

BC INNOVATIONS | EMERGING COMPANY PROFILE

REPAIRE IN PROGRESS

BY KAREN TKACH TUZMAN, SENIOR WRITER

With a \$68 million series A co-led by Versant Ventures and MPM Capital, Repare Therapeutics Inc. emerged from 18 months of stealth today, making a splash in the growing pool of newcos targeting cancer via synthetic lethality. The company thinks its CRISPR screening platform will yield a deep, well-validated pipeline that could bring two lead compounds to the clinic in 2019.

Synthetic lethality occurs when deficiencies in different targets are separately tolerated, but trigger cell death when combined. That concept underlies the success of PARP inhibitors in BRCA1- and BRCA2-deficient ovarian cancers, and has spurred a rush to identify new targets that have synthetic lethal relationships with cancer-associated mutations, particularly in the DNA damage repair pathway.

"Synthetic lethality has the potential to really realize precision oncology, in the sense of being able to target patients with defined genetic alterations," said Dan Durocher, a senior investigator at Lunenfeld-Tanenbaum Research Institute and a scientific founder of Repare. "The issue now is how you find these synthetic lethal interactions in a prospective manner."

Repare's target discovery platform, developed by Durocher, involves conducting a CRISPR-based gene editing screen in two cell lines that are genetically identical except for a single cancer-associated mutation, and identifying which gene perturbations create synthetic lethal interactions in the mutant cell line.

Hits that are validated in primary tumor samples become drug targets for cancers with the mutation.

The newco's first disclosed program targets POLQ, a polymerase that promotes DNA repair via the alternative non-homologous end joining (NHEJ) pathway. A 2015 *Nature* study by co-founder Agnel Sfeir, an assistant professor in cell biology at New York University, showed tumors with BRCA1 or BRCA2 deficiencies require POLQ to repair double-stranded breaks, revealing a targetable synthetic lethality.

"It became obvious that POLQ was a very interesting target, but there were no inhibitors for it," said Sfeir. Her team conducted a small molecule screen for POLQ inhibitors, and the hits provided a starting point for compound development at Repare. The program will target cancers with mutations in other DNA repair proteins, with an initial focus on BRCA-deficient tumors.

Through the CRISPR platform, Repare is building a pipeline of other programs. According to Versant managing director Jerel Davis, the platform has already yielded an undisclosed target whose program is "as far ahead as we are for POLQ in generating an inhibitor that could be a great drug," plus a queue of others that are at earlier stages.

"The quality of the data coming out of the screen is a lot of what got Versant to invest in Repare," said Davis. The company has not disclosed details of the data it has on any of the targets, or what indications it will pursue first.

At least one other company, Artios Pharma Ltd., has a preclinical program inhibiting POLQ to induce synthetic lethality in cancers with defects in DNA damage responses, and at least three -- Metabomed Ltd., Ideaya Biosciences Inc. and Tango Therapeutics Inc. -- are founded on synthetic lethality platforms for cancer. Third Rock-backed Tango is also using a CRISPR-based screen to find synthetic lethal combinations.

But Durocher believes the Repare team's "expertise in DNA repair and DNA damage signaling" gives it a leg up over competitors, and Repare CEO Lloyd Segal said the newco used its time in stealth mode to validate its technology and set up operations at "industrial scale."

Segal said the series A funds should give Repare enough runway to take two compounds -- one against POLQ and another against the company's lead undisclosed target -- into Phase I/II testing in 2019.

He said the company is "collaborating closely with NYU on a range of IP filings around POLQ," and generating new IP covering its candidate compounds.

COMPANY PROFILE

Repare Therapeutics Inc., Montreal, Quebec

Technology: Small molecule therapeutics to induce synthetic lethality in cancers with specific mutations

Disease focus: Cancer

Clinical status: Preclinical

Founded: 2016 by Daniel Durocher, Agnel Sfeir and Frank Sicheri

University collaborators: **New York University, Lunenfeld-Tanenbaum Research Institute**

Corporate partners: None

Number of employees: 20

Funds raised: \$68 million

Investors: **Versant Ventures**, MPM Capital, Fonds de solidarité FTQ, Celgene Switzerland LLC affiliate of **Celgene Corp.**, BDC Capital's Healthcare Venture Fund

CEO: Lloyd Segal

Patents: None issued

COMPANIES AND INSTITUTIONS MENTIONED

Artios Pharma Ltd., Cambridge U.K.
Ideaya Biosciences Inc., South San Francisco, Calif.
Lunenfeld-Tanenbaum Research Institute, Toronto, Ontario
Metabomed Ltd., Yavne, Israel
Repare Therapeutics Inc., Montreal, Quebec
Tango Therapeutics Inc., Cambridge, Mass.

TARGETS

BRCA1 - Breast cancer 1 early onset
BRCA2 - Breast cancer 2 early onset
PARP - Poly(ADP-ribose) polymerase
POLQ - DNA-directed DNA polymerase θ

REFERENCES

Mateos-Gomez, P., et al. "**Mammalian polymerase θ promotes alternative NHEJ and suppresses recombination.**" *Nature* (2015)