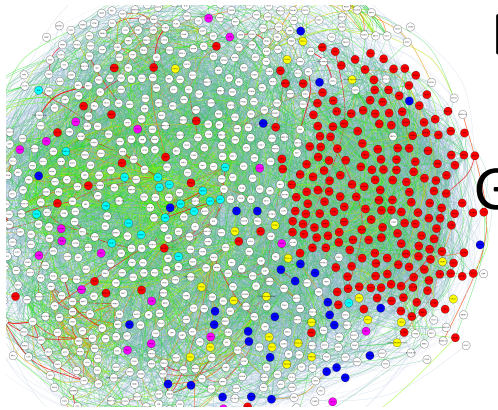
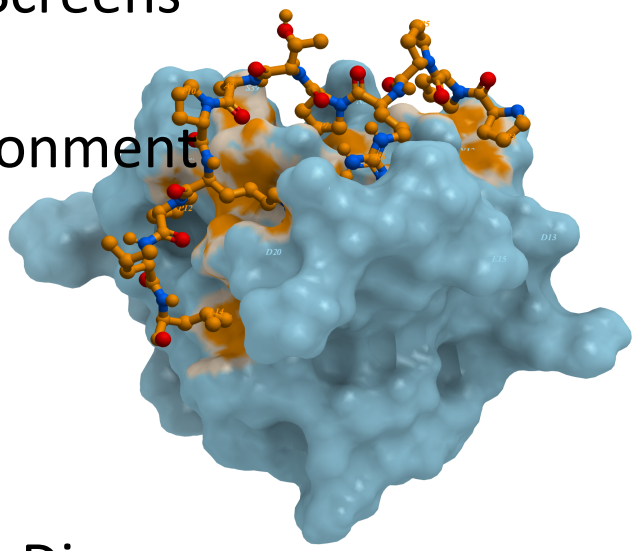
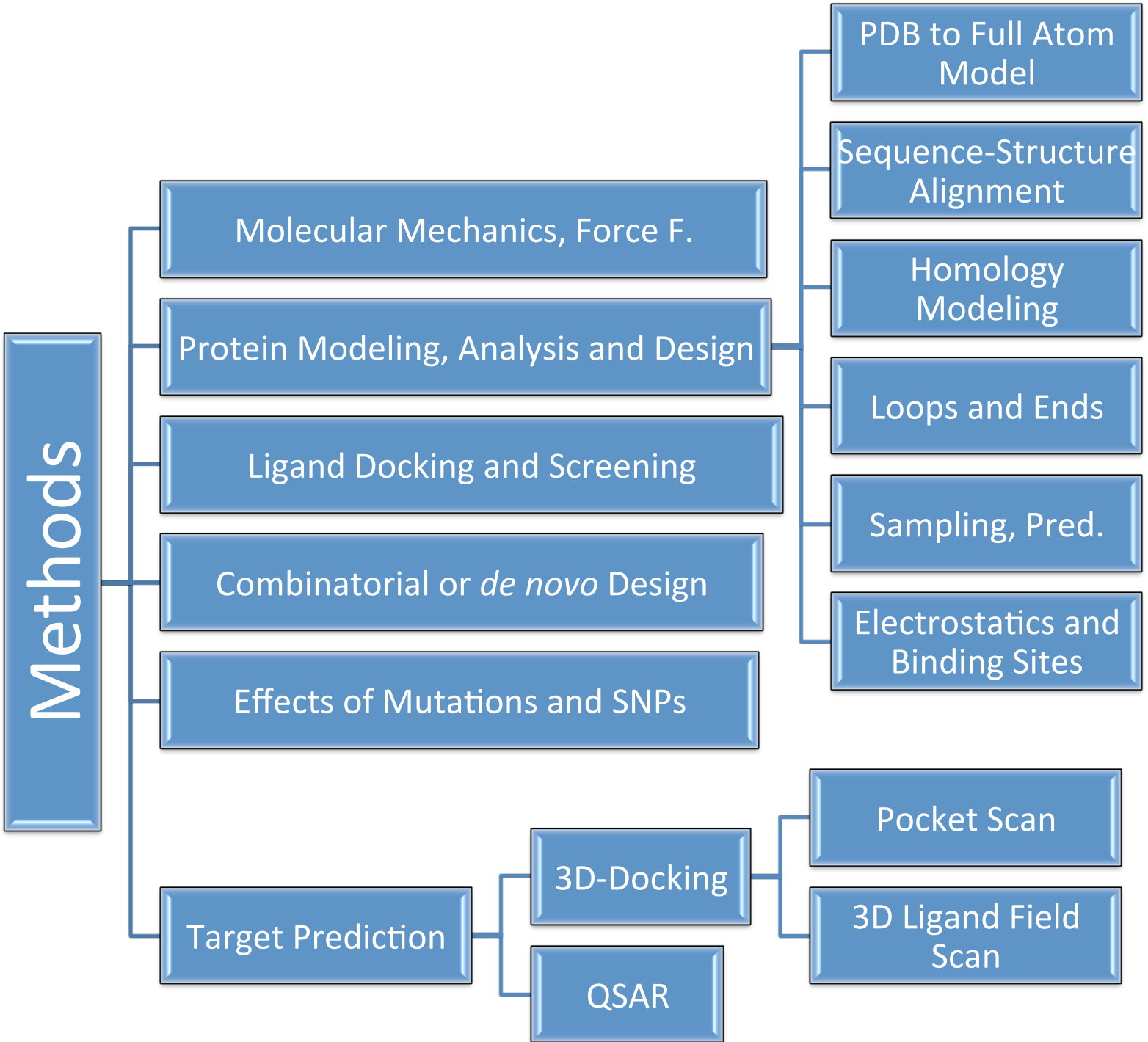
Internal Coordinate Mechanics and ICM

