Drug Transporter Induction:
Can We Leverage P450 Data to Streamline Our Clinical Pharmacology Programs?

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Transporter Induction: Uncertainty Negatively Affects Development/Labeling

- Assumed parity between transporters and CYP3A induction, but what if this isn't true?
  - If DDI study performed: Possibly unnecessary study
  - If DDI study not performed: Conservative labeling

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  - If DDI study performed: Possibly unnecessary study
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- Clinically relevant, known or potential strong CYP3A inducers assumed to be strong P-gp inducers
  - Rifampin
  - St. John's Wort
  - Carbamazepine
  - Rifabutin
  - Rifapentine
  - Tipranavir/Ritonavir
  - Phenytoin
  - Phenobarbital

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  - Tipranavir/Ritonavir
  - Phenytoin
  - Phenobarbital
- Co-regulation of many transporters and P450s
  - Can one P450 induction study tell us anything about transporters?

Overview of Presentation: 3 Questions

1. Can P-gp induction be predicted from CYP3A?
2. Can induction of other transporters/P450s be predicted from CYP3A?
3. What are the implications for clinical development?

Rifampin: Dose Level Titration to Elicit Weak, Moderate, and Strong Induction

Study Design, Part 1

	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	

- Rifampin (RIF) is a prototypical PXR agonist

Kharasch et al. Clin Pharmacol Ther 2011

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Cohort 1, n=20		RIF 10 mg qd		RIF 75 mg qd	
Cohort 2, n=20		RIF 2 mg qd		RIF 600 mg qd	

- Rifampin (RIF) is a prototypical PXR agonist
- Adaptive design attempting to target weak, moderate and strong CYP3A induction

Kharasch et al. Clin Pharmacol Ther 2011

Focused on P-gp vs. CYP3A, But What Else Can We Learn From This Study?

Probe Drug Cassette		Dose	Abbreviation	Transporter/P450	Dosing 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.

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- Are transporters as inducible as P450s?
- Is there a relationship between transporter and P450 induction?

Verification Step 1: Carbamazepine (CBZ) and Rifabutin (RBT)

Study Design, Part 2

	Days 1–9	10–26	27–35
	Cassette		Cassette
Cohort 3, n=24		Escalated to CBZ 300 mg bid	

	Days 1–9	10–20	21–29
	Cassette		Cassette
Cohort 4, n=20		RBT 300 mg qd	

- Do RIF relationships predict other inducers?

Verification Step 2: Sofosbuvir (SOF), a P-gp Substrate

Study Design, Part 2

	Days 1–9	10–26	27–35
	Cassette + SOF		Cassette + SOF
Cohort 3, n=24		Escalated to CBZ 300 mg bid	

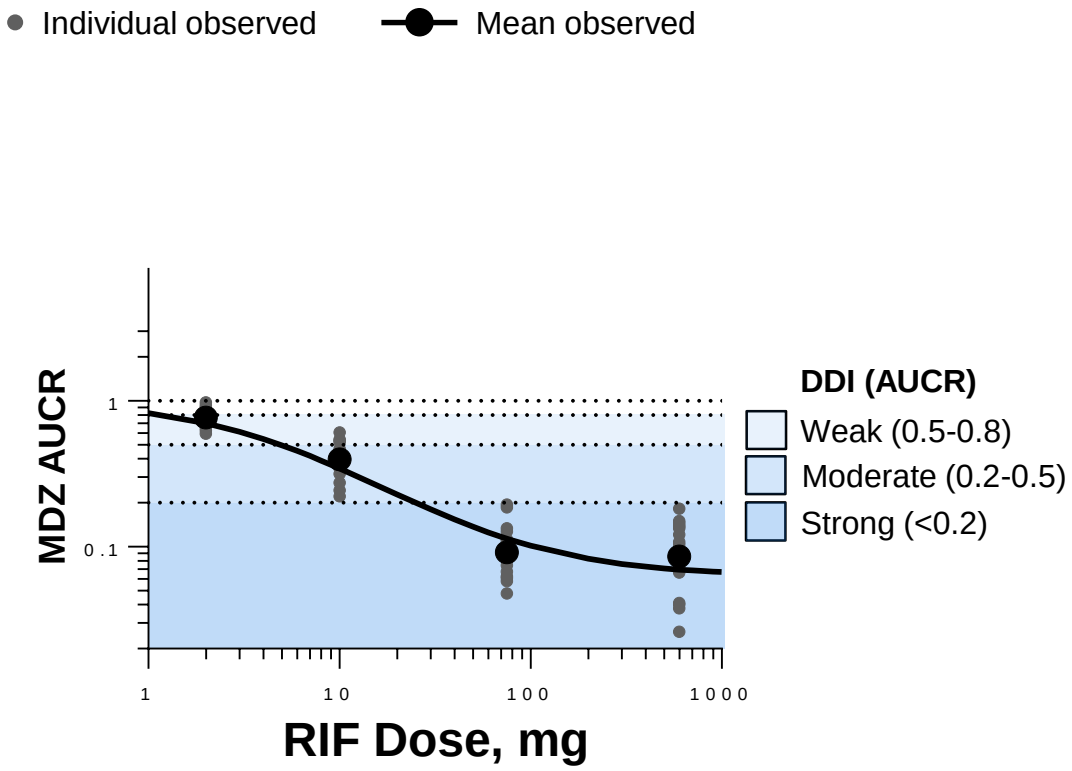
	Days 1–9	10–20	21–29
	Cassette + SOF		Cassette + SOF
Cohort 4, n=20		RBT 300 mg qd	

- Do RIF relationships predict other inducers?
- Do RIF relationships predict other drug transporter substrates?

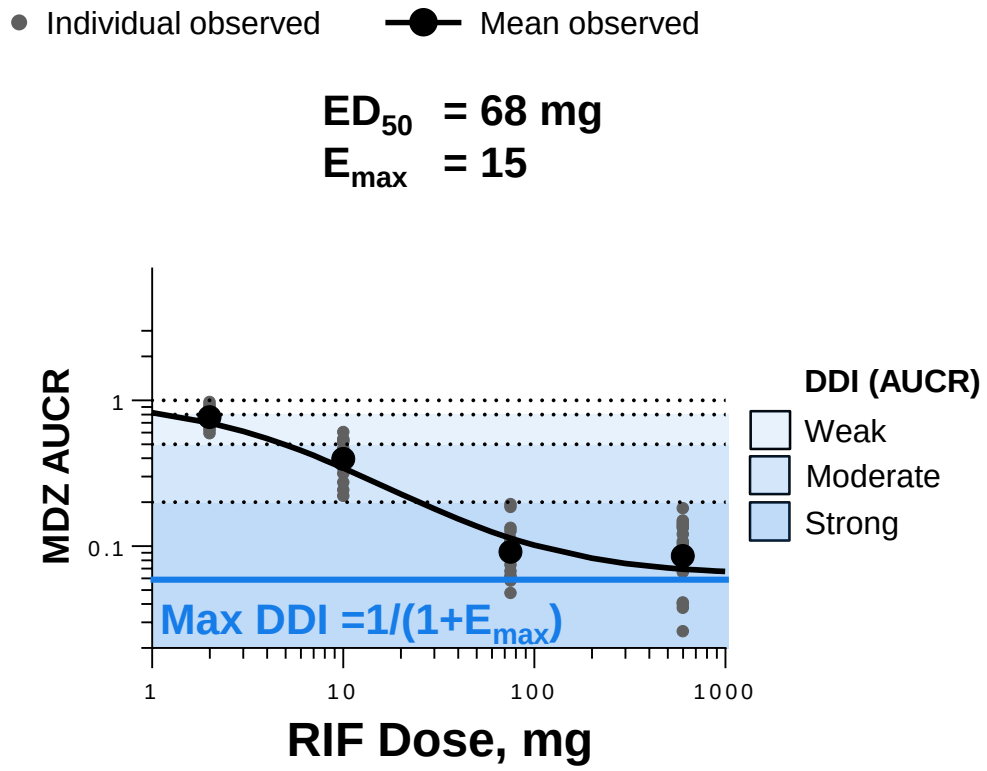
Overview of Presentation: 3 Questions

1. Can P-gp induction be predicted from CYP3A?
   - **Establish:** Relative RIF induction between probes
   - **Verify (Step 1):** P-gp induction by RBT and CBZ
   - **Verify (Step 2):** Decreased SOF exposure
2. Can induction of other transporters/P450s be predicted from CYP3A?
3. What are the implications for clinical development?

