currently available, from a team with over 70 years' experience and a proven track record in neuroscience. We fulfil an unmet need in the contract research market by providing a comprehensive neuroscience research service for pharmaceutical companies wishing to reduce costs by outsourcing expensive testing. Our own neuroscience drug discovery research effort will benefit from screens developed for contract research work".

The other scientists behind the project are Dr Allan Fletcher (Neuropharmacology), Dr Alan Palmer (Neurochemistry), Dr Ian Cliffe (Medicinal Chemistry) and Dr Robin Shepherd (Synthetic Chemistry). Between them, the team has authored more than 475 papers or abstracts, 45 edited books or book chapters and are inventors or coinventors of more than 60 patents.

Peter McPartland, a partner of Schroder Ventures and Chairman of Cerebrus, illustrates Schroder's confidence in working with Chris Evans and the ex-Wyeth team by highlighting the fact that this is the first time that they have backed a life sciences start-up since 1992.

David Hughes

Genomics at the AAAS

Genome science is exerting a profound impact on all areas of biology and biotechnology and is fundamentally changing the drug discovery process. Dr William A. Haseltine (Human Genome Sciences [HGS], Rockville, MD, USA) speaking in February at the *1996 American Association for the Advancement of Science Annual Meeting* (Baltimore, MD, USA), described how it is now possible to derive what he terms 'gene anatomy' – the sequence and relative concentration of every mRNA expressed in a given cell, tissue, organ or organism. Carrying the analogy further he described how changes in gene anatomy during development or upon cell activation yield 'gene physiology', while changes in response to various disease states provide a picture of 'gene pathology'. According to Haseltine, genomics is a reversal of the reductionist approach to biology and begins to build a useful molecular picture of a human being.

The emergence of genomics is due largely to the automation of DNA cloning and sequencing, the use of reverse transcription to convert mRNA into cDNA, and to the advances in bioinformatics required to manipulate enormous amounts of biological data and to compare gene sequences to identify the function of newly discovered genes. These technologies are now so powerful it is possible to sequence the entire genome of a bacterium in just a few weeks, a feat that HGS has just completed for *Staphylococcus aureus*.

Genome science has a totally different goal from gene mapping, which refers to the determination of the address of the various genes on the chromosomes. "If you have a criminal in your hands you do not need to know where he lives," quipped Haseltine as he touted the utility of genomics over mapping. It also avoids having to deal with the huge quantities of noncoding sequences that plague those laboratories sequencing the entire human genetic code.

Rapid sequencing

Dr C. Rosen, also of HGS, indicated that the sequencing of human cDNA is progressing at a furious rate. HGS has the capacity to do as many as 3,000 to 5,000 gene sequences per day, and more than 850,000 cDNA sequences have been completed and incorporated into its database. The company is storing more than 2 million frozen clones that contain specific gene sequences. As a result, when an interesting new sequence is published, HGS scientists can determine within hours whether there are similar sequences present as part of the human gene anatomy,

and frequently pull out a clone expressing the gene of interest.

Using the genomic approach, Rosen claims to have identified a large number of new drug targets. The approach involves looking for cDNA sequences that are specific for a particular cell type or organ or for cDNAs that are present only during cell activation or in association with particular diseases. Once a particular cDNA is selected, its nucleotide sequence is compared with known sequences to determine whether it encodes a protein that has previously been described. If the cDNA is novel, the deduced amino acid sequence of the encoded protein is scrutinized. Homologies to various motifs, such as transmembrane domains, nucleotide binding sites, and other known structural regions from proteins, are relied upon to give clues to function. Ultimately, the protein may be expressed and tested for activity in a battery of routine assays. According to Haseltine, it is just a matter of time to progress from any cDNA sequence to a function. "It's turn-the-crank biology," he said, "but understanding the biochemistry is much more difficult – to identify and understand all the cellular interactions made by the new proteins identified through genomics would keep ten times the present number of biochemists busy for many years to come."

