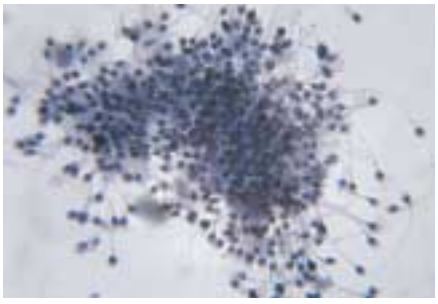
News in brief

Targets and mechanisms

New target for the male contraceptive pill?



The role of oestrogen in male reproduction has been further elucidated and raises the possibility of the oestrogen receptor (ERα) as a target for the development of male contraceptives [1]. Scientists at the University of Illinois College of Veterinary Medicine (Urbana, IL, USA) have studied the molecular mechanism of oestrogen in fluid reabsorption in the male reproductive tract. Oestrogen is essential for the transfer and concentration of sperm in fluid from the testis through the efferent ductules to the epididymis [2].

This latest study demonstrated that oestrogen upregulates the expression of the Na^+/H^+ exchanger-3 (NHE-3) protein. The expression of NHE-3 in the efferent ductules of ERα-null mice was compared with that in wildtype mice using immunohistochemistry and northern blotting. In the ERα-null mice, expression of NHE-3 was almost undetectable and the expression of NHE-3 mRNA was six-times less compared with wildtype mice. In the presence of an NHE inhibitor, the rate of uptake of radiolabelled $^{22}Na^+$ was also four-times less than the uptake measured in wildtype mice. Furthermore, ductal morphology was abnormal only in ERα-null mice.

These findings suggest that oestrogen regulates an important epithelial ion transporter and maintains efferent ductule morphology, implicating ERα as a potential target for male contraceptives.

1 Zhou, Q. *et al.* (2001) Estrogen action and male fertility: Roles of the sodium/hydrogen exchanger-3 and fluid reabsorption in reproductive tract function. *Proc. Natl. Acad. Sci. U. S. A.* 98, 14132–14137

2 Hess, R.A. *et al.* (1997) A role for oestrogens in the male reproductive system. *Nature* 390, 509–512

Gene profiling identifies a unique form of infant leukaemia

Gene expression studies using oligonucleotide arrays have revealed genetic abnormalities in the infant form of acute lymphoblastic leukaemia (ALL) that are dramatically different from adult ALL and acute myelogenous leukaemia (AML). Scientists at the Dana-Farber Cancer Institute (Boston, MA, USA) have found that the rare but lethal form of ALL, which strikes infants of less than one year of age, is a genetically unique form of leukaemia, which they have termed mixed lineage leukaemia (MLL) [3]. It is hoped that this finding will enable the design of specific drugs against this form of cancer.

'This finding is very exciting to us because it forces us to think about this as a separate disease and to think about other therapies that could be designed to attack its specific weak points,' said Scott Armstrong, lead author of the study.

ALLs that carry a chromosomal translocation involving the mixed lineage leukaemia gene (*MLL*, *ALL1*, *HRX*) have a particularly poor prognosis. Affymetrix oligonucleotide arrays were used to study RNA expression profiles in leukaemia samples from bone marrow or peripheral blood.

Analysis of these expression data using clustering algorithms showed that lymphoblastic leukaemias with *MLL* translocations can be distinguished from other forms of ALL and AML. Indeed, the different pattern of gene expression in MLL is so robust that it should enable clinicians to classify leukaemias correctly and make more appropriate treatment decisions, and warrants closer examination of the selectively expressed genes as drug targets.

3 Armstrong, S.A. *et al.* (2001) *MLL* translocations specify a distinct gene expression profile that distinguishes a unique leukaemia. *Nat. Genet.* [epub ahead of print] 10.1038/ng765 (http://www.nature.com)

Bugs go to work against cancer cells

A new therapy that uses anaerobic bacteria to destroy cancer cells in poorly vascularized parts of tumours has been developed by scientists at Johns Hopkins Medical Institute (JHMI; Baltimore, MD, USA) [4].

