

“Functional genomics in *Aspergillus fumigatus* and new strategies to fight against the first fungal pathogen in Europe”: FUMINOMICS

**Third Annual Meeting report on Cell Biology and Biochemistry,
Oct 7-8, 2010,
Institut Pasteur, Paris, France.**



Group picture of the participants of the FUMINOMICS workshop at the Institut Pasteur, Paris

The third annual meeting of FUMINOMICS took place at the Institut Pasteur in Paris, France. Thirty six members of the consortium, including senior and junior scientists from each of the seventeen partner laboratories, met to discuss their experience and results about cell biology and biochemistry. The program of the meeting is included below.

**Third Annual Meeting on Cell Biology and Biochemistry,
Institut Pasteur, Paris, France, Oct 7-8, 2010,
Program**

Day 1 : Thursday October 7 th , 2010	
Introduction	<i>Jean-Paul Latgé</i>
Biochemistry (chair: Javier Arroyo)	
O-Mannosyltransferases	<i>Isabelle Mouyna</i>
MAP kinase signalling pathways in the human-pathogenic fungus <i>Aspergillus fumigatus</i>	<i>Vito Valiante</i>
GliT, a component of the gliotoxin biosynthetic cluster, protects <i>Aspergillus fumigatus</i> against exogenous gliotoxin	<i>Markus Shrettl</i>
Recent insights into the sexual cycle of <i>A. fumigatus</i>	<i>Edyta Szewczyk</i>
Cell wall of <i>Aspergillus fumigatus</i>	<i>Vishukumar Aimananda</i>
Steering Committee meeting	<i>Nathalie Spielesoy (ESF) and Steering Committee members</i>
Biochemistry cont'd (chair: Elaine Bignell)	
<i>Aspergillus fumigatus</i> and Cystic Fibrosis: From clinical features to molecular approaches - Focus on antifungal therapies	<i>Emilie Fréalle</i>
Effects of a bacterial metabolite on function in yeast and filamentous fungi	<i>Danielle Troppens</i>
Identification of novel antifungal cell-wall disrupting compounds	<i>Gabriel Mircus</i>
Azole induced efflux pump expression in <i>Aspergillus fumigatus</i> biofilms	<i>Ranjith Rajendran</i>
System Biology in <i>Af</i> (chair: Jean-Paul Latgé)	
Status of the Transcriptome	<i>Jean-Marie François</i>
Status of the Proteome	<i>Olaf Kniemeyer</i>
Status of the Deletion programme	<i>Guilhem Janbon</i>
Day 2 : Friday October 8 th , 2010	
Cell Biology and Infection (chair: Axel Brakhage)	
Cellular dynamics in the fungal cell: from measuring to modelling	<i>Gero Steinberg, University of Exeter, UK</i>
Developing atomic force microscopy for Biology	<i>Etienne Dague</i>
Functional analysis of DPR proteins in <i>Af</i>	<i>Joanne Wong Sak Hoi</i>
An update on Systematic deletion of <i>A. fumigatus</i> gene clusters	<i>Laura Alcazar-Fuoli</i>
Cell Biology and Infection (chair: Hubertus Haas)	
Response of human dendritic cells to mycelial <i>Aspergillus fumigatus</i> catalase	<i>Michael Ok</i>
NET	<i>Axel Brakhage</i>
Monitoring of experimental <i>Aspergillus fumigatus</i> infection through detection of fungal nucleic acids	<i>Oliver Morton</i>
A new experimental model designed to evaluate the antifungal effect of UVC radiation against some strains of <i>Aspergillus fumigatus</i>	<i>Luminita-Iuliana Ailincai</i>
Pathosystematic analysis of aspergillosis caused by genetically intact, and LaeA methylase-deficient, clinical isolates.	<i>Charlie Cairns</i>
Final Discussion, next meeting,... chaired by the Steering Committee	<i>Steering committee members</i>

Twenty two talks were presented mainly by junior scientists (thirteen out of twenty three). A lot of time was kept for discussions that are essential for the success of such network and have been indeed scientifically very fruitful.

