ERA-NET PathoGenoMics
Consortium: RNAi-Net
Interview with Prof. Thomas F. Meyer

1) If you look back at the first year of funding, what have you managed to achieve?

Firstly, we have realised that bacteriologists are naturally focused on their bacteria rather than on the role of the host cells during infection. Therefore, considerable training is needed to bring into focus the importance as well as the feasibility to perform loss-of-function screens on the host cell side using RNAi. These are challenging learning processes, but we can already see significant advances. Thus, we have seen the first exciting results of our studies, for example with *Helicobacter pylori*. The scientists have discovered that bacterial factors are able to influence host cells in such a way that they detach from neighbouring cells and migrate into tissue. Another group of researchers has analysed bacteria with capsules. Here, first analyses showed that capsules can negatively influence the regulatory signalling pathways of the host cells, thereby preventing recognition and elimination of the bacteria. These are fascinating initial observations that must undergo further detailed analysis.

2) What do you perceive as being the biggest challenge within the consortium?

For us being the coordinator, the whole project is a challenge as well as a small revolution in pathogenomics research. It is now evident that the host plays an equally important role during disease development as compared to the bacterium itself. In this project we focus on the host side of the interaction applying large scale RNAi screens. This innovative approach is new in the pathogenomics field and opens up many new possibilities. However, it is also associated with multiple challenges and questions, for example regarding the most promising research strategies to be taken and how to address the upcoming questions. Here, we can also see differences amongst the participating groups: Some have been engaged for a longer time with these large scale screening approaches. On the other hand, there are groups where this approach has not yet been on the agenda at all. The learning effect is immense. In a big consortium like ours, the challenge is to bring together experienced and less experienced groups in order to spread the existing knowledge and to jointly tackle the most interesting questions in the field.

3) What differences have you observed between the different bacterial species that are being addressed in the consortium?

There are major differences, for example, if you compare intracellular with extracellular bacteria. In contrast to intracellular bacteria, the extracellular pathogens can grow in the absence of human cells and the inter-dependencies between host cells and the bacteria are less pronounced, at least in the in vitro cell culture model. Studies with intracellular bacteria shed light on the mechanisms of the host cell that play a role during bacterial replication and survival within the host cell. Our initial analysis has revealed numerous host cell factors that support or suppress the proliferation of intracellular bacteria, such as *Chlamydia* and *Salmonella*. The analysis of extracellular bacteria, in the other hand, could lead to interesting insights into the host cell signalling pathways and innate defence systems triggered by the adherent pathogens.

4) What do you think about the cooperation within this ERA-NET consortium?

Collaboration within the consortium takes place at multiple levels: Laboratories concerned with the same pathogen collaborate intensively within their respective work packages (WPs). However, while researchers of different WPs might have similar questions, we have implemented four thematic areas (TAs) that laterally connect the various WPs. The TAs thus stimulate the joint development of assay systems, the project design as well as the future data analysis. Finally, all partners intensively interact with the central screening facility in Berlin. Several groups already participated in two training courses provided by the centre. Altogether, the laboratories involved are highly engaged, and take initiatives themselves in establishing fruitful cooperations. We meet regularly, have continuous telephone conferences, and share our results and experiences.

5) What is the therapeutic relevance of the RNAi-Net approach?

We are still in the area of basic research within this ERA-NET consortium. Yet, there are bacterial infections such as acute meningitis for which new therapies are desperately needed that could efficiently block innate reactions of the host cell. In many cases, one cannot sufficiently help these patients with conventional antibiotic therapies because substances released by the killed bacteria have the potential to exacerbate the disease. Another example is chronic infections, such as by *Chlamydia* or *Mycobacteria*, for which no satisfactory therapies exists to clear the chronic state. A promising approach would be to target human signalling pathways or cellular components, exploited by the microorganism for their own advantage.

6) What are your goals for the future?

The RNAi-NET consortium is an important starting point for addressing the host cell to a much greater extent than previously conceivable in pathogenomic research circus. The RNAi-Net also establishes a platform for the comparative analysis of host cell influences on different bacteria. Most importantly, we wish to extend our focus on the clinically most relevant pathogens, including those which belong to the risk group BSL3. Evidently, this would require a screening facility at the corresponding safety level. Moreover, in the very long run, we would wish to include research on fungi, parasites and viruses in conjunction with other research centres in Europe. To reach this goal, we are currently establishing a joint European research network called FuGID (Functional Genomics in Infectious Disease), which also includes colleagues from non-ERA-NET countries.