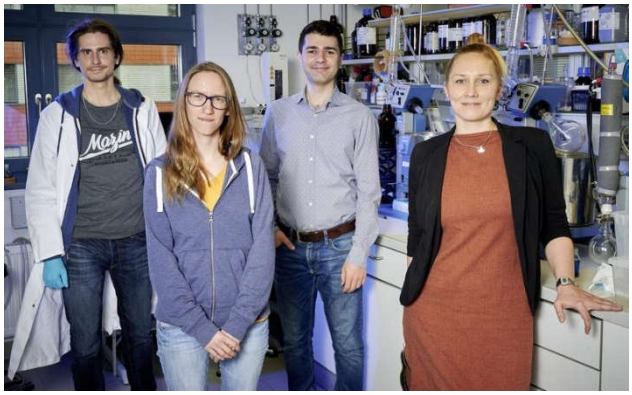
May 2021

Light to get things moving - Excellence Initiative at LIKAT successfully completed

Young researchers at the Leibniz Institute for Catalysis, LIKAT, have completed their part in the state's PePPP excellence initiative with a doctorate and three master's theses. They explored photochemical mechanisms for the synthesis of therapeutics against the so-called copper storage disease. Here, for example, misfolded proteins impair the uptake of copper and promote oxidative stress in the body's cells. LIKAT chemists tested, among other things, catalytic processes to help the proteins fold accurately and become functional again.



In the research alliance, junior researchers from the fields of pharmaceutics, clinical science, chemistry, physics and ethics were to break new ground for the development of therapies for liver and pancreatic diseases. The project was funded by the EU for four years with five million euros. In addition to LIKAT, five partner institutes at the universities of Rostock and Greifswald were involved.

Baseball or tennis ball?

Copper is an important trace element; our organism needs it for cell respiration, among other things. Too much of it, however, is harmful, as shown by the rare metabolic disease Wilson's disease, in which copper accumulates in cells of the liver. This is due to mutations in a single gene, which causes structural defects in the protein responsible. The protein loses its function and is no longer able to capture excess copper atoms.

Junior research group leader Dr. Jola Pospech explains the protein structure responsible, which the chemists had to deal with at the molecular level in the laboratory: "We can imagine the protein like a hand that is supposed to enclose a baseball, in this case the copper atom. If the protein is folded incorrectly, the hand might stay open and not be able to grip the ball or the copper. Or the hand grips the wrong object, say a tennis ball, and the copper has no place to go." In both cases, the copper does not enter the metabolism; it accumulates in the cell.

The task of the LIKAT chemists involved was to get the faulty protein going catalytically, i.e., to get it to move by chemical impulses, in a sense its hand to close the copper or let go of the tennis ball to make room for the baseball.

Metabolism imitated by photocatalysis

Says Dr. Pospech, "We tested a wide variety of substances for their ability to help the protein fold properly." To synthesize these folding helpers, they used catalysts that they activated with light. This allows them to make compounds that are difficult to access by thermal means. Jola Pospech's team used catalysts very similar to the enzymes in this natural process in the liver, which also allowed them to artificially generate oxidative stress in the reaction vessel. Dr. Pospech: "In this way, we gain access to the metabolites of the folding helpers, the so-called metabolites, which can now be specifically produced and tested for their effectiveness."

In addition, the project participants at LIKAT synthesized copper probe molecules, which their partners in the research network can use to determine the amount of copper that accumulates in cells. The probes indicate the findings by fluorescence, and the higher the cellular copper load, the stronger the fluorescence.

Fledged with the project

The researchers are still a long way from developing a new therapeutic for Wilson's disease. That was not the primary goal, as Jola Pospech says. The Excellence Initiative was primarily intended to make young scientists less afraid of neighboring disciplines and to offer them the opportunity to conduct interdisciplinary research.

At LIKAT, the participants, one doctoral student and three master's graduates, have "quite fledged," as their research director Dr. Pospech says. They are now taking the next academic hurdles at universities in Regensburg and Aarhus, including at Bayer AG. "One colleague, a chemist like us, will now do a doctorate in physics."

In total, the PePPP collaborative project in the state supported two junior research group leaders, 9 postdocs, 11 doctoral students and 16 scientific or student assistants.

Scientific contact persons:

Dr. Jola Pospech, e-mail: jola.pospech@catalysis.de, Tel.: +49 (0)381 1281-177