AspMetNet

Presentation
Systematic identification of antifungal drug targets by a metabolic network approach
Thematic:
Fungi
Fungal infections pose an increasing threat for the immunocompromised. Limitations in antifungal therapy arise from non-specific symptoms of infection, poor diagnostics and comparatively few options for treatment. Currently established antifungal drugs interfere with the fungal cell wall or plasma membrane and are characterized by limited efficacy, severe side effects, or emerging pathogen resistance. Despite their promise to serve as highly specific antifungal targets, fungal metabolic pathways have been widely neglected. Because of the fact that Aspergillus, the causative agent of aspergillosis, apparently lacks specific virulence factors, its general characteristics, such as growth and tissue penetration, strongly correlate with the outcome after infection of a susceptible host. These traits strictly rely on nutrient acquisition and metabolic turnover and, therefore, make biosynthetic pathways a prime target in antimycotic therapy.

The basic concept of this proposal is to explore the metabolism of the main pathogenic species A.fumigatus on a comprehensive scale as essential virulence determinant. Emerging from transcriptome profiling data that are mapped on the annotated genome sequence of A. fumigatus, metabolic network reconstruction will serve to identify fungal-specific biosynthetic pathways and key reactions. Predictions for unique enzymes will result in a candidate list of genes, the inactivation of which is likely to result in an auxotrophic phenotype based on conditional essentiality of the biosynthetic reaction. After prioritization of these candidates, gene targeting approaches will result in a collection of deletion strains or conditional expression derivatives. These will be subjected to extensive phenotypic characterization, comprising virulence studies to test infectivity in established animal models of aspergillosis. Based on the resulting data collections, the metabolic network model will be refined in an iterative manner to yield further candidate genes that again will be experimentally validated. In essence, this systematically applied metabolic network approach will yield novel antifungal drug targets based on the metabolism of A. fumigatus that will serve as promising candidates for therapeutic intervention to fight fungal infections.

Administrative Info
AspMetNet starts in March 2014, lasts 36 months and involves the partnerships below.

- **Prof. Sven Krappmann** from University Hospital Erlangen, Friedrich-Alexander-University Erlangen (DE);

- **Prof. Thomas Dandekar** from Julius-Maximilians-University (DE);

- **Prof. Hubertus Haas** from Innsbruck Medical University (AT);

- **Prof. Nir Osherov** from Tel Aviv University (IL)

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- Administration

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