News in brief

Continuing the TRAIL despite potential hepatotoxicity

A recent report by the University of Pittsburgh (Pittsburgh, PA, USA) stated that TRAIL (TNF-related apoptosis-inducing ligand or Apo2L) can cause extensive liver damage in humans even though it appears to be harmless to liver cells from mice and nonhuman primates[1]. This news came just as TRAIL was being proposed to enter clinical trials. However, the two companies conducting the trials, Immunex (San Francisco, CA, USA) and Genentech (Seattle, WA, USA), have reiterated their intention to continue with the preclinical study of TRAIL/Apo2L.

This research from the University of Pittsburgh showed that TRAIL (at concentrations used in previous preclinical studies) induced extensive and rapid apoptosis in cultured human hepatocytes from 20 individuals, causing the characteristic cytoplasmic shrinkage, activation of caspases and DNA fragmentation in >60% of the cells within 10 hours of exposure. This work has not only caused concern over the safety of continuing with the proposed clinical trials, but also highlights the importance of careful extrapolation from preclinical observations using other animal species to humans.

However, Genentech and Immunex say that previous experiments they have conducted have established that different forms of the TRAIL/Apo2L molecule can demonstrate different biological properties. The two companies are therefore collaborating with Stephen Strom (University of Pittsburgh and senior author of the *Nat. Med.* paper) to compare the TRAIL/Apo2L material being used by the two different groups.

1 Jo, M. *et al.* (2000) Apoptosis induced in normal human hepatocytes by tumor necrosis factor-related apoptosis-inducing ligand. *Nat. Med.* 6, 564–567

Drug marketing issues

A recent report by IMS Health, the global healthcare information company, has revealed that growth between April 1999 and March 2000 in 12 key markets has dipped below double-digits to 9% (a figure last recorded in the 12 months previous to November 1999).

General growth, however, continues to be driven by North American sales, which remain at a steady 15%. In the USA, alimentary/metabolism and CNS drugs maintain the fastest growth among the top five drug groups, increasing by 16%. Musculoskeletal drugs demonstrated the highest increase at 48%, boosted by a high growth in anti-rheumatics, which increased by 68%.

European markets

The five leading European markets reported a 7% increase with a pooled value of $53.4 billion. Across Europe, the most rapid growing therapeutic sales areas were cardiovascular products in Italy (13%) and the UK (17%), and CNS drugs in France (11%) and Spain (15%).

A brighter outlook for Japan

Japan recorded a continued steady growth of 6% with sales accumulating to $48.9 billion (in contrast to the −2% decline 12 months previous). Growth here was propelled by a 9% increase for cardiovascular drugs, aided by a 1% incremental increase in growth for the hypolipidaemic/antiatheroma products at 13% and renin–angiotensin agents at 25%. In more global terms, growth in cardiovascular, alimentary/metabolism and CNS drugs remained stable, accumulating $41.4 billion, $32.8 billion and $32.1 billion, respectively.

Nettles take the sting out of arthritis

New research suggests that the common stinging nettle has arthritis pain-relieving properties[2]. The trial, carried out at the University of Plymouth (Plymouth, UK), found that rubbing nettle leaves against the skin of patients with arthritic thumbs significantly reduced the pain associated with the condition as long as the treatment persisted.

Twenty-seven patients with osteoarthritis of the thumb were involved in the trial. Half of the group were told to rub the leaves of stinging nettles (*Urtica dioica*) against their thumbs for a week. The remaining half were given a placebo of the white deadnettle (*Lamium album*). Each patient was told to keep a 'pain diary', and five weeks after treatment had stopped, the groups were reversed and the trial repeated.

Osteoarthritic pain was reduced during most of the treatment. Pain relief was greatest when a sting with weals was produced, but 85% of patients thought that this was an acceptable side effect. In conclusion, most patients said that they preferred this course of therapy to their normal treatment, and 63% said that they would try it again after the study had ended.

These results support anecdotal evidence accumulated since Roman times that nettles can ease pain.

