Heavyweight drugs

Swapping selected hydrogen atoms for deuterium could be a fast route to making safer, longer lasting drugs, Cath O'Driscoll reports

When *C&I* broke the story in 2007 that scientists had significantly extended the lifespan of animals by feeding them natural isotopes (*C&I* 2007, **6**, 7), it sparked a frenzy of interest amongst the national media. Nematode worms fed a diet reinforced with natural isotopes were reported to live 10% longer than animals lacking these isotopes in their diet, according to former Oxford University scientist, Mikhail Shchepinov. And furthermore, Shchepinov speculated that humans might one day benefit from these effects by consuming foods specially reinforced with similar isotopes – 13C, 15N, 18O and 2H – in their diet.

While isotopically enriched foods would be a new diversion, however, scientists have been studying the effects of isotopic substitution for decades in pharmaceuticals. Drug compounds incorporating the hydrogen isotope deuterium are known often to be more stable than their hydrogen equivalents and so are slower to transform to metabolites during digestion by the body's enzymes. Chemists have been exploiting this 'kinetic isotope effect' for years for routine metabolic studies.

But now it appears that some deuterated drugs may be usefully developed in their own right – often with superior properties to their hydrogen equivalents already on the marketplace.

Foodstuffs enriched with deuterium and other isotopes would work along the same principles, says Bob Molinari, ceo of California, US-based Retrotope, the company set up to commercialise Shchepinov's discovery. Once eaten, their constituent proteins and fats would be incorporated in the body tissues where they are expected to be slower to react with damaging free radicals held responsible for many of the processes and diseases of ageing.

The underlying science of isotopic substitution is the same in both cases. 'If you imagine a chemical

In Brief

- **Drug compounds incorporating deuterium isotope are more stable than their hydrogen equivalents**
- **Some deuterated drugs may be safer, longer lasting or more effective than analogues on the marketplace**
- **Researchers have been studying this effect for years during routine metabolic studies**
- **Commercial drugs containing isotopes could be on the marketplace in just four or five years**

Simon Wilkinson

Elixir of youth: to be found in isotopes?

'Certainly, the implication is you can use a lower dose of SD-254 to achieve the same effect and hopefully as the side effects are dose-related one hopes to see lower incidence of side effects'

Auspex Pharmaceuticals ceo Mike Grey

bond as the conventional ball and spring model, then swapping one of the two atoms at either end of the bond by its (heavier) isotope changes the frequency at which the bond vibrates,' Molinari explains. 'The heavier the isotope and the more energy that is needed to make the bond vibrate in order to break it.' And the stronger the bond, the more stable the resulting compound.

Commercial drugs containing isotopes could be on the marketplace in just four or five years, researchers in the field claim. US companies Auspex and Concert Pharmaceuticals between them already have two deuterated compounds in Phase I clinical trials, targeted at depression and menopausal hot flashes, with a third compound targeting HIV slated to begin trials later this year. All of these are analogues of drugs currently on the marketplace and are claimed to be safer, longer lasting or more effective.

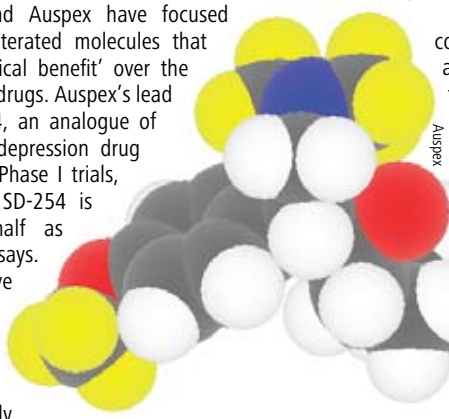
Aside from their different pharmacokinetics, however, these deuterated compounds are virtually indistinguishable from their hydrogen equivalent drugs, says Auspex Pharmaceuticals ceo Mike Grey. Deuterated drugs are made by the careful substitution of a handful of key hydrogen atoms with the heavier, stable, non-radioactive isotope deuterium. 'The resulting molecules therefore have the same physicochemical properties such as melting point and solubility as the originator drugs – and bind to the target receptor proteins in exactly the same way,' he explains.

