**Supplementary Table 2. Publications on HCV using humanized mouse**

| Category | No. of papers | Agents | PXB-mouse | uPA/SCID mouse (CA)*[1] | FRG mouse | TK-NOG mouse | uPA/SCID mouse (BE)*[2] | uPA/SCID mouse (DE)*[3] | uPA/SCID moue (FR)*[4] | Publications |
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| Small molecules | 37 | Daclatasvir plus Asunaprevir; GLE/PIB | O | | | | | | | Osawa M, et al. Efficacy of glecaprevir and pibrentasvir treatment for genotype 1b hepatitis C virus drug resistance-associated variants in humanized miceJ Gen Virol. 2019 Jul;100(7):1123-1131. |
| | | MK-7009, BMS-788329 DAAs | O | | | | | | | Hamdane N, et al. HCV-induced epigenetic changes associated with liver cancer risk persist after sustained virologic response. Gastroenterology. 2019 Jun;156(8):2313-2329.e7. |
| | | Asunaprevir, Beclabuvir, Daclatasvir | O | | | | | | | Teraoka Y, et al. Limitations of daclatasvir/asunaprevir plus beclabuvir treatment in cases of NS5A inhibitor treatment failure. J Gen Virol. 2018 Aug;99(8):1058-1065. |
| | | Glecaprevir+ Pibrentasvir+ Sofosbuvir | O | | | | | | | Teraoka Y, et al. Prevalence of NS5A resistance associated variants in NS5A inhibitor treatment failures and an effective treatment for NS5A-P32 deleted hepatitis C virus in humanized miceBiochem Biophys Res Commun. 2018 Jun 2;500(2):152-157. |
| | | Chlorcyclizine Derivatives | O | | | | | | | Rolt A, et al. Preclinical Pharmacological Development of Chlorcyclizine Derivatives for the Treatment of Hepatitis C Virus Infection. J Infect Dis. 2018 May 5;217(11):1761-1769. |
| | | Daclatasvir, Asunaprevir , Beclabuvir | | | O | | | | | Burchill MA, et al. Rapid reversal of innate immune dysregulation in blood of patients and livers of humanized mice with HCV following DAA therapy. PLoS One. 2017 Oct 17;12(10):e0186213. |
| | | Corilagin | O | | | | | | | Reddy BU, et al. A natural small molecule inhibitor corilagin blocks HCV replication and modulates oxidative stress to reduce liver damage. Antiviral Res. 2017 Dec 7;150:47-59. |
| | | BI-2536 | | | O | | | | | Diab A, et al. Polo-like-kinase 1 is a proviral host-factor for hepatitis B virus replication. Hepatology. 2017 Dec;66(6):1750-1765. |
| | | jumonji domain-containing protein 6 | | | | O | | | | Ganesan M, et al. Demethylase JMJD6 as a New Regulator of Interferon Signaling: Effects of HCV and Ethanol Metabolism. Cell Mol Gastroenterol Hepatol. 2017 Oct 16;5(2):101-112. |
| | | Vaniprevir, BMS-788329 | O | | | | | | | Uchida T, et al. Elimination of HCV via a non-ISG-mediated mechanism by vaniprevir and BMS-788329 combination therapy in human hepatocyte chimeric mice. Virus Res. 2016 Feb 2;213:62-68 |
| | | Daclatasvir Asunaprevir | O | | | | | | | Kan H, et al. Infection of human hepatocyte chimeric mouse with genetically engineered hepatitis B virus. Antivir Ther. 2016;21(4):307-315. |
| | | Legalon SIL | O | | | | | | | DebRoy S, et al. Hepatitis C virus dynamics and cellular gene expression in uPA-SCID chimeric mice with humanized livers during intravenous silibinin monotherapy. J Viral Hepat. 2016 Sep;23(9):708-717. |
| | | B5 | | | O | | | | | Vausselin T, et al. Identification of a new benzimidazole derivative as an antiviral against hepatitis C virus. J Virol. 2016 Sep 12;90(19):8422-8434. |
| | | Ledipasvir/GS-558093, Telaprevir/GS-558093 | | | | O | | | | Kai Y, et al. Emergence of hepatitis C virus NS5A L31V plus Y93H variant upon treatment failure of daclatasvir and asunaprevir is relatively resistant to ledipasvir and NS5B polymerase nucleotide inhibitor GS-558093 in human hepatocyte chimeric mice. Gastroenterol. 2015 Nov;50(11):1145-1151. |
