Induction: Drug Transporters versus Enzymes

Justin D. Lutz, Brian J. Kirby, John Ling, Angela Worth, Brian P. Kearney, Anita Mathias

Gilead Sciences, Inc., Foster City, CA

Transporter Induction:
How Do We Inform Our Labels?

- Difficult to predict in vivo transporter induction liability from in vitro data
- P450 induction parity is assumed

Transporter Induction:
Conservative/Minimal Guidance Due to Lack of Data

- Difficult to predict in vivo transporter induction liability from in vitro data
- P450 induction parity is assumed
- **Ultimately, overly conservative recommendations are adopted**
  - May restrict patient access to still efficacious therapy
- How do we fill in the gaps?
  - We generate data!

FDA

Transporter	Inducer
P-gp	Avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort, tipranavir/ritonavir
BCRP	Not known
OATP1B1	Not known
OATP1B3	Not known

EMA

If there are inducers of the transporter marketed within the EU, an interaction study with such an inducer is recommended.

FDA. Guidance for industry: drug interaction studies 2012;
EMA. Guideline on the investigation of drug interactions 2013.

Rifampin: a Prototypical In Vivo PXR Agonist

Probe Drug Cassette		Dose	Abbreviation	P450/Transporter	Cassette Day
Dabigatran etexilate*		75 mg	DE	P-gp	1
Pravastatin		20 mg	PRA	OATP	3
Rosuvastatin		10 mg	ROS	OATP/BCRP	5
Cocktail	Midazolam	2 mg	MDZ	CYP3A	7
	Tolbutamide	500 mg	TOL	CYP2C9	
	Caffeine	200 mg	CAF	CYP1A2	

*DE was analyzed as total dabigatran (TDAB), the sum of conjugated and unconjugated active species.

- Are transporters as inducible as P450s?
- Can transport induction be predicted from P450s?

Rifampin: Multiple Dose Levels to Elicit Weak, Moderate, and Strong Induction

Study Design

	Days 1–8	9–18	19–26	27–36	37–44
	Cassette		Cassette		Cassette
Cohort 1 n=20		RIF 10 mg qd		RIF 75 mg qd	
Cohort 2 n=20		RIF 2 mg qd		RIF 600 mg qd	

