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A meeting of minds

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The *First Annual Symposium on Neurogenomics* (25–26 April, Chapel Hill, NC, USA) illustrated the range of techniques being brought to bear on the study of the brain. In a single talk, methodologies could range from capillary DNA sequencers to rota-rod behavioural testing apparatus. Depending on the background and scientific interests of the speaker, they might be more impressed by the latter than the former. The meeting brought together leading scientists in the fields of genomics and neuroscience to jointly consider the impact of the human genome sequence on the understanding of brain development and on the underlying basis of neurological and psychiatric disease.

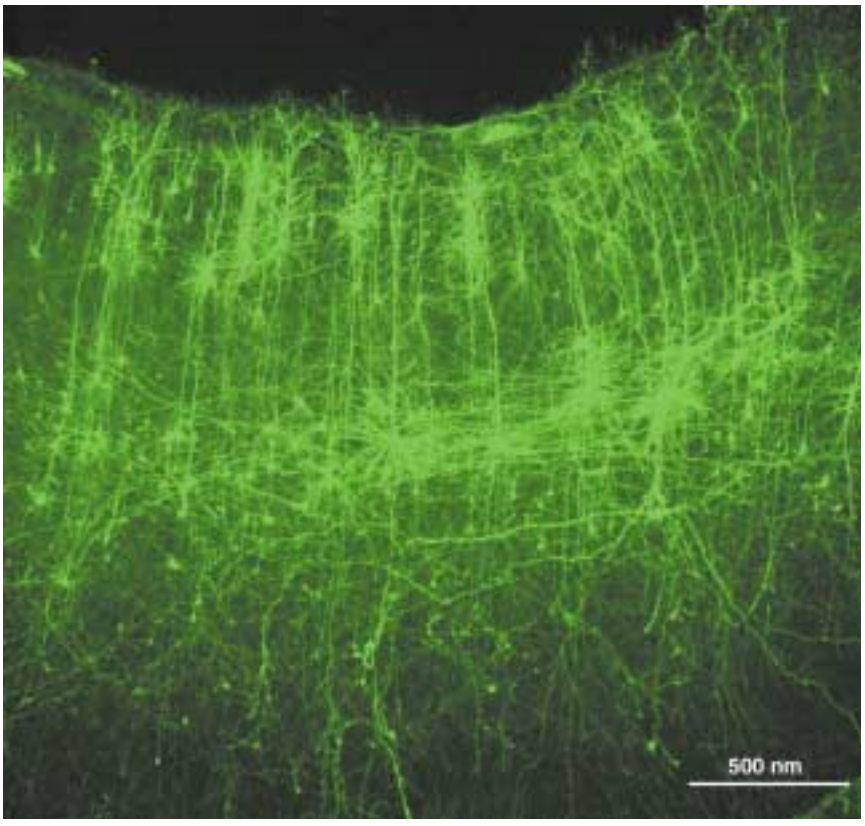

Figure 1. Nanogold particles coated with plasmid DNA encoding a fluorescent reporter protein have been ballistically delivered to cultured slices of rat cortex. Cortical pyramidal neurons hit by nanogold particles, that are also coated with a novel neuroprotective cDNA, are rescued from cell death induced by ischemic damage as occurs in stroke (photomicrograph courtesy of Donald Lo, Cogent Neuroscience, Durham, NC, USA).

The genome

Several presentations focused on the 'Book of Life': the history of our species written in our genome and that of other species in theirs. Lee Hood (Institute for Systems Biology, Seattle, WA, USA) discussed the minimal gene-set for a free-living organism. *Haemophilus influenzae*, the first, whole microbial genome sequenced by Craig Venter and colleagues at The Institute for Genome Research (Rockville, MD, USA), is thought to contain only 1709 protein-coding genes within its 1.8 million bp genome. The minimal gene-set might be considerably smaller, however, and methods are in development for whole-genome synthesis. 'Ink-jet' methods for oligonucleotide synthesis on solid substrates are now accurate enough, give high enough yield and long enough oligomers to enable synthesis of the genome as an overlapping set of oligonucleotides. These might be self-assembled into a complete microbial genome, to allow the characterization of the biology of novel, synthetic genomes.

