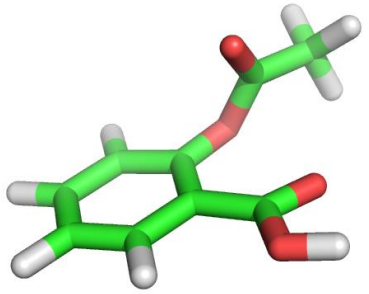
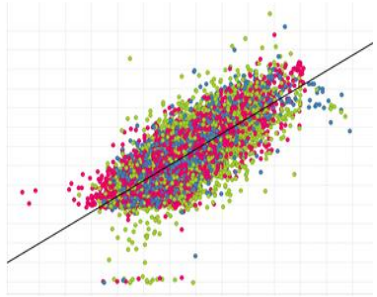
abbvie





Medicinal Chemistry is an art, when you don't understand the data

April 2016

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Director Immunology Chemistry Abbvie

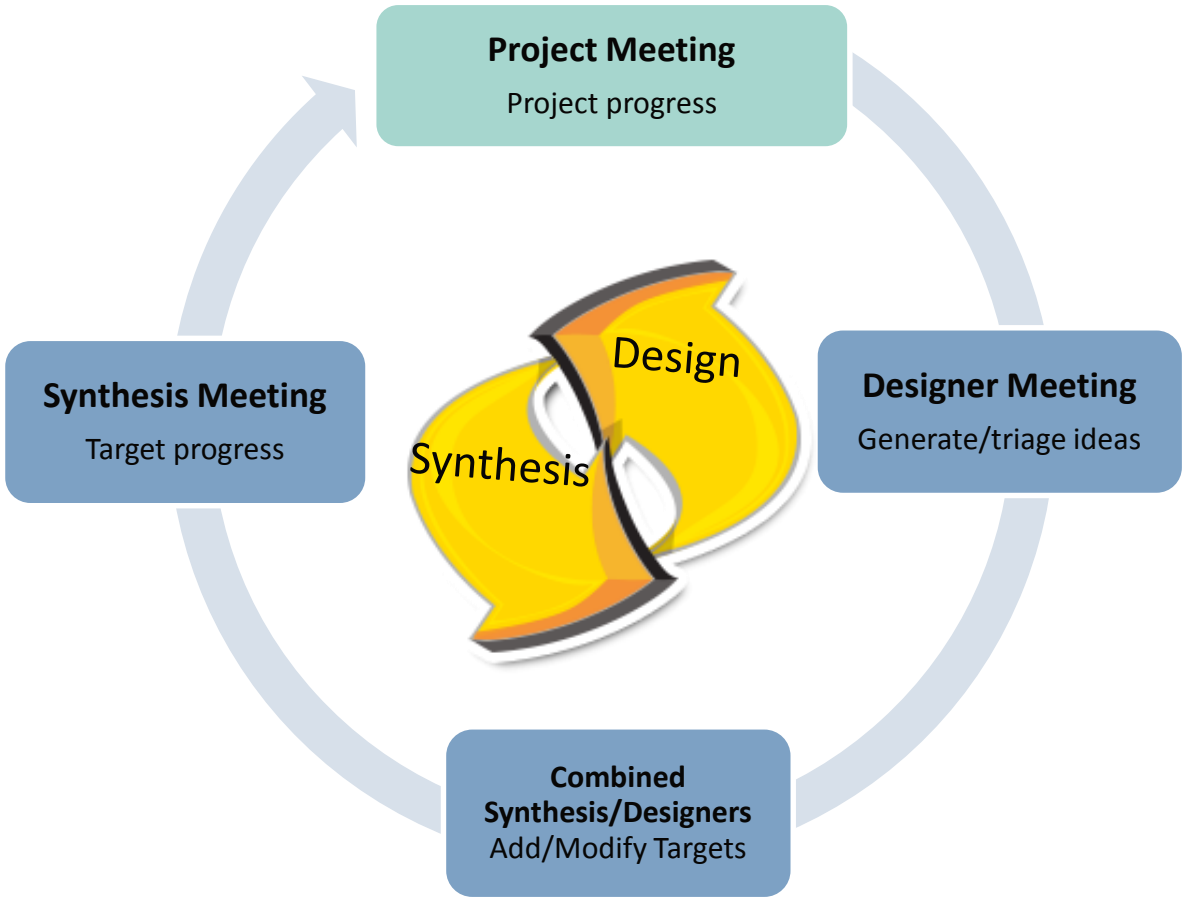
Jeremy.edmunds@abbvie.com

Medicinal Chemists – we (think) we know a lot

- ✓ Thorough knowledge of organic chemistry
- ✓ Knowledge of factors that influence ADME characteristics of compounds in vitro and in vivo
- ✓ Understanding of biology that relates to the disease/target project/ toxicology and safety
  - Relevance of *in vitro* and *in vivo* assays adopted by project
- ✓ Appreciation of patent and literature chemistry/biology information related to competitor compounds
- ✓ Understanding of clinical and regulatory requirements for disease of interest and related drugs
- ✓ Familiarity with new biology and chemistry technologies

Nussbaumer, P., *Medicinal Chemists of the 21st Century—Who Are We and Where to Go?* ChemMedChem, 2015

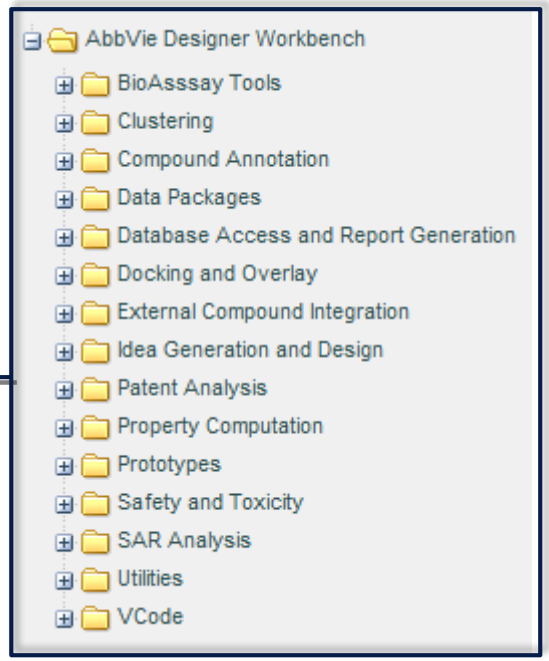
The synthesizer-designer relationship

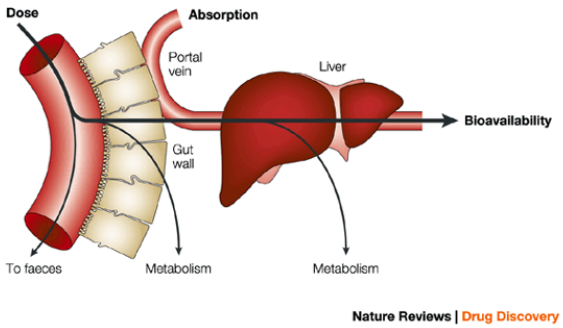


- Designers and synthesizers share project team goals
- Designers and synthesizers refine chemical plan: Add/Modify/Deprioritize/ Reject targets
- Collocated designers and synthesizers for optimal interactions

