

## **Creme de la creme enrichment:**

**Exploiting the synergy between structure-based (SBDD) and ligand-based (LBDD) drug design.**

March 11, 2005



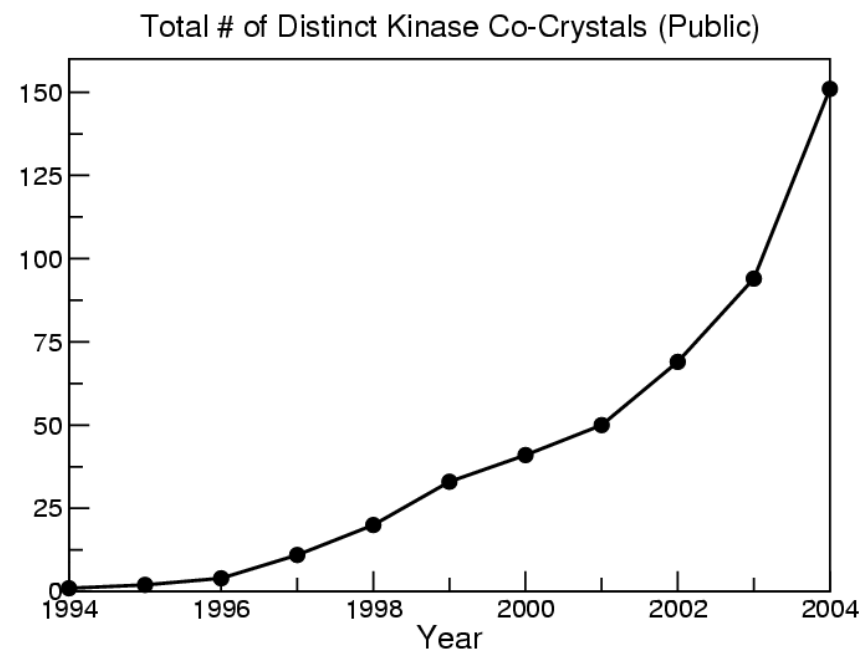
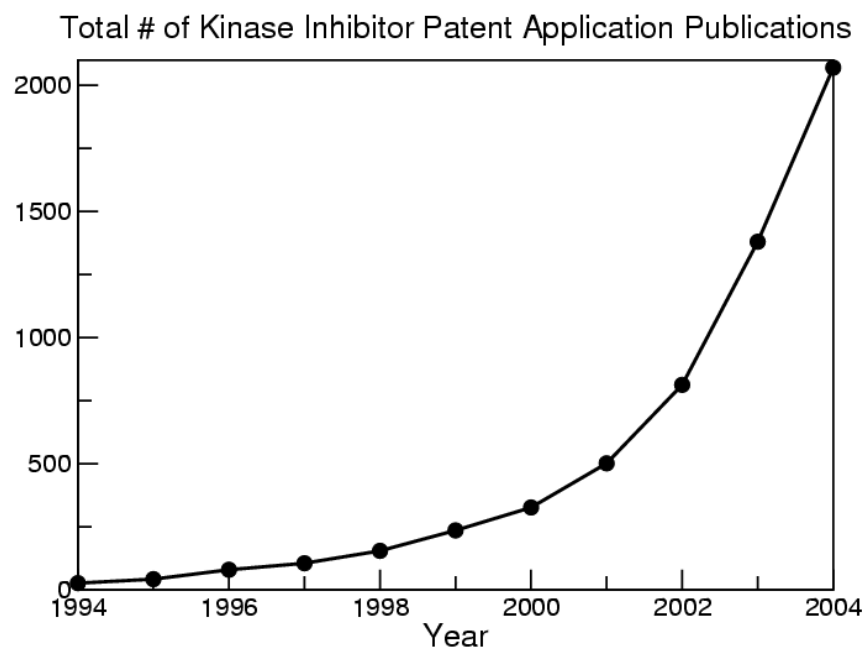
**Steven M. Muskal**  
Chief Executive Officer  
Eidogen-Sertanty, Inc.

# About Eidogen-Sertanty

- Formed from the merger of Eidogen & Sertanty
- Knowledge-based drug discovery solutions provider
  - Target-Based informatics solutions
    - Target Informatics Platform (TIP™)
  - Ligand-Based informatics solutions
    - Kinase Knowledgebase
    - LUCIA™
    - Chemical Intelligence Platform (ChIP™)