| | | GSK8853 | O | | | | | | | Pouliot JJ, et al. Preclinical characterization and in vivo efficacy of GSK8853, a small molecule inhibitor of the Hepatitis C virus NS4B protein. Antimicrob Agents Chemother. 2015 Oct;59(10):6539-6550. |

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| erlotinib and dasatinib combined with Anti-CD81/anti-CLDN1 | | | | | | | O | Xiao F, et al. Synergy of entry inhibitors with direct-acting antivirals uncovers novel combinations for prevention and treatment of hepatitis C. Gut. 2015 Mar;64(3):483-94. |
| Compound 1a | O | | | | | | | Miller JF, et al. Hepatitis C replication inhibitors that target the viral NS4B protein. J Med Chem. 2014 Mar 13;57(5):2107-2120. |
| NA808 and telaprevir | O | | | | | | | Katsume A, et al. A serine palmitoyltransferase inhibitor blocks hepatitis C virus replication in human hepatocytes. Gastroenterology. 2013 Oct;145(4):865-73. |
| 2,3-dihydro-5-hydroxy- 2,2-dipentyl-4,6-di- tert-butylbenzofuran | O | | | | | | | Yasui Y, et al. Synthetic lipophilic antioxidant BO-653 suppresses HCV replication. J Med Virol. 2013 Feb;85(2):241-9. |
| BMS-605339, BMS-788329 or BMS-821095 | O | | | | | | | Shi N, et al. Combination therapies with NS5A, NS3 and NS5B inhibitors on different genotypes of hepatitis C virus in human hepatocyte chimeric mice. Gut. 2013 Jul;62(7):1055-61. |
| SB-431542, LY-364947 | O | | | | | | | Sakata K, et al. HCV NS3 protease enhances liver fibrosis via binding to and activating TGF-beta type I receptor. Sci Rep. 2013 Nov 22;3:3243. |
| LIC-pIC | O | | | | | | | Nakagawa S, et al. Targeted induction of interferon-lambda in humanized chimeric mouse liver abrogates hepatotropic virus infection. PLoS One. 2013;8(3):e59611. |
| Artemisinin analogues | | | | | O | | | Obeid S, et al. Artemisinin analogues as potent inhibitors of in vitro hepatitis C virus replication. PLoS One. 2013 Dec 11;8(12):e81783. |
| RO8191 (small-molecule type I IFN receptor agonist) | O | | | | | | | Konishi H, et al. An orally available, small-molecule interferon inhibits viral replication. Sci Rep. 2012;2:259. |
| Telaprevir and MK-0608 | O | | | | | | | Ohara E, et al. J Elimination of hepatitis C virus by short term NS3-4A and NS5B inhibitor combination therapy in human hepatocyte chimeric mice. Hepatol. 2011 May; 54(5): 872-8. |
| Telaprevir | O | | | | | | | Hiraga N, et al. Rapid emergence of telaprevir resistant hepatitis C virus strain from wildtype clone in vivo. Hepatology. 2011 Sep 2;54(3):781-8. |
| ME3738 | O | | | | | | | Abe H, et al. ME3738 enhances the effect of interferon and inhibits hepatitis C virus replication both in vitro and in vivo. J Hepatol. 2011 Jul;55(1):11-8. |
| MK-3281 | | | | | O | | | Narjes F, et al. Discovery of (7R)-14-cyclohexyl-7-{[2-(dimethylamino)ethyl](methyl) amino}-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylic acid (MK-3281), a potent and orally bioavailable finger-loop inhibitor of the hepatitis C virus NS5B polymerase. J Med Chem. 2011 Jan 13;54(1):289-301. |
| Recombinant griffithsin | | | | | O | | | Meuleman P, et al. Griffithsin has antiviral activity against hepatitis C virus. Antimicrob Agents Chemother. 2011 Nov;55(11):5159-5167. |
| Telaprevir | O | | | | | | | Kamiya N, et al. Practical evaluation of a mouse with chimeric human liver model for hepatitis C virus infection using an NS3-4A protease inhibitor. J Gen Virol. 2010 Jul;91(Pt 7):1668-1677. |
