

Fourth Annual BHIVA Conference for the  
Management of HIV/ Hepatitis Co-infection



# Dr Andri Rauch

University Hospital of Bern, Switzerland

Wednesday 16 November 2011, One Great George Street Conference Centre, London

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Management of HIV/ Hepatitis Co-infection



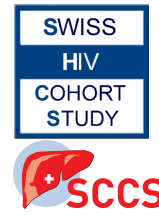
# Dr Andri Rauch

University Hospital of Bern, Switzerland

COMPETING INTEREST OF FINANCIAL VALUE $\geq$ £1,000:	
Speaker Name	Statement
Andri Rauch	Dr Rauch has served as a consultant for GSK and MSD Switzerland, and received a travel grant from MSD, Switzerland. All consultancy fees were paid to his institution.
Date	3 November 2011

Wednesday 16 November 2011, One Great George Street Conference Centre, London

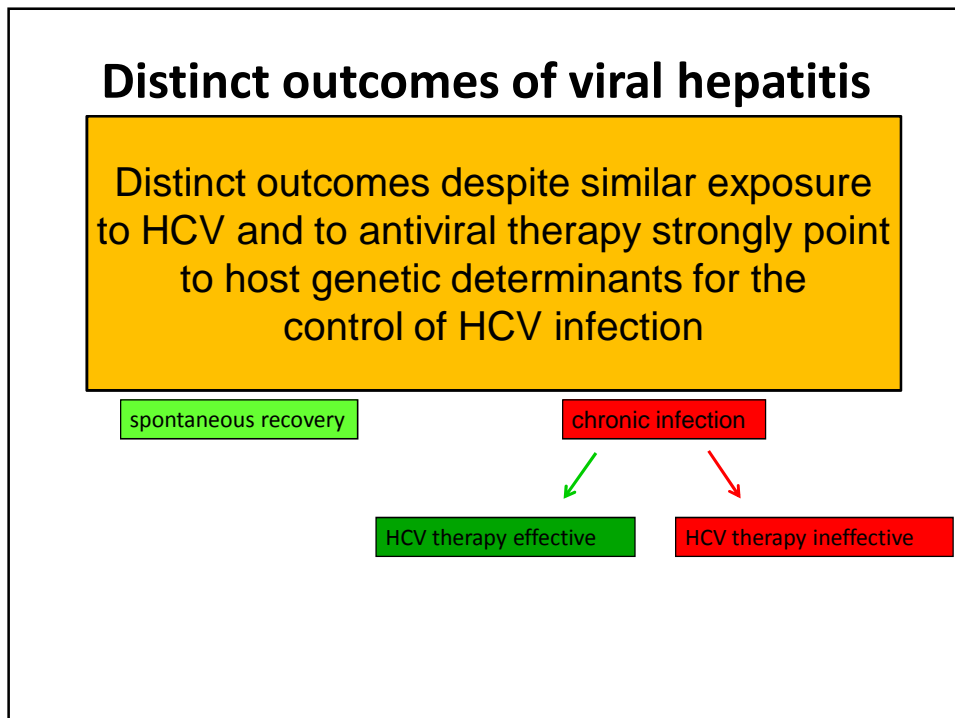
Andri Rauch, MD  
Clinic for Infectious Diseases  
Bern University Hospital - Switzerland  
[Andri.rauch@insel.ch](mailto:Andri.rauch@insel.ch)



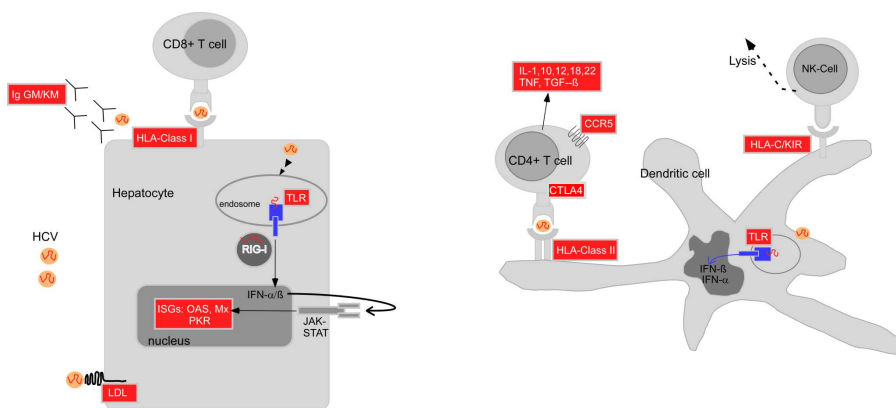
## ***IL28B* and other new predictors of success**

4<sup>th</sup> annual BHIVA Conferene for the managment  
of HIV/Hepatitis co-infection

16 November 2011



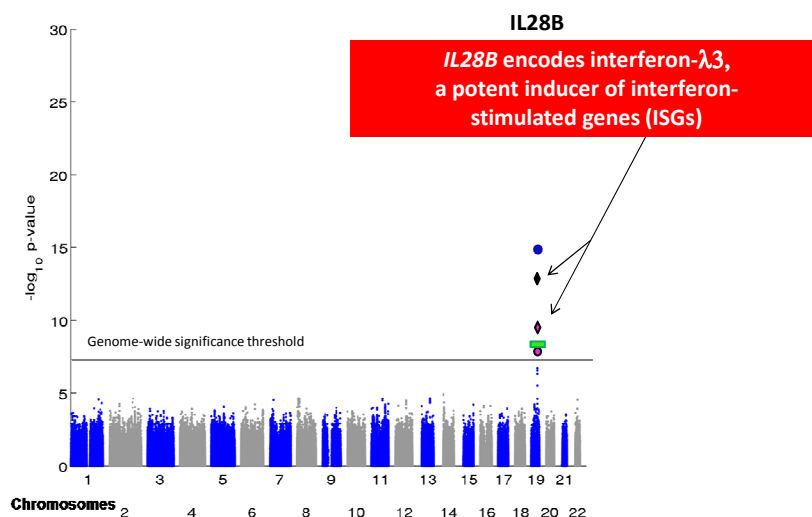
## Host genetic determinants for the control of HCV infection: Candidate gene studies



