

# Aptamers: The New Frontier In Drug Development?

Often called chemical antibodies, aptamers are poised to take on the monoclonal antibodies in therapeutics, diagnostics, and drug development. Stability, low toxicity and immunogenicity, and, perhaps, a higher safety profile – not to mention low-cost advantages – are drawing the attention of big pharma and biotech. **BY BOB CARLSON, MHA**

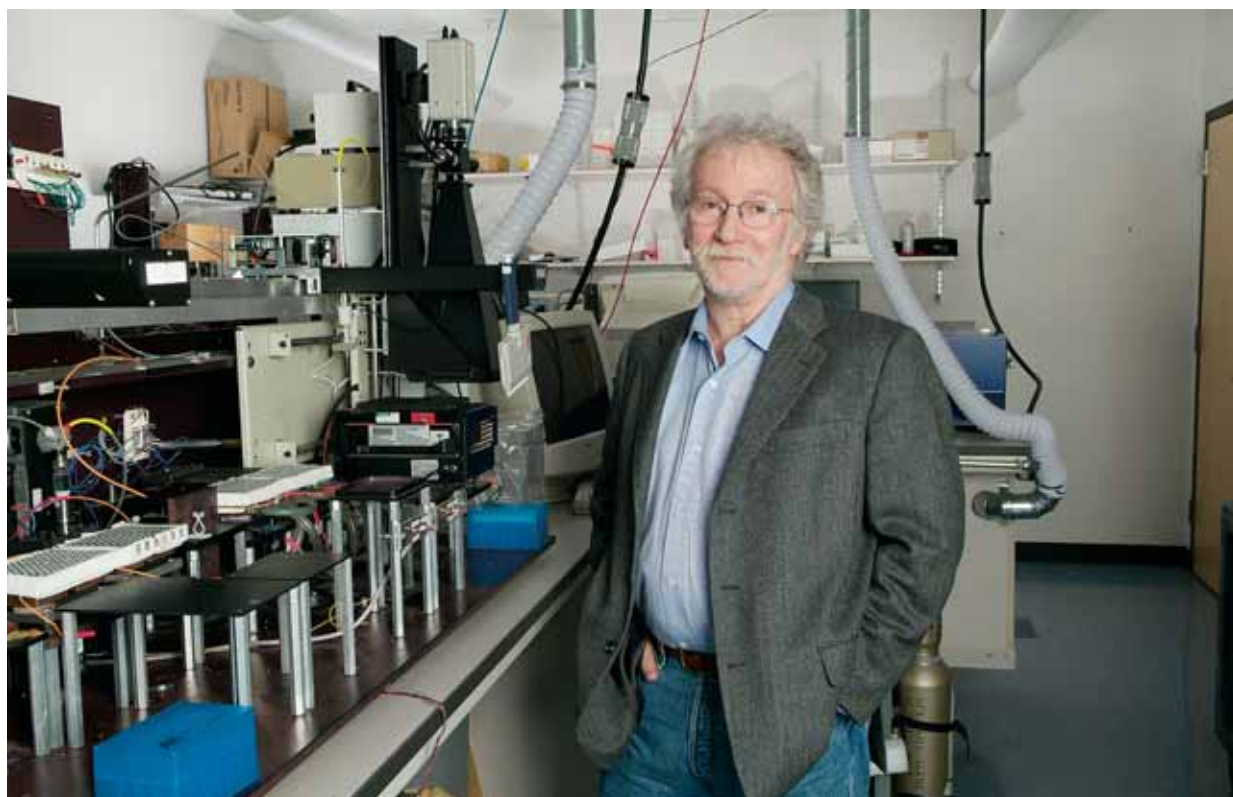
If you're not involved in oligonucleotide research, chances are you have no idea what an aptamer is. And chances are you don't care. Aptamer, schmap-  
tamer, you might say.

Well, Larry Gold, PhD, and Errol

De Souza, PhD, are betting that you'll soon know — and care — because, they say, aptamers are poised to give monoclonal antibodies, or mAbs, a run for the money in therapeutics, diagnostics and drug development.