# Why a Knowledge Driven Approach?

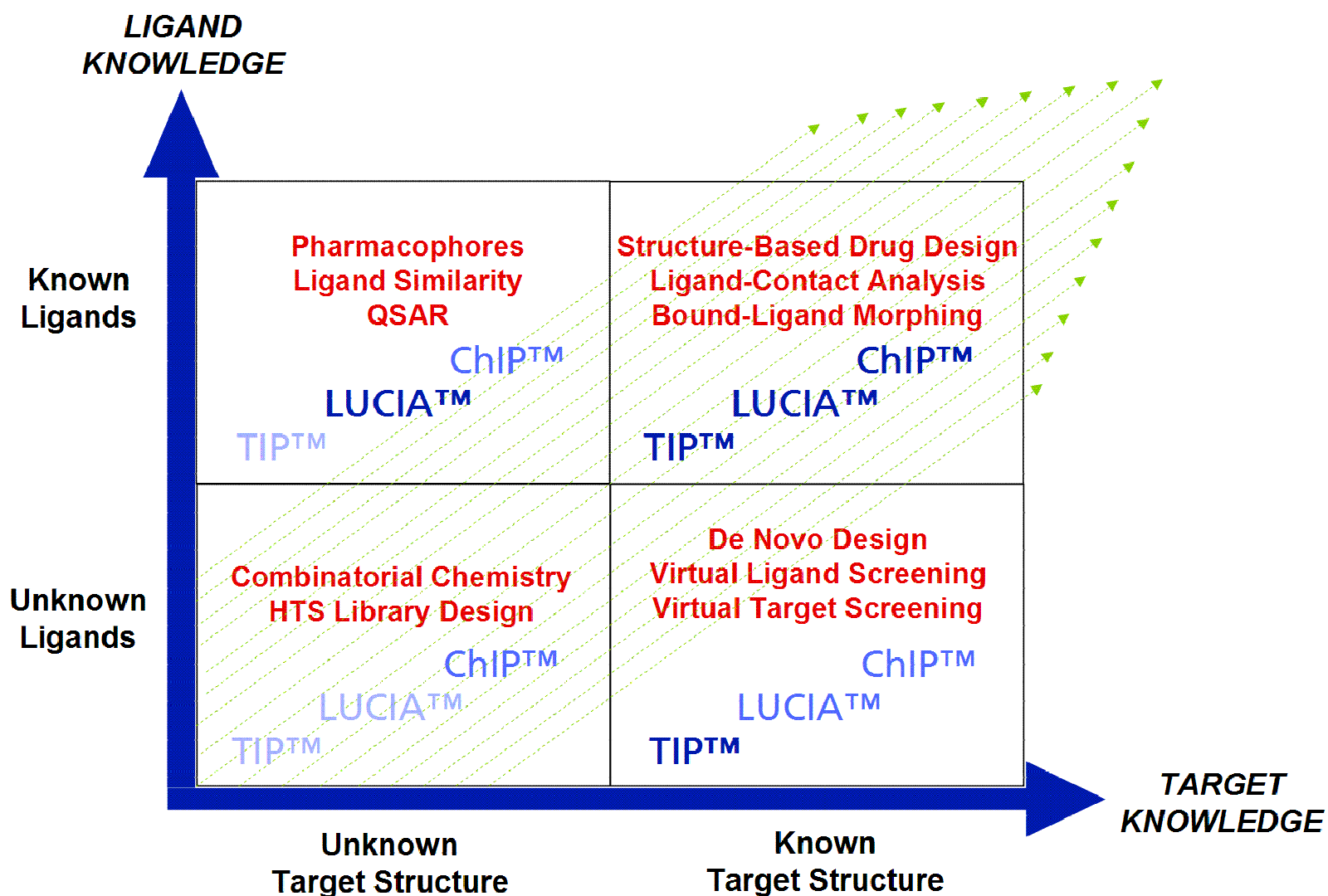
The amount of SAR and structural data available in 2005 dwarfs what was available in the mid 90's



Leveraging earlier successes means reduced costs

Utilizing knowledge means higher success rates

# “Loading the dice of discovery” with knowledge



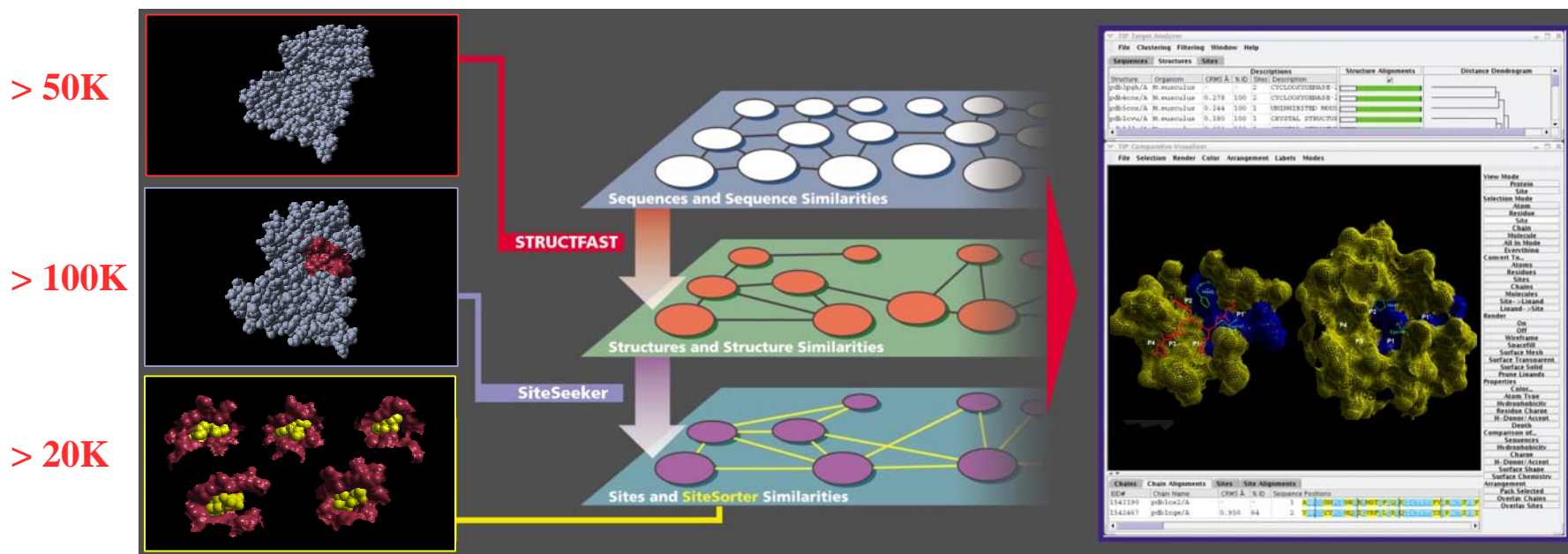
# Integrating Target- and Ligand-based methods

