ERA-NET PathoGenoMics April 2012

NEWSLETTER -10

Hungary Finland Spain Germany Israel France Austria Portugal Slovenia Latvia

ERA-NET PathoGenoMics is a consortium of 13 funding organizations from 9 countries *(Austria, Finland, France, Germany, Hungary, Israel, Slovenia, Spain, and Portugal)* which, among many other activities, implemented 3 transnational joint calls, through which more than 41M € of national funding have been provided to support transnational research projects in the field of genome research on pathogenic microorganisms.

The first joint call for research proposals was launched in 2006, and was followed by two additional joint calls launched in 2008 and 2010. While the first call focused on basic research, the second and third calls extended to applicable research in the prevention, diagnosis, treatment and monitoring of infectious diseases.

Throughout the years of ERA-NET PathoGenoMics funding activities, annual status seminars were organized in which scientists from each funded project presented their results.

On January 23-24, 2012 the final ERA-NET PathoGenoMics status seminar on the projects funded by the 2nd and 3rd joint calls took place, once again, in the beautiful island of Tenerife in the Canary Islands, Spain.

The status seminar consisted of lectures and poster presentations of the research results. The participants were able to get an overall picture of the research undertaken under the framework of the ERA-NET PathoGenoMics and, at the same time, could strengthen existing research collaborations and hopefully create new ones.

The following interviews describe three research projects presented at the 2012 status seminar. These are only examples of the exciting, diverse and leading research supported under the ERA-NET PathoGenoMics collaborative transnational umbrella, which, we believe, could not have been achieved otherwise.

Interview with Dr. Robert Bates, Senior Scientist at GSK Spain

Robert Bates from GlaxoSmithKline (GSK) presented a talk on the project titled **"A genome-wide approach for characterizing the mode of action of novel compounds against tuberculosis (GeMoA)"** which was funded under the 3rd ERA-NET PathoGenoMics joint transnational call.

The project is coordinated by Marc A. Marti-Renom from Centro de Investigacion Principe Felipe, Spain. Other participants in the research are Lluis Ballell-Pages from GlaxoSmithKline, Brigitte Gicquel from Institut Pasteur, Olivier Neyrolles from Institut de Pharmacologie et de Biologie Structurale/CNRS, and Matthias Wilmanns from EMBL Hamburg Unit.

What is the goal of your project?

Dr. Robert Bates: "In this joint industry and academia project our objective is to find new drugs for tuberculosis (TB), which is a disease widely spread in the developing world."

What is your approach to finding new therapies for tuberculosis, and what is the added value of working in a framework of a collaborative consortium?

Dr. Robert Bates: "Our consortium is composed of four academic research groups and one company, representing three European countries that are joining efforts by integrating computational and experimental approaches to create an innovative platform for genome-wide characterization of the mechanism-of-action for selected chemical compounds with activity against *Mycobacterium tuberculosis (Mtb)*, the causative agent of TB. This is a true multidisciplinary approach that is only possible through the cooperation of multiple research groups specializing in different fields including medicinal chemistry, synthetic chemistry, computational chemistry, computational biology, genomics, transciptomics, X-ray crystallography and biochemistry, all working together for identifying new targets and compounds that can lead to new modes-of-action against *Mtb*."

How did GSK get involved in the consortium and what is its contribution?

Dr. Robert Bates: "GSK actively seeks collaborations with academia, especially at our Diseases of the Developing World campus in Tres Cantos, Spain, which employs 200 scientists, and allows GSK researchers to work more collaboratively with scientists from universities, not-for-profit partnerships and other research institutes with the aim of discovering and developing new medicines for diseases of the developing world.

Our aim is to accelerate the development of new and better treatments against diseases that are prevalent in developing countries, such as malaria and tuberculosis, which affect the lives of more than one billion people. By providing a searchable, public database of available assets and resources, we facilitate a coordinated approach to developing new treatments for these diseases, ultimately improving the lives of those most in need. In this project we will adopt an innovative and open approach ensuring that any potential treatments arising from this project will be fully available to countries bearing the greatest TB burden."

Interview with Prof. Sebastian Suerbaum, Hannover Medical school, Germany

Christine Josenhans from Hannover Medical School in Germany, together with Sebastian Suerbaum of Germany and Ivo Boneca from Institute Pasteur, France presented results from the HELDIVPAT project which studies *Helicobacter pylori* diversity in pathogenesis, antibiotic resistance, and immune evasion. The research was conducted under the 3rd call. Other participants in the research include José Machado and Ceu Figueiredo from Portugal, and Rainer Haas, Peter Malfertheiner and Thomax Wex from Germany.

