conference report

However, just like the arteries being treated, the restenosis drug market has plenty of its own scar tissue. *Pharmaprojects* documents the discontinuation of 15 restenosis compounds and a further 45 that are under no active development. Two originally promising candidates, from the AVI Biopharma's NeuGene antisense programme, have become bogged down in the familiar Phase II clinical trial quagmire and are still seeking licensing partners. AVI-4126 and AVI-2221 are both antisense oligonucleotides that inhibit *c-myc* gene expression, with potential in arterial proliferation reduction.

Drug-eluting coronary stents will be increasingly used in the clinical setting despite their high initial outlay because the cost is likely to be compensated for by the reduced need of repeat revascularization. The costs of stents should decrease as more manufacturers enter the market. There are also experiments being conducted into biodegradable stents, especially from Asia, and this will ultimately cut costs. In 2004 >85% (39,000) percutaneous coronary interventions (PCI) performed in the UK involved the placement of a stent and, for the first time, PCIs outnumbered coronary artery bypass graft procedures. The stent has rapidly become popular as a treatment for restenosis, as patients are really taking it to heart.

Sean McDonnell
Pharmaprojects,
PJB Publications,
69–77 Paul Street,
London,
UK, EC2A 4LQ

conference report

Trends in genomic variation: a view of some of the latest technologies

Genomic Variation
San Francisco, CA, USA
15–16 June 2005

Marylyn D. Ritchie, ritchie@chgr.mc.vanderbilt.edu

Capturing information about human genetic variation is a major goal for scientists in several fields. Molecular biologists are constantly developing new ways to explore variation experimentally at the DNA level. Population geneticists are interested in looking at patterns of variation and how different organisms compare in levels of variation. For human genetics and pharmacogenetics, the interest lies in detecting the genetic variations that are associated with clinical outcomes, such as disease and/or drug treatment response.

These topics were discussed at Cambridge Healthtech Institute's Inaugural Conference on *Genomic Variation* on June 15–16 in San Francisco, CA. This event was held in conjunction with *Beyond Genome*, an annual conference held by the Cambridge Healthtech Institute in which several state-of-the-art topics in genome sciences are discussed. The conference on genomic variation will surely become a long standing event in years to come.

The 'one stop shop' for the cutting edge research in genomic variation could be experienced at the 'recent developments in human genomic variation' session. This half-day session covered many of the hot topics in basic science for studying genomic variation to set the stage for the clinical topics that followed for the remaining two days.

Molecular approaches for detecting genomic variation

In recent years, technology has advanced in molecular biology at alarming rates. In the past thirty years, we have seen the development of technology for restriction fragment length polymorphisms, polymerase chain reaction, microsatellite markers or short tandem repeats and variable number of tandem repeat markers, all developed to capture information about variation at the DNA level. However, in the past several years, molecular technology has been advancing even further with the development of genotyping platforms for single nucleotide polymorphisms (SNPs), including many high throughput SNP technologies. Two areas of very recent focus are gene copy number polymorphisms (CNP) and insertion–deletion (indel) polymorphisms.

Charles Lee of the Brigham and Women's Hospital at Harvard Medical School described novel approaches for detecting large-scale gene copy number variants (LCVs) using array-based comparative genomic hybridization. This approach can detect and quantify DNA copy number throughout the entire genome in one analysis, using large DNA clones. He described the arrays developed by Spectral Genomic, which are composed of 2600 large insert clones, spanning 1 Mb intervals. This technology can be used to detect even a single loss or gain in copy number of a particular sequence of DNA. Determining whether these LCVs are important for disease risk and/or drug response will be an enormous task and of great importance. LCVs have been

1359-6446/05/$ – see front matter PII: S1359-6446(05)03578-6

conference report

detected in normal, healthy individuals. Thus, similar to SNPs, these LCVs might or might not have functional consequences. The next major question is whether or not these LCVs are susceptibility factors for disease. Detailed characterization of LCVs will be important for correlating identified genomic imbalances and disease. This will require an enormous amount of additional work, including more individuals from multiple populations, denser arrays and more information regarding genomic structure. To achieve this, an International Consortium has been formed.