Rosen indicated that HGS has discovered 52 novel seven transmembrane G protein-coupled receptors from various human cDNA libraries. These proteins were given special attention because in the past they have been especially rich targets for drug discovery. β-adrenoceptor antagonists, H_1 and H_2 antagonists, α-adrenoceptor antagonists, angiotensin antagonists, 5-HT_3 agonists, and β-agonists all work through this general class of receptor. Such drugs account for more than $20 billion per year in sales.

Rosen believes that the large number of newly identified seven transmembrane G protein-coupled receptors indicates that there are still many useful drugs to be discovered. HGS embarked on a three-year, $125 million collaboration with SmithKline Beecham Pharmaceuticals (King of Prussia, PA, USA) in 1993 to screen for small molecules that interact with such targets. Since then, screening of targets identified through the genomics paradigm has been on the rise, and Haseltine indicated that today at least one major pharmaceutical company is relying upon this approach to generate one-half of new drug leads.

According to Rosen, the sequence information already in hand suggests that there is also an enormous number of new protein therapeutic agents to be discovered. When the cDNAs unique to hematopoietic cells are expressed, for example, most are found to be unknown. The implication is that these proteins likely control different aspects of the intricate mechanisms that regulate the differentiation and production of blood cells. Rosen predicted that many of them may be useful as therapeutic agents.

Prospects for new antibiotics

Genomics may also provide new antibiotics at a time when they are desperately needed to combat the threat from resistant bacteria. "The genome of microbes specify novel antibiotics and it is only a matter of following the genomic paradigm to discover them," said Haseltine. He expressed his sense of amazement upon looking, for the first time, at the entire genome of *Staphylococcus aureus*. "There were many metabolic pathways that no one knew were there. Undoubtedly some, or many, are latent and activated only when the microbe is presented with very specific conditions. Others are likely to be lethal," he said.

New vaccines

The genomic model will also short-circuit time-consuming steps in the development of new vaccines, according to Haseltine. For example, one can easily obtain all of the cDNAs containing the leader sequences needed for proteins to be expressed on the exterior surface of an organism, and then systematically use them to produce the encoded proteins and prepare vaccines. Such an approach may provide much needed new vaccines for staphylococcosis, streptococcosis, tuberculosis, syphilis, Lyme disease, malaria, Chagas' disease and leishmaniasis, he believes.

The result of these developments in genomics is that more targets for drug discovery will soon emerge than can be absorbed into research efforts. Combined with the recent advances in combinatorial chemistry and high-throughput screening automation, genomics "should lead to the discovery of a wonderful new pharmacopoeia," concluded Haseltine.

Other applications

Drug discovery is not the only use for the newly emerging science of genomics. Dr R. Wilson of the Washington University School of Medicine (St Louis, MO, USA) described the effort to complete the entire sequence of expressed genes for *Caeno elegans*, a worm that is used as a model organism. One unique aspect of *C. elegans* is the simplicity of its body of approximately 1,000 cells, which can easily be observed during its three-day development period. The lowly organism has been found to be an excellent choice for correlating gene function with development.

Dr T. Helentjaris (Pioneer Hi-Bred International, Johnston, IA, USA) described how genomics was being applied to agriculture. At Pioneer Hi-Bred, Helentjaris is involved in a program to sequence the corn genome. High rates of internally duplicated gene structure make the corn genome, which is larger than the human genome and contained on ten chromosomes, particularly complex. Therefore, the genomics approach of sequencing only the expressed genes has proven most useful. Helentjaris described the sense of amazement he felt as he sat at the computer and identified corn genes by comparing them to similar sequences from frogs, yeast, *Drosophila* and even humans. He believes that the identification of the expressed genes of corn will lead to strategies for development of new strains with improved growth characteristics and resistance to pests and environmental stresses. As part of this program, Pioneer Hi-Bred has developed a large number of transposon-mutated seed lines, which it maintains and makes available to investigators for the identification of agriculturally useful genes.

Robert W. Wallace