study, using a one-pot synthesis method, they designed several synthetic compounds that bind to 2G12. One-pot synthesis, developed by Wong, enables researchers to assemble carbohydrate structures quickly. 'The one-pot reaction was conducted in such a way that the building blocks were added to the reaction flask in sequence according to their reactivity, with the most reactive one being added first, so the saccharide was assembled with the structure as expected. All the protecting groups were then removed and the product was purified', said Wong. The technique can be automated and programmed. 'All other methods of oligosaccharide syntheses require protection and deprotection in every glycosidic bond formation and thus the process is slow, tedious and expensive', he added.

Retrovaccinology

The synthesis of these antigen-like compounds is the first step in a process called retrovaccinology. Explaining the concept, Burton said 'simply, in vaccinology one typically has a vaccine and puts that in to people to produce neutralizing antibodies. We have the antibodies, but not the vaccine, so we are trying to work in reverse, from antibodies to vaccine'. Spearman is enthusiastic about the approach taken by the Scripps team, 'I think this type of approach is on the cutting edge of vaccinology, and that this is essential because of the marked failure of conventional approaches. gp120 protein vaccines have been a failure, at least as currently constructed. This approach takes the intricate molecular detail of the binding of a neutralizing antibody and tries to re-create the immune response to get there. This is a very clever approach'.

There are many challenges ahead in the road to a HIV vaccine including the variability of HIV, developing immunogens that elicit protective T-cell responses and understanding how attenuated SIV vaccines protect in animal models. Meanwhile, Burton is part of the Neutralizing Antibody Consortium, which supports scientists working to generate immunogens that elicit broadly neutralizing antibodies to HIV. They are exploring the structural interactions between broadly neutralizing monoclonal antibodies and HIV to aid more effective vaccine design.

Next, Wong and his colleagues plan to test their compounds as antigens in mice to see if they can elicit strong antibody production and measure the antibodies binding to HIV. 'We will then develop the good antigens as potential vaccines', he said.

Reference

1 Lee H.K. *et al.* (2004) Reactivity-based one-pot synthesis of oligomannoses: defining antigens recognized by 2G12, a broadly neutralizing anti-HIV-1 antibody. *Angew. Chem. Int. Ed. Engl.* 43, 1000–1003

Parkinson's disease in the PINK

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A new gene has joined the list of genes mutated in hereditary forms of Parkinson's disease (PD). The discovery by European researchers of PD-associated mutations in *PINK1*, which encodes a mitochondrial kinase, provides a direct link between mitochondria and PD pathogenesis and could lead to new treatments for PD.

An unexpected culprit

PD is a common neurodegenerative disorder caused by the progressive loss of dopaminergic neurons. Patients are usually treated with levodopa but, although this initially improves motor symptoms, many patients later develop dyskinesias.

Most cases of PD are sporadic but researchers believe that identifying the genes mutated in rare familial forms of PD will provide insights into how sporadic PD develops. Past genetic studies have identified mutations in parkin, α-synuclein and DJ1. Now, Nicholas Wood, head of the Department of Molecular Neuroscience at the Institute of Neurology, London, UK (http://www.ion.ucl.ac.uk) and co-workers have discovered a fourth mutated gene.

'In 2001, we identified an Italian family with autosomal recessive hereditary early-onset PD,' explains Wood, 'and mapped the affected gene to chromosome 1.' The discovery of a Spanish family and a second Italian family allowed the researchers to home in on a region of chromosome 1 containing 40 genes. 'We ended up sequencing most of these,' says Wood, to find the gene associated with PD.

As the researchers report in *Science* [1], affected individuals in the Spanish family had a homozygous mutation in the putative kinase domain of PINK1 (PTEN-induced putative kinase 1); in both Italian families the kinase domain was truncated. 'We hadn't put *PINK1* at the top of our list

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of candidate genes,' comments Wood, 'and were rather surprised to find a kinase, a mitochondrially located one at that.'

Adding to the jigsaw

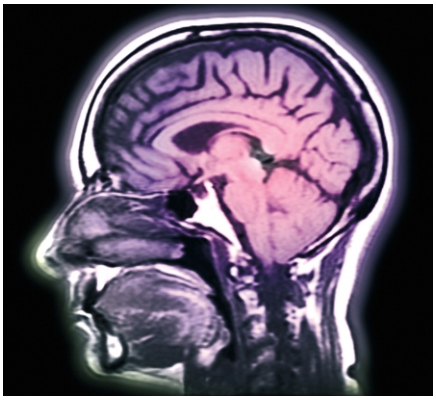
Other researchers, including Serge Przedborski, a professor at Columbia University's Center for Neurobiology and Behavior in New York (http://cumc.columbia.edu/dept/neurobeh), are excited by this discovery. 'We have done little but think about the implications of this result since it came out,' says Przedborski, who is particularly intrigued by results that indicate that loss of PINK1 activity might make neurons susceptible to cellular stress.

PD, explains Przedborski, 'seems to result from an interaction between a person's genetic makeup and some environmental toxin and these new results fit in with that idea.' In addition, mitochondrial defects have been implicated in PD since the 1980s, but although there are biochemical defects in mitochondrial complex 1 in PD, no mutations in the mitochondrially encoded genes for this complex have been found. 'The discovery of the *PINK1* mutation may mean that phosphorylation of complex 1 by PINK1 is essential for the mitochondria to work well under stress,' suggests Przedborski.

Wood agrees that the *PINK1* results put mitochondrial dysfunction right back on the agenda as far as understanding PD is concerned but, he cautions, 'there is a long way to go before it will be clear where PINK1 fits in the PD jigsaw. We don't even know the targets for PINK1.'

Therapeutic implications

For now, treatments for PD based on the discovery of *PINK1* mutations in hereditary PD are a distant hope. 'Until we know more about PINK1, it is difficult to envision any kind of therapeutic strategy,' says Przedborski.



Nevertheless, PINK1, like every piece in the PD jigsaw, is a potential drug target and perhaps more importantly, its identification could help researchers understand exactly how PD develops.

Reference

1 Valente, E. M. *et al.* (2004) Hereditary early-onset Parkinson's disease caused by mutations in *PINK1*. *Science*; DOI 10.1126/science.1096284 (E-pub. ahead of print; http://www.sciencemag.org)

Balancing US patent and FDA approval processes: strategically optimizing market exclusivity

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The patentability of products is essential in the biotechnology field, because limited market exclusivity compensates the investments of biotech companies' in R&D. The biotechnology field also uniquely faces Federal Drug Administration (FDA) approval, which includes considerable additional expense and time issues that a biotech company must address. Although balancing the patent and FDA approval processes might be complex, various strategies of patent extension, of accelerating approval processes, and of prolonging the market entry of generic drug companies can yield higher profit returns and maximize company value.

Biotechnology startups and their investors are primarily concerned with optimizing the value of the company, which can be measured by the quality and lifetime of its patents. Longer patent terms produce longer market exclusivity, which consequentially leads to increased profits and value. In the USA, patents are crucial to protect a company's ideas while FDA approval is necessary to legally market their products. Here, we address and outline strategies to extend patent terms and maximize market

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