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News in brief

Targets and mechanisms

Casanova decides stem-cell fate

Scientists have identified a gene that directs stem cells to become precursors for internal organs. The gene could be exploited to coax cells to produce high levels of differentiated cells, which could then form tissues such as insulin-producing pancreatic islet cells for transplants.

Researchers at the University of California at San Francisco (CA, USA) have been studying genetic loci in the zebrafish, a good model for embryo development, and have identified a gene that is crucial for the development of endoderm, which is the source material for cells of the pancreas, liver, thymus and thyroid. The gene has been called *casanova* (*cas*) because mutant animals lacking the gene have a split heart.

Didier Stainier, lead author of this report[1], believes that: 'By exploiting this master gene, we can control stem cell differentiation from the inside, as opposed to trying to boost differentiation from the outside with growth factors.'

Stainier added: 'If you can gain access to the earliest stages of cell specialization through the genes that directly control the process from within the cell, you have a much more powerful tool to generate desired cells than if you simply try to increase the number of cells after they have specialized.'

This approach could be used to produce cells for several types of transplant material, and could have potential as treatments for type 1 diabetes and various forms of liver disease.

1 Kikuchi, Y. *et al.* (2001) *Casanova* encodes a novel Sox-related protein necessary and sufficient for early endoderm formation in zebrafish. *Genes Dev*. 15, 1493–1505

Reduced BDNF transcription in Huntington's disease

A protein that is mutated in Huntington's disease (HD) regulates the transcription of brain-derived neurotrophic factor (BDNF), a pro-survival factor for neurons[2]. A group of international researchers, led by Elena Cattaneo from the University of Milan (Milan, Italy), has studied the normal and mutant function of a 350 kDa protein called Huntingtin, mutation of which causes a toxic gain-of-function.

The group studied the production of neurotrophins and found that cells expressing normal huntingtin had high levels of the neuron-survival factor BDNF, whereas this effect was absent in cells expressing mutant huntingtin.

For survival, adult neurons need BDNF to be delivered from the cortex to the striatum. In huntingtin-knockout mice this delivery mechanism is disrupted because less BDNF is generated in the cortex. Furthermore, a post-mortem examination of a human brain from a HD patient showed evidence of reduced BDNF transcription in the cortex, correlating with low levels of neurotrophins in the striatum.

Cattaneo believes that this loss of the beneficial function of Huntingtin contributes to HD, but she cautions that: 'There will be no drug ready tomorrow based on this research, but now we have a new idea for how to develop therapies, perhaps in the very close future.' Trials are currently under development to deliver BDNF via gene therapy to HD transgenic mice.

2 Zuccato, C. *et al.* (2001) Loss of Huntington-mediated BDNF gene transcription in Huntington's disease. *Science* 10.11126/science.1059581 (http://www.scienceexpress.org)

Heparin and exercise therapy increases blood flow in children with KD

A new therapy that combines heparin with short bursts of exercise has been shown to promote angiogenesis and widen blocked arteries in children[3].

The study involved seven children with Kawasaki disease (KD; a condition in which the coronary arteries or the heart muscle can be damaged and susceptible to atherosclerosis) who had a totally blocked coronary artery and were ineligible for angioplasty or surgical revascularization. Treatment was given twice-daily for 10 days and consisted of 10 min exercise of gradually increasing intensity. Heparin was given intravenously 10 min before each exercise period.

Angiography was used to evaluate blood flow around the blocked arteries within three months after treatment. The results showed that a network of tiny new blood vessels had formed in two of the patients and the size of the blocked artery had increased in all participants.

Single-photon-emission computed tomography (SPECT) was also used to evaluate the flow and volume of blood in 17 regions in the heart muscle around the occluded artery. Patients underwent SPECT imaging at rest and after taking dipyridamole, which mimics the effects of physical stress on the heart. The heparin and exercise therapy was shown to improve blood flow to the heart muscle in the areas around the blockage compared with control patients.

