genomes from plants and other organisms as an *in vitro* strategy for molecular breeding. A lasting impression was distilled from Scott Uknes (Paradigm Genetics, Research Triangle Park, NC, USA), who described the large-scale biochemical profiling of *Arabidopsis thaliana* knockouts to determine gene function; 5000 data points are taken for each event. This scale of data acquisition requires advancements in computation power to complement the 'big biology' of functional genomics.

Emerging realities

The technical feasibility of applying genomics to crop improvement is rapidly becoming a reality. Beyond the scientific progress in this exciting field and its implications for agriculture are several social issues; these were addressed by Roger Beachy (Donald Danforth Plant Science Center, St Louis, MO, USA). The major challenge is, and will continue to be, engaging the public in the adoption of this technology. Roger Beachy implored delegates to become involved in this dialogue when he said, 'How we tell this story will determine the acceptance and therefore the future of this enterprise. What is produced from this technology, and who benefits from it, are equally essential for the establishment of a safe, secure and nutritious food system'.

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Meeting report

Screen idols: faster, smaller, cheaper and smarter

According to Robin Spencer (Pfizer Central Research, Groton, CT, USA), finding a new drug candidate is like playing golf, where the target is the pin. High-throughput screening techniques using compound libraries can get you to the green; the medicinal chemists will then use different tools to modify the structures of the lead compounds that have been obtained and will thus help you sink the putt. The problem is that we don't know the layout of the course, the golf balls cost US$1 each, and we are blind. Traps (bunkers) lurk everywhere for the unwary, the competition has an unknown handicap, and economics dictate that we can only use a certain number of clubs – this was altogether an appropriate metaphor for the latest meeting* of the Society for Biomolecular Screening held in Edinburgh, Scotland.

To map the course, then, we must have good databases of where the hazards lie, must use intelligent chemoinformatics tools to see whether, and by how much, particular greens overlap (this defines the specificity of a particular pharmaceutical), and must improve the cost:benefit ratios by making our assays faster, smaller, cheaper and smarter.

*The *5th Annual Meeting and Exhibition of the Society for Biomolecular Screening* was held in Edinburgh, UK, 13–16 September 1999.

Getting faster

Of the 10 000 human genes that could realistically form targets, genomics is providing ~100 per year in big Pharma (Paul England, Aurora Biosciences, San Diego, CA, USA), ~20 of which will lead to development compounds, approximately three of which might emerge as new chemical entities. This is still a high attrition rate, and therefore more assays must be carried out not just to find hits that inhibit the desired target but hits that also have desirable pharmacological properties, particularly because we might have run out of decent targets for mammals in <15 years (Alan Binnie, Selectide HMR, Tucson, AZ, USA). With full automation, 100 000 assays can be performed routinely per day.

Getting smaller, getting cheaper

Testing a compound inventory of 500 000 to 1 million compounds can get expensive on reagents, and just as at last year's meeting[1], there is a continuing trend towards miniaturization. Traditional microtitre plates, in which assay volumes of 0.3 ml are typical, are already widely replaced by 384-well plates; 1536-well plates, although only two years old and using assay volumes of 5–10 μl, are now considered to be reliable enough for routine use (Ulrich Haupts, SmithKline Beecham Pharmaceuticals, Harlow, Essex, UK).

Aurora Biosciences (Paul England) and partners (David Mack, Parke–Davis Pharmaceutials, Ann Arbor, MI, USA) are exploiting 3456-well proprietary arrays; wall-less plates were also described (David Burns, Abbott Laboratories, Abbott Park, IL, USA) in which candidate inhibitors are dotted at a density equivalent to 8640 compounds per 96-well footprint, and the enzyme then the substrate are overlaid in continuous gels. Diffusion starts the assay, and the sheets are read with a fluorescent imager.

Another trend is to use 'lab-on-a-chip' technology, in which pneumatic and electro-osmotic forces manipulate reagents through small liquid channels (Robert Pacifici, Amgen, Thousand Oaks, CA, USA); in addition to being high-throughput, less-conventional measurements, such as very rapid DNA sizing, can be performed in this way.

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Smaller assay volumes demand (and in some cases permit) novel assay methods. Fluorescence correlation spectroscopy, using a confocal lens in which the interrogation volume is 1 fl, is especially well-suited to assays being run in only a few μl, and a new variant (fluorescent intensity distribution analysis) extends the range of assays significantly (Manfred Auer, Novartis Research Institute, Vienna, Austria).

Reagent savings in these assays are impressive, with an assay campaign that might have cost US$200 000 in the past being run for US$2000–US$3000 today. Mass spectrometry and fourier transform infrared spectroscopy can be carried out on complex mixtures with no added reagents, and in principle could prove the least expensive of all, although they require the deployment of intelligent software to turn the data into information (Douglas Kell, University of Wales, Aberystwyth, UK).

Getting smarter

Whatever the method, the result of a greater number of assays is a greater amount of data, and the concomitant need to devise information systems that fully exploit them. This involves intelligent data structures and advanced visualization tools for both biology and chemistry (Bryn Roberts, AstraZeneca Pharmaceuticals, Alderley Park, UK), and the integration of lead discovery and optimization (Philip Tagari, Amgen, Thousand Oaks, CA, USA).

Novel parallel expression profiling methods study the pattern generated when each yeast gene is tagged seriatim with green fluorescent protein (Stephen Friend, Rosetta Inpharmatics, Kirkland, WA, USA), and allow the identification of hits not only against specific targets (by comparing patterns with those in a database) but of off-target hits. Even if they don't have brains or livers, yeast are sufficiently similar to people that the patterns of expression from 720 experiments in which the profile matrix was challenged with different drugs, allowed the easy identification and discrimination of neuroactive and hepatotoxic molecules. The trend is towards high-information-content screens and measurements *in vivo*, where transient gene-inactivation methods provide perturbations of considerable power and explanatory value (Julianne Bryan, Scriptgen Pharmaceuticals, Waltham, MA, USA).

The best place to look for a new drug is an old drug, and the discovery (in 1991) that cyclosporin exerts its immunosuppressive effects by inhibiting a protein kinase has led to an explosion of interest in these kinds of molecule, especially because one in three mammalian proteins is phosphorylated (Philip Cohen, University of Dundee, Dundee, UK). However, if we want to isolate agonists, especially for the popular G-protein-coupled receptors, we should screen for agonists, not just binders (Thue Schwartz, The Panum Institute, Copenhagen, Denmark).

Less is more

The aim of having a large compound library is to cover chemical structure space well, but if we are smart we can do this more efficiently. A battery of computer methods allows us to assess chemical diversity based on physical and structural properties (Peter Willett, University of Sheffield, Sheffield, UK), so that if hits cluster together in chemical space we can concentrate our efforts there. Screening libraries intelligently and iteratively, rather than as a blitz, will stop us from doing assays that have no chance of a positive result (Paul Domanico, GlaxoWellcome, Research Trinagle Park, NC, USA); 40% of the hits can come from 10% of the library.

Conclusion

These are exciting times for those involved in the development and validation of new assay technologies, and this meeting has trebled in size in the past four years. As yet there seems to be no diminution in the creativity of screening scientists who exploit all possible disciplines to produce results of a quality, and at a speed and low cost, that would have previously seemed unthinkable.

Reference

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