AGENCE NATIONALE DE LA RECHERCHE

Présentation des projets financés au titre de l'édition 2010 du Programme « ERA-Net PathoGenoMics »

Programme « ERA-Net PathoGenoMics"

Edition 2010

Titre du projet	**ARMSA** - Global analysis of antisense regulatory mechanisms in *Staphylococcus aureus*
Résumé	This research project is dedicated to exploring the effects of antisense RNA transcription on gene expression in *Staphylococcus aureus*, a leading cause of nosocomial and community acquired infections. The project will determine the transcriptome map of S. aureus using tiling arrays and deep sequencing strategies to identify overlapping transcription. The resulting map will be used to analyze the stability of overlapping transcripts; the effect of active replication of pathogenicity islands (PI) or phages on the bacterial transcriptome; and antisense mediated gene regulation in bacterial populations and at single cell level. Mutants deficient in particular antisense transcripts or in proteins involved in antisense mediated gene regulation will be assayed. This work is also anticipated to provide novel S. aureus targets for antibiotics.
Partenaires	Instituto de AgrobiotecnologiaUniversidad Publica de Navarra (ES) Universidade Nova de Lisboa (PT) Université de Strasbourg (FR) Université de Lyon 1, Faculté de médicine RTH Laennec (FR)
Coordinateur	Iñigo Lasa (ES) Correspondants français : Pascal Romby et François Vandenesh/ Tom Geissmann
Aide de l'ANR	316 200 € (partenaires français)
Début et durée	Mars 2011 - 36 mois
Référence	ANR-10-PATH-005

Titre du projet	**AspBIOmics** - Biomarkers for prevention, diagnosis and response to therapy of invasive aspergillosis
Résumé	Invasive aspergillosis (IA) infection-associated mortality incidence is growing and increasingly affecting a broader range of patient groups. A major problem in the management of IA is the poor diagnosis. This consortium proposes to develop and evaluate an efficient diagnostic platform for IA, based on a battery of in vitro assays for a comprehensive multimodality analysis, combining the detection of Aspergillus elements (RNA, polysaccharides, proteins), host factors including cytokine profiles and host genetic susceptibility. This strategy also has the potential to identify patients who are at a high risk of IA infection and to monitor treatment progression.
Partenaires	Insitut Pasteur (FR) bioMérieux (FR) Universaetetklinikum Wuerzburg (DE) Leibnitz Institute for Natural Product Research and Infection Biology Jena (DE) Medizinishe Universitaet Innsbruck (AT) Andalusia Health Public System Granada (ES)
Coordinateur	Hermann Einsele (DE) Correspondants français: Jean Paul Latgé and Alain Troesch
Aide de l'ANR	348 500 € (partenaires français)
Début et durée	Mars 2011 - 36 mois
Référence	ANR-10-PATH-002

Titre du projet	**CANDICOL** - Understanding colonisation and the transition to pathogenic dissemination by Candida species: towards early diagnostic and therapeutic approaches
Résumé	*Candida albicans, Candida glabrata* and *Candida parapsilosis* are the main fungal species of endogenous origin responsible for superficial and disseminated infections. The aim of this project is to identify the attributes that are shared by or distinguish these three fungal pathogen species regarding the mechanisms driving the transition from commensalism to host dissemination. To achieve this goal, we will establish or further develop ex vivo and in vivo models to study host colonisation and systemic infections by *C. albicans, C. glabrata* or *C. parapsilosis*. Using these models, we will identify fungal and host transcriptional patterns, genetic networks and fungal antigens associated with pathological colonisation or bloodstream infections. Furthermore, by developing novel mutant strain collections (gain- and loss-of-function), we will identify sets of fungal genes crucial for colonisation and/or dissemination. We expect to develop the proof of principle for novel diagnostic tools of translational value for discriminating and predicting stages of fungal infection. Finally, identifying Candida genes necessary for various stages of host infection shall also identify feasible targets for novel therapeutic strategies to prevent or interfere with the transition from commensalism to pathological dissemination.
Partenaires	Institut Pasteur (FR) University of Szeged Department of Microbiology (HU) University Medical Center Goettingen (DE) Leibniz Institute of Natural Product research and Infection Biology Jena (DE) Medical University Vienna (AT) Laddia Labordiognostik GmbH Vienna (AT)
Coordinateur	Attila Gacser (HU) Correspondent français : Christophe d'Enfert
Aide de l'ANR	212 160 € (partenaire français)
Début et durée	Mai 2011, 36 mois
Référence	ANR-10-PATH-008

