News in brief

Targets and mechanisms

Mechanism of non-hereditary breast and ovarian cancer revealed

A mechanism of non-hereditary breast cancer was accidentally discovered in a study investigating mutations in the *BRCA1* gene. National Institutes of Health (NIH) human genome researchers at John Hopkins Oncology Center (Baltimore, MD, USA) unexpectedly found that hypermethylation of the breast cancer-associated *BRCA1* gene turned off its tumour suppressor activity thus enabling the progression of cancer[1]. Previously, mutations of the *BRCA1* gene were thought to be the cause of hereditary breast cancer, but this is the first evidence of the gene's involvement in non-hereditary breast cancer.

Almost 15% of breast cancer and 20% of ovarian cancer might be associated with hypermethylation, and this alteration appears to occur in the most common forms of breast and ovarian cancers, rather than the hereditary forms typically associated with mutations in the *BRCA1* gene. At least 200,000 women in the US are affected by breast and ovarian cancer annually, with 60,000 of these cases proving fatal; nearly 80% of these cancers are not the result of an inherited predisposition and, therefore, could be attributed to hypermethylation events.

Brendan Larder, Chief Scientific Officer of Virco (Cambridge, UK), which holds the patent for diagnostic tests based on methylation, commented, 'it appears that the use of methylation as a diagnostic tool may have application in a number of cancers; however, there is a great deal of development work remaining'. However, Virco is already developing a test for hypermethylation of the O^6-methylguanine-DNA methyltransferase (MGMT) gene in glioma patients, after a study showed that glioma patients that tested positive for hypermethylation of this gene were 16-fold more likely to respond favourably to chemotherapy and had a better three-year survival rate[2]. It is hoped, therefore, that a test based on hypermethylation could allow physicians to differentiate between tumours caused by inherited *BRCA1* mutations and those caused by abnormal methylation.

1 Hedenfalk, I. *et al*. (2001) Gene-expression profiles in hereditary breast cancer. *New Engl. J. Med.* 344, 539–548

2 Esteller, M. *et al*. (2000) Inactivation of the DNA-repair gene MGMT and the clinical response of gliomas to alkylating agents. *New Engl. J. Med*. 343, 1350–1354

Childhood seizures increase susceptibility to epilepsy

Fever-induced (febrile) seizures during childhood have been linked to epilepsy in later life. Researchers at the University of California Irvine College of Medicine (Irvine, CA, USA) have shown that long febrile seizures altered the behaviour of h-channels in the brains of baby rats, resulting in further excitation of stimulated nerve cells and increasing the incidence of seizure[3]. This finding might explain the paradox of why a history of prolonged febrile seizures, which typically cause inhibition of nerve cells and thus should reduce further seizures, actually result in increased seizure frequency in later life.

The 'firing' of nerve cells in the brain is a delicate balance between excitation and inhibition, and seizures induced by excessive 'firing' were thought to be a result of peturbing this balance. Within this system, h-channels are thought to sensitively control the excitation–inhibition balance by gently decreasing the excitation of nerve cells, therefore, preventing hyperexcitability. However, when the h-channels become modified by prolonged childhood seizures, they become hypersensitive and are unable to control the excitability of the cells effectively, thus leading to further seizures.

More research will be needed to further characterize the modification of h-channels as a potential target for anti-epileptic therapies. Indeed, h-channels are already a well-studied target in the discovery of drugs to treat heart disease, and it will be important to find therapeutic agents that can alter h-channels in the brain without affecting those in the heart.

Clinical trials

Pfizer restricts use of Pregbalin

Pfizer (New York, NY, USA) have restricted the use of Pregbalin for certain patients in clinical trials following new analysis by the Food and Drug Administration (USA) of previously submitted results from a lifetime mouse study, announced Pfizer recently. The new analysis showed an increased incidence of a specific tumour type, something not seen in a similar previous lifetime dosing study carried out using rats. It is not known whether the new results can be applied to humans as Pregbalin is not a chemical mutagen and was not been found to be genotoxic in preclinical trials. The planned submission of the drug application for neuropathic pain and epilepsy is expected to proceed.

