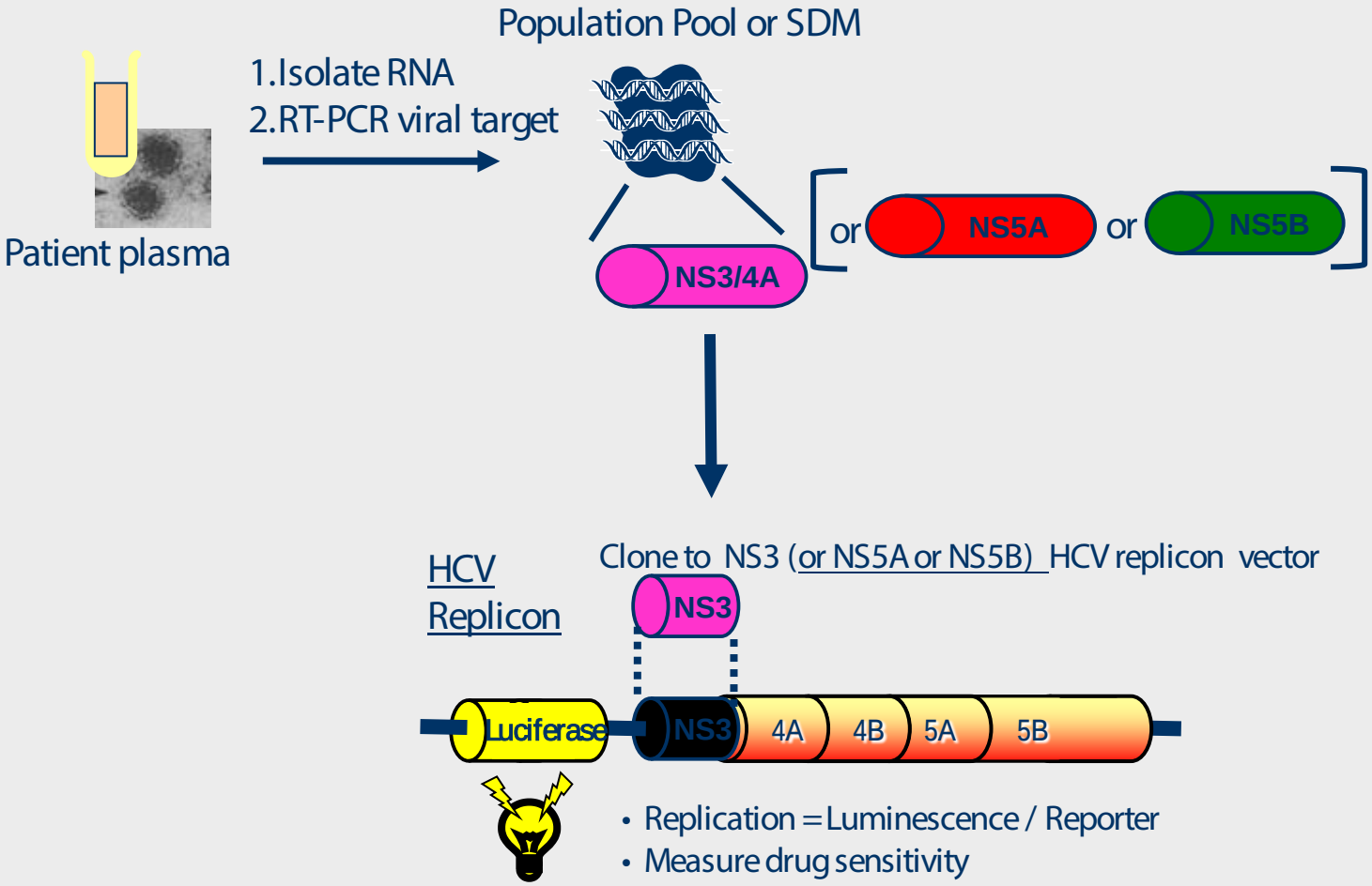
HCV DrAG Meeting #10 , April 23rd 2013

HCV Phenotpying Assays and Clinical Studies

Examples from Boehringer Ingelheim Studies/Analyses

Boehringer Ingelheim

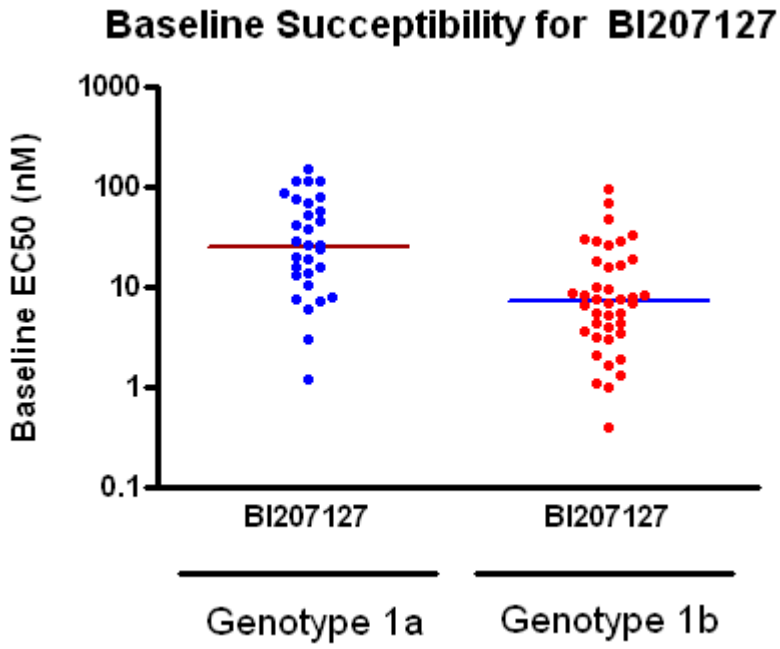
Replicon-based NS-region Phenotyping

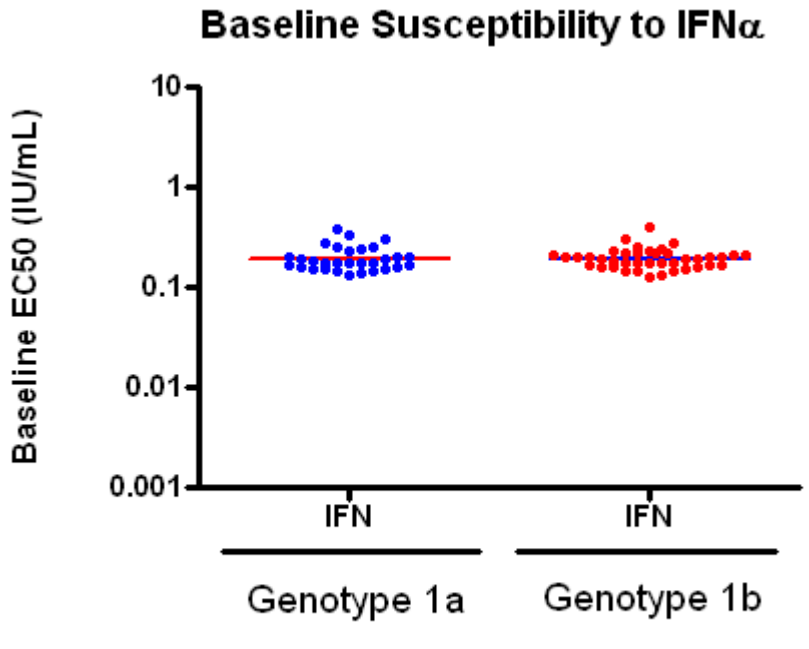


Kukolj et al., 2010 HCV Resistance Workshop

1241.2 Baseline NS5B Phenotyping: Susceptibility to BI207127 and IFNα

Boehringer Ingelheim