Probe Induction As a Function of RIF Dose

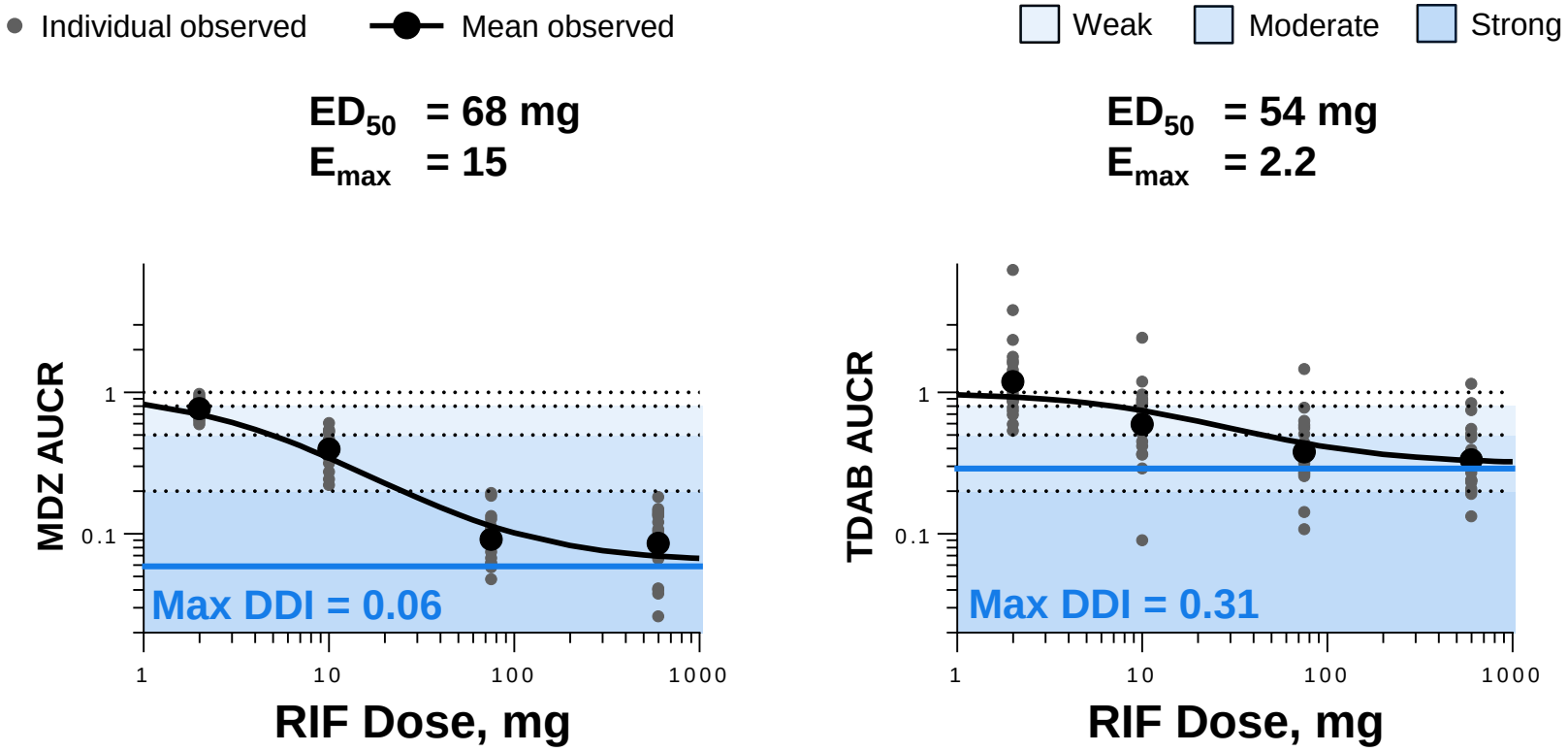


E_{max} and ED_{50} values were estimated for each probe



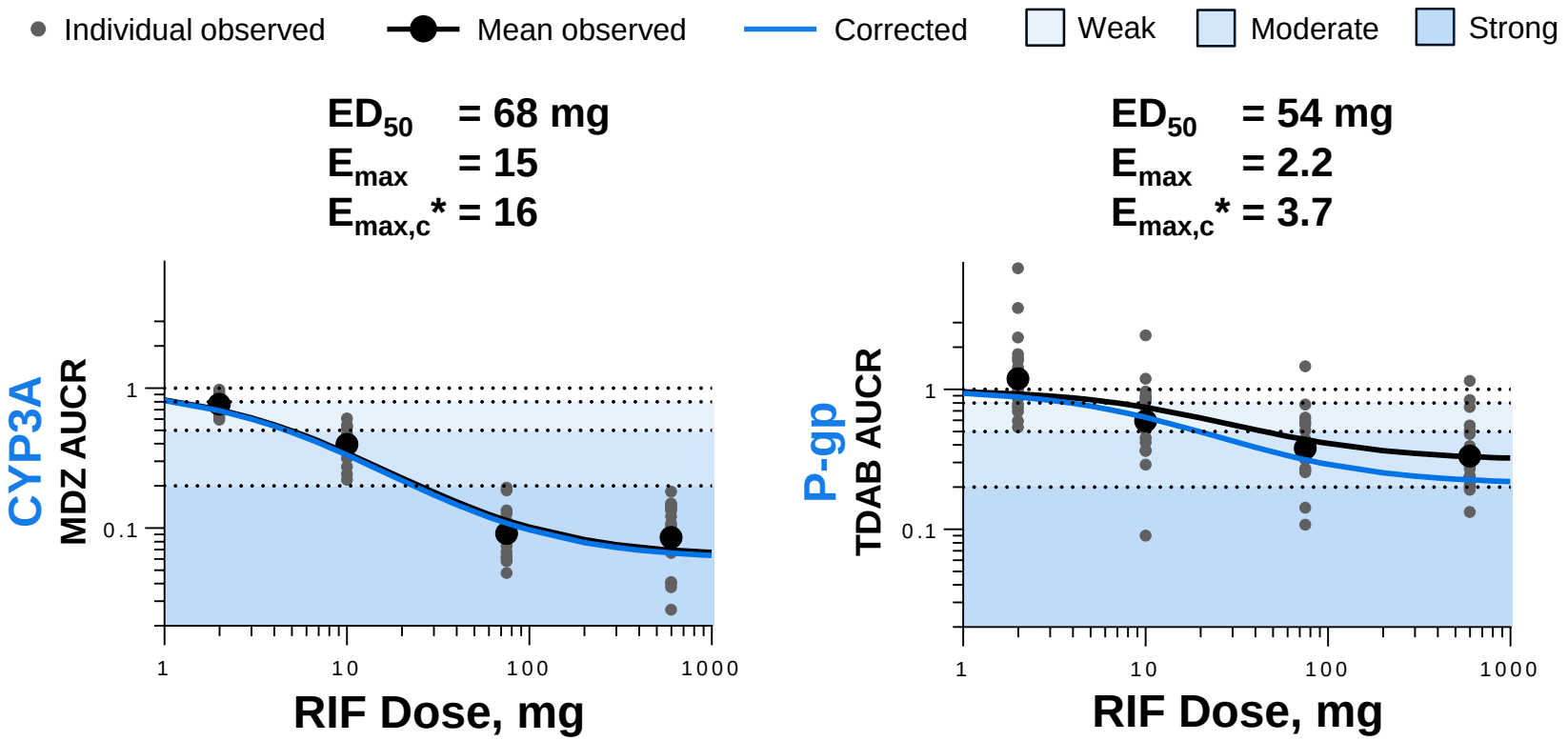
- ED_{50} and E_{max}: Induction affinity versus capacity

Midazolam Exposure is Decreased More Than Dabigatran



- Are differences due to probe sensitivity?

P-gp is Less Inducible than CYP3A

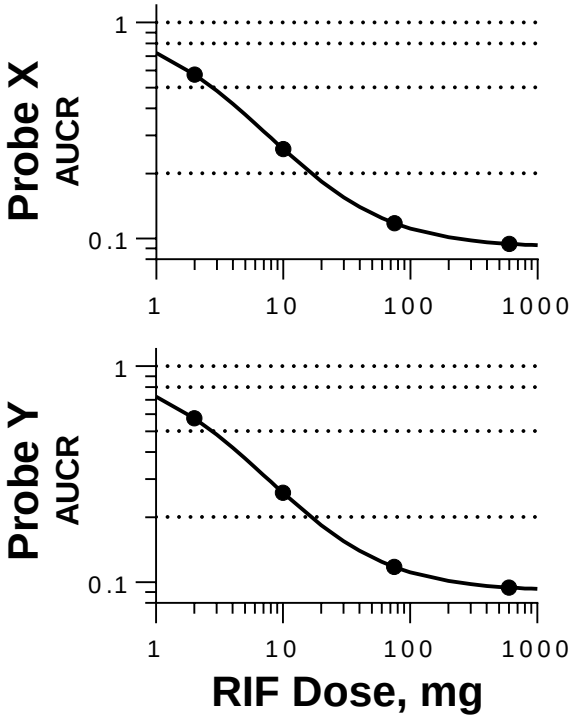


*$E_{max,c}$ = E_{max} corrected for differences in probe sensitivity ($f_{m/t}$)

- Strong P-gp induction (>5-fold CL increase) is unlikely to be observed

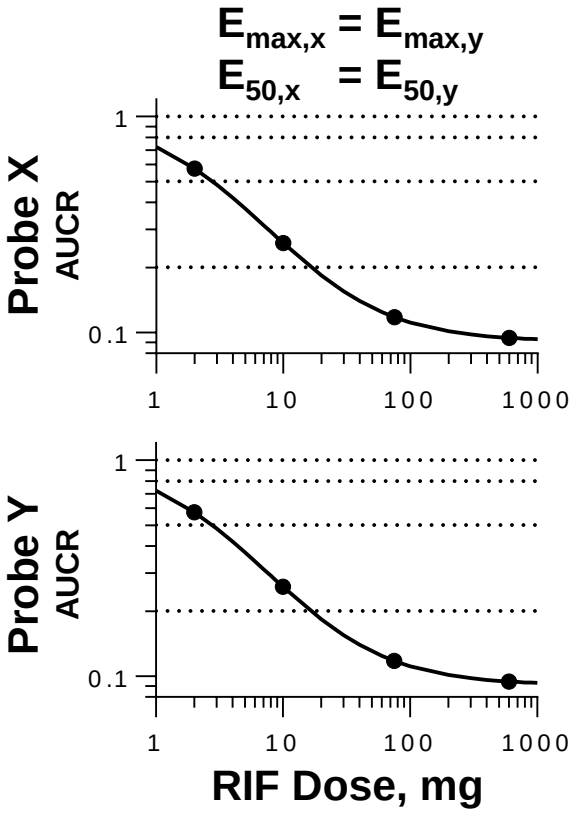
DE f_t: Hartter et al. Br J Clin Pharmacol 2013

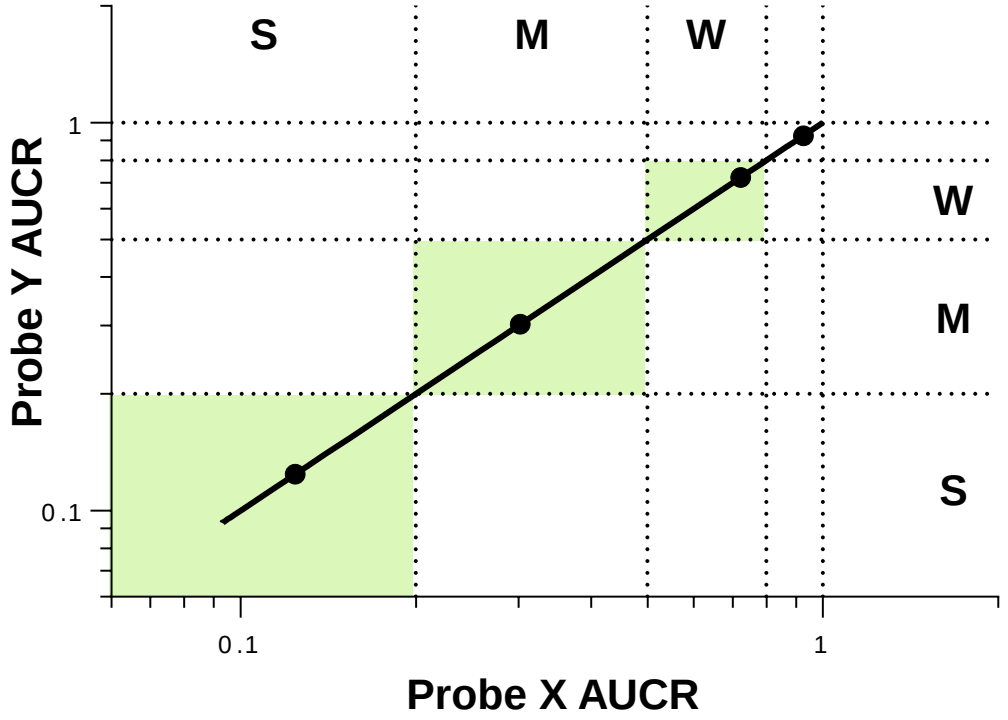
How Do We Characterize and Interpret Relationships Between Probes?



