capsule of semi-permeable membrane. The pore size of the membrane is large enough to allow entry and exit of nutrients, waste products and the target therapeutic protein CNTF. The pore size, however, is too small to admit either antibodies or immune system cells. The implanted cells, and the factors they manufacture, are thus free of immune system attack in any host into which they are placed.

Animal models

Tao and colleagues implanted these capsules into one eye of dogs with the rcd1 model of canine retinitis pigmentosa. The capsules were in place for seven weeks, early in the life cycle of the dog, in which time almost 50% of the photoreceptor cell degeneration takes place. After seven weeks, the eyes with the implants showed an increased survival of photoreceptor cells, compared with the untreated eyes. There was a threshold effect, with CNTF levels below the threshold producing no protection for the photoreceptor cells. There was also a dose-related effect with higher levels of CNTF production providing increased survival of the photoreceptor cells. Perhaps of equal importance to the photoreceptor cell protection was that the eyes with implants showed no adverse effects. Tao, who trained in pediatrics and biophysics, is Vice President for Research and Development of Neurotech USA. She says that based on this and her earlier studies in animals, 'we would like to bring this technology to human clinical trials.'

Cell encapsulation

The technology of encapsulating live cells has been a central interest of Dwaine Emerich for a decade. Emerich, Vice President for Research of Sertoli Technologies (http://www.sertoli.com), says that safety and longevity are important as this work is carried forward in humans. Emerich's work has shown that fouling of the pores of the semi-permeable membrane could be the determining factor for longevity of the implant. His group, as well as Tao's, has shown useful function of encapsulated cells for time periods as long as a year [4]. He says, 'an implant lifetime of several years is entirely possible,' and adds that clinical trials in humans will show if there are unintended results caused by the implants. CNTF, although of human origin, could, when used alone, cause unexpected results as CNTF might require as yet unknown co-factors to be beneficial in the human eye. An equally possible alternative is that substances secreted along with CNTF by the encapsulated cell implant could be harmful to the human eye with long-term exposure.

Paul Sieving, a researcher at the National Eye Institute (NEI; http://www.nei.nih.gov) expects to collaborate with Tao's group in human clinical trials based on this research. He points out that his group at the NEI is increasingly conducting work that is guided by molecular biology and genetics. He welcomes the opportunity to help bring work such as this to clinical fruition, which could keep this type of hereditary blindness under control.

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Asia bioinformatics: a new import–export industry

J.C. Louis, freelance writer

The buzzword in bioinformatics in Asia at the end of 2002 is more 'jump-start' than 'start-up'. Ambitious government programs are providing the impetus for new ventures in Singapore and Japan. The two countries diverge, mirroring nearly opposite approaches: Japan finds off-shore start-ups to partner with its domestic giants, while Singapore spawns start-ups, and imports skilled labor or international partners to match its immense domestic investments.

Three of Japan's big-name computer firms – Fujitsu (http://www.fujitsu.com), Hitachi (http://www.hitachi.com) and Itochu (http://www.itochu.co.jp) – are actively involved in the bioinformatics arena. In July, Fujitsu announced bioinformatics software for high-speed genome analysis, which predicts the function of unknown genes by

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comparing new gene sequences against known gene databases.

Dynamic partnerships

Hitachi has partnered with Yamanouchi Pharmaceutical (http://www.yamanouchi.com/), and Fujitsu with Mitsubishi Chemical (http://www.m-kagaku.co.jp) to undertake genomic research. Concurrently, Hitachi Life Science Group selected Agilent Technology's microarrays (http://www.agilent.com) to search for disease-related genes.

Proteome Systems (http://www.proteomesystems.com), based in New Jersey, USA, has joined with Itochu in a Tokyo-based venture that uses its discovery platform for high-level protein research. The partnership combines the bioinformatic expertise of Proteome Systems with Itochu's strength in information technology. Keith Williams, CEO of Proteome Systems, noted that the convergence of info- and bio-technologies is driving bioinformatics, and believes the partnership complements Proteome Systems' ongoing collaboration with Shimadzu (http://www.shimadzu.com) for next-generation development of proteomics instrumentation.