Current chemotherapeutic approaches are limited in their ability to treat large, advanced cancers because the drug is unable to reach poorly vascularized regions of the tumour. Bert Vogelstein and colleagues have systematically assessed anaerobic bacteria for their ability to grow in the hypoxic compartments of tumours transplanted into mice. Of 26 strains tested, one strain, *Clostridium novyi*, warranted further investigation.

Spores of a strain of *C. novyi* that lacked its lethal toxin (*C. novyi*-NT) were administered intravenously into the avascular regions of tumours in mice and were found to destroy the surrounding viable tumour cells.

Moreover, when coadministered with conventional chemotherapy, extensive haemorrhagic necrosis of >50% of tumours occurred within 24 h, demonstrating a potent antitumour effect of the combined therapies. This strategy, called combined bacteriolytic therapy (COBALT), is hoped to add a new dimension to cancer therapy. However, it will take several years to determine the optimal combination of bacteria and drugs before any attempt will be made to begin clinical trials. Kenneth Kinzler, Professor of Oncology at JHMI, is optimistic about the therapy, but warns that: '[We] realise that the way tumours respond to treatment in mice can be different than in humans.'

4 Dang, L. *et al.* (2001) Combination bacteriolytic therapy for the treatment of experimental tumors. *Proc. Natl. Acad. Sci. U. S. A.* [epub ahead of print] 10.1073/pnas.251543698 (http://www.pnas.org)

Beer belly buster

Recent research has shown that increased activity of a single enzyme, found in fat cells, could be linked to obesity and related diseases, including diabetes [5]. The research was performed at the Beth Israel Deaconess Medical Center (Boston, MA, USA) and the University of Edinburgh (Edinburgh, UK), and could lead to the

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Clinical trials

New drug effective in treating acromegaly

Pegvisomant, one of a new class of compounds, has been shown to be effective in treating the disease acromegaly [13]. The compound, which is a growth hormone receptor antagonist, was shown to normalize the concentration of insulin growth factor-1 (IGF-1) in 97% of patients participating in two 12-month-long open-label trials.

These results are encouraging because there has been 'no significant advance in the medical management of acromegaly in the past decade,' said Michael O. Thorner, Henry B. Mullholland Professor of Internal Medicine and Professor of Neurosurgery at the University of Virginia Health System (Charlottesville, VA, USA), and co-author of the study.

The disease, which is life threatening, is often caused by adenoma of the pituitary and symptoms include progressive coarsening of facial features and an enlargement of the hands, feet and jaw. Growth of the tumour leads to secretion of growth hormone by the pituitary gland, which in turn causes overproduction of IGF-1. Previous treatment has involved surgery to remove cancerous growth, or radiation therapy with drug treatment. 'Pegvisomant has a novel mechanism of action…(as) it blocks the action of growth hormone at the tissue level rather than relying on inhibition of growth hormone secretion,' said Thorner.

One hundred and fifty-two patients with active acromegaly were treated by daily subcutaneous injection for up to 18 months. Mean serum concentrations of IGF-1 fell by at least 50% for patients treated for 6 (by 467 μg), 12 (by 526 μg) and 18 (by 523 μg) months. Growth hormone levels increased by 12.5 μg, 12.5 μg and 14.2 μg at 6, 12 and 18 months, respectively. Antibodies to growth hormone were detected in 27 (16.9%) patients but no tachyphylaxis was seen. Two patients experienced progressive growth of their pituitary tumours, and two other patients were withdrawn from the trial because of their elevated levels of alanine aminotransferase and aspartate transaminase. Generally, the drug was well tolerated, with a 33% rate of mild infections probably reflecting the relatively long period of intense follow-up of patients.

13 Jan van der Lely, A. *et al.* (2001) Long-term treatment of acromegaly with pegvisomant, a growth hormone receptor antagonist. *Lancet* 358, 1754–1759

development of drugs to eradicate visceral obesity – the fat that concentrates around the abdomen, which is often known as a 'beer belly'.