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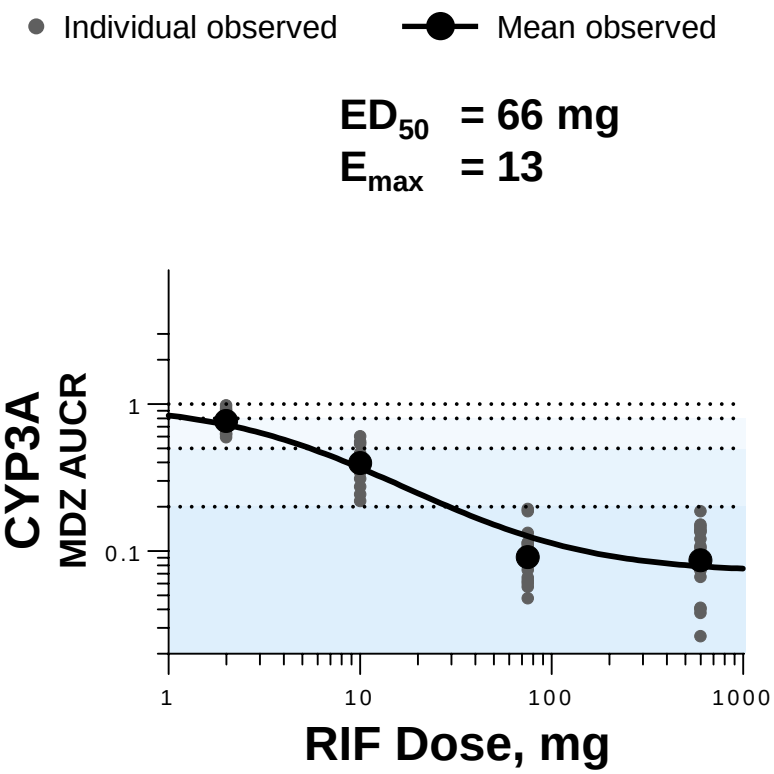
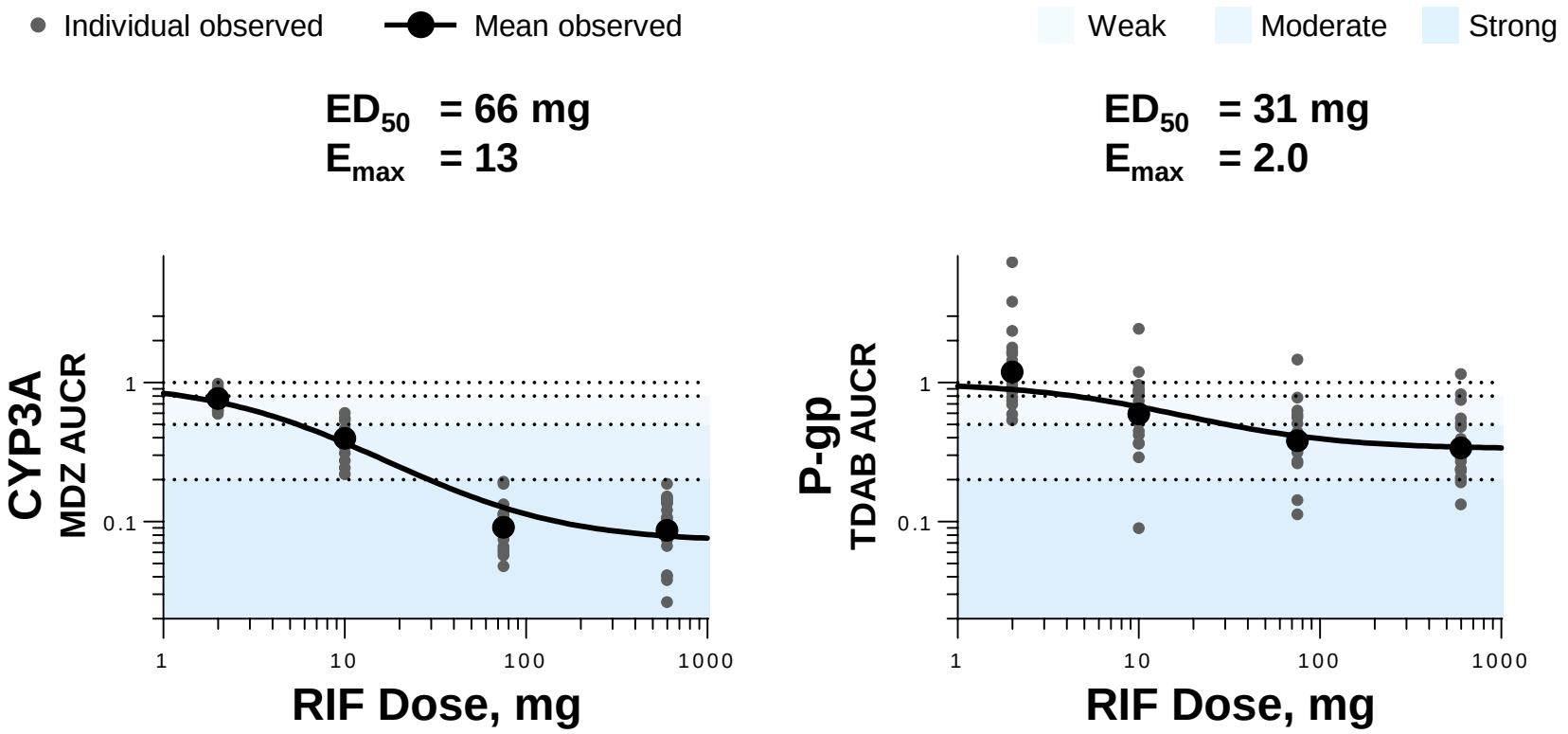
Probe Induction As a Function of RIF Dose



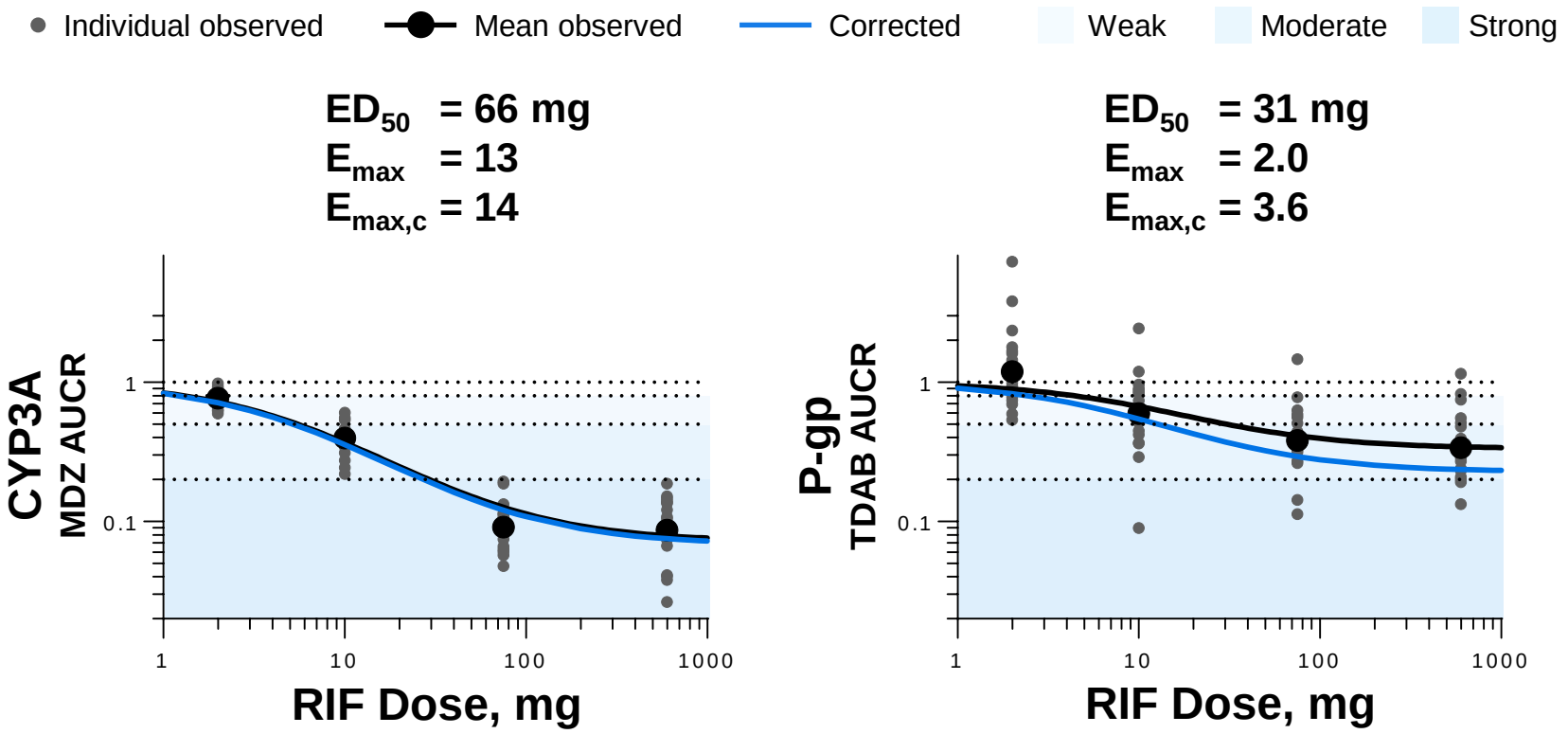
- E_{max} and ED_{50} values were estimated for each probe
- AUC Ratio: Weak (0.5–0.8), moderate (0.2–0.5) and strong (<0.2) induction

