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Participants:
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University of Pennsylvania
Philadelpihia, PA

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DNA 2.0
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RNAi THERAPEUTICS: A TWO-YEAR UPDATE

Two years is a long time in the world of RNAi therapeutics. Since Science last covered the topic in 2007, the first Phase 3 human clinical trial of an siRNA drug has been prematurely terminated; new off-target effects have been identified; and the first miRNA-based therapeutic entered clinical trials. Yet much remains the same, especially the biggest challenge: delivery. As researchers struggle to overcome these obstacles, optimism persists undiminished. By Jeffrey M. Perkel

Optimism over the potential for RNAi therapeutics is emphatic. Says Judy Lieberman, senior investigator at the Immune Disease Institute of Harvard Medical School in Boston, “I think they are potentially superdrugs.” Lieberman, who recently published a paper using intravaginal delivery of short-interfering RNAs (siRNA) to protect mice from herpes virus infection, is not, she says, “being Pollyanna-ish.”

“I am aware of the problems and the obstacles,” she admits. “To get to the superdrug will take a lot of hard work and dedicated development.”

Yet that doesn’t dim her enthusiasm. The fact is that siRNAs—the double-stranded effectors of RNA interference (RNAi)—can “be developed to silence any gene; can be developed incredibly fast; can have picomolar efficacy; [and] can have an effect that lasts for weeks.”

In the lab, they have become invaluable tools, enabling the easy genetic knockdown of any sequence. The problem with migrating to the clinic, she says, is still delivery. “We have to figure out how to get them into cells better.”

Work on that front is proceeding at a rapid clip, in both academia and industry, as a handful of clinical trials attest. At the same time, new problems have cropped up, including unanticipated immunological effects and impacts on endogenous RNA processing. Others are probing the potential of the field as a whole, for instance with so-called “single-stranded” RNAi strategies.

“It’s obvious from what we know about the biology of RNA interference and how we are able to use it as a tool that it has tremendous potential, if we can harness it,” says David Corey, professor of pharmacology at University of Texas Southwestern Medical Center in Dallas. “Good delivery tools will help us do that.”

DELIVERY, DELIVERY, DELIVERY

John Rossi, the Lidow Family Research Chair at the Beckman Research Institute of the City of Hope of Duarte, California, says the three biggest problems with RNAi therapeutics remain “delivery, delivery, and delivery.”

It is, in fact, a multidimensional problem—to achieve RNAi, systemically administered nucleic acids must survive in circulation long enough to reach their target tissue, enter the desired cells, “escape” their endosome and/or delivery packaging, and finally become incorporated into the RNA-induced silencing complex (RISC)—and researchers have advanced a number of solutions over the past two years.

Tekmira Pharmaceuticals’ SNALP (stable nucleic acid–lipid particle) technology is generating excitement in the community, at least if clinical trials and collaborations are any indication: The company, which has partnered with Roche and Alnylam Pharmaceuticals (which uses SNALP technology in its Phase 1 clinical trials of ALN-VSP02 for advanced liver cancer), in July initiated a Phase 1 clinical trial of its own ApoB SNALP for hypercholesteremia.

“Inclusion of companies in this article does not indicate endorsement by either AAAS or Science, nor is it meant to imply that their products or services are superior to those of other companies.”

“I think they are potentially superdrugs.”
According to president and CEO Mark Murray, SNALP particles “contain four distinct lipids, which play distinct roles in the pharmacokinetics and pharmacodynamics of the product.” Mark Kay, director of the program in human gene therapy at Stanford University, who is on the company’s scientific advisory board, calls the technology’s therapeutic window “really the best out there.” He adds, “The doses at which there are clinically relevant responses do not cause toxicity in animal studies.”

Daniel Anderson at the Massachusetts Institute of Technology, collaborating with Alnylam, has broadened the library of compounds that potentially can be incorporated into such systems. His team used combinatorial chemistry to generate “over 1,200 structurally diverse lipid-like molecules,” a subset of which could deliver nucleic acids to cultured cells, mouse, rat, and nonhuman primates—not to mention ovarian cancer molecules, a subset of which could deliver nucleic acids to cultured cells, mouse, rat, and nonhuman primates—not to mention ovarian tumor xenografts in mice. “It really expanded the chemical space people tried,” says Anderson.

Others are investigating nonlipid-based approaches. Steven Dowdy’s lab at the University of California, San Diego School of Medicine, developed a “peptide-transduction domain”/double-stranded RNA-binding domain fusion protein that can both bind siRNA and cross cell membranes. According to Dowdy’s graduate student Bryan Meade, the resulting particles are nontoxic, internalized by macrophagocytes, and then apparently degraded intracellularly, releasing the siRNA. “We can see RNAi as fast as 6 hours after delivery, as measured by quantitative RT-PCR,” he says.

