Perspective from IQ working group on 4β-HC in Drug Development

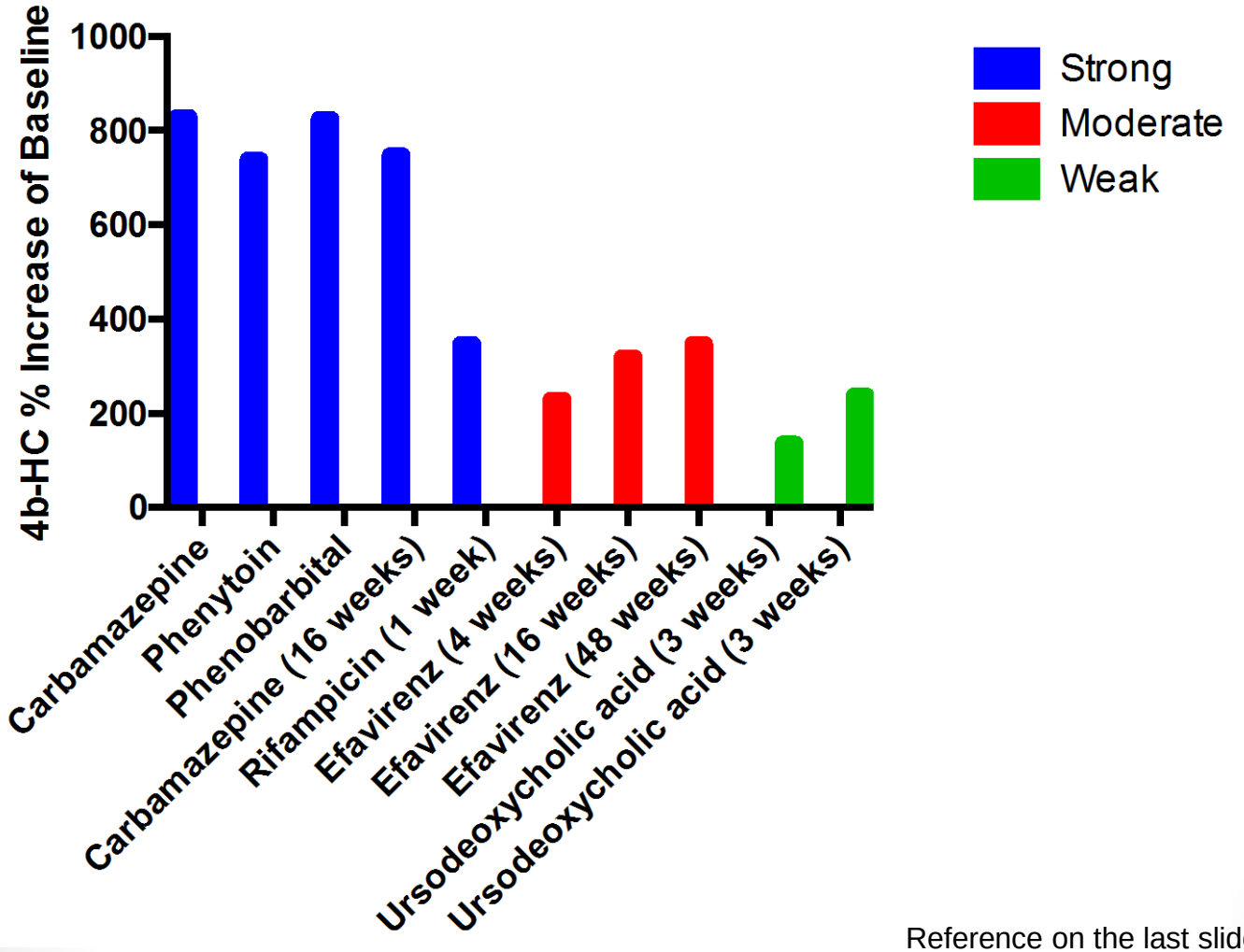
Jialin Mao
Genentech, A Member of the Roche Group
On behalf of the IQ 4β-HC Working Group

