Weinberg's story struck home; we participants had been discussing for days the critical role of cofactors such as CBP and p300 in leukemogenesis. Because these factors regulate p53 as well as interact in both the retinoblastoma and SV40 large T antigen pathways[3], perturbed function, for instance by fusion proteins created by a translocation, could push a cell a long way towards becoming a tumor.

The next 30 years

Will we ablate hematological malignancies in the next 30 years? Although the emerging hypothesis – that alterations in chromatin structure ultimately provide a general mechanism for leukemogenesis – seems too simplistic, the limited clinical data that are available certainly support it. The mood at this meeting ranged from optimistic to giddy, but some scepticism should be in order. Is it premature to call drugs such as TSA and phenylbutyrate HDAC inhibitors? Their mechanism of action in the clinic is unknown, but these drugs do change the course of disease. Nothing is known about the clinical action of As_2O_3 either, although, once again, its efficacy is well documented. A firm understanding of how these drugs target the specific transcriptional profile of each hematological malignancy could bring us closer to remaking *Love Story* with a happy ending.

References

1 Lallemand-Breitenbach, V. *et al.* (1999) **Retinoic acid and arsenic synergize to eradicate leukemic cells in a mouse model of acute promyelocytic leukemia**, *J. Exp. Med.* 189, 1043–1052

2 Hahn, W.C. *et al.* (1999) **Creation of human tumour cells with defined genetic elements**, *Nature* 400, 464–468

3 Giles, R.H., Peters, D.J.M. and Breuning, M.H. (1998) **Conjunction dysfunction: CBP/p300 in human disease**, *Trends Genet.* 14, 178–183

4 Sieweke, M.H. *et al.* (1998) **A transcription factor party during blood cell differentiation**, *Curr. Opin. Genet. Dev.* 8, 545–551

Rachel H. Giles PhD
Postdoctoral Fellow

Department of Human and Clinical Genetics,
Leiden University Medical Center,
Wassenaarseweg 72, 2333 AL Leiden,
The Netherlands.
Tel: +31 71 527 6203
Fax: +31 71 527 6075
e-mail: rachel@ruly46.medfac.leidenuniv.nl

Self-assembly of peptides in medicine: two sides of the coin

Self-assembling Peptide Systems in Biology, Medicine and Engineering*

Aghia Pelagia, Crete, Greece, 1–6 July 1999

Amalia Aggeli, Neville Boden and Shuguang Zhang

One of the major drives in biological research is the establishment of structures and functions of the 80 000 or so proteins in our bodies. Each has a characteristic three-dimensional structure, highly 'ordered', yet 'disordered'. The correct structure is absolutely essential for a protein's function and, significantly, it must be sustained in the competitive and complex environment of the living cell. It is now being recognized that when a cell loses control, proteins undergo self-assembly into more complex supramolecular structures such as the amyloid fibers and plaques associated with the pathogenesis of age related disease (including Alzheimer's disease) and a number of prion diseases (including Creutzfeldt–Jakob disease and bovine spongiform encephalopathy). This is just an indication of the wider significance of the self-assembling properties of polypeptides. It has been long known that, in silk, polypeptides are assembled into β-sheet structures which impart on the material its highly exploitable properties of flexibility combined with high tensile strength. But only now is the recognition that peptides can self-assemble into a wide variety of non-protein-like structures, including fibrils, fibers, tubules, sheets and monolayers, emerging. The potential for exploiting these exciting observations is so wide-ranging that over 80 scientists from around the world met in July to discuss these prospects in the areas of biology, medicine, materials science and engineering.

*The meeting was so successful that a second workshop will be held in summer 2001 at the same venue.

Self-assembly in pathogenesis

Although there was a broad coverage of diverse topics, the self-assembly of proteins resulting in the onset of a number of protein conformational

diseases in medicine was certainly one of the highlights. Nobel Laureate Carleton Gajdusek (Institute of Human Virology, Baltimore, MD, USA) opened the meeting by taking us back to his discovery of the infectious protein conformational diseases, such as Creutzfeldt–Jakob disease and bovine spongiform encephalopathy, and the spontaneous transformation of host precursor proteins to infectious amyloid peptides. Chris Dobson (University of Oxford, Oxford, UK) complemented this historical perspective by explaining the current perceptions of how amyloid can be formed from many proteins, including human lysozyme and the SH3 domain of phosphatidylinositol 3-kinase, in which the structure is a double helix of two protofilament pairs wound around a hollow core[1]. These are among the large number of proteins that undergo self-assembly *in vitro* to form fibril structures (Fig. 1). The self-assembly of proteins such as Sup35 and PrP can also influence the transfer of genetic information and organism development. Susan Lindquist (University of Chicago, Chicago, IL, USA) provided insight into the nature of the conformational changes underlying protein-based mechanisms of inheritance in yeast, and suggested a link between this process and those that produce prion diseases in mammals[2]. Jeff Kelly (Scripps Institute, La Jolla, CA, USA) pointed out that the assembly of misfolded transthyretin, resulting in familial amyloid polyneuropathy and senile systematic amyloidosis, is one of 17 known human proteins that are normally soluble and functional but can aggregate into an alternative conformation that subsequently undergoes self-assembly into pathogenic amyloid fibrils. It is likely that the formation of such fibrils is seeded through minute amounts of abnormal proteins that structurally catalyze similar or dissimilar proteins to undergo conformational change[3]. Self-assembling peptides also have roles in degenerative diseases outside the central nervous system; Aphrodite Kapurniotu (University of Tübingen, Tübingen, Germany) reported that in type II diabetes, pancreatic amyloidosis is characterized by the deposition of amyloid that consists of islet amyloid polypeptide (IAPP) (Ref. 4).

