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encouraging clinical trials in Alzheimer's that reported no toxicity. 'I would say that although the data we have currently suggests Clioquinol interferes with production of the protein, we have more work to do to confirm that and determine the mechanism; also, this data derives from a highly artificial system ... so its applicability to *in vivo*, and particular the human condition remains a question.

'If we can further confirm this mechanism *in vitro*, and demonstrate efficacy in other mouse HD models (and these are large ifs), then Clioquinol would, I believe, be unique amongst small molecules in its direct interference in protein production.' Clioquinol is known to be a chelator, which means it binds metals in body tissues, particularly copper and zinc and removes them when it is excreted. The authors suggested that this chelation effect might interfere with production of the mutant huntingtin protein in some way.

Dexter said that more work needed to be done to uncover the underlying mechanism. 'Although they have weak metal ion chelation capabilities which is the main proposed mechanism of action, they can also affect RNA and protein dynamics. They could utilize more specific metal ion chelators to get a better handle on the mechanism of action of CQ.'

Next steps

Massa and colleagues said their next step would be to create an *in vitro* system in which toxic and non-toxic forms of huntingtin are made in the same cell. This would enable them to evaluate the effects of Clioquinol on several phases of protein synthesis within the cell.

He hopes these experiments would confirm indications that Clioquinol preferentially interferes with synthesis of the toxic form of the protein. A human trial could be organized in 2–3 years but this would depend on confirmatory studies in full length models and perhaps dose ranging studies. However, the manufacturer of the drug, Prana Biotech, recently discontinued development due to manufacturing difficulties and a full, human trial would have to overcome this hurdle.

If drug trials are successful Clioquinol might still only be able to help delay the progression of symptoms of the disease. 'We would not expect this to be a cure, since presumably on stopping the drug the mutant protein synthesis would resume', said Massa. Dexter added that the previous doubts in the USA over Clioquinol had to be weighed against the fact that any drug for Huntington's would have to be given long term and hence the benefits might be restricted by the possible toxic side effects. 'This work should be utilized as an indicator of mechanisms that alter the protein handling in Huntingtons and develop a safer drug for long term use', he suggested.

Reference

1 Nguyen, T. *et al.* (2005) Clioquinol down-regulates mutant huntingtin expression in vitro and mitigates pathology in a Huntington's disease mouse model. *Proc. Natl. Acad. Sci. U. S. A.* 102, 11840–11845

Multiple sclerosis poses tough drug development challenges

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A novel drug that could treat the underlying cause of multiple sclerosis has shown good results in a Phase II study. TFY720, which is taken orally, was found to decrease patients' annual relapse rate by more than 50% compared with a placebo when taken over a 12-month period. Over 80% of patients taking the drug were free from active inflammation as detected by magnetic resonance imaging at the 12-month end point. Novartis, the drug's developer, intends to begin Phase III studies by the end of 2005.

Unique mode of action

'FTY720 is promising oral agent with a unique mode of action, different to all available therapies,' comments Oliver Neuhaus (Department of Neurology, Heinrich Heine University, Düsseldorf, Germany). 'It reversibly sequesters lymphocytes away from blood and susceptible target organs such as the central nervous system, reducing neuroinflammation,' he explains. 'One of the obvious advantages of FTY 720 is that it is an oral immunomodulatory agent, easier on patients than preparations that require infusion', adds Reinhard Hohlfeld of the Institute for Clinical Neuroimmunology (Ludwig Maximilians University, Munich, Germany). However, both agree that, as with the other agents on the horizon, it is important to wait for the results of Phase III trials, because of the history of drug development for this debilitating condition.

Setbacks for MS therapies

Current therapies for MS fall into four groups: steroids, which are used to treat relapses; disease-modifying drugs, including immunomodulators such as interferon beta and the immunosuppressant mitoxantrone; symptomatic treatment, for example, for spasticity, fatigue and depression; and non-drug therapy such as physiotherapy and rehabilitation. Neuhaus says that the currently approved DMDs have limited efficacy 'so new concepts are of high importance'. He had thought that natalizumab, a humanized monoclonal antibody against alpha2-integrin, an adhesion molecule involved in T-cell migration through the blood–brain barrier, was the most promising new drug to date. 'In two Phase III trials, natalizumab has shown dramatic efficacy on all parameters tested (relapse rate, progression, quality of life, MRI)', reports Neuhaus. The drug was approved by the FDA in November 2004. Unfortunately, despite its success in Phase III, it had to be

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removed from the market after three cases of fatal progressive multifocal leukencephalopathy, a rare viral disease of the CNS. 'Currently, a huge safety update on the patients so far treated with natalizumab is taking place, and a new trial assessing safety is being planned. If the adverse event profile is better established, natalizumab may get a second chance to be approved for treatment of MS', says Neuhaus.

