advances in the methods and technology being applied in bioassays. The importance of appropriate statistical analysis of data was demonstrated in a number of presentations. It was emphasized that, for this, it is essential to ensure that the assay design permits the appropriate data to be obtained, and early consultation with a biostatistician can be helpful.

The symposium provided a lively forum for attendees with little previous experience in bioassays who learned about some of the common pitfalls to avoid in assay design and validation, as well as for experienced bioassayists with specific problems to share or resolve. The meetings are currently held annually in the USA and in Europe.

Clinical genomics comes of age

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The promised benefits of clinical genomics stretch from the earliest phase of drug discovery, to the diagnosis and treatment of individuals, and even to already-marketed medications. Clinical genomics investigators apply the large-scale study of genes, using actual clinical materials and associated clinical information, to identify and characterize the genes that are most relevant to the origins and progression of disease. This information can then be used to speed the design and development of new and improved therapeutics, identify novel biomarkers for earlier diagnosis, and select treatments that, based on the patient's genetic makeup, are most likely to succeed and cause the fewest adverse events for that individual. According to the speakers at the *2003 Clinical Genomics Symposium Series* (Princeton, USA; 13 June), clinical genomics and related bioinformatics have matured sufficiently for molecular study of human disease to speed up and improve success rates in discovery and development of novel compounds. At the same time, organizational changes have encouraged the dissemination and application of molecular knowledge to improve pharmaceutical productivity.

Targeting cancer by subtype

The subtyping of cancer, based on differential gene expression profiles, has begun to illuminate the molecular differences between tumours. These differences help to predict individual response to chemotherapy and other medications, and also the likely course of the disease – prognosis provides little solace without the possibility of treatment alternatives. Todd Golub, of the Whitehead Institute (http://www-genome.wi.mit.edu) and the Dana-Farber Cancer Institute (http://www.dfci.harvard.edu), has directed many studies to subtype cancer at the molecular level, to identify novel targets for drug discovery and screening and to improve diagnosis. He presented results showing several cases in which expression-profiling of tumour tissue has enabled rapid identification of molecular targets for screening of novel compounds that are moving rapidly into clinical trials.

Citing more traditional means of classifying hematologic cancers, and using TEL/AML1 translocations in certain childhood leukemias as one example, Golub then demonstrated that identification of such translocations can be predictive of disease outcome. He and his colleagues have extended such molecular–clinical classifications to include global gene expression, and believe that such classifications could also be used to improve diagnosis and treatment. In one example, the FLT3 tyrosine kinase gene was identified as overexpressed in certain leukemias (i.e. mixed lineage leukemia) that are now classifiable with RNA expression profiling. Like the recent success of Gleevec© in treating chronic myelogenous leukemia, in which a translocation event (Bcr-Abl) pointed to an overactive kinase whose inhibition proved to be a successful therapeutic strategy, it was hypothesized that inhibition of FLT3 might be a viable therapy. Subsequent studies of human MLL cells grafted into mice, showed that an available small molecule inhibitor of FLT3 causes regression of the tumour. The stage is now set for testing treatment of MLL patients with a small molecule inhibitor of FLT3: Significant clinical potential with very recent origins in a clinical genomics approach.

Golub described what is now termed a 'Global Cancer Map', showing that the gene-expression profiles of a broad

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array of tumours are a practical tool for improved cancer classification. This approach, developed by his laboratory, has enabled exploration of the molecular differences between cancers, and has most recently been used to uncover gene signatures for metastasis or the metastatic potential of a primary tumour. The demonstrated existence of a generic gene-expression profile for metastasis would, Golub asserted, provide a valuable tool in clinical decision-making early in treatment, and could also help to prevent significant aspects of disease progression. In concluding remarks, he stated that the time has come to systematically validate and integrate the use of molecular profile data in the therapeutic discovery and development process on a consistent basis.

Identifying biomarkers

Many of the emerging clinical and pharmaceutical advances have been enabled by the abundance of independent datasets that are now available for analysis and from bioinformatics tools for large-scale, cross-population, molecular and phenotypic study. In an effort to increase the power of genetic association in complex diseases such as obesity, Eric Schadt (Rosetta Inpharmatics; http://www.rii.com) described his group's novel approach to the use of biologically relevant molecular profiles as a quantitative association phenotype in association analyses within animal and human populations to improve target discovery.

Arul Chinnaiyan (University of Michigan; http://www.umich.edu) described a recently launched web-accessible database, Oncomine, developed and maintained by his laboratory (www.oncomine.org). He explained that meta-analysis of independently derived datasets posted on Oncomine should help investigators validate novel genes they have identified across studies and to address hypotheses across cancer types.