## What follows:

- Enhancing VLS enrichment through combining orthogonal scoring measures from both target-side and ligand-side
- Predicting target cross-reactivity via binding site similarity
- Automated generation of novel inhibitors via recombination of co-crystallized ligands

# Eidogen-Sertanty Target-based Informatics

## Target Informatics Platform™ (TIP™)



## Eidogen Visualization Environment (EVE™)

**ContactSorter**

- Compare Site-Ligand Interaction fingerprints

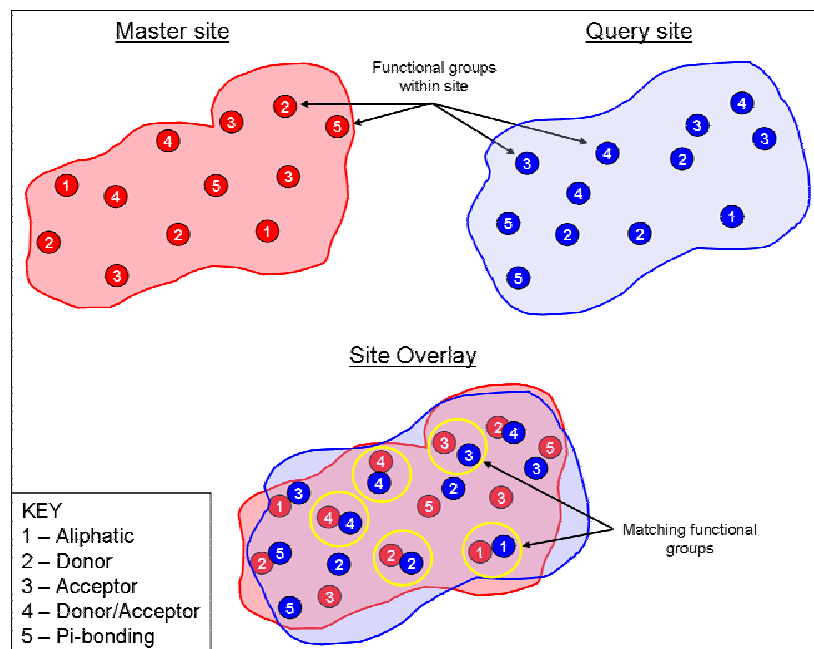
**LigandCross**

- Create novel ligands via recombination of co-crystals



# Target-based: SiteSorter

- Novel algorithm for assessing binding site physicochemical similarity
  - Compare binding sites both within the target family as well as *between* target families



- Explore Target hopping opportunities
- Rationalize unexpected SAR similarity via binding site similarity

# Target-based: ContactSorter

ContactSorter – Re-rank docked ligands relative to other known ligand-target interactions found in co-crystallized examples

Description				Site-Ligand Contacts		Similarity Dendrogram
Site Name	Locus	Description	Contact Similarity			
pdb1di8/s381224 (chain A)	CDK2_HUMAN	DTQ: 4-[3-HYDROXYAN...	-	. I . G T . V . A . K . V . <u>FEFLHOD</u> . K . QN . L . AD . L		
pdb1q3w/s480622 (chain A)	KG3B_HUMAN	ATU: 9-NITRO-5,12-DIH...	0.61	I -- V A K V LDYVP-T R <u>QN</u> L CD E		
pdb1gii/s398693 (chain A)	CDK2_HUMAN	1PU: 1-(5-OXO-2,3,5,9...	0.68	I G- V A K V FEHVHOD T <u>QN</u> L AD -		
pdb1urw/s493669 (chain A)	CDK2_HUMAN	11P: 2-[4-(N-(3-DIMETH...	0.60	I -- V A K V FEFLHOD <u>K</u> <u>QN</u> L AD -		
pdb1gij/s399286 (chain A)	CDK2_HUMAN	2PU: 1-(5-OXO-2,3,5,9...	0.62	I G- V A K V FEHVHOD T <u>QN</u> L AD -		
pdb1e9h/s382695 (chain C)	CDK2_HUMAN	INR: 2',3-DIOXO-1,1',2',...	0.67	I G- V A K V FEFLHOD K QN L AD E		
pdb1e9h/s382694 (chain A)	CDK2_HUMAN	INR: 2',3-DIOXO-1,1',2',...	0.63	I -- V A K V FEFLHOD K QN L AD E		
pdb1v0o/s503736 (chain A)	CC2H_PLAF7	INR: 2',3-DIOXO-1,1',2',...	0.62	I -- V A K V FEHL-QD K <u>QN</u> L AD -		
pdb1v0o/s503737 (chain B)	CC2H_PLAF7	INR: 2',3-DIOXO-1,1',2',...	0.62	I G- V A K V FEHL-QD K <u>QN</u> L AD -		
pdb1fw/s400601 (chain C)	CDK2_HUMAN	107: 4-[(7-OXO-7H-THI...	0.64	<u>I</u> -- V A K V FEFLHOD <u>K</u> QN L AD E		
pdb1vyz/s503568 (chain A)	CDK2_HUMAN	N5B: N-(5-CYCLOPROP...	0.67	I -- V A K V FEFL-QD K Q- L AD -		
pdb1jvp/s424348 (chain P)	CDK2_HUMAN	LIG: 3-PYRIDIN-4-YL-2',...	0.71	I -- V A K V FEFLHOD K QN L AD -		
pdb1uki/s522815 (chain A)	MK08_XENLA	537: 2,6-DIHYDROANT...	0.70	I -- V A K I MELMDAN - S- V L - -		
pdb1pmw/s472060 (chain A)	MK10_HUMAN	537: 2,6-DIHYDROANT...	0.67	I -- V A K I MELMDAN Q S- V L - -		
pdb1ckp/s370369 (chain A)	CDK2_HUMAN	PVB: PURVALANOL_ /1	0.60	I -- V A K V FEFL-QD K Q- L AD -		
pdb1ke5/s424829 (chain A)	CDK2_HUMAN	LS1: N-METHYL-4-[(2-...	0.63	I -- V A K V FEFL-QD <u>K</u> QN L AD -		
pdb1pf8/s453902 (chain A)	CDK2_HUMAN	SU9: (3Z)-3-(1H-IMIDAZ...	0.63	I -- V A K V FEFL-QD K QN L AD -		