March 17, 2017

ASCPT

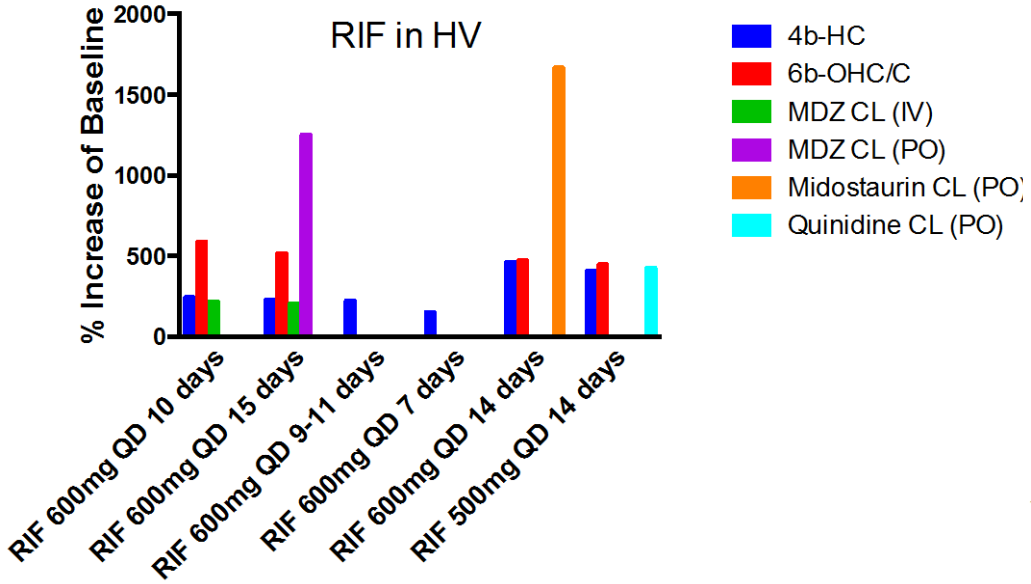
Response of 4β-HC to CYP3A Inducers in Patients

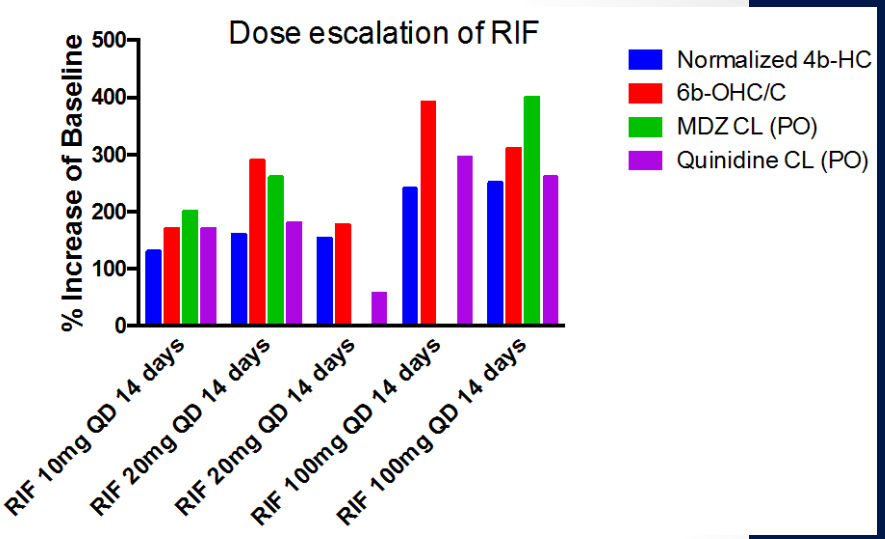
- At least 3 weeks of treatment may be needed to differentiate strong/moderate/weak CYP3A inducers by the 4β-HC increase

