Applying basic science in Hepatology: Addressing the next challenges of hepatitis C virus infection and liver disease

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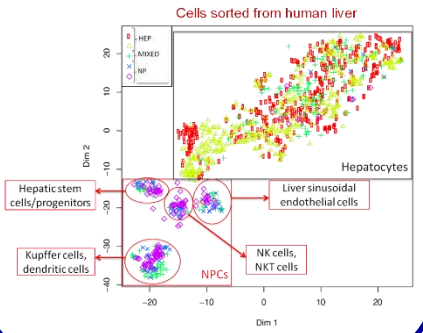
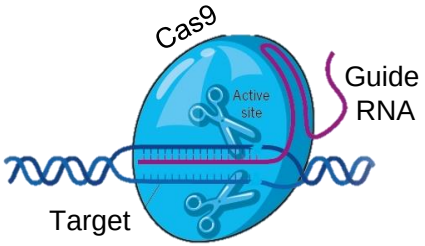
30/06/2107

Novel technologies revolutionizing biomedical research

Single cell RNA-seq analysis

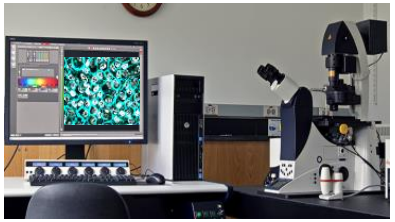


Functional genomics and gene editing

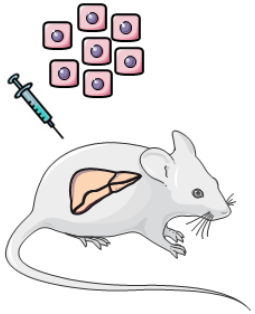


From: Ledford Nature 2016

Advanced live cell imaging



Humanized animal models



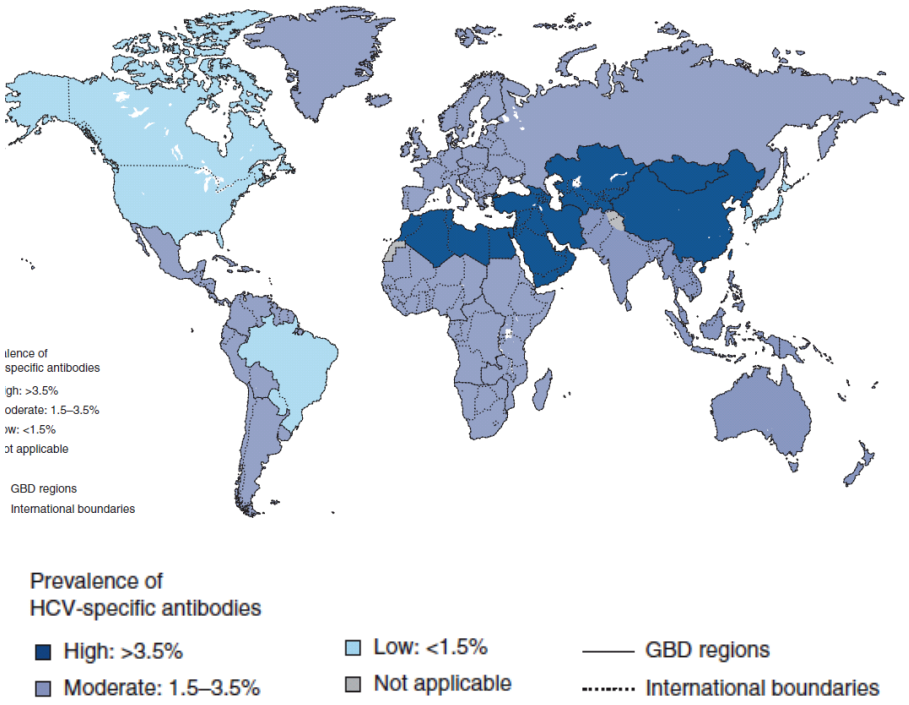
Example for synergy of basic science, technology and clinical development: Cure of HCV infection by DAAs

Key Milestones and Their Effects on the Development of Curative Antiviral Treatment for Chronic Hepatitis C.*	
Key Milestone	**Effects**
Scientific	
Expression cloning of HCV	Discovery of viral genome, genomic organization, and viral genotypes; diagnostic assays; safety of blood products
Model systems for viral replication in cell culture (replicons) and ultrastructural characterization of nonstructural proteins	Screening and discovery of direct-acting antiviral agents targeting the HCV NS3/4A protease, NS5B polymerase, and nonstructural protein NS5A
HCV infectious-tissue culture model	Entry and assembly inhibitors; host-targeting agents as adjunctive therapies
Clinical	
Interferon-based treatment	Discovery that HCV infection is curable; starting point for initial add-on combinations with direct-acting antiviral agents
Successful HIV drug development	Combination of potent agents from two or more classes with nonoverlapping resistance profiles produced effective viral suppression without resistance selection
Regulatory	
FDA policy	Enabled rapid clinical development of direct-acting antiviral agents by permitting phase 2 studies of all oral regimens without standard-of-care comparators

* FDA denotes Food and Drug Administration, HCV hepatitis C virus, and HIV human immunodeficiency virus.

