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FluoroPharma's Bet On Next-Gen Molecular Imaging Agents

Executive Summary

Molecular imaging's technological advances are impressive, but getting the business model right and investors on board has been hard for start ups in the field. FluoroPharma CEO Thijs Spoor believes his company, which has several cardiovascular imaging agents in clinical trials, is on the right track and ripe for partnerships.

Eli Lilly & Co.'s acquisition of molecular imaging start up **Avid Radiopharmaceuticals Inc.** in December 2010 was noteworthy, not only because of its high price tag ("Drug Maker Lilly Buys Alzheimer's Test Developer Avid For Up To $800 Mil." — *"The Gray Sheet,"* Nov. 15, 2010). It also indicated that molecular imaging is gaining the attention of Big Pharma, as it embarks on personalized medicine strategies for serious diseases with a limited arsenal of effective clinical biomarkers. Several companies, in addition to Lilly, reportedly bid for Avid and the industry is watching to see if that deal paves the way for more activities of a similar nature.

Avid was good news for a field characterized by technological advances and struggling business models. A record-breaker for a pre-commercial molecular imaging asset at $300 million upfront plus about $500 million in milestone-related earn-outs, the purchase gave Lilly a diagnostics development platform and florbetapir F18, an imaging agent for Alzheimer's disease facing priority review at FDA. Avid investors earned on average at least three times, if not more, the $69.5 million they had put in aggregate into the company—a return that industry watchers characterized as surprisingly robust.

"Avid was nice exit so there is reason to be optimistic, for the first time in a while," said Robert Weisskoff, a partner at Fidelity Biosciences, who also has a background in academia and industry, where one of his stints was senior director of imaging at **Epix Pharmaceuticals Inc.**, an early molecular imaging start up. Fidelity wasn't an Avid investor but it watches the space closely because of its potential and the Fidelity partners' internal expertise.

Molecular imaging currently consists of contrast agents that can track changes in the bodies of living things at the molecular level using older SPECT technology or positron emissions tomography. SPECT has limited sensitivity and image resolution; PET, while more effective, has been slow to take off, for a variety of reasons, even as the technology behind it advances. It may be coming into its own, however, as a variety of factors come together making the business model more rational and analysts peg global procedure growth in the double digits.

One company banking on Avid's momentum is **FluoroPharma Inc.**, a nine-year-old molecular imaging company founded by a PET pioneer, David Elmaleh. The company got caught in the PET doldrums of the first decade of the 2000s, but has since brought in new management, advanced its pipeline, and shored up its finances, notably through a reverse merger with a shell company in May 2011, that expanded its potential investor base said CEO Thijs Spoor. The reverse merger also helped it raise enough money to meet the terms of a licensing agreement it has with Massachusetts General Hospital. In December, it announced it had raised another $1 million from undisclosed investors, bringing total money raised in 2011 to more than $7 million.

That's not much support in the pharma world, but molecular imaging agents' development costs are much lower

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than those of therapeutics, yet the resulting products have comparative margins. With an established distribution infrastructure finally in place, attractive reimbursement, and huge unmet demand for biomarkers that can accelerate personalized medicine by identifying patient sub-segments that might distinctly benefit from certain therapies, the timing is right for widespread uptake of next-generation PET imaging agents, and for FluoroPharma in particular, insists Spoor, a nuclear pharmacist by training.

Before joining the company in late 2010, the CEO worked in both finance as an equity research analyst and in industry, as an executive at **Amersham Health**, now a subsidiary of **General Electric Co.**, where he ran the nuclear cardiology franchise for 11 years.

FluoroPharma discovers and develops proprietary PET imaging agents, based on technology invented by Elmaleh, a Harvard professor who is the company's chairman and also the director of contrast media chemistry at MGH. It has two Phase II-ready assets directed at cardiovascular disease and a robust early-stage pipeline of first-in-class imaging agents, including one for vulnerable plaque, which builds up in the arterial wall and can cause severe heart attacks or sudden cardiac death if it ruptures, and an Alzheimer's marker in preclinical development. "There is a PET ecosystem waiting for these. There are 7,000 nuclear cardiologists in the U.S, with the infrastructure – software, cameras, reimbursement--in place and they need new tracers to get everyone excited," Spoor argues.