**■** Host genes with polymorphisms that have been associated with the natural and/or treatment-induced control of HCV

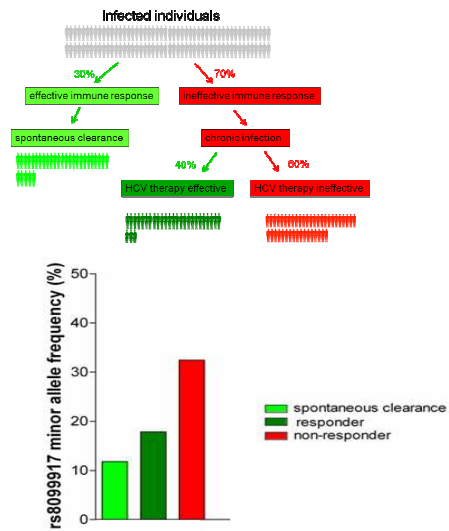
Rauch et al. Pharmacogenomics. 2009 10:1819-37

## Genetic variation in *IL28B* and the control of HCV infection



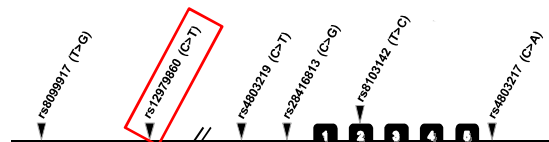
Adapted from Rauch et al., EJC 2010

## IL28B risk allele frequency by HCV infection outcome



Rauch et al, Gastroenterology 2010

## IL28B haplotypes



Di Iulio et al, Hepatology, 2011

## Genetic variation in *IL28B* and the control of HCV infection: **November 2011**

PubMed lists **212** publications

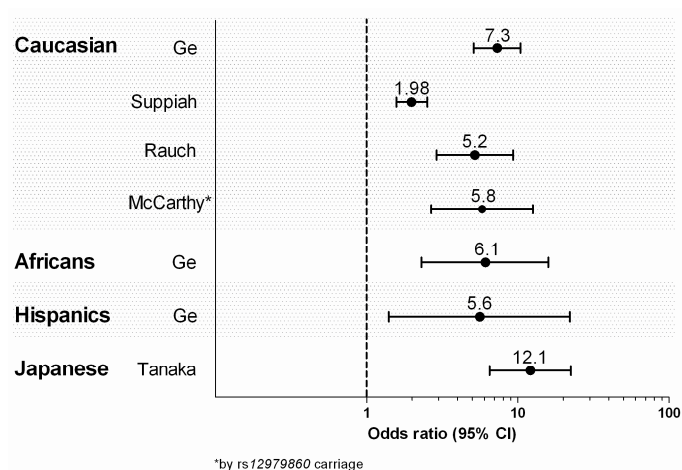
Confirmed influence of *IL28B* in:

- All major ethnicities
- HIV coinfecting population
- Single source cohort
- Recent HCV infection
- HCV Genotype 4, (2 and 3)
- Liver transplantation
- Children
- Response to IFN-based Hepatitis B therapy

New insights in genetics, biology and viral kinetics

+ ITPA and RBV-induced anemia

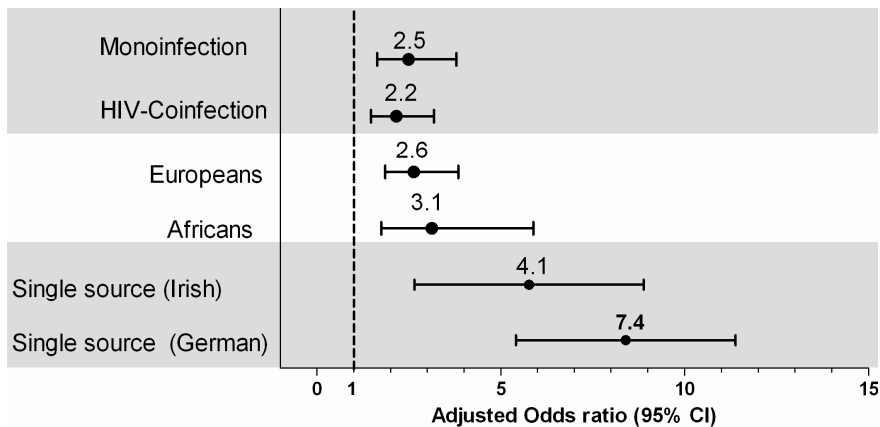
### Consistent effect of *IL28B* on response to HCV therapy in diverse ethnicities



Odds ratios of treatment failure for *rs8099917* G-risk-allele carriers versus non-carriers.

adapted from Rauch et al, EJC 2010

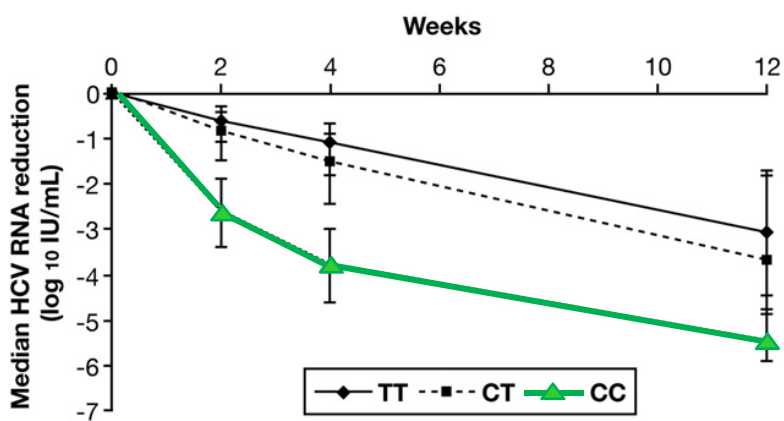
### Consistent effect of *IL28B* on spontaneous HCV infection recovery



Odds ratios for failure to spontaneously clear HCV infection for *IL28B* risk-allele carriers versus non-carriers.

