Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Study of viral pathogenesis in humanized mice
Jenna M Gaska and Alexander Ploss

Many of the viral pathogens that cause infectious diseases in humans have a highly restricted species tropism, making the study of their pathogenesis and the development of clinical therapies difficult. The improvement of humanized mouse models over the past 30 years has greatly facilitated researchers’ abilities to study host responses to viral infections in a cost effective and ethical manner. From HIV to hepatotropic viruses to Middle East Respiratory Syndrome coronavirus, humanized mice have led to the identification of factors crucial to the viral life cycle, served as an outlet for testing candidate therapies, and improved our abilities to analyze human immune responses to infection. In tackling both new and old viruses as they emerge, humanized mice will continue to be an indispensable tool.

Addresses
Department of Molecular Biology, Princeton University, 110 Lewis Thomas Laboratory, Washington Road, Princeton, NJ 08544-1014, USA

Corresponding author: Ploss, Alexander (aploss@princeton.edu)

Introduction
Viruses make a staggering contribution to morbidity and mortality in the human populations of both industrial and developing countries. At least 500 million people are chronically infected with hepatitis B (HBV) or C viruses (HCV), placing them at risk for developing severe liver disease. 33 million individuals are infected with HIV, leading to 1.7 million AIDS-related deaths every year. Of the approximately 400 million people who contract dengue virus (DENV) annually, almost 100 million present with clinical symptoms. 60–90% of the global population is infected with herpes simplex viruses (HSV), resulting in orolabial and genital lesions. Human cytomegalovirus (HCMV), which persistently infects 40% of the world, can be life-threatening for newborns and immunocompromised individuals.

Many of the viruses causing disease in humans have a narrow host range, often limited to humans and closely related non-human primates (NHPs). This has created challenges in studying the pathogenesis of human-tropic viruses as experiments in NHPs are hampered by logistical, financial, and ethical concerns. This creates a pressing need for more tractable small animal models to study existing and emerging viral diseases. In the last few decades, humanized mice have emerged as a solution to this problem. Humanized mice can be generated by expressing human genes whose products are needed for viral infection (Table 1), such as entry factors, or through xenotransplantation of hematopoietic stem cells (creating human immune system mice, known as HIS) and/or other human tissues (Figure 1).

This paper highlights the recent progress and challenges in studying viral pathogenesis in humanized mice. We will discuss four groups of human-tropic viruses — HIV, DENV, herpesviruses, and hepatitis viruses — as examples of diseases for which specific types of humanized mice were and still are enabling experimental platforms. Using these examples, we will provide a general outlook on how humanized mice can be adapted and refined through genetic host adaptations and/or co-engraftment of multiple tissues to facilitate analysis of other viral infections.

Human immunodeficiency virus (HIV)
In 2013 alone, 1.5 million people worldwide died from AIDS, and 33 million were cited as living with HIV. Besides humans, only chimpanzees are readily susceptible to HIV, but since they usually do not progress to AIDS, they have not gained traction as HIV animal models. In searching for alternatives, it was shown that smaller NHPs, specifically rhesus macaques, were susceptible to simian immunodeficiency virus (SIV), leading to AIDS-like symptoms. To improve the utility of this model, chimeric viruses closely resembling HIV-1, namely simian-human immunodeficiency virus (SHIV) and simian-tropic HIV (stHIV), were generated [1].

Despite intense efforts, it has not yet become possible to genetically overcome species barriers and recapitulate the HIV life-cycle in small animal models. Advances have been made, but they are primarily focused on establishing HIV uptake in mice [2]. Since HIV is a lymphotropic virus primarily infecting CD4 T cells, engraftment of human immune system components proved a viable approach to establish HIV infections in a small animal model. Early models pioneered by McCune and colleagues, based on engrafting xenorecipients with human fetal thymic or lymph node implants, demonstrated that an acute infection of human lymphoid organs with HIV-1 can be
followed in humanized mice [3]. With the improvement of xenorecipient strains and humanization protocols (extensively reviewed in [4]), HIS mice have deepened our knowledge about HIV viral transmission, immune responses to HIV and the efficacy of novel therapeutic interventions. The ability of HIV-1-infected cells to form latent reservoirs has been especially challenging in completely curing individuals of the virus [5]. Recently, several groups have shown that HIV-1 latency can be observed in humanized mouse models [6–8]. These mice have made it possible to model in vivo, for example, how treatment using broadly neutralizing antibodies in combination with inducers can prevent viral rebound following removal from antiretrovirals [9]. In hindering transmission, vectored immunophrophylaxis has shown promise as a way to obstruct intravenous [10] and mucosal transmission of HIV in humanized mice [11]. As the latter is the primary route by which individuals become infected, the in vivo model for mucosal HIV transmission is physiologically relevant and provides a venue for testing anti-viral therapies. Immune responses in HIS mice are suboptimal because of a variety of incompatibilities between the mouse and human immune system. Nonetheless, it was shown that in a particular version of HIS mice, so-called bone-marrow liver thymus (BLT) mice, the dynamic interplay of HIV-specific cellular immunity and viral escape from immune pressure can be accurately modeled [12**].

