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News in brief

Targets and mechanisms

Genetic risk factors identified

Osteoporosis outed

deCODE Genetics (Reykjavik, Iceland) and Roche (Basel, Switzerland) have announced the identification of the chromosomal location of a genetic risk factor for osteoporosis by deCODE researchers. A genome-wide screen was carried out with participants of 139 Icelandic families (>430 patients and 600 unaffected relatives), which resulted in the mapping of the osteoporosis gene to a small chromosomal region. This is a major step towards the identification of one of the genes that, if present in a variant form, contributes to osteoporosis.

'The work at deCODE represents important progress towards identifying the nature of one of the genetic factors contributing to osteoporosis, and thus towards the goal of devising new tools for early diagnosis and predisposition testing as well as for therapeutic intervention and prevention. In osteoporosis, as in many chronic diseases that progress over years, we know that early identification of people at risk will have a significant impact,' said Jonathan Knowles, Head of Global Pharmaceutical Research at Roche.

Understanding the cause of peripheral arterial occlusive disease

deCODE Genetics and Roche have also revealed the location of a chromosomal region carrying a putative gene that, in its variant form, contributes to common forms of peripheral arterial occlusive disease (PAOD). This research demonstrates that, in addition to PAOD risk factors such as smoking, lack of exercise, hypertension and a cholesterol-rich diet, genetic factors play a role in this disease.

Researchers at deCODE carried out a genome-wide analysis of 1300 Icelandic PAOD patients and family members. A small section of a single chromosome was identified that demonstrates significant genetic linkage to PAOD.

'We are now one big step closer to understanding the causes of PAOD and to developing more powerful and specific drugs. This discovery will also help us to develop susceptibility screening, allowing those people most at risk to adapt their lifestyles and stay healthier longer,' said Kari Stefansson, CEO of deCODE Genetics.

Under the terms of the alliance between deCODE and Roche, deCODE receive a milestone payment for the location of these new genes; Roche will apply knowledge obtained from this alliance to the development of novel diagnostics and therapeutics.

Cell division puzzle solved

Researchers at the Boehringer Ingelheim-sponsored Research Institute of Molecular Pathology (IMP; Vienna, Austria) have unravelled the 125-year-old mystery of sister-chromatid separation during cell division. During metaphase, sister-chromatids are pulled in opposite directions by the mitotic spindle, before suddenly breaking apart and migrating to opposite poles of the cell during anaphase. The 'glue' holding the sister-chromatids together has been isolated as a protein complex, cohesin, that attaches the sister-chromatids together, but until now, the mechanism by which they are subsequently pulled apart was unknown.

The IMP group has isolated a cysteine protease, separin, that cuts the Scc1 subunit of cohesin and results in the separation of sister-chromatids[1]. Moreover, separin has been shown to be required for cleavage of the meiosis-specific subunit of cohesin, Rec8, at the metaphase–anaphase transition[2]. Importantly, another recent discovery by the IMP group is that the mechanisms that have been identified in yeast are the same as those in humans. In humans, cohesin dissociates from chromatids during prophase and therefore it was unclear how sister-chromatid separation at metaphase was controlled. It has now been shown that a residual quantity of Scc1 remains associated with human centromeres until metaphase, and that separin activation is required for its cleavage[3]. Activation of separin requires the concomitant dissociation of a protein named securin, and this has now been shown to occur both in yeast and vertebrate cells[3]. These findings will contribute to a better understanding of cell division, and hence, inherited genetic diseases and cancer.

1 Uhlmann, F. *et al*. (2000) Cleavage of cohesin by the CD clan protease separin triggers anaphase in yeast. *Cell* 103, 375–386

2 Buonomo, S.B. *et al*. (2000) Disjunction of homologous chromosomes in meiosis I depends on proteolytic cleavage of the meiotic cohesin Rec8 by separin. *Cell* 103, 387–398

Gene therapy

Promising future for stent-mediated gene therapy in heart disease

DNA can be delivered into artery walls by stents implanted in coronary arteries, a recent report has shown. The study carried out at the University of Pennsylvania Medical Center (Philadelphia, PA, USA) has demonstrated for the first time that controlled-release of DNA from a polymer-coated stent is successful *in vivo*.

Stents are used commonly in angioplasty procedures to widen narrowed arteries. Using green fluorescent protein (GFP)-plasmid DNA on an emulsion-coated stent, successful expression was achieved both *in vitro* in rat aortic smooth muscle cells and *in vivo* in porcine coronary arteries (diseased and non-diseased). The presence of GFP-plasmid DNA in the artery wall was confirmed by PCR and in pig coronaries by immunocytochemistry. This method of DNA delivery could be used to release a combination of genes that could reduce blood vessel disease by inhibiting cell growth in the arterial wall. Although further work is needed to identify these genes, the results of this study show that delivery via this mechanism is possible and effective in animals.