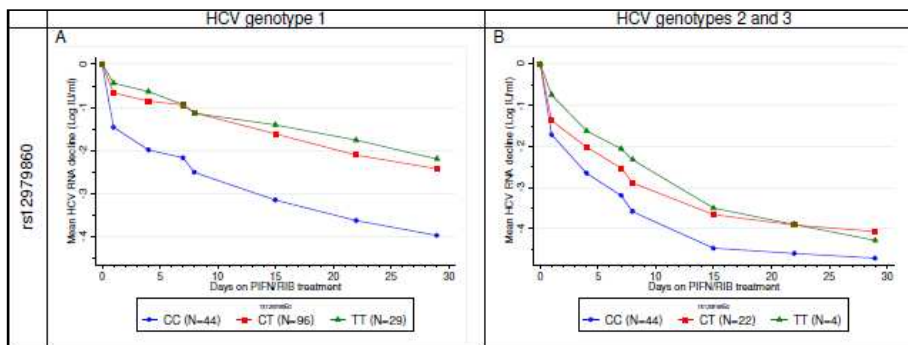
Rauch et al, Gastroenterology 2010, Thomas et al, Nature 2010, di Iulio et al, Hepatology 2011, Tillman et al, Gastroenterology 2010

### *IL28B* and early viral kinetics



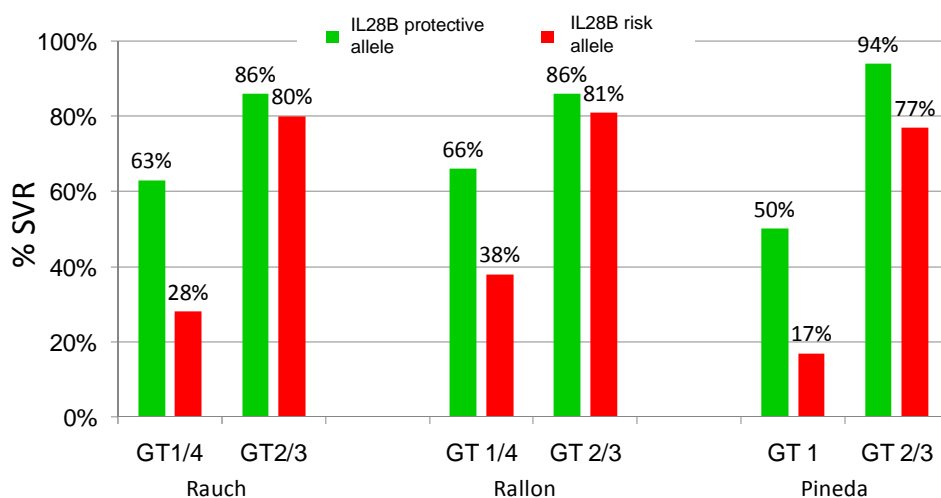
Thompson et al, Gastroenterology 2010

## IL28B and **very** early viral kinetics

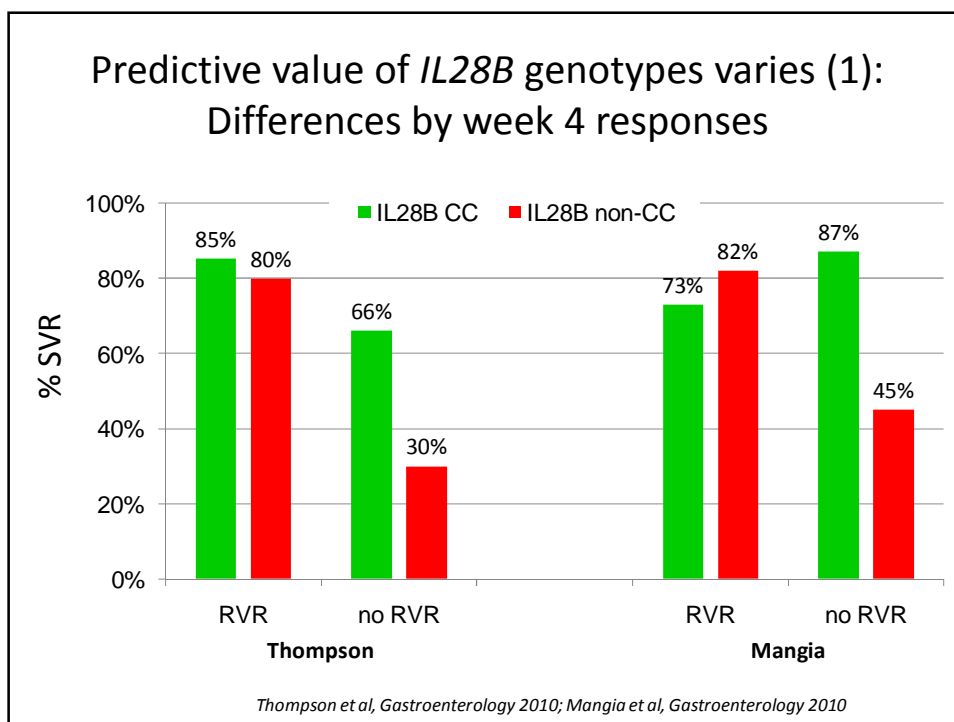
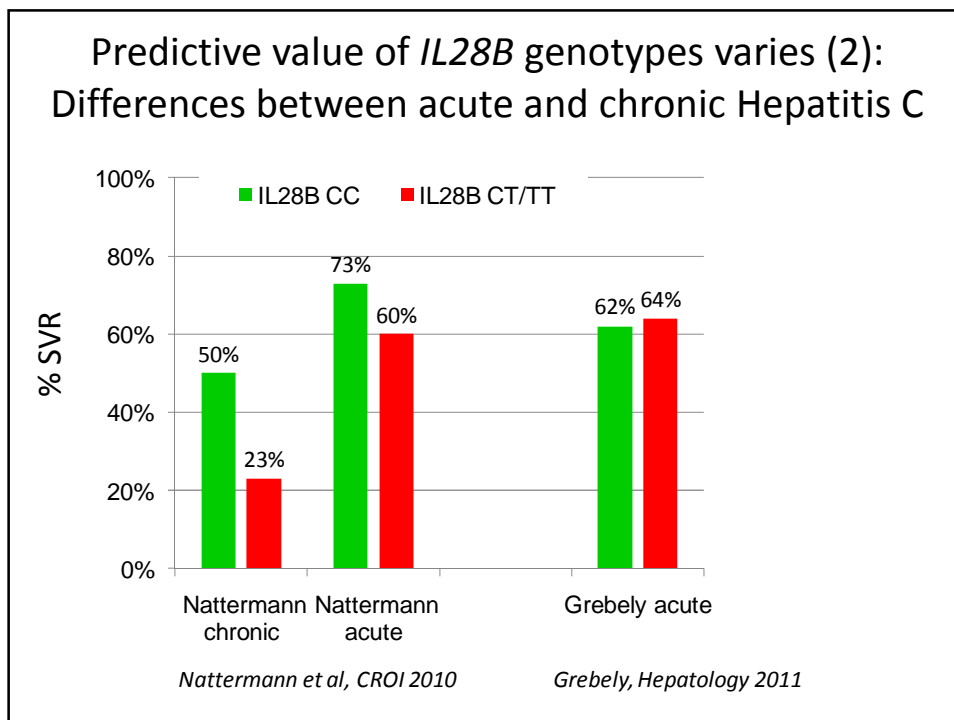