**Dengue virus (DENV)**

Dengue is a mosquito-borne disease, caused by DENV, a positive-sense, single-stranded RNA virus belonging to the family Flaviviridae. Four genetically and antigenically distinct serotypes, DENV-1 to DENV-4, have been described, annually causing ~390 million infections which range in severity from completely asymptomatic to lethal hemorrhagic fever or shock syndrome (DHF and DSS, respectively) [13]. Since a vaccine still does not exist, studying the immune response to DENV is of especial importance, as individuals with previous immunity are more susceptible to developing DHF and DSS [14,15]. Murine xenorecipient strains expressing HLA-A2 were injected with human blood-forming stem cells and demonstrated improved immune responses to tissue-culture derived DENV, especially in assessing human T-cell response to DENV during and after acute infection [16]. Additionally, it was shown that viremia can be suppressed by administration of direct-acting antivirals (DAAs) to humanized mice that displayed symptoms similar to those in humans following infection with a clinical DENV isolate [17], paving the way for creating and testing DAAs that could be utilized in treating DENV. However, while priming of DENV-specific B and T cell responses occurs at some level, it is not sufficiently robust in existing models. This poses challenges for untangling the mechanisms of why DHF/DSS is so much higher in individuals with secondary heterologous DENV infections. Further light has also been shed on identifying the cells targeted by DENV. Past research in humanized mice concluded that T cells were not infected by DENV [18,19], but two groups have recently observed evidence to the contrary [17,20]. Finally, since DENV is mosquito-borne, understanding transmission from host to vector and vice versa is important for examining viral spread in populations and preventing large-scale outbreaks. Thus, the examination for the first time.

**Table 1**

| Pathogen        | Disease/symptoms                                      | Host factors needed at different steps of the viral life cycle in humans                                                                 | Factors restricting infection in mice                                                                 |
|-----------------|-------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| HIV (as reviewed in [39]) | Leads to decreased levels of CD4+ T cells, ultimately resulting in AIDS | Entry: CD4, CCR5, CXCR4 (some T-tropic HIV-1 viruses can use the murine orthology of CXCR4) Post-entry: Cyclin T1 | Transcription: low Tat activity (needs human cyclinT1 as cofactor for successful binding to trans-activation response element) Post-translation: excessive splicing of HIV-1 RNA Poor particle assembly |
| Polio virus [60] | Poliomyelitis, with paralysis in some individuals due to nerve cell damage | Entry: poliovirus receptor |                                                                                                                        |
| Measles virus [61] | Measles (also known as rubeola), which leads to respiratory infection | Entry: CD46 |                                                                                                                        |
| HCV (as reviewed in [42]) | Hepatitis C, which can lead to liver cirrhosis, fibrosis, and hepatocellular carcinoma | Entry: OCLN and CD81 (minimal necessary entry factors) | Replication: Innate immune responses                                                                                     |
| HBV [56**]      | Hepatitis B, which has similar effects on liver health as hepatitis C | Entry: NTCP | Post-entry: no cccDNA formation; other post-entry restrictions unknown Unknown                                                                 |
| Ebola virus [62] | Fever, diarrhea, and disrupted liver and kidney function; can lead to internal and external bleeding | Entry: Niemann-Pick C1 |                                                                                                                        |
of the human immune response in humanized mice following DENV infection by mosquito bite is an encouraging step [21].

