

Structure Activity Relationships and Additivity – Going Beyond Conventional Wisdom

Moderated by: Dr. Samantha Jeschonek of **CDD**

Panel: Dr. James ‘Guy’ Breitenbucher of **Convelo Therapeutics** and Dr. Peter Gedeck of **CDD**

September 19, 2019



Today's Moderator and Panelists



Samantha Jeschonek, PhD
Research Scientist
Collaborative Drug Discovery



James 'Guy' Breitenbucher, PhD
V.P. of Chemistry
Convelo Therapeutics



Peter Gedeck, PhD
Senior Scientist
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Have a question to ask our panel?
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Additivity as the Birth of QSAR

Journal of Medicinal Chemistry

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A Mathematical Contribution to Structure-Activity Studies

SPENCER M. FREE, JR., AND JAMES W. WILSON

Research and Development Division, Smith Kline and French Laboratories, Philadelphia, Pennsylvania



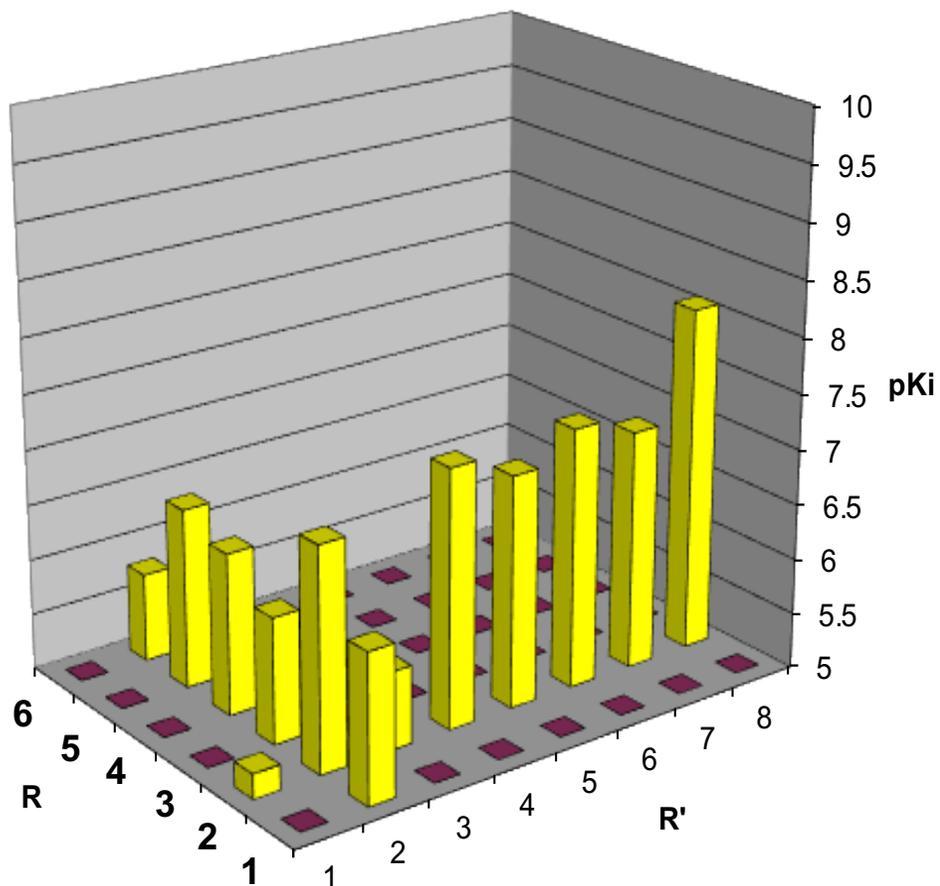
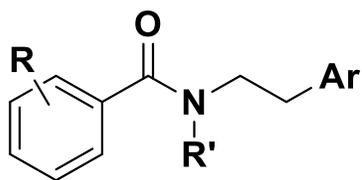
R ₂	R ₁		Average
	H	CH ₂	
N(CH ₃) ₂	2.13	1.64	1.885
N(C ₂ H ₅) ₂	1.28	0.85	1.065
	1.705	1.245	1.475

Red annotations: -0.8 ↓ next to N(CH₃)₂ and N(C₂H₅)₂; -0.5 ⇒ between 2.13 and 1.64; -0.5 ⇒ between 1.28 and 0.85; -0.8 ↓ next to 0.85.

$$\text{Response} = \text{Average} + X_i + Y_j$$

“The proposed models should not be criticized as ignoring the combination of several substituents that produce a biological response in excess of the additive estimation. Such results will appear in some analog series.”

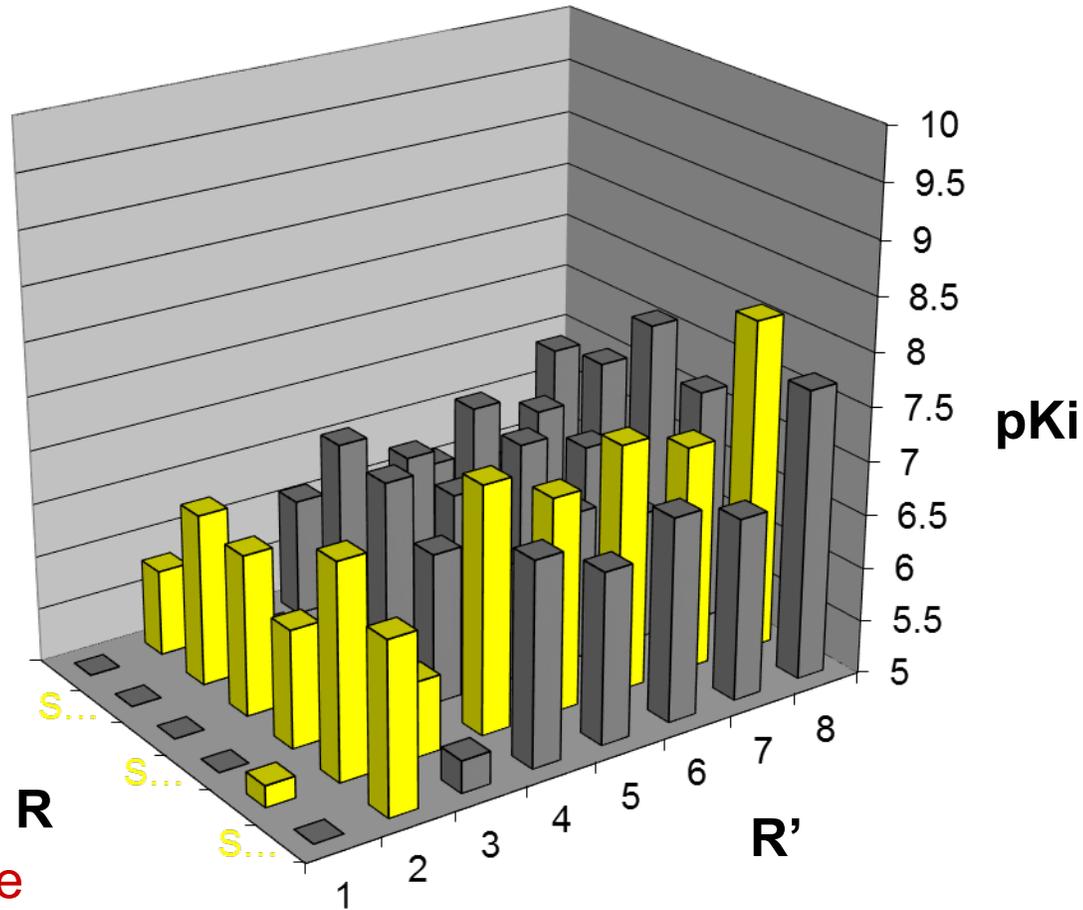
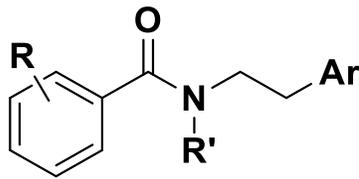
What are we assuming with linear SAR?