A surge of deals with some of the biggest names in biotech and pharma appears to support their optimism about aptamers. And, De Souza promises, even bigger deals are in the works.

Gold, co-inventor of the tech-



PHOTOGRAPH BY DANIEL HIRSCH

**“Between biomarker discovery** and better molecular imaging, what we’re doing is going to change healthcare in an extraordinary way,” says Larry Gold, PhD, SomaLogic’s founder and CEO.

nology for making aptamers from nucleic acids, is founder, chairman of the board, and CEO of SomaLogic, in Boulder, Colo. De Souza is president and CEO of Archemix, in Cambridge, Mass. Between them, these two biotechnology companies own virtually the entire aptamer patent estate.

“We’re feeling pretty good these days, given the huge gaps that you see in the pharma and biotech pipelines,” says De Souza. “One of the big advantages that you have with aptamers is cycle time. We can go from target to candidate in 1 to 2 years. It would take that amount of time just to think about developing an antibody, and it would take 4 to 5 years in the small-molecule world.”

On the diagnostic side, Gold reports that SomaLogic is using its photoaptamer-based microarray technology in biomarker discovery and validation, and is adding to its library of aptamer molecular imaging agents. SomaLogic’s partners include Quest Diagnostics and Tokyo-based Sumitomo Bakelite. Schering AG, in Germany, holds the rights to aptamers for in vivo imaging.

“I think our products will be used in research before they’re used in diagnostics,” says Gold. “We can imagine life science products quite soon, with IVDs [in vitro diagnostics] coming a year or so after that.”

### EUREKA!

It all began in 1989 in a chemistry lab at the University of Colorado when graduate student Craig Tuerk and Professor Larry Gold experienced a simultaneous eureka moment about an experiment

Tuerk had just completed. What followed was “like a Laurel and Hardy movie,” Gold recalls — jumping up and down, slapping each other on the back, then madly scribbling ideas on a whiteboard.

“What we wrote on that whiteboard turned out to be the seminal patent in this field, which we submitted through the University of Colorado,” says Gold, who at the time chaired the department of

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SOMALOGIC

molecular, cellular and developmental biology. “We understood, through what turned out to be the next 17 years of research, that you could do anything with what are now called aptamers that you could with antibodies.”

Tuerk had just discovered what was to be known as SELEX (systematic evolution of ligands by exponential enrichment), the iterative in vitro process for selecting and amplifying RNA molecules to bind with specific molecular targets. The notion that single-stranded, chemically synthesized RNA or DNA molecules could be used like mAbs upset the conventional wisdom that RNA/DNA was a linear configuration of genetic code. To function like mAbs, Tuerk and Gold asserted, aptamers had to be three-dimensional.

“Most people think of nucleic acids as information holders, not globular things like proteins,” Gold explains. “What our work proved is

that when you do SELEX to get aptamers, you get molecules that, even though they’re chemically made out of nucleic acid, are more like proteins than nucleic acids.”

Tuerk and Gold published their findings in *Science* the following year, almost simultaneously with a paper in *Nature* by Harvard researchers Andrew Ellington and John Szostak titled “In Vitro Selection of RNA Molecules That Bind Specific Ligands.” For Ellington and Szostak, these RNA molecules were an intriguing piece of a larger puzzle — the origin of life on earth. Ellington came up with the name “aptamer” (from the Latin *aptus*, meaning fitted or connected) and who cofounded Archemix in 2001.

Gold, who already had a track record in starting successful biotech, founded NeXagen in 1992 to develop aptamers as therapeutic and diagnostic agents. NeXagen later merged with Vestar to become NeXstar, which was acquired by Gilead Sciences in 1999. In 2000, Gilead sold all diagnostic rights to Gold’s start-up SomaLogic, and Archemix acquired therapeutic rights to all aptamers other than those aimed at vascular endothelial growth factor (VEGF).

