Werewolf Therapeutics
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Designing conditionally activated immune stimulators that attack cancer cells

Using its proprietary PREDATOR protein engineering platform, Werewolf designs biotherapeutics that are systemically delivered and activated selectively in the tumor microenvironment to recruit a powerful antitumor immune response.

Cancer cells are able to switch off the body's immune response by inactivating immune cells or avoiding detection. Immunotherapies, such as checkpoint inhibitors, act by switching the immune system back on. These have become an important part of cancer treatment. However, not all tumors respond because there is not enough of an endogenous immune response. Other approaches, such as pro-inflammatory cytokines and costimulatory receptor agonists, are able to stimulate the body's response to cancer. Although this is effective, the clinical use and benefit can be limited; these agents can cause inflammation in healthy tissues, leading to autoimmune or inflammatory side effects and organ toxicity. Historically, it has been challenging to develop these agents with the appropriate pharmaceutical properties and without off-tissue toxicities.

Cambridge, MA-based Werewolf Therapeutics' focus is to create a novel class of proinflammatory immunomodulator therapeutics that act selectively in the tumor, stimulating the body's response against cancer.

Bringing in the PREDATOR

Werewolves are mythological creatures that live unnoticed as humans and then shape-shift to predators at a conditional signal—the full moon. Werewolf's PREDATOR protein engineering technology creates biological prodrugs that remain inactive in the systemic circulation. These prodrugs are activated into immune stimulants only in the tumor microenvironment, where they trigger the immune system to 'predate' on cancer cells (Fig. 1). This has the potential to reduce off-target effects on healthy tissues, while ensuring that the final, activated drug retains full potency for maximum therapeutic potential.

"There are well-validated pro-inflammatory targets and pathways that we know will trigger the tumor immune response, but these are associated with side effects. The PREDATOR technology means that we can tap into these known mechanisms and exploit a wider therapeutic window, with the potential for a greater clinical response and reduced impact on healthy tissue," said Daniel Hicklin, founder, president and CEO.

The PREDATOR technology was developed in-house following the company's launch in 2017, and the tactic has been validated in proof-of-concept studies.

Hunting candidates to build the pipeline

Werewolf's pipeline is made up of prodrugs of pro-inflammatory cytokines and costimulatory multivalent receptor agonists.

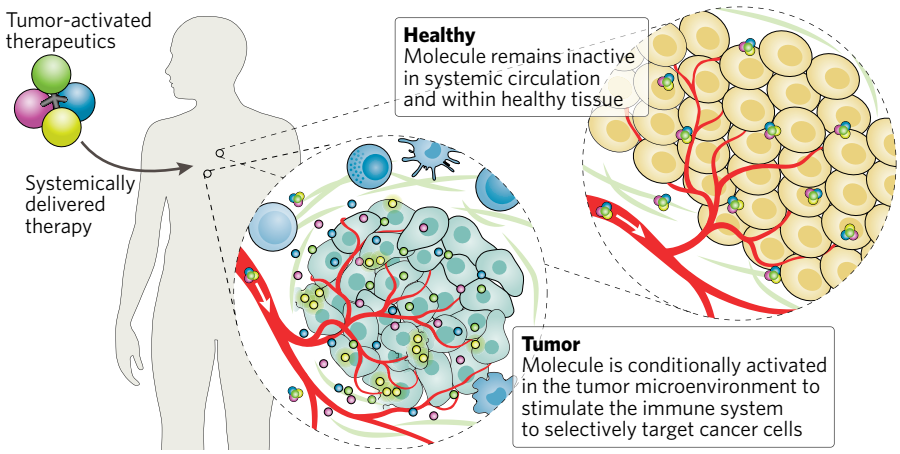

Fig. 1 | The Werewolf molecule in action. The prodrugs are activated into immune stimulants only in the tumor microenvironment, where they trigger the immune system to 'predate' on cancer cells.

"We are currently progressing a number of development candidates, and are near the decision point to prioritize our first IND candidate before the end of the second quarter of 2020," said Hicklin. "These programs cover a diverse set of immune mechanisms so that we can target a broad spectrum of cancer types."

The company's initial approaches are likely to include IL-12, IL-2, interferon and molecules targeting the costimulatory receptor 4-1BB. These are all well-validated pathways that are recognized by biopharma companies, but toxicities limit their ability to be used effectively as systemic drugs.

"Because we know the targets so well and the mechanisms are well-validated, we hope to be able to demonstrate clinical evidence of whether our prodrugs are working early on in development, which could lead to shorter, more efficient clinical trials," said Hicklin.

The majority of experimental immunotherapies are being developed in combination with other immunotherapies and/or traditional chemotherapy. This aims to improve clinical responses but potentially increases the risk of side effects. Hicklin believes that the Werewolf technology will allow its drugs to be developed initially as monotherapies by virtue of controlled delivery of potent immune-activating mechanisms.

Conditional activation of biologics is being pursued by a number of companies for various therapeutic modalities, acknowledges Hicklin. The Werewolf technology uses design elements that address pharmaceutical, potency and tissue selectivity properties, previously a challenge for conditionally activated agents.

Werewolf completed its $56 million Series A financing in November 2019. This financing provided enough capital to progress two molecules into the clinic and progress other molecules in the pipeline, and will also allow the headcount to increase from 17 to around 30. Werewolf expects to conduct its next round of financing in 2021.

Creating the Werewolf pack

According to Hicklin, getting the right people in place has helped Werewolf make its transition from a semi-virtual company in stealth mode to a real-world organization heading rapidly towards a clinical pipeline.

"We have a proven leadership team that includes people with a lot of experience from biotech and big pharma companies, including the development of several approved oncology drugs. Many of us have worked together for a long time—we trust one another to make wise, data-driven decisions that will drive our pipeline forward," said Hicklin.

"Together, we are focused on developing effective drugs against well-validated targets to deliver a clinically meaningful impact for patients," concluded Hicklin.

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