JNJ SAR of Orexin Antagonists

What are we assuming with linear SAR?

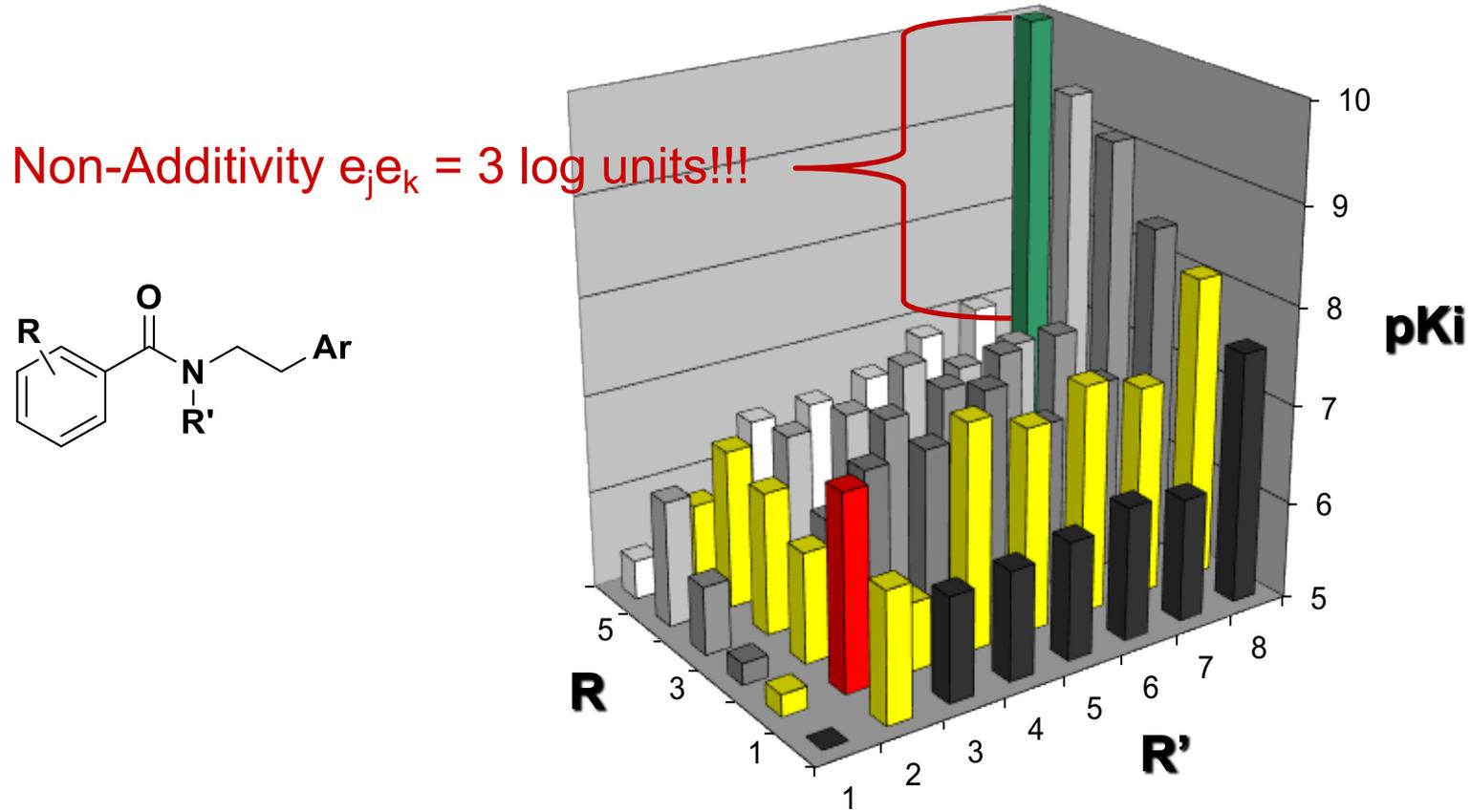
This is a visual quantitative representation of assuming additivity.



$$pK_i = \mu + X_j + Y_k : \text{Additive}$$

SAR of Orexin Antagonists

What if your data looks like this?



