Meeting report

Changing diagnostics and therapeutics forever with cDNA arrays

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A report on the 'cDNA arrays/DNA diagnostics' session at the first meeting of the European Life Scientist Organization (ELSO), Geneva, Switzerland, 2-6 September, 2000.

It has been predicted in numerous reviews that over the next few years there will be an explosion of gene-expression profiling data coming from a number of new technologies that promise 'global' analysis of cellular transcripts. Although complemented by flow-based techniques, the principal technology that is currently generating such data, and which has captured the thinking of many biologists, is the DNA array. Whether it be constructed by spotting cDNA onto immobilized solid supports or through the surface assembly of oligonucleotide probes, it is fundamentally an immobilized array of hundreds to thousands of transcript probes that is being used to explore biological regulation at the level of gene expression.

This conference session brought home the message that this technology is not only changing the pace of discovery but may also be fundamentally altering the paradigms upon which biological experimentation is based. An alternative experimental paradigm to the historical hypothesis-driven research model is the systematic analysis of sets of biological interactions measured against broad comprehensive sets of endpoints: gene expression arrays, proteomics, metabolomics, and so on. After initial experimentation, questions are asked *in silico* and then new hypotheses are generated for focused follow-up testing.

The talk by John Weinstein (National Cancer Institute (NCI), National Institutes of Health, Bethesda, USA) discussed gene expression profiling for cancer drug discovery, in particular the current state of the art at NCI. They have constructed cDNA arrays consisting of approximately 8,000 unique genetic elements and used them in a systematic way to investigate the relationship between candidate therapeutic compounds, cancer tissue type and gene expression regulation. The program currently uses a panel of 60 cultured human cancer cell types which had been characterized pharmacologically against more than 70,000 chemical entities as of March 2000.

Weinstein's group has analyzed large complex data sets and published extensively on the use of two-dimensional clustering techniques to highlight interesting biological phenomena in large systematic biological experiments. He showed examples of how this technique was being used in the therapeutic-compound screening at NCI. To demonstrate the validity of approach, it was shown that cell lines tended to cluster by organ of origin; in other words, the expression profiles of cell lines from the same organ were similar, as expected. Overall, gene expression clusters were much stronger than the activity clusters from growth inhibition assays. Furthermore, the drug-activity gene expression profiles of several tumor lines known to express multi-drug resistance clustered very closely together. In another example, it was shown that when examining a group of 118 'well-known' drugs, five distinct clusters emerged, all clearly based on mechanism of action. For example, one of the clusters contained many Topoisomerase 1 inhibitors, and another contained Topoisomerase 2 inhibitors. Some surprising associations were also observed for compounds not previously known to be related mechanistically. Lastly, one compound in current therapeutic use for one tissue was clearly found to have similar gene expression patterns in a different tissue or cell type. This finding has led to subsequent experimentation and to a possible novel therapeutic use.

This last example, in particular, points to the 'paradigm shift' previously mentioned. By taking a large-scale systematic approach, the NCI researchers were able to capture a biologically relevant answer to a question they hadn't originally asked when setting up the 'experiment'. This answer appeared both by chance and as a result of experimental design. It was by chance that the relevant experimental combination was included in the trial (compound X, cell

type y, and genes a-n), but it was also certainly by design that the NCI researchers had taken great efforts to include a large number of therapeutic compounds, a wide diversity of appropriate cell types, and a large number of genes. In essence, 'genomic level' large-scale biology provides the scale to cover most reasonable experimental combinations of interest, thereby diminishing the chance of missing an important effect. Researchers in large programs, such as those at the NCI or in large pharmaceutical companies, as well as individual investigators in academic labs, are going to have to wrestle with experimental design so as to take best advantage of genomic-scale measurements.

Charles Boone (University of Toronto, Canada) presented work using whole-genome coverage via cDNA arrays in yeast. He explained that *Saccharomyces cerevisiae* provides an opportunity to investigate both intercellular signaling and intracellular signal transduction. Conjugation between different haploid cell types is triggered by the mutual exchange of diffusible peptide pheromones. The pheromones excite surface-localized G-protein-coupled receptors and thereby initiate a signaling pathway that coordinates a set of physiological changes required for mating. These changes include G1-phase arrest of the mitotic cell-division cycle, the increased expression of mating genes, and polarized cell growth directed towards the pheromone source.

Boone's laboratory has been working in collaboration with Rosetta Inpharmatics Inc. (Kirkland, USA) to develop array-based technology as well as the associated bioinformatic tools to handle the highly complex data sets resulting from such experiments. They have elucidated modular response mechanisms - cassettes of genes making up a known metabolic pathway, for example the filamentous growth pathway and the protein kinase C pathway - that coordinate signal transduction and cellular functions controlled by the yeast pheromone response pathway.

Wlodek Mandecki of PharmaSeq Inc., a small start-up company near Princeton, USA, presented a new process of developing detection/labeling technology for 'fluidic' arrays used in gene-expression monitoring. The company's technology employs a small integrated circuit called a microtransponder. This is a miniature transmitter approximately 250 micrometers wide, which is powered by light provided by an interrogating laser. Results were presented indicating that a microfabricated microtransponder could generate a unique electronic signature for thousands of single-oligonucleotide probe platforms within a fluidic chamber. These devices were proposed as a unique platform for performing highly parallel hybridizations, each of which could then be related to a specific oligonucleotide probe via the microtransponder's unique signature. Data from prototypes were presented, indicating that the technology could discriminate between matched and mismatched target oligonucleotides binding to microtransponder-bound probe.

These talks showed that DNA arrays are already becoming very useful tools and may transform the way biological experiments are done and planned in the future.