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Six eminent scientists share the world's largest brain research prize

The Brain Prize - Denmark's 1 million euro brain research prize - is awarded to six leading scientists for the development of 'optogenetics', a revolutionary technique that advances our understanding of the brain and its disorders.

Copenhagen Monday 11 March 2013 - Grete Lundbeck European Brain Research Foundation announced today that The Brain Prize 2013 is awarded to Ernst Bamberg, Edward Boyden, Karl Deisseroth, Peter Hegemann, Gero Miesenböck and Georg Nagel for:

'...their invention and refinement of optogenetics. This revolutionary technique allows genetically specified populations of neurons to be turned on or off with light, offering not only the ability to elucidate the characteristics of normal and abnormal neural circuitry but also new approaches to treatment of brain disorders'

The four European and the two American scientists laid the foundations for 'optogenetics' - one of the most exciting recent technical developments in neuroscience, which allows particular classes of nerve cells to be selectively activated or inhibited by light. This apparently implausible approach to the study of brain function was first suggested by Francis Crick, co-discoverer of the structure of DNA, in 1999.

Over the past decade, Francis Crick's dream has been transformed into the reality of a powerful and versatile technology. In 2010, optogenetics was named Method of the Year across all fields of science by the leading journal Nature Methods, and 'Breakthrough of the Decade' by the journal Science.

The roots of optogenetics were in Europe: German and Austrian researchers discovered molecular constructs capable of changing the activity of cells in response to illumination, and developed methods to use such molecules to exercise selective control over particular classes of neurons.

The story starts with work on tiny single-celled algae that move towards sources of light by beating a whip-like flagellum attached to the cell. In 1992, Peter Hegemann and colleagues at the Max Planck Institute of Biochemistry in Martinsried, Germany, studied the light-sensitive substance in the external membranes of these algae. This substance is very similar to the visual pigment rhodopsin found in the photoreceptors of the human eye. Like rhodopsin, the molecule found in algae responds to blue light, and this causes a change in the permeability of the membrane. Positively charged ions, including calcium, enter the cell of the alga and that activates movement of the flagellum, moving the cell towards the light.

In 2002-3, Hegemann (then at the University of Regensburg), with Georg Nagel and Ernst Bamberg of the Max Planck Institute of Biophysics in Frankfurt, Germany, succeeded in transferring the gene for the algal light-sensitive molecule into eggs of the African clawed frog - a standard technique for genetic expression of substances, so that their properties can be studied in detail. They discovered that, unlike rhodopsin in the eye, algal rhodopsin includes a 'channel', that is a tiny pore through which ions can move. The channel changes its shape when the rhodopsin

portion of the molecule is illuminated and this account for the entry of positive ions. They therefore called the molecule Channelrhodopsin.

In 2003, Nagel, Bamberg, Hegelmann and colleagues described a variant of channelrhodopsin (ChR2), which allowed more rapid light activation of the associated channel. They were able to express ChR2 in the surface membranes of non-neural mammalian cells, and confirmed that exposure to light caused the cells to depolarize - becoming more positively charged inside. Since depolarization of neurons triggers nerve impulses, it was clear that this might provide the key to Francis Crick's dream of turning on nerve cells with light.

In 2002, a group led by the Austrian neuroscientist Gero Miesenböck (who was then working in New York) described a different strategy for optical activation of neurons. They used genetic methods to assemble three different molecules, including true rhodopsin from the eye of the fruit fly, *Drosophila*. In 2005, Miesenböck's group used yet another optogenetic technique to turn on nerve cells in fruit flies and showed that their flying behaviour could be changed by shining a light on them. This was the first demonstration of optogenetic activation in a behaving animal.

In a crucial collaboration, Nagel and Bamberg supplied the ChR2 genetic construct to two young American researchers, Ed Boyden, a graduate student, and Karl Deisseroth, laboratory principal investigator, both at Stanford in California. They successfully used a virus to transfer the ChR2 gene into cultured nerve cells from the rat, and confirmed that brief flashes of light caused impulses in these cells. This result, published in a seminal paper in the journal *Nature Neuroscience* in 2005, opened up the application of optogenetics in mammals.

