TRP Starter Grant: a jump-start to the clinical phase

Non-reclosable – protection against restenosis in CHD

In patients with coronary heart disease (CHD), the coronary arteries narrow due to deposited fatty tissue. When a narrowed blood vessel is reopened, and a stent is placed, small injuries to the inner vessel wall often occur. The body responds by remaking parts of the injured layer. Over time, this causes the blood vessel to narrow again. This process, called restenosis, is one of the most common clinical complications. Zouhair Aherrahrou, a DZHK scientist at the Institute of Cardiogenetics at the University of Lübeck, has been researching a gene related to CHD together with Jeanette Erdmann* since 2011. In collaboration with Oliver Müller from the University Hospital Schleswig-Holstein, Campus Kiel, the team is using a promising RNA-based therapeutic target to prevent such restenosis in the future. The TRP Starter Grant supports Aherrahrou in optimally preparing his treatment idea for the preclinical phase. In addition to financial support for one and a half years, he will also receive expert advice. "When applying for the TRP Starter Grant, you must present the planned clinical follow-up project to a committee. Among others, scientists from industry sit on this committee and assess whether the outlined idea has potential for the preclinical phase, but also provide valuable suggestions for improvement," says Aherrahrou.

Knockout protects against restenosis

Mice lacking the ADAMTS7 gene, known as knock-out mice, are protected from having a blood vessel reocclude. The fact that these knock-out mice were completely healthy made the gene, or its product, an interesting therapeutic target. Aherrahrou and his team developed an inhibitor of

Zouhair Aherrahrou

ADAMTS7 that produces less of the gene product. In a mouse model of atherosclerosis, he has already shown that this inhibitor protects the animals from narrowed vessels. Now, Aherrahrou wants to develop the RNA therapy further to help patients with CHD one day.

Industry contact and patent planned

"The path from basic research to the patient is long, and for me it is also a completely new world," says the biologist from Lübeck. The TRP Starter Grant, which started in 2022, arrived just at the right time for him. He plans to use mini pigs in the preclinical phase to test whether his developed inhibitor protects the animals from restenosis. With the TRP Starter Grant, Aherrarhou can test the inhibitor in the laboratory on tissue from the carotid artery of mini pigs. If the results are as good as the data from the mouse, he would like to apply for a TRP project next year. A company from Braunschweig is already supporting the project, and Aherrarhou is also in the process of patenting his idea.

Inhibition of ADAMTS7 by siRNA to prevent restenosis: first steps towards a preclinical study

Project lead: Zouhair Aherrahrou (Hamburg/Kiel/Lübeck) | Participating scientists: Jeanette Erdmann*, Oliver Müller (both Hamburg/Kiel/Lübeck partner site) | Duration: 2023–2024 | Budget: €147,747

*Jeanette Erdmann passed away unexpectedly in summer 2023. For the obituary dated July 11, 2023, see

dzhk.de/en/the-dzhk/press/article/obituary-of-dzhk-professor-jeanette-erdmann/

These two projects also received a TRP Starter Grant in 2022:

Development of a novel platelet inhibitor for the prevention and treatment of atherothrombosis

Platelet aggregation inhibitors have been shown to protect against heart attacks and are, therefore, a cornerstone of cardiovascular medicine. They prevent coronary arteries from closing when atherosclerosis breaks down and activates platelets. However, the use of conventional platelet aggregation inhibitors does not provide complete protection and is associated with bleeding complications. The project team has developed a new platelet inhibitor that prevents plaque-induced platelet aggregation in vitro and arterial thrombosis in a mouse model without interfering with hemostasis.

The group plans to investigate whether their findings can be translated to the human system. To do so, they plan to reproduce their previous results and generate additional data using alternative measurements of thrombus formation in stromal chamber models. In addition, the scientists will investigate the pharmacodynamics and pharmacokinetics of the new inhibitor.

Project lead: Philipp von Hundelshausen, Christian Weber (Munich) | Participating scientists: Tilman M. Hackeng, Stijn Agten (Cardiovascular Research Institute Maastricht, The Netherlands), Götz Münch (AdvanceCOR GmbH) | Duration: 2023–2024 | Budget: €150,000

Cardiomyocyte-specific restoration of endogenous transcription of KLF15 as a novel therapeutic concept in heart failure

Many factors, including coronary artery disease and hypertension, contribute to a high prevalence of cardiovascular disease. These are characterized by weakening of the myocardium due to a loss of functional cardiomyocytes. The cause may be a dysregulation of healthy gene transcription. Researchers hypothesize that precise restoration of this healthy transcription may prevent the deterioration of cardiomyocyte function or rescue it from failure. Among these factors, the team of scientists has identified a repressor of disease pathways, Krüppel-like factor 15 (KLF15), which is lost during hypertrophic remodeling of the heart. When a genetic system is used to normalize transcription of KLF15 in cardiac muscle cells, attenuation of the pathological response and preservation of cardiac function is observed in mice. The scientists were also able to replicate the loss of KLF15 and repair the loss in a human heart muscle model. In this project, they will test the safety and efficacy of this novel therapeutic principle in a pig model.

Project lead: Laura C. Zelarayán-Behrend (Göttingen) | Participating scientists: Eric Schoger, Rabea Hinkel (both Göttingen partner site), Lorenz Lehmann (Heidelberg/ Mannheim) | Duration: 2023–2024 | Budget: €149,976

Collaboration with Product Development Unit of DZIF

In 2021, the DZHK and the German Center for Infection Research (DZIF) have agreed on closer collaboration in the development of novel drugs and medical devices. The DZHK's project leaders now can call on the DZIF's Product Development Unit (PDU) for expert advice. In the year under review, two ongoing translational research projects used the PDU's advisory services. The PDU supports the projects in project management and regulatory approval issues.