Dabigatran Is Less Inducible Than Midazolam



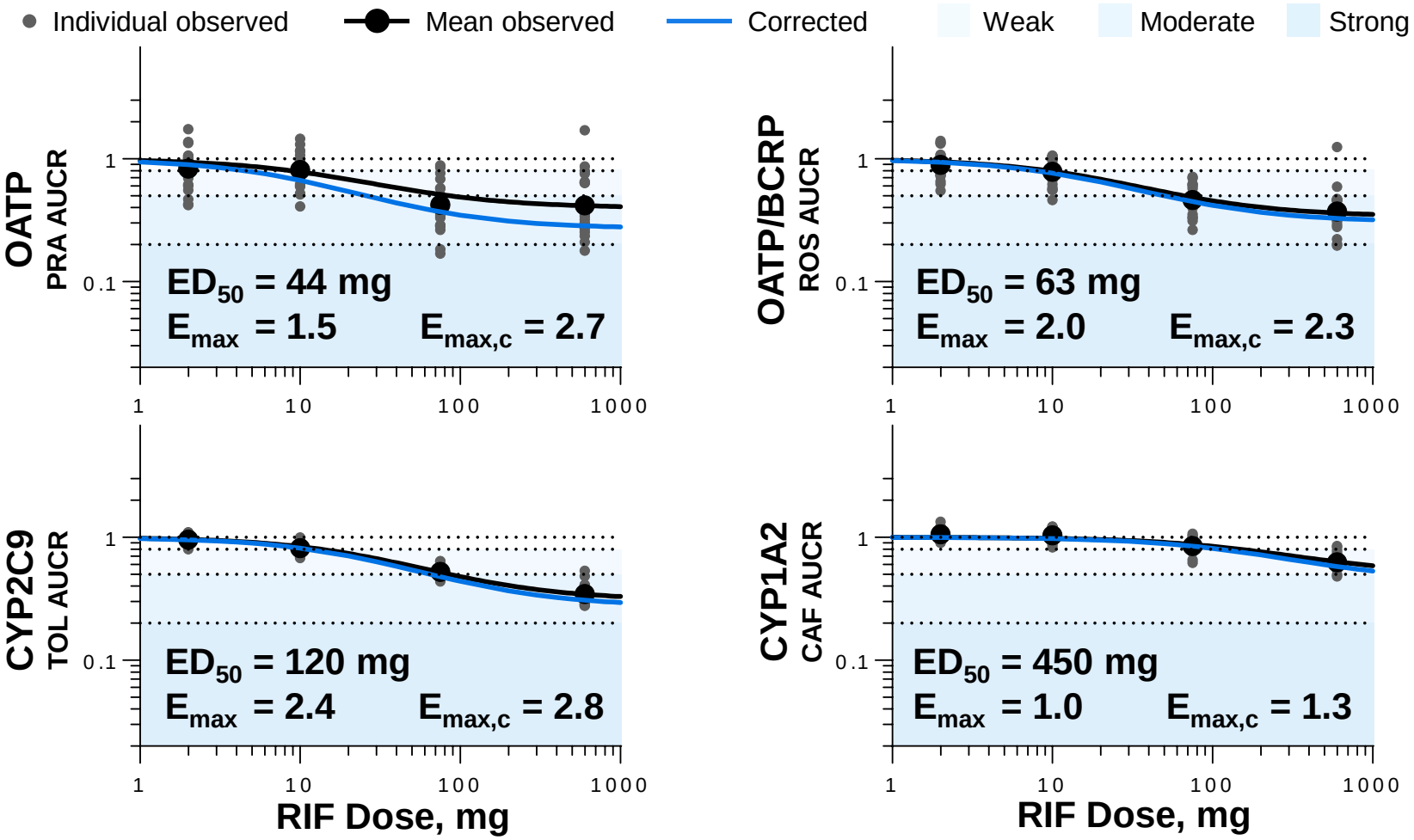
- Are differences due to probe sensitivity?