**Human herpesviruses (HHVs)**

The nine HHVs are prevalent and can establish long-lasting latent infections, leading to skin lesions, epilepsy, cancer, and autoimmune disease (for review see [22]).

Epstein Barr Virus (EBV) is widespread and linked to ~2% of human tumors originating in lymphocytes and epithelial cells [23]. Only B cell EBV infection can be studied in humanized mice, and different stages of the latent and lytic viral life cycle have been observed in these cells [24,25]. EBV-associated malignancies have also been studied in HIS mice. A viral mutant lacking EBV latent nuclear antigen 3B (EBNA3B) led to formation of large B cell lymphomas in HIS mice [26]. Further research on this strain has provided evidence that various EBNA3 antigens regulate expression of the chemokine CXCL10, leading to reduced T cell action [27]. EBV-associated hemophagocytic lymphohistiocytosis, with a pathology highly similar to that seen in humans [28], and erosive arthritis [29] have both been observed in...
humanized mice. Finally, HIS mice have also been a platform for examining the role of innate immunity in EBV infection (reviewed in [30]).

Human cytomegalovirus (HCMV) is the most common causative agent of congenital viral infection, resulting in children with growth defects or, most detrimental, CNS injury. Additionally, immune-compromised patients, such as individuals living with AIDS or recent organ transplant recipients, are also at risk for HCMV-mediated disease [31]. CMV is found in numerous species, but the determinants of species tropism are not yet defined. While rodents and other animals have been utilized to study congenital CMV infection via their species-specific virus [32,33], it is still not possible to specifically model congenital HCMV infection. However, progress is being made — immunocompromised mice engrafted with human CD34+ hematopoietic stem cells were able for the first time to establish both systemic HCMV infection and also viral latency and reactivation [34]. Even more recently, HCMV infection was established in the human hepatocytes of a human liver chimeric mouse, building toward a resource for in vivo testing of candidate therapies [35].

Human T cell leukemia virus type 1 (HTLV-1) is strongly linked to the development of adult T cell leukemia/lymphoma (ATL) and the inflammatory disease HTLV-1-associated myelopathy/tropical spastic paraparesis. HIS mice are primarily used to study human T cells during early HTLV-1 infection and initial stages of HTLV-associated diseases. These mice are able to reproduce some aspects of infection in humans, such as CD4+ T cell lymphomas [36] and symptoms associated with changes in human thymopoiesis [37]. Efforts to improve the adaptive immune response in CD133+ mice by injecting human hematopoietic stem cells into the bone marrow of these mice has led to more consistent B-to-T-cell ratios over time and is thus a better approach for studying ATL development [38].

Finally, immunocompromised mice with human skin transplants have been utilized for studying the herpesviruses most highly associated with skin lesions, such as Kaposi’s sarcoma-associated herpesviruses [39] and Varicella-zoster virus [40].

Hepatitis B and C Virus (HBV and HCV)

HBV and HCV together infect ~490 million individuals worldwide, causing liver cirrhosis, fibrosis, and hepatocellular carcinoma if left untreated. These two viruses robustly infect only chimpanzees and humans. In the absence of a permissive mouse model, numerous transgenic strains expressing individual or combinations of HCV gene products were developed to study HBV and HCV-induced liver disease (Table 2, see [41] for HBV and [42] for HCV for in-depth reviews on existing humanized mouse models for these viruses). HBV transgenic mice have contributed substantially to our understanding of many aspects of HBV biology, immunobiology and pathogenesis (reviewed in [43]). In contrast, reports on the histopathology in HCV transgenic mice differ vastly depending on the expressed HCV gene product, mouse background or differences in the promoters used for the expression of viral proteins. Their utility is further lessened as they are not bona fide infection models as any pathological processes develop in the absence of the inflammatory milieu established during chronic infection.