Please describe your project.

Prof. Sebastian Suerbaum: "We are working on *Helicobacter pylori (H. pylori)*, the most prominent digestive tract bacterial pathogen infecting half of the world's population. It is a potentially deadly infectious agent that can cause multiple pathologies, including cancer. Still, 85% of those infected will remain asymptomatic, and currently there is no way of knowing who will get sick. Therefore, there is a great medical need for a better understanding of this pathogen. The project studies the diversity of the bacterium and its pathogenic mechanisms. One primary goal is to find diagnostic markers that help to predict disease risk. We also want to better understand antibiotic resistance and the mechanisms of immune protection. The current available treatment involves the use of multiple antibiotics to which there are already resistant bacteria. There is frequent failure of the treatment, which is cumbersome to begin with, and there is no vaccine.

The first project we were involved with, which was part of the 1st call and ran from 2007-2010, showed *H. pylori* as an extremely diverse pathogen, characterized by a complex population structure. In this project, we want to exploit this knowledge for practical applications. This is the reason we included a clinician.

One key project is studying bacterial strains isolated during a recent clinical trial performed by our clinical partner, Prof. Malfertheiner, in collaboration with Novartis. We compare the strain that was used to infect human volunteers with bacteria that could be reisolated from the infected individuals. We are using next generation sequencing to sequence the complete genome of the bacteria. We check the number of changes and if they are related to the action of the vaccine. In particular, we ask how several different virulence factors change during the organism's persistence within the stomach.

We also investigate what happens in the initial infection, which is currently not studied at all since it usually happens in childhood."

What are the advantages of performing your research as part of the ERA-NET network?

"In the beginning of the 1st call, the ERA-NET brought us together with scientists from other countries, which resulted in highly publicized discoveries.
The transnational cooperation in the1st call led to exciting discoveries, which we hope now will have applicable implications. The ERA-NET is a very successful framework, which brought us in touch with groups working on other pathogens. It has been truly beneficial."

Interview with Prof. Ulrich Dobrindt, the University of Münster ,Germany

Ulrich Dobrindt presented a talk titled Characterization of fitness traits and genome plasticity of asymptomatic bacteriuria *E. coli* isolates. In his talk he summarized the group's research, which was initiated under the 2nd ERA-NET PathoGenoMics call. Other participants in the research include Levente Emödy from the University of Pécs, Hungary; Timo Korhonen from the University of Helsinki, Finland; Eliora Ron from Tel Aviv University, Israel and Catharina Svanborg from Lund University, Sweden.

What is the focus of your research?

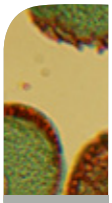
Prof. Dobrindt: "In this project we try to develop a new treatment for recurrent urinary tract infections (UTI) that will provide an alternative to antibiotics and help to circumvent the problem of antibiotic resistance. Antibiotic resistance is an increasing problem in dealing with UTI and new therapeutic concepts are needed. Based on epidemiologic findings that asymptomatic bacterial carriage in the urinary tract is protective in different patient groups, we have developed a technology to deliberately establish asymptomatic bacteriuria in patients who need alternatives to conventional therapy. We have identified bacteria that can grow in the human urinary tract without causing symptoms and placebo-controlled studies have shown that these bacteria protect the patient by competing with the more pathogenic varieties. This approach has systematically been translated into clinical practice and we now have molecular technology to understand in detail how these bacteria protect the host and if molecular tools used by the bacteria can be developed into drugs that modify host resistance to common infections like UTI. We also want to understand why certain bacteria cause symptoms and other don't. If we can determine the pathogenic traits, we can also target them specifically."

Why study urinary tract infections (UTI)?

Prof. Dobrindt: "There are 15 million cases per year in the U.S. alone and only in adults. UTIs are also very common in children. Asymptomatic bacteriuria occurs in 1% of children, more than 2% of pregnant women and in more than 20% of elderly men and women, making this the most common bacterial infection in the industrialized world. While most patients don't die from UTI, the infections drastically impair the quality of life especially in individuals who develop recurrent, chronic disease. It is also a common infection in hospitals, following catheterization, neurogenic damage or surgery. Severe infections in childhood may damage the kidneys, and may even develop into life threatening sepsis, which may be especially fatal in infants and the elderly."

Isn't there a chance that the harmless bacteria that you insert into the body, will transform into harmful ones?

