New screening system for hepatitis C

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A newly designed system of identifying molecules for treating hepatitis C should enable scientists to discover novel and effective therapies for the dangerous and difficult-to-cure disease of the liver, says Zhilei Chen, a Texas A&M University assistant professor of chemical engineering who helped develop the screening system.

The system, Chen explains, enables researchers to study the effects of molecules that obstruct all aspects of the hepatitis C virus (HCV) life cycle. That's a significant milestone in HCV research, says Chen, noting that previous methods of developing drug treatments for the virus have been limited by the fact that researchers were only able to study one aspect of the HCV life cycle. Chen's findings appear in the most recent edition of the scientific journal *Proceedings of the National Academy of Sciences*.

First identified in 1989 and responsible for hepatitis C, an infectious disease affecting the liver, HCV has infected an estimated 180 million people worldwide. Spread by blood-to-blood contact, HCV can cause chronic infection that leads to dangerous scarring of the liver, liver failure, liver cancer and death.

Although new infections resulting from blood transfusions are rare thanks to screening measures that began in 1990, the overall number of people facing death or serious liver disease from HCV is steadily rising because people often live decades with the virus before showing symptoms, Chen says. In addition, injection drug users are at high risk for infection from contaminated needles.

The only existing therapy for HCV is a physically and emotionally taxing 48-week course of treatment that cures less than half of all patients who undergo it, Chen says. The particularly grueling nature of the treatment - it's been compared to chemotherapy - as well as the high financial costs associated with it often result in many patients opting to forego the therapy.

Because Chen's newly developed screening system enables the discovery of small, low-cost molecules that block the HCV life cycle, she believes it could contribute to new, more affordable and more effective therapies for hepatitis C.

The screening system uses an innovative way to "see" cells that are infected with HCV.

"Typically when a virus infects a cell, it's not obvious to detect; it's not easy to distinguish an infected cell from an uninfected cell," Chen says. "Much in the same way a person who is infected with HCV does not initially feel anything, when a cell is initially infected nothing really observable happens. This makes it difficult to distinguish HCV infection in cells."

To address this challenge, Chen "tweaked" the cells she was studying by inserting a gene into them that triggers cell death if HCV enters that cell. This allowed Chen to easily measure the extent of infection in her genetically engineered cells by quantifying the degree of cell death within the cell cultures she was examining.

These engineered cells were grown in miniature compartments in the presence of infectious HCV, and a different chemical was added to each compartment.

"We could then look and see which cells were able to survive because if

you have chemicals that don't inhibit HCV, the cells will die, but if you have a molecule that blocks the HCV life cycle, the cells will grow," Chen says. "And because we were able to look at the complete life cycle of the virus with our system, we discovered inhibitors of the virus across three different stages: entry into cells, reproduction within cells, and final escape from infected cells to attack new cells."

Testing about 1,000 different chemicals, Chen found several that strongly inhibited the HCV life cycle. Some of the inhibitors, she said, obstruct virus entry into a cell. Others inhibit virus replication, meaning that infected cells won't be able to support the reproduction and growth of the virus as much. Chen also found effective inhibitors that keep the virus from escaping the cell even if it grows well inside the cell.

"Since this virus changes all of the time, you really want to hit it across multiple aspects simultaneously," Chen says. "Nevertheless, most current efforts to block the HCV life cycle focus only on its replication within cells due to the long-time absence of a system that allows for convenient screening of molecules blocking other aspects of the virus' life cycle such as entry into cells and release from cells.

"Our system is well-suited to large-scale drug screening efforts because the technology is simple to use and can be easily scaled up to test extremely large collections of compounds using a robotic system," Chen says. "We anticipate that this system will enable the discovery of many more new and more potent HCV antivirals."

Working with Chen to develop the system were Karuppiah Chockalingam and Rudo Simeon, postdoctoral associate and graduate student, respectively, from Texas A&M and Charles Rice, professor from Rockefeller University.