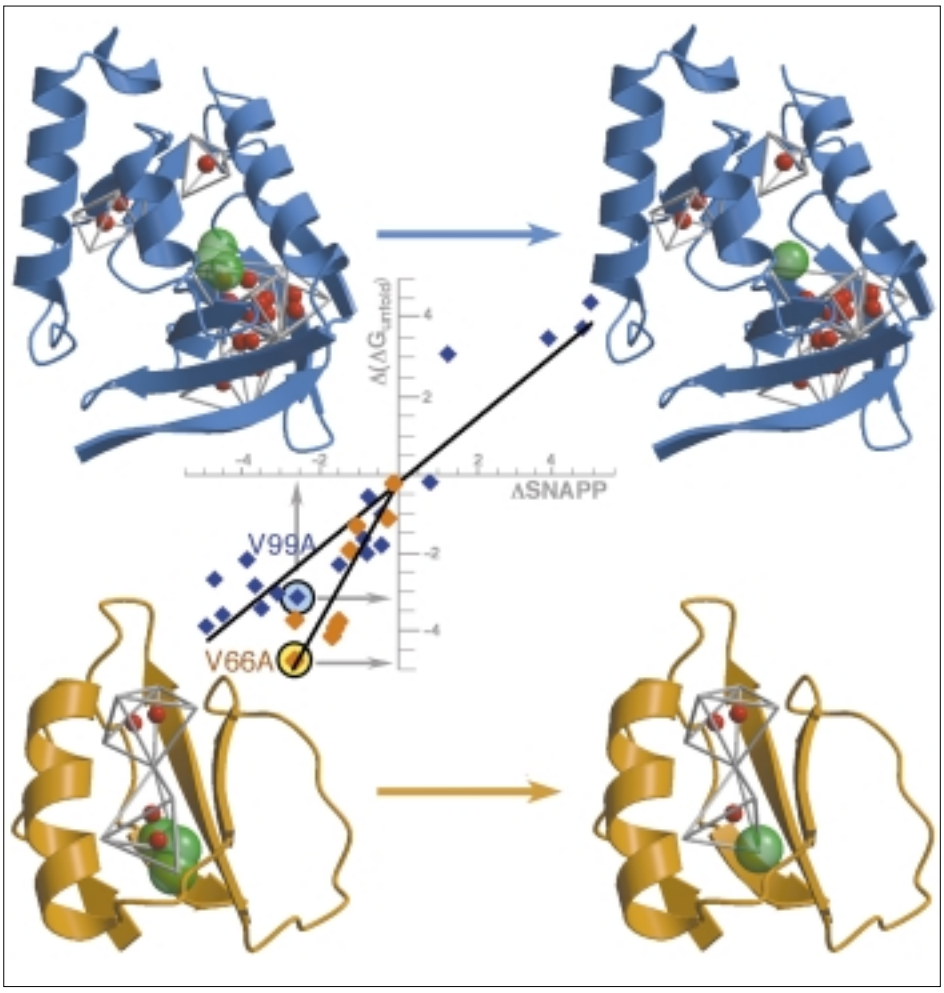

Fig. 1. Identical valine (V) to alanine (A) hydrophobic core mutations (green spheres) change the experimental free energy of unfolding [$\Delta(\Delta G_{unfold}$]; vertical axis) by different amounts at residue 66 of chymotrypsin inhibitor-2 (V66A; gold) and residue 99 of staphylococcal nuclease (V99A; blue). Quantitative analysis of the same mutants using four-body statistical potentials (ΔSNAPP; horizontal axis) suggests that the two mutations should induce the same degree of destabilization. The observed difference is a scaling effect arising systematically from differences in the proportionate impact of mutation indicated by the two slopes. The slopes, in turn, are inversely related to the relative contribution of hydrophobic bonding to stability in the two proteins, suggested graphically here by the density of grey cages and red spheres.

the same. The observed values, however, are different because that in CI2 represents a larger proportionate change than does the same mutation in STN. The differences are reflected in the two slopes relating mutant free-energy changes in the two different proteins to the statistical potential, showing that the two mutations are drawn from systematically distinct populations.