Lead author Jeffrey S. Flier, an endocrinologist at Beth Israel, said: 'Hundreds of studies have led to the conclusion that any fat can be problematic, but it's much, much more dangerous when it's accumulated in the abdomen.' He added, 'Pound for pound, intra-abdominal fat is much more likely to cause diabetes, heart disease and other diseases that make up the metabolic syndrome.'

Flier and colleagues investigated the role of the glucocorticoid hormone cortisol. Previous observations have shown that patients with the endocrine disorder Cushing's syndrome have too much cortisol in their blood, and also have increased intra-abdominal fat, which led Flier to speculate that obese patients – who do not have increased cortisol levels in the blood – could be producing abnormally high levels of cortisol in their fat cells.

The enyme 11β hydroxysteroid dehydrogenase type 1 (11β HSD-1), which produces glucocorticoids, was used to test this hypothesis. Transgenic mice were produced that overexpressed 11β HSD-1 specifically in adipose tissues. These mice had elevated levels of corticosterone and developed visceral obesity, which was further exaggerated by a high-fat diet. The mice also had increased levels of insulin-resistant diabetes and hyperlipidaema. The study showed that increased adipocyte 11β HSD-1 activity could be the common molecular aetiology for visceral obesity and its metabolic syndrome.

5 Masuzaki, H. *et al.* (2001) A transgenic model of visceral obesity and the metabolic syndrome. *Science* 294, 2166–2170

A gut feeling…

Differentiation of stem cells in the intestine could be linked to a gene known to govern the development of neuronal cells [6]. The finding could lead to new treatments for irritable bowel syndrome and other abnormalities of gut motility.

During previous studies, in which *Math1* was found to play a role in the differentiation of neuronal cells, expression of the gene was also detected in intestinal cells. It was therefore thought that it could be involved in the nervous system of the gut.

The researchers used mice in which the coding region of *Math1* was replaced by an enzyme that stained the cells expressing the gene. Instead of detecting expression of the gene in the nervous system of the gut, they found expression in the intestinal epithelium in three kinds of secretory cells: goblet, enteroendocrine and Paneth cells. Mutant mice with no *Math1* gene did not produce the three secretory cells, indicating that *Math1* is important for basic stem cell differentiation. *Math1*-negative progenitor cells instead gave rise to absorptive cells, enterocytes. This suggests that *Math1* plays a role in deciding whether a cell becomes a secretory cell or an absorptive cell.

New treatments could include providing dormant stem cells with a regulatory mechanism that dictates the path of differentiation to replace cells lost to injury. The research could also be applicable to stem cells in other parts of the body.

6 Yang, Q. *et al.* (2001) Requirement of *Math1* for secretory cell lineage commitment in the mouse intestine. *Science* 294, 2155–2158

Defective transport system linked to Alzheimer's disease

Amyloid precursor protein (APP), known for its involvement in the accumulation of β-amyloid in the brain of Alzheimer's disease patients, has been shown to play an important role in molecular transport in the brain [7]. The findings are the first to link APP to cellular trafficking and could explain how and where the harmful β-amyloid plaques build up in the brains of Alzheimer's disease patients.

Researchers at the Howard Hughes Medical Institute (La Jolla, CA, USA) showed that removal of APP in *Drosophila melanogaster* (fruit fly) disrupted the ability

of neurons to transport materials through axons, which enable the transmission of signals throughout the body. When too much APP was introduced, the axonal system became clogged, leading to the death of neurons.

A more recent study using a mouse model showed that the C-terminal portion of APP serves as an attachment point for a molecular motor, kinesin, which transports essential proteins from the main body of the cell along axonal extensions [8]. When enzymes break off this terminus, kinesin is liberated and the transport process is disrupted. It is thought that defects in this transport system cause the cell to send out distress signals that initiate cell death, and that APP might be involved in this signalling process.

