

## EDITORIAL

### Protein Aggregation

Protein aggregation plays a central role in a wide constellation of fields, ranging from bio-materials and biotechnology to food science, human health and physiology. Research in the area has a long history, but has expanded dramatically in the last 25 years. Alois Alzheimer's description of the deposits in the brain which we now recognize as A $\beta$  plaques and tau fibres is often, retrospectively, viewed as the critical starting point of the study of protein aggregation in human disease. However, studies of protein aggregation *in vitro* and in human health pre-date Alzheimer's seminal work and it is interesting to note that Alzheimer's observations had little impact at the time (1). Hofmeister's famous work in the late 19<sup>th</sup> century on the precipitation of proteins by inorganic salts is arguably one of, if not, the first rigorous quantitative physical chemical investigation of protein precipitation/aggregation (2). Opie's observation in 1901 of so called "hyaline lesions", now known to be amyloid, in the pancreas of type-2 diabetes patients actually predates Alzheimer's observation of protein aggregates in the brain and is probably the first reported observation of an amyloid deposit in tissue (3). Despite these early observations, the role of protein aggregation and fiber formation in disease received relatively little attention in the 60 years following Opie and Alzheimer's work, although significant progress was made in defining the cross- $\beta$  structure (4, 5). Glenner and Wong's sequencing of the  $\beta$ -amyloid peptide in 1984 was a significant step forward and led to the birth of the amyloid cascade theory of Alzheimer's disease (6). Since that time, interest in, and the number of groups working on, protein misfolding in human health has exploded. Well over 30 human disorders are now recognized to involve protein aggregation, at least in part.

The growth of biotechnology and the advent of protein based pharmaceuticals has fuelled tremendous interest in practical aspects of protein aggregation. Many new drug filings

are made for protein- or peptide-based therapeutics. Such protein-based pharmaceuticals are typically produced at high yields (1 gram per liter or more) and often require refolding from inclusion bodies. Once refolded and purified, protein-based drugs must be formulated, often at high concentration, under conditions where they remain soluble and do not aggregate for months. An understanding of protein aggregation *in vitro* is critical to the success of these efforts. The deliberate design of self-assembling (aggregating) peptides and proteins to form bio-inspired new materials is also an area of considerable current interest and promise. Studies of protein aggregation have been driven not just by the intrinsic importance of the phenomena and its practical consequences, but also by the development of new methods that are starting to provide high resolution views of the aggregation process on the one hand and increasingly realistic models of disease on the other.

This special issue reflects the diversity of the field and contains examples of the role of protein aggregation in disease, the importance of aggregation in biotechnology, the development of bio-inspired materials and the description of new methods to study aggregation. The diversity of the field is also reflected in the systems described in this issue which span the range from high resolution structural studies of short steric zipper-forming peptides to analysis of weak association of intact IgG molecules (**cite reference for-- or provide the DOI for Eisenberg-1 and for Eisenberg-2 and for Laue**). Included are reviews of the role of protein aggregation and proteotoxicity in type-2 diabetes, and the role of semen-derived enhancer of virus infection (SEVI) amyloid fibers in enhanced HIV infection, articles that discuss the role of TTR and its interactions with abeta, papers on the structural biology of  $\alpha$ -synuclein and the role of post-translation modification in the aggregation of  $\alpha$ -synuclein, and studies of steric zipper models of the amyloid formed by the SOD1 protein that aggregates in Amyotrophic Lateral Sclerosis (**cite or provide doi for papers by**

**Ramamoorthy, by Eliezer, by Abedini , by DOBSON, Eisenberg—1, by Eisenberg-2 and by Pappu).** These articles cover the structural biology of amyloid fibers, the structure of monomeric precursors of amyloid fibers, proteins that sequester amyloid forming polypeptides as well as mechanisms of toxicity and the nature of toxic species.

Progress in the field has been catalysed by the development of new methods and techniques: the special issue describes analytical ultracentrifugation based methods for the analysis of weak interactions in solution, coarse grained MD simulations, advances in aggregation theory, combined methods to study the self-association of therapeutic proteins, and the design of protein scaffolds for the display of amyloidogenic proteins (**cite or provide doi for papers by Laue, by Hall, By Brockwell, Roberts-2, and by Ferrnone**).

Responsive biomaterials and the design of hydrogels that sequester amyloidogenic peptides are illustrated in two contributions. One described a designed hydrogel that removes Abeta from solution and the other highlights the possibility of designing materials whose function can be modulated by controlling the folded state of protein domains displayed on the surface of fibrils. (**cite or provide DOI for paper by Tycko and paper by Schneider**).

The role of aggregation in biotechnology is highlighted by work which examines the role of interfaces and mechanical agitation on the aggregation of recombinant IL-1 $\beta$ , and by studies of the aggregation of single chain Fv antibody fragments. The latter contribution emphasizes the importance of linker regions and shows that seemingly modest changes to a sequence can influence aggregation and self-association. The former illustrates the importance of considering conditions faced by a formulated protein during storage and use. The importance of aggregation in biotechnology is also represented with a study of the use of combined parallel chromatography and *in situ* scattering methods to monitor aggregation in

solution (**CITE or provide doi for paper by Randolph, Paper by Roberts-1 and Roberts-2**).

A recent theme in biophysical studies of protein aggregation is the cross seeding of the aggregation of a polypeptide by a different protein chain. MD simulations which probe this process are reported in the special issue as are experimental studies with a rationally designed pair of peptides that do not aggregate in isolation, but self-assemble to form fibres when mixed (**CITE or provide DOI for the paper by Hall and the paper by Eisenberg and Bowers**).

This special edition highlights the diversity of fields that involve protein aggregation and diversity of the proteins which take part in the process. We hope that the reviews and articles will serve as a reference to readers and provide a platform for further methods developments and studies of aggregation in biophysical chemistry, protein folding disorders, biomaterials, and biotechnology among others.

## **References**

- 1) Cipriani, G. Dolciotti, C., Picchi, L., and Bonuccelli, U. (2011) Alzheimer and his disease: a brief history. *Neurological Sciences*. **32**,275-279.
  
- 2) Hofmeister, F. (1888) Zur Lehre von der Wirkung der Salze, II. Über Regelmässigkeiten in der eiweissfallenden Wirkung der Salze und ihre Beziehung zum physiologischen Verhalten derselben, *Archiv für experimentelle Pathologie und pharmakologie*. **24**, 247–260.

- 3) Opie, E. L (1901) The relation of diabetes mellitus to lesions of the pancreas. Hyaline degeneration of the islands of Langerhans. *The Journal of Experimental Medicine*. **5**, 527–540.
- 4) Eanes, E. D., and Glenner, G.G. (1968) X-ray diffraction studies on amyloid filaments *Journal Histochemistry & Cytochemistry*. **16**, 673-677.
- 5) Sipe J. D., and Cohen A. S. (2000) Review: History of the amyloid fibril. *J. Struct. Biol.* **130**, 88–98.
- 6) Glenner, G.G., and Wong, C. W. (1984) Alzheimer's-disease - initial report of the purification and characterization of a novel cerebrovascular amyloid protein. *Biochemical Biophysical Research Communications*. **120**, 885-890.

Jean Baum  
Department of Chemistry and Chemical Biology,  
Rutgers University  
New Brunswick, NJ 08904  
USA

Daniel Raleigh  
Department of Chemistry Stony Brook University  
Stony Brook, NY, 11794  
USA  
&  
Research Department of Structural and Molecular Biology  
University College London  
London, WC1E 6BT  
United Kingdom