

# Limerick BioPharma Inc.

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**Summary:** Limerick BioPharma is developing drugs that help cells pump unwanted substances away from vulnerable tissues. For diabetes, it is seeking a lead candidate among what it calls Limerick Activators that can increase activation of ATP-binding cassette transporters to promote efflux of lipids from peripheral and pancreatic beta cells, resulting in lowering of serum lipid and glucose.

<b>Further Analysis:</b>	<b>Title</b>	<b>Magazine</b>	<b>Issue</b>	<b>Article ID</b>
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## **Limerick BioPharma Inc.**

### **Molecular transporters expel excess lipids in metabolic disease**

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Industry Segment: Biotechnology

Business: Cellular pump activators

Founded: November 2004

Founders: Wendye Robbins; Ving Lee, PhD, CSO; Leslie Z. Benet, PhD (University of California, San Francisco); Franz Hefti, PhD (Avid Radiopharmaceuticals); Cynthia G. McCormick, MD (McCormick Consultation, LLC)

**Employees:** Undisclosed

**Financing to Date:** \$35.5 million

Investors: Altitude Funds; ARCH Venture Partners; OVP Venture Partners; Sevin Rosen Funds

Board of Directors: Kristina Burow (ARCH Venture Partners); Steve Dow (Sevin Rosen Funds); Corey S. Goodman, PhD; Wendye Robbins; Chad Waite (OVP Venture Partners)

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Cells employ molecular transporters to expel a variety of molecules, including drugs and endogenous substances like fats. Fifty-five known genes produce them, and they can be found in the brain, kidneys, pancreas, liver, skeletal muscles, intestines and immune cells. The pumps operate constantly at between 30 and 70% efficiency, but can be activated under stress conditions to quickly ramp up their capacity.

The pumps have long been a focus in antibiotics resistance, because they can swiftly remove the drugs from the bacterium, averting toxicity. In human cells, the pumps can confer resistance to chemotherapeutic agents or anti-seizure drugs. As a result, most research on cellular pumps (known as ATP-binding cassette transporters) has focused on shutting them down.

**Limerick BioPharma Inc.** takes the opposite tack, developing drugs to activate the pumps to reduce side

effects of drugs. The company was originally founded on the idea of limiting the side effects of pain killers by preventing them from entering the brain stem and causing addiction. "I'm an anesthesiologist by training and every time I walked into a waiting room at Stanford, I saw people who didn't choose to get addicted to opiates, but became addicted anyway. My thought was it would be cool if we could continue to supply the drugs that their peripheral nerves need, but bypass the brain stem to avoid addiction," says Wendye Robbins, president and CEO of Limerick. She is also an assistant professor of anesthesiology at the **Stanford University Stanford School of Medicine** and a founder of NeurogesX, which develops pain therapies.

She points to the example of the anti-diarrheal *Immodium*, which is 10 times more potent than morphine in binding studies. "But it's not a drug of abuse because it doesn't leave the gut," says Robbins.

The pump activators were initially discovered by examining a library of molecules designed to inhibit pumps in an effort to combat antibiotic resistance. The team examined the molecules that had been failures. They reasoned that they had been designed to interact with the pumps, and if they failed to inhibit them, perhaps they would activate them instead. "It was a guess," Robbins says, but it paid off with lead molecules.

The company has identified a molecular scaffold that broadly activates pumps, and researchers are refining compounds and screening them to make them selective. "We are learning the specificity of the different pumps in different tissues," says Robbins.

With drug candidates in hand, Robbins and her colleagues looked for applications. The narcotic space was scientifically promising, but the company was founded in 2004, and the opiate space was politically charged after the market withdrawal of *Vioxx* (rofecoxib) in September of that year. "We made a decision that it was a high risk, low return market," says Robbins. Instead, she and her colleagues turned to chemotherapeutics and immunosuppressive medications. "They can cause permanent damage by getting into the wrong tissues, so it seemed like a more reasonable place to spend time and energy," she says.

The organ transplant space was alluring. Widely used anti-rejection drugs known as calcineurin inhibitors (CNIs) cause a number of side effects, including hyperglycemia, central nervous system irritability, and nephrotoxicity. The side effects of CNIs impact the health of patients, but they can also reduce survival of the graft.

Limerick researchers reasoned that these effects could be countered because they occur when the drug reaches unintended tissues including the pancreas, brain, and kidneys. They set about screening for drugs that could selectively activate pumps in these tissues. Animal studies indicated that pump activators reduced hyperglycemia and kidney toxicity in rats on CNIs, without disrupting the immunosuppressive effects of the drugs.

One drug, LIM-0705, has shown promise in a Phase I human clinical trial in easing the side effects of the drug tacrolimus, which can cause hyperglycemia and diabetes. LIM-0705 conferred improvements in blood sugar levels in the patients. The drug probably works by activating pumps to keep the drug out of the pancreas, Robbins notes.

The drugs don't remove drugs from non-target organs with 100% efficiency. "We're limiting exposure by about 30 to 70%, depending on the ligand that is being chaperoned. It seems to be enough [to improve patient outcomes]," Robbins says.

The technology could be used to limit side effects in other drug classes, including opioids, immunomodulators, selective estrogen receptor modulators, and psychotropics.

And it isn't limited to addressing side effects. Limerick also has a preclinical program in metabolic disease, aimed at pumping triglycerides and other fats out of pancreatic cells. "It seems to make the pancreatic cells

survive longer and make the beta cells in the pancreas more productive," says Robbins. She expects a lead drug to be chosen by the third quarter of 2010, and a Phase I study to start in the first quarter of 2011.

The pump activators are quite specific in the tissues that they affect. That specificity could limit the market of each drug to particular indications, but it also conveys an advantage: "With broad pump activation, if a patient takes your drug and is on some other medication, you worry about the pumps interfering with the other medications. I don't mind that the pump activators appear to be very selective," says Robbins.

The transplant market is \$3.5 billion a year worldwide, with only a few companies involved. Diabetes is also alluring at around \$15 billion a year. "It's a giant field. Some of the drugs work pretty well, but some are also pretty toxic, and we could compete as a monotherapy. It really depends on how effective our drug is in overweight people, but based on what we've seen so far we think it could really work. It's a big risk and a big opportunity," Robbins says.

There are no other companies developing pump activators that Robbins is aware of. In the anti-rejection market, the biggest competitor is likely to be the candidate drug belatacept. It is a protein that selectively blocks T cell activation, it is being developed by **Bristol-Myers Squibb Co.**, and it has less impact on blood sugar than tacrolimus.

Robbins hopes to see the company identify a range of drug candidates, including monotherapies and adjunctive therapies. "Our goal is to do a good job of that so that we'll have a lot of options. It's quite likely that we'll decide to partner."

Limerick has raised \$35.5 million so far, from sources including ARCH Venture Partners, Sevin Rosen Funds, Altitude Funds, and OVP Venture Partners. [W#200930310] – Jm Kling