



Press release

The 27th Colloque Médecine et Recherche of the Fondation Ipsen in the Alzheimer Disease series:

“Proteopathic Seeds and Neurodegenerative Diseases”

Paris (France), February 28, 2012 – In the mid 1980s, Stanley Prusiner startled the scientific world by claiming that transmissible neurodegenerative diseases such as Creutzfeldt-Jakob in humans and Bovine Spongiform Encephalopathy (BSE; ‘mad cow disease’) were caused by self-replicating protein molecules, which he named prions. Painstaking work to establish that prion proteins could replicate without the need for genetic material won him the Nobel prize in 1997. What at first seemed an unusual mechanism restricted to a rather rare group of diseases has now become central to the study of all neurodegenerative conditions: the pathogenic proteins that characterise these diseases all seem to behave like prions. The implications for understanding how these diseases are transmitted through the nervous system and the possibility that environmental contamination may account for the sporadic forms of these diseases, as well as therapeutic possibilities, were among the topics discussed by the thirteen international experts, including two Nobel Prize winners, at the 27th annual colloquium on Alzheimer’s disease, hosted by the Fondation IPSEN. The meeting, held in Paris on February 27, 2012, has been organized by Mathias Jucker (University of Tübingen, Germany) and Yves Christen (Fondation IPSEN, Paris).

Prions are Janus-like proteins synthesised by neurons: in their normal, globular conformation they participate in cellular functions but in certain circumstances they adopt a pleated β -sheet configuration, which forms insoluble fibrous aggregates that disrupt cell function. This aggregated form is found in neurons in a group of neurodegenerative diseases known as the transmissible spongiform encephalopathies, which include Kuru, Creutzfeldt-Jakob disease (CJD) in humans, BSE in cattle and scrapie in sheep. All of these diseases can be transmitted by contact with brain material from affected individuals – the cause of great concern in the late 1980s and early 1990s when people developed a form of CJD after eating products from cows with BSE.

By the 1980s, a long hunt had failed to find either a bacterial or viral agent causing these diseases. Stanley Prusiner and his colleagues proposed instead that the infectious agent was the β -sheet form of the prion protein, which was able to replicate using itself as a template. As the first claim for replication without the need for nucleic acids, this was to say the least controversial. Now it is well accepted that ‘rogue’ molecules in the β -sheet conformation, now known as ‘prions’, can act as a seed, converting normal prion proteins into β -sheet type molecules. These adopt a fibrillar configuration and aggregate into an amyloid-like deposit that disrupts the neuron’s function. Prions released from cells are taken up by neighbours and trigger the same cascade of transformation and aggregation. Genetics still plays a part, because various mutations in the prion protein gene promote this transformation, while some polymorphisms (substitution of one base in the gene sequence for another) make individuals more susceptible to developing a prion disease.



The parallels with Alzheimer's disease (AD) were soon noted: a cellular protein, in this case the amyloid- β peptide, adopts a β -sheet, fibrillar conformation that aggregates in the brain as amyloid plaques; again genetics plays a part, at least in early-onset, familial AD, which is associated with mutations in amyloid- β 's parent protein, the amyloid precursor protein. More recently, it has become clear that this prion-like pattern is common to all the neurodegenerative diseases, including Parkinson's, Huntington's and motor neuron disease (Stanley Prusiner, University of California San Francisco, San Francisco, USA): each is characterised by a disease-specific cellular protein that transforms into a β -sheet configuration that subsequently aggregates. Moreover, mutations associated with familial forms of the diseases have now been identified for all these signature proteins. As a consequence these conditions are now being designated as protein misfolding disorders (Claudio Soto, University of Texas Houston Medical School, Houston, USA) and the proteins responsible could be considered as mammalian prions (Prusiner).

If the misfolded proteins associated with the various neurodegenerative diseases do behave like prions, they should be capable of triggering the transformation of the cellular protein in unaffected cells. Transfer of a systemic (non-neural) amyloidosis between mice was first demonstrated over 40 years ago (Per Westermark, Uppsala University, Uppsala, Sweden). Several speakers at the meeting have presented data supporting this hypothesis for various neurodegenerative diseases, either by injecting a brain homogenate from mice genetically engineered to develop the disease into the brains of susceptible but disease-free animals (Prusiner; Mathias Jucker, Hertie-Institute for Clinical Brain Research and German Center for Neurodegenerative Diseases, Tübingen, Germany; Soto; Michel Goedert, MRC Laboratory of Molecular Biology, Cambridge, UK; Patrik Brundin, Lund University, Lund, Sweden; Virginia Lee, University of Pennsylvania School of Medicine, Philadelphia, USA); by injecting synthetic protein fibrils into brains (Lee); or by testing purified protein extracts on neuron cultures (Anne Bertolotti, MRC Laboratory of Molecular Biology, Cambridge, UK; Ron Kopito, Stanford University, Stanford, USA). Another clear indication of transcellular induction comes from Parkinson's disease patients who have had stem-cell transplants: β -sheet proteins have been found in the neurons derived from the stem cells (Brundin).