Prof. Dobrindt: "We established our consortium in order to study the genomes of these organisms and to address the question whether bacteria evolve towards virulence or commensalism. The current dogma states

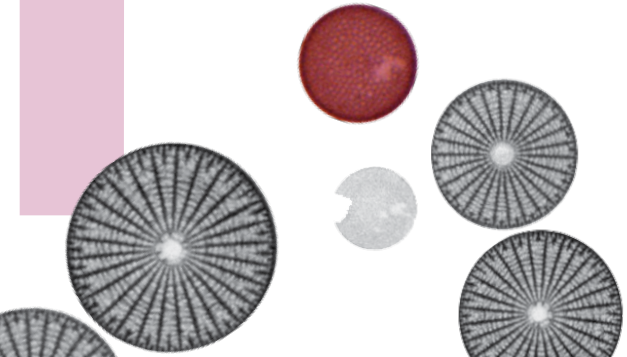


Interview with Prof. Ulrich Dobrindt, the University of Münster ,Germany *Continued*

that evolution favors virulence, but we have found evidence to the contrary. To convert this good strain into a bad one, you need several mutations, so regular gene transfer does not suffice. Not only is the strain safe, but it looses virulence gene content during carriage in human hosts. We have never observed that our strain changes its genome to become more pathogenic."

Have you tried your treatment on people?

Prof. Dobrindt: "The inoculation method has been developed in Sweden over several years but has also been used in other countries, including the US, with evidence of protection against recurrent UTI. Since placebo-controlled studies clearly have demonstrated efficacy and clinical benefit, this is not controversial. The approach has not yet been broadly tested in Europe. Importantly, this is not intended as a replacement for standard therapy. Instead, it provides a tool for prophylaxis, for example in patients with neurogenic bladder disorders, who need alternatives to frequent antibiotic regimens and where intervention by inoculation with this strain may provide long, symptom-free periods. Hopefully our research will help improve confidence in therapy based on our approach. The urologists and clinicians in Sweden that are conducting these studies are optimistic. Patients that have chronic infections report that they are very happy with the results of the treatment. Hopefully, in the future, this will become available to patients more widely."



The future of ERA-NET PathoGenoMics:

Bruck Serawit
Infect-ERA, coordinator. Application pending

The ERA-NET PathoGenoMics: "Genome sequencing and functional genomics of human-pathogenic microorganisms", started in the 6th Framework Programme, in 2004. This coordination action has brought together 10 partner countries and 6 affiliated ones and it is one of the long lasting ERA-NETs, as it will be active until end of August 2012. This platform for cooperation between European research funding bodies established a successful forum of information exchange between participating member states. This concerted action launched three successful joint transnational calls and funded 34 projects with a budget of over 41 M€.

After a thorough evaluation of its activities by the participating agencies and scientists, followed by a S.W.O.T analysis during its seventh year of existence, almost all of the participating ERA-NET PathoGenoMics partners and several other new ones decided to join the application on the continuation ERA-NET on infectious diseases: Infect-ERA.

The Infect-ERA application was submitted to the European Commission on February 20th, 2012. If successful, it will start in January 2013 and end in December 2016. Infect-ERA will build on the achievements and network of PathoGenoMics, such as the establishment of principles, mechanisms for the evaluation of joint calls and management of transnational projects. It plans to have yearly joint transnational calls and to provide support to development and independence of young scientists. With a wide scientific scope, Infect-ERA aims to understand all basic aspects of human infection biology caused by bacteria, fungi, viruses and single cell protozoa.

Infect-ERA is a larger consortium of 15 agencies from 11 countries :The Austrian Science Fund and the Austrian Research Promotion Agency, Austria; The Agency for Innovation by Science and Technology, Belgium; The Danish Agency for Science Technology and Innovation, Denmark; The Forschungszentrum Juelich GmbH, Germany; The Ministry of Economy and Competitiveness and the National Institute of Health Carlos III, Spain; The Agence Nationale de la Recherche, France; The Hungarian Academy of Science and the Hungarian Scientific Research Fund, Hungary; The Chief Scientist Office, Ministry of Health, Israel; The National Science Centre and the National Centre for research and Development, Poland; The Foundation for Science and Technology, Portugal; and the National Authority for Scientific Research, Romania). With an increase of the number of participating agencies, Infect-ERA expects to increase the impact of the joint actions. At the end of Infect-ERA, the European Commission would have funded 12 years of coordination and support action in the area on infectious diseases. In order to further cooperate in a self-sustain basis, the consortium will design a long term sustainable cooperation framework model during the lifetime of Infect-ERA. Furthermore, since the launch of ERA-NET PathoGenoMics, several other European initiatives have come to exist. Hence, Infect-ERA plans to cooperate and complement the ongoing initiatives in the area of infectious diseases.