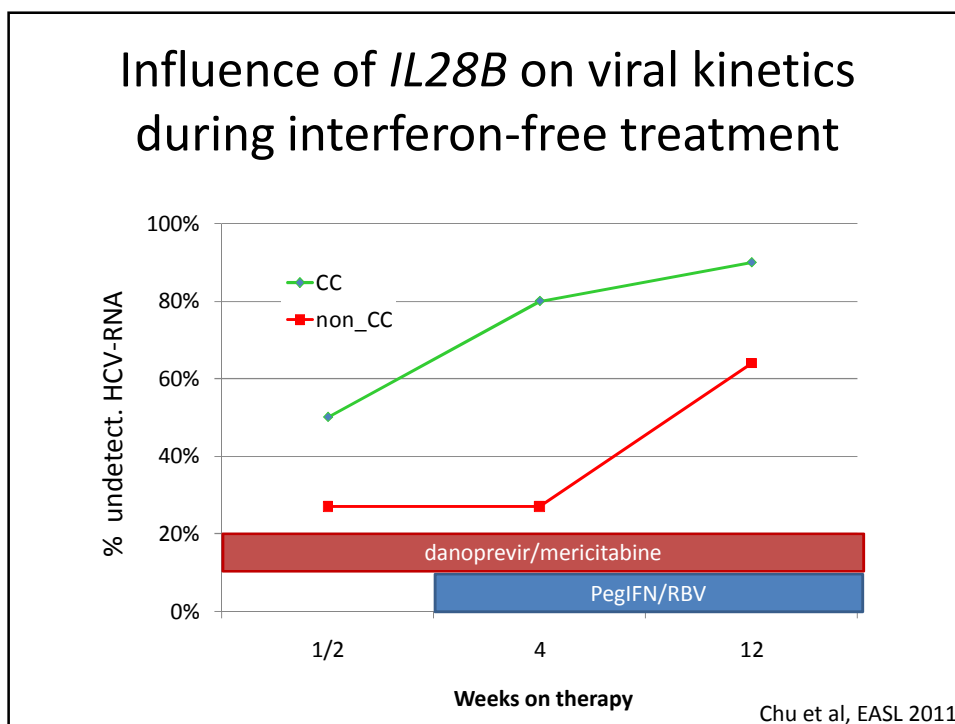
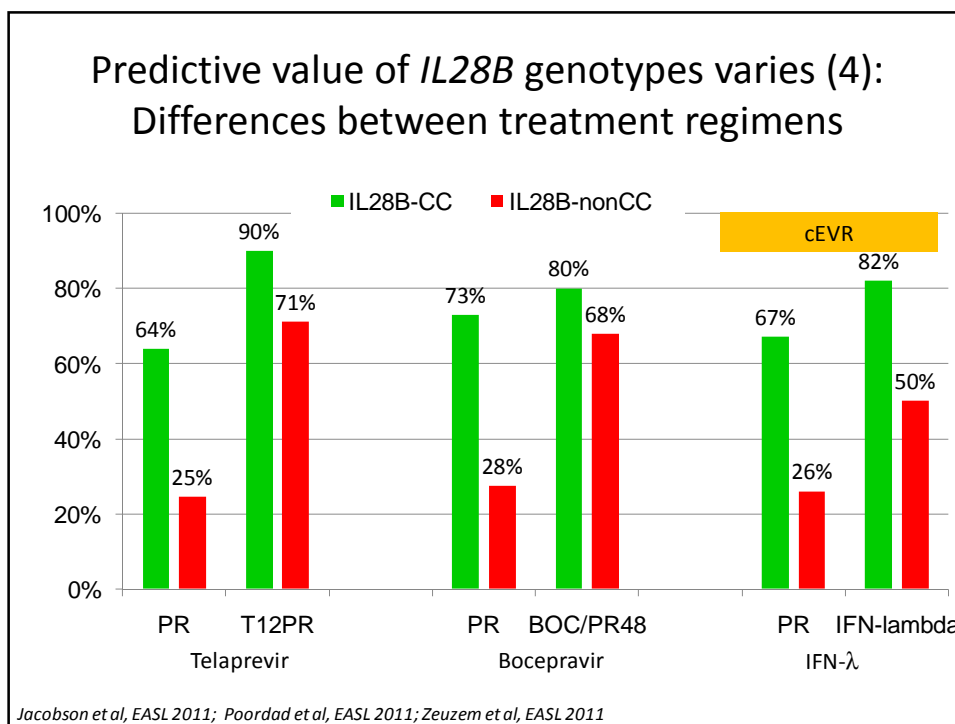
Bochud et al, J Hepatol 2011

## Predictive value of IL28B genotypes varies (1): Differences between HCV genotypes



Rauch et al, Gastroenterology 2010; Rallon et al, AIDS 2010; Nattermann et al, CROI 2010; Pineda et al, CROI 2010





