



Pathogenomics and systems biology of fungal infections - an integrative approach

# Research Summaries

May 2011

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## IRYNA BOHOVYCH (UKRAINE)

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Professor A. Brown, University of Aberdeen, UK



### **A SWEET WAY TO BECOME STRONGER: AN EXAMPLE FROM HUMAN FUNGAL PATHOGEN *CANDIDA ALBICANS***

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There are more than 300,000 known species of fungi, but only a few of them can cause human infections. One of them, *Candida albicans*, is a relatively harmless organism, which can occupy the skin, oral cavity gastrointestinal tract and genitalia of healthy people. However, this fungus can take an advantage of immune system defects and cause a wide range of affections from mild superficial thrush to fatal systemic infections. There are lots of factors which make *C. albicans* so effective pathogen; among them are the ability to consume different nutrients (e.g. sugars) and to resist to different stresses.

When *C. albicans* cells enter the bloodstream, they are attacked by host cells, phagocytes, which cause oxidative stress to fungal cells. Also, in the human they are exposed to glucose in the bloodstream. Thus, we hypothesized that nutrients sensing might influence stress responses. Indeed, in laboratory environment *C. albicans* cell, exposed to glucose, became more resistant to different stresses. Also, it was less sensitive to killing by neutrophils, cells isolated from human donors, when glucose was added. Using different types of modified glucose we have been able to prove that *C. albicans* cells just need to sense glucose, not necessarily to consume it, in order to become more resistant to oxidative stress. *C. albicans*, like other yeasts, has 3 distinct mechanisms for glucose sensing, which form a complicated network. We are now investigating the role of major components of this network in the phenomenon of glucose-enhanced oxidative stress resistance.

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## ИРИНА БОГОВИЧ (UKRAINE)

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Professor A. Brown, University of Aberdeen, UK



### СЛАДКИЙ СПОСОБ СТАТЬ СИЛЬНЕЕ: ПРИМЕР ПАТОГЕНА ЧЕЛОВЕКА *CANDIDA ALBICANS*

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Среди 300 000 известных видов грибов только несколько способны вызывать заболевания человека. В их числе относительно безвредный организм *Candida albicans*, населяющий кожу, ротовую полость, желудочно-кишечный тракт и половые органы человека. В условиях дефектов иммунной системы этот грибок может вызывать целый ряд заболеваний человека, от легкой поверхностной молочницы и до летальных системных инфекций. *C. albicans* является настолько эффективным патогеном благодаря целому ряду факторов, среди которых способность употреблять разнообразные питательные вещества (например, сахара) и противостоять стрессам.

Когда *C. albicans* попадает в кровь, ее сразу же атакуют клетки хозяина, фагоциты, которые подвергают клетки грибка оксидативному стрессу. В то же время в организме человека этот микроорганизм сталкивается с глюкозой. Таким образом, у нас возникла гипотеза о влиянии сенсинга (опознания) питательных веществ на ответ на стресс. Действительно, в лабораторных условиях, клетки *C. albicans* после короткой инкубации с глюкозой ставали более резистентными к разным видам стресса. Также эти клетки были менее чувствительны к уничтожению нейтрофилами, изолированными со здоровых доноров. Используя разные типы модифицированной глюкозы, нам удалось доказать, что для клеток *C. albicans* необходимо всего лишь определить наличие глюкозы в среде для того, чтобы стать более резистентными к оксидативному стрессу. *C. albicans*, как и другие дрожжи, имеет 3 разных пути сенсинга глюкозы, объединенные в сложную сеть. Мы пытаемся изучить роль основных компонентов этой сети в феномене повышенной резистентности к оксидативному стрессу в ответ на наличие глюкозы.

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## ІРИНА БОГОВИЧ (UKRAINE)

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Professor A. Brown, University of Aberdeen, UK



### СОЛОДКИЙ СПОСІБ СТАТИ СИЛЬНІШИМ: ПРИКЛАД ПАТОГЕНА ЛЮДИНИ *CANDIDA ALBICANS*

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З-понад 300 000 відомих видів грибів лише кілька можуть викликати захворювання людини. Одним з них є *Candida albicans*, відносно безпечний організм, що може населяти шкіру, ротову порожнину, шлунково-кишковий тракт та статеві органи здорової людини. Однак за умов порушень роботи імунної системи цей грибок може викликати ряд захворювань, від легкої поверхневої молочниці і до фатальних системних інфекцій. *C. albicans* є настільки ефективним патогеном за рахунок цілої низки факторів, серед яких є здатність споживати різноманітні поживні речовини (наприклад, цукри) та протистояти стресам.

Коли *C. albicans* потрапляє в кров, то її одразу ж атакують клітини господаря, фагоцити, що спричинюють оксидативний стрес клітин грибка. В той же час в організмі людини цей мікроорганізм стикається з глюкозою. Таким чином, у нас виникла гіпотеза про вплив сенсингу (впізнання) поживних речовин на відповідь на стрес. Дійсно, в лабораторних умовах, клітини *C. albicans* після короткої інкубації з глюкозою ставали більш резистентними до різних видів стресу. Також ці ж клітини були менш чутливими до знищення нейтрофілами, ізольованими зі здорових донорів. З використанням різних типів модифікованої глюкози нам вдалося довести, що для клітин *C. albicans* необхідно лише виявити наявність глюкози в середовищі для того, щоб стати більш опірною до оксидативного стресу. *C. albicans*, як і інші дріжджі, має 3 окремі шляхи сенсингу глюкози, що об'єднані в складну сітку. Ми намагаємося з'ясувати роль основних компонентів цієї сітки у феномені підвищеної резистентності до оксидативного стресу у відповідь на наявність глюкози.

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## IULIANA ENE (ROMANIA)

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Professor Al Brown, University of Aberdeen, UK



### DYNAMIC ENVIRONMENTAL RESPONSES OF *C. ALBICANS* THAT CONTRIBUTE TO PATHOGENICITY

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*Candida albicans* is the most common fungal pathogen in humans, causing a variety of health problems ranging from mucosal to systemic infections. Generally harmless, it is present in 40-80% of the normal population, but in immunocompromised individuals it can proliferate and access different internal organs and tissues causing potentially fatal infections. *C. albicans* occupies a number of different niches in the human host. This is where the pathogen is exposed to a variety of nutrients, many of them different from more classical ones (e.g. glucose) which are the basis for most studies conducted so far. The shift from harmless commensal to opportunistic pathogen requires *C. albicans*' ability to grow in poor nutrient niches and survive the diversity of stresses it encounters in the host.

Many of these stresses, such as therapeutic drugs or osmotic stress act on the cell wall of the pathogen. This is the main interface between *C. albicans* and its host, a multi-layered interface which proves to be extremely flexible and dynamic when exposed to different nutrients. We are studying how the variety of nutrients found in the host modulate adaptation and stress responses and how the cell wall must quickly adjust under these conditions. In doing so it relies on mechanisms of constant remodelling and maintenance of cell wall integrity. More importantly we have found that certain nutrients and in particular poor nutrient niches in the host provide a fitness advantage to the pathogen. Having adapted to these niches, *C. albicans* also increases its resistance to a number of antifungals, which are currently the only available weapon against fungal infections.

In this study, we show how the nutrients taken up strongly influence the cell wall architecture and hence resistance of *C. albicans* to certain stresses. These findings are likely to have a major impact on the behaviour of this pathogen inside the human host and may be of major clinical importance.

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## **ABHISHEK SAXENA (INDIA)**

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*Professor Andy Porter, University of Aberdeen, UK*



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### **ANTIFUNGAL BIOLOGICS**

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Fungal diseases are one of the most common infectious problems associated with humans. People with immune dysfunctions or depressed immune status during clinical treatments often get these infections. For last two decades we have been using chemical drugs which lack target specificity and can induce cytotoxicity at various levels. New age modern drugs of Biological origin as monoclonal antibodies, antifungal peptides, vaccines could be better alternatives alone or in combination with existing chemotherapeutic regime. Monoclonal antibodies in particular are very exciting molecules in immune depressed state; they could be supplied passively in the form of injections as during fungal infection the innate antibodies fall with the rise of infections and are largely non protective. We are making better and more efficient experimental monoclonal antibodies against Candidiasis by Phage Display Technology. Antibodies are the most successful class of Biological drugs against number of dreadful diseases, but none of these molecules exists against microbes. We have standardized Ovine model for the generation of antibodies against fungal cell wall glycans and protein epitopes. Recently we have constructed one of the very first and largest scFv Phage Display Library against *Candida albicans* cell wall antigens. We are working on library screen now to develop specific binding motifs from that will have potent antifungal activity by itself.