Using gene-expression profiling and subsequent validation analysis with Oncomine, his laboratory identified novel markers for prostate cancer. These could supplement or possibly replace the current standard prostate cancer test, the Prostate Specific Antigen (PSA) test, which often provides inaccurate and limited information about the presence of cancer and cannot characterize the cancer as benign or aggressive – a major issue in disease prognosis and determination of clinical care. Using high density tissue microarrays, his laboratory found high levels of alpha-Methylacyl Coenzyme A Racemase (AMACR) protein in over 95% of hundreds of prostate tissue samples containing localized cancer, but little or no AMACR protein in normal prostate tissue, making it a likely candidate for use as a biomarker. The Chinnaiyan laboratory and collaborators are now analyzing prostate cancer patient serum for humoral immune response to overexpressed AMACR, and have promising results, suggesting that the presence of antibodies to AMACR may serve as a reliable biomarker for early prostate cancer detection and screening.

Further investigation of prostate cancer samples suggested that the overexpression of polycomb protein EZH2 might distinguish metastatic prostate cancer from localized cancer. Presence of the up-regulated protein associates strongly with lethally aggressive forms of the cancer, and initial studies suggest a correlation of EZH2 expression levels with post-treatment patient survival. A diagnostic test to detect EZH2 protein could help physicians to identify accurately those who need immediate, aggressive treatment to reduce metastasis.

Overcoming bottlenecks within the pharmaceutical environment

Pharmaceutical companies are moving with variable speed toward integrating emerging clinical genomic information into their drug development practices. Several speakers addressed the factors within the industry, that can deter from incorporation of clinical genomic data, such as the high cost of routine molecular analysis, the difficulty of working with non-standardized human tissue and other clinical samples, and the challenges of enabling effective use of the resulting information across discovery and development functions.

Alan Buckler of Ardais (http://www.ardais.com) noted the inherent importance of establishing the clinical relevance of targets early in the drug discovery process, and the importance of standardization in the analysis of human clinical materials, including ethically and technically effective sample and associated clinical data collection methods. He described Ardais' approach to systematically integrating human disease analysis into the discovery process. Pointing to the growing presence of clinical genomics studies in the scientific literature, and the presentations of Golub and Chinnaiyan, he explained that tissue samples and microarrays (as well as molecular derivatives) in combination with structured clinical information, enable researchers to focus on important, disease-specific biological differences. Increasingly, target validation studies with actual human disease tissue are permitting more informed decision-making as target and potential drugs make their way from discovery through clinical development.

Sandra Glucksmann outlined the steps taken by Millennium Pharmaceuticals (http://www.mlnm.com) to apply new technologies and disseminate emerging information. Part of this effort involves the establishment of internal communication programmes

and part of it required integration of multiple information systems across discovery and development departments. The result, according to Glucksmann, has been significantly increased productivity in the discovery process.

Organizational challenges have begun to subside, as the practical business benefits of clinical genomic approaches become clearer. According to Nicholas Dracopoli of Bristol-Myers Squibb (http://www.bms.com), the longstanding approach to drug development in cancer – determination of the maximum tolerable dose – is giving way to a new approach – the maximum biologically effective dose. In the future, new drugs will be prescribed in lower doses, potentially resulting in reduced toxicity. Pharmacogenomics studies that define effective dosages and stratify patient populations according to their likely responses to a drug will be an essential part of this. Predictions will be dependent on the genetic makeup of an individual and the molecular characteristics of the individual's disease.

Dracopoli also described the discovery and validation process in the development of pharmacodynamic marker sets that might be capable of predicting a response and potentially stratifying patient populations for clinical trial enrollment. Converting such profile information to cost-effective assays for large numbers of patients requires the refinement of response-marker identification to a small number of features that could ultimately fit into current diagnostic application methodologies, such as PCR-based or protein detection methods.

Targeting therapeutics to earlier disease stages and to those patient populations most likely to respond, should help improve the current success rates, and reduce the size and cost of clinical trials. Dracopoli contended that the development of more selective, safer and effective treatments, will require adaptation to emerging clinical genomics technologies earlier in the discovery and development process.

The future of clinical genomics

The presentations and discussion at the Clinical Genomics Symposium revealed steady progress in effectively bringing genomic and proteomic technologies into the direct analysis of human disease, ultimately translating these results into clinically useful strategies. Although there are several challenges and opportunities ahead, it appears that the 'humanization of drug discovery' is coming into full swing.

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