Antiviral treatments inspire researchers to develop a new kind of cancer drug

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Jeffrey S. Glenn, M.D., Ph.D. Credit: Jeffrey S. Glenn, M.D., Ph.D.

Stanford virologist Jeffrey Glenn did not set out to tackle cancer. For years, he and his lab have worked to develop new ways of battling viruses like the ones that cause hepatitis delta and the common cold—but the lessons they've learned fighting viruses has led to a new kind of drug that has been effective at treating cancer in mice.

The underlying idea, Glenn said, is to disrupt otherwise normal cellular processes that both viruses and some cancer cells rely on to grow and spread. Now, tests in mice show that drugs based on that idea can shrink tumors and prevent their spread. The scientists from Stanford, the University of Texas, Baylor College of Medicine and the University of California, San Francisco, published their findings Jan. 22 in *Science Translational Medicine*.

Finding the new drug could not have happened without an unusual series of events and collaborations that spanned several academic disciplines, said Glenn, professor of medicine and of microbiology and immunology, whose lab developed the compounds with the assistance of Stanford ChEM-H's Medicinal Chemistry Knowledge Center and support from ViRx@Stanford, an NIH-sponsored Center of Excellence for Translational Research led by Glenn.

"We've been working for many years on potent drugs that we had shown were important for viruses," said Glenn, who is also a member of Stanford Bio-X, the Maternal & Child Health Research Institute and ChEM-H. "This is just an important target that hasn't really been appreciated in cancer, and we had the perfect drugs to get this started."

An antiviral surprise

Originally, when they were looking for new ways to stop viruses such as hepatitis delta, Glenn and colleagues thought they might try a sort of end run around the virus and target cell functions that viruses hijack to replicate and spread. That way, even if a virus does infect a cell, that's more or less the end of it.

Glenn's approach worked. In 2015, he and colleagues at the National Institutes of Health showed that the new approach prevented hepatitis delta from replicating and releasing new copies of the virus in patients.

Later, they modified their strategy to attack enterovirus 71, which is best known for causing hand, foot and mouth disease but can also lead to devastating polio-like paralysis symptoms in children.

Glenn and his lab have continued to develop antiviral drugs, but their focus changed somewhat when their antiviral efforts caught the attention of Jonathan Kurie, a professor of thoracic/head and neck medical oncology at the University of Texas MD Anderson Cancer Center. Kurie had learned that the same cellular processes Glenn and colleagues had successfully shut down was also involved in metastasis. After reading a paper describing the earliest compounds Glenn and his colleagues had developed, he wrote Glenn asking for some of the drug.

"I told him we had much better molecules now, and we have known for a long time that they would also work in cancer," Glenn said, and he sent along two new compounds that he had developed with Mark Smith, who heads the Medicinal Chemistry Knowledge Center.

Cancer translation

In the new paper, the team shows that their hunch was correct—the same drugs Glenn, Smith and colleagues were developing to treat enterovirus can also treat certain kinds of cancers, at least in mice and human cancer cells in a lab dish.

In mouse studies, a drug the team tested reduced how often a human cancer implanted into the mouse in one lung spread to the second lung. With another compound, there were no detectable metastases at all, and both drugs reduced the size of tumors in the first lung. Human breast cancers growing in mice also shrunk in half after just one week of treatment.

The team also looked at an earlier drug developed in collaboration with

Kevan Shokat, a professor of cellular and molecular pharmacology at the University of California, San Francisco, and a professor of chemistry at the University of California, Berkeley. That drug, they found, also curbed cell growth in human lung cancer cell lines. The team also gained some insight into which mice—and one day, they hope, humans—might benefit the most from the new drugs. They found that mice with extra copies of a particular gene responded much better to the drugs.

Now, Glenn said, "My goal is to take this all the way to the clinic."

The right 'brew'

Glenn said the team's success is due in part to a significant shift in the last few years in what his lab does, building on an "infectious brew" of researchers from a range of academic disciplines.

"I think that's the secret thing, having chemists physically in the lab with biologists, virologists and physician-scientists," Glenn said. "We've leveraged the special enabling environment of Stanford to create a unique group that has never existed before here or in academia. It's allowed things to happen that just wouldn't have happened otherwise."

That team is also starting to think about new ways to use their drugs, for example in combination with existing therapies to make them better against drug-resistant tumors, which might be susceptible to a new approach. "We've shown a proof of concept, and I think this could be useful in many cancers."

More information: X. Tan el al., "PI4KIIIβ is a therapeutic target in chromosome 1q–amplified lung adenocarcinoma," *Science Translational Medicine* (2020). stm.sciencemag.org/lookup/doi/ … scitranslmed.aax3772

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