Will new drugs block hepatitis C virus in its tracks?

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Targeted multi-drug treatments for hepatitis C patients that could stop the virus in its tracks have come a step closer, thanks to researchers at the University of Leeds, UK.

The study by Dr Stephen Griffin and colleagues, published in the journal *Hepatology*, reveals how two prototype small molecule drugs, known as p7 inhibitors, can each attack different parts of the hepatitis C virus. Their findings suggest that p7 inhibitors could be a powerful way of suppressing hepatitis C, when used together with the latest generation of 'direct-acting' drugs.

More than 170 million people - or 3% of the world's population - are infected with the hepatitis C virus. The virus causes severe liver disease and is a leading cause of liver-related deaths, organ transplants and liver cancer.

At the moment, patients are typically treated with PEGylated interferon alpha (IFN) and ribavirin (Rib) - drugs that work by boosting the patient's immune system. However, the effects of these drugs can depend on the individual patient's genetic make-up. To make matters worse, hepatitis C is often resistant to the therapy and fails to suppress the virus for long enough. The treatment is also expensive and can trigger unpleasant side effects. Many patients stop taking the drugs or do not take them when they should.

To address this, researchers are looking at new classes of drugs that work

in a different way to either IFN or Rib and target the virus directly. The aim is to find groups of these 'direct-acting' drugs that each attack a different target, making it much, much harder for the virus to fight back.

University of Leeds researchers are focusing on drugs that target the p7 ion channel - a protein made by hepatitis C that allows the virus to continue spreading. In previous studies, Dr Griffin and colleagues worked out how the p7 ion channel could be blocked by certain types of small molecule, stopping the hepatitis C virus in its tracks. Their latest work looks at two particular classes of p7 inhibitor - adamantanes and alkylated imino-sugars – and confirms that these molecules do, indeed, attack their intended target through separate mechanisms.

The researchers used a combination of molecular modelling and lab-based experiments to study the drugs' interaction with hepatitis C. Importantly they observed how the virus responded to the two types of drug and determined that each of these responses was very different. This suggests that the drugs would work well in combination, tackling the virus on a number of fronts.

Lead author, researcher Dr Stephen Griffin, from the University of Leeds' School of Medicine, said: "Hepatitis C has always been an extremely difficult condition to treat effectively because the virus evolves so quickly and develops resistance to drugs that are used to treat it. This new class of small molecule drugs, the p7 inhibitors, attack the virus directly. As we have discovered here, they each do so in quite a different way which allows us to combine their effects.

"By learning how the hepatitis C virus reacts to these molecules, we can design drugs that are likely to be more effective for longer. We can also see how such drugs could be used together with other 'direct-acting' drugs that target alternative viral targets, rather than individually or with IFN/Rib. In other words, a similar approach to treatment as that used for

HIV."

More information: Resistance Mutations Define Specific Antiviral Effects for Inhibitors of the Hepatitis C Virus (HCV) P7 Ion Channel. Toshana L et al. Hepatology; Published Online AOP (DOI: 10.1002/hep.24371); Print Issue Date: July 2011.

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