NeuroCampus – Inside Out:

Søren Riis Paludan

Group leader of Paludan Lab at Department of Biomedicine

Paludan Lab studies viral infections in the brain. They investigate how the brain exerts control over infections as well as the later clearance process and long-term consequen-ces of viral infections.

Søren Paludan. Photo: Pure

Can you describe your research in a nutshell?
One branch of the research in my lab is focused on understanding viral infections in the brain and how the brain exerts control over viral infections. Another branch centers on understanding the clearance of disease and the long-term consequences of viral infections e.g. related to neurodegeneration and inflammation.
One of our current projects investigates how neurons sometimes die, when infected with virus. We investigate the virus-triggered mechanisms that stresses the neuron so much that it may die, and also investigate the molecular mechanisms that occur in the brain, when neurons die or glial cells get immune-activated.

We try to take a very broad methodological approach in our research. A typical process in our lab starts with making an observation in our mice models, which is then studied first in the living organism, then in cells and lastly in terms of molecular mechanisms. Our projects do, however, also sometimes start from the opposite direction. In these cases, we first uncover new molecular mechanisms e.g. using screenings. We conduct exploratory studies using for instance genome-wide CRISPR-screens, which is an unbiased approach, where we do not search for a specific gene. Instead, we set up a search for genes that are essential for the defense against the virus infection, and then knock out all the discovered genes one at a time in order to see which cells are now more susceptible. Thus, we can couple specific genes with specific hypotheses about function in viral infections, which can then be tested experimentally.
At the moment, we work with a newly initiated method, where we use stem-derived brain cell culture systems. This allows us to conduct studies in an environment that has some resemblance to the human brain using primary cells and not just cell lines.

What are the potential clinical impacts of your research?
Our research is very fundamental, and there is thus a rather long way from our discoveries to the development of new therapeutics. One area of our research that I believe could have significant clinical implications in the long run is our studies of the potential link between inflammatory and infection activities and neurodegenerative diseases. Here, there is a profound lack of knowledge. A better understanding of this field can open up new therapeutic possibilities that do not exist today.

How did you end up where you are today?
I trained as an immunologist working with immune responses to infections. As it happened, the virus that I studied, herpes simplex virus, tends to infect neurons, and so, the viruses, rather than an original interest in the brain, thus led my path into neuroscience. Nevertheless, I soon became fascinated by this very fragile organ which can be damaged so easily and moreover with so profound biological consequences, since neurons cannot be replaced to the same extent as other cell types. Another element that makes this work interesting, is the paradox that viruses that can damage the brain, but simultaneously we have immune responses that also easily damage the brain. This means that the immune system and the brain need to be regulated by a very fine balance. This balance also needs to be kept in mind when trying to eliminate infections.

What does a (local) strong neuroscience research network mean for you and your research?
Collaboration is very important for our research, and has become increasingly important during the last few years. Until relatively recently, I worked as an immunologist in the brain without paying much attention to physiological brain function. Today, we do however have an intense focus on the interaction between immune mechanisms and the normal physiological mechanisms, meaning that we need to gain expertise or access into these fields of research.
Moreover, collaboration is essential for studying any translational possibilities of our research. The collaboration with clinicians such as Leif Østergaard and Trine Morgensen is crucial for access to things such as patient materials, scanning and clinical history as well as the required knowledge.
In order to establish fruitful collaborations it is essential to meet each other. I think the neuro-community here in Aarhus is quite good at facilitating meeting-possibilities, but it can of course always be improved. Most importantly, we still need more focus on closing the gap being basic and clinical science.

If you had unlimited resources to conduct a big, multidisciplinary neuroscience project, what would you like to do?
In order to conduct "dream projects", and develop them to the highest level, I see a need to break a lot of existing barriers. We need to get better at interdisciplinary research at several levels, including broadening of our own knowledge but also achieving a better understanding of where our own knowledge ends and where we have to rely on other people's expertise.
With this kind of basis, I would like study how our brain is able to eliminate unwanted things, e.g. infections, cell debris and protein aggregates, all the way from molecular mechanisms to patients. This would require a broad and collaborative research landscape ranging from molecular biology to clinical medicine and from mechanistic studies to very translational activities.

Contact:

- Søren Riis Paludan, PhD, professor
- Address: Høegh-Guldbergs Gade 10, 1115-320, Aarhus C
- E-mail: srp@biomed.au.dk
- PURE profile

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