Meeting report

Protein structure and function by the sea

Trevor Lithgow

Address: Russell Grimwade School of Biochemistry and Molecular Biology, University of Melbourne, Melbourne 3010, Australia.
E-mail: t.lithgow@unimelb.edu.au

Published: 27 March 2002

Genome ***Biology*** 2002, **3(4)**:reports4008.1–4008.2

The electronic version of this article is the complete one and can be found online at http://genomebiology.com/2002/3/4/reports/4008

A report on the 27th Annual Lorne Conference on Protein Structure and Function, Lorne, Australia, 9-13 February 2002.

The Lorne protein structure and function meeting has a proud history of providing a relaxed atmosphere to ensure communication across scientific boundaries: with the waves crashing in the background and a glass of fine wine in hand, biochemists find themselves talking easily with cell biologists and (even) spectroscopists. Bearing this in mind, the organizers of this year's meeting set a theme based on the recent publication of the human genome sequence: stating that this information will "change the way we formulate and address biological questions", the challenge now being to ''address many of the hot issues awaiting protein science in the post-genome era".

Structural genomics

Hailed as a radical departure from our traditional way of thinking about structural biology, the session on structural genomics showed the shape of things to come. Steve Burley (Rockefeller University, New York, USA), on behalf of the New York Structural Genomics Research Consortium (NYSGRC), explained the Consortium's aim to develop the means for high-throughput X-ray crystallographic studies of protein structure. The mission: to expand rapidly the few thousand structures currently available in the Protein Data Bank (PDB) [http://www.rcsb.org/pdb/] towards the 500,000 or so that might exist given the currently available and forecast genome-sequence information. Shigeyuki Yokoyama (RIKEN Genome Sciences Center, Yokohama, Japan) provided a run-down of the RIKEN program for acquiring high-throughput solution structures: 24 on-site nuclear magnetic resonance (NMR) spectrometers (if you include the 920 MHz machine they hope to have up and running soon) will be solving a minimum of one or two new structures per week! Both the NYSGRC and RIKEN groups are focusing first on those proteins for which there is at least some hint of biomedical significance to knowing the structure.

Structural determination of protein complexes

Other highlights of the meeting came in the session on key technologies. Werner Kühlbrandt (Max-Planck Institute, Frankfurt, Germany) presented the structures of several membrane protein complexes derived from analysis of two-dimensional crystals, including the oligomeric SecYEG translocase responsible for bacterial protein secretion. Kühlbrandt warned that, of the several thousand protein structures currently available at PDB, only forty are membrane proteins. This shortfall promises to become an embarrassment given that about 30% of the proteins coded in any genome are membrane proteins. Various specialist approaches will be required if we are to understand the structure of these - often medically important - proteins from any organism. One such approach is the combined use of electron microscopy, for obtaining (relatively) low-resolution information about large complexes, together with X-ray crystallography, for deriving the structures of isolated subunits and domains. Robert Huber (Max-Planck Institute for Biochemistry, Martinsried, Germany) gave a most elegant example, with structural studies of the proteasome: a complex composed of several dozen subunits arranged as a barrel lined with protease activities and capped at each end with chaperone-like subunits restricting entry to only those proteins carefully deemed to be beyond repair. In addition, Huber reported on the soon-to-be-published structure of the bacterial DegP/HtrA. DegP/HtrA is composed of two homotrimeric rings stacked atop to create the active, hexameric protease that mediates quality control of bacterial proteins. Eukaryotic homologs of DegP/HtrA are key control elements of programmed cell death.

Cell biology

It is not only protein structure that gets discussed at Lorne meetings, however. Each year exciting new developments in cell biology are also highlights of the program. John Hancock (University of Queensland, Brisbane, Australia) presented work on the localization of key signaling proteins like H-ras and K-ras to specific microdomains of the plasma membrane and explained the role of lipid rafts in creating and maintaining these discrete protein distributions. Traude Beilharz (University of Melbourne, Australia) reported on a genome-wide search for topology-specific membrane proteins. In the yeast genome, genes encoding 55 tail-anchored proteins were found; their targeting sequences have been analyzed and suggest novel aspects for localization of these proteins. One protein, localized to the inner envelope of the nucleus, contains distinct membrane-integration and nuclear-localization signals. Pam Silver (Harvard University, Cambridge, USA) talked about genome-wide mapping of DNA-binding-protein interactions using technology that is still developing. After cross-linking the DNA-binding protein of interest to chromosomal DNA, and shearing the DNA into short fragments, the bound fragments can be co-immunoprecipitated with the protein and identified by hybridization on oligonucleotide-array 'chips', to yield the total number of sites occupied by the protein either normally or in response to specific stimuli.

As participants for the subsequent Lorne Cancer Conference (on the molecular genetics and biochemistry of cancer) arrive on the last day of the Lorne protein meeting, joint sessions are held and discussions afterwards are always lively. Vickery Arcus (University of Auckland, New Zealand) presented work on structural genomics in relation to bacterial virulence. Arcus is screening bacterial genomes for what might be genes related to superantigens (potent antigens that stimulate a whole subset of T cells), then solving the structures of the proteins encoded by these genes so as to determine whether they might represent novel ways of understanding and conquering virulence. A special session held jointly with the Society for Biomolecular Screening was devoted to the high-throughput screening of drug targets, including presentations from Dirksen Bussiere (Chiron Corporation, Emeryville, USA) who described screening for novel inhibitors of glycogen synthase kinase 3 (GSK3), a key signal transduction enzyme, and Horst Flotow (Institute for Molecular and Cell Biology, Singapore) screening for novel anti-malarial compounds. In both cases their strategy is to take a key enzyme (GSK3 or the protease Plasmepsin II, from *Plasmodium*), and design a simple but robust *in vitro* assay to screen vast libraries of natural products for inhibition. Properties of some first-generation inhibitors, prior to more selective analyses, were presented by both Bussiere and Flotow.

The meeting also served to allow former colleagues, and younger fans, to acknowledge the passing of Max Perutz. In the context of what can become narrow, goal-driven experiments associated with whole-genome, high-throughput research programs, it is worth remembering the philosophies of great men like Perutz. "Discoveries can not be planned; they pop up, like Puck, in unexpected corners... Science has changed the world, but the scientists who changed it rarely foresaw the revolutions to which their research would lead" (From the book by Perutz, MF: *I wish I'd made you angry earlier. Essays on science, scientists and humanity*. New York: Cold Spring Harbor Laboratory Press; 1998).

Information about the 28th Conference to be held at Lorne in February 2003 will be posted on the Annual Protein Structure and Function Conference site at [http://www.biochemistry.unimelb.edu.au/lorne/].