KEY: Yellow = hydrophobic  
 Red = electrostatic  
 Blue = hydrogen bond  
 Purple = H-bond + electrostatic  
 Underline = backbone interaction



# Target-based: ContactSorter – VLS analysis

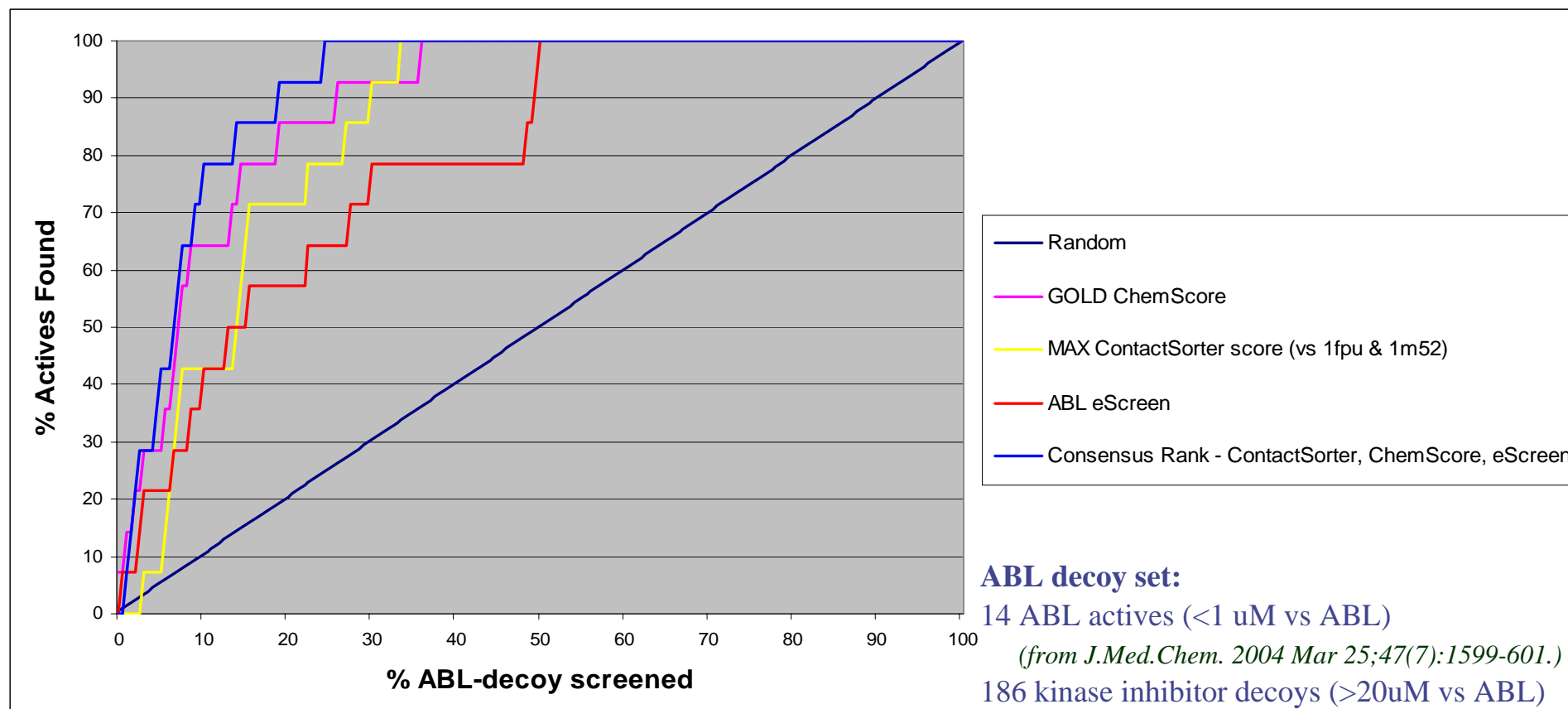
- Load docked compounds and compare contacts to reference ligands

The screenshot displays the ContactSorter software interface. The main window is titled 'Site-Ligand Contacts' and contains a table with the following columns: Site Name, Locus, Description, Contact Similarity, and Docking Score. The table lists 30 docked compounds, each with its corresponding site name, locus, description, contact similarity score, and docking score. To the right of the table is a 'Similarity Dendrogram' showing the hierarchical clustering of the compounds based on their contact similarity scores. The dendrogram shows that compounds with similar contact similarity scores cluster together, indicating similar binding modes.