Optimization of design process – keep what works, improve what doesn't

	Original circa 2010	Design/Synthesis
Data storage and visualization	ISIS, Excel spreadsheets, ppt, cdx (C:drives)	Spotfire data packages: editable/customize views, on demand data update
In silico calculations	Primitive use of chem draw, excel macros, PP tools upon request	Abbvie Designer Workbench: Pipeline pilot - harmonization of calculations
Justification for ideas/ synthesis	Ideas supported by PhD and associate, "Ki is King"	Designer & Chemists ideas supported by prospective calcs/SAR/SPR
Modeling	Primitive Pymol, RocsDoc, Molecular modelers, ChemDraw 2D overlays	Design support specialist, designers tools MAESTRO, CSD, BROOD, TORCH, Water Map, …





$$\text{Efficacious dose} \propto \frac{AUC_{eff,u} \times CL_{int,u} \times \text{target tissue impairment}}{f_a \times f_g}$$

Typical workflow scenario:
Chemical matter analysis for a new target

Dr Recon mentions that he'd like to know what chemical matter exists for the Chemokine receptor CCR007. He couldn't find any chemical matter and now needs your expert help. He mutters something about how exciting the target is, and wonders whether we could start a medicinal chemistry program.

You reply that you'd be happy to review the literature and that you'd get back to him in a few hours/days with some information.

You figure that you'll start by reviewing the biology of CCR007 to make sure that your search terms are accurate, and that it should be trivial to find both internal and external data.

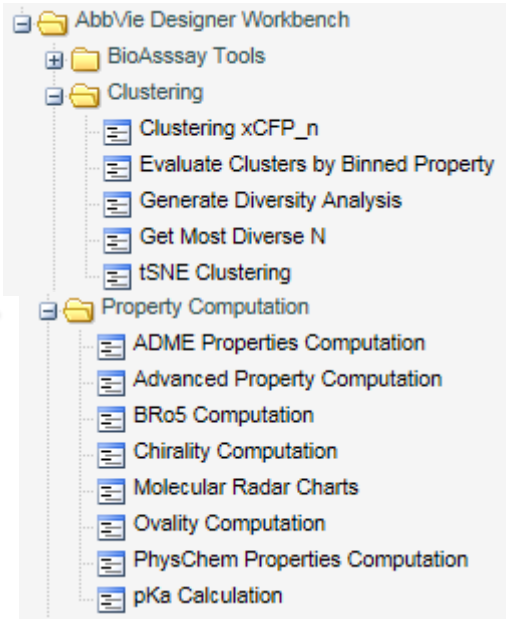
Given that you care about Structure Property Relationships both affinity and property data will be ETL into Spotfire and new ideas of compounds will ultimately be discussed with the synthesis community prior to execution (internally and externally).

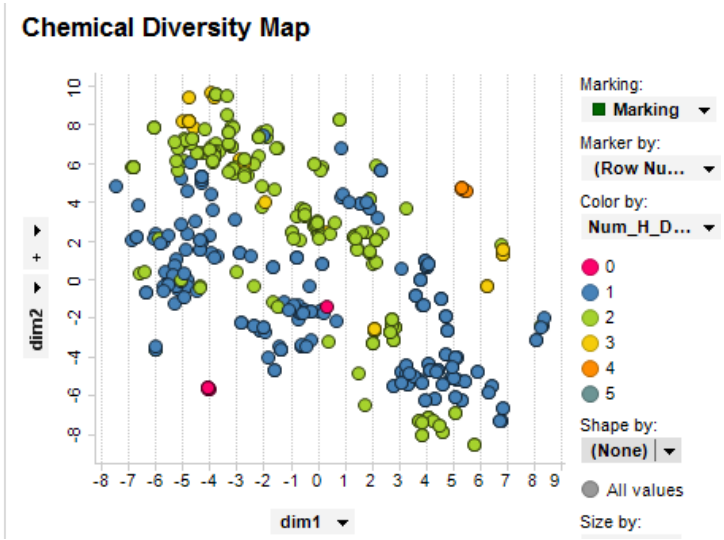
Design workflow (step 1 of 2)
Aggregate internal and external real and calculated data

Data search from ChEMBL, WOMBAT, PubChem, Abbvie Internal Project, TR Integrity & DrugBank

.XLS

TIBCO Spotfire®



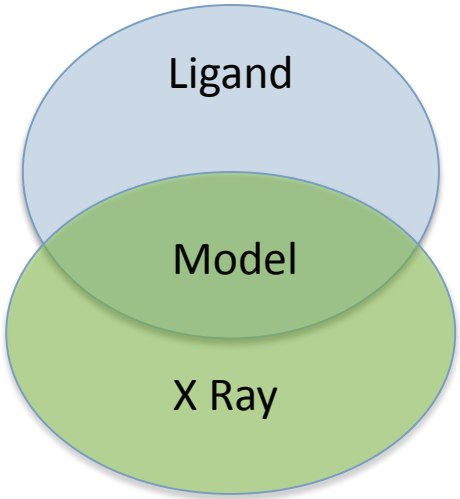


Assess internal and external Structure Activity & Structure Property Relationships to identify potential lead compounds

Design workflow (step 2 of 2)

