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™)

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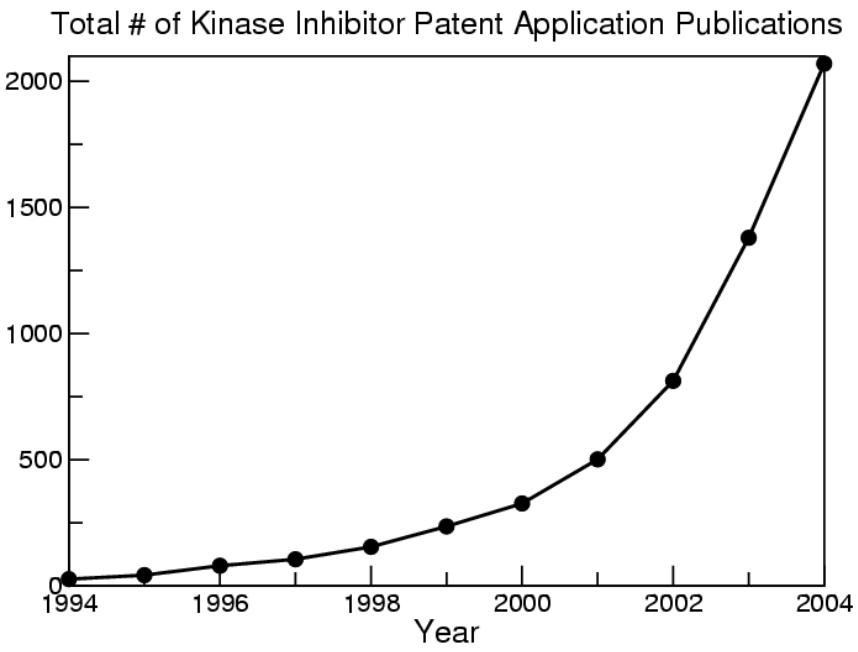
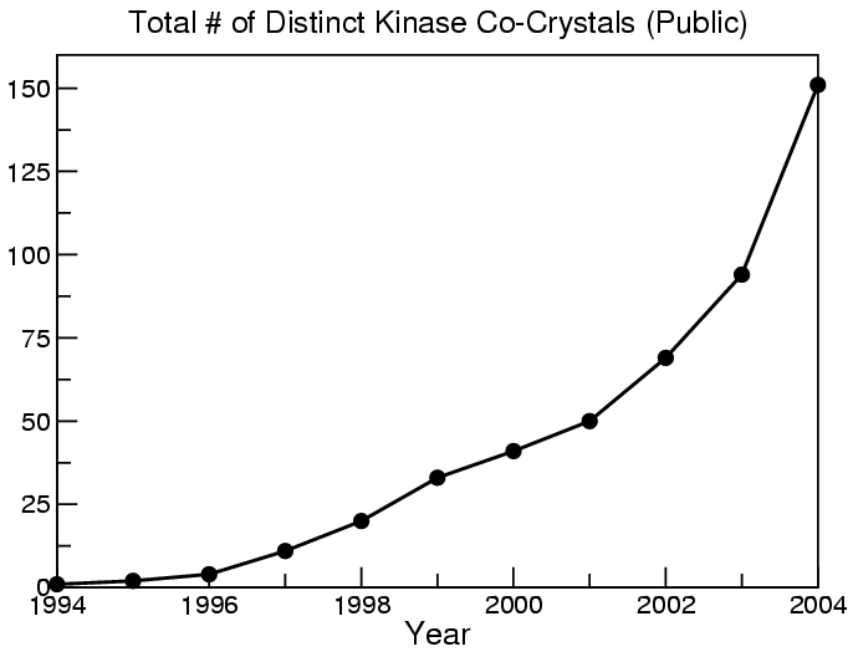
Why a Knowledge Driven Approach?