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

Example 1: Induction Parity Only Occurs When E_{max}/ED_{50} Are Similar

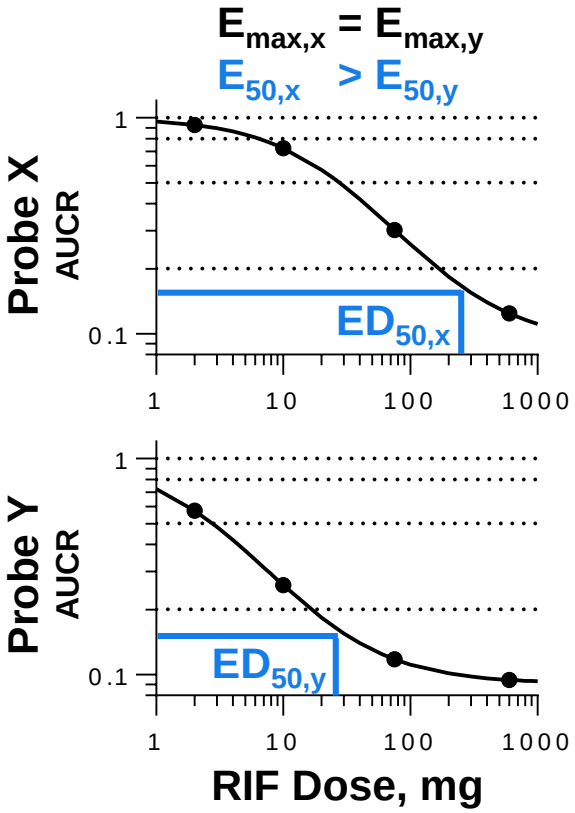


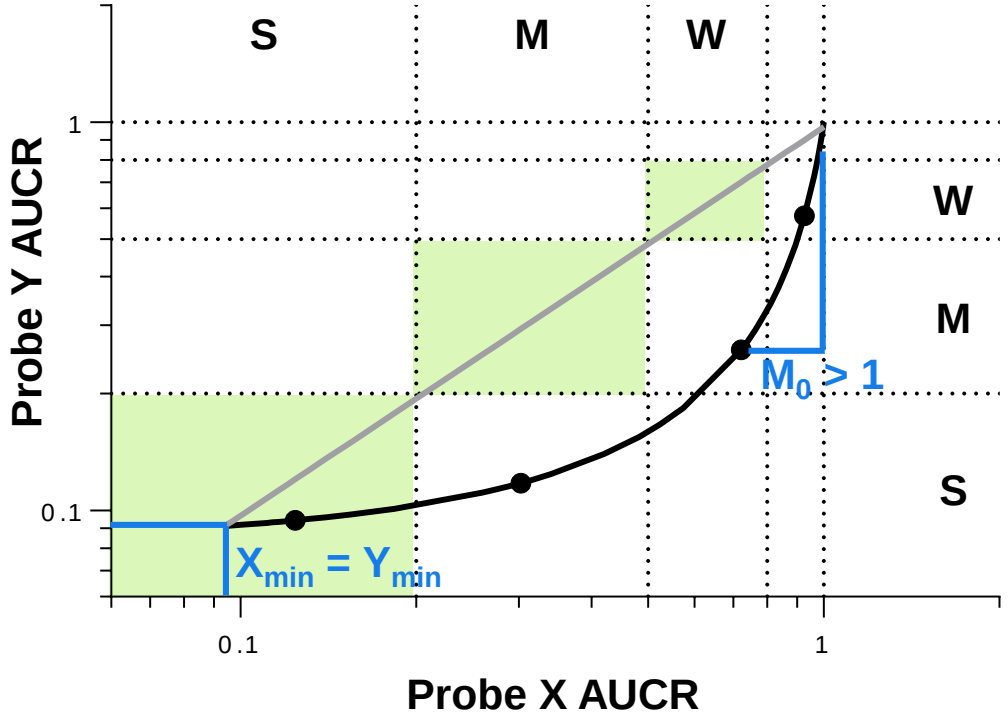


Green areas represent similar induction between probes

- Combining E_{max}/ED_{50} curves allows for evaluation of relative induction, independent of inducer

Example 2: Line Falls Outside of Area of Parity When Induction Affinity is Different

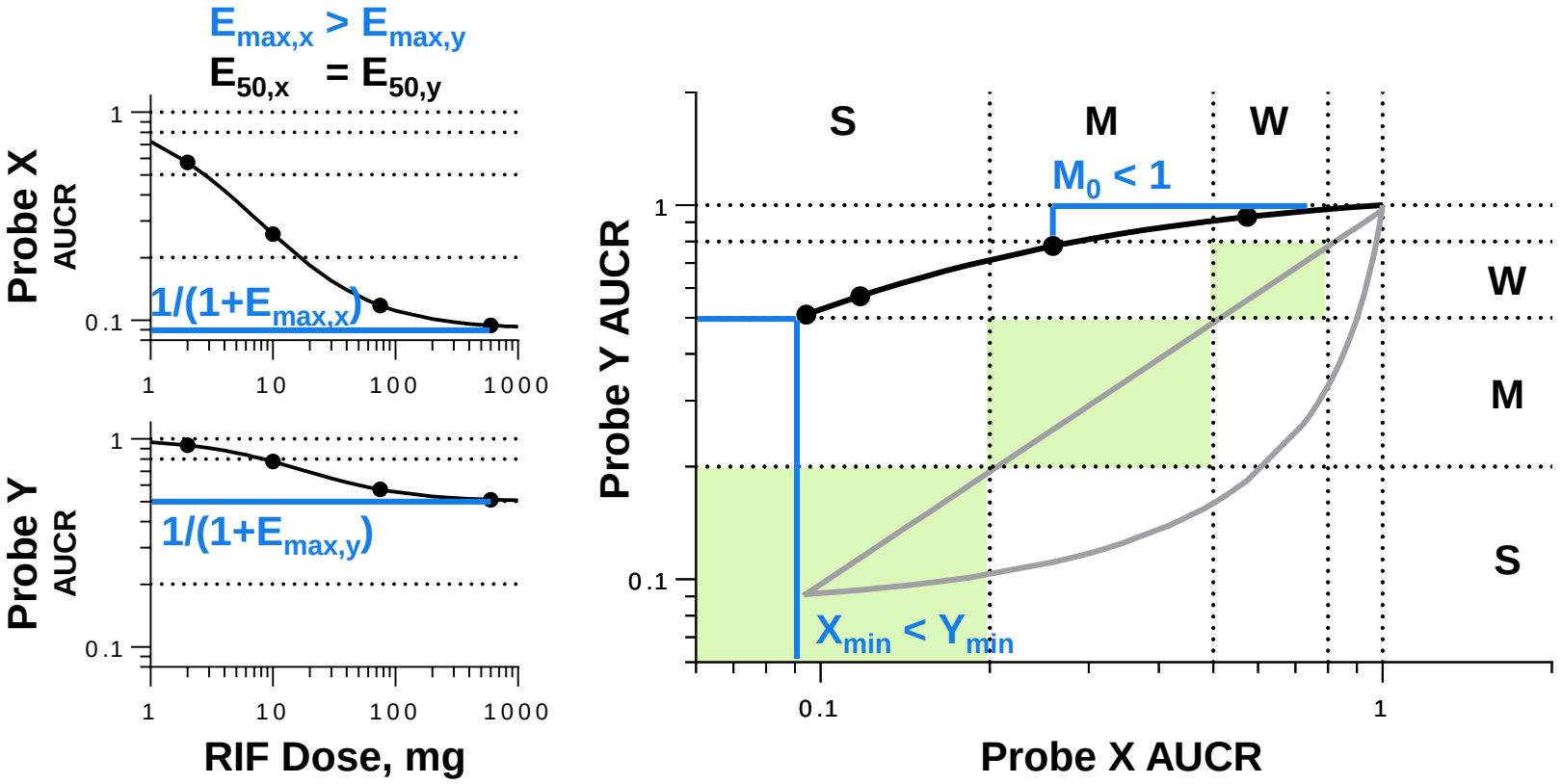




Green areas represent similar induction between probes

- Combining E_{max}/ED_{50} curves allows for evaluation of relative induction, independent of inducer

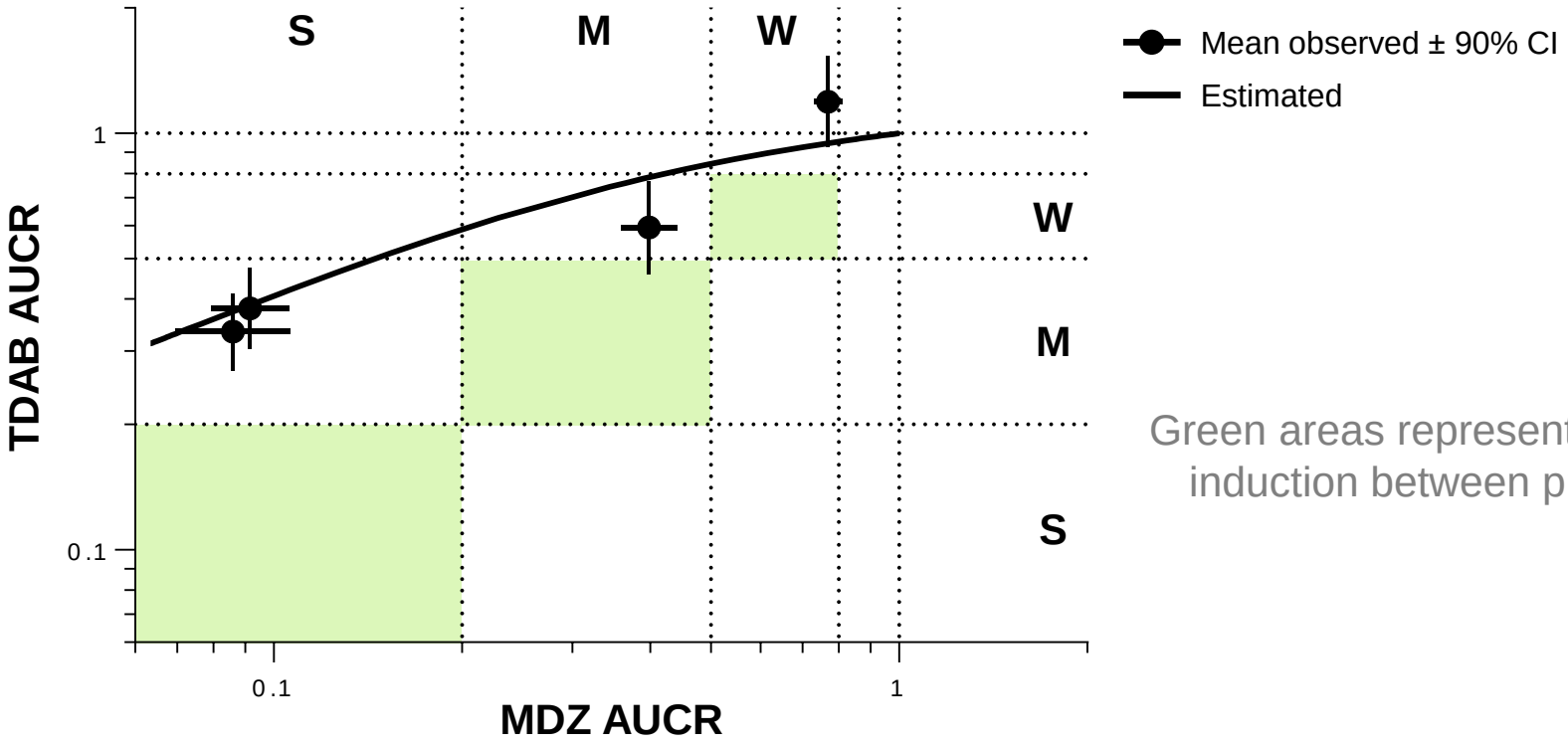
Example 3: Line Falls Outside of Area of Parity When Induction Capacity is Different



