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News in brief

Targets and mechanisms

Pharmacogenomics – proof of the pudding at last?

Virco (Baltimore, MD, USA) is developing a novel test to predict whether patients are likely to respond to the most common drug for the treatment of cancer[1]. This novel test can show whether the *MGMT* gene has a methyl group attached to it. It was shown that brain tumour patients whose *MGMT* gene was methylated were 16-times more likely to respond to alkylating agents, such as Carmustine (BCNU), which are the most common form of chemotherapy. Further, these patients were 10-times less likely to die during three years of follow-up than those patients whose *MGMT* gene was not methylated.

Diagnostic tests based on methylation are being developed for doctors to target alkylating drugs to patients with methylated *MGMT* genes. Alkylating drugs attach to the genes in cancer cells resulting ultimately in cancer cell death. However, if no methyl group is attached, the *MGMT* gene can switch on a repair process, thus rendering this drug ineffective.

This study involved 47 patients; of the 40% who tested positive for *MGMT* gene methylation, 64% demonstrated either complete or partial response to alkylating drugs compared with 4% of the group who tested negative. The average time to tumour progression was 21.4 months in the positive test result group and eight months for the group who tested negative.

The findings of this study could have additional implications in other forms of cancer such as lymphomas, lung, head and neck, and colorectal cancers.

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

Polycystic ovary syndrome linked to early-onset atherosclerosis

Women with polycystic ovary syndrome (PCOS) have an increased risk of developing premature atherosclerosis reports a recent study[2]. PCOS is typified by menstrual irregularities, infertility, insulin resistance, obesity and other cardiovascular risk factors, such as a low ratio of high density lipoprotein (HDL) to low density lipoprotein (LDL) and high systolic blood pressure. Researchers at the University of Pittsburgh (Pittsburgh, PA, USA) evaluated the level of subclinical atherosclerosis in women with PCOS compared with age-matched controls, by measuring carotid intima-media wall thickness (IMT) and plaque formation. A significant difference in carotid plaque distribution and IMT was observed in women with PCOS of all age groups, which was independent of body-mass index (BMI) in women over 45. The study suggests that increased levels of circulating lipids and insulin in women with PCOS is a risk factor for early-onset atherosclerosis, and that symptoms associated with PCOS should be regarded as an early indicator of cardiovascular disease.

2 Talbott, E.O. *et al*. (2000) Evidence for association between polycystic ovary syndrome and premature carotid atherosclerosis in middle-aged women. *Arterioscler. Thromb. Vasc. Biol.* 20, 2414–2421

Fighting infection

The interaction mechanism of two proteins that are involved in regulation of the immune system have been identified by researchers at ZymoGenetics[3] (Seattle, WA, USA). These interleukin 21 (IL-21) and IL-21 receptor proteins (IL-21R), which are naturally occurring cytokine ligand–receptor pairs, are implicated in the growth and activation of red blood cells, white blood cells, antibody-producing cells and other mechanisms crucial for a strong immune response.

This identification of this mechanism involved an integrated genomics approach, incorporating molecular genetics, bioinformatics, protein engineering and functional cloning, to rapidly identify IL-21 and IL-21R. Immunologists and stem-cell biologists at ZymoGenetics then determined the biological roles of thse proteins in immune system regulation. IL-21 was shown to: (1) support production of natural killer immune cells from bone marrow; (2) enhance ability of mature natural killer cells to destroy 'non-self' target cells; and (3) promote expansion of select B and T cell populations.

Herbal medicines

Marigolds could help prevent blindness in the elderly

Supplements of natural lutein esters that are derived from marigolds could reduce the risk of age-related macular pigment degeneration (AMD), which is incurable and the major cause of blindness in the elderly. Researchers from the University Medical Centre Utrecht (Utrecht, The Netherlands) found that oral supplements of lutein esters increased macular pigment optical density in eight male volunteers[1].

Macular pigment is thought to protect the macular region of the retina, which is the small central area responsible for fine, detailed vision, by reducing the damage caused by blue light. Lutein esters are also thought to scavenge free radicals that contribute to aging. Furthermore, in this study, a more accurate method of measuring macular pigment levels has been achieved by using objective measurement techniques. Previously, macular density has been estimated by using heterochromatic flicker photometry, which is dependent on the skill of the subject to produce consistent results. However, two alternative methods have been described that are more accurate, using either a scanning laser ophthalmoscope or a fundus reflectometer to obtain more precise measurements of macular density[4]. This study provides additional evidence that the use of lutein supplements in individuals with low levels of macular pigment could protect against age-related blindness.

4 Berendschot, T.T. *et al*. (2000) Influence of lutein supplementation on macular pigment, assessed with two objective techniques. *Invest. Ophthalmol. Vis. Sci.* 41, 3322–3326

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'Because IL-21 promotes the proliferation and expansion of cells needed to defend against invaders, the molecules may have broad utility in therapeutic applications such as protecting against viral infection, enhancing vaccines, boosting the efficacy of chemotherapy or treating autoimmune disease. Our continued biological studies of IL-21 will clarify which activities will have primary therapeutic value,' said Frank Collins, Senior Vice-President of Research at ZymoGenetics.