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

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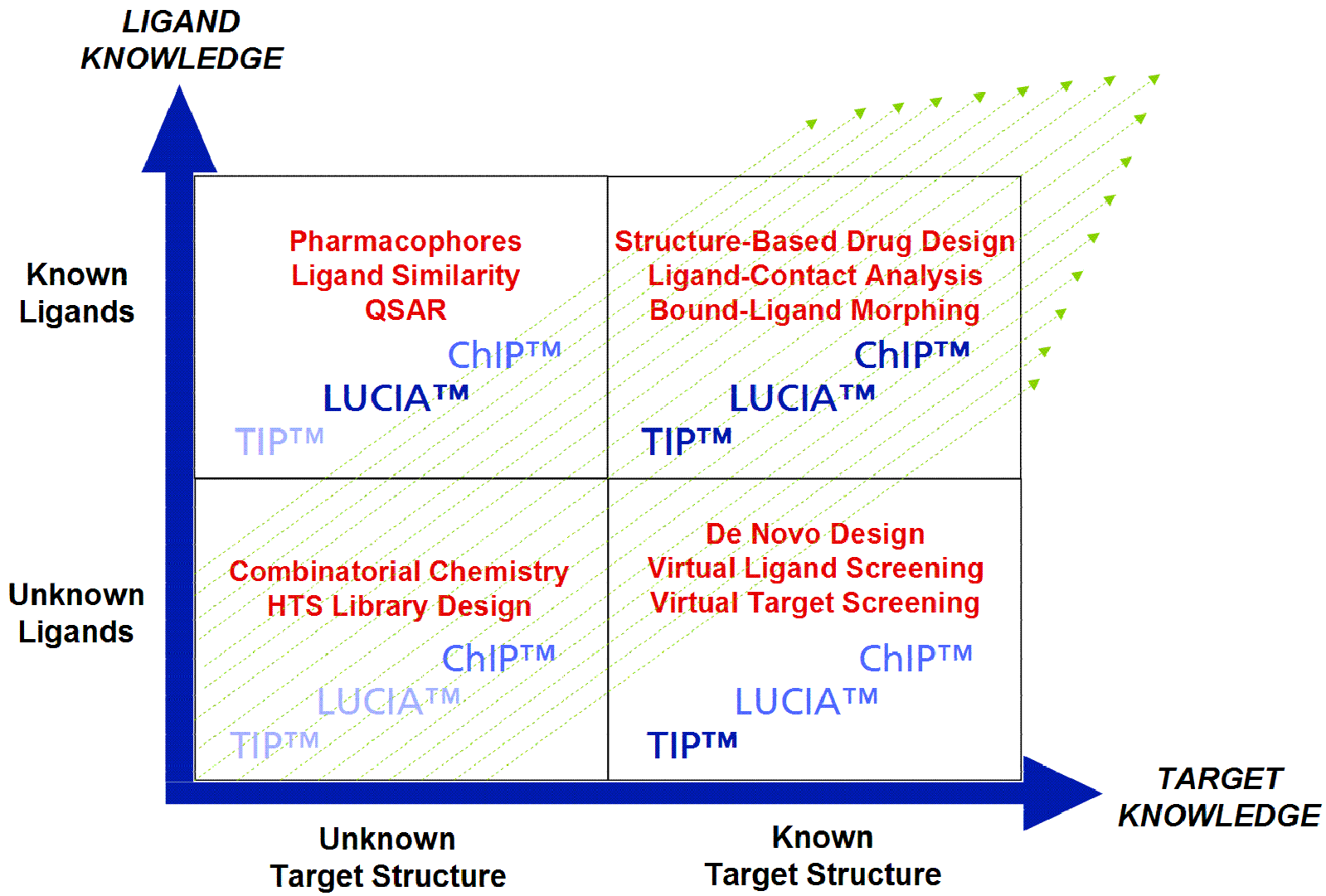
“Loading the dice of discovery” with knowledge



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Integrating Target- and Ligand-based methods

What follows:

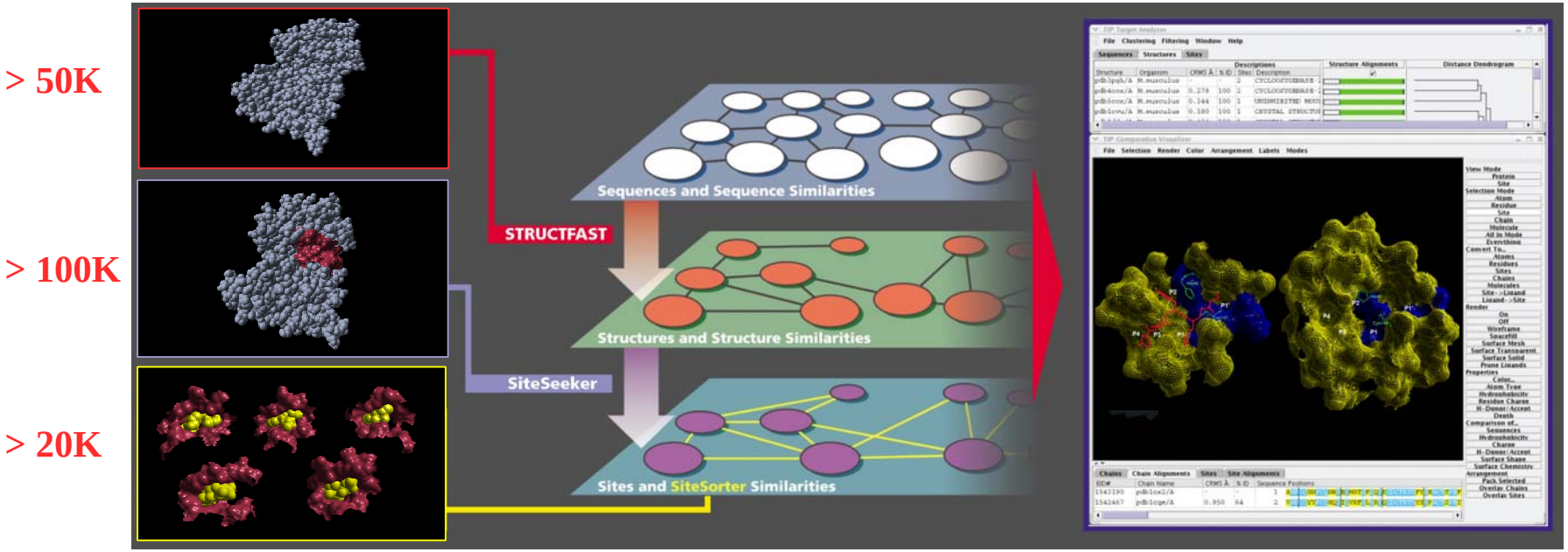
- Enhancing VLS enrichment through combining orthogonal scoring measures from both target-side and ligand-side