This Third Annual Meeting focused on Biochemistry and Cell Biology. Both of these fields are necessary to elucidate protein function, understand their role during host infection and identify novel antifungal targets. The most significant scientific presentations and discussions have been selected to be included in this report.

A. Scientific summary

The Third ESF FUMINOMICS Annual Meeting held in October 2010 was organized by Partner 1 and Chairman of the program at the Institut Pasteur, Paris, France. The meeting gathered young and senior scientists belonging to the 17 laboratories/Partners and allowed them to present their results, discuss together and exchange about their recent studies on *Aspergillus fumigatus*. This year, the presentations and discussions were focused on Biochemistry and Cell Biology. Both disciplines are necessary to elucidate proteins function, understand their role during host infection and identify and characterize novel antifungal targets. The first day was focused on the recent biochemical data about *Aspergillus fumigatus* multi-proteic processes essential for fungal growth: O-Mannosyltransferases as new putative targets for antifungal compounds, MAP kinase signalling pathways, gliotoxin cluster, proteins associated to the sexual cycle of *Aspergillus fumigatus*. During the second day, recent tools for cell biology and functional analysis were presented. Various imaging technologies and their application to monitor cell biology during infection by the pathogenic fungus were described. Development of new imaging technologies was also discussed. On Day 1, a one-hour discussion was scheduled with the Steering Committee members and Mrs Nathalie Spielwoy, ESF Science Officer.

B. Biochemistry

One of the aspects of this research networking program is to understand biochemically the assembly of vital core elements (polysaccharides, proteins, pigment) of the fungal activities of *Aspergillus fumigatus* and the mechanisms that lead to pathogenic status. In FUMINOMICS, biochemical studies were performed using various technical methods.

Partner 1 (Isabelle Mouyna, Vishukumar Aimanianda, Anne Beauvais) determined the composition of the cell wall of *Aspergillus fumigatus* differs in a strain defective in O-mannosyltransferase activity when it is treated or not with Caspofungin (increase in chitin content).

Partner 3 (Vito Valiente) used western blotting analysis to study the expression level of the MpkA MAP kinase as well as its phosphorylation state in strains mutated in three genes (*BKC1*, *MKK2*, *MPKA*) of the hypotonic shock signaling pathway and involved in the cell wall integrity. V. Valiente showed that these genes of the MAP kinase signaling pathway of *A. fumigatus* are essential for normal growth.

HPLC (high pressure liquid chromatography) detection of gliotoxin led Partner 13 (Markus Shrettl) to determine the level of gliotoxin production in a strain lacking GliT, a component of the gliotoxin biosynthetic clusters avoiding the fungal suicide by this toxin.

Finally, Partner 1 (Vishukumar Aimanianda) presented different sets of chemical treatments to efficiently isolate individual cell wall polysaccharides which may be further tested regarding their immunogenicity or tested as putative vaccines. Vishukumar Aimanianda presented also the method to extract cell wall proteins such as hydrophobins and melanin, a green pigment biosynthesized by the fungus.

Advances on the biochemical analysis of *A. fumigatus* will lead to the identification of new therapeutic targets to further develop new antifungal compounds.

Partners 5, 9, 11 and 15 focused on diverse antifungal therapies. From a national, multicenter prospective study on 300 cystic fibrosis patients, partner 11 (Emilie Fréalle) described an emergence of azole resistance in *Aspergillus fumigatus* during azole therapy, associated with change in virulence. Partner 15 (Ranjith Rajendran) also studied azole resistance in *A. fumigatus* biofilms. He described that azole treatment upregulates efflux pump activity. Danielle Troppens (Partner 5) detailed the effects of a bacterial metabolite, 2,4-diacetylphloroglucinol (DAPG), on cell function in yeast and filamentous fungi, especially mitochondria and proteins involved in Ca^{2+} import, as a potential new antifungal drug. Gabriel Mircus (Partner 9) presented an exhaustive work on novel antifungal cell wall disrupting compounds. From a first screening phase of 35,000 drug-like compounds (ChemDiv, 25 μM), he identified 3 novel compounds displaying cell wall damage, equivalent to an *Aspergillus nidulans* Protein Kinase C conditional mutant. The identification of cell-wall targets of these compounds has however still to be done and will be further investigated.

