive regulation of cell-substrate adhesion, positive regulation of growth of symbiont in host, positive regulation of transcription from RNA polymerase II promoter, regulation of single-species biofilm formation in or on host organism, regulation of single-species biofilm formation on inanimate substrate, regulation of transcription from RNA polymerase II promoter, regulation of transcription from RNA polymerase II promoter in response to salt stress, regulation of transcription, DNA-dependent, single-species biofilm formation in or on host organism, single-species biofilm formation on inanimate substrate]	N

ID	Bottleneck	GO_Biological process	Essential
TEC1	52.0	[adhesion to host, cell adhesion, cellular response to biotic stimulus, chronological cell aging, development of symbiont in host, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to biotic stimulus, invasive growth in response to glucose limitation, pathogenesis, positive regulation of filamentous growth of a population of unicellular organisms, positive regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, positive regulation of pseudohyphal growth by positive regulation of transcription from RNA polymerase II promoter, positive regulation of transcription from RNA polymerase II promoter, positive regulation of transcription from RNA polymerase II promoter by pheromones, positive regulation of transcription from RNA polymerase II promoter in response to stress, positive regulation of transposition, RNA-mediated, pseudohyphal growth, regulation of pseudohyphal growth, regulation of single-species biofilm formation on inanimate substrate, regulation of transcription from RNA polymerase II promoter, regulation of transcription, DNA-dependent, single-species biofilm formation on inanimate substrate]	N
CPH1	36.0	[cellular response to biotic stimulus, cellular response to starvation, conjugation with cellular fusion, development of symbiont in host, evasion or tolerance of host immune response, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, fungal-type cell wall organization, galactose metabolic process, growth of unicellular organism as a thread of attached cells, invasive growth in response to glucose limitation, negative regulation of transcription from RNA polymerase II promoter by pheromones, pathogenesis, positive regulation of filamentous growth of a population of unicellular organisms, positive regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, positive regulation of filamentous growth of a population of unicellular organisms in response to starvation, positive regulation of growth of unicellular organism as a thread of attached cells, positive regulation of pseudohyphal growth by positive regulation of transcription from RNA polymerase II promoter, positive regulation of transcription from RNA polymerase II promoter by pheromones, pseudohyphal growth, regulation of filamentous growth of a population of unicellular organisms, regulation of pseudohyphal growth, regulation of single-species biofilm formation on inanimate substrate, regulation of transcription, DNA-dependent, signal transduction, single-species biofilm formation on inanimate substrate]	N
BRG1	33.0	[cellular response to biotic stimulus, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, pathogenesis, positive regulation of filamentous growth of a population of unicellular organisms, positive regulation of single-species biofilm formation on inanimate substrate, regulation of transcription from RNA polymerase II promoter, single-species biofilm formation on inanimate substrate]	N

ID	Bottleneck	GO_Biological process	Essential
CPH2	23.0	[cellular response to chemical stimulus, cellular response to copper ion, cellular response to drug, cellular response to heat, cellular response to neutral pH, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to chemical stimulus, filamentous growth of a population of unicellular organisms in response to neutral pH, positive regulation of filamentous growth of a population of unicellular organisms, positive regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, positive regulation of filamentous growth of a population of unicellular organisms in response to chemical stimulus, positive regulation of filamentous growth of a population of unicellular organisms in response to neutral pH, positive regulation of pseudohyphal growth by positive regulation of transcription from RNA polymerase II promoter, positive regulation of transcription from RNA polymerase II promoter, pseudohyphal growth, regulation of pseudohyphal growth, regulation of transcription from RNA polymerase II promoter, regulation of transcription, DNA-dependent, symbiosis, encompassing mutualism through parasitism]	N
orf19.5953	21.0	[positive regulation of ribosomal protein gene transcription from RNA polymerase II promoter, regulation of cell size]	Y (CGD)
RFG1	21.0	[cellular response to biotic stimulus, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, negative regulation of filamentous growth of a population of unicellular organisms, negative regulation of transcription from RNA polymerase II promoter, negative regulation of transcription from RNA polymerase II promoter in response to stress, negative regulation of transcription, DNA-dependent, pathogenesis, regulation of transcription from RNA polymerase II promoter]	
FGR15	18.0	[cellular response to biotic stimulus, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, regulation of transcription, DNA-dependent]	

Gene essentiality was once more analysed, and in this group of bottlenecks only one gene was pointed as essential, the previously mentioned hub orf19.5953.

Gene Ontology enrichment analysis

The functional enrichment of the integrated network was performed as mentioned before for *P. aeruginosa*, choosing as reference organism *C. albicans*. From this enrichment resulted the following statistics; 1276 nodes (94% genes) out of 1353 nodes of the integrated network have

GO annotation from the existing 6366 ontology annotations for *C. albicans*. Degree distribution was illustrated over the integrated network as it is depicted in Figure 17.

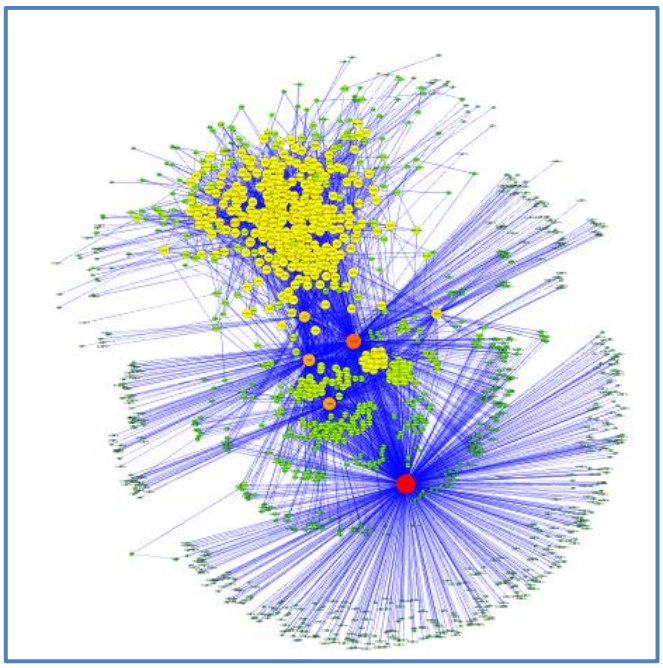

Figure 17: Degree parameter visualisation of the *C. albicans* integrated network.

The filter tool of Cytoscape was used to verify, what were the most representative biological processes annotated within the integrated network. In Figure 18 are the main biological processes annotated in the integrated network, such as *filamentous growth* (GO:0030447) (subnetwork A), *single-species biofilm formation on inanimate substrate* (GO:0044011) (subnetwork B), *pathogenesis* (GO:0009405) (subnetwork C) and *quorum sensing* (GO:0009372) (subnetwork D).

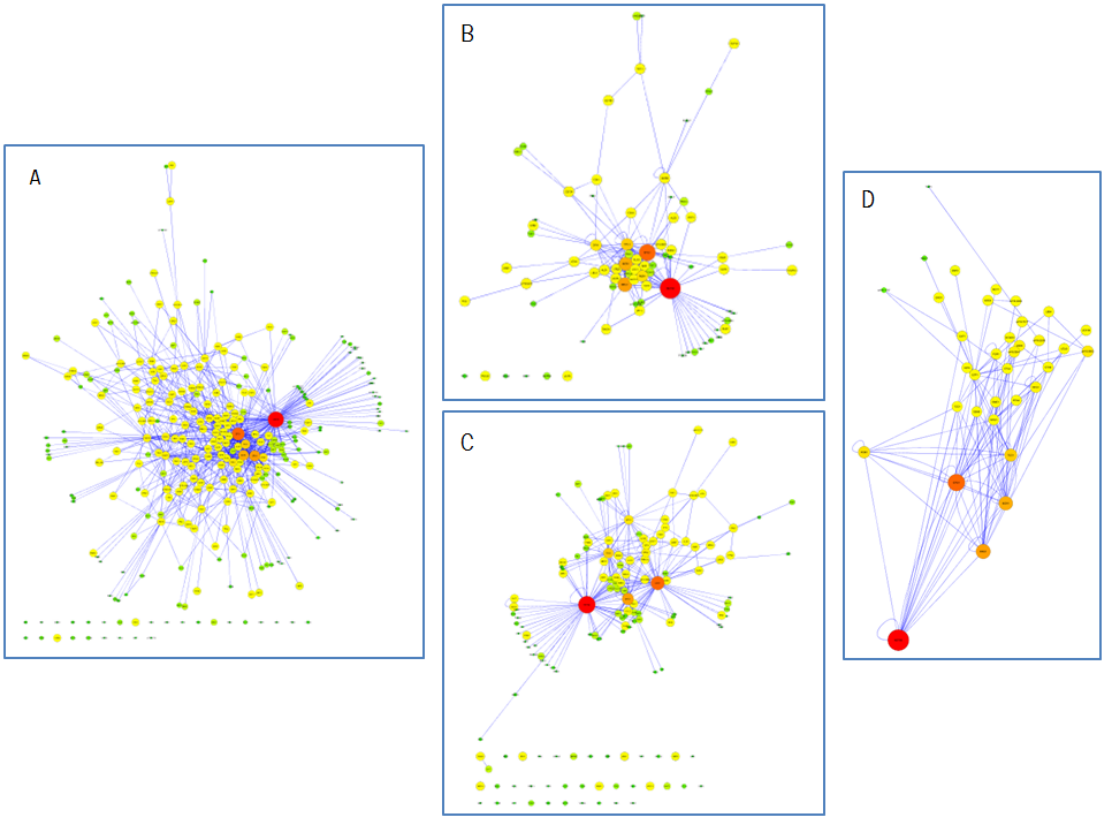

Figure 18: Gene Ontology enrichment analysis the colors of the nodes are the result of the degree visualisation parameter. A - *filamentous growth* (GO:0030447), B - *single-species biofilm formation on inanimate substrate* (GO:0044011), C - *pathogenesis* (GO:0009405) and D - *quorum sensing* (GO:0009372).

Biofilm formation constitutes the most represented biological process within the integrated network, as it is possible to assess by the two subnetworks A and B, with 293 nodes and 797 interactions and 79 nodes and 185 interactions, respectively (Figure 18). The pathogenesis phenomenon itself it is also represented with a subnetwork (C) of 150 nodes and 260 interactions, in which quorum sensing as part as *C. albicans* pathogenesis could be included with a subnetwork (D) of 35 nodes and 119 interactions. Additionally, having in mind the mask of degree distribution previously applied to the integrated network, the top values of degree were checked for each subnetwork. Indeed, some aspects are common to all subnetworks, the first four genes are Ndt80, Efg1, Brg1 and Tec1, but then the next genes differ. In the subnetwork A, related to filamentous growth, the next two most relevant genes are Cph1 and the essential gene Rap1. The subnetwork B, also involved in biofilm formation has Rob1 and Cph1 as the next most important genes. The subnetwork C, representing the broad phenomenon of pathogenesis, has also Cph1, such as the subnetwork A but differ in the next gene which is Rfg1. Finally, the subnetwork D, illustrating quorum sensing phenomenon, by the annotated genes Czf1, Nrg1 and

Tup1 [91,111,112], has also Rob1, like the subnetwork B but differ in the next gene which is orf19.5953 that is consider an essential gene.

The Cytoscape plugin MCODE was applied to the integrated network to search for clusters of related genes, which may potentially share the same biological process. In Figure 19 are illustrated the top three clusters (i.e. with a higher ranking score) of the total five clusters yielded by this plugin. These five clusters comprise 39 nodes and 65 interactions from the integrated network.

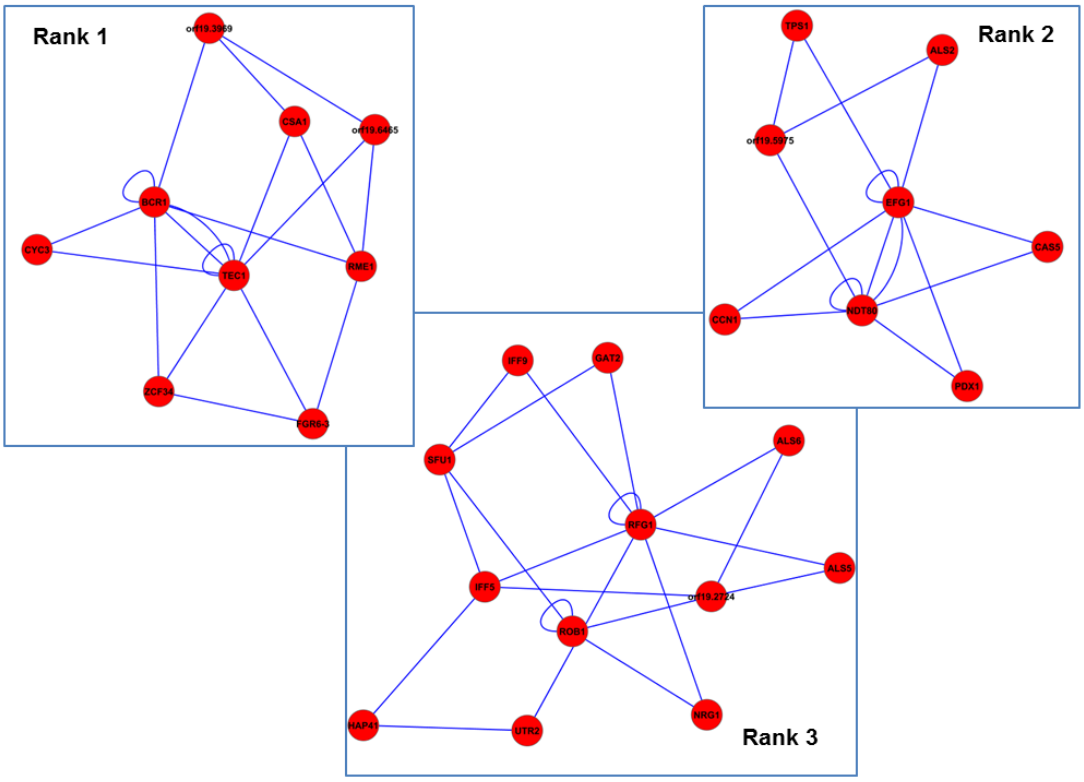

Figure 19: The top three higher ranked clusters afte MCODE application.

The details of the 122 clusters obtained by this method are described in Appendix (Table A 4).

Therefore, after a detail evaluation of the yielded clusters the following features were disclosed; the main biological process, gene essentiality of the nodes within the cluster and its topological importance. Thus, the first cluster is highly enriched in the biological processes, *filamentous growth* (GO:0030447) and *single-species biofilm formation on inanimate substrate* (GO:0044011) and it has two hubs Bcr1 and Tec1. The second cluster is also enriched in the previously mentioned biological processes adding the *pathogenesis* (GO:0009405) process and has as hubs the genes Ndt80 and Efg1. At last, the third cluster is very similar to the previous clusters, in terms of biological processes represented, having *cellular response to biotic stimulus*

(GO:0071216) as an additional process, and Rob1 and Rfg1 as hubs. In fact, only the third cluster has two essential genes, according to CGD, which are the adhesin-like protein Iff5 [113] and the cell-wall protein Iff9 [114].

III.2.3 Discussion

Taken together, the integrated network and analysis obtained in this section is largely interconnected with the two biological networks of origin. In fact, that is mainly reflected in the hubs and bottlenecked found, constituting important genes for the enlightenment on biofilm formation in *C. albicans*. The TFs pointed as key factors in biofilm formation are; Ndt80, Efg1, Brg1, Tec1, Rob1, Efh1, Cph1, orf19.5953 and Rap1, the first five genes were already experimentally validated by the study of Nobile et al and the last four were the result of literature curation by the study of Wang et al, having also pointed the genes Efg1 and Tec1. The network dynamics could be largely affected being translated in bottleneck genes. Likewise, the top ten bottleneck genes are also a reflection of the origin networks, mainly from the Wang et al network. In fact, there are seven bottlenecks, that came from the literature curation of biofilm-related TFs, which are; Efg1, Tec1, Cph1, Cph2, orf19.5953, Rfg1 and Fgr15. On the other hand, other bottlenecks resulting from the Nobile et al study are also pointed, such as Ndt80, Efg1, Tec1 and Brg1, being some of them shared by the study of Wang et al. The biological processes annotated in the integrated network are, as expected, mostly related to biofilm formation being the most significant the *filamentous growth* (GO:0030447) process and the *single-species biofilm formation on inanimate substrate* (GO:0044011). However, there is also a relevant contribution of the biological process *pathogenesis* (GO:0009405), as well as a small fraction of the *quorum sensing* (GO:0009372) process, which is also represented. Gene essentiality is still a subject of concern for *C. albicans*, when it is tried to test the hypothesis of gene essentiality and topological importance and consequently possible drug target discovery. Till now there are not too many sources that could help us in the gene essentiality assignment. However, even with those limitations there were found three essential genes, orf19.5953, classified both as hub and bottleneck and also the genes Iff5 and Iff9, which appeared in a cluster obtained by MCODE plugin. In fact, one could only point orf19.5953 as a possible drug target since it is a highly connected node in the network and it is indicated by Wang et al as a biofilm-related TF.

III.3 Beyond individuality – mining cross-talking

P. aeruginosa and *C. albicans* are commoly found in mixed polymicrobial communities, being frequently identified in cases of hospital-acquired infections, in the lungs of cystic fibrosis patients and in the respiratory tract of ventilated patients [52]. The nature of this interaction and all of the processes involved had been subject of research, and nowadays there are some insights into this phenomenon of cross-talking. *In vitro* studies show the wide spectrucm of this interaction between *P. aeruginosa* and *C. albicans*, some of the most important are depicted in Figure 20.

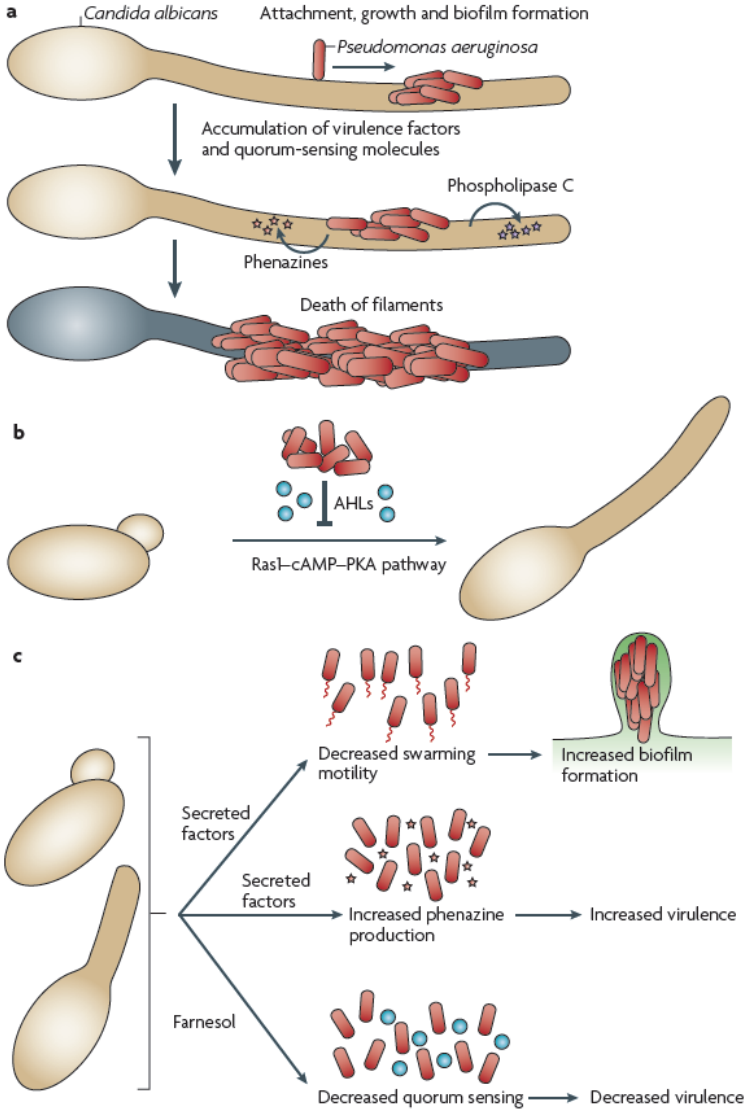

Figure 20: Molecular description of the mechanisms involved in the phenomenon of cross-talking between *P. aeruginosa* and *C. albicans*.

a) *P. aeruginosa* and *C. albicans* attatchament. b) quorum sensing phenomenon and its involment in *C. albicans* cell death. c) modulation of farnesol and secreted factors of *C. albicans* on *P. aeruginosa* [115].

P. aeruginosa adheres to *C. albicans* in its hyphae form, not being able to adhere to the yeast form, forming biofilms in *C. albicans* filaments [116]. Remarkably *P. aeruginosa* appears to limit the growth of *C. albicans in vitro*, this effect is mainly caused by the production of phospholipase C, phenazines (including pycocyanin), and the accumulation of several virulence factors including, GacA, LasR, RhlR and RpoN leading to the death of the fungal cells (Figure 20a) [116–119]. The quorum-sensing system of *P. aeruginosa* is highly involved in this interaction. The *Pseudomonas* QS signal molecule 3OC12HSL (*las* system) not only regulates the adhesion to *C. albicans*, but also modulates the morphological switch by preventing the yeast-to-hypha transition or by the activating the genes promoting the hypha-to-yeast reversion (Figure 20b) [117,120]. *C. albicans* senses the 3OC12HSL as a warning molecule and reacts secreting its QS molecule, farnesol, which in low cell densities inhibits Pseudomonas quinolone signal (PQS) production, responsible for the expression of several virulence factors [118,119]. Additionally, some uncharacterized *C.albicans* secreted factors increase the production of virulence factors, such as phenazines, or lead to the alteration of swarming mobility increasing biofilm formation (Figure 20c). Some insights into these unknown secreted factors are being achieved by some *in vitro* studies which take advantage of the new "Omics" approaches [121,122].

III.3.1 Methods and Results

Literature curation – implicated genes

The pursuit for genes implicated in the phenomenon of cross-talking between *P. aeruginosa* and *C. albicans* passed through several phases. First, a large spectrum research of papers related to this phenomenon was done in Pubmed [123], using simple tags, such as cross-talking and cross-kingdom associated to the names of the two species. Then, after having some papers which fell into these critera, they were read carefully to get more insigths into this phenomenon. In fact, experimental evidences were scavenged in these papers in order to find the original works to be further analysed. Therefore, having in mind the important processes related to this phenomenon, and the papers which described and associate the most important related genes for each microorganism the following Table 5 and

Table 6 were constructed. Thus, these two tables are organized as follow; first the accession, which means, the locus tag or systematic name for *P. aeuginosa* and *C. albicans*, respectively, then the name of the gene or protein, the third column is related to the function of the gene or protein, the next column describe the phenotype associated to the cross-talking phenomenon, the fith column indicates if the present gene or protein is essential, the sixth column points which are the genes present in the two integrated networks and the last one gives the references for the papers in which those genes or proteins were described.

After an analysis of these two tables it was possible to retrieve the following statistics. First and the most important, is the number of gene/proteins which are also identified in the integrated networks, then for *P. aeruginosa* there are 87 genes/proteins (81,3%) from the 107 identified, and for *C.albicans* there are 49 (73,1%) from the 67 identified. Second, there is the number of essential genes, since even in this phenomenon of cross-talking the important of gene essentiality is also tested. Thus, for *P. aeruginosa* there are 13 genes/proteins classified as essential (*acpP*, *trxA*, *argR*, *dnaN*, *glnK*, *groEL*, *groES*, *ndk*, *oprL*, PA0456, PA2659, PA3441, *ppa*) being all represented in the integrated network, and for *C. albicans* the number of essential genes drops to six, in which only two (Cyr1, Nup85) are present in the integrated network. The essential genes identified for *P. aeruginosa* were all identified in the study of Purschke et al, in which the adopted strategy was to study the secretome of the single and mixed biofilms of *P. aeruginosa* and *C. albicans* [122]. In contrast, for *C. albicans* there were two different contributions for each gene, the work of Xu et al, for the gene Cyr1 and the work of Holcombe et al for the gene Nup85 [121,124].

Table 5: *P. aeruginosa* genes involved in the cross-talking phenomenon between *P. aeruginosa* and *C. albicans*, retrieved from literature.

Accession	Name	Function	Phenotype	Essential	Integrated network	References
PA3477	rhlR	N-(butanoyl)-L-homoserine lactone QS system,	delay or attenuate virulence toward *C. albicans*/farnesol stimulate RhlR activiity and the production of C4HSL	N	Y	[125] [117] [126]
PA3476	rhlI	N-(butanoyl)-L-homoserine lactone QS system	defective mutants	N	Y	[117]
PA1430	lasR	N-(3-oxo-dodecanoyl)-L-homoserine lactone QS system,	delay or attenuate virulence toward *C. albicans*/unable to produce 3OC12HSL	N	Y	[125][117]
PA1432	lasI	N-(3-oxo-dodecanoyl)-L-homoserine lactone QS system,	delay or attenuate virulence toward *C. albicans*/unable to produce 3OC12HSL	N	Y	[117]
PA4462	rpoN	RNA polymerase sigma-54 factor	mutants forms poor biofilms in *C.albicans*	N	Y	[125]
PA0844	plcH	Hemolytic phospholipase C	mutants are significantly attenuated in the ability to kill *C. albicans*	N	Y	[125][117]
PA0843	plcR	Hemolytic phospholipase C	mutants are significantly attenuated in the ability to kill *C. albicans*	N	Y	[125][117]
PA1001	phnA	phenazine biosynthesis	defective mutants in redox-active phenazines	N	Y	[125][117]
PA1002	phnB	phenazine biosynthesis	defective mutants in redox-active phenazines	N	Y	[125][117]
PA4526	pilB	Type IV pili biosynthesis and adhesion	initial attachment to *C.albicans* filaments	N	Y	[125]
PA4527	pilC	Type IV pili biosynthesis and adhesion	initial attachment to *C.albicans* filaments	N	Y	[125]

Accession	Name	Function	Phenotype	Essential	Integrated network	References
PA3540	algD	Alginate biosynthesis	defective mutants	N	Y	[117]
PA3724	lasB	Elastase	defective mutants	N	Y	[117] [122]
PA3479	rhlA	Rhamnolipid biosynthesis	defective mutants	N	Y	[117]
PA1716	pscC	Type III secretion outer membrane protein PscC precursor	defective mutants	N	Y	[117]
PA1003	mvfR	TF MfvfR, regulates phnAB operon	farnesol inhibit the production of PQS - phenazines including pyocyanin; farnesol promotes PqsR binding to *pqsA* promoter	N	Y	[118][126]
PA2587	pqsH	Biosynthesis of cofactors also related to quorum sensing	pqsH expression was sufficient to restore pycocyanin and PQS production in *lasR* and *lasI* mutants	N	Y	[126]
PA2966	acpP	Fatty acid and phospholipid metabolism	secreted proteins in mixed biofilms	Y	Y	[122]
PA0283	sbp	Transport of small molecules	secreted proteins in mixed biofilms	N	Y	[122]
PA4366	sodB	Adaptation, Protection	secreted proteins in mixed biofilms	N	Y	[122]
PA0300	spuD		secreted proteins in mixed biofilms	N	Y	[122]
PA1148	toxA	Secreted Factors (toxins, enzymes, alginate)	secreted proteins in mixed biofilms		Y	[122]
PA5240	trxA	Translation, post-translational modification, degradation	secreted proteins in mixed biofilms	Y	Y	[122]
PA2616	trxB1	Nucleotide biosynthesis and metabolism	secreted proteins in mixed biofilms	N	Y	[122]
PA4265	tufA	Translation, post-translational modification, degradation	secreted proteins in mixed biofilms	N	Y	[122]
PA0807	ampDh3	Antibiotic resistance and susceptibility	secreted proteins in mixed biofilms	N		[122]
PA0888	aotJ	Transport of small molecules	secreted proteins in mixed biofilms	N	Y	[122]

Accession	Name	Function	Phenotype	Essential	Integrated network	References
PA1249	aprA	Secreted Factors (toxins, enzymes, alginate)	secreted proteins in mixed biofilms	N	Y	[122]
PA5171	arcA	Amino acid biosynthesis and metabolism	secreted proteins in mixed biofilms	N	Y	[122]
PA5172	arcB	Amino acid biosynthesis and metabolism	secreted proteins in mixed biofilms	N	Y	[122]
PA0893	argR	Amino acid biosynthesis and metabolism	secreted proteins in mixed biofilms	Y	Y	[122]
PA3117	asd	Amino acid biosynthesis and metabolism	secreted proteins in mixed biofilms	N	Y	[122]
PA4922	azu	Energy metabolism	secreted proteins in mixed biofilms	N	Y	[122]
PA1074	braC	Transport of small molecules	secreted proteins in mixed biofilms	N	Y	[122]
PA0852	cbpD	Secreted Factors (toxins, enzymes, alginate)	secreted proteins in mixed biofilms	N	Y	[122]
PA4625	cdrA	Secreted Factors (toxins, enzymes, alginate)	secreted proteins in mixed biofilms	N	Y	[122]
PA2787	cpg2	Central intermediary metabolism	secreted proteins in mixed biofilms	N	Y	[122]
PA4648	cupE1	Cell wall / LPS / capsule	secreted proteins in mixed biofilms	N	Y	[122]
PA4761	dnaK	DNA replication, recombination, modification and repair	secreted proteins in mixed biofilms	N	Y	[122]
PA0002	dnaN	DNA replication, recombination, modification and repair	secreted proteins in mixed biofilms	Y	Y	[122]
PA1982	exaA	Carbon compound catabolism	secreted proteins in mixed biofilms	N	Y	[122]
PA1086	flgK	Cell wall / LPS / capsule	secreted proteins in mixed biofilms	N	Y	[122]
PA1092	fliC	Motility & Attachment	secreted proteins in mixed biofilms	N	Y	[122]
PA1094	fliD	Cell wall / LPS / capsule	secreted proteins in mixed biofilms	N	Y	[122]
PA2398	fpvA	Transport of small molecules	secreted proteins in mixed biofilms	N	Y	[122]
PA4266	fusA1	Translation, post-translational modification, degradation	secreted proteins in mixed biofilms	N	Y	[122]
PA5214	gcvH1	Central intermediary metabolism	secreted proteins in mixed biofilms	N	Y	[122]

Accession	Name	Function	Phenotype	Essential	Integrated network	References
PA5288	glnK	Central intermediary metabolism	secreted proteins in mixed biofilms	P	Y	[122]
PA0347	glpQ	Fatty acid and phospholipid metabolism	secreted proteins in mixed biofilms	N	Y	[122]
PA4385	groEL	Chaperones & heat shock proteins	secreted proteins in mixed biofilms	P	Y	[122]
PA4386	groES	Chaperones & heat shock proteins	secreted proteins in mixed biofilms	Y	Y	[122]
PA3407	hasAp	Transport of small molecules	secreted proteins in mixed biofilms	N	Y	[122]
PA2623	icd	Carbon compound catabolism	secreted proteins in mixed biofilms	N	Y	[122]
PA4370	icmP	Membrane proteins	secreted proteins in mixed biofilms	N	Y	[122]
PA4694	ilvC	Biosynthesis of cofactors, prosthetic groups and carriers	secreted proteins in mixed biofilms	N	Y	[122]
PA4236	katA	Adaptation, Protection	secreted proteins in mixed biofilms	N	Y	[122]
PA1871	lasA	Secreted Factors (toxins, enzymes, alginate)	secreted proteins in mixed biofilms	N	Y	[122]
PA3361	lecB	Motility & Attachment	secreted proteins in mixed biofilms	N		[122]
PA2493	mexE	Transport of small molecules	secreted proteins in mixed biofilms	N	Y	[122]
PA3029	moaB2	Biosynthesis of cofactors, prosthetic groups and carriers	secreted proteins in mixed biofilms	N	Y	[122]
PA3807	ndk	Nucleotide biosynthesis and metabolism	secreted proteins in mixed biofilms	Y	Y	[122]
PA1777	oprF	Membrane proteins	secreted proteins in mixed biofilms	N	Y	[122]
PA0973	oprL		secreted proteins in mixed biofilms	Y	Y	[122]
PA2760	oprQ	Transport of small molecules	secreted proteins in mixed biofilms	N		[122]
PA0456	PA0456	Transcriptional regulators	secreted proteins in mixed biofilms	Y	Y	[122]
PA0572	PA0572	Hypothetical, unclassified, unknown	secreted proteins in mixed biofilms	N	Y	[122]
PA0622	PA0622	Related to phage, transposon, or plasmid	secreted proteins in mixed biofilms	N	Y	[122]
PA0623	PA0623	Related to phage, transposon, or plasmid	secreted proteins in mixed biofilms	N	Y	[122]

Accession	Name	Function	Phenotype	Essential	Integrated network	References
PA1342	PA1342	Transport of small molecules	secreted proteins in mixed biofilms	N	Y	[122]
PA1486	PA1486	Hypothetical, unclassified, unknown	secreted proteins in mixed biofilms	N	Y	[122]
PA1733	PA1733	Hypothetical, unclassified, unknown	secreted proteins in mixed biofilms	N		[122]
PA2377	PA2378	Hypothetical, unclassified, unknown	secreted proteins in mixed biofilms	N		[122]
PA2439	PA2439	Membrane proteins	secreted proteins in mixed biofilms	N	Y	[122]
PA2451	PA2451	Hypothetical, unclassified, unknown	secreted proteins in mixed biofilms	N	Y	[122]
PA2452	PA2452	Hypothetical, unclassified, unknown	secreted proteins in mixed biofilms	N	Y	[122]
PA2453	PA2453	Hypothetical, unclassified, unknown	secreted proteins in mixed biofilms	N		[122]
PA2462	PA2462	Hypothetical, unclassified, unknown	secreted proteins in mixed biofilms	N		[122]
PA2659	PA2659	Hypothetical, unclassified, unknown	secreted proteins in mixed biofilms	Y		[122]
PA2758	PA2758	Transcriptional regulators	secreted proteins in mixed biofilms	N		[122]
PA2939	PA2940	Secreted Factors (toxins, enzymes, alginate)	secreted proteins in mixed biofilms	N		[122]
PA3031	PA3032	Hypothetical, unclassified, unknown	secreted proteins in mixed biofilms	N		[122]
PA3123	PA3124	Hypothetical, unclassified, unknown	secreted proteins in mixed biofilms	N		[122]
PA3181	PA3181	Central intermediary metabolism	secreted proteins in mixed biofilms	N	Y	[122]
PA3190	PA3190	Transport of small molecules	secreted proteins in mixed biofilms	N	Y	[122]
PA3301	PA3301	Putative enzymes	secreted proteins in mixed biofilms	N		[122]
PA3313	PA3313	Transport of small molecules	secreted proteins in mixed biofilms	N	Y	[122]
PA3441	PA3441	Transport of small molecules	secreted proteins in mixed biofilms	Y	Y	[122]
PA3529	PA3529	Adaptation, Protection	secreted proteins in mixed biofilms	N		[122]
PA3785	PA3785	Hypothetical, unclassified, unknown	secreted proteins in mixed biofilms	N		[122]
PA3836	PA3836	Hypothetical, unclassified, unknown	secreted proteins in mixed biofilms	N	Y	[122]
PA3922	PA3922	Hypothetical, unclassified, unknown	secreted proteins in mixed biofilms	N		[122]

Accession	Name	Function	Phenotype	Essential	Integrated network	References
PA4792	PA4793	Hypothetical, unclassified, unknown	secreted proteins in mixed biofilms	N		[122]
PA5033	PA5033	Hypothetical, unclassified, unknown	secreted proteins in mixed biofilms	N		[122]
PA5076	PA5076	Transport of small molecules	secreted proteins in mixed biofilms	N	Y	[122]
PA5153	PA5153	Transport of small molecules	secreted proteins in mixed biofilms	N	Y	[122]
PA5303	PA5303	Hypothetical, unclassified, unknown	secreted proteins in mixed biofilms	N	Y	[122]
PA5339	PA5339	Hypothetical, unclassified, unknown	secreted proteins in mixed biofilms	N	Y	[122]
PA5359	PA5359	Hypothetical, unclassified, unknown	secreted proteins in mixed biofilms	N		[122]
PA5505	PA5505	Membrane proteins	secreted proteins in mixed biofilms	N	Y	[122]
PA5545	PA5545	Hypothetical, unclassified, unknown	secreted proteins in mixed biofilms	N	Y	[122]
PA0423	pasP		secreted proteins in mixed biofilms	N	Y	[122]
PA4228	pchD	Secreted Factors (toxins, enzymes, alginate)	secreted proteins in mixed biofilms	N	Y	[122]
PA3166	pheA	Amino acid biosynthesis and metabolism	secreted proteins in mixed biofilms	N	Y	[122]
PA4554	pilY1		secreted proteins in mixed biofilms	N	Y	[122]
PA4175	piv		secreted proteins in mixed biofilms	N	Y	[122]
PA4031	ppa	Central intermediary metabolism	secreted proteins in mixed biofilms	P	Y	[122]
PA0122	rahU	Adaptation, Protection	secreted proteins in mixed biofilms	N		[122]

Table 6: *C. albicans* genes involved in the cross-talking phenomenon between *P. aeruginosa* and *C. albicans*, retrieved from literature.