Chung RT & Baumert TF, N Engl J Med 2014

Hepatitis C – Future challenges

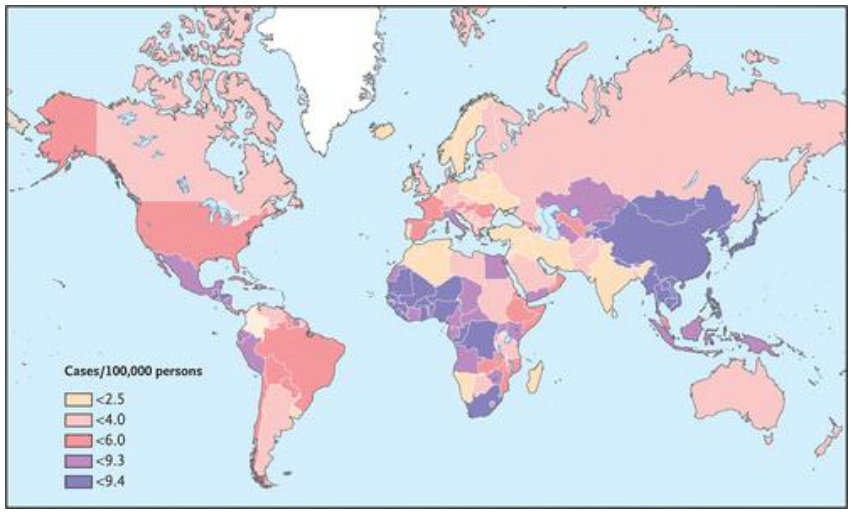


From: Thomas DL Nat Med 2013

- **Absent vaccine**
- **Limited or absent access to therapy in majority of infected patients**
- **DAA failure and resistance in a significant subset of patients**
- **Areas of uncertainty: advanced liver disease, graft infection, renal failure**
- **HCC risk persists post SVR in patients with advanced liver disease (“point of no return”)**
- **HCC recurrence and DAAs**

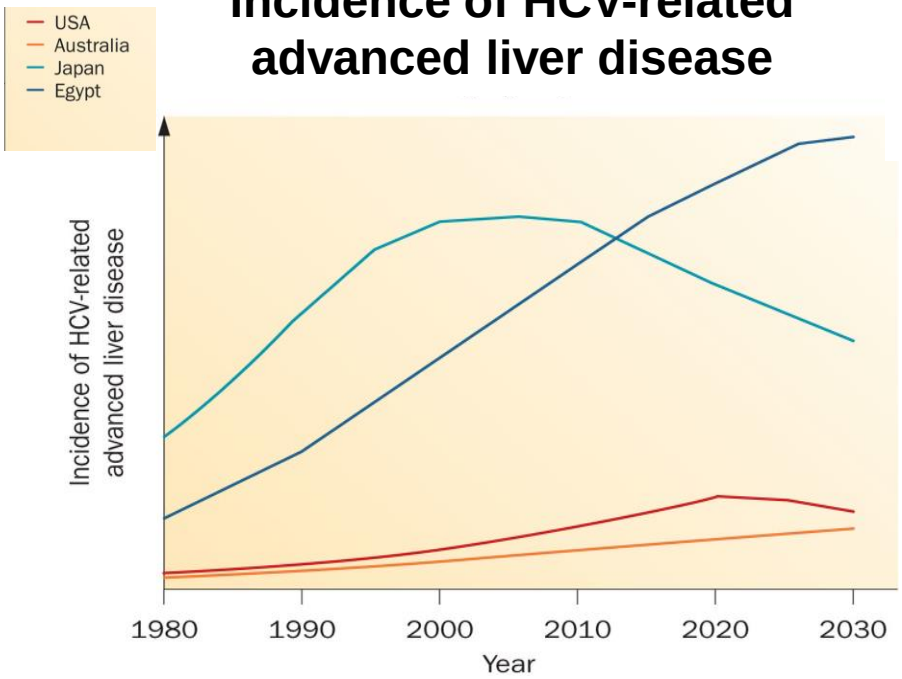
Limited impact of DAAs on HCC on a global scale