Read Outs On Phase II Cardiac Assets Expected in Mid-2012

PET has come a long way since the 1970s, when a handful of scientists, including Elmaleh, began using it in their pre-clinical and clinical research. The utility of the technology and its chief imaging agent fludeoxyglucose (FDG) is now better understood scientifically; moreover, some of the reimbursement and intellectual property uncertainties have been addressed. PET is an improvement over traditional cardiac imaging because it can assess molecular metabolism of living things—animals and people—in real time, with high resolution, even while other imaging modalities, such as MRI, offer only static views of physiological structures.

Although almost all of the clinical use is currently for diagnosing and monitoring cancer, FluoroPharma and others are betting that new agents will expand the opportunity broadly to include cardiovascular and neurological applications ("The Pace of Development of Molecular Imaging Agents" — *IN VIVO*, May 2009). The U.S. now has a geographically dispersed network of several thousand PET facilities, supplied by local cyclotrons, where FDG and other molecular agents must be made, making the technology essentially ubiquitous, Spoor says.

On the other hand, the regulatory process remains a quagmire, experts say, although FDA is slowly clarifying its demands for approval ("FDA Develops Separate Set Of GMP Requirements For PET Drug Makers" — *"The Pink Sheet,"* Dec. 21, 2009). Currently, by dint of the field's idiosyncrasies and relative youth, many PET agents in commercial use do not have FDA approval, although the agency has set a deadline of Dec. 9, 2015 for all PET drugs in commercial use to obtain approval ("PET Drugs May Get Shorter Path To FDA Approval" — *"The Pink Sheet"* DAILY, Mar. 3, 2011).

The result is, from an investor's perspective, clinical development is somewhat faster than it is for therapeutics, although both kinds of compounds follow the same broad regulatory pathway. But the regulatory and commercial processes for molecular imaging in particular remain big hurdles, says Fidelity Biosciences' Weisskoff, who has looked at business plans of most of the current crop of molecular imaging companies. Some animal reagent imaging companies have succeeded in the marketplace, demonstrating the technology's scientific value, but "translating that into clinical imaging drugs has been a challenge," he said. "We still look at imaging companies because we have internal expertise and are seduced by the early-stage data. The early data has a good correlation for success in Phase III trials, but not very well correlated to regulatory approval or commercial success"

Weisskoff didn't comment specifically on FluoroPharma or other companies, but FluoroPharma now has enough funding to take its two most advanced assets, *Cardio*PET (Trans-9 [18F] Fluoro-3, 4-Methyleneheptadecanoic Acid) and *BFPET* (18F-labeled cationic lipophilic tetraphosphonium) through Phase II, an important check point for attracting partners, Spoor says. Data is expected on the two Phase II trials by mid-2012.

Although Phase I by definition consists of small sample sizes, it is an accurate barometer of efficacy as well as safety for contrast agents, enabling the Phase II trials to be somewhat de-risked, Spoor points out. If the drugs get to market, moreover, they ultimately aim to categorize patients who might benefit the most from particular therapeutic regimens, an attractive pharmacoeconomic proposition to bring to managed care.

As he sees, it therefore, FluoroPharma, with a current market cap of $23 million, is undervalued, and worth $40 million to $80 million, given the stage of its R&D portfolio. That valuation could triple if the products now moving through development succeed in Phase II.

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A Low-Cost, Robust Opportunity Business Model

Part of that overhang may be related to the spectacular bust of Molecular Insights, an early molecular imaging company that raised $65.1 million in a highly visible February 2007 initial public offering, only to file for Chapter 11 bankruptcy three years later, despite the support of some of the industry's top investors, scientists, and managers [See Deal]. The company emerged from bankruptcy in May 2011, after restructuring and reaching an agreement with bondholders.

