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Ressort: Special interest

A new approach to studying proteins in action

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Proteins are the building blocks of life – and the docking sites for pharmaceutical compounds. Therefore, understanding exactly how proteins function and react to stimuli opens up new possibilities in pharmaceutical research. Four researchers have now been awarded a prestigious ERC Synergy Grant to investigate how proteins respond to electric fields. Their method will be prototyped using the X-ray free-electron laser

Four researchers have been awarded an ERC Synergy Grant by the European Research Council for their joint project SPARX. The grant will provide approximately CHF 8.5 million over the next six years. The researchers are John Beale from the PSI Center for Photon Science, Doeke Hekstra from Harvard University with the University of Hamburg as his host institution, Thomas J. Lane from the Deutsches Elektronen-Synchrotron (DESY) in Hamburg and Guido Meier from the Max Planck Institute for the Structure and Dynamics of Matter (MPSD) in Hamburg. Together, they aim to develop a new capability to study how proteins — the building blocks of life — respond to electric fields.

SPARX, which stands for Structural Perturbations by Applied electRic-field Xtallography, builds on established serial crystallography techniques and the emerging domain of electric-field crystallography. In serial crystallography, crystals are first grown from proteins that can then be illuminated with X-rays. By analysing the resulting diffraction patterns, it is possible to determine the location of every individual atom within a protein.

“If we can understand the structure of proteins down to the level of individual atoms, we can better understand their functions within living organisms,” explains John Beale, whose research takes place at the X-ray free-electron laser SwissFEL at PSI.

Electric fields to investigate protein dynamics

“This knowledge can then be used to develop new pharmaceutical compounds in a targeted way.” Proteins are not static structures: they change their shape to initiate processes in our bodies. Therefore, researchers aim to study proteins in action. Until now, laser pulses have typically been used to trigger protein dynamics, which are then observed using X-rays like the ones from SwissFEL.

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However, Doeke Hekstra explains: “Only a small number of proteins in our bodies respond directly to light. We therefore want to use electric fields instead of laser pulses to trigger these protein dynamics.” This approach would actually reproduce conditions found in living organisms. Our bodies use electric fields in many contexts, for example when nerve cells transmit signals in our brains. Regions of enzymes also change their electrical charge to initiate chemical reactions in the body. “If we use electric fields to stimulate proteins, we can investigate a broader range of protein dynamics,” Hekstra sums up.

Infrastructure for SwissFEL and other research facilities

The researchers have several objectives. First, they will use part of the ERC Synergy Grant to develop and test devices that complement existing serial crystallography techniques by incorporating the use of electric fields to trigger protein dynamics.

They will subsequently use the devices at SwissFEL to investigate proteins of interest. “One thing we’re really interested in is using the electric field to investigate proteins that cannot currently be targeted with pharmaceutical compounds. These are known as undruggable proteins,” says Thomas J. Lane.

The researchers hypothesise that their new method could reveal so-called ‘cryptic binding pockets’ that emerge during protein dynamics and might provide novel docking sites for new therapeutics. “We particularly hope to understand signaling proteins and ion channels – knowledge that will inform the development of future treatments for cancer and neurological disorders, such as Parkinson’s disease,” Lane adds.

Finally, the researchers plan for their devices to serve as a model for similar setups at synchrotron light sources, which also provide X-rays for scientific research. “Naturally, we have the Swiss Light Source SLS at PSI in Switzerland and the PETRA III synchrotron source of DESY in Hamburg, Germany, in mind,” says Guido Meier. In the longer term, these types of devices could be installed at synchrotron facilities around the world, further advancing the study of protein dynamics. “Achieving the goal of SPARX requires an international collaboration bringing together researchers from different institutions, each with their respective expertise,” emphasises Meier.

About PSI

The Paul Scherrer Institute PSI is the largest research institute for natural and engineering sciences in Switzerland. It is the central location of Switzerland’s large research facilities, available to both the scientific community and industry. Its research spans future technologies, energy and climate, health innovation and fundamentals of nature. The annual budget is CHF 450 million. PSI employs 2300 people;

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around a quarter of these are postdoctoral researchers, PhD students or apprentices. PSI is part of the ETH Domain, which also includes ETH Zurich and ETH Lausanne, as well as the other federal research institutes Empa, Eawag and WSL. (SOURCE: Paul Scherrer Institute PSI, Laura Hennemann)

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