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Pushing the viral envelope

By Kai-Jye Lou, Staff Writer

Researchers at the **University of California, Los Angeles** have identified small molecules that exploit the inability of a virus to repair its envelope. The compounds, which target the lipid component of the envelope and irreversibly block a virus' ability to enter the host cell, could represent a new class of broad-spectrum antivirals.[1]

The viral envelope is found in many types of viruses including influenza, HIV and HCV, and it helps the virus fuse with and infect host cells. Those viruses use lipids from the host cell plasma membrane to build their envelopes. However, viruses can neither repair their envelopes nor synthesize lipids on their own. Mammalian cells, on the other hand, can rapidly replenish and repair damage to the lipid component of their membranes.

The UCLA group thus searched for compounds that could exploit the difference in reparative capacity between a virus and its host cell.

In a high throughput screen for inhibitors of viral entry, the group identified a small molecule rhodanine derivative. *In vitro*, the compound, called LJ001, inhibited the entry and spread of 20 enveloped viruses from 9 different families.

LJ001 disrupted virus–host cell fusion and irreversibly rendered the viral particles noninfectious. Cell-cell fusion was not significantly affected and the compound was safe in mice at therapeutic concentrations.

The compound did not show significant antiviral activity against nonenveloped viruses.

Results were published in the *Proceedings of the National Academy of Sciences*.

"LJ001 is exploiting the reparative processes of the cellular membrane that viruses do not have," said Benhur Lee, corresponding author on the *PNAS* paper and an associate professor in the Department of Microbiology, Immunology and Molecular Genetics at UCLA. "The effect is specific to the virus because the body's cells can efficiently repair the effects caused by LJ001."

When the researchers co-treated cells with LJ001 and an inhibitor of fatty acid synthesis, they saw a synergistic increase in cellular toxicity. Cells use fatty acids to make the lipids in their membranes.

Lee, who declined to disclose LJ001's specific molecular mechanism of action for IP reasons, also has a joint appointment in the Department of Pathology and Laboratory Medicine at UCLA's David Geffen School of Medicine.

"This story reveals a new approach to prevent the cellular entry of enveloped viruses," said Erik De Clercq, a professor emeritus in the Department of Microbiology and Immunology at the **Catholic University Leuven**'s Rega Institute for Medical Research. "The most fascinating aspect of LJ001 is its broad-spectrum antiviral activity."

However, because the lipid composition of viral envelopes could be highly variable and dependent on the virus' host cell type, De Clercq cautioned that LJ001's potency "may be strongly dependent on the nature of the host cells and their [membrane's] lipid composition."

He added that the researchers did not evaluate LJ001's efficacy against several major families of enveloped viruses, including *Herpesviridae*, which is one of the largest virus families. He added that LJ001 should be tested in different clades of HIV-1.

Irresistible potential

In addition to its broad-spectrum activity, LJ001 could have reduced potential for eliciting resistance. Because the lipid component of the viral envelope is derived from the host and not the virus, it should be less prone to mutation.

"There is a preliminary but tempting suggestion that drug resistance may be minimal with LJ001," said Michael Kinch, VP of R&D at **Functional Genetics Inc.** He thinks host-based antiviral targets are less likely to elicit resistance because they are not under the virus' direct control.

> **"The virus has control over the glycoproteins that it uses to attach to and enter the cell, but its lipids are determined by the host cell."**
> *—Benhur Lee, University of California, Los Angeles*

Functional Genetics identifies host-specific molecules that are essential for the viral lifecycle but not for normal host cell functions. The company has filed an IND for FGI-103, a host-directed small molecule with broad-spectrum antiviral activity.

FG-103 is being developed to treat Ebola in collaboration with the **U.S. Department of Defense**'s **Defense Threat Reduction Agency**. The compound also is in preclinical testing for HBV and respiratory syncytial virus (RSV) infections.

"A key challenge in the development of any antiviral has been the relative ease by which viruses evade treatment," Kinch told *SciBX*. "History has shown us that such escape events are inevitable when targeting viral mechanisms, since Darwinian-like pressure is placed on the virus itself to select for mutants that do not respond to a drug. This potential to evade therapy is compounded further by the fact that viral nucleic acid polymerases are notoriously error-prone and because infection of a single cell can yield thousands or millions of progeny."

"Since LJ001 is targeting the lipid components of the envelope, it's not attacking something that is under the control of the viral genome," said Lee. "The virus has control over the glycoproteins that it uses to attach to and enter the cell, but its lipids are determined by the host cell."

Lee thinks optimized derivatives of LJ001 could become alternatives

to the few marketed drugs that have broad-spectrum antiviral activity, like interferon and ribavirin.

"Using interferon to rev up the immune system is like using a sledgehammer to take out a virus—the drug comes with strong side effects and is also very expensive," he said. "With ribavirin, even though the exact mechanism is not yet known, the drug has been shown to affect viral polymerases and resistant viral strains have been identified."

Going analog

Two potential formulation issues are the compound's lipophilic structure and its specificity.

De Clercq said that because LJ001 appears to interact with lipids, it must have a highly lipophilic structure. This could create formulation problems for its practical application, he said.

"One prominent question will be whether the molecule is taken up by cells nonspecifically," Kinch added. He said that if LJ001 nonspecifically targets lipids, the bulk of the compound could be taken up by host cell membranes and not by viral envelopes.

According to Lee, his group has synthesized 30–40 analogs of LJ001 and is continuing to optimize the potency, pharmacokinetics and bioavailability of the compounds. The team is also trying to improve the delivery and safety profile of its compounds.

"At this stage, the compounds appear to be promising microbicides," he said. "They could also be used to reduce pathogen contamination by enveloped viruses like HIV and HCV and could help make the blood supply safer."

In the *PNAS* paper, the authors also noted that the compounds could be used as topical treatments against mucosally-transmitted enveloped viruses or as inhalants for enveloped respiratory viruses.

UCLA has filed a patent application covering the use of the compounds as broad-spectrum antivirals. The work is available for licensing from UCLA's Office of Intellectual Property.

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