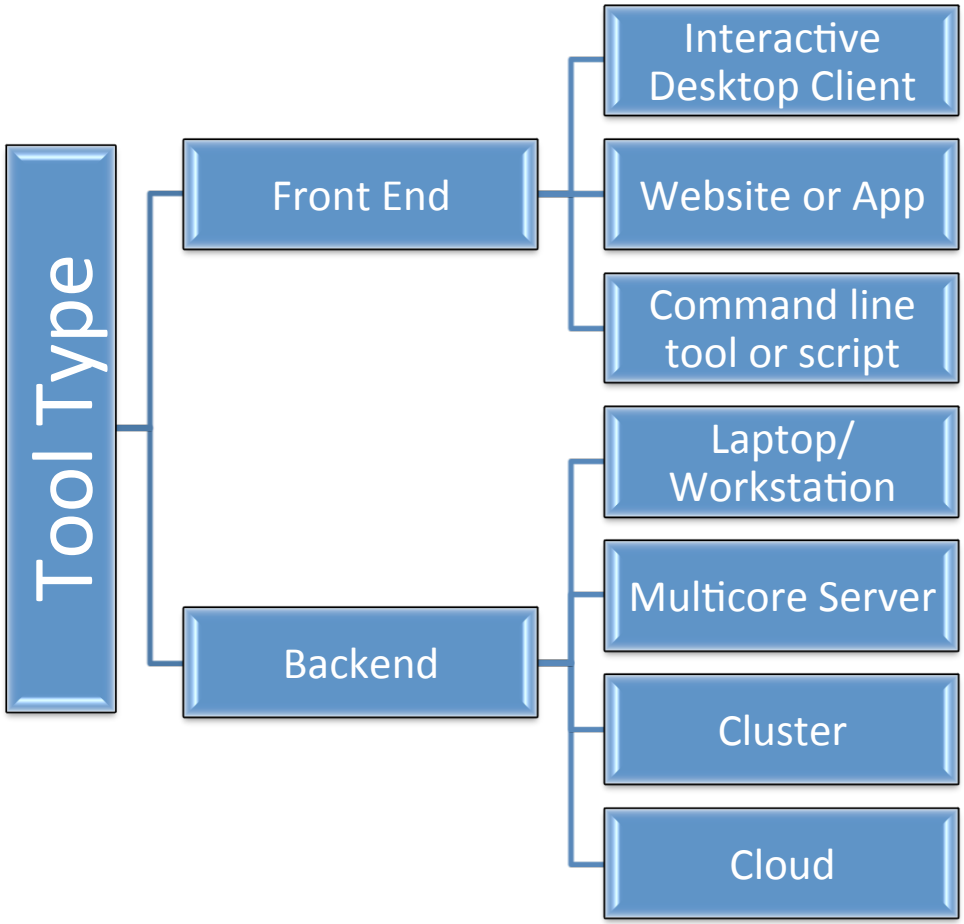
Modeling
Docking, Ligand and Target Screens
Cheminformatics
Graphical and Scripting Environment
Big Structural Data