| Amphipathic DNA polymers | O | | | | | | | Matsumura T, et al. Amphipathic DNA polymers inhibit hepatitis C virus infection by blocking viral entry. Gastroenterology. 2009 Aug;137(2):673-681. |
| DEBIO-025 | O | | | | | | | Inoue K, et al. Evaluation of a cyclophilin inhibitor in hepatitis C virus-infected chimeric mice in vivo. Hepatology. 2007 Apr;45(4):921-928. |
| BILN 2061 | | | | | O | | | Vanwolleghem T, et al. Ultra-rapid cardiotoxicity of the hepatitis C virus protease inhibitor BILN 2061 in the urokinase-type plasminogen activator mouse. Gastroenterology. 2007 Oct;133(4):1144-55. |

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| | | Myriocin | O | | | | | | | Umehara T, et al. Serine palmitoyltransferase inhibitor suppresses HCV replication in a mouse model. Biochem Biophys Res Commun. 2006 Jul 21;346(1):67-73. |
| | | BH3 interacting domain death agonist | | O | | | | | | Hsu EC, et al. CD Richardson. Modified apoptotic molecule (BID) reduces hepatitis C virus infection in mice with chimeric human livers. Nat Biotechnol. 2003 May;21(5):519-525. |
| Interferon | 8 | IFN-alpha | O | | | | | | | Miyaki E, et al. Interferon alpha treatment stimulates interferon gamma expression in type I NKT cells and enhances their antiviral effect against hepatitis C virus. PLoS One. 2017 Mar 2;12(3):e0172412. |
| | | IFN-α2, IFN-γ, IFN-λ1 | O | | | | | | | Hamana A, et al. Evaluation of antiviral effect of type I, II, and III interferons on direct-acting antiviral-resistant hepatitis C virus. Antiviral Res. 2017 Aug 31;146:130-138. |
| | | biliverdin & PEG-IFNα | | | | | | O | | Kah J, et al. Heme oxygenase-1 polymorphisms can affect HCV replication and treatment responses with different efficacy in humanized mice. Liver Int. 2017 Aug;37(8):1128-1137. |
| | | IFNα-2b | | O | | | | | | Chen R, et al. Intrinsic Viral Factors Are the Dominant Determinants of the Hepatitis C Virus Response to Interferon Alpha Treatment in Chimeric Mice. PLoS One. 2016 Jan 14;11(1):e0147007. doi: 10.1371 |
| | | IFN-gamma gene transfer | O | | | | | | | Takahashi Y,et al. Long-Term Elimination of Hepatitis C Virus from Human Hepatocyte Chimeric Mice After Interferon-gamma Gene Transfer. Hum Gene Ther Clin Dev. 2014 Mar;25(1):28-39. |
| | | PEG-IFN-alpha | O | | | | | | | Watanabe T, et al. Hepatitis C virus kinetics by administration of pegylated interferon-alpha in human and chimeric mice carrying human hepatocytes with variants of the IL28B gene. Gut. 2013 Sep;62(9):1340-1346. |
| | | Interferon alpha | O | | | | | | | Hiraga N, et al. Infection of human hepatocyte chimeric mouse with genetically engineered hepatitis C virus and its susceptibility to interferon. FEBS Lett. 2007 May 15;581(10):1983-1987. |
| | | IFN-alpha | | O | | | | | | Kneteman NM, et al. Anti-HCV therapies in chimeric scid-Alb/uPA mice parallel outcomes in human clinical application. Hepatology. 2006 Jun;43(6):1346-1353. |
| Small molecule+Interferon | 5 | Ledipasvir /GS-558093, simeprevir / GS-558093 + PEG-IFN | | | | O | | | | Doi A, et al. Combinations of two drugs among NS3/4A inhibitors, NS5B inhibitors and non-selective antiviral agents are effective for hepatitis C virus with NS5A-P32 deletion in humanized-liver mice. J Gastroenterol. 2019 May;54(5):449-458. |
| | | Simeprevir Daclatasvir Asunaprevir +IFN | O | | | | | | | Kan H, et al. Protease inhibitor resistance remains even after mutant strains become undetectable using deep sequencing. J Infect Dis. 2016 Dec 1;214(11):1687-1694. |
| | | Telaprevir and MK-0608 & IFN | O | | | | | | | de Jong YP, et al. Evaluation of combination therapy against hepatitis C virus infection in human liver chimeric mice. J Hepatol. 2011 May;54(5):848-850. |