- 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

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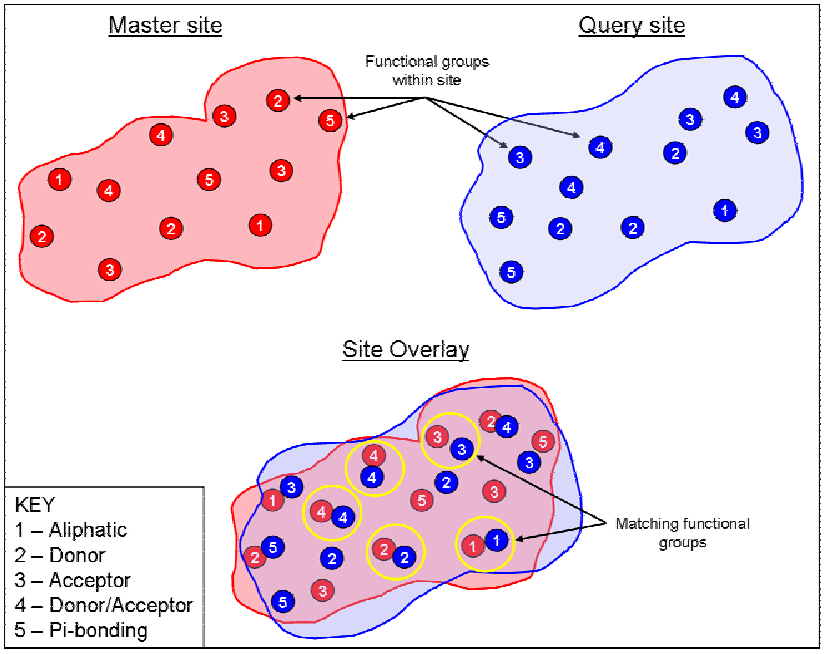
Target-based: SiteSorter

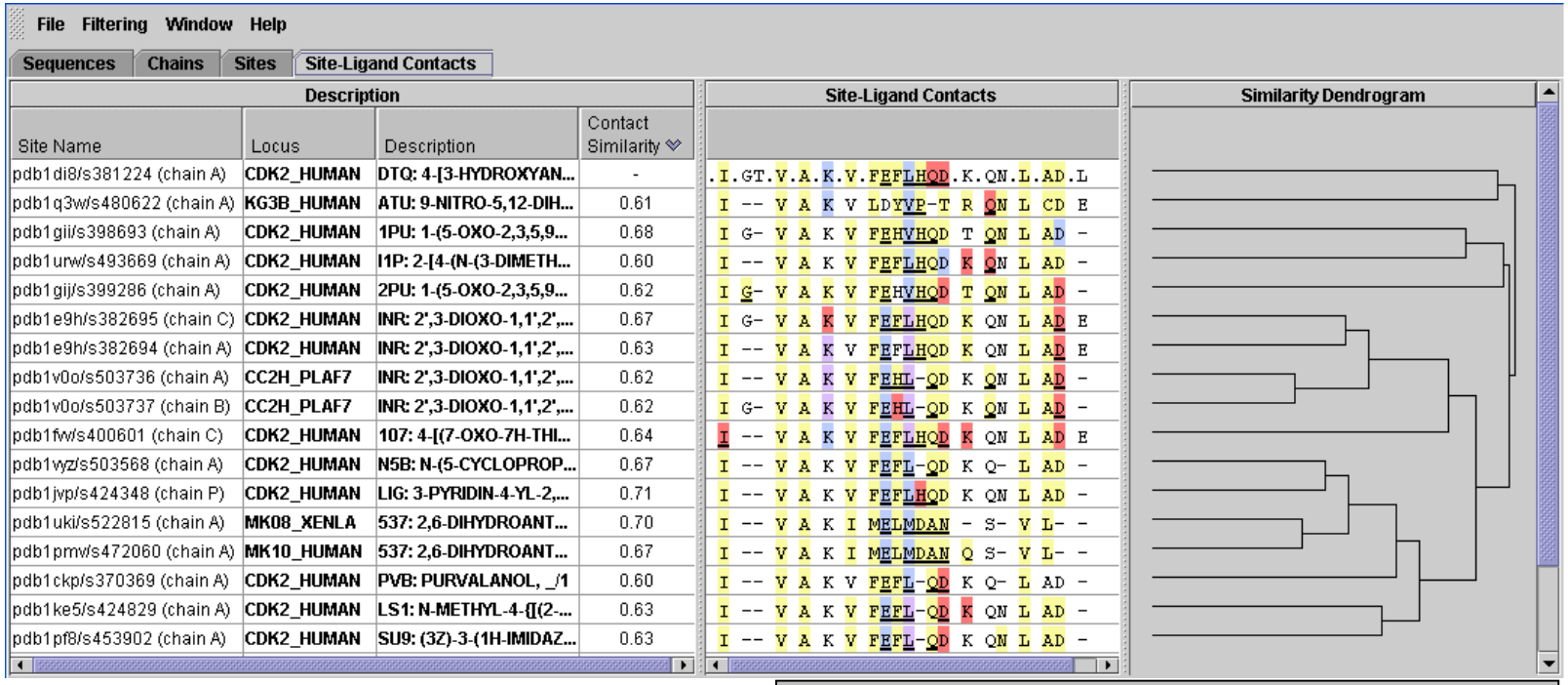
- Novel algorithm for assessing binding site physicochemical similarity
  - Compare binding sites both within the target family as well as *between* target families