Between 2005 and 2007, Hegemann, Boyden, Bamberg, Nagel and Deisseroth worked to develop optogenetic methods for silencing, as well as exciting neurons. Two different genes, introduced into the same nerve cells, allow them to be activated or silenced by illumination, depending on the colour of the light. Additional genetic techniques allow the light sensitive molecules to be selectively expressed only in certain classes of nerve cells - inhibitory neurons, or neurons producing a particular type of chemical transmitter substance, for example. Light to trigger the activation or silencing of particular cells can be delivered either from outside, in the case of small, translucent animals, or through a tiny fibre-optic probe inserted into the brain. In this way, specific types of nerve cells, in very localised points in the brain, can be rapidly tuned on or off, exactly as Francis Crick had proposed.

The reaction to these demonstrations of the effectiveness of optogenetics has been rapid and far-reaching. In the past few years optogenetic manipulation has been used to study the way in which nerve circuits control such functions as learning, arousal, tactile and visual sensation, breathing, and movement. Attention is now focusing on the use of optogenetic methods to understand disorders of neural circuitry, for instance in addiction and anxiety.

The potential medical applications are also exciting. Research is already underway to use optogenetic techniques to restore some sort of vision after age-related degeneration of the retina of the eye. And optogenetic methods, combined with fibre-optic probes, offer a possible sophisticated alternative to deep brain stimulation with metal electrodes for treatment of Parkinson's disease, intractable pain, depression and other psychiatric disorders.

Professor Colin Blakemore, Chairman of the Selection Committee for the Brain Prize said: "Optogenetic control of nerve cells is arguably the most important technical advance in neuroscience in the past 40 years. It offers a revolution in our understanding of the way in which circuits of neurons carry out complex functions, such as learning and controlling movement. And it could provide an entirely new approach to the restoration of function in blindness or brain degeneration, and to the treatment of conditions as varied as pain, depression, addiction and

Parkinson's disease. The Brain Prize honours four European scientists who laid the foundations of optogenetics, and two young Americans who, in collaboration with the Europeans, launched the technology that is having such a huge impact in neuroscience."

About the Brain Prize

The Brain Prize - € 1 million is awarded annually by Grete Lundbeck European Brain Research Foundation, a charitable, non-profit organization.

The Brain Prize is a personal prize awarded to one or more scientists who have distinguished themselves by an outstanding contribution to European neuroscience.

For more information please contact:

Kim Krogsgaard, MD, DMSc	or	Nils Axelsen, MD, DMsc
Director		Chairman
Mobile: +45 2014 8384		Mobile: +45 40548646
Phone: +45 3917 8240		
kk@thebrainprize.org		

Grete Lundbeck European Brain Research Foundation
Ole Maaløes Vej 3
2200 N
Copenhagen
Denmark
www.thebrainprize.org

Biographies

Ernst Bamberg

Born November 09, 1940

Professor, Head of the Dept. of Biophysical Chemistry and Director at the Max Planck Institute of Biophysics, Frankfurt am Main, Germany

Honours and awards

1987	Boris Rajewsky Prize for Biophysics
2009	Wissenschaftspreis des Stifterverbands für die Deutsche Wissenschaft
2010	Wiley Prize in Biomedical Sciences
2010	Karl Heinz Beckurts Prize for technical innovation
2011	Member of the Leopoldina National Academy of Sciences
2012	K.-J. Zülch Prize for basic Neuroscience

Current research interests

Functional analysis of membrane proteins with biophysical methods as electrophysiology, spectroscopy and structural methods for deeper understanding of the molecular mechanism of these proteins. The focus lies on microbial rhodopsins, the light gated ion channels (channelrhodopsins) and the light driven ion pumps, which are used as optogenetic tools for the light control of electrically excitable cells. Goal of these studies is the development of improved

tools with respect to light sensitivity, speed and ion selectivity in order to make them more applicable to the brain. Within an international consortium the “new” rhodopsins are used for the recovery of vision on blind animals with a biomedical perspective.

Edward S. Boyden III

Born August 18, 1979; Plano, Texas, USA

BS Physics, BS Electrical Engineering Computer Science, MEng Electrical Engineering Computer Science, MIT PhD, Neurosciences, Stanford University, California, USA

Associate Professor, MIT Media Lab and McGovern Institute, Departments of Biological Engineering and Brain and Cognitive Sciences, MIT, Cambridge, Massachusetts, USA

Honors and awards

2007 NIH Director's New Innovator Award
2007 Society for Neuroscience, Research Award for Innovation in Neuroscience
2010 Paul Allen Distinguished Investigator Award in Neuroscience
2011 Perl/UNC Neuroscience Prize
2011 The AF Harvey Prize

Current research interests

My group at MIT develops tools for analyzing and engineering brain circuits. Driven by the goal of optical control of targeted neurons, in 2000 Deisseroth and I began to discuss using opsins to manipulate neural activity, and in early 2004 we established a collaboration with Nagel and Bamberg that led to a successful demonstration of opsin-mediated neural activation that summer. My group continues to introduce optogenetic tool classes into neuroscience, including halorhodopsins (2007) and bacteriorhodopsins (2010) for optical neural silencing. We optimize these opsins for novel neuroscientific applications, and develop complementary technologies such as scalable neural recording technologies.

