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PRO LOEWE NEWS

The LOEWE research initiatives report

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Cover photo: Rocaglates specifically and efficiently inhibit the RNA helicase eIF4A: this enzyme is required by many viruses and other pathogens for replication. The picture shows Dr. Francesca Magari – postdoc in the Grünweller lab – purifying the enzyme. Photo: Regina Gerlach-Riehl

PROF. ARNOLD GRÜNWELLER OF LOEWE-DRUID PUBLISHES A COMPREHENSIVE PICTURE OF THE POTENTIAL OF PLANT-BASED COMPOUNDS TO COMBAT VIRUSES AND OTHER PATHOGENS

Based on synergies of several groups in the **LOEWE Centre DRUID**, a study on the broad-spectrum antipathogenic effect of rocaglates (compounds isolated from plants) could be published in June 2023, the results of which could be groundbreaking for the treatment of severe infectious diseases.

Rocaglates, a group of substances originally isolated from plants of the genus *Aglaia* (belonging to the mahogany family), play a key role in this study. Rocaglates are known for their high efficacy against RNA viruses, including highly infectious (highly pathogenic) viruses such as Ebola-, Lassa-, Crimean-Congo- and Coronaviruses. Rocaglates inhibit the RNA helicase eIF4A, which is required to unwind stable RNA structures at the beginning of protein synthesis, by fixing the bound mRNA to the surface of the enzyme. This mechanism is also known as RNA clamping. Stable RNA structural elements and/or polypurine sequences are required for clamping of the mRNA. Inhibition of eIF4A prevents these RNA structures from being unwound and, as a consequence, ribosomes cannot bind to the corresponding mRNAs. This prevents their translation into a protein and the pathogen is no longer "viable".

Important: Viruses very often form highly structured regions in untranslated mRNA regions that are essential for their own replication. Therefore, a large number of viruses are dependent on the unwinding activity of eIF4A. Rocaglates are relatively well tolerated by humans and are already under investigation in clinical trials, which has brought this substance class into the focus of drug development during the last years and could represent a significant step forward in the treatment of viral infections and other pathogenic diseases.

Within the DRUID Centre, Prof. Arnold Grünweller has already investigated and characterized the antiviral activity of rocaglates in collaboration with various virological groups of the DRUID consortium (labs of Professors John Ziebuhr, Eberhard Hildt, Stephan Becker, Friedemann Weber). In a recent study regarding neglected tropical infectious diseases (Obermann et al., 2023), the concept of inhibition of eIF4A by rocaglates has now been extended to other pathogens, such as *Schistosoma mansoni* (a blood fluke that causes schistosomiasis), *Trypanosoma brucei brucei* (parasite that transmits African sleeping sickness), *Toxoplasma gondii* or *Plasmodium falciparum* (causative agents of toxoplasmosis or malaria), but also to the vector of yellow fever, the tiger mosquito *Aedes aegypti*.

Commenting on the content and results of the study, Prof. Grünweller says: "We have succeeded for the first time in providing a comprehensive picture of the antipathogenic potential of rocaglates. With the data obtained, it is in principle possible to distinguish between pathogens that are sensitive or resistant to inhibition of eIF4A by rocaglates. In addition, our results reveal potential evolutionary scenarios for the development of rocaglate resistance and provide insights into structure-activity relationships that might be useful in the synthesis of new rocaglates or other eIF4A inhibitors."

Interestingly, the first studies with rocaglates were conducted in the context of cancer. The rocaglate zotatifin (developed by *eFFECTOR Therapeutics*) is currently in a Phase 2 clinical trial in patients with solid tumor diseases. Inhibition of the helicase eIF4A during protein synthesis is thus not only relevant in the fight against viruses and other pathogens but is also of central importance in the field of cancer therapies.

In addition to the lab of Professor Grünweller, the labs of Professors Andreas Heine, Carlos Hermosilla, Anja Taubert, Simone Häberlein and Christoph G. Grevelding as part of the DRUID consortium were also involved in the study. The project was led by Dr. Gaspar Taroncher-Oldenburg (Philadelphia, USA) with the participation of the Sarawak Biodiversity Centre, Kuching, Malaysia.

