The Brain Prize 2018:

Four neuroscientists receive The Brain Prize for crucial research on Alzheimer's

The tireless efforts of these four leading scientists to understand Alzheimer's have provided the foundation for treatment of one of the most devastating diseases of our era. For this, they are receiving the world's most valuable prize for brain research, The Lundbeck Foundation Brain Prize, worth 1 million euros.

Denmark sees 7,500 new cases of dementia every year, changing the lives of Danish families for ever. People with dementia gradually lose their memories, their personalities change and they lose the ability to function in their daily lives. In Denmark, 80,000 patients already live with some form of dementia – and, little by little, their brain cells are destroyed. Around 50,000 of these patients have Alzheimer's disease.

There is still no cure for dementia such as Alzheimer's; we can only provide medication for temporary alleviation of symptoms. But thanks to four leading European scientists and their many years of intense research in the laboratory, the way is now paved for better treatment and, in time, prevention.

The four scientists are Bart De Strooper from Belgium, Michel Goedert from Luxembourg, Christian Haass from Germany and John Hardy from the UK. They are recognised for their highly specialised studies of Alzheimer's disease and other dementia disorders and are now being awarded the world's most valuable prize for brain research, The 2018 Brain Prize, worth 1 million euros (approximately 7.5 million Danish kroner). This year's prizewinners were announced on Tuesday, 6 March at the spring meeting of the Danish Society for Neuroscience.

Together, these four internationally respected neuroscientists have revolutionised our understanding of the harmful changes in the brain that lead to Alzheimer's disease. Their research achievements form the basis for development of the drugs that are currently tested as therapies for the disease.

The organisation behind the prize is the Lundbeck Foundation, one of Denmark's largest sponsors of biomedical research. The chairman of the foundation's Selection Committee, Professor Anders Björklund, explains the reasoning behind the award:

"The research of the four prizewinners has far-reaching perspectives for our understanding not only of Alzheimer's disease but of other dementia disorders, too. Their research has provided a foundation for the design of drugs to counter the pathogenic processes. This gives us hope that we will be able to slow Alzheimer's disease and, perhaps, even prevent it."

One of the most expensive disorders

Alzheimer's disease is the most common cause of dementia and the total cost of treatment and care makes it one of the most expensive disorders in the western world. In Denmark alone, the costs associated with dementia disorders are estimated at more than DKK 20 billion annually.

Incidence of Alzheimer's disease is expected to treble over the next 30 to 40 years, unless we can develop medical therapies that slow down or arrest progress of the disease.

Consequently, we urgently need to develop and strengthen brain research. "At the Lundbeck Foundation, brain research is our focus area, and we're the country's main provider of funds for brain research. Our aim is for Denmark to become a magnet for the most talented, international neuroscientists and for Denmark to become one of the world's leading brain research nations. The Brain Prize provides a perfect supplement to the 250 million Danish kroner granted by the Lundbeck Foundation to brain research each year," says Kim Krogsgaard, Director of The Brain Prize.

No-one knows the cause

German doctor Alois Alzheimer described the disease as far back as 1906, but no-one yet knows what causes its onset. Alzheimer's primarily affects older people but is seen in adults of all ages.

Once the disease develops, brain cells gradually die and proteins accumulate both between the brain cells (beta-amyloid plaques) and inside the brain cells (tau tangles). These proteins have a function in the normal brain, but in Alzheimer's patients they are produced in an abnormal form, causing them to accumulate which leads to the disease.

Four significant contributions

By the nineties, prizewinner *Christian Haass* already knew that beta-amyloid is not the result of a pathogenic process but that the protein forms naturally from precursors. Haass also identified and

described the secretase enzymes which control its formation. Thanks to Haass' research, we now know that the accumulation of beta-amyloid between brain cells is due to an imbalance in the production and the clearance of amyloid.

Bart De Strooper's significant contribution was to describe in detail how the secretases are constructed and how they function. This insight led to the development of drugs which either lower production or increase clearance of beta-amyloid.

Michel Goedert has proved that the tau protein is the most important constituent of the tangles we see inside the neurons in Alzheimer's. Goedert was also instrumental in proving it likely that tau itself plays a role in the development of Alzheimer's.

Steen Hasselbalch, Professor at the University of Copenhagen and Alzheimer's specialist, says:

"Goedert's most recent and very exciting discovery is that tau can spread within the brain. With this discovery, Goedert has shown that Alzheimer's is more than just an accumulation of beta-amyloid. It has given us valuable new ideas for the development of therapies."

Finally, *John Hardy*'s work focuses on the genetic mutations that can cause Alzheimer's. In rare cases, Alzheimer's disease is inherited, and there are families in which the risk of contracting the disease from one parent is 50%. Based on his genetic studies, John Hardy and his co-workers were the driving force behind the hypothesis that accumulation of beta-amyloid is the cause of Alzheimer's disease.

Prizewinners to visit Denmark

The Brain Prize, which honours the world's best neuroscientists, is being awarded for the eighth successive year. The prizewinners are invited to Denmark to deliver lectures and to participate in conferences, meetings and workshops together with Danish brain researchers. The programme is organised in partnership with the three largest Danish universities, the Danish Society for Neuroscience and the Federation of European Neuroscience Societies (FENS).

