Work on rare molecule aims to enhance cell therapy and deliver functional cure for HIV

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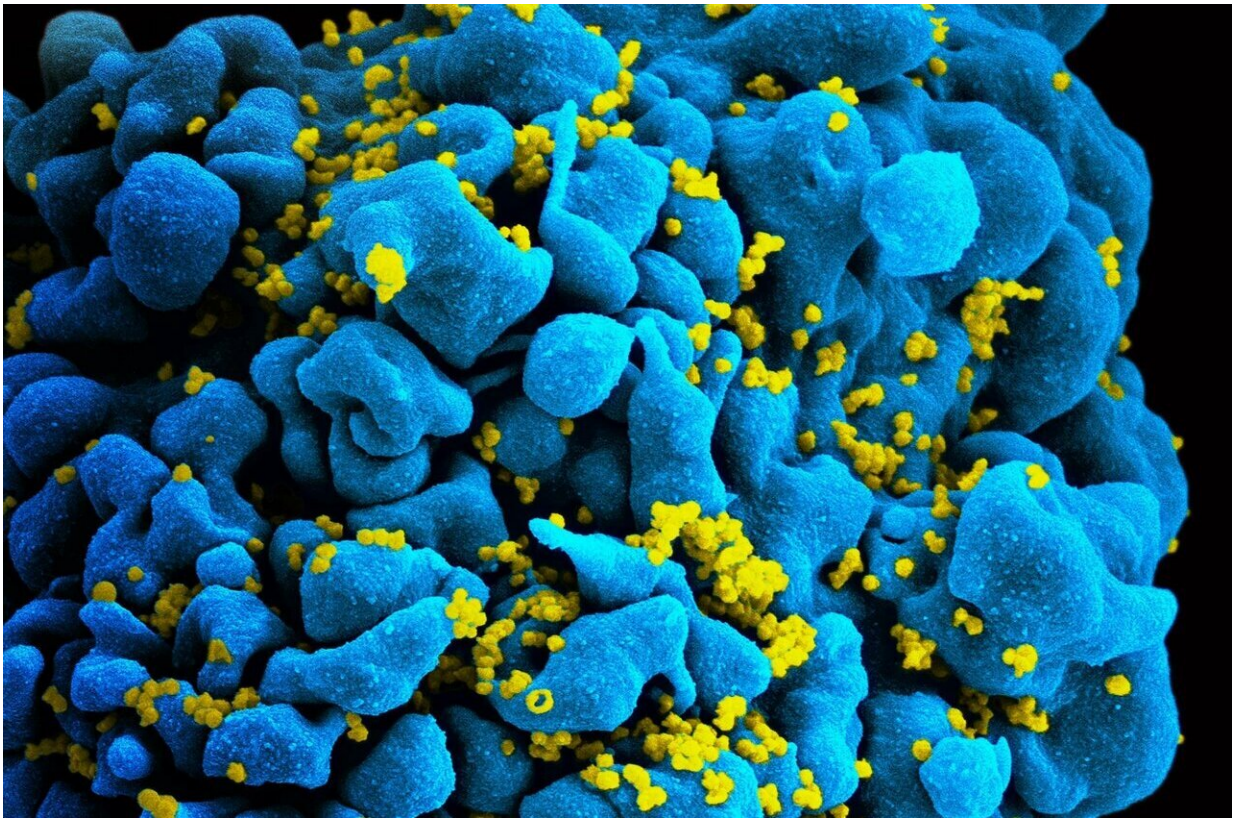

Scanning electromicrograph of an HIV-infected T cell. Credit: NIAID

Stanford University chemist Paul Wender and his colleagues are working to improve treatments for cancer, HIV and Alzheimer's—and they are betting that a drab, weedy marine invertebrate is the means to achieving

that end. They have focused on this seemingly unremarkable organism, called *Bugula neritina*, because it cooperates with a bug in its gut to produce bryostatin (specifically, bryostatin-1), a molecule that can manipulate cellular activity in crucial and controllable ways.

Faced with dwindling natural supplies, the Wender lab produced synthetic bryostatin in 2017. Now, they are developing a suite of related synthetic analogs while continuing to explore the many uses of bryostatin for medical treatments, such as enhanced cancer immuno-therapy and eradication of HIV/AIDS.

"If you search long enough, somewhere, someplace, somehow you're going to find a solution to a problem that originally appeared impossible, and our work with bryostatin has led to those kinds of moments many times," said Wender, who is the Francis W. Bergstrom Professor of Chemistry. "What we have now are pretty remarkable results that will hopefully be driving clinical trials. I think this research exemplifies how much scientific and societal benefit can be derived from higher education and research."

