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Red Queen: A new approach to viral fusion proteins

Apple Tree Partners launches infectious disease company with stapled lipopeptide tech for blocking viral fusion

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October 28, 2024 7:51 PM GMT+1

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Launched in August with $55 million from Apple Tree Partners and a BARDA contract to develop a pan-influenza therapy, Red Queen aims to overcome the efficacy and stability problems of past programs targeting viral fusion proteins.

Red Queen Therapeutics Inc. is developing small molecules that inhibit viral fusion to stop entry into host cells, an approach it's applying to at least four viral families. Its lead program for COVID-19 is nearing Phase II, while the others, including the pan-influenza program, are preclinical.

Viral fusion proteins often take center stage in vaccine development but have had less success in therapeutics development. Only one, Fuzeon enfuvirtide, has achieved FDA approval. The 36-amino acid peptide targeting HIV gp41 was approved in 2003 but failed to become a mainstream treatment. Genentech Inc. is discontinuing the drug next year.

"It's not that stable," CEO and ATP venture partner Mark Mitchnick told BioCentury. "You need a big dose. We fixed those problems."

Red Queen's solution is to use stapled lipopeptides developed by Dana-Farber Cancer Institute's Loren Walensky, the biotech's scientific founder. The molecules comprise a cholesterol moiety conjugated to a peptide bearing unsaturated hydrocarbon chains that can be chemically 'stapled' to produce macrocyclic rings.

Mitchnick said the lipopeptides are uniquely well-suited to targeting viral fusion proteins because their ring structure confers rigidity and protease resistance, while their lipophilic cholesterol moiety homes to the cell wall.

"We've given it enough hydrophobicity that it's going to be happy staying where it needs to stay, which is right at that membrane interface," he said. "A very water-soluble molecule is not going to stay there."

The staples also hold the peptide moiety in a conformation that's complementary to the viral fusion protein target. This allows the lipopeptides to act like molecular mimics that prevent key interactions within the viral fusion protein or between the virus and its host cell.

In the case of SARS-CoV-2, Red Queen's candidate, RQ-01, binds to the HR1 domain of the spike protein, preventing an interaction between HR1 and the spike's HR2 domain, a required step in the process of viral fusion.

"HR1 and HR2 have areas that fold on each other and bind," said Mitchnick. "There's a part of HR1 that is complementary to HR2. What we do is mimic HR2."

Red Queen programs its lipopeptides to target a specific fusion protein. "We start with the native sequence, and then we iterate on that," he said. "We start changing amino acids, we alter where we provide our cross-link. Every time we do this, we look to see if we made our peptide more or less efficacious."

Mitchnick cited several advantages of stapled lipopeptides over other means of inhibiting viruses.

First, the company doesn't expect the viruses to develop resistance because the lipopeptides are relatively large, and the viral fusion proteins are highly conserved across whole families of viruses.

A high level of conservation should bring with it another benefit — broad efficacy.

"RQ-01, our drug for COVID, has worked on every coronavirus we've looked at, and there's been dozens at this point," said Mitchnick. "We have every reason to believe that in the next nasty one that pops up, this machinery will remain conserved."

Conservation of fusion proteins is observed in other viral families the company is exploring. It's got programs for pan-influenza, herpes, and a group of viruses that includes respiratory syncytial virus, human metapneumovirus and parainfluenza.

Other companies are blocking viral fusion from the host side, targeting viral receptors on host cells or host immune proteins. Mitchnick noted a benefit of inhibiting a viral protein rather than a host protein is that Red Queen's therapies should be better suited to patients who are immune compromised.

The company plans to enroll immunosuppressed patients in its upcoming Phase II trial of RQ-01, in which the therapy will be administered intranasally as add-on therapy to standard of care. The study is expected to read out in 1Q26.

Red Queen hopes to be in the clinic with its influenza product, which is also inhaled, in 4Q25. The BARDA contract, worth just under $750,000, is partially funding the preclinical work on that program.

One of Red Queen's long-term goals is to develop combination products, which Mitchnick believes will be practical because the high potency of the lipopeptides should allow them to be mixed and inhaled.

COMPANY PROFILE

Red Queen Therapeutics Inc.
Cambridge, Mass.
Technology: Stapled lipopeptides targeting viral fusion proteins
Origin of technology: In-licensed from Dana-Farber
Disease focus: Infectious
Clinical status: Phase I
Founded: 2021 by Loren Walensky and Apple Tree Partners
Academic collaborators: Dana-Farber Cancer Institute
Corporate partners: Undisclosed
Number of employees: 7
Funds raised: $55 million
Investors: Apple Tree Partners
CEO: Mark Mitchnick
Issued Patents: 1 covering use of stapled peptides to prevent and/or treat respiratory syncytial virus

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