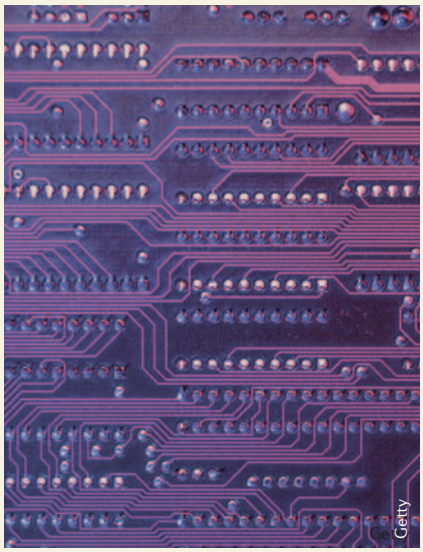
NEWS IN BRIEF

Network pharmacology moves into the clinic



e-Therapeutics has pushed its lead candidate into Phase I trials, hoping to validate network pharmacology as a drug discovery tool.

The lowdown: When e-Therapeutics set out to develop an anticancer drug, it took an unconventional approach: rather than starting with a promising protein target or phenotypic screen result, it mapped out 103 protein networks that help cancer cells to evade apoptosis, and then delved into biological data from 15 million compounds to figure out which ones best modulated network activity. The winner was ETS2101 (also known as dexanabinol), a cannabinoid that has previously been shown to be safe but ineffective in a Phase III trial of traumatic brain injury. The drug has no clear anticancer targets, says e-therapeutics CEO Malcolm Young, but instead affects apoptotic networks, and kills cancer cell lines, through multiple binding partners and downstream activities. The company has now launched a first clinical trial of the drug in up to 24 glioma patients, and results are expected by the end of the year. An all-comers oncology Phase I trial of the drug is also planned for later this year.

Young argues, moreover, that a molecular reductionist approach that dominates in the industry is in part responsible for the low success rate of drug developers in past decades. He points to preclinical data as evidence that it is easier to drive biology by modulating the activity of several — rather than a single — targets, though concedes that network pharmacology has yet to prove itself in the clinic. "We need to demonstrate success, and the only type of success that industry understands is clinical success. Network pharmacology has to put up or shut up." ETS2101 provides one such opportunity to test the hypothesis.

Another company that is also hoping that network pharmacology will pay off is Pharnext. Its lead candidate PXT3003 — a combination of the GABA (γ-aminobutyric acid) receptor agonist baclofen, opioid receptor antagonist naltrexone and the sugar alcohol sorbitol, at relatively low doses — is in a Phase II trial in neuropathic Charcot–Marie–Tooth disease. Results are expected in early 2013.

Obesity drugs prevail

The FDA has approved two obesity drugs, the first since 1999.

The lowdown: When the US Food and Drug Administration (FDA) rejected three obesity drugs in a matter of months in 2010–2011, some experts thought that high safety standards made the area a lost cause. Two recent approvals now show the tide has turned.

The first new approval in 13 years fell to Arena and Eisai's lorcaserin, a serotonin receptor agonist. Although the drug was previously rejected owing to uncertainty over its efficacy and because it seemed to be associated with mammary masses in female rats, further preclinical and clinical data allayed these fears. The drug was approved at the end of June. Vivus's Qsymia, a combination of phentermine and topiramate, was approved a few weeks later. Vivus's candidate was similarly rejected in 2010, but re-submitted data and marketing plans were able to dispel concerns that the drug can cause birth defects and may lead to an increased risk of cardiovascular events. The FDA is requiring sponsors of both drugs to complete post-marketing studies that will confirm the cardiovascular safety of the drugs, as long-term data remain lacking.

Although industry experts view the approvals as a sign that the agency has become more amenable to the development of obesity therapies, some questions still remain over the extent to which future drug developers will have to rule out excess cardiovascular risk.

Orexigen faced a similar setback in 2011, when its obesity candidate Contrave, a combination of naltrexone and bupropion, was rejected by the FDA. Whereas Arena and Vivus re-submitted their candidates, Orexigen initiated an outcomes study to assess its drug's cardiovascular safety. It also posted positive news in the past month, noting that the safety study is progressing faster than anticipated: results from the 10,000-patient trial are now due by the end of 2013.

Antibacterial mAb heads back to the FDA

Human Genome Sciences has resubmitted its anthrax therapy raxibacumab to the FDA, eying a first approval for an antibacterial monoclonal antibody.

The lowdown: Human Genome Sciences' raxibacumab is a monoclonal antibody (mAb) that binds to the *Bacillus anthracis* protective antigen: a bacterial toxin that enables two other bacterial toxins to enter and kill host cells. The neutralizing mAb was developed under the animal rule, which is reserved for drugs that are unethical to test for efficacy in humans. Although it was first filed in May 2009 for the treatment of anthrax inhalation, an independent advisory committee voted 17–6 against approval and said that further data were needed to test whether the therapy could be combined with traditional antibiotics to better treat anthrax inhalation. The FDA rejected the drug 1 month later.

Nearly 3 years on, Human Genome Sciences has resubmitted the drug. The approval package now includes further analysis of the histopathology of the animals used in the efficacy studies that supported the filing, as well as an evaluation of raxibacumab when used in combination with other antibiotics. A decision is due by the end of this year.

If approved, the drug would be the first antibacterial mAb to make it to market. Various other companies are developing their own antibacterial mAbs, although for indications in which the animal rule does not apply. Most of the clinical-stage antibacterial mAb candidates are in Phase II development, but Merck & Co. and Bristol-Myers Squibb's MK-3415A — which combines two mAbs against *Clostridium difficile* toxins A and B — is in two Phase III trials that are due to be completed in 2014.