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## VITOR CABRAL (PORTUGAL)

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*Dr. Ch. d'Enfert, Pasteur Institute, Paris, France*



### IDENTIFICATION OF NOVEL *CANDIDA ALBICANS* GENES INVOLVED IN BIOFILM FORMATION

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*Candida albicans* is a fungus that lives within the human body, usually without causing any health problems. Nevertheless, under certain conditions, mainly deficiencies of the immune system, it can turn into a major health issue. This is because its growth can become uncontrolled and reach the blood stream, causing a systemic infection that spreads throughout the entire body. In severe cases an infection by *Candida albicans* frequently results in the death of the patient. A feature of *Candida albicans* is the formation of a particular structure that is denominated biofilm, found in catheters used for treatment of patients. Since in this state *C. albicans* is more resistant to antifungals, the removal of the device is the only option to avoid greater problems to the patient's life. *C. albicans* biofilms include round (yeast) or long (hypha) shaped cells as well as a sugar matrix surrounding these cells. In order to increase our presently limited knowledge of *C. albicans* biofilms and to seek new and more efficient ways to avoid or fight them, my project aims at defining the genetic basis of this *C. albicans* life style, that is to identify the genes that *C. albicans* requires to build biofilms, and to understand how they're used. I intend to do so using a genetic tool created in my host laboratory and that consists of a collection of *C. albicans* overexpression strains. Using this tool I shall identify genes whose over-expression modifies the formation of biofilms or their organization. Through the characterization of these genes and their products, I hope to increase our understanding of biofilms, as well as that of biofilm-associated infections, giving us an advantage in the fight against these perilous situations.

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## VITOR CABRAL (PORTUGAL)

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*Dr. Ch. d'Enfert, Pasteur Institute, Paris, France*



### IDENTIFICAÇÃO DE NOVOS GENES DE *CANDIDA ALBICANS* ENVOLVIDOS NA FORMAÇÃO DE BIOFILMES

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*Candida albicans* é um fungo que vive no corpo humano, normalmente sem causar qualquer problema de saúde. No entanto, sob certas condições, principalmente relacionadas com o deficiências do sistema imunitário, pode tornar-se um sério risco para a saúde, porque o seu crescimento pode tornar-se descontrolado e chegar à corrente sanguínea, causando uma infecção sistémica que se espalha por todo o corpo. Em casos extremos uma infecção por *Candida albicans* pode, frequentemente, resultar na morte do paciente. Uma capacidade inerente a *Candida albicans* é a formação de uma estrutura particular denominada de biofilmes, que se encontra, entre outros locais, em catéteres usados para o tratamento de pacientes e, devido à resistência aos medicamentos disponíveis apresentada pelo organismo quando nesta forma, a remoção do catéter é a única opção para evitar maiores perigos para a vida do paciente. Nesta estrutura particular podemos encontrar ambas as formas redonda (levedura) e alongada (hifa) de *C. albicans*, isto porque este fungo tem a capacidade de alterar a sua forma, rodeadas por uma matriz de açúcares. De forma a aumentar o nosso actualmente limitado conhecimento sobre biofilmes de *C. albicans* e procurar novas e mais eficientes estratégias para o evitar ou combater, o meu projecto tem como objectivo definir a base genética deste tipo de estrutura, ou seja os genes que *C. albicans* precisa para formar biofilmes e e compreender como. A minha intenção passa por usar uma ferramenta genética criada no nosso laboratório e que consiste numa colecção de sobre-expressão de estirpes de *C. albicans*. Usando esta ferramenta tenciono identificar os genes cuja sobre-expressão modifica a formação de biofilmes ou a sua organização. Através da caracterização destes genes e dos seus produtos, espero aumentar o nosso conhecimento sobre biofilmes, assim como sobre infecções associadas a biofilmes, oferecendo-nos uma vantagem na luta contra estas perigosas situações.

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# PEDRO MIRAMÓN (MEXICO)

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Professor B. Hube, HKI, Jena, Germany



## UNDERSTANDING THE RESPONSE OF THE HUMAN PATHOGEN *CANDIDA ALBICANS* TO THE ATTACK BY IMMUNE CELLS

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*Candida albicans* is a fungus commonly associated with humans without causing any harm. The reason this fungus is usually harmless is because immune cells constantly patrol the sites in the body where the fungus lives; for example, the oral cavity or the gut. However, under certain circumstances, *C. albicans* is able to surpass the vigilance of the immune system, causing a variety of diseases ranging from superficial non-lethal manifestations to life-threatening deep-seated infections.

The purpose of this project is to understand how *C. albicans* is recognised and eliminated from the host. To this end, we are studying how the cells of the immune system fight against the pathogen. The key players involved in eliminating not only fungal, but pathogens in general, are phagocytes – specialised cells from the immune system which engulf and kill microorganisms. We know that *C. albicans* responds differently to the several kinds of cells found in blood. The cells that evoke the most dramatic response from the fungus are the so called neutrophils, cells of the immune system that play a major role in inflammation and the clearance of pathogens.

We aim to identify components of the fungal cell (proteins or enzymatic activities) that are involved in the response towards the attack by neutrophils, in order to better understand the response of the fungus and the strategies it uses to overcome and survive attack by neutrophils.

We have found that *C. albicans* responds in a different manner depending on whether it is inside or only touching the neutrophils. For instance, inside the neutrophils, we have observed that *C. albicans* produces proteins that neutralise potent oxidants that could kill the fungus. Some of these proteins are produced even before the fungus comes in contact with the neutrophil, preparing itself to encounter the oxidants and hence, survive. When the fungus is unable to produce these proteins, its survival is decreased in the presence of neutrophils. We have also observed that the fungus changes its metabolism to adapt to the nutrient-deficient environment inside the neutrophil.

Understanding the response of the fungus when confronted with phagocytes will allow us to identify the most important steps that lead to a proper response in order to contain the growth and dissemination of this opportunistic pathogen.

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# PEDRO MIRAMÓN (MEXICO)

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Professor B. Hube, HKI, Jena, Germany



## WIE DER HUMANPATHOGENE PILZ *CANDIDA ALBICANS* DIE ATTACKEN DES IMMUNSYSTEMS ÜBERSTEHT

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*Candida albicans* ist ein Hefepilz, der häufig als harmloser Besiedler der menschlichen Haut und Schleimhäute vorkommt und unter normalen Umständen keinerlei gesundheitliche Schäden verursacht. In der Mundhöhle oder im Darm verhindern die Zellen des menschlichen Immunsystems effektiv, dass der Pilz Schaden anrichtet. Unter bestimmten Bedingungen kann *C. albicans* aber der Kontrolle des Immunsystems entgehen und dann verschiedenste Erkrankungen hervorrufen. Diese reichen von oberflächlichen und vergleichsweise harmlosen Verlaufsformen bis hin zu lebensbedrohlichen, systemischen Infektionen, die den ganzen Körper und verschiedene Organe betreffen.

In diesem Projekt soll daher versucht werden, die Erkennung und die Bekämpfung von *C. albicans* durch den Wirt besser zu verstehen. Wir untersuchen dazu, welche Mechanismen die Zellen des Immunsystems entwickelt haben, um *C. albicans* zu kontrollieren. Besonders wichtig sind dabei die sogenannten Phagozyten, Fresszellen des angeborenen Immunsystems, die Mikroorganismen in sich aufnehmen und dann zerstören können. Sie sind auch die ersten Immunzellen, mit denen *C. albicans* (und auch andere Krankheitserreger) im Wirt in Kontakt kommen sobald der Pilz in Gewebe eindringt. Dabei reagiert *C. albicans* in unterschiedlicher Weise auf die einzelnen Zelltypen der Immunabwehr. Besonders die neutrophilen Granulozyten, die an Entzündungsprozessen und an der Beseitigung von Pathogenen beteiligt sind, führen zu einer deutlichen Antwort des Pilzes.

