treatment options currently being explored. However, one of the major problems in neural transplantation is finding an ample supply of viable cells, Borlongan points out.

The demonstration that DADLE produces extended survival of cells has direct clinical application for transplantation therapy, he claims. 'With DADLE being able to prolong survival of nerve cells, pooling of viable cells is possible', he said.

Furthermore, when (in an extension of the above study) the harvested foetal cells were transplanted into the brains of parkinsonian rats, the DADLE-treated cells not only survived better than the non-treated cells, but they also promoted enhanced behavioral recovery in the transplanted animals. 'These results suggest that DADLE should be considered as an adjunctive agent for neural transplantation therapy in Parkinson's disease', the researchers concluded.

How does it work?

Although no one knows exactly how this compound exerts its neuroprotective effects, DADLE appears to be a powerful antioxidant, and this might partially explain why it protects nerve cells.

According to Borlongan, 'the aberrant accumulation of free radicals has been documented in Parkinson's disease and other neurological disorders'. Therefore, he argues that the most plausible explanation for the neuroprotective effects of DADLE is 'via its free radical scavenging property'.

Tsung-Ping Su, Chief of the Cellular Pathobiology Unit at NIDA, agrees with Borlongan, but thinks that there are other processes involved as well: 'DADLE can also block the translocation of a Bax protein from the cytosol into the mitochondria, the consequence of which is to cause a release of cytochrome c that can activate all sorts of caspase enzymes to kill cells', he explained.

Looking ahead

Whatever the mechanism behind it, there is convincing evidence that DADLE is an effective neuroprotector, according to Su. Therefore, he suggests that it could be used as a therapeutic agent for various neurological and aging-related diseases in the future.

Su admits that several things must happen before clinical studies involving humans can take place. First, the bioavailability and biosafety of DADLE must be tested after intravenous administration in animals, he contends. However, if all of the initial tests are successful this unique substance, which triggers hibernation in squirrels, might one day be used to prevent or treat several neurological diseases, including stroke and PD, he says.

References

1 Borlongan, C.V. *et al.* (2002) Hibernation-inducing trigger (delta opioid peptide): A therapeutic agent for aging-related disorders. Poster presented at the 2002 Annual Meeting of the International College of Geriatric Psychoneuropharmacology, Barcelona, Spain (see http://www.icgp.org/PosAbstracts.htm)

2 Tsao, L. *et al.* (1999) Reversal by [D-ala2, D-leU5]enkephalin of the dopamine transporter loss caused by methamphetamine. *Eur. J. Pharmacol.* 372, R5–R7

3 Borlongan, C.V. *et al.* (2000) Treatment with delta opioid peptide enhances *in vitro* and *in vivo* survival of rat dopaminergic neurons. *NeuroReport* 11, 923–926

4 Borlongan, C.V. *et al.* (2001) Delta opioid peptide augments functional effects and intrastriatal graft survival of rat fetal ventral mesencephalic cells. *Cell Transplant.* 10, 53–58

Mistletoe compound enters clinical trials

Martina Habeck, freelance writer

For many years, mistletoe extract has been popular with cancer patients, but not with scientists. Now, there is a drug in clinical trials that contains a recombinant version of the extract's main active ingredient [1,2].

Under the mistletoe

Extract from the mistletoe plant (*Viscum album*) is widely used as an alternative complementary therapy, especially in German-speaking countries (this is a result of the proposition, by Austrian Rudolf Steiner in the early 1920s, that misletoe could be used as a therapeutic agent for the treatment of cancer). However, scientists have traditionally been skeptical about this treatment approach. So is Patrick Schöffski, a hematologist at Hannover Medical School (http://www.mh-hannover.de): 'Natural extracts have the disadvantage that they contain many ingredients at varying concentrations. I am very excited to have the chance to study one ingredient, genetically engineered mistletoe lectin 1, in conventional clinical studies.'