Reference:
Obermann W, Azri MFD, Konopka L, Schmidt N, Magari F, Sherman J, Silva LMR, Hermosilla C, Ludewig AH, Houhou H, Haeberlein S, Luo MY, Häcker I, Schetelig MF, Grevelding CG, Schroeder FC, Lau GSK, Taubert A, Rodriguez A, Heine A, Yeo TC, Grünweller A, Taroncher-Oldenburg G. Broad anti-pathogen potential of DEAD box RNA helicase eIF4A-targeting rocaglates. Sci Rep. 2023 13(1):9297. doi: 10.1038/s41598-023-35765-6.

PS: On 05/09/2023 Prof. Arnold Grünweller will give a lecture on the subject of topic under the title „Promising herbal active substances from Asian mahogany plants", online, 5 pm. Further info at https://www.loewe-druid.de/

From left: Prof. Dr. Arnold Grünweller, Dr. Francesca Magari, postdoc and project leader, both working for LOEWE-DRUID and Dr. Stefan Merkl from LOEWE-CoroPan in front of the Institute of Pharmaceutical Chemistry in Marburg. Photo: Regina Gerlach-Riehl

SPECIAL HONOUR: GIESSEN-BASED ANIMAL VENOM RESEARCHER DR. TIM LÜDDECKE OF LOEWE-TBG WAS INVITED TO THE 72ND LINDAU NOBEL LAUREATE MEETINGS

Dr. Tim Lüddecke is researching the potential applications of natural substances produced by snakes, spiders, and insects, some of which are still unknown. Photo: Désirée Schulz

He will probably always remember this conference: Together with more than 600 other young scientists, Dr. Tim Lüddecke was invited to this year's Lindau Nobel Laureate Meetings. From June 25 to 30, 2023, the researchers had the unique opportunity to exchange ideas with Nobel laureates in the small Bavarian town on Lake Constance. The conferences rotate thematically between the Nobel Prize disciplines of physics, chemistry and – as this year – physiology/medicine. The participants can further benefit: They stay connected within the Lindau Alumni Network for life afterwards.

"The discussions and exchanges were very enriching and opened new perspectives for me. I look forward to staying in contact with Nobel laureates and young scientists," said Lüddecke, an animal venom researcher.

Lüddecke is a junior research group leader in the "Animal Venomics" research group at the Department of Bioresources of the Fraunhofer Institute for Molecular Biology and Applied Ecology IME, as well as a scientist at the Institute for Insect Biotechnology at Justus Liebig University Giessen (**LOEWE-ZIB** funded until 2022). At the **LOEWE Centre for Translational Biodiversity Genomics (LOEWE-TBG)** he is project area spokesman for Natural Product Genomics.

Lüddecke conducts research in the field of biology and biochemistry on possible applications of animal venoms, especially those from arthropods such as insects and spiders. He uses systems biology and biotechnology methods to identify and characterize previously unknown natural products. The applied aspect of his work is particularly important to him, be it for plant protection, industrial goods production, or biomedicine. Together with other **LOEWE-TBG** researchers, Lüddecke has already succeeded in isolating new biomolecules from the venoms of spiders, ants, or bees that are effective against (multi-resistant) pathogens or breast cancer.

AROUND 29 MILLION EUROS IN STATE FUNDING FOR OUTSTANDING RESEARCH IN HESSE: FROM JANUARY 1, 2024, A NEW LOEWE CENTRE AND THREE NEW CLUSTER WILL BE FUNDED

DYNAMIC, TRIO, ADMIT and **HABITAT**, these are the names of the **LOEWE** research Centre and the three new **LOEWE** research clusters, which will be funded with around 29 million euros of state money from January 1, 2024 for a period of four years. This was decided by the LOEWE Administrative Commission on the basis of the evaluations of the external experts and the recommendations of the LOEWE Program Advisory Board. All five Hessian universities, two universities of applied sciences, Geisenheim University and three non-university research institutions were involved in the applications submitted. The four selected research projects will receive project funding for a period of four years in the 16th season of the Hessian research funding program LOEWE. In the process, the new LOEWE Centre will then have the chance to apply for funding for another three years in 2027. "New approaches for the diagnosis and treatment of mental illnesses and in cancer, adaptation to global warming in agriculture and in medical care - these are important topics for our society, triggered by changing environmental and working conditions," explains Science Minister Angela Dorn. "The applications for these research fields show that Hessian universities and research institutions are leading the way here - we are happy to support them with our LOEWE funding program in finding solutions to these burning problems. [...]" "Once again, the program advisory board intensively deliberated on very high-ranking applications in order to select the best projects for multi-year LOEWE funding in the strictly science-led process," added Prof. Dr. Stefan Treue, chairman of the advisory board. "All the research projects are characterized by their high scientific level and very current topics, but also by their embedding in the long-term development plans of the cooperating universities and research institutions."