Site Name	Locus	Description	Contact Similarity	Docking Score
pdb1m52s449830 (chain A)	ABL_MLVAB	P17: 6-(2,6-DICHLORO...	-	-
pdb1m52s449830_137 (chain A)	ABL_MLVAB	9871	0.68	29.340
pdb1m52s449830_138 (chain A)	ABL_MLVAB	9871_2	0.69	27.810
pdb1m52s449830_136 (chain A)	ABL_MLVAB	50004919_5	0.71	32.010
pdb1m52s449830_135 (chain A)	ABL_MLVAB	50004919_4	0.75	32.580
pdb1m52s449830_43 (chain A)	ABL_MLVAB	50004902_3	0.66	31.190
pdb1m52s449830_153 (chain A)	ABL_MLVAB	9872_9	0.69	31.980
pdb1m52s449830_145 (chain A)	ABL_MLVAB	9872	0.65	33.820
pdb1m52s449830_147 (chain A)	ABL_MLVAB	9872_3	0.69	33.090
pdb1m52s449830_26 (chain A)	ABL_MLVAB	11115_2	0.54	22.540
pdb1m52s449830_27 (chain A)	ABL_MLVAB	11115_3	0.57	21.600
pdb1m52s449830_141 (chain A)	ABL_MLVAB	9871_5	0.57	26.010
pdb1m52s449830_67 (chain A)	ABL_MLVAB	2425902_5	0.57	35.950
pdb1m52s449830_68 (chain A)	ABL_MLVAB	2425902_6	0.50	35.330
pdb1m52s449830_25 (chain A)	ABL_MLVAB	11115	0.38	23.240
pdb1m52s449830_64 (chain A)	ABL_MLVAB	2425902_2	0.57	37.440
pdb1m52s449830_19 (chain A)	ABL_MLVAB	7233	0.55	26.340
pdb1m52s449830_21 (chain A)	ABL_MLVAB	7233_3	0.48	25.740
pdb1m52s449830_20 (chain A)	ABL_MLVAB	7233_2	0.59	25.840
pdb1m52s449830_65 (chain A)	ABL_MLVAB	2425902_3	0.57	36.820
pdb1m52s449830_63 (chain A)	ABL_MLVAB	2425902	0.54	37.780
pdb1m52s449830_66 (chain A)	ABL_MLVAB	2425902_4	0.55	36.640
pdb1m52s449830_139 (chain A)	ABL_MLVAB	9871_3	0.62	27.350
pdb1m52s449830_31 (chain A)	ABL_MLVAB	50004869_3	0.70	30.430
pdb1m52s449830_111 (chain A)	ABL_MLVAB	50004917_3	0.67	29.260
pdb1m52s449830_157 (chain A)	ABL_MLVAB	50004862_3	0.68	32.560
pdb1m52s449830_58 (chain A)	ABL_MLVAB	50004924_3	0.68	32.690
pdb1m52s449830_42 (chain A)	ABL_MLVAB	50004902_2	0.70	31.840
pdb1m52s449830_54 (chain A)	ABL_MLVAB	50004884_2	0.68	30.960

- Re-rank docking poses using Contact Similarity scores
- Group molecules by binding mode
- Compare contacts to multiple structure conformations
  - Understand which compounds are binding to which conformation (e.g. DFG-out vs. DFG-in conformations of ABL)

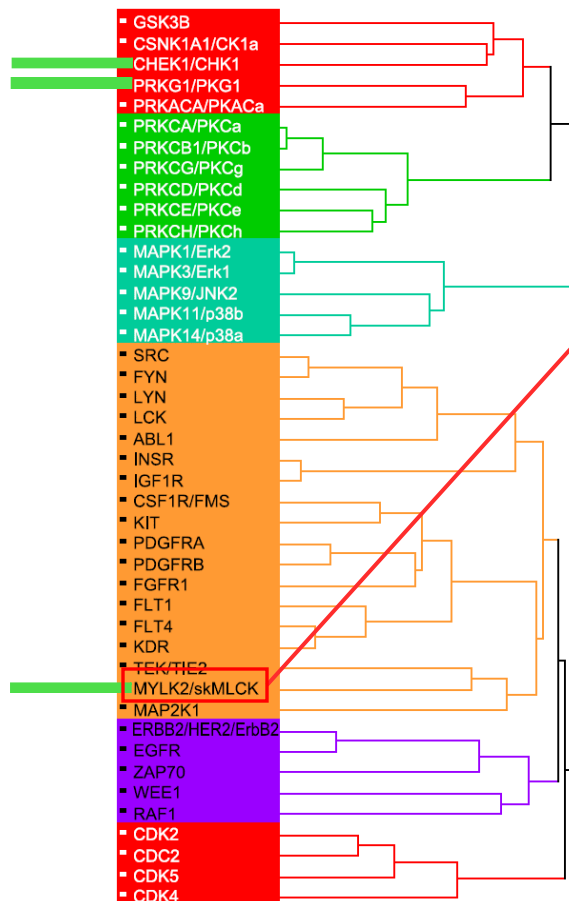
# Target- and Ligand-based Enrichment - ABL