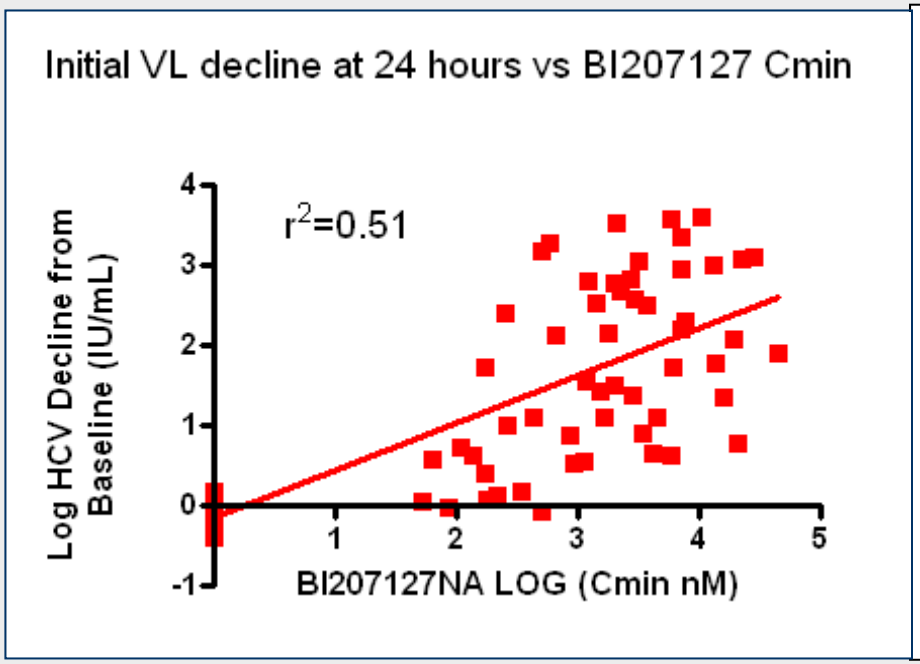


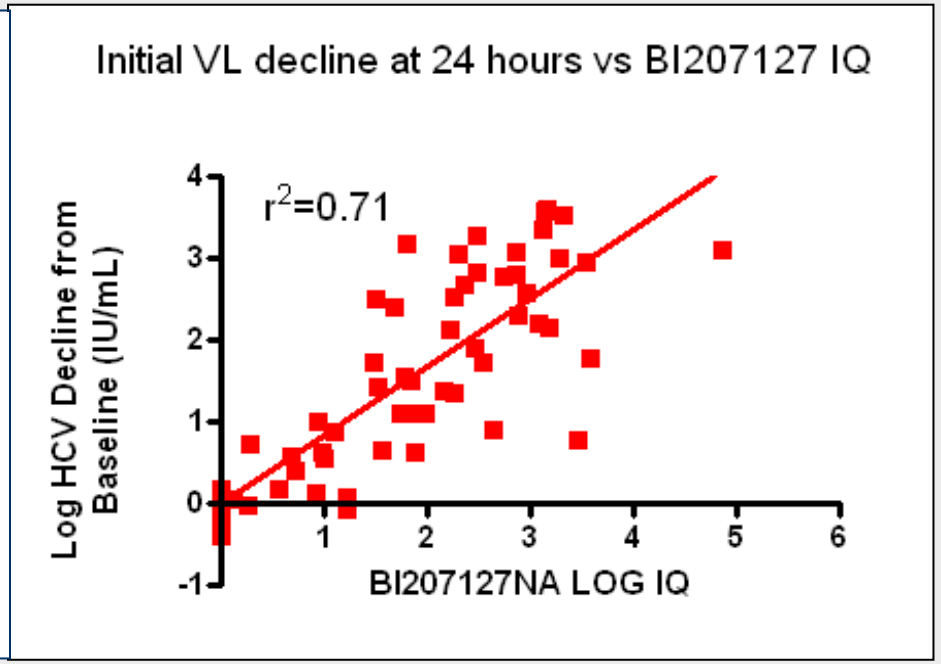


	Genotype 1a	Genotype 1b
gMean (range)	25.7 (1.2 - 150) nM	7.3 (0.4 – 94) nM
Mean	0.20 +/-0.06 IU/ml	0.20 +/-0.05 IU/ml

Marquis et al., 2011 HCV Resistance Workshop

1241.2 PK/PD Analysis: Individual VL Decline vs. IQ (Cmin/EC_{50})





Cmin

IQ : Cmin / EC_{50}

- Adjustment of PK values with individual BI 207127 EC_{50} baseline NS5B phenotype improves PK/PD correlation
- Relationship between baseline viral phenotypic variants and clinical response

Marquis et al., 2011 HCV Resistance Workshop

Liver Corrected Inhibitor Quotients (LCIQ)

Boehringer Ingelheim

	Telaprevir	BILN 2061	BILB 1941
Dose (mg)	750 (tid)	25 (bid)	300 (tid)
% Patients >3 log_{10} VL reduction (day 2)	75	33	12
EC_{50} (μM)	0.30	0.001	0.074
C_{min} / EC_{50}, plasma IQ	6	6	21
Est. Human Liver Kp	38	20	3
Liver Corrected IQ	228	120	63

