New artificial model validates antibodies' ability to reach the brain

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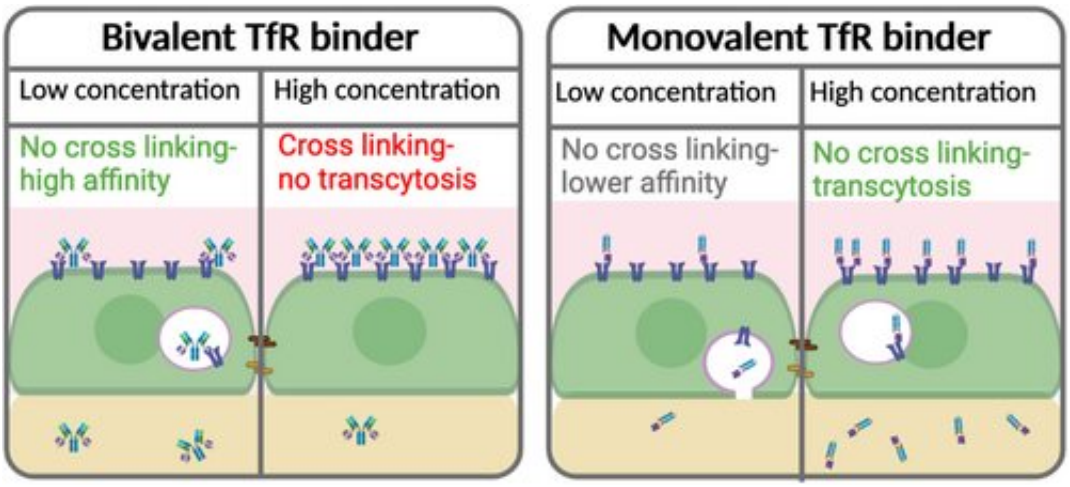

Graphical abstract. Credit: *Journal of Neurochemistry* (2023). DOI: 10.1111/jnc.15768

A research group at Uppsala University has developed a simple and effective artificial blood-brain barrier model that can be used to determine how well antibody-based therapies can enter the brain. Today animal experimentation is the most common method for testing an antibody's function and the new model could reduce the need for animal testing.

Protein-based biopharmaceuticals or biologics, such as antibodies, are promising therapeutic tools to specifically target clumps of protein found in neurodegenerative diseases such as Alzheimer's disease and

Parkinson's disease. However, the blood-brain barrier (BBB) provides a significant hurdle when trying to deliver biologics to areas of the brain to stop these large molecules causing disease.

Greta Hultqvist's research group at Uppsala University has recently published an article in *Molecular Pharmaceutics* highlighting the development of an artificial BBB model that can be used to determine how well antibody-based therapies can enter the brain.

One of the most effective ways of delivering large antibodies into the brain is to piggyback existing pathways within the body that are designed to deliver essential molecules. Antibodies can be re-designed to essentially trick the BBB into thinking the antibody needs to enter the brain via an existing pathway.

Animal experimentation is the most common method for testing whether an antibody can penetrate the BBB. However, aside from the cost in terms of time and money, there is an ethical requirement to reduce the amount of animal experiments. The artificial BBB model developed by the Hultqvist group can now instead be used to validate the antibody's ability to cross the BBB.

"There are many different cell culture-based BBB models published, but most try to mimic the complex functions of the BBB, making them harder to work with when compared to the artificial BBB model we have developed that primarily focuses on studying how biologics are transported," says Jamie Morrison, lecturer at the Department of Pharmacy at Uppsala University.

"Our goal was to develop a robust and simple mouse cell culture model system, where multiple antibodies could be tested in a relatively short period of time. Our results show a clear distinction between antibodies that are able to cross the BBB and those that cannot. Our findings from

the new model have been validated in mice," says Morrison.

The research group has also developed a new in-house designed antibody that has been shown to have a better uptake into the brain compared to traditional antibodies. The new antibody was tested using the artificial BBB model and later confirmed in mice studies. The new antibody was presented in *Journal of Neurochemistry*.

"We validated the results using the artificial BBB model multiple times, but it was still somewhat surprising to see just how well the results mimicked what we saw when conducting brain uptake studies in mice using our antibody. It was exciting to see a significant improvement in brain uptake using the new antibody format," says Nicole Metzendorf, researcher at the Department of Pharmacy at Uppsala University and first author on the antibody study.

Even though the artificial BBB model is new, it has already become ingrained in many of the new research projects within the research group.

More information: Jamie I. Morrison et al, Standardized Preclinical In Vitro Blood–Brain Barrier Mouse Assay Validates Endocytosis-Dependent Antibody Transcytosis Using Transferrin-Receptor-Mediated Pathways, *Molecular Pharmaceutics* (2023). DOI: 10.1021/acs.molpharmaceut.2c00768

Jamie I. Morrison et al, A single-chain fragment constant design enables easy production of a monovalent blood–brain barrier transporter and provides an improved brain uptake at elevated doses, *Journal of Neurochemistry* (2023). DOI: 10.1111/jnc.15768

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