The scientists will come to Denmark on 9 May to receive the Brain Prize at a ceremony in the Royal Danish Library Black Diamonds Building.

Press contact:

Dr Kim Krogsgaard, Director of The Brain Prize
Tel. +45 3397 0001 or +45 2014 8384
Email: kk@thebrainprize.org

www.thebrainprize.org

www.lundbeckfonden.com

Facts

- The one million euro Brain Prize is awarded by the Lundbeck Foundation, which each year distributes grants of almost half a billion Danish kroner to biomedical research. Around half of this amount is donated to brain research, which is the Foundation's focus area.
- The Brain Prize was established by the Lundbeck Foundation in 2010 as a European prize and was awarded for the first time in 2011.
- From 2018, the Brain Prize will be international.
- This year, the prize goes to research on the genetic conditions and disease mechanisms that are the basis of Alzheimer's disease. This research has far-reaching perspectives for our understanding of the causes and development of Alzheimer's disease and other dementia disorders and has enabled us to design the drugs which are now being tested for treatment and prevention of Alzheimer's.
- The Brain Prize is a personal prize, awarded annually to one or more scientists who have distinguished themselves by outstanding contributions to neuroscience.
- The Prize will be presented on 9 May 2018 in Copenhagen.

About the prizewinners' research

According to the so-called amyloid hypothesis, the accumulation of beta-amyloid in the brain is a key mechanism involved in the development of Alzheimer's disease. The amyloid protein (Amyloid Precursor Protein, or APP) is a normal constituent of the surface membrane of the brain cell. When APP is broken down by the secretase enzymes (alpha, beta and gamma secretase), fragments of the protein are produced. One of these fragments, the so-called beta-amyloid 42, has a tendency to accumulate in clusters between the brain cells. These clusters of beta-amyloid, also known as plaques, are a significant marker of the disease.

The amyloid hypothesis was originally formulated based on genetic studies of the inherited form of Alzheimer's disease. The inherited form the disease is relatively rare (approximately 1% of all cases of Alzheimer's disease), and onset is earlier than in the case of non-hereditary Alzheimer's. Mutations of the three genes that lead to early-onset Alzheimer's disease all result in an over-production of toxic beta-amyloid in the brain. The various genetic mutations that lead to early-onset Alzheimer's disease change either production or breakdown of amyloid and cause an accumulation of beta-amyloid in the brain.
Another of the classic characteristics of Alzheimer's disease is the occurrence of so-called neurofibrillary filaments. These filaments are formed by tau protein, which, under normal circumstances, plays a key role in the structure of brain cells by stabilising the microtubules of the cells. In Alzheimer's disease, this structure is destroyed and fibrous clumps – also known as tangles – are formed. Whereas plaques consisting of beta-amyloid are found *between* the brain cells, tau tangles are found *inside* the cells. Tangles are usually first found in the part of the brain important to memory. From here, they spread to other areas of the brain as the disease progresses.

All four of the prizewinners have contributed to our understanding of the genetic basis and molecular mechanisms not only of Alzheimer's disease but of a range of other neurodegenerative disorders. Their research has also been key to the development of drugs to treat Alzheimer's disease.

John Hardy

Based on his genetic studies, John Hardy was the driving force behind formulation of the amyloid hypothesis of the cause of Alzheimer's disease. His research team has contributed to this field at each step of the development, from identification of a genetic link between early-onset Alzheimer's disease and mutations located on chromosome 21 to development of (transgenic) animal models for studying the significance of mutations. These models have provided a foundation for development of new drugs to treat Alzheimer's disease. Hardy also identified the first rare genetic risk factor for Alzheimer's, a genetic defect in the TREM2 protein found in the neuron supporting cells called microglia. Microglia and TREM2 are part of the brain's immune system and it is presumed that the defect reduces the ability to clear beta-amyloid. In addition to his ground-breaking work on Alzheimer's disease, Hardy has played an important role in our understanding of the genetics behind other neurodegenerative diseases such as frontotemporal dementia, Parkinson's disease and progressive supranuclear palsy (an atypical variant of Parkinson's disease).

Christian Haass

When Christian Haass began his research career in the USA in the 1990s, very little was known about the molecular mechanisms involved in Alzheimer's disease. It was widely thought that amyloid beta was pathogenic and therefore not present under normal physiological circumstances. Using cellular models, Haass was the first to prove that amyloid beta is also produced and released in normal conditions. He continued investigating and describing the enzymes behind the production and release of beta-amyloid, so-called secretases. Haass has shown that the way in which two of these secretases – beta-secretase and gamma-secretase – cleave APP is instrumental in the formation of beta-amyloid, whereas alpha-secretase cleavage of APP inhibits formation of beta-amyloid. This research has paved the way for the development of numerous drug candidates, all of which inhibit either beta- or gamma-secretase. However, so far, none of these drug candidates have succeeded in slowing down Alzheimer's disease once it has been diagnosed. This has resulted in several new clinical trials involving early treatment of healthy individuals predisposed to Alzheimer's disease or healthy individuals showing signs of beta-amyloid deposition.