Furthermore, two other proteins, β-secretase and presenilin-1, were also found within the body of the cell. These are thought to be the main enzymes that process APP to create β-amyloid. This suggests that APP processing might be an essential part of normal cell transport function and that this process is disrupted in individuals with Alzheimer's disease.

Although the results are not definitive, they provide important clues to which protein pathways lead to the cell death observed in Alzheimer's disease. Future research could lead to new therapies that target APP.

7 Gunawardena, S. and Goldstein, L.S.B. (2001) Disruption of axonal transport and neuronal viability by amyloid precursor protein mutations in *Drosophila*. *Neuron* 32, 389–401

8 Kamal, A. *et al.* (2001) Kinesin-mediated axonal transport of a membrane compartment containing β-secretase and presenilin-1 requires APP. *Nature* 414, 643–648

The waste is over

Scientists have discovered a biochemical mechanism that could explain the disease 'wasting syndrome', which is characterized by severe weight loss and weakness in patients with chronic inflammatory diseases, and which often hastens their demise [9].

The researchers, from the Salk Institute for Biological Studies (La Jolla, CA, USA), the University of California, La Jolla (CA, USA) and the Veterans Association Medical Center (San Diego, CA, USA), pinpointed the biochemical events that occur in mice with this syndrome, and identified the same processes in liver samples from cancer patients.

Mario Chojkier, senior author of the study, said 'When we saw that it was virtually identical in animals and humans, we were ecstatic.' He added, 'What we've described in animals has much greater relevance than we ever thought to human wasting syndrome. We're optimistic this will bring hope and relief very quickly to the bedside.'

The research concentrated on the decreased levels of albumin, which is a frequent feature of patients with acute diseases, including cancer, and is a major contributor to their deaths. It was shown that tumour necrosis factor-α (TNF-α) can prevent albumin production. In a mouse model, overexpression of TNF-α induces oxidative stress, nitric oxide synthase expression and phosphorylation of the protein C/EBPβ on Ser239, which induces its nuclear export, thus, inhibiting transcription from the albumin gene. 'We found that this phosphorylation makes the C/EBPβ exit the nuclear area and go into the cytosol, where there is no DNA for it to bind with. This means it can no longer produce protein,' said Chojkier.

The group found that treatment of TNF-α mice with vitamin E and other antioxidants prevented C/EBPβ phosphorylation on Ser239 and restored normal albumin expression. According to Chojkier, antioxidants could have the potential to halt human wasting syndrome, especially if targeted to the liver. 'One solution will be to find a liver-specific antioxidant. With the technology we have today, this is very feasible. We believe this will provide an exciting new avenue for intervention,' he said.

9 Buck, M. *et al.* (2001) Nuclear export of phosphorylated C/EBPβ mediates the inhibition of albumin expression by TNF-α. *EMBO J.* 20, 6712–6723

Enzyme mimic to ease joint pain

Scientists have shown that the inflammation and joint damage seen in rheumatoid arthritis can be lessened, or even prevented, using novel small-molecule enzyme mimetics [10]. The groups, at Metaphore Pharmaceuticals (St Louis, MO, USA) and the University of Messina (Messina, Italy), investigated the drug M40403, which is a synthetic mimetic of superoxide dismutase (SOD), on collagen-induced arthritis (CIA) in rats.

The SOD mimetic was shown to effectively reduce cartilage and bone erosion, and also decreased chronic inflammation in the rat model. Other effects were the reduction of the levels of two pro-inflammatory cytokines, tumour necrosis factor-α (TNF-α) and interleukin-1α (IL-1α), which are implicated in the development of arthritis. Results from the study were the reduction of inflammation by up to 56% and a 70% reduction in joint erosion in animals treated with M40403 compared with untreated animals.