Wir wollen deshalb Bestandteile der Pilzzelle (insbesondere Proteine und aktive Enzyme) identifizieren, die an der Interaktion von *C. albicans* mit neutrophilen Granulozyten beteiligt sind. Das soll uns ermöglichen, die Reaktionen des Pilzes besser zu verstehen – und damit seine Strategien, den Kontakt mit Immunzellen zu überleben.

Wir konnten schon zeigen, dass *C. albicans* – je nachdem, ob sich der Pilz im Inneren der Neutrophilen befindet oder nur an deren Oberfläche – unterschiedlich reagiert. Beispielsweise haben wir beobachten können, dass *C. albicans* innerhalb der Immunzellen ein Protein bildet, das Oxidantien unschädlich macht, die sonst den Pilz abtöten können. Einige dieser Proteine werden vom Pilz sogar schon gebildet, bevor er überhaupt mit Neutrophilen in Kontakt kommt. So kann er sich vor oxidativem Stress schützen und sein Überleben sichern. Ohne diese Proteine überleben deutlich weniger *C. albicans*-Zellen den Kontakt mit neutrophilen Granulozyten. Außerdem haben wir beobachten können, dass *C. albicans* seinen Stoffwechsel an die nährstoffarme Umgebung innerhalb der Neutrophilen anpassen kann.

In Zukunft wollen wir so die Reaktion von *C. albicans* auf Immunzellen besser verstehen und dadurch diejenigen Mechanismen identifizieren, die das Wachstum und die Ausbreitung des Pilzes im Körper ermöglichen.

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## PEDRO MIRAMÓN (MEXICO)

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Professor B. Hube, HKI, Jena, Germany



### ENTENDIENDO LA RESPUESTA DEL PATÓGENO HUMANO *CANDIDA ALBICANS* AL ATAQUE DE CÉLULAS DEL SISTEMA INMUNE.

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*Candida albicans* es un hongo comúnmente asociado a los humanos sin causar daño alguno. La razón por la cual este hongo es generalmente inofensivo es porque las células del sistema inmune vigilan constantemente los sitios del cuerpo donde el hongo vive, por ejemplo, la cavidad oral o el intestino. Sin embargo, bajo ciertas circunstancias, *C. albicans* es capaz de evadir la vigilancia del sistema inmune, provocando una variedad de enfermedades que van desde manifestaciones superficiales no letales hasta infecciones profundas que ponen en riesgo la vida.

El objetivo de este proyecto es entender cómo *C. albicans* es reconocida y eliminada del huésped. Para este fin estamos estudiando cómo las células del sistema inmune luchan contra el patógeno. Los principales actores involucrados en la eliminación de patógenos en general, no solo hongos, son los fagocitos – células especializadas del sistema inmune, encargadas de atrapar y matar microorganismos. Sabemos que *C. albicans* responde diferencialmente a los distintos tipos de células que se encuentran en la sangre. El tipo de células que induce la respuesta más dramática por parte del hongo son los llamados neutrófilos, células del sistema inmune que juegan un papel muy importante durante procesos inflamatorios y durante la eliminación de patógenos.

Nuestro objetivo es identificar componentes del hongo (proteínas o actividades enzimáticas) involucrados en la respuesta hacia el ataque de los neutrófilos para comprender mejor esta respuesta, así como las estrategias empleadas para superar y sobrevivir al ataque de los neutrófilos.

Hemos encontrado que *C. albicans* responde de formas distintas dependiendo de si se encuentra dentro o sólo en contacto con los neutrófilos. Por ejemplo, dentro de los neutrófilos, hemos observado que *C. albicans* produce proteínas que neutralizan potentes oxidantes capaces de matar al hongo. Algunas de estas proteínas son producidas incluso antes de que el hongo entre en contacto con el neutrófilo, preparándose para encontrarse con oxidantes y, de esta manera, sobrevivir. Cuando el hongo es incapaz de producir estas proteínas, su sobrevivencia está disminuida en presencia de los neutrófilos. Hemos observado también que el hongo cambia su metabolismo para adaptarse a las condiciones deficientes en nutrientes dentro del neutrófilo.

Al comprender la respuesta del hongo cuando se enfrenta a los fagocitos, podremos identificar los eventos clave que llevan a una respuesta correcta para contener el crecimiento y la diseminación de este patógeno oportunista.

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## QUENTIN LAGADEC (FRANCE)

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Professor Joachim Ernst, University of Dusseldorf, Germany



### **CANDIDA ALBICANS FILAMENTATION REGULATION: THE MAJOR CROSSROAD, EFG1**

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With the raising number of immunodeficient patients due to HIV, transplantation or major surgery, some pathogens like the fungus *Candida albicans* (fourth most isolated pathogen in nosocomial infections) have increased in importance. *C. albicans* is an opportunistic pathogen, meaning that a large part of the population with normal immune systems is carrying it with few or no symptoms. A good understanding of the virulence mechanisms could help treating the potentially deadly cases of *Candida* infections. One of the essential virulence factors is the ability of *C. albicans* to switch between unicellular form (yeast form) and filamentous form (hyphal growth). We are trying to understand the regulation mechanism underlying this transition. Some factors can induce hyphal formation (serum ...). We are interested in the signal cascade following those signals especially in Efg1, a key regulator of the yeast to hyphae transition. Efg1 is a transcription factor: a protein influencing the expression of genes.

Efg1 is a central regulator of the yeast to hyphae transition; therefore it is regulating a lot of other genes. To get a better understanding of Efg1 action on those genes, we tried to reconstitute the regulation system in *S. cerevisiae*. We managed to reconstitute the action of Efg1 on its own gene and on another gene (*YWP1*). In an attempt to understand Efg1 role, we are working at the same time on three other projects:

Firstly, we are modifying Efg1 protein. The modification mimics activation of Efg1 by the signalling cascade following a signal inducing hyphal growth. We want to observe the influence of these modifications on Efg1 self-regulation.

Secondly, it has been observed in previous studies that one of the main targets of Efg1 was *TCC1* gene - a gene repressing hyphal growth. We want to measure the influence of Efg1 presence on *TCC1* expression level. We use a reporter indicating the expression of *TCC1*. We then measure the expression level of *TCC1* with or without Efg1 (using a mutant strain of *C. albicans* lacking *EFG1*) to observe Efg1 influence.

The last project is involving luminescent proteins - proteins that produce light in the presence of a specific chemical. We have created a chimaera protein by fusing Efg1 with a red luminescent protein. This will allow us to follow Efg1 expression over time. To be able to measure simultaneously the expression of another gene, we are introducing in *C. albicans* a new green luminescent protein.

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## QUENTIN LAGADEC (FRANCE)

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Professor Joachim Ernst, University of Duesseldorf, Germany



### LA FILAMENTATION DE *CANDIDA ALBICANS*: EFG1, UN CARREFOUR MAJEUR

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Le nombre croissant de patients immunodéficients dûs au virus du SIDA, aux greffes ou aux interventions chirurgicales lourdes induit une importance accrue de certains organismes pathogènes comme le champignon *Candida albicans* (quatrième organisme le plus isolé dans les cas d'infections nosocomiales). *C. albicans* est un pathogène opportuniste c'est-à-dire qu'une grande partie de la population ayant un système immunitaire fonctionnel est porteuse avec peu ou pas de symptômes. Une bonne compréhension des mécanismes de virulence pourrait aider au traitement des infections par *C. albicans* souvent mortelles. Un des facteurs de virulence fondamentaux est la capacité de *C. albicans* à passer d'une forme levure, unicellulaire à une forme filamenteuse pluricellulaire (hyphes). Nous essayons de comprendre les mécanismes de régulation permettant cette transition. Certains facteurs environnementaux peuvent induire la filamentation (présence de sérum...). Nous nous intéressons à la voie de signalisation activée par ces signaux, notamment à Efg1, un régulateur clef de la transition levure/hyphe. Efg1 est un facteur de régulation, c'est-à-dire une protéine influençant l'expression d'autres gènes.

Efg1 est un régulateur clef pour l'induction de la filamentation, il régule donc logiquement de nombreux autres gènes. Pour mieux comprendre l'action de Efg1, nous avons essayé de reconstituer la régulation induite par Efg1 sur l'expression d'autres gènes dans l'organisme modèle *S. cerevisiae*. Nous sommes parvenus à démontrer l'action de Efg1 sur son propre gène et sur un autre gène (*YWP1*). Pour essayer de mieux comprendre le rôle de Efg1, nous travaillons également sur trois autres projets.