To study HBV and HCV infection in mice, humanization of the mouse liver by xenograftment of permissive human primary hepatocytes has been explored. Most of the commonly used xenorecipients share common features: they are immunodeficient to prevent xenograft rejection and often suffer from an endogenous liver injury to promote hepatocyte proliferation and provide human donor cells a competitive growth advantage over mouse hepatocytes. In 2001, the development of an Alb-uPA/Rag-2 mouse, which could be engrafted with primary human hepatocytes, was successfully infected with

| Pathogen | Component of virus expressed | Resultant phenotype in mouse |
|----------|------------------------------|-----------------------------|
| HCV (as reviewed in [42]) | Core, NS4B, E1-E2-NS2, Core-E2 | Apoptosis of hepatocytes, lipogenesis, no liver disease observed, liver injury, no liver disease observed |
| HBV (as reviewed in [41]) | HBV surface antigen (HBsAg) and pre-S and X antigens, X gene, Hepatitis B core antigen (HBcAg), 1.3 HBV-DNA | No viral replication or signs of liver disease, tumor formation in the liver, T cell tolerance in response to HBcAg, but no liver disease observed, high viral particle production |
HBV [44] and also HCV [45]. To improve robustness and throughput, several other immunodeficient liver injury models, including fumaryl acetoacetate hydrase deficient mice (FAH−/− [46]), MUP-uPA [47] and Alb-HSV1-tk [48], have been generated. These mice can be engrafted to very high levels with human hepatocytes and subsequently become susceptible to HBV and HCV infection. Human liver chimeric mice have been critical tools for studying HBV, HCV and HDV infections but also serve as important tools for preclinically assessing the efficacy of novel therapeutics. However, HBV and HCV pathogenesis, human adaptive immune responses and vaccine development can only be studied in a mouse model harboring both a human liver graft and a functional human immune system. Several groups have now reported that dual engraftment of components of a human immune system and a (matching) human liver can be achieved in a single recipient [49,50]. When infected with HBV [51] or HCV [52], dually engrafted mice indeed mount virus-specific immune responses and develop histopathological features reminiscent of liver disease in humans. However, the differences of donor matching for the two tissue compartments, variation in the level of engraftment, the low throughput and the limited functionality of the engrafted human immune system lessen the utility of this model.

An inbred mouse model with inheritable susceptibility to HBV or HCV would overcome the technical difficulties of the xenotransplantation model. The challenge is to systematically identify and overcome any restrictions to viral growth in murine cells. Both the HBV and HCV life-cycles are blocked at numerous steps. For HCV, the minimal set of human specific entry factors, that is human CD81 and occludin (OCLN) have been identified, facilitating HCV uptake into mouse cells in vitro [53] and in vivo [54]. The entire HCV life-cycle can be recapitulated in mice transgenically expressing human CD81 and OCLN with severely impaired antiviral innate immunity [55**]. The recent identification of human taurocholate co-transporting polypeptide (hNTCP) as an HBV receptor [56**] is a promising first step toward creation of a mouse model with inheritable susceptibility to HBV infection. However, it should be noted that there are still numerous blocks to overcome. While HBV assembly and release are supported in mouse hepatocytes, expression of hNTCP does not render mouse cells permissive for HBV uptake, pointing toward post-attachment and post-entry blocks. These include, but are not limited to, the inability of HBV to form covalently closed circular DNA, its main transcriptional template.

Conclusions
The use of humanized mice in infectious disease research provides a forum for studying viruses previously less accessible due to their species tropism. With so many types of humanized mice now available, researchers will continue to improve and expand upon these models. The research discussed here has provided invaluable lessons for handling emerging viral threats, as exemplified by the quick development of a humanized mouse for studying Middle Eastern Respiratory Syndrome (MERS [57]) and a lung xenotransplantation model for the emerging Nipah Virus [58**]. As viruses continue to evolve and adapt to new hosts, humanized mice will be an indispensable tool for studying pathogenesis and will increase the likelihood of developing more efficacious therapeutics.

Acknowledgements
We would like to thank Florian Douam, Benjamin Winer, and Qiang Ding for their helpful discussion and comments on drafts of this paper. Work in the laboratory is in part supported by grants from the National Institutes of Health (2 R01 AI079301-05A1, 1 R01 AI107301-01, 1 R56 AI106005-01), the Walter Reed Army Institute of Research, the Bill and Melinda Gates Foundation and the Grand Challenge Program of Princeton University. JMG is supported by co-funding from NIAID on iNRS A 5T32GM007388. We apologize to all colleagues whose work could not be cited due to space constraints.