The projects of the 16th LOEWE funding round at a glance:

DYNAMIC – Dynamic Network Approach of Mental Health to Stimulate Innovations for Change.
Scientific coordination: Prof. Dr. Winfried Rief.
Lead management: Philipps University of Marburg. Project partners: Goethe University Frankfurt, Justus Liebig University Giessen, Technical University Darmstadt, Leibniz Institute for Educational Research and Educational Information DIPF, Ernst Strüngmann Institute for Neuroscience ESI.
LOEWE research Centre, funding: 14.7 million euros.

TRIO – Transformative Mixed Culture Systems for One Health.
Scientific coordination: Prof. Dr. Miriam Athmann.
Lead: University of Kassel. Project partners: Justus Liebig University Giessen, Geisenheim University of Applied Sciences.
LOEWE research cluster, funding: 4.8 million euros.

ADMIT – Advanced Medical Physics in Imaging and Therapy.
Scientific coordination: Prof. Dr. Boris Keil.
Lead management: Technical University of Central Hesse.
Project partners: Philipps University Marburg, Justus Liebig University Giessen.
LOEWE research cluster, funding: 4.8 million euros.

HABITAT – Health Affected by Climate Change and Air Pollution – Pathophysiology and Regional Management.
Scientific coordination: Prof. Dr. Dr. Thomas Brenner.
Lead management: Philipps University Marburg.
Project partner: Fulda University of Applied Sciences.
LOEWE research cluster, funding: 4.8 million euros.

MELEK CANAN ARKAN APPOINTED LOEWE-FCI PROFESSOR FOR TUMOR METABOLISM

Melek Canan Arkan has been appointed Professor for Tumor Metabolism of the **LOEWE Centre FCI** at the Institute of Tumor Biology and Experimental Therapy, at Georg-Speyer-Haus in Frankfurt am Main, in August 2023.

In tumor metabolism, the aim is to investigate how tumors obtain their energy, which metabolites are formed in the process, and how these metabolites influence growth and neighboring cells. The interaction of the metabolic function of the microbiome (community of all living microorganisms in a specific habitat, e.g. the human intestine) with the tumor also plays a crucial role in this context. Trillions of bacteria colonize the human gut and contribute significantly to the regulation of metabolic functions and immune homeostasis. Microbial community dynamics are of critical importance, as the composition and functional profile of the microbiota influence cancer susceptibility and response to therapy. Diet can directly or indirectly modulate the microbiome, playing a critical role in disease outcome.

Research from Canan Arkan's lab aims to unravel the effects of dietary intake on microbiota structure and function during cancer and therapy. They are clarifying whether targeted nutrition (precision nutrition) can pave the way for individualized interventions in cancer by regulating the microbiome.

One more layer of complexity in Tumor Metabolism is the circadian rhythm: that is, it matters not only what we eat and how food is metabolized, but also what time of day we eat. The lab explores whether dietary interventions can be used to prevent cancer, and how to time the treatment.

Canan Arkan combines all these layers and employs state-of-the-art methods to decipher the simplicity in the complexity that can be used as preventive or therapeutic measures to fight cancer.

LOEWE-WHITE BOX FEATURED AT WISSEN ANIMIERT – A NEW SERIES BY HESSEN SCHAFFT WISSEN

Artificial Intelligence and Machine Learning are becoming increasingly important. However, there is often a lack of transparency and understanding of how these models arrive at their decisions. This is where the **LOEWE research cluster WhiteBox** at TU Darmstadt comes into play: it aims to make AI models more comprehensible and explainable – also with the help of Cognitive Science.

Until a few years ago, intelligent systems had to be precisely programmed for their task and environment by experts. For some years now, however, a paradigm shift has been taking place in AI: Instead of manually coding all the steps of knowledge processing, machines are now being programmed with the ability to learn. With the help of Machine Learning, robots, for example, are trained with a very large number of example situations and can then act as learned in similar situations. Deep Neural Networks, which are inspired by the structure of the human brain, achieve great success in this. A large number of artificial neurons, organised and networked in layers, process a large amount of data with a high computing effort. At the same time, the learned, intelligent behaviour of such an AI system can often no longer be (fully) understood or predicted, even by the experts who built it, due to the great complexity of the system. The model becomes a black box – just as human intelligence, based on biological neuron networks, is.