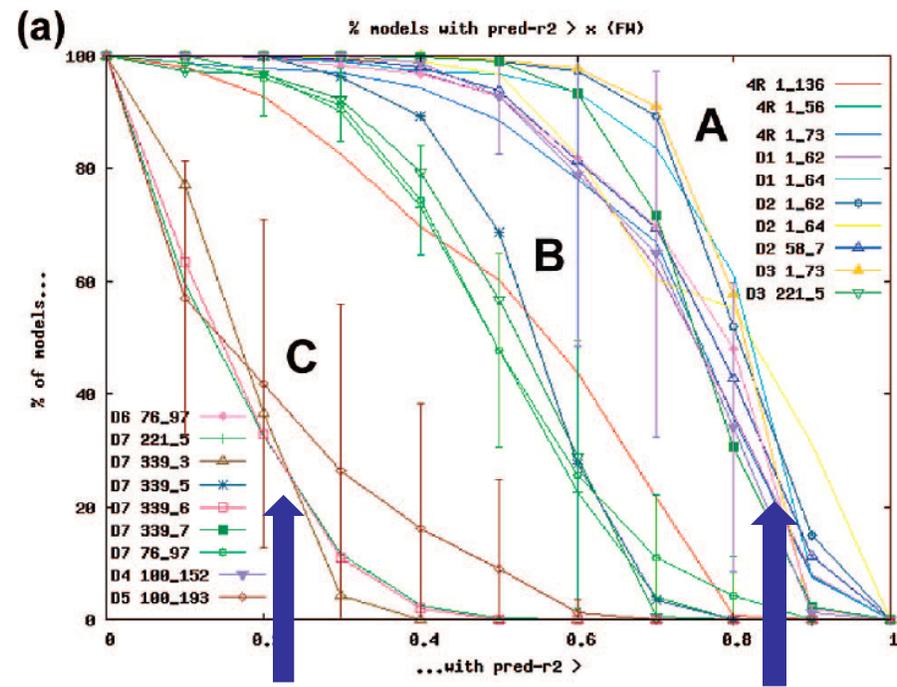
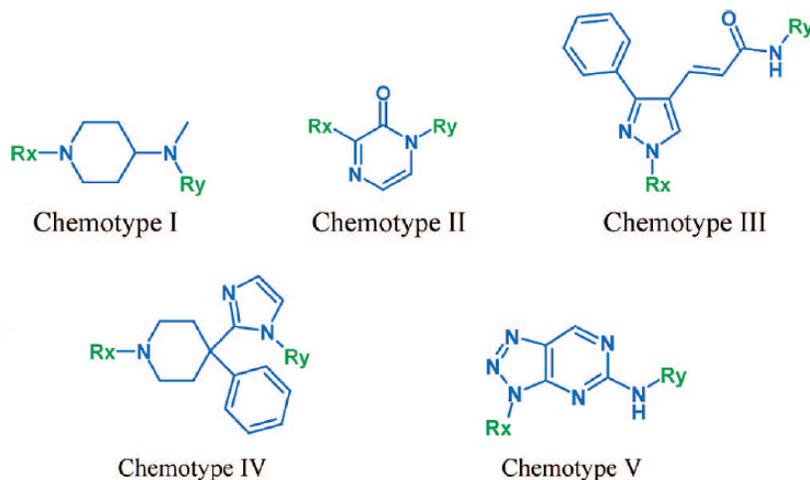
2 other Orexin libraries showed a similar lack of additivity.

We did not have structural information to know why this was happening

How general is additivity in SAR?

- Janssen data mining exercise.
 - 19 SAR data sets
 - Sets had 40-178 members
 - At least 2 variable groups
 - Range of data values >2 log units
 - Sets were 80-66% complete

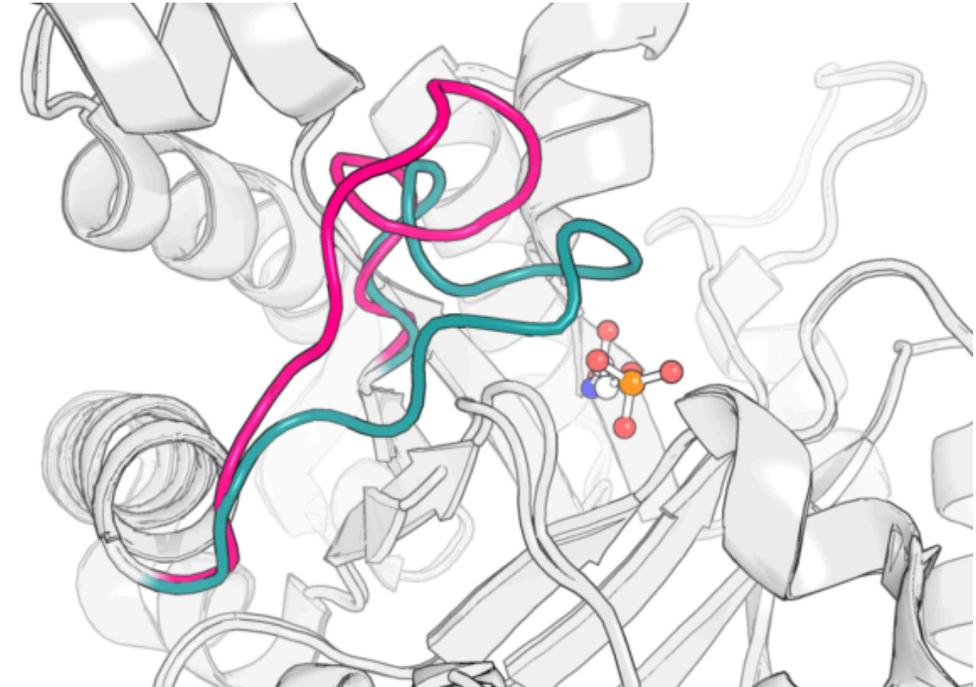
$$y = C + \sum_{i=1}^n a_i X_i + \sum_{j=1}^m b_j Y_j$$



4 Clearly non-additive

10 Mostly additive

- Defined pockets
- Internal ligand flexibility
 - Internal H-bonds
- Protein flexibility
 - Side chains
 - Loops with distinct conformation.
- Full ligand rearrangements
 - Flips, mostly fragments



<https://www.blopig.com/>

Poll the Audience!



Have you seen non-additivity in your SAR?