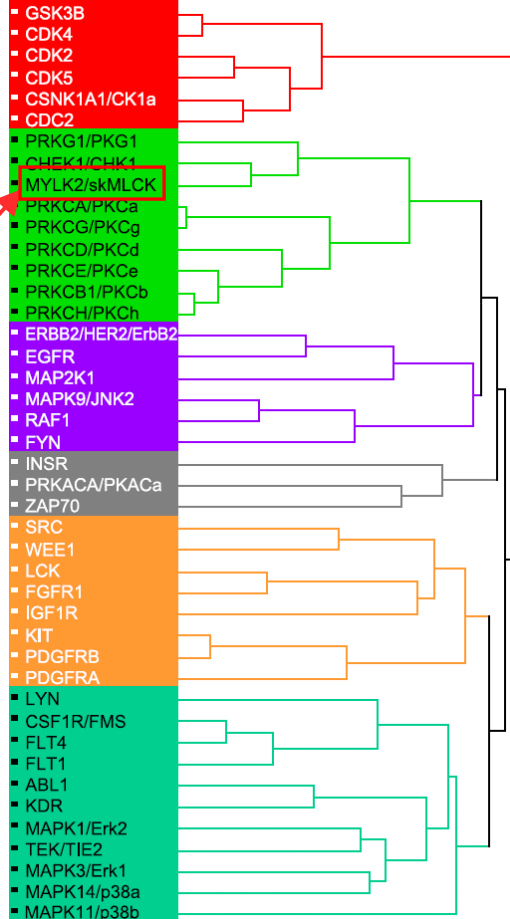
**Consensus ranking of ligand- and target-based methods  
gives best enrichment**

# Binding site cross-reactivity prediction

## Kinase Sequence Similarity



## Experimental SAR Data



## 10 Most Similar by Binding Site %ID

MYLK2/skMLCK

PRKACA/PKACa

PRKCG/PKCg

CHEK1/CHK1

PRKCE/PKCe

PRKCH/PKCh

PRKCD/PKCd

FGFR1

ZAP70

MAP2K1/MEK1

PRKCA/PKCa

71%

67%

63%

63%

63%

63%

63%

63%

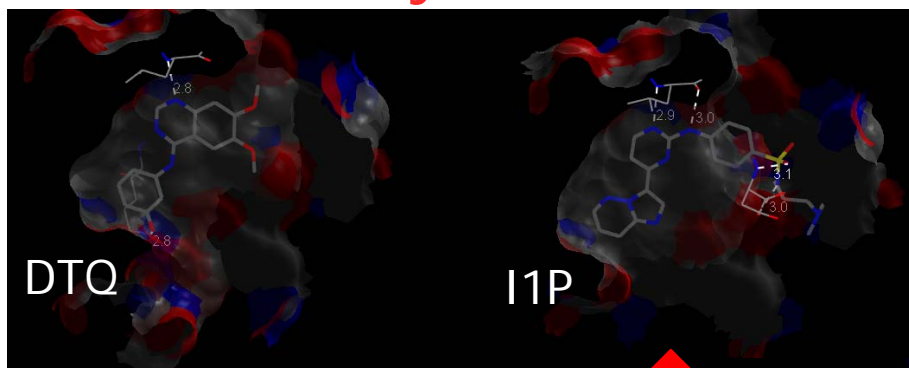
63%

58%

Global annotation of binding site similarity leads to more accurate predictions of cross-reactivity

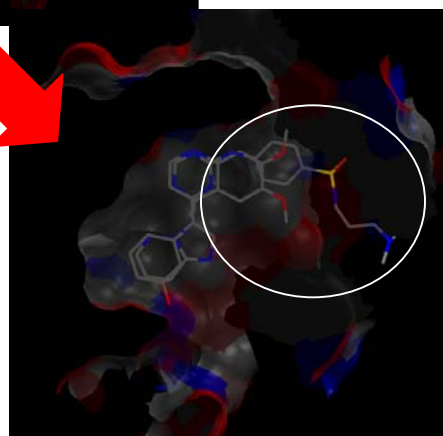
# Integrating Target-Based and Ligand-Based: LigandCross

## CDK2 co-crystal sites



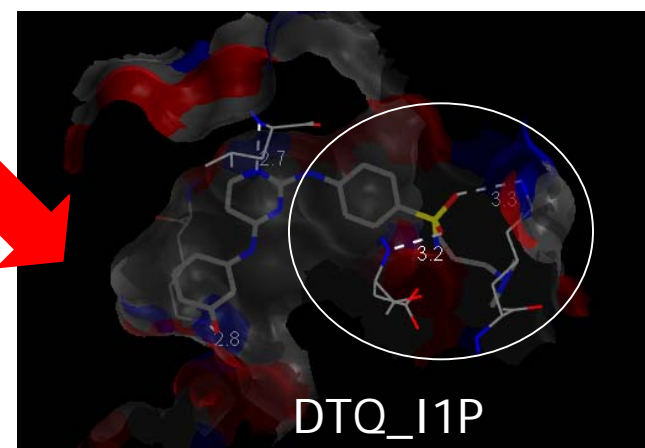
Generate novel ligands by recombining known binding fragments from co-crystal structures

