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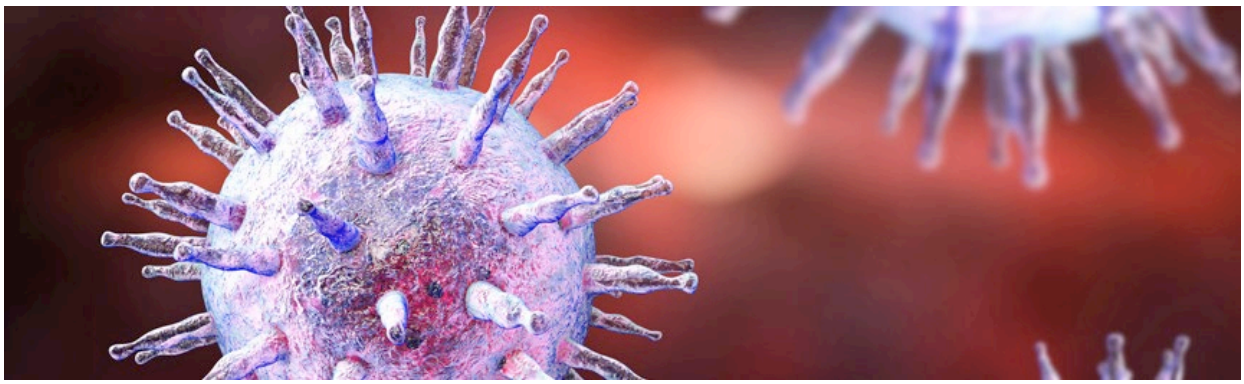

PRODUCT DEVELOPMENT

VIRAL VULNERABILITY

BY EMILY CUKIER-MEISNER, SENIOR WRITER

Persistent viral infection, even those that are undetectable or asymptomatic, can cause some cancers and contribute to their severity. Viracta Therapeutics Inc. is treating virus-associated cancers by forcing them to re-express latent viral proteins that make cancerous cells vulnerable to antiviral treatment.

In November, Viracta acquired lead program VRx-3996 from Chroma Therapeutics Ltd. in exchange for an undisclosed equity stake. Chroma had been studying the HDAC inhibitor in Phase Ib testing to treat solid tumors but sold it to Viracta because its efficacy was not great enough to raise funds for its development, according to Viracta CBO David Slack.

Viracta will combine it with the nucleoside analog prodrug valganciclovir to treat Epstein-Barr virus (EBV)-positive lymphoma, and possibly to treat nasopharyngeal carcinoma and gastric carcinomas and for prophylaxis of post-transplant lymphoproliferative disease (PTLD).

VRx-3996 induces EBV to express the thymidine kinase enzyme. The enzyme in turn catalyzes the addition of a phospate group to nucleoside antivirals — the initial step in activating valganciclovir after first-pass metabolism. Non-specific intracellular kinases then add a second and a third phosphate to form the active triphosphate form of the drug, which inhibits viral DNA synthesis.

Slack said the combination of HDAC inhibition and valganciclovir is lethal only in rapidly dividing cells that harbor the virus. In infected cells that are not rapidly dividing, VRx-3996 inhibits viral replication but does not harm the host cell.

"In cancer and other diseases, there is clonal proliferation driven by the virus — those are the bad actors we'd wipe out," he said.

Slack said even though the treatment can also affect rapidly dividing non-cancerous EBV-positive cells, the latent virus is typically only found in B cells.

The combination is not expected to be immunosuppressive because less than 5% of B cells tend to harbor latent EBV, and the Viracta team did not see immunosuppression in a proof-of-concept study using arginine butyrate, a pan-HDAC inhibitor.

GETTING SPECIFIC

Slack said Viracta's founders got as far as a Phase I/II trial with arginine butyrate plus ganciclovir while at predecessor company HemaQuest Pharmaceuticals Inc. There were four complete responses and six partial responses among 15 patients with EBV-associated lymphoid malignancies.

However, giving arginine butyrate required hospitalization and continuous infusion over three weeks, which made recruiting for additional trials difficult. In addition, a sickle cell program consumed most of the company's resources until its Phase II failure in 2013 made it difficult to raise additional funds.