“I think of Archemix as the therapeutic extension of what used to be NeXstar, and SomaLogic as the diagnostic and research arm,” says Gold, who serves on the Archemix Scientific Advisory Board with six other PhDs.

### APTAMER DIAGNOSTICS — READY FOR PRIME TIME

Gold is especially energized by two diagnostic applications of aptamers.

Because aptamers with special photoreactive adducts bind covalently with their target proteins in the presence of a specific wavelength of light, microarrays based on these photoaptamers don't need the secondary reagents that antibody-based arrays do (the probe-analyte-secondary reagent "sandwich" configuration). That, in turn, decreases the "noise" generated by cross-reactions and vastly increases the scale of a photoaptamer array. Gold claims that all 23,710 proteins in the human genome could be measured on one SomaLogic photoaptamer array, thanks to its scale and the specificity and affinity of photoaptamer probes. SomaLogic is partnering with Sumitomo Bakelite to develop optimal surfaces for photoaptamer arrays.

"We started SomaLogic because we knew we could make a big array, and that the antibody guys could not," says Gold. "Biomarker discovery and validation has become a really big deal, and we think we have used these aptamers to make the best biomarker discovery weapon there is."

SomaLogic's partnership with Quest Diagnostics is about biomarkers, but Gold declines to go into detail, explaining, "We first have to find biomarkers that meet the requirements" and "make sure that the markets are big enough."

"We know where we'd like to be," adds Gold, who lost both parents to lung cancer. "We'd like to be helping with early detection of cancer because cancer is one of the diseases where early detection makes a huge difference in your prognosis."

High specificity and affinity also figure prominently in NeXstar's de-

velopment of aptamer-based molecular imaging agents with Bayer Schering. And, the short circulating half-life of "untuned" aptamers turns out to be an important advantage over antibody-based imaging agents, which may circulate in the body for days or weeks.

"Imaging is all about signal to noise," says Gold, "and we've done 3,600 SELEX experiments to identify aptamers with the proper biochemical properties for both biomarker discovery and molecular imaging. We're ready for prime time."

#### APTAMER THERAPEUTICS — THE RIGHT CHEMISTRY

"Functionally, we can do anything antibodies can do and stay in the chemistry space, which obviously has lots of advantages," says De Souza, at Archemix. "We sort of represent the best of antibodies, of biologics, and the best of small molecules."

The "chemistry space" De Souza refers to differentiates aptamers and mAbs right at the point of origin. Monoclonal antibodies are derived from living organisms such as mice. An immune response to the target protein is induced in the mouse, and the resulting antibodies are then cultured in big fermentation plants. The process can take years, and the investment in manufacturing alone can reach \$500 million.

Aptamers are oligonucleotides synthesized in vitro from nucleic acids produced in commercially available automated systems that fit into an office-sized space. Making aptamers at manufacturing scale requires an investment of about \$50 million, although synthesis costs are declining.

De Souza, who is widely published and has held high-profile academic appointments and senior positions with DuPont Merck Pharmaceutical, Neurocrine Biosciences (which he founded), Neuroscience Pharma, Hoechst Marion Roussel, and Aventis, clearly enjoys enumerating what he believes are other advantages of aptamers over antibodies:

- Initial therapeutic leads for an aptamer drug can be generated in as little as two weeks
- Because they are chemically synthesized (and amplified in the SELEX process), aptamers have demonstrated extraordinary specificity for their molecular targets, which have included growth factors, enzymes, immunoglobulins, receptors, and viral proteins
- Ditto for aptamer affinity (binding strength)
- Aptamers can disrupt protein-protein interactions
- Aptamer therapeutics can be administered subcutaneously
- Aptamers are stable molecules that can be stored at room temperature

Also, the pharmacologic properties of aptamers include wide therapeutic margins,<sup>1</sup> stability, modulatable pharmacokinetics, and very low immunogenicity and toxicity. Pure RNA/DNA are degraded within minutes in the bloodstream, and aptamers have long had a reputation for short half-lives. That stability problem has apparently been

<sup>1</sup> The therapeutic margin of a drug is the difference between the optimal effective dose and the dose at which unacceptable adverse effects occur.

solved by “civilizing” chemistries that can “tune” in vivo aptamer half-lives to match their indication.