LOEWE-WhiteBox is therefore grounded in both AI research and Cognitive Science and develops methods at the interface of these disciplines to better understand human and artificial intelligence. A central thesis is that only the two-way exchange of these research directions will provide deep insight into intelligent systems and enable artificial and human intelligence to work together in partnership in the future.

"Wissen animiert" is a series by "Hessen schafft Wissen". The 3D animated films provide brief insights into the world of research in Hessen. They aim to arouse interest in science and invite further exploration of the topic depicted.

Canan Arkan is a newly appointed Professor of Tumour Metabolism, advertised as part of the LOEWE Centre FCI at the Institute of Tumour Biology and Experimental Therapy, Georg-Speyer-Haus, with Goethe University. She is researching metabolic processes in connection with tumour diseases, the microbiome, nutrition and the circadian rhythm. Photo: FCI

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ProLOEWE. LOEWE Research Initiatives Network
Phone: +49 561.804-2348
kontakt-proloewe@uni-kassel.de
www.proloewe.de

Postal address:
ProLOEWE
c/o Universität Kassel
Mönchebergstrasse 19
34125 Kassel
Germany

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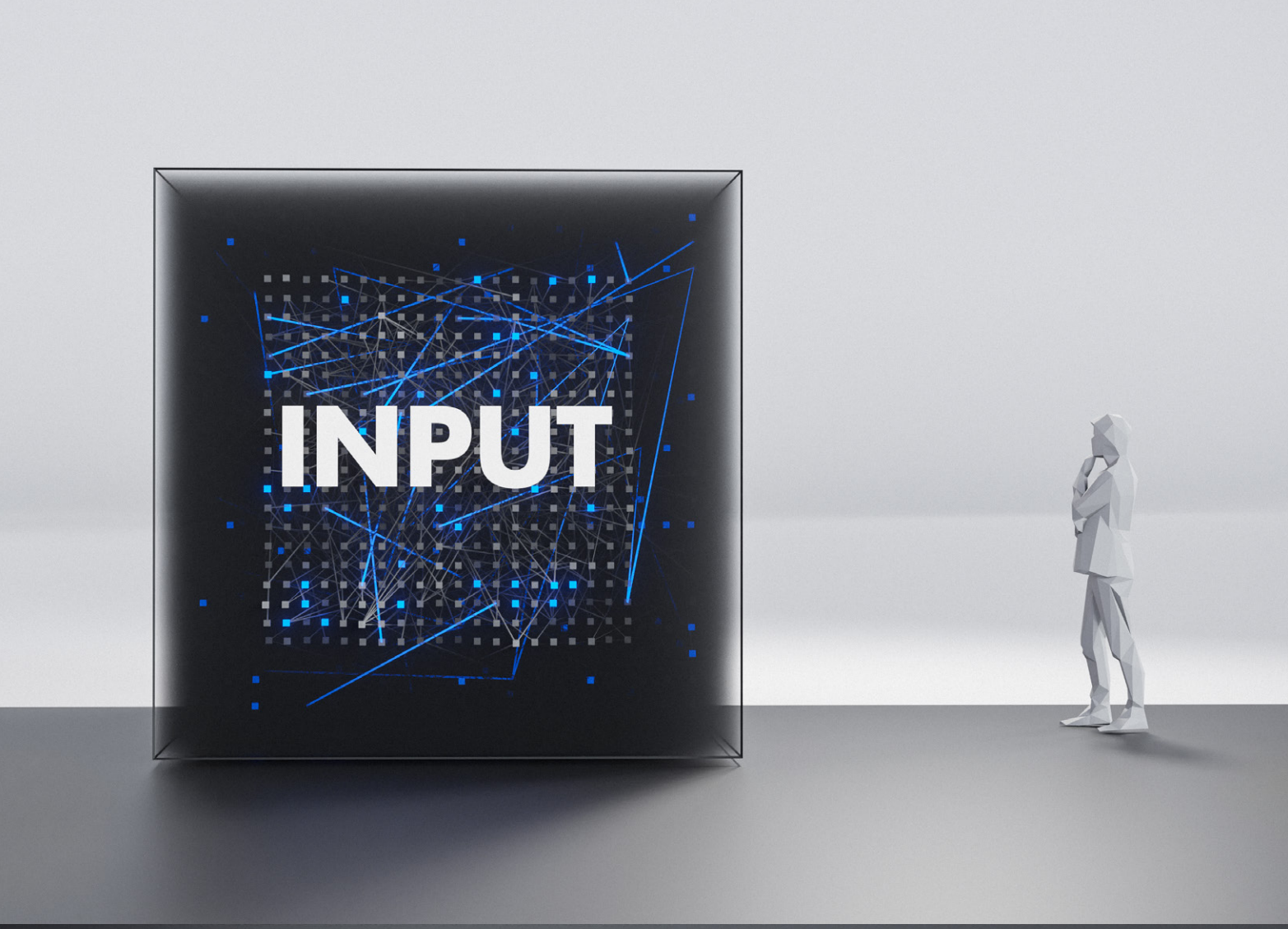

