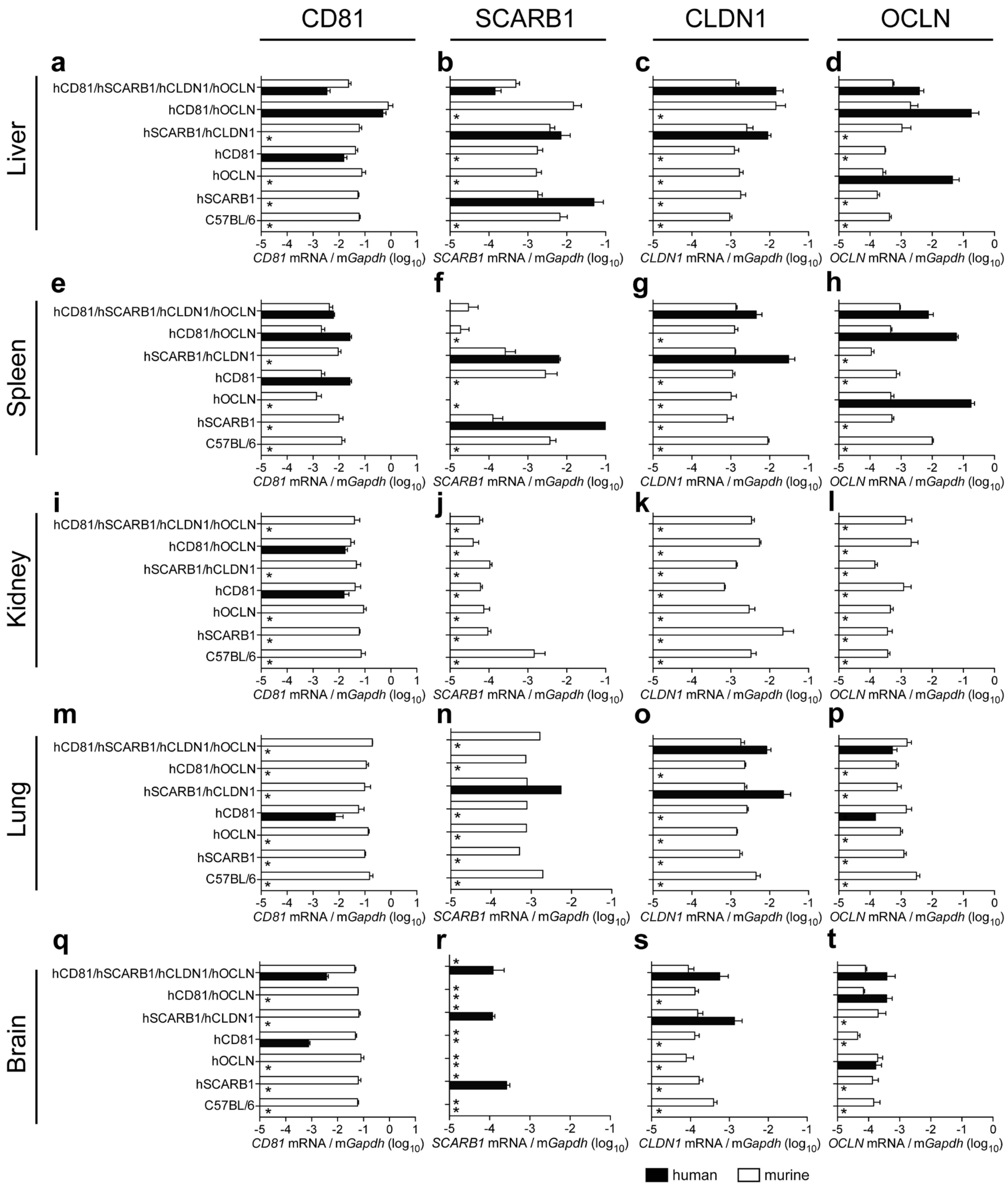
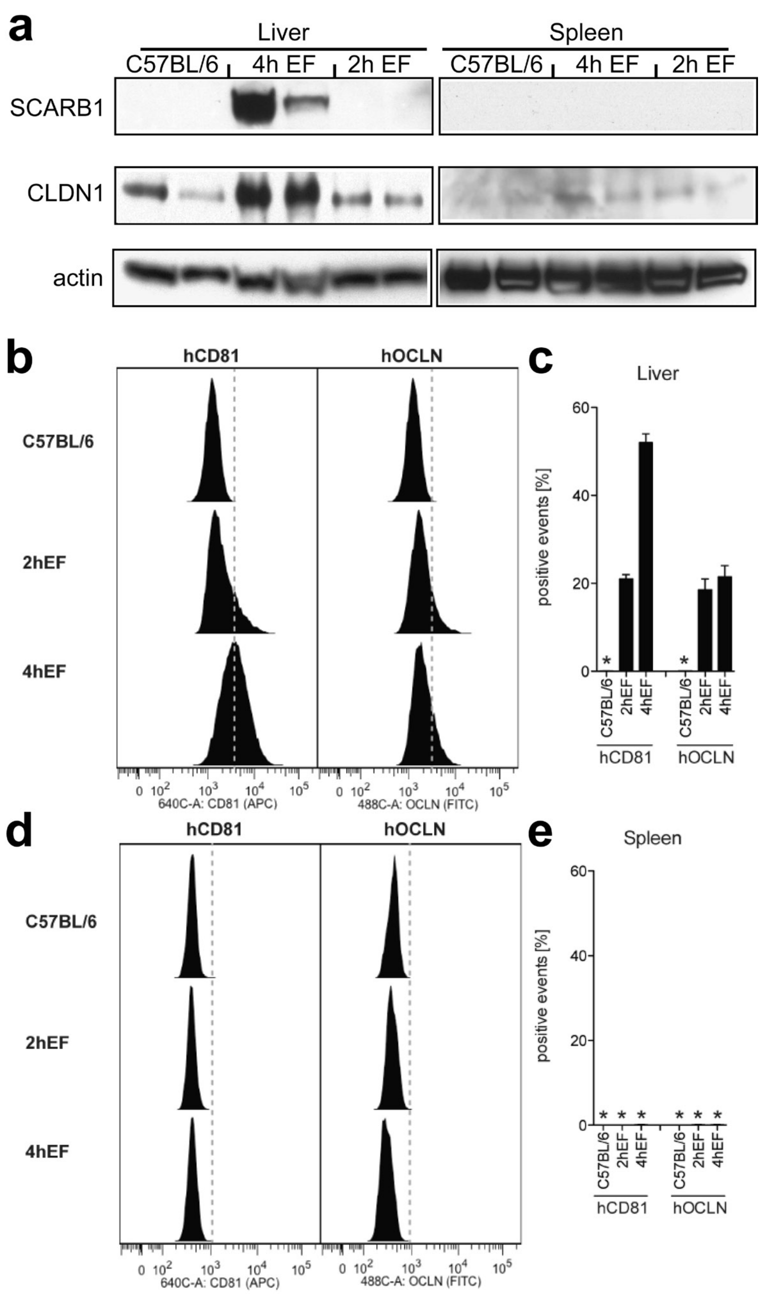
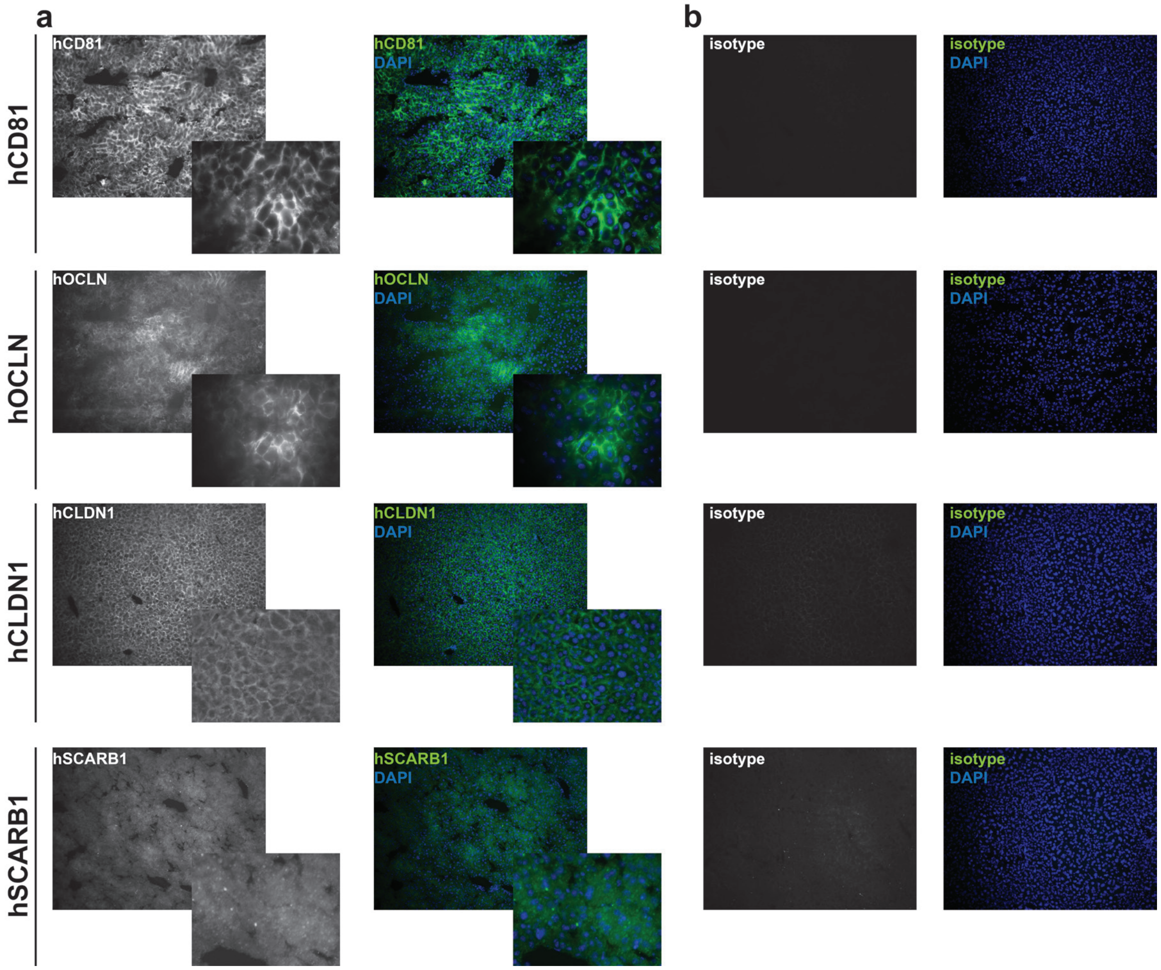
doi:10.1038/nature12427