“You want aptamers to be cleared in two minutes? That’s easy,” says De Souza. “If you want them to hang around for a week, we can do that, too.”

When asked about aptamer disadvantages, De Souza responds that they can’t get into cells. “But neither can antibodies,” he adds.

Should payers be excited about aptamers?

“I think so, and I’ll tell you why,” De Souza responds. “A drug like Avastin [bevacizumab] is selling for \$50,000 to \$100,000. We can bring [the price of treatment] down because of our lower manufacturing costs and cost of goods — less than 10 percent. By comparison, the cost of goods of an antibody usually runs 20 to 30 percent. That’s why insurance companies should be excited. Aptamers are doing the same thing as an antibody, but bringing the cost of goods down.”

Early this year, Archemix launched a phase 1 trial for ARC 1779, which reduces platelet aggregation and thrombosis by inhibiting the von Willebrand Factor (vWF). Planning is underway for phase 2 for cardiology and hematology-related indications late this year. The goal is to improve care for patients with life-threatening thrombosis by offering a better risk-to-benefit ratio between antithrombotic efficacy and treatment-related bleeding than treatments that are currently available. The company also has candidates for oncology and inflammatory indications, including an aptamer against immunoglobulin E for asthma.

Last July, Archemix started cash-

ing in on its aptamer expertise and patent estate. It closed a three-year deal with Dublin-based Elan to develop drugs targeting the interleukin-23 cytokine in autoimmune inflammatory conditions. In August, it expanded its collaboration with Nuvelo, in San Carlos, Calif., to develop and market aptamers targeting the coagulation cascade in cardiovascular procedures. More recently, in January, Archemix agreed to provide product candidates for targets identified by Pfizer, and agreed to collaborate with Merck KGaA, in Darmstadt, Germany, to discover, develop, and commercialize aptamer cancer drugs.

So why did it take 17 years after Tuerk and Gold’s eureka moment for the first aptamer-based drug to hit the market? Gold says that’s still less time than it took for the first mAb drug to hit the market after César Milstein discovered how to make antibodies.

“If you think about where antibodies were around 1996 and ’97, when you had one or two antibodies on the market and people clearly realized their potential, aptamers are probably on an even more accelerated trajectory now,” says De Souza.

### BULLISH ON APTAMERS

Anthony P. Adamis, MD, Harvard specialist in ocular neovascularization, and his team searched in the late ’90s for anti-VEGF drugs after they discovered that VEGF played an important role in macular degeneration. They happened on NeXstar, a small company in Colorado, and liked what they learned about aptamers.

Then in April 2000, Adamis, who was working as a consultant to

NeXstar, teamed with colleagues David Guyer, John McLaughlin, and Marty Glick to acquire the rights to NX1838 (the future pegaptanib) and created Eyetech Pharmaceuticals, the company that developed and launched the first aptamer-based drug. Pegaptanib (Macugen) was approved by the U. S. Food and Drug Administration in 2004 for all types of neovascular age-related macular degeneration.<sup>2</sup>

“I’m bullish on aptamers,” says Adamis. “I think they’re going to be an important, big class of molecules. That’s why the next drug we’re developing is an aptamer.”

Adamis anticipates a phase 1 initiation for E10030, a new aptamer-based macular degeneration therapy targeting platelet-derived growth factor that could be used in combination with any anti-VEGF agent, by the middle of this year.

### SAFER DRUGS?

In its collaboration with Nuvelo, Archemix is responsible for discovering multiple short-acting aptamers that target the proteins in the coagulation cascade. The first molecule, developed under a prior agreement, demonstrated proof of concept but lacked the necessary potency.