- 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



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

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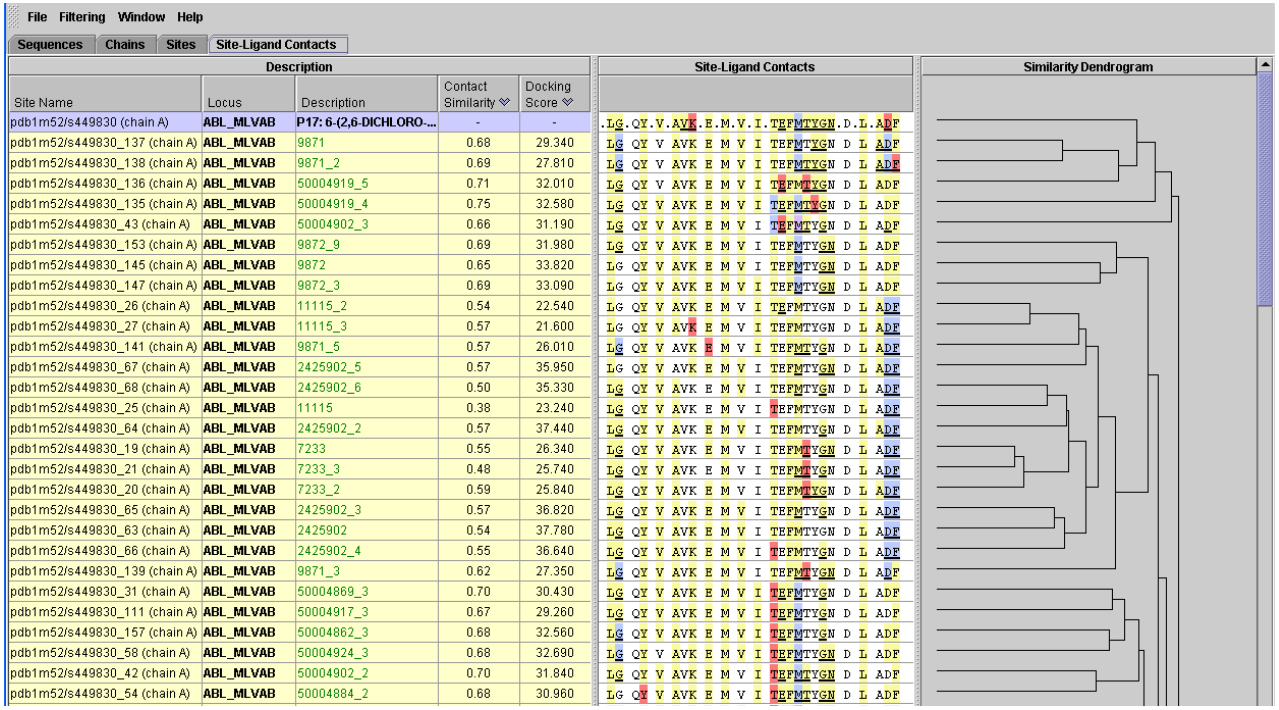
Target-based: ContactSorter – VLS analysis

- Load docked compounds and compare contacts to reference ligands



- 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)

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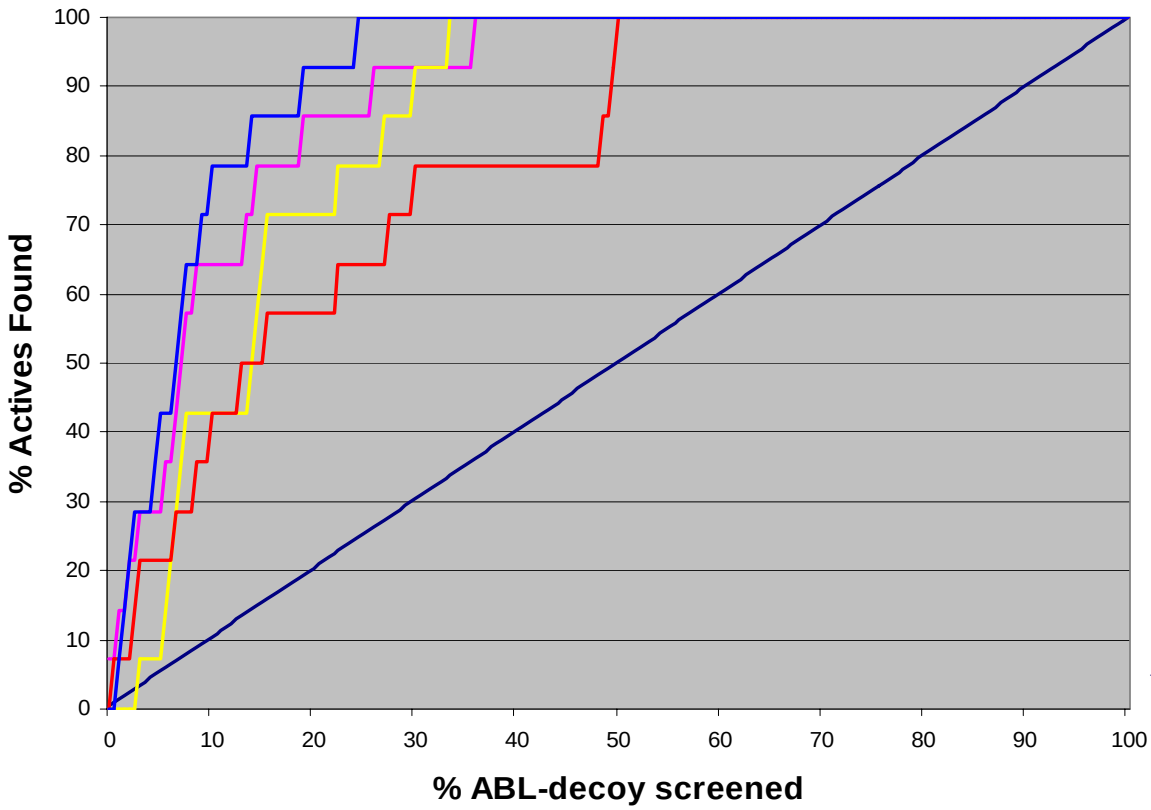
Target- and Ligand-based Enrichment - ABL