HCC prevalence



El-Serag HB, N. Engl. J. Med. 2011

Incidence of HCV-related advanced liver disease



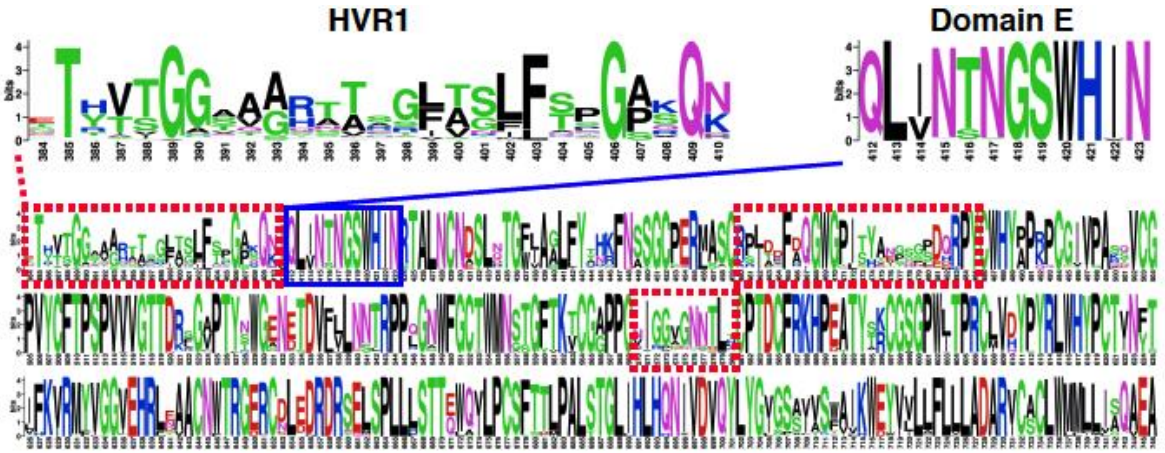
Hajarizadeh et al.. Nat. Rev. Gastroenterol. Hepatol. 2013

- **Absence of vaccine and limited access to DAAs for the majority of patients**
- **Absence of screening: detection of chronic HCV infection often late or absent**
- **HCV-associated disease burden will still remain substantial in the era of oral DAAs including high resource countries such as the US**

Morgan et al. Ann. Intern. Med. 2013; Harris et al. J. Hepatol. 2014, Chhatwal et al. Hepatology 2016

Future challenges: need for a vaccine

Genetic variability of the HCV envelope proteins



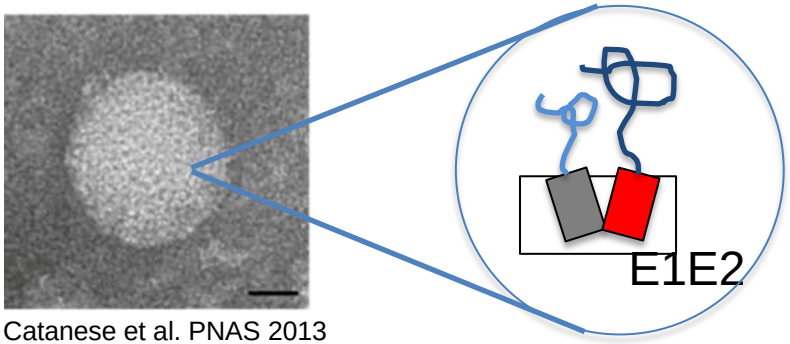
Pierce et al. Curr Opin Virol 2016

- **Despite the arrival of DAAs, development of a safe and effective vaccine remains a key goal for global control and eradication of HCV infection**
- **Viral diversity and immune evasion remain greatest challenges**
- **A detailed understanding of innate and adaptive immune responses is required for rational vaccine design**

Bukh J. J. Hepatol. 2016, Freedman et al. ACS Infectious Dis. 2016, Baumert et al. J. Hepatol. 2014, Liang TJ Nat. Med. 2013

Examples for vaccine candidates in clinical development

B cell vaccine

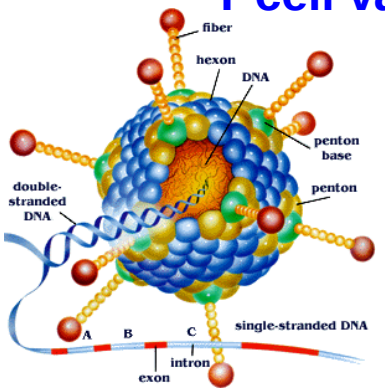


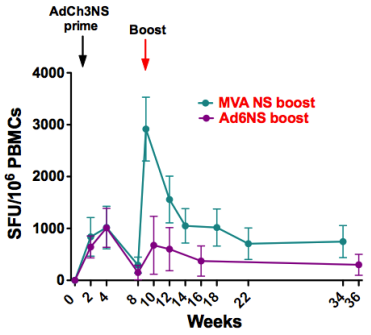
Catanese et al. PNAS 2013

- Immunogen: recombinant gpE1/E2 isolated from mammalian cells
- Reduces chronicity in chimps (Choo et al. PNAS 1991)
- Immunogenic and safe in man (Frey et al. Vaccine 2010, Law et al. PLoS One 2013; Wong et al. J. Virol. 2014)
- Second generation in progress

