

2001 Hans Sigrist Prize



Jan Johansson

The Hans Sigrist Prize awarded to me in 2001 made it possible to expand already ongoing research on mechanisms underlying formation of amyloid fibrils and to study protein misfolding diseases more generally. Amyloid fibrils are polymers, which are insoluble and harmful to cells, and can be formed when certain proteins lose their native, monomeric and soluble structures. Well-known examples of proteins that can form amyloid fibrils are the amyloid-peptide (A), which is associated with Alzheimer's disease, and the prion protein that forms amyloid in spongiform encephalopathies like Creutzfeldt-Jakob disease in humans and BSE (mad cow disease) in cattle. Important questions that remain to be solved regarding fibril formation include the detailed structure of an amyloid fibril and what determinants give rise to fibril formation from certain proteins, while most proteins do not appear to form fibrils under physiological conditions.

The Hans Sigrist Prize made it possible for me to work at the Department of Structural Medicine, Cambridge University in 2002. During that visit I initiated structural studies of amyloid fibrils formed from a designed peptide containing a sequence motif present in A and other fibril-forming peptides. Fibrils formed from that peptide are very regular and crystalline, and thus amenable to diffraction studies. Electron and X-ray diffraction studies carried out in collaboration with Lousie Serpell and her colleagues have very recently resulted in the determination of the first atomic level structure of an amyloid fibril. The interactions between amino acid side-chains observed in this structure explain the outstanding stability of the amyloid fibril. In addition to working on amyloid fibrils in Cambridge, I also started work on another family of proteins associated with human disease, the serin protease inhibitors (serpins). Serpins can form polymers

in which the reactive loop of one molecule inserts into another molecule. These polymers are retained intracellularly and thereby cause cellular damage and deficiency of circulating serpins. Neuroserpin is specifically expressed in the central nervous system and familial forms of dementia have recently been described, in which mutant neuroserpin form polymers. We have studied in detail the stability and polymer formation of two neuroserpin mutants, from which we have proposed a model that explains loss of inhibitory activity as well as the increased tendency to form polymers.

As described above the Hans Sigrist Prize allowed me to work at another University for a longer time and made it possible to develop novel lines of research. Without the freedom offered by the prize, this may not have happened. The results that emanated from these new projects are potentially important for finding ways to inhibit fibril formation, and thereby possible prevent or cure amyloid diseases. From my personal point of view, the Hans Sigrist Prize as such and the possibility to expand my research profile contributed very positively when applying for a new position as professor of medical biochemistry.

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