PAUL EHRLICH FOUNDATION

JOHANN WOLFGANG GOETHE
UNIVERSITÄT
FRANKFURT AM MAIN

The Chairman of the Scientific Council

Press Release • Press Release • Press Release • Press Release

Frankfurt am Main, September 28, 2005

RNA Interference: Dicing and Slicing for the Sake of Healthy Cells

Paul Ehrlich and Ludwig Darmstaedter Prize 2006 goes to Craig Mello and Andrew Fire / invitation to compete for the generously endowed prize for young researchers issued for the first time this year

FRANKFURT. Biochemist **Professor Dr. Craig C. Mello** (44), Howard Hughes Medical Institute at the Massachusetts Medical School in Worcester, U.S.A., and biologist **Professor Dr. Andrew Z. Fire** (46), School of Medicine of Stanford University, California, U.S.A., will receive the Paul Ehrlich and Ludwig Darmstaedter Prize 2006, endowed with a total of € 100,000, for the discovery of so-called non-coding double-stranded interfering RNAs (***r**ibo**n**ucleic **a**cids*), also known as agents of RNA interference (RNAi)**.** This was resolved by the Scientific Council of the Paul Ehrlich Foundation. The announcement states: "RNA interference is a relatively simple and universal method of silencing individual genes by selectively knocking out their messenger RNA through a complex mechanism with the help of double-stranded small RNA molecules. It has become an indispensable tool of fundamental research in the last few years and has already made an invaluable contribution to the understanding of how molecules work, making it relevant to medicine. The work done by Andrew Fire and Craig Mello laid the foundations for this."
With RNA interference, Andrew Fire and Craig Mello discovered a universal system of gene regulation. The technique can be applied in principle to any RNA sequence and is thus an ideal tool for temporarily silencing cellular genes for a functional genome analysis in order to understand their function. The possibilities for using this method are so diverse that in December 2002 the magazine "Science" celebrated the interfering RNAs discovered by Mello and Fire as the "breakthrough of the year".
The Paul Ehrlich and Ludwig Darmstaedter Prize, to be presented in the Frankfurter Paulskirche on March 14, 2006, is one of the highest and most internationally renowned awards conferred in the Federal Republic of Germany in the field of medicine.
For the first time, the Paul Ehrlich Prize for Young Researchers, endowed with € 60,000, will also be awarded on March 14, 2006. The prize, for which candidates were invited to compete this year, is intended for young scientists, aged less than 40 years, for outstanding biomedical research at German research institutions.

Importance of RNA interference

The DNA of any animal and plant cell contains thousands of genes. The cell uses various protective mechanisms to ensure that only those genes which are needed at any given time are

Senckenberganlage 31 · 60325 Frankfurt am Main · E-Mail: Paul-Ehrlich-Stiftung@pvw.uni-frankfurt.de

translated into proteins. These mechanisms effectively regulate which genes are transcribed into messenger RNA which serves as a blueprint for protein synthesis by ribosomes, the cellular protein factories. However, not only endogenous genes have to be silenced, depending on their development level and the cell function. It is even more important that the cell should intercept and inactivate harmful genes, for example the genes of pathogenic organisms. To be able to do this, the cell has developed – in the course of evolution – highly effective security systems, including RNA interference discovered in 1998 by Craig Mello and Andrew Fire. Almost all plant and animal cells use this protective mechanism to destroy the RNA transcripts of potentially dangerous genes before the latter can be translated into proteins. With the help of RNA interference, the cell also regulates the activity of normal genes in the course of growth and development, because the genes active in a muscle cell are different, for example, from those in a nerve cell.

How does RNA interference work?

In RNA interference, the cell inhibits gene expression by forming double-stranded RNA molecules. Interference arises when an enzyme called "dicer" cuts longer double-stranded RNA molecules – viral RNA molecules, regulatory RNA sequences or synthetic RNAs introduced into the cell from outside – into fragments of a standard length (21 to 23 base pairs). All of these RNA pieces are subsequently cleft into their two single strands. One of them then combines with proteins to form the so-called "RNA-inducing silencing complex" (RISC). This complex intercepts messenger RNAs with complementary sections. If their sequence is a relatively perfect match with the original, the captured messenger RNA molecule is sliced in the middle by an RISC complex enzyme called "slicer" and rendered inoperable. As a result, the protein coded by this messenger RNA can no longer be formed. If the intercepted messenger RNA is only a partial match with the sequence of the RISC-bound siRNA, RISC simply retains the messenger RNA. Because of this, the ribosomes are held up by the messenger RNA in protein synthesis and also fail to form a functioning protein. Depending on the siRNA, therefore, the protein synthesis of certain genes can be completely shut off. This also applies to siRNA introduced into the cell from outside. "And that is where the great potential of RNA interference lies in its medical application", explains Dr. Rino Rappuoli, Institute for Immunological Research in Siena, Italy, and Member of the Paul Ehrlich Foundation's Scientific Council. "The point is that, through the synthesis of certain RNA double-stranded chains, you can determine precisely which target messenger RNA is to be destroyed."

Therapeutic potential

Through the introduction of defined siRNA molecules into human cell cultures (a technique pioneered by Dr. Thomas Tuschl's group, then at the Max Planck Insitute in Gottingen), thousands of research teams have succeeded in carrying out genetic interference experiments. These experiments have shown feasibility (at least in culture) of inhibiting the spread of viruses, including those responsible for aids, infantile paralysis and hepatitis C, at least temporarily, by stopping the production of viral proteins indispensable for the reproduction of pathogenic organisms. But the road to the therapeutic use of RNA interference on human beings is still long. The reason is that while the inhibiting effect of siRNAs spreads throughout the entire organism in the case of the roundworm *Caenorhabditis elegans* and in plants, there are local limits to this effect in mammals, including human beings. Just how siRNA can be transported to defined targets is the object of intensive research.

The Paul Ehrlich Foundation

The Paul Ehrlich Foundation is a legally dependent foundation of the Association of Friends and Patrons of the Johann Wolfgang Goethe University Frankfurt am Main e. V. The Honorary President of the Foundation, which was set up in 1929 by Hedwig Ehrlich, is the

President of the Federal Republic of Germany, who also appoints the elected members of the Scientific Council and the Board of Trustees. The Chairman of the Association of Friends and Patrons is at the same time the Chairman of the Scientific Council of the Paul Ehrlich Foundation. This committee, comprised of 12 nationally and internationally reputed scientists from five countries, selects the prizewinners. The President of the Johann Wolfgang Goethe University is ex officio member of the Board of Trustees. The prize is financed by tied donations, one half from companies and one half from the Federal Ministry of Health.

Further information
Further background texts, personal biographies, selected publications, lists of publications and photos of the prizewinners can be obtained from the Press Office of the Paul Ehrlich Foundation (c/o Dr. Monika Mölders, Telephone: 069/798-23266 or 06238/982783, Telefax: 06238/982784, E-Mail: Paul-Ehrlich-Stiftung@pvw.uni-frankfurt.de).
You can find more information on the websites of
Professor Dr. Andrew Fire, Departments of Pathology and Genetics, Stanford University School of Medicine: http://genome-www.stanford.edu/group/fire and
Professor Dr. Craig Mello, Howard Hughes Medical Institute, University of Massachusetts: http://www.hhmi.org/research/investigators/mello.html