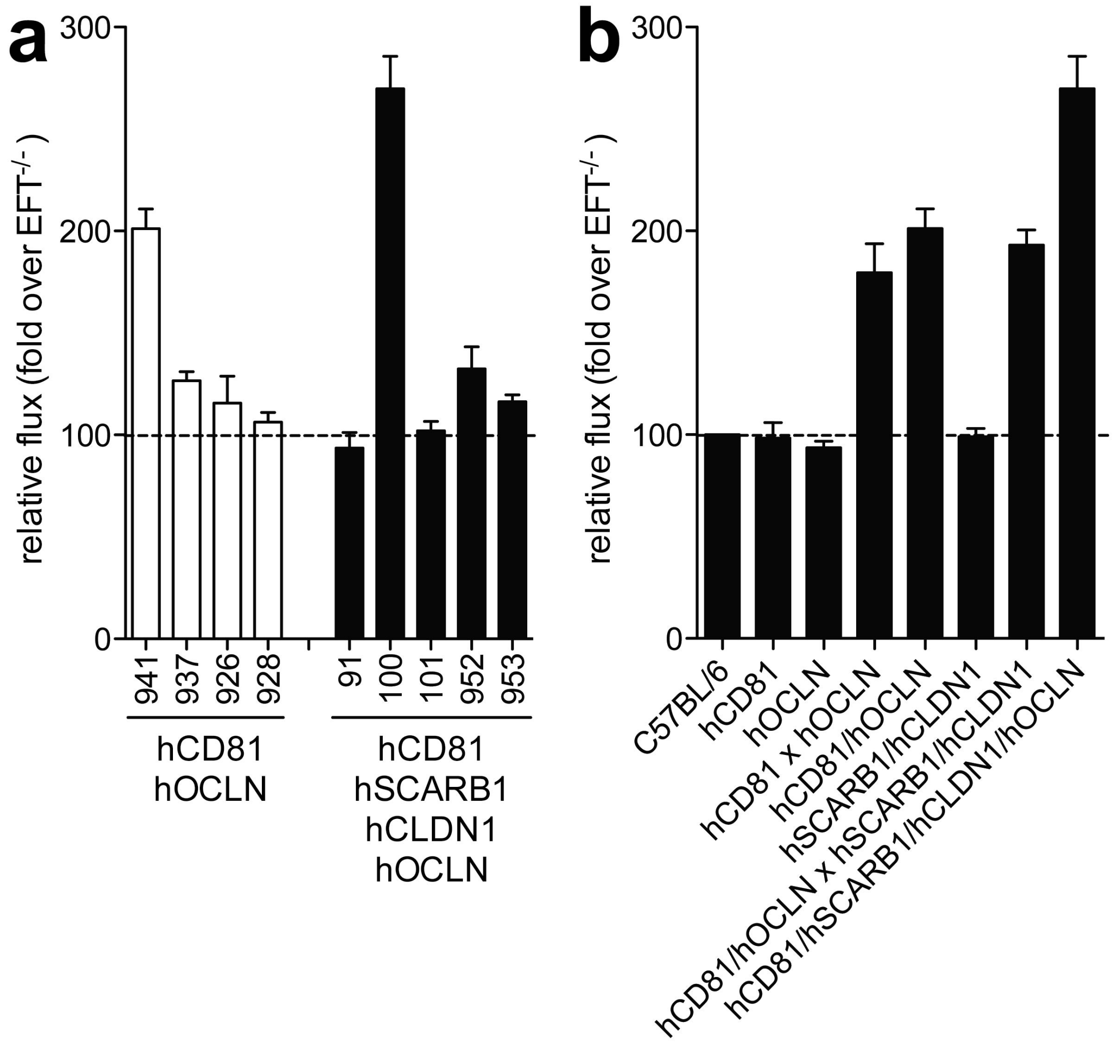
Supplementary figure 1. Liver-specific expression of HCV entry factors in entry factor-transgenic mice. (a-t) Expression of the human and murine HCV entry factors **(a, e, i, m, q)** *CD81*, **(b, f, j, n, r)** *SCARB1*, **(c, g, k, o, s)** *CLDN1*, and **(d, h, l, p, t)** *OCLN* mRNAs in **(a, b, c, d)** liver, **(e, f, g, h)** spleen, **(I, j, k, l)** kidney, **(m, n, o, p)** lung, and **(q, r, s, t)** brain of mice transgenically expressing either all HCV entry factors (hCD81/hSCARB1/hCLDN1/hOCLN1), hCD81 and hOCLN, hSCARB1 and hCLDN1, hCD81, hOCLN, hSCARB1 or in wild-type control animals (C57BL/6) as determined by quantitative real-time PCR. Data shown are mean ± SD of four individual animals.