Nanotechnology in Japan

Japan's track record in nanotechnology also has importance. 'Nanotechnology has just begun to contribute to drug development and delivery in pharma,' says Robert Burrows, spokesman for GeneLogic (http://www.genelogic.com), a Maryland-based provider of genomics-based information, and bioinformatics products and services to the pharma and biotech industries. In October 2002, Mitsubishi and Fujisawa (http://www.fujisawa.com) joined other major Japanese drug companies as subscribers to Gene Logic's drug discovery tool.

Burrows does not see imminent global competition from Asian bioinformatics start-ups. 'Faced with the rapid development curve and uncertainties over emerging protocols, the Japanese will remain net importers of bioinformatics technologies for some time,' he predicts.

Investment opportunities

Japan's approach builds from the depths of its historic strengths in protein science. By contrast, Singapore's style lies in its breadth; matching brainpower and technical partners from abroad with heavy domestic investment – a model that remains a promising bioscience infrastructure. The Economic Development Board (EDB; http://www.sedb.com), the lead agency driving industrial investments, assists companies considering strategic location to Singapore. Since the early 1990s, the EDB has single-mindedly sought to transform Singapore into a life-science colossal.

In 2000, the EDB redoubled its effort with the launch of the National Biomedical Science Strategy, pumping an estimated US$2 billion into the endeavour. The results were almost immediate. By November 2000, Lynk Biotechnologies (http://www.lynk-biotech.com), one of the first life-science start-ups spun-off from the National University of Singapore (NUS; http://www.nus.edu.sg), opened its research facilities in Singapore Science Park.

Bioinformatics start-ups

The brainchild of Professor Lee Chee Wee (NUS), Lynk's drug discovery platform claims to 'tailor-make' novel molecules that bind irreversibly to selected proteins. These molecules can be simulated and designed to bind to specific target sites and produce desired pharmacological effects.

'We can zoom in on the active-site of the protein where binding of particular drug occurs,' says Gurinder Shahi, CEO of BioEnterprise Asia (BEA; http://www.bioenterprise.org), an incubator of life-science ventures, and co-founder of Lynk. 'We know what proteins the drug is binding to, and where the key fits the lock.'

Two other start-ups exemplify BEA's flare for discovering high-growth opportunities that can be supported by its domain expertise. ReceptorScience (http://www.receptorscience.com), a bioinformatics venture (and sister company to Lynk Biotech), uses proteomics, data mining, 3D visualization, and artificial intelligence to investigate the molecular physiology and pharmacology of receptors and active targeted sites for rational drug design and development.

AP Genomics (http://www.apgenomics.com) has developed a diagnostic test for dengue virus that uses bioinformatics to zoom-in on gene sequences and identify a specific signature. 'We can say, "if you have the signature for dengue fever or West Nile virus", for example, "then you must have this condition and nothing else",' says BEA's Shahi.

Big pharma

Big pharma has also shown involvement in Singapore ventures. Novartis (http://www.novartis.com) set up its Institute for Tropical Disease in Singapore, with 70 scientists researching treatments for dengue, malaria and other diseases. Eli Lilly (http://www.lilly.com) joined with the EDB to launch the Center for Systems Biology, a US$140 million project that represented the first venture of the new EDB initiative. The project will use bioinformatics to study whole biological systems.

Aligning the public and private sectors

John Wooley, Vice Chancellor at the University of California, San Diego (http://www.ucsd.edu/), and a scientific advisory board member for the Singapore Bioinformatics Institute (BII; http://www.bii-sg.org), believes that bioinformatics has a pivotal role to play in aligning public-sector research

with private-sector R&D. 'Bioinformatics operates at the interface between active experimentation (including data mining and other analyses) and computation,' he says.

Wooley sees the rising importance of bioinformatics as based on its linkage of the computational orientation of basic research and the experimental practice within applied R&D. Biopolis, a biomedical R&D campus located alongside NUS, will house the Genome Institute of Singapore (GIS) and the Institute of Bioengineering (IBE), as well as the BII. The GIS develops core technology platforms to bridge clinical and basic research, including high-throughput sequencing and SNP analysis.

