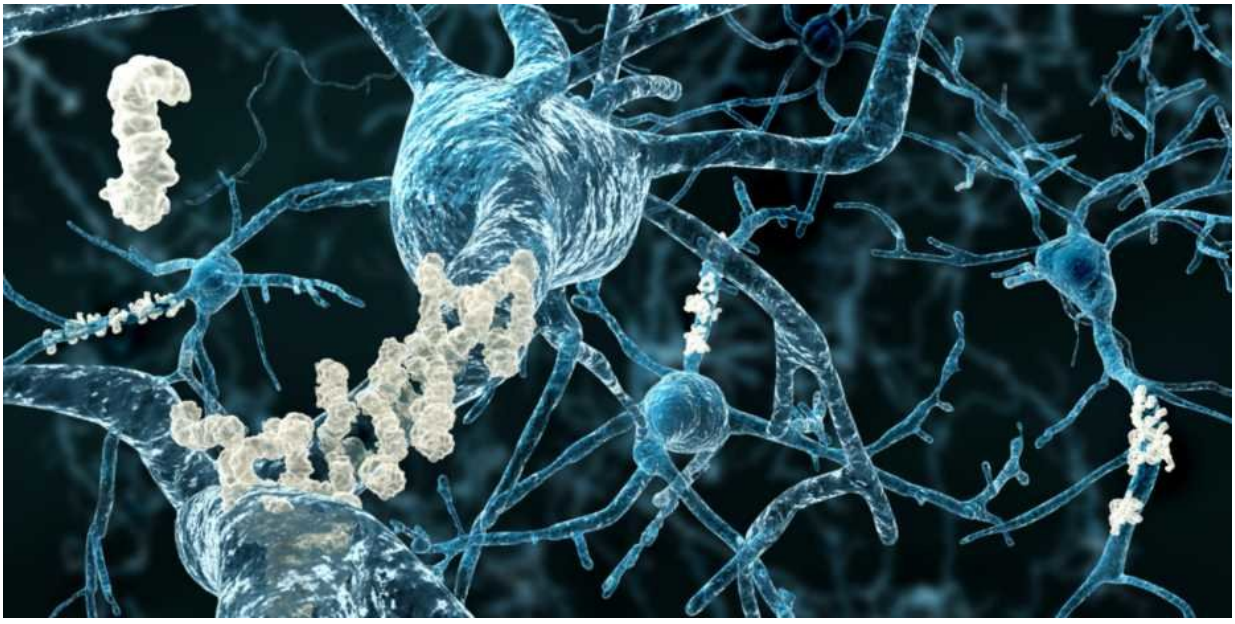
Protein analysis for personalised medicine

March 16 2018, by Peter Rüegg



At the axons of neurons, plaques of strucutrally modified proteins (grey) accumulate and are the root cause of neurodegenerative diseases such as Parkinson's or Alzheimer's disease. Credit: selvanegra / istockphoto.com

New knowledge about proteins helps researchers develop innovative solutions for clinical practice, for example to the benefit of patients with Parkinsons's disease.

To this day, there are no therapies that work equally well for all patients diagnosed with the same disease. Many conventional therapies are effective in only a limited proportion of cases. And some patients who

initially respond to a specific medication later suffer an inexplicable relapse. The one-size-fits-all pill remains an illusory dream.

Take the example of Parkinson's disease: Doctors generally prescribe Levodopa, a drug that relieves some patients of their tremors. In certain cases, however, it accelerates the loss of cognitive functions, thus impairing rather than improving the patient's condition. None of the diagnostic methods available at present enables doctors to predict how or whether a patient will respond to the prescribed treatment – or decide which cases call for an alternative therapeutic approach.

Biomarkers for Parkinson's

This is the point of departure for protein scientist Paola Picotti's work as part of the ETH Domain's strategic focus area Personalized Health and Related Technologies (PHRT). A professor at the Institute of Molecular Systems Biology, Picotti plans to set up a research project to develop biomarkers for the early detection and subtype classification of Parkinson's disease. The underlying technology comes from the field of proteomics.

While the genome represents the complete set of genetic information that defines a living organism or a virus, the proteome represents the entire set of proteins expressed by a given individual at a given time, under defined conditions: for example, a patient's protein profile as recorded during a health check-up. Proteins, and the amino acids they consist of, are complex molecules that perform many different functions, such as fighting infections (antibodies) or regulating metabolic processes (enzymes). Proteomics is the field of research in which mass spectrometry-based and bioinformatic methods are used to investigate the proteome.

Unlike the genome (the complete set of an organism's DNA sequences),

the proteome (the collective term for all proteins in an organism) changes dynamically in response to environmental stimuli, diseases and active drug ingredients. "Specific proteins often provide an indication of whether an organism is healthy or sick," says Picotti. She laid the foundations for her new project a few years ago by developing a protein measurement method that makes it possible to identify not only all "normal" proteins in a random biological sample but also those that are misshapen. This is important when designing systems for the early diagnosis of Parkinson's disease.

It is thought that Parkinson's disease is caused by the formation of amyloid plaques in the brain, which in turn damage the nerve cells. Amyloid plaques are clusters of degenerate proteins that gradually clump together to form insoluble deposits. In her preliminary study of samples obtained from Parkinson's patients, Picotti was able to detect such defective proteins. However, the number of test subjects was too low to produce statistically significant results.

As the next stage in her quest to identify biomarkers for use in the early detection and diagnosis of Parkinson's disease, Picotti now intends to analyse and compare proteins in samples obtained from a large cohort of Dutch patients on two separate occasions: once shortly after the onset of symptoms and the second time ten years later. "We are looking for correlations between structural changes in the proteins and the appearance of symptoms such as loss of cognitive functions," Picotti explains. The study also included a control group of healthy subjects.

The ETH professor hopes this will lead to improved therapy for Parkinson's patients. Most drugs are developed in vitro, i.e. in the laboratory, and may seem to work at this stage but often fail when used to treat real patients. Picotti's approach allows drug candidates to be tested on human tissue and determine how and whether they interact with proteins. The results will allow specialists to distinguish between

effective and ineffective drugs, and help tailor solutions to suit individual patients.

Provided by ETH Zurich