Random
GOLD ChemScore
MAX ContactSorter score (vs 1fpu & 1m52)
ABL eScreen
Consensus Rank - ContactSorter, ChemScore, eScreen

ABL decoy set:

14 ABL actives (<1 uM vs ABL)

(from J.Med.Chem. 2004 Mar 25;47(7):1599-601.)

186 kinase inhibitor decoys (>20uM vs ABL)

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

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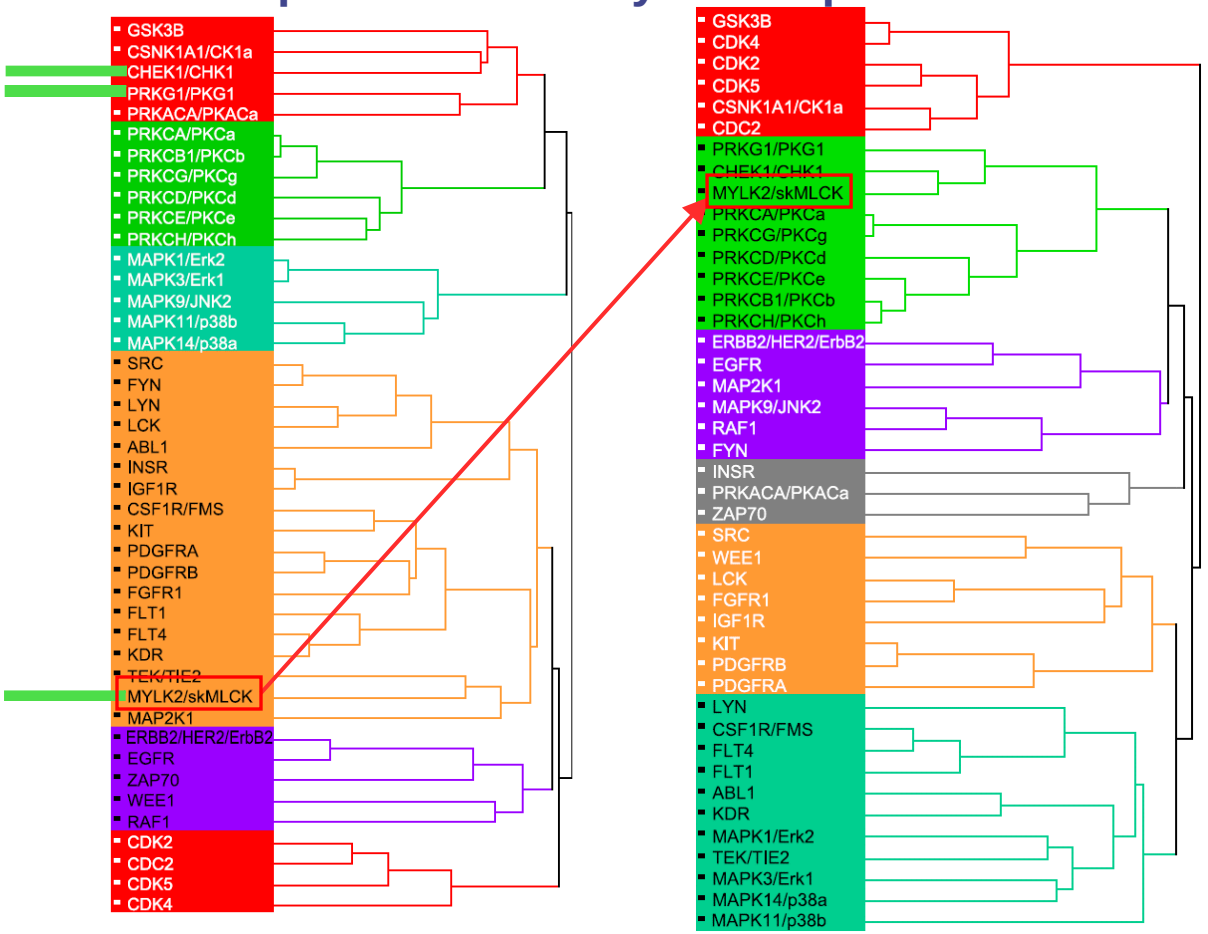
Binding site cross-reactivity prediction