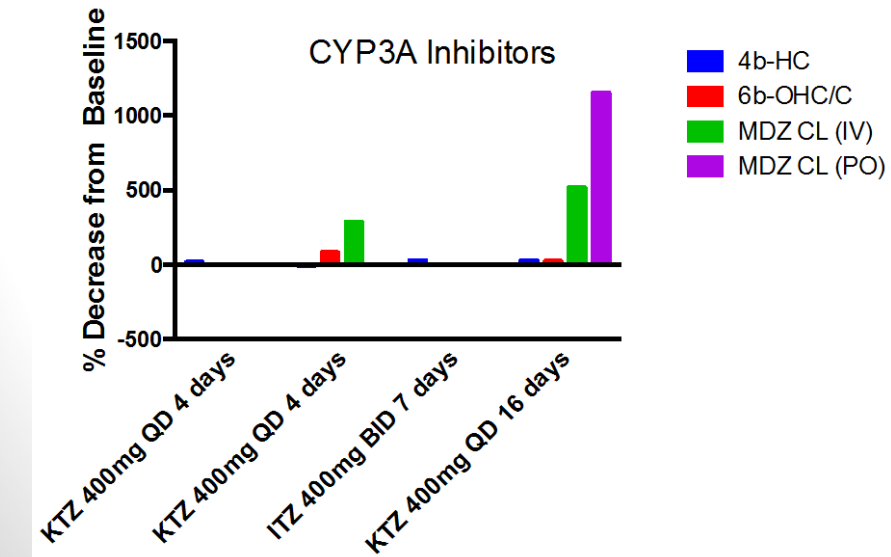


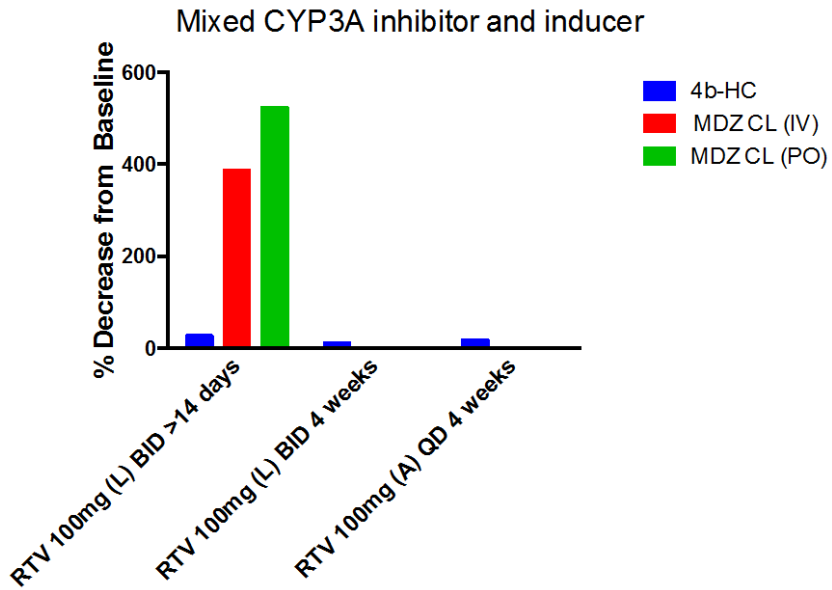
Reference on the last slide

Response of 4β-HC to CYP3A Inducers, Inhibitors and Mixed inhibitor/inducer in Healthy Volunteers and Patients









Reference on the last slide

Recommendations for the Application of 4β-HC in Drug Development

Advantages of 4β-HC
Minimally invasive
Cost-effective biomarker of hepatic CYP3A

- Applications for CYP3A induction:
  - Multiple dose study
  - Replace dedicated midazolam DDI study?
  - CYP3A activity at baseline and during efficacy studies

Recommendations: Multiple dose study

Advantages

- In a study with at least 6 subjects and one week of treatment, an increase in 4β-HC provides an early signal for strong hepatic CYP3A inducers
- If the NME is not a CYP3A inducer *in vitro*, monitoring 4β-HC may confirm the absence of hepatic CYP3A induction in an appropriately designed study

Limitations

- The magnitude of the 4β-HC change is smaller than the magnitude of an oral midazolam clearance change
- If no change in 4β-HC is observed, one cannot rule out the risk of weak and moderate hepatic CYP3A induction, intestinal CYP3A induction or CYP3A inhibition

Recommendations: Replace Dedicated Midazolam DDI study?

Limitations

- 4β-HC is unlikely to replace an oral midazolam DDI study because 4β-HC is insensitive to acute CYP3A inhibition or short-term treatment and will not reflect intestinal CYP3A DDIs

Advantages

- 4β-HC may be used for long-term treatment studies or in patient populations where a midazolam DDI study is not feasible/practical
- Normalized 4β-HC is recommended when the treatment affects cholesterol levels

Recommendations:
CYP3A Activity at Baseline and During Efficacy Studies

Advantages

- Reflects inter-individual variability in hepatic CYP3A
- Maybe suitable for chronic condition in which hepatic CYP3A activity is altered by disease

Limitations

- Does not reflect intestinal CYP3A activity
- May be insensitive to mild disease states or diseases involving acute or local inflammation

