IN brief

Orphans' matchmaker

The London-based charity Wellcome Trust launched a new scheme to fund industry-academia collaborations in orphan and neglected diseases. The Pathfinder Awards will provide up to £100,000 ($159,000) for four projects a year, and private partners will match the money. The aim is to de-risk and kick-start promising projects deemed too early for other funding models. The projects funded are those likely to lead to innovative products—from biologics and vaccines to software solutions. The first two awards were announced in September. One is the development of a human pluripotent stem cell line by Lilly of Indianapolis and University College London to study the disease mechanisms of the disorder 'neurodegeneration with brain iron accumulation'. The other project is a study of the enzyme affected in homocystinuria by researchers at Pfizer of New York and the Structural Genomics Consortium at Oxford University. "The Pathfinder Awards are an excellent vehicle for stimulating academic-industrial collaborations in areas of medical need that are not given much attention either academically or industrially," says Steve Projan, senior vice president of R&D at MedImmune, Gaithersburg, Maryland. In the scheme, an academic lead builds on or establish a partnership with a company with specialist knowledge and technologies. After 18 months, it is hoped the project will attract further investment. The partners can negotiate collaboration terms, but the company would typically have first refusal to further development, according to Bethan Hughes, who manages the Pathfinder scheme. *Emma Dorey*

IN their words

"In most industries something that offers no advantage over its competitors and yet sells for twice the price would never even get on the market. But that is not how things work for drugs." Peter Bach, Leonard Saltz and Robert Wittes of Memorial Sloan-Kettering Cancer Center in New York explain why their cancer center will not offer a high-priced cancer therapy to patients. (*The New York Times*, 14 October 2012)

"Cystic fibrosis gene discovery 1989; 1st drug approved 2012; Duchenne muscular dystrophy gene dsvy [discovery] 1987; 1st + drug 2012. Need to rev up." *Eric Topol tweets on drug discovery timelines.* (Eric Topol@Eric Topol, 13 October 2012)

system and to potentiate extravasation and tissue penetration.

Several delivery vehicles are being explored to boost siRNA potency for systemic indications, but lipid nanoparticles are the furthest along in terms of clinical development (**Table 1**). In September, Watertown, Massachusetts–based Dicerna disclosed some preliminary results using its Encore lipid nanoparticle delivery system (S.K. Basu *et al.*, poster P-004, International Liver Cancer Association Sixth Annual Conference, 14–16 September 2012). But three companies are blazing the trail into the clinic using such systems: Alnylam and Tekmira, which use SNALPs to encapsulate siRNA, and Silence, which embeds its siRNAs into lipid bilayers.

Lipid nanoparticles fully encapsulate and protect the siRNA oligos, enabling systemic delivery. They are often mixtures of cationic and neutral lipids, with PEGylated lipids on the external surface to increase serum half-life. They naturally accumulate at sites of vascular leak—such as those found in areas of tumor cell growth, infection or inflammation—and in the liver, which makes diseases of the liver preferable targets (hence their use in Alnylam's ALN-TTR02).

Alnylam licensed Tekmira's LPN technology in 2008 and has made improvements since then, according to Alnylam CEO John Maraganore. The company is developing second-generation SNALPs using a novel lipid dilinoleylmethyl-4-dimethylaminobutyrate (DLin-MC3-DMA), which has allowed siRNAs to remain efficacious at doses approaching single-digit micrograms per kilogram of body weight in animals. "This is a clear and demonstrable potency compared with the first-generation SNALPs," says Maraganore. He claims that the company has continued to improve the technology by developing a "biodegradable liposome component," which provides the same potency but a broader therapeutic index.

Silence, on the other hand, creates cationic lipid complexes using three components that each have specific functions: a 'masking' lipid increases the drug's half-life in the bloodstream, a second lipid preferentially delivers the siRNA oligonucleotide to certain tissues and the third 'helper lipid' promotes release from the endosome. For example, the company's AtuPLEX is a combination of a masking PEGylated lipid (*N*-(carbonyl-methoxypolyethyleneglycol-2000)-1,2-distearoyl-*sn*-glycero-3-phospho-ethanolamine sodium salt; DSPE-PEG), a tissue-targeting β-L-arginyl-2,3-L-diaminopropionic acid-*N*-palmityl-*N*-oleylamide trihydrochloride and the neutral phospholipid 1,2-diphytanoyl-*sn*-glycero-3-phosphoethanolamine (DPhyPE) in a molar ratio of 1:50:49 in 300 mM sucrose. According to Giese, this combination allows preferential targeting of endothelial cells in the vascular system. Giese says the company does not have a clear-cut explanation for why some lipids preferentially target some tissues. "At the moment, we can't design lipids that target any specific organ. We make different lipids and see which organs they end up in," he says.

Silence's lead internal therapeutic candidate, Atu027, uses the company's AtuPLEX technology to deliver an siRNA targeting protein kinase N3 and is in phase 1 testing for solid tumors. Working with MiReven, Silence will evaluate AtuPLEX and its 'proprietary' lung-targeting cationic lipid technologies as vehicles for delivering MiReven's miR-7, a microRNA that knocks out epidermal growth factor receptor and associated signaling pathways promoting cancer development.

Close behind the lipid particles as delivery vehicles are the linear and branched polymers. These include such molecules as polyethyleneimine (PEI), polyspermine, polyproplyenimine, poly(lactic-co-glycolic acid) (PLGA), cyclodextrin, dendrimers (such as polyamidoamine (PAMAM)) and more exotic polymers, such as chitosan, atelocollagen and hyaluronic acid.

The cationic polymer PEI is widely used as a nonviral vector for delivering gene therapies and has been studied since 2003 as a potential delivery vehicle for siRNA molecules. Similar to cationic lipids, PEI binds siRNA and forms self-assembled nanoparticles owing to its positive charge. Because it can accept protons at physiological pH, it has a high buffering capacity, and the acidic environment of the endosome promotes release of its siRNA cargo (the 'proton sponge effect'). The architecture (that is, linear or branched), side chains and molecular weight of the PEI particle or micelle all influence delivery (PEIs under 25 kDa with branched chains are thought to be superior). Knowledge about even this comparatively well-characterized cationic molecule continues to evolve, however; in September, for example, it was shown that PEI is a potent mucosal adjuvant (*Nat. Biotechnol.* **30**, 883–888, 2012).

One company that has focused on PEI delivery systems is Senesco of Bridgewater, New Jersey. Senesco is using PEI to deliver SNS01-T, a therapy combining a DNA plasmid and an siRNA. The plasmid expresses a modified version of human eukaryotic translation initiation factor 5A-1 (eIF5A) that upregulates the apoptotic pathway and is under the control of the B29 promoter and enhancer, which restricts its expression to B cells. The siRNA component