

Emerging Company Profile**CalciMedica: CRACKing toxicity**

By Matthew Mikulski
Staff Writer

Calcineurin inhibitors are effective in preventing acute organ transplant rejection and treating autoimmune diseases, but their long-term use is associated with renal and hepatic toxicities. CalciMedica Inc. hopes to sidestep these toxicities by developing therapeutics that modulate calcium release-activated calcium channels, key upstream regulators of calcineurin activity.

Both of the calcineurin inhibitors approved to protect against transplant rejection have black box warnings. Prograf tacrolimus from Astellas Pharma Inc. (Tokyo:4503, Tokyo, Japan) has a warning for increased risk of hematological malignancies. The label for generic cyclosporin A warns of the potential for systemic hypertension and nephrotoxicity. Exactly how long-term inhibition of calcineurin generates these unwanted effects is not known.

CalciMedica (La Jolla, Calif.) is working upstream from calcineurin in calcium-dependent immune activation, developing inhibitors of the complex formed by stromal interaction molecule-1 (STIM-1) and ORAI1.

The company, which was co-founded by the CBR Institute and TorreyPines Therapeutics Inc. (TPTX, La Jolla, Calif.), has rights to TPTX's patent applications covering uses of STIM-1 and ORAI1 to regulate calcium release-activated calcium (CRAC) channel activity.

Recent studies have shown that transmembrane protein 142A (ORAI1, TMEM142A) forms a complex with STIM-1 that is needed for the CRAC channel to function. It is believed that STIM-1 senses calcium depletion within the endoplasmic

CalciMedica Inc.

La Jolla, Calif.

Technology: Inhibition of calcium release-activated calcium (CRAC) channels

Disease focus: Transplant, autoimmune

Clinical status: Lead optimization

Founded: 2006 by Gonul Velicelebi, Ken Stauderman and Jack Roos

University collaborators: CBR Institute for Biomedical Research

Corporate partners: None

Number of employees: 8

Funds raised: Not disclosed

Investors: SR One and Sanderling Ventures

CEO: Gonul Velicelebi

Patents: None issued

reticulum and communicates the need for calcium influx into the cell to ORAI1, a Ca²⁺-selective ion channel. Calcium influx is necessary for the activation of calcineurin.

President and CEO Gonul Velicelebi told BioCentury that case studies of two patients with rare loss-of-function mutations in ORAI1 offer evidence that inhibiting CRAC function might be safer than targeting calcineurin.

A paper published in *Nature* in May 2006 describes two patients with severe combined immune deficiency (SCID) syndrome who had defective CRAC function as a result of mutations in the ORAI1 gene. Velicelebi said although the patients suffer

from a chronically compromised immune system, they exhibit no organ toxicities.

CalciMedica has completed preclinical proof-of-concept studies in rheumatoid arthritis (RA), ulcerative colitis and delayed-type hypersensitivity. The company is holding off from additional animal studies until it has optimized lead candidates.

"Once we identify leads, we will conduct studies in organ transplant rejection and psoriasis, and additional studies in rheumatoid arthritis," Velicelebi said.

In addition to the compound series acquired from TPTX, CalciMedica is using proprietary cell lines as a screening platform to discover new molecular scaffolds that can modulate the activity of the STIM-1/ORAI1 complex.

CalciMedica raised \$1.5 million in a series A round and has completed an undisclosed first tranche of series B funding, with a second tranche expected to close early next year.

The funds are expected to take the company into early 2009, by which time it hopes to have submitted an IND for at least one compound and identified one or more follow-on molecules using its STIM-1/ORAI1 discovery platform.

CalciMedica is interested in partnering both the discovery platform and its development programs. But, Velicelebi told BioCentury, "if we don't find the right partnership, we can do it on our own."

At least two other companies are developing CRAC channel inhibitors: Synta Pharmaceuticals Corp. (SNTA, Lexington, Mass.) and Astellas. SNTA is in preclinical development. The pharma would not disclose the status of its program.

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