3 Parrish-Novak, J. (2000) Interleukin 21 and its receptor are involved in NK cell expansion and regulation of lymphocyte function. *Nature* 408, 57–63

Clinical trials

Total spending on clinical trials in 2000 to reach $4.5 billion

Pharmaceutical, biotechnology and medical device companies will contribute more than 80% of the $4.5 billion that has been spent on clinical trials in 2000, says a recent report by CenterWatch (Boston, MA, USA). The remainder of the money will come from US government bodies such as the National Institutes of Health. The market is expected to be growing at a rate of 18% per year.

UK website lists all cancer clinical trials

The Cancer Research Campaign (CRC; London, UK) is to list every cancer-related clinical trial occurring the UK, it was announced at a recent press briefing. The list, available at http://www.cancerhelp.org.uk, will enable patients to request to be referred by their doctor onto commercial or non-commercial trials. 'A similar list is already available in the US and has enabled patients to get the very best treatment,' says Gordon McVie, Director General of the CRC. The benefit of this service will be two-fold. It will enable patients to gain access to the very latest drugs and best available quality care.

Thalidomide as an anti-cancer drug?

The use of Thalidomid® (Celgene, Warren, NJ, USA) as an anti-cancer agent warrants further investigation according to the results of ongoing clinical trials reported recently. At the Chemotherapy Foundation Symposium XVIII (8–11 November 2000, New York, NY, USA), researchers from the Arkansas Cancer Research Center (ACRC, Little Rock, AR, USA), Cedars-Sinai Medical Center (Los Angeles, CA, USA), M.D. Anderson Cancer Center (Houston, TX, USA) and the National Cancer Institute (NCI, Bethesda, MD, USA) presented clinical trial data from studies assessing the use of Thalidomid in various cancers and immune disorders. The published abstracts of the meeting report suggest clinical trial results are consistent with previous studies of Thalidomid in conditions such as multiple myeloma, colon cancer and prostate cancer.

Bart Barlogie (Director, ACRC) reported that, as a single agent, Thalidomid substantially reduced paraproteins and improved bone marrow histology in patients with multiple myeloma, consistent with previous clinical results.

James Berenson (Cedars-Sinai Medical Center) presented results from studies of Thalidomid in treatment of primary amyloidosis, which is a non-cancerous disorder that results in the deposition of insoluble protein fibres in tissues and organs and impairs their function. The results of this study showed that in five of six patients, Thalidomid induced a marked improvement in symptoms such as impaired speech, gastrointestinal problems and renal impairment.

Rangaswamy Govindarajan (University of Arkansas for Medical Sciences, Little Rock, AR, USA) evaluated the use of Thalidomid in combination with irinotecan (Camptosar®) for the treatment of metastatic colorectal cancer. Eleven of seventeen patients had a reduction in the severe gastrointestinal side effects associated with irinotecan, and a Phase II trial is now underway. The results of a trial to investigate Thalidomid as a treatment for acute myeloid leukaemia were discussed by Jorge Cortes (M.D. Anderson Cancer Center). Administration of Thalidomid in combination with ara-C and liposomal daunorubicin caused a transient improvement (reduction of blasts) in three

Markets

Europe lags behind US when embracing Web Technology

The US is leading Europe in embracing Web technologies, with over twice as many (68%) of its pharmaceutical R&D executives believing that they will fundamentally change the R&D process. The results, from Andersen Consulting Research (London, UK), revealed that only 32% of European respondents felt the same way.

A similar difference emerged when participants were asked how they file new drug approval applications with government regulatory agencies, with 45% of US respondents saying they would use the Internet compared with 5% of Europeans. Similarly, 71% of US interviewees said they use the Internet to communicate with partners or suppliers outside of the company compared with a mere 16% of Europeans. The situation in Europe is likened to that in the US in early 1999, with Europe expected to catch up rapidly within the next 12 months.

Drug delivery industry heading for consolidation

The drug delivery industry is currently highly fragmented, full of too many small unprofitable companies, and is heading for a phase of consolidation, concludes a recent report by CMR International (Epsom, Surrey, UK) entitled *The Application of Drug Delivery Systems: Current Practices and Future Strategies*. This will result in market domination by a few multi-technology drug delivery companies.

Despite 13% of the current $337 billion global pharmaceutical market being accounted for by sales of products incorporating a drug delivery system, actual utilization of novel delivery technologies by the pharmaceutical industry lags behind for several possible reasons. There is concern that using novel drug delivery technologies could delay products because of technical or regulatory reasons and oral delivery remains a preferred option despite novel alternatives. Furthermore, only 40% of drug delivery projects currently underway within large pharmaceutical companies are focused on novel compounds and this is compounded by a decline in new collaborations between pharmaceutical and drug delivery companies.

of nine patients and a complete response in one patient.