Premièrement, nous modifions la protéine Efg1 pour imiter son activation par la cascade de signalisation. Nous voulons observer l'influence de ces modifications sur l'auto régulation de Efg1.

Deuxièmement, il a été observé dans de précédentes études qu'une des principales cibles de Efg1 était le gène *TCC1*, un gène réprimant la croissance filamenteuse. Nous voulons évaluer l'influence de la présence de Efg1 sur le niveau d'expression du gène *TCC1*. Nous disposons d'un marqueur de l'activité du gène *TCC1* et nous allons en mesurer le niveau d'expression avec ou sans Efg1, en utilisant une souche mutante de *C. albicans* dépourvue de Efg1.

Le dernier projet concerne des protéines luminescentes, ces protéines produisent de la lumière lorsqu'elles sont mises au contact d'un réactif particulier. Nous avons créé une protéine chimère consistant en la fusion de Efg1 et d'une protéine luminescente rouge. Cette protéine chimère devrait nous permettre de suivre le niveau d'expression de Efg1 au cours du temps. Nous sommes également en train d'introduire dans *C. albicans* une protéine luminescente verte qui devrait nous permettre de suivre de manière simultanée le niveau d'expression d'un autre gène.

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# IAROSLAVA KOS (UKRAINE)

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Dr M. Lavie-Richard, INRA, France



## **CANDIDA ALBICANS CELL WALL PROTEINS AND THEIR ROLE IN THE COLONIZATION OF HUMAN HOST**

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Serious fungal infections identified at the hospital have increased considerably since the 80s; they have become a major concern for health care facilities given the relatively poor means of diagnosis and treatment accessible to practitioners. It has been shown that *Candida albicans* is the first fungal pathogen of humans, and that this yeast, usually commensal, can cause deep infections that can be life threatening. The incidence of candidiasis continues to rise with the increasing number of patients at risk (immuno-compromised). The virulence of *C. albicans* is due to its ability to invade and colonize many tissues of the body corresponding to very different microenvironments. Currently in the lab we try to answer several key questions to enhance our means against this pathogen: how one organism present in low concentrations can so effectively colonize and persist in the host? What are the molecular mechanisms developed to adhere to the different substrates encountered (plastic, human cell)? Are there surface proteins involved in these mechanisms?

To answer these questions we have specifically targeted a class of proteins: proteins attached to the cell surface by a molecule called GPI anchor, this molecule is the link between the protein and the cell wall covering the surface of the pathogen. Indeed, we hypothesized that these surface proteins at the interface with the outside world could play a role in all these mechanisms of interaction and adhesion, helping *C. albicans* to invade and colonize its host. We describe in this yeast more than 100 proteins displayed on the surface by this GPI anchor. Our initial strategy was to create a collection of 105 strains of this organism with mutants for each of these 105 genes encoding different GPI-anchored proteins. We then studied the consequences of the absence of each gene during the interaction of each mutant with the host or during development of *C. albicans* to identify genes essential for these mechanisms. Now that we have selected these few genes we try to understand what are their specific roles in these phenomena and hopefully we will be able to describe the nature of the mechanisms involved and their relationship to the virulence of this fungus. For instance, we are currently particularly interested in studying a protein that seems to possess a function of adhesion and thus participate in the colonization of *C. albicans*.

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# IAROSLAVA KOS (UKRAINE)

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Dr M. Lavie-Richard, INRA, France



## LES PROTEINES DE PAROI DE *CANDIDA ALBICANS* ET LEUR ROLE DANS LA COLONISATION DE LEUR HOTE L'HOMME.

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Les infections fongiques graves identifiées à l'hôpital ont considérablement augmenté depuis les années 80, elles sont devenues aujourd'hui une préoccupation importante pour les établissements de soin étant donnés les moyens relativement pauvres de diagnostic et de traitement accessibles aux praticiens. Or *Candida albicans* est le premier pathogène fongique de l'homme. Cette levure, habituellement commensale, peut être à l'origine d'infections profondes mettant en jeu le pronostic vital. L'incidence des candidoses profondes ne cesse d'augmenter parallèlement à l'augmentation du nombre de patients à risque. La virulence de *C. albicans* s'explique par sa capacité à coloniser puis envahir de nombreux tissus de l'organisme qui constituent autant de microenvironnements différents. Actuellement au laboratoire nous essayons de répondre à plusieurs questions essentielles pour améliorer notre lutte contre ce pathogène : comment un organisme présent en faible concentration peut-il si efficacement coloniser et persister dans l'hôte ? Quels mécanismes moléculaires a-t-il mis en place pour adhérer aux différents substrats rencontrés (plastique, cellule humaine) ? Y-a-t-il des protéines de surface impliquées dans ces mécanismes ?

Pour répondre à ces questions nous avons ciblés spécifiquement une classe de protéines : les protéines attachées à la surface cellulaire par une molécule appelée ancre GPI, cette molécule fait le lien entre la protéine et la paroi recouvrant la surface de ce organisme pathogène, *C. albicans*. En effet nous avons émis l'hypothèse que ces protéines de surface à l'interface avec l'extérieur pourraient jouer un rôle dans tous ces mécanismes d'interactions, d'adhésion permettant à *C. albicans* de coloniser puis d'envahir son hôte. Cette levure posséderait plus de 100 protéines présentées à la surface par cette ancre. Notre stratégie de départ a été de créer une collection de 105 souches de ce micro-organisme comportant les mutants pour chacune de ces 105 gènes codant des protéines à ancre GPI différentes. Nous avons ensuite étudié les conséquences de l'absence de ces gènes lors de l'interaction avec l'hôte ou lors du développement de *C. albicans* afin d'identifier des gènes essentiels à ces mécanismes. Maintenant que nous avons sélectionné ces quelques gènes nous essayons de comprendre quel est leur rôle spécifique dans ces phénomènes et nous espérons pouvoir décrire la nature du mécanisme impliqué et son lien avec la virulence de ce pathogène. Nous sommes par exemple actuellement particulièrement intéressé par l'étude d'une protéine qui semble posséder une fonction d'adhésine et qui participerait donc à la colonisation de *C. albicans*.

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# IAROSLAVA KOS (UKRAINE)

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Dr M. Lavie-Richard, INRA, France



## РОЛЬ БІЛКІВ КЛІТИННОЇ СТІНКИ *CANDIDA ALBICANS* У КОЛОНІЗАЦІЇ ЛЮДСЬКОГО ОРГАНІЗМУ

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В останні десятиліття спостерігається значне зростання випадків діагностування небезпечних грибкових інфекцій. Ця тенденція викликає серйозну заклопотаність у зв'язку з вельми обмеженими можливостями діагностики та лікування.

Першість серед збудників грибкових захворювань належить *Candida albicans*. Ці дріжджі можуть вести коменсальний спосіб життя, але в певних умовах також викликають небезпечні системні захворювання. Частота кандидозів зростає з одночасним збільшенням випадків розладів імунної системи. Вірулентність *C. albicans* обумовлена здатністю вторгуватися і колонізувати різноманітні тканини людини, адаптуючись до найрізноманітніших умов мікросередовища. У нашій лабораторії ми намагаємося знайти відповіді на кілька ключових питань для озброєння знаннями проти цього патогена: як організм в таких малих кількостях здатний настільки ефективно колонізувати і перебувати в тканинах господаря? Які молекулярні механізми використовуються для адгезії до різних субстратів (пластик, клітини людини)? Чи беруть у цих процесах участь поверхневі білки?

Щоб відповісти на ці питання, ми обрали своєю мішенню специфічний клас білків: молекули поверхні клітини, так звані GPI-якорі, що є зв'язковими ланками між білками і клітинною стінкою, що вкриває поверхню патогена. Ми припустили, що ці поверхневі білки інтерфази із зовнішнім світом можуть відігравати важливу роль у механізмах взаємодії та адгезії, сприяючи колонізації *C. albicans*. Нами було описано більше 100 білків, що виводяться на поверхню за допомогою GPI-якоря. Наша початкова стратегія передбачала створення колекції з 105 штамів цього організму з мутаціями в кожному з 105 генів, що кодують різні GPI-якірні білки. Далі ми вивчили наслідки відсутності кожного з цих генів для взаємодії мутантів з хазяїном або ж протягом розвитку *C. albicans* для ідентифікації обов'язкових для цих механізмів генів. На даний час ми намагаємося зрозуміти специфічну роль кількох відібраних генів в цьому феномені, сподіваючись, що незабаром ми зможемо пояснити природу залучених механізмів, а також їхнє відношення до вірулентності цього грибка. Наприклад, ми особливо зацікавлені у білку, який, можливо, є адгезином, і таким чином приймає участь в колонізації *C. albicans*.

