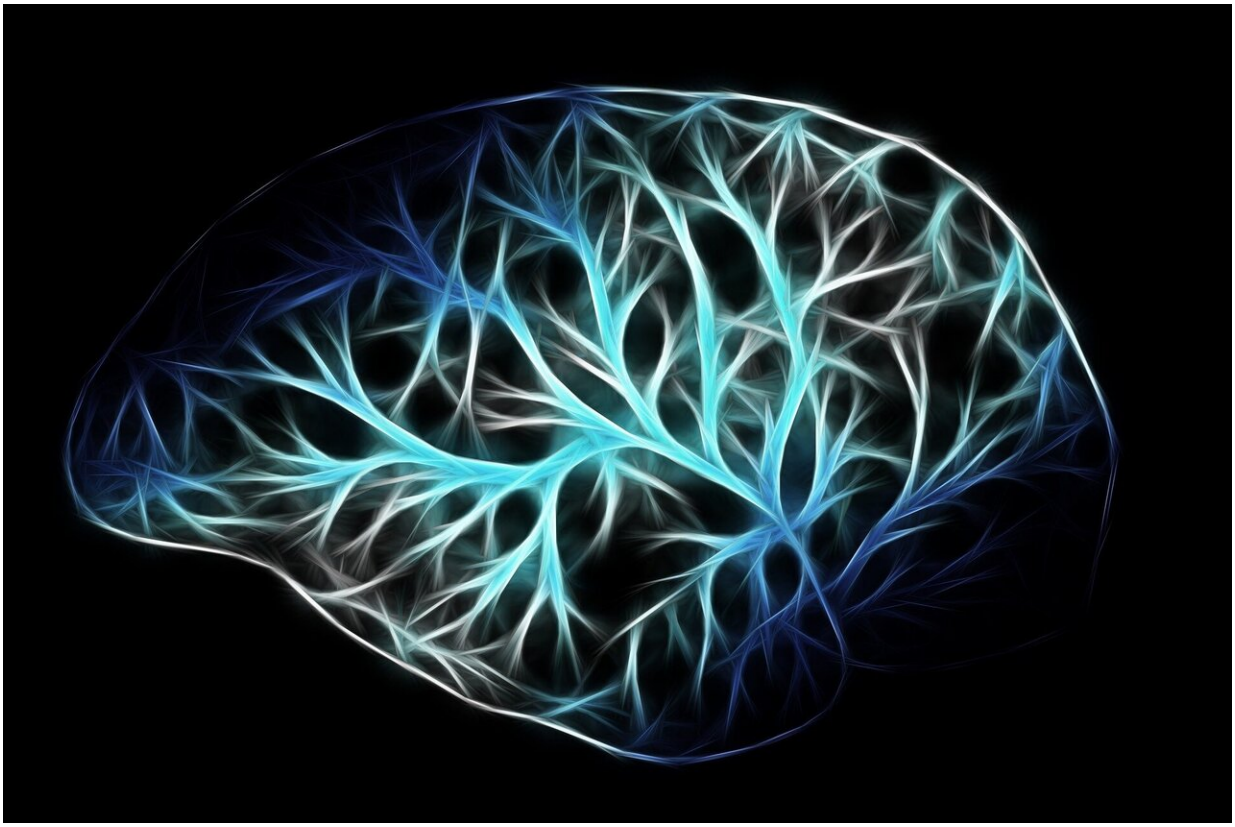
Preventing cell death in the brain calls for a new perspective on drug development

July 29 2021



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Parkinson's disease and Alzheimer's disease are neurodegenerative diseases whose progression cannot be stopped with the currently available drug therapies. Numerous new drug candidates have proved

disappointing in clinical trials. According to Myöhänen, one of the reasons for this could be that drugs are often targeted at one disease mechanism only, such as protein deposits in the brain, which are typical of these diseases. In Parkinson's disease, a protein called alpha-synuclein accumulates in the brain, while in Alzheimer's disease, deposits are formed by beta-amyloid and tau proteins.

"I personally think that drug development should focus on targets that have the potential to affect several disease mechanisms at the same time. This may help to achieve sufficient effectiveness and, in a best-case scenario, to find a treatment that is suitable for several diseases, since different neurodegenerative diseases share many similar mechanisms."

A strong candidate for this type of a drug target is the PREP enzyme, which can be found in brain cells and other parts of the body as well. In neurodegenerative diseases, the activity of PREP changes. Myöhänen and his research group have shown that PREP can affect several factors that promote cell death in the brain, such as the emergence and spread of protein deposits from one cell to another, the decline of cell waste removal, and oxidative stress.

The research group has developed compounds that regulate the activity of PREP and tested them in, e.g., mouse models of Parkinson's disease with promising results: motor symptoms typical of the disease subsided and protein accumulations were cleared from the brain. It is significant that this response was seen in animals whose treatment was begun only after symptoms emerged.

"When symptoms start to show, the disease is already well advanced. However, it is at this point when people, too, start to seek treatment, so it is not realistic to develop treatments that would be initiated earlier, unless a good biomarker is found. Currently, Parkinson's disease is difficult to predict from genes or other biomarkers," Myöhänen says.

The research group is currently looking for partners in the pharmaceutical industry to commercialize promising, yet unpatented PREP regulators in a Research to Business project funded by Business Finland.

For PREP, this is a second coming as a target of drug development. At the turn of the millennium, it looked like clinical trials with PREP inhibitors had come a dead end worldwide, failing to produce the expected results. According to Myöhänen, this was partially caused by the research settings used.

"For example, efforts were made to improve the memory of healthy older people, which I would say is an impossible goal.

There has also been a change in our understanding of PREP's activity in neurodegenerative diseases.

"In the past, PREP was mainly thought to degrade small mediators affecting signaling pathways, and efforts in drug development sought to prevent this. Now, however, we know that PREP works in many other ways, too. Based on our own research, the interactions of PREP with other proteins, such as alpha-synuclein and tau, are probably more significant, and may prove to be a better starting point for drug development than old PREP inhibitors."

The research findings are based on persistent work, as Myöhänen has studied the topic already in his Master's and doctoral theses in the then University of Kuopio. Following the transfer of Myöhänen's Ph.D. supervisor, Professor Pekka Männnistö, to the University of Helsinki, Myöhänen also ended up there, continuing his research on PREP. For the past ten years, he has led a research group focusing on PREP at the University of Helsinki and, since last year, also at the University of Turku.

In addition to working in three universities in Finland, Myöhänen has also been a post doc researcher at the University of Antwerp in Belgium and at Georgetown University in the United States.

"New perspectives, operating models and partners gained from different research environments have been very useful for my own research, and as a professor, I will certainly try to encourage young researchers to go abroad. However, if cuts in the funding of science continue at the current rate in Finland, there is a risk that they will not be tempted to return and to advance research in Finland," he points out.

Myöhänen will start as Professor of Pharmacology and Drug Development at the University of Eastern Finland in the beginning of August. Once in Kuopio, he will also focus his PREP research increasingly on Alzheimer's disease.

"This aspect has risen alongside Parkinson's disease in recent years, and the preliminary results encourage us to continue. Kuopio is a great place to conduct research on Alzheimer's disease in particular: there are extremely good research groups and networks working around the theme. On a compact campus, everything is easily accessible, including the university hospital that has a positive attitude to research."

"Alongside PREP, the idea is also to look for other similar drug targets that affect several disease mechanisms. I think this could be the key to effective treatments unless clinical trials prove otherwise."

Provided by University of Eastern Finland