Acknowledgements

- Yvonne Lin (Univ of Washington, co-lead)
- Iain Martin (Merck)
- James McLeod (Galleon Pharmaceuticals)
- Gail Nolan (GlaxoSmithKline)
- Robert van Horn (Sanofi)
- Manoli Vourvahis (Pfizer)
- Team members from IQ companies for their input
- IQ DMLG and CPLG for their guidance and support

Reference

Shin CPT 2013
Kasichayanula BJCP 2014
Niemi Pharma 2006
Goodenough CRT 2011
Dutreix EJCP 2014
Kanebratt CPT 2008
Marde Arrhen CPT 2008

Bjorkhem-Bergman DMD 2013
Goodenough CRT 2011
Lutjohann IJCPT 2009
Kasichayanula BJCP 2014
Tomalik-Scharte CPT 2009
Josephson EJCP 2008
Mao DMR 2016

A Case Example of Application of 4β-HC in a Discovery Project: How to Translate the Preclinical in vitro and in vivo Data to Assess Human CYP3A Induction Risk?

Jialin Mao

March 17, 2017

ASCPT

Genentech
A Member of the Roche Group

Compound X: exposure of Day 7 significant lower than Day 1 in cynomolgus monkey toxicology study

Dose 100mg/kg	Day 1	Day 7	Day7/Day1 %
$AUC_{0\text{-}12}$ free (µM*h)	45.4	9.9	-78.2
C_{max} free (µM)	7.0	2.1	-70.0

Questions:

- What is the main cause in the decreased exposure in monkey?
- Will it occur in human?

Overall Strategy for CYP3A induction risk assessment

Cyno induction risk

Monitor hepatic CYP3A biomarker 4ß-HC in the toxicology studies

Observed D7 vs. D1 exposure

CYP3A biomarker helps to understand whether the decreased exposure of D7 compared to D1 is related to CYP3A8 induction in cynomolgus monkey

If yes, it is important to find means to increase the dose in order to cover the high dose for toxicology studies

Human induction risk

Build model using human in vitro data

Measured induction potency in validated human hepatocytes

PBPK (Simcyp)