Discussions around the research themes showed that important advances in biochemistry of *A. fumigatus* required strong collaborations between partners. For instance collaborations between Partners 1 (Isabelle Mouyna, Vishukumar Aimanianda, Anne Beauvais), 3 (Olaf Kniemeyer, Dirk Wartenberg, Axel Brakhage) and 16 (Emilia Mellado) have provided an in-depth analysis of Pmt proteins necessary for protein O-mannosylation, an essential process to maintain cell wall integrity, cell morphology and cell stability in *Aspergillus fumigatus*. After completing the different deletions of *PMT* genes, Partner 1 performed most phenotype analysis (growth, conidiation, germination, morphology). Virulence was undertaken by Partner 16 and proteomics analysis by Partner 3.

C. Cell Biology and Infection

a. Cell biology imaging technologies

Gero Steinberg, an invited speaker at our Third Annual FUMINOMICS Meeting, described the up to date tools to study cellular dynamics in the fungal cell using *Ustilago maydis* as a pathogenic model fungus. Simple fungal organisms use similar core transport machineries as mammals (Figure 1) and can therefore serve as model systems to address fundamental questions concerning intracellular motility and the cytoskeleton. Focusing on the cellular role of cytoskeleton-based dynamics in *U. maydis*, Gero Steinberg and coworkers tagged the protein of interest with GFP, and could visualize signalling transport along the cytoskeleton. Using photo-activable GFPs, he could analyse bi-directional motility of early endosomes. After quantification of GFP signals and use of the rapid bleaching of GFP, he could mathematically model motor behaviour.

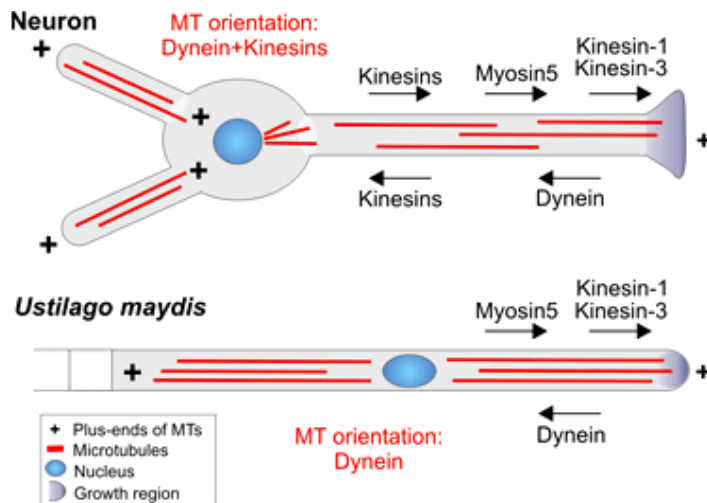


Figure 1: Comparison of the microtubule-based transport machinery in neurons and in *Ustilago maydis*. Note that neurons have many more kinesin motors being involved in microtubule organization and trafficking. Taken from [Steinberg and Perez-Martin (2008), Trends Cell Biol.]

In another presentation, Partner 2 (Etienne Dague) illustrated the potential of real-time atomic force microscopy (AFM) imaging and force spectroscopy for tracking cell-surface dynamics on alive fungi. For instance, in collaboration with Partner 1, Partner 2 could determine through AFM the structural and physicochemical dynamics of single *Aspergillus fumigatus* conidia during germination (Figure 2). Thus, nanoscale topographic images of dormant spores revealed the presence of a layer of rodlets made of hydrophobins. Within the 3-h germination period, progressive disruption of the rodlet layer was observed, revealing hydrophilic inner cell wall structures.