Create a potential list of target compounds for synthesis

Type of design → Create Filter → Generate Compounds → Prioritize



Pharmacophore Map

Docking Grid

Forge

- Field based alignment
- Common substructure

Maestro 10.4

Singleton & Library Idea Generation

BROOD

LeadIT: Recore

sparkVI0

Schrodinger Core Hopping

LEAD HOPPER

Score & Review

jmp

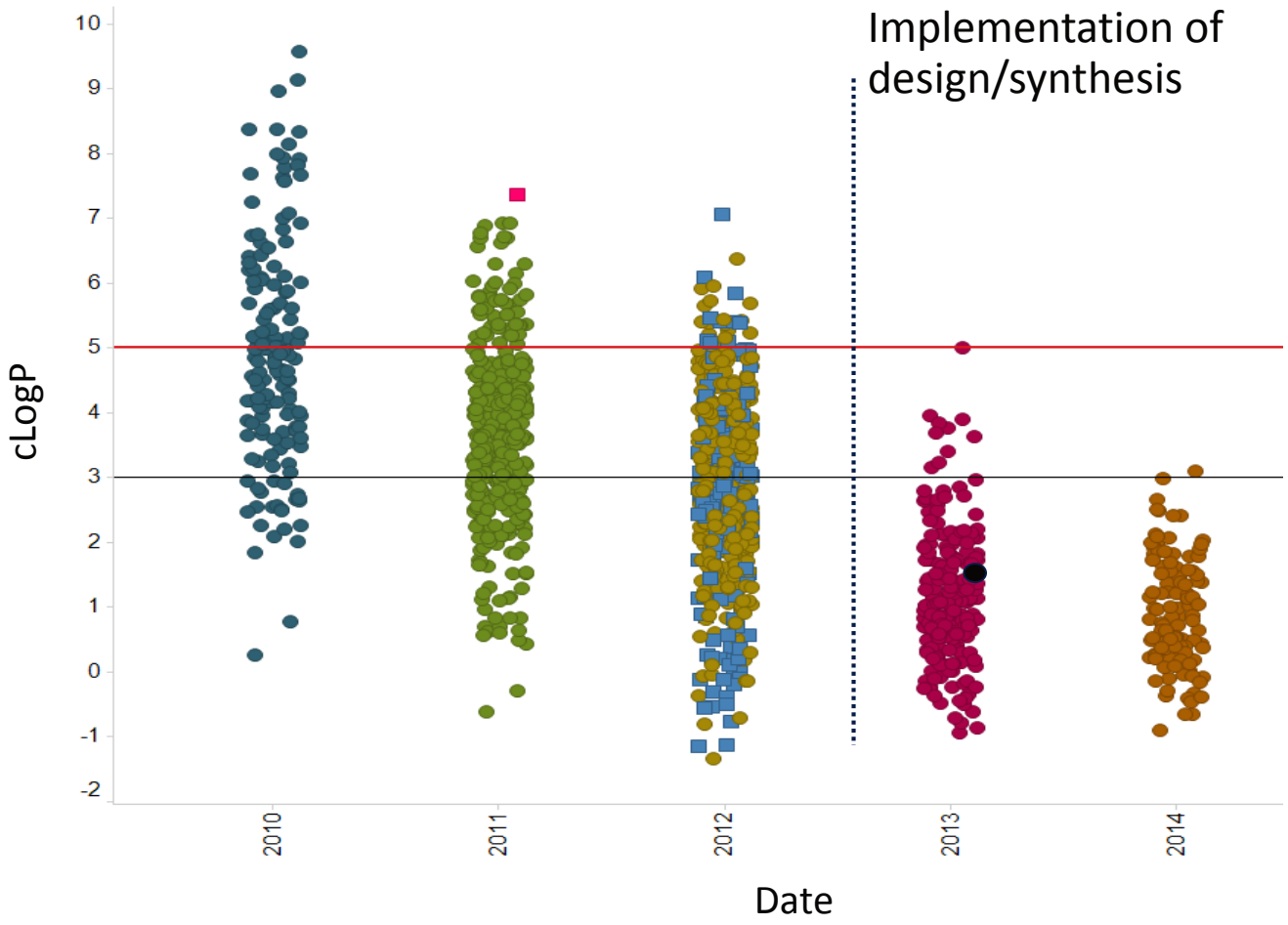
Schrodinger: Glide

BioSolveIT

Hyde - SeeSAR

OpenEye SCIENTIFIC ROCS

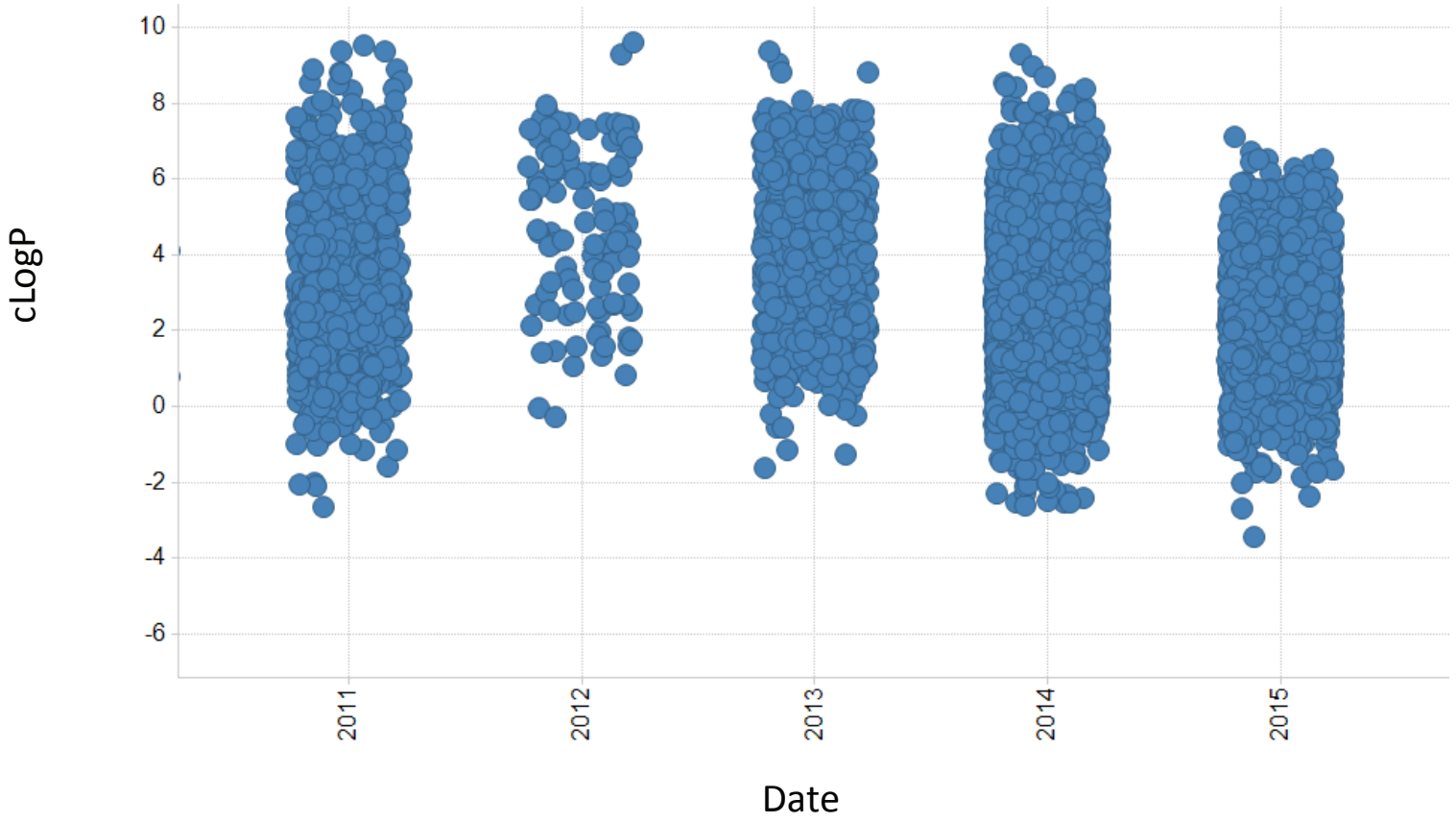
Example 1: Kinase project



- Clear trend into more optimal drug like space over time in parallel with achievement of project goals.