## „Modulators“ of *IL28B* effects

### Strong influence of *IL28B*

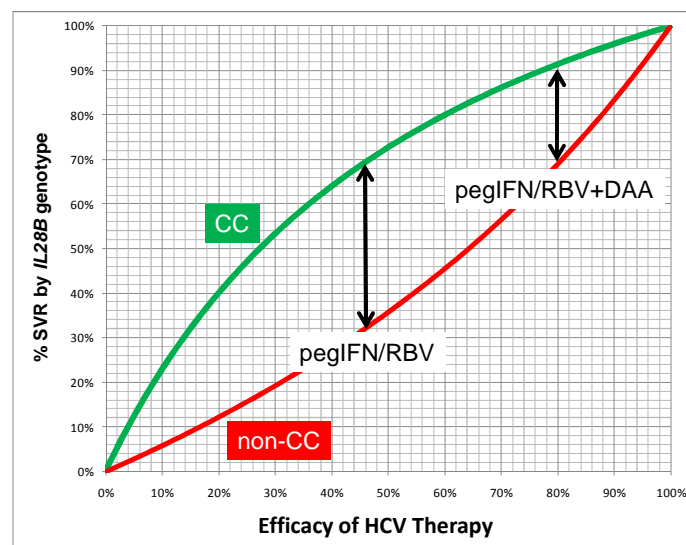
- HCV genotype 1/4
- chronic infection
- non-RVR
- conventional therapy

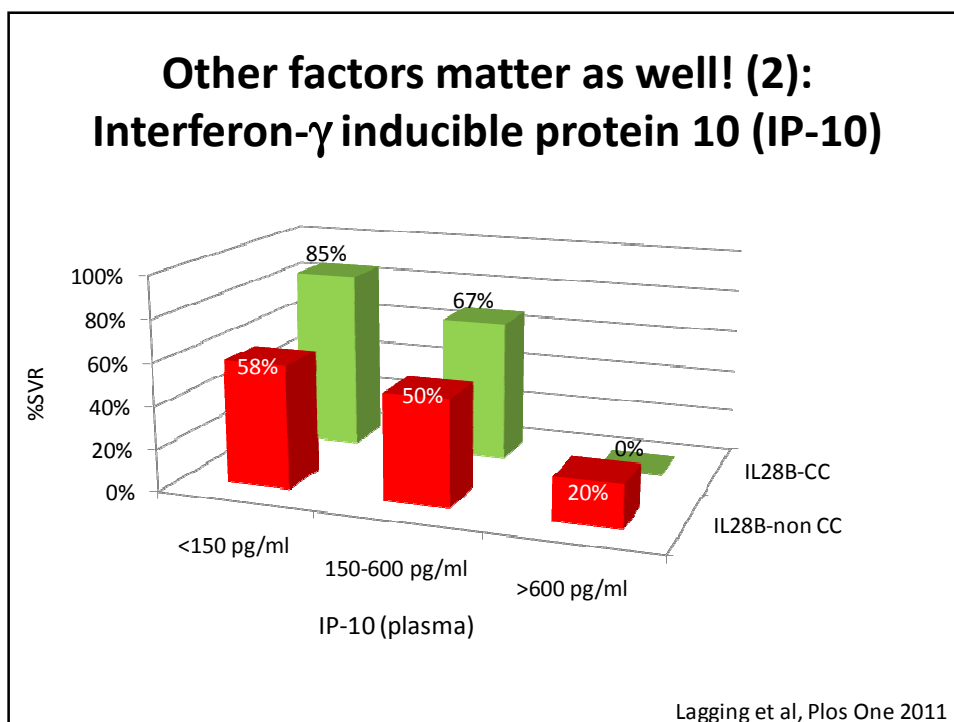
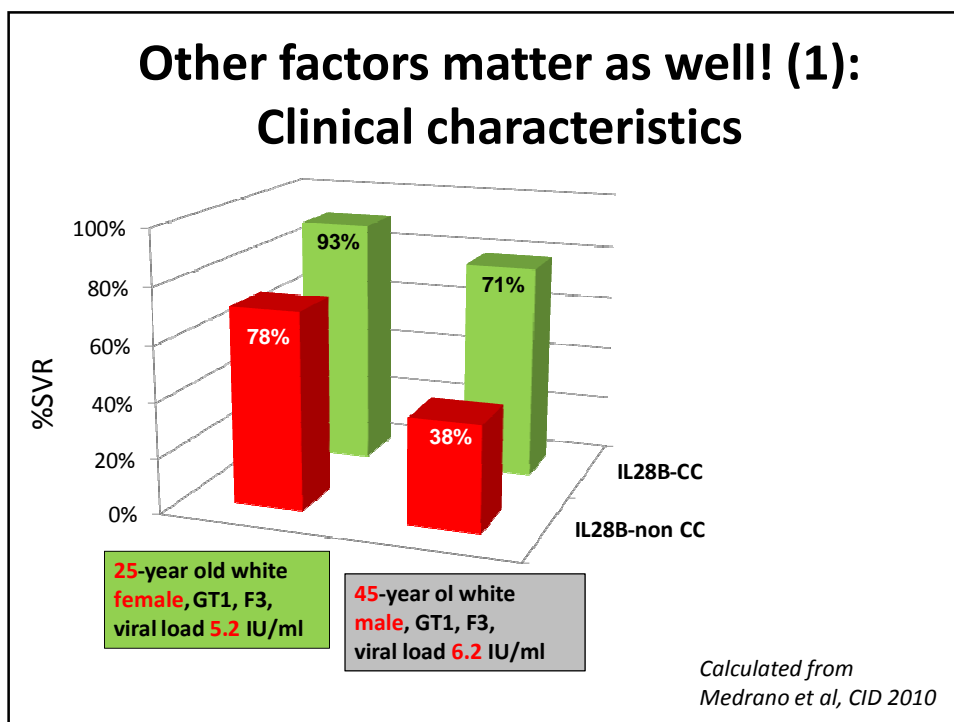
### Moderate influence of *IL28B*