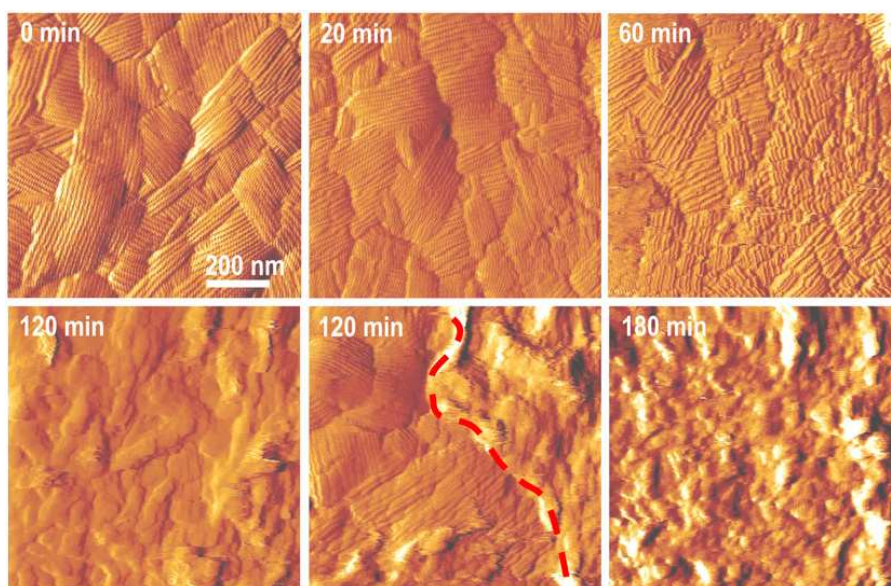


Figure 2: Structural dynamics of single germinating conidia. Series of high-resolution deflection images recorded on a single spore during germination. Within 3 h, the crystalline rodlets layer changes into a layer of amorphous material, presumably reflecting inner cell wall polysaccharides. After 2 h, both rodlets and amorphous regions were found to coexist (lower middle panel, left and right, respectively, of dashed line).

During her exchange visit (ESF grant) at Dr. Nick Read’s laboratory in Edinburgh, United Kingdom, Joanne Wong Sak-Hoi (Partner 1) could work further on the functional analysis of DPR proteins in *A. fumigatus*, especially by determining their subcellular localization using eGFP and DsRed tagging. These DPR proteins, a novel family of stress response proteins,

seem to be regulated by MAPK-, cAMP- and Pal-related pathways. Their peroxisomal localization led Partner 1 to identify impaired peroxisomal functions in the DPR mutants. The molecular mechanisms involved still need to be determined.

b. Cell biology imaging technologies during infection and infection itself

Additional talks presented applications of imaging technologies to monitor cell biology during infection by the pathogenic fungus.

Axel Brakhage (Partner 3) showed that human neutrophils produce, *in vitro*, neutrophil extracellular traps (NETs), consisting of nuclear DNA decorated with fungicidal proteins when encountering *A. fumigatus*. Time-lapse movies showed that NET production was a highly dynamic process which, however, was only exhibited by a sub-population of cells. NETosis was maximal against hyphae, but reduced against resting and swollen conidia (Figure 3).