| | | Ribavirin +IFN | O | | | | | | | Kurbanov F, et al. Positive selection of core 70Q variant genotype 1b hepatitis C virus strains induced by pegylated interferon and ribavirin. J Infect Dis. 2010 Jun 1;201(11):1663-1671. |
| | | Hsp90 inhibitor and PEG-IFN | O | | | | | | | Nakagawa S, et al. Hsp90 inhibitors suppress HCV replication in replicon cells and humanized liver mice. Biochem Biophys Res Commun. 2007 Feb 23;353(4):882-8. |
| **siRNA** | 5 | RRM2-siRNA | O | | | | | | | Kitab B, et al. Ribonucleotide reductase M2 promotes RNA replication of hepatitis C virus by protecting NS5B protein from hPLIC1-dependent proteasomal degradation. J Biol Chem. 2019 Apr 12;294(15):5759-5773. |
| | | siRNA target HCV 5'UTR | O | | | | | | | Watanabe T, et al. In vivo therapeutic potential of Dicer-hunting siRNAs targeting infectious hepatitis C virus. Sci Rep. 2014 Apr 23;4:4750. |
| | | LNP- sshRNAs | O | | | | | | | Ma H, et al. Formulated minimal-length synthetic small hairpin RNAs are potent inhibitors of hepatitis C virus in mice with humanized livers. Gastroenterology. 2014 Jan;146(1):63-66.e5. |

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| | | LNP- sshRNAs | O | | | | | | | Dallas S, et al. Inhibition of hepatitis C virus in chimeric mice by short synthetic hairpin RNAs: sequence analysis of surviving virus shows added selective pressure of combination therapy. J Virol. 2014 May;88(9):4647-4656. |
| | | thromboxane A2 synthase | | | O | | | | | Abe Y, et al. Combinatorial RNA Interference Therapy Prevents Selection of Pre-existing HBV Variants in Human Liver Chimeric Mice. Gastroenterology. 2013 Sep;145(3):658-667. |
| **Antibody** | 19 | Anti-E2 &anti-claudin 1 | | | O | | | | | Mailly L, et al. In vivo combination of human anti-envelope glycoprotein E2 and -Claudin-1 monoclonal antibodies for prevention of hepatitis C virus infection . Antiviral Res. 2019 Feb;162:136-141. doi: 10.1016/j.antiviral.2018.12.018. |
| | | claudin-1-specific monoclonal Ab | | | | | | | O | Colpitts CC, et al. Humanisation of a claudin-1-specific monoclonal antibody for clinical prevention and cure of HCV infection without escape. Gut. 2018 Apr;67(4):736-745. |
| | | mAb 2A5 | | | | | O | | | Desombere I, et al. A novel neutralizing human monoclonal antibody broadly abrogates hepatitis C virus infection in vitro and in vivoAntiviral Res. 2017 Dec;148:53-64. |
| | | human mAb | | O | | | | | | O'Shea D, et al. Prevention of hepatitis C virus infection using a broad cross-neutralizing monoclonal antibody (AR4A) and epigallocatechin gallate. Liver Transpl. 2016 Mar;22(3):324-332. |
| | | HC84.26 | | O | | | | | | Keck Z, et al. Affinity maturation of a broadly neutralizing human monoclonal antibody that prevents acute hepatitis C virus infection in mice. Hepatology. 2016 Dec;64(6):1922-1933. |
| | | mAb E6F6 | | | O | | | | | Zhang TY, et al. Prolonged suppression of HBV in mice by a novel antibody that targets a unique epitope on hepatitis B surface antigen. Gut. 2016 Apr;65(4):658-71. doi: 10.1136 |
| | | mAb16-71 | | | | | O | | | Vercauteren K, et al. Targeting a host-cell entry factor barricades antiviral-resistant HCV variants from on-therapy breakthrough in human-liver mice. Gut. 2016 Dec;65(12):2029-2034. |
| | | mAbs AP33 | | | | | O | | | Desombere I, et al. Monoclonal anti-envelope antibody AP33 protects humanized mice against a patient-derived hepatitis C virus challenge. Hepatology. 2016 Apr;63(4):1120-1134. |
