Back to Nature?

Some commentators believe that in the next few years we'll see the emergence of a new wave of pharmaceuticals based on natural products. In this special feature we meet two companies in the ERBI Network that are working on natural products. First we hear from Biotica's Business Development Manager Melanie McCullagh.

Melanie – most companies take the traditional fragment-based medicinal chemistry approach to drug discovery so why did Biotica opt for natural products?

Compounds derived from natural products (NPs) have made a big impact on the pharmaceutical industry. About 1,000 NCEs were approved between January 1981 and June 2006, and of these over 250 were NPs or NP derivatives . Famous examples include the cancer drugs Taxol (paclitaxel) and its derivative Taxotere (docetaxel) and the antibiotic erythromycin and its derivatives Biaxin (clarythromycin) and Zithromax (azithromycin). Less well known is that the 'statin' class of anti-cholesterol drugs was also based on NPs, with the originals being Mevacor (lovastatin) and its two derivatives Pravachol (pravastatin) and Zocor (simvastatin).

NPs can have very high affinity to the target that they are naturally evolved to bind, very distinct from low-affinity synthetic fragments. Furthermore, NPs seem to be able to address a different range of targets from combinatorial chemistry-derived small molecules. Calcineurin, for example, is the target of the major immunosuppressant drugs Sandimmune/ Neoral (cyclosporine), Prograf/Protopic (tacrolimus, FK506) and Elidel (pimecrolimus). Even though cyclosporine was approved in 1983, there are still no approved small molecule inhibitors of calcineurin in the market. Targeting of mTOR is similarly dominated by rapamycin and its analogues. The large size and complex structure of NPs may make them especially suitable for traditionally difficult targets, such as protein-protein interactions.

But aren't natural products difficult to make and undrug-like?

Although NPs can be large in molecule size and complex in structure with multiple chiral centres and do not comply with the Lipinski's rule-of-five, these molecules tend to have well balanced conformational pre-organisation and flexibility. They bind to protein targets with little loss of entropy and in the meantime are bioavailable because of their flexibility in adopting different conformations in aqueous and lipophilic environments.

Because they are large and complex molecules, NPs can be difficult to make by total synthesis, especially at commercially viable yields. However many, especially those that are produced in bacteria rather than in plants, can be made through culturing a producer organism. Sometimes the original producer organism is suitable for production at commercial scale. This is true of many of the approved polyketide pharmaceuticals, for example. Alternatively, if the natural producer cannot be cultured, or the yield is too low, NPs can often be made through heterologous expression of the gene product in a host organism optimised for high yield.

What is different about Biotica's approach to natural products?

The first generation of NPs, such as erythromycin and Taxol, involved developing an unmodified NP as a pharmaceutical. A second generation of compounds relied upon improving the NP using semi-synthesis, often to optimise physico-chemical properties. Biotica is taking advantage of advances in genomics to develop a third generation of NPs, in which the producer organism is genetically modified to produce a novel polyketide compound. Because this can result in chemical structures that are not practically achievable by semi-synthesis, the new compounds can have different characteristics from those achievable using other methods. For example, in our drug discovery programmes we have been able to make compounds that are more metabolically stable than the parent, and can cross the blood brain barrier. In some of these programmes, decades of research hasn't been able to achieve with medicinal chemistry what we have done using bioengineering.

How has Biotica used its technology to build a pipeline?

Biotica has a growing pipeline of novel pharmaceutical projects, all of which are based on our bioengineering technology. We have focused on a particular class of NPs called polyketides, which has a rich history of yielding high-value pharmaceuticals. Erythromycin is one example; we have a programme based on erythromycin analogues where we are optimising the molecules for their anti-inflammatory properties. In January 2009 we announced a partnership with GSK on this programme, in which we will collaborate for three years on lead optimisation, with GSK developing and commercialising any resulting drugs. We have a second partnered programme, where we're working with Wyeth on optimisation of rapamycin analogues for use in a range of therapeutic indications.

Then we have a number of internal development projects which we're planning to take to preclinical proof of concept, or even to early clinical studies, before partnering. Of these, the most advanced is based on tacrolimus, an immunosuppressant marketed by the Japanese company Astellas for use in organ transplantation and as a topical cream for atopic dermatitis. Unfortunately, the mechanism of action of tacrolimus, calcineurin inhibition, is associated with undesirable side effects, such as nephrotoxicity, which limit the indications it can be used in. Biotica is creating novel analogues of tacrolimus optimised for inhaled use, which we are testing as possible treatments for asthma. If our drugs are approved, their mechanism of action will be novel in the asthma field. Our technology enables us to solve the problem of toxicity inherent to the calcineurin-inhibiting activity of tacrolimus, so they will also be extremely safe. Furthermore, the immune-suppression will be limited to the site of inflammation – the lung. We believe that our drugs will offer hope to moderate to severe asthma patients – a population that is currently very poorly treated and often resistant to current standard of care treatments such as steroids.

What is the future of natural products in the pharmaceutical industry?

NPs have the potential to make a huge difference to medical science, but they have previously been underexploited, due to the issues discussed earlier. Technologies like Biotica's enable us to take NPs with novel mechanisms of action but drawbacks such as toxicity or poor physico-chemical characteristics and turn them into viable, valuable pharmaceuticals. We believe that the next few years could bring a new wave of NP-based pharmaceutical products addressing diseases including cancer, viral infections and immune disorders. Of course this is great for Biotica, but it's even better for patients, since these NPs will offer new ways of treating all kinds of diseases that we may not identify by sticking to more conventional chemistry-based drug discovery.