After Accounting for Probe Sensitivity: P-gp is Less Inducible than CYP3A



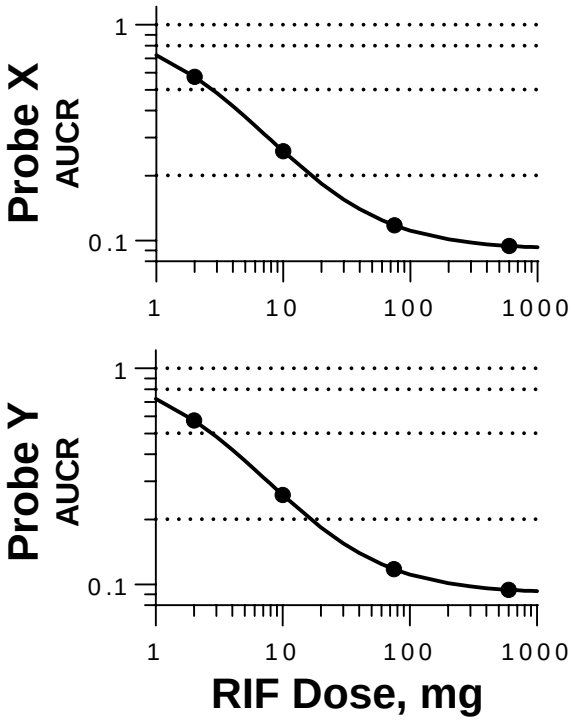
- $E_{max,c}$ = E_{max} corrected for (divided by) differences in probe sensitivity ($f_{m/t}$)
- Strong P-gp induction (>5-fold CL increase) is unlikely to be observed

Similar to P-gp, Only Moderate Induction of OATP and CYP2C9 Is Observed



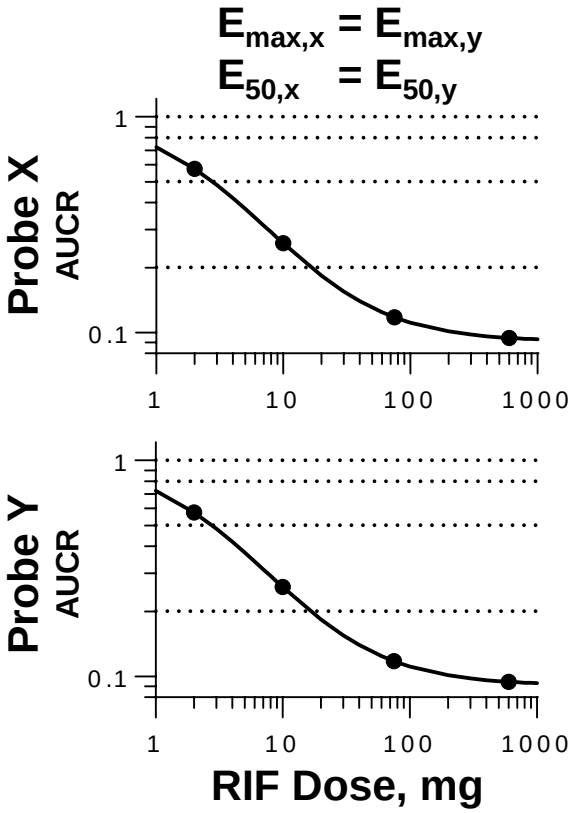
- PRA and ROS results suggest that OATP, but not BCRP, is induced
- RIF may elicit weak induction of CYP1A2 via PXR crosstalk or weak AHR agonism

