

NURIX: TWO SIDES OF PROTEIN DEGRADATION

BY CHRIS LIEU, STAFF WRITER

Nurix is flipping the concept of targeted protein degradation on its head. In addition to the usual approach of inducing target destruction, the company has technology that can block E3 ligase activity and increase a protein's levels. The latter is the basis of its preclinical immuno-oncology partnership with Celgene Corp.

Backed by a \$25.1 million series B from Third Rock Ventures and The Column Group and funds from Celgene, Nurix Therapeutics Inc. has developed two platforms that differentially modulate E3 ligases. Although founded in 2009, Nurix CEO Arthur Sands said the company "launched in earnest" in 2014 with the series B round, after it had gained a better understanding of E3 ligase biochemistry to enable screening and developed hit-to-lead programs to discover E3 ligase binders.

Nurix's first platform generates small molecules that inhibit E3 ligases, blocking target protein ubiquitination and subsequent degradation of the protein, which leads to increases in target protein levels.

Nurix signed its deal with Celgene in 2015 to develop these E3 ligase inhibitors for cancer, inflammation and immunology indications. The deal included \$150 million up front, an undisclosed series C investment and option fee, \$405 million in milestones per program and royalties.

The partners disclosed data from the program's first target, the E3 ligase Cbl-b, in an **abstract** released last month ahead of the American Association for Cancer Research (AACR) meeting. In T cells, Cbl-b inhibitors increased cytokine secretion and surface markers of activation, and showed efficacy in an ex vivo model of exhausted T cell function. In a syngeneic mouse model of colon cancer, a Cbl-b inhibitor decreased tumor growth.

According to Sands, the ligase appears to degrade proteins that are important in boosting T cell activity. "By preventing Cbl-b from doing its job, specific protein levels accumulate and cause T cells to be supercharged."

The company hopes to begin Phase Ia testing of its lead Cbl-b inhibitor in relapsed or refractory solid tumors in 2H20, then Phase Ib testing in 2021 for melanoma, lung cancer, clear cell renal cell carcinoma (ccRCC) and head and neck cancer.

Nurix's second platform generates linker small molecules, known as chimeric targeting molecules (CTM), that bind a disease-associated dysregulated protein and an E3 ligase. The E3 ligase ubiquitinates the target protein, which can then be degraded by the proteasome, and leads to decreases in protein levels.

In unpublished data, Nurix's lead CTM targeting Btk decreased tumor growth in a xenograft mouse model of lymphoma compared with vehicle, with potency comparable to the small molecule Btk inhibitor Imbruvica ibrutinib.

The company hopes to begin Phase I testing of its lead Btk CTM in relapsed or refractory B cell malignancies in 2H20.

According to BioCentury's BCIQ database, there are at least five other protein degradation companies, most of which are focused on targeted protein degradation.

Arvinas Inc.'s degraders are based on its proteolysis-targeting chimera (PROTAC) technology. The company has the androgen receptor protein degrader, ARV-110, in Phase I testing for metastatic castration-resistant prostate cancer (CRPC). According to Arvinas, this is the first protein degradation therapy to enter clinic. Arvinas also has six other degraders in preclinical testing for cancers and neurodegenerative diseases.

Kymera Therapeutics Inc. has an IRAK4-targeting heterobifunctional degrader in preclinical testing for MYD88-mutant lymphoma.

Other preclinical protein degradation companies include Third Rock-backed Cedilla Therapeutics Inc., C4 Therapeutics Inc. and Cullgen Inc., which have not yet disclosed pipeline products.

Sands said while other companies focus primarily on binders for CRBN and vHL, Nurix has identified binders for those and 12 other ligases. He added that Nurix's DNA-encoded library of compounds has given the company access to novel chemical matter to discover new ligases.

Cullgen told BioCentury the company is looking at undisclosed ligases besides CRBN and vHL.

According to Sands, there are no other companies that are attempting to inhibit E3 ligases to boost protein levels.

“We can push activity of these ligases in either direction.”

COMPANY PROFILE

Nurix Therapeutics Inc.

San Francisco, Calif.

Technology: Protein degradation platforms that can inhibit E3 ligase activity or promote E3 ligase targeted degradation

Disease focus: Cancer

Clinical status: Preclinical

Founded: 2009 by John Kuriyan, Michael Rapé and Arthur Weiss

University collaborators: None

Corporate partners: Celgene Corp.

Number of employees: 80

Funds raised: At least \$31.3 million

Investors: Third Rock Ventures, The Column Group and Celgene

CEO: Arthur Sands

Patents: None issued

COMPANIES AND INSTITUTIONS MENTIONED

American Association for Cancer Research (AACR), Philadelphia, Pa.

Arvinas Inc. (NASDAQ:ARVN), New Haven, Conn.

C4 Therapeutics Inc., Watertown, Mass.

Cedilla Therapeutics Inc., Cambridge, Mass.

Celgene Corp. (NASDAQ:CELG), Summit, N.J.

Cullgen Inc., San Diego, Calif.

Kymera Therapeutics Inc., Cambridge, Mass.

Nurix Therapeutics Inc., San Francisco, Calif.

TARGETS

Btk - Bruton's tyrosine kinase

Cbl-b - Casitas B cell lymphoma-b

CRBN - Cereblon

IRAK4 - Interleukin-1 receptor-associated kinase 4

MYD88 - Myeloid differentiation primary response gene 88

vHL - von Hippel-Lindau tumor suppressor