

wall. “There is a shift underway in the thinking that most heart attacks occur because of vessel narrowing,” says Roy. “Now it seems [that] even with a wide open coronary artery, [an unstable plaque can] present significant danger.”

Roy’s group has developed tiny intravascular ultrasound transducers that can be placed at the tip of a catheter used during angioplasty to probe the structure of the arterial plaque, so that cardiac surgeons can place their stents appropriately. These tools have yet to be tested in vivo, but a related catheter-based drug delivery system that uses an array of silicon microneedles is now being studied in animals.

A Biomedical Revolution?

While each new bioMEMS application that takes aim at the patient may be a leap forward, the real revolution will only come about with a full integration of the various areas of bioMEMS, such as microfluidics, biosensors, and micro and DNA chips, says Ferrari. “What we need is a true blending that uses this technology to combine diagnostics with therapeutics in the same way as nature does in the body. Now that microtechnology [can reach] down to the nanoscale level of individual molecules, the possibilities are incredible.”

—Margaret A. Woodbury

RIDING THE ANTISENSE ROLLER COASTER

Antisense technology has been vaunted as a hot new therapeutic approach for almost 15 years. In principle, short antisense oligonucleotides, which are designed to act on mRNAs and prevent them from making proteins, have significant advantages over more standard small molecule drugs. For example, there are no “undruggable” targets that are beyond the reach of antisense therapies, notes Frank Bennett, Vice President of Antisense Research at Isis Pharmaceuticals (Carlsbad, CA). “It doesn’t matter what [a] protein does, because antisense [works] on the protein before it is even made.”

Then too, generating an antisense compound is lightning fast once you know the relevant cDNA sequence. “All you have to do is go to a machine and you can get a lead molecule,” David Corey (UT Southwestern) says. “Instead of spending months or years to get a lead compound, you can get it in a few days.” Indeed, AVI BioPharma (Portland, OR) recently announced that they had a lead antisense compound targeted against the human coronavirus implicated in severe acute respiratory syndrome (SARS) only 10 days after receiving the virus sequence.

Still, therapeutic failures with antisense have greatly outnumbered successes—even for Isis, which holds over 1000 antisense-related patents and has been the most steadfast corporate proponent of the technology. Isis developed the only antisense drug ever approved by the FDA, Vitravene®, which inhibits replication of the human cytomegalovirus that causes retinitis in AIDS patients. The company is now testing 13 other antisense drugs in clinical development.

So far, the road has been rocky. Isis first tasted phase III failure 3 years ago with its antisense drug for Crohn’s disease, which was directed against intercellular adhesion molecule-1 (ICAM-1). Bad went to worse when Novartis International AG (Basel, Switzerland) pulled out of a partnership with the company, leaving Isis to lay off 40% of its workforce and sharpen its focus. Isis just got kicked in the gut again, when their phase III trial of Affinitak for lung cancer failed to meet its primary end points.

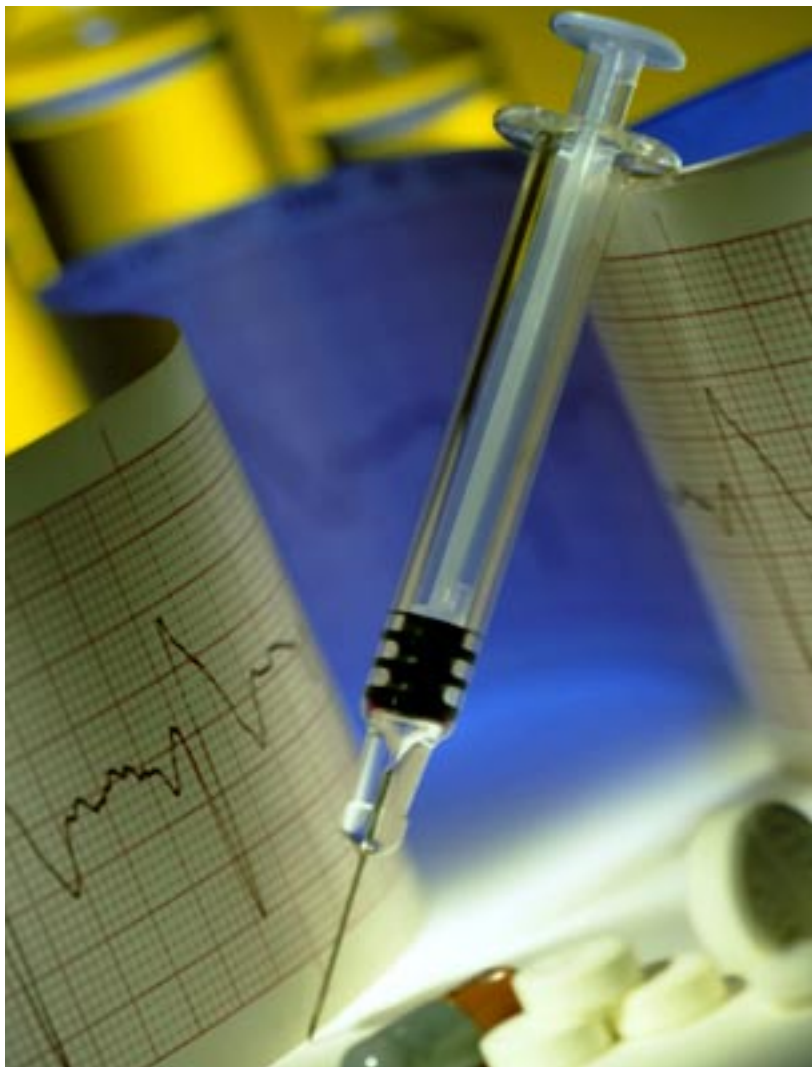
Bennett Weintraub, a senior analyst at Biotech Tracker, is harsh in his general assessment of the sector: “Antisense is a lot like sugar pills; [at least] there doesn’t seem to be any problem with safety.”

