

START-UP

Emerging Medical Ventures

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10 Health Care Information Technology: Venture's New Darling?

As traditional venture-like returns are harder to generate from drug development and medtech plays, some frustrated VCs see new opportunities in health care information technology, an area many have traditionally avoided.

BY PAUL BONANOS

16 Drug-Eluting Balloons: Promise Versus Practicalities

Drug-eluting balloons might someday pick up where drug-eluting stents leave off, promising to solve problems not addressed – and even created - by DES. But despite what interventional cardiology companies have learned about device and drug combinations, the drug-eluting balloon markets aren't as simple as they might at first seem.

BY MARY STUART

PROFILES Novel Respiratory Therapies: Moving Beyond Symptomatic Relief

- 24 Current drugs for major chronic respiratory disorders relieve symptoms but do little to slow progression. The presence of mature products means new agents in development will only enjoy commercial success if they clear high safety and outcomes-based hurdles – and that's a bet few are willing to make.
- 28 **Pearl Therapeutics** develops combination therapies for respiratory disorders.
- 30 **Protectimmun** bets a bacterium can be an allergy prophylactic.
- 32 **Pulmatrix** alters airway fluid to treat respiratory disorders.

Start-Ups Across Health Care

- 34 **3WIN** precisely targets deep brain stimulation.
- 36 **Cianna Medical's** multi-catheter device delivers accelerated partial breast irradiation.
- 38 **GlySure** offers optical technology for continuous glucose monitoring in the ICU.
- 40 **Promedior** advances a pentraxin platform against fibrosis.

- 42 **EMERGINGS IN BRIEF:** BioCritica, Entericon, Radisens Diagnostics and Sovia Pharmaceuticals

1 VALUATION WATCH

Corporate VC Backing Influences
Private Biotech M&A Step-Ups

3 VENTURE 'ROUND

Radius Raises \$91 Million, Moves
Toward Public Listing

In Deep Brain Stimulation,
Sapiens Adopts Wise Model

8 CAPITAL MATTERS

Safeguard Jumps Into Life Science
But Leaves Behind Early-Stage Risk

43 SCIENCE MATTERS

Evidence Of Lung Stem Cells In Adults

44 ON THE MOVE

Who's Going Where In Biopharma
And Medtech Start-Ups

55 EXECUTIVE SUMMARIES

46 DEALS

Recent Financings Of
Private Companies And
Tech Transfers Between
Academia And Industry

Pulmatrix Inc.

Altering airway fluid to treat respiratory disorders

Pulmatrix Inc. was founded early in 2003 to develop technology meant to prevent individuals exposed to airborne pathogens from infecting others. In the wake of the attacks at New York's World Trade Center on September 11, 2001 and anthrax-by-mail scares the following month, more than a few health-industry executives and investors began to see "inescapable opportunities" in the prospect of bioterrorism. Robert Clarke, PhD, the first PhD employee at Pulmatrix and its current chief scientific officer recalls, "our idea was to develop something so that contaminated individuals, whether soldiers or civilians, could self-administer to the lungs and stop contagion."

Now Pulmatrix believes it has a much broader bailiwick than biodefense. Though still pursuing the premise of protecting US soldiers and civilians, supported in part by government grants, the company now aspires to treat a variety of respiratory disorders where infectious agents and associated airway inflammation cause or exacerbate symptoms. If the company's current thinking and early clinical data bear out, a single compound could treat acute infections as well as prevent exacerbations of chronic disorders including asthma, chronic obstructive pulmonary disease (COPD) and cystic fibrosis (CF). Flare-ups in these disorders are often caused by airborne pathogens.

The new vision arises from the company's efforts to broaden the market potential of its original drug candidate, described as an "inhaled cationic airway lining modulator (iCALM)." A "cation" is another word for a positively charged molecule. The molecules Pulmatrix has been working on all along are GRAS (generally recognized as safe) compounds: calcium and other elements in combinations and ratios the company has not disclosed publicly. "When we started out, many people doubted that these simple cationic salts could impact the airway

lining," Clarke says, "but then the data started coming in."

Research in recent years makes the company think that its original iCALM formulation and subsequent ones may be acting on calcium ion channels, and so changing calcium flux into cells or possibly influencing calcium-sensing at the cell surface. "We believe we are triggering and enhancing the antimicrobial peptides that cells are secreting," Clarke declares, adding, "We are also seeing reductions in pro-inflammatory cytokines and chemokines."

Pulmatrix spent six years working to develop a liquid formulation of one particular cationic combination it calls PUR003, which is delivered in aerosol form through a nebulizer during 12 to 15 minute sessions. Other drugs for serious respiratory disorders such as CF are delivered this way, but patients often resent and resist spending time sitting with a nebulizer. "It's fairly obvious that kind of product does not create vast market opportunity or patient compliance," says Robert Connelly, CEO of Pulmatrix since January 2008. Connelly was formerly the founding CEO and first employee of Domantis, an antibody-fragment company acquired in 2007 by GlaxoSmith-Kline PLC.