Accession	Name	Function	Phenotype	Essential	Integrated network	References
orf19.7218	RBE1	Pry family cell wall protein	yeast-associated transcripts levels of expression increased after 3OC12HSL addition	N	Y	[117]
orf19.54	RHD1	regulated on yeast-hypha and white-opaque switches	yeast-associated transcripts levels of expression increased after 3OC12HSL addition	N	Y	[117]
orf19.1321	HWP1	Hyphal cell wall protein	farnesol induced inhibition of filamentation and a decrease in expression/filament-transcript levels greatly decrease after 3OC12HSL	N	Y	[117]
orf19.1327	RBT1	Cell wall protein with similarity to Hwp1	filament-transcript levels of expression greatly decrease after 3OC12HSL/Pseudomonas supernatants lead to its significant downregulation	N	Y	[117,121]
orf19.3374	ECE1	Hypha-specific protein	filament-transcript levels greatly decrease after 3OC12HSL	N	Y	[117,122]
orf19.3618	YWP1	Secreted yeast wall protein	yeast-associated transcripts levels of expression increased after 3OC12HSL addition	N	Y	[117,122]
orf19.5148	CYR1	adenylyl cyclase/role in macrophage sensitivity	bacterial peptidoglycan (PNG)-like molecules can strongly promote *C.albicans* hyphal growth	Y (OGEE)	Y	[124]
orf19.5741	ALS1	Cell-surface adhesin	*Pseudomonas* supernatants lead to its significant downregulation	N	Y	[121,122]
orf19.1097	ALS2	Cell-surface adhesin	*Pseudomonas* supernatants lead to its downregulation	N	Y	[121,122]
orf19.1816	ALS3	Cell-surface adhesin	*Pseudomonas* supernatants lead to its significant downregulation	N	Y	[121,122]

Accession	Name	Function	Phenotype	Essential	Integrated network	References
orf19.4555	ALS4	Cell-surface adhesin	*Pseudomonas* supernatants lead to its significant downregulation	N	Y	[121]
orf19.5636	RBT5	Cell wall protein	*Pseudomonas* supernatants lead to its significant downregulation	N	Y	[121,122]
orf19.5674	PGA10	Membrane protein	*Pseudomonas* supernatants lead to its significant downregulation	N	Y	[121,122]
orf19.6202	RBT4	Localized in hyphal tips	*Pseudomonas* supernatants lead to its significant downregulation	N	Y	[121,122]
orf19.6109	TUP1	represses filamentous growth	*Pseudomonas* supernatants lead to its upregulation	N	Y	[121]
orf19.7150	NRG1	hyphal gene induction	*Pseudomonas* supernatants lead to its upregulation	N	Y	[121]
orf19.896	CHK1	cell wall synthesis	*Pseudomonas* supernatants lead to its significant downregulation	N	Y	[121]
orf19.5908	TEC1	involved in biofilm formation	*Pseudomonas* supernatants lead to its significant downregulation	N	Y	[121]
orf19.610	EFG1	involved in biofilm formation	*Pseudomonas* supernatants lead to its downregulation	N	Y	[121]
orf19.4969	KEM1	role in filamentous growth	*Pseudomonas* supernatants lead to its downregulation	N		[121]
orf19.6760	MDS3	role in chlamydospore formation	*Pseudomonas* supernatants lead to its downregulation	N	Y	[121]
orf19.4519	SUV3	role in chlamydospore formation	*Pseudomonas* supernatants lead to its significant downregulation	N	Y	[121]
orf19.723	BCR1	involved in biofilm formation and adhesion	*Pseudomonas* supernatants lead to its downregulation	N	Y	[121]
orf19.5604	MDR1	multidrug efflux pump	*Pseudomonas* supernatants lead to its downregulation	N	Y	[121]

Accession	Name	Function	Phenotype	Essential	Integrated network	References
orf19.6000	CDR1	Multidrug transporter of ABC superfamily	*Pseudomonas* supernatants lead to its significant downregulation	N	Y	[121]
orf19.5958	CDR2	Multidrug transporter of ABC superfamily	*Pseudomonas* supernatants lead to its significant downregulation	N		[121]
orf19.5887	NUP85	structural constituent of the nuclear pore	*Pseudomonas* supernatants lead to its downregulation	Y (OGEE)	Y	[121]
orf19.4433	CPH1	for mating and filamentation on solid media	*Pseudomonas* supernatants lead to its downregulation	N	Y	[121]
orf19.1401	EAP1	cell wall adhesin	*Pseudomonas* supernatants lead to its downregulation	N		[121]
orf19.7523	MKC1	role in biofilm formation	*Pseudomonas* supernatants lead to its significant downregulation	N	Y	[121]
orf19.1358	GCN4	amino acid control response	*Pseudomonas* supernatants lead to its significant downregulation	N	Y	[121]
orf19.5736	ALS5	Cell-surface adhesin	*Pseudomonas* supernatants lead to its downregulation	N	Y	[121]
orf19.7414	ALS6	Cell-surface adhesin	*Pseudomonas* supernatants lead to its downregulation	N	Y	[121]
orf19.7400	ALS7	Cell-surface adhesin	*Pseudomonas* supernatants lead to its downregulation	N	Y	[121]
orf19.5742	ALS9	Cell-surface adhesin	*Pseudomonas* supernatants lead to its downregulation	N	Y	[121]
orf19.2681	RBT7	putative secretion signal	*Pseudomonas* supernatants lead to its downregulation	N		[121]
orf19.1110	orf19.1110	produce the coenzyme thiamine pyrophosphate	secreted proteins in mixed biofilms	N		[122]
orf19.1490	MSB2	cell wall damage sensor	secreted proteins in mixed biofilms	N	Y	[122]

Accession	Name	Function	Phenotype	Essential	Integrated network	References
orf19.1671	UTR2	role in adhesion	secreted proteins in mixed biofilms	N	Y	[122]
orf19.1690	TOS1		secreted proteins in mixed biofilms	N	Y	[122]
orf19.1779	MP65	role in adhesion	secreted proteins in mixed biofilms	N	Y	[122]
orf19.2060	SOD5	protects against oxidative stress	secreted proteins in mixed biofilms	N		[122]
orf19.2941	SCW4	putative cell wall protein	secreted proteins in mixed biofilms	Y (CGD)		[122]
orf19.2990	XOG1	Exo-1,3-beta-glucanase	secreted proteins in mixed biofilms	N	Y	[122]
orf19.3445	HOC1	similarity to mannosyltransferases	secreted proteins in mixed biofilms	N		[122]
orf19.3642	SUN41	role in biofilm formation and cell separation	secreted proteins in mixed biofilms	N	Y	[122]
orf19.3829	PHR1	Cell surface glycosidase	secreted proteins in mixed biofilms	N	Y	[122]
orf19.3893	SCW11	Cell wall protein	secreted proteins in mixed biofilms	Y (CGD)		[122]
orf19.3895	CHT2	equired for normal filamentous growth	secreted proteins in mixed biofilms	N	Y	[122]
orf19.4565	BGL2	Cell wall 1,3-beta-glucosyltransferase	secreted proteins in mixed biofilms	N	Y	[122]
orf19.4781	GRP1		secreted proteins in mixed biofilms	N		[122]
orf19.6274	PBR1	required for cohesion, adhesion	secreted proteins in mixed biofilms	N	Y	[122]
orf19.6673	HEX1	may have role in carbon or nitrogen scavenging	secreted proteins in mixed biofilms	Y (CGD)		[122]
orf19.7586	CHT3	hyphal-repressed	secreted proteins in mixed biofilms	N	Y	[122]

Accession	Name	Function	Phenotype	Essential	Integrated network	References
orf19.2706	CRH11	cell wall transglycosylase	secreted proteins in mixed biofilms	N		[122]
orf19.3066	ENG1	endo-1,3-beta-glucanase	secreted proteins in mixed biofilms	N		[122]
orf19.4035	PGA4	cell surface protein	secreted proteins in mixed biofilms	N		[122]
orf19.5542	SAP6	Secreted aspartyl protease	secreted proteins in mixed biofilms	N	Y	[122]
orf19.5716	SAP4	Secreted aspartyl protease	secreted proteins in mixed biofilms	N	Y	[122]
orf19.5760	IHD1	GPI-anchored protein	secreted proteins in mixed biofilms	N	Y	[122]
orf19.1589	orf19.1589		secreted proteins in mixed biofilms	N		[122]
orf19.3010.1	ECM33	host cell damage, and endocytosis	secreted proteins in mixed biofilms	N	Y	[122]
orf19.7030	SSR1	cell-wall protein with a role in cell wall structure	secreted proteins in mixed biofilms	N		[122]
orf19.3117	CSA2	extracellular-associated protein	secreted proteins in mixed biofilms	N	Y	[122]
orf19.4899	GCA1	extracellular/plasma membrane-associated glucoamylase	secreted proteins in mixed biofilms	N		[122]
orf19.999	GCA2	extracellular/plasma membrane-associated glucoamylase	secreted proteins in mixed biofilms	Y (CGD)		[122]
orf19.4975	HYR1	hyphal cell wall protein	secreted proteins in mixed biofilms	N	Y	[122]

Cross-talking subnetworks

The main objective was to obtain a representation of the subnetwork formed by the cross-talking genes presented in the two integrated networks. Therefore, the following steps were applied: first a list of the genes/proteins, involved in cross-talking, for each species was transferred for a simple .txt document and then using the Select option from the menu tool bar of Cytoscape, the nodes with a direct match against that list were selected from the whole integrated network. The second step was to save that information regarding the specific genes for cross-talking phenomenon, so a new argument (type string) was created and the value Y (i.e. Yes) was attributed. Additionally, those nodes were further highlighted with the color red, allowing the possibility to distinguish the nature of the nodes. The third step was to pull these nodes from the integrated network in order to create a subnetwork. Thus, these nodes were filtered and then the adjacent edges were selected as well as the nodes connected by the selected nodes giving raise to a full subnetwork for each of the species. In Figure 21, it is depicted the two integrated networks with the highlighted red nodes (i.e. the cross-talking genes/proteins) and then the subnetworks comprising the cross-talking genes/proteins and the related genes within the integrated network. In terms, of network dimensions the results for *P. aeruginosa* are as follow: 993 nodes, in which 87 are assigned as cross-talking genes, and 8430 interactions. Then, for *C. albicans* the subnetwork dimension is of 718 nodes, in which 49 are assigned as cross-talking genes, and 2886 interactions. Furthermore, these subnetworks were anlysed in terms of topological features, such as top hubs and top bottlenecks, and also for gene ontology enrichment.

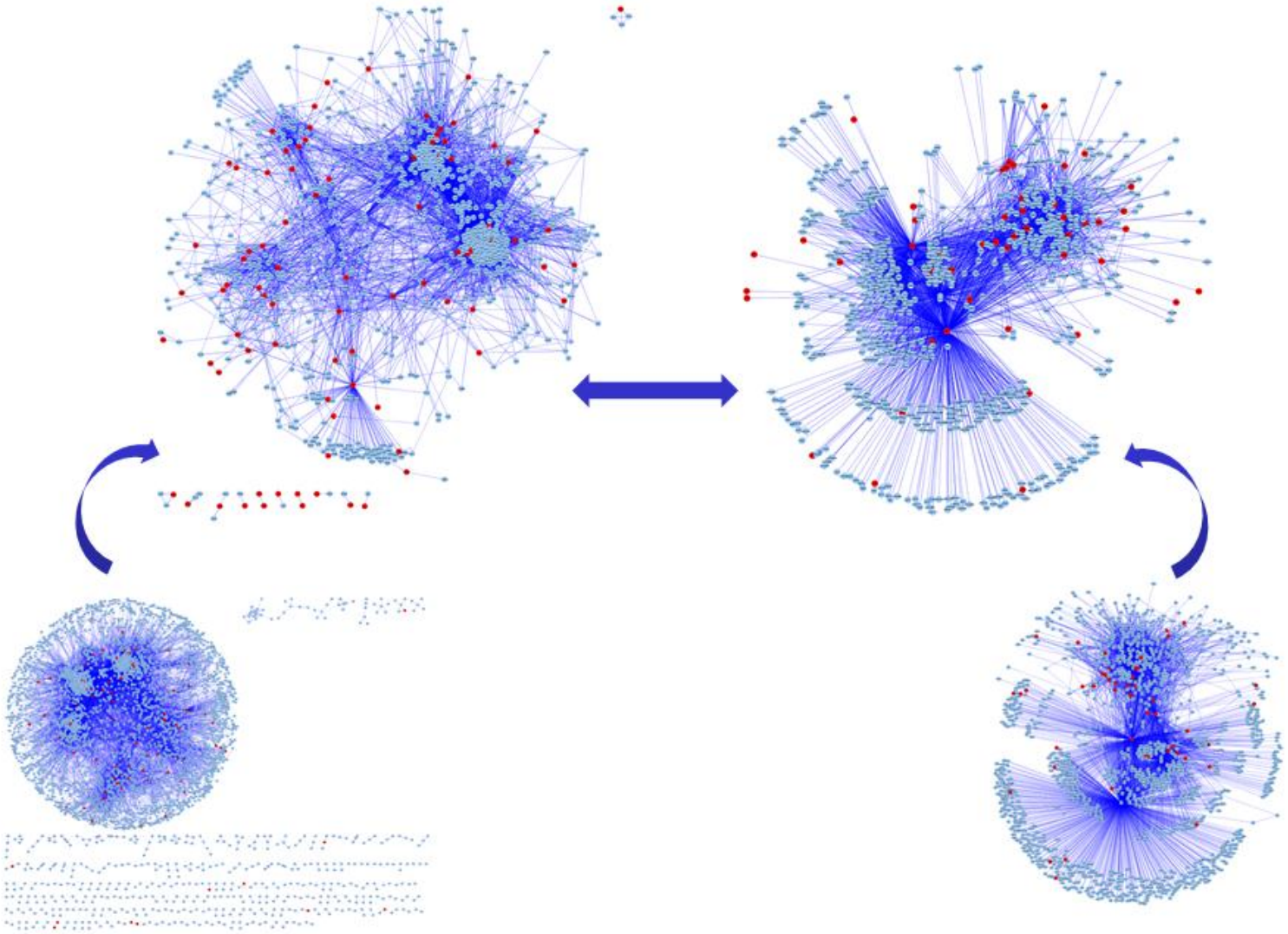

Figure 21: Cross-talking subnetworks for *P. aeruginosa* (subnetwork in the right conner of superior layer) and *C.albicans* (subnetwork in the left conner of superior layer). The nodes highlighted in red are the ones related to cross-talking in the subnetworks (superior layer) and the integrated networks (inferior layer).
The subnetworks depicted in the superior layer are detailed in the Appendix (Table A 5 and Table A 6).

Topological analysis – hubs and bottlenecks

In terms of topological analysis the two subnetworks were subject to the Cyto-Hubba plugin, being the results were computed for the two networks. In Figure 22 it is depicted the top ten hubs (A and B) for the cross-talking subnetworks, as well as the top ten bottlenecks (C and D) for *P. aeruginosa* and *C. albicans*.

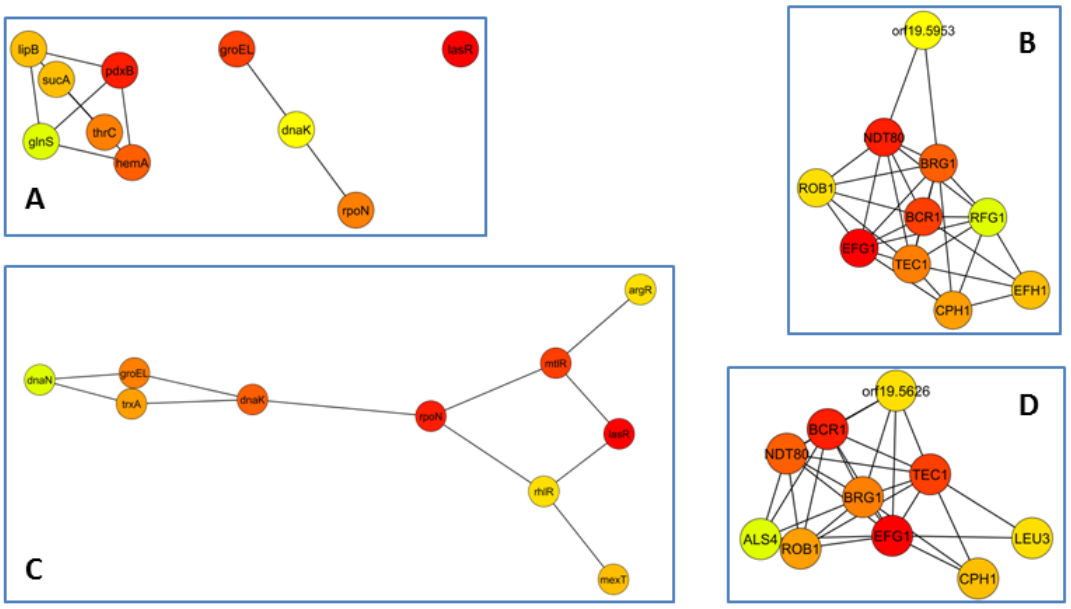

Figure 22: Cyto-Hubba results for the cross-talking subnetworks of *P. aeruginosa* and *C.albicans*. The top ten hubs of *P.aeruginosa* (A) and *C.albicans* (B) and the top ten bottlenecks (C) and (D), respectively.

The top ten hubs for the subnetwork of *P. aeruginosa* are the following; *lasR*, *pdxB*, *groEL*, *hemA*, *rpoN*, *thrC*, *lipB*, *sucA*, *dnaK* and *lpdG* (Figure 22A), in which four were assigned as cross-talking genes (*lasR*, *groEL*, *rpoN* and *dnaK*) and six were classified as essential genes (*pdxB*, *groEL*, *hemA*, *thrC*, *lipB* and *sucA*). In terms of the top ten bottlenecks the following nodes were assigned; *lasR*, *rpoN*, *mtlR*, *dnaK*, *groEL*, *trxA*, *mexT*, *argR*, *rhlR* and *aceE* (Figure 22C), in which seven were assigned as cross-talking genes (*lasR*, *rpoN*, *dnaK*, *groEL*, *trxA*, *argR* and *rhlR*) and three (*groEL*, *trxA* and *mexT*) as essential genes. The cross-talking subnetwork of *C. albicans* was also subject to a topological analysis, and the top ten hubs are the following; Efg1, Ndt80, Bcr1, Tec1, Cph1, Efh1, Rob1, orf19.5953 and Rfg1 (Figure 22B), in which four were assingned as cross-talking genes (Efg1, Bcr1, Tec1, Cph1) and only one is considered essential (orf19.5953). The top ten bottlenecks assigned are; Efg1, Bcr1, Tec1, Ndt80, Brg1, Rob1, Cph1, Leu3,

orf19.5626 and Als4, in which five are assigned as cross-talking genes (Efg1, Bcr1, Tec1, Cph1 and Als4) and none is considered an essential gene.

Gene Ontology enrichment analysis

In this section the imported Gene Ontology annotation data previously imported for the integrated network was used here for each of the cross-talking subnetworks. The filters to identify the most represented biological processes were used for each subnetwork, as well as the MCODE plugin to detect the presence of clusters created according to the functional proximity of the nodes.

In the subnetwork of *P. aeruginosa* for the cross-talking phenomenon the most represented biological processes were the following; the *cellular amino acid metabolic process* (GO:0006520), with 159 nodes, the *cellular protein metabolic process* (GO:0044267), with 90 nodes, the *transport* process (GO:0006810), with 83 nodes, the cofactor biosynthetic process (GO:0051188), with 71 nodes, the *reponse to stimulus* (GO:0050896) and *generation of precursor metabolites and energy* (GO:0006091) with the same contribution of 64 nodes and then the *regulation of transcription, DNA-dependent* (GO:0006355) with 58 nodes. Additionaly, the subnetwork of *C. albicans* presents the following processes; the *filamentous growth* process (GO:0030447), with 171 nodes, the *pathogenesis* (GO:0009405), with 93 genes, the *single-species biofilm formation on inanimate substrate* (GO:0044011), with 62 nodes, the *hyphal growth* process (GO:0030448), with 35 nodes and the *transcription, DNA-dependent* (GO:0006351) with 18 nodes. From the application of the MCODE plugin resulted 26 clusters for the subnetwork of *P. aeruginosa* comprising 413 nodes and 1188 interactions from the subnetwork, being highly enriched in the following biological processes; *reponse to stimulus* (GO:0050896) and in the *cellular protein metabolic process* (GO:0044267). On the other hand, the subnetwork for *C. albicans* droped this number of clusters with only five clusters, the same number as the one yielded for the integrated network, comprising 39 nodes and 67 interactions. The main biological processes represented in these clusters were the *filamentous growth* process (GO:0030447) and the *single-species biofilm formation on inanimate substrate* (GO:0044011).

III.3.2 Discussion

In conclusion one could say that the cross-talking phenomenon has a high rate of coverage in the tow involved species. Thus, the percentages of genes involved in cross-talking, which are represented in the subnetworks of *P. aeruginosa* and *C. albicans* are 81,3% (87 from 107 identified) and 73,1% (49 from 67 identified), respectively. The strategy, adopted to highlight and extract the subnetworks related to cross-talking enables a wider prespective of the genes involved (marked as red) and the connected genes and interactions. In terms of the topological analysis, the hubs and bottlenecks found revealed some interesting aspects. First, for the subnetwork of *P. aeruginosa*, there where five hubs that were exactly the same as the main integrated subnetwork. Moreover, this fact points to the importance of these nodes (*lasR*, *pdxB*, *hemA*, *lipB* and *lpdG*) in this process of cross-talking making them worthy of further attention. The bottlenecks changed, as expected since this is a measure of dynamics, although four genes were still conserved (*lasR*, *rpoN*, *mexT* and *argR*) between the two networks. Otherwise, for the subnetwork of *C. albicans* the top ten hubs were almost intact among the two networks, with only one gene was different. In contrast, the bottlenecks only presented five genes (Efg1, Tec1, Brg1 and Cph1) in common, revealing that the dynamics of the network changed. The gene ontology enrichment procedure also followed the tendency in the orign networks. The subnetwork of *P. aeruginosa* revealed to be highly enriched in the same biological processes as the integrated network only adding the following processes; *transport* (GO:0006810) and *regulation of transcription, DNA-dependent* (GO:0006355). Likely, the subnetwork of *C. albicans* also follows the same pattern as the integrated network, being additionaly influenced by the *transcription, DNA-dependent* (GO:0006351) process. The application of the MCODE plugin to this two subnetworks, revealed only 26 clusters for *P. aeruginosa*, with the same biological processes described for the integrated network, and the same, previously identified five clusters for *C. albicans*.

Chapter IV – Conclusions and future perspectives

The integration process for the two pathogenic microorganisms was accomplished in two networks of considereable size and quality. The two integrated networks were treated as PPI networks, opening the possibility of having a preliminary study of these networks and of the cross-talking phenomenon. The cross-talking subnetworks obtained revealed the importance of the cross-talking genes and also the related genes connected, giving some insights to future work, pointing also some new potential drug targets.

This thesis might be ameliorated starting from the origin represented by the networks which gave raise to the two integrated networks. In fact, the networks which are since the beginig TRN could maintain their nature, if it is made a proper literature curation of the regulatory interactions since it is a key step for the comparison against a PPI network. The objective of having integrated networks with an entire coverage for the nodes transcription regulatory interaticon (i.e. activation or inhibition) could be achieved through: literature curation and databases curation (STRING and STITCH). In fact, a further enrichment of these networks could be made by exploring different coditions, such as antimicrobial stress, among others important for the cross-talking phenonemenon. Thus, specific databases of “Omics” data could be used to accomplish this goal, such as GEO and ArrayExpress. Nevertheless, having the two integrated networks with a final nature of TRN, one could explore different metrics of Cytoscape and different Cytoscape plugins comparing to the results obtained in this thesis.

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Appendix

Table A 1: Expanded subnetwork description for *P. aeruginosa*, obtained by the Cyto-Hubbba plugin for the topological feature degree. This description is based in the biological process, gene essentiality and drug taget.

ID	Degree	Object_name	GO_Biological process	Essential	Drug target
pdxB	143.0	erythronate-4-phosphate dehydrogenase	[cellular amino acid metabolic process, cellular catabolic process, cofactor biosynthetic process]	Y	N
lpdG	127.0	lipoamide dehydrogenase-glc	[cellular amino acid metabolic process, generation of precursor metabolites and energy]	N	N
hemA	121.0	glutamyl-tRNA reductase	[cellular amino acid metabolic process, cellular protein metabolic process, cofactor biosynthetic process, porphyrin-containing compound biosynthetic process]	Y	N
rpsB	121.0	30S ribosomal protein S2	[cellular protein metabolic process]	Y	Y
aceE	116.0	pyruvate dehydrogenase	[acetyl-CoA biosynthetic process from pyruvate, cellular amino acid metabolic process, generation of precursor metabolites and energy]	N	N
lipB	116.0	lipoate-protein ligase B	[cellular amino acid metabolic process, cofactor biosynthetic process, folic acid biosynthetic process, lipoate biosynthetic process, lysine catabolic process, ubiquinone biosynthetic process]	Y	N
folD	114.0	5,10-methylene-tetrahydrofolate dehydrogenase / cyclohydrolase	[10-formyltetrahydrofolate biosynthetic process, cellular protein metabolic process, cofactor biosynthetic process, histidine biosynthetic process, methionine biosynthetic process, nucleotide metabolic process, pantothenate biosynthetic process, purine nucleobase biosynthetic process]	Y	N

ID	Degree	Object_name	GO_Biological process	Essential	Drug target
gshB	112.0	glutathione synthetase	[cellular amino acid metabolic process, cofactor biosynthetic process, glutathione biosynthetic process]	Y	N
rplA	112.0	50S ribosomal protein L1	[cellular protein metabolic process]	Y	Y
lasR	112.0	transcriptional regulator LasR	[regulation of transcription, DNA-dependent, response to stimulus]	N	N
rplC	107.0	50S ribosomal protein L3	[cellular protein metabolic process]	N	Y
rplV	100.0	50S ribosomal protein L22	[cellular protein metabolic process]	Y	Y
rpsG	96.0	30S ribosomal protein S7	[cellular protein metabolic process]	Y	Y
dnaK	81.0	DnaK protein	[DNA metabolic process, protein folding, response to stimulus]	N	N
spoT	75.0	guanosine-3',5'-bis(diphosphate) 3'-pyrophosphohydrolase	[cellular response to starvation, nucleotide metabolic process, purine nucleotide metabolic process, response to stimulus]	Y	N
fur	72.0	ferric uptake regulation protein	[regulation of transcription, DNA-dependent]	N	N
PA2840	71.0		[]	N	N
rpsF	69.0	30S ribosomal protein S6	[cellular protein metabolic process]	N	Y
rpoA	68.0	DNA-directed RNA polymerase alpha chain	[RNA metabolic process]	Y	Y
dnaJ	65.0	DnaJ protein	[DNA metabolic process, protein folding, response to stimulus]	N	N
rpoB	58.0	DNA-directed RNA polymerase beta chain	[RNA metabolic process]	Y	Y
exsA	56.0	transcriptional regulator ExsA	[regulation of transcription, DNA-dependent, secretion]	Y	N
secA	52.0	secretion protein SecA	[secretion]	Y	N
rhlR	49.0	transcriptional regulator RhlR	[regulation of transcription, DNA-dependent, response to stimulus]	N	N
fabZ	48.0	(3R)-hydroxymyristoyl-[acyl carrier protein] dehydratase	[cellular lipid metabolic process]	Y	N

ID	Degree	Object_name	GO_Biological process	Essential	Drug target
pqsD	47.0	3-oxoacyl-[acyl-carrier-protein] synthase III	[cofactor biosynthetic process]	N	N
narL	47.0	two-component response regulator NarL	[generation of precursor metabolites and energy, nitrogen compound metabolic process, phosphorelay signal transduction system, regulation of transcription, DNA-dependent]	N	N
lpxD	47.0	UDP-3-O-[3-hydroxylauroyl] glucosamine N-acyltransferase	[]	N	N
pvdS	44.0	sigma factor PvdS	[regulation of transcription, DNA-dependent]	N	N
cspD	43.0	cold-shock protein CspD	[regulation of transcription, DNA-dependent, response to stimulus]	Y	N
lexA	42.0	repressor protein LexA	[cellular protein metabolic process, regulation of DNA repair, regulation of transcription, DNA-dependent, response to stimulus]	N	N
rpoC	41.0	DNA-directed RNA polymerase beta* chain	[RNA metabolic process]	N	Y
uvrC	40.0	excinuclease ABC subunit C	[DNA metabolic process, DNA repair]	N	N
rpoD	38.0	sigma factor RpoD	[DNA-dependent transcription, initiation, regulation of transcription, DNA-dependent]	Y	N
secY	37.0	secretion protein SecY	[secretion]	N	N
parE	37.0	topoisomerase IV subunit B	[DNA metabolic process, DNA topological change]	Y	Y
rpmF	34.0	50S ribosomal protein L32	[cellular protein metabolic process]	N	Y
gltR	34.0	two-component response regulator GltR	[cellular catabolic process, phosphorelay signal transduction system, regulation of transcription, DNA-dependent]	N	N
acpP	34.0	acyl carrier protein	[cellular lipid metabolic process]	Y	N
gacA	31.0	response regulator GacA	[regulation of transcription, DNA-dependent]	N	Y
ihf	30.0		[]		
lspA	29.0	prolipoprotein signal peptidase	[cellular protein metabolic process, proteolysis, secretion]	Y	N
PA3972	25.0		[]	N	N

ID	Degree	Object_name	GO_Biological process	Essential	Drug target
glmU	23.0	glucosamine-1-phosphate acetyltransferase/N-acetylglucosamine-1-phosphate uridyltransferase	[lipopolysaccharide biosynthetic process]	Y	
pqsA	23.0	probable coenzyme A ligase	[cofactor biosynthetic process]	N	N
parC	22.0	topoisomerase IV subunit A	[DNA metabolic process, DNA topological change]	Y	
gbuR	21.0	GbuR	[arginine metabolic process, proline metabolic process, regulation of transcription, DNA-dependent]	N	N
cheZ	18.0	chemotaxis protein CheZ	[chemotaxis, response to stimulus]	N	N
pqsE	15.0	Quinolone signal response protein	[cofactor biosynthetic process]	N	N
vfr	15.0	transcriptional regulator Vfr	[regulation of transcription, DNA-dependent]	N	N
algQ	15.0	Alginate regulatory protein AlgQ	[regulation of transcription, DNA-dependent]	N	N
PA5180	11.0		[]	N	N
secE	11.0	secretion protein SecE	[secretion]	Y	N
xcpP	9.0	secretion protein XcpP	[secretion]	N	N
dinB	8.0		[]	N	N
xcpQ	6.0	general secretion pathway protein D	[secretion]	N	N
PA5181	3.0		[]	N	N

Table A 2: Expanded subnetwork description for *P. aeruginosa*, obtained by the Cyto-Hubbba plugin for the topological feature bottleneck. This description is based in the biological process, gene essentiality and drug taget.

ID	Bottleneck	Object_name	GO_Biological process	Essential	Drug target
lasR	163.0	transcriptional regulator LasR	[regulation of transcription, DNA-dependent, response to stimulus]	N	N
metK	114.0	methionine adenosyltransferase	[S-adenosylmethionine biosynthetic process, cellular amino acid metabolic process, metabolic process]	N	N
fur	79.0	ferric uptake regulation protein	[regulation of transcription, DNA-dependent]	N	N
lpdG	67.0	lipoamide dehydrogenase-glc	[cellular amino acid metabolic process, generation of precursor metabolites and energy]	N	N
mexT	66.0	transcriptional regulator MexT	[regulation of transcription, DNA-dependent]	Y	N
gabT	63.0	4-aminobutyrate aminotransferase	[cellular amino acid metabolic process, cellular catabolic process, gamma-aminobutyric acid catabolic process, metabolic process]	N	N
exsA	61.0	transcriptional regulator ExsA	[regulation of transcription, DNA-dependent, secretion]	Y	N
gabD	59.0	succinate-semialdehyde dehydrogenase	[cellular amino acid metabolic process, cellular catabolic process, gamma-aminobutyric acid catabolic process, metabolic process]	N	N
argR	55.0	transcriptional regulator ArgR	[cellular amino acid metabolic process, regulation of transcription, DNA-dependent]	N	N
rpoN	54.0	RNA polymerase sigma-54 factor	[regulation of transcription, DNA-dependent]	N	Y
dnaK	49.0	DnaK protein	[DNA metabolic process, protein folding, response to stimulus]	N	N
phoP	49.0	two-component response regulator PhoP	[phosphorelay signal transduction system, regulation of transcription, DNA-dependent]	N	N
algR	45.0	alginate biosynthesis regulatory protein AlgR	[phosphorelay signal transduction system, regulation of transcription, DNA-dependent]	N	N
gacA	42.0	response regulator GacA	[regulation of transcription, DNA-dependent]	N	Y

ID	Bottleneck	Object_name	GO_Biological process	Essential	Drug target
pmrA	39.0	PmrA: two-component regulator system response regulator PmrA	[phosphorelay signal transduction system]	Y	N
glnS	35.0	glutaminyl-tRNA synthetase	[cellular amino acid metabolic process, cellular protein metabolic process, glutaminyl-tRNA aminoacylation]	Y	N
pvdS	35.0	sigma factor PvdS	[regulation of transcription, DNA-dependent]	N	N
cysB	34.0	transcriptional regulator CysB	[cellular amino acid metabolic process, regulation of transcription, DNA-dependent]	N	N
fleQ	34.0	transcriptional regulator FleQ	[cellular component movement, ciliary or bacterial-type flagellar motility, regulation of transcription, DNA-dependent]	N	N
secA	29.0	secretion protein SecA	[secretion]	Y	N
hemA	29.0	glutamyl-tRNA reductase	[cellular amino acid metabolic process, cellular protein metabolic process, cofactor biosynthetic process, porphyrin-containing compound biosynthetic process]	Y	N
aceE	27.0	pyruvate dehydrogenase	[acetyl-CoA biosynthetic process from pyruvate, cellular amino acid metabolic process, generation of precursor metabolites and energy]	N	N
aceF	27.0	dihydrolipoamide acetyltransferase	[acetyl-CoA biosynthetic process from pyruvate, cellular catabolic process, generation of precursor metabolites and energy, gluconeogenesis, glycolysis, pyruvate metabolic process]	Y	N
acpP	25.0	acyl carrier protein	[cellular lipid metabolic process]	Y	N
rpoD	22.0	sigma factor RpoD	[DNA-dependent transcription, initiation, regulation of transcription, DNA-dependent]	Y	N
dnr	21.0	transcriptional regulator Dnr	[denitrification pathway, regulation of transcription, DNA-dependent]	N	N
dxs	17.0	1-deoxyxylulose-5-phosphate synthase	[cofactor biosynthetic process]	Y	N

ID	Bottleneck	Object_name	GO_Biological process	Essential	Drug target
phnB	16.0	anthranilate synthase component II	[L-phenylalanine metabolic process, cellular amino acid metabolic process, response to stimulus, tryptophan biosynthetic process, tyrosine metabolic process, ubiquinone biosynthetic process]	N	N
cheY	16.0	two-component response regulator CheY	[chemotaxis, phosphorelay signal transduction system, regulation of transcription, DNA-dependent]	Y	N
PA3806	15.0		[]	N	N
pqsD	15.0	3-oxoacyl-[acyl-carrier-protein] synthase III	[cofactor biosynthetic process]	N	N
rpoB	15.0	DNA-directed RNA polymerase beta chain	[RNA metabolic process]	Y	Y
pstB	15.0	ATP-binding component of ABC phosphate transporter	[phosphate ion transport, transport]	N	N
groEL	14.0	GroEL protein	[protein folding]	P	N
dnaJ	12.0	DnaJ protein	[DNA metabolic process, protein folding, response to stimulus]	N	N
lysC	12.0	aspartate kinase alpha and beta chain	[cellular amino acid metabolic process, lysine biosynthetic process via diaminopimelate]	Y	N
algB	12.0	two-component response regulator AlgB	[alginic acid biosynthetic process, phosphorelay signal transduction system, regulation of transcription, DNA-dependent]	N	N
rplA	12.0	50S ribosomal protein L1	[cellular protein metabolic process]	Y	Y
rhlR	12.0	transcriptional regulator RhlR	[regulation of transcription, DNA-dependent, response to stimulus]	N	N
tufB	12.0	elongation factor Tu	[cellular protein metabolic process]	Y	N
fleR	12.0	two-component response regulator	[cellular component movement, ciliary or bacterial-type flagellar motility, phosphorelay signal transduction system, regulation of transcription, DNA-dependent]	N	N