Kinase Sequence Similarity

Experimental SAR Data



10 Most Similar by Binding Site %ID

MYLK2 / skMLCK	
PRKACA / PKACa	71 %
PRKCG / PKCg	67 %
CHEK1 / CHK1	63 %
PRKCE / PKCe	63 %
PRKCH / PKCh	63 %
PRKCD / PKCd	63 %
FGFR1	63 %
ZAP70	63 %
MAP2K1 / MEK1	63 %
PRKCA / PKCa	58 %

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

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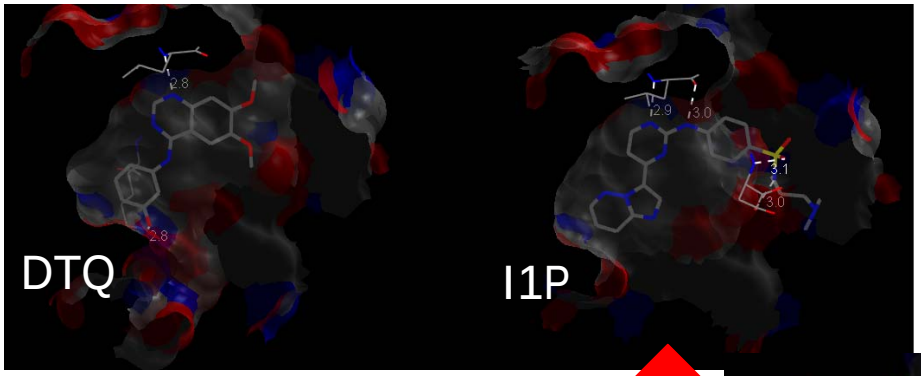
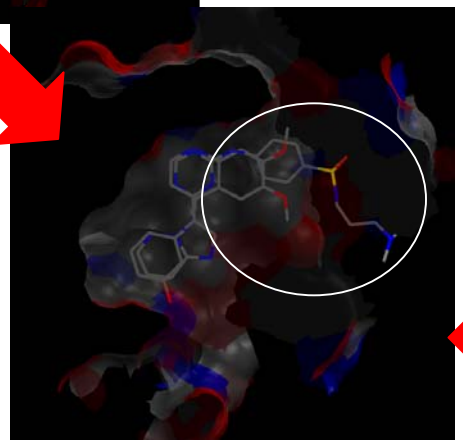
Integrating Target-Based and Ligand-Based: LigandCross