1359-6446/02/$ – see front matter PII: S1359-6446(02)02571-0

Mistletoe lectin I (ML I, or viscumin) was identified in the late 1980s as the main pharmacologically active ingredient of the extract [3]. It belongs to the family of type II ribosome-inactivating proteins (RIPs), which have a domain with enzymatic activity (the A-chain) and another domain that is responsible for binding to the surface of the target cell (the B-chain) [4,5]. As a result of the enzymatic activity of the A-chain, protein synthesis is interrupted, which induces a cellular stress response that triggers the release of cytokines and, at high ML1 concentrations, apoptosis.

Because mistletoe extract contains ML1 in low concentrations, the type II RIP acts as an immune stimulant. However, in high concentrations, ML1 is a potent cytotoxin. Therefore, the German company Viscum (http://www.viscum-ag.de) decided to make an anti-cancer drug from it.

Recombinant protein

Using recombinant technology in *Escherichia coli*, scientists at Viscum produced a protein with structural similarity to the original viscumin (designated rViscumin). Josef Beuth (Institute for the Scientific Evaluation of Naturopathic Therapies at the University of Cologne; http://www.uni-koeln.de) believes the investigators might have been better off expressing the recombinant product in plant cells, rather than bacterial cells. Bacterial proteins are not glycosylated and the rViscumin differs in this respect from its natural cousin.

However, this difference does not seem to affect the efficacy of the drug. Animal studies indicated that rViscumin has cytotoxic activity against various types of cancer. The drug is now in several Phase I clinical trials in Europe. First results from a dose-escalation study that is under way in Hannover (Germany) and in Nantes (France) were presented recently at

the 14th EORTC–NCI–AACR symposium in Frankfurt, Germany (19–22 November 2002).

In the study, patients with a solid malignant tumor receive 60 minute infusions of rViscumin twice a week. Schöffski, who is supervising the trial in Hannover, says that analysis of data from 28 patients showed an 'ideal pharmacokinetic scenario'. The treatment was well tolerated even at high concentrations.

Preliminary findings

The investigators also presented immunological data from 14 patients. 'According to our preliminary findings, rViscumin stimulates the immune system over a broad range of doses with the release of IL-1β, IL-6, IFN-γ and TNF-α,' says Schöffski. He adds that the recombinant protein also induces IgG and IgM antibodies, but the clinical relevance of this finding is not known.

Schöffski believes that rViscumin might act as a double whammy: although it is mainly seen as a cytotoxic therapy, the immunological action of the drug could enhance its efficacy in fighting cancer.

Eventually, hopes Beuth, rViscumin could become 'an alternative to currently used chemotherapies, such as Taxol®'. Like viscumin, Taxol (paclitaxel) was isolated from a plant; it is found in the bark of the Pacific yew tree (*Taxus brevifolia*).

Future prospects

However, at present, the specificity of the treatment remains a concern with Beuth. Viscum is already working on rViscumin-based fusion proteins that contain a monoclonal antibody that should direct the drug to cancer cells.

Time will tell whether this treatment approach will become another natural-product success story. At present, the investigators have not even got efficacy data in humans. 'If you are at ASCO next year [American Society of Clinical Oncology, 31 May–3 June 2003, Chicago, IL, USA], you will find out whether there have been tumor remissions,' promises Schöffski.

References

1 Schöffski, P. *et al.* (2002) The intravenous administration of rViscumin induces cytokine release and antibody formation. Results of EORTC New Drug development Group Trial 16002. *Eur. J. Cancer* 38, (Suppl. 7), S154

2 Schöffski, P. *et al.* (2002) Pharmacokinetics of the intravenous administration of rViscumin in patients with solid tumours. First results of EORTC Phase I Study 16002. *Eur. J. Cancer* 38, (Suppl. 7), S154

3 Hajto, T. (1989) Modulatory potency of the b-galactoside-specific lectin from mistletoe extract (Iscador) on the host defense system *in vivo* in rabbits and patients. *Cancer Res.* 49, 4803–4808

4 Eck, J. *et al.* (1999) Cloning of the mistletoe lectin gene and characterization of the recombinant A-chain. *Eur. J. Biochem.* 264, 775–784

5 Eck, J. *et al.* (1999) Characterization of recombinant and plant-derived mistletoe lectin and their B-chains. *Eur. J. Biochem.* 265, 788–797