Green areas represent similar induction between probes

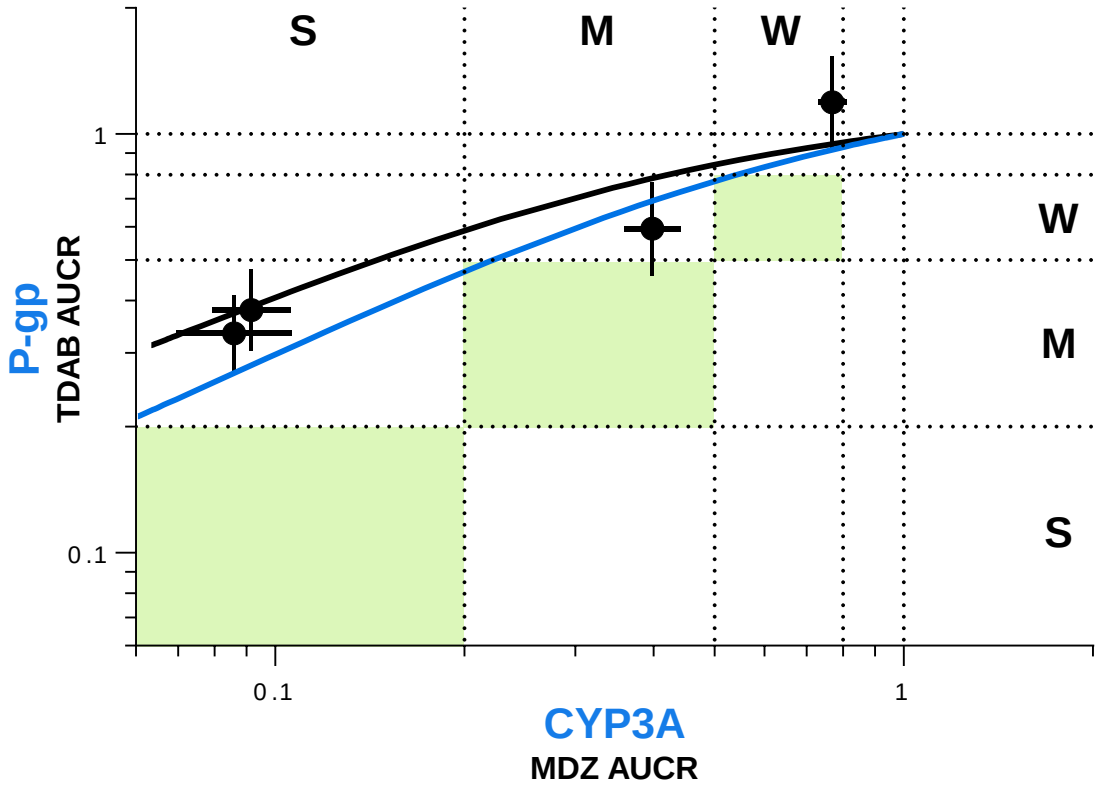
- Combining E_{max}/ED_{50} curves allows for evaluation of relative induction, independent of inducer

MDZ AUCR is Decreased More Than TDAB AUCR Across DDI Categories



Green areas represent similar induction between probes

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

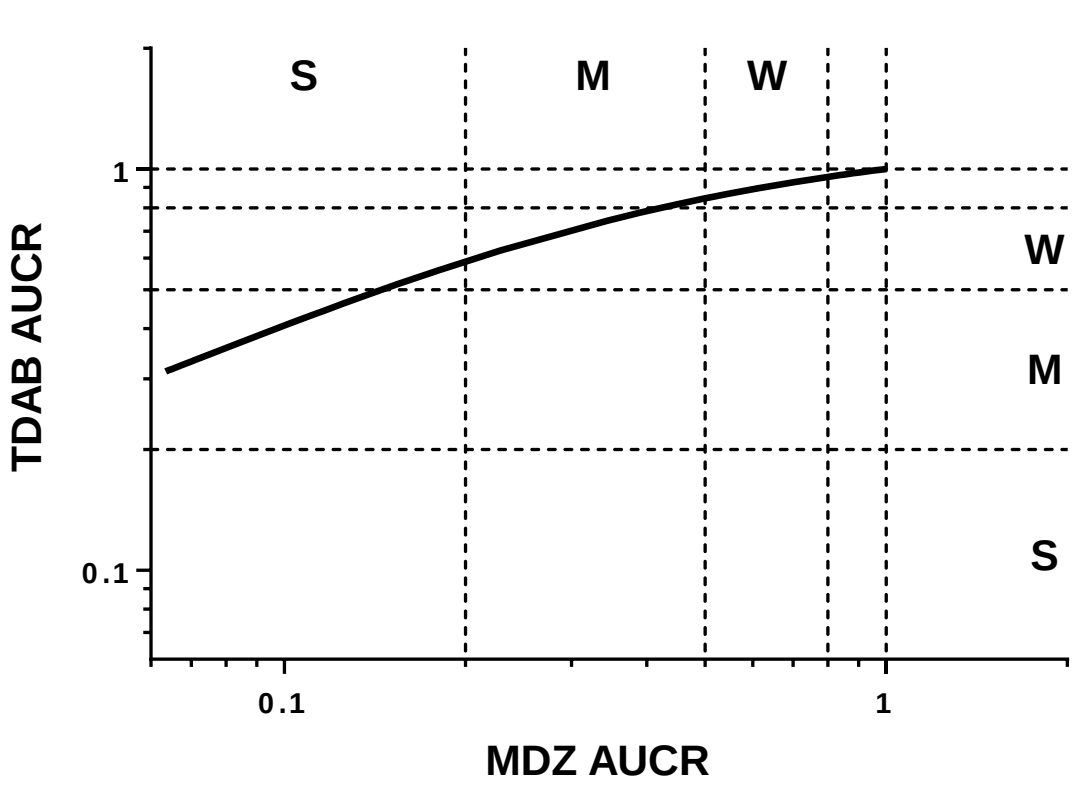


Mean observed ± 90% CI
Estimated
Corrected

Green areas represent similar induction between probes

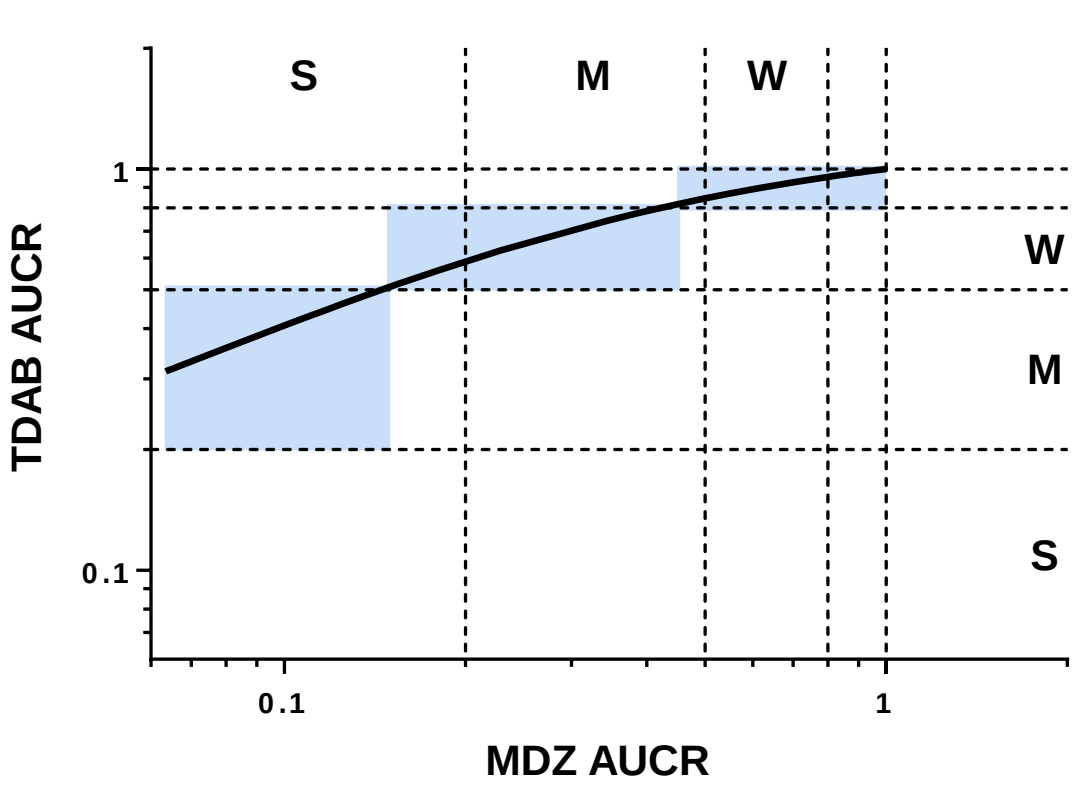
- This relationship holds true when correcting for probe fraction metabolized/transported ($f_{m/t}$)

