

March 14, 2023

## **Paul Ehrlich and Ludwig Darmstaedter Prize: Insights into the Origin, Evolution and Development of our Immune System**

*Award ceremony in Frankfurt's Paulskirche – Acknowledgement of Frederick W. Alt and David G. Schatz, winners of the main prize, and of Leif S. Ludwig, winner of the Early Career Award*

**The 2023 Paul Ehrlich and Ludwig Darmstaedter Prize, worth €120,000, will today be awarded to immunologists Frederick W. Alt and David G. Schatz in Frankfurt's Paulskirche for their discovery of molecules and mechanisms that enable our immune system to perform the astonishing feat of recognizing billions of different bacterial, viral and other antigens on first contact. The Early Career Award goes to Leif S. Ludwig, biochemist and physician, for a method he has devised to analyze the origin and development of human blood cells, which also include the cells of the immune system.**

FRANKFURT. Unlike more primitive organisms, jawed vertebrates like we humans not only have an innate immune system but also an adaptive one that is capable of preparing itself for all kinds of invaders. This is because – at some point in the course of evolution – one of our ancestors apparently succeeded in taming a DNA parasite that had implanted itself in his genome. This is how the parasite became the gene for an enzyme that advanced to become the command center of immunological diversity. This enzyme, RAG1/2, excises fragments from the DNA of certain chromosomes in maturing immune cells (lymphocytes) and recombines them to form functional genes in a random process. This somatic recombination multiplies the variability of antibodies and T cell receptors. It is a prerequisite for our body's ability to build around ten billion different antibodies, although it only has about 20,000 protein blueprints in the form of genes. **David G. Schatz** discovered the RAG1/2 enzyme, **Frederick W. Alt** the enzymes that repair the DNA excised by it. "In decades of research, Alt and Schatz have shed light on the previously hidden evolution of our adaptive immunity, and in so doing they have raised our knowledge of the development of the immune system to a new level," says Professor Thomas Boehm, Chairman of the Scientific Council of the Paul Ehrlich Foundation, commending the achievements of the two winners of the main prize.

The RAG1/2 enzyme is the motor for somatic recombination. Without it, neither functional B and T cells nor effective adaptive immunity can develop. Many cases of severe immunodeficiency are caused by mutations of the RAG genes, and some lymphomas and leukemias are associated with malfunctions of the enzymes encoded by these genes. This makes understanding not only the molecular mechanism but also their evolutionary origin and how they behave in the living cell nucleus even more important. According to **Schatz's** findings, RAG1/2 originates from a gene that began

jumping at will through the genome of our very early ancestors millions of years ago, like a kind of selfish parasite. In structural biology studies, Schatz has traced these jumps (transposons) over several stages of evolution. He has shown which biochemical tricks vertebrates used to fix the jumping RAG1/2 gene at a certain position and harness it for the immune system.

As they migrate through the cell nucleus of immature lymphocytes, RAG enzymes draw together chromatin clusters, in which the DNA is coiled up in a space-saving way, temporarily and again and again to form recombination centers. There, they perform chromatin scanning, which **Alt** has described for the first time. They draw a chromatin thread, which can be over a million DNA letters long, through the recombination center like a loop. The result is that gene segments previously far apart are suddenly opposite each other and can be joined firmly together.

The B and T lymphocytes, on which acquired immunity rests, are components of our blood, in which at least 500 billion old cells per day are replaced by new ones in a healthy person. They originate from hematopoietic stem cells in the bone marrow and then mature on divergent developmental trajectories over several stages, like all other blood cells. Determining the resulting lineages and relationships is highly interesting for medicine, for example for identifying at which branch point a leukemia cell forms. **Leif S. Ludwig**, the winner of this year's Early Career Award, has devised a method that opens up the possibility for the first time for medicine to do this relatively inexpensively, quickly and reliably. Ludwig's method, which has already been tested on individual patients, combines the analysis of mutations in mitochondria with the latest technologies for the gene sequencing of individual cells.

### **2023 Paul Ehrlich and Ludwig Darmstaedter Prize**

[https://www.uni-frankfurt.de/124912621/2023\\_Alt\\_Schatz](https://www.uni-frankfurt.de/124912621/2023_Alt_Schatz)

Dr. Frederick W. Alt is *Charles A. Janeway Professor of Pediatrics* and *Director of the Program in Cellular and Molecular Medicine* at Boston Children's Hospital, a *Howard Hughes Medical Institute Investigator*, and *Professor of Genetics* at Harvard Medical School. <https://www.childrenshospital.org/research/labs/alt-laboratory-research>

Dr. David G. Schatz is *Professor of Molecular Biophysics and Biochemistry* at Yale University and *Chairperson of the Department of Immunobiology* at Yale School of Medicine. <https://medicine.yale.edu/profile/david-schatz/>