ID	Bottleneck	Object_name	GO_Biological process	Essential	Drug target
pdxB	11.0	erythronate-4-phosphate dehydrogenase	[cellular amino acid metabolic process, cellular catabolic process, cofactor biosynthetic process]	Y	N
icd	11.0	isocitrate dehydrogenase	[cellular amino acid metabolic process, cellular catabolic process, generation of precursor metabolites and energy]	N	N
gbuR	10.0	GbuR	[arginine metabolic process, proline metabolic process, regulation of transcription, DNA-dependent]	N	N
fliG	10.0	flagellar motor switch protein FliG	[cellular component movement, chemotaxis, ciliary or bacterial-type flagellar motility]	N	N
fabH2	10.0	3-oxoacyl-[acyl-carrier-protein] synthase III	[cellular lipid metabolic process, fatty acid biosynthetic process]	N	N
narL	10.0	two-component response regulator NarL	[generation of precursor metabolites and energy, nitrogen compound metabolic process, phosphorelay signal transduction system, regulation of transcription, DNA-dependent]	N	N
capB	9.0	cold acclimation protein B	[regulation of transcription, DNA-dependent, response to stimulus]	Y	N
ubiE	9.0	ubiquinone biosynthesis methyltransferase UbiE	[cofactor biosynthetic process, generation of precursor metabolites and energy, ubiquinone biosynthetic process]	Y	N
cheZ	9.0	chemotaxis protein CheZ	[chemotaxis, response to stimulus]	N	N
pfeR	9.0	two-component response regulator PfeR	[phosphorelay signal transduction system, regulation of transcription, DNA-dependent]	N	N
rnhA	9.0	ribonuclease H	[DNA metabolic process]	Y	N
purB	9.0	adenylosuccinate lyase	[cellular amino acid metabolic process, nucleotide metabolic process, purine ribonucleotide biosynthetic process]	Y	N
glpD	8.0	glycerol-3-phosphate dehydrogenase	[generation of precursor metabolites and energy, glycerol metabolic process, glycerolipid metabolic process, metabolic process]	Y	

ID	Bottleneck	Object_name	GO_Biological process	Essential	Drug target
aguB	8.0	N-carbamoylputrescine amidohydrolase	[arginine metabolic process, cellular amino acid metabolic process, proline metabolic process]	N	N
gcp	8.0	O-sialoglycoprotein endopeptidase	[cellular protein metabolic process]	Y	N
lipB	8.0	lipoate-protein ligase B	[cellular amino acid metabolic process, cofactor biosynthetic process, folic acid biosynthetic process, lipoate biosynthetic process, lysine catabolic process, ubiquinone biosynthetic process]	Y	N
carB	7.0	carbamoylphosphate synthetase large subunit	[arginine metabolic process, cellular amino acid metabolic process, glutamate metabolic process, nucleotide metabolic process, proline metabolic process, pyrimidine nucleotide metabolic process, pyrimidine ribonucleotide biosynthetic process]	N	N
znuC	7.0	zinc transport protein ZnuC	[transport, zinc ion transport]	N	N
parE	7.0	topoisomerase IV subunit B	[DNA metabolic process, DNA topological change]	Y	Y
zwf	7.0	glucose-6-phosphate 1-dehydrogenase	[cellular catabolic process, generation of precursor metabolites and energy, pentose-phosphate shunt]	N	N
msuE	7.0	NADH-dependent FMN reductase MsuE	[cellular catabolic process, metabolic process, sulfur compound metabolic process]	Y	N
fruR	7.0	fructose transport system repressor FruR	[carbohydrate metabolic process, cellular catabolic process, regulation of transcription, DNA-dependent, transport]	N	N
PA0929	7.0	two-component response regulator	[phosphorelay signal transduction system, transport]	N	N
rplL	7.0	50S ribosomal protein L7 / L12	[cellular protein metabolic process]	Y	Y
trpB	7.0	tryptophan synthase beta chain	[L-phenylalanine biosynthetic process, cellular amino acid metabolic process, tryptophan biosynthetic process, tyrosine biosynthetic process]	N	N

ID	Bottleneck	Object_name	GO_Biological process	Essential	Drug target
rpoC	6.0	DNA-directed RNA polymerase beta* chain	[RNA metabolic process]	N	Y
flhA	6.0	flagellar biosynthesis protein FlhA	[cellular component movement, chemotaxis, ciliary or bacterial-type flagellar motility, response to stimulus]	N	N
fleS	6.0	two-component sensor	[cell adhesion, cellular component movement, phosphorelay signal transduction system]	N	N
iscS	6.0	L-cysteine desulfurase (pyridoxal phosphate-dependent)	[cellular amino acid metabolic process, cofactor biosynthetic process, cysteine metabolic process, sulfur compound metabolic process]	Y	N
oprL	6.0	Peptidoglycan associated lipoprotein OprL precursor	[transport]	Y	N
hcnC	6.0	hydrogen cyanide synthase HcnC	[metabolic process]	N	N
pcaR	6.0	transcriptional regulator PcaR	[cellular catabolic process, regulation of transcription, DNA-dependent]	N	N
glgB	6.0	1,4-alpha-glucan branching enzyme	[generation of precursor metabolites and energy, glycogen biosynthetic process]	Y	N
gshB	6.0	glutathione synthetase	[cellular amino acid metabolic process, cofactor biosynthetic process, glutathione biosynthetic process]	Y	N
lexA	6.0	repressor protein LexA	[cellular protein metabolic process, regulation of DNA repair, regulation of transcription, DNA-dependent, response to stimulus]	N	N
algA	5.0	phosphomannose isomerase / guanosine 5'-diphospho-D-mannose pyrophosphorylase	[fructose metabolic process, mannose metabolic process, response to stimulus]	N	N
PA1618	5.0		[]	Y	N
rpoS	5.0	sigma factor RpoS	[DNA-dependent transcription, initiation, regulation of transcription, DNA-dependent, response to stress]	N	N

ID	Bottleneck	Object_name	GO_Biological process	Essential	Drug target
fliP	5.0	flagellar biosynthetic protein FliP	[cellular component movement, chemotaxis, ciliary or bacterial-type flagellar motility, response to stimulus]	N	N
edd	5.0	phosphogluconate dehydratase	[Entner-Doudoroff pathway, cellular catabolic process, generation of precursor metabolites and energy, pentose-phosphate shunt]	N	N
fumC2	5.0	fumarate hydratase	[cellular catabolic process, generation of precursor metabolites and energy, tricarboxylic acid cycle]	N	N
pqsA	5.0	probable coenzyme A ligase	[cofactor biosynthetic process]	N	N
amgR	5.0		[]	N	N
ubiG	5.0	3-demethylubiquinone-9 3-methyltransferase	[cofactor biosynthetic process, generation of precursor metabolites and energy]	Y	N
alg8	5.0	alginate biosynthesis protein Alg8	[response to stimulus]	N	N
acoB	5.0	acetoin catabolism protein AcoB	[cellular catabolic process]	N	N
recJ	5.0	single-stranded-DNA-specific exonuclease RecJ	[DNA metabolic process, DNA recombination]	N	N
maiA	4.0	maleylacetoacetate isomerase	[L-phenylalanine catabolic process, cellular catabolic process, tyrosine catabolic process]	Y	N
fliA	4.0	sigma factor FliA	[DNA-dependent transcription, initiation, regulation of transcription, DNA-dependent]	N	N
argG	4.0	argininosuccinate synthase	[alanine metabolic process, arginine biosynthetic process, arginine metabolic process, aspartate metabolic process, cellular amino acid metabolic process, proline metabolic process]	N	N
pscL	4.0	type III export protein PscL	[secretion]	N	N
rluC	4.0	ribosomal large subunit pseudouridine synthase C	[RNA metabolic process]	N	N
polA	4.0	DNA polymerase I	[DNA metabolic process, DNA replication]	N	N

ID	Bottleneck	Object_name	GO_Biological process	Essential	Drug target
glcB	4.0	malate synthase G	[cellular catabolic process, metabolic process, tricarboxylic acid cycle]	N	N
ffh	4.0	signal recognition particle protein Ffh	[secretion]	P	N
proC	4.0	pyrroline-5-carboxylate reductase	[cellular amino acid metabolic process, proline biosynthetic process]	N	
coxB	4.0	cytochrome c oxidase, subunit II	[generation of precursor metabolites and energy]	N	N
fbp	4.0	fructose-1,6-bisphosphatase	[cellular catabolic process, gluconeogenesis, metabolic process]	Y	N
adhA	4.0	alcohol dehydrogenase	[cellular catabolic process, fatty acid metabolic process, generation of precursor metabolites and energy, gluconeogenesis, glycerolipid metabolic process, glycolysis, tyrosine metabolic process]	N	N
trpA	4.0	tryptophan synthase alpha chain	[L-phenylalanine biosynthetic process, cellular amino acid metabolic process, tryptophan biosynthetic process, tyrosine biosynthetic process]	N	N
hisE	4.0	phosphoribosyl-ATP pyrophosphohydrolase	[cellular amino acid metabolic process, histidine biosynthetic process]	Y	N
algK	4.0	alginate biosynthetic protein AlgK precursor	[response to stimulus]	N	N
tolB	4.0	TolB protein	[transport]	Y	N
ppsA	4.0	phosphoenolpyruvate synthase	[cellular catabolic process, generation of precursor metabolites and energy, gluconeogenesis, metabolic process, phosphoenolpyruvate-dependent sugar phosphotransferase system]	N	N
hcnB	3.0	hydrogen cyanide synthase HcnB	[metabolic process]	N	N
fliI	3.0	flagellum-specific ATP synthase FliI	[cellular component movement, ciliary or bacterial-type flagellar motility, generation of precursor metabolites and energy]	N	N

ID	Bottleneck	Object_name	GO_Biological process	Essential	Drug target
amiR	3.0	aliphatic amidase regulator	[cellular catabolic process, regulation of transcription, DNA-dependent]	N	N
rpsG	3.0	30S ribosomal protein S7	[cellular protein metabolic process]	Y	Y
PA1095	3.0		[]	N	N
rpoA	3.0	DNA-directed RNA polymerase alpha chain	[RNA metabolic process]	Y	Y
gcvP1	3.0	glycine cleavage system protein P1	[L-serine metabolic process, cellular amino acid metabolic process, glycine metabolic process, metabolic process, threonine metabolic process]	N	N
tolA	3.0	TolA protein	[transport]	Y	N
ampR	3.0	transcriptional regulator AmpR	[regulation of transcription, DNA-dependent]	N	N
clpX	3.0	ATP-dependent Clp protease ATP-binding subunit ClpX	[protein folding]	Y	N
mvfR	3.0	Transcriptional regulator	[cofactor biosynthetic process, regulation of transcription, DNA-dependent]	N	N
phhC	3.0	aromatic amino acid aminotransferase	[cellular amino acid metabolic process]	N	N
trpE	3.0	anthranilate synthetase component I	[L-phenylalanine metabolic process, cellular amino acid metabolic process, generation of precursor metabolites and energy, tryptophan biosynthetic process, ubiquinone biosynthetic process]	N	N
fliJ	3.0	flagellar protein FliJ	[cellular component movement]	N	N
nadE	3.0	NH3-dependent NAD synthetase	[cellular amino acid metabolic process, cofactor biosynthetic process]	P	N
PA2812	3.0		[]	N	N
gshA	3.0	glutamate–cysteine ligase	[cellular amino acid metabolic process, cofactor biosynthetic process, glutathione biosynthetic process]	N	N
ptsN	2.0	nitrogen regulatory IIA protein	[nitrogen compound metabolic process, transport]	P	N

ID	Bottleneck	Object_name	GO_Biological process	Essential	Drug target
fliF	2.0	Flagella M-ring outer membrane protein precursor	[cellular component movement, ciliary or bacterial-type flagellar motility]	N	N
PA3981	2.0		[]	N	N
fliD	2.0	flagellar capping protein FliD	[cellular component movement, ciliary or bacterial-type flagellar motility]	N	N
lpdV	2.0	lipoamide dehydrogenase-Val	[cellular amino acid metabolic process, generation of precursor metabolites and energy]	N	N
lysS	2.0	lysyl-tRNA synthetase	[cellular amino acid metabolic process, cellular protein metabolic process, lysine biosynthetic process, lysyl-tRNA aminoacylation, tRNA aminoacylation]	Y	N
gyrA	2.0	DNA gyrase subunit A	[DNA metabolic process, DNA topological change]	Y	Y
plsX	2.0	fatty acid biosynthesis protein PlsX	[cellular lipid metabolic process, lipid biosynthetic process]	N	N
bkdA2	2.0	2-oxoisovalerate dehydrogenase (beta subunit)	[cellular amino acid metabolic process]	N	N
sahH	2.0	S-adenosyl-L-homocysteine hydrolase	[cellular amino acid metabolic process, one-carbon metabolic process]	Y	N
oprE	2.0	Anaerobically-induced outer membrane porin OprE precursor	[transport]	N	N
arcD	2.0	arginine/ornithine antiporter	[cellular amino acid metabolic process, transport]	N	N
asd	2.0	aspartate semialdehyde dehydrogenase	[L-serine metabolic process, cellular amino acid metabolic process, glycine metabolic process, isoleucine biosynthetic process, lysine biosynthetic process, lysine biosynthetic process via diaminopimelate, methionine biosynthetic process, threonine biosynthetic process, threonine metabolic process]	Y	N
glyQ	2.0	glycyl-tRNA synthetase alpha chain	[cellular amino acid metabolic process, cellular protein metabolic process, glycyl-tRNA aminoacylation]	Y	N

ID	Bottleneck	Object_name	GO_Biological process	Essential	Drug target
gyrB	2.0	DNA gyrase subunit B	[DNA metabolic process, DNA topological change]	N	Y
purF	2.0	amidophosphoribosyltransferase	[cellular amino acid metabolic process, glutamate metabolic process, nucleotide metabolic process, purine nucleotide metabolic process, purine ribonucleotide biosynthetic process]	N	N
algF	2.0	alginate o-acetyltransferase AlgF	[response to stimulus]	N	N
pchD	2.0	pyochelin biosynthesis protein PchD	[transport]	N	
pchR	2.0	transcriptional regulator PchR	[regulation of transcription, DNA-dependent]	N	N
gltR	2.0	two-component response regulator GltR	[cellular catabolic process, phosphorelay signal transduction system, regulation of transcription, DNA-dependent]	N	N
secE	2.0	secretion protein SecE	[secretion]	Y	N
gdhB	2.0	NAD-dependent glutamate dehydrogenase	[biological_process, cellular amino acid metabolic process]	N	N
pnp	2.0	polyribonucleotide nucleotidyltransferase	[RNA metabolic process]	Y	N
fepB	2.0	ferrienterobactin-binding periplasmic protein precursor FepB	[transport]	N	N
algG	2.0	alginate-c5-mannuronan-epimerase AlgG	[response to stimulus]	N	N
mtlR	2.0	transcriptional regulator MtlR	[regulation of transcription, DNA-dependent]	N	N
algI	2.0	alginate o-acetyltransferase AlgI	[alginic acid biosynthetic process, response to stimulus]	N	N
hisI	2.0	phosphoribosyl-AMP cyclohydrolase	[cellular amino acid metabolic process, histidine biosynthetic process]	N	N
pscF	2.0	type III export protein PscF	[secretion]	N	N
pqsE	2.0	Quinolone signal response protein	[cofactor biosynthetic process]	N	N
trpF	2.0	N-(5'phosphoribosyl)anthranilate (PRA) isomerase	[cellular amino acid metabolic process, tryptophan metabolic process]	N	N

ID	Bottleneck	Object_name	GO_Biological process	Essential	Drug target
PA0930	2.0	two-component sensor	[phosphorelay signal transduction system, transport]	N	N
hpd	2.0	4-hydroxyphenylpyruvate dioxygenase	[L-phenylalanine catabolic process, cellular amino acid metabolic process, tyrosine catabolic process]	N	N
poxB	2.0	pyruvate dehydrogenase (cytochrome)	[generation of precursor metabolites and energy, metabolic process, pyruvate metabolic process]	N	N
flhB	2.0	flagellar biosynthetic protein FlhB	[cellular component movement, chemotaxis, ciliary or bacterial-type flagellar motility, response to stimulus]	N	N
panD	2.0	aspartate 1-decarboxylase precursor	[cellular amino acid metabolic process, cofactor biosynthetic process]	N	N
algJ	2.0	alginate o-acetyltransferase AlgJ	[alginic acid biosynthetic process, response to stimulus]	N	N
phnA	1.0	anthranilate synthase component I	[response to stimulus]	N	N
PA1442	1.0		[]	Y	N
pqsH	1.0	probable FAD-dependent monooxygenase	[aromatic compound catabolic process, cofactor biosynthetic process, quorum sensing]	N	N
fliQ	1.0	flagellar biosynthetic protein FliQ	[cellular component movement, chemotaxis, ciliary or bacterial-type flagellar motility, response to stimulus]	N	N
proA	1.0	gamma-glutamyl phosphate reductase	[cellular amino acid metabolic process, cofactor biosynthetic process, proline biosynthetic process]	N	N
PA1103	1.0		[]	N	N
fliO	1.0	flagellar protein FliO	[cellular component movement, chemotaxis, response to stimulus]	N	N
fliE	1.0	flagellar hook-basal body complex protein FliE	[cellular component movement, ciliary or bacterial-type flagellar motility]	N	N
PA3899	1.0		[]	N	N

ID	Bottleneck	Object_name	GO_Biological process	Essential	Drug target
fliN	1.0	flagellar motor switch protein FliN	[cellular component movement, chemotaxis, ciliary or bacterial-type flagellar motility, response to stimulus]	N	N
pchB	1.0	salicylate biosynthesis protein PchB	[transport]	Y	N
recN	1.0	DNA repair protein RecN	[DNA metabolic process, DNA recombination, DNA repair]	N	N
pscJ	1.0	type III export protein PscJ	[secretion]	N	N
argF	1.0	ornithine carbamoyltransferase, anabolic	[arginine biosynthetic process, arginine metabolic process, cellular amino acid metabolic process, proline metabolic process]	N	N
alg44	1.0	alginate biosynthesis protein Alg44	[alginic acid biosynthetic process, response to stimulus]	N	N
rhlI	1.0	autoinducer synthesis protein RhlI	[response to stimulus]	N	N
ilvI	1.0	acetolactate synthase large subunit	[cellular amino acid metabolic process, cofactor biosynthetic process, isoleucine biosynthetic process, valine biosynthetic process]	N	N
PA3297	1.0		[]	N	N
lldD	1.0	L-lactate dehydrogenase	[generation of precursor metabolites and energy]	N	N
ltaA	1.0	low specificity l-threonine aldolase	[L-serine metabolic process, cellular amino acid metabolic process, glycine metabolic process, threonine metabolic process]	N	N
oprD	1.0	Basic amino acid, basic peptide and imipenem outer membrane porin OprD precursor	[transport]	N	N
fleN	1.0	flagellar synthesis regulator FleN	[cellular component movement]	N	N
algL	1.0	poly(beta-d-mannuronate) lyase precursor AlgL	[response to stimulus]	N	N
acsB	1.0	acetyl-coenzyme A synthetase	[cellular catabolic process, metabolic process, propionate metabolic process]	N	N

ID	Bottleneck	Object_name	GO_Biological process	Essential	Drug target
foaB	1.0	fatty-acid oxidation complex beta-subunit	[L-phenylalanine metabolic process, cellular amino acid metabolic process, cellular lipid metabolic process, fatty acid biosynthetic process, isoleucine catabolic process, leucine catabolic process, valine catabolic process]	N	N
glpK	1.0	glycerol kinase	[glycerol metabolic process, glycerolipid metabolic process, metabolic process]	N	N
rplJ	1.0	50S ribosomal protein L10	[cellular protein metabolic process]	Y	Y
lldP	1.0	L-lactate permease	[transport]	N	N
algX	1.0	alginate biosynthesis protein AlgX	[alginic acid biosynthetic process, response to stimulus]	N	N
PA4724	1.0		[]	N	N
toxR	1.0	transcriptional regulator ToxR	[regulation of transcription, DNA-dependent]	N	N
ilvC	1.0	ketol-acid reductoisomerase	[cellular amino acid metabolic process, cofactor biosynthetic process, isoleucine biosynthetic process, valine biosynthetic process]	N	N
PA3961	1.0		[]	N	N
leuD	1.0	3-isopropylmalate dehydratase small subunit	[cellular amino acid metabolic process, isoleucine biosynthetic process, leucine biosynthetic process, regulation of flower development]	N	N
acoR	1.0	transcriptional regulator AcoR	[regulation of transcription, DNA-dependent]	N	N
pqsB	1.0	Homologous to beta-keto-acyl-acyl-carrier protein synthase	[cofactor biosynthetic process]	N	N
dapB	1.0	dihydrodipicolinate reductase	[cellular amino acid metabolic process, lysine biosynthetic process, lysine biosynthetic process via diaminopimelate]	Y	N
mqoB	1.0	malate:quinone oxidoreductase	[generation of precursor metabolites and energy, metabolic process, tricarboxylic acid cycle]	N	N

ID	Bottleneck	Object_name	GO_Biological process	Essential	Drug target
aspA	1.0	aspartate ammonia-lyase	[alanine metabolic process, aspartate metabolic process, cellular amino acid metabolic process, nitrogen compound metabolic process]	N	N
arcA	1.0	arginine deiminase	[arginine metabolic process, cellular amino acid metabolic process, proline metabolic process]	N	N
rpsE	1.0	30S ribosomal protein S5	[cellular protein metabolic process]	N	Y
prtN	1.0	transcriptional regulator PrtN	[regulation of transcription, DNA-dependent]	Y	N
hisH1	1.0	glutamine amidotransferase	[cellular amino acid metabolic process, histidine biosynthetic process]	N	N
nadA	1.0	quinolinate synthetase A	[cellular amino acid metabolic process, cofactor biosynthetic process, pyridine nucleotide biosynthetic process]	N	N
pqsC	1.0	Homologous to beta-keto-acyl-acyl-carrier protein synthase	[cofactor biosynthetic process]	N	N
pvdQ	1.0	PvdQ	[antibiotic biosynthetic process, pyoverdine biosynthetic process, response to stimulus]	N	N
glk	1.0	glucokinase	[carbohydrate metabolic process, cellular catabolic process, generation of precursor metabolites and energy, pentose-phosphate shunt]	N	
PA1697	1.0	ATP synthase in type III secretion system	[protein secretion by the type III secretion system, secretion]	N	N
argE	1.0	acetylornithine deacetylase	[arginine biosynthetic process, cellular amino acid biosynthetic process, cellular amino acid metabolic process]	N	N
PA5428	1.0		[]	N	N
algQ	1.0	Alginate regulatory protein AlgQ	[regulation of transcription, DNA-dependent]	N	N
aruC	1.0	N-succinylglutamate 5-semialdehyde dehydrogenase	[arginine biosynthetic process, cellular amino acid metabolic process]	N	N
algE	1.0	Alginate production outer membrane protein AlgE precursor	[alginic acid biosynthetic process, response to stimulus]	N	N

ID	Bottleneck	Object_name	GO_Biological process	Essential	Drug target
bkdB	1.0	branched-chain alpha-keto acid dehydrogenase (lipoamide component)	[cellular amino acid metabolic process]	N	N
ppc	1.0	phosphoenolpyruvate carboxylase	[carbon fixation, generation of precursor metabolites and energy, metabolic process, oxaloacetate metabolic process, pyruvate metabolic process, reductive tricarboxylic acid cycle]	N	N
ilvA2	1.0	threonine dehydratase, biosynthetic	[L-serine metabolic process, cellular amino acid metabolic process, glycine metabolic process, threonine metabolic process]	N	N
trpI	1.0	transcriptional regulator TrpI	[cellular amino acid metabolic process, regulation of transcription, DNA-dependent]	N	N
rnpA	1.0	ribonuclease P protein component	[cellular protein metabolic process]	N	N
hasR	1.0	Haem uptake outer membrane receptor HasR precursor	[transport]	N	N
ureC	1.0	urease alpha subunit	[metabolic process, nitrogen compound metabolic process]	N	N
fliM	1.0	flagellar motor switch protein FliM	[cellular component movement, chemotaxis, ciliary or bacterial-type flagellar motility, response to stimulus]	N	N
coIII	1.0	cytochrome c oxidase, subunit III	[generation of precursor metabolites and energy]	N	N
oruR	1.0	transcriptional regulator OruR	[regulation of transcription, DNA-dependent]	N	N
fliR	1.0	flagellar biosynthetic protein FliR	[cellular component movement, chemotaxis, response to stimulus]	N	N
lrp	1.0	leucine-responsive regulatory protein	[metabolic process, regulation of transcription, DNA-dependent]	N	N
glnA	1.0	glutamine synthetase	[cellular amino acid metabolic process, glutamine biosynthetic process]	Y	N
ppk	1.0	polyphosphate kinase	[nucleotide metabolic process, response to stimulus]	N	N

ID	Bottleneck	Object_name	GO_Biological process	Essential	Drug target
dksA	1.0	suppressor protein DksA	[DNA metabolic process, regulation of transcription, DNA-dependent, response to stimulus]	N	N
pcaQ	1.0	transcriptional regulator PcaQ	[cellular catabolic process, regulation of transcription, DNA-dependent]	N	N
aroQ1	1.0	3-dehydroquinate dehydratase	[cellular amino acid metabolic process, chorismate biosynthetic process]	N	N
rplM	1.0	50S ribosomal protein L13	[cellular protein metabolic process]	Y	Y
topA	1.0	DNA topoisomerase I	[DNA metabolic process, DNA replication, DNA topological change]	P	N
proB	1.0	glutamate 5-kinase	[cellular amino acid metabolic process, proline biosynthetic process]	N	N

Table A 3: Description of the 122 clusters yielded by the MCODE pluging comprising the information of genes, nodes, edges, score, topological features degree and bottleneck, gene essentiality, drug targets and the main biological processes [106].

Cluster	GeneList	Nodes	Edges	Score	Degree	Bottleneck	Essentia	DrugTarget	Biological process
1	rplA	22	183	8,773	112.0		Y	Y	cellular protein metabolic process
	rplC				107.0		N	Y	
	rpsC				100.0		Y	Y	
	rpsE						N	Y	
	rpsJ						Y	Y	
	rplX						Y	Y	
	rpsT						Y	Y	
	rpsD						Y	Y	
	rplD						N	Y	
	rplN						Y	Y	

Cluster	GeneList	Nodes	Edges	Score	Degree	Bottleneck	Essentia	DrugTarget	Biological process
	rplQ						Y	Y	
	rplW						N	Y	
	PA2840					15.0	N	N	
	rplP						Y	Y	
	rpmG						Y	Y	
	rplU						Y	Y	
	rplF						Y	Y	
	rpsQ						Y	Y	
	rplR						Y	Y	
	rpmD						Y	Y	
	rpsH						N	Y	
	rpsB				121.0		Y	Y	
	rplV				100.0	13.0	Y	Y	
	rpsG				96.0		Y	Y	
	rpsA						Y	Y	
	rplL					34.0	Y	Y	
	rplM						Y	Y	
	spoT					21.0	Y	N	
2	rpsM	30	230	7,667			Y	Y	cellular protein metabolic process
	rpsS						Y	Y	
	rpsF						N	Y	
	rpoA						Y	Y	
	rplE						Y	Y	
	PA3806					17.0	N	N	
	rpsR						Y	Y	
	rpmH						Y	Y	

Cluster	GeneList	Nodes	Edges	Score	Degree	Bottleneck	Essentia	DrugTarget	Biological process
	rnr						N	N	
	rplS						N	Y	
	rpsO						Y	Y	
	rpsU						Y	Y	
	rplT						Y	Y	
	rplO						Y	Y	
	nusG						Y	N	
	rpsK						Y	Y	
	rluC						N	N	
	rpmE						Y	Y	
	rpsI						N	Y	
	rpmJ						Y	Y	
	pnp						N	Y	
	PA2812						N	N	
	secY					37.0	N	N	
3	algR	15	16	6,4	65.0	23.0	N	N	response to stimulus
	algU				60.0	20.0	Y	N	
	algA						N	N	
	algF						N	N	
	algK						N	N	
	algG						N	N	
	algD						N	N	
	algX						N	N	
	algL						N	N	
	alg8						N	N	
	algJ						N	N	

Cluster	GeneList	Nodes	Edges	Score	Degree	Bottleneck	Essentia	DrugTarget	Biological process
	alg44						N	N	
	amrZ						N	N	
	algI						N	N	
	algE						N	N	

Table A 4: Description of the 5 clusters yielded by the MCODE pluging comprising the information of genes, nodes, edges, score, topological features degree and bottleneck, gene essentiality and the main biological processes [106].

Cluster	GeneList	Nodes	Edges	Score	Degree	Bottleneck	Essential	Biological process
1	BCR1	9	19	1,889	271.0	254.0		regulation of transcription from Rna polymerase II promoter; filamentous growth; single-species biofilm formation on inanimate substrate
	TEC1				162.0	52.0	N	
	ZCF34							
	CSA1							
	RME1						N	
	orf19.6465							
	FGR6-3							
	CYC3						N	
	orf19.3969							
2	NDT80	8	15	1,625	839.0	1353.0	N	filamentous growth; single-species biofilm formation on inanimate substrate; pathogenesis
	EFG1				507.0	526.0	N	
	orf19.5975							

Cluster	GeneList	Nodes	Edges	Score	Degree	Bottleneck	Essential	Biological process
	ALS2							
	TPS1						N	
	CAS5							
	CCN1							
	PDX1						N	
3	ROB1	12	20	1,5	100.0	16.0		negative regulation of transcription from RNA polymerase II promoter; pathogenesis; filamentous growth; cellular response to biotic stimulus
	RFG1				43.0	21.0		
	GAT2						N	
	ALS6							
	UTR2						N	
	SFU1							
	IFF5						Y*	
	IFF9						Y*	
	orf19.2724							
	HAP41							
	NRG1						N	
	ALS5							
4	CRZ1	4	5	1			N	cellular response to starvation
	GLN3						N	
	orf19.4972							
	RAS2						N	
5	SWI4	6	6	1	39.0		N	cellular response to biotic stimulus; filamentous growth of a population of unicellular organisms in response to biotic stimulus

Cluster	GeneList	Nodes	Edges	Score	Degree	Bottleneck	Essential	Biological process
	INO4				27.0		N	
	orf19.5855				21.0			
	HGC1							
	FGR6-10							
	ESC4						N	

Table A 5: Description of the nodes comprising the cross-talking subnetwork for *P. aeruginosa*.

ID	Go_Biological process	Cross-talking
acpP	[cellular lipid metabolic process]	Y
algD	[response to stimulus]	Y
aotJ	[transport]	Y
aprA	[]	Y
arcA	[arginine metabolic process, cellular amino acid metabolic process, proline metabolic process]	Y
arcB	[arginine metabolic process, cellular amino acid metabolic process, proline metabolic process]	Y
argR	[cellular amino acid metabolic process, regulation of transcription, DNA-dependent]	Y
asd	[L-serine metabolic process, cellular amino acid metabolic process, glycine metabolic process, isoleucine biosynthetic process, lysine biosynthetic process, lysine biosynthetic process via diaminopimelate, methionine biosynthetic process, threonine biosynthetic process, threonine metabolic process]	Y
azu	[generation of precursor metabolites and energy]	Y
braC	[transport]	Y
cbpD	[biological_process]	Y

ID	Go_Biological process	Cross-talking
cdrA	[]	Y
cpg2	[metabolic process]	Y
cupE1	[]	Y
dnaK	[DNA metabolic process, protein folding, response to stimulus]	Y
dnaN	[DNA metabolic process, DNA replication]	Y
exaA	[cellular catabolic process]	Y
flgK	[cellular component movement, ciliary or bacterial-type flagellar motility]	Y
fliC	[cellular component movement]	Y
fliD	[cellular component movement, ciliary or bacterial-type flagellar motility]	Y
fpvA	[transport]	Y
fusA1	[cellular protein metabolic process]	Y
gcvH1	[cellular amino acid metabolic process, glycine decarboxylation via glycine cleavage system, metabolic process]	Y
glnK	[metabolic process, regulation of nitrogen utilization]	Y
glpQ	[cellular lipid metabolic process]	Y
groEL	[protein folding]	Y
groES	[protein folding]	Y
hasAp	[transport]	Y
icd	[cellular amino acid metabolic process, cellular catabolic process, generation of precursor metabolites and energy]	Y
icmP	[biological_process]	Y
ilvC	[cellular amino acid metabolic process, cofactor biosynthetic process, isoleucine biosynthetic process, valine biosynthetic process]	Y
katA	[]	Y
lasA	[cellular protein metabolic process]	Y
lasB	[cellular protein metabolic process, proteolysis]	Y
lasI	[response to stimulus]	Y

ID	Go_Biological process	Cross-talking
lasR	[regulation of transcription, DNA-dependent, response to stimulus]	Y
mexE	[drug transmembrane transport, response to antibiotic, transport]	Y
moaB2	[cofactor biosynthetic process, molybdopterin cofactor metabolic process, pteridine-containing compound biosynthetic process]	Y
mvfR	[cofactor biosynthetic process, regulation of transcription, DNA-dependent]	Y
ndk	[nucleobase-containing small molecule interconversion, nucleotide metabolic process, purine nucleotide metabolic process, pyrimidine nucleotide metabolic process]	Y
oprF	[transport]	Y
oprL	[transport]	Y
PA0456	[]	Y
PA0572	[]	Y
PA0622	[]	Y
PA0623	[]	Y
PA1342	[]	Y
PA1486	[]	Y
PA2439	[]	Y
PA2451	[]	Y
PA2452	[]	Y
PA3181	[Entner-Doudoroff pathway, cellular catabolic process, metabolic process]	Y
PA3190	[]	Y
PA3313	[]	Y
PA3441	[]	Y
PA3836	[]	Y
PA5076	[]	Y
PA5153	[]	Y
PA5303	[]	Y

ID	Go_Biological process	Cross-talking
PA5339	[]	Y
PA5505	[]	Y
PA5545	[]	Y
pasP	[]	Y
pchD	[transport]	Y
pheA	[aromatic amino acid family biosynthetic process, prephenate pathway, cellular amino acid metabolic process]	Y
phnA	[response to stimulus]	Y
phnB	[L-phenylalanine metabolic process, cellular amino acid metabolic process, response to stimulus, tryptophan biosynthetic process, tyrosine metabolic process, ubiquinone biosynthetic process]	Y
pilB	[cellular component movement, pilus assembly, protein secretion by the type II secretion system]	Y
pilC	[cellular component movement, pilus assembly]	Y
pilY1	[cellular component movement]	Y
piv	[]	Y
plcH	[]	Y
plcR	[]	Y
ppa	[metabolic process, phosphorus metabolic process]	Y
pqsH	[aromatic compound catabolic process, cofactor biosynthetic process, quorum sensing]	Y
pscC	[secretion]	Y
rhlA	[]	Y
rhlI	[response to stimulus]	Y
rhlR	[regulation of transcription, DNA-dependent, response to stimulus]	Y
rpoN	[regulation of transcription, DNA-dependent]	Y
sbp	[transport]	Y
sodB	[removal of superoxide radicals, response to stimulus]	Y
spuD	[transport]	Y
toxA	[]	Y

ID	Go_Biological process	Cross-talking
trxA	[cellular protein metabolic process, generation of precursor metabolites and energy, nucleotide metabolic process]	Y
trxB1	[nucleotide metabolic process, pyrimidine nucleotide metabolic process]	Y
tufA	[cellular protein metabolic process]	Y
aat	[cellular protein metabolic process, proteolysis]	
accA	[cellular catabolic process, cellular lipid metabolic process, fatty acid biosynthetic process, propionate metabolic process, pyruvate metabolic process]	
accC	[cellular lipid metabolic process]	
aceE	[acetyl-CoA biosynthetic process from pyruvate, cellular amino acid metabolic process, generation of precursor metabolites and energy]	
aceF	[acetyl-CoA biosynthetic process from pyruvate, cellular catabolic process, generation of precursor metabolites and energy, gluconeogenesis, glycolysis, pyruvate metabolic process]	
aceK	[carboxylic acid metabolic process, glyoxylate metabolic process, metabolic process]	
acnB	[generation of precursor metabolites and energy, tricarboxylic acid cycle]	
acoB	[cellular catabolic process]	
acpP2	[]	
acsB	[cellular catabolic process, metabolic process, propionate metabolic process]	
adcA	[]	
adcB	[]	
adhA	[cellular catabolic process, fatty acid metabolic process, generation of precursor metabolites and energy, gluconeogenesis, glycerolipid metabolic process, glycolysis, tyrosine metabolic process]	