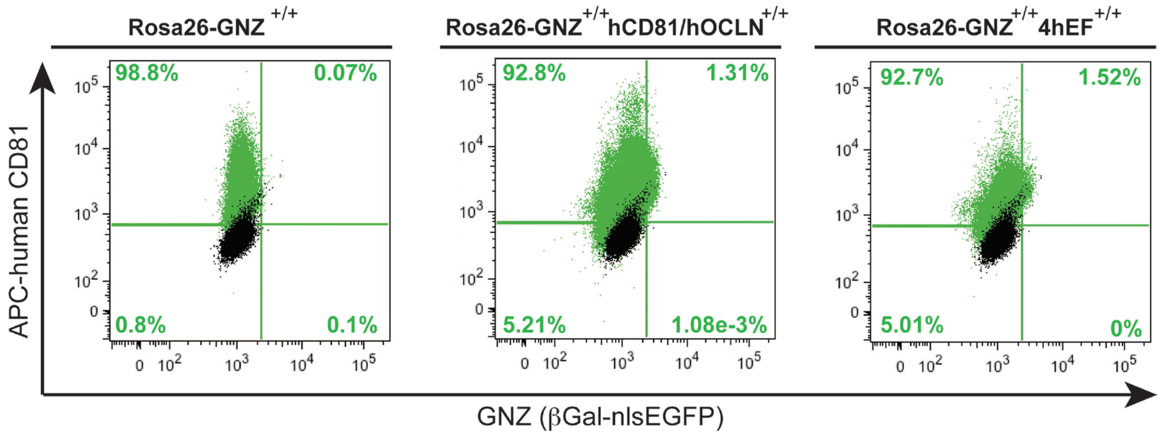
Supplementary figure 2. Protein expression of human HCV entry factors. (a). **(a)**. Protein expression of human SCARB1 and OCLN in the liver and spleen of wild-type animals (C57BL/6), and mice transgenically expressing either all four human HCV entry factors (4h EF) or human CD81 and OCLN (2hEF) as determined by Western blot. Data shown are from two independent animals. Actin was used as a loading control. Flow-cytometric analysis of human CD81 and human OCLN protein expression in livers **(b, c)** and spleens **(d, e)** of non-transgenic control mice (C57BL/6), mice expressing human CD81 and OCLN (2hEF) or all four entry factors (hCD81/hSCARB1/hCLDN1/hOCLN1). **(b, d)** Representative histogram plots, **(c, e)** Frequency of entry factor positive cells (hCD81 or hOCLN as indicated).