Daniela Salvemini, principal investigator of the study and Metaphore's Vice President of Pharmacology, said: 'The findings of this study suggest a potentially novel therapeutic for rheumatoid arthritis, combining anti-inflammatory and disease-modifying properties into a single drug. The SOD mimetic possesses both of these properties because superoxide plays a dual role, acting both as a direct inflammatory molecule, as well as stimulating the release of the inflammatory cytokines TNF-α and IL-1α. This contrasts with the current generation of disease-modifying arthritis drugs, which attempt to control the cytokines after their release.'

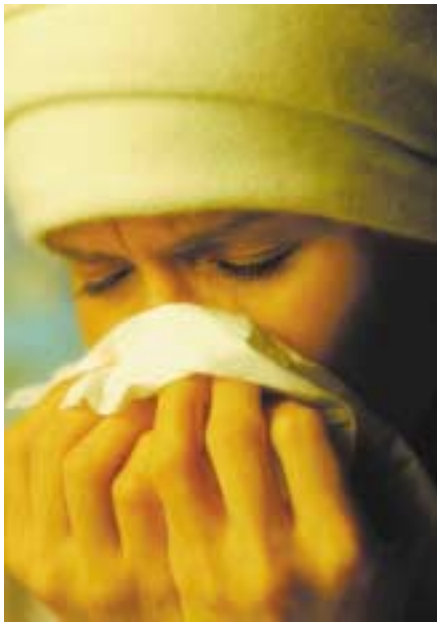
10 Salvemini, D. *et al.* (2001) Amelioration of joint disease in a rat model of collagen-induced arthritis by M40403, a superoxide dismutase mimetic. *Arthritis Rheum.* 44, 2909–2921

Infectious diseases

Influenza's jewel among the junk

A new 'hidden' influenza A virus protein has been found that could herald a groundbreaking advance in understanding the virus' virulence [11]. For almost 20 years, scientists have believed that the influenza virus consists of only ten proteins. However, Jonathan Yewdell and colleagues at the National Institute of Allergy and Infectious Diseases (Bethesda, MD, USA) accidentally found an additional protein while sifting through 'junk' peptides – short proteins that the virus makes after it begins replicating inside a cell.

'We weren't looking for new proteins at all,' says Yewdell, 'we just wanted to know



whether immune system cells had learned to recognize any of these junk peptides.' Indeed, the $CD8^+$ cells of mice did recognize one of the peptides, but on further examination, the gene encoding the peptide was 'suspiciously long' to be mere junk.

Yewdell and colleagues then went on to quantify expression of the peptide using immunofluorescence and found large amounts of the protein in the mitochondria of influenza A-infected cells. 'It was one of those ''Eureka'' moments of discovery you live for in science,' said Yewdell.

Further investigation has revealed that the protein is created when ribosomes begin reading the influenza A *PB1* gene from a different start codon. Yewdell believes that this gene might have started out as a mistake, but because it proved useful, it has been conserved and improved throughout evolution.

The 87-residue protein, termed PB1-F2, is unusual compared with other influenza A gene products – it is absent from swine isolates, has variable expression between individual cells, undergoes rapid proteasome-dependent degradation and is localized to the mitochondria of host cells. Yewdell and colleagues have found that exposure of cells to synthetic PB1-F2 induces apoptosis and, further, that viruses with mutant PB1-F2 induce less extensive apoptosis in human monocytes than those with the wildtype protein. These findings suggest that this novel protein functions by killing immune cells that respond to influenza A infection.

11 Chen, W. *et al.* (2001) A novel influenza A virus mitochondrial protein that induces cell death. *Nat. Med.* 7, 1306–1312

Natural hydrolase attacks bacteria

Scientists have shown that a natural enzyme from viruses that live inside bacteria can kill pathogenic bacteria, including those with developed resistance to drugs [12]. The group, at the Laboratory of Bacterial Pathogenesis, The Rockefeller University (New York, NY, USA), used the recently discovered 'bacteriophage' enzymes, which kill pathogenic bacteria that lie on the surface of cells, to eliminate *Streptococcus pneumoniae* (in mice), which is present in the nasal passages.