WhiteBox brings more transparency to the performance of AI models. To this end, the project also uses the comparison of approaches to explain human intelligence on the one hand and artificial intelligence on the other. Photos: Hessen schafft Wissen / Moritz Mohr

Prof. Dr. Florian Greten, here in the museum of the Georg-Speyer-Haus (GSH), is spokesman of the LOEWE Centre FCI and director of the GSH in Frankfurt am Main. His scientific focus is on research into the development of colorectal cancer and the development of new therapeutic approaches. For this, he was awarded the Advanced Grant – the EU's most highly endowed science prize – by the European Research Council (ECR) in 2021. Photo: Steffen Böttcher

Prof. Dr. Florian R. Greten
Cancer researcher with passion

Professor Greten, you are the spokesperson for the LOEWE Centre FCI, which has been funded since 2019. Can you tell us something about how you came up with the idea to apply for a LOEWE Centre? *The idea for the Frankfurt Cancer Institute (FCI) came very early on. Shortly after I started here in Frankfurt in 2013, together with colleagues at the University Hospital (Professors Hubert Serve, Ivan Đikić and Karlheinz Plate), I thought about how we could better connect the interaction of basic science with clinical research and improve so-called translational research. We then came up with the idea of working together on an interdisciplinary basis within the framework of a new building that was to be constructed, and we contacted the state government to this end. The then Minister of Science, Boris Rhein, was very quickly convinced by our concept of constructing such a building. Fortunately, the German Cancer Aid also liked our project and supported us with a donation of 20 million euros. In order to implement the FCI's content-related concept, we have submitted an application for a LOEWE Centre below.*

What exactly does the LOEWE Centre Frankfurt Cancer Institute deal with and why is it so important? *We try to mechanistically investigate relevant observations from the clinic, such as a lack of or different response to therapy, and to develop new therapy concepts that we then test clinically. It is important that clinical scientists and basic scientists, bioinformaticians and pharmaceutical chemists work closely together on the projects from the beginning and exchange information regularly. Only in this way can we learn from each other: the basic scientists from the clinicians about the relevant problems and the clinicians from the basic scientists with regard to preclinical methods. It is particularly important to integrate bioinformaticians into the respective projects at an early stage in order to be able to carry out appropriate analyses together and to plan experimental approaches.*

Why did you decide to become a physician, especially with a focus on cancer research? *Studying medicine was the only thing that came into question for me. Even at school I had a great interest in science but just as great was the interest in being clinically active and being able to treat and help patients. Studying medicine combines this in an ideal way.*

At the end of 2022, you received the very pleasant news that the funding for LOEWE-FCI was extended by the Hessian Ministry of Science and Arts until 2025. Can you give us an insight: What have you been able to achieve so far through LOEWE and what do you hope to achieve in the following years? *We have succeeded in proving that our new interdisciplinary concept supported by the newly established technology platforms works. In addition to a large number of excellent publications, we have already been able to initiate several clinical studies to test our new results directly on patients. Some of these studies have already provided us with very promising data for cancer therapy, so that we are now planning to pursue these in further studies.*

Is there already an idea of how things will continue after the funding? *The LOEWE Centre and the technology platforms are to be integrated into the Georg-Speyer-Haus. Next year, we (GSH including LOEWE-FCI) intend to apply for membership of the Gottfried-Wilhelm-Leibniz Science Association (WGL). As soon as the new building is ready for occupancy, we will then be able to fully implement the original idea and work on our projects in a joint building.*

The Hessian LOEWE programme is unique in Germany – also because it funds basic research in particular. Why would you say it is so important? *Without the generous state support, we would never have been able to put our idea into practice. The funds required to set up such a Centre with all its platforms, professorships, working groups and projects are enormous and there is no other funding instrument in Germany or Europe that would otherwise have been considered for such a project.*

The entire interview is available online at proloewe.de