'Previous studies of patients with angina have shown that exercise capacity was not improved by heparin or exercise alone,' says Masaru Terai, co-author of the study and Head of the Cardiology Division at Chiba University School of Medicine (Chiba, Japan). 'This implies that the combination of heparin and physical stress is required for improvement in collateral circulation.'

3 Tateno, S. *et al.* (2001) Alleviation of myocardial ischemia after Kawasaki disease by heparin and exercise therapy. *Circulation* 103, 2591–2597

Soy extract might prevent prostate cancer but cause uterine cancer

Genistein, a chemical found in soy, has recently been shown to reduce prostate cancer growth in mice.

The research, performed at the UC Davis Cancer Center (Sacramento, CA, USA) showed that genistein slowed prostate cancer growth in mice and caused prostate cancer cells to die. The results were presented at the *American Urological Association* meeting in Anaheim, CA, USA, 2–7 June 2001.

Genistein belongs to a family of chemicals known as isoflavones – plant-based chemicals that mimic the effects of oestrogen in the body.

The researchers tested commercially manufactured genistein on mice bred to develop prostate cancer and on metastatic prostate cell lines. In the mice, genistein reduced cancer growth, and in tissue culture, it increased the production of p21 (a gene that regulates cell growth) and reduced the production of vascular endothelial growth factor (VEGF), resulting in apoptosis.

The researchers are now evaluating the effects of genistein in men who have slow-growing prostate cancer. There will be a pilot study to determine whether genistein reduces levels of prostate-specific antigen (PSA), a marker for prostate cancer.

The trial will recruit men who have declined treatment for prostate cancer or who have received treatment and whose PSA levels are rising slowly. Volunteers will take up to 5 g (depending on their body weight) of genistein every day for six months and results will be obtained a year later.

It is thought that the low incidence of prostate cancer in Asian men is a result of the high soy content in their diets and thus, if the study indicates that genistein does lower PSA, it is hoped that it could be used as a preventative drug as well as in conjunction with conventional therapy in the treatment of prostate cancer.

However, scientists at the National Institute of Environmental Health Studies (Research Triangle Park, NC, USA) have reported that genistein causes infant mice to develop uterine cancer later in life[4]. Female mice were treated with genistein for five days after birth in doses thought to be similar to those that human infants might receive in a soy-based infant formula. Infants receive the formula by mouth, whereas in the study the mice were injected with genistein and, therefore, more research is needed.

Retha Newbold, who led the study, previously discovered the carcinogenic effect of prenatal exposure of diethylstilbestrol (DES, a synthetic oestrogen), which led to its use in the USA being discontinued.

The authors recommend that use of soy-based infant formulas in the absence of medical necessity, and the marketing of soy products, should be examined closely.

4 Newbold, R.R. *et al.* (2001) Uterine adenocarcinoma in mice treated neonatally with genistein. *Cancer Res.* 61, 4325–4328

Genomics

Human genome: bigger than we thought?

Two recent reports offer conflicting evidence for the size of the human genome. In the first[5], researchers from the University of Ohio (Columbus, OH, USA) present a third map of the genome comprising 65,000–75,000 genes, more than twice the number previously proposed by two earlier reports[6,7]. Bo Yuan, Head of Ohio State's Division of Human Cancer Genetics, led the project: 'We ended up with a higher estimated number of genes than the other two teams because we compared 13 different gene databases with the DNA sequences in the draft genome produced by the Human Genome Project.'

The report consists of a functionally annotated gene index, based on the integration of published transcript, protein and mapping information. Initial sequence analysis has revealed highly ordered chromosomal landscapes associated with paralogous gene clusters and distinct functional compartments. Of the estimated 65,000–75,000 transcriptional units reported by this group, 4% is thought to consist of exon sequences. The full 19-page annotation is available online at http://genomebiology.com (Ref. 5).