CDK2 co-crystal sites



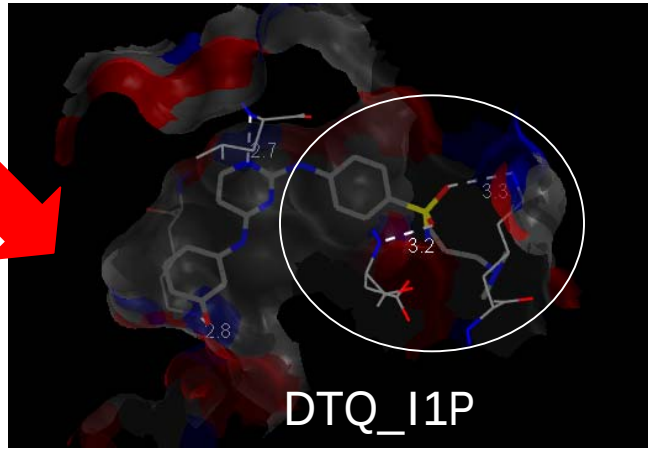
Load multiple co-crystal sites

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



Overlay sites

ITERATION 1



Recombine ligands

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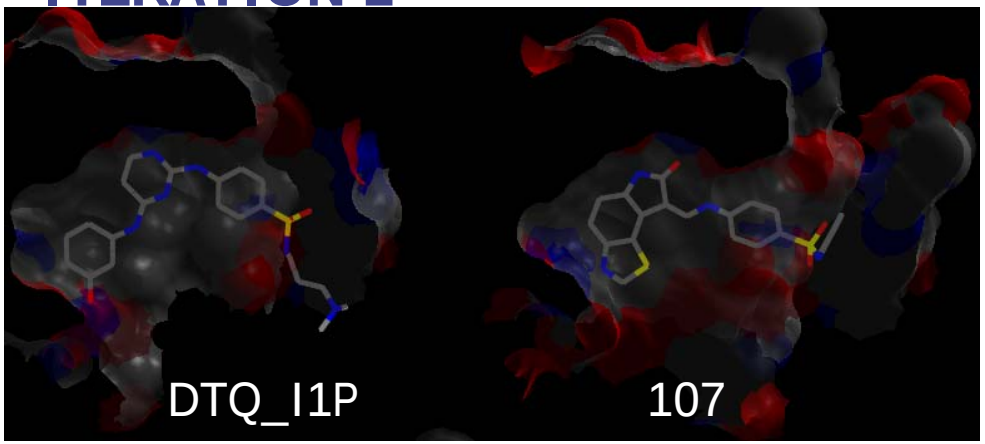
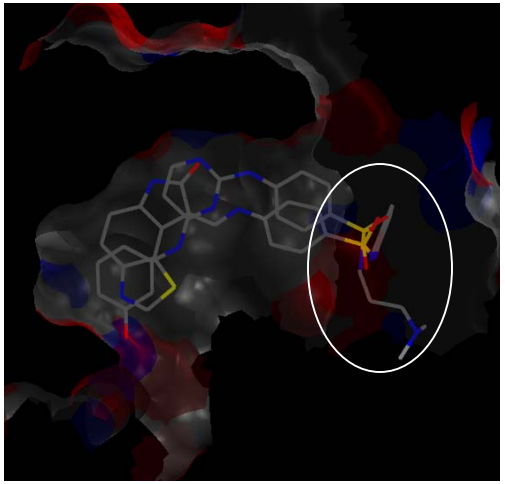
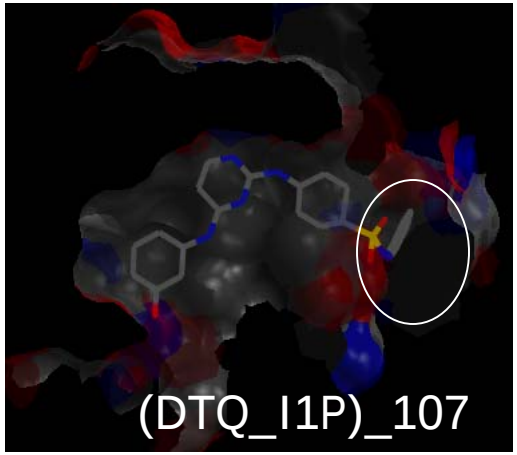
LigandCross

ITERATION 2

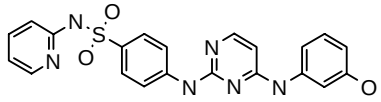


Leverage co-crystal and docked structural information to build libraries of likely binders