ID	Go_Biological process	Cross-talking
aer	[aerotaxis, chemotaxis, response to stimulus, signal transduction]	
aguB	[arginine metabolic process, cellular amino acid metabolic process, proline metabolic process]	
alg44	[alginic acid biosynthetic process, response to stimulus]	
alg8	[response to stimulus]	
algA	[fructose metabolic process, mannose metabolic process, response to stimulus]	
algB	[alginic acid biosynthetic process, phosphorelay signal transduction system, regulation of transcription, DNA-dependent]	
algC	[carbohydrate metabolic process, cellular amino acid metabolic process]	
algE	[alginic acid biosynthetic process, response to stimulus]	
algF	[response to stimulus]	
algG	[response to stimulus]	
algI	[alginic acid biosynthetic process, response to stimulus]	
algJ	[alginic acid biosynthetic process, response to stimulus]	
algK	[response to stimulus]	
algL	[response to stimulus]	
algP	[alginic acid biosynthetic process, regulation of transcription, DNA-dependent]	
algQ	[regulation of transcription, DNA-dependent]	
algR	[phosphorelay signal transduction system, regulation of transcription, DNA-dependent]	
algR4	[]	
algU	[regulation of transcription, DNA-dependent]	
algW	[cellular protein metabolic process, response to stimulus]	
algX	[alginic acid biosynthetic process, response to stimulus]	
alkA	[DNA metabolic process]	
amgR	[]	
amiC	[regulation of transcription, DNA-dependent]	

ID	Go_Biological process	Cross-talking
amiR	[cellular catabolic process, regulation of transcription, DNA-dependent]	
amn	[nucleotide metabolic process, purine nucleotide metabolic process]	
ampR	[regulation of transcription, DNA-dependent]	
amrZ	[]	
amtB	[ammonium transport, transport]	
anr	[regulation of transcription, DNA-dependent]	
ansB	[alanine metabolic process, cellular amino acid metabolic process, nitrogen compound metabolic process]	
aotM	[transport]	
aotP	[histidine transport, transport]	
aotQ	[transport]	
aprD	[secretion]	
aprE	[secretion]	
aprF	[secretion]	
aprI	[]	
aprX	[]	
apt	[nucleotide metabolic process, purine ribonucleoside salvage]	
arcC	[cellular amino acid metabolic process, nitrogen compound metabolic process]	
arcD	[cellular amino acid metabolic process, transport]	
argB	[arginine biosynthetic process, arginine metabolic process, cellular amino acid metabolic process, proline metabolic process]	
argC	[cellular amino acid metabolic process]	
argE	[arginine biosynthetic process, cellular amino acid biosynthetic process, cellular amino acid metabolic process]	

ID	Go_Biological process	Cross-talking
argF	[arginine biosynthetic process, arginine metabolic process, cellular amino acid metabolic process, proline metabolic process]	
argG	[alanine metabolic process, arginine biosynthetic process, arginine metabolic process, aspartate metabolic process, cellular amino acid metabolic process, proline metabolic process]	
argH	[arginine biosynthetic process, arginine metabolic process, cellular amino acid metabolic process, proline metabolic process]	
argS	[arginyl-tRNA aminoacylation, cellular protein metabolic process]	
arnT	[response to antibiotic]	
aroB	[L-phenylalanine biosynthetic process, cellular amino acid metabolic process, chorismate biosynthetic process, tryptophan biosynthetic process, tyrosine biosynthetic process]	
aroC	[L-phenylalanine biosynthetic process, aromatic amino acid family biosynthetic process, cellular amino acid metabolic process, tryptophan biosynthetic process, tyrosine biosynthetic process]	
aroE	[L-phenylalanine biosynthetic process, cellular amino acid metabolic process, chorismate biosynthetic process, tryptophan biosynthetic process, tyrosine biosynthetic process]	
aroK	[cellular amino acid metabolic process]	
aroP2	[transport]	
aroQ1	[cellular amino acid metabolic process, chorismate biosynthetic process]	
aroQ2	[L-phenylalanine biosynthetic process, cellular amino acid metabolic process, tryptophan biosynthetic process, tyrosine biosynthetic process]	
arsB	[response to arsenic-containing substance, transport]	

ID	Go_Biological process	Cross-talking
aruB	[cellular amino acid metabolic process]	
aruC	[arginine biosynthetic process, cellular amino acid metabolic process]	
aruD	[cellular amino acid metabolic process]	
aruE	[cellular amino acid metabolic process]	
aruF	[arginine catabolic process, cellular amino acid metabolic process]	
aruG	[arginine catabolic process, cellular amino acid metabolic process]	
aruH	[]	
aspA	[alanine metabolic process, aspartate metabolic process, cellular amino acid metabolic process, nitrogen compound metabolic process]	
aspS	[RNA metabolic process, aspartyl-tRNA aminoacylation, cellular protein metabolic process]	
astA	[]	
astB	[]	
atoB	[cellular lipid metabolic process, metabolic process]	
atpD	[ATP synthesis coupled proton transport, generation of precursor metabolites and energy]	
atpE	[ATP synthesis coupled proton transport, generation of precursor metabolites and energy]	
bacA	[response to antibiotic, response to stimulus]	
bauA	[]	
bcp	[response to stimulus]	
betA	[cellular amino acid metabolic process, fermentation, response to stimulus]	
betB	[cellular amino acid metabolic process, fermentation, response to stimulus]	
bexR	[]	
bioF	[biotin metabolic process, cofactor biosynthetic process]	
bkdA1	[cellular amino acid metabolic process]	
bkdA2	[cellular amino acid metabolic process]	

ID	Go_Biological process	Cross-talking
bkdB	[cellular amino acid metabolic process]	
bkdR	[isoleucine catabolic process, leucine catabolic process, regulation of transcription, DNA-dependent, valine catabolic process]	
bphO	[]	
bphP	[]	
bqsR	[]	
bqsS	[]	
braD	[transport]	
braE	[transport]	
braF	[transport]	
braG	[transport]	
braZ	[branched-chain amino acid transport, transport]	
capB	[regulation of transcription, DNA-dependent, response to stimulus]	
carA	[cellular amino acid metabolic process, glutamate metabolic process, nucleotide metabolic process, pyrimidine ribonucleotide biosynthetic process]	
carB	[arginine metabolic process, cellular amino acid metabolic process, glutamate metabolic process, nucleotide metabolic process, proline metabolic process, pyrimidine nucleotide metabolic process, pyrimidine ribonucleotide biosynthetic process]	
catB	[cellular catabolic process]	
cbrB	[cellular catabolic process, phosphorelay signal transduction system, regulation of transcription, DNA-dependent]	
cc4	[generation of precursor metabolites and energy]	
ccmB	[heme transport, transport]	
ccmC	[heme transport, transport]	
ccmE	[cytochrome complex assembly, generation of precursor metabolites and energy]	
ccpR	[generation of precursor metabolites and energy]	

ID	Go_Biological process	Cross-talking
cdrB	[]	
cheZ	[chemotaxis, response to stimulus]	
cioB	[generation of precursor metabolites and energy]	
clpA	[cellular protein metabolic process]	
clpB	[cellular protein metabolic process]	
clpP	[protein folding]	
clpP2	[]	
clpX	[protein folding]	
cmk	[nucleobase-containing small molecule interconversion, nucleotide metabolic process]	
coaC	[DNA metabolic process, cofactor biosynthetic process]	
coaD	[metabolic process]	
coaE	[cofactor biosynthetic process]	
cobB	[cobalamin biosynthetic process, cofactor biosynthetic process]	
cobC	[cobalamin biosynthetic process, cofactor biosynthetic process]	
cobD	[cobalamin biosynthetic process, cofactor biosynthetic process]	
cobL	[cofactor biosynthetic process]	
cobM	[cofactor biosynthetic process]	
cobO	[cobalamin biosynthetic process]	
cobV	[cobalamin biosynthetic process, cofactor biosynthetic process]	
codA	[nucleotide metabolic process]	
crc	[DNA repair, cellular catabolic process, generation of precursor metabolites and energy]	
creB	[phosphorelay signal transduction system, regulation of transcription, DNA-dependent]	
cspD	[regulation of transcription, DNA-dependent, response to stimulus]	
cupE2	[]	
cupE5	[]	

ID	Go_Biological process	Cross-talking
cycH	[generation of precursor metabolites and energy]	
cyoB	[generation of precursor metabolites and energy]	
cysA	[transport]	
cysB	[cellular amino acid metabolic process, regulation of transcription, DNA-dependent]	
cysC	[cellular amino acid metabolic process, metabolic process, nucleotide metabolic process, sulfur compound metabolic process]	
cysE	[cellular amino acid metabolic process, cofactor biosynthetic process, cysteine biosynthetic process from serine]	
cysK	[cellular amino acid metabolic process, cysteine biosynthetic process from serine]	
cysN	[cellular amino acid metabolic process, metabolic process, sulfur compound metabolic process]	
cysP	[transport]	
cysS	[cellular amino acid metabolic process, cellular protein metabolic process, cysteine metabolic process, cysteinyl-tRNA aminoacylation, tRNA aminoacylation]	
cysT	[transport]	
cysW	[transport]	
dadA	[L-phenylalanine metabolic process, cellular amino acid metabolic process, generation of precursor metabolites and energy, nitrogen compound metabolic process]	
dadX	[D-alanine metabolic process, aspartate metabolic process, cellular amino acid metabolic process]	
dapA	[cellular amino acid metabolic process, lysine biosynthetic process, lysine biosynthetic process via diaminopimelate]	
dapB	[cellular amino acid metabolic process, lysine biosynthetic process, lysine biosynthetic process via diaminopimelate]	

ID	Go_Biological process	Cross-talking
dapD	[lysine biosynthetic process via diaminopimelate]	
dapE	[cellular amino acid metabolic process, lysine biosynthetic process via diaminopimelate, lysine catabolic process]	
dapF	[cellular amino acid metabolic process, lysine biosynthetic process via diaminopimelate]	
def	[cellular protein metabolic process, cellular protein modification process]	
dgkA	[cellular lipid metabolic process, glycerolipid metabolic process, phospholipid biosynthetic process]	
dht	[nucleotide metabolic process]	
dinB	[]	
dksA	[DNA metabolic process, regulation of transcription, DNA-dependent, response to stimulus]	
dnaA	[DNA metabolic process, DNA replication initiation, regulation of DNA replication]	
dnaE	[DNA metabolic process, DNA replication]	
dnaJ	[DNA metabolic process, protein folding, response to stimulus]	
dnaQ	[nucleotide metabolic process]	
dnaX	[DNA metabolic process, DNA replication]	
dps	[]	
dsdA	[cellular amino acid metabolic process]	
dxr	[cofactor biosynthetic process, isopentenyl diphosphate biosynthetic process, methylerythritol 4-phosphate pathway]	
dxs	[cofactor biosynthetic process]	
eco	[cellular protein metabolic process]	
eno	[cellular catabolic process, cellular protein metabolic process, generation of precursor metabolites and energy, glycolysis]	
epd	[cofactor biosynthetic process, gluconeogenesis, glycolysis]	

ID	Go_Biological process	Cross-talking
era	[cell growth, cellular protein metabolic process, cytokinesis by binary fission]	
erbR	[]	
estX	[]	
etfA	[generation of precursor metabolites and energy]	
exoS	[]	
exsA	[regulation of transcription, DNA-dependent, secretion]	
fabA	[cellular lipid metabolic process, fatty acid biosynthetic process]	
fabB	[cellular lipid metabolic process]	
fabD	[cellular lipid metabolic process]	
fabF1	[cellular lipid metabolic process]	
fabG	[cellular lipid metabolic process]	
fabI	[cellular lipid metabolic process]	
fabZ	[cellular lipid metabolic process]	
fadD1	[cellular lipid metabolic process, fatty acid metabolic process]	
fadH1	[cellular lipid metabolic process, fatty acid catabolic process]	
fahA	[L-phenylalanine catabolic process, cellular catabolic process, tyrosine catabolic process]	
fdhA	[metabolic process, methane metabolic process]	
fdhE	[generation of precursor metabolites and energy]	
fdnH	[generation of precursor metabolites and energy]	
fdxA	[generation of precursor metabolites and energy]	
fecA	[transport]	
fepB	[transport]	
fepC	[transport]	
fgtA	[]	
fhp	[generation of precursor metabolites and energy]	
fhpR	[]	
fhpR_Tá	[]	

ID	Go_Biological process	Cross-talking
figA	[]	
fis	[DNA metabolic process, RNA metabolic process, regulation of transcription, DNA-dependent]	
fklB	[cellular protein metabolic process, protein folding]	
fleN	[cellular component movement]	
fleQ	[cellular component movement, ciliary or bacterial-type flagellar motility, regulation of transcription, DNA-dependent]	
fleR	[cellular component movement, ciliary or bacterial-type flagellar motility, phosphorelay signal transduction system, regulation of transcription, DNA-dependent]	
fleS	[cell adhesion, cellular component movement, phosphorelay signal transduction system]	
flgB	[cellular component movement, ciliary or bacterial-type flagellar motility]	
flgC	[cellular component movement, ciliary or bacterial-type flagellar motility]	
flgD	[cellular component movement]	
flgE	[cellular component movement]	
flgF	[cellular component movement, ciliary or bacterial-type flagellar motility]	
flgG	[cellular component movement, ciliary or bacterial-type flagellar motility]	
flgH	[cellular component movement, ciliary or bacterial-type flagellar motility]	
flgI	[cellular component movement, ciliary or bacterial-type flagellar motility]	
flgJ	[cellular component movement]	
flgL	[cellular component movement, ciliary or bacterial-type flagellar motility]	
flgM	[]	
flhA	[cellular component movement, chemotaxis, ciliary or bacterial-type flagellar motility, response to stimulus]	

ID	Go_Biological process	Cross-talking
flhB	[cellular component movement, chemotaxis, ciliary or bacterial-type flagellar motility, response to stimulus]	
flhF	[cellular component movement, chemotaxis, response to stimulus]	
fliA	[DNA-dependent transcription, initiation, regulation of transcription, DNA-dependent]	
fliE	[cellular component movement, ciliary or bacterial-type flagellar motility]	
fliF	[cellular component movement, ciliary or bacterial-type flagellar motility]	
fliG	[cellular component movement, chemotaxis, ciliary or bacterial-type flagellar motility]	
fliI	[cellular component movement, ciliary or bacterial-type flagellar motility, generation of precursor metabolites and energy]	
fliJ	[cellular component movement]	
fliK	[]	
fliM	[cellular component movement, chemotaxis, ciliary or bacterial-type flagellar motility, response to stimulus]	
fliN	[cellular component movement, chemotaxis, ciliary or bacterial-type flagellar motility, response to stimulus]	
fliO	[cellular component movement, chemotaxis, response to stimulus]	
fliP	[cellular component movement, chemotaxis, ciliary or bacterial-type flagellar motility, response to stimulus]	
fliQ	[cellular component movement, chemotaxis, ciliary or bacterial-type flagellar motility, response to stimulus]	
fliR	[cellular component movement, chemotaxis, response to stimulus]	
flp	[]	
fmt	[cellular amino acid metabolic process, cellular protein metabolic process, methionyl-tRNA aminoacylation]	

ID	Go_Biological process	Cross-talking
foaB	[L-phenylalanine metabolic process, cellular amino acid metabolic process, cellular lipid metabolic process, fatty acid biosynthetic process, isoleucine catabolic process, leucine catabolic process, valine catabolic process]	
folD	[10-formyltetrahydrofolate biosynthetic process, cellular protein metabolic process, cofactor biosynthetic process, histidine biosynthetic process, methionine biosynthetic process, nucleotide metabolic process, pantothenate biosynthetic process, purine nucleobase biosynthetic process]	
folE2	[cofactor biosynthetic process, folic acid-containing compound metabolic process]	
folK	[cofactor biosynthetic process]	
foxA	[]	
fpvI	[]	
frr	[cellular protein metabolic process]	
ftsE	[cytokinesis, cytokinesis by binary fission, transport]	
ftsH	[cytokinesis, cytokinesis by binary fission]	
ftsZ	[cytokinesis, cytokinesis by binary fission]	
fur	[regulation of transcription, DNA-dependent]	
fusA2	[cellular protein metabolic process]	
gabT	[cellular amino acid metabolic process, cellular catabolic process, gamma-aminobutyric acid catabolic process, metabolic process]	
gacA	[regulation of transcription, DNA-dependent]	
gatB	[cellular protein metabolic process, glutamyl-tRNA aminoacylation]	
gbuR	[arginine metabolic process, proline metabolic process, regulation of transcription, DNA-dependent]	
gcdH	[cellular amino acid metabolic process, cellular catabolic process, cellular lipid metabolic process]	
gcpE	[]	

ID	Go_Biological process	Cross-talking
gcvP1	[L-serine metabolic process, cellular amino acid metabolic process, glycine metabolic process, metabolic process, threonine metabolic process]	
gcvP2	[L-serine metabolic process, cellular amino acid metabolic process, glycine decarboxylation via glycine cleavage system, glycine metabolic process, metabolic process, threonine metabolic process]	
gcvT1	[cellular amino acid metabolic process, glycine decarboxylation via glycine cleavage system, metabolic process]	
gdhA	[cellular amino acid metabolic process]	
gdhB	[biological_process, cellular amino acid metabolic process]	
gidA	[biological_process, cytokinesis by binary fission]	
glcF	[cellular catabolic process, metabolic process]	
glmU	[lipopolysaccharide biosynthetic process]	
glnA	[cellular amino acid metabolic process, glutamine biosynthetic process]	
glnS	[cellular amino acid metabolic process, cellular protein metabolic process, glutaminyl-tRNA aminoacylation]	
gloA1	[metabolic process]	
glpK	[glycerol metabolic process, glycerolipid metabolic process, metabolic process]	
glpT	[glycerol-3-phosphate transport, transport]	
gltA	[carboxylic acid metabolic process, generation of precursor metabolites and energy, glyoxylate metabolic process, tricarboxylic acid cycle]	
gltB	[cellular amino acid metabolic process, glutamate biosynthetic process]	
gltD	[cellular amino acid metabolic process, glutamate biosynthetic process]	

ID	Go_Biological process	Cross-talking
gltR	[cellular catabolic process, phosphorelay signal transduction system, regulation of transcription, DNA-dependent]	
gltX	[cellular protein metabolic process, glutamate metabolic process, glutamyl-tRNA aminoacylation]	
glyA1	[cellular amino acid metabolic process, glycine biosynthetic process, one-carbon metabolic process]	
glyA2	[L-serine metabolic process, cellular amino acid metabolic process, glycine metabolic process, lysine catabolic process, methane metabolic process, threonine metabolic process]	
glyA3	[L-serine metabolic process, cellular amino acid metabolic process, glycine biosynthetic process, glycine metabolic process, lysine catabolic process, methane metabolic process, one-carbon metabolic process, threonine metabolic process]	
glyQ	[cellular amino acid metabolic process, cellular protein metabolic process, glycyl-tRNA aminoacylation]	
glyS	[cellular amino acid metabolic process, cellular protein metabolic process, glycyl-tRNA aminoacylation]	
gmd	[polysaccharide biosynthetic process]	
gmk	[nucleobase-containing small molecule interconversion, nucleotide metabolic process]	
gor	[cellular amino acid metabolic process, cofactor biosynthetic process, glutamate metabolic process, glutathione metabolic process]	
greA	[DNA-dependent transcription, elongation, RNA metabolic process]	
grpE	[DNA metabolic process, protein folding]	
gshA	[cellular amino acid metabolic process, cofactor biosynthetic process, glutathione biosynthetic process]	
gshB	[cellular amino acid metabolic process, cofactor biosynthetic process, glutathione biosynthetic process]	

ID	Go_Biological process	Cross-talking
guaA	[cellular amino acid metabolic process, nucleotide metabolic process, purine ribonucleotide biosynthetic process]	
guaB	[nucleotide metabolic process, purine nucleotide metabolic process, purine ribonucleotide biosynthetic process]	
gyrA	[DNA metabolic process, DNA topological change]	
gyrB	[DNA metabolic process, DNA topological change]	
hasD	[secretion, transport]	
hasE	[secretion]	
hasR	[transport]	
hcnA	[biological_process, metabolic process]	
hcnB	[metabolic process]	
hcnC	[metabolic process]	
hemA	[cellular amino acid metabolic process, cellular protein metabolic process, cofactor biosynthetic process, porphyrin-containing compound biosynthetic process]	
hemC	[cofactor biosynthetic process]	
hemE	[cofactor biosynthetic process, porphyrin-containing compound biosynthetic process]	
hemF	[chlorophyll metabolic process, cofactor biosynthetic process]	
hemH	[cofactor biosynthetic process, porphyrin-containing compound biosynthetic process]	
himA	[DNA recombination, RNA metabolic process, cellular protein metabolic process, regulation of transcription, DNA-dependent]	
hisA	[cellular amino acid metabolic process, histidine biosynthetic process, histidine metabolic process]	
hisC2	[cellular amino acid metabolic process]	
hisE	[cellular amino acid metabolic process, histidine biosynthetic process]	

ID	Go_Biological process	Cross-talking
hisF1	[cellular amino acid metabolic process, histidine biosynthetic process, histidine metabolic process]	
hisF2	[cellular amino acid metabolic process, histidine metabolic process]	
hisG	[cellular amino acid metabolic process, histidine biosynthetic process]	
hisH1	[cellular amino acid metabolic process, histidine biosynthetic process]	
hisH2	[cellular amino acid metabolic process, histidine metabolic process]	
hisI	[cellular amino acid metabolic process, histidine biosynthetic process]	
hisJ	[cellular amino acid metabolic process, transport]	
hisM	[cellular amino acid metabolic process, transport]	
hisP	[cellular amino acid metabolic process, transport]	
hisQ	[cellular amino acid metabolic process, transport]	
hisS	[cellular protein metabolic process, histidyl-tRNA aminoacylation]	
holA	[DNA metabolic process, DNA replication]	
holB	[DNA metabolic process, DNA replication]	
holC	[DNA metabolic process, DNA replication]	
hom	[L-serine metabolic process, aspartate family amino acid biosynthetic process, cellular amino acid metabolic process, glycine metabolic process, lysine biosynthetic process, threonine metabolic process]	
hpd	[L-phenylalanine catabolic process, cellular amino acid metabolic process, tyrosine catabolic process]	
hprA	[metabolic process]	
hrlA	[]	
hrlB	[]	
hscA	[protein folding]	
htpG	[protein folding]	
hupB	[DNA metabolic process, DNA packaging]	

ID	Go_Biological process	Cross-talking
hutH	[cellular amino acid metabolic process, histidine catabolic process]	
hutI	[cellular amino acid metabolic process, histidine catabolic process]	
hutU	[cellular amino acid metabolic process, histidine catabolic process]	
iciA	[DNA metabolic process]	
ihf	[]	
ileS	[cellular amino acid metabolic process, cellular protein metabolic process, isoleucyl-tRNA aminoacylation]	
ilvA1	[L-serine metabolic process, cellular amino acid metabolic process, glycine metabolic process, isoleucine biosynthetic process, threonine metabolic process]	
ilvA2	[L-serine metabolic process, cellular amino acid metabolic process, glycine metabolic process, threonine metabolic process]	
ilvE	[branched-chain amino acid biosynthetic process, cellular amino acid metabolic process]	
ilvH	[cellular amino acid metabolic process, cofactor biosynthetic process, isoleucine biosynthetic process, valine biosynthetic process]	
ilvI	[cellular amino acid metabolic process, cofactor biosynthetic process, isoleucine biosynthetic process, valine biosynthetic process]	
infB	[cellular protein metabolic process]	
ipk	[cofactor biosynthetic process, isopentenyl diphosphate biosynthetic process, methylerythritol 4-phosphate pathway]	
irlR	[phosphorelay signal transduction system, regulation of transcription, DNA-dependent]	

ID	Go_Biological process	Cross-talking
iscS	[cellular amino acid metabolic process, cofactor biosynthetic process, cysteine metabolic process, sulfur compound metabolic process]	
iscU	[]	
ispA	[cofactor biosynthetic process]	
katB	[response to oxidative stress, response to stimulus]	
katE	[response to oxidative stress, response to stimulus]	
kdpB	[potassium ion transport, transport]	
kdpC	[potassium ion transport, transport]	
kdsA	[cellular catabolic process, keto-3-deoxy-D-manno-octulosonic acid biosynthetic process]	
kdsB	[fructose metabolic process, lipopolysaccharide core region biosynthetic process, mannose metabolic process]	
kefB	[potassium ion transport, transport]	
kinB	[]	
kinU	[]	
kynB	[biological_process, cellular amino acid metabolic process]	
lecA	[]	
lepA	[cellular protein metabolic process, secretion]	
leuA	[cellular amino acid metabolic process, isoleucine biosynthetic process, leucine biosynthetic process, regulation of flower development]	
leuB	[cellular amino acid metabolic process, isoleucine biosynthetic process, leucine biosynthetic process, regulation of flower development]	
leuC	[cellular amino acid metabolic process, isoleucine biosynthetic process, leucine biosynthetic process, regulation of flower development]	
leuD	[cellular amino acid metabolic process, isoleucine biosynthetic process, leucine biosynthetic process, regulation of flower development]	

ID	Go_Biological process	Cross-talking
leuS	[cellular amino acid metabolic process, cellular protein metabolic process, leucyl-tRNA aminoacylation]	
lexA	[cellular protein metabolic process, regulation of DNA repair, regulation of transcription, DNA-dependent, response to stimulus]	
lipB	[cellular amino acid metabolic process, cofactor biosynthetic process, folic acid biosynthetic process, lipoate biosynthetic process, lysine catabolic process, ubiquinone biosynthetic process]	
lis	[cofactor biosynthetic process, lipoate biosynthetic process]	
liuD	[]	
lldD	[generation of precursor metabolites and energy]	
lnt	[cellular protein metabolic process, cellular protein modification process]	
lon	[cellular protein metabolic process, proteolysis, response to stimulus]	
lpd3	[generation of precursor metabolites and energy]	
lpdG	[cellular amino acid metabolic process, generation of precursor metabolites and energy]	
lpdV	[cellular amino acid metabolic process, generation of precursor metabolites and energy]	
lpxC	[lipid A biosynthetic process]	
lpxD	[]	
lrp	[metabolic process, regulation of transcription, DNA-dependent]	
ltaA	[L-serine metabolic process, cellular amino acid metabolic process, glycine metabolic process, threonine metabolic process]	
lysA	[cellular amino acid metabolic process, lysine biosynthetic process via diaminopimelate]	
lysC	[cellular amino acid metabolic process, lysine biosynthetic process via diaminopimelate]	

ID	Go_Biological process	Cross-talking
lysS	[cellular amino acid metabolic process, cellular protein metabolic process, lysine biosynthetic process, lysyl-tRNA aminoacylation, tRNA aminoacylation]	
lytB	[response to antibiotic, response to stimulus, stringent response]	
masA	[cellular amino acid metabolic process]	
mdcC	[cellular catabolic process]	
mdcD	[cellular catabolic process]	
mdlC	[aromatic compound catabolic process, cellular catabolic process]	
metE	[cellular amino acid metabolic process, methionine biosynthetic process]	
metF	[cellular amino acid metabolic process, metabolic process, methionine biosynthetic process]	
metH	[cellular amino acid metabolic process, methionine biosynthetic process]	
metK	[S-adenosylmethionine biosynthetic process, cellular amino acid metabolic process, metabolic process]	
metY	[cellular amino acid metabolic process, sulfur compound metabolic process]	
mexB	[response to antibiotic, transport]	
mexH	[quorum sensing, transport]	
mexR	[regulation of transcription, DNA-dependent]	
mexT	[regulation of transcription, DNA-dependent]	
micA	[DNA metabolic process]	
migA	[]	
minD	[cytokinesis by binary fission]	
mmsA	[cellular amino acid metabolic process, cellular catabolic process, isoleucine catabolic process, leucine catabolic process, propionate metabolic process, valine catabolic process]	

ID	Go_Biological process	Cross-talking
mmsB	[cellular catabolic process, isoleucine catabolic process, leucine catabolic process, valine catabolic process]	
moaA2	[cofactor biosynthetic process]	
moaC	[]	
moaE	[cofactor biosynthetic process]	
mobA	[]	
moeA2	[cofactor biosynthetic process]	
mqoB	[generation of precursor metabolites and energy, metabolic process, tricarboxylic acid cycle]	
mraY	[]	
mreB	[cytokinesis by binary fission]	
msbA	[cellular lipid metabolic process, lipid transport, transport]	
mscL	[response to stimulus, transport]	
msuD	[cellular catabolic process, metabolic process, sulfur compound metabolic process]	
msuE	[cellular catabolic process, metabolic process, sulfur compound metabolic process]	
mtlR	[regulation of transcription, DNA-dependent]	
mtlZ	[cellular catabolic process, fructose metabolic process, mannose metabolic process]	
mtr	[transport]	
murA	[]	
murB	[amino sugar metabolic process, peptidoglycan biosynthetic process]	
murC	[]	
murG	[cellular catabolic process]	
mutM	[DNA metabolic process, DNA repair]	
nadA	[cellular amino acid metabolic process, cofactor biosynthetic process, pyridine nucleotide biosynthetic process]	

ID	Go_Biological process	Cross-talking
napA	[generation of precursor metabolites and energy, nitrogen compound metabolic process]	
napB	[generation of precursor metabolites and energy, nitrogen compound metabolic process]	
napE	[generation of precursor metabolites and energy]	
narG	[generation of precursor metabolites and energy, nitrogen compound metabolic process]	
narJ	[generation of precursor metabolites and energy]	
narL	[generation of precursor metabolites and energy, nitrogen compound metabolic process, phosphorelay signal transduction system, regulation of transcription, DNA-dependent]	
nasA	[nitrogen compound metabolic process, transport]	
nhaP	[hydrogen transport, transport]	
nirB	[metabolic process]	
nirD	[metabolic process, nitrogen compound metabolic process]	
nirJ	[cofactor biosynthetic process, generation of precursor metabolites and energy, heme biosynthetic process]	
norB	[generation of precursor metabolites and energy]	
norC	[generation of precursor metabolites and energy]	
nosD	[generation of precursor metabolites and energy]	
nosR	[generation of precursor metabolites and energy]	
nosZ	[generation of precursor metabolites and energy]	
nqrA	[generation of precursor metabolites and energy]	
nqrB	[generation of precursor metabolites and energy]	
nrdA	[2'-deoxyribonucleotide biosynthetic process, nucleotide metabolic process]	
nrdB	[2'-deoxyribonucleotide biosynthetic process, nucleotide metabolic process, purine nucleotide metabolic process, pyrimidine nucleotide metabolic process]	
ntrB	[phosphorelay signal transduction system, regulation of nitrogen utilization]	

ID	Go_Biological process	Cross-talking
nuh	[nucleotide metabolic process]	
nuoI	[generation of precursor metabolites and energy, oxidative phosphorylation]	
nusA	[RNA metabolic process]	
nusG	[RNA metabolic process]	
obg	[biological_process, response to stimulus]	
ogt	[DNA metabolic process]	
oprB	[transport]	
oprD	[transport]	
oprE	[transport]	
oprJ	[response to antibiotic, transport]	
oprM	[response to antibiotic, transport]	
orfB	[]	
orfC	[]	
orfD	[]	
orfE	[]	
orfF	[]	
orfG	[]	
orfH	[]	
orfI	[]	
orfJ	[]	
orfK	[]	
orfL	[]	
orfM	[]	
orfN	[]	
oruR	[regulation of transcription, DNA-dependent]	
PA0027	[]	
PA0028	[]	
PA0122	[]	
PA0128	[]	
PA0144	[]	
PA0313	[]	

ID	Go_Biological process	Cross-talking
PA0328	[]	
PA0399	[cellular amino acid metabolic process]	
PA0422	[]	
PA0575	[]	
PA0588	[]	
PA0606	[]	
PA0656	[]	
PA0805	[]	
PA0855	[]	
PA0858	[]	
PA0891	[]	
PA0900	[]	
PA0929	[phosphorelay signal transduction system, transport]	
PA0935	[]	
PA0947	[]	
PA0968	[]	
PA0976	[]	
PA1059	[]	
PA1093	[]	
PA1095	[]	
PA1103	[]	
PA1159	[]	
PA1204	[]	
PA1296	[]	
PA1339	[]	
PA1340	[]	
PA1341	[]	
PA1419	[]	
PA1442	[]	
PA1485	[]	
PA1616	[]	
PA1640	[]	

ID	Go_Biological process	Cross-talking
PA1656	[]	
PA1657	[]	
PA1658	[]	
PA1659	[]	
PA1697	[protein secretion by the type III secretion system, secretion]	
PA1779	[metabolic process]	
PA1782	[]	
PA1784	[]	
PA1833	[]	
PA1914	[]	
PA2022	[]	
PA2042	[]	
PA2142	[]	
PA2188	[]	
PA2197	[]	
PA2204	[]	
PA2302	[]	
PA2303	[]	
PA2304	[]	
PA2305	[]	
PA2307	[]	
PA2339	[]	
PA2351	[]	
PA2437	[]	
PA2438	[]	
PA2483	[]	
PA2588	[]	
PA2591	[]	
PA2812	[]	
PA2840	[]	
PA2939	[]	

ID	Go_Biological process	Cross-talking
PA2943	[L-phenylalanine biosynthetic process, cellular amino acid metabolic process, chorismate biosynthetic process, tryptophan biosynthetic process, tyrosine biosynthetic process]	
PA2987	[]	
PA3017	[]	
PA3034	[]	
PA3040	[]	
PA3119	[]	
PA3187	[]	
PA3261	[]	
PA3314	[]	
PA3315	[]	
PA3316	[]	
PA3326	[]	
PA3404	[]	
PA3443	[]	
PA3444	[]	
PA3521	[]	
PA3534	[]	
PA3535	[]	
PA3538	[]	
PA3618	[]	
PA3628	[]	
PA3714	[]	
PA3799	[]	
PA3800	[]	
PA3801	[]	
PA3804	[]	
PA3806	[]	
PA3808	[]	
PA3837	[]	

ID	Go_Biological process	Cross-talking
PA3904	[]	
PA3905	[]	
PA3906	[]	
PA3907	[]	
PA3908	[]	
PA3913	[]	
PA3934	[]	
PA3972	[]	
PA3980	[]	
PA4061	[]	
PA4133	[generation of precursor metabolites and energy]	
PA4153	[cellular catabolic process]	
PA4222	[]	
PA4223	[]	
PA4395	[]	
PA4445	[]	
PA4456	[]	
PA4463	[]	
PA4465	[]	
PA4466	[]	
PA4668	[]	
PA4677	[]	
PA4753	[]	
PA4754	[]	
PA4757	[]	
PA4778	[]	
PA4841	[]	
PA4907	[]	
PA4948	[]	
PA5019	[]	
PA5074	[]	
PA5080	[cellular protein metabolic process]	

ID	Go_Biological process	Cross-talking
PA5152	[]	
PA5154	[]	
PA5155	[]	
PA5180	[]	
PA5181	[]	
PA5184	[]	
PA5228	[]	
PA5230	[]	
PA5231	[]	
PA5232	[]	
PA5275	[]	
PA5281	[]	
PA5298	[nucleotide metabolic process, purine ribonucleoside salvage]	
PA5428	[]	
PA5503	[]	
PA5504	[]	
PA5521	[]	
PA5543	[]	
PA5544	[]	
PA5567	[]	
PA5568	[]	
pabB	[cofactor biosynthetic process, folic acid-containing compound metabolic process]	
pabC	[cofactor biosynthetic process]	
panC	[cofactor biosynthetic process, pantothenate biosynthetic process]	
panD	[cellular amino acid metabolic process, cofactor biosynthetic process]	
parE	[DNA metabolic process, DNA topological change]	
pcaC	[cellular catabolic process, protocatechuate catabolic process]	

ID	Go_Biological process	Cross-talking
pcaD	[catechol-containing compound catabolic process, cellular catabolic process]	
pcaF	[cellular catabolic process, cellular lipid metabolic process]	
pcaQ	[cellular catabolic process, regulation of transcription, DNA-dependent]	
pcaR	[cellular catabolic process, regulation of transcription, DNA-dependent]	
pchA	[pyochelin biosynthetic process, transport, ubiquinone biosynthetic process]	
pchB	[transport]	
pchC	[transport]	
pchE	[pyochelin biosynthetic process, transport]	
pchF	[pyochelin biosynthetic process, transport]	
pchR	[regulation of transcription, DNA-dependent]	
pcm	[cellular protein metabolic process, protein repair, response to stimulus]	
pdxA	[cofactor biosynthetic process, pyridoxine biosynthetic process, vitamin B6 metabolic process]	
pdxB	[cellular amino acid metabolic process, cellular catabolic process, cofactor biosynthetic process]	
pepN	[cellular protein metabolic process, proteolysis]	
pfeR	[phosphorelay signal transduction system, regulation of transcription, DNA-dependent]	
pfpI	[cellular protein metabolic process]	
pgi	[cellular catabolic process, generation of precursor metabolites and energy, glycolysis]	
pgl	[metabolic process, pentose-phosphate shunt]	
pheC	[cellular amino acid metabolic process, response to stimulus]	