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# IAROSLAVA KOS (UKRAINE)

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Dr M. Lavie-Richard, INRA, France



## РОЛЬ БЕЛКОВ КЛЕТОЧНОЙ ОБОЛОЧКИ *CANDIDA ALBICANS* В КОЛОНИЗАЦИИ ЧЕЛОВЕЧЕСКОГО ОРГАНИЗМА

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В последние десятилетия наблюдается значительное возрастание случаев диагностирования опасных грибковых инфекций. Эта тенденция вызывает серьезную озабоченность в связи с весьма ограниченными возможностями диагностики и лечения.

Первенство среди возбудителей грибковых заболеваний принадлежит *Candida albicans*. Эти дрожжи могут вести комменсальный образ жизни, но в определенных условиях также вызывают опасные системные заболевания. Частота кандидозов возрастает с одновременным увеличением случаев расстройств иммунной системы. Вирулентность *C. albicans* обусловлена способностью вторгаться и колонизировать разнообразные ткани человека, адаптируясь к самым разным условиям микросреды. В нашей лаборатории мы пытаемся найти ответы на несколько ключевых вопросов для вооружения знаниями против этого патогена: как организм в столь малых количествах способен настолько эффективно колонизировать и пребывать в тканях хозяина? Какие молекулярные механизмы используются для адгезии к разным субстратам (пластик, клетки человека)? Берут ли в этих процессах участие поверхностные белки?

Чтобы ответить на эти вопросы, мы избрали своей мишенью специфический класс белков: молекулы поверхности клетки, так называемые GPI-якори, являющиеся связным звеном между белком и клеточной стенкой, покрывающей поверхность патогена. Мы предположили, что эти поверхностные белки интерфейсы с внешним миром могут играть важную роль в механизмах взаимодействия и адгезии, способствуя колонизации *C. albicans*. Нами было описано более 100 белков, выводимых на поверхность с помощью GPI-якоря. Наша начальная стратегия предполагала создание коллекции из 105 штаммов этого организма с мутациями в каждом из этих 105 генов, кодирующих разные GPI-якорные белки. Далее мы изучили последствия отсутствия каждого из этих генов для взаимодействия мутантов с хозяином или же на протяжении развития *C. albicans* для идентификации генов, обязательных для этих механизмов. В данное время мы пытаемся понять специфическую роль нескольких отобранных генов в этом феномене, надеясь, что в скором времени мы сможем объяснить природу вовлеченных механизмов, а также их отношение к вирулентности этого грибка. Например, мы в особенности заинтересованы в белке, который возможно является адгезином и таким образом принимает участие в колонизации *C. albicans*.

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## ALICE SORGO (AUSTRIA)

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Dr. Frans Klis, University of Amsterdam, The Netherlands



### DYNAMICS OF CELL WALL AND SECRETED PROTEINS OF THE PATHOGENIC FUNGUS *CANDIDA ALBICANS* IN RESPONSE TO CLINICALLY RELEVANT STRESS CONDITIONS

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The fungus *Candida albicans* is living in the majority of the human population usually without having any effect on their health. Sometimes it causes relatively mild superficial infections. Nevertheless, when the host's immune system is severely weakened, *C. albicans* can gain access to the bloodstream and spread throughout the whole body. If not detected and properly treated in time a bloodstream infection is able to rapidly kill the patient. Conventional methods for diagnosis take two days, making faster diagnostics necessary. New resistances emerge against the already existing antifungal drugs resistances, hence new antifungal treatments are needed.

The wall proteins and secreted proteins of *C. albicans* are very dynamic under changing environmental conditions. These proteins play an important role for *C. albicans* fitness and virulence. They serve fundamental roles, like tissue adhesion and invasion, biofilm formation, nutrient acquisition and defense against the host's immune system. In the human host *C. albicans* has to cope with a variety of challenges. It grows in sites where oxygen levels are high, like on the skin, as well in niches where very low oxygen levels are found, such as in the gut. *C. albicans* is able to acquire iron, which is rarely found in a freely available form in the human body but is essential for its survival. It also adapted to survive in the presence of antifungal drugs and at high temperatures, like during fever.

We are investigating how the cell wall and secreted proteins of *C. albicans* contribute to the fungus' survival and virulence under these medically relevant stress conditions. We are applying mass spectrometry to measure qualitative as well as quantitative changes of these proteins that might help *C. albicans* adapting to these conditions. Our research will improve the understanding of how *C. albicans* copes with various infection-associated stress conditions as well as how cell wall and secreted protein levels are controlled. Importantly it might lead to the identification of new potential targets for vaccine development and diagnostic markers.

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## ALICE SORGO (AUSTRIA)

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Dr. Frans Klis, University of Amsterdam, The Netherlands



### **DYNAMIK DER ZELLWANDPROTEINE UND SEKRETIERTEN PROTEINE DES PATHOGENEN PILZES *CANDIDA ALBICANS* ALS ANTWORT AUF KLINISCH RELEVANTE STRESSBEDINGUNGEN.**

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*Candida albicans* ist ein Pilz der in den meisten Menschen lebt ohne Einfluss auf deren Gesundheit zu haben. Manchmal kann er jedoch eine oberflächliche Infektion der Schleimhäute verursachen. Bei Patienten deren Immunsystem ernsthaft geschwächt ist kann *C. albicans* bis in die Blutbahn vordringen und sich im ganzen Körper ausbreiten. Wenn eine solche Infektion nicht rasch diagnostiziert und richtig behandelt wird endet das in den meisten Fällen tödlich für den Patienten. Herkömmliche Diagnosen nehmen zwei Tage in Anspruch, was die Entwicklung schnellerer Methoden notwendig macht. Gegen die kommerziell verfügbaren Antimykotika entwickeln sich immer mehr resistente Pilzstämme, somit ist es notwendig ständig nach neuen Antimykotika and Behandlungsarten zu suchen.

Die Zusammensetzung der Zellwandproteine und sekretierten Proteine ändert sich je nach der Umgebung in der *C. albicans* sich befindet. Außerdem sind diese Proteine unverzichtbar für Fitness und Virulenz des Pilzes. Sie dienen grundlegenden Funktionen, wie etwa der Anhaftung und Einwanderung in das Gewebe, der Bildung von Biofilmen, der Aufnahme von Nährstoffen und der Verteidigung gegen das Immunsystem des Wirtes. Das Leben in einem Wirt bringt viele Herausforderungen mit sich. *C. albicans* wächst an sauerstoffreichen Orten, wie etwa der Haut, aber auch an Orten an denen Sauerstoffarmut vorherrscht, wie etwa im Darm. *C. albicans* ist außerdem in der Lage das für das Überleben notwendige Eisen zu erlangen, obwohl dieses im Wirt kaum frei zugänglich ist. Der Pilz hat sich so weit angepasst, dass es ihm sogar möglich ist in der Gegenwart von Antimykotika und hohen Temperaturen, wie zum Beispiel während eines Fiebers, zu überleben.

Wir erforschen wie Zellwandproteine und sekretierte Proteine dem Überleben und der Virulenz dieses Pathogens während medizinisch relevanter Stressbedingungen dienen. Mittels Massenspektrometrie messen wir qualitative und quantitative Veränderungen in der Zusammensetzung dieser Proteine, welche dem Pilz bei der Anpassung an diese Bedingungen hilft. Unsere Forschung wird das generelle Verständnis darüber verbessern wie *C. albicans* verschiedene Stressbedingungen bewältigt und wie Zellwandproteine und sekretierte Proteine kontrolliert werden. Schlussendlich könnten neue Angriffspunkte für die Impfstoffentwicklung und Diagnose von Candida Infektionen ermittelt werden.

