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By establishing Nanomedicine Development Centers, they hope to encourage the development of technologies that can destroy cancer cells, repair broken cellular machinery, deliver medicines with precision, and more.

In October 2005, scientists gathered in Cambridge, Massachusetts, for a conference on Nanomedicine. Discussions ranged broadly, from imaging technologies to exotic nanomaterials for sealing a surgical field from contamination. One of the presenters was Mansoor Amiji, an Associate Professor at Northeastern University in Boston, Massechussetts. Amiji is working on various strategies for using nanotechnology to deliver drugs or other payloads to target sites in the body. Amiji has already had success targeting cancer drugs to human tumors growing on the backs of nude mice using polymer-based nanoparticles. The particles are about 150 nanometers in diameter and can entrap or encapsulate hydrophobic drugs. Amiji has also developed a gelatin-based nanoparticle that can be used as a safe delivery vector for DNA. He and his colleagues at Northeastern have recently begun working on combination methods for delivering more than one agent to a drug-resistant tumor, in an attempt to reprogram the cell so that it can once more respond to treatment. 'By using the nanotechnology and combining more than one agent, you are able to literally reengineer the whole apoptotic mechanism back into a cell, which...has lost the apoptotic state.'

Molecular imaging

One of the most promising areas of nanomedicine is in optics and imaging. Nano-sized imaging agents that can be targeted to tumors or other areas of interest in the body could provide a faster, less invasive, and more accurate way to diagnose disease. Rebekah Drezek, assistant professor of Bioengineering at Rice University in Houston, Texas, specializes in developing novel optical imaging technologies for *in vivo* tissue pathology. One project in her laboratory focuses on molecular imaging. A fundamental limitation of molecular imaging is the signal to background ratio. When brightly glowing nanoparticles are targeted to diseased tissue, there will be a certain proportion that do not arrive at the target zone, resulting in a background illumination that can make it difficult to identify a low-intensity signal. Says Drezek, 'We're trying to get around that by developing a class of imaging agents that's completely dark and only lights up when a particular molecular event happens.' By using quantum dots attached to gold nanoparticles through a degradable peptide linker, Drezek gets a molecular imaging agent that only changes color when it comes in contact with the correct cleavage enzyme.

Changing the rules in drug discovery

Developments in nanomedicine are distinctly threatening to the traditional paradigm in drug discovery, which is predicated on finding druggable compounds. Poor solubility and limited bioavailability are the major reasons that most compounds do not advance to lead status. Changing the rules at this stage would result in a major reorganization and reconceptualizing of the drug discovery process that could be both expensive and uncomfortable. But the benefits in salvaging millions of discarded compounds are undeniable. A larger hurdle is untangling the regulatory issues surrounding nanomedical devices. In some cases, they could be regulated as drugs. In others, regulation as a device would seem more appropriate. And the safety issues surrounding many of these new nanomaterials are not well understood. Until regulatory agencies respond to the new technologies, there will be some confusion.

Hope for Huntington's from an old antibiotic

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US researchers have reported that an antibiotic for internal use might block the action of Huntington's disease in mice and cell culture. Huntington's disease is a hereditary, degenerative, and fatal disease of the brain that causes changes in personality, progressive loss of memory and cognitive ability, and a characteristic uncontrolled jerking motion known as Huntington's chorea. There is no known cure or effective treatment.

Less huntingtin

The Huntington's gene causes the production of a toxic protein, mutant huntingtin, which eventually kills neurons, causing the disease's degenerative effects. The research team led by neurologist Stephen Massa (San Francisco VA Medical Center, California, USA) said Clioquinol, an antibiotic banned for internal use in the USA in 1971 but still allowed for topical applications, interrupted the production of mutant huntingtin. In the first part of their study the team tested the effect of Clioquinol on neurons in cell culture that contained a form of the mutant Huntington's gene [1]. 'We found that not only did cells look better and survive a bit longer when exposed to the drug, but they also seemed to make less of the toxic protein', said Massa.

These tests were followed by animal studies where mice bred to express the toxic huntingtin protein were given 1 milligram of Clioquinol per day in water. After eight weeks of treatment, they had accumulated four times less toxic protein in their brains compared with control mice given water alone. The experimental animals lived 20% longer than the control animals, did better on tests of motor coordination, and had less weight loss, they reported.

Senior lecturer in neuropharmacology David Dexter (Imperial College, London, UK) said that the results backed an increasingly supported hypothesis. 'It is becoming very clear that many neurodegenerative disorders are being associated with altered protein formation and these can often interact with metal ions to produce free radicals and oxidative stress or alternately oxidative stress can cause misfolding of proteins making them toxic.'

'The implications of this work do add some credence to the theory and hence are and important indicator of potential mechanisms and drug targets, said Dexter, who is also scientific director of the Parkinson's Disease Society Tissue Bank.

Efficacy *in vivo*

Massa said that he was cautious about over interpreting the results for Clioquinol, which he decided to try after reading about

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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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