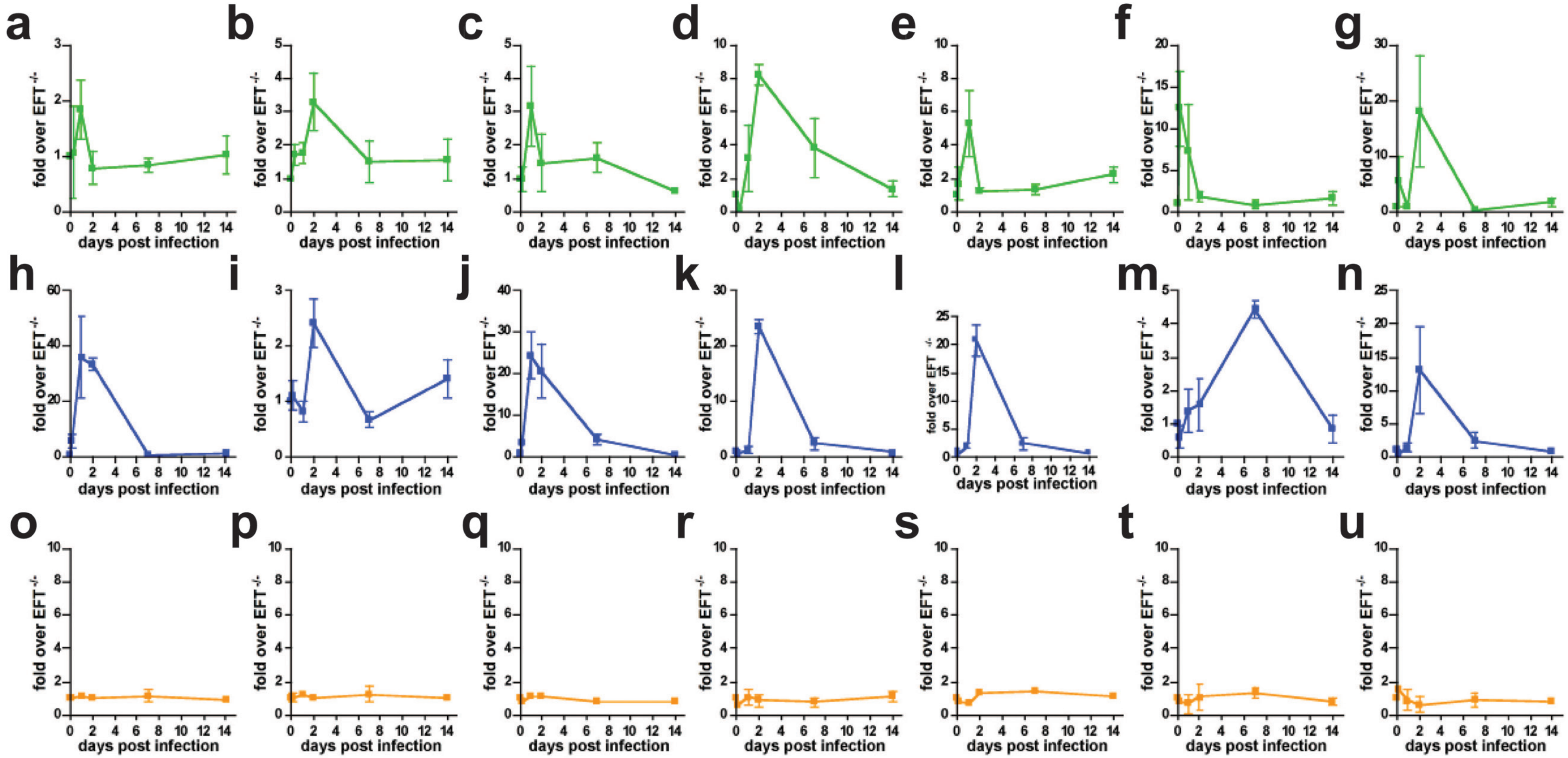
Supplementary figure 3. Histological analysis of human HCV entry factor expression in the liver of entry factor transgenic animals. Expression of human CD81, OCLN, CLDN1 and SCARB1 in the liver of mice transgenically expressing all four human HCV entry factors. Data shown are from one of four representative animals.



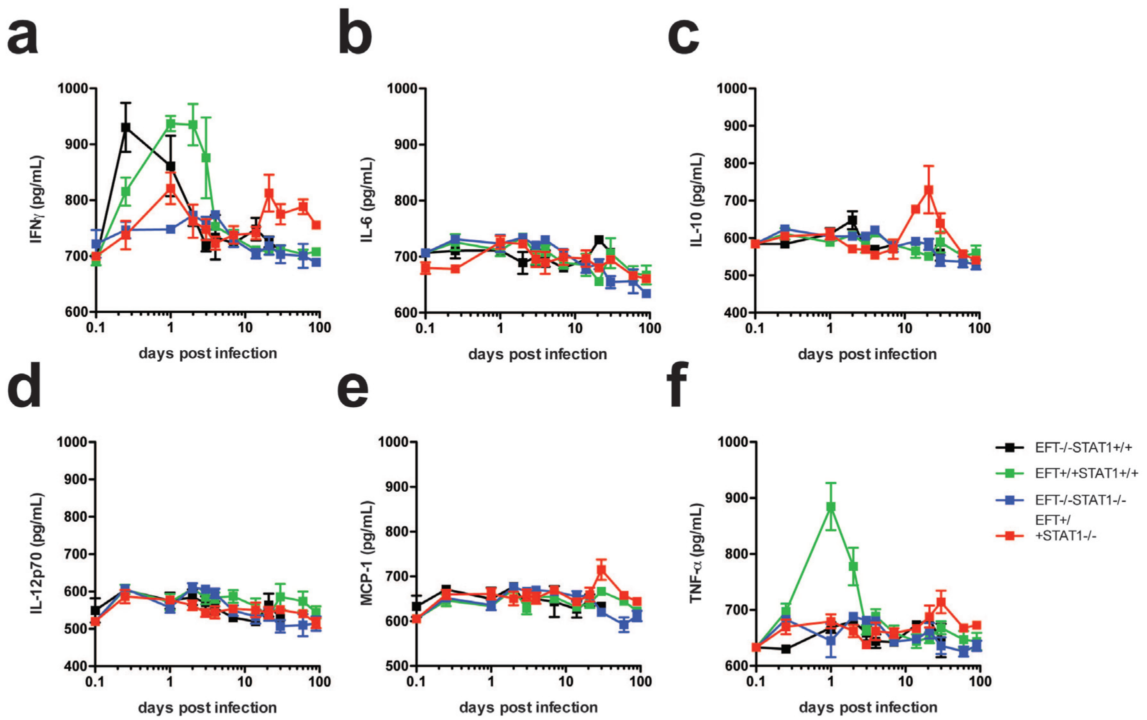
Supplementary figure 4. Analysis of HCV entry into different founder animals transgenically expressing HCV entry factors. (a) HCV entry efficiency in distinct founder animals on the Rosa26-LSL-Fluc background expressing either human CD81 and OCLN or all four HCV entry factors. **(b)** HCV entry in mice expressing either human CD81, human OCLN, human CD81 and human OCLN as individual transgenes (hCD81 x hOCLN), human CD81 and human OCLN as a combined transgene (hCD81/hOCLN), human SCARB1 and human CLDN1, all four HCV entry factors as individual transgenes (hCD81/hOCLN x hSCARB1/hCLDN1) or as combined transgenes (hCD81/hSCARB1/hCLDN1/hOCLN). Mice were injected with $2x10^7$ $TCID_{50}$ BiCre-Jc1 and analyzed by in vivo bioluminescence imaging 72h post infection. Data shown are means ± SD from two independent experiments (n=6-8 mice per experiment).