Example 2: Protein – Protein interaction

Compounds prepared by 2 groups of medicinal chemists (same project)



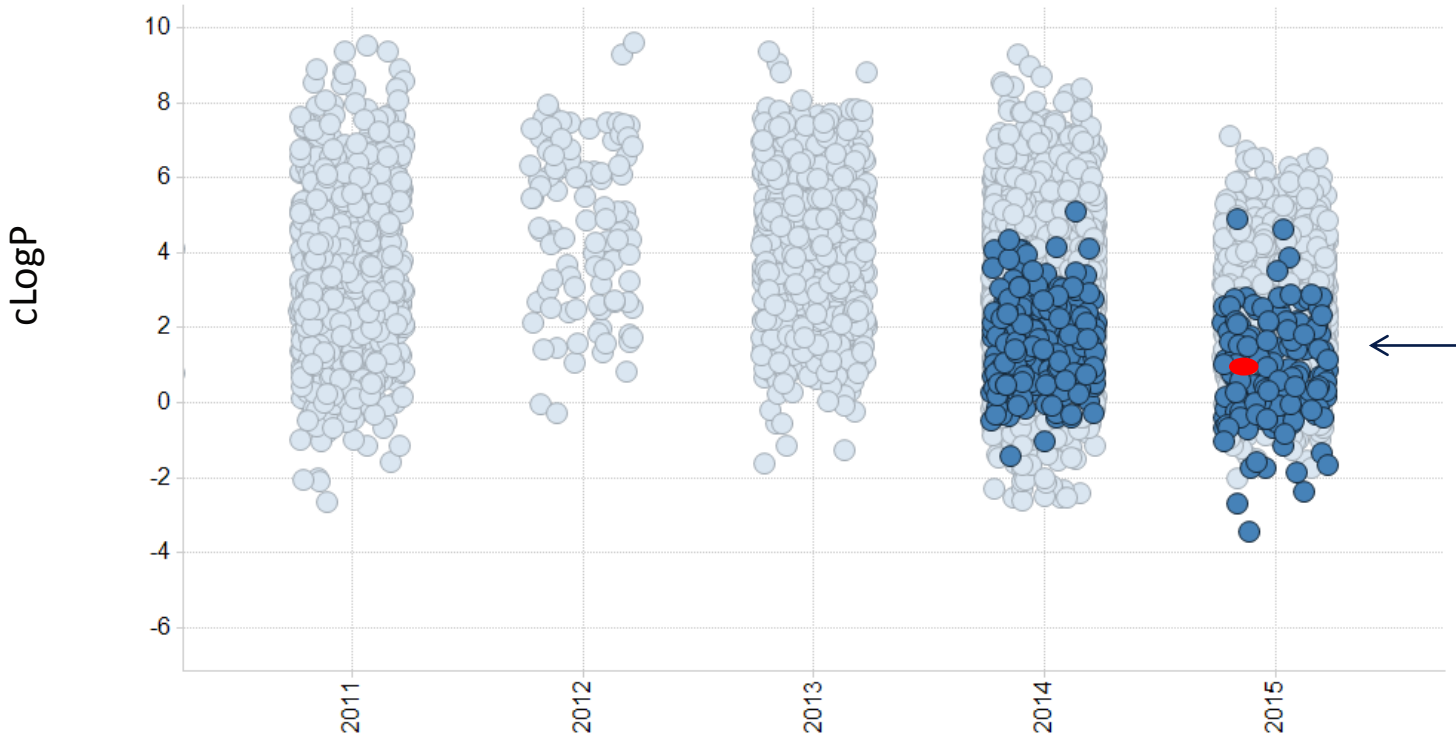
"… but we didn't need umpteen years of upheaval to tell us that making compounds that weight 910 with logP values of 8 are less likely to be successful. Did we?"

Waring, M.J., et al., *An analysis of the attrition of drug candidates from four major pharmaceutical companies.* Nat Rev Drug Discov, 2015. **14**(7): p. 475-486.

Example 2: Protein – Protein interaction

First control physico chemical properties!

What you work on is just as important as what you won't work on:



Chemists working in Design/Synthesis mode

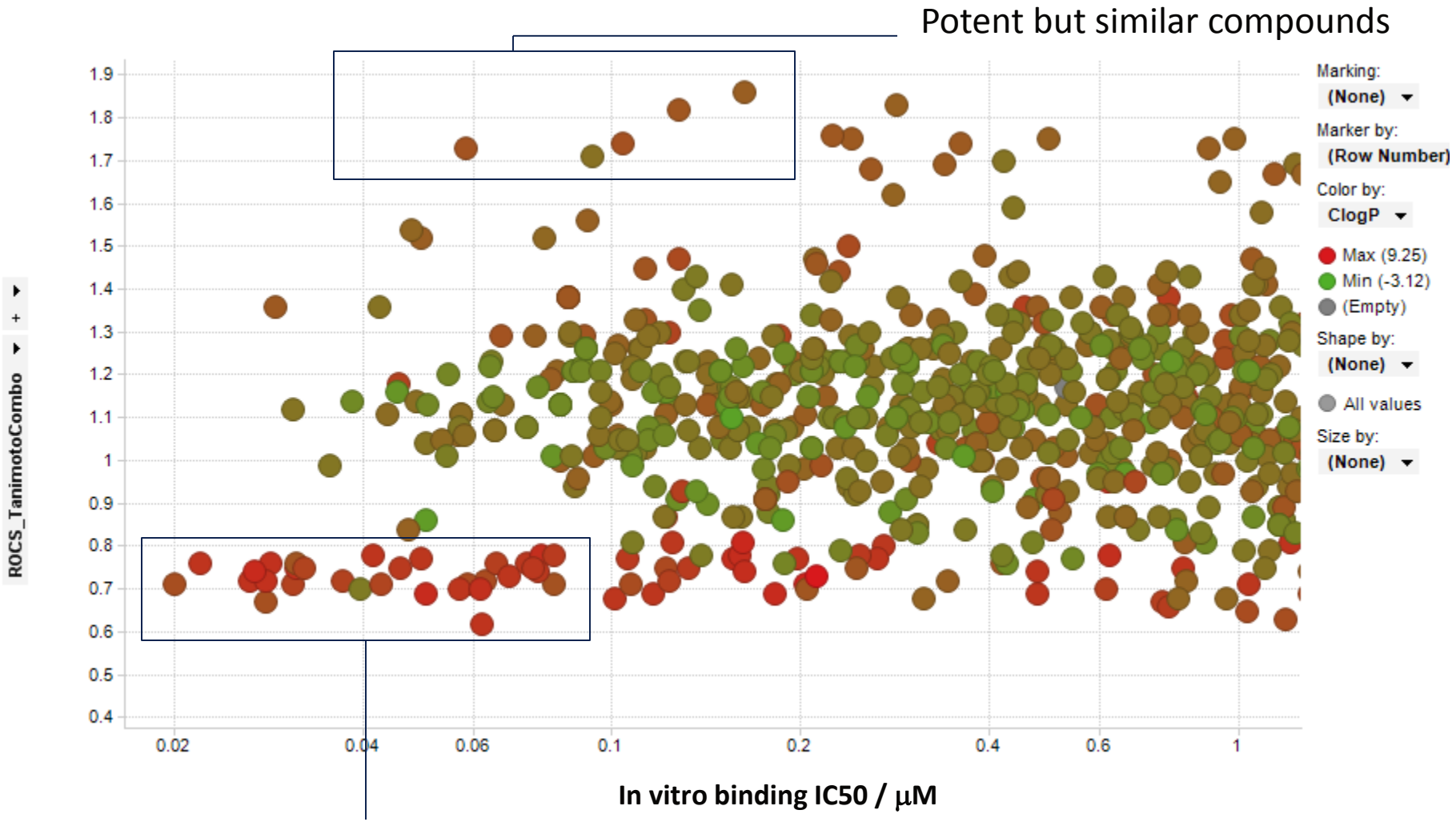
Lead

"… but we didn't need umpteen years of upheaval to tell us that making compounds that weight 910 with logP values of 8 are less likely to be successful. Did we?"

Waring, M.J., et al., *An analysis of the attrition of drug candidates from four major pharmaceutical companies.* Nat Rev Drug Discov, 2015. **14**(7): p. 475-486.

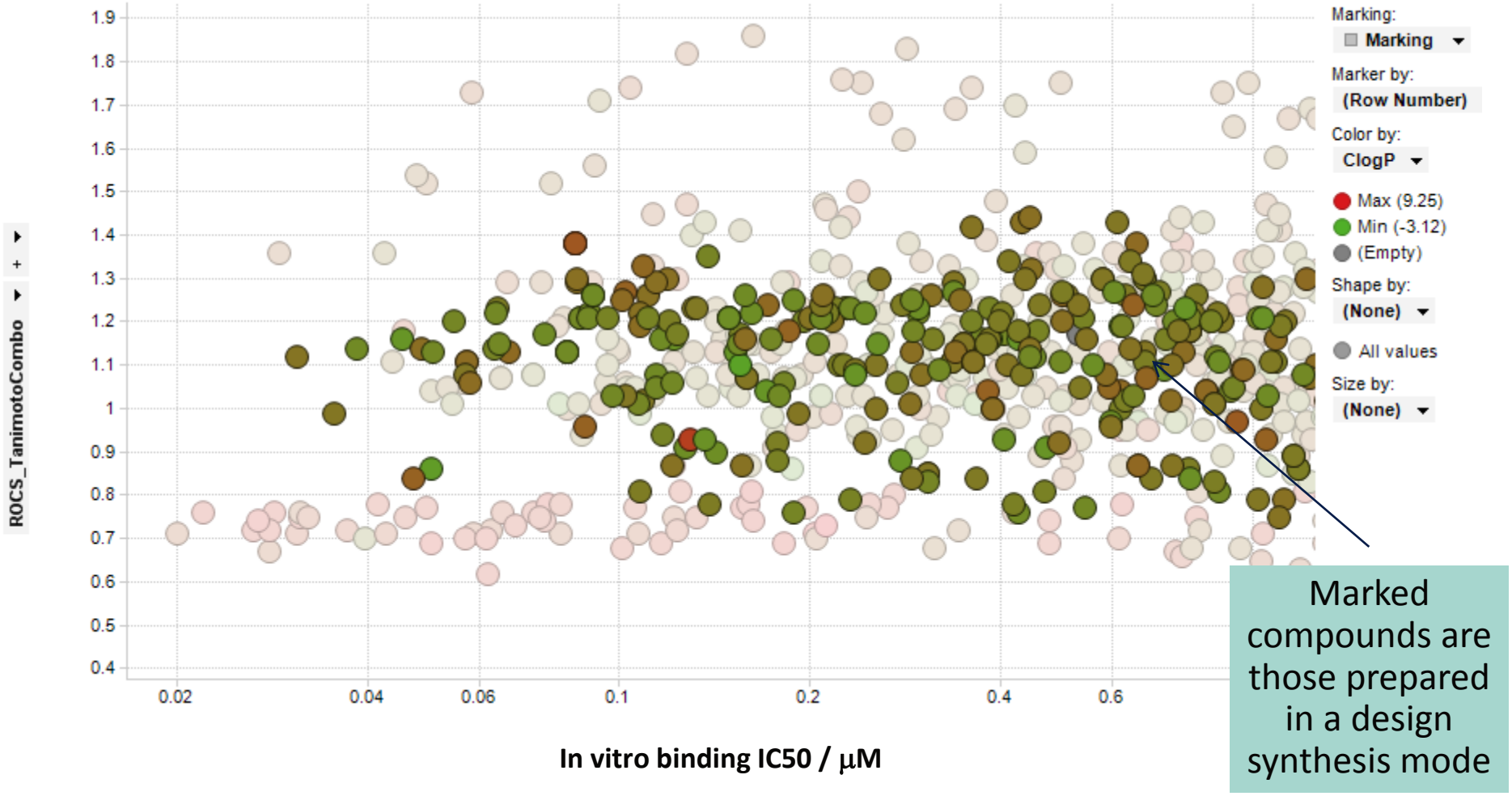
Chemical Structure Similarity – 800 days of compounds

RocsOverlay comparing 3D shape and color to a reference lead



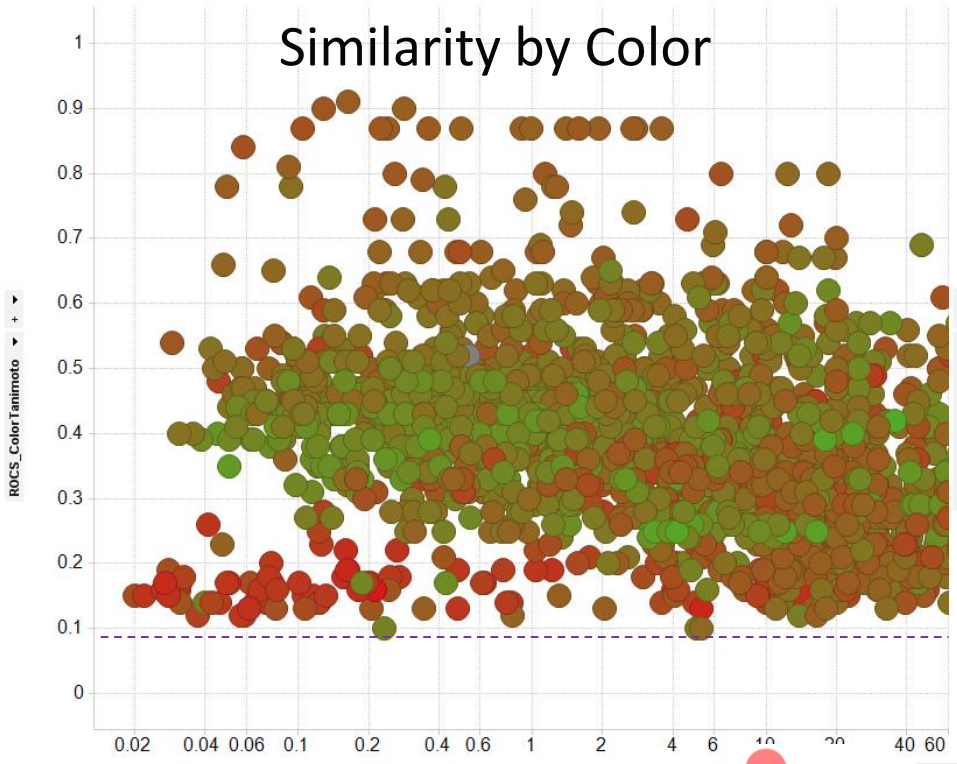
Potent, Lipophilic (~ 7), dissimilar compounds