3 Chen, K. *et al*. (2001) Persistently modified h-channels after complex febrile seizures convert the seizure-induced enhancement of inhibition to hyperexcitability. *Nat. Med*. 7, 331–337

Attractive therapy for pain relief

Magnets have provided clinically significant pain relief in sufferers of fibromyalgia, a recent study has shown[4]. Researchers at the University of Virginia (Charlottesville, VA, USA) conducted a study using three measurements of pain: functional status of patients (as reported by study participants), the number of tender points on the body and pain intensity ratings. Almost one-hundred patients were randomly divided into four groups; one control group received their normal fibromyalgia treatment, a second control group received demagnetized sham pads, and the two test groups received either an active magnetized pad A, which provided a low level of uniformly static negative-polarity to the whole body, or pad B, which provided a low level static magnetic field that varied both spatially and in polarity.

Although no significant differences were observed for most of the pain measurements, the groups of patients that

1359-6446/01/$ – see front matter PII: S1359-6446(01)01767-6

slept on pads with active magnets showed a general improvement in pain intensity levels, the number of tender points on the body and functional status after six months when compared with both control groups. The study's principal investigator, Alan P. Alfano concluded that, 'The results tell us maybe this therapy works, and that maybe more research is justified… there are no standards for magnets yet, so researchers need to find what dosage, field strength and period of exposure is proper, what side-effects may occur and what conditions benefit most.' Further studies are currently underway at the University of Virginia to investigate the effects of pulsed and static magnetic fields on neural processes and microvascular capillary blood flow.

4 Alfano, A.P. *et al*. (2001) Static magnetic fields for treatment of fibromyalgia: a randomized controlled trial. *J. Altern. Complem. Med*. 7, 53–64

Phantom kidney disease to be fought by non-profit foundation

Research into a frequently mis-diagnosed kidney condition in children and young adults is to be funded by a non-profit organization called the NephCure Foundation (NCF). The group intend to raise public awareness of a complex set of overlapping diseases that ultimately cause breakdown of the nephron, the filter component of the kidney. The causes of these diseases are unknown, and for the tens of thousands of young people that are sufferers there is currently no cure.

Among the diseases to be targeted is Nephrotic Syndrome, which is typified by a significant loss of protein via the urine resulting in oedema, swelling (particularly around the eyes in the morning) and high cholesterol levels. Another condition that will be investigated is Focal Segmental Glomerulosclerosis (FSGS), which causes scarring of the filtering units of the glomerulus and can destroy the kidney. Funding into FSGS has been encouraged because of recent breakthroughs in research into inherited forms of FSGS and the identification of a protein that might cause the disease. Unlike the National Kidney Foundation (New York, NY, USA) and the Polycystic Kidney Disease Foundation (Kansas City, MO, USA), NCF is dedicating itself to fighting Nephrotic Syndrome, FSGS and related conditions.

Markets

Global market contribution of Brazilian generics

Despite the recent worries of many western pharmaceutical companies, generic medicines produced by Brazilian companies still only make up 1.6% of the $7.5 billion global pharmaceutical market, reported the *Gazeta Mercantil* (Brazil; courtesy of John P. Stewart). However, this sector is expected to grow as investments in such centres accredited by the Brazilian Health Ministry totalled $2 million in the year 2000.

Furthermore, approximately 200 of the 360 laboratories in Brazil are requesting permission from the Finance Ministry to raise the prices of their medications. However, as they are only entitled to increase the cost of their medicines by an average of 4.4% and many companies have already reached the maximum level, it is anticipated by some analysts that many of these requests will be refused.

Treatment of arrhythmias an untapped market

The anti-arrhythmia drug treatment market has a large untapped sales potential, claims a recent Decision Resources (Waltham, MA, USA) report. The report, entitled *Arrhythmias,* has based its predictions on a number of factors: these treatments target a large patient population; there is a high rate of drug treatment; the need for therapies that prevent reoccurrence of atrial fibrillation and other arrhythmias; the need for non-pharmacological alternatives; and the need for safer drugs.

Sales are expected to increase modestly from US$1.8 billion to US$2.6 billion (for the forecast period 1999–2009) in the major markets (USA, France, Germany, Italy, Spain, UK and Japan). This will mainly be driven by small increases in prevalence and diagnosis rates in most countries and a higher use of device/drug combination therapy and expensive novel therapies.