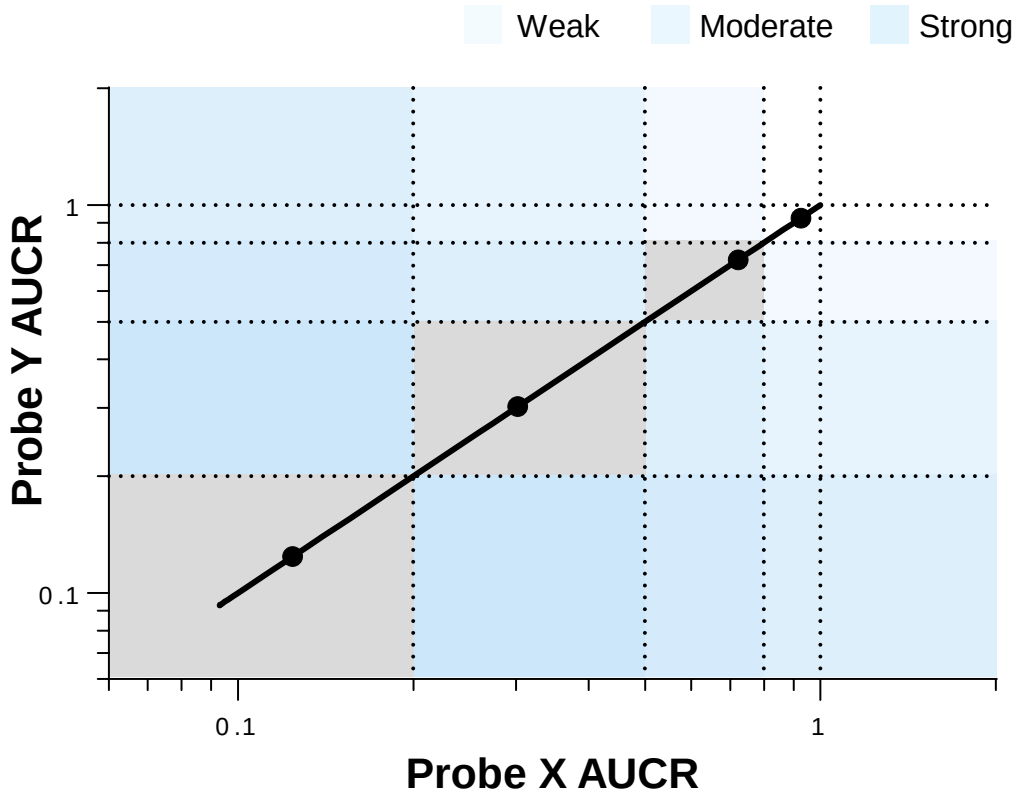
How Do We Characterize and Interpret Relationships Between Probes?



- Can we predict Probe Y induction based on Probe X?

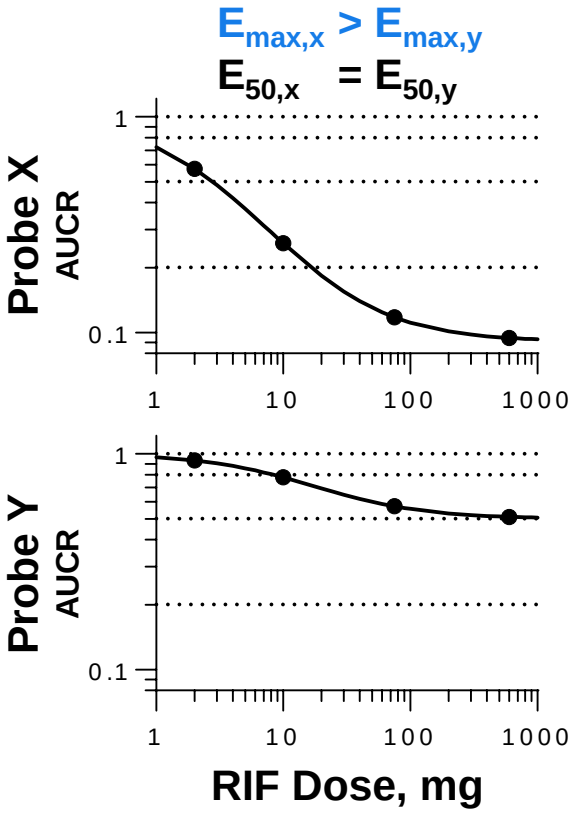
Linear Relationships Only Occur When E_{max}/ED_{50} Are Similar