Meanwhile, at the University of Massachusetts Medical School, Michael Czech, professor and chair of molecular medicine, has developed what he calls, “to our knowledge, the only technology that has been published that allows oral delivery of siRNA.”

GeRPs—or beta-1,3-D-glucan-encapsulated siRNA particles—are “solid but porous shells composed almost entirely” of a specific yeast cell wall component, says Czech. Within the glucan shell, the particles wrap siRNA in a transfection reagent, cationic polyethyleneimine. Delivered orally to mice, the GeRPs can silence tumor necrosis factor-alpha expression in gut macrophages.

RNAi therapeutics firm RXi Pharmaceuticals is using GeRPs in its in-house development efforts, says Tod Woolf, president and CEO, as well as so-called “self-delivering rRNAs”—chemically modified RNAs that can enter cells without a vehicle. Though he declines to describe the enabling chemistry, Woolf does say rRNA technology involves three different kinds of modifications: “They make compounds bind cells, get taken up, and get released into cells.”

LOCAL VICTORIES

Companies have also had success with local delivery strategies.

Completed in spring 2008, Alnylam’s 88-patient Phase 2 GEMINI trial of ALN-RSV01, a naked, chemically modified siRNA delivered intranasally against respiratory syncytial virus (RSV), “provided the first human proof of principle results showing statistically significant antiviral efficacy [from RNAi],” says John Maraganore, CEO of Alnylam.

Specifically, ALN-RSV01 produced “an approximately 40 percent reduction in RSV infection rate and 95 percent increase in infection-free subjects,” according to a corporate statement. Data from a second, 24-patient Phase 2 trial, announced in July, indicated it too “achieved its primary objective of demonstrating safety and tolerability” over 90 days posttreatment. But, Maraganore clarified, “[That] study wasn’t powered to show activity.”

TransDerm, with the International Pachyonychia Congenita (PC) Consortium and the PC Project, found smaller-scale success with a one-patient, placebo-controlled Phase 1b trial of TD101, a naked, unmodified siRNA for treatment of PC.

A painful genetic disorder, PC causes blisters and thickened skin on the soles of the foot, says company CEO Roger Kaspar; just to administer the drug intradermally required pain medication. Following injection, “we saw what appeared to be pink skin that was no longer tender to the touch,” Kaspar says.

However, as injections are especially problematic for PC patients, TransDerm is investigating other delivery options, including dissolvable microneedle arrays and even a skin cream dubbed “GeneCreme.”

With so many available options, it’s unlikely any one will dominate the RNAi landscape. “There’s not going to be a one-size-fits-all solution,” says Beverly Davidson, the Roy J. Carver Biomedical Research Chair of Internal Medicine at the University of Iowa, who pursues both naked and viral-mediated RNAi approaches to central nervous system disorders. “It’s more likely that one technology will be better for one application than another.”

THREE STEPS FORWARD, ONE STEP BACK

Unfortunately, as with any new science, unexpected roadblocks inevitably arise on the way to the clinic. “With every three steps forward, there is a step back,” Davidson says.

Christina Leslie of the Memorial Sloan-Kettering Cancer Center and Debora Marks of Harvard Medical School exposed one such setback this year when they showed that transfection of siRNA into cells tends to upregulate microRNA-controlled genes, suggesting that the exogenous nucleic acids can swamp intracellular RNA-processing machinery.

Jayakrishna Ambati’s lab exposed another one, in March 2008, they demonstrated that a naked siRNA, injected into the eye, could block angiogenesis in mouse models of age-related macular degeneration regardless of its sequence. Whether targeting vascular endothelial growth factor or green fluorescent protein, a random sequence or firefly luciferase, every siRNA seemed to block choroidal neovascularization, says Ambati, the Dr. E. Vernon Smith and Eloise C. Smith Endowed Chair at the University of Kentucky.

The findings seemed to fly in the face of accepted RNAi wisdom—and directly into the path of an ongoing human clinical trial. Opko Health’s bevasiranib, a naked siRNA targeting vascular endothelial growth factor for age-related macular degeneration (AMD), was on track to become the first FDA-approved siRNA therapeutic.

The drug had ridden into Phase 3 trials on the basis of animal data indicating it could block the subretinal vasculature that causes blindness in AMD. But those studies used a transfection reagent not used in the human trials. Ambati’s results suggested the drug’s efficacy had nothing to do with RNAi, but rather with an innate immune reaction to double-stranded RNAs mediated by the Toll-like receptor-3 (TLR3).

Ambati says the findings are not terribly surprising; researchers knew that in general, cells don’t take up naked siRNA. “It seems to me that there was an irrational exuberance about the technology, and to be frank, the science behind these [original bevasiranib animal studies] is not sound and contradicts very good science showing that double-stranded siRNAs don’t get into cells.”