1 Klugherz, B.D. *et al*. (2000) Gene delivery from a DNA controlled-release stent in porcine coronary arteries. *Nat. Biotechnol*. 18, 1181–1184

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3 Waizenegger, I.C. *et al*. (2000) Two distinct pathways remove mammalian cohesin from chromosome arms in prophase and from centromeres in anaphase. *Cell* 103, 399–410

Aiming at Alzheimer's

Clioquinol, which was used in the 1970s but was linked to a rare neurological disorder found only in Japan, has recently been suggested to be a potential treatment for Alzheimer's disease. Ashley Bush (Scientific Adviser to Prana Biotechnology, Melbourne, Australia) presented this potential treatment at the annual meeting of the Society for Neurosciences (New Orleans, LA, USA). Clioquinol is currently being tested on 36 patients moderately affected by Alzheimer's.

Genetically manipulated mice overproducing β-amyloid (this creates the sticky plaques that are a major feature of Alzheimer's) were used in the experiments. Clioquinol strips copper and zinc away and prevents them from decorating the sticky plaques; mice administered with this drug demonstrated a 51% reduction in plaques compared with untreated mice.

'The drug was effective in the mice experiments not because it kills germs but because it binds two metals,' said Bush. 'In a third of the younger animals, it eliminated the plaques, even though the animals continued to overproduce β-amyloid.' According to Bush, depending on how advanced the Alzheimer's disease is, if the plaque is removed, the brain can heal and repair the damage. Clinical trials, sponsored by Prana Biotechnology, are currently being carried out at the University of Melbourne (Melbourne, Australia).

Markets

Bioindustry Association welcomes UK Pre-Budget Report

Tax and share option concessions included in the Chancellor of the Exchequer's Pre-Budget Report have been welcomed by the Bioindustry Association (BIA, London, UK). However, the BIA is concerned over a continued complex tax system for growing biotechnology companies and yet more detailed legislative proposals. A cap on the National Insurance liabilities on stock options and the relaxation of the conditions attached to the grant of options under the Enterprise Management Incentive Scheme were seen as positive steps toward the encouragement of high-technology companies in the UK. Similarly proposals to withdraw withholding tax on interest and royalty payments were greeted favourably by companies dealing in intellectual property and goodwill.

'Overall the Pre-budget statement is good news… however it does not go as far as we would like in removing altogether the tax liabilities that would help… rapid expansion', said Crispin Kirkman, CEO of BIA. 'We would now urge the Chancellor to extend equivalent privileges beyond the small companies targeted by the existing scheme,' says Daniel Abrams, Head of the Finance and Taxation Committee at the BIA.

For more information, see a more detailed report in the next issue of *Drug Discovery Today*.

News in Brief was written by *Annabel Hinde, Ben Ramster, Joanna Owens and Rebecca N. Lawrence*

People

New CEO and SVP of R&D at Genome Therapeutics

Stephen M. Rauscher has been appointed as CEO of Genome Therapeutics, with Richard Labaudiniere taking up the position of Senior Vice-President of R&D for the company. Robert J. Hennessey will remain Chairman of the Board of Directors while Richard D. Gill's position of COO has been discontinued because of the new management appointments.

Rauscher has been a member of the Board of Directors of the company since 1993. He was previously CEO of AmericasDoctor.com during the period when the company revenues grew from $500,000 to more than $56 million. Rauscher has also held a number of senior leadership positions at Abbott Laboratories including Vice-President of Corporate Licensing, Vice-President of Business Development and Vice-President of Sales US Pharmaceutical Products Division.

Labaudiniere has significant drug discovery executive experience being a former Head of Lead Generation for Rhône-Poulenc Rorer (RPR; now Aventis). Other previous senior R&D leadership positions he has held include Senior Director for Worldwide Lead Discovery at RPR, Head of Medicinal Chemistry and Cardiovascular Project Leader at Glaxo.

New Board member for Variagenics

Ellen M. Zane has recently been appointed to the Board of Directors of Variagenics (Cambridge, MA, USA). David Shortland and Mark Carthy, both venture capitalists, have stepped down after helping the company through its initial public offering. Zane is renowned as a leader in healthcare delivery and policy and it is hoped that her experience of the pharmacogenomic market will help in Variagenic's aim to apply the company's technologies to the development of drugs and related diagnostics to enable individualized therapy and improve patient care.

Zane is currently Network President of Partners HealthCare System and is responsible for the development of a physician and hospital network comprising 4000 physicians and administrators from Brigham and Women's Hospital, Massachusetts General Hospital (MA, USA). Zane also recently led negotiations of the agreement between Partners and Tufts HMO.

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