associated with oxidative stress to endothelial cells, such as stroke, gut ischaemia, kidney ischaemia or lung ischaemia. Currently there are no other therapies that inhibit the lectin complement pathway activation.'

Commenting on the study, Malcolm Turner, Professor of Molecular Immunology and Head of Immunobiology at the Institute of Child Health (University College London, London, UK) said the findings were 'extremely interesting and underscore the possibility that important pathological consequences might be associated with MBL-mediated complement activation.' He added, 'Research on MBL is, however, still in its infancy and much remains to be elucidated about the protein and its disease associations.'

Turner highlighted that another recently published study concluded that severe atherosclerosis is associated with MBL deficiency[5]. He said, 'The authors of this paper have interpreted this as possible evidence implicating chlamydial infections in coronary heart disease, because MBL is known to bind to various strains of *Chlamydia*. The findings from the two studies serve to emphasize the fact that the role of MBL in health and disease is more complex than was first anticipated.'

### Future projects

Stahl's next project is to map the epitope of the mAbs, to determine how they inhibit MBL. 'We are also generating mAbs to the MBL of other animal species, so that we can use animal models of human disease to firmly establish what we have discovered *in vitro*,' Stahl said. 'We are further characterizing what MBL is binding to, so that we can develop novel inhibitors to that molecule.'

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*Sharon Kingman*

# SNPs; windows of opportunity in the human genome

In April, the SNP Consortium issued a Request for Applications to determine how frequently single nucleotide polymorphisms (SNPs) occur in major human population groups (e.g. Caucasian, Afro-Caribbean). SNPs are single base pair (bp) differences that occur between individuals, such as the variations that lead to different blood types or the inheritance of the different alleles APOE3 or APOE4, both involved in susceptibility to Alzheimer's disease[1].

Although the majority of SNPs do not produce obvious physical changes or cause disease directly, they might be located close to deleterious mutations in the genome that are involved. Furthermore, because they occur at a

relatively high frequency in the genome (approximately one SNP for every 1000 bp), SNPs can be used as markers for these more important genetic alterations. 'The full genome SNP map will allow geneticists to identify areas of interest in the genome much more precisely than has been possible,' says Arthur Holden, CEO of the SNP Consortium.

### SNP mapping targets

The SNP Consortium is a private, non-profit alliance of 13 leading multinational pharmaceutical companies and the Wellcome Trust (London, UK). It was established in April 1999 with a budget of $45 million and a two-year programme to identify 300,000 SNPs and to map at least half of them. Although the first year's target was to identify just under 100,000 SNPs, Holden confirms that 'outstanding progress has been made, primarily due to the use that we have been able to make of the constantly updated public draft of the human genome.' By April 2000, 149,000

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SNPs had been identified and 105,000 of those had been mapped to a resolution of 100 kb. With the publication of the 'working draft' of more than 90% of the human genome expected in June 2000, Holden is confident that the consortium will continue to progress at a faster rate than anticipated. 'We expect to reach our original targets by the end of this calendar year,' he says.

The database, which has been produced by sequencing the DNA of 24 ethnically diverse individuals using restriction enzyme libraries, has been placed in the public domain since its inception. The SNP mapping data has been released onto the consortium website (http://snp/cshl/org; Box 1) and has been frequently updated over the past year. With significant advancements one year into the project, the SNP Consortium decided that enhancement of the SNP map could provide significant long-term benefits. They launched a request for applications to submit SNP data from academic centres and commercial organizations worldwide to determine the allele frequency of at least 60,000 mapped SNPs in at least three major human populations. Applications are being reviewed and projects will start later this year subject to the review outcome.

'The denser the SNP map, the greater the number of markers we will have to detect disease-causing mutations,' comments Holden. Although the database project itself is public and is not a profit-making exercise, Holden anticipates that all the companies within the consortium will derive commercially valuable products from the venture. Allen Roses, Vice-President and Worldwide Director of Genetics at GlaxoWellcome (Greenford, UK) and the Duke University Medical Center (Durham, NC, USA) and Board member of the SNP Consortium confirms that 'GlaxoWellcome has been using high-density SNP mapping to reduce the time between linkage analysis and gene identification.' He adds that the consortium is producing data that will 'form the basis for new opportunities for drug surveillance, efficacy and safety in the development and dispensing of medicines.'

**Box 1. The SNP Consortium**

**Companies involved in the SNP Consortium Ltd:**

| | | |
|---|---|---|
| APBiotech | AstraZeneca | Aventis |
| Bayer | Bristol-Myers Squibb | F. Hoffman-La Roche |
| GlaxoWellcome | IBM | Motorola |
| Novartis | Pfizer | Searle |
| SmithKline Beecham | Wellcome Trust | |

**The data is available from:**

- Browsable Web pages http://snp.cshl.org/db/map/snp
- Bulk downloads ftp://stein.cshl.org/pub/SNP/
- Entries on NCBI's dbSNP database http://www.ncbi.nlm.nih.gov/SNP

## Using SNPs in drug development

Roses believes that pharmacogenetics will become an increasingly important part of drug development in the next few years[2]. 'Pharmacogenetics has the promise of removing much of the uncertainty involved in choosing the right drug for a particular patient', he predicts. Physicians will be able to use a medicine response profile to predict an individual's likely response to a drug on the basis of their genetic data. In the long term, the data generated by the Human Genome Project and the consortium will enable pharmaceutical companies to run faster and more efficient clinical trials and to produce new drugs at a reduced cost, enabling expansion of research into mechanisms of disease. 'Using pharmacogenetics to identify potential non-responders to new drugs will be a major step forward,' says Roses. If, for example, a Phase II trial of a new drug in 750–1300 patients demonstrated efficacy in only 30% of those patients, then a Phase II trial would need to be extensive because 70% of the subjects would be expected to be non-responders. If an SNP profile was available to identify those patients in the Phase II study that were likely to respond, the Phase III trial could recruit only patients with the same profile. The Phase III trial could be smaller, faster and less expensive, but would yield the same quantity of useful data on the drug.

Although this field shows great promise for the future, Roses warns that pharmacogenetics will raise its own distinct set of ethical, legal, social and regulatory variables. 'These cannot be ignored, but with the rapid emergence of data from the Human Genome Project, the SNP Consortium and other initiatives, we will soon have the tools to make drug development and delivery more effective. We must find acceptable ways to use them,' he concludes.

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