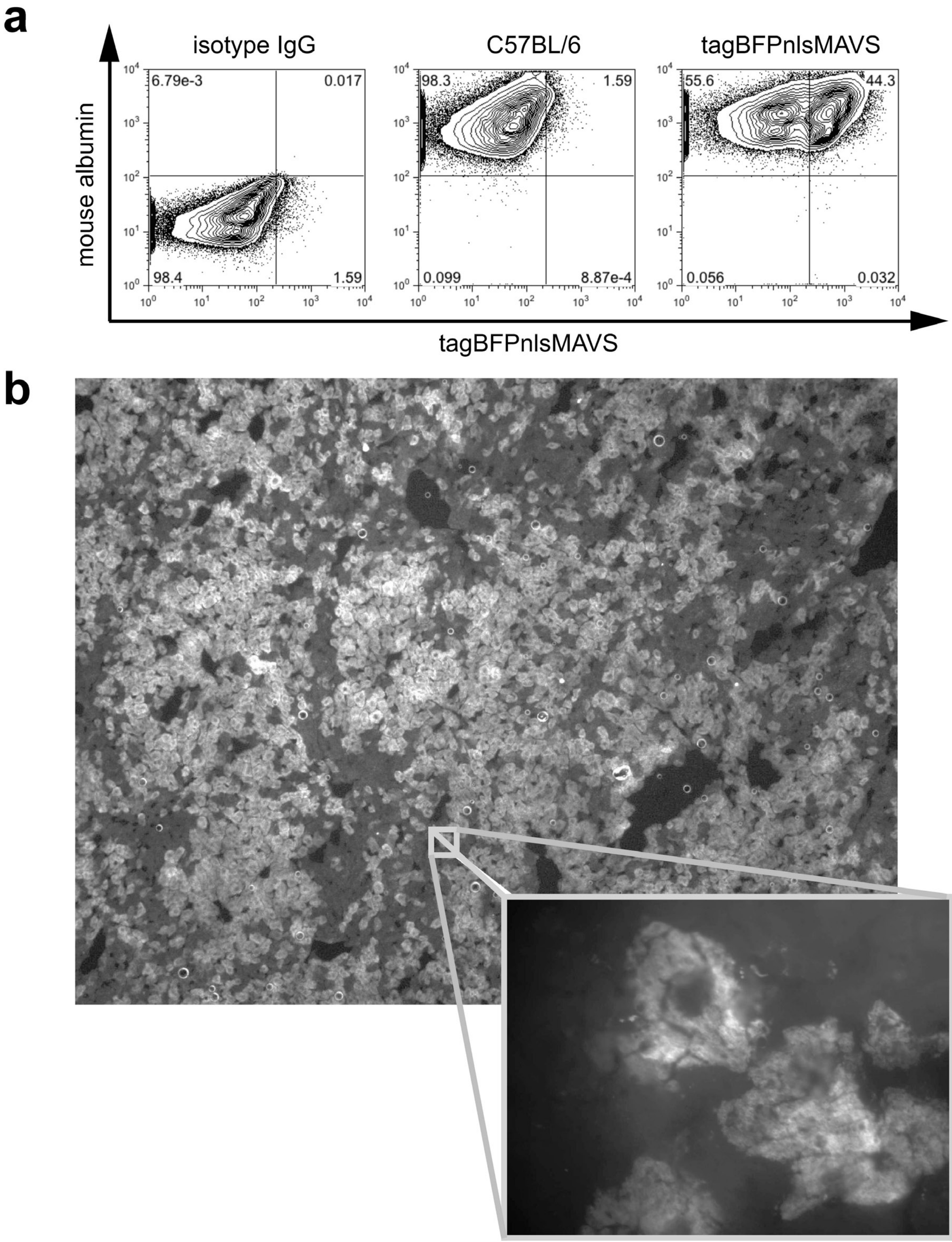
Supplementary figure 5. Quantification of HCV-infected hepatocytes in HCV entry factor transgenic mice. Rosa26-GNZ mice or Rosa26-GNZ mice expressing either human CD81 and human OCLN or all four human HCV entry factors were infected with $2x10^7$ $TCID_{50}$ BiCre-Jc1 72h prior to analysis by flow cytometry. Hepatocytes were isolated by a two-step perfusion, stained for human CD81 prior to analysis. Data shown are from one of four representative experiments.



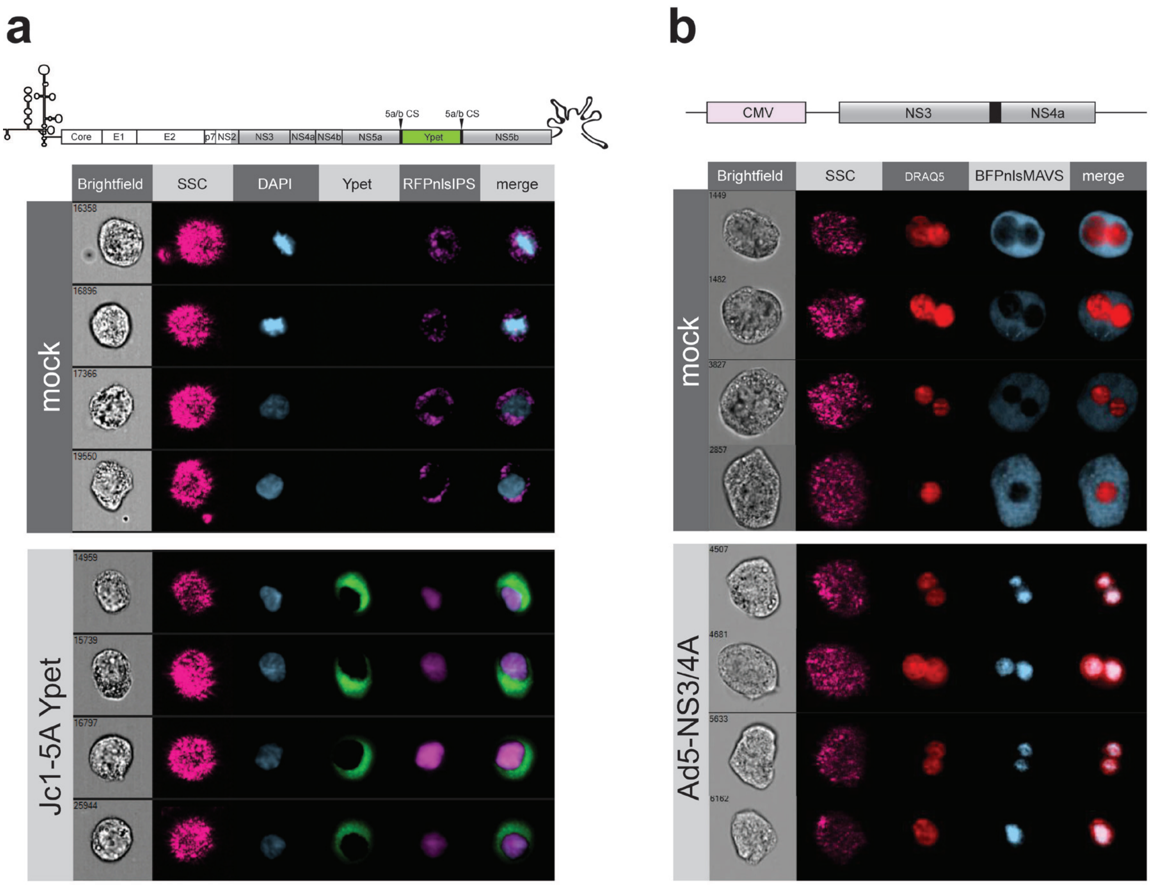
Supplementary figure 6. HCV infection induces interferon stimulated genes in HCV entry factor transgenic mice. (a-u) Longitudinal expression of interferon-stimulated genes **(a, h, o)** *mx-1*, **(b, I, p)** *2'OAS*, **(c, j, q)** *viperin*, **(d, k, r)** *ifi27i2a*, **(e, l, s)** *ifi44*, **(f, m, t)** *eif2ak2*, **(g, n, u)** *cxcl10* in the **(a-g)** liver, **(h-n)** spleen and **(o-u)** brain of mice infected with Con1/Jc1. Data shown are presented as mean ± SD of fold over entry factor negative mice (C57BL/6) from three independent experiments.



