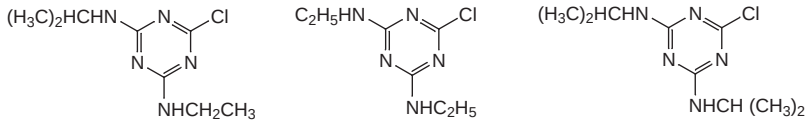

Figure 1. *Molecular structures of atrazine, simazine and propazine, chloro-s-triazine herbicides, the former currently in development as an antimalarial drug.*

of antimalarial drugs and the use of combination chemotherapy will also slow the rate of resistance development,' says Hacker.

Mechanism

The team is currently working hard to explain the mechanism of action of atrazine and related compounds against the malaria parasite. They also hope that their studies will shed light on the role of the apicoplast itself.

Antimalarial drugs with triazine nuclei, such as proguanine, are already in clinical use and they act by inhibiting parasitic dihydrofolate reductase (DHFR), thus preventing the formation of tetrahydrofolates and limiting DNA synthesis[3]. However, atrazine does not affect either mammalian or microbial DHFR *in vitro*, nor does it affect the activity of yeast transfected with malarial DHFR, which requires functional malarial DHFR to grow. 'While pyrimethamine and cycloguanil, both malarial antifolates, inhibit yeast growth in this assay, neither the triazines nor chloroquine affect growth, demonstrating that atrazine is not another triazine antifolate,' explains Hacker.

In vitro, Hacker's group has shown that atrazine also acts in synergy with chloroquine and, *in vivo*, it appears to be as effective as chloroquine against *Plasmodium berghei*. Hacker says, 'Our data clearly demonstrate the efficacy of atrazine and suggest a novel mechanism of action for the drug. The latter is extremely important as it indicates that atrazine will be useful in parasites resistant to currently used medications.'

Safety

Commenting on the safety of atrazine, Hackers says: 'We are testing other triazines to see if we can find a more effective molecule and, perhaps, a less toxic one. However, it is unlikely that we will find a safer drug than atrazine with such significant antimalarial activity.'

Future research

Hacker and his team now hope to work with other pharmaceutical companies to develop atrazine as an antimalarial drug. If they can find a suitable collaborator, they hope to begin clinical trials within two years. In the meantime, they are continuing their basic research into the mechanism of action of the triazines. 'At present, we are concentrating all our efforts on the malaria parasite, but we feel that there may well be a much larger spectrum of antiparasitic activity, given that there are a number of parasites in the apicomplexan family. This family includes several parasites of human and veterinary importance, such as *Toxoplasmodia*, *Cryptosporidia*, *Emeria* and *Babesia*,' says Hacker. 'We hope to form collaborations with other groups working with such parasites to assess the spectrum of activity of the triazines in treating apicomplexan diseases,' he concludes.

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3 Yeo, A.E. *et al.* (1997) Effects of folic acid and folinic acid in the activities of cycloguanil and WR 99210 against *Plasmodium falciparum* in erythrocyte culture. *Am. Trop. Med. Parasitol.* 91, 17–23

Sharon Dorrell

News in brief

Potential for improved pig-to-human xenotransplantation success rate

Research funded by ML Laboratories PLC (London, UK) has shown that the rejection of foreign cells by a host's immune system can be prevented by donor-specific costimulatory blockade[1]. Robert Lechler and colleagues investigated mice transplanted with pig pancreatic xenografts, and reported that these mice showed a significant increase in survival time after immunization to induce an antibody blocking response. This research might consequently eliminate the current need for long-term immunosuppression following transplantation.

Robert Lechler, Head of the Immunology team at Hammersmith Hospital (London, UK), said 'Our first models using cells from the pancreas have been successful and we are now taking these findings on to further,

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more complex models. Eventually, we hope that using foreign organs in humans may start to solve the huge shortage of organ donors across the world.'

1 Rogers, N.J. *et al.* (2000) Costimulatory blockade by the induction of an endogenous xenospecific antibody response. *Nat. Immun.* 1, 163–168

Plans for rhIGF-1 in osteoarthritis seize up after Phase IIa trials

Further clinical development of rhIGF-I in osteoarthritis has been cancelled following poor results from two Phase IIa proof-of-concept trials, announced Chiron Corporation (Emeryville, CA, USA) recently. The two 13-week trials evaluated the effect of rhIGF-I in patients with mild-to-moderate osteoarthritis undergoing knee arthroscopy, and the effect of intra-articular rhIGF-I in patients with severe osteoarthritis of the knee who planned to undergo knee replacement surgery. Both studies compared the histology of cartilage biopsies and both studies produced results that were not deemed worthy of further clinical development.