The second report[8], by scientists at the Joint Genome Institute (Walnut Creek, CA, USA), compares sections of the mouse and human genome sequences, and has confirmed the original size estimate of 33,000 genes. The study, led by Lisa Stubbs (Livermore National Laboratory, Livermore, CA, USA) studied chromosome 19 and related regions, and used comparative sequence alignment to identify exons, regulatory elements and candidate genes that had been previously missed by predictive methods.

'There had been speculation that aligning the human and mouse DNA sequence might reveal many more genes,' Stubbs says. 'However, if chromosome 19 is indicative of other chromosomes, the estimate of 30,000 genes is fairly accurate.' The group revealed high-level conservation of certain genes in the mouse compared with human genes, and differences (e.g. number, coding capacity and organization) in genes residing in familial clusters. Sequencing of breakpoints of the 15 evolutionary rearrangements in chromosome 19 also revealed clues of the forces that drive chromosome evolution in mammals.

5 Wright, F.A. *et al*. (2001) A draft annotation and overview of the human genome. *Genome Biol*. 2, research0025.1-0025.18 (http://genomebiology.com/2001/2/7/research/0025)

6 International Human Genome Sequencing Consortium (2001) Initial sequencing and analysis of the human genome. *Nature* 409, 860–921

7 Venter, J.C. *et al*. (2001) The sequence of the human genome. *Science* 291, 1304–1351

8 Dehal, P. *et al*. (2001) Human chromosome 19 and related regions in mouse: conservative and lineage-specific evolution. *Science* 293, 129–141

Oxford GlycoSciences to construct 'protein atlas' of human genome

Oxford GlycoSciences (OGS; Oxford, UK) is to be the first to use sequence information obtained directly from naturally occurring human proteins to unambiguously identify all protein-coding genes in the human genome.

The database, to be constructed over the next 24 months, is expected to generate £22.5 million (depending on results) over the next three years. A newly announced company, Confirmant, joint-owned by OGS and Marconi (London, UK), is expected to commercialize and distribute the data in early 2002. Each company will pay an initial investment of £30 million in cash.

By combining Marconi's broadband services with OGS' proteome databases, Confirmant will aim to offer substantial computing power and the means with which to manipulate the data in a secure environment.

'…Because HUGO [the Human Genome Project] relied on computational methods and expressed sequence tag (EST) information, the resulting data are more predictive than absolute,' said Andrew Lyall of OGS. 'This uncertainty… will be addressed by the Protein Atlas.'

Miscellaneous

American Cancer Society criticized for trying to hijack National Cancer Program

The American Cancer Society (ACS; Atlanta, GA, USA) is forging a legally questionabe alliance with the federal Centers for Disease Control and Prevention (CDC; Atlanta, GA, USA) and is virtually neglecting cancer prevention, claimed Samuel Epstein, Chairman of the Cancer Prevention Coalition (Chicago, IL, USA), and Quentin Young, Chairman of the Health and Policy Research Group and past president of the American Public Health Association (APHA; Washington, DC, USA), recently.

Members of the National Dialogue on Cancer (NDC), a body created by the ACS, are advising Congress to re-write the National Cancer Act, the cornerstone of the National Cancer Institute's (NCI; Bethesda, MD, USA) war on cancer, claim Epstein and Young.

Epstein and Young claim that, in return for a US$3 million co-operative agreement, the ACS has made strong efforts to upgrade the CDC's role in the National Cancer Program, increase its appropriations for CDC's non-peer-reviewed community programmes, (which focus on community screening, behavioural intervention and tobacco cessation) and facilitate its access to tobacco litigation money.

Further, they say that patronage of the public relations firms Shandwick International and Edelman by the ACS is inconsistent with their tobacco cessation programmes and the firms' other clients R.J. Reynold's and Brown & Williamson Tobacco.