ID	Go_Biological process	Cross-talking
pheS	[L-phenylalanine biosynthetic process, cellular protein metabolic process, phenylalanyl-tRNA aminoacylation, tRNA aminoacylation, tryptophan biosynthetic process, tyrosine biosynthetic process]	
pheT	[DNA metabolic process, cellular protein metabolic process, phenylalanyl-tRNA aminoacylation]	
phhA	[L-phenylalanine biosynthetic process, L-phenylalanine catabolic process, cellular amino acid metabolic process, tryptophan biosynthetic process, tyrosine biosynthetic process]	
phhC	[cellular amino acid metabolic process]	
phnC2	[]	
phnE	[transport]	
phnW	[cellular catabolic process]	
phnX	[cellular catabolic process]	
phoB	[phosphate ion transport, phosphate-containing compound metabolic process, phosphorelay signal transduction system, regulation of transcription, DNA-dependent]	
phoP	[phosphorelay signal transduction system, regulation of transcription, DNA-dependent]	
phzA1	[]	
phzB1	[]	
phzC1	[]	
phzC2	[]	
phzD1	[]	
phzE1	[]	
phzF2	[]	
phzG	[]	
pilA	[cellular component movement]	
pilD	[cellular component movement, pilus assembly, secretion]	
pilI	[cellular component movement, chemotaxis]	

ID	Go_Biological process	Cross-talking
pilR	[cellular component movement, phosphorelay signal transduction system, pilus assembly, regulation of transcription, DNA-dependent]	
pilT	[cellular component movement]	
pilX	[cellular component movement]	
plcB	[biological_process]	
plsB	[cellular lipid metabolic process]	
pnp	[RNA metabolic process]	
pobA	[cellular catabolic process]	
potC	[transport]	
potD	[transport]	
poxB	[generation of precursor metabolites and energy, metabolic process, pyruvate metabolic process]	
ppc	[carbon fixation, generation of precursor metabolites and energy, metabolic process, oxaloacetate metabolic process, pyruvate metabolic process, reductive tricarboxylic acid cycle]	
ppiB	[cellular protein metabolic process, protein folding]	
ppiC1	[cellular protein metabolic process, protein folding]	
ppiC2	[cellular protein metabolic process, protein folding]	
ppk	[nucleotide metabolic process, response to stimulus]	
ppsA	[cellular catabolic process, generation of precursor metabolites and energy, gluconeogenesis, metabolic process, phosphoenolpyruvate-dependent sugar phosphotransferase system]	
ppyR	[]	
pqqA	[cofactor biosynthetic process]	
pqqC	[cofactor biosynthetic process]	
pqsA	[cofactor biosynthetic process]	
pqsB	[cofactor biosynthetic process]	
pqsC	[cofactor biosynthetic process]	
pqsD	[cofactor biosynthetic process]	
pqsE	[cofactor biosynthetic process]	

ID	Go_Biological process	Cross-talking
proA	[cellular amino acid metabolic process, cofactor biosynthetic process, proline biosynthetic process]	
proB	[cellular amino acid metabolic process, proline biosynthetic process]	
proC	[cellular amino acid metabolic process, proline biosynthetic process]	
proS	[arginine metabolic process, cellular amino acid metabolic process, cellular protein metabolic process, proline metabolic process, prolyl-tRNA aminoacylation]	
prpC	[cellular catabolic process, fermentation, metabolic process]	
prs	[cellular catabolic process, nucleotide metabolic process, pentose-phosphate shunt, purine ribonucleotide biosynthetic process]	
prtN	[regulation of transcription, DNA-dependent]	
pscB	[secretion]	
pscD	[secretion]	
pscF	[secretion]	
pscH	[secretion]	
pscJ	[secretion]	
pscL	[secretion]	
psd	[cellular amino acid metabolic process, cellular lipid metabolic process, phospholipid biosynthetic process]	
psIA	[]	
psIB	[]	
psIC	[]	
psID	[]	
psIE	[]	
psIF	[]	
psIG	[]	
psIH	[]	
psII	[]	
psIJ	[]	

ID	Go_Biological process	Cross-talking
pslK	[]	
pslL	[]	
pssA	[cellular lipid metabolic process, phospholipid biosynthetic process]	
pstA	[phosphate ion transport, transport]	
pstB	[phosphate ion transport, transport]	
pstC	[phosphate ion transport, transport]	
pstI	[]	
pta	[acetyl-CoA biosynthetic process from pyruvate, cellular catabolic process, pyruvate metabolic process]	
ptpA	[cellular protein metabolic process, response to stimulus]	
ptsN	[nitrogen compound metabolic process, transport]	
ptsP	[phosphoenolpyruvate-dependent sugar phosphotransferase system, transport]	
ptxR	[regulation of transcription, DNA-dependent]	
purB	[cellular amino acid metabolic process, nucleotide metabolic process, purine ribonucleotide biosynthetic process]	
purC	[nucleotide metabolic process, purine nucleotide metabolic process, purine ribonucleotide biosynthetic process]	
purD	[nucleotide metabolic process, purine nucleotide metabolic process, purine ribonucleotide biosynthetic process]	
purE	[nucleotide metabolic process, purine nucleotide metabolic process, purine ribonucleotide biosynthetic process]	
purK	[nucleotide metabolic process, purine nucleotide metabolic process, purine ribonucleotide biosynthetic process]	
purM	[nucleotide metabolic process, purine ribonucleotide biosynthetic process]	

ID	Go_Biological process	Cross-talking
purT	[L-serine metabolic process, cellular amino acid metabolic process, glycine metabolic process, nucleotide metabolic process, threonine metabolic process]	
purU2	[carboxylic acid metabolic process, glyoxylate metabolic process, nucleotide metabolic process, purine ribonucleotide biosynthetic process]	
putA	[cellular amino acid metabolic process, proline catabolic process]	
pvdD	[response to stimulus, siderophore biosynthetic process]	
pvdE	[response to stimulus, transport]	
pvdF	[pyoverdine biosynthetic process, response to stimulus]	
pvdG	[response to stimulus]	
pvdS	[regulation of transcription, DNA-dependent]	
pykA	[carbon fixation, cellular catabolic process, generation of precursor metabolites and energy, gluconeogenesis, glycolysis, purine nucleotide metabolic process, pyruvate metabolic process]	
pykF	[cellular catabolic process, generation of precursor metabolites and energy]	
pyrB	[alanine metabolic process, aspartate metabolic process, cellular amino acid metabolic process, nucleotide metabolic process, pyrimidine nucleotide metabolic process, pyrimidine ribonucleotide biosynthetic process]	
pyrC	[nucleotide metabolic process, pyrimidine ribonucleotide biosynthetic process]	
pyrD	[nucleotide metabolic process, pyrimidine nucleotide metabolic process, pyrimidine ribonucleotide biosynthetic process]	
pyrE	[nucleotide metabolic process, pyrimidine ribonucleotide biosynthetic process]	

ID	Go_Biological process	Cross-talking
pyrF	[nucleotide metabolic process, pyrimidine ribonucleotide biosynthetic process]	
pyrH	[nucleobase-containing small molecule interconversion, nucleotide metabolic process]	
qor	[generation of precursor metabolites and energy]	
qsc102	[]	
qscR	[regulation of transcription, DNA-dependent]	
rbfA	[cellular protein metabolic process, response to stimulus]	
rbsA	[D-ribose transport, transport]	
rbsB	[transport]	
recA	[DNA metabolic process, DNA recombination, SOS response]	
recD	[DNA metabolic process, DNA recombination, DNA repair]	
recF	[DNA metabolic process, DNA repair, DNA replication, SOS response]	
recG	[DNA metabolic process, DNA recombination]	
recJ	[DNA metabolic process, DNA recombination]	
recO	[DNA metabolic process, DNA recombination, DNA repair]	
resR	[]	
resS	[]	
rfaD	[fructose metabolic process, mannose metabolic process]	
rhdA	[metabolic process]	
rhlB	[]	
rhlG	[cellular lipid metabolic process]	
rho	[DNA-dependent transcription, termination, RNA metabolic process]	
ribD	[cofactor biosynthetic process, riboflavin biosynthetic process]	

ID	Go_Biological process	Cross-talking
ribE	[cofactor biosynthetic process, riboflavin biosynthetic process]	
ribF	[FAD biosynthetic process, FMN biosynthetic process, cofactor biosynthetic process, riboflavin biosynthetic process]	
rimK	[RNA metabolic process, cellular protein metabolic process]	
rmlC	[O antigen biosynthetic process, dTDP-rhamnose biosynthetic process]	
rnhB	[DNA metabolic process, RNA catabolic process]	
rnpA	[cellular protein metabolic process]	
rnr	[RNA metabolic process]	
rnt	[DNA metabolic process, RNA metabolic process]	
rocS1	[]	
rpe	[generation of precursor metabolites and energy, pentose-phosphate shunt]	
rph	[RNA metabolic process]	
rplA	[cellular protein metabolic process]	
rplB	[cellular protein metabolic process]	
rplC	[cellular protein metabolic process]	
rplD	[RNA metabolic process, cellular protein metabolic process]	
rplE	[cellular protein metabolic process]	
rplI	[cellular protein metabolic process]	
rplK	[cellular protein metabolic process]	
rplL	[cellular protein metabolic process]	
rplM	[cellular protein metabolic process]	
rplN	[cellular protein metabolic process]	
rplQ	[cellular protein metabolic process]	
rplS	[cellular protein metabolic process]	
rplV	[cellular protein metabolic process]	
rplX	[cellular protein metabolic process]	
rpmF	[cellular protein metabolic process]	

ID	Go_Biological process	Cross-talking
rpmG	[cellular protein metabolic process]	
rpmH	[cellular protein metabolic process, metabolic process]	
rpoA	[RNA metabolic process]	
rpoB	[RNA metabolic process]	
rpoC	[RNA metabolic process]	
rpoD	[DNA-dependent transcription, initiation, regulation of transcription, DNA-dependent]	
rpoH	[regulation of transcription, DNA-dependent]	
rpoS	[DNA-dependent transcription, initiation, regulation of transcription, DNA-dependent, response to stress]	
rpsA	[cellular protein metabolic process]	
rpsB	[cellular protein metabolic process]	
rpsC	[cellular protein metabolic process]	
rpsD	[cellular protein metabolic process]	
rpsE	[cellular protein metabolic process]	
rpsF	[cellular protein metabolic process]	
rpsG	[cellular protein metabolic process]	
rpsJ	[RNA metabolic process, cellular protein metabolic process]	
rpsM	[cellular protein metabolic process]	
rpsN	[cellular protein metabolic process]	
rpsP	[DNA metabolic process, cellular protein metabolic process]	
rpsR	[cellular protein metabolic process]	
rpsT	[cellular protein metabolic process, metabolic process]	
rsaL	[quorum sensing, regulation of transcription, DNA-dependent, response to stimulus]	
ruvA	[DNA metabolic process, DNA recombination]	
ruvB	[DNA metabolic process, DNA recombination]	
ruvC	[DNA metabolic process, DNA recombination]	
sadB	[]	
sahH	[cellular amino acid metabolic process, one-carbon metabolic process]	

ID	Go_Biological process	Cross-talking
secA	[secretion]	
secB	[protein stabilization, secretion]	
secF	[intracellular protein transport, secretion]	
secG	[secretion]	
secY	[secretion]	
selB	[cellular protein metabolic process]	
serC	[L-serine biosynthetic process, cellular amino acid metabolic process, cofactor biosynthetic process]	
serS	[cellular amino acid metabolic process, cellular protein metabolic process, seryl-tRNA aminoacylation]	
slyD	[cellular protein metabolic process, protein folding]	
sodM	[response to stimulus]	
soxA	[cellular catabolic process]	
soxB	[cellular catabolic process]	
soxG	[cellular catabolic process]	
speA	[cellular amino acid metabolic process, polyamine biosynthetic process]	
speE	[beta-alanine metabolic process, cellular amino acid metabolic process, spermidine biosynthetic process, urea cycle]	
spoT	[cellular response to starvation, nucleotide metabolic process, purine nucleotide metabolic process, response to stimulus]	
spuA	[cellular amino acid metabolic process]	
spuB	[glutamine biosynthetic process]	
spuE	[transport]	
spuF	[putrescine transport, transport]	
spuG	[transport]	
spuH	[transport]	
sspB	[cellular response to starvation, response to stimulus]	
sth	[nucleotide metabolic process]	
stk1	[cellular protein metabolic process]	

ID	Go_Biological process	Cross-talking
sucA	[cellular amino acid metabolic process, generation of precursor metabolites and energy, lysine catabolic process, tricarboxylic acid cycle, tryptophan metabolic process]	
sucD	[generation of precursor metabolites and energy, tricarboxylic acid cycle]	
tauD	[cellular catabolic process]	
thiD	[cofactor biosynthetic process]	
thiG	[cofactor biosynthetic process]	
thiL	[cofactor biosynthetic process, thiamine biosynthetic process]	
thrB	[cellular amino acid metabolic process, threonine biosynthetic process]	
thrC	[L-serine metabolic process, cellular amino acid metabolic process, cofactor biosynthetic process, glycine metabolic process, threonine biosynthetic process, threonine metabolic process, vitamin B6 metabolic process]	
thrH	[L-serine metabolic process, cellular amino acid metabolic process, glycine metabolic process, threonine metabolic process]	
thrS	[L-serine metabolic process, cellular amino acid metabolic process, cellular protein metabolic process, glycine metabolic process, tRNA aminoacylation, threonine metabolic process, threonyl-tRNA aminoacylation]	
thyA	[2'-deoxyribonucleotide biosynthetic process, cofactor biosynthetic process, nucleotide metabolic process]	
tig	[cytokinesis by binary fission, protein folding]	
tmk	[nucleobase-containing small molecule interconversion, nucleotide metabolic process]	
tolA	[transport]	
tolB	[transport]	

ID	Go_Biological process	Cross-talking
tolQ	[antibiotic transport, transport]	
tolR	[transport]	
tonB1	[]	
toxR	[regulation of transcription, DNA-dependent]	
tpbA	[]	
tpiA	[generation of precursor metabolites and energy, glycolysis, metabolic process]	
tpx	[response to stimulus]	
trpA	[L-phenylalanine biosynthetic process, cellular amino acid metabolic process, tryptophan biosynthetic process, tyrosine biosynthetic process]	
trpB	[L-phenylalanine biosynthetic process, cellular amino acid metabolic process, tryptophan biosynthetic process, tyrosine biosynthetic process]	
trpD	[cellular amino acid metabolic process, tryptophan biosynthetic process]	
trpF	[cellular amino acid metabolic process, tryptophan metabolic process]	
trpG	[cellular amino acid metabolic process, cofactor biosynthetic process, generation of precursor metabolites and energy, tryptophan biosynthetic process]	
trpI	[cellular amino acid metabolic process, regulation of transcription, DNA-dependent]	
trpS	[cellular amino acid metabolic process, cellular protein metabolic process, tryptophanyl-tRNA aminoacylation]	
tufB	[cellular protein metabolic process]	
typA	[biological_process, response to stimulus]	
tyrS	[L-phenylalanine biosynthetic process, cellular amino acid metabolic process, cellular protein metabolic process, tRNA aminoacylation, tryptophan biosynthetic process, tyrosine biosynthetic process]	

ID	Go_Biological process	Cross-talking
tyrZ	[tRNA aminoacylation, tryptophan metabolic process, tyrosyl-tRNA aminoacylation]	
ubiA	[cofactor biosynthetic process, generation of precursor metabolites and energy, ubiquinone biosynthetic process]	
ubiE	[cofactor biosynthetic process, generation of precursor metabolites and energy, ubiquinone biosynthetic process]	
ubiG	[cofactor biosynthetic process, generation of precursor metabolites and energy]	
ubiH	[cofactor biosynthetic process, generation of precursor metabolites and energy, ubiquinone biosynthetic process]	
upp	[nucleotide metabolic process, pyrimidine nucleotide metabolic process, pyrimidine-containing compound salvage]	
uppS	[cofactor biosynthetic process]	
ureB	[metabolic process, nitrogen compound metabolic process]	
ureD	[metabolic process]	
uvrC	[DNA metabolic process, DNA repair]	
valS	[cellular amino acid metabolic process, cellular protein metabolic process, isoleucine biosynthetic process, leucine biosynthetic process, regulation of flower development, tRNA aminoacylation, valyl-tRNA aminoacylation]	
vfr	[regulation of transcription, DNA-dependent]	
vioA	[]	
waaA	[lipopolysaccharide core region biosynthetic process]	
wbpM	[lipopolysaccharide biosynthetic process]	
wrbA	[RNA metabolic process, tryptophan metabolic process]	
wzm	[lipopolysaccharide biosynthetic process, transport]	
wzt	[lipopolysaccharide biosynthetic process, transport]	

ID	Go_Biological process	Cross-talking
wzx	[transport]	
xcpP	[secretion]	
xcpQ	[secretion]	
xdhA	[nucleotide metabolic process]	
xenB	[metabolic process, response to antibiotic, response to stimulus]	
xerD	[DNA integration, DNA metabolic process, DNA recombination]	
xseA	[DNA catabolic process, DNA metabolic process]	
xylS	[regulation of transcription, DNA-dependent]	
xylX	[cellular catabolic process]	
xylZ	[cellular catabolic process, generation of precursor metabolites and energy]	
ygbB	[cofactor biosynthetic process, isopentenyl diphosphate biosynthetic process, methylerythritol 4-phosphate pathway]	
ygdP	[metabolic process, nucleotide metabolic process]	
znuC	[transport, zinc ion transport]	
zwf	[cellular catabolic process, generation of precursor metabolites and energy, pentose-phosphate shunt]	

Table A 6: Description of the nodes comprising the cross-talking subnetwork for *C. albicans*.

ID	Go_Biological process	Cross-talking
ALS1	[adhesion to host, cell adhesion, cell adhesion involved in multi-species biofilm formation, cell adhesion involved in single-species biofilm formation, cell-cell adhesion, cell-cell adhesion involved in flocculation, cellular response to neutral pH, entry into host cell, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to neutral pH, hyphal growth, induction by symbiont of host defense response, pathogenesis, positive regulation of flocculation, single-species biofilm formation on inanimate substrate]	Y

ID	Go_Biological process	Cross-talking
ALS2	[adhesion to host, adhesion to other organism involved in symbiotic interaction, agglutination involved in conjugation with cellular fusion, cell adhesion, cell adhesion involved in biofilm formation, cell adhesion involved in multi-species biofilm formation, cell adhesion involved in single-species biofilm formation, cell-cell adhesion, endocytosis, entry into host cell, filamentous growth of a population of unicellular organisms, hyphal growth, iron assimilation by reduction and transport, pathogenesis, single-species biofilm formation on inanimate substrate]	Y
ALS3	[cell adhesion]	Y
ALS4	[adhesion to host, cell adhesion, cell-cell adhesion, cellular response to temperature stimulus, hyphal growth]	Y
ALS5	[adhesion to host, cell adhesion, cell adhesion involved in multi-species biofilm formation, cell adhesion involved in single-species biofilm formation, cell-cell adhesion, cell-matrix adhesion, entry into host cell]	Y
ALS6	[cell adhesion, cell adhesion involved in multi-species biofilm formation, cell adhesion involved in single-species biofilm formation]	Y
ALS7	[cell adhesion involved in multi-species biofilm formation, cell adhesion involved in single-species biofilm formation]	Y
ALS9	[cell adhesion, cell adhesion involved in multi-species biofilm formation, cell adhesion involved in single-species biofilm formation, cellular response to stress, flocculation via cell wall protein-carbohydrate interaction]	Y
BCR1	[carbon catabolite activation of transcription from RNA polymerase II promoter, cell-abiotic substrate adhesion, filamentous growth, growth of symbiont in host, positive regulation of cell adhesion involved in single-species biofilm formation, positive regulation of cell-substrate adhesion, positive regulation of growth of symbiont in host, positive regulation of transcription from RNA polymerase II promoter, regulation of single-species biofilm formation in or on host organism, regulation of single-species biofilm formation on inanimate substrate, regulation of transcription from RNA polymerase II promoter, regulation of transcription from RNA polymerase II promoter in response to salt stress, regulation of transcription, DNA-dependent, single-species biofilm formation in or on host organism, single-species biofilm formation on inanimate substrate]	Y
BGL2	[adhesion to host, carbohydrate metabolic process, fungal-type cell wall organization, growth of symbiont in host, pathogenesis, single-species biofilm formation in or on host organism, single-species biofilm formation on inanimate substrate]	Y

ID	Go_Biological process	Cross-talking
CDR1	[azole transport, cellular response to drug, cellular response to oxidative stress, cellular response to steroid hormone stimulus, drug export, drug transmembrane transport, fluconazole transport, phospholipid translocation, transport]	Y
CHK1	[cellular response to biotic stimulus, cellular response to farnesol, cellular response to oxidative stress, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, fungal-type cell wall biogenesis, negative regulation of calcium-independent cell-cell adhesion, negative regulation of phagocytosis, pathogenesis, phosphorelay signal transduction system, positive regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, protein phosphorylation, regulation of conjugation with cellular fusion, regulation of mitotic cell cycle, regulation of single-species biofilm formation on inanimate substrate, regulation of transcription, DNA-dependent, single-species biofilm formation on inanimate substrate, stress-activated protein kinase signaling cascade]	Y
CHT2	[carbohydrate metabolic process, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to starvation]	Y
CHT3	[carbohydrate metabolic process, cellular bud site selection, chitin catabolic process, cytokinesis, completion of separation]	Y

ID	Go_Biological process	Cross-talking
CPH1	[cellular response to biotic stimulus, cellular response to starvation, conjugation with cellular fusion, development of symbiont in host, evasion or tolerance of host immune response, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, fungal-type cell wall organization, galactose metabolic process, growth of unicellular organism as a thread of attached cells, invasive growth in response to glucose limitation, negative regulation of transcription from RNA polymerase II promoter by pheromones, pathogenesis, positive regulation of filamentous growth of a population of unicellular organisms, positive regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, positive regulation of filamentous growth of a population of unicellular organisms in response to starvation, positive regulation of growth of unicellular organism as a thread of attached cells, positive regulation of pseudohyphal growth by positive regulation of transcription from RNA polymerase II promoter, positive regulation of transcription from RNA polymerase II promoter by pheromones, pseudohyphal growth, regulation of filamentous growth of a population of unicellular organisms, regulation of pseudohyphal growth, regulation of single-species biofilm formation on inanimate substrate, regulation of transcription, DNA-dependent, signal transduction, single-species biofilm formation on inanimate substrate]	Y
CSA2	[single-species biofilm formation on inanimate substrate]	Y

ID	Go_Biological process	Cross-talking
CYR1	[Ras protein signal transduction, adenylate cyclase-modulating G-protein coupled receptor signaling pathway, cAMP biosynthetic process, cAMP-mediated signaling, cell adhesion involved in single-species biofilm formation, cell-abiotic substrate adhesion, cellular response to biotic stimulus, cellular response to carbon dioxide, cellular response to chemical stimulus, cellular response to drug, cellular response to starvation, conidium formation, evasion or tolerance of host immune response, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to chemical stimulus, filamentous growth of a population of unicellular organisms in response to starvation, growth of unicellular organism as a thread of attached cells, negative regulation of conidium formation, negative regulation of induction of conjugation with cellular fusion, negative regulation of transcription from RNA polymerase II promoter by glucose, pathogenesis, phenotypic switching, positive regulation of apoptotic process, positive regulation of filamentous growth of a population of unicellular organisms, positive regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, positive regulation of filamentous growth of a population of unicellular organisms in response to chemical stimulus, positive regulation of filamentous growth of a population of unicellular organisms in response to starvation, positive regulation of growth of unicellular organism as a thread of attached cells, positive regulation of phenotypic switching, positive regulation of protein import into nucleus, regulation of glycogen biosynthetic process, regulation of phenotypic switching, regulation of single-species biofilm formation on inanimate substrate, response to heat, signal transduction involved in filamentous growth, single-species biofilm formation on inanimate substrate, spore germination, sporocarp development involved in sexual reproduction, trehalose catabolic process]	Y
ECE1	[single-species biofilm formation on inanimate substrate]	Y
ECM33	[adhesion to host, ascospore wall assembly, biological_process, cell morphogenesis, cellular response to biotic stimulus, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, fungal-type cell wall organization, pathogenesis, single-species biofilm formation on inanimate substrate]	Y

ID	Go_Biological process	Cross-talking
EFG1	[adhesion to host, cell adhesion, cell growth mode switching, budding to filamentous, cell migration, cell morphogenesis, cell-cell adhesion involved in flocculation, cell-substrate adhesion, cellular developmental process, cellular response to N-acetyl-D-glucosamine, cellular response to biotic stimulus, cellular response to chemical stimulus, cellular response to drug, cellular response to neutral pH, cellular response to starvation, chlamydospore formation, development of symbiont in host, entry into host, evasion or tolerance of host immune response, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to chemical stimulus, filamentous growth of a population of unicellular organisms in response to neutral pH, filamentous growth of a population of unicellular organisms in response to starvation, fungal-type cell wall organization or biogenesis, hyphal growth, negative regulation of transcription from RNA polymerase II promoter, pathogenesis, phenotypic switching, positive regulation of cell-substrate adhesion, positive regulation of filamentous growth of a population of unicellular organisms, positive regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, positive regulation of filamentous growth of a population of unicellular organisms in response to chemical stimulus, positive regulation of filamentous growth of a population of unicellular organisms in response to neutral pH, positive regulation of filamentous growth of a population of unicellular organisms in response to starvation, positive regulation of phenotypic switching, positive regulation of pseudohyphal growth, positive regulation of pseudohyphal growth by positive regulation of transcription from RNA polymerase II promoter, positive regulation of transcription from RNA polymerase II promoter, pseudohyphal growth, regulation of cell differentiation, regulation of phenotypic switching, regulation of pseudohyphal growth, regulation of single-species biofilm formation on inanimate substrate, regulation of transcription from RNA polymerase II promoter, regulation of transcription, DNA-dependent, single-species biofilm formation on inanimate substrate]	Y

ID	Go_Biological process	Cross-talking
GCN4	[cellular response to N-acetyl-D-glucosamine, cellular response to amino acid starvation, cellular response to biotic stimulus, cellular response to neutral pH, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to chemical stimulus, filamentous growth of a population of unicellular organisms in response to neutral pH, negative regulation of ribosomal protein gene transcription from RNA polymerase II promoter in response to nutrient levels, nitrogen catabolite activation of transcription from RNA polymerase II promoter, positive regulation of RNA polymerase II transcriptional preinitiation complex assembly, positive regulation of filamentous growth of a population of unicellular organisms in response to neutral pH, positive regulation of single-species biofilm formation on inanimate substrate, positive regulation of transcription from RNA polymerase II promoter, positive regulation of transcription initiation from RNA polymerase II promoter, positive regulation of transcription, DNA-dependent, regulation of transcription from RNA polymerase II promoter, regulation of transcription, DNA-dependent, single-species biofilm formation on inanimate substrate]	Y
HWP1	[adhesion to host, cell adhesion, cell adhesion involved in biofilm formation, cell adhesion involved in single-species biofilm formation in or on host organism, cell-cell adhesion, filamentous growth of a population of unicellular organisms, fungal-type cell wall organization, growth of symbiont in host, pathogenesis, single-species biofilm formation on inanimate substrate]	Y
HYR1	[avoidance of host defenses, cell-substrate adhesion, cellular response to hydrogen peroxide, oxidation-reduction process, pathogenesis, single-species biofilm formation in or on host organism]	Y
IHD1	[biological_process]	Y
MDR1	[cellular response to drug, cellular response to oxidative stress, drug export, drug transmembrane transport, drug transport, fluconazole transport, intracellular protein transport, pathogenesis, regulation of Rab GTPase activity, response to drug]	Y

ID	Go_Biological process	Cross-talking
MDS3	[TOR signaling cascade, cellular response to chemical stimulus, cellular response to heat, cellular response to pH, chlamydospore formation, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to chemical stimulus, filamentous growth of a population of unicellular organisms in response to heat, filamentous growth of a population of unicellular organisms in response to pH, filamentous growth of a population of unicellular organisms in response to starvation, negative regulation of sporulation resulting in formation of a cellular spore, pathogenesis, positive regulation of cell-substrate adhesion, positive regulation of filamentous growth of a population of unicellular organisms in response to chemical stimulus, signal transduction involved in conjugation with cellular fusion, single-species biofilm formation on inanimate substrate]	Y
MKC1	[MAPK cascade, UFP-specific transcription factor mRNA processing involved in endoplasmic reticulum unfolded protein response, activation of bipolar cell growth, ascospore formation, barrier septum assembly, cell wall macromolecule catabolic process involved in fungal-type cell wall disassembly, cellular hyperosmotic salinity response, cellular response to biotic stimulus, cellular response to drug, cellular response to glucose starvation, cellular response to heat, cellular response to non-ionic osmotic stress, cellular response to oxidative stress, cellular response to reactive oxygen species, conidiophore development, conidium formation, filamentous growth, filamentous growth of a population of unicellular organisms in response to starvation, fungal-type cell wall biogenesis, fungal-type cell wall organization, hyphal growth, pathogenesis, peroxisome degradation, positive regulation of calcium ion transport into cytosol, positive regulation of calcium-mediated signaling, positive regulation of filamentous growth of a population of unicellular organisms in response to starvation, protein phosphorylation, regulation of cell shape, regulation of cell size, regulation of fungal-type cell wall organization, regulation of single-species biofilm formation on inanimate substrate, regulation of transcription factor import into nucleus, response to acid, signal transduction, single-species biofilm formation on inanimate substrate, sporocarp development involved in sexual reproduction, stress-activated protein kinase signaling cascade, syncytium formation by plasma membrane fusion]	Y
MP65	[carbohydrate metabolic process, cell adhesion, cell adhesion involved in single-species biofilm formation, cell-cell adhesion, cell-substrate adhesion, cellular glucan metabolic process, cellular response to glucose starvation, cellular response to neutral pH, conjugation with cellular fusion, filamentous growth, filamentous growth of a population of unicellular organisms in response to neutral pH, filamentous growth of a population of unicellular organisms in response to starvation, induction by symbiont of host defense response, pathogenesis]	Y

ID	Go_Biological process	Cross-talking
MSB2	[establishment of cell polarity, filamentous growth, filamentous growth of a population of unicellular organisms, fungal-type cell wall organization, hyperosmotic response, osmosensory signaling pathway via Sho1 osmosensor, positive regulation of MAPK cascade, positive regulation of filamentous growth of a population of unicellular organisms, positive regulation of single-species biofilm formation on inanimate substrate, signal transduction involved in filamentous growth]	Y
NRG1	[biofilm formation, cellular response to N-acetyl-D-glucosamine, cellular response to biotic stimulus, cellular response to drug, cellular response to neutral pH, cellular response to starvation, chlamydospore formation, development of symbiont in host, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to chemical stimulus, filamentous growth of a population of unicellular organisms in response to neutral pH, filamentous growth of a population of unicellular organisms in response to pH, filamentous growth of a population of unicellular organisms in response to starvation, negative regulation of cellular hyperosmotic salinity response by negative regulation of transcription from RNA polymerase II promoter, negative regulation of filamentous growth of a population of unicellular organisms, negative regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, negative regulation of filamentous growth of a population of unicellular organisms in response to chemical stimulus, negative regulation of filamentous growth of a population of unicellular organisms in response to neutral pH, negative regulation of filamentous growth of a population of unicellular organisms in response to starvation, negative regulation of invasive growth in response to glucose limitation by negative regulation of transcription from RNA polymerase II promoter, negative regulation of isoprenoid metabolic process, negative regulation of transcription from RNA polymerase II promoter, negative regulation of transcription from RNA polymerase II promoter by glucose, negative regulation of transcription, DNA-dependent, pathogenesis, pseudohyphal growth, quorum sensing, regulation of transcription, DNA-dependent]	Y
NUP85	[cellular response to pH, filamentous growth, filamentous growth of a population of unicellular organisms in response to pH, mRNA export from nucleus, nuclear pore distribution, positive regulation of transcription, DNA-dependent, protein import into nucleus, ribosomal large subunit export from nucleus, single-species biofilm formation on inanimate substrate]	Y
PBR1	[cell adhesion, single-species biofilm formation on inanimate substrate]	Y
PGA10	[cellular iron ion homeostasis, hemoglobin import, single-species biofilm formation on inanimate substrate]	Y

ID	Go_Biological process	Cross-talking
PHR1	[adhesion to other organism involved in symbiotic interaction, carbohydrate metabolic process, cell-substrate adhesion, cellular response to drug, cellular response to pH, development of symbiont in host, entry into host, filamentous growth, filamentous growth of a population of unicellular organisms, fungal-type cell wall organization, growth of symbiont in host, hyphal growth, pathogenesis, response to salt stress, single-species biofilm formation in or on host organism, single-species biofilm formation on inanimate substrate]	Y
RBE1	[pathogenesis, sterol transport]	Y
RBT1	[fungal-type cell wall organization, pathogenesis]	Y
RBT4	[cellular response to drug, pathogenesis]	Y
RBT5	[cell adhesion involved in single-species biofilm formation, cellular iron ion homeostasis, hemoglobin import, single-species biofilm formation on inanimate substrate]	Y
RHD1	[beta-1,2-oligomannoside metabolic process]	Y
SAP4	[activation of immune response, adhesion to host, cellular nitrogen compound catabolic process, evasion or tolerance of host immune response, induction by symbiont of defense-related host calcium ion flux, nitrogen compound metabolic process, pathogenesis, protein catabolic process, proteolysis, signal peptide processing]	Y
SAP6	[activation of immune response, adhesion to host, cellular nitrogen compound catabolic process, induction by symbiont of defense-related host calcium ion flux, induction by symbiont of host defense response, nitrogen compound metabolic process, pathogenesis, protein catabolic process, protein metabolic process, proteolysis, signal peptide processing]	Y
SUN41	[adhesion to host, cellular response to biotic stimulus, cytokinetic cell separation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, fungal-type cell wall biogenesis, fungal-type cell wall organization, pathogenesis, single-species biofilm formation in or on host organism, single-species biofilm formation on inanimate substrate]	Y
SUV3	[Group I intron splicing, aerobic respiration, cell growth mode switching, budding to filamentous, cellular response to biotic stimulus, cellular response to drug, cellular response to pH, chlamydospore formation, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to pH, mitochondrial DNA replication, mitochondrial RNA 3'-end processing, mitochondrial RNA catabolic process, single-species biofilm formation on inanimate substrate]	Y

ID	Go_Biological process	Cross-talking
TEC1	[adhesion to host, cell adhesion, cellular response to biotic stimulus, chronological cell aging, development of symbiont in host, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to biotic stimulus, invasive growth in response to glucose limitation, pathogenesis, positive regulation of filamentous growth of a population of unicellular organisms, positive regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, positive regulation of pseudohyphal growth by positive regulation of transcription from RNA polymerase II promoter, positive regulation of transcription from RNA polymerase II promoter, positive regulation of transcription from RNA polymerase II promoter by pheromones, positive regulation of transcription from RNA polymerase II promoter in response to stress, positive regulation of transposition, RNA-mediated, pseudohyphal growth, regulation of pseudohyphal growth, regulation of single-species biofilm formation on inanimate substrate, regulation of transcription from RNA polymerase II promoter, regulation of transcription, DNA-dependent, single-species biofilm formation on inanimate substrate]	Y
TOS1	[biological_process]	Y

ID	Go_Biological process	Cross-talking
TUP1	[cell-cell adhesion, cellular response to biotic stimulus, cellular response to copper ion, cellular response to drug, cellular response to farnesol, cellular response to starvation, chromatin remodeling in response to cation stress, chromatin silencing, cleistothecium development, conidium formation, development of symbiont in host, entry into host, evasion or tolerance of defenses of other organism involved in symbiotic interaction, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to chemical stimulus, filamentous growth of a population of unicellular organisms in response to starvation, histone exchange, hyphal growth, negative regulation of dipeptide transport by negative regulation of transcription from RNA polymerase II promoter, negative regulation of filamentous growth of a population of unicellular organisms, negative regulation of isoprenoid metabolic process, negative regulation of mating-type specific transcription from RNA polymerase II promoter, negative regulation of transcription from RNA polymerase II promoter, negative regulation of transcription from RNA polymerase II promoter by glucose, negative regulation of transcription from RNA polymerase II promoter during mitosis, negative regulation of transcription, DNA-dependent, nucleosome positioning, pathogenesis, phenotypic switching, positive regulation of sexual sporulation resulting in formation of a cellular spore, positive regulation of sterigmatocystin biosynthetic process, quorum sensing, regulation of fatty acid biosynthetic process by regulation of transcription from RNA polymerase II promoter, regulation of glycogen metabolic process, regulation of response to DNA damage stimulus, regulation of transcription from RNA polymerase II promoter in response to hypoxia, regulation of transcription from RNA polymerase II promoter in response to osmotic stress, sporocarp development involved in asexual reproduction, sterigmatocystin biosynthetic process, syncytium formation by plasma membrane fusion]	Y
UTR2	[adhesion to host, cell wall chitin metabolic process, fungal-type cell wall organization, growth of unicellular organism as a thread of attached cells, pathogenesis]	Y
XOG1	[cell-substrate adhesion, cellular glucan metabolic process, fungal-type cell wall organization, single-species biofilm formation in or on host organism, single-species biofilm formation on inanimate substrate]	Y
YWP1	[adhesion to host, single-species biofilm formation]	Y
AAF1	[adhesion to host, cell adhesion, cell-cell adhesion, filamentous growth, regulation of transcription, DNA-dependent]	
AAT1	[aspartate biosynthetic process, chronological cell aging, replicative cell aging]	