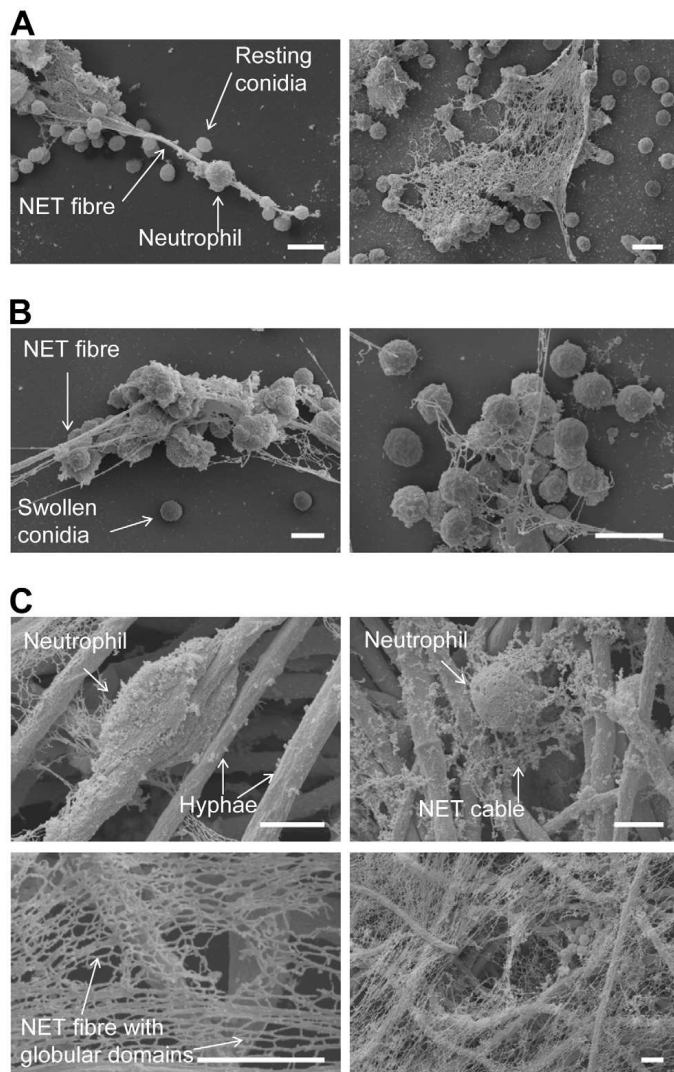


Figure 3: Scanning electron microscopy (SEM) micrographs of conidia and hyphae trapped in NETs. NET formation of human neutrophils after co-incubation with *A. fumigatus*. Microscopic pictures were taken after 3 hours. Neutrophils were co-incubated with resting conidia (A), swollen conidia (B) and hyphae (C). All scale bars represent 5 μm length.

A screening of recombinant *A. fumigatus* antigens, done by Michael Ok (Partner 7) revealed the mycelial catalase 1 as a potent immunogenic stimulator for human monocyte-derived and myeloid dendritic cells. Catalase 1 was shown to be uptaken and processed while cytokines were upregulated.

Having a closer look on infection itself, Partner 10 (Charlie Cairns) focused on a $\Delta laeA$ methyltransferase mutant strain lacking LaeA, a global regulator of secondary metabolite

biosynthesis. A comparative analysis of wild type and $\Delta laeA$ gene expression during infection revealed a wide up-regulation of mobile genetic elements during early neutropenic infection.

Partner 6 (Oliver Morton) monitored experimental *Aspergillus fumigatus* infection through detection of fungal DNA. He determined that *Aspergillus fumigatus* DNA can be detected in the sera and blood of infected animals by real time PCR after intranasal inoculation of the fungi to mice, but also in the brain (96%) and spinal cord (96%) after intracranial inoculation. Finally, Luminita-Iuliana Ailincăi described the effects of ultraviolet radiation on *A. fumigatus*. UV rays may have a fungicidal and fungistatic effect on the fungi but it depends on the distance and irradiation time, the best parameters being an irradiation time of at least one hour and a UV source over one meter high.

D. Omics in *A. fumigatus*

All these large biological state experiments have been only possible when a community is gathered together, that has been the main focus of this ESF grant.

a. Status of the transcriptome

Table 1 presents the transcriptome analysis steps which were optimized during the first two years of the ESF program. The best protocol is now established, based on RT-PCR results. Final validation will be performed through a comparison with RNAseq analysis of the RNA samples from Partner 1 and obtained during shaken and static growth culture conditions.

