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Selection waits on efficacy data from trial of Kv1.3 ion channel blocker in atopic dermatitis

By Cormac Sheridan, Staff Writer

The coming months represent a crucial phase in the development of Selection Inc., a U.S.-German firm that is tackling a target in autoimmune disease that has evaded the best efforts of many other drug developers.

A recent interim readout from a phase Ib trial of si-544, a selective peptide-based blocker of the voltage-gated potassium ion channel Kv1.3, provided preliminary evidence that its drug candidate is safe and well-tolerated in patients with atopic dermatitis. It plans to evaluate its efficacy after three months' follow-up. "In a couple of months, we will have data from what we believe is the complete treatment cycle," Antonius Schuh, CEO of Selection (pronounced Select-ion) told *BioWorld*. If it can replicate in patients its preclinical findings in animal models, it could have a very valuable asset on its hands.

Antonius Schuh, CEO, Selection

Schuh credits George Chandy, of the University of California at Irvine, with identifying Kv1.3 as a target in autoimmune disease back in the 1980s. Chandy and colleagues identified and characterized the voltage-gated potassium ion channel properties of T-cells and then reported their role in human T-cell activation.

The interest in Kv1.3, in particular, stems from its role in the chronic activation of effector memory T-cells (TEM cells) in autoimmune disease, which offers a highly selective route to targeting a disease-associated T-cell population. That's because expression of other potassium ion channels becomes dysregulated once these cells are chronically activated. They become exquisitely dependent on Kv1.3 to maintain activation and ion homeostasis. What's more, the same dependency does not occur in healthy T-cells. "Typically, Kv1.3 is one of a group of redundant potassium channels," said Schuh. That difference gives drug developers a hook for selective targeting of these disease-associated T-cells.

Chandy and colleagues were first to demonstrate the clinical possibilities. "He got as far as bringing a poorly selective peptide into the clinic and showed durable efficacy," said Schuh. However, it was not feasible to take the molecule any further, because its lack of selectivity resulted in an excessive burden of side effects.

In 2017, Kineta Inc., of Seattle, reported data from a phase Ib trial of dalazatide in patients with mild plaque psoriasis. The drug exhibited a high response rate and modest levels of activity, even at the very low doses employed, but the company did not develop it further. "This was a homeopathic dose," said Schuh. "We can, of course, raise our dose dramatically higher."

The desired therapeutic effect can only be attained if developers can uncover a molecule with the necessary selectivity. The structure of the ion channel – and its resemblance to potassium ion channels expressed in other tissues – makes it challenging to achieve this. Targeting a single epitope is not sufficient. "The structural differentiation is in the collar of the channel," Schuh said. "That has been the entry point for the company." It refers to the region external to the central pore, which shows little variation across different potassium ion channels. "The pore is always the same," Selection's chief scientific officer and co-founder Andreas Klostermann told *BioWorld*.

Andreas Klostermann, co-founder and chief scientific officer, Selection

Klostermann has led an extensive discovery effort to find a molecule with the desired attributes of selective, high-affinity binding. This involved studying and learning from natural products, including venoms secreted by scorpions, sea anemones and conus snails, which also act on potassium channels; leveraging computer-based simulation data on the interactions between the target and binders; leveraging X-ray structural data; and studying the genetics of Kv1.3. These efforts then fed into the construction of a phage-display library that expressed peptides likely to have the desired properties. Its screening campaigns generated multiple selective binders,

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Continued from previous page

but si-544 "took the biscuit," said Schuh. It offers four orders of magnitude more selectivity than what has previously been reported in the literature, he said.

It has also demonstrated dramatic effects in both cell culture studies and animal models of autoimmune disease. "When you introduce si-544 into a culture of chronically activated effector memory T-cells, you see rapid and durable, dose-dependent deactivation of these cells," he said. In a rat model of arthritis, treatment resulted in an overnight improvement in mobility and a 75% reduction in joint swelling, Schuh said. "If that experiment is any indication, then we are good."

Moreover, the therapy, which has a half-life of just thirty minutes, appears to work as a switch, by turning off the pathological activation and restoring immune homeostasis. That may obviate the need for chronic dosing, the current paradigm for treating autoimmune disease, which creates significant safety concerns. "We absolutely believe you don't have to permanently suppress your immune system to control symptoms," said Schuh.

The company is headquartered in San Diego but was originally founded in Martinsried, Germany, where it retains its R&D functions. It has raised modest amounts of equity and debt financing so far. Schuh, a serial entrepreneur and investor, joined the company five years ago, along with chief financial officer Stephen Zaniboni. The pair have previously led several ventures together, including Sequenom Inc., Trovagene Inc. (now Cardiff Oncology), and Sorrento Therapeutics Inc., among others. Prospective pharma partners and investors have been skeptical about the program in the past. That is now beginning to change.