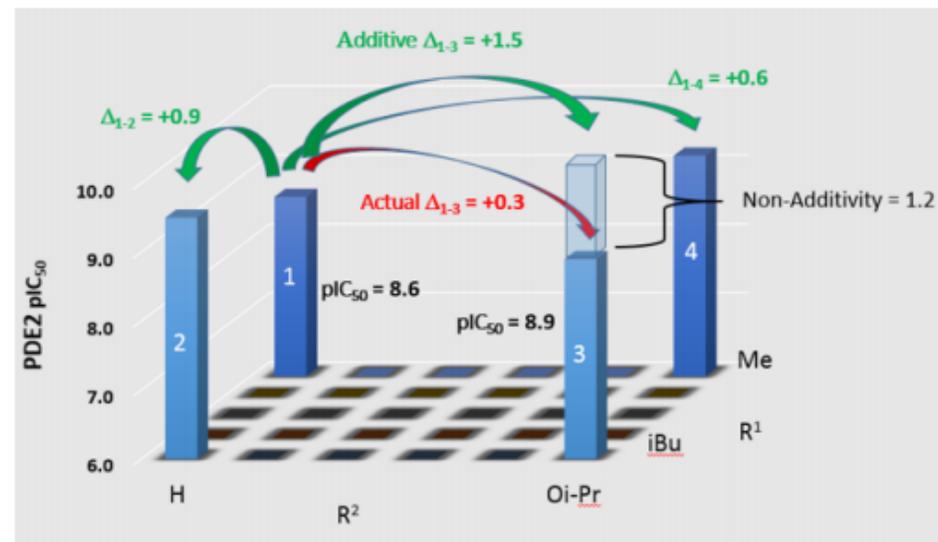
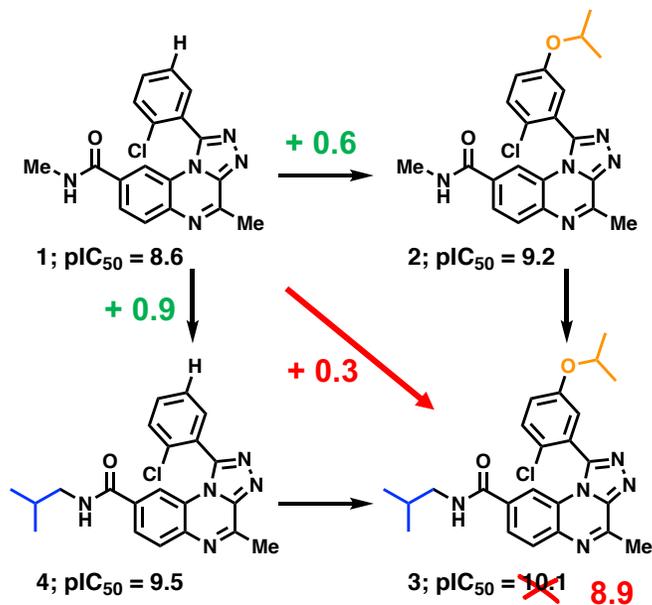
- a) Yes
- b) No
- c) I've seen it in other's SAR
- d) I haven't thought about it, but I'd like to know more

Assuming Additivity by Inference

- *We analyzed 500 SAR papers (JMC, BOMCL, ACSMCL) and found only 4 where the additive assumption was checked!!*
- *I think chemists are aware of the possibility that non-additivity exists, but they are so comfortable with the assumption that they don't think it is important to check.*
- *I will contend that checking additivity not only prevents chemists from missing good compounds but also highlights critical changes in SAR.*

PDE2 Case Study

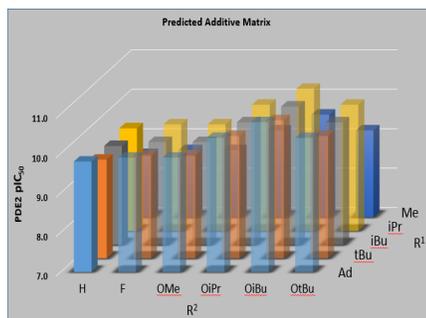
Phosphodiesterase 2 (PDE2) inhibitors for the treatment of memory disorders



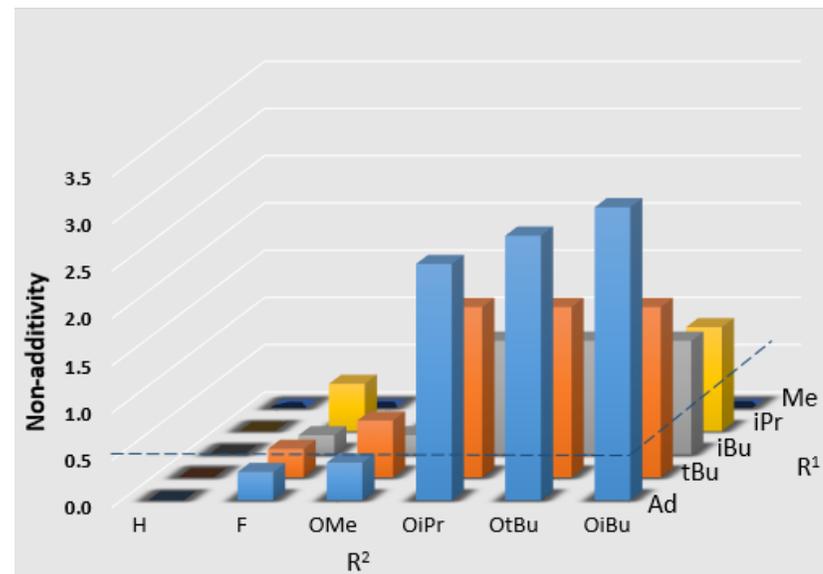
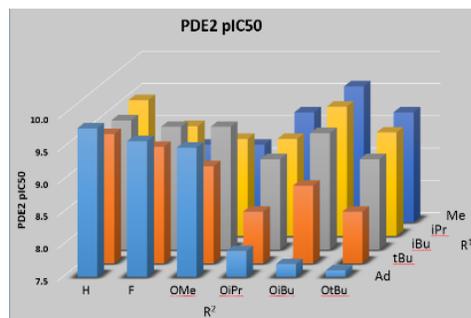
- Evidence for non-additive SAR early (< 10 analogs)
- Can this data provide insights into ligand-protein interactions?