Other genome sequencing efforts currently under way or under consideration, such as the compact genome of the puffer fish or a genome closely related to ours (the chimpanzee *Pan troglodytes*), should allow us to study similarities between species and to understand the differences between humans and primates that determine the rich heritage of our species, its intelligence, its language skills and, ultimately, its organization into social units, and the influence of both the genome and the environment.

Insights provided by flies and worms

Gerald Fischbach (Columbia University, New York, NY, USA) argued that, given the miracles of modern neurology, we have the greatest opportunity to understand neurodegenerative disorders. The study of rare Mendelian phenocopies of Alzheimer's disease caused by mutations in the amyloid protein precursor (APP)

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protein, ultimately led to large-scale projects in most major pharmaceutical companies at design inhibitors of key enzymes that lead to the production of amyloid-β peptide. Advances in technology also allow novel and rapid screens for neuroprotective genes to be undertaken, based on knowledge of the genome sequences (Fig. 1). The real challenge of the next millennium will be to understand the characteristics of cells that give rise to emergent properties of the brain. These will underlie the changes occurring in neuropsychiatric illnesses, which are currently only addressed by symptomatic treatments

For some areas of interest to neurogenomics scientists, however, there is remarkable convergence across distinct phyla. For example, fruit flies (*Drosophila melanogaster)* do not normally express α-synuclein, a protein associated with the neurodegeneration of dopaminergic neurons in the substantia nigra of Parkinson's disease patients. Yet, transgenic expression of the human protein in all neural tissues causes the selective degeneration of fruit flies' dopaminergic neurons.

Cornelia Bargmann (University of California at South Francisco, CA, USA) described an even more remarkable example of social convergence. The phylogenetically lowly nematode, *Caenorhabditis elegans*, has strains that are solitary feeders or social feeders. Solitary feeders, as the name suggests, graze on lawns of nutritious *Escherichia coli* bacteria in isolation from their neighbours, whereas social feeders writhe in ecstatic balls of happily feeding worms. The nematodes regard *E. coli* as foul smelling, but good tasting, food. This difference in behaviour can be traced to a single amino-acid polymorphism in a neuropeptide-Y-receptor homologue. This receptor belongs to the class of G-protein-coupled receptors (GPCRs) with which the worm genome is richly endowed. Worms devote nearly 10% of their ~19,000 protein-coding genes to chemoreceptors and other GPCRs.

Why so few genes?

James Watson (Cold Spring Harbor Laboratory, Long Island, NY, USA) reviewed almost 50 years of research since his discovery of the DNA double-helix with Francis Crick in 1953. In a wonderfully idiosyncratic after-dinner speech (more social feeding), Watson wondered why fruit flies, being such intricate and adaptable organisms, needed only ~13,500 protein-coding genes in their genome compared with the nematode, which needs ~19,000, and a plant, the yellow mustard *Arabidopsis*, which needs ~25,000. Indeed, the number of genes in the *Arabidopsis* genome comes close to the ~35,000 protein-coding genes in our own genomes. Perhaps the number of genes needed by an organism is proportional to the degree to which adaptation to the environment is strictly genetic. Plants and nematodes that, because of size or predilection, are anchored to one particular site, need greater adaptability programmed within their genomes. By contrast, flies and humans rely more on behavioural adaptation to their environment. Flies and humans are mobile, foraging organisms, which seek out hospitable environments, whereas nematodes and plants rely on genomic solutions.

Human genetics

Allen Roses (GlaxoSmithKline, Research Triangle Park, NC, USA) began with the observation that the title of the theme of the symposium, 'After the genome' might be a little optimistic. Although the public and private efforts continue in their attempt to fill in the many gaps in the human genome, how will that knowledge impact on the time and effectiveness of drug discovery? One area of societal concern is managing the risk of medical product use. The USA Food and Drug Administration (Rockville, MD, USA), for example, estimates that morbidity and mortality from the use of medical products cost US$76 billion in 1999. Such adverse drug reactions (ADR) in many cases have a genetic basis. For example, individuals could be poor metabolizers of particular drugs because of polymorphisms in the cytochrome P450 enzymes that their genomes encode.