Step	Q	A	Comment
RNA samples	Quality	Yes	The best quality of RNAs was obtained after extraction using trizol and purification using the Qiagen kit (removal of ribosomal RNA).
	Amplification	No/Yes	Amplification of RNAs should not be used except if it is required (samples with very low concentration in <i>Af</i> such as biological tissues). The limit of RNAs detection has to be validated for indirect and direct labelling with either 500 ng or 5-15 μ g respectively.
Labelling	Direct		Primers: polyT and Random Method: Chip Shot labelling kit (Promega) at 38°C
Hybridization	Automatic	Yes	Hybridization is performed at 38°C; automatic hybridization was preferred to a manual technique to allow a standardization of the experiment.
	Formamide	20-50 %	60% formamide is recommended.
Image analysis	Bioplot software	Yes	Bioplot (Genepix) is the best software to analyse images. Spotfinder or Midas can also be used. One centre has to be defined to store all the images and associated analysis in the same database.

Table 1: Questions and Answer for the final validation of the *Af* Biochip from Toulouse

b. Proteome advancement

Proteome advancement has been summarized by O. Kniemeyer (Partner 3) and showed the new proteome methodologies implemented in Jena including data analysis that are available to all members of the consortium.

c. Status of the deletion program

The ESF project has also fostered the development of ambitious projects such as the undertaking of a mass gene disruption program as a unique European initiative (as discussed in the previous meeting in 2009). Program will be initiated in two institutions (University of Jena, Institut Pasteur) to show the feasibility of the program on 200 mutants, and then the deletion of all genes will be undertaken to have a fully comprehensive library of mutants. During this Third Annual FUMINOMICS Meeting, the methodology was presented by Guilhem Janbon (Partner 1). Four main steps have been highlighted: 1) Gene identification, 2) Construction of the bar coded markers, 3) Construction of the deletion cassettes, 4) Gene deletion *per se*. Similar disruption programs have been undertaken with a few fungi: it has been completed in *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe* and *Neurospora crassa* and partially done in *Candida albicans* and *Cryptococcus neoformans*. Preliminary meetings to discuss the most efficient strategy to construct the mutant library will be organized in Paris in November 2011. First meeting sponsored by ESF will gather Axel BRAKHAGE (University of Jena, P2), Guilhem JANBON and Jean-Paul LATGE (Institut Pasteur, P1) and Jay DUNLAP (Dartmouth Medical School), who has been responsible for the mass gene disruption in *Neurospora crassa* (an ascomycetous fungus, closed taxonomically to *A. fumigatus*). A second meeting which has not been fixed yet will allow discussing the practical follow up of the deletion program (strains, storage, optimization...) and will be sponsored by ESF. Several steps will be undertaken to reach this goal.

1. Gene identification

From now on, two genomes have been sequenced in *A. fumigatus*: AF293 (9630 genes) and A1163 (9929 genes). Moreover, the analysis of the genome has been mainly done through automatic annotation: no cDNA library has been sequenced although 77% of the identified genes have introns. The genome possesses a lot of small genes; there are a lot of *A. fumigatus* specific genes.

During the Meeting, several partners planned to use the RNAseq strategy for cDNA sequencing to re-annotate the genome of *Aspergillus fumigatus*.

2. Construction of the bar coded markers

As shown in Figure 4, the gene of interest will be deleted through homologous recombination of a bar coded marker cassette to a specific locus. This bar coded marker cassette consists in a GFP tag followed of the hygromycin marker gene and a bar code. This type of cassette will allow discovering additional information about the deleted genes by the visualization of gene expression thanks to GFP fluorescent marker and by a phenotypic analysis of transformants.