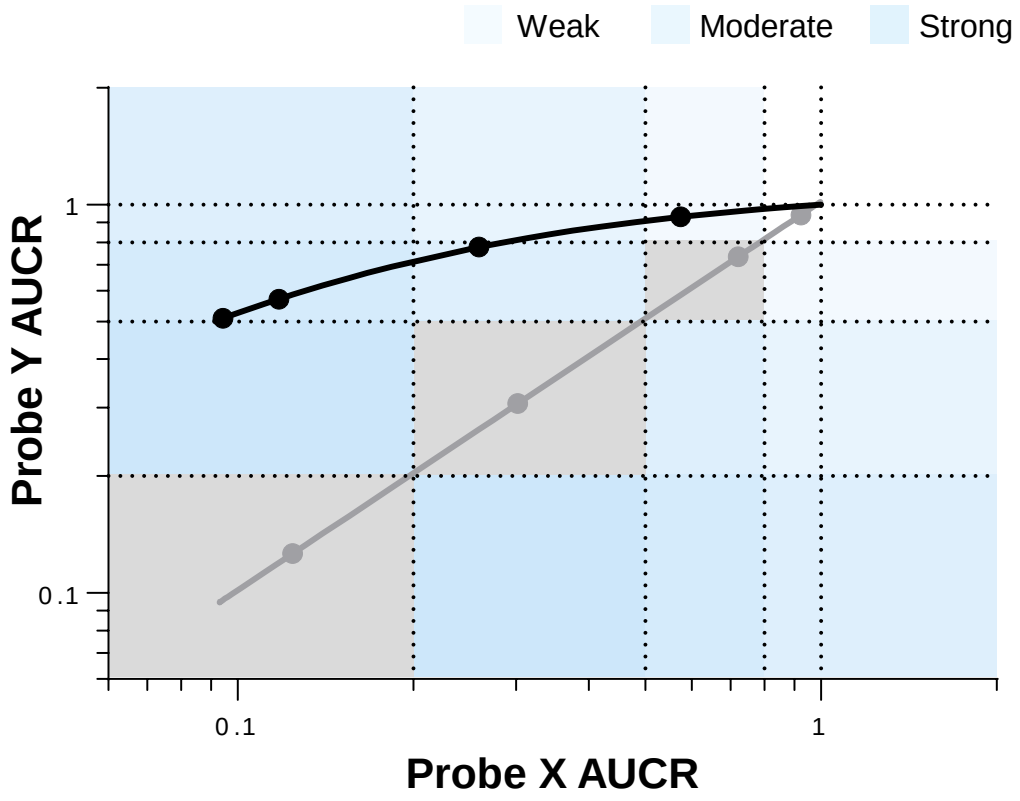




- **Combining E_{max}/ED_{50} curves allows for evaluation of PXR agonism, independent of RIF**
- Gray areas represent similar induction between probes