Stinging nettles contain serotonin and histamine and one suggested mechanism of action is that these neurotransmitters affect pain perception or transmission. Alternatively, the nettle sting could function with an acupuncture-like effect or possibly as a counter-irritant (as seen with the capsicum-derivative, capsaicin).

2 Randall, C. *et al.* (2000) The randomised controlled trial of nettle sting for treatment of base of thumb pain. *J. R. Soc. Med.* 93, 305–309

Mouse models and microarrays to understand Huntington's disease

A collaboration between the Fred Hutchinson Cancer Research Center

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(FHCRC; Seattle, WA, USA) and Massachusetts General Hospital (MGH; Boston, MA, USA) has led to the identification of changes that occur in nerve cells in the early stages of Huntington's disease. Using the R6/2 and N171-82Q transgenic Huntington's disease (HD) mouse models, researchers identified several signalling molecules[3] that could potentially be used as drug targets for the development of future therapies for this devastating, inherited neurological disorder.

Researchers surveyed the patterns of active and non-active genes at early and late symptomatic stages points (6 and 12 weeks of age) in the mouse models using microarrays. Such a process would previously have taken a period of years. The group found a small subset of genes to be affected by the disease, only 2% of the total. However, many of these affected genes are involved in signalling pathways known to be crucial to striatal neuron function.

Olsen commented, 'We confirmed that the mice had genetic changes similar to humans with Huntington's disease and we also identified changes not previously associated with the disease. Understanding how nerve cells are damaged before symptoms occur is the first step toward developing therapies to forestall the onset of Huntington's disease.'

For a more in-depth report, see the next issue of *Drug Discovery Today* (September 2000 issue).

3 Olson, J.M. *et al.* (2000) Decreased expression of striatal signaling genes in a mouse model of Huntington's disease. *Hum. Mol. Genet.* 9, 1259–1271

Positive Phase I results for non-small cell lung cancer

Final results from a Phase I clinical trial on the novel anticancer compound ZD1839 (IRESSA™, AstraZeneca, New Orleans, LA, USA) have showed encouraging antitumour activity and disease stabilization, especially in non-small cell lung cancer [Ferry, D. *et al.* Intermittent oral ZD1839 (Iressa), a novel epidermal growth factor receptor tyrosine kinase inhibitor (EDFR-TK), shows evidence of good tolerability and activity: Final results from a Phase I study. *American Society of Clinical Oncology Annual Meeting*, 23 May 2000, New Orleans, LA, USA, Abstract]. This compound is thought to inhibit TK, blocking the signal sent from the complexed EGFR via tyrosine kinase to promote cell growth and division.

The study examined the effect of ZD1839 in 64 patients with solid malignant tumours known to express or over-express EDFRs, who had failed at least one prior chemotherapy regimen. After treatment, 15 of the patients with a range of tumour types had stable disease or a response at ⩾4 months, while antitumour activity was most evident in 16 non-small cell lung cancer patients. Side effects were limited, with the most common being mild to moderate diarrhoea and acne-like skin rash. Further clinical trials are now being planned.

Tumour necrosis factor inhibitors lead fight against rheumatoid arthritis

The tumour necrosis factor (TNF) inhibitors, etanercept and infliximab, which have been shown to be much more effective in treating rheumatoid arthritis (RA) than the current gold standard, methotrexate, are transforming the RA market, as reported by a recent Decision Resources (Waltham, MA, USA) study. These two new genetically engineered recombinant proteins function by inhibiting TNFα activity, a proinflammatory cytokine central to inflammation and joint destruction in RA. While prescription of both agents has previously been restricted because of their expense and safety concerns, the US Food and Drug Administration has recently relaxed the regulations governing prescription of etanercept to include early active RA.

The report suggests that TNFα inhibitors will remain the most prominent new drug class for at least the next five years. More specific agents, such as the novel cytokine inhibitors (e.g. interleukin-1 receptor antagonists), should reach the market by 2004. These new drugs target the joints with a higher specificity and might be used in conjunction with other types of inhibitors (such as TNF inhibitors) to inhibit multiple inflammatory pathways. Selective and second-generation, cyclooxygenase-2 inhibitors will further contribute to growth in the RA market.