In 2015, HemaQuest investors Forward Ventures and Latterell Venture bought out the other investors and rebooted the company as Viracta to develop the viral activation platform.

Slack said in the interim, Viracta and HemaQuest scientific founder Douglas Faller determined that a selective inhibitor of class I HDAC isoforms would have a superior therapeutic window because it would reactivate the desired genes without restoring pathological infectiousness. Faller is a professor of medicine at Boston University School of Medicine.

"You need to hit certain HDACs, and we know which ones to hit to turn on certain viral genes," Slack said.

> "YOU NEED TO HIT CERTAIN HDACS, AND WE KNOW WHICH ONES TO HIT TO TURN ON CERTAIN VIRAL GENES."
>
> DAVID SLACK, VIRACTA

VRx-3996 inhibits class I HDACs. It can be given orally and on a similar schedule as valganciclovir, which could enable formulation in a once- or twice-daily pill.

MANAGING TOXICITY

The most common severe adverse events in the Phase I/II study of arginine butyrate plus ganciclovir were somnolence and confusion; however, three patients who achieved complete responses went on to die of complications of tumor lysis.

Slack said those deaths were related to tumor involvement in a large portion of a major body system — the carotid artery or the GI tract — leading to structural destabilization once the tumor was lysed. In its next trial Viracta may exclude, carefully monitor or titrate therapy in patients with tumor involvement in major structures.

He said it is also possible that some of the structural destabilization could relate to off-target effects of butyrate that would not be expected with VRx-3996.

In 2Q Viracta plans to begin a Phase II study of VRx-3996 plus valganciclovir in at least 30 patients with EBV-positive lymphoma. Response rate data are expected by year end.

Viracta is also considering finding a partner to develop the program in China, where EBV infection occurs in a high proportion of certain cancers. About 100% of NK/T cell lymphomas and 90-100% of nasopharyngeal cancers in China are EBV-positive.

At least two other companies are developing therapies that target EBV-positive cells. Atara Biotherapeutics Inc.'s EBV-CTL (ATA 129) is in Phase II testing to treat EBV-positive lymphomas and lymphoproliferative disorders. Early this year the company plans to meet with FDA to discuss a pair of Phase III registrational studies in patients with rituximab-refractory EBV-associated PTLD (EBV-PTLD).

Atara has exclusive worldwide rights to the donor-derived EBV-specific cytotoxic T lymphocytes (CTLs) from Memorial Sloan Kettering Cancer Center.

Cell Medica Ltd.'s baltaleucel-T (CMD-003) is an autologous EBV-specific CTL product in Phase II testing to treat EBV-positive extranodal NK/T cell lymphoma. Cell Medica in-licensed exclusive worldwide rights to baltaleucel-T from Baylor College of Medicine in 2011.

Slack said Viracta's small molecule approach could act faster than a cell therapy because it doesn't rely on cells growing in the body to induce an immune response to the cancer. Fast therapeutic onset could be especially helpful for rapidly progressive indications like PTLD. Furthermore, he said immunotherapy approaches may have difficulty targeting latent virus.

Atara declined to compare the programs, and Cell Medica did not respond to requests for comment.

Viracta began with undisclosed bridge financing at the reboot and hopes to raise at least $10 million in a series A round to take the company at least through the Phase II study.

Slack said issued patents covering VRx-3996 extend at least through 2026. The company also plans to seek Orphan Drug designation in the U.S. and other geographies for select indications. bc

COMPANIES AND INSTITUTIONS MENTIONED

Atara Biotherapeutics Inc. (NASDAQ:ATRA), South San Francisco, Calif.
Baylor College of Medicine, Houston, Texas
Boston University School of Medicine, Boston, Mass.
Cell Medica Ltd., London, U.K.
Chroma Therapeutics Ltd., Abingdon, U.K.
Memorial Sloan Kettering Cancer Center, New York, N.Y.
Viracta Therapeutics Inc., San Diego, Calif.
U.S. Food and Drug Administration (FDA), Silver Spring, Md.

REFERENCES

Perrine, S. et al. "A phase 1/2 trial of arginine butyrate and ganciclovir in patients with Epstein-Barr virus–associated lymphoid malignancies." *Blood* (2007)

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