LigandCross + ContactSorter

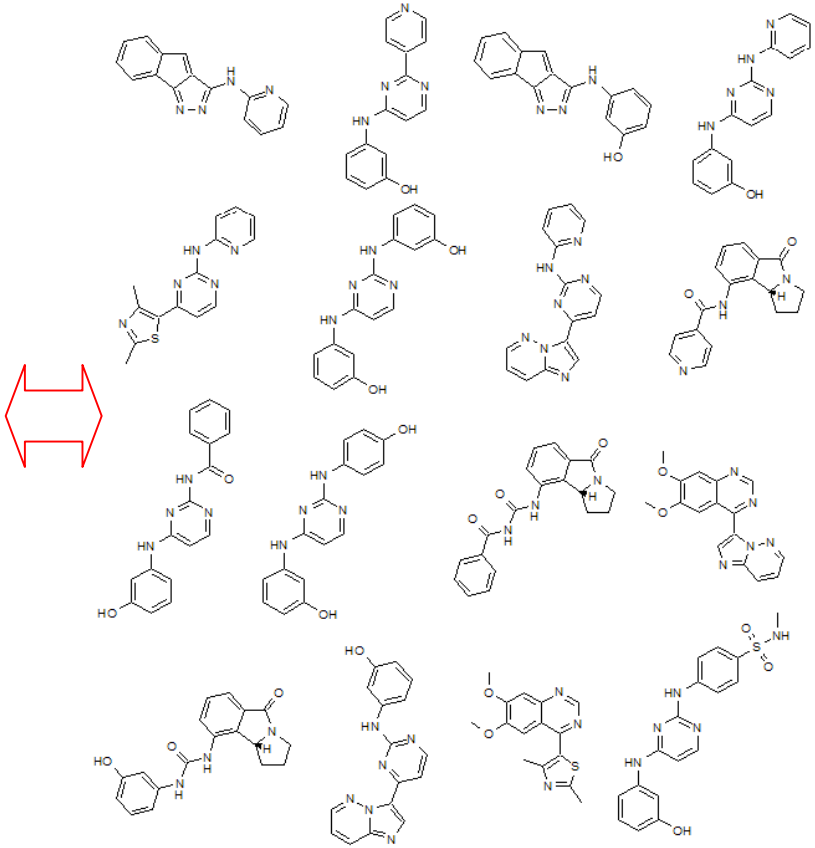


File Filtering Window Help

Sequences | Chains | Sites | Site-Ligand Contacts

Description				Site-Ligand Contacts	Similarity Dendrogram
Site Na...	Locus	Description	Contact Similarity		
pdb1di...	CDK2...	DTQ: 4-[3-HYDROXYANILINO]...	-	.I.GT.V.A.K.V.FEFLHQD.K.QN.L.AD.L	
pdb1di...	CDK2...	DTQ_I1P_1	0.85	I -- V A K V FEFLHQD - Q- L AD L	
pdb1di...	CDK2...	(((DTQ_I1P_2)_107_1)_ALH_1	0.80	I G- V A K V FEFLHQD K -N L AD L	
pdb1di...	CDK2...	((((DTQ_I1P_2)_107_1)_LS1...	0.67	I -- V A K V FEFLHQD K -- L AD -	
pdb1di...	CDK2...	(((DTQ_I1P_2)_107_1)_LS1...	0.71	I -- V A K V FEFLHQD K -- L AD -	
pdb1di...	CDK2...	(((DTQ_I1P_2)_107_1)_LS1...	0.68	I -- V A K V FEFLHQD - -- L AD -	
pdb1di...	CDK2...	((((DTQ_I1P_2)_107_1)_LS1...	0.71	I -- V A K V FEFLHQD - -- L AD -	
pdb1di...	CDK2...	((((DTQ_I1P_2)_107_1)_LS1...	0.73	I -- V A K V FEFLHQD K -- L AD -	
pdb1di...	CDK2...	((((DTQ_I1P_2)_107_1)_LS1...	0.67	I -- V A K V FEFLHQD - -- L AD -	
pdb1di...	CDK2...	((((DTQ_I1P_2)_107_1)_LS1...	0.71	I -- V A K V FEFLHQD K -N L AD -	
pdb1di...	CDK2...	((((DTQ_I1P_2)_107_1)_LS1...	0.68	I -- V A K V FEFLHQD - -- L AD -	
pdb1di...	CDK2...	((((DTQ_I1P_2)_107_1)_LS1...	0.64	I -- V A K V FEFLHQD - -- L AD -	
pdb1di...	CDK2...	((((DTQ_I1P_2)_107_1)_LS1...	0.63	I -- V A K V FEFLHQD K -N L AD -	
pdb1di...	CDK2...	(DTQ_I1P_2)_107_2	0.67	I -- V A K V FEFLHQD K -N L AD -	
pdb1di...	CDK2...	(((DTQ_I1P_2)_107_1)_LS1...	0.67	I -- V A K V FEFLHQD K -- L AD -	
pdb1di...	CDK2...	((((DTQ_I1P_2)_107_1)_LS1...	0.62	I -- V A K V FEFLHQD K -- L AD -	
pdb1di...	CDK2...	((((DTQ_I1P_2)_107_1)_LS1...	0.65	I -- V A K V FEFLHQD K -- L AD -	
pdb1di...	CDK2...	((DTQ_I1P_2)_107_1)_LS1_2	0.58	I -- V A K V FEFLHQD K -- L AD -	
pdb1di...	CDK2...	((((DTQ_I1P_2)_107_1)_LS1...	0.58	I -- V A K V FEFLHQD K -- L AD -	
pdb1di...	CDK2...	(((DTQ_I1P_2)_107_1)_LS1...	0.57	I -- V A K V FEFLHQD K -- L AD -	
pdb1di...	CDK2...	(DTQ_I1P_2)_107_1	0.64	I G- V A K V FEFLHQD K -N L AD L	
pdb1di...	CDK2...	(((DTQ_I1P_2)_107_1)_I1P_1	0.54	I -- V A K V FEFLHQD K -- L AD L	
pdb1di...	CDK2...	(((DTQ_I1P_2)_107_1)_LS1...	0.46	I -- V A - V FEFLHQD K -N L AD -	
pdb1di...	CDK2...	(((DTQ_I1P_2)_107_1)_LS1...	0.50	I -- V A - V FEFLHQD K -N L AD -	
pdb1di...	CDK2...	(((DTQ_I1P_2)_107_1)_ALH_2	0.43	I -- V A - V FEFLHQD K -N L AD -	
pdb1di...	CDK2...	(((DTQ_I1P_2)_107_1)_LS1_1	0.70	I G- V A K V FEFLHQD K -N L AD L	
pdb1di...	CDK2...	DTQ_I1P_2	0.74	I G- V A K V FEFLHQD K -N L AD L	
pdb1di...	CDK2...	(((DTQ_I1P_2)_107_1)_LS1...	0.58	I -- V A K V FEFLHQD K -- L AD L	

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



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

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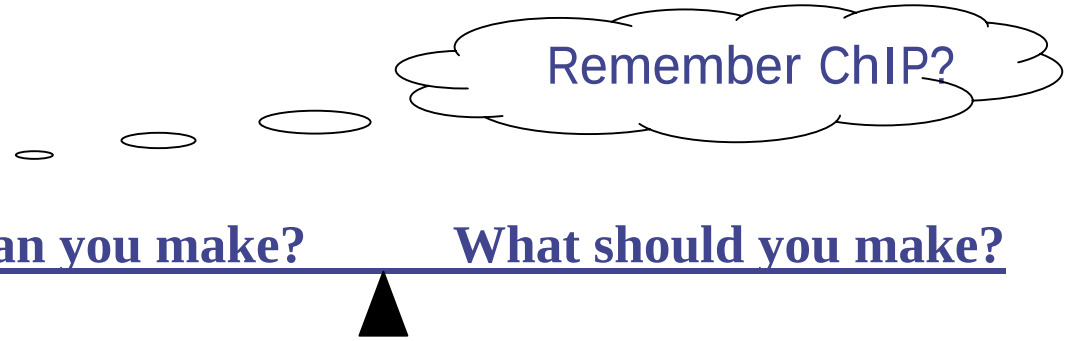
LigandCross → ChIP

➢ 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

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