How Do We Predict P-gp Induction by CBZ and RBT? Back to Basics



Black line is RIF
MDZ – TDAB relationship

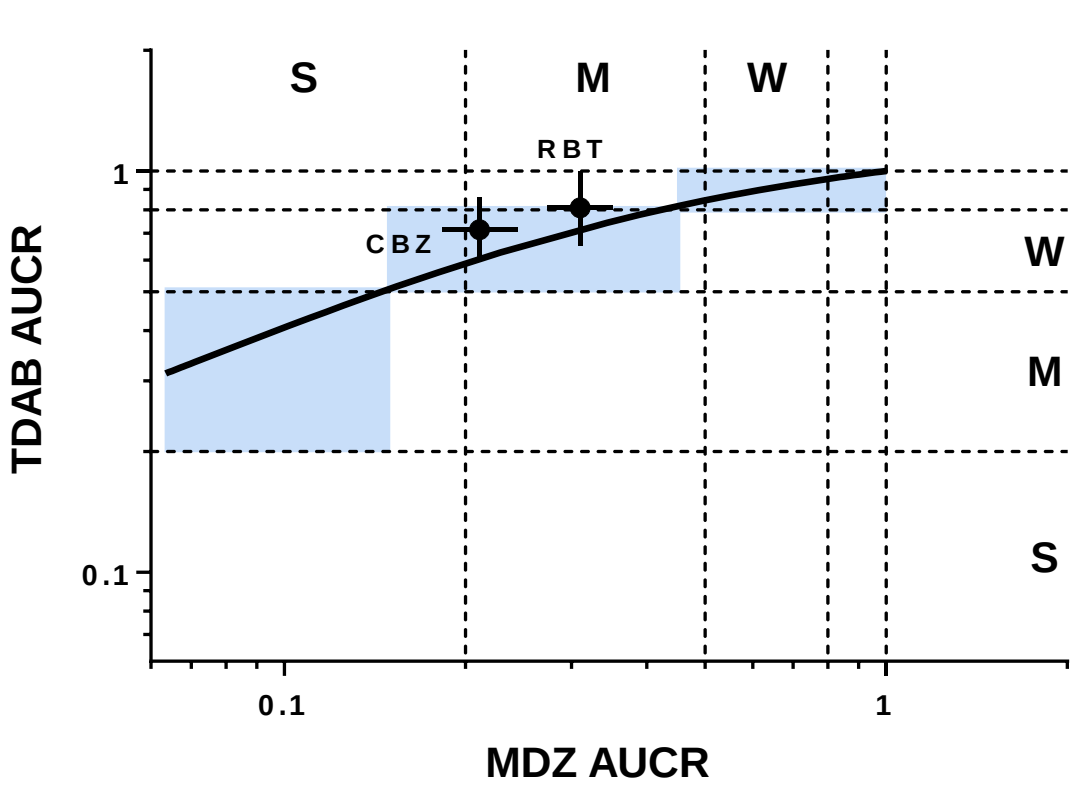
RIF Induction Relationship: Directly Applied for CBZ and RBT Prediction



Black line is RIF MDZ – TDAB relationship

Blue area is predicted TDAB DDI category based on observed MDZ DDI

P-gp Induction by CBZ and RBT is Predicted by the RIF CYP3A – P-gp Relationship



Estimated

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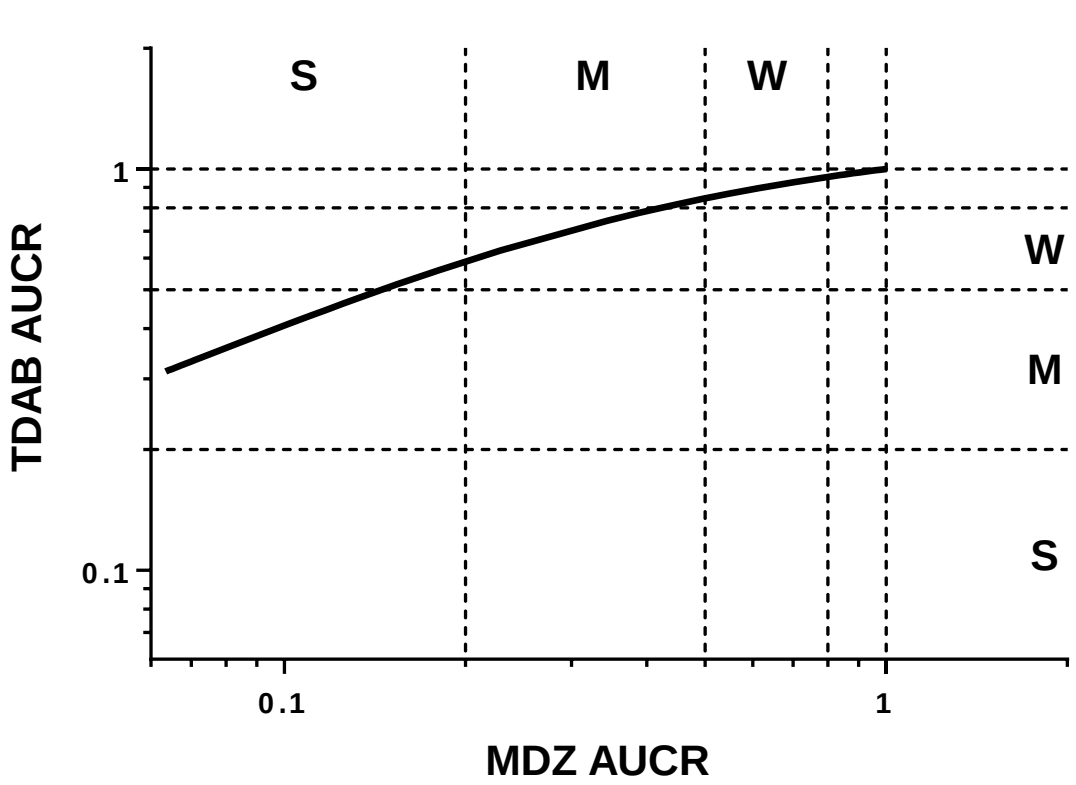
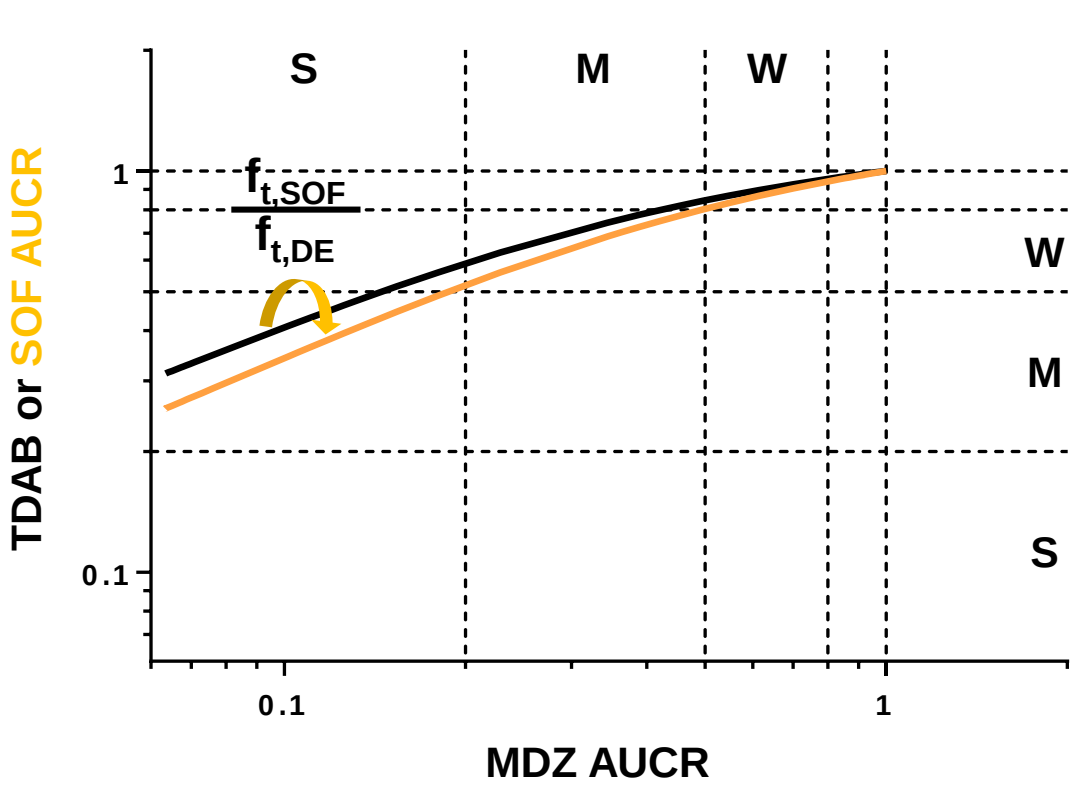
How Do We Predict SOF Exposure Decrease? Back to Basics



Black line is RIF
MDZ – TDAB relationship

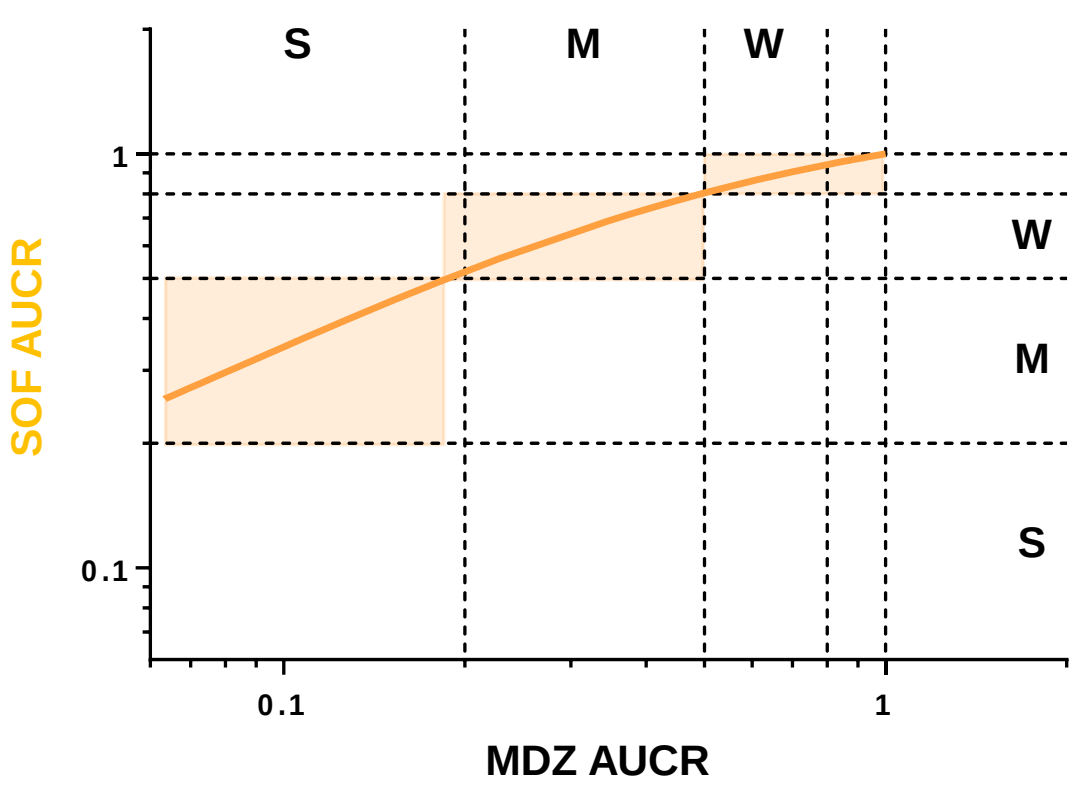
SOF AUCR Can Be Predicted From TDAB AUCR