M. Houghton, Edmonton, Canada

T cell vaccine



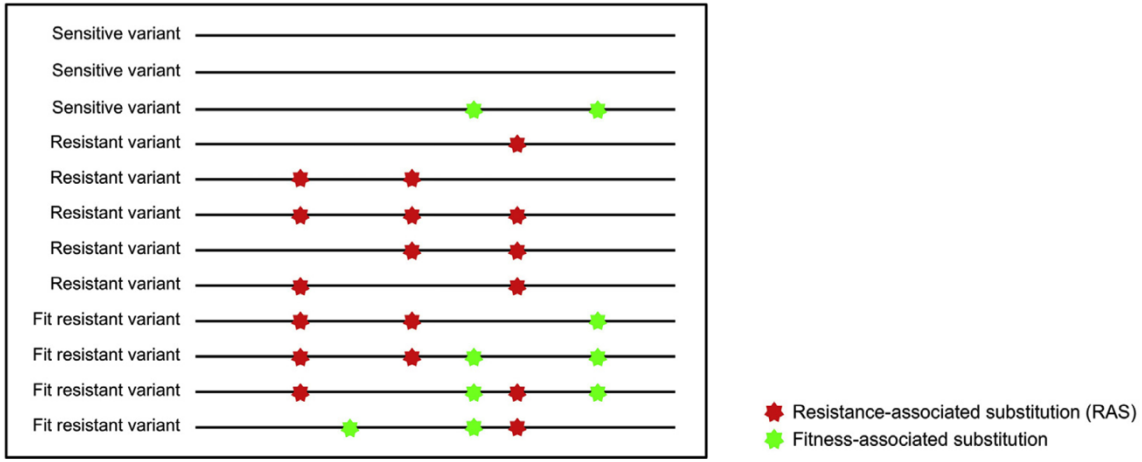


- Immunogen: simian adenoviral vector-boosted with MVA HCV NS proteins
- Protection against chronic infection chimps (Folgori et al. Nat. Med. 2010)
- Immunogenic and safe in man (Colloca et al. Sci. Transl. Med. 2012; Swadling et al. Sci. Transl. Med. 2014)
- Clinical trial in IVDU ongoing

E. Barnes, P. Klenerman, Oxford, UK

Future challenges: DAAs and their limitations

Viral quasispecies and resistance



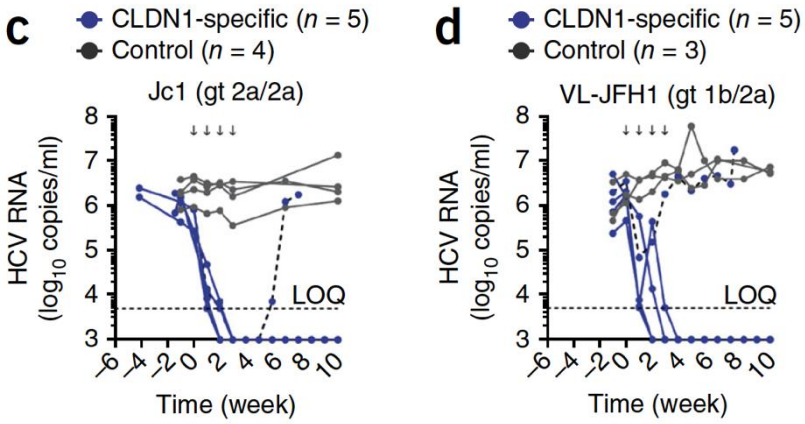
JM Pawlotsky Gastroenterology 2016

- **Although most treated patients achieve virological cure, HCV resistance to DAAs has an important role in the failure of interferon-free treatment regimens.**
- **Genotype 1a or 3, cirrhosis, and/or prior nonresponders to pegylated interferon regimens, transplantation.**
- **Decompensated liver disease, renal failure areas of uncertainty**

C. Sarrazin J. Hepatol. 2016, JM Pawlotsky Gastroenterology 2016, Roche et al. Viruses 2016

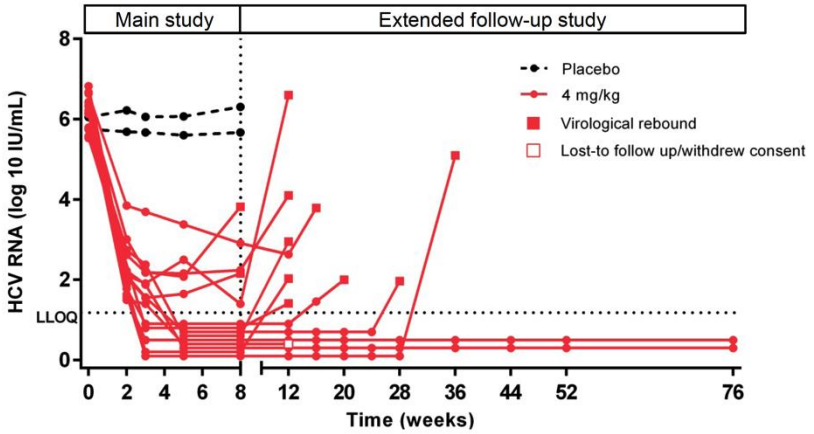
Host-targeting agents for prevention and treatment