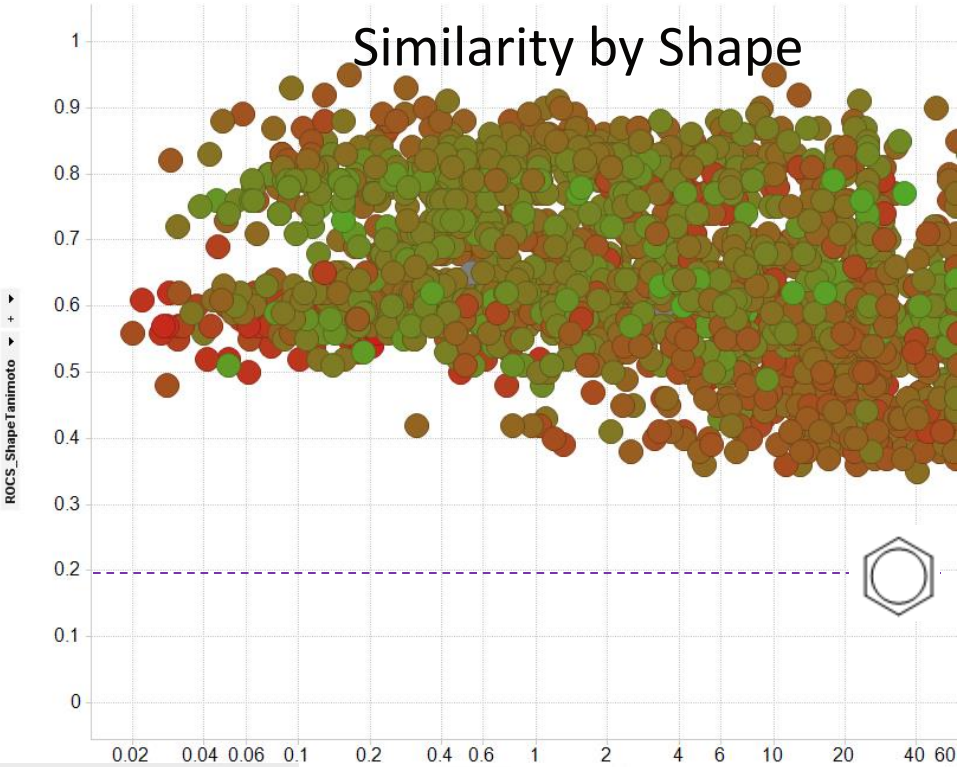
RocsOverlay comparing 3D shape and color of compounds prepared in a design/synthesis mode

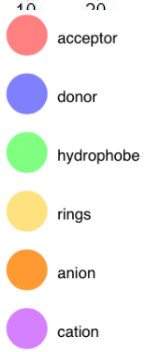


Program maintains a focus on appropriate physico chemical properties, while maximizing dissimilarity from literature lead

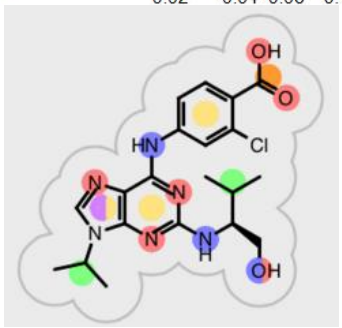
Similarity allows an assessment of the degree of diversity of compounds synthesized in H2L and LO programs