References and recommended reading
Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Hatziioannou T, Ambrose Z, Chung NPY, Piatak M, Yuan F, Trubey CM, Coalter V, Kisier R, Schneider D, Smedley J et al.: A macaque model of HIV-1 infection. Proc Natl Acad Sci U S A 2009, 106:4426-4429.
2. Pietzsch J, Gnuel H, Bourmassos S, Donovan BM, Klein F, Diskin R, Seaman MS, Bjorkman PJ, Ravetch JV, Pierson A et al.: A mouse model for HIV-1 entry. Proc Natl Acad Sci U S A 2012, 109:15859-15864.
3. Namikawa R, Kaneshima H, Lieberman M, Weissman IL, McCune JM: Infection of the SCID-hu mouse by HIV-1. Science 1988, 242:1684-1686.
4. Shultz LD, Brehm MA, Garcia-Martinez JV, Greiner DL: Humanized mice for immune system investigation: progress, promise and challenges. Nat Rev Immunol 2012, 12:786-798.
5. Marsden MD, Zack JA: HIV/AIDS eradication. Bloomberg Med Chem Lett 2013, 23:4003-4010.
6. Choudhary SK, Archin NM, Cheema M, Dahl NP, Garcia JV, Margolis DM: Latent HIV-1 infection of resting CD4+ T cells in the humanized Rag2−/−, IL-2Rg−/−, mouse. J Virol 2012, 86:114-120.
7. Denton PW, Olesen R, Choudhary SK, Archin NM, Wahl A, Swanson MD, Chateau M, Nodji T, Krisko JF, Spagnuolo RA et al.: Generation of HIV latency in humanized BLT mice. J Virol 2012, 86:630-634.
8. Marsden MD, Kovochich M, Suey N, Shimizu S, Mehta R, Cortado R, Bristol G, An DS, Zack JA: HIV latency in the humanized BLT mouse. J Virol 2012, 86:339-347.
9. Halper-Stromberg A, Lu CL, Klein F, Horwitz JA, Bourmassos S, Noguera L, Eisenreich TR, Liu C, Gazumyan A, Schafer U et al.: Broadly neutralizing antibodies and viral inducers decrease rebound from HIV-1 latent reservoirs in humanized mice. Cell 2014 http://dx.doi.org/10.1016/j.cell.2014.07.043.
10. Balazs AB, Chen J, Hong CM, Rao DS, Yang L, Baltimore D: Antibody-based protection against HIV infection by vectored immunoprophylaxis. Nature 2011, 481:81-84.
11. Balazs A, Ouyang Y, Hong C, Chen J, Nguyen S, Rao D, An D, Baltimore D: Vectored immunoprophylaxis protects humanized mice from mucosal HIV transmission. Retrovirology 2014, 20:296-300.
12. Dudek TE, No DC, Seung E, Vrublansky T, Fadda L, Brounkin P, Botwell CJ, Power KA, Gladden AD, Battis L et al.: Rapid evolution of HIV-1 to functional CD8+ T cell responses in humanized BLT mice. Sci Transl Med 2012, 4:143ra96.

Analyzing HIV-1 infection in humanized BLT mice, this study observed CD8+ T cell responses that were highly similar in their specificity, kinetics and magnitude to those observed in humans. The rapid appearance of viral escape mutations from host immune responses, as also seen in humans, further underscored the utility of humanized BLT mice for studying human-specific immunopathology of pathogens.

13. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, Drake JM, Brownstein JS, Hoen AG, Sankoh O et al.: The global distribution and burden of dengue. Nature 2013, 496:504-507.

14. Costa VV, Fagundes CT, Souza DG, Teixeira MM: Inflammatory and innate immune responses in dengue infection: protection versus disease induction. Am J Pathol 2013, 182:1950-1961.

15. Guabiraba R, Ryffel B: Dengue virus infection: current concepts in immune mechanisms and lessons from murine models. Immunology 2014, 141:135-156.

16. Jaiswal S, Paozles P, Woda M, Shultz LD, Greiner DL, Brehm MA, Mathew A: Enhanced humoral and HLA-A2-restricted dengue virus-specific T cell responses in humanized BLT NSG mice. Immunology 2012, 136:334-343.

17. Frias-Staheli N, Donner M, Marukian S, Billerbeck E, Labbet RN, Rice CM, Ploss A: Utility of humanized BLT mice for analysis of dengue virus infection and antiviral drug testing. J Virol 2014, 88:2205-2218.