ID	Go_Biological process	Cross-talking
AAT21	[aspartate biosynthetic process, biosynthetic process]	
ABG1	[cytokinetic cell separation, endocytosis, fungal-type cell wall organization, hyphal growth, protein complex assembly, vacuole organization]	
ACE2	[cell adhesion involved in single-species biofilm formation, cellular response to chemical stimulus, cellular response to drug, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to chemical stimulus, fungal-type cell wall organization, pathogenesis, positive regulation of cell adhesion involved in single-species biofilm formation, positive regulation of cell-substrate adhesion, positive regulation of cytokinetic cell separation, positive regulation of filamentous growth of a population of unicellular organisms in response to chemical stimulus, positive regulation of transcription from RNA polymerase II promoter, single-species biofilm formation in or on host organism]	
ACO1	[induction by symbiont of host defense response, mitochondrial genome maintenance, tricarboxylic acid cycle]	
ADAEC	[DNA repair, regulation of transcription, DNA-dependent]	
ADE2	['de novo' IMP biosynthetic process, adenine biosynthetic process, detoxification of cadmium ion, hydrogen sulfide biosynthetic process, pathogenesis, phytochelatin biosynthetic process, purine nucleobase metabolic process, purine nucleotide biosynthetic process]	
ADH1	[NADH oxidation, amino acid catabolic process to alcohol via Ehrlich pathway, ethanol biosynthetic process involved in glucose fermentation to ethanol, ethanol catabolic process, glycolysis, induction by symbiont of host defense response, interaction with host, oxidation-reduction process, single-species biofilm formation in or on host organism, single-species biofilm formation on inanimate substrate, threonine catabolic process]	

ID	Go_Biological process	Cross-talking
ADR1	[cellular response to biotic stimulus, cellular response to oleic acid, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, negative regulation of chromatin silencing, peroxisome organization, positive regulation of ethanol catabolic process by positive regulation of transcription from RNA polymerase II promoter, positive regulation of fatty acid beta-oxidation by positive regulation of transcription from RNA polymerase II promoter, positive regulation of peroxisome organization by positive regulation of transcription from RNA polymerase II promoter, positive regulation of transcription from RNA polymerase II promoter by oleic acid, positive regulation of transcription from RNA polymerase II promoter in response to ethanol, regulation of carbohydrate metabolic process, regulation of transcription by chromatin organization, regulation of transcription, DNA-dependent]	
AGA1	[biological_process]	
AGP3	[amino acid transmembrane transport, amino acid transport, sulfur utilization, transmembrane transport]	
ALG6	[aerobic respiration, oligosaccharide-lipid intermediate biosynthetic process, protein glycosylation]	
ANB1	[peptidyl-lysine modification to hypusine, positive regulation of translational elongation, positive regulation of translational initiation, positive regulation of translational termination, translational frameshifting]	
ARG81	[cellular response to drug, filamentous growth, filamentous growth of a population of unicellular organisms, nitrogen utilization, positive regulation of cell adhesion involved in single-species biofilm formation, positive regulation of cell-substrate adhesion, regulation of arginine metabolic process, regulation of transcription from RNA polymerase II promoter, regulation of transcription, DNA-dependent, single-species biofilm formation on inanimate substrate]	
ARG83	[filamentous growth, proline catabolic process, regulation of transcription, DNA-dependent]	
ARO80	[aromatic amino acid family catabolic process, positive regulation of transcription from RNA polymerase II promoter, transcription, DNA-dependent]	
ARP8	[cellular response to cadmium ion, cellular response to drug, chromatin remodeling, detoxification of cadmium ion, mitotic recombination, response to DNA damage stimulus]	

ID	Go_Biological process	Cross-talking
ASC1	[G-protein coupled receptor signaling pathway, cell adhesion, cellular protein localization, cellular response to biotic stimulus, cellular response to neutral pH, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to neutral pH, filamentous growth of a population of unicellular organisms in response to starvation, glucose mediated signaling pathway, intracellular signal transduction, invasive growth in response to glucose limitation, negative regulation of translation, pathogenesis, positive regulation of conjugation with cellular fusion, regulation of actin cytoskeleton organization, regulation of fungal-type cell wall biogenesis]	
ASH1	[cellular response to biotic stimulus, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to neutral pH, filamentous growth of a population of unicellular organisms in response to starvation, negative regulation of G1/S transition of mitotic cell cycle by negative regulation of transcription from RNA polymerase II promoter, negative regulation of mating type switching by negative regulation of transcription from RNA polymerase II promoter, negative regulation of transcription from RNA polymerase II promoter, pathogenesis, positive regulation of filamentous growth of a population of unicellular organisms, positive regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, positive regulation of filamentous growth of a population of unicellular organisms in response to neutral pH, positive regulation of filamentous growth of a population of unicellular organisms in response to starvation, positive regulation of pseudohyphal growth by positive regulation of transcription from RNA polymerase II promoter, regulation of pseudohyphal growth, response to neutral pH]	
BEM1	[cell budding, cell communication, cell morphogenesis involved in conjugation with cellular fusion, cytokinetic cell separation, filamentous growth, hyphal growth, pathogenesis, regulation of conjugation with cellular fusion, regulation of establishment or maintenance of cell polarity regulating cell shape]	

ID	Go_Biological process	Cross-talking
BMH1	[DNA damage checkpoint, DNA replication initiation, Ras protein signal transduction, ascospore formation, cellular protein localization, cellular response to UV, cellular response to biotic stimulus, cellular response to calcium ion, cellular response to heat, cellular response to neutral pH, cellular response to salt stress, cellular response to starvation, chlamydospore formation, cytokinesis checkpoint, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to heat, filamentous growth of a population of unicellular organisms in response to neutral pH, fungal-type cell wall chitin biosynthetic process, glycogen metabolic process, negative regulation of induction of conjugation with cellular fusion, negative regulation of sequence-specific DNA binding transcription factor activity, negative regulation of transcription during meiosis, negative regulation of transcription from RNA polymerase II promoter, negative regulation of ubiquitin-protein ligase activity involved in mitotic cell cycle, pathogenesis, positive regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, positive regulation of filamentous growth of a population of unicellular organisms in response to neutral pH, positive regulation of septation initiation signaling cascade, pre-replicative complex assembly involved in nuclear cell cycle DNA replication, pseudohyphal growth, regulation of carbohydrate metabolic process, signal transduction, signal transduction involved in filamentous growth, spore germination]	
BMT1	[beta-1,2-oligomannoside metabolic process, biological_process]	
BMT7	[biological_process]	
BMT9	[biological_process]	
BRG1	[cellular response to biotic stimulus, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, pathogenesis, positive regulation of filamentous growth of a population of unicellular organisms, positive regulation of single-species biofilm formation on inanimate substrate, regulation of transcription from RNA polymerase II promoter, single-species biofilm formation on inanimate substrate]	
BUD20	[cellular bud site selection, cellular response to biotic stimulus, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, ribosomal large subunit export from nucleus]	

ID	Go_Biological process	Cross-talking
BUD31	[cellular bud site selection, mRNA splicing, via spliceosome]	
CAN1	[amino acid transmembrane transport, arginine transport, basic amino acid transport, transmembrane transport]	
CAN2	[]	
CAN3	[amino acid transmembrane transport]	
CAP1	[Ras protein signal transduction, actin filament severing, apoptotic process, asexual sporulation, asperthecin biosynthetic process, cAMP-mediated signaling, cell growth mode switching, budding to filamentous, cell morphogenesis, cellular response to biotic stimulus, cellular response to cadmium ion, cellular response to caffeine, cellular response to drug, cellular response to heat, cellular response to hydrogen peroxide, cellular response to neutral pH, cellular response to oxidative stress, cellular response to starvation, cytoskeleton organization, detoxification of cadmium ion, emericellin biosynthetic process, evasion or tolerance of host immune response, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to heat, filamentous growth of a population of unicellular organisms in response to neutral pH, negative regulation of asperthecin biosynthetic process, negative regulation of emericellin biosynthetic process, negative regulation of sterigmatocystin biosynthetic process, pathogenesis, positive regulation of filamentous growth of a population of unicellular organisms in response to heat, positive regulation of filamentous growth of a population of unicellular organisms in response to neutral pH, positive regulation of transcription from RNA polymerase II promoter in response to arsenic-containing substance, positive regulation of transcription from RNA polymerase II promoter in response to heat stress, positive regulation of transcription from RNA polymerase II promoter in response to increased salt, positive regulation of transcription from RNA polymerase II promoter in response to menadione, positive regulation of transcription from RNA polymerase II promoter in response to oxidative stress, regulation of adenylate cyclase activity, regulation of ascospore formation, regulation of conjugation with cellular fusion, regulation of transcription from RNA polymerase II promoter in response to oxidative stress, regulation of transcription, DNA-dependent, response to methylglyoxal, response to neutral pH, response to singlet oxygen, sexual sporulation resulting in formation of a cellular spore, shamixanthone biosynthetic process, sterigmatocystin biosynthetic process]	

ID	Go_Biological process	Cross-talking
CAS5	[cellular hyperosmotic response, cellular response to cold, cellular response to drug, development of symbiont in host, filamentous growth, fungal-type cell wall organization, negative regulation of ergosterol biosynthetic process, negative regulation of transcription from RNA polymerase II promoter, pathogenesis, positive regulation of cell adhesion involved in single-species biofilm formation, positive regulation of cell-substrate adhesion, positive regulation of transcription from RNA polymerase II promoter, regulation of transcription from RNA polymerase II promoter, regulation of transcription, DNA-dependent, single-species biofilm formation on inanimate substrate]	
CAT2	[acetate catabolic process, acetyl-CoA metabolic process, carbon utilization, carnitine metabolic process, cellular respiration, fatty acid beta-oxidation, pathogenesis, single-species biofilm formation on inanimate substrate]	
CAT8	[acetate catabolic process, carbon utilization, conidiophore development, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, growth of unicellular organism as a thread of attached cells, negative regulation of growth of unicellular organism as a thread of attached cells, negative regulation of invasive growth in response to glucose limitation, positive regulation of gluconeogenesis, positive regulation of gluconeogenesis by positive regulation of transcription from RNA polymerase II promoter, positive regulation of glyoxylate cycle by positive regulation of transcription from RNA polymerase II promoter, positive regulation of transcription from RNA polymerase II promoter, positive regulation of transcription from RNA polymerase II promoter by a nonfermentable carbon source, regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, transcription, DNA-dependent]	

ID	Go_Biological process	Cross-talking
CBK1	[budding cell apical bud growth, cell morphogenesis, cellular response to biotic stimulus, cellular response to drug, cellular response to heat, cellular response to neutral pH, cellular response to osmotic stress, cellular response to starvation, cortical actin cytoskeleton stabilization, cytokinesis after mitosis checkpoint, cytokinetic cell separation, establishment or maintenance of actin cytoskeleton polarity, establishment or maintenance of bipolar cell polarity regulating cell shape, establishment or maintenance of cell polarity, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to heat, filamentous growth of a population of unicellular organisms in response to neutral pH, filamentous growth of a population of unicellular organisms in response to starvation, fungal-type cell wall assembly, fungal-type cell wall organization, maintenance of protein location in cell cortex of cell tip, membrane raft organization, positive regulation of bipolar cell growth, positive regulation of filamentous growth of a population of unicellular organisms in response to heat, positive regulation of filamentous growth of a population of unicellular organisms in response to neutral pH, positive regulation of single-species biofilm formation on inanimate substrate, protein phosphorylation, regulation of establishment or maintenance of bipolar cell polarity regulating cell shape, regulation of fungal-type cell wall organization, regulation of transcription from RNA polymerase II promoter, single-species biofilm formation on inanimate substrate]	
CCE1	[DNA recombination, mitochondrial genome maintenance]	
CCH1	[calcium ion import, calcium ion transport, cellular response to drug, cellular response to mechanical stimulus, conidium formation, fungal-type cell wall organization, hyphal growth, positive regulation of calcium-mediated signaling, positive regulation of phosphoprotein phosphatase activity, regulation of protein phosphatase type 2B activity, unidimensional cell growth]	
CCN1	[G1/S transition of mitotic cell cycle, cellular response to biotic stimulus, cellular response to drug, cellular response to neutral pH, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to neutral pH, hyphal growth, maintenance of cell polarity, positive regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, positive regulation of filamentous growth of a population of unicellular organisms in response to neutral pH, regulation of cell cycle, regulation of cyclin-dependent protein serine/threonine kinase activity]	

ID	Go_Biological process	Cross-talking
CCT8	[cellular response to N-acetyl-D-glucosamine, cellular response to biotic stimulus, cellular response to drug, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to chemical stimulus, filamentous growth of a population of unicellular organisms in response to starvation, protein folding]	
CDC19	[cellular response to biotic stimulus, cellular response to nitrogen starvation, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, glycolysis, induction by symbiont of host defense response, negative regulation of G0 to G1 transition, pyruvate metabolic process]	
CDC34	[G2/M transition of mitotic cell cycle, SCF-dependent proteasomal ubiquitin-dependent protein catabolic process, protein autoubiquitination, protein polyubiquitination, protein ubiquitination involved in ubiquitin-dependent protein catabolic process]	
CDC68	[DNA replication-independent nucleosome organization, DNA-dependent DNA replication, nucleosome assembly, positive regulation of RNA polymerase II transcriptional preinitiation complex assembly, positive regulation of transcription initiation from RNA polymerase II promoter, regulation of DNA-dependent transcription, elongation, regulation of transcription by chromatin organization, transcription elongation from RNA polymerase II promoter]	
CDG1	[L-cysteine catabolic process to pyruvate, using cysteine dioxygenase, oxidation-reduction process]	
CDR3	[drug export, phospholipid translocation, transport]	
CDS1	[CDP-diacylglycerol biosynthetic process, cellular response to biotic stimulus, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, phosphatidylinositol metabolic process, phosphatidylserine metabolic process]	
CEF3	[translational elongation, translational termination]	

ID	Go_Biological process	Cross-talking
CEK1	[MAPK cascade, ascospore formation, cell cycle arrest, cellular hyperosmotic salinity response, cellular response to biotic stimulus, cellular response to drug, cellular response to non-ionic osmotic stress, cellular response to starvation, conidiophore development, conidium formation, conjugation with cellular fusion, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, fungal-type cell wall biogenesis, fungal-type cell wall organization, hyphal growth, invasive growth in response to glucose limitation, negative regulation of MAPK cascade, negative regulation of transposition, RNA-mediated, pathogenesis, penicillin biosynthetic process, pheromone-dependent signal transduction involved in conjugation with cellular fusion, positive regulation of ascospore formation, positive regulation of filamentous growth of a population of unicellular organisms, positive regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, positive regulation of filamentous growth of a population of unicellular organisms in response to starvation, positive regulation of penicillin metabolic process, positive regulation of sterigmatocystin biosynthetic process, protein phosphorylation, regulation of growth rate, spore germination, sporocarp development involved in sexual reproduction, sterigmatocystin biosynthetic process, syncytium formation by plasma membrane fusion, tube fusion]	
CEK2	[cellular response to biotic stimulus, cellular response to starvation, conjugation with cellular fusion, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, protein phosphorylation]	
CFL2	[cellular iron ion homeostasis, oxidation-reduction process]	
CFL4	[copper ion import, iron ion transport, oxidation-reduction process]	
CHA1	[L-serine catabolic process, cellular amino acid metabolic process, filamentous growth, threonine catabolic process]	
CHS2	[ascospore wall assembly, ascospore wall chitin biosynthetic process, cell septum assembly, cell wall chitin biosynthetic process, conidium formation, cytokinesis, completion of separation, hyphal growth]	
CIT1	[acetyl-CoA catabolic process, cellular carbohydrate metabolic process, citrate metabolic process, tricarboxylic acid cycle]	

ID	Go_Biological process	Cross-talking
CLA4	[ascospore formation, cellular response to biotic stimulus, cellular response to drug, cellular response to starvation, chlamydospore formation, conidiophore development, conidium formation, development of symbiont in host, establishment or maintenance of cell polarity, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, hyphal growth, negative regulation of gene expression, pathogenesis, positive regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, positive regulation of filamentous growth of a population of unicellular organisms in response to starvation, protein phosphorylation, regulation of exit from mitosis, response to pheromone, septin ring organization, sporocarp development involved in sexual reproduction, sterol import, vacuole inheritance]	
CLB2	[G2/M transition of mitotic cell cycle, cellular protein localization, cellular response to drug, cellular response to nitrogen starvation, filamentous growth, microtubule cytoskeleton organization, negative regulation of G0 to G1 transition, negative regulation of induction of conjugation with cellular fusion, positive regulation of protein localization to nucleus, positive regulation of spindle pole body separation, regulation of G2/M transition of mitotic cell cycle, regulation of cyclin-dependent protein serine/threonine kinase activity, regulation of mitotic cell cycle]	
CLN3	[G1/S transition of mitotic cell cycle, cell budding, cellular response to biotic stimulus, cellular response to drug, cellular response to neutral pH, development of symbiont in host, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to neutral pH, hyphal growth, negative regulation of filamentous growth of a population of unicellular organisms, positive regulation of filamentous growth of a population of unicellular organisms, positive regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, positive regulation of filamentous growth of a population of unicellular organisms in response to neutral pH, re-entry into mitotic cell cycle after pheromone arrest, regulation of cell cycle, regulation of cell size, regulation of cyclin-dependent protein serine/threonine kinase activity, regulation of transcription involved in G1/S transition of mitotic cell cycle, single-species biofilm formation on inanimate substrate, vacuole fusion, non-autophagic]	
COX19	[metal ion transport, mitochondrial respiratory chain complex IV assembly]	

ID	Go_Biological process	Cross-talking
CPH2	[cellular response to chemical stimulus, cellular response to copper ion, cellular response to drug, cellular response to heat, cellular response to neutral pH, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to chemical stimulus, filamentous growth of a population of unicellular organisms in response to neutral pH, positive regulation of filamentous growth of a population of unicellular organisms, positive regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, positive regulation of filamentous growth of a population of unicellular organisms in response to chemical stimulus, positive regulation of filamentous growth of a population of unicellular organisms in response to neutral pH, positive regulation of pseudohyphal growth by positive regulation of transcription from RNA polymerase II promoter, positive regulation of transcription from RNA polymerase II promoter, pseudohyphal growth, regulation of pseudohyphal growth, regulation of transcription from RNA polymerase II promoter, regulation of transcription, DNA-dependent, symbiosis, encompassing mutualism through parasitism]	
CPP1	[adaptation of signaling pathway by response to pheromone involved in conjugation with cellular fusion, cellular response to biotic stimulus, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, hyphal growth, inactivation of MAPK activity involved in cell wall biogenesis, inactivation of MAPK activity involved in conjugation with cellular fusion, negative regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, negative regulation of filamentous growth of a population of unicellular organisms in response to starvation, pathogenesis, protein dephosphorylation, regulation of MAPK export from nucleus, regulation of fungal-type cell wall organization, signal transduction, signal transduction involved in filamentous growth]	

ID	Go_Biological process	Cross-talking
CRZ1	[DNA repair, bipolar cellular bud site selection, calcium-mediated signaling, cell wall chitin biosynthetic process, cellular cation homeostasis, cellular response to acidity, cellular response to biotic stimulus, cellular response to blue light, cellular response to drug, cellular response to mechanical stimulus, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, fungal-type cell wall organization, hyphal growth, mRNA catabolic process, pathogenesis, positive regulation of cellular response to drug, positive regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, positive regulation of filamentous growth of a population of unicellular organisms in response to starvation, positive regulation of sodium ion transport by positive regulation of transcription from RNA polymerase II promoter, positive regulation of transcription from RNA polymerase II promoter by calcium-mediated signaling, positive regulation of transcription from RNA polymerase II promoter by pheromones, positive regulation of transcription from RNA polymerase II promoter in response to alkalinity, positive regulation of transcription from RNA polymerase II promoter in response to calcium ion, positive regulation of transcription from RNA polymerase II promoter in response to increased salt, regulation of apoptotic process, regulation of potassium ion concentration by positive regulation of transcription from RNA polymerase II promoter, regulation of transcription, DNA-dependent, response to endoplasmic reticulum stress, thigmotropism]	
CRZ2	[cellular response to acidity, cellular response to cold, cellular response to copper ion, positive regulation of cell adhesion involved in single-species biofilm formation, positive regulation of cell-substrate adhesion, regulation of single-species biofilm formation on inanimate substrate, regulation of transcription from RNA polymerase II promoter, regulation of transcription, DNA-dependent, single-species biofilm formation on inanimate substrate]	
CSA1	[cellular iron ion homeostasis, single-species biofilm formation on inanimate substrate]	
CSH1	[cell-matrix adhesion, pathogenesis, single-species biofilm formation on inanimate substrate]	
CSP37	[pathogenesis]	
CTA2	[biological_process, positive regulation of transcription, DNA-dependent]	
CTA24	[positive regulation of transcription, DNA-dependent]	

ID	Go_Biological process	Cross-talking
CTA4	[cellular response to biotic stimulus, cellular response to oleic acid, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, growth of unicellular organism as a thread of attached cells, positive regulation of chromatin silencing at telomere, positive regulation of fatty acid beta-oxidation, positive regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, positive regulation of growth of unicellular organism as a thread of attached cells, positive regulation of transcription from RNA polymerase II promoter, positive regulation of transcription, DNA-dependent, response to defense-related host nitric oxide production, transcription, DNA-dependent]	
CTA8	[cellular response to heat, negative regulation of TOR signaling cascade, positive regulation of transcription from RNA polymerase II promoter, positive regulation of transcription, DNA-dependent, spindle pole body duplication]	
CUP9	[filamentous growth, regulation of transcription, DNA-dependent]	
CYC3	[aerobic respiration, cytochrome c-heme linkage, filamentous growth of a population of unicellular organisms, sporocarp development involved in sexual reproduction]	
CZF1	[cellular response to biotic stimulus, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, phenotypic switching, positive regulation of cell adhesion involved in single-species biofilm formation, positive regulation of cell-substrate adhesion, positive regulation of phenotypic switching, quorum sensing, regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, regulation of phenotypic switching, regulation of single-species biofilm formation on inanimate substrate, regulation of transcription from RNA polymerase II promoter, regulation of transcription, DNA-dependent, single-species biofilm formation on inanimate substrate]	
DAL4	[allantoin assimilation pathway, allantoin transport, nucleobase transport]	
DAL81	[nitrogen catabolite activation of transcription from RNA polymerase II promoter, nitrogen utilization, positive regulation of cell adhesion involved in single-species biofilm formation, positive regulation of cell-substrate adhesion, positive regulation of gamma-aminobutyric acid catabolic process, positive regulation of transcription from RNA polymerase II promoter, positive regulation of urea catabolic process, regulation of transcription from RNA polymerase II promoter, single-species biofilm formation on inanimate substrate, transcription, DNA-dependent]	
DAP2	[proteolysis]	

ID	Go_Biological process	Cross-talking
DBF2	[conidium formation, cytokinesis, fungal-type cell wall biogenesis, hyphal growth, maintenance of endoplasmic reticulum location involved in endoplasmic reticulum polarization at cell division site, mitotic spindle organization, nuclear division, protein phosphorylation, regulation of exit from mitosis, regulation of protein localization, septation initiation signaling cascade, sporocarp development involved in sexual reproduction, vacuolar acidification]	
DCK1	[cellular response to biotic stimulus, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, fungal-type cell wall organization, small GTPase mediated signal transduction]	
DDR48	[DNA repair, biological_process, cellular response to biotic stimulus, cellular response to oxidative stress, cellular response to starvation, cellular response to stress, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation]	
DEF1	[cell adhesion involved in single-species biofilm formation, development of symbiont in host, filamentous growth, filamentous growth of a population of unicellular organisms, positive regulation of cell adhesion involved in single-species biofilm formation, positive regulation of filamentous growth of a population of unicellular organisms, single-species biofilm formation on inanimate substrate]	
DFG16	[cellular response to pH, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to pH, pathogenesis, protein processing, pseudohyphal growth, regulation of intracellular pH]	
DIP5	[L-aspartate transport, L-glutamate transport, amino acid transmembrane transport, cellular response to drug]	
DOT6	[chromatin silencing at rDNA, chromatin silencing at telomere, filamentous growth, regulation of transcription from RNA polymerase II promoter, unidimensional cell growth]	
DPP1	[biological_process, phospholipid metabolic process]	
EAF6	[DNA repair, histone H4 acetylation]	

ID	Go_Biological process	Cross-talking
ECM22	[cellular response to drug, cellular response to hypoxia, ergosterol biosynthetic process, ergosterol metabolic process, growth of unicellular organism as a thread of attached cells, negative regulation of transcription, DNA-dependent, positive regulation of ergosterol biosynthetic process by positive regulation of transcription from RNA polymerase II promoter, positive regulation of growth of unicellular organism as a thread of attached cells, positive regulation of sterol import by positive regulation of transcription from RNA polymerase II promoter, positive regulation of transcription from RNA polymerase II promoter, regulation of transcription, DNA-dependent, sterol metabolic process]	
ECM29	[cellular response to biotic stimulus, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, proteasome assembly]	
ECM4	[cellular response to biotic stimulus, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation]	
EFH1	[growth of symbiont in host, negative regulation of transcription from RNA polymerase II promoter, phenotypic switching, positive regulation of phenotypic switching, positive regulation of transcription from RNA polymerase II promoter, pseudohyphal growth, regulation of cell differentiation, regulation of transcription from RNA polymerase II promoter]	
EMC9	[biological_process]	
ENA2	[calcium ion transmembrane transport, cation transport, hyphal growth, potassium ion transport, sodium ion transport]	
ENO1	[carbon utilization, cellular response to biotic stimulus, entry into host, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, gluconeogenesis, glycolysis, induction by symbiont of host defense response, regulation of vacuole fusion, non-autophagic]	
ERG13	[acetyl-CoA metabolic process, cellular response to biotic stimulus, cellular response to drug, cellular response to nitrogen starvation, cellular response to starvation, ergosterol biosynthetic process, establishment or maintenance of cell polarity, farnesyl diphosphate biosynthetic process, mevalonate pathway, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, negative regulation of G0 to G1 transition]	

ID	Go_Biological process	Cross-talking
ERG24	[cellular response to drug, ergosterol biosynthetic process, filamentous growth of a population of unicellular organisms in response to biotic stimulus, pathogenesis]	
ERG3	[cellular response to biotic stimulus, cellular response to drug, ergosterol biosynthetic process, establishment of protein localization to plasma membrane, fatty acid biosynthetic process, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to biotic stimulus, oxidation-reduction process, pathogenesis, protein insertion into membrane raft]	
ERG7	[ergosterol biosynthetic process]	
FAA4	[long-chain fatty acid metabolic process, long-chain fatty acid transport, long-chain fatty-acyl-CoA metabolic process]	
FAD2	[asexual sporulation resulting in formation of a cellular spore, pathogenesis, unsaturated fatty acid biosynthetic process]	
FAT1	[long-chain fatty acid transport, very long-chain fatty acid metabolic process]	
FCR1	[cellular response to biotic stimulus, cellular response to drug, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, regulation of transcription, DNA-dependent]	
FCR3	[positive regulation of cell adhesion involved in single-species biofilm formation, positive regulation of cell-substrate adhesion, regulation of glycogen metabolic process, regulation of transcription from RNA polymerase II promoter, regulation of transcription, DNA-dependent, single-species biofilm formation on inanimate substrate]	
FCY2	[cellular response to biotic stimulus, cellular response to drug, cellular response to starvation, cytidine transport, cytosine transport, drug transport, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, nucleobase transport, purine nucleobase transport, purine-containing compound transmembrane transport, pyrimidine-containing compound salvage]	
FCY23	[nucleobase transport, transport, vitamin transport]	
FET3	[cellular response to drug, ferrous iron import, high-affinity iron ion transport, oxidation-reduction process, prostaglandin biosynthetic process]	

ID	Go_Biological process	Cross-talking
FET34	[cellular response to iron ion, cellular response to iron ion starvation, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, high-affinity iron ion transport, iron assimilation by reduction and transport, iron ion transmembrane transport, oxidation-reduction process, pathogenesis, response to copper ion]	
FGR15	[cellular response to biotic stimulus, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, regulation of transcription, DNA-dependent]	
FGR17	[cellular response to biotic stimulus, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, growth of unicellular organism as a thread of attached cells, negative regulation of growth of unicellular organism as a thread of attached cells, regulation of transcription, DNA-dependent, transcription, DNA-dependent]	
FGR23	[cellular response to biotic stimulus, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation]	
FGR27	[cellular response to biotic stimulus, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, positive regulation of cell adhesion involved in single-species biofilm formation, positive regulation of cell-substrate adhesion, regulation of transcription from RNA polymerase II promoter, regulation of transcription, DNA-dependent, single-species biofilm formation on inanimate substrate, transcription, DNA-dependent]	
FGR28	[cellular response to biotic stimulus, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation]	
FGR34	[cellular response to biotic stimulus, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation]	

ID	Go_Biological process	Cross-talking
FGR37	[cellular response to biotic stimulus, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation]	
FGR41	[cellular response to biotic stimulus, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation]	
FGR42	[filamentous growth]	
FGR47	[cellular response to biotic stimulus, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation]	
FGR6-10	[cellular response to biotic stimulus, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation]	
FGR6-3	[cellular response to biotic stimulus, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation]	
FIL1	[adenine biosynthetic process, filamentous growth, mitochondrial translation, positive regulation of transcription from RNA polymerase II promoter, purine nucleobase biosynthetic process, regulation of transcription, DNA-dependent]	
FIL2	[adenine biosynthetic process, chromatin remodeling, filamentous growth, filamentous growth of a population of unicellular organisms, histidine biosynthetic process, positive regulation of DNA binding, positive regulation of phosphate metabolic process, positive regulation of transcription from RNA polymerase II promoter]	
FKH2	[biological_process, cell morphogenesis, cellular response to methylmercury, chromatin remodeling, donor selection, filamentous growth, filamentous growth of a population of unicellular organisms, mRNA 3'-end processing, negative regulation of pseudohyphal growth, negative regulation of transcription elongation from RNA polymerase II promoter, negative regulation of transcription involved in G2/M transition of mitotic cell cycle, positive regulation of chromatin silencing at silent mating-type cassette, positive regulation of transcription involved in G2/M transition of mitotic cell cycle, regulation of transcription from RNA polymerase II promoter, termination of RNA polymerase II transcription]	
FLC1	[FAD transport, heme transport]	
FLC3	[FAD transport, heme transport]	

ID	Go_Biological process	Cross-talking
FLO8	[biofilm formation, cell growth mode switching, budding to filamentous, cellular developmental process, cellular response to biotic stimulus, cellular response to chemical stimulus, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to chemical stimulus, pathogenesis, positive regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, positive regulation of filamentous growth of a population of unicellular organisms in response to chemical stimulus, positive regulation of flocculation via cell wall protein-carbohydrate interaction by positive regulation of transcription from RNA polymerase II promoter, positive regulation of invasive growth in response to glucose limitation by positive regulation of transcription from RNA polymerase II promoter, positive regulation of phenotypic switching, positive regulation of pseudohyphal growth by positive regulation of transcription from RNA polymerase II promoter, positive regulation of starch catabolic process by positive regulation of transcription from RNA polymerase II promoter, positive regulation of transcription from RNA polymerase II promoter]	
FMO2	[biological_process]	
FRE10	[iron ion transport, oxidation-reduction process]	
FRP3	[ammonium transport, nitrogen utilization, plasma membrane acetate transport]	
GAC1	[glycogen metabolic process, meiosis, mitotic spindle assembly checkpoint, response to heat]	
GAL1	[carbohydrate phosphorylation, galactose catabolic process, galactose catabolic process via UDP-galactose, galactose transport, positive regulation of transcription by galactose]	
GAL10	[cellular response to glucose starvation, cellular response to oxidative stress, filamentous growth, filamentous growth of a population of unicellular organisms, fungal-type cell wall biogenesis, galactose catabolic process, galactose catabolic process via UDP-galactose, invasive growth in response to glucose limitation, negative regulation of filamentous growth of a population of unicellular organisms, negative regulation of flocculation, protein galactosylation]	
GAL102	[cellular response to drug, fungal-type cell wall biogenesis, nucleotide-sugar metabolic process]	
GAL7	[UDP-D-galactose biosynthetic process, galactose catabolic process via UDP-galactose, protein galactosylation]	

ID	Go_Biological process	Cross-talking
GAP1	[L-arginine import, adhesion to host, amino acid transmembrane transport, amino acid transport, apoptotic process, cell-matrix adhesion, filamentous growth, filamentous growth of a population of unicellular organisms, glycolysis, induction by symbiont of host defense response, interaction with host, lysine import, oxidation-reduction process, reactive oxygen species metabolic process, regulation of nitrogen utilization]	
GAP4	[amino acid transmembrane transport]	
GAT2	[]	
GFA1	[cell wall chitin biosynthetic process, cellular response to drug, chitin biosynthetic process, establishment or maintenance of cell polarity, fungal-type cell wall chitin biosynthetic process, glucosamine biosynthetic process, hyphal growth, protein N-linked glycosylation]	
GIT1	[glycerol-3-phosphate transport, glycerophosphodiester transport, phosphate ion transport, transmembrane transport]	
GLN3	[cellular response to drug, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to starvation, nitrogen catabolite activation of transcription from RNA polymerase II promoter, pathogenesis, positive regulation of transcription from RNA polymerase II promoter, positive regulation of transcription, DNA-dependent, regulation of nitrogen utilization]	
GLY1	[glycine metabolic process, one-carbon metabolic process]	

ID	Go_Biological process	Cross-talking
GPA2	[G-protein coupled receptor signaling pathway, GTP catabolic process, adenylate cyclase-activating G-protein coupled receptor signaling pathway, ascospore formation, cAMP-mediated signaling, cellular copper ion homeostasis, cellular response to biotic stimulus, cellular response to glucose stimulus, cellular response to neutral pH, cellular response to starvation, conidium formation, detection of nutrient, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to heat, filamentous growth of a population of unicellular organisms in response to neutral pH, filamentous growth of a population of unicellular organisms in response to starvation, glucose mediated signaling pathway, invasive growth in response to heat, negative regulation of G2/M transition of mitotic cell cycle, negative regulation of conidium formation, negative regulation of transcription from RNA polymerase II promoter by glucose, pathogenesis, positive regulation of cAMP biosynthetic process, positive regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, positive regulation of filamentous growth of a population of unicellular organisms in response to heat, positive regulation of filamentous growth of a population of unicellular organisms in response to neutral pH, positive regulation of filamentous growth of a population of unicellular organisms in response to starvation, pseudohyphal growth, regulation of adenylate cyclase activity, regulation of cell size, regulation of cellular amino acid metabolic process, replicative cell aging, response to pheromone involved in conjugation with cellular fusion, signal transduction involved in filamentous growth, spore germination, sporocarp development involved in sexual reproduction, trehalose catabolic process]	
GPD1	[NADH oxidation, cell-abiotic substrate adhesion, glycerol biosynthetic process, glycerol metabolic process, glycerol-3-phosphate catabolic process, intracellular accumulation of glycerol]	
GPD2	[carbohydrate metabolic process, glycerol-3-phosphate catabolic process, oxidation-reduction process]	

ID	Go_Biological process	Cross-talking
GPR1	[G-protein coupled receptor signaling pathway, cellular response to biotic stimulus, cellular response to chemical stimulus, cellular response to glucose stimulus, cellular response to heat, cellular response to starvation, detection of glucose, detection of sucrose stimulus, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to chemical stimulus, filamentous growth of a population of unicellular organisms in response to heat, filamentous growth of a population of unicellular organisms in response to starvation, glucose mediated signaling pathway, invasive growth in response to glucose limitation, negative regulation of filamentous growth of a population of unicellular organisms in response to heat, positive regulation of filamentous growth of a population of unicellular organisms in response to chemical stimulus, pseudohyphal growth, replicative cell aging, response to glucose stimulus, signal transduction involved in filamentous growth, sucrose mediated signaling]	
GPX2	[cellular response to hydrogen peroxide, cellular response to oxidative stress, oxidation-reduction process, peptidyl-cysteine oxidation, positive regulation of transcription from RNA polymerase II promoter in response to hydrogen peroxide, response to oxidative stress]	
GRP2	[cellular metabolic process]	
GSC1	[(1->3)-beta-D-glucan biosynthetic process, ascospore wall assembly, cell wall (1->3)-beta-D-glucan biosynthetic process, cellular response to drug, cytokinesis, fungal-type cell wall organization, pathogenesis, regulation of cell shape]	
GSL1	[(1->3)-beta-D-glucan biosynthetic process, cellular response to drug]	
GSY1	[glycogen biosynthetic process]	
GUT2	[NADH oxidation, glycerol metabolic process, glycerol-3-phosphate metabolic process, replicative cell aging]	
HAC1	[cellular response to stress, fungal-type cell wall organization, hyphal growth, negative regulation of transcription from RNA polymerase II promoter during meiosis, positive regulation of transcription from RNA polymerase II promoter involved in unfolded protein response, regulation of transcription, DNA-dependent]	
HAL9	[filamentous growth of a population of unicellular organisms in response to biotic stimulus, growth of unicellular organism as a thread of attached cells, negative regulation of growth of unicellular organism as a thread of attached cells, regulation of transcription, DNA-dependent]	
HAP41	[regulation of transcription from RNA polymerase II promoter in response to iron ion starvation]	