Karl Deisseroth

Born November 18, 1971; Boston, USA

MD PhD, is the DH Chen Professor of Bioengineering and of Psychiatry and Behavioral Sciences at Stanford University, California, USA

Honors and awards

Member of the National Academy of Sciences, and of the US Institute of Medicine
2005 The NIH Director's Pioneer research award funding
2010 The Nakasone Prize,
2011 The Alden Spencer Prize
2012 The UNC/Perl and the Zuelch Prize
2013 The Richard Lounsbery Prize

Current research interests:

My work is focused on developing and applying methods for studying intact biological systems with fine spatiotemporal resolution, and high molecular and genetic specificity. In developing optogenetics between 2004 and 2013, my team integrated genetics and optics to enable experimental gain- or loss-of-function of well-defined events in specific cell-types within intact systems, using genes taken from evolutionarily distant organisms such as algae and archaeobacteria. Since my transduction of microbial opsins into neurons in 2004, my applications of my technologies have spanned from basic work on motivated behavior to disease-focused work on Parkinsonism, anxiety, social dysfunction, depression, and other neuropsychiatric diseases.

Peter Hegemann

Born December 11, 1954; Münster, Germany

Prof. Dr., Professor, Head of experimental biophysics, Humboldt University, Berlin, Germany

Honors and awards

- 2010 Wiley Prize for Biomedical innovation
- 2010 Karl Heinz Beckurts Preis for technical innovation
- 2012 Zülch Prize for fundamental work in Neuroscience
- 2013 The Leibniz Prize of the German Research Foundation (DFG)
- 2013 The Louis-Jeantet Award

Current research interests

My group studies the photobiology of green algae including phototaxis and developmental processes. We are expecting to improve reverse genetics and structure function analysis of photoreceptors by establishing nuclear gene targeting in these lower plants. We are especially interested in unusual sensory photoreceptors including channelrhodopsins, enzyme rhodopsins, and flavin-based photoreceptors using electrophysiology, protein structure function analysis time resolved spectroscopy for the analysis. We work on photoreceptor design and engineering for optogenetic applications.

Gero Miesenböck

Born July 15, 1965; Braunau, Austria

MD, Waynflete Professor of Physiology, Director, Centre for Neural Circuits and Behaviour, University of Oxford, United Kingdom

Honors and awards

- 2009 Bayliss-Starling Prize Lecture
- 2012 Inbev-Baillet Latour International Health Prize

Current research interests

My research seeks to identify elementary neural circuits that perform fundamental operations, such as integrating information over time, applying decision thresholds, computing error signals, and storing memories. Much of this work is done in fruit flies, where principles of brain function

with direct relevance to human health can be dissected with unparalleled precision. Optogenetic control has been a key enabling technology in this research. It has allowed us to link activity in defined neuronal populations causally to the expression of behavior, delineate how neurons are wired into circuits, and test ideas about how these circuits work.

Georg Nagel

Born August 24, 1953; Weingarten, Germany

Professor, Dr. phil., Full professor at University of Würzburg, Germany

Honors and awards

James Hudson Brown - Alexander B. Coxe Fellowship of Yale University (1988-1989)
2010 Wiley Prize in Biomedical Sciences
2010 Karl-Heinz-Beckurts-Preis
2012 Klaus Joachim Zülch-Preis
2013 Louis Jeantet Prize

Current research interests:

My research deals with natural photoreceptors, especially channelrhodopsins and other rhodopsins but also flavoproteins. We characterize membrane transport with electrophysiology and biophysical techniques. The investigated flavoproteins are Light-activated adenylyl cyclases which we study in-vivo (i.e. in living cells or organisms) and in-vitro (after heterologous expression and protein purification). We like to cooperate with physiologists who use these photoreceptors as tools to modulate cellular function by visible light (optogenetics). For this purpose we also mutate and engineer existing natural photoreceptors to award them novel functions. Currently we are also working on generating channelrhodopsin- or foreign-flavoprotein-expressing plants to study signalling in plant cells ("green optogenetics").