Vincent Fischetti, principal investigator of the study, said: 'A nasal spray containing this enzyme would prevent infections before they start.' He adds, 'Resistance to antibiotics is rapidly becoming a serious public health concern. These enzymes offer an alternative method for combating resistant pathogens.'

The group showed that, seconds after contact, a pneumococcal bacteriophage lytic enzyme (Pal) can eliminate 15 common serotypes of pneumococci, including those that have previously been shown to be penicillin-resistant. *In vivo,* mice had undetectable levels of pneumococcal titres following colonization, five hours after treatment with the enzyme. Even Pal-resistant strains of pneumococci could not be detected after extensive enzymatic exposure.

Jutta Loeffler, first author of the paper, and a post-doctoral research fellow at Rockefeller, said: 'This enzyme will kill pneumococci on mucous membranes within seconds. By treating individuals carrying this bacterium with the enzyme, you could significantly reduce the reservoir of these bugs in the population and consequently reduce infection rates.'

As *S. pneumoniae* remains one of the most challenging pathogens known to man, this decrease in the number of infections worldwide could decrease the requirements for antibiotics, and thus contribute to eliminating the current escalating problem of drug resistance.

12 Loeffler, J.M. *et al.* (2001) Rapid killing of *Streptococcus pneumoniae* with a bacteriophage cell wall hydrolase. *Science* 294, 2170–2172

NIAID funds new functional genomics centre

The National Institute of Allergy and Infectious Diseases (Bethesda, MD, USA) has awarded a US$25 million five-year grant to The Institute for Genomic Research (TIGR, Rockville, MD, USA) to fund a new centre for functional genomics.

The Pathogen Functional Genomics Resource Center (PFGRC; http://pfgrc.tigr.org/) will be based at TIGR and aims to centralize production, access and training in the use of resources for exploring the roles of genes and gene products in many microbes known to cause disease. The short-term goals are to provide researchers with microarray and genotyping technology, genomic DNA, type strains and access to clone sets. Data analysis and storage will be provided by TIGR's bioinformatics services and a centre–client web-based interface will also be set up to enable scientists to easily access and acquire resources.

Miscellaneous

New therapeutic approaches for respiratory disorders

Several new products using new ways of treating asthma and chronic obstructive pulmonary disease (COPD) will reach the market by 2005 and fuel significant market growth, says a recent Decision Resources report entitled *Next-Generation Respiratory Disease Therapeutics: An Analysis of Key Competitor Pipelines.*

The most significant development is the use of combinations of corticosteroids with long-acting β_2-adrenoceptor agonists, which have proven more effective when treating asthma than each factor alone. Although asthma and COPD do not produce similar disease symptoms or patient population distributions, similar treatments might be effective for both diseases and marketing approval could be sought for treating COPD if existing asthma drugs prove effective.

Hence, sales of GlaxoSmithKline's (London, UK) Advair/Seretide (fluticasone plus salmeterol) and AstraZeneca's (London, UK) Symbicort (budesonide plus formoterol) combination asthma treatments might be boosted by their future use for COPD if they become approved for this condition.

The launch of a long-acting anticholinergic drug is expected to cement Boehringer Ingelheim's (Ingelheim, Germany) control of the COPD treatment market. Spirivia (tiotropium bromide) has been formulated as a once-daily formulation and is expected to greatly increase patient compliance. Meanwhile, the PDE_4 inhibitors Ariflo (cilomilast; GlaxoSmithKline) and roflumilast (Byk Gulden, Konstanz, Germany) are expected to reach the market in 2005.

Biotech bounces back at end of 2001

Biotechnology shares performed well throughout November 2001 in all sectors, claim Burrill and Company (San Francisco, CA, USA). The Burrill Biotech Select Index was up by 12% (down 19% YTD) and the NASDAQ was up by nearly 14% at month's end (down 22% YTD), both outperforming the DOW, which rose 9% (down 9% YTD). This was despite nationwide downsizing, revenue and earnings shortfalls, and budget deficits in the USA.