Forthcoming trends are expected to be the appearance of novel anticoagulants, as an alternative to warfarin (such as Dupont's Coumadin); the reduction in the overall proportion of drug-treated patients due to increases in the use of new devices and techniques opening opportunities for adjuvants to device implantation; and the replacement of Class I drugs by Class III drugs driven by growing evidence of the efficacy of amiodarone (Sanofi-Synthelabo/American Home Products's Codarone) and of newer drugs.

Oranges are not the only fruit

Purple grape juice is a more effective antioxidant than orange juice, it has recently been reported. Researchers at the University of Scranton (Scranton, PA, USA) have been comparing the antioxidant qualities of the two fruits and have found that a glass of purple grape juice in the morning could significantly reduce levels of oxidized low density lipoprotein (LDL)[5]. Elevated levels of LDL is a proven risk factor in cardiovascular disease, and it has recently been hypothesized that oxidation of this form of lipoprotein is a preliminary event in the progression of atherosclerosis[6].

In this study, 16 participants were given two glasses of either grape or orange juice daily for one week and the LDL lag-time was measured by taking blood samples. Measurement of LDL lag-time is an established method for determining the efficacy of antioxidants: LDL is isolated and exposed to the antioxidant, and the duration of time between exposure and oxidation is referred to as the lag-time. A long lag-time, therefore, reduces the potential for LDL to contribute to the atherogenic process. Subjects who consumed purple grape juice exhibited a 27% increase in LDL lag time, whereas those individuals who consumed orange juice failed to demonstrate any such increase. These new findings suggest that a daily glass of purple grape juice as part of a healthy diet could help to prevent coronary heart disease.

5 Vinson, J.A. *et al*. (2001) Grape juice, but not orange juice, has *in vitro*, *ex vivo* and *in vivo* antioxidant properties. *J. Med. Food* 5, 167–171

6 Hakamata, H. *et al*. (1998) Cytotoxic effect of oxidized low density lipoprotein on macrophages. *J. Atheroscler. Thromb*. 5, 66–75

Genomics

Register for arrhythmic side effects

A register has been established by researchers and physicians in Lake Buena Vista (FL, USA) to collect clinical information and genetic data on people who have developed potentially fatal arrhythmias from taking medications. The registry, which can be found at http://www.qtdrugs.org, was initiated by Michael Kilborn (Georgetown University, Washington D.C., MD, USA) and aims to collate ECG and genetic features of these individuals to aid in the development of prediction tests.

Kilborn says that almost any type of drug can cause arrhythmias, although probably the commonest are anti-arrhythmics, antipsychotics, antibiotics, antihistamines and some analgesics. He anticipates that the project is likely to last for 10 years but hopes to gain valuable insights from the growing information as new data is submitted and analysed.

Genetic predictor found for effectiveness of diuretic drug

A recent article in *Hypertension*[7] is one of the first to demonstrate the isolation of a gene polymorphism that has a direct impact on the effectiveness of a medicine. Researchers at the Mayo Clinic, Emory University School of Medicine (Rochester, MN, USA) and the University of Texas Health Sciences (Houston, TX, USA) showed that the T allele of the C825T polymorphism of the gene encoding the β(3)-subunit of G proteins is associated with increased responsiveness to the diuretic, hydrochlorothiazide (HCTZ). This increase in responsiveness is thought to be because of increased sodium–hydrogen exchange and low renin levels in these patients with essential hypertension.

The study examined the effect of 4 weeks treatment with HCTZ on the systemic and diastolic blood pressures of 197 blacks and 190 non-Hispanic whites with essential hypertension. Blood pressure changes were monitored in patients with different combinations of the two variations of the *GNB3* (C and T) gene. Results showed that HCTZ was 60–78% more effective in reducing blood pressure in those with two copies of the T-variant of the gene compared with those with two copies of the C-variant of the gene.