18. Blackley S, Kou Z, Chen H, Quinn M, Rose RC, Schlesinger JJ, Coppage M, Jin X: Primary human splenic macrophages, but not T or B cells, are the principal target cells for dengue virus infection in vitro. J Virol 2007, 81:13325-13334.

19. Kou Z, Quinn M, Chen H, Rodrigo WWII, Rose RC, Schlesinger JJ, Jin X: Monocytes, but not T or B cells, are the principal target cells for dengue virus (DV) infection among human peripheral blood mononuclear cells. J Med Virol 2008, 80:134-146.

20. Mota J, Rico-Hesse R: Humanized mice show clinical signs of dengue fever according to infecting virus genotype. J Virol 2009, 83:9638-9645.

21. Cox J, Mota J, Sukupolvi-Petty S, Diamond MS, Rico-Hesse R: Mosquito-borne delivery of dengue virus enhances immunogenicity and pathogenesis in humanized mice. J Virol 2012, 86:7637-7649.

22. Berges BK, Tanner A: Modelling of human herpesvirus infections in humanized mice. J Gen Virol 2014, 95:2106-2117.

23. Cohen Ji, Fauci AS, Varhous H, Nabel GJ: Epstein-Barr virus: an important vaccine target for cancer prevention. Sci Transl Med 2011, 3:10767.

24. Chijioke O, Azzi T, Nadal D, Münz C: Innate immune responses against Epstein-Barr virus infection. J Leukoc Biol 2013, 94:1185-1190.

25. Heuts F, Rotenberg ME, Salamon D, Rasul E, Adori M, Klein G, Klein E, Nagy N: T cells modulate Epstein-Barr virus latency phenotypes during infection of humanized mice. J Virol 2014, 88:3325-3324.

26. White RE, Rämer PC, Naresh KN, Meixlsperger S, Pinaud L, • Rooney C, Savoldo B, Coutinho R, Böddör C, Gribben J et al.: EBNA3B-deficient EBV promotes B cell lymphomagenesis in humanized mice and is found in human tumors. J Clin Invest 2012, 122:1487-1502.

27. Harth-Hertle ML, Scholz BA, Erhard F, Glaser LV, Döhlen K, Zimmer R, Kempkes B: Inactivation of intergenic enhancers by EBNA3A initiates and maintains polycomb signatures across a chromatin domain encoding CXCL10 and CXCL9. PLoS Pathog 2013, 9.

28. Sato K, Misawa N, Nie C, Satou Y, Iwakiri D, Matsuoka M, Takahashi R, Kuzushita K, Ito M, Takada K et al.: A novel animal model of Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis in humanized mice. Blood 2011, 117:5663-5673.

29. Kuwana Y, Takei M, Yajima M, Inamada KI, Inomata H, Shiozaki M, Ikumi N, Nozaki T, Shirawa H, Kitamura N et al.: Epstein-Barr virus induces erosive arthritis in humanized mice. PLoS ONE 2011, 6.

30. Chatterjee B, Laung CS, Münn C: Animal models of Epstein Barr virus infection. J Immunol Methods 2014 http://dx.doi.org/10.1016/j.jim.2014.04.009.

31. Söderberg-Naucler C: Does cytomegalovirus play a causative role in the development of various inflammatory diseases and cancer? J Intern Med 2006, 259:219-246.

32. Slavuljica I, Kveščak D, Huzsthy PC, Britt KK, Jonići WS: Immunobiology of congenital cytomegalovirus infection of the central nervous system—the murine cytomegalovirus model. Cell Mol Immunol 2014 http://dx.doi.org/10.1038/cmi.2014.51. Epub ahead of print.

33. Schleiss MR: Developing a vaccine against congenital cytomegalovirus (CMV) infection: what have we learned from animal models? Where should We Go Next?. Future Virol 2013, 8:1161-1182.

34. Smith MS, Goldman DC, Bailey AS, Pfaffle DL, Kreklywich CN, Spencer DB, Othieno FA, Strebel DW, Garcia JV, Fleming WH et al.: Granulocyte-colony stimulating factor reactivates human cytomegalovirus in a latently infected humanized mouse model. Cell Host Microbe 2010, 8:284-291.

