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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stable, the dendritic spines were dynamic, with ~20% of spines disappearing (and an equivalent number forming) between one day and the next.

Subsequent electron microscopy revealed that the new spines had formed connections that appeared to be functional synapses. Svoboda and colleagues suggest that the spines could be sampling potential synaptic partners. Turnover of spines was increased when certain whiskers (and, thus, input to the barrel cortex) was removed, indicating that spine motility was affected by what the mice experienced.

These groundbreaking findings show that, although the gross organization of adult brain cells does not change, adult synaptic connectivity can still be modified by experience. As commented by Paul Adams, a neurobiologist at the State University of New York at Stony Brook (http://www.sunysb.edu/): 'If a few years ago you could have imagined in your wildest dreams any experiment you wanted to do, it would be this one.'

3 Trachtenberg, J. *et al.* (2002) Long-term *in vivo* imaging of experience-dependent synaptic plasticity in adult cortex. *Nature* 420, 788–794

Thrombospondin-1: respondin' to *Id1*

When activated, cancer-causing gene *Id1* has been found to regulate production of thrombospondin-1 (TSP-1), a naturally occurring suppressor of tumour angiogenesis, by transcriptional regulation [4].

Researchers at Northwestern University Medical School (http://www.nums.nwu.edu) have used mouse embryonic fibroblasts (MEFs) and whole animal models for their studies. They revealed that levels of the Id1 target, TSP-1, are increased by three- to fivefold) in *Id1* knockout mice, compared with control littermates. Accordingly, growth of blood vessels is minimal in the null mice; however, vascularization can be resumed by addition of a TSP-1 neutralising antibody.

Manipulating the blood supply, which is essential for tumour growth, could lead to a massive increase in suppression of certain tumours. However, "because TSP-1 occurs naturally throughout the body, it can't be used as a drug" reports Robert Pili of the Kimmel Cancer Center, "but, it could potentially be paired with another molecule and programmed to be released only in tumors", giving more great promise for the future of cancer therapeutics.

4 Volpert, O.V. *et al.* (2002) Id1 regulates angiogenesis through transcriptional repression of thrombospondin-1. *Cancer Cell* 2, 473–483

Zebrafish can mend their broken hearts

New research shows that zebrafish are able to regenerate their hearts after injury; understanding just how this can be achieved could lead to new strategies for repairing damage in human hearts [5].

Although many invertebrates are known to be able to regenerate vital organs after injury, the zebrafish is one of the first vertebrates to be shown to also have this ability. The researchers, led by Mark T. Keating at the Howard Hughes Medical Institute, removed 20% of tissue from the heart of several zebrafish. When the fish were checked two months later, they were found to have regrown the missing portions. When the gene responsible for this regeneration was mutated, the heart tissue did not regenerate, and scarring occurred instead.

Keating reports that, following the removal of the heart tissue, erythrocytes begin to clot at the wound site, and this is followed by the addition of fibrin, a thick tissue that forms a mature clot. However, the fibrin is gradually replaced by cardiomyocytes; cells that normally comprise heart muscle. After a month, a new piece of tissue is formed and, after two months, all evidence of scarring is gone and the heart resembles a normal heart that is no different physically or functionally from a normal healthy zebrafish heart.

The process of regeneration is similar to that seen in other vital organs although the scarring that is a major problem in other vertebrate tissue does not appear to be a problem in zebrafish. Keating suggests that there is competition between tissue regeneration and scar tissue formation, the second being overcome by tissue regeneration. It might be that there is a similar competition within human hearts, which results in scarring being more common than regeneration. 'If one enhances the regenerative potential in humans', says Keating, 'perhaps one can overcome the fibrotic potential'. This could lead to specific strategies for repairing damaged human hearts, following heart surgery, for example.

5 Poss, K.D. *et al.* (2002) Heart regeneration in zebrafish. *Science* 298, 2188–2190

Males and females have different feelings of pain

A major role for GIRKs in sex-based differences in pain sensitivity and the effects of pain-killing drugs has been reported [6,7].

Opioid analgesics exhibit different efficiency in men and women, and pain threshold is typically lower in women than in men. Opioids and other analgesics activate signal transduction cascades that culminate in the activation of both pre- and post-synaptic effectors, including the post-synaptic decrease in excitability through the activation of G-protein-coupled inwardly rectifying potassium channels (GIRKs).

Mitrovic and colleagues [6] at the University of California, Los Angeles (http://www.ucla.edu/), used mutant mice lacking GIRK2 (which is important in electrical communication between neurons) to examine pain sensitivity and reactivity to analgesic drugs. Morphine and clonidine, the analgesics tested, both had reduced efficacy in mice lacking GIRK2. Pain thresholds in male mutants only were reduced compared with controls, effectively eliminating sex differences in baseline pain sensitivity.

Blednov and colleagues. [7] at the University of Texas (http://www.uth.tmc.edu/) used the same GIRK2 mutant mice to demonstrate the role of GIRK2 in the analgesic effects of several other drug types – alcohol, nicotine and cannabinoids. The analgesic effects of some of the drugs tested were completely abolished in male mutants but not in females, correlating with Mitrovic's data.

GIRK2 could thus be a crucial component of the pain pathway that accounts for the differential pain and analgesic sensitivity between the sexes. Both these studies show GIRK2 channels as crucial targets for transduction of central analgesia mediated by a variety of neurotransmitter systems and GIRK2 might, therefore, provide an attractive new target for the treatment of pain.