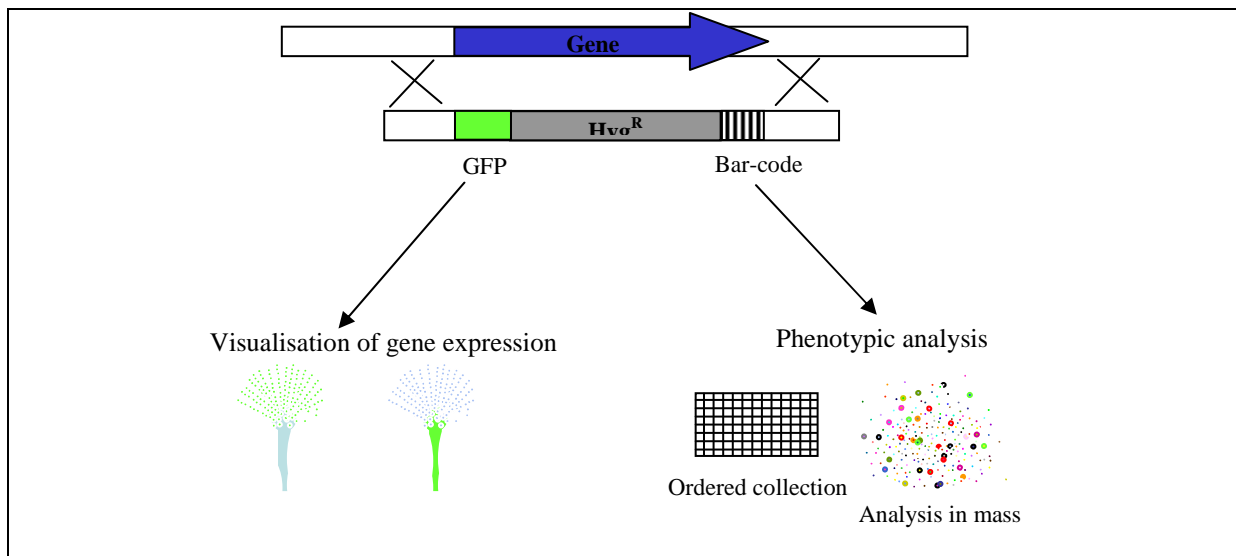


Figure 4: Bar coded markers construction

3. Deletion cassette construction

For construction of the deletion cassettes (Figure 5), 3-step PCR fusions will be performed, which shortens the cloning time. All 3 PCR fusion fragments as well as a plasmid will then be co-transformed into the yeast *S. cerevisiae* as developed for *Neurospora crassa*.

4. The deletion per se

For the deletion process itself into *Aspergillus fumigatus*, the final PCR cassettes amplified from plasmid DNA will be transformed by electroporation into the *ku80Δ* mutant strain (da Silva Ferreira *et al.* EC 2006) enabling to delete genes with probability of more than 50%.