Titre du projet	**CELLPATH** - Characterization of host cell pathways altered by effectors of *Brucella*, *Chlamydia* and *Coxiella*: identification of novel therapeutic targets
Résumé	Brucella spp., Chlamydia trachomatis, and Coxiella burnetii are intracellular bacterial pathogens causing human infections of clinical and public health relevance. As many other Gram-negative bacterial pathogens, they use specialised secretion systems to manipulate eukaryotic host cells by injection of bacterial virulence proteins (effectors). However, current knowledge about how these pathogens establish infection is limited. The overall purpose of this proposal is to characterise the molecular and cellular function of effector proteins from Brucella, Chlamydia and Coxiella. The expected results will likely lead to the discovery of novel therapeutic approaches and may help in the design of vaccines and novel diagnostics. In particular, the host signalling pathways altered by one (or more) effector(s) will be excellent candidates as novel therapeutic targets. Furthermore, the knowledge that we will produce could also lead to the identification of inhibitors targeting the effectors directly.
Partenaires	Université de la Méditerranée aix Marseille 2 – Centre d'immunologie de Marseille Luminy (FR) Universidade Nova de Lisboa (PT) National Institute of Health Lisboa (PT) Universaetetklinikunt Erlangen (DE) AROMICS Barcelona (ES) Universidad Complutense de Madrid (ES)
Coordinateur	Luís Jaime Mota (PT) Correspondent français : Suzana Salcedo
Aide de l'ANR	170 000 € (partenaire français)
Début et durée	Mars 2011, 36 mois
Référence	ANR-10-PATH-006

Titre du projet	**GeMoA** - A genome-wide approach for characterizing the mode of action of novel compounds against Tuberculosis
Résumé	One third of the world's overall population is infected with Mycobacterium tuberculosis (Mtb), the causing agent of Tuberculosis (TB). About 95% of those are thought to be in latent infection wherec Mtb rarely replicates. Nevertheless, ~10% of latent infections eventually progresses to active disease, which, if left untreated, kills more than half of the infected patients. Mtb infection is best described as an equilibrium involving a balance of activation and suppression of host responses, orchestrated by a complex and dynamic series of interactions between multiple host and bacterial components. Therefore, it is not unsurprising that single-target approaches for the identification of lead compounds, followed by establishment of pipelines for drug discovery, have had limited success. To address such limitation, we plan to apply genome-wide approaches to characterize the mode-of-action of a compound library, which has been validated for its activity against Mtb by GlaxoSmithKline (GSK, Partner 3), a major player in the pharmaceutical industry. Our approach uses an alternative and highly promising route by starting rather than finishing an initial process for lead compound characterization. Our teams will combine medicinal chemistry, synthetic chemistry, computational chemistry, computational biology, genomics, transciptomics, X-ray crystallography and biochemistry to address the need for identifying new targets and compounds that can lead to unexplored new mode-of-action against Mtb.
Partenaires	CNRS - Institut de Pharmacologie et de Biologie Structurale (FR) Institut Pasteur (FR) Centro de Investigacion Principe Felipe Valencia (ES) EMBL Hamburg Unit (DE) GSK TCMDC Madrid (ES)
Coordinateur	Marc A. Marti-Renom (ES) Correspondant français : Olivier Neyrolles et Brigitte Gicquel
Aide de l'ANR	440 000 € (partenaires français)
Début et durée	Mars 2011, 36 mois
Référence	ANR-10-PATH-007

Titre du projet	**HELDIVPAT** – Helicobacter pylori diversity in pathogenesis, antibiotic resistance, and evasion from natural and vaccine-induced immune responses
Résumé	Helicobacter pylori chronically infect more than one half of the world's human population. The chronic gastritis that this infection always induces remains asymptomatic in the majority of individuals, but can give rise to important complications, ranging from peptic ulcer disease to malignancies (gastric carcinoma, MALT lymphoma). Despite the fact that H. pylori is responsible for an estimated 590,000 cases of gastric cancer per year, treatment remains difficult, with a rising rate of antibiotic resistance, and a vaccine is currently unavailable. Very high genetic diversity and variability are hallmarks of H. pylori. In a previous project funded within the ERA-NET PathoGenoMics, entitled "Parasite and host genetic diversity in Helicobacter infections" (HELDIVNET), fundamental aspects of the mechanisms leading to genetic diversity of H. pylori, its global population structure, and the variability of host interaction factors (in particular, the cag pathogenicity island), were studied. The HELDIVPAT project will build on the results of HELDIVNET to address important questions with direct relevance to treatment and prevention of H. pylori by antibiotics and vaccines, respectively. In a closely networked approach, we will address the question how the genetic diversity/variability of H. pylori is connected to a) pathogenesis, b) its ability to evade immune responses raised during natural infections as well as those induced by currently available vaccines, c) resistance against antibiotics. To reach this ambitious goal, the consortium partners not only have a highly complementary set of technologies and expertise at their disposal, but also have access to unique resources, including a previously uncharacterized strain collection from a human volunteer challenge study performed with a cagPAI carrying strain of H. pylori in the context of a vaccine trial, as well as one the largest available globally representative collection of MLST-characterized H. pylori strains, including 30 strains whose complete cagPAI sequences are available.
Partenaires	Hanover Medical School (DE) Institut Pasteur (FR) University of Porto IPATIMUP (PT) University of Munchen Max von Pettenkofer Institute (DE) University of Magdeburg (DE)
Coordinateur	Sebastian Suerbaum (DE) Correspondent français : Ivo G. Boneca