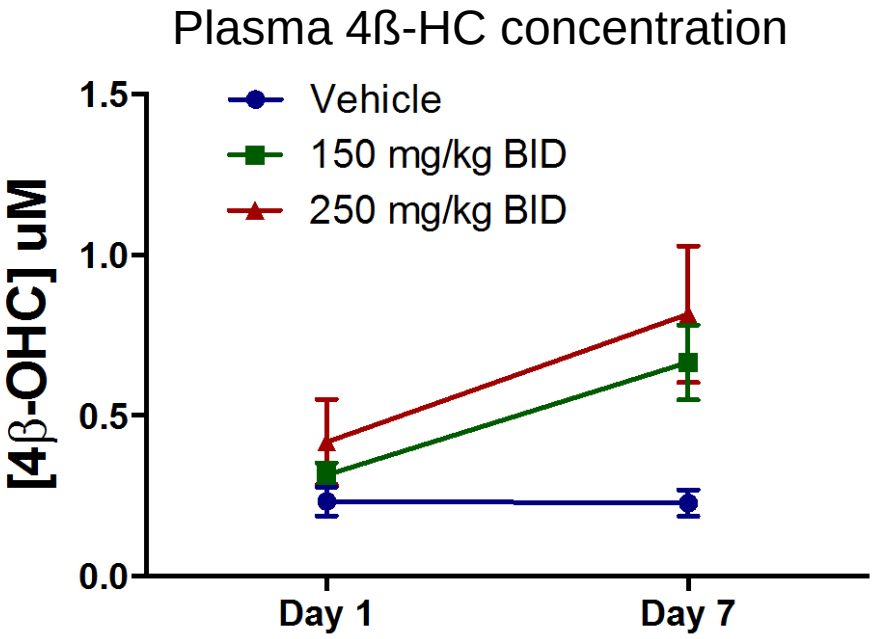
Predict human PK

Predict MDZ-DDI

Observed exposure in multiple dose study

Monitor hepatic CYP3A biomarker 4ß-HC in multiple dose study in Phase I

Auto-induction was confirmed by the increase in 4ß-HC

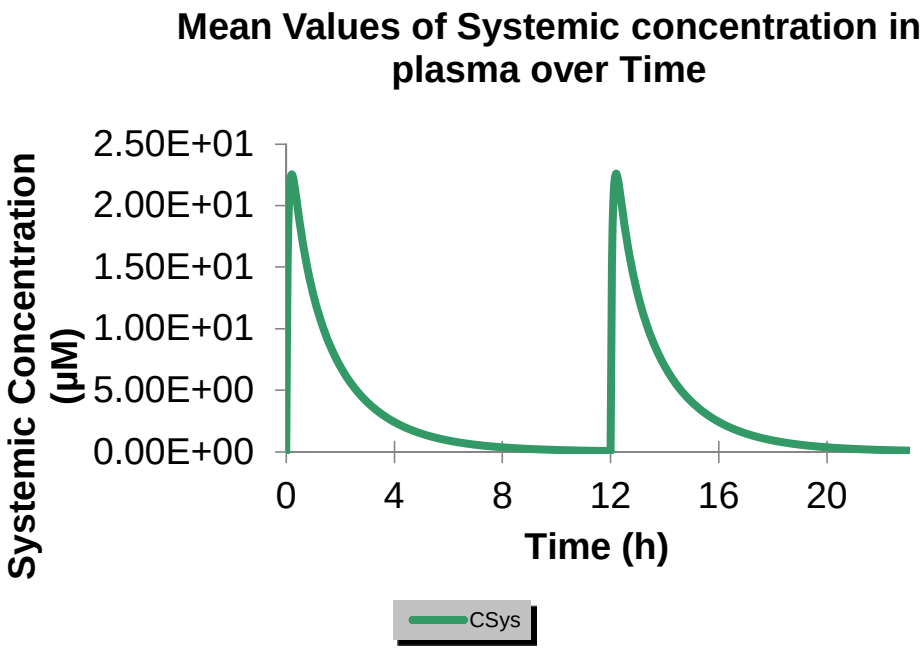


- Two fold increase of plasma 4ß-HC concentration confirmed the auto-induction hypothesis.
- Put into context: Four fold increase was observed for 16 days of RIF treatment @15 mpk/day (DMD 42: 839-43)

	D1 150 mg/kg	D7 150 mg/kg	D7/ D1 %	D1 250 mg/kg	D7 250 mg/kg	D7/ D1 %
AUC_{0-12} free (µM*h)	38.5	8.9	-76.9	52.3	9.3	-82.2
C_{max} free (µM)	5.0	1.9	-62	5.8	2.4	-58.7

Genentech
A Member of the Roche Group

Human PK and DDI prediction of compound X



PK

- Compound X was predicted with a moderate clearance and low Vss, considered a reasonable IVIVE in preclinical species
- No impact of auto-induction on its PK was predicted with the worst case scenario.

DDI

- Low CYP3A induction risk was predicted at the efficacious dose.

	D1	D7	D7/D1%
Scenario fmcyp3A=0.9 with mRNA induction data*			
AUC_{0-12} free (µM.h)	4.9	4.8	-3
C_{max} free (µM.h)	2.7	2.7	-1
C_{min} free (µM.h)	0.0088	0.0079	-10

CYP3A probe Midazolam	Geometric mean % (95% CI)
AUC ratio	-16 (-18, -15)
C_{max} ratio	-12 (-13, -11)

* Compound X mRNA CYP3A EC50=41.2-77.6 µM, Emax= 17.8-25.9

Conclusion

- 4ß-HC is minimally invasive and cost-effective biomarker of hepatic CYP3A in both monkey and human.
- Monitoring the change of 4ß-HC can serve as a practical solution to understand whether the CYP3A8 induction is contributing to the exposure decrease in monkey.
- A positive readout of 4ß-HC in monkey provides the valuable insight in a timely manner without performing the isolation of liver tissue or monkey hepatocyte induction study or monkey DDI study.
- By applying PBPK approach in preclinical species with the measured in vitro data and observed PK profiles, one can form a strategy with a relatively higher confidence on key parameter prediction for human PK and DDI risk assessment.

Acknowledgements

Peter Fan

Susan Wong

Jonathan Wang

Brian Dean

Cornelis E. C. A. Hop

Matthew Wright

Yuan Chen

Back-up

Human PK prediction strategy using PBPK approach

Observed IV and PO PK profile in preclinical Species

Form a PBPK strategy on key parameters prediction for human based on four preclinical species

Measured in vitro data for preclinical

IVIVE Confidence

Predict human PK

Measured in vitro data for human