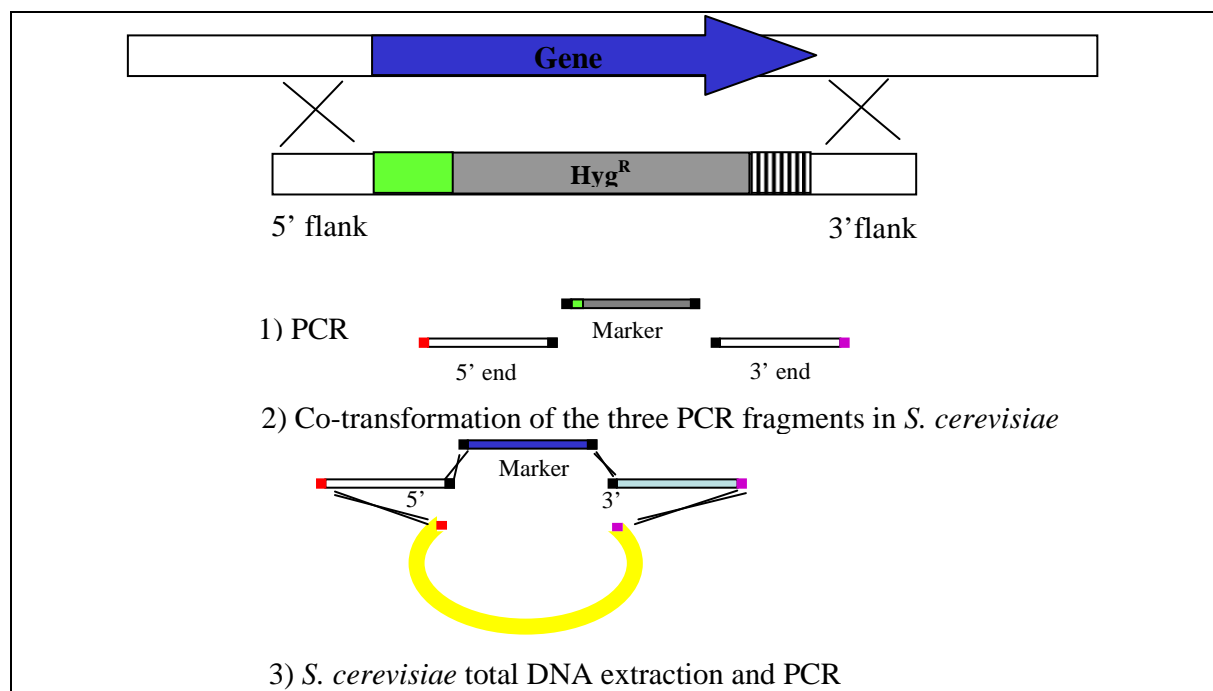


Figure 5: Construction and assembly of the deletion cassette in *S. cerevisiae* (Oldenburg *et al.*, NAR, 1997)

Conclusion: Impact of the event on future research directions in the study of *A. fumigatus*

Thanks to ESF, 17 European research groups have openly shared their experience in biochemistry and cell biology and infection fields. Like the two last years, this Third Annual Meeting offered the opportunity to junior scientists to present their research data. Collaborations at the EU level were strengthened at this meeting in a very friendly and cooperative atmosphere.

A major achievement of the meeting was the exchange of all data and protocols recently developed in the *A. fumigatus* biochemistry, cell biology and infection science. One of the major achievements of the past two years of the ESF-Fuminomics program is the validation of the *A. fumigatus* Biochip from Toulouse and the proteome from Jena. Thanks to ESF, short visit has been granted by the ESF for Véronique Le Berre (Partner 2, INSA Toulouse) in January 2009 at the Rockville J. Craig Venter Institute (William Nierman's lab). During the second year validation was completed and the protocol was agreed by all partners of FUMINOMICS. From now on Partners 2 and 3 can receive samples from members of the community to perform transcriptome and proteome analysis respectively. Results will be published further on a public website.

The strategy to undertake a mass gene disruption in *A. fumigatus* has been discussed this year and workshops have been planned. The deletion program should start in January 2011 with cDNA sequencing, genome re-annotation and a proof of concept of the deletion program on 200 genes. Most of the work will be initiated by Partner 1. Once the deletion strategy is in hands of Partner 1, the deletion program will be extended to the whole genome of *Aspergillus fumigatus* and will involve at a European level other partners of the Fuminomics program. The deletions *per se* will be done at two places: the *Aspergillus* unit of the Institut Pasteur in Paris, France (Partner 1) and the Department of Molecular and Applied Microbiology of the Hans-Knoell-Institute in Jena, Germany (Partner 3). The deletion program will be initiated with internal money and grants applications will be formatted to cover a budget roughly estimated around 1.5 million of Euros.

Review of the Mid-term report has been received in September 2010. Reports from both reviewers were extremely positive. Two minor criticisms were already partially corrected during the last meeting in Paris (7-8 Oct. 2010): it was recommended to all members to increase the number of exchanges and to increase outstanding scientist visits. This year an international expert on Cell Biology (theme of the last meeting) Gero Steinberg (Exeter) was invited and an international expert in mass gene disruption, Jay Dunlap, has been invited for the next meeting.

Next annual and final meeting will be held in October 2011. An « ESF day » on *A. fumigatus* to be sponsored by Fuminomics, will be organized close to the **5th Trends in Medical Mycology** conference in Valencia (Spain). It will be organized by Partner 1 and will group all topics examined these last three years in *Aspergillus fumigatus*.

Annexe:

- p.12, List of participants

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