Black line is RIF
MDZ – TDAB relationship

Orange line is predicted
MDZ – SOF Relationship

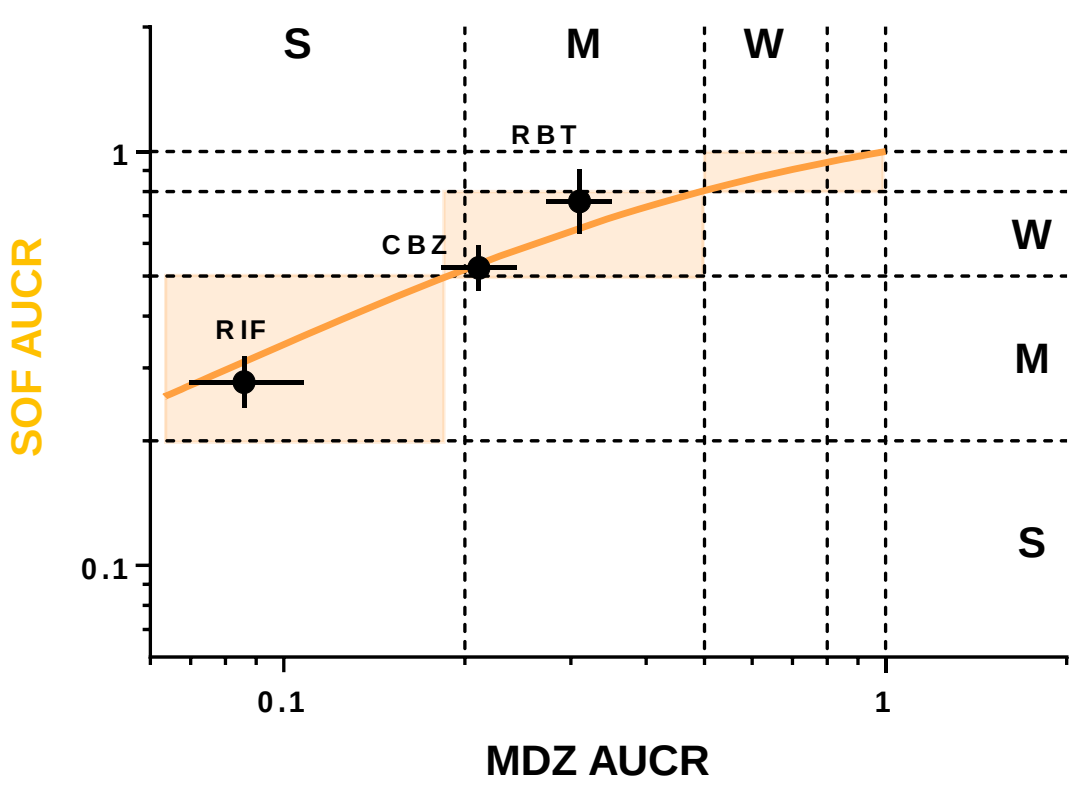
“New SOF Relationship” Determines the SOF DDI Category at any MDZ AUCR

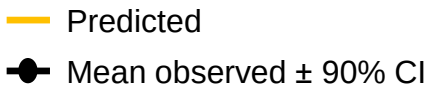


Orange line is predicted MDZ – SOF relationship

Orange area is predicted SOF DDI category based on observed MDZ DDI

Effect of RIF, CBZ and RBT on SOF is Predicted by MDZ – TDAB Relationship





Orange line is predicted MDZ – SOF relationship

Orange area is predicted SOF DDI category based on observed MDZ DDI

- CBZ and RBT considered moderate CYP3A inducers based on MDZ
  - Elicit weak induction of SOF CL/F (AUC ≥0.50)

RIF-SOF DDI: Kirby et al. Clin Pharmacokinet 2015

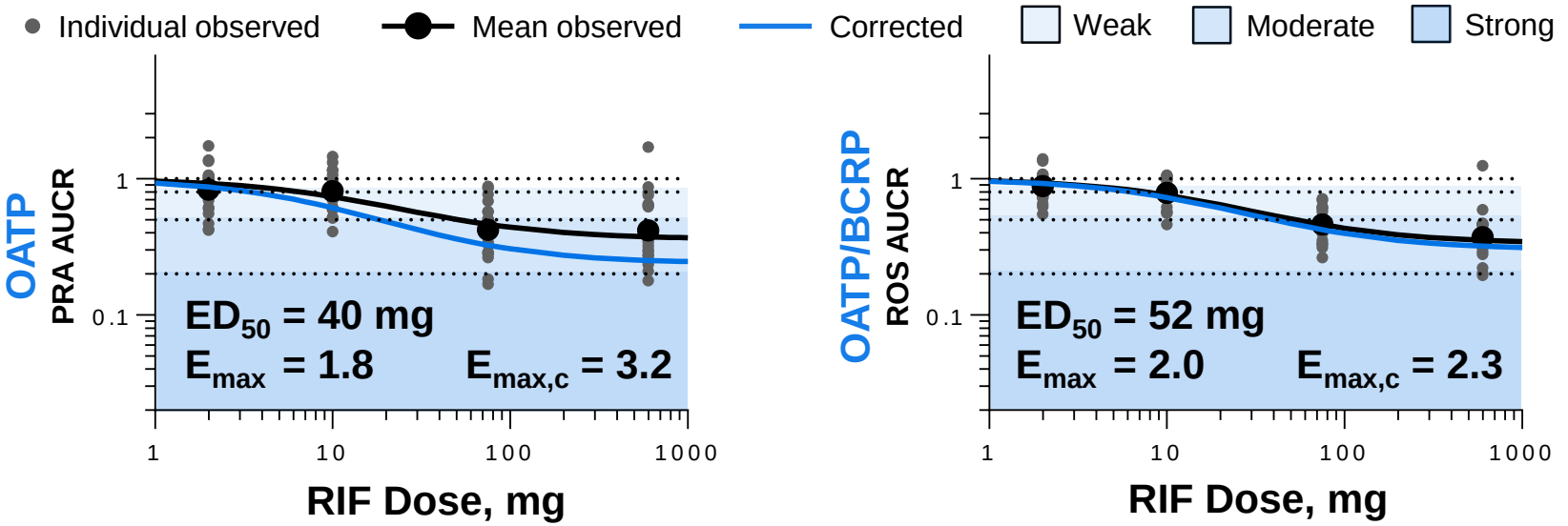
Overview of Presentation: 3 Questions

1. Can P-gp induction be predicted from CYP3A?
   - **Defined induction relationship between CYP3A and P-gp**
   - **Accurate prediction of RBT and CBZ induction**
   - **Accurate prediction of SOF exposure decrease**
2. Can induction of other transporters/P450s be predicted from CYP3A?
3. What are the implications for clinical development?

Overview of Presentation: 3 Questions

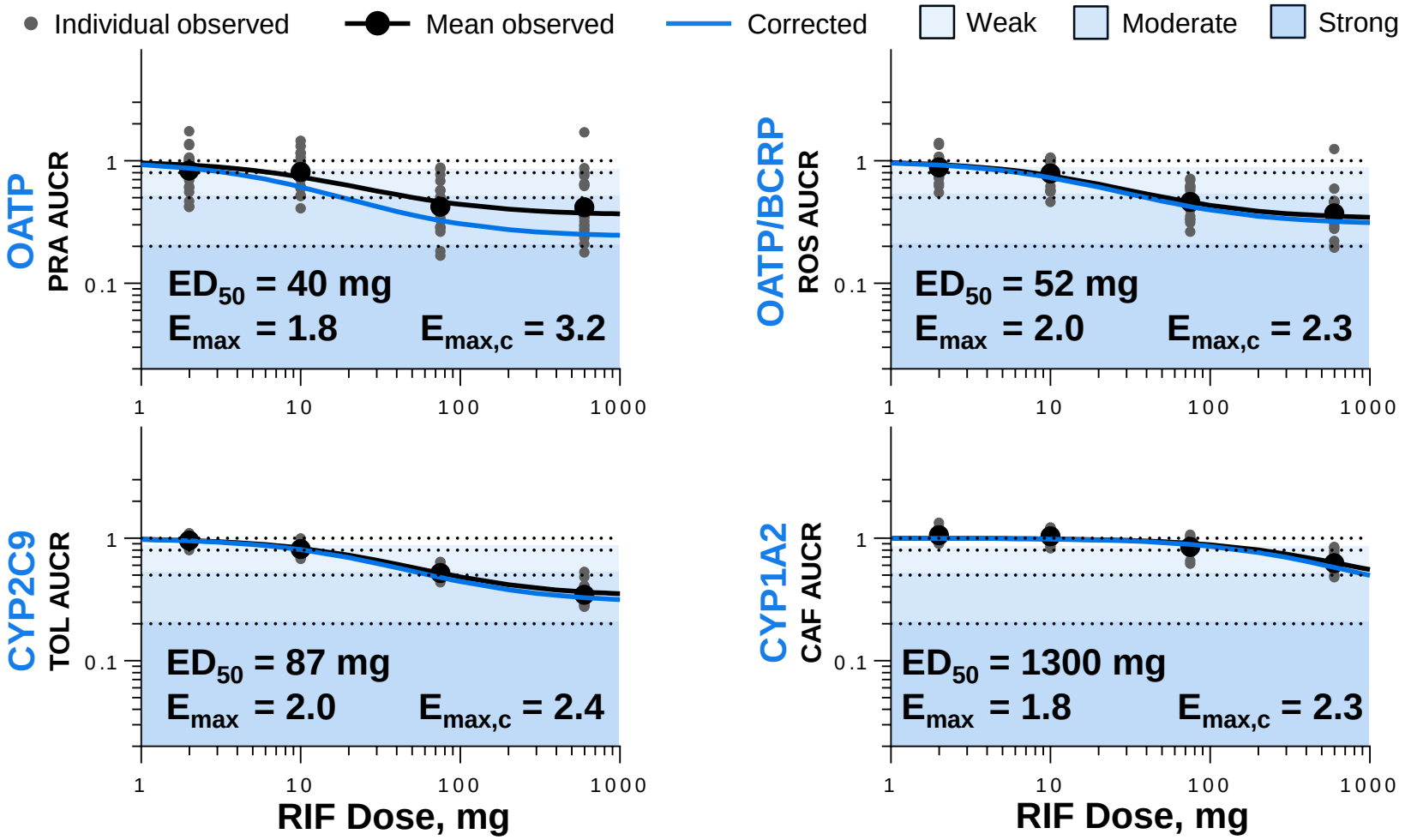
1. Can P-gp induction be predicted from CYP3A?
2. Can induction of other transporters/P450s be predicted from CYP3A?
   - **Establish:** Relative RIF induction between probes
   - **Verify:** Transporter/P450 induction by RBT and CBZ
3. What are the implications for clinical development?