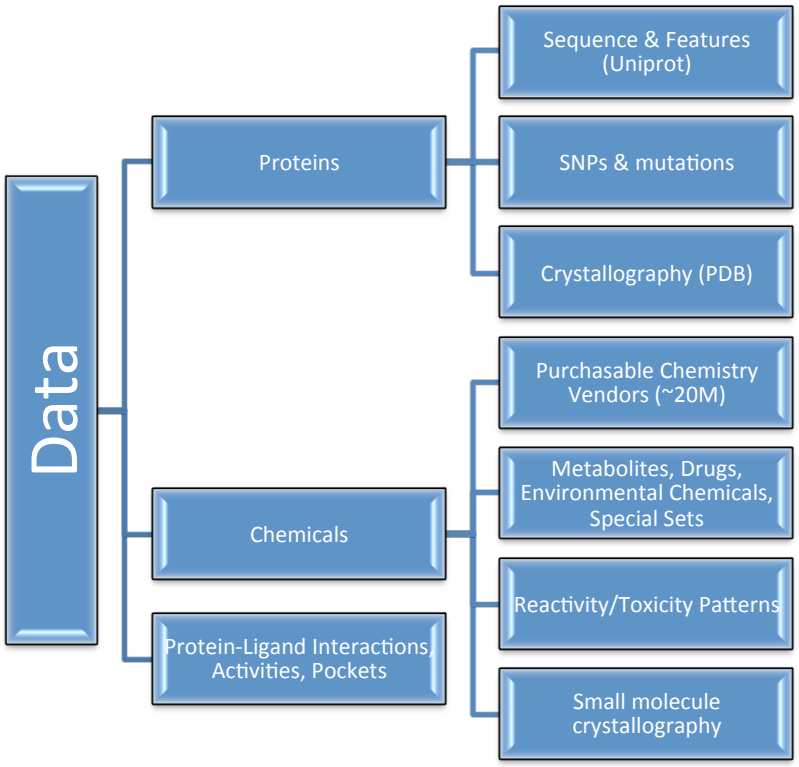




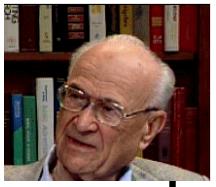
Ruben Abagyan
University of California, San Diego
Skaggs School of Pharmacy & Pharm. Sciences
Molsoft, LLC
ruben@ucsd.edu


Methods
Molecular Mechanics, Force F.
Protein Modeling, Analysis and Design
Ligand Docking and Screening
Combinatorial or *de novo* Design
Effects of Mutations and SNPs
Target Prediction
PDB to Full Atom Model
Sequence-Structure Alignment
Homology Modeling
Loops and Ends
Sampling, Pred.
Electrostatics and Binding Sites
3D-Docking
QSAR
Pocket Scan
3D Ligand Field Scan


Tool Type
Front End
Backend
Interactive Desktop Client
Website or App
Command line tool or script
Laptop/ Workstation
Multicore Server
Cluster
Cloud


Data
Proteins
Chemicals
Protein-Ligand Interactions, Activities, Pockets
Sequence & Features (Uniprot)
SNPs & mutations
Crystallography (PDB)
Purchasable Chemistry Vendors (~20M)
Metabolites, Drugs, Environmental Chemicals, Special Sets
Reactivity/Toxicity Patterns
Small molecule crystallography

Internal Coordinate Mechanics for modeling&docking biological complexes



Harold Scheraga

Energy, FF **X**, E(x, y, z) **Q** E(φ)
E (b, α, φ, ϕ)