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## CLEMENS HEILMANN (GERMANY)

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*Dr. Frans Klis, University of Amsterdam, The Netherlands*



### DEVELOPMENT OF CWP-BASED VACCINES AGAINST CANDIDIASIS AND DETECTION OF DIAGNOSTIC MARKERS

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Patients with a weakened immune system and especially in intensive care units are increasingly contracting fungal infections. These infections are often life-threatening. *Candida albicans* is the most common of these infectious fungi. Depending on how suppressed the immune response is, this can lead to unpleasant infections of the skin and mucosa, but also invasive, blood stream infections. Usually, almost half of these infections are fatal within a week, highlighting the need for faster diagnostics and better preventative measures, i.e. a vaccine.

The first contact with the host cell is established by proteins on the wall of the fungus. They have been shown to play a crucial role in both infections and resistance to the immune system. We are particularly interested in this layer of proteins that is directly attached to the cell wall of the fungus or is released into the environment. Environment specific changes are important for *C. albicans* to thrive in different niches in the host during an infection. We also are interested in how the predominant growth form change in *C. albicans*, from spheric yeast cells to elongated hyphal cells, affect the proteins on the wall.

The goals of my project are three fold. Firstly, we want to increase the basic understanding of these attached wall proteins and the secreted proteins and how their composition and abundance changes in infection related conditions. To this end, we want to quantify the wall proteins using mass spectrometry. Secondly, we want to develop methods that allow faster diagnostics based on these secreted proteins that are abundant in many growth conditions. Thirdly, we want to identify targets for the development of a vaccine against *C. albicans*. To identify parts of the proteins that are suitable for vaccine development, we will use prediction algorithms to assess their ability to elicit an immune response. Using these results we will assemble and test a vaccine protein that is comprised of the most immune-stimulating peptides of these proteins.

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# CLEMENS HEILMANN (GERMANY)

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Dr. Frans Klis, University of Amsterdam, The Netherlands



## ZELLWANDPROTEINE ALS ZIELE FÜR NEUE DIAGNOSE- UND THERAPIEANSÄTZE GEGEN SYSTEMISCHE PILZINFEKTIONEN DURCH *CANDIDA ALBICANS*

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Patienten mit geschwächtem Immunsystem und speziell auf Intensivstationen erkranken immer häufiger an Pilzinfektionen. Diese Infektionen sind oft lebensbedrohlich. *Candida albicans* ist der am häufigsten vorkommende Erreger von Pilzkrankungen. Abhängig vom Immunstatus der Patienten können unangenehme, aber relativ harmlose Infektionen der Haut und Schleimhäute, aber auch zu invasive, lebensbedrohliche Blutbahninfektionen auftreten. Üblicherweise verlaufen fast die Hälfte aller Blutstrominfektionen bei nicht rechtzeitiger Behandlung innerhalb einer Woche tödlich. Diese Tatsache unterstreicht die Notwendigkeit zur Entwicklung neuer und schnellerer Diagnoseverfahren und besseren Präventionsstrategien, zum Beispiel durch die Entwicklung eines Impfstoffes.

Der Erstkontakt zur Wirtszelle wird durch Proteine auf der Zellwand des Pilzes etabliert. Es wurde bereits gezeigt dass, diese Proteine eine essentielle Rolle beim Widerstand von *C. albicans* gegen das Immunsystem und bei Infektionen spielen. Unserer besonderes Interesse gilt hierbei jenen Proteinen, welche direkt an die Zellwand gebunden sind oder in die Umgebung abgegeben werden. Umgebungsbedingte Veränderungen dieser Proteine sind wichtig für *C. albicans* um in den verschiedensten Nischen des Wirts während einer Infektion zu florieren. Weiterhin sind wir daran interessiert, wie die wichtigste Veränderung in der Wuchsform, von runden Hefezellen zu verlängerten Hyphen, die Proteine der Zellwand beeinflusst.

Es gibt drei Hauptziele meines Projekts. Erstens, wollen wir die gebundenen Zellwandproteine und die sekretierten Proteine sowie Änderungen in ihrer Zusammensetzung und Menge unter Infektionsbedingungen grundlegend besser verstehen. Zu diesem Zweck setzen wir Massenspektrometrie ein um die Zellwandproteinmenge zu bestimmen. Zweitens, wollen wir basierend auf sekretierten Proteinen, die in vielen Wachstumsbedingungen gehäuft vorkommen, diagnostische Marker und Methoden entwickeln. Drittens, wollen wir vielversprechende Ziele zur Impfstoffentwicklung identifizieren. Mithilfe von Prognosealgorithmen, bestimmen wir Teile dieser Proteine die in der Lage sind eine starke Immunreaktion auszulösen. Basierend auf diesen Ergebnissen stellen wir ein Impfstoffprotein zusammen, das aus den am immune-stimulierendsten Teilen dieser Proteine besteht, um es anschliessend zu testen.

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## NEELAM PANDEY (INDIA)

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Professor A. Vechiarelli, University of Perugia (Italy)



### CELL SIGNALING PATHWAYS INDUCED BY *C. ALBICANS* IN THE PRESENCE OR ABSENCE OF PROTECTIVE ANTIBODIES - IMPLICATIONS FOR THERAPY

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What if a commensal turns into a pathogen? For example, the fungus *Candida albicans* normally dwells in the oral and genital tracts as harmless microflora. It becomes pathogenic and even causes systemic infections if the balance of the normal flora is disrupted or the immune defences are compromised. In its pathogenic form, candida has a diverse armoury to cause infection, such as phenotype switching, adhesins, secreted aspartic proteases, phospholipases etc. which facilitate adhesion, invasion of immune cells and infection by overriding the host immune response.

Among these virulence factors, the secretion of aspartyl proteases (Saps) has long been recognized as a virulence-associated trait of *C. albicans*. We therefore analysed the inflammatory response of human immune cells following interaction with candida Saps. We have observed that recombinant Saps have differing abilities to induce pro-inflammatory cytokine secretion by human monocytes. Individual Saps can induce an inflammatory response which is independent from the pH of a specific host niche and from Sap enzymatic activity. Saps stimulate inflammasome complexes, which catalyses the maturation and secretion of pro-inflammatory cytokines from immune cells. These cytokines further attract other immune cells to the infection sites, where they engulf the pathogenic cells and/or produce antibodies against them.

Saps' ability to induce a pro-inflammatory effect in the host makes them important candidates for immunotherapeutic studies. More research is needed to investigate the immune response to candida Saps *in vivo*. This will further enhance our knowledge for developing vaccine strategies against candida.

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## JAMES CHENG (TAIWAN)

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Dr. M. Netea, Radboud University Nijmegen, The Netherlands



### ESCAPE MECHANISMS OF *C. ALBICANS* FROM HOST DEFENCES

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*C. albicans* is one of most common pathogens present in human. It colonizes the mucosal surface of many healthy individuals without causing any symptom. Some risk factors, such as overuse of antibiotics, diabetes, stress and compromised immune system, however, predispose individuals to *C. albicans* infection. Although there are some anti-fungal drugs available to treat *C. albicans* infection, the mortality rate of disseminated candidiasis remains in the range of 30-40%. Therefore, it is crucial to develop a new type of anti-fungal drug to fight against *C. albicans* infection.

The key feature of immune system is to distinguish self and non-self antigen. Upon recognition of the non-self antigen/pathogen, the immune system could readily respond and be triggered to alarm, control and eventually eliminate the non-self antigen/pathogen. However, as a successful pathogen, *C. albicans* can actively evade or disarm the immune response for its own benefit. My goal is to unravel the mechanisms that *C. albicans* uses to escape host immune systems.

By studying the interaction between *C. albicans* and peripheral blood mononuclear cells (PBMCs), the main immune cells in the blood, I have identified two major active roles of *C. albicans*. First, *C. albicans* secretes soluble factors to actively modulate the cytokine production of PBMCs. Second, *C. albicans* represses IL-17 production, which is crucial for anti-*C. albicans* infection, by modulating tryptophan metabolism in the PBMCs.

These findings clearly demonstrate the ability of *C. albicans* to escape the immune system by modulating host cytokine production. By further understanding the escape mechanism utilized by *C. albicans* would eventually lead to translate the basic knowledge into an applicable intervention to disarm the defensive shield of *C. albicans* and to strengthen host immune system to cure *C. albicans* infection.