Although society debates the ethics, policy concerns and legal regulation of predictive genetic testing for susceptibility to common diseases, the genetics of adverse drug reactions might well be 'politically correct'. In this case, the interest of patients, physicians, medical-care providers and insurers all converge on the common goal of tailoring medical treatment to the individual patient. Thus, genetic testing for ADR might engender fewer privacy concerns than the diagnosis of disease susceptibility. From the genetics of ADR, such a program might extend to the genetics of efficacy. In fragmented markets such as that for rheumatoid arthritis, where several different (and expensive) biological drugs are, or will, become available, but yet only 40–50% of treated patients respond, it might make sense to look for genetic predictors of efficacy as early as Phase II clinical trials. The great financial risks of drug development today could be lessened by identifying genetic markers that correlate with clinical response in early clinical trials, and then using that information to design and conduct smaller, faster Phase III registration trials. If the expense of clinical trials could be reduced, it might stimulate the interest of pharmaceutical companies in 'orphan' diseases that affect smaller groups of patients.

Too many genes, too little time

A highlight of the meeting was a panel discussion led by Anthony Butler of Lehman Brothers (New York, NY, USA) that included Francis Collins (National Human Genome Research Institute, Bethesda, MD, USA), Eric Lander (Whitehead Institute, Cambridge, MA, USA), Steven Hyman (National Institute of Mental Health, Besthesda, MD, USA),

Steve Paul (Eli Lilly, Indianapolis, IN, USA), and Laura Coruzzi from the patent firm Pennie and Edmonds (New York, NY, USA). Butler and his colleagues at McKinsey & Company (New York, NY, USA) suggest that the novel target genes discovered through genome sequencing present a challenge to the pharmaceutical industry as they will actually decrease the probability of success in Phase II clinical trials. Because they are novel, less will be known about these targets and their relation to disease. That will result in an increase in attrition rate and could double the cost of drug development. Francis Collins suggested that perhaps only recent investors thought that the whole endeavour would pay off within one year. If attrition comes from lack of information about the biology of targets, perhaps the solution is for industry, academia and government to work together pre-competitively in a similar way to the SNP Consortium and the expressed sequence tag (EST) sequencing carried out by the IMAGE consortium. Eric Lander suggested that this reinforced the need to move beyond the handful of deeply validated targets that are addressed by currently marketed drugs. He felt that the industry will change dramatically around a broad waterfront where companies will take greater risk and work on targets where years of biological study have not been completed. As Steve Paul pointed out, the days of *in homo validatus* are over. The industry is transitioning from, for example, 3-hydroxy-3-methyl-glutaryl (HMG)-CoA-reductase inhibitors and the next generation of serotonin reuptake inhibitors, to targets such as the Alzheimer's disease β-secretase. In that instance, the genetics has taught a great deal about amyloid deposition in the context of disease and, without the genetics, there would not be the focus in the industry on this target. Of course, targets are only one side of the equation, the fraction of the human genome that can be addressed with chemistry is the other.

Compete in the courts or compete in the marketplace?

Multiple scientific teams at Amgen (Thousand Oaks, CA, USA), GlaxoSmithKline, Elan Pharmaceuticals (Dublin, Ireland) and Pharmacia (Peapack, NJ, USA) converged nearly simultaneously on the β-secretase gene. Presumably, most major pharmaceutical companies are now screening against this target. One issue, however, is if intellectual property issues might inhibit therapeutic development. According to Laura Coruzzi (Pennie & Edmonds), patents can be 'swords, shields, bargaining chips or vehicles for financing'. Lander and Collins both felt that the bar for utility in a patent has been increased. However, utility is a changing target and probably most appropriately reflects the state of knowledge at the time the patent was filed. Of more concern are the types of claims appearing in patents that attempt to reach through to therapeutics against that target and its utility in treating disease. Does this break the social contract and, as a public policy issue, should such claims be allowed? Perhaps society is best served by allowing multiple drugs to compete in the marketplace and to let clinical practice show, as in the case of lipid-lowering HMG-CoA-reductase inhibitors, which drugs have greatest efficacy and lowest cost.

Conclusion

One can only wait happily for the second instalment of the *Annual Symposium on Neurogenomics*. By next year, the human genome sequence might be more complete, and this knowledge will advance our understanding of the human brain and how it functions in disease.