Load multiple co-crystal sites



Overlay sites

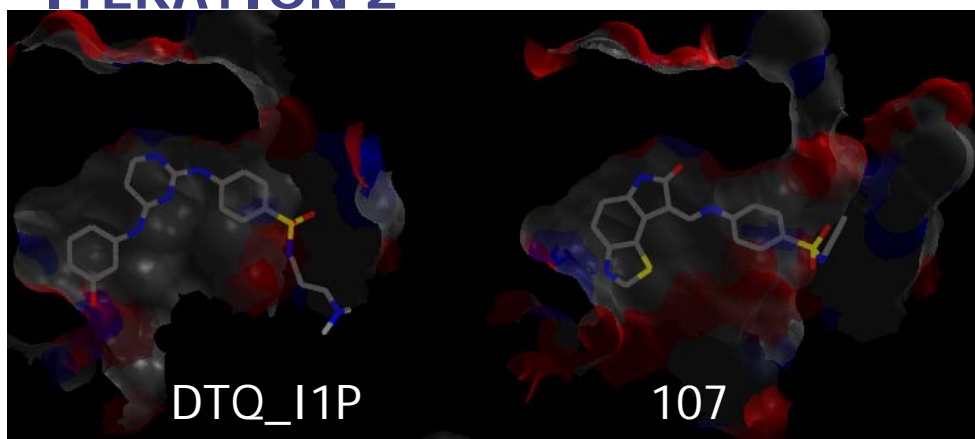
ITERATION 1



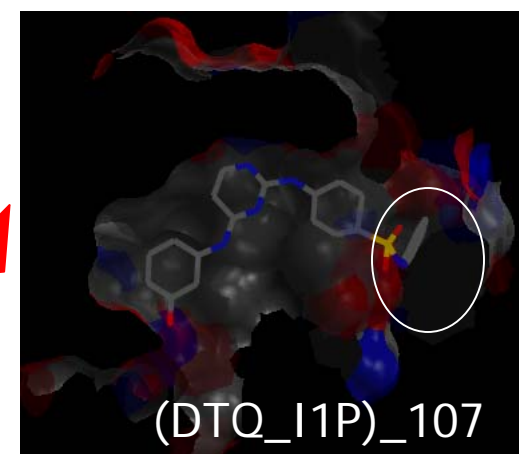
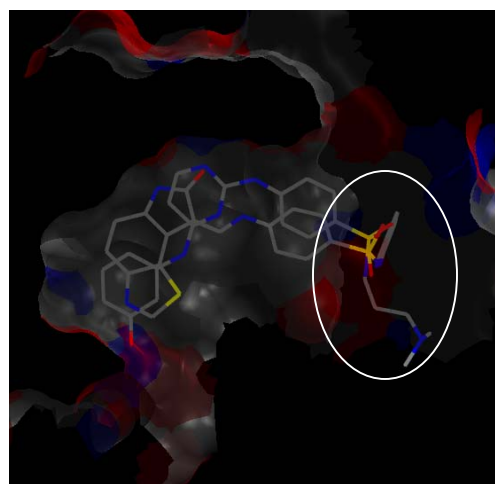
Recombine ligands

# LigandCross

## ITERATION 2

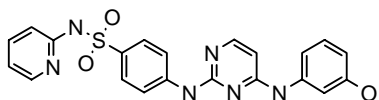


Leverage co-crystal and docked structural information to build libraries of likely binders



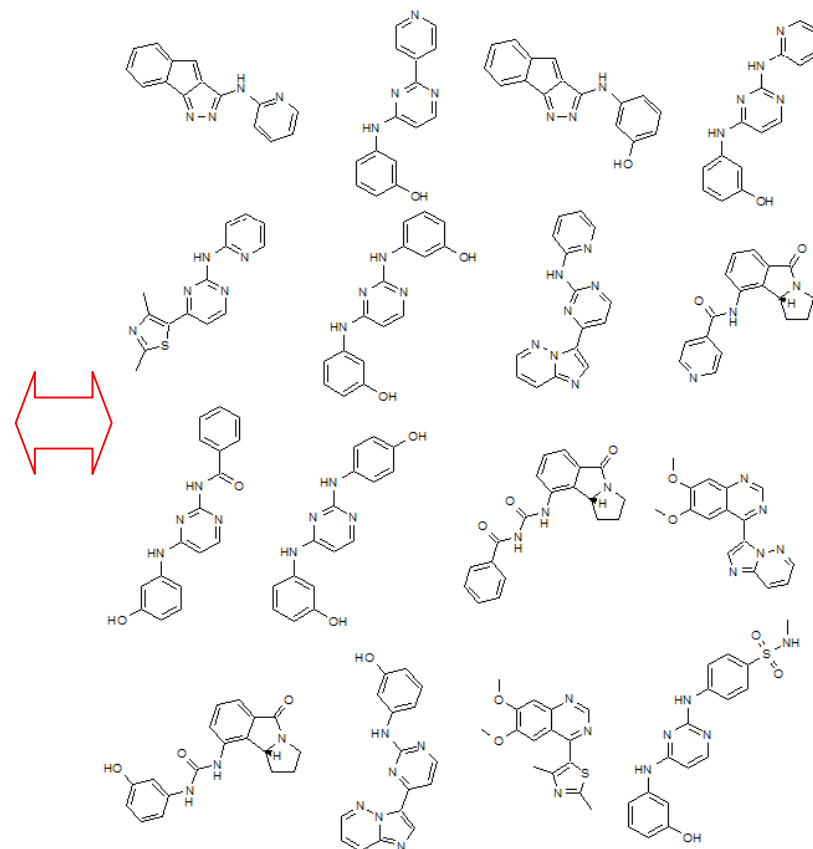


# LigandCross + ContactSorter



Sample CDK2 LigandCross molecules after 3 iterations (15 starting co-crystals)