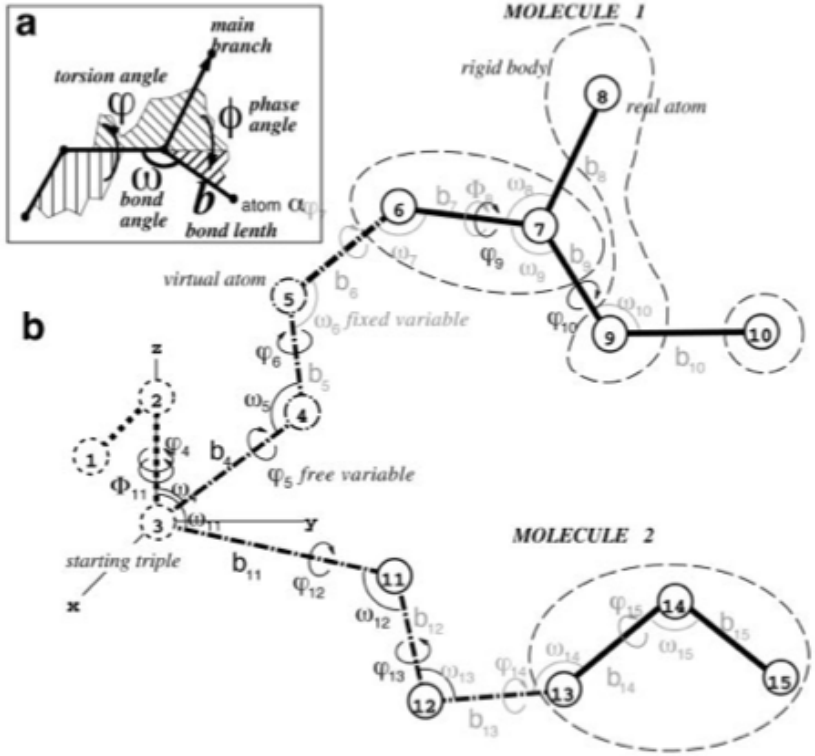
Dynamics Newton

F = ma

Stochastic sampling

Inefficient,

Sample in IC

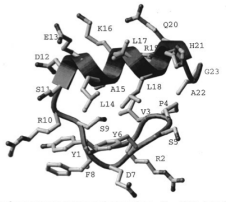


Square-Root Sampling

Ab initio folding of peptides with the Optimal Bias Monte Carlo Minimization Procedure

Abagyan, Totrov *J. Comp. Physics*, 1999

Optimal Sampling: *discrete states*



The lowest energy conformation, E=-385.4 kc/m

ampling function

IS

apter in

lications, Kluwer

THEOREM. *The optimal random guessing strategy minimizing the average number of guesses is to guess with relative frequencies f_1 and f_2 so that*

$$\frac{f_1}{f_2} = \sqrt{\frac{s_1}{s_2}}.$$

Proof. Let us calculate the average number of guesses N_{guesses} until the correct answer is given, provided that previous guesses are forgotten and thus each guess is independent. If in our random guessing strategy the probability of a correct guess in a single trial is f, and the successful result can be achieved through the first correct guess ($p_1 = f$), the first incorrect guess and the second correct guess ($p_2 = (1-f)f$), the first two incorrect guesses and the correct guess ($p_3 = (1-f)^2 f$), etc., the average number of guesses reads

$$\begin{aligned} N_{\text{guesses}} &= p_1 + 2p_2 + 3p_3 + \cdots \\ &= f + 2(1-f)f + 3(1-f)^2 f + \cdots + n(1-f)^{n-1} + \cdots = 1/f, \end{aligned}$$