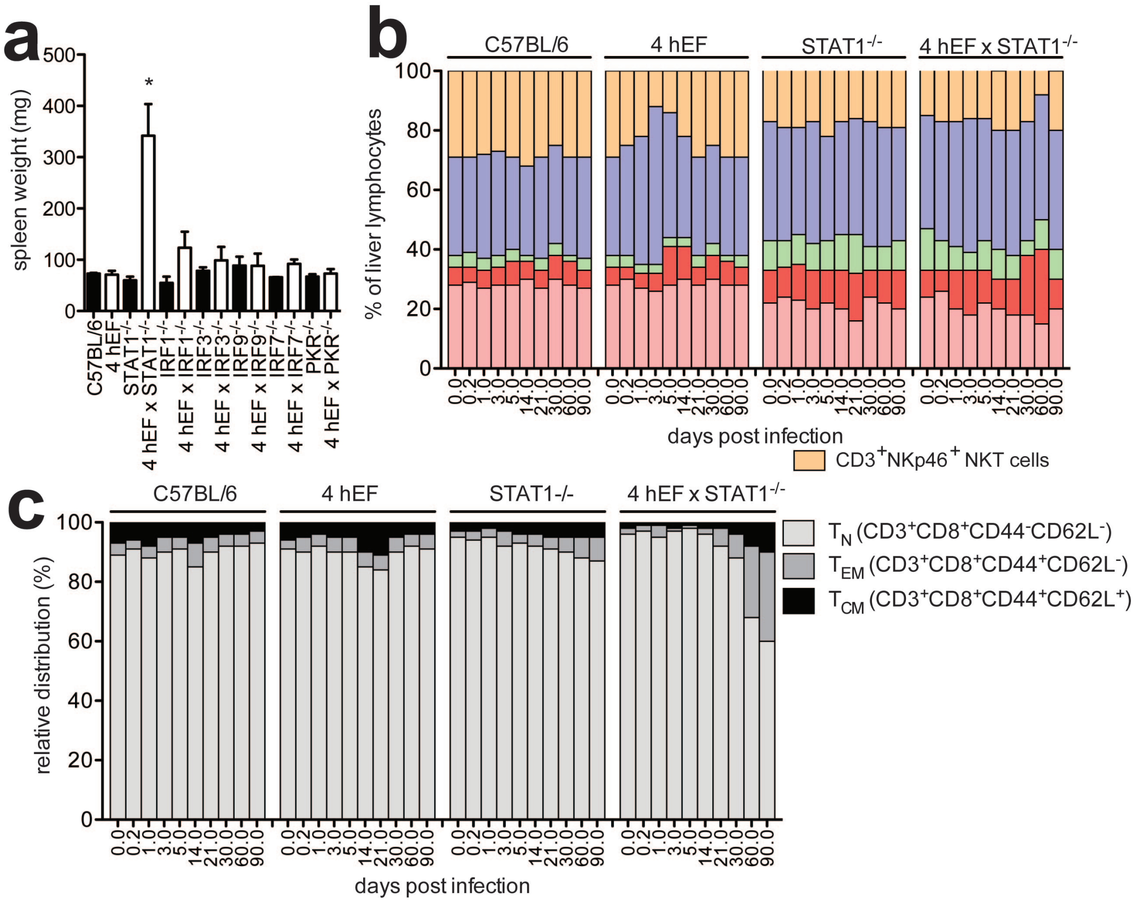
Supplementary figure 7. HCV infection induces proinflammatory cytokines and interferons in entry factor transgenic mice. (a-f) Kinetic of the induction of **(a)** IFNγ, **(b)** IL-6, **(c)** IL-10, **(d)** IL-12p70, **(e)** MCP-1, and **(f)** TNF-α in the serum of either wild-type mice ($EFT^{-/-}$ $STAT1^{+/+}$), STAT1-deficient mice ($EFT^{-/-}$ $STAT1^{-/-}$), HCV entry factor transgenic mice ($EFT^{+/+}$ $STAT1^{+/+}$) or HCV entry factor transgenic STAT1-deficient mice ($EFT^{+/+}$ $STAT1^{-/-}$) following infection with Con1/Jc1. Data shown are mean ± SD of three independent experiments.



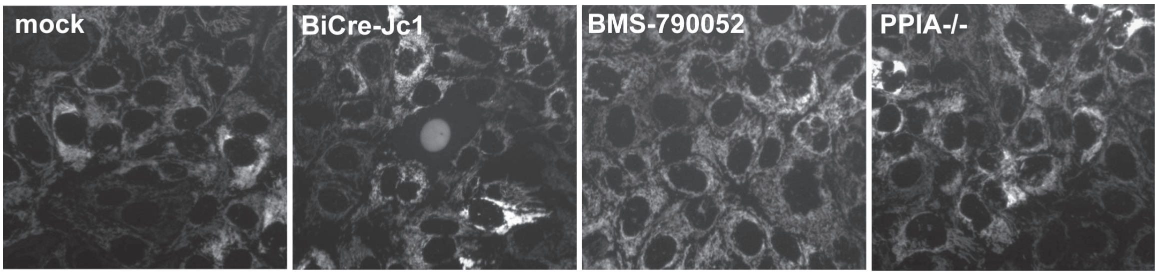
Supplementary figure 8. Characterization of tagBFPnlsMAVS-transgenic mice. (a) Expression levels of the tagBFPnlsMAVS transgene on albumin-positive hepatocytes isolated from either wild-type mice or tagBFPnlsMAVS-transgenic mice. **(b)** Histology of the distribution of tagBFPnlsMAVS-expressing hepatocytes in the liver of tagBFPnlsMAVS-transgenic mice. Data shown are from one of four representative experiments.



