Meeting report

Macromolecular technologies: applications and improvements

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Published: 2 May 2001

Genome ***Biology*** 2001, **2(5)**:reports4012.1–4012.3

The electronic version of this article is the complete one and can be found online at http://genomebiology.com/2001/2/5/reports/4012

A report on the Association of Biomolecular Resource Facilities (ABRF) meeting, San Diego, USA, 24-27 February, 2001.

Approximately 1,000 scientists arrived in San Diego for the annual ABRF meeting, which was entitled "The new biology: technologies for resolving macromolecular communications". An online version of the meeting abstracts will be available through the ABRF journal, the *Journal of Biomolecular Techniques* [http://www.abrf.org/JBT/JBTindex.html], and more details can be found at the ABRF website [http://www.abrf.org]. This meeting was, as in previous years, a great place to learn about both new technologies and recently developed modifications that improve existing research methods. A regular meeting highlight is the recognition of an outstanding contributor to technology development. This year, Csaba Horvath (Yale University, New Haven, USA) was recognized for his contributions to the evolution of modern chromatography.

The plenary talks provided an appropriate backdrop to illustrate how basic science drives the discovery and development of the many research methods and technologies that were discussed in detail during the smaller concurrent sessions. Ronald Evans (Salk Institute, La Jolla, USA) presented the intricacies of nuclear hormone receptor action and illustrated potential effects that can result from drug-drug interactions. He described an interesting adaptation mechanism that enables the body to increase resistance to an introduced chemical, and outlined how this 'xenobiotic response' facilitates detoxification and clearance of the chemical from the body. This response can be triggered by substances present in non-prescription compounds (such as St John's Wort) and, once activated, removes a variety of substances from the body. Examples of drugs that can be eliminated from the body by the xenobiotic response include the active ingredient in birth control pills (thus providing a scientific explanation for many 'miracle' babies), and protease inhibitors, which are used to treat HIV.

Roger Brent (Molecular Sciences Institute, Berkeley, USA) discussed the development of a computer program to predict how a biological system will respond to a particular stimulus. Brent said that accurate modeling of cellular behavior will ultimately be made possible by combining advances in computing power, computational methods, and biological understanding. As an example, the group is generating datasets from cells treated with varying amounts of a signal (such as yeast mating pheromone). Expression of various fluorescent protein constructs provides information about the promoters that are activated, and facilitates quantification of the biological response to the signal.

Andrew Marks (Columbia University, New York, USA) described a series of essential protein-protein interactions between proteins that form and regulate calcium-release channels in heart muscle. These intracellular (sarcoplasmic reticulum) channels have huge cytoplasmic domains that act as scaffolds for the additional proteins that determine pore structure and channel activity. If these interactions are disturbed by hyperphosphorylation, heart failure can occur. Thus, the proteins involved in these contacts are targets for potential therapeutic agents.

Other plenary talks were given by Robert Lehrer (University of California Los Angeles, USA), Roger Kornberg (Stanford University School of Medicine, USA), and Alan Wolffe (Sangamo BioSciences, Inc., Richmond CA, USA). Lehrer described protegrins, a fascinating class of broad-spectrum antibiotics that quickly disrupt the bacterial outer membrane, killing cells within minutes. Kornberg presented a three-dimensional structure of the RNA polymerase II transcription system from *Saccharomyces cerevisiae*, which contains approximately 50 polypeptides. Finally, Wolffe discussed a strategy using engineered zinc-finger proteins as transcription factors to activate

or repress specific genes, an exciting advance with both medical and biotechnological potential.

ABRF research groups conduct studies to assess and compare the core facilities provided by member laboratories. The research group presentations stimulated lively discussions of both cutting-edge and established technologies. Four of the most interesting DNA-related presentations were on sequencing, microarrays, nucleic-acid synthesis, and detection of dinucleotide repeats.

Dina Leviten presented the ABRF DNA Sequencing Research Group's studies assessing the capabilities of DNA sequencing core laboratories. The bacterial artificial chromosome (BAC) study has two aims: to determine a robust protocol for BAC sequencing and to identify a protocol or kit that produces high-quality BAC DNA for sequencing. A protocol for sequencing has been determined (see the poster, which can be found on the group's website [http://abrf.org/ABRF/ResearchCommittees/dsrg_members.html#Electronic_Posters]), but the second part of the study is still accepting submissions and the results will be disseminated at a later date. The group has also conducted a general survey to describe the composition and configuration of an average DNA sequencing core facility.