Systematic Deviation from Additivity

Predicted Data

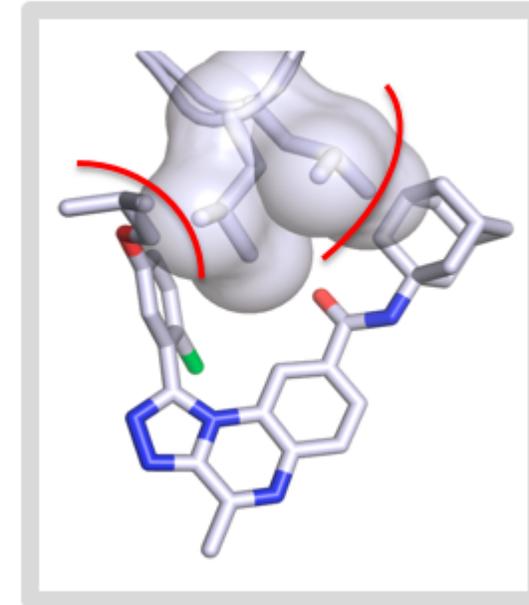
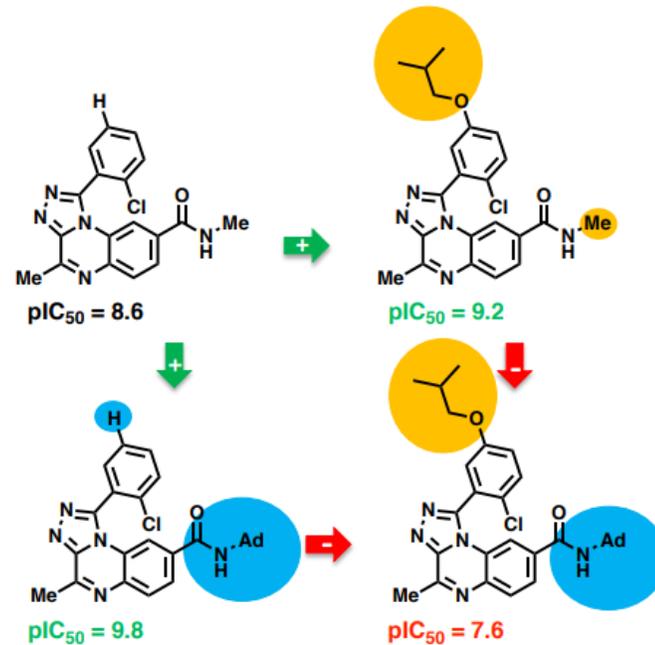
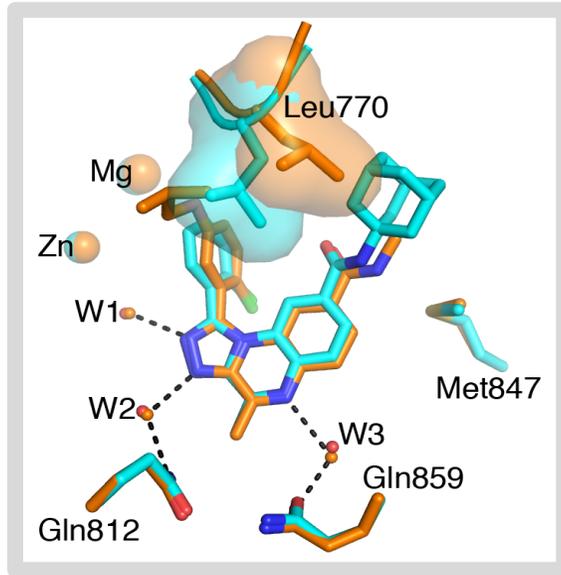


Actual Data



54% of the data is non-additive (99% confidence)

Protein Conformational Changes!



Leu770 works as a molecular divider that distributes ligand binding volume between R_1 and R_2 pockets.

First documented case of large non-additive SAR effects being confirmed as resulting from changes in protein conformation.

Poll the Audience!



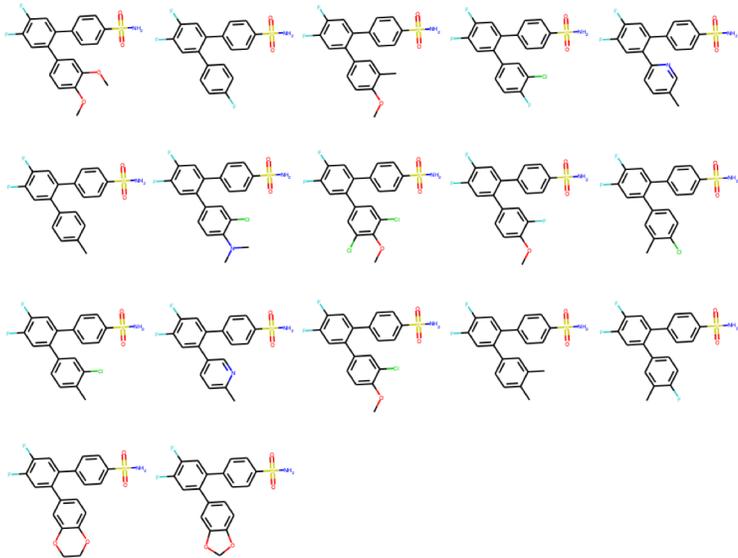
What's the hardest part about optimizing SAR Patterns?

- a) Logic: Multi-parameter optimization
- b) Synthesis: Picking a “drug-like” lead series that is relatively easy to optimize
- c) Biology: Target identification with a biological assay that is an indicative model of the disease
- d) Informatics: Discerning the most informative patterns in complex, multi-dimensional data

Have a question to ask our panel?
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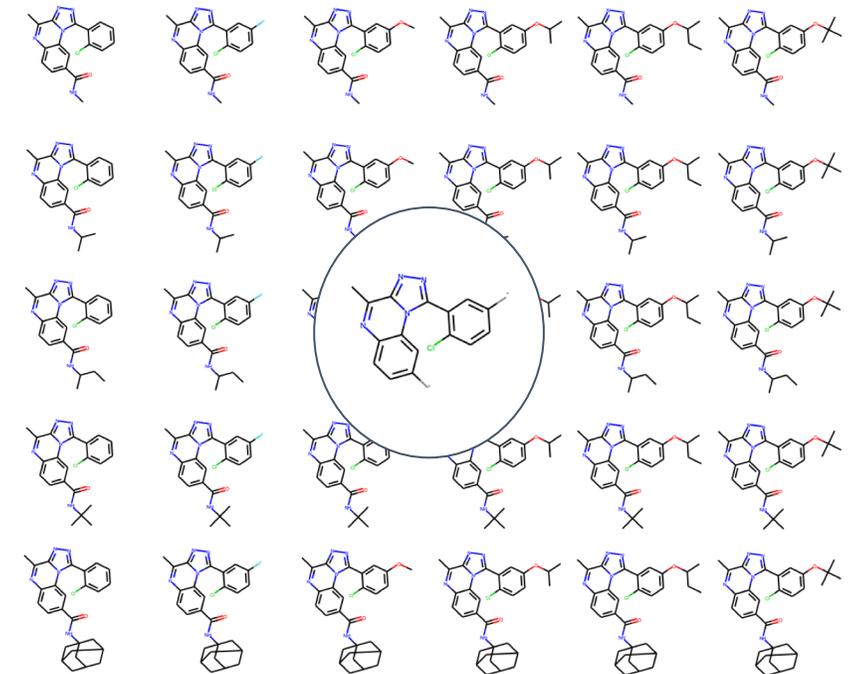
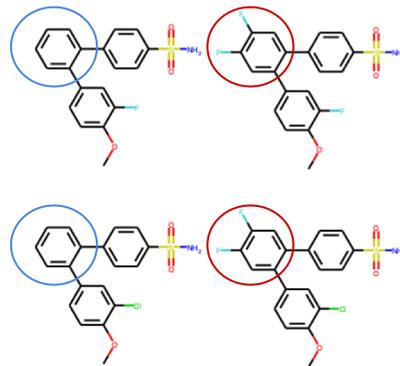