### **2023 Paul Ehrlich and Ludwig Darmstaedter Early Career Award**

[https://www.uni-frankfurt.de/131228185/2023\\_Ludwig](https://www.uni-frankfurt.de/131228185/2023_Ludwig)

Dr. Leif S. Ludwig is the leader of the Emmy Noether Junior Research Group "Stem Cell Dynamics and Mitochondrial Genomics" at the Berlin Institute of Health at Charité and the Max Delbrück Center. <https://www.mdc-berlin.de/de/ludwig>

**Further information:**

Press Office Paul Ehrlich Foundation  
Joachim Pietzsch  
Tel.: +49 (0)69 36007188  
[j.pietzsch@wissenswort.com](mailto:j.pietzsch@wissenswort.com)  
[www.paul-ehrlich-stiftung.de](http://www.paul-ehrlich-stiftung.de)

The **Paul Ehrlich and Ludwig Darmstaedter Prize** is Germany's most renowned medical award, endowed with €120,000. It is traditionally awarded on Paul Ehrlich's birthday, 14 March, in Frankfurt's Paulskirche. It honours scientists who have made special contributions in areas of research represented by Paul Ehrlich's achievements, namely in immunology, cancer research, haematology, microbiology and chemotherapy. The prize, which has been awarded since 1952, is funded by the Federal Ministry of Health, the German Association of Research-based Pharmaceutical Companies (Verband Forschender Arzneimittelhersteller e.V.) and by earmarked donations from the following companies, foundations and institutions: Else Kröner-Fresenius-Foundation, Sanofi-Aventis Deutschland GmbH, C.H. Boehringer Sohn AG & Co. KG, Biotest AG, Hans und Wolfgang Schleussner-Foundation, Fresenius SE & Co. KGaA, F. Hoffmann-LaRoche Ltd., Grünenthal Group, Janssen-Cilag GmbH, Merck KGaA, Bayer AG, Georg von Holtzbrinck GmbH & Co.KG, GlaxoSmithKline GmbH & Co. KG, B. Metzler seel. Sohn & Co KGaA. The award winners are selected by the Scientific Council of the Paul Ehrlich Foundation. A list of the members of the Scientific Council is available on the website of the Paul Ehrlich Foundation.

The **Paul Ehrlich and Ludwig Darmstaedter Prize for Young Researchers**, first awarded in 2006, is presented once a year by the Paul Ehrlich Foundation to a young scientist working in Germany for outstanding achievements in biomedical research. The prize money of €60,000 must be used for research-related purposes. University professors and senior scientists at German research institutions are eligible to nominate candidates. The award winners are selected by the Foundation Council on the recommendation of an eight-member selection committee.

The **Paul Ehrlich Foundation** is a legally dependent foundation administered in trust by the Association of Friends and Sponsors of Goethe University. Honorary President of the Foundation, which was established in 1929 by Hedwig Ehrlich, is Professor Katja Becker, President of the German Research Foundation, who also appoints the elected members of the Scientific Council and the Board of Trustees. The Chairman of the Scientific Council of the Paul Ehrlich Foundation is Professor Thomas Boehm, Director at the Max Planck Institute for Immunobiology and Epigenetics in Freiburg; Chairman of the Board of Trustees is Professor Jochen Maas, Managing Director Research & Development, Sanofi-Aventis Deutschland GmbH. In his function as Chairman of the Association of Friends and Benefactors of Goethe University, Professor Wilhelm Bender is also a member of the Scientific Council of the Paul Ehrlich Foundation. The President of Goethe University is in this capacity also a member of the Board of Trustees.

**Goethe University** is a research-oriented university in the European financial centre Frankfurt am Main. The university was founded in 1914 through private funding, primarily from Jewish sponsors, and has since produced pioneering achievements in the areas of social sciences, sociology and economics, medicine, quantum physics, brain research, and labour law. It gained a unique level of autonomy on 1 January 2008 by returning to its historic roots as a "foundation university". Today, it is one of the three largest universities in Germany. Together with the Technical University of Darmstadt and the University of Mainz, it is a partner in the inter-state strategic Rhine-Main University Alliance. **Internet:** [www.uni-frankfurt.de](http://www.uni-frankfurt.de)

**Publisher:** The President of Goethe University **Editors:** Joachim Pietzsch / Dr Markus Bernards, Science Editor, PR & Communication Department, Theodor-W.-Adorno-Platz 1, 60323 Frankfurt am Main, Tel: -49 (0) 69 798-12498, Fax: +49 (0) 69 798-763 12531, [bernards@em.uni-frankfurt.de](mailto:bernards@em.uni-frankfurt.de).