Claudin-1 specific mAb – chimeric mice



Mailly / Baumert Nat. Biotech. 2015

miR122 inhibitor – phase I RCT



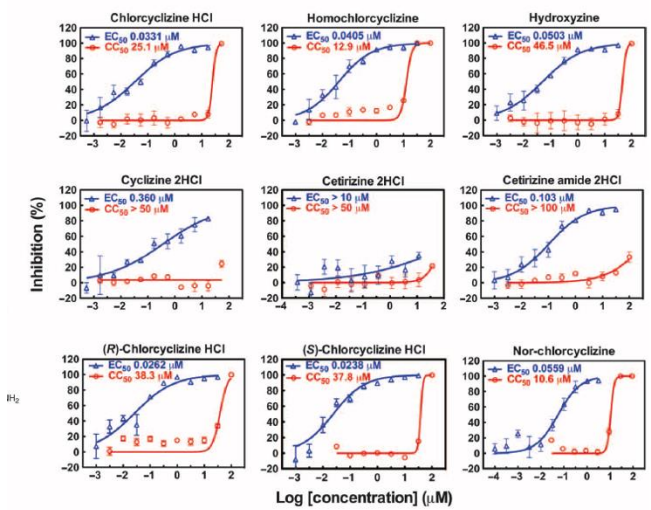
Van de Ree / Reesink Lancet 2017

- **Study of virus-host interactions has identified novel targets and compounds for antiviral therapy: host-targeting agents**
- **Complementary mechanism of action, synergistic with DAA**
- **Shorting treatment duration**
- **Prevention and treatment of DAA resistance**
- **Prevention of HCV infection in HCV+ organ transplatation**

Zeisel and Baumert Lancet 2017, Zeisel et al. Viruses 2016, Felmlee et al. Lancet Infect. Dis. 2016, Vercauteren K et al. Gut 2015, Yamashita et al. J. Exp. Pharm. 2015, Xiao et al. Gut 2014

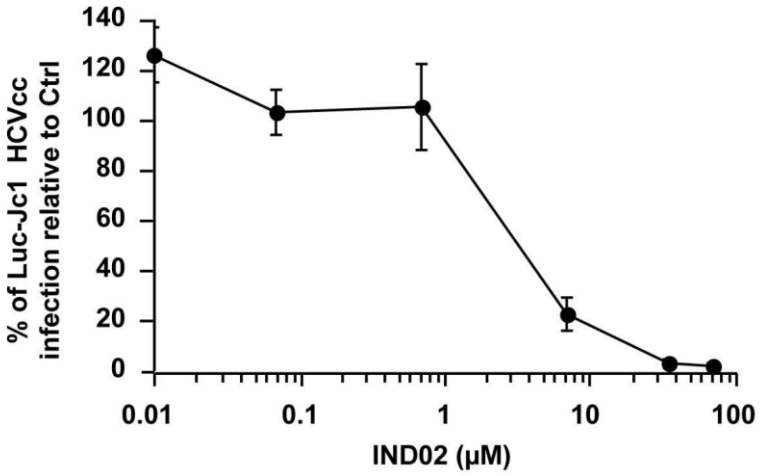
Improve access to antiviral therapy

Approved Antihistamines



He et al. Sci. Transl. Med. 2015

Cinnamon-Derived Compound



Fauvelle et al. 2017, in press

- **Repurposing of clinically licensed, FDA-approved drugs**
- **Natural compounds (e. g. EGCG, silymarin, silibinin, cinnamon)**
- **Discovery and development of low cost antivirals**

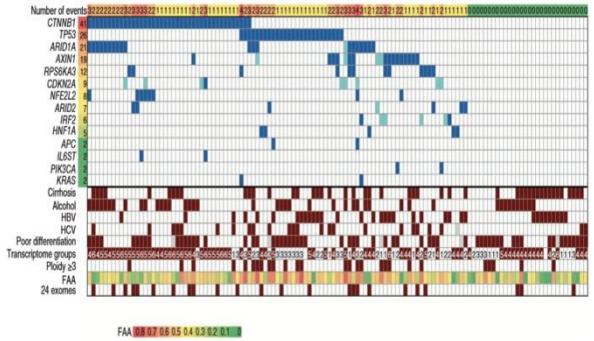
Vausselin et al. J. Virol. 2016, Perin PM et al. Hepatology 2015, Lin LT, Chung CY, Hsu WC, et al. J Hepatol 2015, He S, Lin B, Chu V, et al. Sci Transl Med 2015, Ciesek S et al. Hepatology 2011, Calland N et al. Hepatology 2012, Wagoner J et al. Hepatology 2010, Blaising J et al. Cell Microbiol. 2013 , Gastaminza P et al. PNAS 2010, Chockalingam K et al. PNAS 2010