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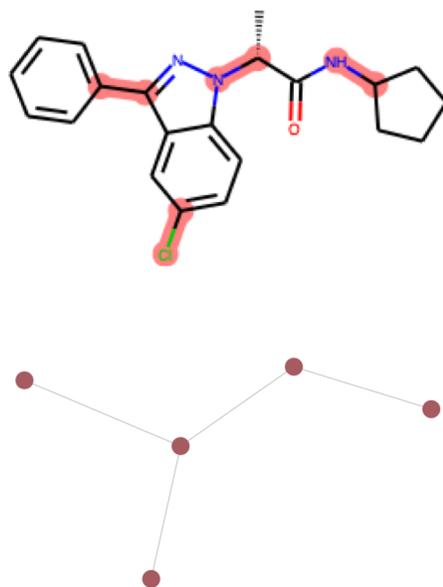


How does activity change when we modify the ring system?

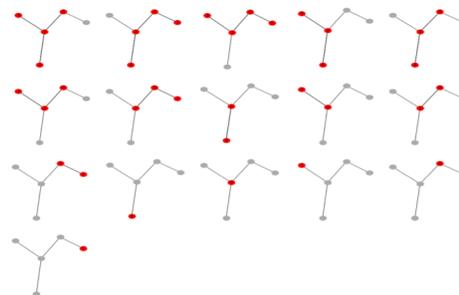
What is the effect of changing the core?



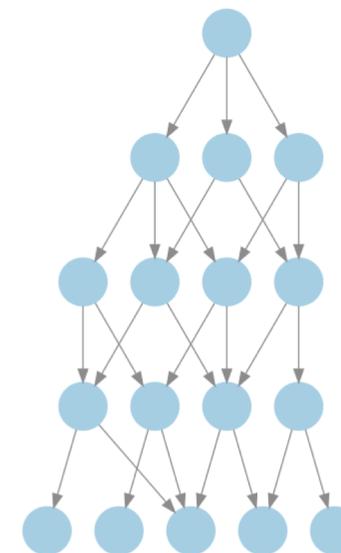
Are modifications on two sides of a core additive or not?



Split molecule into fragments
into a simplified representation

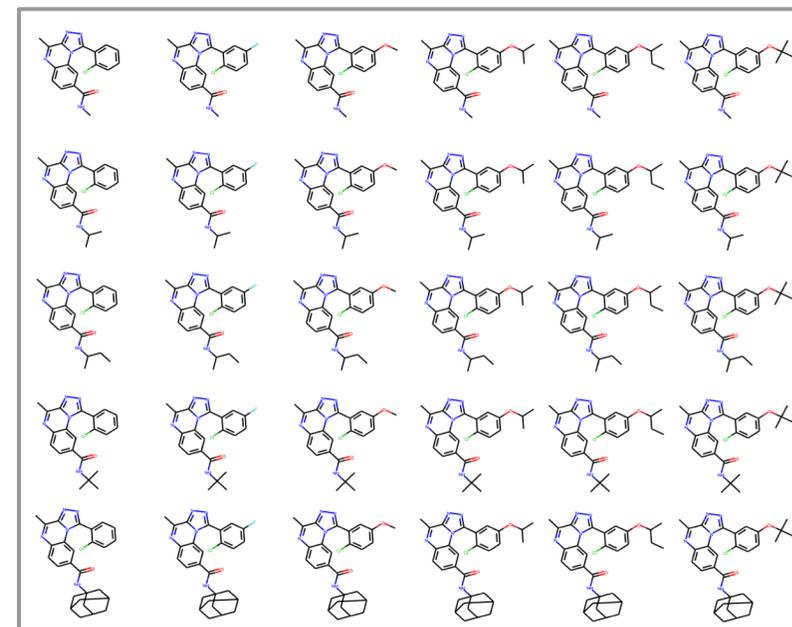
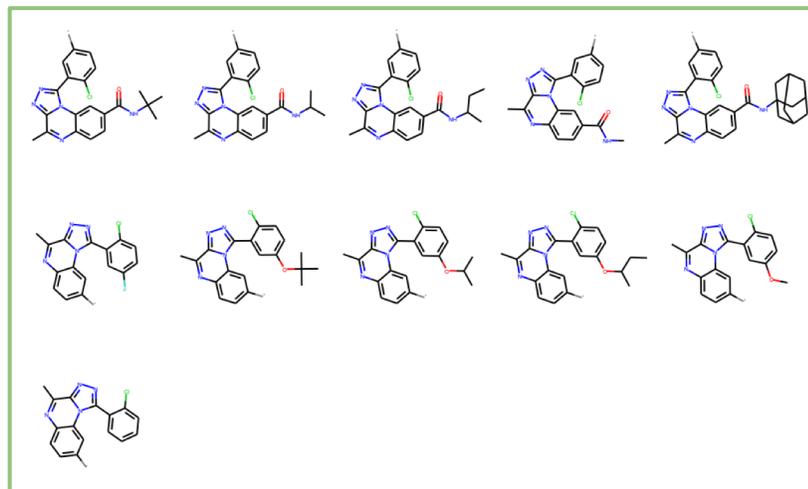
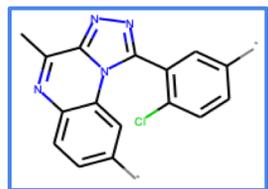
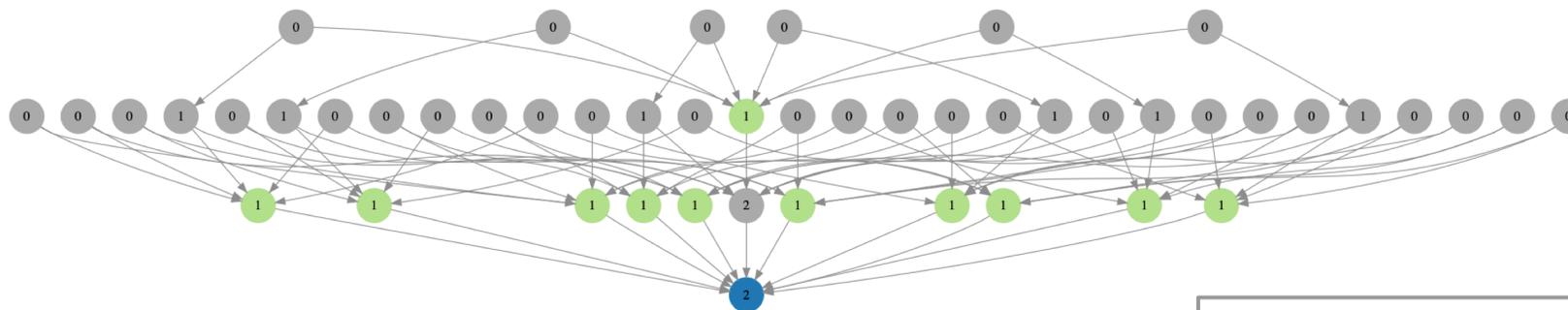