Like P-gp, Only Moderate Induction of OATP After High Dose RIF



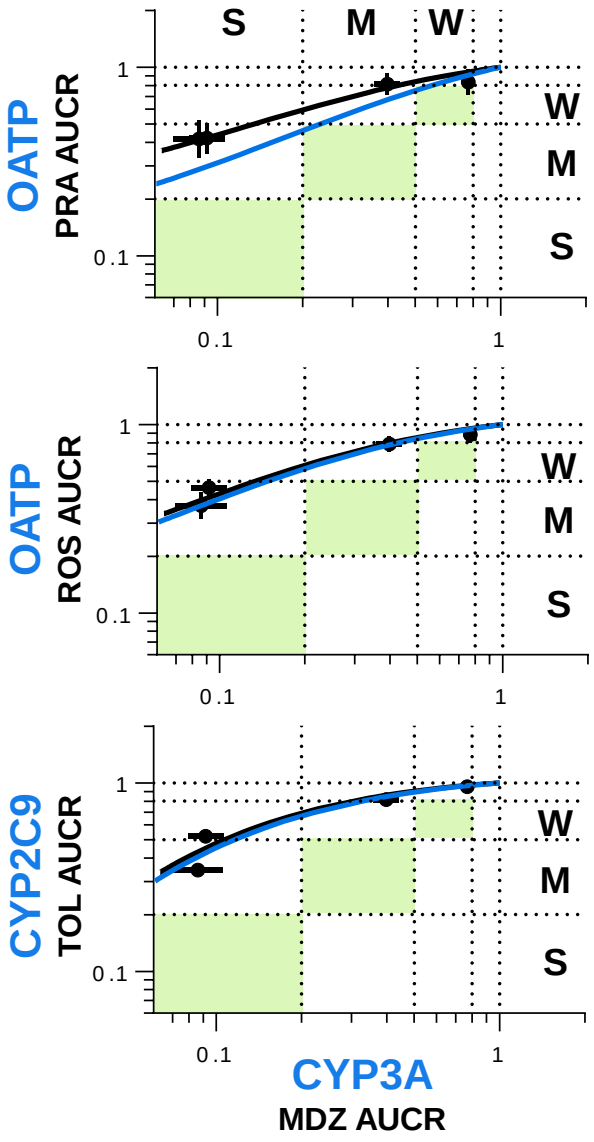
- PRA and ROS results suggest that OATP, but not BCRP, is induced
- OATP induction is a working hypothesis
  - No change in PRA/ROS renal CL
  - More data is needed to substantiate

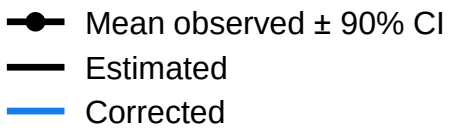
Like P-gp and OATP, Only Moderate Induction of CYP2C9 After High Dose RIF



- Weak induction of CYP1A2 was expected

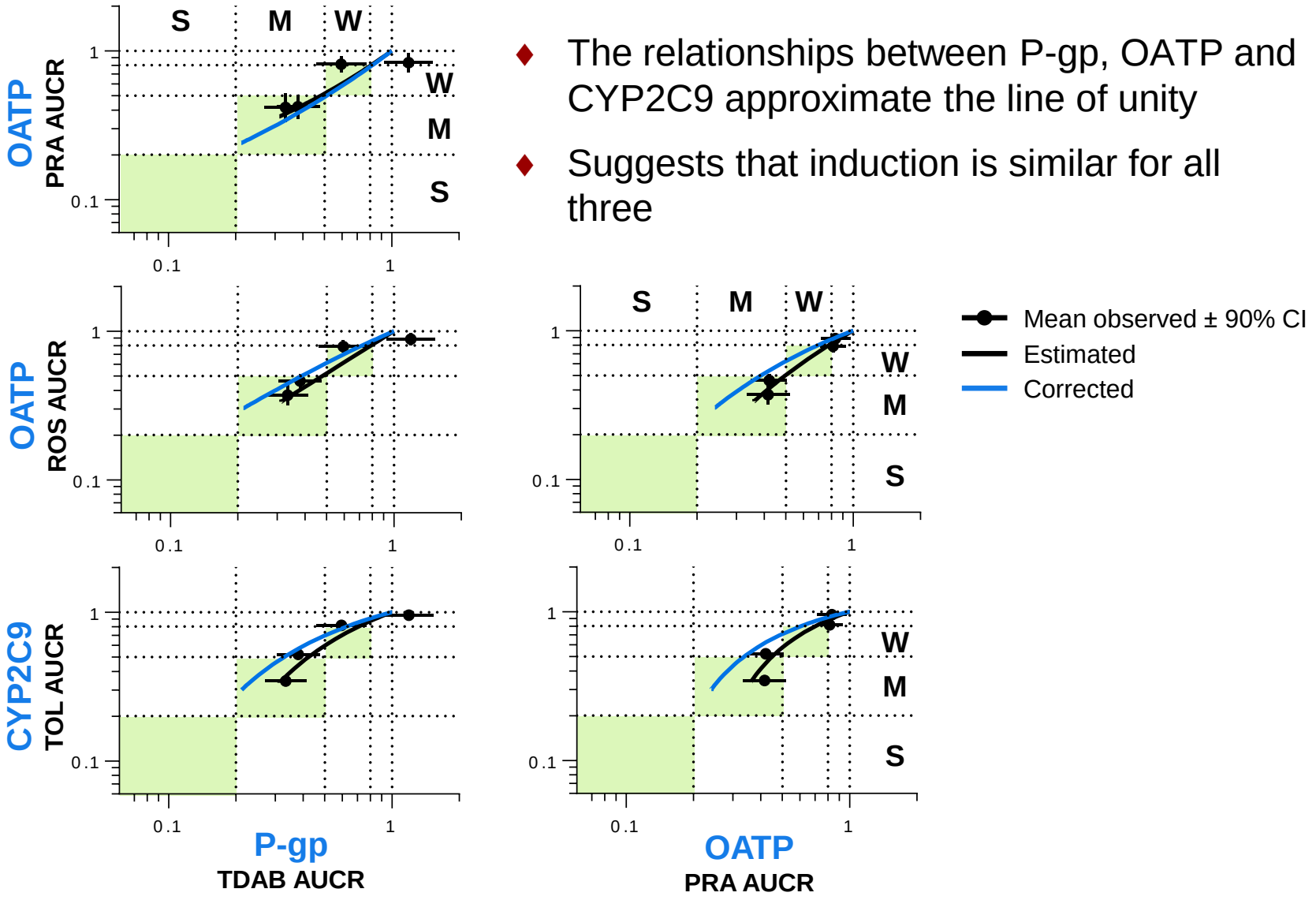
OATP and CYP2C9 Induction Is Less than CYP3A





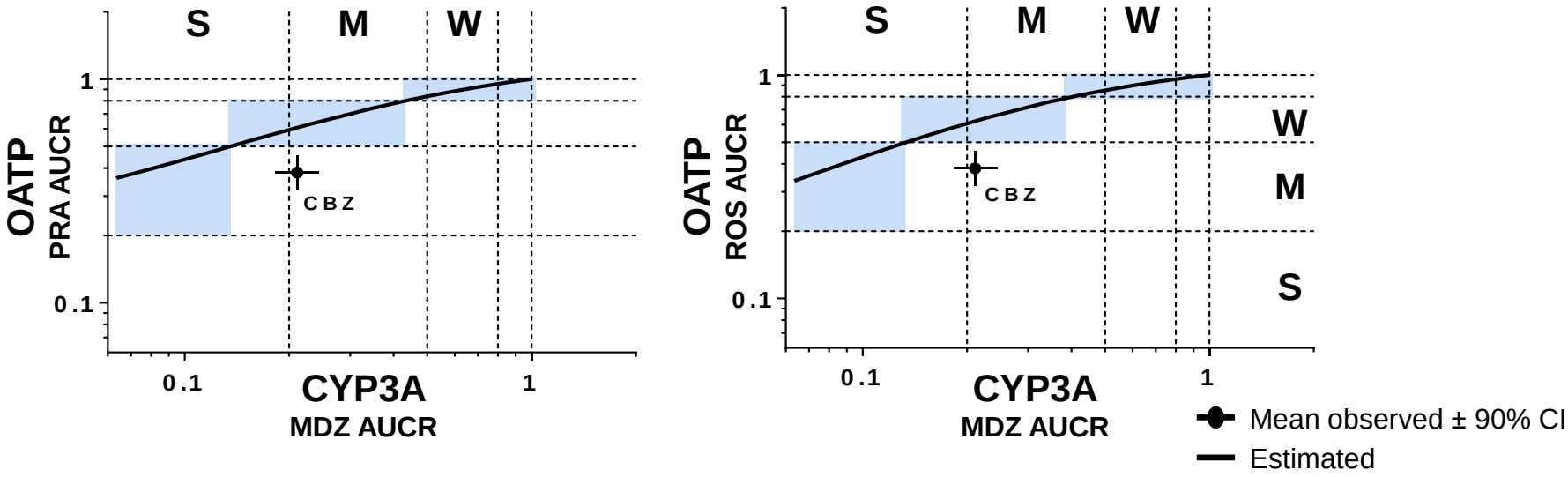
- Both observed and corrected relationships fall above the area of parity

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



- The relationships between P-gp, OATP and CYP2C9 approximate the line of unity
- Suggests that induction is similar for all three