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## DIANA ROSENTUL (VENEZUELA)

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Dr. M. Netea, Radboud University Nijmegen, The Netherlands



### FINDING HUMAN GENES THAT PREDISPOSE TO INFECTION

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Some environmental factors (such as the exposure to certain toxic compounds or microorganisms that can cause disease) might be generalized and relatively similar to everybody. However, some people have a higher risk to become ill than others. The protective shields of our bodies against infection consist of our anatomical barriers, the secretion of some substances and, of course the immune system. The information of how all of this mechanisms work is stored in our genetic material. The heritable information is kept in our genes in the form of a code, the genetic code, consisting on the DNA nucleotides 4 letters alphabet. Small changes in this sequence may alter the structure, function or quantity of a protein. If the affected protein belongs to the “defensive shields” the person may be more vulnerable to infection. The goal of our research is to determine whether the individual differences in the genetic information lead to a higher susceptibility to get infections with *Candida albicans*. *Candida albicans* is a yeast (comparable to the one used to produce beer) that causes several types of infection. Skin, tongue (especially in patients with AIDS), the gastrointestinal tract and the female genitals are common sites of infection. More dramatically, a disseminated infection in the bloodstream may affect several organs being a possible cause of death. The research is made by comparing the genetic code with the clinical information and the functioning of the immune cells.

Multiple variations were not responsible to increase the probability to have an infection with *Candida albicans*, but some of them were. In our previous work, we have determined a variation in the gene coding for a receptor in the cells of the immune system. This receptor can detect a component of the *Candida albicans* surface,  $\beta$ -glucan, and it is called dectin-1. The patients having this nucleotide change have non functional receptors presenting *Candida albicans* recurrent vulvo-vaginal infections as well as infections in the nail bed. Conversely, in our current work we have determined that the same variation does not affect the predisposition of *Candida albicans* bloodstream infection as well as in the infection in the tongue (in HIV positive patients). In addition, a variation in the sequence of the CARD9 protein (the protein that transmits the dectin-1 signal to the rest of the cell), did not affect the predisposition of these infections. On the other hand, a variation on the NLRP12 gene had an effect on the apparition of the infection on the tongue on HIV positive patients when the level of CD4+ cells was low. The CD4+ are some kind of white blood cells affected by the HIV virus but essential to avoid the *Candida albicans* tongue infection. The NLRP12 protein is involved in inflammation, which is an important process of the immune response. Analyses of more genes related to other processes are still in progress.

The results of this research will help people to develop new detection tools and treatments.

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## KATARZYNA TYC (POLAND)

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Professor E. Klipp, Humboldt University, Berlin, Germany



### MODELLING OF REGULATORY NETWORKS RESPONSIBLE FOR *CANDIDA ALBICANS* VIRULENCE

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Systems Biology is a relatively new field that combines two different sciences: mathematics and biology as means to decipher the mechanisms that underlie experimental observations. There are currently many mathematical concepts developed for such a purpose and depending on the availability and quality of the experimental data different techniques can be applied. Emerging data sets in the area of *Candida* research call out mathematics to increase our understanding.

The pathogen *C. albicans* can adapt to different environmental conditions and can respond to stress signals like osmotic changes, oxidative stress, nutritional stress, etc. This plasticity plays an important role in the fungus virulence. The interaction between *C. albicans* virulence factors (yeast-to-hyphae transition, adhesion to epithelial cells, secretion of different hydrolytic enzymes) and human defence strategies determine whether to act as a commensal or foe.

I am studying the adaptation of the yeast *C. albicans* to external stresses. We consider heat shock as a stress, where upon exposure of cells to elevated temperature the proteins unfold and cause malfunction of many signalling and regulatory pathways. This can also end in death of the cell. To survive many organisms have developed an appropriate response. Part of my research program is to establish a mathematical dynamic model of the molecular mechanism activated during the heat shock, responsible for the capability of the pathogen to survive at elevated temperature, e.g. induction of fever, which is one of the first host defence response. I validate the model with additional experimental time series data from my collaboration partner Michelle Leach (AFG, Aberdeen UK). The model predicts behaviour of thermal adaptation system under medically relevant conditions.

I am also establishing a mathematical model of *C. albicans* response to osmotic stress. Such a response has been intensively studied but it is still poorly understood the capacity of cells to adapt to the osmotic stress when grown on different carbon sources. The carbon sources are chosen to be relevant to conditions present on the host side at different stages and sites of infection. This will again increase our understanding of *C. albicans* strength when invading the host.

The pathogen *C. albicans* is a habitant of the human flora. When a patient is weakened, the fungus can cross the host barriers (epithelial and endothelial cells) and disseminate all over the body leading to systemic disease. I will focus on an early stage infection model, e.g. interaction of the pathogen with epithelial cells using the agent based modelling approach as another method widely used in biology and medicine.

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## KATARZYNA TYC (POLAND)

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Professor E. Klipp, Humboldt University, Berlin, Germany



### MODELOWANIE SIECI REGULATORYCH ODPOWIEDZIALNYCH ZA WIRULENJCĘ *CANDIDA ALBICANS*

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Biologia systemów jest względnie nową dziedziną, która łączy w sobie dwie odmienne nauki: matematykę oraz biologię, jako środki do zidentyfikowania mechanizmów opisujących eksperymentalne obserwacje. Obecnie istnieje wiele matematycznych metod rozwiniętych szczególnie w tym celu, stosowane w zależności od dostępności i jakości danych eksperymentalnych. Metody matematyczne są naturalnym narzędziem służącym do lepszego zrozumienia stale przybywających danych eksperymentalnych w środowisku *Candida*.

Patogen *C. albicans* potrafi się dostosować do zmieniających się warunków w otoczeniu oraz jest w stanie szybko odpowiadać na różne sygnały z zewnątrz, które są uznawane za stres, np. zmiany osmotyczne, stres oksydacyjny, niedobór pożywienia, itp. Ta elastyczność odgrywa ogromną rolę w wirulencji patogena. Wzajemne interakcje między czynnikami wirulencyjnymi *C. albicans* (filamentacja, adhezja do ścianki nabłonkowej, sekrecja hydrolazy), a strategią obronną człowieka mają wpływ na to czy ten grzyb zaatakuje swojego gospodarza, czy też pozostanie komensalem.

W mojej pracy badam zdolność przystosowania się *C. albicans* do zmian np. cieplnych w otoczeniu. Szok cieplny jest uznawany za formę stresu, gdzie podwyższona temperatura powoduje denaturację białek w komórce i, co za tym idzie, wadliwe funkcjonowanie wielu szlaków sygnałowych oraz regulatorowych. Takie zmiany mogą również doprowadzić do śmierci komórki. Aby przeżyć, wiele organizmów wyspecjalizowało stosowną odpowiedź. Część mojej pracy doktorskiej skupia się wokół budowy molekularnego modelu matematycznego opisującego mechanizm umożliwiający przeżycie patogena w podwyższonych temperaturach np. podczas gorączki broniącego się gospodarza. Model jest oceniany przy użyciu danych eksperymentalnych dostarczonych od mojego współpracownika Michelle Leach (AFG, Aberdeen UK). Ten model jest w stanie przewidzieć zachowanie się systemu w odpowiednich warunkach medycznych.

Pracuję również nad modelem matematycznym odpowiedzi *C. albicans* na stres osmotyczny. Mimo iż temat ten jest chętnie badany, wciąż pozostaje niejasne, jak rodzaj źródła węgla, użyty przy hodowaniu komórek, wpływa na odpowiedź na zmiany osmotyczne w otoczeniu. Źródła węgla zostały tak dobrane, by odpowiadały warunkom obecnym po stronie gospodarza na różnych etapach infekcji.

Grzyb *C. albicans* zamieszkuje florę fizjologiczną człowieka. W przypadku osłabionej odporności, patogen jest w stanie przekroczyć naturalne bariery gospodarza (tkankę nabłonkową i śródbłonek) oraz rozprzestrzenić się po całym organizmie powodując chorobę. Zamierzam również sformułować model opisujący wczesny etap infekcji tj. penetrację komórek nabłonka. Jako narzędzie wybrałam programowanie agentowe, które ma szerokie zastosowanie w biologii i medycynie.