Aide de l'ANR	212 932 € (partenaires français)
Début et durée	Mars 2011, 36 mois
Référence	ANR-10-PATH-004

Titre du projet	**LISTRESS** - Analysis of the cellular mechanisms underlying the early response of the host to stress induced by *Listeria* infection

Résumé

The intracellular pathogen, *Listeria monocytogenes* breaches tissular barriers to replicate within many cell types in the infected host. During cellular infection, microbial presence is continuously monitored by intracellular pattern recognition receptors (PRRs) that recognize evolutionary conserved structures (peptidoglycan, nucleic acids etc.,) and lead to the induction of ubiquitous cytoplasmic quality and quantity control pathways such as the ubiquitin-proteasome-system (UPS), endoplasmic reticulum stress (ER stress), and autophagy. Our studies have revealed that these processes are subverted by listerial factors at early time points following infection of the cell. The molecular interaction required for this subversion involve reciprocal modulation of bacterial or host cell proteins using post-translational modifications (PTMs), thus enabling rapid, local and specific modification of key processes in both the host and bacterium. In this proposal we build on resources developed in our previous proposal, including mutant libraries for all cell wall-associated proteins, to analyse the role of the Listeria factors that induce post-translational modifications and organelle remodelling to overcome ER stress and autophagy. Our studies are aimed at identifying bacterial ligands as well as their intracellular PRRs and interacting targets, and to connect them to downstream events leading to the induction of cell autonomous defences and innate immune signalling pathways. By combining functional genomic strategies to examine bacterial and host factors we wish to identify and map interactions between listerial effector ligands and host proteins in these processes. We will use state-of-the-art 3D- and 2- photon imaging technologies to examine the role of these processes during Lm infection in a transgenic rodent model of gastrointestinal infection. In addition, clinical material deriving from patients with inflammatory bowel disease harbouring mutations in predisposition loci involving nucleotidebinding oligomerization domain NOD genes, ER stress (XBP-1) and autophagy (ATGL16L) will be used to examine the contribution of these processes to limiting bacterial replication in a clinical setting. Augmentation of protective host cell pathways represents a novel therapeutic option to efficiently eliminate the invading pathogen.

Partenaires	Institut Pasteur (FR) Justus Liebig University Gessen (DE) Helmholtz Centre for infection Research Braunchweig (DE) Condejo Superior de Investigaciones Cientificas Madrid (ES) Institute for Molecular and Cell Biology Porto (PT) Tel Aviv University Department of Molecular Microbiology and Biotechnology (IL)
Coordinateur	Trinad Chakraborty / Torsten Hain (DE) Correspondents français: Pascale cossart et Marc Lecuit
Aide de l'ANR	255 000 € (partenaires français)
Début et durée	Mars 2011, 36 mois
Référence	ANR-10-PATH-001

Titre du projet	**MobileGenomics**: Impact of mobile genetic elements and horizontal gene transfer on bacteria-host adaptation: a genomic view
Résumé	This project aims to study horizontal gene transfer (HGT) and mobile genetic elements (MGE) in the human gut environment and in the upper and lower respiratory tracts. Commensals, probiotics and important opportunistic bacterial pathogens are present in both niches. The study will analyze niche-specific representatives of these three classes. The aims of this project are to increase basic knowledge on genome variability, on the mechanism leading to this variability and on the impact it has on host adaptation, colonization and virulence. The research is expected to impact our understanding on niche adaptation, bacterial survival in harsh conditions, colonization and virulence acquisition related to MGE and HGT, and to help decipher the impact of antibiotics and screen for more efficient probiotics and vaccines.
Partenaires	Insitut Pasteur (FR) Danone Research (FR) Universaetet Wuerzburg Institut fur Molecular Infektionsbiologie (DE) Ludwig Maximilian Universitaet Munenchen Max von Pettenkofer Institute (DE) Karl Franzes Universitaet Graz (AT)
Coordinateur	Carmen Buchrieser (FR)
Aide de l'ANR	524 052 € (partenaires français)
Début et durée	Septembre 2011, 36 mois
Référence	ANR-10-PATH-004