- Genotype 2/3
- acute infection
- RVR
- therapy with PI

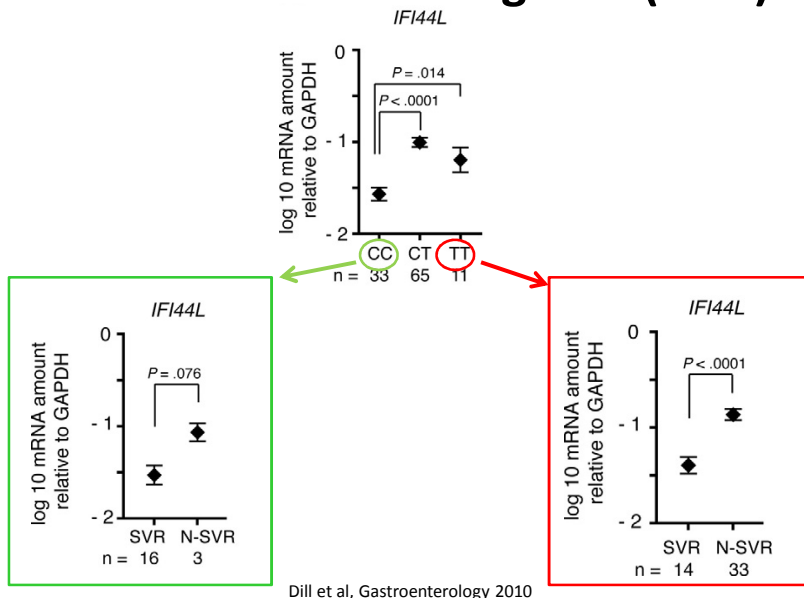
→ Favorable clinical and therapeutic predictors can at least partly overcome the effect of *IL28B* variation.

## Genetic effect is attenuated with more effective treatment

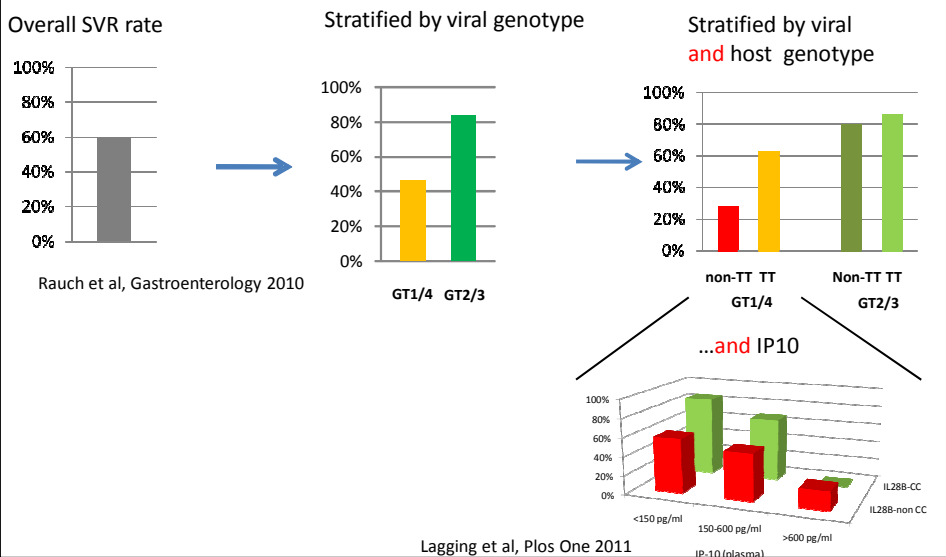


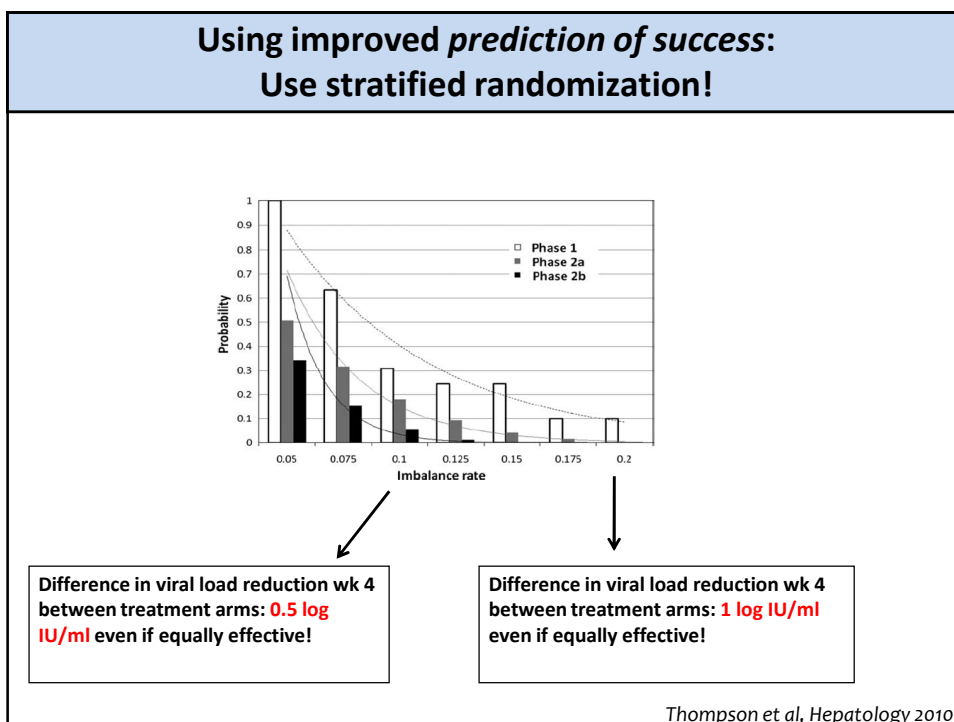
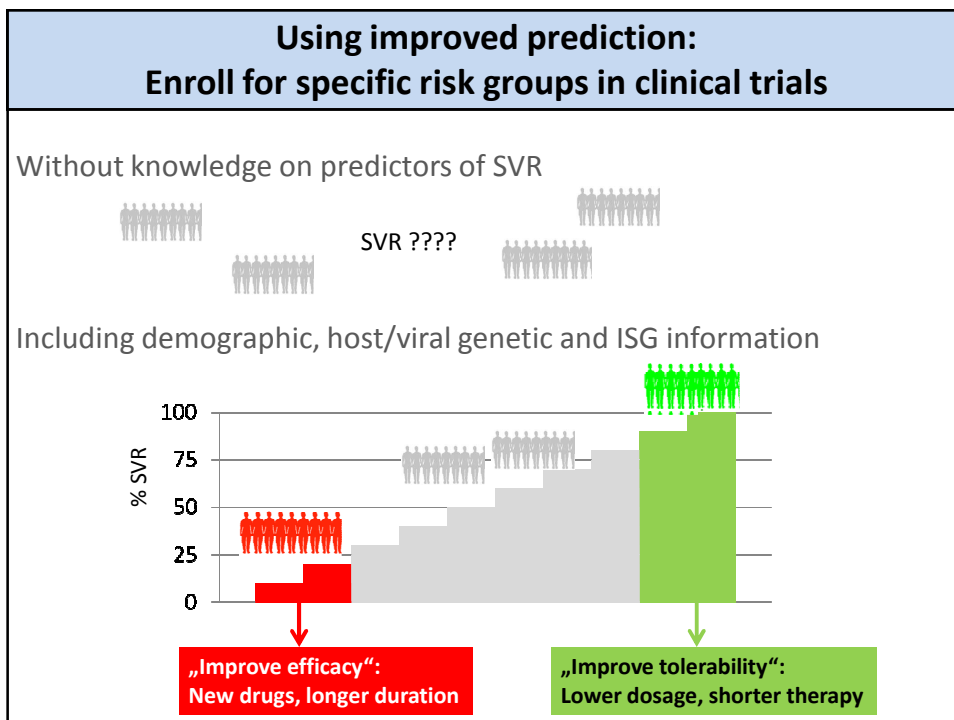