Plasma exposure and potency alone do not α VL reduction

LCIQ correlates VL reductions

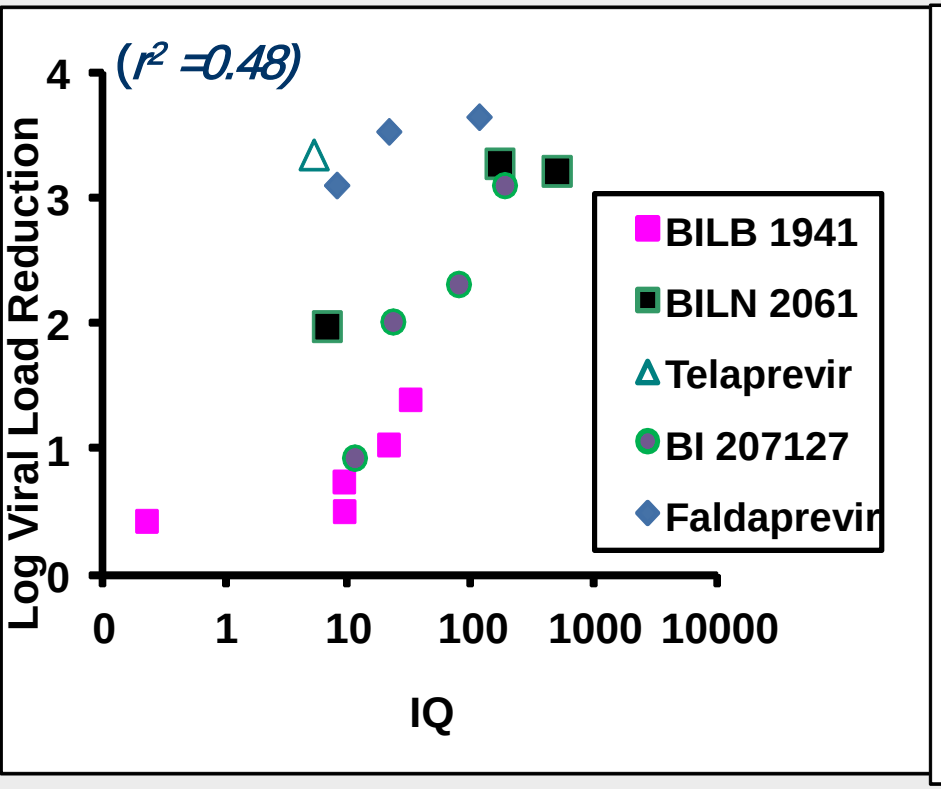
BI developed model to estimate human liver partitioning (Kp):

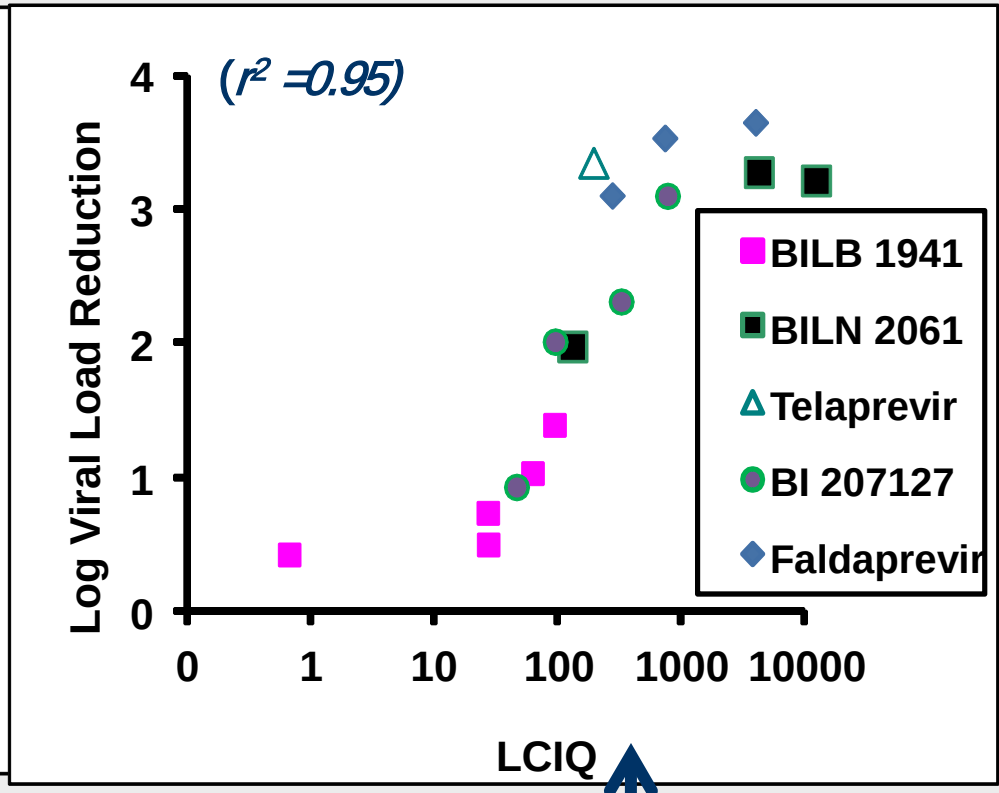
$$\text{human } Kp_{liver} = \frac{1}{n}\sum_{i=1}^{n}[(Kp_{hep},\ human\ /\ Kp_{hep},\ animal_i) * Kp_{liver},animal_i].$$

Duan et al., 2012 Antimicrob. Agents Chemother. 56(10):5381.

LCIQ vs Viral Load Reduction for HCV DAAs

Boehringer Ingelheim





Achieving > $LCIQ_{500}$: Maximal short term antiviral potency

Duan et al., 2012 Antimicrob. Agents Chemother. 56(10):5381.