Shifting the Balance

Researchers like Alan Gewirtz (University of Pennsylvania) share some of Weintraub’s skepticism, if not his vehemence. “[Clinical] trials... really haven’t produced very much.... Clear-cut demonstrations of utility have been hard to come by,” says Gewirtz, noting that delivery remains a fundamental problem. “It’s not clear [the antisense molecules] are really hitting their targets.” In most cases, in fact, it isn’t known whether the trials failed because of some weakness in the underlying antisense technology or because of a problem with the target. Still, Gewirtz and others believe that incomplete blockade of the target protein’s expression is a frequent problem. For many genes, protein production at even 10% of normal levels suffices for function.

Companies are increasingly stacking the odds in their favor by going after targets that don’t need to

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be shut down completely. “You really want to look for a drug where you’re tipping a balance,” Weintraub says. In cancer, for instance, cells walk a fine line between apoptosis and proliferation. Antisense Bcl-2 (brand name Genasense™; Genta, Berkeley Heights, NJ), which pushes cancer cells toward apoptosis and sensitizes them to chemotherapy, has been successful in clinical trials so far. In autoimmune disease, likewise, clinically meaningful effects could come from subtly shifting lymphocyte responses from self-reactivity toward self-tolerance. “[Isis] has some... good ideas, like inhibiting TNF α [tumor necrosis factor α] to tip the balance away from autoimmunity,” Weintraub notes approvingly.

Delivering the Goods

Getting the antisense oligonucleotides into the right cells can also be a problem. Corey notes that although the oligonucleotides are small compared to the (notoriously in-

tractable) plasmids used for gene therapy, they are strongly negatively charged and are larger than a typical small molecule drug. “We know very little about how these big charged molecules get into cells,” he says. Still, as Bennett stresses, researchers have clarified which tissues are the most welcoming to antisense oligonucleotides. Antisense molecules don’t seem to cross the blood-brain barrier, and they can have a slow onset of action; so neurological and acute conditions are areas to avoid. Conversely, Bennett says, “the drugs get into the liver, kidney, and adipose tissue, so we can focus there.”

Other advances, particularly the means to stabilize the oligonucleotides in the bloodstream, promise to help address the delivery problem. Chemists have designed modifications to the antisense backbone that greatly reduce the turnover of the molecules in circulation. “Unmodified DNA degrades within 3 to 4 minutes in plasma... Now we have a half-life of 2 to 3 days,” notes Bennett. Unfortunately, the benefits of these innovations won’t be realized immediately. Isis’ best-studied drugs, like Genta’s Genasense (whose phase III studies are the next big trials scheduled to report results), use oligonucleotide chemistry over a decade old, as Corey observes. “The chemistries that are in phase I and phase II trials now are much more potent, more specific... It would be a huge mistake for the community to give up on antisense just because there have

been some negative [trial] results.”

Gewirtz, too, remains positive about the long-term prospects for antisense. “It’s a lot like monoclonal antibodies were,” he notes (see “Therapeutic Monoclonal Antibodies (Finally) Poised for Commercial Success,” page 91). “They got hyped up to the sky, then they were a bust; but people kept working on them and now they are making a big contribution. It’s a question of hanging in there and solving the problems.”

—Mignon Fogarty