A group at Cold Spring Harbor is also performing gene copy number studies. Jonathan Sebat described their approach for identifying CNP. ROMA (representational oligonucleotide microarray analysis) is another array-based technology that allows the identification of chromosomal imbalances. However, there is yet to be a definitive conclusion on whether these CNPs have any clinical relevance, as they are also detected in healthy controls. Although this technology has advanced, it needs to move even further to become useful for disease association studies. Researchers hope to develop an ultra-high resolution ROMA probe set, which will contain ~380,000 probes, far exceeding the current 85,000 probes. This might allow for the detection of disease susceptibility CNPs. Sebat noted that CNP variants are more likely to be rare observations detected in few individuals. Therefore, it might be useful for those studying the rare-variant common-disease hypothesis. It will be difficult to make statistically significant interpretations of CNPs because of small sample sizes. Based on this rare-variant phenomenon, it is unclear how useful CNPs will be, especially if common diseases are the result of multiple common variants.

Although CNPs gained significant attention, SNPs are still the overwhelming technology for most genetic and pharmacogenetic studies. The recent advances of the 100K and 500K SNP technologies, by companies such as Affymetrix, Illumina and Perlegen, have made it possible to measure a great deal of genomic variation on a single sample in a single experiment. Kelly Frazer from Perlegen Sciences spoke about the Perlegen technology and some new advances related to indel polymorphisms. Frazer showed evidence that a dense SNP panel is able to capture the genomic variation due to indels by proxy. That is, common intermediate length indels are in linkage disequilibrium with SNPs in the dense panels and thus, through the use of a whole-genome association study, it is possible to detect genetic variation associated with indels. Her results are based on a sample of 71 individuals (24 European American, 23 African American and 24 Han Chinese). These studies will need validation and follow-up by other teams of molecular biologists, as the assays for indels are not high throughput similar to SNPs. If we can use SNPs as proxys for indels, this will be a major advance in whole-genome association studies.

Bioinformatics approaches for genomic variation: access to information and analysis

Generating a wealth of information to capture genomic variation has developed faster than anticipated. This is an exciting time to be in the field of human genetics and/or pharmacogenetics because we have never before had access to so much data. This influx of data generated numerous bioinformatics challenges. Russ Altman of Stanford University demonstrated the latest bioinformatics support for the discovery and use of pharmacogenomic information: PharmGKB (www.pharmgkb.org). This internet research tool was developed as part of the NIH Pharmacogenetics Research Network (PGRN), which is a US-wide collaborative research consortium focused on understanding how genetic variation among individuals contributes to differences in drug treatment response. PharmGKB is the central data repository for genetic and clinical information, as well as molecular and cellular phenotype data for detailed analyses for the scientific community. This research tool is the first of its kind to provide detailed, curated genomic and phenotypic information on millions of data points through a user friendly, easily navigated website. PharmGKB demonstrates the power of bioinformatics and the utility of such approaches to improve and facilitate large-scale studies of genomic variation.

The final step in processing data on genomic variation involves analyzing genotype to phenotype associations across the numerous genetic variants. In the quest for disease susceptibility genes associated with disease or drug response, the reality of gene–gene interactions creates difficult challenges for many current statistical approaches. In an attempt to overcome limitations with current disease gene detection methods, myself and colleagues from Vanderbilt University have developed the multifactor dimensionality reduction (MDR) approach. MDR is a novel computational method developed for the analysis of gene–gene interactions in association with clinical endpoints. Genetic variation associated with drug response is likely due to a combination of genes, rather than a single large effect gene. MDR provides statistical power to elucidate such epistatic effects in relatively small sample sizes. In brief, MDR reduces the dimensionality of multi-locus information to identify polymorphisms associated with an increased risk of disease or adverse drug-response. This approach takes multi-locus genotypes and develops a model for defining disease risk by pooling high-risk genotype combinations into one group and low-risk combinations into another group. In my presentation, I described the methodology and provided information regarding how researchers can obtain the software for their own analysis (http://sourceforge.net/projects/mdr/). The open source software package is being developed and distributed by Jason Moore from Dartmouth Medical School.

Conclusion

Recent developments in genomic variation sparked a lot of conversation and interest in the audience. This field is moving rapidly and the ability to generate, store and analyze genomic variation to detect associations with disease and drug response phenotypes has become a major focus of research institutions around the world. Conferences like this inspire and invigorate the community to strive to new heights and rejuvenate the creativity to make novel discoveries and advances.

Marylyn D. Ritchie
Assistant Professor,
Vanderbilt University,
Department of Molecular Physiology & Biophysics,
Center for Human Genetics Research,
519 Light Hall,
Nashville, TN 37232, USA