FluoroPharma differs from Molecular Insights in key ways, notably its business model, which is built around a low-cost, largely virtual, infrastructure, including five full time staffers, outsourcing clinical trials and tying variable costs to particular projects development needs, says Spoor. Recently, Ascent Biomedical Ventures partner Lawrence Atinsky joined the board, which remains small due in part to constraints that the number can't be expanded without preferred stockholder approval.

Still, the scientific advisory board is a virtual who's who of the molecular imaging field, including Peter Conti, a nuclear physician at the University of Southern California, Elazer Edelman, of MIT, Daniel Berman of Cedar Sinai Heart Center, and Andrew Selwyn of Harvard. "The cardiovascular imaging field has been stagnant for some time…If we can find imaging agents that can better identify patients with disease abnormalities, or monitor their treatments," that would more the field forward, said Conti in an interview.

FluoroPharma's three clinical-stage assets include BFPET, a perfusion imaging agent, which tracks adequacy of blood flow in the heart, and CardioPET, which assesses myocardial metabolism for detection of ischemic and infracted tissue in patients suspected of having CAD for prediction of functional improvement prior to, or following, revascularization in patients with acute CAD including heart attacks. If approved, it may have several important advantages over SPECT or anatomical imaging, including more reliable reagent supply and improved accuracy.

The third agent, VasoPET (diadenosine 5'5'"-P1, P4-tetraphosphate analogs), an adenosine analog with the tracer F18 tacked on, is in preparation to begin Phase 1 trials for evaluation of risk of recurrence in patients who have had an acute heart attack or stroke; the company expects to submit an IND this year. It identifies vulnerable coronary artery plaques that are likely to rupture and cause heart attacks or strokes.

If approved, it would be the first PET agent to reliably image inflamed plaque and differentiate between vulnerable and stable coronary artery plaque. One potential drawback to date for adoption: therapies don't yet exist to stop vulnerable plaques from rupturing. At the same time, it's a Catch-22 because, in general, the lack of easy to use, non-invasive biomarkers to identify vulnerable plaques and monitor responses to treatment has slowed progress on therapeutic research in the field.

Still it's not clear that Big Pharma has an interest in imaging beyond certain very specific applications. Many companies have cut back on cardiovascular research because of the complexity and cost of doing large clinical trials that FDA requires for approval, so their interest in cardiac imaging agents subsequently might be lower than their current clinical trial activities would indicate.

Even Lilly is circumspect in how it views Avid's role in its overall corporate strategy. The acquisition gave the Big Pharma a "diagnostics development platform covering several therapeutic areas, including Alzheimer's disease, Parkinson's disease, and diabetes," a spokesperson said in an email, adding, while it "provides us with a good foundation, and we will look at other opportunities in diagnostics that closely align with our core therapeutic areas, we have no near-term plans to create a stand-alone diagnostics business."

AstraZeneca PLC, in fact, in December, out-licensed a potential Alzheimer's marker to Neoprobe Corp., another molecular imaging agent biotech. The marker, a fluorine-18-labeled radiotracer, has potential to aid in the diagnosis of the disease, with a Phase III trial expected to begin in 2013. To date, however, aside from the Avid deal, financing activities in the field appear to be small, often in the mid single digits; the AstraZeneca-Neoprobe deal included a $5 million upfront to AstraZeneca and contingent milestone payments totaling $6.5 million, based on clinical development and regulatory progress, as well as another $11 million for post-regulatory milestones.

And much may hinge on how the Lilly/Avid drug, *Amyvid*, does before FDA. The company received a not entirely unexpected "Complete Response" Letter for the drug from FDA in March 2011, asking for a training process for physicians to be sure they can accurately read and interpret the data emerging from the scan. The drug detects beta-amyloid in the brain. "Everyone is holding their breath on this one," said Weisskoff.

-Wendy Diller (w.diller@elsevier.com)

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