

Supplementary information S1 | Further reading

Virology

Choo Q. L., *et al.* Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. *Science* **244**, 359–362 (1989).

Lohmann V., *et al.* Replication of subgenomic hepatitis C virus RNAs in a hepatoma cell line. *Science* **285**, 110–113 (1999).

Wakita, T. *et al.* Production of infectious hepatitis C virus in tissue culture from a cloned viral genome. *Nature Med.* **11**, 791–796 (2005).

Lindenbach B. D., *et al.* Complete replication of hepatitis C virus in cell culture. *Science* **309**, 623–626 (2005).

Moaradpour, D., Penin, F. & Rice, C. M. Replication of hepatitis C virus. *Nature Rev. Microbiol.* **5**, 453–463 (2007).

Drug Discovery

Pawlotsky, J.-M., Chevaliez S., & McHutchison, J. G. The hepatitis C virus life cycle as a target for new antiviral therapies. *Gastroenterol.* **132**, 1979–1998 (2007).

Asselah, R., Benhamou, Y. & Marcellin, P. Protease and polymerase inhibitors for the treatment of hepatitis C. *Liver International* **29**, 57–67 (2009).

Entry

Pileri P. *et al.* Binding of hepatitis C virus to CD81. *Science* **282**, 938–941 (1998).

Scarselli, E. *et al.* The human scavenger receptor class B type I is a novel candidate receptor for the hepatitis C virus. *EMBO J.* **21**, 5017–5025 (2002).

Lozach P.Y. *et al.* DC-SIGN and L-SIGN are high affinity binding receptors for hepatitis C virus glycoprotein E2. *J. Biol. Chem.* **278**, 20358–20366 (2003).

Cormier E.G. *et al.* L-SIGN (CD209L) and DC-SIGN (CD209) mediate transinfection of liver cells by hepatitis C virus. *Proc. Natl Acad. Sci. USA* **101**, 14067–72 (2004).

Evans, M.J. *et al.* Claudin-1 is a hepatitis C virus co-receptor required for a late step in entry. *Nature* **446**, 801–805 (2007).

Dubuisson, J., Helle F. & Cocquerel L. Early steps of the hepatitis C virus life cycle. *Cell. Microbiol.* **10**, 821–827 (2008).

Assembly

Miyanari Y., *et al.* The lipid droplet is an important organelle for hepatitis C virus production. *Nature Cell Biol.* **9**, 1089–1097 (2007).

Roingard P, Hourieux C, Blanchard E & Prensier G. Hepatitis C virus budding at lipid droplet-associated ER membrane visualized by 3D electron microscopy. *Histochem. Cell Biol.* **130**, 561–566 (2008).

Targets — Host**Cyclophilin**

Crabbe, R. *et al.* An evaluation of the cyclophilin inhibitor Debio 025 and its potential as a treatment for chronic hepatitis C. *Expert Opin. Investig. Drugs* **18**, 211–220 (2009).

Targets — Viral**IRES**

Lukavsky, P. J. (2009). Structure and function of HCV IRES domains. *Virus Res.* **139**, 166–171

McHutchison, J. G. *et al.* A phase I trial of an antisense inhibitor of hepatitis C virus (ISIS 14803), administered to chronic hepatitis C patients. *J. Hepatol.* **44**, 88–96 (2006).

Core

Murray, C. L., Jones, C. T., Tassello, J. & Rice, C. M. Alanine scanning of the hepatitis C virus core protein reveals numerous residues essential for production of infectious virus. *J. Virol.* **81**, 10220–10231 (2007).

Hourieux, C. *et al.* Core protein domains involved in hepatitis C virus-like particle assembly and budding at the endoplasmic reticulum membrane. *Cell. Microbiol.* **9**, 1014–1027 (2007).

Ivanyi-Nagy, R., Lavergne, J.-P., Gabus, C., Ficheux, D., Darlix, J.-L. RNA chaperoning and intrinsic disorder in the core proteins of *Flaviviridae*. *Nucl. Acids Res.* **36**, 712–725 (2008).

p7

Steinmann, E. *et al.* Hepatitis C virus p7 protein is crucial for assembly and release of infectious virions. *PLoS Path.* **3**, 962–971 (2007).

Griffin, S. *et al.* Genotype-dependent sensitivity of hepatitis C virus to inhibitors of the p7 ion channel. *Hepatology* **48**, 1779–1790 (2008).

NS2

Welbourn, S. *et al.* Hepatitis C virus NS2/3 processing is required for NS3 stability and viral RNA replication. *J. Biol. Chem.* **280**, 29604–29611 (2005).

Schregel, V., Jacobi, S., Penin, F. & Tautz, N. Hepatitis C virus NS2 is a protease stimulated by cofactor domains in NS3. *Proc. Natl Acad. Sci. USA* **106**, 5342–5347 (2009).

Lorenz, I. C., Marcotrigiano, J., Dentzer, T. G. & Rice, C. M. Structure of the catalytic domain of the hepatitis C virus NS2–3 protease. *Nature* **442**, 831–835 (2006).