Source of neurons from bone marrow stem cells for brain repair

Research carried out by Juan Sanchez-Ramos and co-researchers at the University of South Florida (Tampa, FL, USA) has shown that mouse and human bone marrow stem cells (stromal cells) can be reprogrammed *in vitro* to develop into immature nerve cells[2]. When these stromal cells are cultured *in vitro* with retinoic acid and growth factor, their bone marrow features are lost and they start to look like immature neurons. When these cells were joined with fetal rat brain tissue in a petri dish, the number of neuron-like cells doubled. The researchers have started to clone and transplant the stem cells into an animal model for stroke to investigate whether or not it is possible to replace damaged brain tissue.

'More studies are needed to determine whether the bone marrow-derived stem cells triggered to resemble early nerve cells can actually develop into functioning neurons,' said Sanchez-Ramos. These cells might ultimately provide a supply of neurons for the treatment of neurodegenerative disorders.

2 Sanchez-Ramos, J. *et al.* (2000) Adult bone marrow stromal cells differentiate into neural cells *in vitro*. *Exp. Neurol.* 164, 247–256

Bright future predicted for angiogenesis inhibitors

The development of the anti-cancer drugs, angiogenesis inhibitors, is now reaching clinical trials stage in many cancer care facilities. The drugs, which work by affecting the supply of blood to newly forming cancer cells, are currently one of the most dynamic areas in cancer research, stated a recent Decision Resources (Waltham, MA, USA) report entitled *Angiogensis Inhibition in Cancer Therapy*.

Conservative estimates predict that their market could be worth $503 million by 2004 (based on US, European and Japanese markets). However, the study says that if there is rapid introduction of matrix metalloproteinase inhibitors and signal transduction inhibitors, the market could increase to $2.7 billion by 2004, with possible total market sales for angiogenesis inhibitors surpassing $12 billion by 2009.

Of these drugs, the matrix metalloproteinases inhibitors (marimastat and prinomastat) and receptor tyrosine kinase inhibitors (e.g. SU5416) are currently farthest down the development pathway. Both offer the advantage of oral bioavailability. There are also several other classes of angiogenesis inhibitor currently undergoing clinical trials, such as those that reduce growth factor expression or interaction with its receptor (IM862, Angiozyme, rhuMAb-VEGF), interfere with integrin signalling (Vitaxin, cilengitide), or work by as yet unknown mechanisms (e.g. combretastatin, squalamine, thalidomide).

Benefits of Copaxone for MS patients continue for six years

A six-year investigation has demonstrated that the prolonged use of Copaxone (glatiramer acetate) by patients diagnosed with the relapsing–remitting form of multiple sclerosis (MS) significantly reduces their relapse rate and delays disability[3]. This investigation is the longest, to date, of an approved MS drug, and is programmed to carry on until mid-2002; the study will have been carried out for 10 years.

A total of 101 participants were administered daily with injections of Copaxone during the past six years; 77 experienced three or less relapses and 26 experienced none. On average, there was a 72% reduction in the annual relapse rate.

'Over time, people with relapsing–remitting MS experience fewer relapses, even if they are not taking medication. But they go on to have increasing permanent disability,' said Kenneth Johnson, Chairman of Neurology at the University of Maryland School of Medicine (Baltimore, MD, USA). 'This study showed that there was a beneficial effect of treatment with Copaxone on neurological disability, which continued over six years when patients were regularly evaluated by their examining neurologist,' Johnson added.

3 Johnson, K.P. *et al.* (2000) Sustained clinical benramer acetate in relapsing multiple sclerosis patients observed for 6 years. *Mult. Scler.* 6, 255–266

Attention deficit drug shows no benefit over placebo

The attention deficit hyperactivity disorder (ADHD) treatment drug Provigil (modafinil; Cephalon, West Chester, PA, USA) has been shown to be of no benefit when compared with placebo. The results, taken from a 113-patient, double-blind, placebo-controlled trial,

were described by the company's Chairman as disappointing. Provigil obtained favourable results earlier this year in trials investigating excessive sleepiness associated with obstructive sleep apnea and shift work, and fatigue associated with multiple sclerosis, and the drug will continue to be marketed as a treatment for narcolepsy.