This likeness to the original drugs may also allow researchers to bring deuterated analogues to market much faster than conventional drugs as much of the toxicological data are already known. Grey estimates that the initial R&D stage typically takes a few months to identify six or seven deuterated analogues for evaluation as potential leads, for example, while human pharmacokinetic data should be available in under a year.

Further along the development process, researchers are hopeful that it should be feasible to foreshorten some of the conventional clinical trial steps. 'We're in the process of initiating a dialogue with regulators for submissions in the US, but the advice from experts is we may not need to repeat all these studies,' Grey says. 'The question is do we need to repeat all the non-clinical studies, how many clinical studies do we need to do?'

According to Concert Pharmaceuticals ceo Roger Tung: 'Our hope is that we could shave a year or more off the development process. We could be much more aggressive in developing compounds by moving forward into very late stage studies directly after Phase I.'

Both Concert and Auspex have focused their efforts on deuterated molecules that deliver a 'clear medical benefit' over the equivalent hydrogen drugs. Auspex's lead compound is SD-254, an analogue of Wyeth's top-selling depression drug *Effexor*; currently in Phase I trials, initial results show SD-254 is metabolised only half as fast as *Effexor*, Grey says. Moreover, effective levels of drug were maintained after 24 hours, considerably longer than observed with *Effexor*. 'Certainly, the implication is you can use a lower dose of SD-254 to achieve the same effect and hopefully as the side effects are dose-related one hopes to see lower incidence of side effects.'



Auspex

Model drug: SD-254

If successful, Grey adds that SD-254 could be the first drug that combines the effectiveness of the so-called serotonin norepinephrine reuptake inhibitor (SNRI) class of depression drugs but with the improved side effect profile of the selective serotonin reuptake inhibitor (SSRI) class – potentially making it very attractive for first line use.

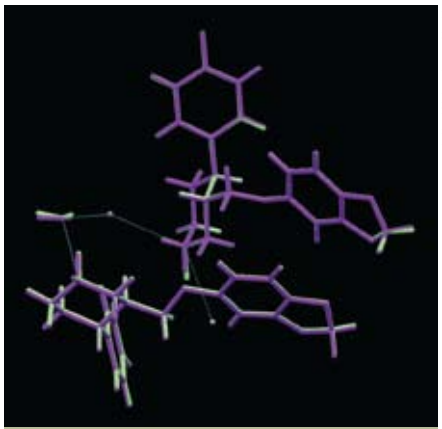
'Our hope is that we could shave a year or more off the development process. We could be much more aggressive in developing compounds by moving forward into very late stage studies directly after Phase I'

Concert Pharmaceuticals ceo Roger Tung

At Concert, researchers will be concentrating resources this year on developing the HIV protease inhibitor CTP-518, Tung says. The compound holds promise as the first HIV protease inhibitor capable of being administered without an expensive booster agent alongside to raise blood levels. 'What we have done is to create changes in one of the market leading protease inhibitors to stabilise and optimise the drug without boosting agents,' Tung explains. 'It could be the first in class non boosted HIV protease inhibitor and that may improve tolerability too.'

The company's other clinical compound, CTP-347, is targeted against menopausal hot flashes for women unsuitable for hormone replacement therapy, including those with breast cancer. The compound is based on paroxetine, a molecule shown to be effective for treating hot flashes, but which irreversibly inactivates a key cytochrome P450 liver enzyme. With CTP 347, this inhibition reaction is observed to 'shut down altogether' in animal studies and in *in vitro* studies with human liver microsomes, Tung says. 'We are the first group to observe changes in drug-drug interactions in terms of D modification.'