Under Connelly, by the fourth quarter of 2009, Pulmatrix got iCALM reformulated as a dry powder that can be delivered through a standard dry powder inhaler. By doing so, Pulmatrix believes it has produced a more convenient and possibly more potent drug candidate with a strong patent position. In the course of its efforts, Pulmatrix developed technology it calls iSPERSE for Inhaled Small Particles Easily Respirable and Emittable. Connelly says the method provides enhanced aerodynamic properties to dry powders, because of salts present in small amounts. He sees iSPERSE as "a discovery engine distinct from iCALM," noting

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Contact: Robert Connelly, CEO

Business: Therapeutics for respiratory diseases

Founded: April 2003

Founders: David Edwards, PhD (Harvard University); Mark Gabrielson (Ore Pharmaceutical Holdings); Alexander Klibanov, PhD (Massachusetts Institute of Technology); Robert Langer, ScD (MIT)

Employees: 35

Financing to Date: \$45 million

Investors: Polaris Venture Partners; 5AM Ventures; Novartis Venture Fund

Board of Directors: Robert Connelly; David Edwards; Steven Gillis, PhD (ARCH Venture Partners); Kurt Graves (Intarcia); David Maki (Altitude Life Sciences Ventures); Terry McGuire (Polaris Venture Partners); Scott Rocklage, PhD (5AM Ventures); Lauren Silverman, PhD (Novartis Option Fund)

Scientific Advisory Board: David Edwards; Robert Langer; Dennis A. Ausiello, MD (Harvard Medical School, Massachusetts General Hospital); Steve Calderwood, MD (MGH); Peter Palese, PhD (Mount Sinai School of Medicine); Richard Ulevitch, PhD (5AM and Chairman Emeritus, Scripps Research Institute); Tony Hickey, PhD (University of North Carolina); Sanjay Sethi, MD (SUNY Buffalo); David Clapham, MD, PhD (Howard Hughes Medical Institute, Children's Hospital Boston, Harvard Medical School); Ric Boucher, MD (UNC School of Medicine); Chuck Wira, PhD (Dartmouth University)

that Pulmatrix can now prepare in just days or weeks spray-dried formulations of marketed respiratory drugs and proprietary molecules, suitable for in vivo testing.

The new dry powder formulation of iCALM, coupled with positive results in animal models of disease plus adequate human safety data from the original liquid formulation, helped attract fresh capital. In November 2009, a group of investors joined in a financing the com-

pany says is worth \$30.3 million.

Connelly says Pulmatrix is now investigating combinations of iCALM with marketed respiratory drugs, including fluticasone and salmeterol, the ingredients in GSK's *Advair*. That blockbuster combination of a corticosteroid and a long-acting beta agonist is used to prevent asthma attacks and to treat COPD. It generated \$8.4 billion in 2010 for GSK, which in early June announced positive data on *Relovair* (fluticasone/vilanterol), the once-daily drug candidate being groomed as *Advair*'s successor. "It's next to impossible to create inhaled dry-powder generic drugs due to current regulations and device-patent hurdles," Connelly points out. But iSPERSE gives Pulmatrix opportunity to try.

In June 2011, Pulmatrix announced a new slate of scientific advisors that have agreed to help Pulmatrix plan and carry out clinical trials, understand more about the biological effects of iCALM and iSPERSE, and pursue new commercial opportunities.

Connelly and Clarke acknowledge it is only recently that Pulmatrix has been looking closely at the biological effects of iCALM. Previously, the company had a more biophysical orientation shaped by its founders, who include three world-class experts in materials science from the **Massachusetts Institute of Technology** and **Harvard University**: Robert Langer, Alexander Klivanov and David Edwards.

Whereas most biotechnology start-ups develop drug candidates against specific molecular targets, the founding team of

Pulmatrix set out to trap infectious organisms by making the airway lining stickier. The scientists figured that intruding organisms, once caught, could be cleared from the respiratory system as they normally are, by the motions of the minute hairs known as cilia. The founders realized that mucins, glycoproteins that line the airways, are negatively charged and become more elastic when cationically triggered. Making the mucus stickier at its surface does not make the lung abnormal, and may actually enhance airway clearance, Connelly says: "While the surface of the airway lining fluid may be more elastic, underneath the mucus remains thin and fluid."

In the first quarter of 2011, Pulmatrix began its first Phase I trial of the dry-powder formulation PUR118 in healthy normal volunteers in England. At the beginning of May 2011, the company began a Phase IB trial of PUR118 in patients with mild COPD. Beyond assessing the safety of the dry powder formulation, Pulmatrix is also looking at biomarkers of inflammation and innate immunity along with the drug's impact on mucociliary clearance. Pulmatrix expects this trial to complete

by the end of the third quarter. By the end of 2011 Connelly says the company hopes to begin a Phase IIa trial of patients with moderate to severe COPD at the **State University of New York, Buffalo** (SUNY Buffalo) and other sites.

Pulmatrix also expects to soon start a Phase I trial of PUR118 in cystic fibrosis at **Johns Hopkins University** and the **University of North Carolina**.

The iSPERSE formulation of iCALM is doing more than increase the number of disorders the drug candidate can potentially treat; Connelly says it is also creating a business development challenge "because we want value for all the indications." As for every other start-up seeking partnerships, the market will determine how much Pulmatrix has to de-risk its assets before

it can strike a deal.

To date, Pulmatrix has raised \$45 million from investors including ARCH Venture Partners, Polaris Venture Partners, 5AM Ventures and Novartis Venture Fund. [\[A#2011900133\]](#)

— DEBORAH ERICKSON

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