ID	Go_Biological process	Cross-talking
HGC1	[cellular response to biotic stimulus, cellular response to neutral pH, development of symbiont in host, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to neutral pH, positive regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, positive regulation of filamentous growth of a population of unicellular organisms in response to neutral pH, re-entry into mitotic cell cycle after pheromone arrest, regulation of cyclin-dependent protein serine/threonine kinase activity, single-species biofilm formation on inanimate substrate]	
HGT1	[carbohydrate transport, cellular response to drug, cellular response to heat, cellular response to neutral pH, filamentous growth, filamentous growth of a population of unicellular organisms in response to heat, filamentous growth of a population of unicellular organisms in response to neutral pH, glucose transport, negative regulation of complement activation, transmembrane transport]	
HGT10	[D-xylose transport, carbohydrate transport, glucose transport, glycerol transport, transmembrane transport]	
HGT17	[carbohydrate transport, glucose transport, transmembrane transport]	
HGT19	[carbohydrate transport, glucose transport, transmembrane transport]	
HGT2	[carbohydrate transport, glucose transport, transmembrane transport]	
HGT7	[carbohydrate transport, cellular response to drug, fructose import, glucose import, glucose transport, transmembrane transport]	
HGT8	[carbohydrate transport, glucose transport, transmembrane transport]	
HIP1	[amino acid transmembrane transport]	
HIS1	[histidine biosynthetic process]	
HIS4	[adhesion to host, cell adhesion, histidine biosynthetic process, oxidation-reduction process]	
HIT1	[biological_process]	
HSL1	[G2/M transition of mitotic cell cycle, cellular response to drug, cellular response to glucose starvation, cytokinesis checkpoint, filamentous growth, filamentous growth of a population of unicellular organisms, growth of symbiont in host, invasive growth in response to glucose limitation, negative regulation of filamentous growth of a population of unicellular organisms, negative regulation of pseudohyphal growth, pathogenesis, protein autophosphorylation, protein phosphorylation, pseudohyphal growth, regulation of cell cycle]	

ID	Go_Biological process	Cross-talking
HSP12	[cell adhesion, cellular response to heat, cellular response to osmotic stress, cellular response to oxidative stress, cellular response to stress, cytokinesis, actomyosin contractile ring assembly, plasma membrane organization]	
HST7	[MAPK cascade, MAPK cascade involved in cell wall biogenesis, MAPK cascade involved in conjugation with cellular fusion, activation of MAPK activity involved in conjugation with cellular fusion, ascospore formation, cellular hyperosmotic salinity response, cellular response to drug, cellular response to nitrogen starvation, cellular response to non-ionic osmotic stress, cellular response to starvation, conidiophore development, conidium formation, conjugation with cellular fusion, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to starvation, fungal-type cell wall organization, hyphal growth, invasive growth in response to glucose limitation, positive regulation of filamentous growth of a population of unicellular organisms in response to starvation, positive regulation of pseudohyphal growth by positive regulation of transcription from RNA polymerase II promoter, protein phosphorylation, pseudohyphal growth, regulation of pseudohyphal growth, regulation of secondary metabolite biosynthetic process, regulation of transposition, RNA-mediated, signal transduction involved in filamentous growth, sporocarp development involved in sexual reproduction, syncytium formation by plasma membrane fusion]	
HXK1	[N-acetylglucosamine catabolic process, adhesion to host, adhesion to other organism involved in symbiotic interaction, development of symbiont in host, filamentous growth, filamentous growth of a population of unicellular organisms, fructose import, fructose metabolic process, glucosamine catabolic process, glucose import, glycolysis, growth of symbiont in host, hyphal growth, mannose metabolic process, pathogenesis]	
HYM1	[budding cell apical bud growth, cellular response to biotic stimulus, cellular response to drug, cellular response to neutral pH, cellular response to starvation, conidium formation, cytokinesis, completion of separation, cytokinetic cell separation, establishment or maintenance of cell polarity, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to neutral pH, filamentous growth of a population of unicellular organisms in response to starvation, fungal-type cell wall organization, hyphal growth, regulation of cell shape, regulation of transcription, DNA-dependent]	
IAH1	[acetate metabolic process, cellular response to biotic stimulus, cellular response to drug, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation]	

ID	Go_Biological process	Cross-talking
IFF4	[cell-substrate adhesion, pathogenesis]	
IFF5	[biological_process]	
IFF8	[biological_process]	
IFF9	[biological_process]	
ILV5	[branched-chain amino acid biosynthetic process, mitochondrial genome maintenance, oxidation-reduction process]	
INO1	[inositol biosynthetic process, phospholipid biosynthetic process]	
INO2	[inositol biosynthetic process, phospholipid biosynthetic process, positive regulation of transcription from RNA polymerase II promoter, regulation of gene expression]	
INP51	[cellular response to neutral pH, filamentous growth, filamentous growth of a population of unicellular organisms in response to neutral pH, fungal-type cell wall organization, pathogenesis, phosphatidylinositol dephosphorylation]	
IPL1	[attachment of spindle microtubules to kinetochore, cytokinesis, histone H3-S10 phosphorylation involved in chromosome condensation, homologous chromosome segregation, meiotic sister chromatid segregation, mitotic DNA integrity checkpoint, mitotic sister chromatid segregation, mitotic spindle disassembly, negative regulation of protein import into nucleus during spindle assembly checkpoint, protein localization to kinetochore, protein localization to nucleolar rDNA repeats, regulation of cytokinesis]	
IPT1	[cell growth mode switching, budding to filamentous, cellular response to biotic stimulus, cellular response to chemical stimulus, cellular response to drug, cellular response to starvation, development of symbiont in host, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to chemical stimulus, filamentous growth of a population of unicellular organisms in response to starvation, localization within membrane, mannosyl diphosphorylinositol ceramide metabolic process, single-species biofilm formation on inanimate substrate, sphingolipid biosynthetic process]	
ISU1	[cellular iron ion homeostasis, iron-sulfur cluster assembly, protein maturation by iron-sulfur cluster transfer, tRNA wobble uridine modification]	

ID	Go_Biological process	Cross-talking
ISW2	[ATP-dependent chromatin remodeling, cellular response to copper ion, cellular response to drug, chlamydospore formation, chromatin remodeling, chromatin silencing at rDNA, chromatin silencing at telomere, filamentous growth, negative regulation of antisense RNA transcription, negative regulation of transcription from RNA polymerase II promoter by pheromones, nucleosome positioning, regulation of transcription by chromatin organization, termination of RNA polymerase II transcription]	
JEN2	[dicarboxylic acid transport, transmembrane transport]	
KGD2	[2-oxoglutarate metabolic process, mitochondrial genome maintenance, tricarboxylic acid cycle]	
KIP4	[cellular response to biotic stimulus, cellular response to starvation, exocytosis, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, microtubule-based movement]	
KIS2	[protein phosphorylation, regulation of carbohydrate metabolic process, regulation of protein complex assembly, signal transduction]	
KRE5	[(1->6)-beta-D-glucan biosynthetic process, cellular response to biotic stimulus, cellular response to drug, cellular response to neutral pH, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to neutral pH, filamentous growth of a population of unicellular organisms in response to starvation, fungal-type cell wall organization, protein glycosylation]	
LEU3	[conidiophore development, hyphal growth, negative regulation of transcription from RNA polymerase II promoter, positive regulation of cell adhesion involved in single-species biofilm formation, positive regulation of cell-substrate adhesion, positive regulation of leucine biosynthetic process, positive regulation of transcription from RNA polymerase II promoter, regulation of transcription from RNA polymerase II promoter, single-species biofilm formation on inanimate substrate]	
LIG4	[DNA recombination, DNA replication, double-strand break repair via nonhomologous end joining, filamentous growth, filamentous growth of a population of unicellular organisms, pathogenesis, replicative cell aging]	
LIP3	[lipid catabolic process]	

ID	Go_Biological process	Cross-talking
LIP5	[cellular response to biotic stimulus, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, lipid catabolic process]	
LPD1	[2-oxoglutarate metabolic process, G1/S transition of mitotic cell cycle, L-serine biosynthetic process, cell redox homeostasis, cellular amino acid metabolic process, cellular response to biotic stimulus, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to biotic stimulus, glycine catabolic process, hydrogen peroxide metabolic process, isoleucine catabolic process, leucine catabolic process, oxidation-reduction process, pyruvate metabolic process, valine catabolic process]	
LPI9	[chromosome segregation, regulation of phosphoprotein phosphatase activity]	
LSC1	[succinyl-CoA metabolic process]	
MAL2	[cellular response to biotic stimulus, cellular response to starvation, dextrin catabolic process, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, maltose catabolic process, starch catabolic process, sucrose catabolic process]	
MAL31	[carbohydrate transport, transmembrane transport]	
MEP2	[ammonium transmembrane transport, ammonium transport, cellular response to nitrogen starvation, cellular response to nutrient, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to starvation, invasive growth in response to glucose limitation, methylammonium transmembrane transport, nitrogen utilization, pseudohyphal growth, signal transduction involved in filamentous growth]	
MET10	[cellular response to cadmium ion, detoxification of cadmium ion, oxidation-reduction process, sulfate assimilation]	
MET28	[positive regulation of transcription regulatory region DNA binding, regulation of sulfur amino acid metabolic process, regulation of transcription from RNA polymerase II promoter]	
MHP1	[cellular response to biotic stimulus, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, fungal-type cell wall organization, negative regulation of microtubule depolymerization]	

ID	Go_Biological process	Cross-talking
MIG1	[carbon utilization, cellular response to drug, hyphal growth, negative regulation of transcription from RNA polymerase II promoter by glucose, negative regulation of transcription, DNA-dependent, positive regulation of filamentous growth of a population of unicellular organisms in response to starvation, positive regulation of transcription from RNA polymerase II promoter, regulation of growth rate, regulation of protein secretion, regulation of transcription from RNA polymerase II promoter, regulation of transcription, DNA-dependent, response to fructose stimulus]	
MIT1	[glycosphingolipid biosynthetic process, inositolphosphoceramide metabolic process, mannosyl-inositol phosphorylceramide metabolic process, pathogenesis, sphingolipid biosynthetic process]	
MLP1	[cell division, negative regulation of protein import into nucleus during spindle assembly checkpoint, nuclear retention of unspliced pre-mRNA at the site of transcription, poly(A)+ mRNA export from nucleus, protein import into nucleus, protein localization to nuclear pore, telomere tethering at nuclear periphery, transcriptional activation by promoter-terminator looping]	
MLS1	[acetate catabolic process, carbon utilization, fatty acid catabolic process, glyoxylate cycle]	
MLT1	[cellular response to biotic stimulus, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, organic anion transport, pathogenesis, transmembrane transport, transport]	
MNL1	[cellular response to acid, cellular response to drug, regulation of transcription from RNA polymerase II promoter in response to stress]	
MNN1	[protein glycosylation]	
MNN4	[biological_process, cell wall mannoprotein biosynthetic process, fungal-type cell wall biogenesis, pathogenesis, protein N-linked glycosylation, protein O-linked glycosylation, response to stress]	
MNN4-4	[]	
MNT1	[N-glycan processing, cell wall mannoprotein biosynthetic process, cell-cell adhesion, cell-matrix adhesion, evasion or tolerance of defenses of other organism involved in symbiotic interaction, filamentous growth, fungal-type cell wall organization, mannoprotein biosynthetic process, pathogenesis, protein O-linked glycosylation, protein O-linked mannosylation]	
MOH1	[biological_process]	
MRR1	[cellular response to drug, positive regulation of transcription from RNA polymerase II promoter, transcription, DNA-dependent]	
MSB1	[adhesion to host, cell adhesion, establishment of cell polarity, regulation of transcription, DNA-dependent]	

ID	Go_Biological process	Cross-talking
MSN4	[age-dependent response to oxidative stress involved in chronological cell aging, cellular response to blue light, cellular response to methylmercury, cellular response to oxidative stress, chromatin remodeling, positive regulation of transcription from RNA polymerase II promoter in response to a hypotonic environment, positive regulation of transcription from RNA polymerase II promoter in response to acidity, positive regulation of transcription from RNA polymerase II promoter in response to alkalinity, positive regulation of transcription from RNA polymerase II promoter in response to amino acid starvation, positive regulation of transcription from RNA polymerase II promoter in response to arsenic-containing substance, positive regulation of transcription from RNA polymerase II promoter in response to ethanol, positive regulation of transcription from RNA polymerase II promoter in response to freezing, positive regulation of transcription from RNA polymerase II promoter in response to glucose starvation, positive regulation of transcription from RNA polymerase II promoter in response to heat stress, positive regulation of transcription from RNA polymerase II promoter in response to hydrogen peroxide, positive regulation of transcription from RNA polymerase II promoter in response to hydrostatic pressure, positive regulation of transcription from RNA polymerase II promoter in response to increased salt, positive regulation of transcription from RNA polymerase II promoter in response to nitrosative stress, positive regulation of transcription from RNA polymerase II promoter in response to zinc ion starvation, regulation of replicative cell aging by regulation of transcription from RNA polymerase II promoter in response to caloric restriction, regulation of transcription, DNA-dependent, replicative cell aging]	
NCE103	[carbon utilization, cellular response to carbon dioxide, cellular response to oxidative stress, phenotypic switching, regulation of phenotypic switching]	

ID	Go_Biological process	Cross-talking
NDT80	[cellular response to N-acetyl-D-glucosamine, cellular response to biotic stimulus, cellular response to copper ion, cellular response to drug, cellular response to lithium ion, cellular response to oxidative stress, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to chemical stimulus, filamentous growth of a population of unicellular organisms in response to pH, hyphal growth, meiosis, pathogenesis, positive regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, positive regulation of filamentous growth of a population of unicellular organisms in response to chemical stimulus, positive regulation of filamentous growth of a population of unicellular organisms in response to pH, positive regulation of transcription from RNA polymerase II promoter, positive regulation of transcription from RNA polymerase II promoter in response to stress, regulation of single-species biofilm formation on inanimate substrate, regulation of transcription from RNA polymerase II promoter, single-species biofilm formation on inanimate substrate, transcription, DNA-dependent]	
NOT4	[cellular response to biotic stimulus, cellular response to neutral pH, deadenylation-independent decapping of nuclear-transcribed mRNA, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to neutral pH, pathogenesis, positive regulation of transcription elongation from RNA polymerase II promoter, protein polyubiquitination, protein ubiquitination, single-species biofilm formation on inanimate substrate]	
OLE1	[cellular response to abiotic stimulus, cellular response to biotic stimulus, cellular response to hydrogen peroxide, cellular response to neutral pH, cellular response to salt stress, cellular response to starvation, chlamydospore formation, filamentous growth, filamentous growth of a population of unicellular organisms in response to neutral pH, filamentous growth of a population of unicellular organisms in response to starvation, lipid particle organization, oxidation-reduction process, pathogenesis, pseudohyphal growth, unsaturated fatty acid biosynthetic process]	
OPI1	[endoplasmic reticulum unfolded protein response, negative regulation of transcription from RNA polymerase II promoter, negative regulation of transcription, DNA-dependent, phospholipid biosynthetic process, phospholipid metabolic process, positive regulation of transcription from RNA polymerase II promoter]	
orf19.1066	[N-acetylglucosamine metabolic process]	
orf19.1105.3	[biological_process]	
orf19.1106	[biological_process]	

ID	Go_Biological process	Cross-talking
orf19.1122	[biological_process]	
orf19.1124	[biological_process]	
orf19.1150	[regulation of transcription, DNA-dependent]	
orf19.1189	[biological_process]	
orf19.1228	[carbon catabolite activation of transcription from RNA polymerase II promoter, cellular response to alkalinity, cellular response to copper ion, regulation of cellular respiration]	
orf19.1253	[cellular response to copper ion, cellular response to phosphate starvation, chromatin remodeling, filamentous growth, filamentous growth of a population of unicellular organisms, phosphate-containing compound metabolic process, positive regulation of phosphatase activity, positive regulation of phosphate metabolic process, positive regulation of transcription from RNA polymerase II promoter]	
orf19.1265	[CVT pathway, early endosome to Golgi transport, intra-Golgi vesicle-mediated transport, macroautophagy, regulation of Rab GTPase activity]	
orf19.1277	[biological_process]	
orf19.1285	[biological_process]	
orf19.1286	[]	
orf19.1287	[biological_process]	
orf19.1326	[biological_process]	
orf19.1350	[biological_process]	
orf19.1351	[biological_process]	
orf19.1363	[ascospore formation, positive regulation of transcription from RNA polymerase II promoter]	
orf19.1486	[biological_process]	
orf19.1488	[biological_process]	
orf19.1535	[biological_process]	
orf19.1562	[biological_process]	
orf19.1604	[regulation of transcription, DNA-dependent]	
orf19.1617	[cellular response to biotic stimulus, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation]	
orf19.1687	[maturation of 5.8S rRNA from tricistronic rRNA transcript (SSU-rRNA, 5.8S rRNA, LSU-rRNA), maturation of LSU-rRNA from tricistronic rRNA transcript (SSU-rRNA, 5.8S rRNA, LSU-rRNA), maturation of SSU-rRNA from tricistronic rRNA transcript (SSU-rRNA, 5.8S rRNA, LSU-rRNA), spliceosomal complex disassembly]	

ID	Go_Biological process	Cross-talking
orf19.1718	[filamentous growth of a population of unicellular organisms in response to biotic stimulus, positive regulation of cell adhesion involved in single-species biofilm formation, positive regulation of cell-substrate adhesion, regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, regulation of transcription from RNA polymerase II promoter, single-species biofilm formation on inanimate substrate]	
orf19.1720	[mitotic recombination]	
orf19.1728	[biological_process]	
orf19.173	[cellular response to carbohydrate stimulus, cellular response to drug, regulation of fungal-type cell wall organization, regulation of transcription from RNA polymerase II promoter, regulation of transcription, DNA-dependent]	
orf19.1735	[biological_process]	
orf19.1736	[biological_process]	
orf19.177	[cell communication]	
orf19.1777	[endocytosis, protein deubiquitination, ubiquitin-dependent protein catabolic process]	
orf19.1793	[cellular response to nitrogen starvation, piecemeal microautophagy of nucleus]	
orf19.1814	[establishment or maintenance of cell polarity, invasive filamentous growth, phosphatidylinositol phosphorylation, phosphatidylinositol-mediated signaling]	
orf19.1815	[maturation of 5.8S rRNA from tricistronic rRNA transcript (SSU-rRNA, 5.8S rRNA, LSU-rRNA), maturation of LSU-rRNA from tricistronic rRNA transcript (SSU-rRNA, 5.8S rRNA, LSU-rRNA), mature ribosome assembly, ribosomal subunit export from nucleus]	
orf19.1821	[]	
orf19.1830	[biological_process]	
orf19.1842	[axial cellular bud site selection, bipolar cellular bud site selection, regulation of small GTPase mediated signal transduction, small GTPase mediated signal transduction]	
orf19.1897	[biological_process]	
orf19.1906	[]	
orf19.1958	[]	
orf19.1959	[protein deubiquitination]	
orf19.1961	[biological_process]	
orf19.1963	[aerobic respiration]	
orf19.2049	[biological_process]	
orf19.2050	[cellular lipid metabolic process, sterol metabolic process]	
orf19.2124	[oxidation-reduction process]	

ID	Go_Biological process	Cross-talking
orf19.2125	[biological_process]	
orf19.2169	[biological_process]	
orf19.217	[biological_process]	
orf19.2178.1	[biological_process]	
orf19.2236	[negative regulation of ribosomal protein gene transcription from RNA polymerase II promoter, positive regulation of ribosomal protein gene transcription from RNA polymerase II promoter, positive regulation of transcription from RNA polymerase II promoter, rRNA transcription, regulation of ribosome biogenesis, regulation of transcription, DNA-dependent]	
orf19.2272	[cell adhesion, cellular iron ion homeostasis, cellular response to biotic stimulus, cellular response to oxidative stress, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, invasive filamentous growth, pathogenesis, positive regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, positive regulation of filamentous growth of a population of unicellular organisms in response to starvation, positive regulation of transcription from RNA polymerase II promoter in response to iron ion starvation, regulation of transcription, DNA-dependent]	
orf19.2308	[fructose 2,6-bisphosphate metabolic process, fructose metabolic process, regulation of glycolysis]	
orf19.2332	[biological_process]	
orf19.2333	[oxidation-reduction process, retrograde transport, endosome to Golgi]	
orf19.2350	[cellular response to biotic stimulus, cellular response to starvation, drug transport, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, transmembrane transport]	
orf19.2397.3	[filamentous growth]	
orf19.2398	[biological_process]	
orf19.2430	[biological_process]	
orf19.2431	[]	
orf19.2457	[biological_process]	
orf19.2506	[biological_process]	
orf19.2529.1	[biological_process]	
orf19.255	[growth of symbiont in host, regulation of transcription, DNA-dependent]	
orf19.258	[biological_process]	
orf19.2612	[regulation of transcription, DNA-dependent]	

ID	Go_Biological process	Cross-talking
orf19.2638	[biological_process]	
orf19.2639	[biological_process]	
orf19.2653	[biological_process]	
orf19.2686	[nitrogen compound metabolic process, proteolysis involved in cellular protein catabolic process]	
orf19.2724	[biological_process]	
orf19.2725	[]	
orf19.2726	[actin cytoskeleton organization, inositol lipid-mediated signaling, vacuole organization]	
orf19.2766	[]	
orf19.2822	[CVT pathway, ER to Golgi vesicle-mediated transport, macroautophagy, peroxisome degradation, retrograde transport, vesicle recycling within Golgi]	
orf19.2848	[CVT pathway, activation of protein kinase activity, macroautophagy, mitochondrion degradation, piecemeal microautophagy of nucleus, protein localization to pre-autophagosomal structure]	
orf19.2892	[biological_process]	
orf19.2943.5	[]	
orf19.2962	[biological_process]	
orf19.3134	[]	
orf19.3135	[ER-associated protein catabolic process, lipid particle organization]	
orf19.314	[biological_process]	
orf19.3148	[biological_process]	
orf19.3264.1	[biological_process]	
orf19.3302	[biological_process]	
orf19.3325	[glycogen biosynthetic process]	
orf19.3328	[RNA polymerase II transcriptional preinitiation complex assembly, cellular hyperosmotic salinity response, positive regulation of transcription from RNA polymerase II promoter in response to osmotic stress]	
orf19.3335	[biological_process]	
orf19.3336	[]	
orf19.3337	[biological_process]	
orf19.3338	[]	
orf19.334	[biological_process]	
orf19.335	[biological_process]	
orf19.3368	[]	
orf19.3378	[biological_process]	

ID	Go_Biological process	Cross-talking
orf19.34	[]	
orf19.3434	[positive regulation of cell adhesion involved in single-species biofilm formation, positive regulation of cell-substrate adhesion, regulation of transcription from RNA polymerase II promoter, single-species biofilm formation on inanimate substrate]	
orf19.3439	[biological_process]	
orf19.344	[biological_process]	
orf19.345	[cellular response to oxidative stress, gamma-aminobutyric acid catabolic process, glutamate decarboxylation to succinate, oxidation-reduction process]	
orf19.3469	[positive regulation of mating type switching by positive regulation of transcription from RNA polymerase II promoter, regulation of transcription involved in G1/S transition of mitotic cell cycle]	
orf19.3475	[biological_process]	
orf19.3499	[biological_process]	
orf19.35	[protein phosphorylation]	
orf19.3501	[maintenance of cell polarity, regulation of Rho protein signal transduction]	
orf19.3555	[cytoskeleton organization, negative regulation of actin filament polymerization, regulation of cell shape during vegetative growth phase, regulation of protein localization, regulation of transcription, DNA-dependent]	
orf19.3603	[biofilm formation, filamentous growth, pathogenesis]	
orf19.3643	[biological_process]	
orf19.3711	[metabolic process]	
orf19.3742	[biological_process]	
orf19.3793	[biological_process]	
orf19.3865	[negative regulation of transcription from RNA polymerase II promoter, positive regulation of exit from mitosis, positive regulation of transcription from RNA polymerase II promoter]	
orf19.3868	[]	
orf19.3869	[biological_process]	
orf19.3897	[biological_process]	
orf19.3928	[regulation of transcription, DNA-dependent]	
orf19.3968	[]	

ID	Go_Biological process	Cross-talking
orf19.3969	[cellular response to biotic stimulus, cellular response to neutral pH, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to neutral pH, flocculation, negative regulation of filamentous growth of a population of unicellular organisms, negative regulation of flocculation, pathogenesis, regulation of transcription from RNA polymerase II promoter]	
orf19.3971	[biological_process]	
orf19.3982	[sucrose catabolic process]	
orf19.4000	[]	
orf19.4081	[]	
orf19.4153	[protein neddylation]	
orf19.4166	[regulation of transcription, DNA-dependent]	
orf19.4167	[biological_process]	
orf19.4210	[cardiolipin acyl-chain remodeling]	
orf19.4214	[]	
orf19.4234	[biological_process]	
orf19.4245	[biological_process]	
orf19.4246	[cellular response to biotic stimulus, cellular response to starvation, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, metabolic process]	
orf19.4280	[biological_process]	
orf19.4281	[positive regulation of transcription from RNA polymerase II promoter, rRNA transcription, regulation of ribosome biogenesis, regulation of transcription, DNA-dependent]	
orf19.4282	[]	
orf19.4320	[]	
orf19.4321	[]	
orf19.4342	[positive regulation of sterol import by positive regulation of transcription from RNA polymerase II promoter]	
orf19.4390	[biological_process]	
orf19.4394	[biological_process]	
orf19.4439.1	[nucleotide-excision repair, phosphorylation of RNA polymerase II C-terminal domain, transcription from RNA polymerase II promoter]	

ID	Go_Biological process	Cross-talking
orf19.4459	[cellular response to biotic stimulus, cellular response to starvation, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, oxygen transport]	
orf19.4461	[biological_process]	
orf19.4463	[biological_process]	
orf19.4478	[mitochondrial aspartyl-tRNA aminoacylation]	
orf19.450	[biological_process]	
orf19.4528	[vacuolar protein processing]	
orf19.4531	[transport]	
orf19.4553	[biological_process]	
orf19.467	[establishment or maintenance of cell type involved in phenotypic switching, phenotypic switching, positive regulation of phenotypic switching]	
orf19.4672	[]	
orf19.4684.2	[translation]	
orf19.4725	[DNA replication, positive regulation of reciprocal meiotic recombination, positive regulation of transcription from RNA polymerase II promoter in response to heat stress, positive regulation of transcription involved in G1/S transition of mitotic cell cycle, regulation of transcription during meiosis, regulation of transcription during mitosis, regulation of transcription involved in G1/S transition of mitotic cell cycle]	
orf19.474	[mRNA export from nucleus, nuclear envelope organization, protein export from nucleus]	
orf19.475	[pre-replicative complex assembly involved in nuclear cell cycle DNA replication, rRNA processing, regulation of DNA-dependent DNA replication initiation, ribosomal large subunit assembly]	
orf19.4792	[termination of G-protein coupled receptor signaling pathway]	
orf19.4793	[biological_process]	
orf19.4818	[biological_process]	
orf19.4857	[protein dephosphorylation]	
orf19.4883	[signal transduction]	
orf19.4900	[protein O-linked glycosylation]	
orf19.4907	[regulation of cell size]	
orf19.4908	[]	
orf19.4921.1	[biological_process]	
orf19.4936	[]	
orf19.4936.1	[biological_process]	

ID	Go_Biological process	Cross-talking
orf19.4942	[]	
orf19.4952	[biological_process]	
orf19.4960	[pantothenate biosynthetic process, spermine biosynthetic process]	
orf19.4966	[L-glutamate transport, aspartate transport, cellular nitrogen compound biosynthetic process, transmembrane transport]	
orf19.4972	[regulation of transcription, DNA-dependent]	
orf19.5022	[cellular cobalt ion homeostasis, cellular manganese ion homeostasis, cobalt ion transport, manganese ion transport]	
orf19.5026	[regulation of transcription, DNA-dependent]	
orf19.5041	[biological_process]	
orf19.5105	[RNA polymerase II transcriptional preinitiation complex assembly, negative regulation of transcription from RNA polymerase II promoter, positive regulation of transcription from RNA polymerase II promoter]	
orf19.5114	[cell communication, late endosome to Golgi transport, protein localization]	
orf19.5114.1	[biological_process]	
orf19.5131	[negative regulation of gluconeogenesis, proteasomal ubiquitin-dependent protein catabolic process]	
orf19.5132	[biological_process]	
orf19.5203	[biological_process]	
orf19.5210	[regulation of transcription, DNA-dependent, response to stress]	
orf19.5210.1	[biological_process]	
orf19.5233	[]	
orf19.5237	[vacuolar acidification, vacuolar proton-transporting V-type ATPase complex assembly]	
orf19.5238	[biological_process]	
orf19.5264	[]	
orf19.5267	[biological_process]	
orf19.5288.1	[biological_process]	
orf19.5289	[]	
orf19.529	[biological_process]	
orf19.53	[generation of catalytic spliceosome for first transesterification step, mRNA cis splicing, via spliceosome]	

ID	Go_Biological process	Cross-talking
orf19.5300	[ER-associated protein catabolic process, apoptotic process, cell wall organization or biogenesis, endoplasmic reticulum unfolded protein response, misfolded or incompletely synthesized protein catabolic process, protein folding in endoplasmic reticulum]	
orf19.5308	[biological_process]	
orf19.5311	[biological_process]	
orf19.5312	[positive regulation of cell adhesion involved in single-species biofilm formation, positive regulation of cell-substrate adhesion, positive regulation of transcription from RNA polymerase II promoter, regulation of transcription from RNA polymerase II promoter, response to arsenic-containing substance, response to cadmium ion, single-species biofilm formation on inanimate substrate, sulfur amino acid metabolic process]	
orf19.5326	[cellular response to drug, regulation of transcription, DNA-dependent]	
orf19.533	[]	
orf19.5431	[biological_process]	
orf19.5449	[biological_process]	
orf19.5465	[generation of catalytic spliceosome for first transesterification step]	
orf19.5537	[Rho protein signal transduction, fungal-type cell wall organization, response to heat]	
orf19.5539	[retrograde vesicle-mediated transport, Golgi to ER]	
orf19.5555	[biological_process]	
orf19.5556	[]	
orf19.5576	[cellular response to biotic stimulus, cellular response to starvation, coenzyme A biosynthetic process, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation]	
orf19.5625	[biological_process]	
orf19.5626	[biological_process]	
orf19.5711	[Golgi to plasma membrane protein transport, negative regulation of fatty acid biosynthetic process, negative regulation of phosphatidylglycerol biosynthetic process, phosphatidylinositol metabolic process, phospholipid transport, positive regulation of phosphatidylcholine biosynthetic process]	
orf19.5717	[]	
orf19.5728	[oxidation-reduction process]	
orf19.583	['de novo' NAD biosynthetic process from tryptophan, NAD metabolic process, filamentous growth of a population of unicellular organisms in response to chemical stimulus, tryptophan catabolic process to kynurenine]	

ID	Go_Biological process	Cross-talking
orf19.5844	[meiotic DNA recombinase assembly, reciprocal meiotic recombination]	
orf19.5855	[positive regulation of transcription involved in G1/S transition of mitotic cell cycle, regulation of transcription involved in G1/S transition of mitotic cell cycle]	
orf19.5917.3	[negative regulation of ATP-dependent RNA helicase activity, poly(A)+ mRNA export from nucleus, transcription-coupled nucleotide-excision repair]	
orf19.5924	[cellular response to copper ion, cellular response to drug, positive regulation of cell adhesion involved in single-species biofilm formation, positive regulation of cell-substrate adhesion, regulation of transcription from RNA polymerase II promoter, single-species biofilm formation on inanimate substrate]	
orf19.5933	[biological_process]	
orf19.5953	[positive regulation of ribosomal protein gene transcription from RNA polymerase II promoter, regulation of cell size]	
orf19.5975	[positive regulation of cell adhesion involved in single-species biofilm formation, positive regulation of cell-substrate adhesion, regulation of transcription from RNA polymerase II promoter, regulation of transcription, DNA-dependent, single-species biofilm formation on inanimate substrate]	
orf19.5991	[maturation of 5.8S rRNA from tricistronic rRNA transcript (SSU-rRNA, 5.8S rRNA, LSU-rRNA), maturation of LSU-rRNA from tricistronic rRNA transcript (SSU-rRNA, 5.8S rRNA, LSU-rRNA)]	
orf19.6071	[N-terminal peptidyl-methionine acetylation, cytoskeleton organization, mitochondrion inheritance]	
orf19.6082	[protein folding, protein localization to cell surface]	
orf19.6084	[biological_process]	
orf19.6169	[biological_process]	
orf19.6309	[biofilm formation, cellular response to neutral pH, filamentous growth, filamentous growth of a population of unicellular organisms in response to neutral pH, positive regulation of filamentous growth of a population of unicellular organisms in response to neutral pH, positive regulation of flocculation via cell wall protein-carbohydrate interaction by positive regulation of transcription from RNA polymerase II promoter, positive regulation of invasive growth in response to glucose limitation by positive regulation of transcription from RNA polymerase II promoter, positive regulation of pseudohyphal growth by positive regulation of transcription from RNA polymerase II promoter, positive regulation of starch catabolic process by positive regulation of transcription from RNA polymerase II promoter, positive regulation of transcription from RNA polymerase II promoter]	
orf19.6311	[biological_process]	

ID	Go_Biological process	Cross-talking
orf19.6326	[biological_process]	
orf19.6342	[biological_process]	
orf19.6343	[fatty acid elongation, sphingolipid biosynthetic process, vesicle-mediated transport]	
orf19.6408	[protein folding]	
orf19.6465	[biological_process]	
orf19.6487	[biological_process]	
orf19.6501	[biological_process]	
orf19.6503	[mitochondrial translation]	
orf19.6530	[biological_process]	
orf19.6547	[]	
orf19.6555	[protein import into mitochondrial intermembrane space]	
orf19.6556	[biological_process]	
orf19.6585	[biological_process]	
orf19.6586	[cellular response to drug]	
orf19.6660	[biological_process]	
orf19.6687	[biological_process]	
orf19.6688	[biological_process]	
orf19.6713	[biological_process]	
orf19.6715	[]	
orf19.6719	[DNA replication-independent nucleosome assembly, chromatin silencing at centromere, filamentous growth, mitotic sister chromatid segregation, negative regulation of transcription from RNA polymerase II promoter during mitosis, regulation of mitotic cell cycle, regulation of transcription involved in G1/S transition of mitotic cell cycle, transcription elongation from RNA polymerase II promoter]	
orf19.6736	[maturation of SSU-rRNA]	
orf19.6737	[biological_process]	
orf19.6754	[biological_process]	
orf19.6783	[ER to Golgi vesicle-mediated transport, activation of Rab GTPase activity, protein geranylgeranylation, protein targeting to membrane]	
orf19.6805	[biological_process]	
orf19.6818	[biological_process]	
orf19.6840	[biological_process]	
orf19.6852	[biological_process]	

ID	Go_Biological process	Cross-talking
orf19.6869	[oxidation-reduction process, protein targeting to membrane]	
orf19.6871	[biological_process]	
orf19.6873.1	[peptidyl-diphthamide biosynthetic process from peptidyl-histidine, tRNA wobble uridine modification]	
orf19.6874	[filamentous growth]	
orf19.6882.1	[cytoplasmic translation]	
orf19.6973	[protein catabolic process, proteolysis]	
orf19.6982	[biological_process]	
orf19.6983	[biological_process]	
orf19.6984	[biological_process]	
orf19.7017	[]	
orf19.7027	[biological_process]	
orf19.7054	[]	
orf19.7055	[]	
orf19.7056	[amino acid transmembrane transport]	
orf19.7077	[copper ion import, iron ion transport, oxidation-reduction process]	
orf19.7078	[meiosis]	
orf19.7084	[cell adhesion]	
orf19.7085	[biological_process]	
orf19.7110	[tRNA modification]	
orf19.7111	[chronological cell aging, hyphal growth, mitochondrial fission, peroxisome fission]	
orf19.7151	[]	
orf19.7152	[cellular response to cadmium ion, cysteine biosynthetic process, detoxification of cadmium ion]	
orf19.721	[centromeric heterochromatin assembly, chromatin silencing at centromere, cleavage in ITS2 between 5.8S rRNA and LSU-rRNA of tricistronic rRNA transcript (SSU-rRNA, 5.8S rRNA, LSU-rRNA), termination of RNA polymerase I transcription]	
orf19.7239	[pheromone-dependent signal transduction involved in conjugation with cellular fusion]	
orf19.7250	[biological_process]	
orf19.7279.1	[biological_process]	
orf19.7296	[biological_process]	
orf19.732	[metabolic process]	
orf19.733	[transmembrane transport]	