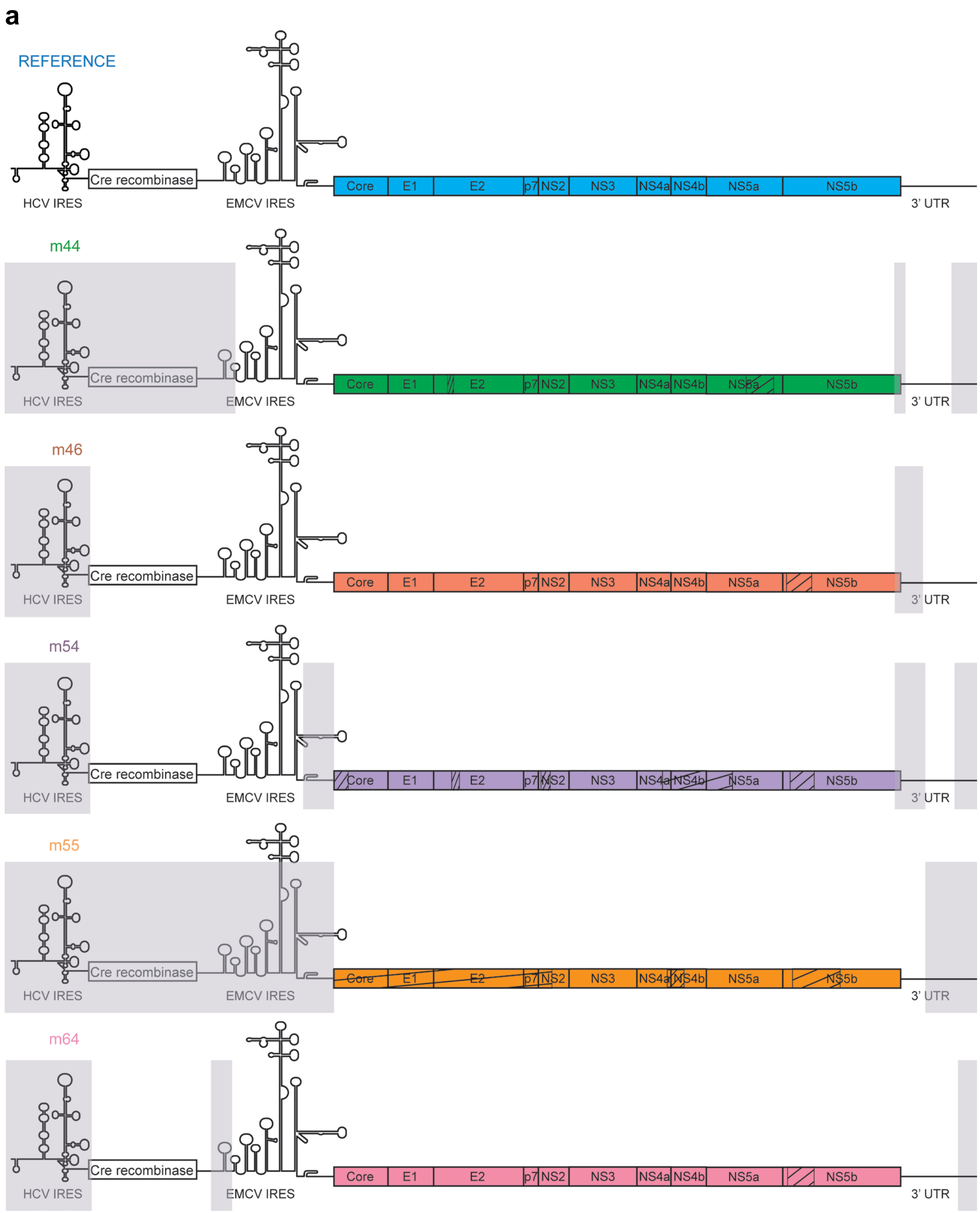
Supplementary figure 9. Validation of Imagestream X to determine the HCV infection frequency in hepatocytes. (a) Huh7.5 cells stably expressing the RFPnlsMAVS cell-based HCV infection reporter system were either mock electroporated or electroporated with Jc1-5AB Ypet. 72h post electroporation cell nuclei were counterstained with DAPI and images were acquired using Imagestream X. **(b)** Mice transgenically expressing tagBFPnlsMAVS were injected with 10^{10} adenoviral particles expressing the HCV protease (NS3-4A). 24h post infection hepatocytes were isolated and nuclei were counterstained using DRAQ5. Data shown are one representative of three experiments.



Supplementary figure 10: HCV infection in 4hEF STAT1$^{-/-}$ mice leads to splenomegaly and immune activation. **(a)** weights of spleens of mice with the indicated genotype 90 days post infection with BiCre-Jc1. **(b)** Relative frequencies of the indicated lymphocyte subsets **(b)** CD8^{+} T cell memory and effector cells **(c)** in livers of wild-type, 4hEF, STAT1$^{-/-}$, STAT1$^{-/-}$ 4hEF mice isolated at the indicated time-points post infection with Con1/Jc1.