Enlisting endothelial cells to fight glioblastoma

Phase I/II trials of a novel treatment for high-grade glioblastoma, the most aggressive form of human brain cancer, have recently been initiated by Neurotech (Evry, France) and involves the treatment of 16 patients.

The therapeutic strategy involves developing an endothelial cell line that could be genetically engineered to express interleukin 2 (IL-2). Endothelial cells migrate to sites where active blood vessel growth is occurring and are attracted to a glioblastoma because of the excessive angiogenic activity of the tumour. Preclinical studies *in vitro* and in a rat model of glioblastoma showed promising results. The NTC-121 cells did indeed migrate towards tumour cells and expressed high levels of IL-2. This stimulated the immune system by overwhelming the immunosuppressive factors secreted by the tumour and by enlisting immune cells to the tumour site. In the rat model used, human transformed cells are injected into rats brains to induce development of aggressive glioblastomas that are usually fatal within 19 days. Treatment with NTC-121 cells at the time of the tumour cell injection doubled the average survival time. Most significantly, ≈25% of the rats treated survived long term.

The human trials are still in the preliminary stages and have been designed primarily to assess safety. The therapeutic strategy and the trials show potential but the concept of endothelial cell therapy with glioblastoma has yet to be proved.

For additional reading see Ref. 4.

4 Quinonero, J. *et al.* (1997) Gene transfer to the central nervous system by transplantation of cerebral endothelial cells. *Gene Ther.* 4, 111–119

Value of global E-commerce healthcare market to rise

The Internet market for healthcare products and services is expected to be worth $370 billion by 2004 according to research published recently in *e-Healthcare Market Reporter* (Manasquan, NJ, USA). Most of this revenue ($15 billion) will be created by sales of prescription drugs, with smaller contributions from nutraceutical sales ($3.3 billion), over-the-counter drugs ($1.9 billion) and health and beauty aids ($900 million), Forrester Research (Cambridge, MA, USA) predicts. The research also confirmed news in the July issue of *Drug Discovery Today*[5] that Europe will be the focus of intense B2B (business-to-business) e-commerce expansion in the next few years. It is thought that European companies will use online services in a bid to control their costs, improve information flow and gain transaction efficiency.

5 Hughes, D. (2000) E-commerce turns to PriceWaterhouseCoopers. *Drug Discovery Today* 5, 268–269

Key breast cancer target patented

The US Patent and Trademark Office has granted a patent to Prolifix (Abingdon, UK), which covers a novel target for breast cancer therapies. The target was discovered by research at the Netherlands Cancer Institute (Amsterdam, The Netherlands), which revealed that the cell cycle control protein cyclin D1 interacts directly with oestrogen receptors and stimulates the proliferation of breast cancer tumour cells. HTS was used to identify molecules that disrupt the cyclin D1–oestrogen receptor interaction and hence preclude proliferation. The properties of these compounds are now being optimized to identify a drug development candidate.

Amyloid inhibitors favoured for treating Alzheimer's disease

Amyloid inhibitors are the favoured therapeutic approach for treating Alzheimer's disease (AD), announced a recent Decision Resources (Waltham, MA, USA) report. The inhibitors, in the form of α-, β- and γ-secretase inhibitors, are anticipated to overtake other new treatments, such as vaccination and gene therapy, in the race to the marketplace by going on sale in the next few years.

The report found that changes in the treatment of AD were likely to be evolutionary. Increases in the use of acetylcholinesterase inhibitors (AChEIs) are expected, stemming from the new alternative to donepezil, galantamine, and a use of AChEIs as a basis for multidrug treatment of the disease. New agents that reach the market are expected to demonstrate a high degree of efficacy to qualify for reimbursement, a prerequisite for widespread prescribing.

Increased gonadotrophin levels in Alzheimer's disease?