This triggering ability of the aberrant proteins, which has gained them the label of proteopathic seeds, also seems to be responsible for the temporal spread of degeneration through the brain that is typical of the neurodegenerative diseases (Jucker; Brundin; Lee). Perhaps more significant, the aberrant proteins have been found in the brain after intraperitoneal injection or blood transfusion (Soto); as with prions, transport along the vagal nerve seems to be the most likely route into the brain (Prusiner; Brundin). This opens up the possibility of an environmental causation for the many patients with a neurodegenerative disease who do not have hereditary links (Jucker; Soto; Westermark).

The mechanisms underlying proteopathic seeding are still unclear. The spread of the β -sheet transformation seems to depend on both the configuration of the seed itself and the genetic constitution of the animal – again very like the prion diseases (Jucker; Goedert). The uptake of the seed proteins into neurons is being examined in culture (Bertolotti; Kopito) and model systems (Brundin). The key seems to be in the interaction between the seed protein and cell membranes and, in some cases at least, helper proteins are required (Brundin).

To understand how seeding works, it is essential to know the structure of the β -sheet proteins. Taking amyloid- β as an example, the conditions that determine what type of fibril and aggregates will form, and how this relates to the mutations in the amyloid precursor protein will be discussed (Robert Tycko, National Institutes of Health, NIDDK, Bethesda,



USA). Cooperativity between β -sheet molecules may also be important in aggregation (Roland Riek, ETH Zürich, Zürich, Switzerland). Helpful insights can also come from systemic diseases in which amyloid accumulates, such as AA amyloidosis. Amyloid, a generic term for protein aggregates, is in this case produced by the inflammatory protein serum amyloid A (Westermarck). There is evidence that AA amyloid formation can be triggered by other types of amyloid molecule, leading to speculation that amyloid fibrils found in the environment and food could cross-seed amyloid formation in the body or brain.

As knowledge about proteopathic seeding accumulates, new prospects for therapeutic intervention open up (Peter Lansbury, Brigham and Women's Hospital, Boston, USA). The initial conversion of functional globular protein into potentially pathogenic β -sheet form, the seeding cascade that converts further globular protein to β -sheet, and the mechanisms by which neurons take up prion-like β -sheet molecules are all potential targets. The discovery that amyloid- β seeds are partly soluble and may be present in body fluids offers a possible alternative strategy for an early diagnostic (Jucker).

At the same time, it is essential to remember that prion-like molecules have biological functions, which poses further challenges in the design of therapeutics. A form of amyloid seems to participate in the storage of hormones in secretory granules and in skin pigmentation (Riek), while self-replicating prion-like proteins are a necessary part of the molecular mechanism for long-term memory storage in both the fly and the mouse (Eric Kandel, Columbia University, New York, USA). Intervention to prevent the spread of a β -sheet protein like amyloid- β through the nervous system that interfere with important biological mechanisms, particularly those involved in memory storage, obviously need to be avoided. Despite these caveats, the unfolding of yet another significant aspect of neurodegeneration offers exciting prospects for both the basic understanding of these devastating diseases and their treatment.

About the Fondation Ipsen

Established in 1983 under the aegis of the Fondation de France, the mission of the Fondation Ipsen is to contribute to the development and dissemination of scientific knowledge. The long-standing action of the Fondation Ipsen aims at fostering the interaction between researchers and clinical practitioners, which is indispensable due to the extreme specialisation of these professions. The ambition of the Fondation Ipsen is to initiate a reflection about the major scientific issues of the forthcoming years. It has developed an important international network of scientific experts who meet regularly at meetings known as Colloques Médecine et Recherche, dedicated to six main themes: Alzheimer's disease, neurosciences, longevity, endocrinology, the vascular system and cancer science. Moreover the Fondation Ipsen has started since 2007 several meetings in partnership with the Salk Institute, the Karolinska Institutet, the Massachusetts General Hospital, the Days of Molecular Medicine Global Foundation as well as with the science journals Nature, Cell and Science. The Fondation Ipsen produced several hundreds publications; more than 250 scientists and biomedical researchers have been awarded prizes and research grants.

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