CBZ-Mediated OATP Induction is Under-Predicted

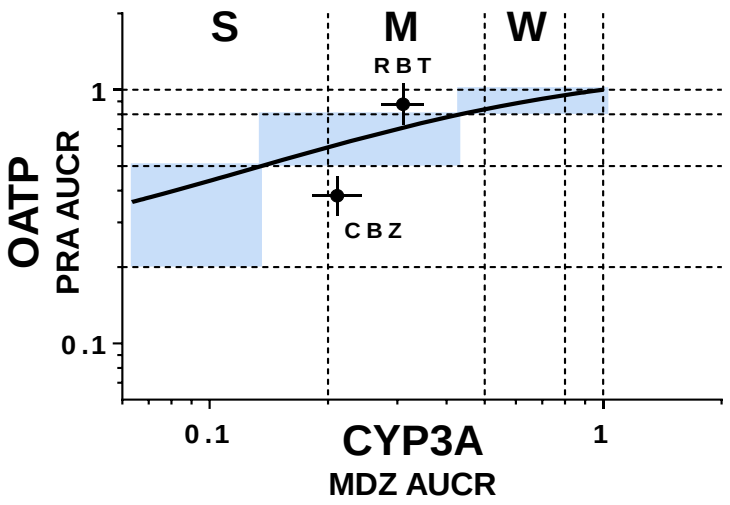


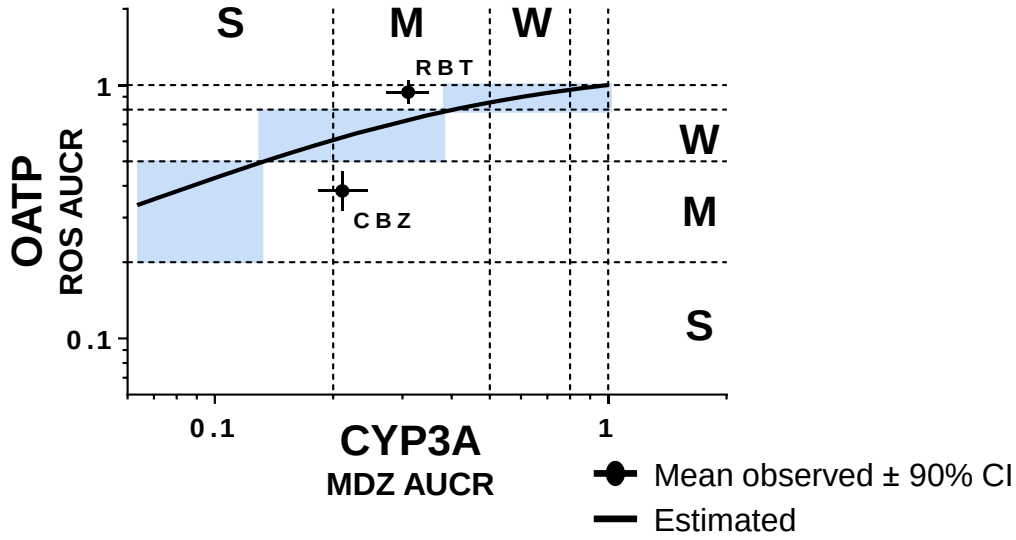
- CBZ: CYP3A – OATP parity
  - Both moderate
  - Is CBZ inducing via a non-PXR pathway?

    OATP is regulated by several non-PXR pathways

Faucette et al. J Pharmacol Exper Ther 2007; Svoboda et al. Curr Drug Metab 2011.

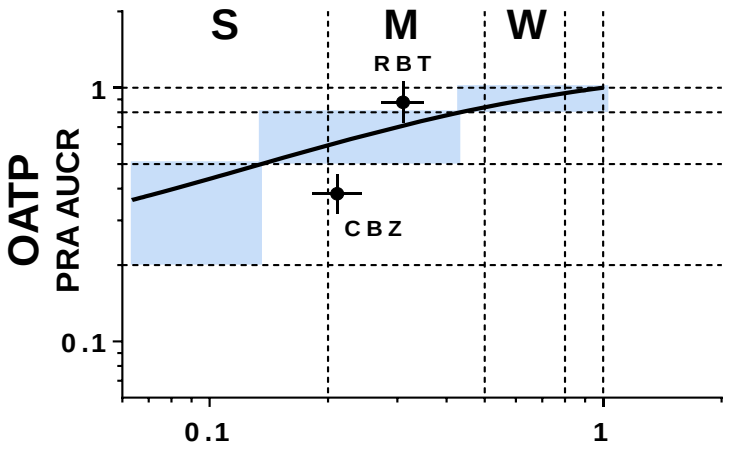
CBZ-Mediated OATP Induction is Under-Predicted, Unlike RBT

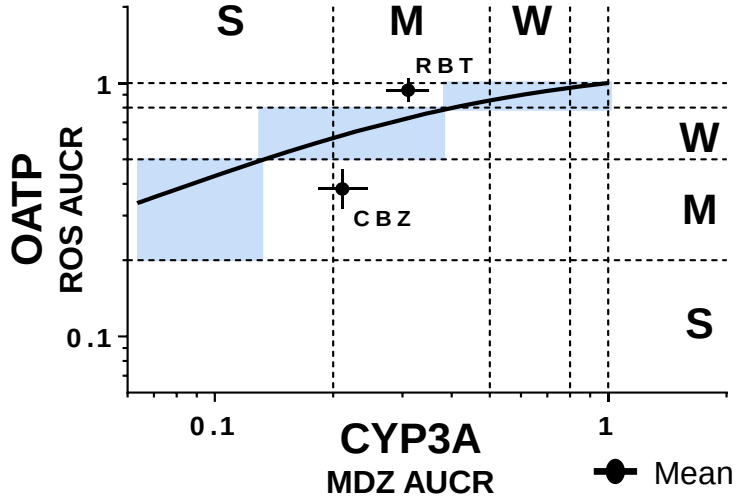


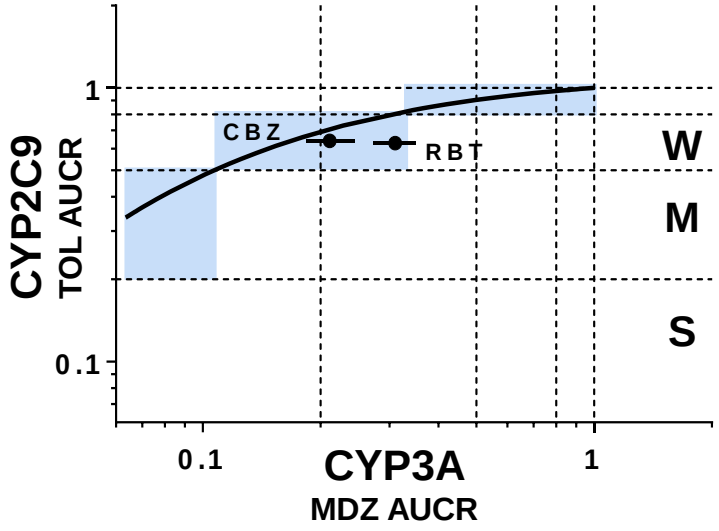


- RBT: Induction follows RIF CYP3A – OATP relationship
  - Over-prediction is of less concern than under-prediction

RBT Induces OATP and CYP2C9 As Expected From the RIF Induction Relationships







- P-gp, CYP2C9 and CYP3A are all primarily PXR regulated
  - Simple co-regulatory system allows for accurate predictions

Overview of Presentation: 3 Questions

1. Can P-gp induction be predicted from CYP3A?
2. Can induction of other transporters/P450s be predicted from CYP3A?
   - **Defined relationships between transporters and P450s**
   - **Accurate prediction of RBT induction**
   - **Presence and prediction of OATP induction is uncertain**
3. What are the implications for clinical development?

Hypothesis and Mechanistic Interpretation

- Nuclear receptor involvement is important for predictability
  - Primarily PXR involvement:

    Strong CYP3A = Moderate P-gp, OATP, CYP2C9

***If* NCE is an agonist of:**	***Then* CYP3A Induction Can Predict Induction of:**	
Primarily PXR	**P-gp/CYP2C9 OATP**	True

Hypothesis and Mechanistic Interpretation

- Nuclear receptor involvement is important for predictability
  - Primarily PXR involvement:

    Strong CYP3A = Moderate P-gp, OATP, CYP2C9
  - Additional non-PXR agonism:

    CYP3A may mispredict OATP induction magnitude

***If* NCE is an agonist of:**	***Then* CYP3A Induction Can Predict Induction of:**	
Primarily PXR	**P-gp/CYP2C9** **OATP**	True
PXR and Non-PXR	**P-gp/CYP2C9**	True
	OATP	Maybe true; misprediction could occur

Hypothesis and Mechanistic Interpretation

- Nuclear receptor involvement is important for predictability
  - Primarily PXR involvement:
    Strong CYP3A = Moderate P-gp, OATP, CYP2C9
  - Additional non-PXR agonism:
    CYP3A may mispredict OATP induction magnitude
  - Little to no PXR involvement:
    More study is warranted

***If* NCE is an agonist of:**	***Then* CYP3A Induction Can Predict Induction of:**	
Primarily PXR	**P-gp/CYP2C9** **OATP**	True
PXR and Non-PXR	**P-gp/CYP2C9**	True
	OATP	Maybe true; misprediction could occur
Primarily Non-PXR	**P-gp/CYP2C9** **OATP**	Unknown if true or false; not tested but not recommended

Overview of Presentation: 3 Questions

1. Can P-gp induction be predicted from CYP3A?
2. Can induction of other transporters/P450s be predicted from CYP3A?
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Clinical Development Implications: Increased Utility of DDI Data

- RIF dose can be titrated to elicit weak, moderate and strong PXR-dependent induction as desired for DDI assessment

  Standardized DDIs and better facilitate transporter/P450 induction extrapolation

Clinical Development Implications: Strong Transport Induction Unlikely

- Doses of <600 mg RIF can be tailored to represent weak, moderate and strong PXR-dependent induction
  - Standardized DDIs facilitate transporter induction database development
- In contrast to P-gp, OATP and CYP2C9, only strong induction was observed with CYP3A after potent PXR agonism

Clinical Development Implications: Increased CBZ and RBT DDI Categorization

- Doses of <600 mg RIF can be tailored to represent weak, moderate and strong PXR-dependent induction
  - Standardized DDIs facilitate transporter induction database development
- In contrast to P-gp, OATP and CYP2C9, only strong induction was observed with CYP3A after potent PXR agonism
- Carbamazepine and rifabutin induction categorization:

	CYP3A	P-gp	OATP	CYP2C9	CYP1A2
Carbamazepine	Moderate*	Weak	Moderate	Weak	Weak
Rifabutin	Moderate	Weak	None	Weak	None

*Strong CYP3A inducer as per FDA DDI Guidance

CBZ-Quetiapine DDI: Grimm et al. Br J Clin Pharmacol 2006

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Lutz JD, *et al*. Cytochrome P450 3A Induction Predicts P-glycoprotein Induction; Part 1: Establishing Induction Relationships Using Ascending Dose Rifampin. *Clin Pharmacol Ther* 2018; 104(6):1182-1190

Lutz JD, *et al*. Cytochrome P450 3A Induction Predicts P-glycoprotein Induction; Part 2: Prediction of Decreased Substrate Exposure After Rifabutin or Carbamazepine. *Clin Pharmacol Ther* 2018; 104(6):1191-1198