File Filtering Window Help			
Sequences Chains Sites Site-Ligand Contacts			
Description		Site-Ligand Contacts	
Site No.	Locus	Description	Contact Similarity
pdb1 di...	CDK2...	DTQ: 4-[3-HYDROXYANILINO]...	-
pdb1 di...	CDK2...	DTQ_H1P_1	0.85
pdb1 di...	CDK2...	((DTQ_H1P_2)_107_1)_ALH_1	0.80
pdb1 di...	CDK2...	((((DTQ_H1P_2)_107_1)_LS1...	0.67
pdb1 di...	CDK2...	((((DTQ_H1P_2)_107_1)_LS1...	0.71
pdb1 di...	CDK2...	((DTQ_H1P_2)_107_1)_LS1...	0.68
pdb1 di...	CDK2...	((((DTQ_H1P_2)_107_1)_LS1...	0.71
pdb1 di...	CDK2...	((((DTQ_H1P_2)_107_1)_LS1...	0.73
pdb1 di...	CDK2...	((((DTQ_H1P_2)_107_1)_LS1...	0.67
pdb1 di...	CDK2...	((((DTQ_H1P_2)_107_1)_LS1...	0.71
pdb1 di...	CDK2...	((((DTQ_H1P_2)_107_1)_LS1...	0.68
pdb1 di...	CDK2...	((((DTQ_H1P_2)_107_1)_LS1...	0.64
pdb1 di...	CDK2...	((((DTQ_H1P_2)_107_1)_LS1...	0.63
pdb1 di...	CDK2...	((DTQ_H1P_2)_107_2	0.67
pdb1 di...	CDK2...	((DTQ_H1P_2)_107_1)_LS1...	0.67
pdb1 di...	CDK2...	((((DTQ_H1P_2)_107_1)_LS1...	0.62
pdb1 di...	CDK2...	((((DTQ_H1P_2)_107_1)_LS1...	0.65
pdb1 di...	CDK2...	((DTQ_H1P_2)_107_1)_LS1_2	0.58
pdb1 di...	CDK2...	((((DTQ_H1P_2)_107_1)_LS1...	0.58
pdb1 di...	CDK2...	((DTQ_H1P_2)_107_1)_LS1...	0.57
pdb1 di...	CDK2...	(DTQ_H1P_2)_107_1	0.64
pdb1 di...	CDK2...	((DTQ_H1P_2)_107_1)_H1P_1	0.54
pdb1 di...	CDK2...	((DTQ_H1P_2)_107_1)_LS1...	0.46
pdb1 di...	CDK2...	((((DTQ_H1P_2)_107_1)_LS1...	0.50
pdb1 di...	CDK2...	(DTQ_H1P_2)_107_1)_ALH_2	0.43
pdb1 di...	CDK2...	((DTQ_H1P_2)_107_1)_LS1_1	0.70
pdb1 di...	CDK2...	DTQ_H1P_2	0.74
pdb1 di...	CDK2...	((DTQ_H1P_2)_107_1)_LS1...	0.58

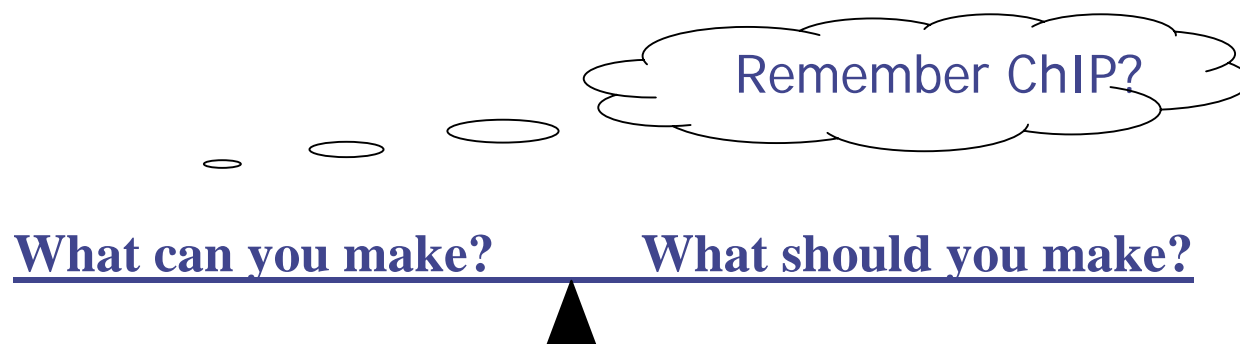


Fast, scalable method suitable for any target where multiple co-crystal or docked structures are available



# LigandCross → ChIP

➤ **ChIP** with LigandCross(ed) molecules to create synthetically accessible libraries with likely binding affinity toward target(s) of interest



- Forward, prospective exploration of existing and newly coupled synthetic strategies
- “Mixing-n-matching” synthetic protocols to generate novel, synthetically accessible molecules

# Future Directions

- Combine docking, ContactSorter, and eScreen data *across multiple targets* to further enhance enrichment factors
- Customizable ContactSorter scoring tuned for specific targets or compound classes
- Integrate technologies to produce automated feedback loop of: compounds → eScreen → Dock → Contact Similarity analysis → Automated recombination of ligands → ChIP Simulation → Design focused, synthetically accessible libraries

# Acknowledgements

- Kevin Hambly
- Stephan Schürer
- Joe Danzer
- Brian Palmer
- Aleksandar Poleksic
- Derek Debe