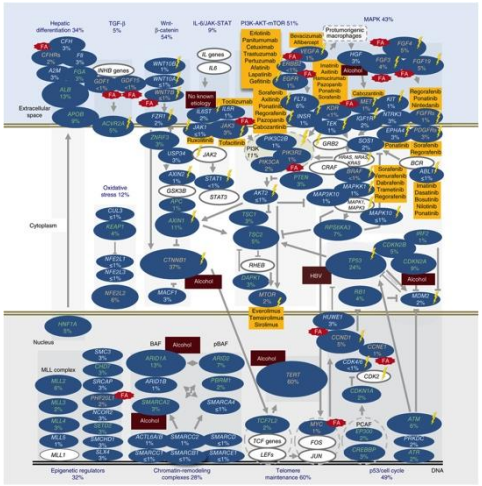
HCV and HCC

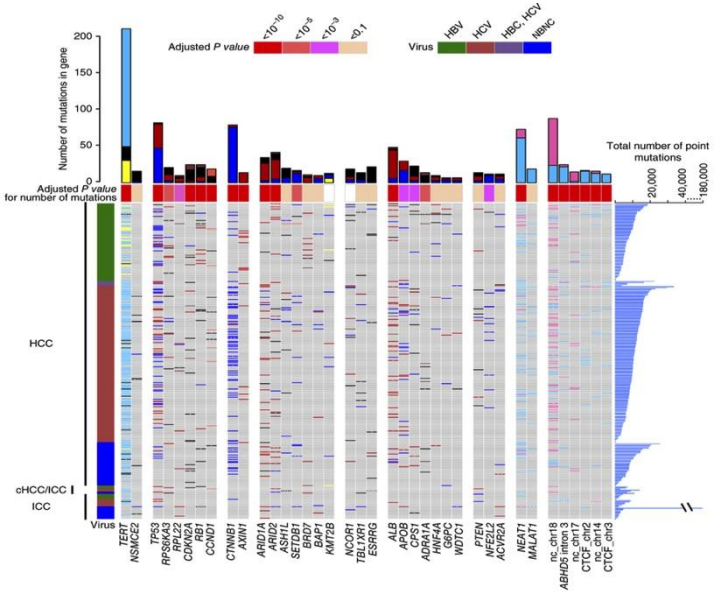
- **HCV – major cause of HCC world-wide including Japan, Europe and the US**
- **Global cancer death rates : ↘ 1.5 percent/year (2003-2012)**
- **Death rates due to liver cancer : ↗ 2.3 percent/year**
- **Hepatocellular carcinoma (HCC) is the second leading and fastest rising cause of cancer death worldwide**
- **Strategies to prevent HCC in advanced fibrosis are limited**
- **While early stage HCC can be treated by surgical intervention, curative strategies for advanced HCC are not available**
- **Novel strategies to prevent and treat HCC are urgently needed**

Center of Diseases Control and Prevention Annual Report on Cancer March 9, 2016

Chronic hepatitis C virus infection as a model to understand hepatocarcinogenesis in general







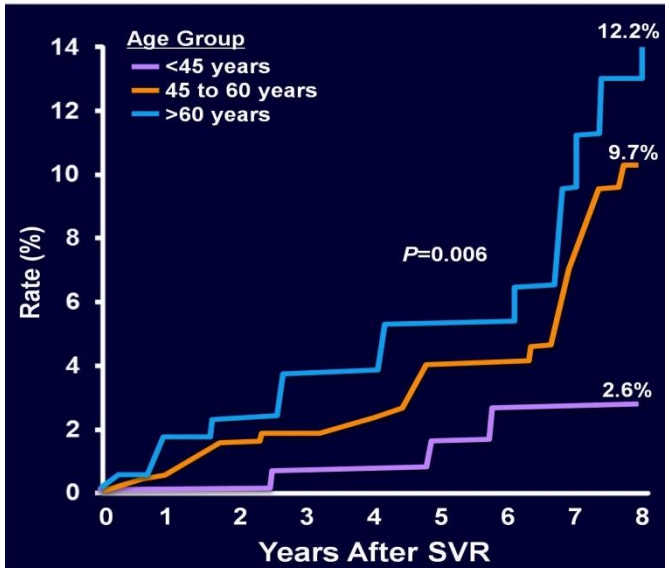
Guichard et al. Nature Genetics 2012 *Schulze et al. Nature Genetics 2015* *Fujimoto et al. Nature Genetics 2016*

