BioWorld™
The news source of record covering the development of innovative human therapies for 30 years

Clarivate™

February 14, 2023
Volume 34, No. 30
Special Reprint

‘Rip’ it up and start again: Halda Therapeutics unveils Riptac platform, $76M investment

By Cormac Sheridan, Staff Writer

A preclinical data presentation at the American Society of Clinical Oncology Genitourinary Cancers (ASCO GU) Symposium later this week has prompted Halda Therapeutics Inc. to emerge from stealth and unveil its novel Riptac (Regulated Induced Proximity Targeting Chimera) platform for creating heterobifunctional small molecules designed to kill cancer cells selectively. The New Haven, Conn.-based company has been quietly refining the technology since its formation in 2019 and has already secured $76 million in series A and B rounds.

Craig Crews, scientific founder, Halda

Halda has obvious echoes of another New Haven-based firm, Arvinas Inc., which has pioneered the Protac (Proteolysis Targeting Chimera) drug class. They share the same scientific founder, Craig Crews, of Yale University, and chairman Tim Shannon, of Canaan Partners. Riptac’s roster of investors has strong overlaps with the syndicate that originally backed Arvinas a decade ago. But there the similarities end. “There’s a clear distinction between Riptacs and Protacs,” Crews told *BioWorld*.

Protacs, which Crews, Raymond Deshaies, now at Amgen Inc., and Kathleen Sakamoto, now at Stanford University, co-invented over two decades ago, earmark target proteins for degradation by bringing the protein of interest and an E3 ubiquitin ligase into close proximity. The formation of a ternary complex between the Protac and the two proteins to which it binds initiates degradation of the target protein through the ubiquitin-proteasome system.

Riptac molecules do not harness the ubiquitin-proteasome pathway. Instead, they tether a target protein that is overexpressed in cancer cells to a protein that mediates a function essential for cell survival. By sequestering that essential protein in a complex with the Riptac and target protein, they smother it in “a big hug,” Crews said, and prevent it from functioning. Cell death follows quickly – from what the company calls a “hold-and-kill” mechanism.

Crews and colleagues described the approach in a chemical biology proof-of-concept study they posted on the Biorxiv repository last month. At the ASCO GU meeting, Halda will present a poster describing the effects of a Riptac molecule targeting androgen receptor and an undisclosed protein involved in transcriptional regulation in a rodent model of enzalutamide-insensitive prostate cancer.

A key feature of the Riptac approach is that it need not target oncogenic drivers of the cancer that is being addressed, a feature that may slow the emergence of drug resistance, although Crews did not rule out the possibility that Riptacs could also select for escape variants. “We recognize, as powerful as this new modality is, the cells are likely to come up with ways to develop resistance,” he said.

Another theoretical concern is the possibility of unwanted effects arising from binding of a Riptac molecule to the essential protein in healthy cells, even if a ternary complex involving the target protein does not form. “We have been able to tune it, so it has very weak activity,” Kat Kayser-Bricker, chief scientific officer at Halda, told *BioWorld*. Initial in vivo studies have not raised any concerns. “So far, the early data look really good,” she said.

Kat Kayser-Bricker, chief scientific officer, Halda

The apparent efficacy of Riptacs stems in large part from a cooperative binding effect between the molecules and their protein ligands. The interactions – which can be covalent or non-covalent – between the three are far stronger than those between a Riptac and either one of the proteins it binds. “That is what leads to tumor-selective death,” Crews said.

Part of Halda’s “secret sauce,” Kayser-Bricker said, lies in its ability to predict a successful pairing between a target and an essential protein. “We have a portfolio of essential proteins we look at,” she said. In terms of targeting, the field is wide open. Unlike other therapeutic modalities that combine a targeting and killing activity – such as antibody-drug conjugates, bispecific T-cell engagers, targeted radiopharmaceuticals, or chimeric antigen receptor T cells – Riptacs engage intracellular rather than extracellular targets. They are also easier to produce and administer, being orally available.

Continues on next page

Continued from previous page

The company is not yet disclosing the likely timing of a first clinical trial, but as it is already in in vivo studies in prostate cancer, formal entry into IND-enabling studies cannot be too far away. Its second lead program also targets a drug-resistant solid tumor indication, but Riptacs can also be deployed in liquid tumors and in earlier treatment lines, Kayser-Bricker said.

Kayser-Bricker has been involved with the company since shortly after its inception. She previously had a front-row view of the emergence of Protacs, she recalled, as she completed PhD and post-doctoral research in different labs at Yale during that period. Prior to joining Halda in 2019, she spent a decade at Forma Therapeutics (now part of Novo Nordisk A/S), which included a stint as head of early discovery chemistry.

Halda's investors include Canaan Partners, Access Biotechnology, Elm Street Ventures and Connecticut Innovations.