William Figg (NCI) presented data on the effects of Thalidomid in the treatment of androgen-independent prostate cancer, and reported that 58% of patients on low-dose treatment and 68% of patients on high-dose treatment had a reduction in prostate-specific antigen (PSA). Based on these data, he suggested that Thalomid can affect PSA levels and might influence tumour metabolism and metabolic volume. Phase II trials are underway in his group to assess the effects of Thalidomid in combination chemotherapy for prostate cancer.

Several side effects of Thalidomid treatment were noted by the researchers including constipation, somnolence, numbness, tingling, tremor, rash, bradycardia, fatigue and peripheral neuropathy. On the basis of the presented data, Thalidomid is in ongoing trials for the treatment of several types of cancer, immune and metabolic diseases.

Mergers and acquisitions

Merged company focuses on cell transplantation and heart disease therapies

Cardiogene (Erkrath, Germany) and Intracardia (Cincinnati, OH, USA) have recently announced that they have merged to form a transatlantic biopharmaceutical company, renamed Cardion. The new company will retain corporate headquarters in Erkrath but establish US operations in Boston (MA, USA).

The focus of the new company will be to develop new drugs for heart disease and cell transplantation. This will be done using the gene therapy platform created by Cardiogene, together with expertise in stem cell differentiation and graft enhancement from Intracardia. One of the new company's main aims will be to move some new products through clinical development. These will include NOStentin, a nonviral gene therapy for the treatment of restenosis and Cardioprotectin for heart tissue regeneration using stem cells for use in myocardial infarction. NOStentin is hoped to enter clinical trials in early 2001 for restenosis and re-narrowing of arteries previously dilated using angioplasty.

Acquisition of small-molecule protein kinase inhibitor company

Amgen (Thousand Oaks, CA, USA) has recently acquired Kinetix Pharmaceuticals (Medford, MA, USA) to enhance Amgen's small-molecular drug discovery programme. Kinetix was a small company (~40 employees) that focussed on the discovery of small-molecule protein kinase inhibitors. The acquisition is hoped to enhance Amgen's lead identification and optimization programmes and strengthen their preclinical and clinical development programmes, as well as combining strong oncology and inflammation expertise from both companies. 'Kinetix is one of the real innovations in the emerging field of protein kinase inhibition,' said Kevin Sharer, CEO and President of Amgen.

Nick Lydon, CEO and President at Kinetix, David Armistead, Vice-President of R&D and CSO, and other members of Kinetix have joined the enhanced company, where Lydon will become Vice-President of small-molecule drug discovery and Armistead will become Vice-President of Chemistry and oversee research at the Boston site. Amgen paid approximately $170 million in stock for all the outstanding shares of Kinetix and the transaction invoked a one-off charge of ≈$30 million to write-off acquired in-process R&D.

Enhancement of oncology franchise

Neurovir Therapeutics (San Diego, CA, USA) has been acquired by MediGene (Martinsried, Germany) to strengthen its oncology franchise. NeuroVir was a biopharmaceutical company that developed herpes simplex virus vectors for cancer therapeutics, and currently has two products, G207 and NV1020, in clinical trials. G207 is a potential treatment for malignant brain tumours such as glioblastoma and brain metastases and has successfully completed Phase I/II trials with Phase II trials planned for 2001. NV1020 is a locoregional therapy for colorectal cancer that has metastasized to the liver and is currently in Phase I/II studies at the Memorial Sloan-Kettering Medical Center (New York, NY, USA).

'With its potential blockbuster product candidate Etomoxir, MediGene's cardiology already is a strong point of the company,' says Peter Heinrich, CEO of MediGene. 'The acquisition of NeuroVir now moves MediGene into the league of major international biotechnology players in oncology and establishes a foothold for Medigene in the US.'

The transaction will be stock-for-stock, with the issuance of 996,631–1,009,999 new MediGene shares to NeuroVir's shareholders in exchange for ~91% of shares that NediGene does not already own on a fully diluted basis. MediGene previously purchased ~9% of NeuroVir before its IPO in June 2000.

Acquisition of protein drug target expertise and knowledge

PanVera Corporation (Madison, WI, USA) has been acquired by Aurora Biosciences (San Diego, CA, USA) to extend Aurora's expertise in protein drug target solutions, as well as to establish a strong sales and marketing infrastructure to commercialize bioassay technologies. The protein expression and purification expertise of PanVera is also hoped to provide protein drug targets for Aurora's target-based drug discovery initiative called the Big Biology™ program.

The transaction will be stock-for-stock using the pooling-of-interests method. PanVera shareholders will receive ~1.34 shares of Aurora common stock for every share of PanVera common stock. Aurora will issue 1,900,000 shares of Aurora common stock to the security holders of PanVera. The transaction has been unanimously approved by the Board of Directors of both companies and is subject to regulatory approvals and PanVera shareholder approvals, and is hoped to close in the first quarter of 2001.

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