- **HCV and other HCC etiologies involve shared pathways and produce similar genetic footprints** ***(Guichard et al. Nat. Genet. 2012, Schulze et al. Nat. Genet. 2015, Fujimoto et al. Nat. Genet. 2016)***

- **Chronic HCV infection - a model for understanding progression of liver disease and hepatocarcinogenesis in general**

Clinical challenge: risk of HCC persists following HCV cure in patients with advanced fibrosis

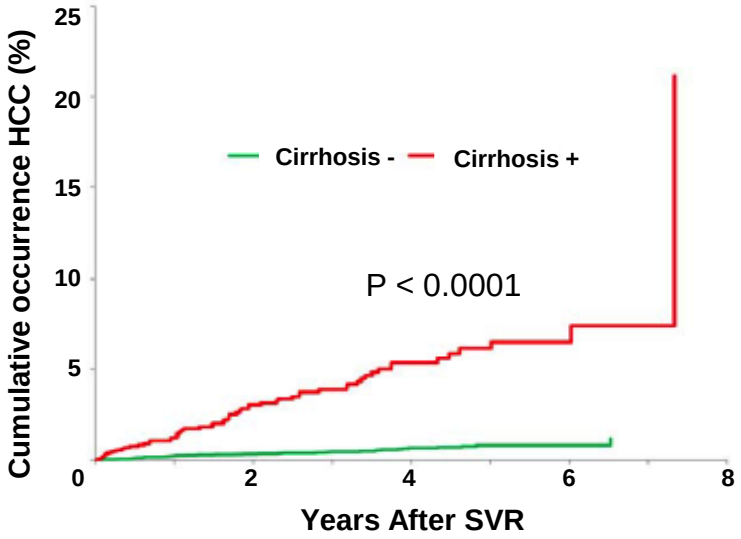
Meta-analysis



van der Meer et al. JAMA 2012

- 10 cohorts, individual patient data
- 5.1 y follow-up
- SVR with IFN-based therapy
- HCC risk decreased but not eliminated
- Risk increased with age, severity of liver disease, and presence of diabetes mellitus

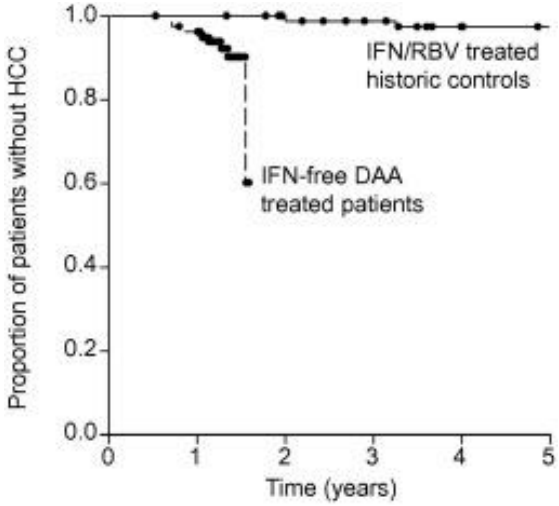
Retrospective cohort study



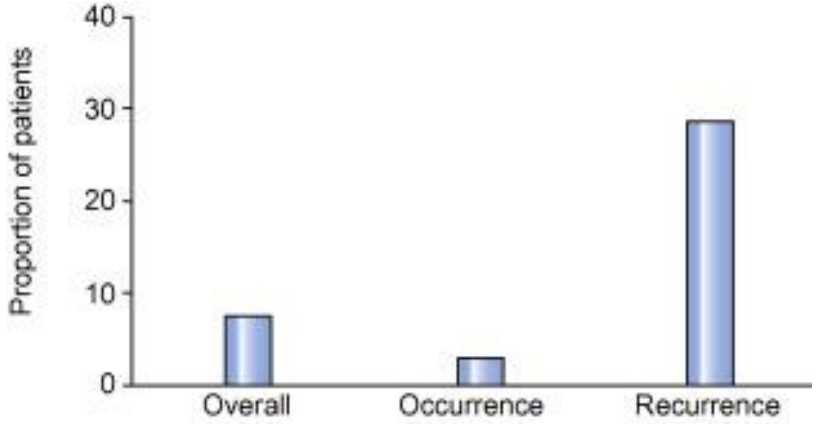
El Serag et al. Hepatology 2016

- US Veterans HCV RNA positive (n=33005)
- 10 y follow-up
- SVR with IFN-based therapy
- Risk of HCC postcure, though considerably reduced, remains relatively high
- Cirrhosis, cure after age 64, diabetes, gt 3 infection risk factors for post-SVR HCC