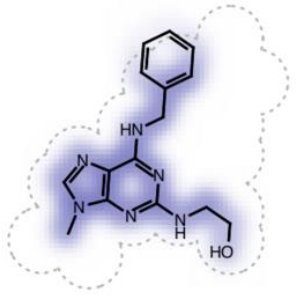




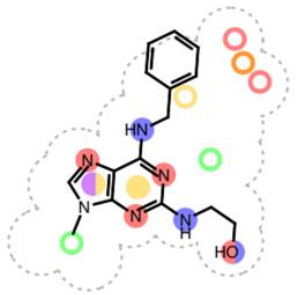


Small changes influence biological activity





Shape Tanimoto = 0.648

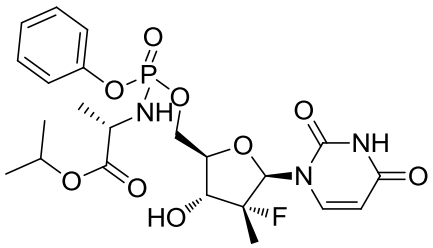


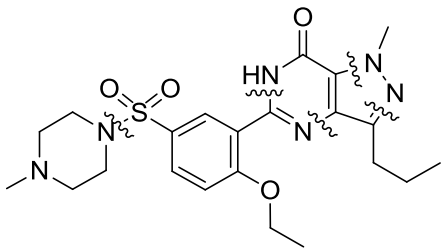
Color Tanimoto = 0.574

Synthesis is design made real

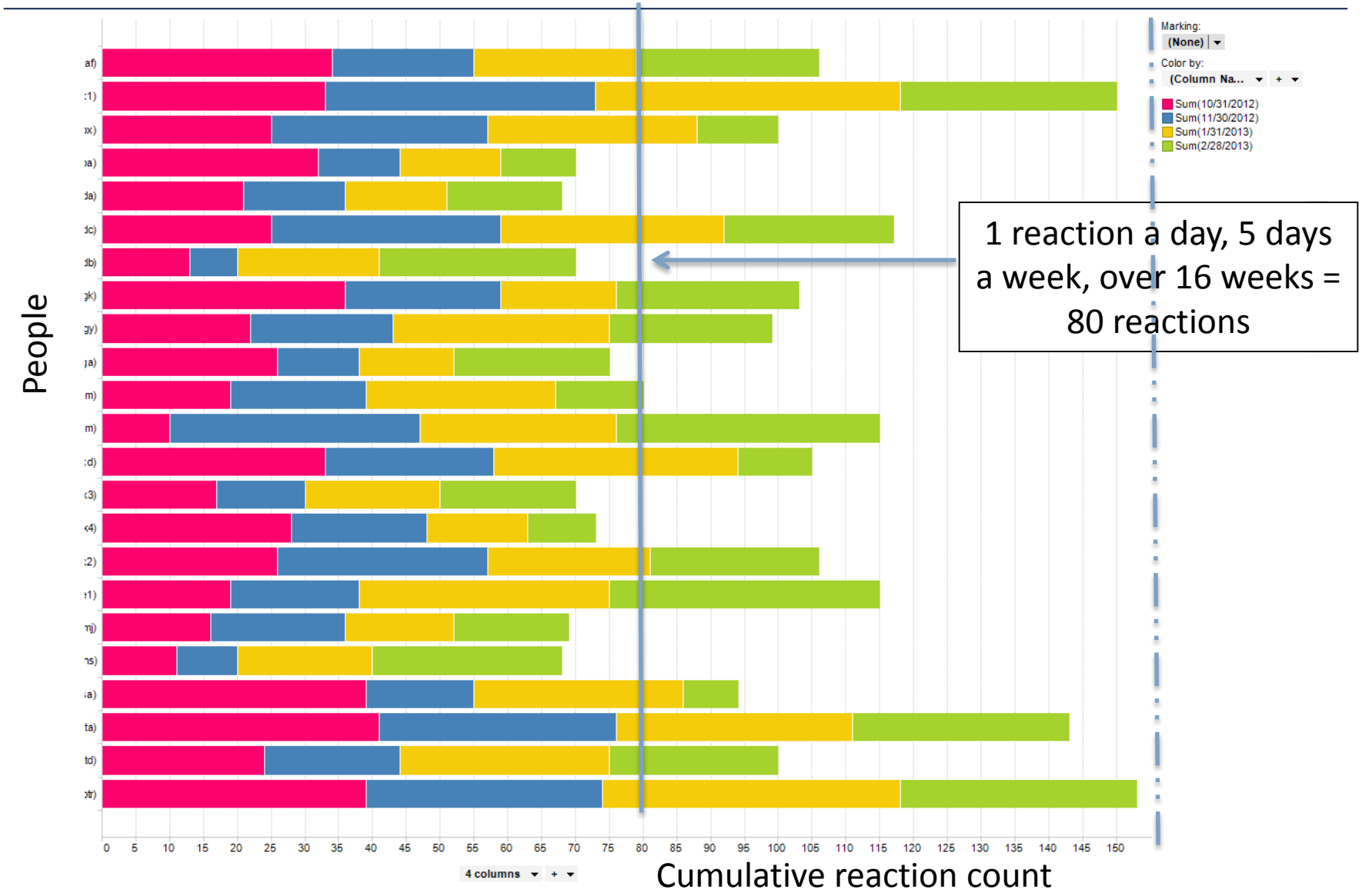
The quality of synthesis depends upon the wisdom/ knowledge of the chemist and their practical skill to complete the synthesis

- Synthetic chemistry knowledge requires familiarity with organic chemistry literature, disconnection skill, and functional group compatibility
- Applicability of flow chemistry, resin supported procedures, parallel synthesis and purification approaches
- Requires experience in triaging multiple potential routes



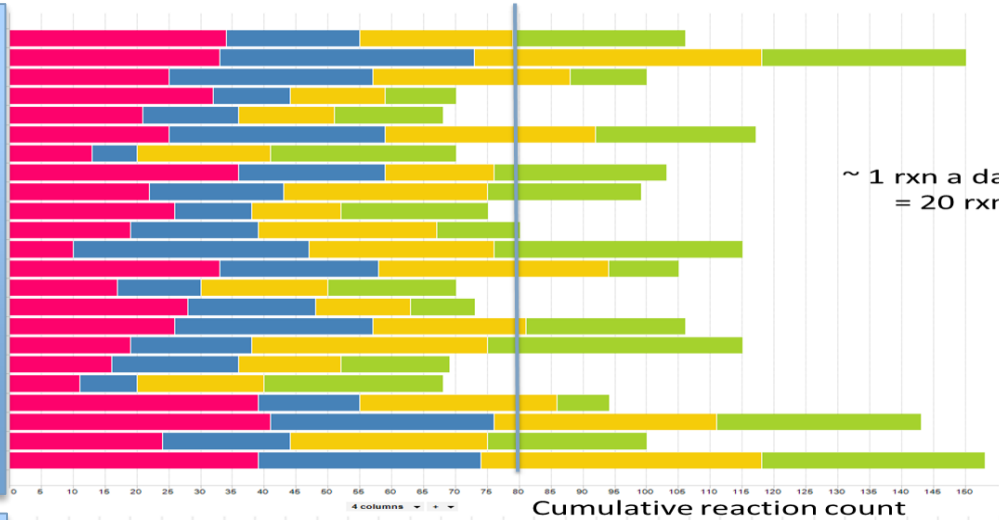


Cumulative number of reactions performed over a 4 month period by traditional medicinal chemists