Preliminary results of a study into the effects of Lupron (a currently available prostate cancer drug; TAP Pharmaceuticals, Deerfield, IL, USA) on Alzheimer's disease (AD) have supported the recent suggestion that elevated serum gonadotrophin levels are involved in AD (Ref. 6). This suggestion was supported by the fact that significantly higher levels of follicle-stimulating hormone and luteinizing hormone were found in patients with dementia. However, oestrogen replacement appears to have a protective effect against AD, possibly because it lowers circulating gonadotrophin levels[6]. This latest study, carried out by the Mayo Clinic (San Diego, CA, USA), found that gonadotrophin concentrations in the blood were significantly higher in a group of women with AD compared with a similar group of control women. Another study is now planned to see if these results can be reproduced and to further examine the effect of Lupron on AD (for more information, see http://alzheimerstrial.com).

6 Bowen, R.L. *et al.* (2000) An association of elevated serum gonadotrophin concentrations and Alzheimer's disease? *J. Neuroendocrinol.* 12, 351–354

Cranberries reduce human breast cancer cell growth in mice

Recent research showed that cranberry juice and cranberry products significantly reduced the number of breast cancer tumors that occurred compared with a control group of mice, as reported by researchers at the University of Western Ontario (Lakeville-Middleboro, MA, USA) at the *Experimental Biology* meeting in San Diego (CA, USA). The research, funded by Ocean Spray Cranberries (Lakeville-Middleboro, MA, USA), also showed tumor development to be delayed and a marked reduction in metastasis to the lungs and lymph nodes in cranberry-fed subjects.

Cranberries have also been making the news with other health-promoting claims. While it is common knowledge that cranberries can alleviate urinary problems caused by *Escherichia coli* infection, there have been subsequent claims recently that the berry is effective against a wider range of bacteria, including *Staphylococcus aureus* and *Salmonella enteritidis*[7]. Other research

at the University of Wisconsin-LaCrosse (La Crosse, WI, USA) suggests cranberries might be beneficial in preventing cardiovascular disease, possibly owing to an inhibitory effect on LDL cholesterol oxidation.

7 Lee, Y-L. *et al.* (2000) Does cranberry juice have antibacterial activity? *J. Am. Med. Assoc.* 283, 1691

Functional consequences of SNP changes in GPCRs

Systematic evaluation of the functional consequences of single nucleotide polymorphisms (SNPs) in G protein-coupled receptors (GPCRs) associated with neuropsychiatric disorders has revealed an unexpectedly high frequency of genetic variation (estimated to be one difference in every 500 base pairs). This study by Acadia PharmacoGenomics (San Diego, CA, USA) suggests that in the human population, changes in the encoded proteins of drug targets are likely to be very common. By contrast, many of the results they have obtained from pharmacological evaluation of the genetic variation in most drug target genes has shown that many of the SNPs that result in an amino acid change do not have a functional effect. These data are being used to create a database for prediction of variability in drug response.

Mark R. Brann (President and CSO of Acadia) said, 'Our results have important implications for the allocation and focus of resources for pharmacogenomic studies.' He further commented that, 'The expense of clinical linkage and association studies makes selection and prioritization of SNPs essential, such that the functionally relevant SNPs are given the highest priority. Most of the SNPs in GPCRs that we have studied do nothing to biological function and drug response.'

p10 gene patented: good news for cancer therapeutic and diagnostic strategies?

The p10 gene, a member of a small family of key tumour suppressor genes that are mutated in many cancers such as melanoma, leukaemia, lymphoma and testicular cancer, has been patented. Myriad Genetics (Salt Lake City, UT, USA) has been awarded the patent by the US Patent and Trademark office. The identification of mutations in the gene could provide the basis of molecular diagnostic tests for predisposition to various cancers. The gene also could become the basis for the development of novel therapeutics to treat many types of cancer. Therapeutic approaches covered under the patent include gene therapy, protein replacement, protein mimetics and small-molecule drugs.

Rebecca N. Lawrence, Ben Ramster and Deborah Tranter