Recurrence of HCC in DAA-treated patients



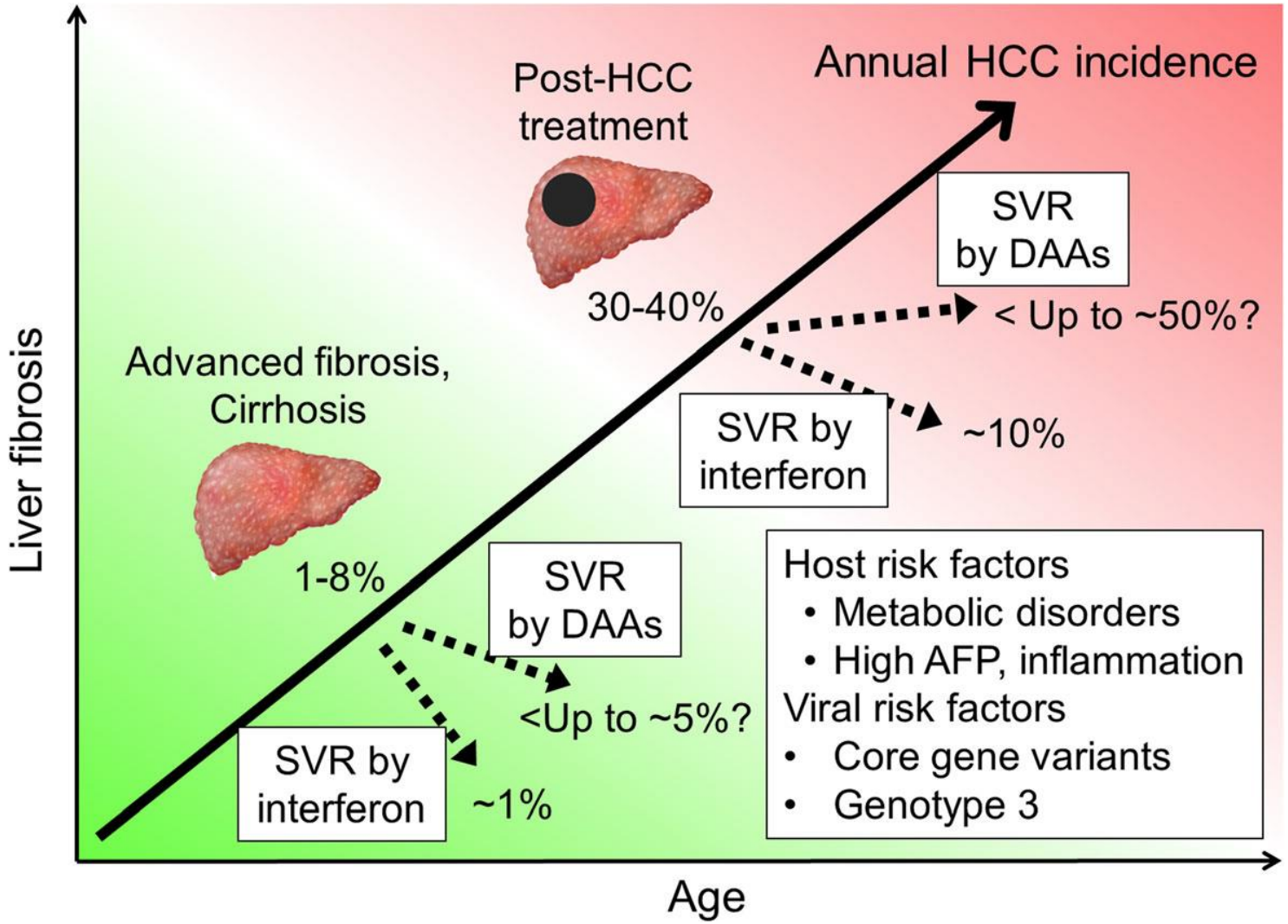
Kozbial et al. J Hepatol 2016



Conti et al. J Hepatol 2016

- **Unexpected high rate and pattern of tumor recurrence in DAA-treated patients in at least three independent cohorts (Reig et al. J. Hepatol. 2016, Kozbial et al. J. Hepatol. 2016; Conti et al. J. Hepatol. 2016)**
- **HCC recurrence not increased in another cohort (Pol et al. ANRS collaborative study group on HCC J. Hepatol. 2016)**
- **Potential differences in HCC incidence in DAA and IFN-based regimens (Kobayashi et al. J. Med. Virol. 2016, Toyoda H et al. Hepatology 2016)**
- **Consideration of a hypothetical "oncogenic" activity of novel HCV drugs (Llovet JM and Villanueva A Nat. Rev. Gastro Hepatol 2016).**

Modulation of HCC risk by anti-HCV therapies



Baumert/Hoshida BMC Medicine 2016