# PRESS RELEASE

## Human Frontier Science Program funds transatlantic research project

### Tuning Brain Cells with Light

**Berlin/Bonn, 5. Mai 2023 - An international research team, comprising scientists from University Hospital Bonn, DZNE, the Netherlands, and the US has been awarded a US$ 1.3 million grant by the "Human Frontier Science Program" to investigate brain immune cells and manipulate them via light irradiation. This will involve using gene transcripts (mRNAs) as molecular mediators. From these laboratory studies, the scientists aim to gain new insights into how these cells change their shape in response to hazards and the role they play in neurodegenerative diseases such as Alzheimer's.**

The brain houses a special class of immune cells called "microglia" that eliminate toxins, remove cellular debris, and fight pathogens, helping to keep the brain healthy. "These immune cells move through the tissue, surveying the local environment with little processes. When the microglia sense a danger, they are activated, which is associated with changes in their morphology. First, the dimensions and branching of their projections change and eventually, the microglia take on a blob-like shape," said Dr. Dragomir Milovanovic, a biochemist and research group leader at DZNE's Berlin site. "This transformation is essential for the immunological function of microglia. However, how this dynamic behavior is achieved is unclear. With our studies, we hope to learn more about the mechanisms involved in this. It is known that in Alzheimer's microglia become overactive and that their initially beneficial effect escalates into a chronic inflammatory response. Thus, a better understanding of microglia could help in devising new therapies."

#### A Switch for Microglia Behavior

For this endeavor, Milovanovic is cooperating with three colleagues, including Prof. Kathrin Leppek from University Hospital Bonn in Germany, as well as fellow researchers from University of Utrecht in the Netherlands, and from University of California, Berkeley. "We are an interdisciplinary team, with each member bringing their specific expertise to the table. This includes cell biology, RNA and protein biochemistry, synthetic chemistry and other areas," the DZNE scientist explained. Supported by an "Early Career Research Grant" of the Human Frontier Science Program (HFSP), the international collaboration aims to study microglia in mouse brains and to manipulate microglia behavior in cell cultures by means of photosensitive molecules and laser light. "We intend to develop compounds that influence

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the production of proteins. Specifically, proteins significant to changes in microglia morphology. The key point is that the compounds we will synthesize are photoswitchable. Thus, their effect on protein production can be controlled with an appropriate light source. This will allow us to specifically manipulate the morphology of microglia and hence their immunological function with light", Milovanovic noted. He and his colleagues are looking forward to joining forces for this project. The grant will enable them to recruit PhD students or postdocs who will work highly collaboratively.

**Targeting Protein Production**

Recent studies suggest that the morphological transformation of microglia is regulated by proteins that are produced in the cell's periphery, including its processes. This requires gene transcripts called "mRNAs" as well as molecular machines that "translate" mRNA molecules into proteins. "It seems, and this is something we want to investigate in detail, that the mRNAs relevant for morphological changes are packaged together with protein factories into so-called granules. This happens close to the cell's nucleus. From there, these granules that resemble tiny droplets suspended in a different liquid, are transported to other sites", Milovanovic explained.

"Therefore, our collaboration aims to identify mRNAs involved in the morphological changes and develop light-sensitive compounds that can attach to mRNAs to regulate their transport and protein production at specific places in the cell. For this, we need to identify and characterize microglia mRNAs that we can specifically target with light-switchable RNA tools," said Prof. Kathrin Leppek, an RNA biochemist and research group leader at the Institute of Clinical Chemistry and Clinical Pharmacology of University Hospital Bonn. "With this innovative approach, we want to contribute to a better understanding of the biology of microglia and their role in diseases. Our studies may pave the way to novel therapies."

**A Competitive Selection Procedure**

The project is set to run for three years. Acquiring the grant was a highly competitive process, as the success rate for applications was only 6.5 percent. "The winners in this year's HFSP Research Grant Program are remarkable scientists pioneering life science research that needs international collaboration and basic science in frontier subjects – that is, investigations for which there are no prior studies," said Pavel Kabat, HFSP Secretary-General. "I was thrilled with the proposals we received and look forward to the ground-breaking discoveries that will be revealed."

**Further Information**

The funded project is called "Switchable immunomodulation of mRNA transport and local translation in microglia by bioactive RNAs", principal investigators (alphabetical order): Prof. Dr. Daniël L.J. Broere (University of Utrecht, NL), Prof. Dr. Meng-Meng Fu (University of California, Berkeley, USA), Prof. Dr. Kathrin Leppek (Institute of Clinical Chemistry and

Clinical Pharmacology of University Hospital Bonn, Germany) and Dr. Dragomir Milovanovic (DZNE, Bonn, Germany).

The “Human Frontier Science Program” funds pioneering research in the life sciences. It is run by the “International Human Frontier Science Program Organization”, an international, non-profit entity:
https://www.hfsp.org & https://www.hfsp.org/awardees/newly-awarded

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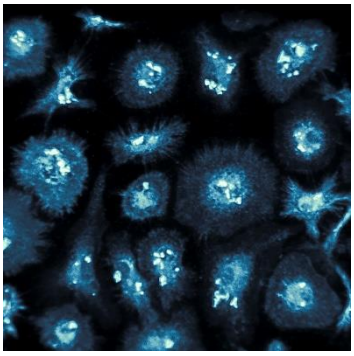

**Caption:** Brain immune cells (“microglia”) in culture exposed to amyloid-beta proteins which are involved in Alzheimer’s disease. Note the heterogeneous shape of microglia, where some contain longer, intricate processes, whereas the others are more blob-like. The ability of microglia to surveil the brain and ingest cellular debris and aggregates relies on their ability to rapidly change shape.

**Credits:** E. Novakova and R. Sansevrino, DZNE/Milovanovic Lab

**Caption:** Dr. Dragomir Milovanovic, research group leader at DZNE’s Berlin site.

**Credits:** DZNE/Frommann

**Caption:** Prof. Kathrin Leppek, an RNA biochemist and research group leader at the Institute of Clinical Chemistry and Clinical Pharmacology of University Hospital Bonn

**Credits:** University Hospital Bonn (UKB) / J.F. Saba

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**About the University Hospital Bonn:** The UKB cares for about 500,000 patients per year, employs 8,800 people and has a balance sheet total of 1.5 billion euros. In addition to the more than 3,300 medical and dental students, a further 580 people are trained each year in numerous healthcare professions. The UKB is ranked first among university hospitals in NRW in the science ranking and in the Focus clinic list and has the third highest case mix index in Germany.

**About the Deutsches Zentrum für Neurodegenerative Erkrankungen, DZNE (German Center for Neurodegenerative Diseases)**
The DZNE is a research institute funded by the German federal and state governments, comprising ten sites across Germany. It is dedicated to diseases of the brain and nervous system, such as Alzheimer's, Parkinson's, and ALS, which are associated with dementia, movement disorders and other serious health impairments. To date, there are no cures for these diseases, which represent an enormous burden for countless affected individuals, their families, and the healthcare system. The aim of DZNE is to develop novel strategies for prevention, diagnosis, care, as well as treatment, and to transfer them into practice. To this end, DZNE cooperates with universities, university hospitals, research centers and other institutions in Germany and abroad. The institute is a member of the Helmholtz Association and belongs to the German Centers for Health Research. www.dzne.de/en