In less than a year, Archemix developed NU172, a potent anti-coagulant in animal studies that has demonstrated a rapid onset and offset of action and reduced bleeding. Those are precisely the characteristics you’d find on a cardiovascular surgeon’s wish list for a drug to re-

<sup>2</sup> OSI Pharmaceuticals acquired Eyetech in 2005 and put pegaptanib up for sale last year. Ironically, Genentech’s mAb for wet age-related macular degeneration, ranibizumab (Lucentis), has taken significant market share from pegaptanib.

place the current combination of heparin and protamine. In fact, the global market for antithrombotics is estimated at \$10 billion, and injectable antithrombotics are the fastest growing segment.

In coronary artery bypass surgery, for example, the current standard is heparin, followed by protamine to reverse the heparin. Not only are both drugs plagued by significant side effects, heparin is long acting and brings with it the risk of heparin-induced thrombocytopenia.

“NU172 is an aptamer that binds to thrombin and creates a profound anti-coagulant effect as long as it’s being infused, and rapidly self-eliminates once you turn the infusion off,” says Ted Love, MD, chairman and CEO of Nuvelo, which is focused on cardiovascular and cancer therapies. “We think this is an ideal profile for surgery, and we plan to start the phase 1 clinical trial in Q4 of this year or Q1 of next year.”

In the still relatively uncrowded aptamer therapeutics space, what are the chances that another biotech is working on the same indication, using aptamer technology but with another mechanism to stop the antithrombotic drug’s activity?

“At Duke, we would rather give the physician active control by administering an antidote to rapidly shut off the drug’s effect, rather than having the patient’s body clear the compound and be subject to whatever variation you have between patients,” explains Bruce Sullenger, PhD, professor in the department of surgery, chief of experimental surgery, and director of the Duke Translational Research Institute at

Duke University. Sullenger performed the first therapeutic aptamer studies in 1990 showing that a viral-derived aptamer could inhibit HIV replication. He subsequently learned the SELEX technique from Tuerk and Gold while a postdoctoral fellow in Colorado. Sullenger is a scientific founder of Regado Biosciences in Research Triangle Park, N.C., and serves as a consultant.

Regado, an Archemix licensee, successfully completed a phase 1 trial of REG1, a Factor IX anti-coagulant/antidote combination, and published the results in the December 2006 issue of *Circulation*. The company describes itself as “a bio-

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DUKE UNIVERSITY

pharmaceuticals company developing antidote-controlled therapeutics via simultaneous rational design of drug-antidote pairs.”

“One major advantage in using aptamers as drugs is the ability to design antidotes rationally,” Sullenger adds. “That’s tough to do with antibodies or small molecules. The take-home message might be that aptamers may actually improve the safety side of the patient outcome equation, and hopefully be as efficacious, if not more so, than some of these other modalities.”

### A SUBSTANTIAL NICHE

Cy Stein, MD, PhD, has been in the therapeutic oligonucleotide field for 20 years and has published ex-

tensively. Oligonucleotides include aptamers, siRNA, and antisense. This gives him a certain credibility on the topic of aptamers in a world divided between aptamer enthusiasts — most of whom are affiliated with Archemix or SomaLogic — and everyone else.

Stein is professor of medicine, urology, and molecular pharmacology at Albert Einstein College of Medicine in New York, and is most closely associated with oblimersen sodium (Genasense), an anti-Bcl2 antisense oligonucleotide currently awaiting approval by European regulators.

“I think that aptamers have a very big potential,” says Stein, “Aptamers are going to be another weapon in the therapeutic armamentarium.”

Then he adds two caveats.

Caveat 1: He does not expect aptamers to replace antibodies. For one thing, there are no guarantees that an aptamer will produce the same effect on a given target as an antibody.

“There is so much nuance in the target, I don’t think you’re going to replace drugs that have clinical records and that physicians and patients trust,” says Stein. “Aptamers ... are going to find their own niche, which I think could be very substantial.”

Caveat 2:

“Until you get aptamers into human beings and do the pharmacokinetics and the pharmacodynamics, you don’t know. We’ll see.”

**BH**

*Contributing editor Bob Carlson writes exclusively about healthcare. He lives near Zionsville, Ind., and received his MHA from Indiana University.*