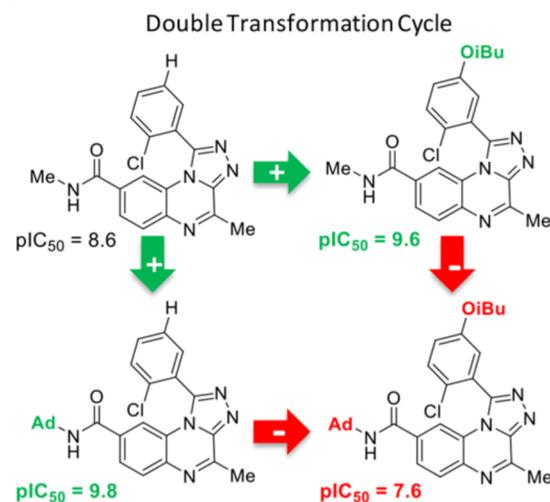
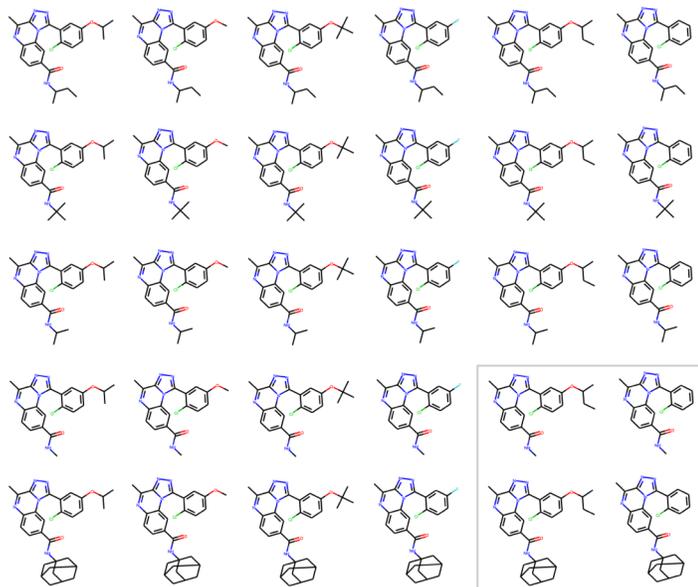
Enumerate all possible
substructures



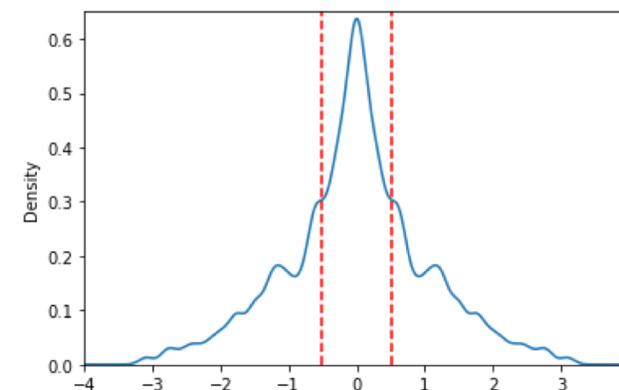
Arrange subgraphs in lattice using
substructure relationship

- Identify cores: fragments with many associated structures
- Single point changes: start from fragments with one connection point
- Identify core replacements
- Two-dimensional libraries: start from fragments with two connection points
- Automated additivity analysis

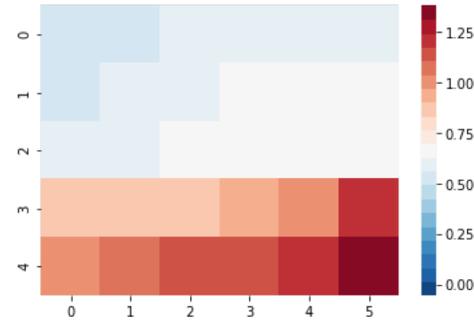




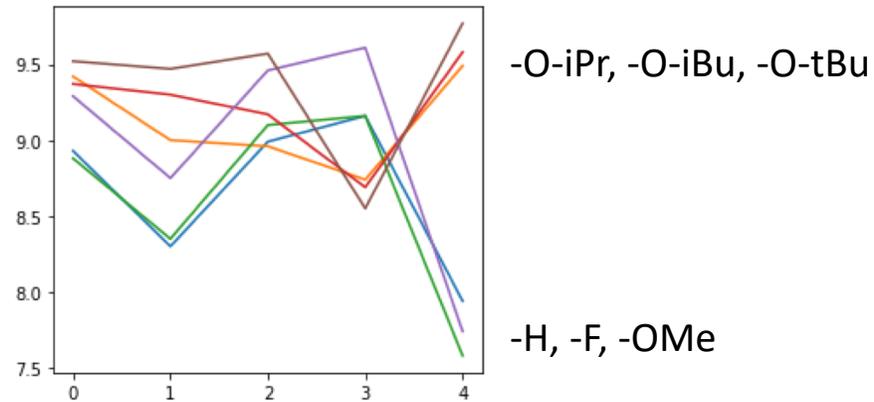
Enumerate all transformation cycles in sublibrary and calculated non-additivity:
 $(7.74 - 9.77) - (9.61 - 8.55) = -3.09$

