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Emerging Company Profile

Calithera: Activating caspases

By Chris Cain
Staff Writer

Unlike most companies working on inducing apoptosis to treat cancer, which have focused on upstream components of the pathway, **Calithera Biosciences Inc.** has identified small molecules that work far downstream to activate caspases. The company thinks the ability to precisely target specific caspases may yield treatments that are highly selective for specific cancers.

The main challenge to overcome is finding the right caspase targets and optimizing dosing to preferentially kill cancer cells without harming healthy tissues, where caspases are broadly expressed.

Doing that will require extensive pre-clinical investigation, but the challenge is not foreign to President and CEO Susan Molineaux. As CEO and CSO of Proteolix Inc., she developed inhibitors of the proteasome, another enzyme that is ubiquitously expressed, and is essential to regulating the cell cycle.

Proteolix was acquired by **Onyx Pharmaceuticals Inc.** for \$276 million in cash and up to \$575 million in milestones last year (see *BioCentury*, Oct. 19, 2009).

Calithera's investors are obviously confident the company will solve the problem: The newco raised \$40 million in a

Calithera Biosciences Inc.

South San Francisco, Calif.
Technology: Small molecule caspase activators
Disease focus: Cancer
Clinical status: Preclinical
Founded: June 2010 by Susan Molineaux and Jim Wells
University collaborators: None
Corporate partners: None
Number of employees: 22
Funds raised: \$40 million
Investors: Morgenthaler Ventures, U.S. Venture Partners, Advanced Technology Ventures, Delphi Ventures and Mission Bay Capital
CEO: Susan Molineaux
Patents: None issued

series A round led by U.S. Venture Partners and Morgenthaler Ventures in July.

"One reason we have significant funding is because our backers have faith that we have the desire and ability to thoroughly investigate the safety of these compounds," Molineaux told *BioCentury*.

Caspases are a group of 12 cysteine proteases that are initially synthesized in

an inactive procaspase form. Many intra- and extracellular signals feed into and activate caspases. A subset of these enzymes, known as executioner caspases, trigger apoptosis by cleaving hundreds of downstream proteins essential for cell survival.

It is well established in the literature that most cytotoxic drugs ultimately work by activating caspases and causing apoptosis. But according to Molineaux, "one of the challenges of cytotoxic drugs is they work upstream of many pathways, and mutations in key genes such as p53 or Bcl-2 block the signals leading to caspase activation, causing the tumors to become resistant to the drugs."

In search of a more direct route, scientific founder Jim Wells screened 62,000 small molecules to identify compounds that could convert an inactive procaspase to its active caspase form.

Wells is director of the Small Molecule Discovery Center and professor of pharmaceutical chemistry and cellular and molecular pharmacology at the **University of California, San Francisco**. Calithera has rights to patent applications covering caspase activators from UCSF.

Wells identified compounds that could potentially kill multiple cancer cell lines —

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Calithera Biosciences Inc.,
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including p53-deficient breast cancer cells and p53-proficient breast cancer cells — by activating caspase-3, an executioner caspase. The work was published in *Science* last year.

But the compounds also potently induced cell death in non-cancerous cells. This non-discriminatory cytotoxicity could result in a therapeutic index too narrow to be used in humans.

Calithera believes it can overcome this potential toxicity. Preliminary proof of principle was provided by cell culture data from Wells' lab suggesting that a cancerous B cell line was more sensitive to caspase activation than normal B cells.

In addition, some tumors express higher levels of specific caspases than healthy cells, suggesting that targeting the correct caspase with the correct dose might preferentially kill tumor cells. The company plans to conduct studies of its compounds in various cell lines and animal models of cancer to test this hypothesis.

Calithera is not the first company to attempt to directly activate the apoptotic pathway in cancer.

BioLineRx Ltd. thought it had licensed a caspase activator from the **University of Illinois, Urbana Champaign** in 2007. But further studies demonstrated the compound, dubbed BL-4030, worked more generally by chelating zinc, a metal required for numerous cellular processes (see *BioCentury*, July 30, 2007).

According to the university, BioLineRx returned rights to the

compound in 2009.

At least eight companies have compounds in preclinical or clinical development that target the pathway through upstream regulators of apoptosis. The most advanced is **Aegera Therapeutics Inc.**'s AEG35156, a second-generation antisense oligonucleotide targeting XIAP mRNA, which is in Phase II testing to treat liver cancer.

In addition, several companies are developing caspase inhibitors. The most advanced of these is emricasan, a pan-caspase inhibitor from **Conatus Pharmaceuticals Inc.** in Phase II testing to treat HCV.

Molineaux said Calithera is interested in developing its compounds itself, although it may consider partnering if the compounds show efficacy in multiple types of cancer.

The company also plans to pursue the activation of enzymes other than caspases, but Molineaux said those plans are in early stages.

She expects the series A funding to last about four years and to allow the completion of at least one Phase I study.

COMPANIES AND INSTITUTIONS MENTIONED

Aegera Therapeutics Inc., Montreal, Quebec

BioLineRx Ltd. (Tel Aviv:BLRX), Jerusalem, Israel

Calithera Biosciences Inc., South San Francisco, Calif.

Conatus Pharmaceuticals Inc., San Diego, Calif.

Onyx Pharmaceuticals Inc. (NASDAQ:ONXX), Emeryville, Calif.

University of California, San Francisco, San Francisco, Calif.

University of Illinois, Urbana Champaign, Urbana, Ill.