Two studies are being prepared by this group for launch this year. One is a continuing analysis of the effect of different DNA-sequencing methods on the quality of the resulting data using a standard template (see the group's website [http://nes.biotech.cornell.edu/nes]). The second will determine the accuracy of single-nucleotide polymorphisms (SNP) sequencing using the equipment and chemistries available in participating laboratories. The group is particularly interested in assessing detection of mutations and mixed bases and may include insertions and deletions in the study.

George Grills of the ABRF Microarray Research Group (MARG) described the results of a web-based survey that assessed the current state of 78 laboratories that use microarray technologies. The study focused on Affymetrix GeneChip oligonucleotide technology and on spotting microarray technologies that use oligonucleotides, cDNA, or protein as the spotted material. Labs from academic, pharmaceutical, and commercial sectors that offer microarray technologies as a shared resource or as an individual lab provided data for the survey, including information on instrumentation, protocols, staffing, funding, and throughput. The results describe the equipment being used in labs doing their own spotting, including types of DNA-handling robots, slide arrayers, and scanners, and the levels of satisfaction and types of technologies being used. For example, the current survey shows that users of the Affymetrix GeneChip technology report higher satisfaction with the platform than in a previous MARG survey. More laboratories with spotting technologies are spotting oligonucleotide probes. The most commonly reported challenge in using microarray technologies is bioinformatics. The MARG plans to post a detailed description of the survey results on the ABRF website [http://www.abrf.org]. Results from the previous survey are available from the MARG's 2000 poster [http://abrf.org/ABRF/ResearchCommittees/MARG/MARG_Survey_2000_Poster.pdf]. The MARG intends to follow up its general survey with a study involving comparative analysis of data from different microarray technologies.

Martha Gunthorpe and Anthony Yeung, representing the ABRF Nucleic Acid Research Group (NARG), presented their 2001 DNA-synthesis facility survey and a benchmarking study of the quality control (QC) of oligonucleotide synthesis in ABRF facilities. DNA-synthesis machines that appear to produce functional short primers can nevertheless be non-optimal for the synthesis of one or more of the four nucleotides, and these instruments may thus be unable to make good long or modified oligonucleotides (which are important in several DNA-based technologies). In this study, homopolymers of each of the four nucleotides were used to evaluate the synthesis efficacy of each nucleotide by about 31 DNA synthesizers. Moreover, six methods of quality control were compared in a high-throughput environment. Analysis of the resulting 744 QC chromatograms showed that routine QC would lead to DNA synthesizers that make oligonucleotides better, cheaper, and faster. In the future, the specific factors that lead to more efficient and economical synthesis will be distributed. The group invites all DNA synthesis facilities contact each other through the NARG, in order to help each other maintain a uniformly high standard of oligonucleotide synthesis. The results of this study are available from Yeung's ftp site [ftp://ftp.fccc.edu/yeung/outgoing/] and at the ABRF site [http://www.abrf.org].

Doug Bintzler, representing the ABRF Fragment Analysis Research Group (FARG), presented the results of their current study, in which participating labs submitted results from the sequencing of two DNA samples, each containing a dinucleotide-repeat marker generated with both untailed primers and a tailed reverse primer (tailing optimizes incorporation of a non-templated 3′ base at the end of the DNA strand). A tetranucleotide was also included in the samples for comparison. The study clearly demonstrates that using tailed primers increases the accuracy of detecting and calling dinucleotide repeats. When assessed by allelic differential, participating laboratories were able to distinguish the correct alleles 97% of the time when tailed primers were used to generate the dinucleotide repeat, as opposed to only 44% of the time when untailed primers were used. Tetranucleotide repeats were detected with 98% accuracy. The details of the study are available online on the poster [http://www.abrf.org/ABRF/ResearchCommittees/FARG/POSTER_farg2001.pdf].

This ABRF meeting was a wonderful opportunity to learn about a wide variety of research methods from the hands-on

experts who routinely use or improve them. Mark your calendars: ABRF 2002, "Biomolecular technologies: tools for discovery in proteomics and genomics" will be held in Austin, Texas, USA, 9-12 March, 2002.

Acknowledgements

I thank Pamela Scott Adams, George Grills, Dina Leviten, and Anthony Yeung for providing summaries of their presentations.