Potential cancer link found between SV40 and asbestos fibres

Recent research carried out by Michele Carbone (Cardinal Bernardin Cancer Centre, Loyola University Medical Centre, Maywood, IL, USA) has indicated a potential cancer-causing link between a monkey virus, Simian virus 40 (SV40) and asbestos fibres[4]. Preliminary evidence was reported suggesting that SV40 and asbestos fibres act together to convert healthy cells into malignant cells resulting in mesothelioma, which is a rare and fatal type of cancer.

Typically, SV40 kills the human cells that it enters; however, mesothelial cells can live after infection with SV40 because of the strong presence of p53 (a tumour-fighting protein), which slows SV40 replication by connecting to the cancer-promoting protein of the virus. The combination of p53 and SV40 disturbs the anti-tumour effect the latter, and there is therefore an increased chance that the cell will become malignant.

Further, this risk of malignancy is increased if cells are exposed to both SV40 and asbestos fibres. 'The transformation process from healthy cell to malignant cell is enhanced in the presence of asbestos fibres,' Carbone said. 'Asbestos fibres alone are unable to transform the cell, but they seem to promote the cancer-causing work of SV40, thereby increasing the cell's potential for becoming malignant.'

4 Bocchetta, M. *et al.* (2000) From the cover: human mesothelial cells are unusually susceptible to simian virus 40-mediated transformation and asbestos co-carcinogenicity. *Proc. Natl. Acad. Sci. U. S. A.* 18, 10214–10219

Evidence for efficacy of patented Ginkgo extract

Recent research has provided evidence that the Ginkgo extract, EGb761®, can enhance the mental performance of patients with Alzheimer's disease and multi-infarct dementia. This improvement was seen within the first 26 weeks of treatment.

A double-blind, placebo-controlled, parallel group, multicentre study was carried out, in which the mental performance, daily living and social behaviour of 309 patients were assessed using the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), Geriatric Evaluation by Relative's Rating Instrument (GERRI) and Clinical Global Impression of Change[5] (CGIC).

It was reported that patients administered with 120 mg per day of EGb761® demonstrated improvements in their ADAS-Cog (26% improved by at least 4-point) and GERRI (30%) evaluations that were clinically relevant, whereas the same evaluations of the placebo group were significantly worse. There were no differences observed between these groups with regard to safety.

The study states: 'Comparison of the current results with those reported in a German study testing a higher dose of EGb might suggest that an increased EGb dose would result in an even more favourable treatment effect. After a similar treatment duration ... 240 mg EGb showed ... a higher percentage of improved patients, i.e. 38% of the EGb group reached the highest cut-off point on the cognitive scale versus 26% in the current study.'

5 Le Bars, P.L. *et al.* (2000) A 26-week analysis of a double-blind, placebo-controlled trial of the ginkgo biloba extract EGb 761 in dementia. *Dement. Geriatr. Cogn. Disord.* 11, 230–237

Orphan drug status for short bowel syndrome drug

The US Food and Drug Administration (FDA) have designated ALX0600, active in alleviating short bowel syndrome (SBS), an orphan drug. ALX0600, produced by NPS Pharmaceuticals (Salt Lake City, UT, USA), is an analogue of glucagon-like peptide 2, a hormone that regulates growth, proliferation and maintenance of the mucosal lining of the small intestine. The drug has recently moved into a pilot Phase II clinical trials for SBS to measure safety, tolerability and improvements in nutrient absorption. SBS only affects 200,000 people in the US but is a debilitating condition that prevents sufferers from adequately absorbing nutrients, electrolytes and fluids from the small intestine.

Vibrio cholerae genome sequenced

The genome of the cholera bacterium *Vibrio cholerae* has been sequenced by The Institute for Genomic Research (TIGR, Rockville, MD, USA)[6]. The achievement, the result of collaborations with the Harvard Medical School, National Science Foundation and the University of Maryland, with funding from the National Institute of Allergy and Infectious Diseases (NIAID), will hopefully facilitate the development of an effective vaccine for this epidemiologically important human pathogen. Furthermore, the information will provide a model for the study of multi-chromosomal prokaryotic organisms and provide clues for understanding the metabolic and regulatory networks represented by genes linked on one or both chromosomes. Moreover, it provides potential for learning how multiple horizontally acquired loci located on separate chromosomes can interact efficiently at the regulatory, cell biology and biochemical levels of organization.

6 Waldor, M.K. and RayChaudhuri, D. (2000) Treasure trove for cholera research. *Nature* 406, 469–470

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