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## KATE DOBB (UK)

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*Dr. Jason Oliver, F2G Ltd., Manchester, UK*



### INVESTIGATING NEW DRUG LEADS FOR FUNGAL INFECTIONS

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*Aspergillus fumigatus* and *Candida albicans* are fungal species that can cause serious, often fatal, disease in the vulnerable, especially cancer and AIDS patients. Current medicines to treat these infections have many drawbacks including serious side effects and limited effectiveness. This project aims to find new leads in the fight against these kinds of infection. A molecular approach has been used to find proteins that are essential for the survival of both *A. fumigatus* and *C. albicans*. The theory is that if these essential proteins are disabled the fungal cells will die. Therefore it is hoped that finding chemicals that disrupt these proteins will provide chemical leads for antifungal drug discovery. To date 3 proteins have been identified that are essential for the survival of both types of fungi. The 3 essential proteins have been made in large quantities using bacterial cells and screens are being developed to test for activity of the protein. Measuring activity of the protein in the presence of a library of small molecule compounds will enable identification of chemical inhibitors. Chemicals that disrupt both *A. fumigatus* and *C. albicans* proteins will be analysed in further detail to identify the best starting points for drug design. It is important that a new drug has the ability to enter cells in order to disrupt the protein inside the cell and cause cell death. This will be tested by mixing the chemicals of interest with whole cells to see if they can enter and then kill the cells. It is also important that the chemicals are not toxic to human cells. One way of testing this is to grow mammalian cells in a test tube in the presence of the chemicals and see if the cells stay alive. Other considerations are how easily the drug compounds can be manufactured, costs and intellectual property surrounding the work.

This study should result in new broad-spectrum antifungal drug leads to fight two of the most medically important fungi. Newer, effective antifungal medicines will result in huge benefits to human health.

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## FRANCESCO CITIULO (ITALY)

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Professor B. Hube, HKI, Jena, Germany



### CHARACTERIZATION OF MOLECULAR MECHANISM USED BY FUNGAL PATHOGENS TO UPTAKE ZINC FROM HOST CELLS DURING THE INFECTION

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Fungal pathogens are a significant cause of morbidity and mortality and resistance to current antifungals limits the effectiveness of treatment. Targeting the access of the fungus to host nutrients represents an exciting new area of therapeutic development. A variety of metals are important for pathogenic fungi to grow and to establish an infection. For example, iron is known to be sequestered by the host to prevent the growth of pathogens in a process known as nutritional immunity. However, *Candida albicans* is able to acquire host iron, and the molecular mechanisms underlying this have begun to be unraveled.

Zinc is an important metal for both the host and any invading pathogen. Recently, it has been shown that the natural antimicrobial peptide, calprotectin, is highly expressed in the human body in response to infection and chelates zinc. This points to the possibility of an important role of host zinc for the pathogen to establish an infection.

Using *C. albicans* as a model, our aim is to characterize the molecular mechanisms that pathogenic fungi use to acquire zinc from the host. By an *in silico* analysis on the *C. albicans* secretome we identified multiple Zn binding domains in 35 kD secreted protein, this protein is interestingly highly conserved throughout the fungal kingdom. Using a deletion strain for this protein and other molecular tools, including a gene reporter we have already shown that zinc is important for *C. albicans* growth and that the 35 kD secreted protein plays a pivotal role in host cell damage via Zn-acquisition.

Therefore, we have begun to uncover the molecular mechanism by which *C. albicans* acquires Zn from host cells. The future goal will be to fully characterize the molecular bases of the mechanism that *C. albicans* uses to sequester Zn, useful for growth, from the host. The knowledge obtained from these studies will lay the foundation for the future creation of peptides that could inhibit Zn uptake from the host by pathogenic fungi restricting their ability to establish an infection.

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## FRANCESCO CITIULO (ITALY)

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Professor B. Hube, HKI, Jena, Germany



### CARATTERIZZAZIONE DEI MECCANISMI MOLECOLARI USATI DAI FUNGHI PATOGENI PER CATTURARE ZINCO DALL'OSPITE DURANTE IL PROCESSO D'INFEZIONE.

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I funghi patogeni sono una significativa causa di malattia e mortalità, la resistenza che essi sviluppano agli antifungini limita l'efficacia dei trattamenti odieramente usati per eradicarne l'infezione. Un'interessante area di ricerca sullo sviluppo di nuove terapie per le infezioni fungine è basata sulla creazione di molecole che impediscono al fungo l'acquisizione di nutrienti dall'ospite. L'accesso ai metalli dell'ospite da parte del fungo è, infatti, uno step molto importante per il processo d'infezione; per esempio il ferro è sequestrato dall'ospite per prevenire la crescita del patogeno, in un processo conosciuto come immunità nutrizionale. *Candida albicans* ha sviluppato meccanismi per circonvenire questo processo e acquisire ferro dall'ospite; le basi molecolari di questo meccanismo sono in corso di studio.

Lo zinco è un metallo importante sia per l'ospite sia per il patogeno. Recentemente è stato dimostrato che la calprotettina, un peptide a funzione antibiotica prodotto dall'uomo, è altamente espressa durante un'infezione microbica o fungina ed essa sequestra lo zinco. Questo mette in evidenza la possibilità che l'accesso allo zinco dell'ospite da parte del patogeno giochi un ruolo chiave nell'infezione.

Usando *C. albicans* come organismo modello, il nostro scopo è quello di caratterizzare i meccanismi molecolari che i funghi patogeni usano per acquisire lo zinco dall'ospite. Mediante un'analisi *in silico* del secretoma di *C. albicans* abbiamo identificato una proteina di 35kD, con omologhi in altri funghi patogeni, che contiene multipli siti di legame per lo zinco. Usando un ceppo di *C. albicans* depresso per questa proteina e altri tool molecolari incluso un gene reporter, abbiamo dimostrato che lo zinco è essenziale per la crescita di *C. albicans* e che la proteina 35kD ha un ruolo chiave nel processo d'infezione, rendendo lo zinco dell'ospite accessibile al fungo.

Il nostro futuro goal è quello di caratterizzare le basi molecolari di questo meccanismo che permette a *C. albicans* di sequestrare lo zinco dell'ospite. Le conoscenze derivanti da questo studio saranno le basi per la sperimentazione di nuovi composti che consentiranno di bloccare l'accesso di varie specie di funghi patogeni allo zinco dell'ospite limitando così la loro capacità di creare un'infezione.

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## MALCOLM MCLEAN (AUSTRALIA)

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Dr. N. Barkai, Weizmann Institute, Rehovot, Israel



### USING COMPUTERS TO ANALYSE BIOLOGICAL DATA

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I am a bioinformatician, who supports experimental biologists in their work. Modern biologists perform a lot of so-called "high throughput" experiments, created by DNA sequencing and "lab on a chip" technology. We can now obtain the entire sequence of all the proteins in an organism and their flanking regulatory regions. The cost is ever falling; the first human genome cost 3 billion dollars, now people are talking seriously of the \$1000 genome.

Complete DNA sequences for the fungal pathogen *Candida albicans* are available, also for its relatives. We also have information about which genes are turned on under certain conditions, for instance under stress. As a computer programmer, it is my job to turn data into information. I do this partly by writing tools to visualise data, for instance highlighting regions of a DNA sequence that are of interest, or automatically searching for repeated motifs which may be of biological significance. The information of interest needs to leap out from what to a human eye are just a meaningless series of letters.

My main goal is to read the regulatory code. We only have a very rough idea how the flanking regions of genes determine when they are to be switched on. It is thought that proteins called transcription factors recognise and bind short control sequences in these flanking regions. However computer programs to extract the control sequences only have limited success so far. There is also the issue of how the transcription factors themselves are controlled.

So I also look for patterns in the data. For instance we find that DNA is very non-random around the beginnings of genes. One strand has more cytosine and less guanine than we would expect by chance. Towards the ends of genes, this pattern is reversed, the strand that was rich in cytosine is now rich in guanine. For reasons we don't understand these patterns are not found in the related organism, baker's yeast. The guanine / cytosine biases might be part of the regulatory code, or they might be entirely irrelevant. We do not know which pieces of the puzzle are important and which are not. It is important to always keep an open mind, and be very flexible in what analyses of data we perform.

Ultimately organisms are not bags of enzymes, which was the way old style biochemists tended to view them. They are systems that respond to challenges to defend themselves and obtain nutrients, in *Candida albicans'* case, often at the expense of the host, and we have to understand them as systems to fight them.

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