References

1 Carter, C.W. *et al.* (2001) Four-body potentials reveal protein-specific correlations to stability changes caused by hydrophobic core mutations. *J. Mol. Biol.* 311, 625–638

2 Cammer, S. *et al.* Identification of sequence-specific tertiary packing motifs in protein structures using Delaunay tessellation. In *Lecture Notes in Computational Science and Engineering* (Schlick, T., ed). Springer-Verlag, New York (in press)

Charles W. Carter, Jr.*
Dept of Biochemistry and Biophysics, CB 7260, University of North Carolina, Chapel Hill, NC 27599-7260, USA.
*e-mail: carter@med.unc.edu

Alex Tropsha
Laboratory for Molecular Modeling, CB 7360, University of North Carolina, Chapel Hill, NC 27599-7360, USA.

Marshall Edgell
Dept of Microbiology and Immunology, CB 7290, University of North Carolina, Chapel Hill, NC 27599-2790, USA.

Meeting Report

Honey I've shrunk biomedical technology!

Suzanne Berry

The Second Annual BioMEMS and Biomedical Nanotechnology World 2001 conference was held 22–25 September in Columbus, Ohio, USA. The conference was organised by Mauro Ferrari and the Cambridge Healthtech Institute.

Biomedical devices are getting smaller and the time when tiny machines will be flowing through our bloodstream targeting cells for treatment is not as far away as we might think. Neither are point-of-care diagnostic and analytical devices. Bio-microelectromechanical systems (bioMEMS) usually contain sensors, actuators, mechanical structures and electronics and are, in general, made from silicon. Such systems are being developed as diagnostic and analytical devices at an incredibly rapid speed. BioMEMS sensors and tools such as lab-on-a-chip will not only lead to 'point-of-care' assessments but also will take diagnosis out of the doctor's hands and into the hands of the patient.

This conference covered topics including micro- and nanotechnologies for drug discovery, tissue engineering, proteomics, microfluidics, biosensors, molecular assembly and integrated systems.

Bioassays and chips of the future

Many technologies from the field of electronics have not been exploited in biomedical fields, but bioassays of the future will integrate fluid, electronic and optical tools. Researchers are now moving from conventional microfluidics to polymer

 0167-7799/02/$ – see front matter PII: S0167-7799(01)01901-1

systems and minor adaptations can lead to the miniaturization of existing technologies. George Whitesides (Harvard University, Cambridge, MA, USA) discussed the need to develop news types of assays and tools to improve the validation of targets to streamline the drug development process. He described the five main techniques that are providing a new set of tools: (1) self assembled monolayers (SAMs) of alkanethiolates on gold to control the character of interfaces; (2) inert surfaces that do not adsorb proteins and therefore do not allow cells to attach; (3) the use of surface plasmon resonance to observe the kinetics and thermodynamics of adsorption of macromolecules at the surface of SAMs; (4) soft lithography to pattern the interface in its plane and (5) controlled laminar flows in microchannels.

Advances in chip technology have resulted in high signal-to-noise ratios, very small amounts of material are required, the assays are extremely sensitive and the chips are cheap to make. Stephen Quake (California Institute of Technology, Pasadena, CA, USA) discussed advances in fabricating chips out of polymeric materials. His group has developed novel pinch valves and peristaltic pump components for on-chip fluidic manipulation that will be useful in future chip designs and biotech applications. Heng Zhu (Yale University, New Haven, CT, USA) has developed a novel protein chip technology that allows the high-throughput analysis of biochemical activities and has used the approach to analyze nearly all the protein kinases from *Saccharomyces cerevisiae*. His studies show that microarrays of an entire eukaryotic proteome can be created and screened for large numbers of biochemical activities resulting in the identification of novel protein functions and interactions.