Supplementary figure 11: Virus assembly and release in mice expressing all four human HCV entry factors as evidenced by nuclear translocation of the tagRFPnlsMAVS reporter. HCV infectious particles released into the serum of 4hEF STAT$^{-/-}$ mice, 4hEF STAT$^{-/-}$ PPIA$^{-/-}$ or 4hEF STAT1$^{-/-}$ mice treated with BMS-790052 for 20 days visualized by nuclear translocation in Huh-7.5 TagRFPnlsMAVS reporter cells.


a
REFERENCE
Cre recombinase
HCV IRES
EMCV IRES
Core
E1
E2
p7
NS2
NS3
NS4a
NS4b
NS5a
NS5b
3' UTR
m44
m46
m54
m55
m64

b

Genomic Region	44	46	54	55	64
5'UTR					
nlsCRE			G715A (1/5)		
			T862C (1/5)		
EMCV IRES			C1775T (1/4)		T1885C (1/5)
			T1875C (2/4)		
core	C2289T (1/7)				
E1	C2656T (3/14)		C2909T (1/5)		
	C3037T(2/12)		C2993T (5/5)		
	T3073C (2/12)				
	T3169A (1/12)				
E2	A4221G (7/15)		T3694C (1/5)		G3911A (1/12)
p7					
NS2	G4616A(1/15)	G4616A (1/10)	C4657T (1/8)		G4612A (1/12)
	C4785T (1/15)	C4905T (1/6)			G4685A (1/12)
		G5064A (1/5)			
NS3	C5312T (1/23)	C5595T (1/8)	C5208T (1/2)		C5175T (1/6)
		G6118A (1/11)			C5457T (1/10)
		A6225G (1/11)			A5571G (1/11)
		T6672C (1/6)			C5668T (1/12)
		T6853C (1/6)			C6939T (2/10)
		G6995T (1/6)			G6995T (2/10)
					T7013C (1/10)
NS4A					
NS4B	G7916A(2/11)			C7895T (1/8)	
NS5A	A8049G(1/12)	C8379T (1/15)	C8957G (5/5)	T8144C (1/8)	T8178C (1/11)
	G8304A (1/13)	T8602C (1/15)	T8958A (5/5)	A8323G (1/8)	G8304A (1/11)
		G8906A (1/7)			G8615A (1/15)
		C8957G (3/7)			T8878C (1/5)
		T8958A(3/7)			
		C9109T (1/7)			
NS5B	C10244T (1/12)	C10214T (1/3)			
	C10922G (1/3)				
3'UTR					

c

Bi-nlsCre-Jc1Flag2

m44 **m46** **m54** **m55** **m64** **more than one mouse sample with mutation**

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CCACACCAAAGCCGTTTTTCCGGGATGAGGTCTCGTTCTGCGTTGGGCTTAATTCCTAT
GCTGTCGGGTCCCAGCTTCCCTGTGAACCTGAGCCCGACGCAGACGTATTGAGGTCCAT
GCTAACAGATCCGCCCCACATCACGGCGGAGACTGCGGCGCGGCGCTTGGCACGGGGAT
CACCTCCATCTGAGGCGAGCTCCTCAGTGAGCCAGCTATCAGCACCGTCGCTGCGGGCC
ACCTGCACCACCCACAGCAACACCTATGACGTGGACATGGTCGATGCCAACCTGCTCAT
GGAGGGCGGTGTGGCTCAGACAGAGCCTGAGTCCAGGGTGCCCGTTCTGGACTTTCTCG
AGCCAATGGCCGAGGAAGAGAGCGACCTTGAGCCCTCAATACCATCGGAGTGCATGCTC
CCCAGGAGCGGGTTTCCACGGGCCTTACCGGCTTGGGCACGGCCTGACTACAACCCGCC
GCTCGTGGAATCGTGGAGGAGGCCAGATTACCAACCGCCCACCGTTGCTGGTTGTGCTC
TCCCCCCCCCAAGAAGGCCCCGACGCCTCCCCCAAGGAGACGCCGGACAGTGGGTCTG
AGCGAGAGCACCATATCAGAAGCCCTCCAGCAACTGGCCATCAAGACCTTTGGCCAGCC
CCCCTCGAGCGGTGATGCAGGCTCGTCCACGGGGGCGGGCGCCGCCGAATCCGGCGGTC
CGACGTCCCCTGGTGAGCCGGCCCCCTCAGAGACAGGTTCCGCCTCCTCTATGCCCCCC
CTCGAGGGGGAGCCTGGAGATCCGGACCTGGAGTCTGATCAGGTAGAGCTTCAACCTCC
CCCCCAGGGGGGGGGGTAGCTCCCGGTTCGGGCTCGGGGTCTTGGTCTACTTGCTCCG
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GCGATACCATAACAAGGTGTACTGTACAACATCAAAGAGCGCCTCACAGAGGGCTAAAA
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GCTTGTCCGGGAGGGCCGTTAACCACATCAAGTCCGTGTGGAAGGACCTCCTGGAAGAC
CCACAAACACCAATTCCCACAACCATCATGGCCAAAAATGAGGTGTTCTGCGTGGACCC
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TCACTGAGAGAGACATCAGGACCGAGGAGTCCATATACCAGGCCTGCTCCCTGCCCGAG

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GAGGCCCGCACTGCCATACACTCGCTGACTGAGAGACTTTACGTAGGAGGGCCCATGTT
CAACAGCAAGGGTCAAACCTGCGGTTACAGACGTTGCCGCGCCAGCGGGGTGCTAACCA
CTAGCATGGGTAACACCATCACATGCTATGTGAAAGCCCTAGCGGCCTGCAAGGCTGCG
GGGATAGTTGCGCCCACAATGCTGGTATGCGGCGATGACCTAGTAGTCATCTCAGAAAG
CCAGGGGACTGAGGAGGACGAGCGGAACCTGAGAGCCTTCACGGAGGCCATGACCAGGT
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TGTTCCTCAAATGTGTCTGTGGCGTTGGGCCCGCGGGGCCGCCGCAGATACTACCTGAC
CAGAGACCCAACCACTCCACTCGCCCGGGCTGCCTGGGAAACAGTTAGACACTCCCCTA
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TTTTTTTTTTTCCCTCTTTCTTCCCTTCTCATCTTATTCTACTTTCTTTCTTGGTGGCT
CCATCTTAGCCCTAGTCACGGCTAGCTGTGAAAGGTCCGTGAGCCGCATGACTGCAGAG
AGTGCCGTAACTGGTCTCTCTGCAGATCATGT
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Supplementary figure 12. Analysis of HCV genomes isolated from HCV entry factor transgenic mice deficient in STAT1. (a-c) Sequence analysis of HCV genomes isolated 4 weeks post infection from the serum of five individual STAT1-deficient mice transgenically expressing the HCV entry factors. **(a)** Schematic representation of the BiCre-Jc1 genomes used for inoculation of five individual mice including regions not covered in sequencing reactions (grey boxes). Genomes from the different animals are coded in different colors. The reference sequences derived from sequencing the inoculum matches the sequences of infectious cDNA clone of BiCreJc1 used to generate the virus stock. Hatched areas in the genome indicate regions within the different genomes in which mutations were identified. **(b)** Common mutations identified in more than one clonal sequence. **(c)** Sequence of BiCre-Jc1 with marked mutations identified in vivo. The color code of the mutation in the sequence matches the genome color scheme in supplementary figure 10a.