Nonlinear Relationships Occur When Induction Capacity is Different





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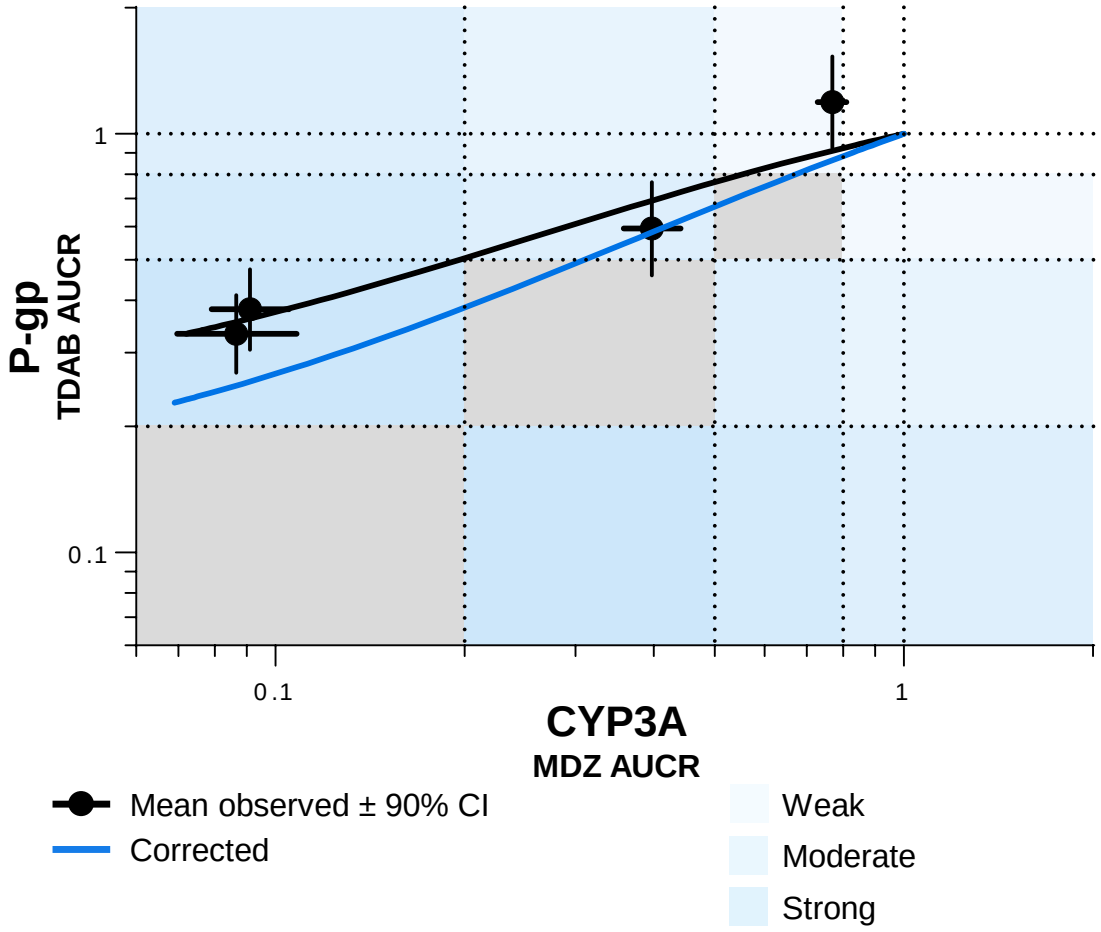
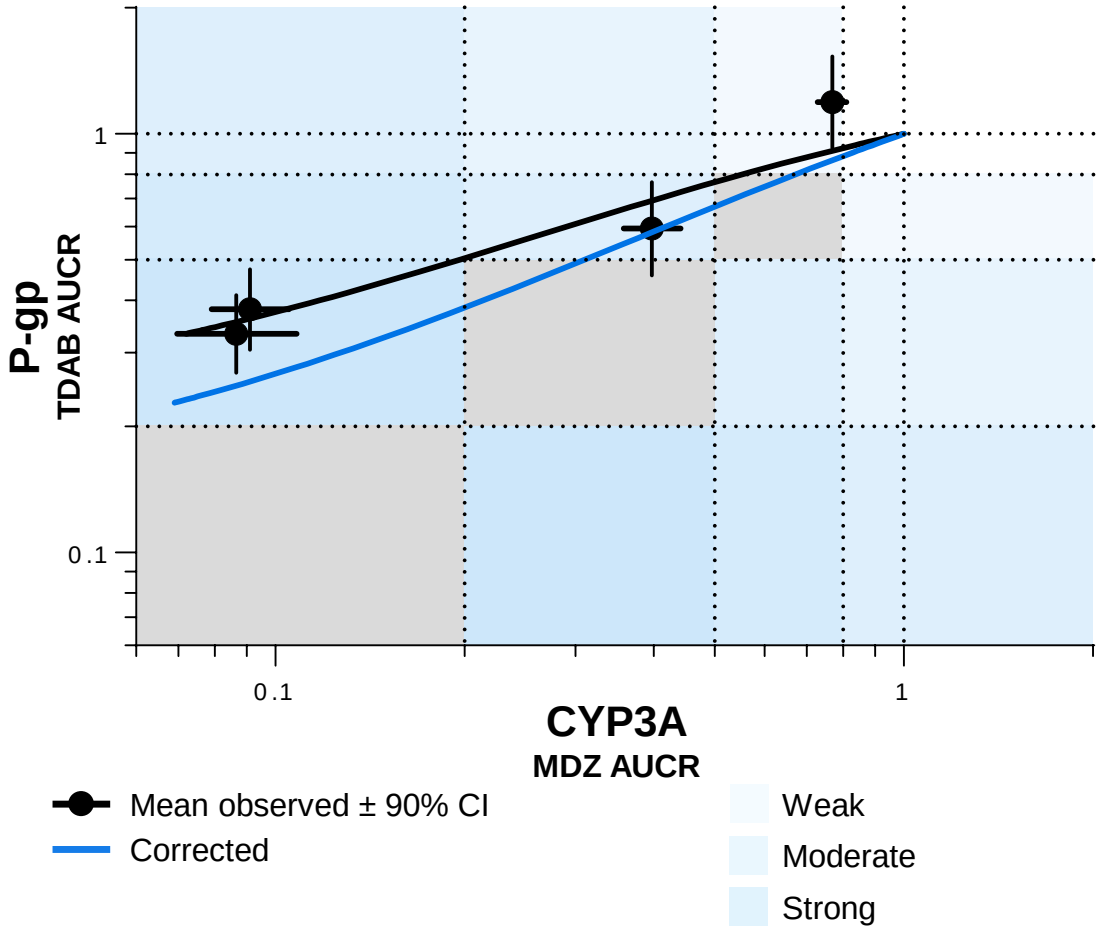
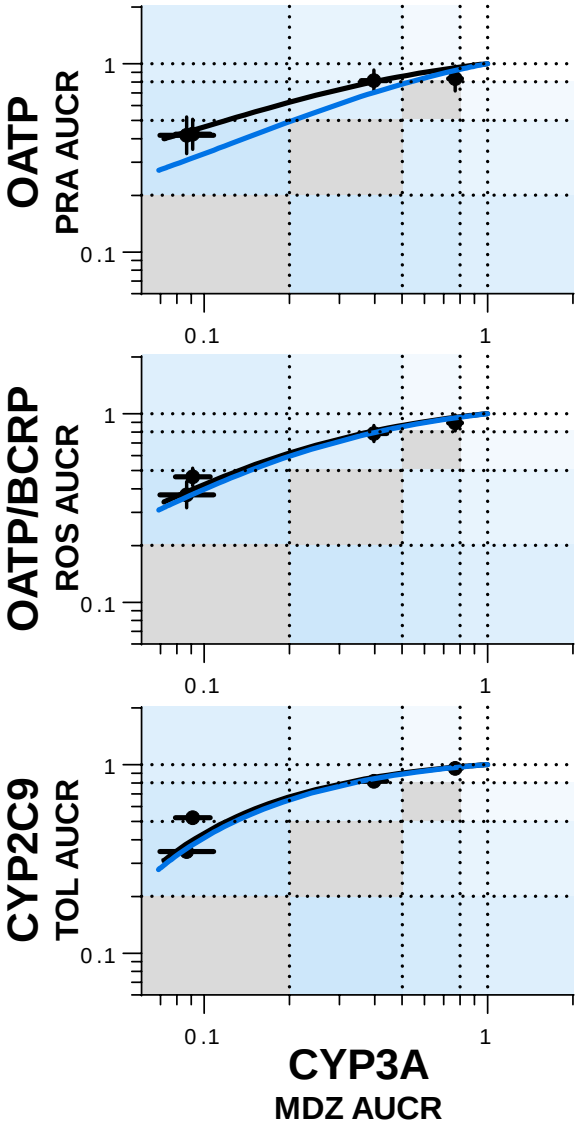
Induction of P-gp is One DDI Category Weaker Than CYP3A



