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Emerging Company Profile

Verastem: Cancer stem cell engine

By Andrew Fisher
Staff Writer

Cancer stem cells have long been recognized as important therapeutic targets, but growing enough of them to allow for screening with typical drug discovery methods has been a challenge. **Verastem Inc.** believes its techniques have removed the bottleneck to high throughput screening.

Cancer stem cells (CSCs), which often remain after treatment with chemo- or radiotherapies, are believed to be responsible for disease recurrence and can migrate through the body to form metastases.

Verastem uses a procedure developed by co-founder Piyush Gupta and colleagues that forces cancer cells to undergo epithelial-mesenchymal transition (EMT). Co-founder Robert Weinberg said cells undergoing EMT “acquire a ‘stem-ness’” that includes increased motility, the ability to form new cancers, and an increased resistance to chemotherapies — all properties of CSCs.

With the ability to drive cells through EMT, Verastem can produce an almost unlimited number of its CSCs for screening.

Researchers from the **Broad Institute** and Verastem have screened more than 300,000 compounds from libraries at Broad, the **Whitehead Institute for Biomedical Research** and Verastem. Several small molecule leads with increased selectivity for CSCs over normal cancer cells have been identified.

One of the Verastem compounds, VS-507, is a proprietary formulation of salinomycin being developed to treat breast cancer. The selective potassium ionophore is marketed as a generic veteri-

Verastem Inc.

Boston, Mass.

Technology: Therapeutics targeting cancer stem cells

Disease focus: Cancer

Clinical status: Preclinical

Founded: 2010 by Richard Aldrich, Piyush Gupta, Satish Jinal, Eric Lander, Robert Weinberg and Christoph Westphal

University collaborators: Harvard University and Massachusetts Institute of Technology

Corporate partners: NA

Number of employees: 15

Funds raised: \$48 million

Investors: Advanced Technology Ventures, Astellas Venture Management, Bessemer Venture Partners, Cardinal Partners, Longwood Founders Fund and MPM Capital

CEO: NA

Patents: 3 issued covering methods for screening for compounds that target cancer stem cells and use of these compounds to treat cancer

nary antibiotic. Verastem said the exact mechanism by which VS-507 kills CSCs has not been determined.

Weinberg and colleagues have shown that salinomycin reduced the proportion of CSCs in breast cancer cells by more than 100-fold compared with paclitaxel.

In a mouse model of breast cancer, salinomycin inhibited tumor growth and metastasis compared with paclitaxel. Data were published in *Cell* in 2009.

COO Robert Forrester said the company is screening for additional compounds, including NCEs.

While Verastem has not picked a lead, the company hopes to begin Phase I/II testing next year of at least one molecule to treat triple-negative breast cancer in patients with low levels of claudin. Low levels of claudin-1 (CLDN1) have been implicated in increased risk of metastasis.

According to Forrester, these patients have few treatment options because their cancers are resistant to current therapies, and because CSCs make up 30-50% of their tumors.

Forrester said Verastem likely will pursue subsets of patients with other types of solid tumors based on the “biology underlying tumor recurrence and the role of cancer stem cells within the most aggressive tumors.” Weinberg added that the company plans to pair its anti-CSC agents with chemotherapy to kill both CSCs and conventional cancer cells.

Verastem also is developing a proprietary EMT signature as a companion diagnostic to monitor patients during clinical trials. The company envisions using biomarkers of mesenchymal cells instead of reduced tumor volume to measure the effect of its compounds. The assay also could be used to identify tumors that have a high proportion of CSCs.

Verastem has about \$45 million in
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cash, which Forrester said should take one to two compounds through Phase II testing in the next 2-3 years. The company plans on taking its compounds through Phase II without a partner.

At least two other companies targeting CSCs have compounds in the clinic. **Boston Biomedical Inc.**'s BBI608 is in Phase Ib/II testing for solid tumors and Phase I for colorectal cancer. **Dainippon Sumitomo Pharma Co. Ltd.** has an option to the small molecule CSC inhibitor against an undisclosed molecular target.

This year, **OncoMed Pharmaceuticals Inc.** began a Phase I trial of OMP-59R5 to treat advanced solid tumors. **GlaxoSmithKline plc** has an option to the mAb that binds selected Notch receptors under a 2007 deal to identify mAbs against CSCs.

According to Forrester, other companies targeting CSCs design molecules against a specific target. In contrast, Verastem thinks its ability to generate a stable pool of CSCs will allow it to look for compounds that show activity against the tumor, regardless of the specific target.

"We're taking the premise that we'll let the biology direct us to the right chemistry," he said.

COMPANIES AND INSTITUTES MENTIONED

Boston Biomedical Inc., Norwood, Mass.

Broad Institute, Cambridge, Mass.

Dainippon Sumitomo Pharma Co. Ltd. (Tokyo:4506; Osaka:4506), Osaka, Japan

GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.

OncoMed Pharmaceuticals Inc., Redwood City, Calif.

Verastem Inc., Boston, Mass.

Whitehead Institute for Biomedical Research, Cambridge, Mass.

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