### Other factors matter as well! (3): Interferon-stimulated genes (ISGs)



### Combining ,predictors of success'





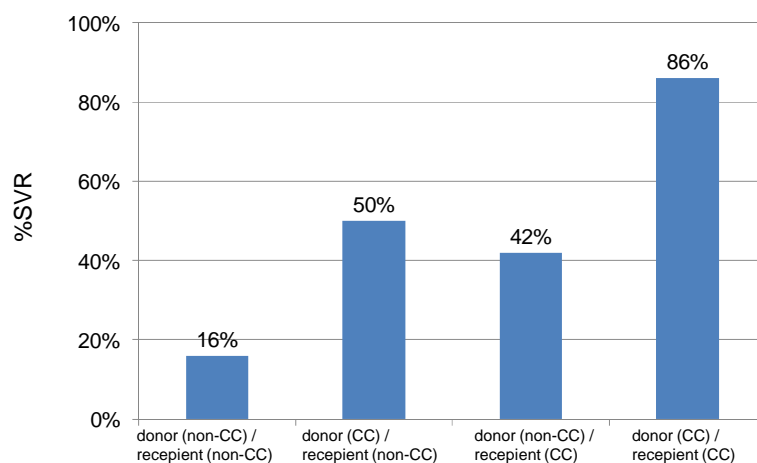
**Using improved *prediction of success*:  
Consider lead-in for CC genotypes**

Use lead in for patients with *IL28B* CC (RVR in ~30%) before starting telaprevir

- RVR → PegIFN/RBV (SVR ~80%)
- no RVR → add protease inhibitor

No lead in for patients with *IL28B* non-CC (RVR in ~5%) before starting telaprevir

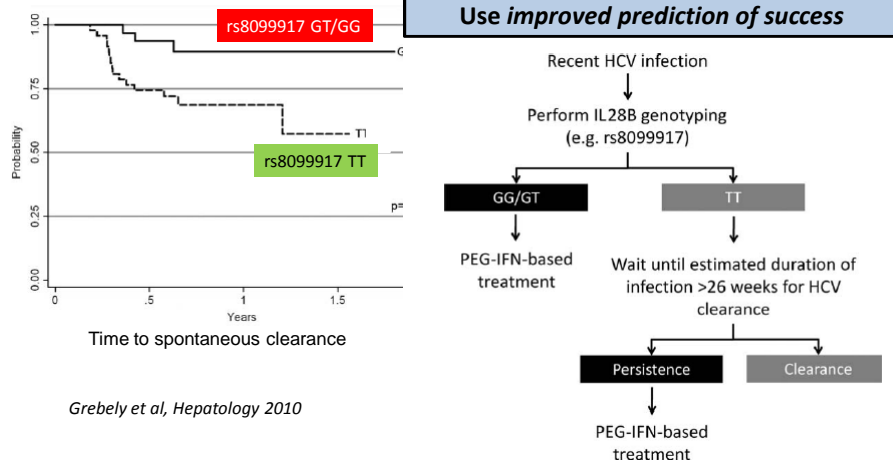
***IL28B* in liver transplantation**



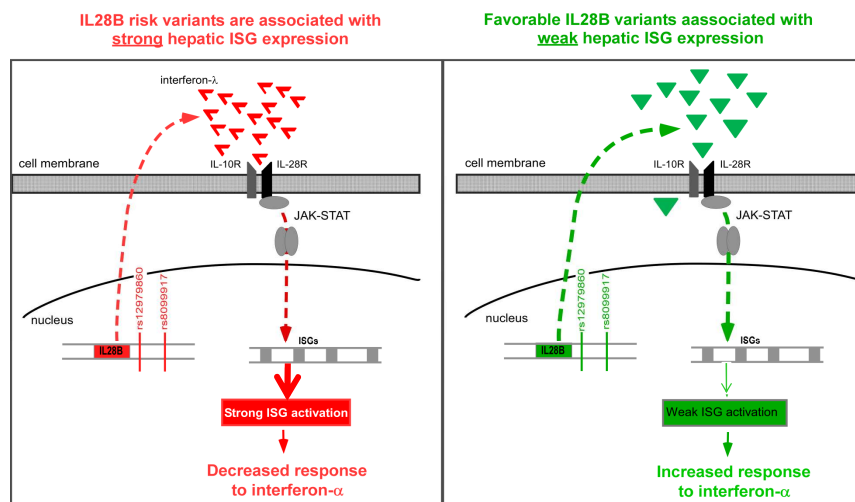
**Use improved *prediction of success*:**  
Allocate donors with favorable *IL28B* variants to HCV-infected recipients.

