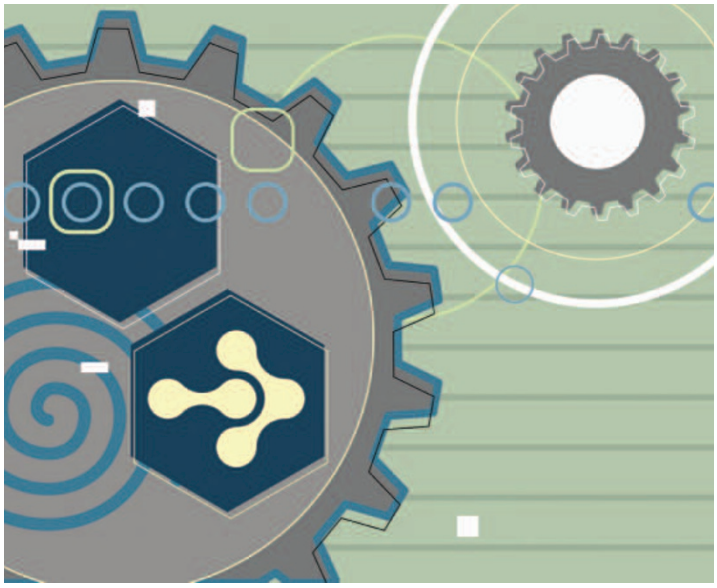
ANTIVIRAL DRUGS

Macrocyclic inhibitor for hepatitis C

Across the globe an estimated 170 million people are chronically infected with hepatitis C virus (HCV), and the development of effective HCV therapies continues to be a challenge due to the lack of adequate animal models and tissue-culture systems for analysis and propagation of the virus. A new drug, BILN 2061, has been developed to treat those infected with HCV, according to research published in the 13 November issue of *Nature*. The molecule, which prevents virus particles from being produced, greatly reduced viral load in a small sample of infected patients.



The non-structural (NS) proteins are enzymes or accessory factors that catalyse and regulate the replication of the HCV genome; the NS3 serine protease is essential for replication, which makes it an attractive target for therapeutic intervention. Daniel Lamarre and colleagues used a substrate-based approach to design inhibitors of the NS3 active site. The protease is prone to inhibition by specific penta- or hexapeptides derived from the amino-terminal NS3 cleavage products, and these provided the basis for lead optimization of peptidomimetic inhibitors. Using a structure–activity-relationship (SAR) approach, the authors identified tripeptide mimetics that maintained potent and specific activity against the NS3 protease. Strengthening of the scaffold by intramolecular linking of each terminal amino-acid side chain produced novel macrocyclic inhibitors with desirable drug-like activities. Further SAR analysis produced a subset of inhibitors, including BILN 2061, that possessed the targeted low-nanomolar cellular potency and a good oral pharmacokinetic profile in animals.

In a clinical study, BILN 2061 or placebo was orally administered to healthy volunteers at 5–2,400 mg; it was well tolerated up to 2,000 mg and no serious side effects were identified. In a small proof-of-concept study with placebo controls, eight people infected with HCV took four doses of the drug over 48 hours. Two days later virus levels had dropped by 100–1,000-fold. No side effects were reported.

The efficacy of BILN 2061 in humans establishes a new class of selective anti-HCV agent, as well as the further potential of other such selective and potent agents. In the case of BILN 2061, longer trials are now needed to assess how its antiviral activity holds up over time and whether drug resistance will become an issue.

Melanie Brazil

References and links

ORIGINAL RESEARCH PAPER Lamarre, D. *et al.* An NS3 protease inhibitor with antiviral effects in humans infected with hepatitis C virus. *Nature* **426**, 186–189 (2003)

FURTHER READING Tan, S.-L. *et al.* Hepatitis C therapeutics: current status and emerging strategies. *Nature Rev. Drug Discov.* **1**, 867–881 (2002) | Tsantrizos, Y. S. *et al.* Macrocyclic inhibitors of the NS3 protease as potential therapeutic agents of hepatitis C virus infection. *Angew. Chem. Int. Ed. Engl.* **42**, 1356–1360 (2003)