ID	Go_Biological process	Cross-talking
orf19.7336	[drug transport, transmembrane transport]	
orf19.7337	[biological_process]	
orf19.7380	[biological_process]	
orf19.7381	[cell adhesion, cell adhesion involved in single-species biofilm formation, cellular response to biotic stimulus, cellular response to drug, cellular response to glucose starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, invasive growth in response to glucose limitation, pathogenesis, positive regulation of cell adhesion involved in single-species biofilm formation, positive regulation of transcription from RNA polymerase II promoter, regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, regulation of phenotypic switching]	
orf19.7489	[actin cortical patch localization, actin cytoskeleton organization, barrier septum assembly, fungal-type cell wall biogenesis, regulation of cell shape, small GTPase mediated signal transduction]	
orf19.750	[biological_process]	
orf19.7502	[biological_process]	
orf19.7512	[oxidation-reduction process]	
orf19.7539.1	[biological_process]	
orf19.7545	[biological_process]	
orf19.7624	[rRNA processing]	
orf19.77.1	[biological_process]	
orf19.828	[translation]	
orf19.849	[]	
orf19.850	[cellular protein modification process, nitrogen compound metabolic process, protein catabolic process]	
orf19.851	[biological_process]	
orf19.86	[]	
orf19.861	[regulation of transcription, DNA-dependent]	
orf19.867	[apoptotic process, oxidation-reduction process, regulation of actin cytoskeleton organization]	
orf19.89	[fatty acid metabolic process, protein import into peroxisome matrix, docking, protein targeting to peroxisome]	
orf19.90	[biological_process]	

ID	Go_Biological process	Cross-talking
orf19.921	[cellular response to chemical stimulus, cellular response to heat, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to chemical stimulus, filamentous growth of a population of unicellular organisms in response to heat, positive regulation of filamentous growth of a population of unicellular organisms, positive regulation of filamentous growth of a population of unicellular organisms in response to chemical stimulus, positive regulation of filamentous growth of a population of unicellular organisms in response to heat, signal transduction involved in filamentous growth]	
orf19.933	[UV-damage excision repair, free ubiquitin chain polymerization, postreplication repair, protein K63-linked ubiquitination]	
orf19.938	[biological_process]	
orf19.948	[]	
orf19.949	[biological_process]	
orf19.952	[biological_process]	
OSH3	[endocytosis, exocytosis, filamentous growth, filamentous growth of a population of unicellular organisms, invasive growth in response to glucose limitation, karyogamy involved in conjugation with cellular fusion, maintenance of cell polarity, positive regulation of phosphatase activity, pseudohyphal growth, sterol transport]	
OYE23	[oxidation-reduction process]	
PDE1	[adhesion to host, cAMP catabolic process, cAMP-mediated signaling, cellular response to glucose stimulus, cellular response to nitrogen starvation, filamentous growth, filamentous growth of a population of unicellular organisms, negative regulation of cAMP biosynthetic process, pathogenesis, positive regulation of filamentous growth of a population of unicellular organisms, positive regulation of transcription from RNA polymerase II promoter, regulation of conjugation with cellular fusion]	
PDX1	[acetyl-CoA biosynthetic process from pyruvate, filamentous growth, single-species biofilm formation on inanimate substrate]	
PFK26	[fructose 2,6-bisphosphate metabolic process, fructose metabolic process]	
PGA1	[adhesion to host, cell adhesion involved in single-species biofilm formation, filamentous growth, filamentous growth of a population of unicellular organisms, fungal-type cell wall organization, negative regulation of filamentous growth of a population of unicellular organisms]	
PGA13	[filamentous growth, filamentous growth of a population of unicellular organisms, fungal-type cell wall organization, negative regulation of flocculation]	

ID	Go_Biological process	Cross-talking
PGA16	[biological_process]	
PGA23	[cellular response to drug]	
PGA30	[biological_process]	
PGA31	[cellular response to drug, fungal-type cell wall organization]	
PGA32	[biological_process]	
PGA34	[biological_process]	
PGA54	[biological_process]	
PGA56	[L-sorbose catabolic process]	
PGA59	[cellular response to neutral pH, filamentous growth, filamentous growth of a population of unicellular organisms in response to neutral pH, fungal-type cell wall organization]	
PGA62	[cellular response to drug, fungal-type cell wall organization]	
PHM7	[biological_process]	
PHO84	[cellular response to biotic stimulus, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, manganese ion transport, organic cation transport, phosphate ion transport, plasma membrane selenite transport, polyphosphate metabolic process, transmembrane transport]	
PHO86	[ER to Golgi vesicle-mediated transport, protein folding, regulation of phosphate transport]	
PHR2	[carbohydrate metabolic process, cellular response to pH, chromatin silencing, filamentous growth, fungal-type cell wall organization, pathogenesis]	
PIR1	[biological_process, cellular response to temperature stimulus, fungal-type cell wall organization, intracellular protein transport]	
PLD1	[ascospore-type prospore assembly, cell morphogenesis involved in conjugation with cellular fusion, cellular response to chemical stimulus, cellular response to starvation, exocytosis, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to chemical stimulus, filamentous growth of a population of unicellular organisms in response to starvation, pathogenesis, phosphatidylinositol metabolic process]	
PMA1	[ATP biosynthetic process, ATP catabolic process, proton transport, regulation of intracellular pH, response to osmotic stress, transmembrane transport]	
PMC1	[calcium ion transmembrane transport, calcium ion transport, cellular calcium ion homeostasis, cellular response to drug, transmembrane transport]	

ID	Go_Biological process	Cross-talking
PMR1	[calcium ion transmembrane transport, cellular calcium ion homeostasis, cellular manganese ion homeostasis, cellular response to cadmium ion, cellular response to mechanical stimulus, detoxification of cadmium ion, exocytosis, filamentous growth, filamentous growth of a population of unicellular organisms, fungal-type cell wall organization, hyphal growth, manganese ion transmembrane transport, positive regulation of calcium-mediated signaling, protein glycosylation]	
PMT2	[ER-associated misfolded protein catabolic process, cellular response to drug, conidiophore development, establishment or maintenance of cell polarity, filamentous growth of a population of unicellular organisms in response to neutral pH, fungal-type cell wall organization, hyphal growth, protein O-linked glycosylation, protein O-linked mannosylation, protein exit from endoplasmic reticulum, regulation of endoplasmic reticulum unfolded protein response, single-species biofilm formation on inanimate substrate]	
POP3	[intronic box C/D snoRNA processing, mRNA cleavage, rRNA processing, tRNA processing]	
PSA2	[biosynthetic process]	
PST3	[cellular response to brefeldin A, chromatin silencing at silent mating-type cassette]	
PTH2	[biological_process, negative regulation of proteasomal ubiquitin-dependent protein catabolic process]	
PTR2	[dipeptide transmembrane transport, dipeptide transport, oligopeptide transport, tripeptide transport]	
PUT3	[positive regulation of proline catabolic process to glutamate, positive regulation of transcription from RNA polymerase II promoter, transcription, DNA-dependent, transcription-dependent tethering of RNA polymerase II gene DNA at nuclear periphery]	
RAD32	[error-free translesion synthesis, error-prone translesion synthesis, establishment of mitotic sister chromatid cohesion, peptidyl-lysine N6-acetylation, positive regulation of maintenance of mitotic sister chromatid cohesion, centromeric]	
RAM1	[cellular response to nitrogen starvation, protein farnesylation, protein prenylation, regulation of amino acid import, regulation of cell proliferation]	

ID	Go_Biological process	Cross-talking
RAP1	[chromatin silencing at silent mating-type cassette, establishment of chromatin silencing at telomere, establishment of protein localization to chromatin, establishment of protein localization to telomere, filamentous growth, filamentous growth of a population of unicellular organisms, negative regulation of chromatin silencing, negative regulation of pseudohyphal growth, negative regulation of transcription from RNA polymerase II promoter, protection from non-homologous end joining at telomere, pseudohyphal growth, regulation of glycolysis by positive regulation of transcription from RNA polymerase II promoter, regulation of transcription by chromatin organization, regulation of transcription, DNA-dependent, telomere capping, telomere maintenance, telomere maintenance via telomere lengthening]	
RAS2	[GTP catabolic process, Ras protein signal transduction, cellular response to biotic stimulus, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, protein transport]	
RAX1	[cellular bud site selection, termination of G-protein coupled receptor signaling pathway]	
RBD1	[filamentous growth, filamentous growth of a population of unicellular organisms, negative regulation of filamentous growth of a population of unicellular organisms, proteolysis]	
RBR1	[cellular response to neutral pH, filamentous growth, filamentous growth of a population of unicellular organisms in response to neutral pH]	
RBR2	[fungal-type cell wall organization, response to stress]	
RBR3	[biological_process]	
RDI1	[actin filament organization, cellular response to biotic stimulus, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, hyphal growth, regulation of cytolysis, regulation of growth rate, regulation of vacuole fusion, non-autophagic, small GTPase mediated signal transduction]	
REG1	[cellular response to glucose starvation, regulation of carbohydrate metabolic process, vacuolar protein catabolic process]	

ID	Go_Biological process	Cross-talking
RFG1	[cellular response to biotic stimulus, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, negative regulation of filamentous growth of a population of unicellular organisms, negative regulation of transcription from RNA polymerase II promoter, negative regulation of transcription from RNA polymerase II promoter in response to stress, negative regulation of transcription, DNA-dependent, pathogenesis, regulation of transcription from RNA polymerase II promoter]	
RGS2	[adenylate cyclase-modulating G-protein coupled receptor signaling pathway, termination of G-protein coupled receptor signaling pathway]	
RGT1	[filamentous growth, filamentous growth of a population of unicellular organisms, glucose metabolic process, glucose transport, growth of symbiont in host, negative regulation of filamentous growth of a population of unicellular organisms, negative regulation of transcription from RNA polymerase II promoter, positive regulation of transcription from RNA polymerase II promoter, positive regulation of transcription, DNA-dependent]	
RHB1	[GTP catabolic process, arginine transport, cell cycle arrest in response to nitrogen starvation, cellular response to chemical stimulus, cellular response to drug, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to chemical stimulus, filamentous growth of a population of unicellular organisms in response to starvation, fungal-type cell wall organization, intracellular protein transport, lysine transport, nucleocytoplasmic transport, regulation of L-arginine import, retrograde transport, endosome to Golgi, signal transduction, small GTPase mediated signal transduction]	
RHD3	[fungal-type cell wall organization, pathogenesis]	

ID	Go_Biological process	Cross-talking
RIM101	[ascospore formation, barrier septum assembly, cellular response to alkalinity, cellular response to anoxia, cellular response to biotic stimulus, cellular response to copper ion, cellular response to drug, cellular response to iron ion starvation, cellular response to lithium ion, cellular response to neutral pH, cellular response to pH, chlamydospore formation, entry into host, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to chemical stimulus, filamentous growth of a population of unicellular organisms in response to neutral pH, filamentous growth of a population of unicellular organisms in response to pH, fungal-type cell wall biogenesis, induction by symbiont of host defense response, meiosis, negative regulation of transcription from RNA polymerase II promoter, pathogenesis, positive regulation of T cell tolerance induction, positive regulation of filamentous growth of a population of unicellular organisms, positive regulation of filamentous growth of a population of unicellular organisms in response to chemical stimulus, positive regulation of transcription from RNA polymerase II promoter, regulation of transcription from RNA polymerase II promoter, regulation of transcription, DNA-dependent, signal transduction]	
RIM8	[cellular response to biotic stimulus, cellular response to pH, entry into host, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to pH, filamentous growth of a population of unicellular organisms in response to starvation, invasive growth in response to glucose limitation, meiosis, pathogenesis, penicillin biosynthetic process, positive regulation of filamentous growth of a population of unicellular organisms, positive regulation of penicillin biosynthetic process, protein processing]	
RLM1	[biological_process, cellular response to drug, fungal-type cell wall organization, positive regulation of transcription from RNA polymerase II promoter in response to stress, regulation of transcription from RNA polymerase II promoter, signal transduction]	
RME1	[negative regulation of meiosis, negative regulation of transcription during meiosis, negative regulation of transcription from RNA polymerase II promoter, positive regulation of invasive growth in response to glucose limitation by positive regulation of transcription from RNA polymerase II promoter, positive regulation of transcription involved in G1/S transition of mitotic cell cycle]	
RMT2	[peptidyl-arginine methylation]	
RNR3	[DNA replication, oxidation-reduction process]	

ID	Go_Biological process	Cross-talking
ROB1	[cellular response to biotic stimulus, chromatin remodeling, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, nucleosome positioning, positive regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, regulation of nitrogen utilization, regulation of single-species biofilm formation on inanimate substrate, regulation of transcription from RNA polymerase II promoter, single-species biofilm formation on inanimate substrate, transcription, DNA-dependent]	
RPN4	[negative regulation of transcription from RNA polymerase II promoter in response to stress, positive regulation of proteasomal ubiquitin-dependent protein catabolic process, positive regulation of transcription from RNA polymerase II promoter in response to arsenic-containing substance, proteasomal ubiquitin-dependent protein catabolic process, regulation of DNA repair, regulation of transcription from RNA polymerase II promoter]	
RPS1	[maturation of SSU-rRNA from tricistronic rRNA transcript (SSU-rRNA, 5.8S rRNA, LSU-rRNA), translation]	
RPS21	[positive regulation of translational fidelity, rRNA export from nucleus, translation]	
RPS8A	[maturation of SSU-rRNA from tricistronic rRNA transcript (SSU-rRNA, 5.8S rRNA, LSU-rRNA), translation]	
RTA4	[cellular response to biotic stimulus, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation]	
SAP2	[adhesion to host, cellular protein catabolic process, induction by symbiont of defense-related host calcium ion flux, induction by symbiont of host defense response, nitrogen compound metabolic process, pathogenesis, protein catabolic process, protein metabolic process, proteolysis, signal peptide processing]	
SAP5	[adhesion to host, cellular nitrogen compound catabolic process, nitrogen compound metabolic process, pathogenesis, protein catabolic process, proteolysis]	
SAP7	[pathogenesis, proteolysis]	
SBP1	[negative regulation of translation in response to stress]	

ID	Go_Biological process	Cross-talking
SCH9	[G-protein coupled receptor signaling pathway, age-dependent response to oxidative stress involved in chronological cell aging, cellular response to chemical stimulus, cellular response to starvation, chlamydospore formation, conidiophore development, development of symbiont in host, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to chemical stimulus, filamentous growth of a population of unicellular organisms in response to starvation, hyphal growth, intracellular signal transduction, negative regulation of filamentous growth of a population of unicellular organisms in response to chemical stimulus, pathogenesis, positive regulation of filamentous growth of a population of unicellular organisms in response to starvation, positive regulation of ribosomal protein gene transcription from RNA polymerase II promoter, positive regulation of transcription from RNA polymerase I promoter, positive regulation of transcription from RNA polymerase III promoter, protein phosphorylation, regulation of cell size, regulation of conjugation with cellular fusion, regulation of protein localization, regulation of response to osmotic stress, regulation of transcription from RNA polymerase II promoter in response to oxidative stress, regulation of trehalose metabolic process, replicative cell aging, response to salt stress, spore germination, trehalose catabolic process]	
SER33	[oxidation-reduction process, serine family amino acid biosynthetic process]	
SFL1	[cellular response to drug, filamentous growth, filamentous growth of a population of unicellular organisms, flocculation, gene silencing, negative regulation of filamentous growth of a population of unicellular organisms, negative regulation of invasive growth in response to glucose limitation by negative regulation of transcription from RNA polymerase II promoter, negative regulation of pseudohyphal growth by negative regulation of transcription from RNA polymerase II promoter, negative regulation of transcription from RNA polymerase II promoter, positive regulation of transcription from RNA polymerase II promoter]	
SFU1	[cellular iron ion homeostasis, cellular response to copper ion, cellular response to iron ion, negative regulation of transcription from RNA polymerase II promoter, positive regulation of transcription from RNA polymerase II promoter, regulation of transcription from RNA polymerase II promoter in response to iron ion starvation]	
SGA1	[glycogen catabolic process]	

ID	Go_Biological process	Cross-talking
SHA3	[cellular response to biotic stimulus, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, glucose transport, negative regulation of induction of conjugation with cellular fusion, negative regulation of meiosis, negative regulation of transcription from RNA polymerase II promoter during mitosis, positive regulation of transcription from RNA polymerase II promoter, protein phosphorylation, response to glucose stimulus]	
SIM1	[fungal-type cell wall biogenesis, fungal-type cell wall organization, mitochondrion degradation, regulation of DNA replication]	
SIT1	[cellular response to drug, ferrichrome transport, siderophore transport, transmembrane transport]	
SIT4	[DNA repair, G1/S transition of mitotic cell cycle, TOR signaling cascade, actin cytoskeleton organization, cellular response to biotic stimulus, cellular response to chemical stimulus, cellular response to neutral pH, cellular response to oxidative stress, dephosphorylation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to chemical stimulus, filamentous growth of a population of unicellular organisms in response to heat, filamentous growth of a population of unicellular organisms in response to neutral pH, filamentous growth of a population of unicellular organisms in response to starvation, fungal-type cell wall organization, intracellular protein kinase cascade, pathogenesis, positive regulation of filamentous growth of a population of unicellular organisms in response to chemical stimulus, positive regulation of filamentous growth of a population of unicellular organisms in response to neutral pH, positive regulation of filamentous growth of a population of unicellular organisms in response to starvation, positive regulation of hydroxymethylglutaryl-CoA reductase (NADPH) activity, positive regulation of isopentenyl diphosphate biosynthetic process, mevalonate pathway, positive regulation of protein dephosphorylation, protein phosphorylation, regulation of cell shape, regulation of chromosome segregation, regulation of mitotic cell cycle, replicative cell aging, tRNA wobble uridine modification]	

ID	Go_Biological process	Cross-talking
SKN7	[cellular hyperosmotic response, cellular response to biotic stimulus, cellular response to drug, cellular response to hydrogen peroxide, cellular response to oxidative stress, cellular response to starvation, conidium formation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, pathogenesis, phosphorelay signal transduction system, positive regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, positive regulation of filamentous growth of a population of unicellular organisms in response to starvation, pseudohyphal growth, regulation of cell size, regulation of cellular response to oxidative stress by regulation of transcription from RNA polymerase II promoter, regulation of conidium formation, regulation of conjugation with cellular fusion by regulation of transcription from RNA polymerase II promoter, regulation of transcription from RNA polymerase II promoter in response to oxidative stress, response to singlet oxygen, transcription, DNA-dependent]	
SKO1	[biological_process, cellular response to copper ion, cellular response to stress, filamentous growth, filamentous growth of a population of unicellular organisms, negative regulation of filamentous growth of a population of unicellular organisms, negative regulation of transcription from RNA polymerase II promoter, positive regulation of transcription from RNA polymerase II promoter in response to osmotic stress, regulation of transcription from RNA polymerase II promoter in response to stress, stress-activated MAPK cascade]	
SMM1	[oxidation-reduction process, tRNA modification]	
SOD3	[oxidation-reduction process, superoxide metabolic process]	
SOD4	[cellular response to superoxide, evasion or tolerance by symbiont of host-produced reactive oxygen species, oxidation-reduction process, superoxide metabolic process]	
SOK1	[cAMP-mediated signaling]	
SPE2	[pantothenate biosynthetic process, spermidine biosynthetic process, spermine biosynthetic process]	
SPO75	[ascospore wall assembly]	

ID	Go_Biological process	Cross-talking
SRR1	[apoptotic process, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to neutral pH, filamentous growth of a population of unicellular organisms in response to starvation, pathogenesis, phosphorelay signal transduction system, positive regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, positive regulation of filamentous growth of a population of unicellular organisms in response to neutral pH, positive regulation of filamentous growth of a population of unicellular organisms in response to starvation, regulation of transcription, DNA-dependent, response to osmotic stress, response to oxidative stress]	
SSA2	[SRP-dependent cotranslational protein targeting to membrane, translocation, establishment or maintenance of cell polarity, interaction with host, peptide transport, protein folding, protein import into mitochondrial matrix, response to stress, response to toxic substance]	
SSK1	[activation of MAPKKK activity involved in osmosensory signaling pathway, cellular hyperosmotic salinity response, cellular response to biotic stimulus, cellular response to cadmium ion, cellular response to heat, cellular response to hydrogen peroxide, cellular response to neutral pH, cellular response to oxidative stress, cellular response to starvation, conidium formation, detoxification of cadmium ion, evasion or tolerance of host immune response, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to neutral pH, filamentous growth of a population of unicellular organisms in response to starvation, fungal-type cell wall organization, osmosensory signaling via phosphorelay pathway, pathogenesis, phosphorelay signal transduction system, positive regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, positive regulation of filamentous growth of a population of unicellular organisms in response to neutral pH, positive regulation of filamentous growth of a population of unicellular organisms in response to starvation, positive regulation of protein autophosphorylation, regulation of conidium formation, regulation of filamentous growth of a population of unicellular organisms, regulation of mitotic cell cycle, regulation of transcription, DNA-dependent, response to arsenic-containing substance, stress-activated protein kinase signaling cascade]	

ID	Go_Biological process	Cross-talking
SSN6	[cellular response to drug, chromatin remodeling, filamentous growth, filamentous growth of a population of unicellular organisms, negative regulation of dipeptide transport by negative regulation of transcription from RNA polymerase II promoter, negative regulation of filamentous growth of a population of unicellular organisms, negative regulation of transcription from RNA polymerase II promoter, negative regulation of transcription from RNA polymerase II promoter during mitosis, nucleosome positioning, pathogenesis, regulation of fatty acid biosynthetic process by regulation of transcription from RNA polymerase II promoter, regulation of response to DNA damage stimulus, regulation of transcription from RNA polymerase II promoter in response to osmotic stress]	
SSU1	[cellular response to abiotic stimulus, cellular response to biotic stimulus, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, sulfite transport, transmembrane transport]	
SSU81	[cell morphogenesis, cellular response to biotic stimulus, cellular response to heat, cellular response to neutral pH, cellular response to oxidative stress, cytokinesis, establishment of cell polarity, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to neutral pH, fungal-type cell wall biogenesis, fungal-type cell wall organization, osmosensory signaling pathway via Sho1 osmosensor, positive regulation of filamentous growth, positive regulation of filamentous growth of a population of unicellular organisms, signal transduction involved in filamentous growth]	
STE2	[G-protein coupled receptor signaling pathway, cell projection assembly, cell-cell adhesion, cell-substrate adhesion, cellular response to pheromone, cytogamy, negative regulation of signal transduction in absence of ligand, pheromone-dependent signal transduction involved in conjugation with cellular fusion, positive regulation of conjugation with cellular fusion, positive regulation of diacylglycerol biosynthetic process, positive regulation of pheromone-dependent signal transduction involved in conjugation with cellular fusion, protein homooligomerization, receptor transactivation, regulation of single-species biofilm formation on inanimate substrate, response to pheromone involved in conjugation with cellular fusion, single-species biofilm formation on inanimate substrate, sporocarp development involved in sexual reproduction]	

ID	Go_Biological process	Cross-talking
STP2	[amino acid import, cellular response to alkalinity, cellular response to chemical stimulus, cellular response to drug, cellular response to heat, filamentous growth, filamentous growth of a population of unicellular organisms in response to chemical stimulus, positive regulation of filamentous growth of a population of unicellular organisms in response to chemical stimulus, positive regulation of transcription from RNA polymerase II promoter]	
STP3	[cellular response to drug, filamentous growth of a population of unicellular organisms, positive regulation of protein catabolic process, positive regulation of pseudohyphal growth by positive regulation of transcription from RNA polymerase II promoter, positive regulation of transcription from RNA polymerase II promoter, regulation of pseudohyphal growth]	
STP4	[filamentous growth, regulation of transcription, DNA-dependent]	
SUL2	[sulfate transport, transmembrane transport]	
SUR7	[ascospore formation, cellular response to biotic stimulus, cellular response to chemical stimulus, cellular response to glucose starvation, cellular response to neutral pH, cortical actin cytoskeleton organization, endocytosis, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to chemical stimulus, filamentous growth of a population of unicellular organisms in response to neutral pH, filamentous growth of a population of unicellular organisms in response to starvation, fungal-type cell wall organization, septin cytoskeleton organization, single-species biofilm formation on inanimate substrate]	
SWE1	[G2/M transition of mitotic cell cycle, cell morphogenesis, cellular response to drug, cytokinesis after mitosis checkpoint, negative regulation of spindle pole body separation, pathogenesis, protein phosphorylation, re-entry into mitotic cell cycle, regulation of cell size, regulation of cyclin-dependent protein serine/threonine kinase activity, regulation of meiosis]	
SWI4	[cellular response to cadmium ion, detoxification of cadmium ion, positive regulation of transcription from RNA polymerase II promoter in response to heat stress, positive regulation of transcription involved in G1/S transition of mitotic cell cycle, regulation of transcription during meiosis, regulation of transcription during mitosis, regulation of transcription involved in G1/S transition of mitotic cell cycle]	
TCC1	[cellular response to pH, filamentous growth, filamentous growth of a population of unicellular organisms in response to pH, negative regulation of transcription from RNA polymerase II promoter, negative regulation of transcription, DNA-dependent, pathogenesis]	
TEF4	[biological_process, translational elongation]	

ID	Go_Biological process	Cross-talking
TEM1	[GTP catabolic process, cellular protein localization, intracellular protein transport, mitotic M phase, nucleocytoplasmic transport, positive regulation of barrier septum assembly, septation initiation signaling cascade]	
TLO1	[]	
TLO10	[biological_process]	
TLO9	[biological_process]	
TOP1	[DNA strand elongation involved in DNA replication, DNA topological change, chromatin assembly or disassembly, chromatin silencing at rDNA, hyphal growth, mitotic chromosome condensation, nuclear migration, pathogenesis, regulation of mitotic recombination, regulation of transcription from RNA polymerase II promoter, transcription elongation from RNA polymerase II promoter, transcription of nuclear large rRNA transcript from RNA polymerase I promoter]	
TOR1	[Rho protein signal transduction, TOR signaling cascade, cell cycle arrest in response to nitrogen starvation, cellular response to drug, establishment or maintenance of actin cytoskeleton polarity, negative regulation of autophagy, negative regulation of cell cycle arrest in response to nitrogen starvation, negative regulation of induction of conjugation with cellular fusion, positive regulation of endocytosis, positive regulation of transcription from RNA polymerase II promoter, rRNA transcription, ribosome biogenesis]	
TPI1	[cellular response to biotic stimulus, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, glycolysis, induction by symbiont of host defense response]	

ID	Go_Biological process	Cross-talking
TPK2	[G-protein coupled receptor signaling pathway, Ras protein signal transduction, activation of bipolar cell growth, asexual sporulation resulting in formation of a cellular spore, cell adhesion involved in single-species biofilm formation, cell morphogenesis, cell-abiotic substrate adhesion, cellular age-dependent response to reactive oxygen species, cellular response to biotic stimulus, cellular response to salt stress, cellular response to starvation, cellular response to stress, chronological cell aging, conidiophore development, conidium formation, development of symbiont in host, entry into host, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, fungal-type cell wall organization, hyphal growth, induction of conjugation upon nitrogen starvation, invasive growth in response to glucose limitation, negative regulation of G2/M transition of mitotic cell cycle, negative regulation of ascospore formation, negative regulation of induction of conjugation with cellular fusion, negative regulation of sterigmatocystin biosynthetic process, negative regulation of transcription by glucose, pathogenesis, positive regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, positive regulation of filamentous growth of a population of unicellular organisms in response to starvation, protein kinase A signaling cascade, protein phosphorylation, regulation of circadian rhythm, regulation of single-species biofilm formation on inanimate substrate, single-species biofilm formation on inanimate substrate, spore germination, sporocarp development involved in sexual reproduction, stress granule assembly, trehalose catabolic process]	
TPO4	[drug transport, spermidine transport, spermine transport, transmembrane transport]	
TPS1	[ascospore formation, cellular response to biotic stimulus, cellular response to desiccation, cellular response to ethanol, cellular response to freezing, cellular response to heat, cellular response to stress, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to heat, pathogenesis, positive regulation of trehalose catabolic process, trehalose biosynthesis in response to heat stress, trehalose biosynthetic process]	
TPS2	[cellular response to heat, cellular response to osmotic stress, cellular response to oxidative stress, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to starvation, fungal-type cell wall organization, negative regulation of flocculation, pathogenesis, trehalose biosynthetic process]	

ID	Go_Biological process	Cross-talking
TYE7	[carbon catabolite activation of transcription, cellular response to hypoxia, filamentous growth, filamentous growth of a population of unicellular organisms, negative regulation of filamentous growth of a population of unicellular organisms, positive regulation of glycolysis, positive regulation of single-species biofilm formation on inanimate substrate, single-species biofilm formation on inanimate substrate, transcription, DNA-dependent]	
UBI4	[cell morphogenesis, cellular response to heat, cellular response to stress, filamentous growth, filamentous growth of a population of unicellular organisms, pathogenesis, phenotypic switching, protein ubiquitination]	
UME6	[cellular response to biotic stimulus, cellular response to neutral pH, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to neutral pH, filamentous growth of a population of unicellular organisms in response to starvation, pathogenesis, positive regulation of filamentous growth of a population of unicellular organisms, positive regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, positive regulation of filamentous growth of a population of unicellular organisms in response to neutral pH, positive regulation of filamentous growth of a population of unicellular organisms in response to starvation, regulation of transcription, DNA-dependent]	
URA2	['de novo' pyrimidine nucleobase biosynthetic process, carbamoyl phosphate biosynthetic process, glutamine catabolic process, glutamine metabolic process, negative regulation of pyrimidine nucleobase metabolic process]	
URA3	['de novo' UMP biosynthetic process, 'de novo' pyrimidine nucleobase biosynthetic process, UMP biosynthetic process, adhesion to host, cell migration, filamentous growth, filamentous growth of a population of unicellular organisms, pathogenesis, pyrimidine nucleobase biosynthetic process, sporocarp development involved in sexual reproduction, uracil biosynthetic process, uridine biosynthetic process]	
UTP22	[rRNA processing, response to drug, tRNA export from nucleus]	
VCX1	[calcium ion transport, cellular calcium ion homeostasis, transmembrane transport]	

ID	Go_Biological process	Cross-talking
VPS36	[cellular response to alkalinity, cellular response to lithium ion, cellular response to pH, filamentous growth, filamentous growth of a population of unicellular organisms in response to neutral pH, filamentous growth of a population of unicellular organisms in response to pH, negative regulation of transcription from RNA polymerase II promoter by glucose, protein processing, protein retention in Golgi apparatus, protein targeting to vacuole, protein targeting to vacuole involved in ubiquitin-dependent protein catabolic process via the multivesicular body sorting pathway]	
VPS41	[cellular response to biotic stimulus, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, intracellular protein transport, piecemeal microautophagy of nucleus, protein transport, regulation of SNARE complex assembly, regulation of vacuole fusion, non-autophagic, vacuolar protein processing, vacuole fusion, non-autophagic, vacuole inheritance, vesicle-mediated transport]	
WH11	[pathogenesis, phenotypic switching, response to stress, single-species biofilm formation on inanimate substrate]	
WOR1	[adhesion to host, cell adhesion, conjugation with cellular fusion, filamentous growth of a population of unicellular organisms, phenotypic switching, positive regulation of phenotypic switching, positive regulation of pseudohyphal growth by positive regulation of transcription from RNA polymerase II promoter, positive regulation of transcription from RNA polymerase II promoter, regulation of phenotypic switching, regulation of pseudohyphal growth, regulation of single-species biofilm formation on inanimate substrate, regulation of transcription, DNA-dependent, single-species biofilm formation on inanimate substrate]	
WOR2	[filamentous growth, growth of unicellular organism as a thread of attached cells, negative regulation of growth of unicellular organism as a thread of attached cells, phenotypic switching, positive regulation of phenotypic switching, regulation of transcription, DNA-dependent]	
WSC4	[protein targeting to ER, protein targeting to membrane, response to heat]	
XUT1	[nucleobase transport, transmembrane transport, urate transport, xanthine transport]	
YAK1	[activation of bipolar cell growth, cellular response to biotic stimulus, cellular response to neutral pH, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to neutral pH, protein phosphorylation, single-species biofilm formation on inanimate substrate]	
YCP4	[negative regulation of transcription, DNA-dependent]	

ID	Go_Biological process	Cross-talking
YHB1	[cellular response to nitrosative stress, filamentous growth, filamentous growth of a population of unicellular organisms, nitric oxide catabolic process, oxidation-reduction process, oxygen transport, pathogenesis, response to defense-related host nitric oxide production, response to toxic substance]	
YHB5	[oxidation-reduction process, oxygen transport]	
YIM1	[oxidation-reduction process, response to DNA damage stimulus]	
YNK1	[CDP phosphorylation, CTP biosynthetic process, GTP biosynthetic process, UTP biosynthetic process, anisotropic cell growth, hyphal growth, nucleoside diphosphate phosphorylation, protein autophosphorylation, response to DNA damage stimulus, response to oxidative stress]	
ZAP1	[cellular response to biotic stimulus, cellular response to starvation, cellular zinc ion homeostasis, filamentous growth, filamentous growth of a population of unicellular organisms, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, iron assimilation, positive regulation of transcription from RNA polymerase II promoter, regulation of single-species biofilm formation on inanimate substrate, regulation of transcription from RNA polymerase II promoter, regulation of transcription from RNA polymerase II promoter in response to zinc ion starvation, single-species biofilm formation on inanimate substrate]	
ZCF10	[filamentous growth of a population of unicellular organisms in response to biotic stimulus, positive regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, positive regulation of transcription from RNA polymerase II promoter, quinate catabolic process, regulation of transcription, DNA-dependent, transcription, DNA-dependent]	
ZCF11	[carbon utilization, cellular response to biotic stimulus, cellular response to starvation, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, filamentous growth of a population of unicellular organisms in response to starvation, regulation of transcription, DNA-dependent]	
ZCF16	[]	
ZCF2	[filamentous growth of a population of unicellular organisms in response to biotic stimulus, regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, regulation of transcription, DNA-dependent]	
ZCF20	[carbon catabolite activation of transcription from RNA polymerase II promoter, establishment of protein localization to chromatin, negative regulation of transcription from RNA polymerase II promoter in response to hypoxia, regulation of cellular respiration]	

ID	Go_Biological process	Cross-talking
ZCF25	[conidiophore development, regulation of transcription, DNA-dependent, transcription, DNA-dependent]	
ZCF26	[regulation of transcription, DNA-dependent, transcription, DNA-dependent]	
ZCF27	[filamentous growth, growth of unicellular organism as a thread of attached cells, positive regulation of growth of unicellular organism as a thread of attached cells, regulation of transcription, DNA-dependent]	
ZCF29	[cellular response to biotic stimulus, cellular response to drug, cellular response to oxidative stress, filamentous growth, filamentous growth of a population of unicellular organisms in response to biotic stimulus, growth of symbiont in host, positive regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, regulation of transcription, DNA-dependent, transcription, DNA-dependent]	
ZCF34	[cellular response to drug, growth of symbiont in host, positive regulation of cell adhesion involved in single-species biofilm formation, positive regulation of cell-substrate adhesion, regulation of transcription from RNA polymerase II promoter, regulation of transcription, DNA-dependent, single-species biofilm formation on inanimate substrate, transcription, DNA-dependent]	
ZCF39	[filamentous growth of a population of unicellular organisms in response to biotic stimulus, positive regulation of cell adhesion involved in single-species biofilm formation, positive regulation of cell-substrate adhesion, regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, regulation of transcription from RNA polymerase II promoter, regulation of transcription, DNA-dependent, single-species biofilm formation on inanimate substrate]	
ZCF5	[filamentous growth of a population of unicellular organisms in response to biotic stimulus, positive regulation of filamentous growth of a population of unicellular organisms in response to biotic stimulus, regulation of transcription, DNA-dependent, transcription, DNA-dependent]	
ZRT2	[cellular response to zinc ion starvation, conidium formation, high-affinity zinc ion transmembrane import, low-affinity zinc ion transport, regulation of growth rate, regulation of transcription from RNA polymerase II promoter in response to iron ion starvation]	