Homing in on delivery

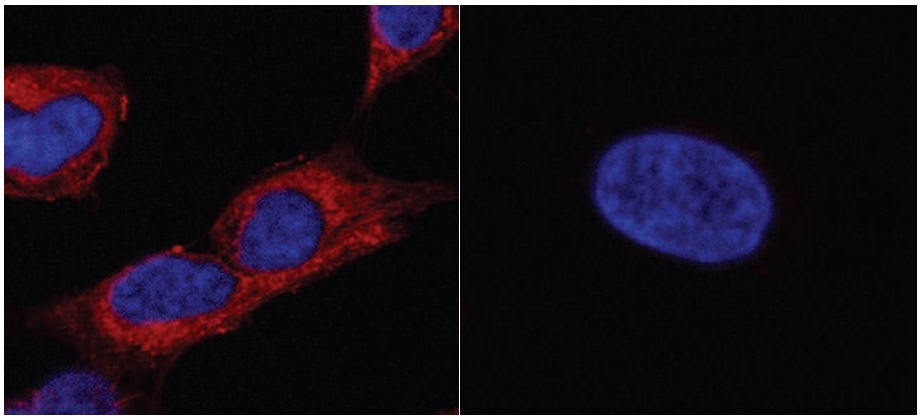
The scientific community now seems convinced that small RNAs will become therapies, if new tools can help these large molecules to make it safely into cells. Monya Baker reports.

Researchers in the field of small RNAs have been on a wild ride. Twenty years ago, RNA was considered a passive conveyer of information between DNA and protein. Now it is understood that RNA controls and coordinates almost everything that goes on in a cell. From being long unrecognized, then heralded as a convenient tool for screening gene function, small RNAs are now hotly pursued as therapies.

Advocates of using small RNAs to treat disease like to tick off the hurdles that were anticipated but seem to have been cleared: that the computational techniques for predicting appropriate RNA sequences would be overwhelming, that synthetic oligonucleotides would be too expensive to manufacture, that the problems uncovered with earlier RNA drugs would crop up again, and that there would be no way of mitigating 'off-target' (or nonspecific) effects.

The field has moved fast. The complex process by which small RNAs are able to silence genes by targeting complementary messenger RNA molecules for destruction was recognized and named RNA interference (RNAi) in 1998 (ref. 1). In 2004, the first RNAi-based experimental therapies entered clinical trials.

For the past few years, though, researchers have been stalled by the challenge of delivering small RNA molecules *in vivo*. "It's still the place where the most important innovations are being made," says Phillip Sharp, a researcher at the Massachusetts Institute of Technology (MIT) in Cambridge and one of the founders of Alnylam Pharmaceuticals in Cambridge, Massachusetts, the first company explicitly founded to harness RNAi. Delivery is also a stumbling block for researchers hoping to use small RNAs to carry out basic research into diseases in living mammals (see 'From tools to therapies').



RXI

Small RNAs (red) don't usually enter cells by themselves (right) but can when chemically modified (left).

Getting in

For many experimental RNA therapies, synthetically produced oligonucleotides are somehow delivered into the desired cells in the body by way of targeting agents, chemical modifications or administration directly to the organ of interest. To test this approach, various clinical trials are in progress, involving many

FROM TOOLS TO THERAPIES

It's not only clinical researchers who are looking for the best ways to get synthetic oligonucleotides into cells in living mammals. If the delivery problem were solved, says Phillip Sharp, who studies RNA interference (RNAi) at the Massachusetts Institute of Technology (MIT) in Cambridge, the ability to use animals to study physiology and disease would expand dramatically. "You can't make a knockout dog, but you could probe genetic function with RNAi." He is optimistic that in a few years researchers will have worked out ways to exploit RNAi in the immune system and the digestive system, at least. It's an open question whether all tissues will be accessible, he says. "Formulating nanoparticles for certain tissue types is still a pretty sophisticated business."

The challenge of delivering the molecules has not stopped companies from producing *in vivo* research tools. Those offering products for animal RNAi studies include Ambion, part of Applied Biosystems in Austin, Texas; Exiqon in Vedbaek, Denmark; Integrated DNA Technologies, headquartered in Coralville, Iowa; and Thermo Fisher Scientific, headquartered in Waltham, Massachusetts. These products are widely used in mice, but they lack some of the tissue or organ specificity that researchers desire. Companies are listening: in December last year, in what it announced as the first targeted delivery vehicle to hit the market, Bioo Scientific in Austin launched a kit containing a proprietary linking modality that allows researchers to conjugate RNA molecules of their choice to antibodies, in this way targeting them to specific cells.

BIOO SCIENTIFIC

Bioo Scientific's T3 Conjugation Kit can be used to target RNAs to specific cells in the body.

This is still a young field, however, and scientists may rightfully feel that the PubMed database is a better source of such technology than product catalogues. In fact, many of the best encapsulation tools are not readily available, given that the tools companies are now seeding therapeutics companies with technologies and expertise, says Mark Behlke, one of the founders of Dicerna Pharmaceuticals in Watertown, Massachusetts. Dicerna is pursuing RNA drugs built on the same platform as some of the research tools offered by Integrated DNA Technologies, of which he is chief scientific officer. Matt Winkler says that he decided to sell Ambion, the research tools company he founded, and launch a therapeutics-focused company after a chance discovery with enormous therapeutic potential. Ambion scientists who were characterizing small RNAs for the company catalogue realized that cancer tissues were surprisingly deficient in certain RNA molecules.

There are other examples. William Marshall co-founded tools company Dharmacon (now owned by Thermo Fisher Scientific) before co-launching miRagen Therapeutics in Boulder, Colorado. Exiqon and Santaris Pharma, headquartered in Hoersholm, Denmark, are commercializing the tool and therapeutic aspects of similar nucleic-acid technologies. And scientists who a few years ago were developing tools are at other companies thinking about the best approaches for clinical trials. M.B.