$$\prod_{i=1}^{n} f_j^{-1}(\mathbf{x}_i^0)d\mathbf{x}_i^0,$$

$$\langle N_{\text{guesses}} \rangle = S_1/f_1 + S_2/f_2.$$

, let us set the derivative of ⟨

$$S_1/f_1^2 - S_2/f_2^2 = 0,$$

$$S_1/f_1^2 = S_2/f_2^2,$$

$$f_1/f_2 = (S_1/S_2)^{1/2}.$$

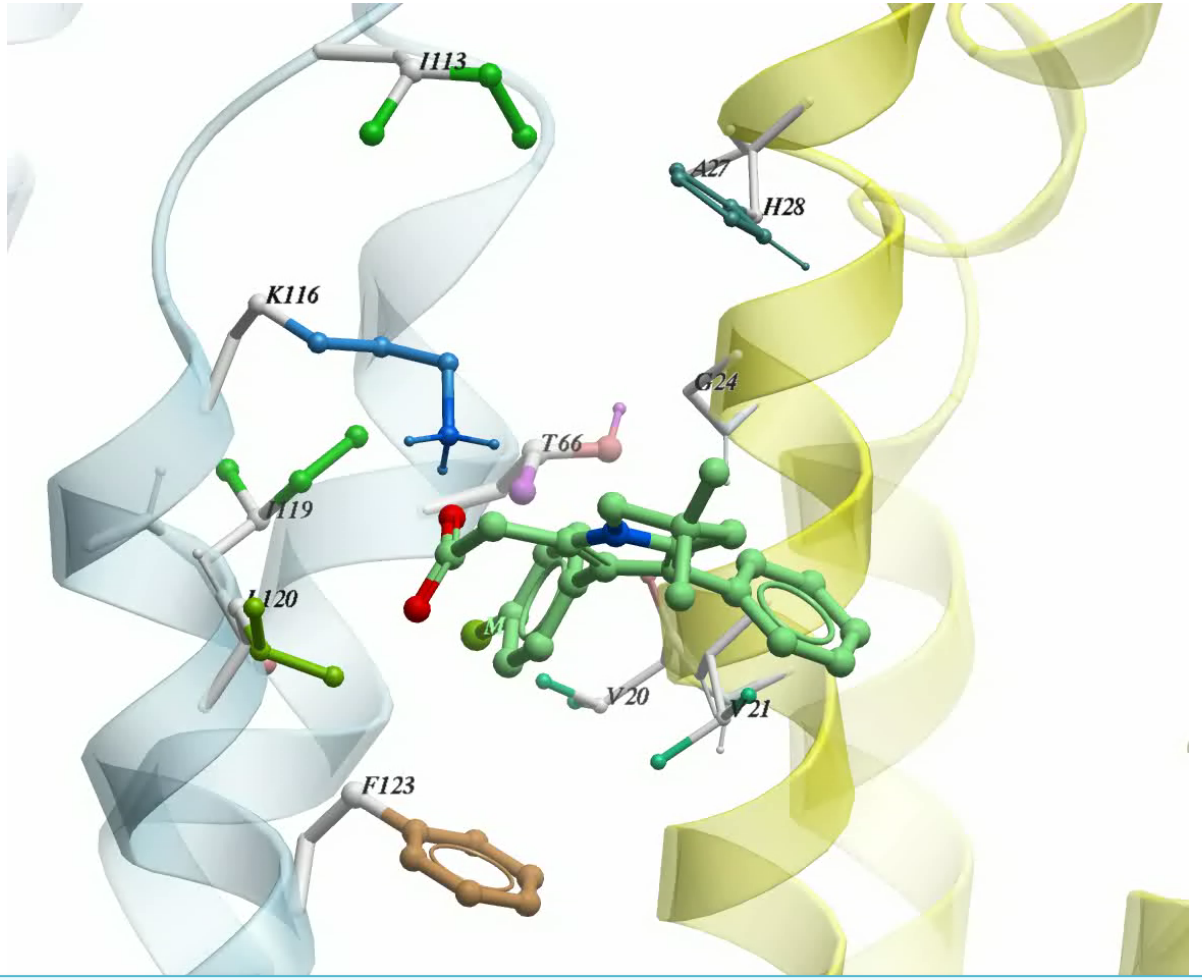
order for the above equation to hold for any arbitrary function δf_j, we have

$$f_j(\mathbf{x}) = \frac{1}{c'}\sqrt{S_j(\mathbf{x})},$$

where c' is the normalization constant equal to $\int \sqrt{S_j(\mathbf{x})}d\mathbf{x}$.