That perception seemed vindicated March 6 when Opko Health, citing the recommendation of its Independent Data Monitoring Committee, announced it was terminating its Phase 3 trial of bevasiranib because “the trial, as structured, was unlikely to meet its primary...
RNAi Therapeutics

end point.”

But Phillip Sharp, Institute Professor at the Massachusetts Institute of Technology, cautions against drawing a straight line from Ambati’s findings to Opko’s announcement. “The TLR studies were interesting, but small RNAs interacting with TLRs had been described before,” he says. “That does not in any way qualify the utilization of small RNAs in clinical studies.”

For its part, Opko remains bullish on RNAi, says Jamie Freedman, executive vice president of research and development and business development. Though no siRNA trials are ongoing, the company has not abandoned bevasiranib, he says. It is, however, pursuing other delivery options, as well as other siRNA targets. But Opko also is not putting all its eggs in one basket; the company “is also expanding its portfolio with other kinds of therapeutics, both in and outside of ophthalmology.”

GOING SINGLE-STRANDED

Though researchers have identified ways to circumvent the TLR3 effect (using siRNAs shorter than 21 bases, for instance), just as they have ways to avoid miRNA swamping, it’s also true that not all oligonucleotide structures elicit these responses.

Double-strand RNAs also present fundamentally different—and more complex—manufacturing and delivery challenges than single-strand molecules. “A double-stranded structure is structurally and functionally as different from a single strand as night and day,” says Isis CEO Stan Crooke. Rigid where a single strand is relatively flexible, hydrophilic rather than amphipathic, and with double the mass and volume of a single-stranded molecule, double-stranded RNAs—unlike their single-stranded counterparts—are not readily distributed to most organs in vivo, Crooke says.

For these reasons, some are pursuing single-strand RNAi strategies instead of double-stranded ones. The technique differs from traditional antisense RNA, in that antisense RNA targets RNAs for degradation via RNase H, while RNAi does the same using RISC.

According to Crooke, that distinction is one of semantics, not science. “I don’t believe the field has broadened. I believe RNAi researchers’ understanding has broadened. siRNA is an antisense mechanism: The active moiety is the antisense strand, and the sense strand is a drug-delivery device.”

Developer of Vitravene, the first FDA-approved antisense therapeutic, Isis now appears poised for the agency’s next oligonucleotide approval, as well: mipomersen. One of 19 drugs in Isis’ pipeline, mipomersen is a “first-in-class” ApoB synthesis inhibitor “to reduce LDL-C in patients with high cholesterol and who have high cardiovascular risk.” In May the company disclosed Phase 3 clinical data of individuals with familial hypercholesteremia indicating that the drug had “met its primary endpoint, with a 25 percent reduction in LDL cholesterol after 26 weeks of treatment, versus 3 percent for placebo.” According to Crooke, the company plans to file an NDA in 2010.

Regulus Therapeutics and Santaris Pharma are also pursuing antisense strategies, but directed at microRNAs rather than messenger RNAs.

“miRNA inhibition provides a way to affect multiple gene pathways that have evolved together and are regulated by the target miRNA,” says Henrik Ørum, Santaris’s chief scientific officer. “This pathway modulation is fundamentally different from the single-gene approach achieved by targeting and reducing the expression of an mRNA.”

Santaris achieved an industry milestone in 2008 when it initiated a Phase 1 clinical trial of SPC3649, a locked nucleic acid–based antisense molecule targeting miR-122, a host RNA required for hepatitis C replication, and the first microRNA-targeted therapeutic to reach the clinic.

Regulus achieved a milestone of its own when it helped show the therapeutic benefits of antagonizing miR-21 in a mouse model of heart failure. According to Kleanthis Xanthopoulos, Regulus president and CEO, the study “demonstrates for the first time that inhibition of an overexpressed miRNA has a therapeutic effect in a mouse model of human disease.”

For Xanthopoulos, microRNA represents the “third column” of what he calls the “genus [of] ‘RNA therapeutics’” (the others being antisense RNA and RNAi). And, with the constant discovery of new roles and species of noncoding RNAs, that genus is growing—as is its potential. That’s because unlike monoclonals, which can target only extracellular proteins, oligonucleotide therapeutics “can touch every single gene, and every miRNA,” Xanthopoulos says. It is an idea Maraganore calls, “drugging the undruggable genome,” and it could be huge. “If proteins and monoclonal antibodies are a $40 billion industry, RNA therapeutics can be significantly higher,” says Xanthopoulos.

It won’t happen overnight—it took two decades to turn monoclonals into an approved therapeutic—but with some two-dozen oligonucleotide compounds in clinical trials, including at least eight siRNAs (two each from Alnylam and Quark Pharmaceuticals, plus one each from Calando Pharmaceuticals, Tekmira, TransDerm, and Silence Therapeutics), and around 10,000 people having been dosed in those and previous trials, “We are not talking about potential, we are at a tipping point,” says Xanthopoulos.

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