DeVita, the Legislative Committee co-chair of the ACS, is also Chairman of the Medical Advisory Board of CancerSource.com, a website that is receiving business from the ACS, they say, and they suggest that this represents the development of business interests in a publicly funded forum.

The fact that the ACS also devotes less than 0.1% of its US$700 million annual budget to environmental and occupational causes of cancer disqualifies it from a leadership role in the National Cancer Program, says Epstein and Young. 'The ACS political agenda reveals a pattern of self interest, conflicts of interest, lack of accountability and non-transparency,' said Young.

Serono to appeal Swiss Rebif ban

Serono Pharmaceuticals is to appeal the decision of a Swiss court preventing it from advertizing the benefits of its multiple sclerosis (MS) treatment Rebif.

The court, in Geneva (Switzerland), issued a provisional civil action stopping Serono advertizing the results of its EVIDENCE study, which compared its drug Rebif with Avonex, produced by Biogen (Cambridge, MA, USA).

Serono says that: 1) patients treated with Rebif have a 90% greater chance of remaining relapse-free during the observation period than those being treated with Avonex (Interferon β-1a); 2) patients treated with Avonex had 50% more brain lesions than those using Rebif; and 3) the Food and Drug Administration (FDA) has agreed to the design of the study.

'The validity of relapse-related statistics is seriously compromized by Serono's short-term 'snapshot' approach that accentuates random relapses which are unrelated to treatment effects,' said Biogen in a recent press release. The real difference between the efficacy of the two drugs is not 90% but 12% (74.9% for Rebif, 63.3% for Avonex) the company says.

'They are trying to make life uncomfortable for us because they feel commercially threatened,' Nick Miles of Serono told *Drug Discovery Today*. 'It's all a bit of a storm in a tea cup.'

New HIV initiatives in Africa

Two new initiatives to enable HIV treatments to reach those in need in the poorest countries have recently been launched.

The first initiative is that The Pfizer Foundation (New York, NY, USA) is to fund a study in collaboration with UNAIDS, UNICEF and the Uganda AIDS Commission to determine what measures have been most effective in preventing the spread of HIV in Uganda. Conducted over an 18-month period, the study will identify the best practices in several districts of the country with a view to recommending that they could be used countrywide and also adopted in other countries.

'What we learn about best practices in Uganda can be immensely important throughout Africa,' said Dr Sedibe of UNICEF. 'There is still a great deal of misunderstanding and confusion about HIV/AIDS. The more we learn, especially about what works in reducing infection at a community-based level, will be invaluable in controlling this epidemic.'

The second initiative, a method devised in the 1980s to provide the poorest people in the USA with HIV and AIDS treatments, is to be applied by AIDS Empowerment and Treatment International (AIDSETI, New York, NY, USA) to 14 of the poorest African and Caribbean nations.

In the scheme, unused drugs collected from developed countries will be given to poorer countries for free. The model will be piloted and then expanded to more than 6000 patients in Africa and the Caribbean over the next 12 months, said AIDSETI.

Platform survival requires good product-pipeline

Platform-technology companies will hold no value for investors in the future unless the company has a well-established product-pipeline, Ian Smith of Lehman Brothers (London, UK) told European healthcare professionals recently.

The comments, at a recent dinner arranged by Cambridge Consultants (CC; Cambridge, UK), prompted discussion on whether a technology platform can be a sustainable business-model in the biotechnology sector, or whether product companies will become more attractive for investors again.

'Clearly, it is going to take some time for platform technology companies to really deliver. To date, there are only two potential products that have entered clinical trial despite the millions of pounds and time and effort that has been invested,' said Monika Green of CC.

The general consensus from the meeting was that smaller genomics companies and large pharmaceutical companies should share more information in the future.

The pharmaceutical industry was suggested as the best tool for the future of functional genomics because of the billions of dollars it invests in the search for new drug targets.

News in Brief was written by *Joanna Owens, Suzanne Berry* and *Ben Ramster*