| | | anti-human CD81 mAb | O | | | | | | | Ji C, et al. Prevention of hepatitis C virus infection and spread in human liver chimeric mice by an anti-CD81 monoclonal antibody. Hepatology. 2015 Apr;61(4):1136-1144. |
| | | claudin-1-targeting monoclonal Ab | | | | | | O | | Mailly L, et al. Clearance of persistent hepatitis C virus infection in humanized mice using a claudin-1-targeting monoclonal antibody. Nat Biotechnol. 2015 May;33(5):549-554. |
| | | SR-BI mAbs | | | | | O | | | Vercauteren K, et al. Successful anti-scavenger receptor class B type I (SR-BI) monoclonal antibody therapy in humanized mice after challenge with HCV variants with in vitro resistance to SR-BI-targeting agents. Hepatology. 2014 Nov;60(5):1508-1518. |
| | | IgG purified from the sera of HCV-particle-immunized mice | O | | | | | | | Akazawa D, et al. Neutralizing antibodies induced by cell culture-derived hepatitis C virus protect against infection in mice. Gastroenterology. 2013 Aug;145(2):447-455 |
| | | SR-BI, mAb16-71 | | | | | O | | | Meuleman P, et al. A human monoclonal antibody targeting scavenger receptor class B type I precludes hepatitis C virus infection and viral spread in vitro and in vivo. Hepatology. 2012 Feb;55(2):364-372. |
| | | anti-SR-BI mAbs | | | | | O | | | Lacek K, et al. Novel human SR-BI antibodies prevent infection and dissemination of HCV in vitro and in humanized mice. J Hepatol. 2012 Jul;57(1):17-23. |
| | | H06-antibodies | | | | | O | | | Meuleman P, et al. In vivo evaluation of the cross-genotype neutralizing activity of polyclonal antibodies against hepatitis C virus. Hepatology. 2011 Mar;53(3):755-762. |
| | | Polyclonal IgG | | | | | O | | | Vanwolleghem T, et al. Polyclonal immunoglobulins from a chronic hepatitis C virus patient protect human liver-chimeric mice from infection with a homologous hepatitis C virus strain.Hepatology. 2008 Jun;47(6):1846-1855. |

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| | | Anti-CD81 | | | | | O | | | Meuleman P, et al. Anti-CD81 antibodies can prevent a hepatitis C virus infection in vivo. Hepatology. 2008 Dec;48(6):1761-1768. |
| | | BILN-2061; HCV371 | | O | | | | | | Kneteman NM, et al. Anti-HCV therapies in chimeric scid-Alb/uPA mice parallel outcomes in human clinical application. Hepatology. 2006 Jun;43(6):1346-1353. |
| | | anti-CLDN1 Mabs | O | | | | | | | Fukasawa M, et al. Monoclonal Antibodies against Extracellular Domains of Claudin-1 Block Hepatitis C Virus Infection in a Mouse Model. J Virol. 2015 May 1;89(9):4866-4879. |
| Others | 2 | ribonucleotide reductase M2 | O | | | | | | | Kitab B, et al. Ribonucleotide reductase M2 promotes RNA replication of hepatitis C virus by protecting NS5B protein from hPLIC1-dependent proteasomal degradation. J Biol Chem. 2019 Apr 12;294(15):5759-5773. |
| | | peroxisomal biogenesis impaired by HCV | O | | | | | | | Lupberger J, et al. Combined Analysis of Metabolomes, Proteomes, and Transcriptomes of HCV-infected Cells and Liver to Identify Pathways Associated With Disease Development. Gastroenterology. 2019 Aug;157(2):537-551.e9. |
| | | Griffithsin, Scytovirin | | O | | | | | | Takebe Y, et al. Antiviral lectins from red and blue-green algae show potent in vitro and in vivo activity against hepatitis C virus. PLoS One. 2013 May 21;8(5):e64449. |
| | | HCV796 | | O | | | | | | Kneteman NM, et al. HCV796: A selective nonstructural protein 5B polymerase inhibitor with potent anti-hepatitis C virus activity in vitro, in mice with chimeric human livers, and in humans infected with hepatitis C virus. Hepatology. 2009 Mar;49(3):745-752. |

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