Molecular Lego

Through molecular design and combinatorial selection, artificial proteins can be produced that form amyloid fibrils (Michael Hecht, Princeton University, Princeton, NJ, USA)[5]. Artificial proteins seem to assemble by making a rapid transition from an α-helix to a β-sheet conformation (Hisakazu Mihara, Tokyo Institute of Technology, Tokyo, Japan)[6]. This conformational change can be brought about by changes in temperature or pH (Shuguang Zhang, Massachusetts Institute of Technology, Cambridge, MA, USA). Amalia Aggeli (University of Leeds, Leeds, UK)[7] suggested a role for peptide chirality in stabilizing fibrils and fiber-like polymeric structures, to facilitate their assembly. Although these designed proteins share no similarity at all in sequence, structure and function to their naturally occurring counterparts, one common feature is a segment of short repeats that might nucleate the formation of stable β-sheet structures, ultimately resulting in fibril formation. These findings reinforce the hypothesis that when proteins lose control of their folded native structure – by genetic mutation, misfolding, ageing or during normal function – they can self-assemble into insoluble amyloid fibrils. But, apart from elucidating mechanisms of pathogenesis, such self-assembling peptides could have enormous value in medicine, as biodegradable scaffolds for tissue engineering (Shuguang Zhang)[8].

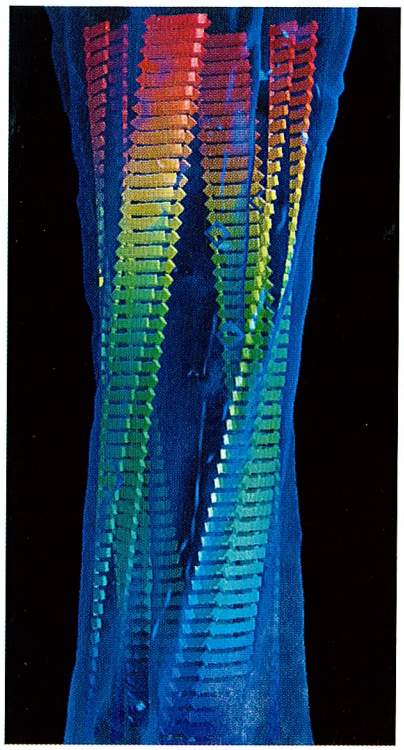

Figure 1. Model of the structure of amyloid fibrils formed from the SH3 domain of phosphatidylinositol 3-kinase, derived from a low-resolution cryo-electron microscopy image[1]. Kindly provided by Jose Jimenez and Helen Saibil, Birkbeck College, London, UK.

Concluding remarks

There was a spirit of excitement about the workshop indicative of an important new endeavor that is bringing together a group of scientists from a broad range of disciplines to form a new area of research. The emerging perception is that these new insights into the molecular mechanisms that lead to seemingly diverse diseases might also lead to the discovery of new therapies. As Francis Crick put it: 'In Nature, hybrid species are usually sterile, but in science the reverse is often true. Hybrid subjects are often astonishingly fertile, whereas if a scientific discipline remains too pure it usually wilts'.

References

1 Jimenez, J.L. *et al.* (1999) **Cryo-electron microscopy structure of an SH3 amyloid fibril and model of the molecular packing**, *EMBO J.* 18, 815–821

2 Liu, J.J. and Lindquist, S. (1999) **Oligopeptide-repeat expansions modulate 'protein-only' inheritance in yeast**, *Nature* 400, 573–576

3 Lansbury, P.T., Jr (1999) **Evolution of amyloid: what normal protein folding may tell us about fibrillogenesis and disease**, *Proc. Natl. Acad. Sci. U. S. A.* 96, 3342–3344

4 Kayed, R. *et al.* (1999) **Conformational transitions of islet amyloid polypeptide (IAPP) in amyloid formation *in vitro***, *J. Mol. Biol.* 287, 781–796

5 West, M.W. *et al.* (1999) ***De novo* amyloid proteins from designed combinatorial libraries**, *Proc. Natl. Acad. Sci. U. S. A.* 96, 11211–11216

6 Takahashi, Y., Ueno, A. and Mihara, H. (1999) **Optimization of hydrophobic domains in peptides that undergo transformation from alpha-helix to beta-fibril**, *Bioorg. Med. Chem. Lett.* 7, 177–185

7 Aggeli, A. *et al.* (1997) **Responsive gels formed by the spontaneous self-assembly of peptides into polymeric beta-sheet tapes**, *Nature* 386, 259–262

8 Zhang, S. *et al.* (1999) **Biological surface engineering: a simple system for cell pattern formation**, *Biomaterials* 20, 1213–1220

Amalia Aggeli PhD
Royal Society Research Fellow

Neville Boden PhD
Director

Centre for Self-Organising Systems, The University of Leeds, Leeds, UK LS2 0JT.

Shuguang Zhang* PhD
Associate Director

Center for Biomedical Engineering, Massachusetts Institute of Technology, Cambridge, MA 02139, USA.
Tel: +1 617 258 7514
Fax: +1 617 258 0204
***e-mail: Shuguang@MIT.EDU**