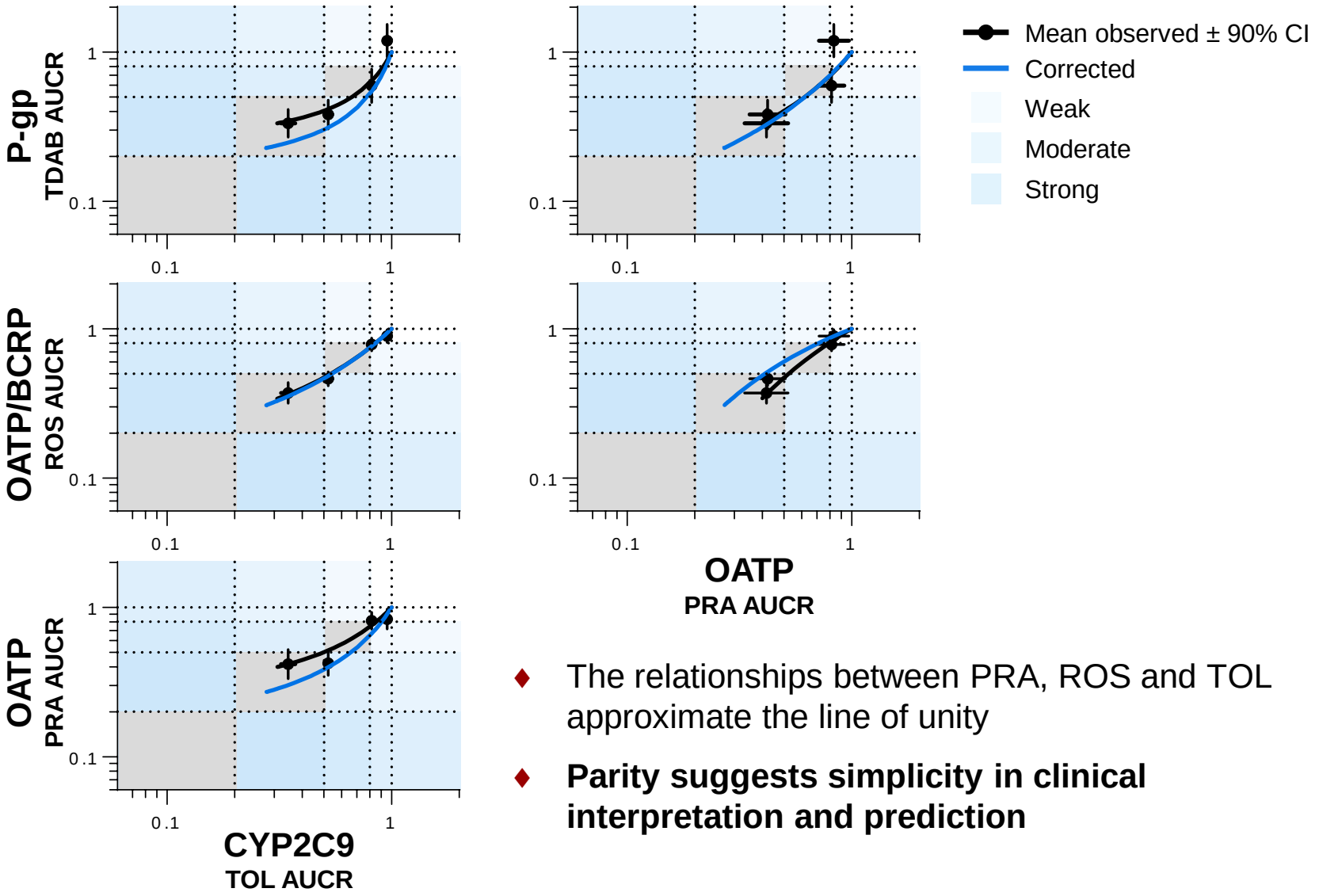
Similarly, OATP and CYP2C9 Induction Is Always Less than CYP3A





- This relationship holds true even after accounting for probe sensitivity

P-gp, OATP and CYP2C9 Demonstrate Induction DDI Classification Equivalence



- The relationships between PRA, ROS and TOL approximate the line of unity
- **Parity suggests simplicity in clinical interpretation and prediction**

What are the Clinical Implications?

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  Standardize DDIs and facilitates extrapolation

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- Observed relationships should apply to other inducers

  This hypothesis is currently being tested with rifabutin and carbamazepine

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  - Standardize DDIs and facilitates extrapolation
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- Observed relationships should apply to other inducers
  - This hypothesis is currently being tested with rifabutin and carbamazepine
- Application of these results could provide for
  - **More informed labeling recommendations**
  - **Decreased # of DDI studies via better leveraging of available data**

Acknowledgments

We extend our thanks to the study subjects.

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$E_{max,c}$ is P450/transporter (not probe) specific
$f_{m/t}$ only attenuates (not limits) AUCR