In a paper published on April 20 in *Nature Communications*, researchers from the Wender lab and the labs of Jerome Zack and Matthew Marsden at the University of California, Los Angeles describe the first synthetic forms of bryostatin that are subtly different from the natural molecule—called "close-in analogs." Tests of these 18 analogs on lab-grown human cancer cells indicated that many could boost the effectiveness of cell therapies at a level similar to or better than bryostatin, opening the door for disease-specific optimization.

In a second study, published April 27 in *Proceedings of the National Academy of Sciences*, the same researchers collaborated with Tae-Wook Chun at the National Institutes of Health to modify bryostatin into a prodrug that can pay out the active drug—and its medicinal effect—over

time. This prodrug was found to be significantly more effective and better tolerated than bryostatin in animal models and infected cells from HIV positive individuals. The same success in humans would mean a reduction in treatment frequency and drug side effects for patients with HIV.

More precious than gold

In 1968, naturalist Jack Rudloe provided the National Cancer Institute with the first sample of *Bugula neritina*. Scientists later processed 14 tons of the invertebrate—only to produce a mere 18 grams of bryostatin. That makes bryostatin nearly 350,000 times more valuable than gold (at current prices).

Scientists continue to be interested in this scarce material because bryostatin-based drugs have the potential to make existing state-of-the-art cell and combination therapies more effective for a wider diversity of people and diseases. Bryostatin and its analogs could also serve as treatments on their own.

Bryostatin's exciting prospects come from its ability to alter signaling pathways in cells to promote or block genes involved in protein production. And it can make these changes in several different ways that could be useful for a wide range of medical applications. In the case of cancer and HIV, increasing certain proteins improves drug treatments by enhancing the immune system's ability to identify potential drug targets (antigens) on infected cells. Other bryostatin-initiated changes in protein expression may reduce symptoms of other diseases, including Alzheimer's, Parkinson's and Fragile X.

Attempts to bulk up reserves of bryostatin through further harvesting, aquaculture and biosynthesis have been unsuccessful. Then, in 2017, the Wender lab outlined a new way to create synthetic bryostatin in 29

steps—half as many as the only other synthetic route. But even with the new process, they were able to increase the stock of the precious molecule by only 2 grams, or enough to treat about 2,000 patients, based on current clinical trials.

Fortunately, the team has been able to use their additional reserve to develop new versions of bryostatin in a remarkably short time, and they are now working to scale up their manufacturing process.

"If we still had to collect bryostatin from the ocean, we wouldn't have had enough of it to conduct these studies," said Nancy Benner, a postdoctoral research scholar in the Wender lab and co-lead author of the *PNAS* paper. "It really opened up the doors for the optimization of different synthetic forms of bryostatin."

Many paths forward

Bryostatin did not evolve to treat human diseases, which motivates efforts to optimize it for that purpose. These researchers have produced bryostatin analogs that are more effective and better tolerated than the natural product, two lofty goals "that have been argued about in hotel lobbies since the beginning of bryostatin time," said Wender, who is senior author of both papers. Given the number of biological pathways that bryostatin influences, it is expected that its clinical potential will only grow now that synthetic bryostatin and its analogs are available.

Based on the successful production and testing of the analogs outlined in the *Nature Communications* study, Wender and his team are increasingly confident that they have a good understanding of how to best utilize their valuable resource.

"If you were part of the team that spent years building up all the synthetic bryostatin, you really appreciate how precious it is and you're

really sensitive to not trying to lose any of it," said Clayton Hardman, a graduate student in the Wender lab and lead author of the *Nature Communications* paper. "Even doing routine chemistries, my hands were kind of the shaky the first couple of times I did those reactions."

The team's *PNAS* paper also points to effective ways of administering bryostatin-based drugs to patients. The delayed-release method they designed for bryostatin could someday lead to improved treatments that avoid prolonged administration times, which would benefit both patients and practitioners.

Considered together, the two papers mark the beginning of exciting research paths that will open new opportunities in the coming months and years, the researchers say. They're already planning to further design and investigate bryostatin analogs and delivery methods, while pushing the most promising leads toward real-world, clinical applications.

"In both of these studies, we're bringing to bear design and chemistry principles to solve big problems," said Jack Sloane, a former graduate student in the Wender lab who is co-lead author of the *PNAS* paper and co-author of the *Nature Communications* paper. "Chemistry is a fundamental science that seems very esoteric when you first learn about it, but it has allowed us to synthesize new compounds for novel drug therapeutic opportunities and improve upon existing ones in a way no other field can."

More information: Jack L. Sloane el al., "Prodrugs of PKC modulators show enhanced HIV latency reversal and an expanded therapeutic window," *PNAS* (2020). www.pnas.org/cgi/doi/10.1073/pnas.1919408117

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