NS3 protease

Kim, J. L., *et al.* Crystal structure of the hepatitis C virus NS3 protease domain complexed with a synthetic NS4A cofactor peptide. *Cell* **87**, 343–355 (1996).

Yao, N., Reichert, P., Taremi, S. S., Prosis, W. W. & Weber, P. C. Molecular views of viral polyprotein processing revealed by the crystal structure of the hepatitis C virus bifunctional protease-helicase. *Structure* **7**, 1353–1363 (1999).

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

Hinrichsen, H., *et al.* Short-term antiviral efficacy of BILN 2061, a hepatitis C virus serine protease inhibitor, in hepatitis C genotype 1 patients. *Gastroenterology* **127**, 1347–1355 (2004).

Gentile, I., Viola, C., Borgia, F., Castaldo, G. & Borgia, G. Telaprevir: a promising protease inhibitor for the treatment of hepatitis C virus infection. *Curr. Med. Chem.* **16**, 1115–1121 (2009).

Njoroge, F. G., Chen, K. X., Shih, N.-Y. & Piwinski, J. J. Challenges in modern drug discovery: a case study of boceprevir, an HCV protease inhibitor for the treatment of hepatitis C virus infection. *Accts. Chem. Res.* **41**, 50–59 (2008).

NS3 helicase

Frick, D. N. The hepatitis C virus NS3 protein: a model RNA helicase and potential drug target. *Curr. Issues Mol. Biol.* **9**, 1–20 (2007).

Mackintosh, S. G., *et al.* Structural and biological identification of residues on the surface of NS3 helicase required for optimal replication of the hepatitis C virus. *J. Biol. Chem.* **281**, 3528–3535 (2006).

NS4A

Yang, W., *et al.* Selection of replicon variants resistant to ACH-806, a novel hepatitis C virus inhibitor with no cross-resistance to NS3 protease and NS5B polymerase inhibitors. *Antimicrob. Agents Chemother.* **52**, 2043–2052 (2008).

NS4B

Jones, D. M., Patel, A. H., Targett-Adams, P. & McLauchlan, J. The hepatitis C virus NS4B protein can *trans*-complement viral RNA replication and modulates production of infectious virus. *J. Virol.* **83**, 2163–2177 (2009).

Thompson, A. A., *et al.* Biochemical characterization of recombinant hepatitis C virus non-structural protein 4B: evidence for ATP/GTP hydrolysis and adenylate kinase activity. *Biochemistry* **48**, 909–916 (2009).

Einav, S., *et al.* Discovery of a hepatitis C target and its pharmacological inhibitors by microfluidic affinity analysis. *Nature Biotech.* **26**, 1019–1027 (2008).

NS5A

Macdonald A. & Harris, M. Hepatitis C virus NS5A: tales of a promiscuous protein. *J. Gen. Virol.* **85**, 2485–2502 (2004).

Tellinghuisen, T. L., Foss, K. L. & Treadaway, J. Regulation of hepatitis C virus production via phosphorylation of the NS5A protein. *PLoS Path.* **4**(3), e1000032 (2008).

Appel, N., *et al.* Essential role of domain III nonstructural protein 5A for hepatitis C virus infectious particle assembly. *Plos Path.* **4**(3), e1000035 (2008).

Tellinghuisen, T. L., Marcotrigiano, J. & Rice, C. M. Structure of the zinc-binding domain of an essential component of the hepatitis C virus replicase. *Nature* **435**, 374–379 (2005).

Love, R. A., Brodsky, O., Hickey, M. J., Wells, P. A. & Cronin, C. N. Crystal structure of a novel dimeric form of NS5A domain I protein from hepatitis C virus. *J. Virol.* **83**, 4395–4403 (2009).

Schmitz, U. & Tan, S.-L. NS5A: from obscurity to new target for HCV therapy. *Recent Pat. Anti-Inf. Drug Disc.* **3**, 77–92 (2008).

Nettles, R., *et al.* BMS-790052 is a first-in-class potent hepatitis C virus (HCV) NS5A inhibitor for patients with chronic HCV infection: results from a proof-of-concept study. *AASLD Annual Meeting* LB12 (2008).

NS5B

Behrens SE, Tomei L & De Francesco R. Identification and properties of the RNA-dependent RNA polymerase of hepatitis C virus. *EMBO J.* **15**, 12–22 (1996).

Lohmann V, Körner F, Herian U & Bartenschlager R. Biochemical properties of hepatitis C virus NS5B RNA-dependent RNA polymerase and identification of amino acid sequence motifs essential for enzymatic activity. *J. Virol.* **71**, 8416–8428 (1997).

De Francesco R, Carfi A. Advances in the development of new therapeutic agents targeting the NS3–4A serine protease or the NS5B RNA-dependent RNA polymerase of the hepatitis C virus. *Adv Drug Deliv Rev.* **59**, 1242–1262 (2007).