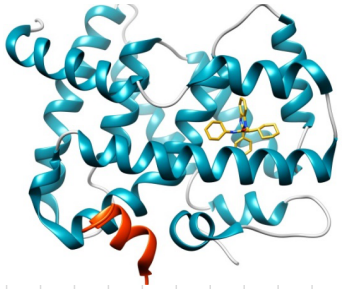
Fast Conformation Sampler and Optimizer in Internal Coordinates

- A minimal subset of internal variables
- Collective moves
- Optimal Square-root sampling
- Stochastic global optimizer with history feedback



Abagyan R., Totrov M. 1994, ICM *JCC,* BPMC *JMB*, 1997 Ligand Docking, *Proteins*.
Neves et al., 2011: Top scoring pose: 91% <2A cognate docking for 165 tasks, 71% <1A
Bottegoni G et al. ..multiple receptor conformations for VLS. *PLoS One*, 2011, Activity Cliffs 2015

D3R Grand Docking Challenge: 2017



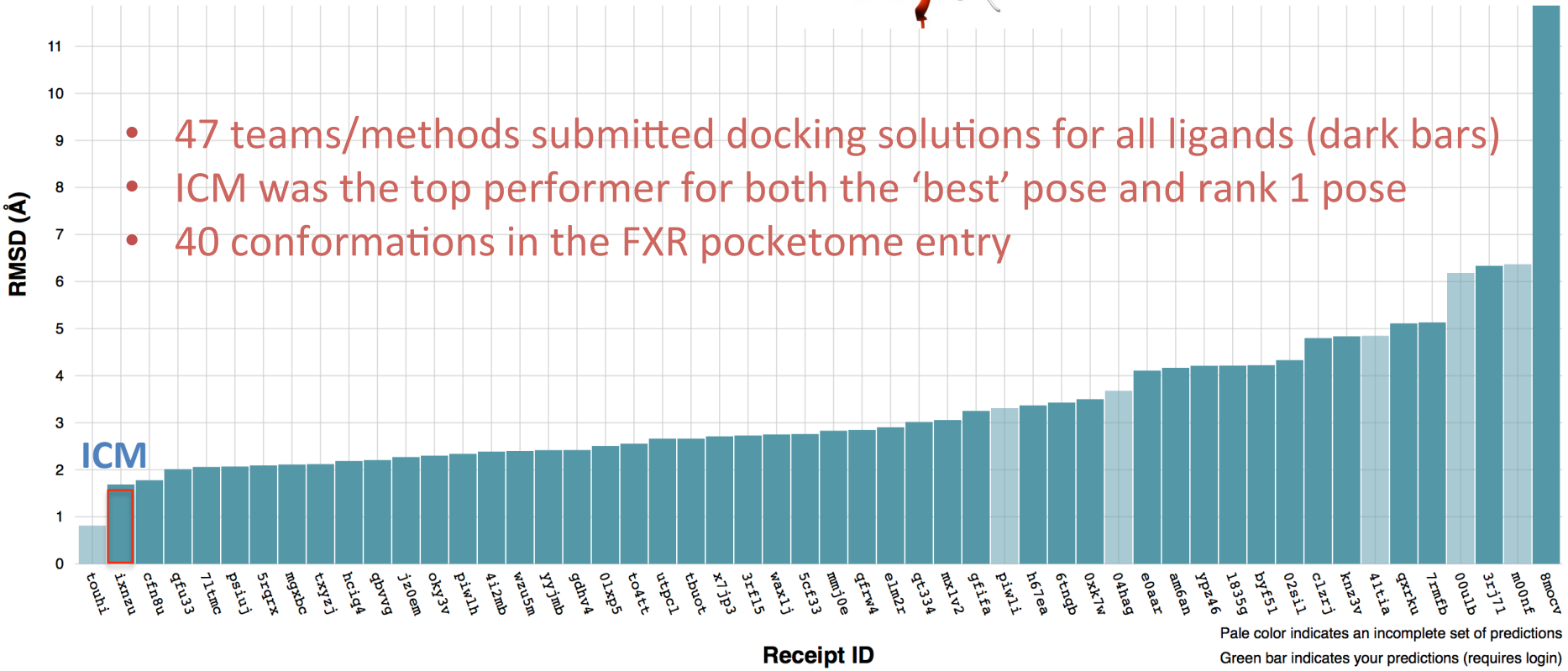
Predict the crystallographic poses of 36 **ligands** to FXR