These clear medical benefits with deuterated drugs, the researchers say, should more than offset the estimated 20-30% extra manufacturing costs, particularly as many of them should be useful at lower doses. Costs are also expected to come down as deuterium becomes more readily available. Although not rare – the human body typically contains roughly 2g of D for example – D is currently sourced as D_2O from the distillation of water, a process used by the nuclear industry.



Concert Pharmaceuticals

Same but different: An overlay of the crystal structures of CTP-347 hydrochloride hemihydrate (in purple) and paroxetine hydrochloride hemihydrate from the Cambridge database (in pale green)

Victor Watts

High fat diets: Isotopes could help to understand the consequences

> **'What we have done is to create changes in one of the market leading protease inhibitors to stabilise and optimise the drug without boosting agents'**
>
> Concert Pharmaceuticals ceo Roger Tung

One possible obstacle to progress, however, could be the robustness of the intellectual property. Between them Auspex and Concert currently have lodged more than 300 patent applications, while Auspex has recently received its first patent issue, on SD-254 in the US. Concert has received its first notice of allowance for a D-modified compound from the US Patent and Trademark Office. 'Because the changes in pharmacokinetic profile can be so dramatic – as we have seen with SD-254 – we believe we will have strong arguments to support the patentability of our product candidates,' Grey says.

According to Alan Johnson, a partner at London law firm Bristows, however, 'there will undoubtedly be considerable scope for lengthy and doubtless expensive legal wrangles if the deuterated drugs have some real advantage'. As in the biotech arena, Johnson says it will be the processes for manufacture that are the real key. 'Once disclosed it would seem surprising if the use of those processes to obtain countless variants of existing drugs could really justify patents,' he cautions.

Retrotope's targeted 'nutraceuticals', by contrast, may be on safer ground, according to Molinari. The company will not only own the molecules but has also filed for patents worldwide on the overall technology behind ageing and isotopic substitution of essential nutrients. And while longevity and ageing are longer term goals, Molinari says the near term plan is to explore the usefulness of the approach for preventing or slowing some of the associated diseases.

Many of the common diseases of ageing – cancer, Parkinson's disease, cardiovascular disease and Alzheimer's – are known to involve some form of oxidation reaction, he points out. Parkinson's starts with the oxidation of a fatty acid, for example, while some cancer metastases are seen to involve the oxidation of the amino acid lysine. Retrotrope hopes to be able to target these pathways by making deuterated or other isotopic analogues of some of the so-called essential fatty acids and amino acids – ones that need to be ingested in the diet – and so slow down some of these undesirable these oxidation processes.

Whether the resulting compounds would be classed as drugs or nutraceuticals is a moot point, Molinari says. 'At some concentration this may be classed as a nutraceutical, at others as a drug. Regulatory strategies and guidelines vary and are not yet worked out. However, for now the objective is simply to obtain proof of principle that the idea works.'

The company has just started work with the Institute of Ageing in Russia to investigate the potential of a deuterated lysine compound, and is currently seeking grants with various US organisations for studies with deuterated linoleic acid. 'If you review the literature on ageing, one of the key mechanisms in its onset is that membranes like the mitochondrial membrane are bombarded with reactive oxygen species [ROS] and eventually fail,' Schepinov explains. 'When they fail, they release ROS into the cell, which bombard cells and this is how you age. It's the chemical equivalent of rusting to death'.

Linoleic acid is a key component of cell membranes, and so should be an early step in this process. This and other deuterated fatty acids could also be helpful in understanding the progression of non-alcoholic liver necrosis – a disease of 'epidemic proportions' being fuelled by high fat diets, Molinari says. Caused by build up of fatty acids around the liver, necrosis occurs as a consequence of the increased expression of liver enzymes that promote oxidative damage and ultimately liver failure.

Further into the future, meanwhile, Molinari has his sights on an even bigger prize. Deuterated versions of nucleic acids that comprise the genes could stabilise the body's genome, with almost limitless possibilities, he enthuses. 'If we can lower the mutation rate in the genome, potentially we might have a handle on a whole host of different diseases.'