Bart De Strooper

Bart De Strooper has focused on investigating the molecular mechanisms behind the formation of amyloid beta to increase our understanding of the development of Alzheimer's disease. He has identified a protein known as presenilin. Presenilin is a key constituent of the gamma secretase and is necessary for formation and release of beta-amyloid. These results have given further support to the development of secretase inhibitors for the treatment of Alzheimer's. De Strooper has also shown that mutations in both APP and presenilin have an impact on the length of the individual beta-amyloid protein strings. In behavioural studies of animals, he has shown that the qualitative changes in beta-amyloid, including the length of the protein strings, rather than the actual amount of beta-amyloid itself play the primary role in clinical symptoms such as impaired memory.

Michel Goedert

In addition to plaques of beta-amyloid, so-called neurofibrillary tangles are also found in Alzheimer's patients. Michel Goedert and his research team have identified the tau protein as the main constituent of the neurofibrillary tangles of Alzheimer's disease. They have shown that the tau protein spreads within the neurons of the brain and from neuron to neuron, as is seen in the so-

called prion diseases. These discoveries have given us a new and better understanding of the gradual spread of symptoms in the brain, as described many years ago.

Together with other research teams, Goedert has also shown that mutations of the tau gene give rise to various inherited forms of dementia - so-called tauopathies. These diseases are characterised by clumping of tau, but without accumulation of beta-amyloid. There are numerous types of mutations, all of which result in abnormal tau filaments. The individual mutations give rise to well-defined clinical diseases, each with characteristic clumping of tau protein.

Goedert has also contributed to our understanding of the group of neurodegenerative diseases in which the alpha-synuclein protein forms clumps of so-called Lewy bodies, as seen in Parkinson's disease, Lewy body dementia and multiple system atrophy.

About the prizewinners

Biographies

John Hardy received his PhD from Imperial College London in 1981. He did postdoctoral research at the MRC Neuropathogenesis Unit in Newcastle upon Tyne, and then at the Swedish Brain Bank in Umeå, Sweden where he started to work on Alzheimer's disease. At St. Mary's Hospital, Imperial College London in 1985 he initiated genetic studies of Alzheimer's disease. He took the Pfeiffer Endowed Chair of Alzheimer's Research at the University of South Florida in Tampa in 1992. In 1996, he moved to Mayo Clinic in Jacksonville, Florida, and became Chair of Neuroscience in 2000. He moved to National Institute on Aging, Bethesda, Maryland in 2001 as Chief of the Laboratory of Neurogenetics. He returned to the UK in 2007 to take up the Chair of Molecular Biology of Neurological Disease at the Reta Lila Weston Institute of Neurological Studies, University College London. He is a Fellow of the Royal Society.

Bart De Strooper became Doctor of Medicine (MD) in 1985 at KU Leuven, Belgium. In 1988, he received his Master of Medical Sciences at Leuven, and completed his PhD in 1991 at the same university. He is currently Full Professor of Molecular Medicine at KU Leuven, Belgium and a Group Leader at the VIB Center for Brain & Disease Research. In 2016, he was appointed Director of the UK Dementia Research Institute at UCL London, UK. Professor De Strooper has received several distinguished awards for his research, including the Potamkin Prize in 2002 (together with Haass), the Alois Alzheimer Award in 2003, the FWO-Joseph Maisin Prize in 2005, the MetLife Foundation

Award in 2008 and the European Grand Prix for Research by the Foundation for Research on Alzheimer's disease in 2018.

Michel Goedert, a Luxembourg national, received an MD from the University of Basel (Switzerland) in 1980 and a PhD from the University of Cambridge in 1984. He has worked at the Medical Research Council Laboratory of Molecular Biology in Cambridge as a Programme Leader since 1984 and was Head (joint or sole) of its Neurobiology Division between 2003 and 2016. Since 2014, he has also been an Honorary Professor of Experimental Molecular Neurology at Cambridge University. Goedert received a number of honours, including the MetLife Foundation Award in 1996, the Potamkin Prize in 1998 and the European Grand Prix for Research from the French Foundation for Alzheimer's disease in 2014. He is a member of the European Molecular Biology Organization, a Fellow of the Royal Society and a Fellow of the Academy of Medical Sciences of the United Kingdom.

Christian Haass is a professor at the Ludwig-Maximilians-University and the speaker of the German Center for Neurodegenerative Disorders, DZNE, in Munich. He got his PhD in 1989 and became a postdoctoral fellow at the Center for Neurologic Diseases of Harvard Medical School. In 1995 he went back to Germany to become a Professor of Molecular Biology at the University of Heidelberg. Since 1999, he has been Professor of Biochemistry and head of the Department of Metabolic Biochemistry at the Biomedical Research Center (BMC) and since 2009 he is also the speaker of the DZNE Munich. Professor Haass has received several honors including the Potamkin Award in 2002 (together with De Strooper), the MetLife Award in 2015 and the Gottfried Wilhelm Leibniz-Award of the German Research Foundation in 2006.