'Even though we are in recession…'healthcare' continues to perform well,' said G. Steven Burrill, CEO of Burrill & Company. 'Venture capitalists and other financial institutions are not paid to sit on their cash…so investment is returning to the sector,' he said.

Nexell Therapeutics saw their shares rise by more than 200% on the news that they had received orphan drug status for their experimental treatment for chronic granulomatous disease. Burrill commented that 'This therapy is based on stem cell technology. The agency's decision underscores the importance of sustaining strong R&D in the stem cell arena.'

Other stem cell company stocks were temporarily buoyed by the announcement of the successful cloning of a human embryo by researchers at Advanced Cell Technologies and led to the increase of shares in Geron (by 8%), StemCells (by 9%) and Aastrom (by 9%). However, by the end of the month, these shares had moved to –13%, +4% and +5%, respectively.

Two recent medical technology IPOs saw their company's stock rise in November. Given Imaging's (Yoqneam, Israel) stock increased from US$12 to US$14.56 at the end of November, while Therasense (Alameda, CA, USA) went up from US$19 to US$23.20.

Meanwhile, the new biodefense industry did not perform as well with the stocks falling to readdress gains made in the previous month. After increasing 178% in October, Cepheid (Sunnyvale, California) stocks dropped 36% to US$4.10. Similarly, shares in Nanogen (San Diego, CA, USA) fell 30% to US$6.32. Despite the turbulence, this new industry was not a 'flash in the pan' said Burrill. 'A number of companies are swiftly adapting their platform and human therapeutics technologies to address the urgent and growing needs of our battle against terrorism.'

News in Brief was written by *Joanne Clough, Joanna Milburn, Joanna Owens and Ben Ramster*

People

Appointments

Completion of appointments program at Elan

Elan Corporation (Dublin, Ireland) has announced the appointment of Alison Pilgrim to the position of Senior Vice-President, Clinical Development, Biopharmaceuticals and Michael George as President, North America. Pilgrim was most recently Head of Clinical Development for DuPont Pharmaceuticals. She has also previously held senior clinical positions at Glaxo and Sanofi, where she was responsible for the development of the blockbuster products Sumatriptan (for Glaxo) and Plavix (for Sanofi).

Meanwhile, George comes from being CEO of UroCor for two years, during which time the company's revenue increased by 50% and its market capitalization quadrupled, after which he presided over the company's acquisition of Dianon Systems. Previously, George held several positions at DuPont Pharmaceuticals including Director of Worldwide Marketing, President of European Operations, and President, North America, and has also held several senior marketing and management positions with Sandoz Pharmaceuticals and Bristol-Myers Squibb.

Donal J. Geaney, Chairman and CEO of Elan commented that: 'The addition of Alison Pilgrim and Mike George marks the completion of an important ongoing process... In the past year, other key external recruitments of senior executives included Daniel Welch, President, Worldwide Pharmaceuticals; Lars Ekman, President, Biopharmaceuticals R&D; Timothy Wright, President, Europe/ROW; and David Silver, Senior Vice-President, Global Pharma Strategy.'

New VP Business Development at Transgene

Michel Hubert has been appointed as Vice-President, Business Development at Transgene (Strasbourg, France) and moves from Laboratoires Fournier (Paris, France) where he was Executive Director, Business Development & Licensing. In this role, he created and managed the Business Development and Licensing Department, negotiating licensing agreements, co-marketing agreements for pharmaceutical products, joint venture agreements, and R&D agreements, and completed acquisitions of products and companies.

He was previously Business Development Manager for Rhone-Poulenc Sante (now Aventis). Giles Belanger, CEO of Transgene, commented that: 'Transgene will benefit greatly from Michel Hubert's experience and knowledge as we accelerate our development efforts in an environment characterized by more complex relationships between pharmaceutical companies and biotechnology companies