35. Kawahara T, Lisboa LF, Cader S, Douglas GN, Nourbakhsh M, Pu CH, Lewis JT, Churchill TA, Human A, Kneteman NM: Human cytomegalovirus infection in humanized liver chimeric mice. Hepatol Res 2013, 43:679-684.

36. Banerjee P, Tripp A, Laimore MD, Crawford L, Sieburg M, Ramos JC, Harrington W, Beilke MA, Feuer G: Adult T-cell leukemia/lymphoma development in HTLV-1-infected humanized SCID mice. Blood 2010, 115:2640-2648.

37. Villaudy J, Wencker M, Gadot N, Gillet NA, Scoazec YJ, Gazzolo L, Manz MG, Bangham CRM, Dodon MD: HTLV-1 propels thymic human T cell development in ‘human in mouse’ system 2/3—gamma c/-/ mice. PLoS Pathog 2011, 7.

38. Tezuka K, Xun R, Tei M, Ueno T, Tanaka M, Taneuchi N, Fujisawa S: JM: An animal model of adult T-cell leukemia: humanized mice with HTLV-1-specific immunity. Blood 2014, 123:346-355.

39. Foreman KE, Friborg J, Chandran B, Katano H, Sata T, Mercader M, Nabel GJ, Nickoloff BJ: Injection of human herpesvirus-6 in human skin engrafted on SCID mice induces Kaposi’s sarcoma-like lesions. J Dermatol Sci 2001, 26:182-193.

40. Moffat JF, Zanzonii L, Kimchitch P, Grose C, Kaneshima H, Arvin AM: Attenuation of the vaccine Oka strain of Varicella-zoster virus and role of glycoprotein C in alpha-herpesvirus virulence demonstrated in the SCID-hu mouse. J Virol 1998, 72:965-974.

41. Dandi M, Lütgertkamm M: Mouse models of hepatitis B and delta virus infection. J Immunol Methods 2014 http://dx.doi.org/10.1016/j.jim.2014.03.002.

42. Billerbeck E, De Jong Y, Dorner M, De La Fuente C, Ploss A: Animal models for hepatitis C. Curr Top Microbiol Immunol 2013, 369:49-56.

43. Chisari FV: Hepatitis B virus transgenic mouse: models of viral immunobiology and pathogenesis. Curr Top Microbiol Immunol 1996, 206:149-173.

44. Dandi M, Burda MR, Torok E, Pollok JM, Iwanek A, Sommer G, Rogiers X, Rogier CE, Gupta S, Will H et al.: Repopulation of mouse liver with human hepatocytes and in vivo infection with hepatitis B virus. Hepatology 2001, 33:981-988.
20 Viral pathogenesis

45. Mercer DF, Schiller DE, Elliott JF, Douglas DN, Hao C, Rinfret A, Addison WR, Fischer KP, Churchill TA, Lakey JR et al.: Hepatitis C virus replication in mice with chimeric human livers. Nat Med 2001, 7:927-933.

46. Bissig K-D, Wieland SF, Tran P, Isogawa M, Le TT, Chisari FV, Verma IM: Human liver chimeric mice provide a model for hepatitis B and C virus infection and treatment. J Clin Invest 2010, 120:924-930.

47. Tesfaye A, Stift J, Maric D, Cui Q, Dienes HP, Feinestone SM: Chimeric mouse model for the infection of hepatitis B and C viruses. PLOS ONE 2013:8.

48. Kosaka K, Hiraga N, Imamura M, Yoshimi S, Murakami E, Nakahara T, Honda Y, Oto A, Kawakata T, Tsuge M et al.: A novel TK-NOG based humanized mouse model for the study of HBV and HCV infections. Biochem Biophys Res Commun 2013, 441:230-235.

49. Guti-TL, Knibbe JS, Makarov E, Zhang J, Yannam GR, Gorantla S, Sun Y, Mercer DF, Suemizu H, Wisecarver JL et al.: Human hepatocytes and hematolymphoid dual reconstitution in treosulfan-conditioned uPA-NOG mice. Am J Pathol 2014, 184:101-109.

50. Wilson E, Bial J, Bial G, Jensen B, Greiner D, Brehm M, Grompe M: Extensive double humanization of both liver and hematopoiesis in FRGN mice. Stem Cell Res 2014, 13:404-412.