*Charlton et al, Hepatology 2011*

## IL28B in recent HCV infection



## Mechanism

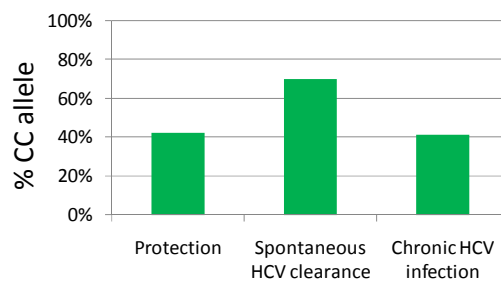


## Protection from HCV infection

*KIR2DL3-HLA-C1* homozygosity associated with:

- protection from HCV infection
- spontaneous HCV clearance

*IL28B* CC not associated with protection



Knapp et al, EASL 2011

## *IL28B* and Hepatitis B

No impact of *IL28B* on natural history

→ Martin et al, JID 2010

No influence of *IL28B* on HBsAg clearance after interferon therapy

→ Mangia et al, EASL 2011

*IL28B* CC genotype associated with HBeAg seroconversion during interferon therapy

<i>IL28B</i> CC	50% HBe Seroconversion
<i>IL28B</i> CT	29% HBe Seroconversion
<i>IL28B</i> TT	10% HBe Seroconversion

(Sonneveld et al, EASL 2011)

### Summary: *Improved prediction of success*

- Improved prediction of spontaneous and treatment-induced HCV clearance by combining host and viral determinants
- Personalized treatment decisions according to clinical and host and viral genetic characteristics (→ avoid unnecessary toxicity, lead-in in patients with *IL28B* CC?)

### Summary: *Improved prediction of success*

Predict spontaneous HCV clearance in acute infection:

- „Watch-and-wait“ strategy in patients with favorable *IL28B* genotypes

Predict treatment response after liver transplantation

- Allocate livers of *IL28B*-CC donors to HCV-infected patients?

Predict toxicity

- Expand access to therapy for favorable ITPA genotypes in anemic patients

## Avoid pitfalls

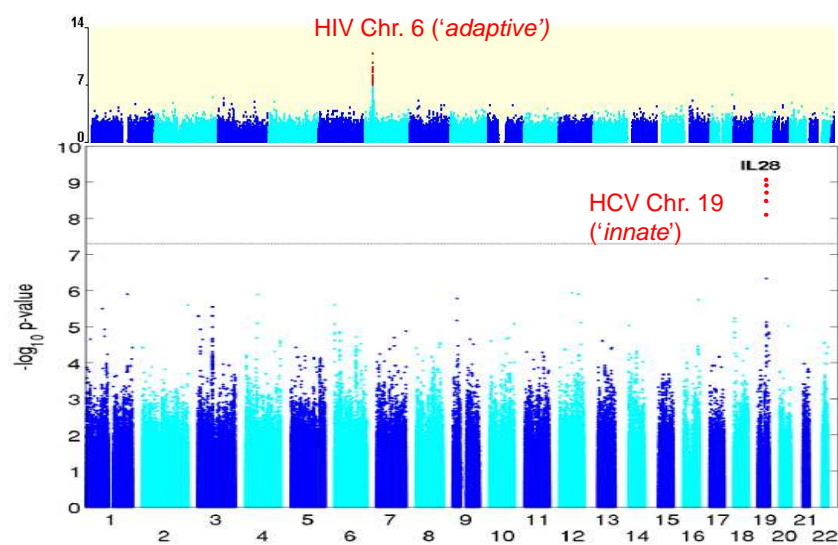
Avoid misunderstandings of patients and health care providers:

- the genetic variants have strong effects at the population level, but are imperfect predictors at the individual level.
- Genotypes can be used to improve clinical decisions, but will not replace a global clinical assessment.
- Avoid inappropriate denial of HCV therapy to individuals who would have responded to treatment despite carrying *IL28B* risk alleles.

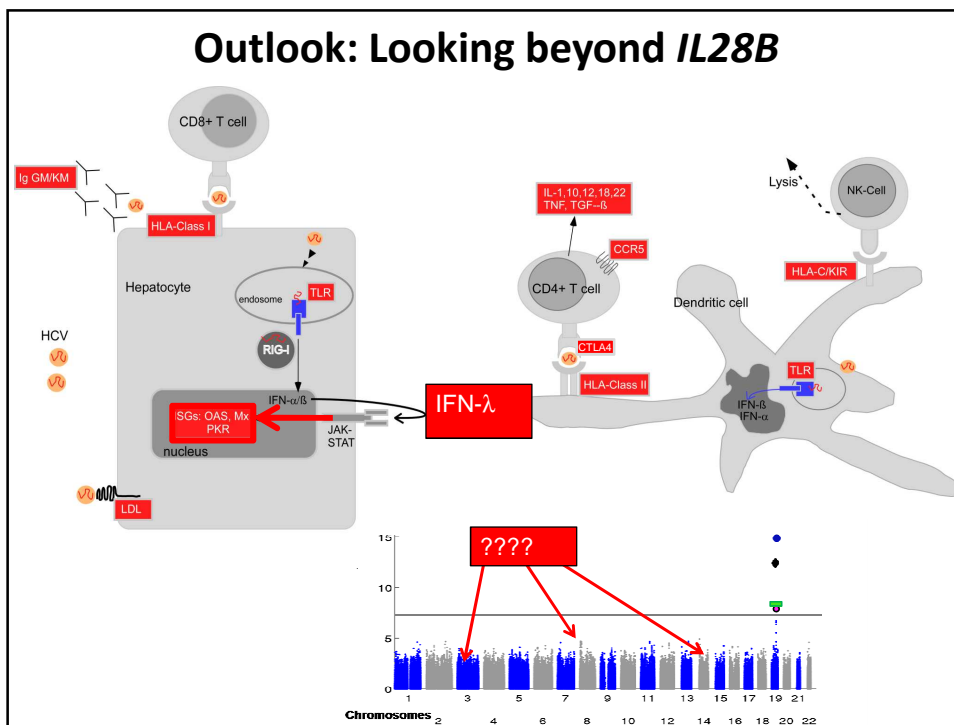
Genetic effects are attenuated by more effective HCV therapies

Rauch and Fellay, Exp Rev Mol Med 2011

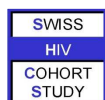
## Chromosomal location of locus of susceptibility to HIV-1 and to HCV



Slide A. Telenti



## Acknowledgements



Amalio Telenti, Julia di Iulio, Hansjakob Furrer, Huldrych Günthard  
 Janine Rohrbach, Jacques Fellay  
 SHCS participants and representatives



The Swiss Hepatitis C Cohort Study

Pierre-Yves Bochud, Francesco Negro  
 Zoltan Kutalik  
 SCCS participants and representatives

Swiss National Science Foundation, Essex Chemie Switzerland, Novartis Foundation, Infectigen Foundation