Stephen Turner, lead author of the study and a hypertension specialist at the Mayo Clinic points out that only ~50% of patients will respond to drugs such as HCTZ and hopes that understanding the variations in these responses will enable the prescription of medicines that are more likely to be effective and avoid the current trial and error process of drug selection. However, Turner realises that this current research only provides part of the solution: 'This single gene does not explain all of the variation in response to HCTZ… with all known factors combined, we can account for about 32% of blood pressure variation among individuals.' However, he is optimistic: 'The current study provides a solid basis for further investigation into other genes that might explain the rest, and which might someday enable us to choose medications that will have a much higher probability of effectiveness for a given patient.'

7 Turner, S.T. *et al.* (2000) C825T polymorphism of the G protein β(3)-subunit and antihypertensive response to a thiazide diuretic. *Hypertension* 37, 739–743

'Ethnic divide' over gene research in UK

Women and people from an Asian background are more likely to believe that research into genetics is unethical, reported a Mori opinion poll for the UK government's Human Genetics Commission. The findings from the poll of 1000 people also showed that Black and Asian people were significantly less optimistic than White participants that new genetic improvements would bring cures for many diseases.

Answers also varied on account of age and gender. Older people (over 65) tended to have more faith in controls governing research, although about 75% of those questioned felt they did not know enough about the controls on biological developments. The proportion of women concerned that human genetics research was tampering with nature was greater (37%) than that of men (28%). 'The variations between different groups of people in our society are enlightening and it is important that we and others take careful note of these views', said Baroness Helena Kennedy, Chair of the Human Genetics Commission.

Genome sequencing collaborations

Rat genome

Following the recent advances in sequencing of the mouse genome by the public–private Mouse Sequencing Consortium[8] and Celera Genomics (Rockville, MD, USA), Celera and the Baylor College of Medicine (Houston, TX, USA) have been awarded grants totaling US$58 million by the National Heart Lung and Blood Institute (NHLBI; Bethesda, MD, USA) and the National Human Genome Research Institute (NHGRI; Bethesda, MD, USA) to expand their ongoing efforts to sequence the laboratory rat genome.

Further funding has also been awarded by these institutes to the Genome Therapeutics Corporation (Waltham, MA, USA), The Institute for Genomic Research (TIGR; Rockville, MD, USA) and the University of British Columbia (Vancouver, Canada), to accelerate the rat genome project. The collaboration aims to provide a draft of the genome sequence within two years. The complete sequence is estimated to be similar to the size of the human genome, ~2 million base pairs, and the project will utilize several methods, including shotgun and map-based approaches, while taking advantage of lessons learned from the sequencing of the human genome.

Streptomyces diversa *genome*

Diversa Corporation (San Diego, CA, USA) and Celera Genomics have announced their completion of the sequencing of the *Streptomyces diversa* genome. *S. diversa* belongs to the actinomycetes, a class of microorganisms that produces the majority of commonly used antibiotics, as well as immunosuppressants, anti-parasitic agents and herbicides. Knowledge of the genome sequence will enable Diversa to fully exploit *S. diversa* for the production of antibiotics and other novel small-molecule therapeutics.

Helicobacter hepaticus *genome*

A consortium formed between MWG-Biotech (High Point, NC, USA) and the University of Würzburg (Würzburg, Germany), the Massachusetts Institute of Technology (MIT; Cambridge, MA, USA) and GeneData (Basel, Switzerland) aims to determine the whole genome sequence of *Helicobacter hepaticus*, using MWG-Biotech and GeneData's proprietary sequencing and annotation technology. *H. hepaticus* is

a pathogen belonging to the Enterohepatic Helicobacter Species (EHS) class, and causes chronic active hepatitis, hepatocellular carcinoma and inflammatory bowel disease in mice, and has recently been linked to liver cancer and chronic cholecystitis in humans. The consortium is aiming to provide an overview of the whole genome and identify genes involved in pathogenicity by comparing the genome with that of *H. pylori*, which is thought to be a causative agent in stomach cancer.