6 Mitrovic, I. *et al.* (2003) Contribution of GIRK2-mediated postsynaptic signaling to opiate and α_2-adrenergic analgesia and analgesic sex differences. *Proc. Natl Acad. Sci. U. S. A.* 100, 271–276

7 Blednov, Y.A. *et al.* (2003) A pervasive mechanism for analgesia: activation of GIRK2 channels. *Proc. Natl Acad. Sci. U. S. A.* 100, 277–282

Viral targets and mechanisms

Visualizing HIV

The earliest stages of HIV infection in living cells have now been recorded using time-lapse microscopy, enabling researchers to see how HIV particles take over the genetic machinery of a living cell [8].

Researchers at the University of Illinois at Chicago (http://www.uic.edu) labeled individual virus particles with green fluorescent protein (GFP). The researchers, led by David MacDonald and Thomas Hope, were then able to film the virus traveling along the cytoskeletal framework of the cell after it had hitched a ride on dynein, which is a multi-unit protein that acts as a molecular motor. The process is not as smooth as it could be: 'They don't make a beeline for the nucleus,' reported MacDonald, 'Their progress is somewhat halting…but they eventually reach their destination'. The whole journey takes between two and four hours, covering a distance that can be up to 500 times the size of the virus particle. By attaching themselves to dynein, the HIV particles are able to reach their destination and get around the various cellular components that might otherwise block their way, such as mitochondria.

The researchers hope that such dynamic methods of studying HIV will one day lead to new targets for drug therapy against HIV. Hope also plans to extend this technique to study Ebola, a virus that could be used in a bioterrorist attack. Little is known about how Ebola enters and moves around a cell, and it is hoped that this technique could also be used to shed more light on the basic biology of this virus.

8 MacDonald, D. *et al.* (2002) Visualization of the intracellular behavior of HIV in living cells. *J. Cell Biol.* 159, 441–452

Secret armour of West Nile revealed

West Nile virus (WNV), a potent but poorly understood pathogen, has finally given up one of its secrets. The protective capsid (WNV-Cp) surrounding its genetic material is so deadly that it can single-handedly initiate a cascade of reactions leading an infected cell to destroy itself [9].

The lack of information about the virus, which was introduced to the USA in 1999 and has since killed over 200 people, underlines the significance of the findings, made by researchers at the Pennsylvania School of Medicine (http://www.med.upenn.edu/). 'Since there is currently no specific treatment for WNV,' said David Weiner, one of the authors of the study, 'it is important to understand the biology of this virus to help us devise vaccines and new treatment for WNV infection.'

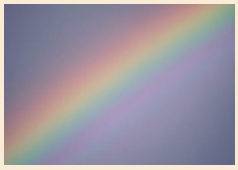
When introduced to tissue culture, WNV-Cp led to rapid nuclear condensation and cell death. The team think they also understand how the deadly protein works. 'Apoptosis is induced through the mitochondrial pathway resulting in caspase-9 activation and downstream caspase-3 activation,' they said. By delivering WNV-Cp directly into the striatum of mouse brain or interskeletal muscle, they induced cell death and inflammation.

The next step, according to Weiner, will be to identify the proteins that interact with WNV-Cp once inside the cell. This, he said, 'will give more insight into the biology of West Nile.'

9 Yang, J-S. *et al.* (2002) Induction of inflammation by West Nile virus capsid through the caspase-9 apoptotic pathway. *Emerg. Infect. Dis.* 8, 1379–8

Miscellaneous

Quantum dots head over the rainbow



The dream of watching proteins and cells moving and interacting in their natural environment has moved one step closer thanks to recent research by two independent groups of scientists from Rockefeller University (http://www.rockefeller.edu/) and the Quantum Dot Corporation (http://www.qdots.com/). The two papers [10,11] demonstrate for the first time how fluorescent nanocrystals (called quantum dots) can be used to simultaneously track multiple living proteins or cells for up to days at a time. A fluorescent microscope is all that is required to follow the minute-by-minute activities of the colour-coded proteins and cells.

The unique physical properties of quantum dots offer several advantages over more traditional methods of visualising proteins and cells (e.g. green fluorescent protein). Simply by altering their size, scientists can manufacture quantum dots to produce light in any colour of the rainbow, and only one wavelength of light is required to illuminate all of the different-coloured dots. Thus, spectral overlap does not limit the number of colours that can be used at once in an experiment. In addition, quantum dots do not stop glowing even after being visualised for very long periods of time: compared with most known fluorescent dyes, they shine for an average of 1000 times longer.

Previous studies have overcome the problems of hydrophobicity and specificity associated with quantum dots by developing hydrophilic coats and using antibodies to provide protein specificity. This recent work has now gone on to show the specific labelling of targets at a subcellular level and demonstrated the long-term multicolour imaging of live cells. This type of cell-tracking approach would allow researchers to study cell fate either outside the body in culture or in whole developing organisms. "With quantum dots, you could follow each cell in the worm *C. elegans* continuously from its birth in an embryo to its final destination in an adult three and a half days later," says Jaiswal, the lead author of the Rockerfeller study. The potential of these reagents is immense, as they are likely to find both medical and biological applications.

10 Jaiswal, J.K. *et al.* (2002) Long-term multiple color imaging of live cells using quantum dot bioconjugates *Nat. Biotechnol.* 21, 47–51

11 Wu, X. *et al.* (2002) Immunofluorescent labeling of cancer marker Her2 and other cellular targets with semiconductor quantum dots. *Nat. Biotechnol.* 21, 41–46.

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