A long term effort

Reinhard Hohlfeld of the Institute for Clinical Neuroimmunology (Ludwig Maximilians University, Munich, Germany), who recently reviewed monoclonal development for MS therapy, was also disappointed that natalizumab ran into such problems. 'The history of drug development is beset with failures and MS therapy has provided some spectacular examples', he says wryly. Although therapeutic mAbs have shown much promise, several such potential therapies based on mAbs have had unexpected and unexplained severe side effects and, like Natalizumab, have had to be withdrawn, he adds. 'A new generation of neuroprotective and repair strategies, which might even reverse disability in MS patients, is on the horizon, but currently at a very early stage of development. With so many setbacks, it will be some years before we even come close to success', he concludes.

Medicinal mushroom cuts off prostate cancer cells' blood supply

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Ganoderma lucidum, a medicinal mushroom, is a widely popular dietary supplement in East Asia, taken to enhance health and longetivity. Its use in traditional Chinese medicine, including the treatment of cancers, is backed by two thousand years of anecdotal evidence and ever-increasing scientific data. Now, Daniel Sliva and colleagues at the Methodist Research Institute (www.clarian.org) and Indiana University in Indianapolis, IN, USA, (www.indiana.edu) have discovered how *G. lucidum* inhibits prostate cancer cell proliferation [1].

Potent anticancer agent

Triterpenes and polysaccharides are the biologically active components of *G. lucidum*, and are known to inhibit cancer growth and metastasis by modulating the immune system, inducing cell cycle arrest and triggering apoptosis. Sliva and colleagues have now discovered that *G. lucidum* halts prostate cancer cell proliferation by suppressing angiogenesis as well.

'My major interest is in how to stop the invasive behavior of cancers', explains Sliva, whose research focuses on identifying and characterizing anticancer compounds from nutritional sources. Indeed, previous studies by the authors showed that *G. lucidum* could suppress the movement and growth of highly invasive breast and prostate cancer cells and could trigger apoptosis and halt proliferation in prostate cancer cells.

In their latest study, Sliva and colleagues examined the effect of *G. lucidum* on prostate cancer cell angiogenesis. They found that mushroom extracts inhibited capillary morphogenesis (tube formation during angiogenesis) in human endothelial cells in a dose-dependent manner.

Suppressing angiogenesis

To study the effects of VEGF (vascular endothelial growth factor) and TGF-β1 (transforming growth factor), angiogenic factors involved in angiogenesis, they then added *G. lucidum* to prostate cancer cells and saw that it inhibited VEGF and TGF-β1 secretion in a dose-dependent manner, accounting for the inhibition of capillary morphogenesis.

Using *G. lucidum* preparations containing standardized amounts of triterpenes and polysaccharides, they then characterized how *G. lucidum* inhibits VEGF and TGF-β1 secretion by exerting its affects on both Erk1/2 and Akt signaling pathways, suggesting potential targets for therapeutic intervention. The result is inhibition of DNA-binding and activation of a transcription factor, resulting in downregulated expression of VEGF and TGF-β1.

***G. lucidum* extracts as chemotherapeutics**

'Since most of the chemical structures of *G. lucidum*'s antitumor triterpenes and polysaccharides have now been characterized, its chemopreventive and therapeutic potentials, mechanisms of action, efficacy and side effects should now be investigated', says Vay Liang W. Go, professor of medicine at UCLA (http://dgsom.healthsciences.ucla.edu/) in Los Angeles, CA, USA.

Sliva says they are currently focusing efforts on further characterizing and synthesizing these biologically active compounds responsible for the mushroom's anticancer properties. Yet, despite their promise, pharmaceutical companies are not currently taking any steps to develop these molecules as chemotherapeutics. 'They're interested but unlikely to vigorously pursue them since the bioactive phytochemicals in *G. lucidum* cannot be patented', explains Go.

If these compounds can be synthesized and thus patented, their development as actual chemotherapeutics seems likely, says Sliva. However, isolating the individual compounds and synthesizing them will prove to be an onerous task, he adds. In the meantime, he envisions *G. lucidum* as a dietary supplement and adjunct to cancer therapy. He and his colleagues anticipate beginning clinical safety trials in the next six months.

While *G. lucidum* can be obtained around the world and through the internet, Sliva advises that buyers beware. 'Not all (preparations) on the market have these active ingredients so the anticancer activity is not there', he says.

References

1 Stanley, G. *et al.* (2005) *Ganoderma lucidum* suppresses angiogenesis through the inhibition of secretion of VEGF and TGF-β1 from prostate cancer cells. *Biochem. Biophys. Res. Commun.* 330, 46–52

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