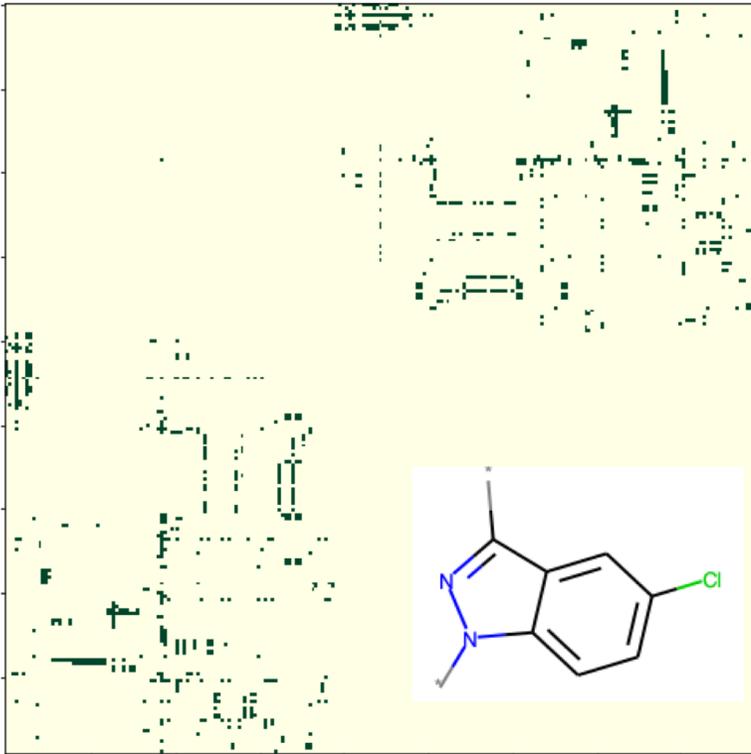


Average non-additivity of compound



Identify additive subsets



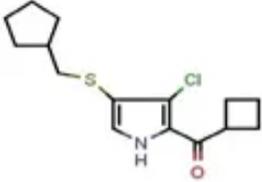
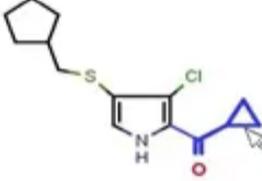
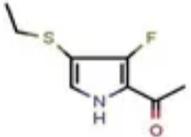


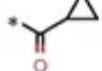
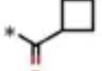
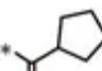
4 x 8: (0, 3, 6, 7), (99, 103, 107, 108, 109, 110, 114, 115)
3 x 10: (0, 3, 6), (99, 103, 106, 107, 108, 109, 110, 114, 115, 116)
3 x 2: (1, 3, 6), (109, 113)
3 x 2: (1, 3, 7), (101, 109)
2 x 5: (1, 3), (101, 109, 111, 113, 119)
2 x 2: (2, 3), (102, 199)
2 x 4: (3, 4), (102, 118, 119, 159)
5 x 2: (3, 5, 46, 54, 57), (111, 199)

...

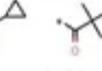
109 fully enumerated sub-libraries

There is no need to associate the R-groups with either one of the connection points

Compound	ID	IC50	Peff	HLM
	XYZ123	3.2	88	
	XYZ124	1.3	16	
				

Activity/Property scores				
Fragment	ID	IC50	Peff	HLM
	Frag 23	3.7	29	88
	Frag 24	-6.2	-12	-75
	Frag 25	5.5	16	12

Series summary

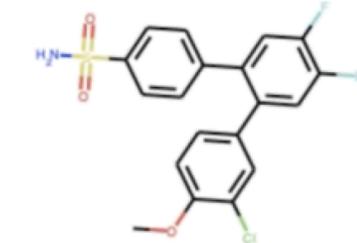
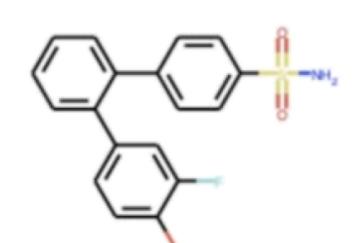
R ₁	R ₂	R ₃	R ₄	R ₅
				
				

Sibling compounds

- Add to favorites
- Show Result Data
- Related compounds with this group replaced (2)
- Related compounds with this group kept same (3)
- All compounds with this group (985492)
- Related compounds with one group replaced
- Related compounds with two groups replaced
- View summary of series
- All compounds in the series (588)
- Include virtual compounds from series expansion (37394)
- Compare with reference compound

Composite of several screens from a preliminary UI Mock-up

45 Selected: [Launch Vision](#) [Plot](#) [Export](#) [Add to collection](#) [Build model](#) [Flag outliers](#) [Customize your report](#) [Save this search](#)

Select...	Molecule	Chemical Properties				Lipinski violations	
all · none		Molecular weight (g/mol)	log P	H-bond donors	H-bond acceptors		
<input checked="" type="checkbox"/>	 HA-0146032 Heather Arnal Testing		246.200	3.00	0	0	0
<input checked="" type="checkbox"/>	 HA-0145934 Heather Arnal Testing	222.150	3.34	1	1	0	
<input checked="" type="checkbox"/>	 HA-0145935 Heather Arnal Testing	234.360	3.54	1	1	0	

Poll the Audience!



If Free-Wilson together with more sophisticated additivity analyses similar to what was just shown were automated so you could just click on your data to pull it up, how impactful would it be?

- a) Game changer: would greatly enhance SAR optimization – I would use it frequently
- b) Moderately impactful: nice to have, might help somewhat, but impact would be small or infrequent
- c) Not impactful
- d) Not sure because I'm not involved with SAR optimization
- e) Not sure for other reasons

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Kiev Ly
Richard Truong

Biology teams (JNJ and Dart) and Structural Biology team (Dart)



Questions?



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