8 Marshall, E. (2000) Public–private project to deliver mouse genome in 6 months. *Science* 287, 1723–1725

Regulatory affairs

Bristol-Myers Squibb accused of deceiving federal agencies

Bristol-Myers Squibb (BMS) have been accused of fraudulently obtaining an extension to the patent they hold on the anxiety treatment BuSpar, reported the SPAN (Stop Patient Abuse Now; Pennsylvania, PA, USA) coalition recently. SPAN, who have referred the matter to the Federal Trade Commission, are accusing the company of obtaining the patent extension under the false premise that it would only cover new uses of the drug, currently worth $700 million a year. The US Patent and Trade Organisation (PTO) indicated that it would not have otherwise issued the patent extension, which protects the drug from competitors. A similar case occurred previously when BMS were accused of fraudulently extending the patent for its breast cancer drug Taxol. It was ruled in March 2000 that BMS had demonstrated an intent to deceive. 'There can be no question… that Bristol took one position before the PTO, and another before the FDA,' said Judge William H. Walls.

In March, the FDA objected to the listing of a Biovail Corporation patent for the antihypertensive drug, Tiazac, on similar grounds. Tim Fuller, Executive Director of the Gray Panthers, a national seniors organization said: 'The FDA moved against a smaller company that tried this – it should not be afraid to move against BMS.'

FDA follows through on warnings to Schering-Plough

Three years of formal Food and Drug Administration (FDA) warning letters issued to Schering-Plough (Camp Hill, PA, USA) have culminated in the agency withholding approval of Clarinex (desloratidine), the company's successor to the allergy drug Claritin. The action follows a recent 31-day inspection of Schering-Plough's Kenilworth plant (NJ, USA) by FDA officials, which found 'no assurance that the manufacturing process, parameters, equipment of protocols… conducted at multiple sites for the production of Clarinex… are equivalent or capable of producing products of the same quality.' They concluded that the 'process validation for many products fails to support claims that manufacturing processes were capable of consistently producing products with the same quality, purity and safety.'

Warning letters are the highest level of regulatory action against a company the FDA can take prior to beginning federal court proceedings. Former FDA district director, John Scharmann, described Schering-Plough's response to FDA criticisms of the manufacturing practices as 'not the way to go'.

Schering-Plough have also received criticism from the website Public Citizen (http://www.publiccitizen.org) regarding allegations of negligence in its manufacturing of asthma inhalers and other drugs. In a recent letter sent to the Department of Health and Human Services (Washington D.C., MD, USA), it is claimed that during the past 15 months the company has recalled 59 million asthma inhalers (produced at Kenilworth, NJ, USA) because many lacked their active ingredient albuterol (brand name Proventil).

It is also alleged that the company was aware of quality control problems a year ago when a previous external audit found significant problems at the site. A second external audit, leaked from AAC Consulting Group (Rockville, MD, USA) earlier this year, was extremely critical of the general attitude of managers, who told of 'an imbalance between quality and production, leaning considerably toward production'. The problems with inhalers indicated 'insufficient technical expertise and managerial oversight' they said. Public Citizen is now calling on the FDA to consider whether criminal charges are appropriate because of the possibility that the company was aware of their quality control problems when it shipped some of the defective inhalers.

These criticisms have decreased sales of certain product lines in the US, resulting in lower first quarter and full-year 2001 sales and earnings than previously expected (Schering-Plough Press Release, 15 February 2001). In response to these sales figures, the company said that it was confident that all its prescription and OTC products currently in the marketplace were safe and effective. They pointed to their commitment to spend $50 million on new equipment, process and system improvements, to increase the number of personnel dedicated to quality control and compliance and blamed certain manufacturing and shipping problems on the temporary interruption of some production lines for the installation of system upgrades. However, there are currently no dates available for when the company will discuss these issues with the FDA or when Clarinex may gain approval, Bob Consaldo (Schering-Plough, Kenilworth) told *Drug Discovery Today*.

Miscellaneous

Blue genes in Taiwan

IBM plans to provide the necessary hardware and technical support for Taiwan's booming biotechnology sector, as well as to provide super-computers for the necessary bioinformatics tasks. These super-computers are already being used by Academica Sinica, the National Center for High-Performance Computing and the Institute of Biochemical Sciences in Taiwan. IBM is claiming that its super-computer, Blue Gene, can run 100-times faster than the Deep Blue computer used to take on Garry Kasporov at chess. The company has already invested US$10 billion in Blue Gene, which contains 186 central processing units.

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