Paper of the Quarter

Outstanding 3R-Research from North Rhine-Westphalia
- 3rd Quarter of 2024 -

The quarterly distinction 'Paper of the Quarter' of the 3R-Competence Network NRW recognizes outstanding contributions to the 3R principles. We are delighted to announce the winner for the third quarter of 2024.

Congratulations to

Selene Lickfett

Heinrich Heine University Düsseldorf

for their publication

"Mutant huntingtin impairs neurodevelopment in human brain organoids through CHCHD2-mediated neurometabolic failure"

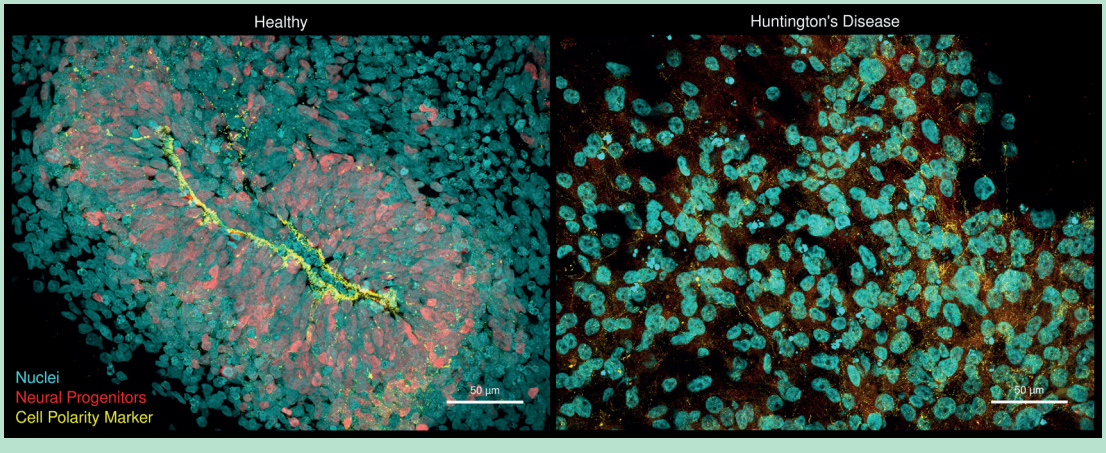
The „Paper of the Quarter" award was given to her publication because she strives in a special way to further develop the 3R principle—"Replace, Reduce, Refine"—which has been applied in laboratory animal science for more than 60 years.

With its innovative approach of using human brain organoids as a model for Huntington's disease, with her research group, she has developed **a non-animal method that reproduces human development and disease processes**. Therefore, they are making an essential contribution to the replacement of animal experiments. At the same time, by establishing a standardized model, they reduce the need for animal experiments in research and improve the quality of the knowledge gained. This paper sets **new standards for the modeling of neurodegenerative diseases**.

The model presented is suitable for leading to an improved implementation of the 3R principle and thus fulfills the requirements of the Scientific Advisory Board of the 3R Competence Network NRW for a Paper of the Quarter in the best possible way.

▶ You can read the original article here

Lisowski P, **Lickfett S**, Rybak-Wolf A, et al. Mutant huntingtin impairs neurodevelopment in human brain organoids through CHCHD2-mediated neurometabolic failure. Nat Commun. 2024;15(1):7027.



The author and her colleagues developed a human cell-based Huntington's disease model using iPSCs (induced pluripotent stem cells) and cerebral organoids, uncovering disrupted neural precursor cell organization (right panel) and gene regulation, offering key insights without animal experiments
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Q&A with the Winner
- 3rd Quarter of 2024 -

How did this research come about?

Most people know about Huntington's Disease (HD), but it remains incurable and not well understood. Over the last decade, research revealed that HD disrupts mitochondria, which provide energy to brain cells, and that some effects may begin pre-natally. To investigate this, we combined genome editing with stem cell-derived brain organoids. With expertise in mitochondria and neuronal models, Prof. Prigione started this project with colleagues in Berlin, introducing the HD mutation and finding it impairs neurodevelopment by disrupting the mitochondrial protein CHCHD2. The project began nearly 10 years ago, so when I joined Prof. Prigione's group in Düsseldorf, there was already a lot of data. Sorting through it took time but gave me a strong base to start my own experiments, and we published this great paper last year.

All members of the research group "Stem Cell Metabolism" led by Prof. Alessandro Prigione (in the middle) ©Selene Lickfett, HHU Düsseldorf

What is the contribution of this research to the 3Rs?

Huntington's Disease does not occur naturally in animals, so it needs to be induced to study it. This can be done using toxins or by developing transgenic models. However, animal models may not be sufficient to fully understand the impact of the disease on the human brain, which exhibits unique features. With the emergence of human pluripotent stem cell-derived neuronal models, it is now possible to study human neuronal cells carrying specific genetic defects, either by deriving them from reprogrammed patient somatic cells or by engineering them using genome editing. With the emergence of brain organoids, these neuronal models can also reproduce key aspects of the three-dimensional features of the human brain. With our research, we modelled HD using brain organoids and found that the mutation may impair human brain development. These results helped us to identify the protein CHCHD2 as a potential novel target for early therapeutic intervention. Therefore, we could show that it is possible to model Huntington's Disease using human stem cell-derived brain organoids to unveil disease mechanisms and detect innovative treatment targets. Such human-driven approaches may not only reduce reliance on animals but could also enhance the precision and translational relevance of findings in human neurobiology.

What is your next 3R research question that you would like to answer?

I want to continue working with human stem cell-derived neuronal models to enhance their physiological relevance, making them even more accurate representations of human brain function. By refining these models, we can significantly reduce the reliance on animal testing, particularly in drug discovery and repurposing. These human in vitro models offer a faster and more precise path to identifying and validating potential treatments, providing insights that are more likely to translate to human clinical outcomes. Additionally, human stem cell-derived models open the door to exploring personalized medicine, tailoring treatment options to individuals or to specific patient groups. This approach not only aligns with the 3R principle by replacing animal models and therefore reducing the number of animals in research, but also holds promise for more effective and inclusive therapeutic strategies.

What is "Paper of the Quarter"?

The quarterly distinction „Paper of the Quarter" serves to recognize outstanding publications in the field of 3R principle of the 3R Competence Network NRW. The aim is to recognize the diversity of research achievements and in particular those publications for which the extraordinary quality cannot be adequately reflected by quantitative evaluation criteria such as the Journal Impact Factor (JIF). A high JIF is not an exclusion criterion, but it is not a selection criterion either.

The award is presented as part of a quarterly open competition. The decision on the publication to be awarded is made by the network's Steering Committee which is formed by the representatives of the eight faculties of medicine in NRW. Each location represented on the Steering Committee has one vote, so that the winner is determined by a simple majority of votes. The selection can be made if at least 50% of the site representatives are present at the relevant meeting. The selected paper will be made visible as „Paper of the Quarter" by the network. The award is also recognized with a certificate.

For more information and submissions for the next round **until February 28th, 2025**, please visit
► **PAPER OF THE QUARTER**

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