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# Chip, chip, array! Three chips for post-genomic research

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Cambridge Healthtech Institute recently held the Fourth instalment of their popular *Lab-on-a-Chip* series in Zurich, Switzerland (14–16 January 2002). As usual, it was enthusiastically received and >225 people attended the meeting to see and hear about some of the latest developments and applications of biochip and array technology.

## Protein chips

The post-genomic era has seen a rapidly increasing need and desire to enhance and support genomic studies with proteomic data. Consequently the development of protein array technology is beginning to move forward rapidly. Perhaps because of the variability and complexity of proteins, proteomic studies are generally lagging a few years behind their genomic counterparts. Nevertheless, there are already several examples of lab-on-chip type devices available for proteomic analysis. This could be because certain aspects of protein technology are relatively mature, for example, antibody technology, and can be readily adapted to automated miniaturized array formats, albeit on a low density scale.

Thus, many of the presentations on protein analysis described technologies based on antibody–antigen binding. For example, Ken Beuchler (Biosite, San Diego, CA, USA) gave a detailed presentation of Biosite's microfluidics chip for assessing heart damage. Built into a portable hand-held instrument, the chip uses a few microliters of whole blood and works via immobilized immunoassays. Although the current version measures only three products of heart damage, the next iteration will be able to measure up to 100 analytes and will thus be amenable to measuring the presence and extent of numerous other conditions. Similarly, Sara Mangialaio (Novartis Pharmaceuticals, Basel, Switzerland) is heading up a project using chip-based antibody arrays to detect rheumatoid arthritis in human patients.

Tito Bacarese-Hamilton (Imperial College of Science, London, UK) has approached the antibody–antigen paradigm from the opposite direction. He described the development of antigen-based microarray immunoassays for the simultaneous determination of IgG and IgM antibodies against various pathogenic antigens present in serum samples. Likewise, Michael Seul (BioArray Solutions, Piscataway, NJ, USA) described bead arrays, arranged on a chip, which display a multi-functional antigen panel for quantitative profiling of antibodies in patient sera. This approach is also versatile in that it can be adapted to carry out DNA polymorphism analysis, or indeed, to any assay designed to monitor the binding of one molecule (ligand) to another (receptor).

Of course, antibodies can also be generated against chemical epitopes, and this property is being used by Claus Christenson (University of Copenhagen, Denmark) to develop antibody-based assays for groundwater pesticides and their breakdown products. Christenson described how an array-based enzyme-linked immunosorbent assay (ELISA) of this nature would offer an inexpensive, sensitive and rapid replacement for traditional test systems such as HPLC. Such arrays could be incorporated into portable instruments for testing for the presence of pesticides at individual waterworks or wells.

## Phenotype chips

According to Barry Bochner (Biolog, Hayward, CA, USA), phenotype microarrays are a new technology platform that enable the simultaneous testing of up to 2000 cellular properties. The arrays themselves are 96-well plates, with each well containing a different cell-culture medium that is designed to test a unique phenotype or cell function. Biolog is developing a battery of ~2000 tests for examining, among other things, carbon and nitrogen metabolism, biosynthetic pathways, osmotic and ionic effects, pH effects, and sensitivity to chemicals such as heavy metals and drugs. Bacterial or *in vitro* cultured cells are added to each well, and incubated for a short period. The phenotype is reported by the presence or absence of a color change in the growth media. The phenotype arrays can be used to discover drug targets, determine gene function, and fingerprint the effects of drug leads to determine mode of action, side effects, and synergy or antagonism with other drugs.

## DNA arrays

The use of phenotype arrays makes sense, because in most cases we do not understand the biology of a system sufficiently well to make decisions on the meaning and usefulness of gene expression changes and other genomic measurements, nor how gene expression

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networks are modulated or interact. The issue becomes yet more complicated in the emerging area of surrogate tissue analysis, and this new approach to monitoring the effects of drugs and environmental toxicants was discussed by John Rockett (author of this report). The premise is that for all toxic endpoints (except perhaps necrosis), clinical manifestation is preceded by gene expression changes, thus providing a mechanism for the early detection of biomarkers of exposure and/or effect. Although it is clearly not possible to biopsy apparently healthy inaccessible tissue such as testis or liver to determine its status, the use of accessible 'surrogate' tissues (e.g. blood, hair follicles) as a 'window' into the molecular events occurring in these and other inaccessible tissues might be a viable approach for monitoring at-risk populations.

One of the most stimulating presentations (as measured by the throngs of delegates subsequently gathered about their exhibition stand during the breaks) was by a small biotech company, Febit (Mannheim, Germany). Febit has developed the first fully integrated DNA array platform, Geniom 1®, which could move the field of DNA microarray analysis forward into the next generation. The key is the flexibility of the system and the ease of operation. The user simply inputs the oligonucleotide sequences (15–60 base pairs) of the genes they wish to study, and their RNA samples. Up to 48,000 oligonucleotides (eight subarrays of 6000 oligonucleotides each) are then synthesized *in situ* on a disposable substrate. Hybridization of up to eight samples can then be carried out simultaneously, and Geniom 1 measures the fluorescence signals using an inbuilt CCD-camera. The hybridization data is delivered in digital format. One user can, therefore, examine gene expression analysis in the whole yeast genome, whereas another could subsequently genotype HIV strains. The next user could carry out SNP analysis of pufferfish CYP450s, and then conduct sequence analysis of sheepshead minnow genes induced by estrogen. This versatility could prove invaluable for high-throughput research.

New insight into biological function is one of the most widespread applications of biochips. Gene arrays bring a new dimension to research because they often provide new information about gene function, expression and interaction; information that could reveal unknown, unexpected or unanticipated relationships. As Shu Ye (University of Southampton, Hampshire, UK) pointed out, hypothesis-driven studies of one or a few genes based on *a priori* knowledge is unlikely to lead to the identification of novel candidate genes involved in a model of interest. This was exemplified in his own work examining the effect of nicotine on endothelium. Because the regulatory pathways mediating the effect of nicotine on gene expression in endothelial cells are unknown, Ye used DNA array analysis to provide the leads into what molecular mechanisms might be involved. He went on to provide evidence that nicotine could increase the permeability of the endothelial barrier by downregulating endothelial junction protein expression, and that the effect might be modulated through the inositol phospholipid signaling pathway.

## Informatics

Information, they say, is power. If this is true, then Jutta Bachmann and her colleagues at Bachmann Science Information Service (BSIS, Nesoddtangen, Norway) have developed a website that goes a long way to empower scientists working in the biochip technology sector. Until now, a researcher interested in the latest products, patent applications, publications or meetings associated with the biochip sector, has been forced to visit at least several of the eclectic multitude of websites that currently exist in cyberspace. BSIS have compiled a unique and complete resource for biochip information that includes all of this information and more in an easy-to-navigate website (www.biochipnet.de). Further good news is that a sponsor has recently stepped forward so that access to all areas of the site will soon be free for all.

It is clear from meetings such as this that lab-on-a-chip and array technology has gained much interest and support. Although we are far from the end of the learning curve, the technology has already been used successfully in basic and applied research and in diagnostic tools. The post-genomic era promises to be a period in which the 'omic' fields, such as genomics, proteomics and phenomics, will be combined with miniaturization technology and advanced computing power to provide a hitherto unprecedented resource for biological research.

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