'Biopolis is a city-state within a city-state,' observes Wooley. 'It's built around bioinformatics, but is broader in its likely impact. Its institutes are essential to global competitiveness in biotechnology.'

News in brief

Targets and mechanisms

Roadmap to culprits for Down syndrome

Scientists say they have drawn up a 'road map with clear signposts to the culprits of Down syndrome' [1]. Their findings are to offer a glimmer of hope to sufferers of the disorder, the most common cause of mental retardation in humans and, until now, a mystery to medical research.

The group identified mouse counterparts to human chromosome 21 (HSA21), which, when found in triplicate, causes individuals to develop the disease and its characteristic signs including abnormalities of the head, face and heart. They used a sophisticated method of scientific detective work, combining large-scale mRNA *in situ* hybridization at crucial stages of embryonic and brain development in the mouse with *in silico* mining of expressed sequence tags.

'There are now clearly defined candidate genes in the brain, heart and elsewhere that we can look at,' explained Ariel Ruiz i Altaba, a cell biologist at the New York University School of Medicine (http//www.med.nyu.edu) and co-author of the study. 'The next step is to understand how these genes function normally,' he added. 'Once we know which ones cause defects in the brain when their expression is altered, we will be in a position to see if rational therapies for Down syndrome are possible.' The disease is estimated to affect more than 350 000 people in the USA alone.

1 Gitton, Y. *et al.* (2002) A gene expression map of human chromosome 21 orthologues in the mouse. *Nature* 420, 586–590

MHC trains immune cells

Major histocompatability complex (MHC) encoded molecules provide a two-step approach to fighting off infection, say scientists [2]. They have shown that MHC molecules provide 'training' to a wide and diverse collection of T-cells, which helps the body to destroy a pathogen at the beginning of an infection.

Team leader Janko Nikolich-Zugich of the Oregon Health and Science University Vaccine and Gene Therapy Institute (http://www.ohsu.edu/research) said they already knew that MHC molecules acted as 'traffic cops, [which] look for invaders and, once they find them, call in T-cells to defeat the pathogen.' But, he said, the ability to 'train' T-cells when the pathogen is not present had previously been overlooked. 'What we [have] determined [is] that the 'training function' [is] exquisitely important,' he explained. Following the latest findings, it is now thought that MHC molecules specifically select the T-cells best able to destroy a pathogen when it invades.

Nikolich-Zugich and collaborators have linked polymorphisms in MHC molecules to a varied collection of T-cells, which provide what they call 'a superior antiviral defence.'

The group says their research is of particular interest to vulnerable individuals, such as the elderly, who are thought to have a less varied complement of T-cells. They also hope that with a better understanding of the importance of diversity in cytotoxic T-cells, scientists will be more able to deal with rapidly mutating viruses such as HIV.

2 Messaoudi, I. *et al.* (2002) Direct link between MHC polymorphism, T cell avidity, and diversity in immune defense. *Science* 298, 1797–1800

New connections in old brains

It has long been thought that adult brain cells are unable to form new connections, or synapses. Researchers led by Karel Svoboda of the Cold Spring Harbor laboratory (http://www.cshl.org/) now present results indicating that this is not the case [3], radically changing the way we think of brain connectivity and learning, and offering hope for the future treatment of brain damage.

Neurons receive input from other neurons through their dendrites. It has been shown that tiny protrusions on dendrites, called spines, grow and retract over the course of tens of minutes in the developing cerebral cortex. However, observations made on a similar time-scale have previously indicated that such changes do not occur in the adult brain.

Now, Trachtenburg *et al.* have used longer-term imaging to show that dendritic spines can also appear and disappear in the adult cortex. They studied young adult mice expressing green-fluorescent protein in a subset of cortical neurons, focussing on the barrel cortex (a region of the brain that processes information from the whiskers). Although the overall dendritic structure of the barrel-cortical neurons was largely

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