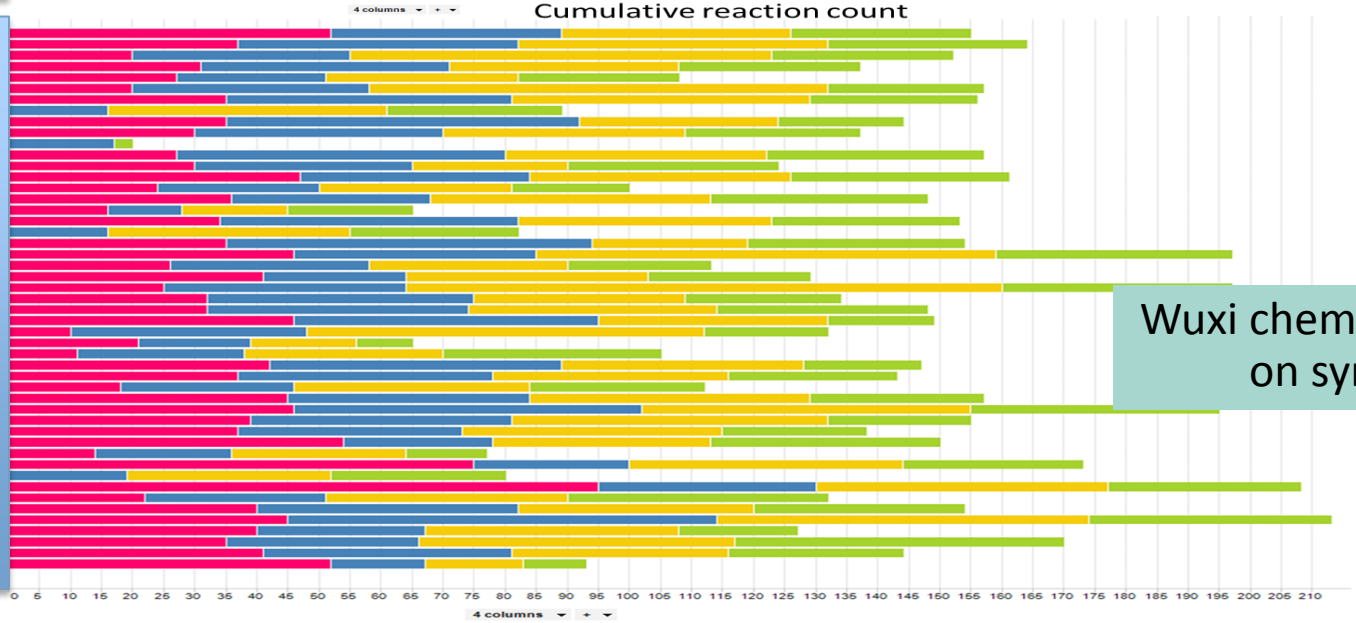
Wuxi and Abbvie Chemistry – same scale

Abbvie Chemistry



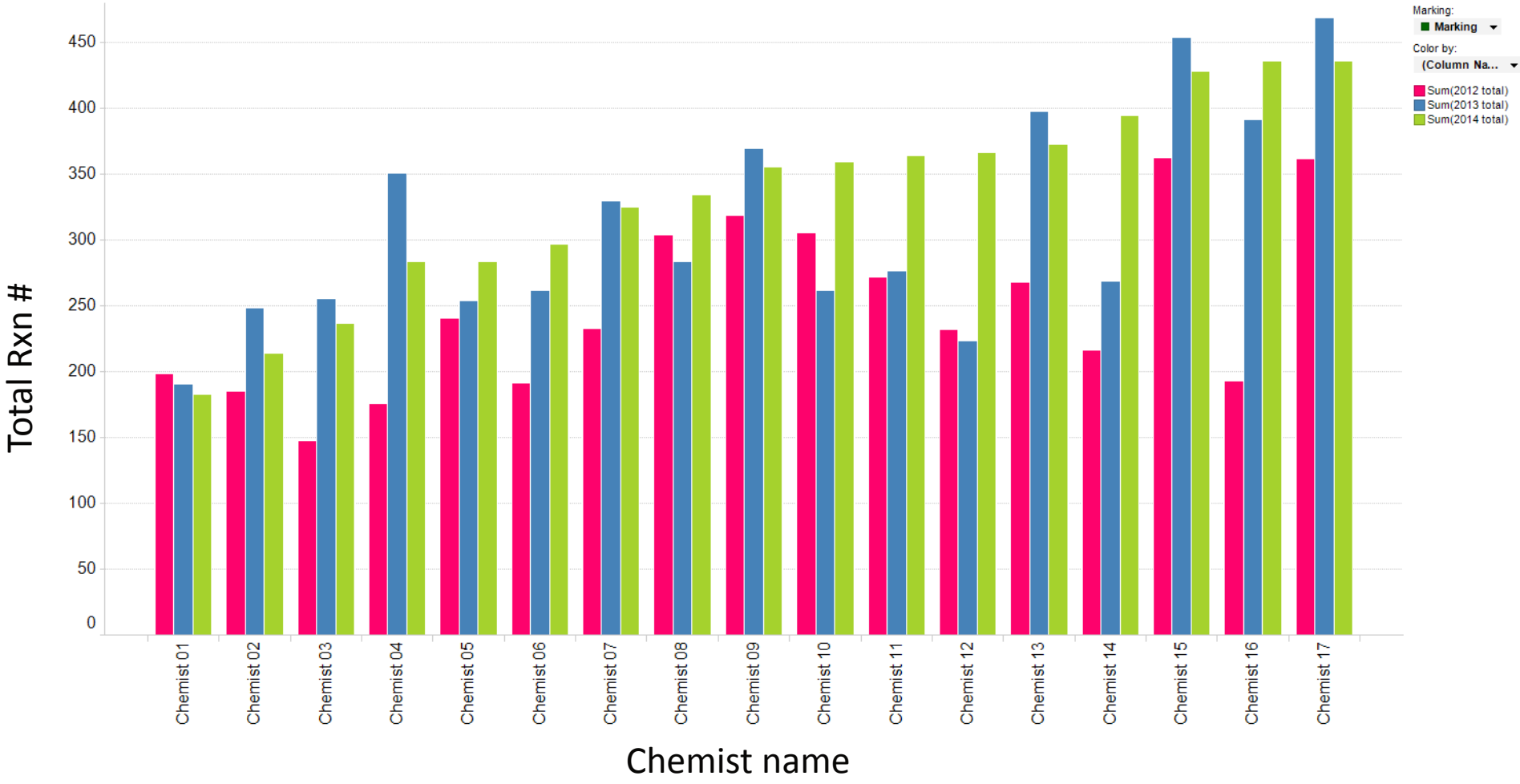
~ 1 rxn a day, 5 days a week
= 20 rxns per month

Wuxi Chemistry



Wuxi chemistry focuses on synthesis

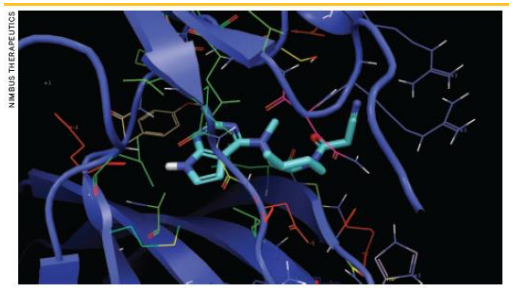
Reaction count Pre-Design/Synthesis (2012) and Post Design/Synthesis (2013, 2014)



Design/Synthesis allowed chemists to focus more effort in the lab synthesizing compounds of increasing complexity

Summary

- ✓ Appropriate application of design tools improves the quality of compounds that are prepared
- ✓ Expertise in synthesis enables the preparation of preferred compounds



NIMBUS THERAPEUTICS

COMPUTATIONAL COMEBACK

COMPUTER MODELING is emerging from the valley of despair in drug discovery

RICK MULLIN, C&EN NEW YORK CITY

C&EN.ACS.ORG 19 JANUARY 25, 2016

If you think you can walk from the lab and do design in your office for a couple of hours and then go back to synthesis, you don't understand the complexity of design or synthesis

Abstract

When one considers the considerable expense that is associated with developing a drug, it is clearly the responsibility of the chemist to ensure that they are preparing the most optimal compound. To achieve this we have focused our efforts within Abbvie medicinal chemistry toward excellence in design and excellence in synthesis. Here we will describe the trials and tribulations of this approach.

Talk title: Medicinal Chemistry is an art, when you don't understand the data. Jeremy J Edmunds, Ph.D., Director, Immunology Medicinal Chemistry, Abbvie