51. Blitty MT, Cheng L, Zhang Z, Luan Y, Li F, Chi L, Zhang L, Tu Z, Gao Y, Fu Y et al.: Hepatitis B virus infection and immunopathogenesis in a humanized mouse model: induction of human-specific liver fibrosis and M2-like macrophages. PLoS Pathog 2014:10.

52. Washburn ML, Blitty MT, Zhang L, Kovalev GI, Buntzman A, Frellinger JA, Barry W, Ploss A, Rice CM, Su L: A humanized mouse model to study hepatitis C virus infection, immune response, and liver disease. Gastroenterology 2011, 140:1334-1344.

53. Ploss A, Evans MJ, Gaysinskaya VA, Panis M, You H, de Jong YP, Rice CM: Human occludin is a hepatitis C virus entry factor required for injection of mouse cells. Nature 2009, 457:882-886.

54. Dornier M, Horvitz JA, Robbins JB, Barry WT, Feng Q, Mu K, Jones CT, Schoggins JW, Catanese MT, Burton DR et al.: A genetically humanized mouse model for hepatitis C virus infection. Nature 2011, 474:208-211.

55. Dornier M, Horvitz JA, Donovan BM, Labitt RN, Budell WC, Frilling T, Vogt A, Catanese MT, Satoh T, Kawai T et al.: Completion of the entire hepatitis C virus life cycle in genetically humanized mice. Nature 2013, 501:237-241.

Using mice with diminished antiviral immunity that also stably expressed the minimal human factors, human CD81 and OCLN, for viral uptake in murine cells, this study was the first to reproduce the entire HCV life cycle in mice with inheritable susceptibility to HCV. This is a significant improvement upon previous xenotransplant mouse models, allowing for higher throughput work and decreased variabilities between experiments.

56. Yan H, Zhong G, Xu G, He W, Jing Z, Gao Z, Huang Y, Qi Y, Peng B, Wang H et al.: Sodium taurocholate cotransport polypeptide is a functional receptor for human hepatitis B and D virus. PLoS 2012:12.

This paper identified the first HBV and HDV receptor, sodium taurocholate cotransport polypeptide (NTCP), using tandem affinity purification and mass spectrometry. This finding greatly enhances researchers’ abilities to create in vitro platforms and small-animal models for studying these two viruses.

57. Zhao J, Li K, Wohlford-Lenane C, Agnihotram SS, Fett C, Zhao J, Gale MJ, Baric RS, Enjuanes L, Gallagher T et al.: Rapid generation of a mouse model for Middle East respiratory syndrome. Proc Natl Acad Sci U S A 2014, 111:4970-4975.

Following transduction of mice with a recombinant, nonreplicating adenovirus expressing the human receptor for MERS, DPP4, these mice were successfully infected with MERS-CoV, developing pneumonia. The quick timeline of 2-3 weeks to create such a model is a promising approach for rapid study of emerging pathogens.

58. Valbuena G, Halliday H, Borisevich V, Goez Y, Rockx B: A human lung xenograft mouse model of Nipah Virus infection. PLoS Pathog 2014:10.

Here, the first human lung xenograft model in mice was made and successfully infected with Nipah Virus, which replicated to high titers in the lungs. This is a promising, more physiologically relevant approach for studying the pathogenesis of other respiratory viruses in the context of the human lung microenvironment.

59. Takeuchi H, Matano T: Host factors involved in resistance to retroviral infection. Microbiol Immunol 2008, 52:318-325.

60. Ren RB, Costantini F, Gogacz EJ, Lee JJ, Racaniello VR: Transgenic mice expressing a human poliovirus receptor: a new model for poliomyelitis. Cell 1990, 63:353-362.

61. Oldstone MB, Lewicki H, Thomas D, Tishon A, Dales S, Patterson J, Manchester M, Homann D, Nancie D, Holz A: Measles virus infection in a transgenic model: virus-induced immunosuppression and central nervous system disease. Cell 1999, 98:629-640.

62. Carette JE, Raaben M, Wong AC, Herbert AS, Obermoser G, Mulherkar N, Kuehne AI, Kranzusch PJ, Griffin AM, Ruthel G et al.: Ebola virus entry requires the cholesterol transporter Niemann-Pick C1. Nature 2011, 477:340-343.