Small therapy

Micro- and nanodevices are in demand in the therapeutic arena because they minimise material, can mimic the size-scale of the biological world and can have integrated functionality. There is an unmet medical need in the drug delivery field with respect to the unsatisfactory treatment of patients with chronic illnesses that require multiple injections – bioMEMS could provide the answer. Tejal Desai (Boston University, Boston, MA, USA) described how nanoporous interfaces that are selectively permeable to biomolecular species can be fabricated using sacrificial lithography and that nanoporous cylinders containing semiporous regions can be used for drug delivery. Mauro Ferrari (Ohio State University, Columbus, OH, USA) described the implantable 'stealth bioreactor', an immunoisolated cell transplantation biochip technology, and targeted micropills for the oral delivery of biotech molecules. He also described a novel nanopump (patent pending), an externally controlled, implantable drug delivery device for the long-term release of drugs, which is targeted for use in programmable drug delivery systems. Nanopore membranes, which act as sieves for the selective passage of molecules, can be used in capsules with cells for transplantation and in drug delivery and release. Previously, the limitations in biocapsule development have been premature biodegradation, the need for precision and the requirement of protein resistance so that the implants don't get stuck to proteins.

Nanotechnology can be used to target the drug discovery market. The potential applications of combining MEMS with biological systems has become increasingly apparent. Sangeeta Bhatia (University of California, San Diego, CA, USA) is specifically interested in integrating microtechnology tools with live mammalian cells for applications in drug discovery, functional genomics and tissue engineering. Cell-based strategies for assays mean that drugs fail earlier, before they enter expensive animal and clinical trials. Ravi Kapur (Cellomics Inc. Pittsburgh, PA, USA) described a new approach, termed high content screening (HCS) which uses cells as biosensors, exploiting the sensitive and specific molecular detection and amplification system that cells use to sense changes in their external environment. HCS results in a complete description of cell functions and activity of bioactive molecules or drugs and in the future, cell arrays and microfluidics will be integrated to produce a faster and cheaper miniaturised HCS platform. Cell-based biosensors are also being used as generalised toxicity sensors.

Tissue engineering

Tissue engineering is a promising technology that can be used in place of animal experiments. Potential applications include drug testing and screening, drug delivery, cell-based micro-actuators, hybrid biomimetic robotics, hybrid prosthetic devices and surgical transplantation. Paul Kosnik (Brown University, Providence, RI, USA) discussed how engineered skeletal muscle is qualitatively similar to native muscle and the many uses it could be put to, and Jeffrey Borenstein (Charles Stark Draper Laboratory, Cambridge, MA, USA) discussed how microfluidic designs that replicate key aspects of physical circulation have been developed.

Small chemistry

The increased surface area to volume ratio associated with miniaturization enhances surface-based reactions but surface interactions are not always desirable. Johan Roeraade (Royal Institute of Technology, Stockholm, Sweden) described the use of static and microfluidic systems, new sampling devices for liquids and solids, methods to avoid solvent evaporation from nanosystems and the applications. He has combined chip-based chemistry with analytical tools such as capillary electrophoresis.

Summary

The conference provided an excellent forum at which to find out what is happening at the forefront of small technology. Improved therapeutic technologies and new approaches are emerging from the alliances between biomedical engineers and molecular biologists, and materials science and engineering researchers, all working together to solve problems and create nanotech devices. One of the main bottlenecks in biomedical nanotechnology is that many of the technologies and functionalities that have been developed have not been fully integrated and are difficult to use. Also, many of the devices are already working in the labs now and it will be the process of getting them accepted into society and into doctor's surgeries that will be the bottleneck, rather than the technology behind the devices.

Suzanne Berry
Trends in Biotechnology, Elsevier Science London, 84 Theobald's Road, London, UK WC1X 8RR.
e-mail: suzanne.berry@eslo.co.uk