Grand Challenge 2

Pose - RMSD - Compound: AVG - Best

Compound: AVG | Best | Average | Pose 1

- 47 teams/methods submitted docking solutions for all ligands (dark bars)
- ICM was the top performer for both the 'best' pose and rank 1 pose
- 40 conformations in the FXR pocketome entry

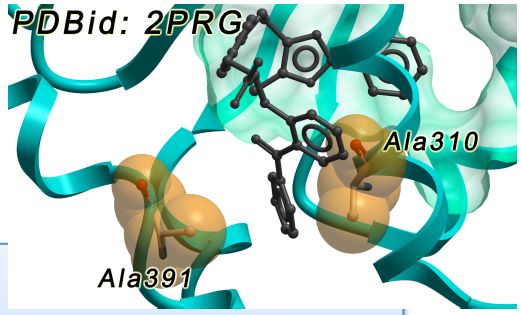


Docking: 7 Types of Pocket Flexibility

- Explicit Side Chains in LigEdit and _dockScan
- 4D Docking / Ensemble Docking
- SCARE (SCan Alanines & Refine)
- NMA or ICM Ligand-guided pocket variations
- Full ICM simulations with custom defined space and restraints
- Hybrid protocols

Max

Giovanni



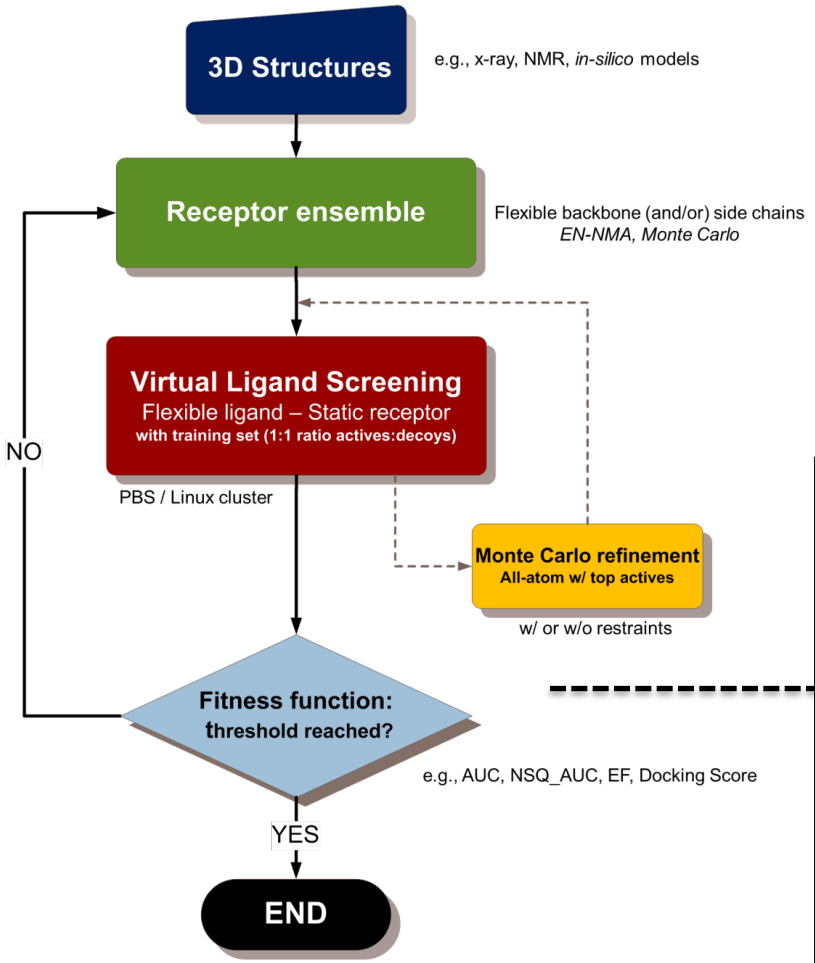
Irina

Bottegoni et al. 2008 **"SCARE.."** *JCAMD*

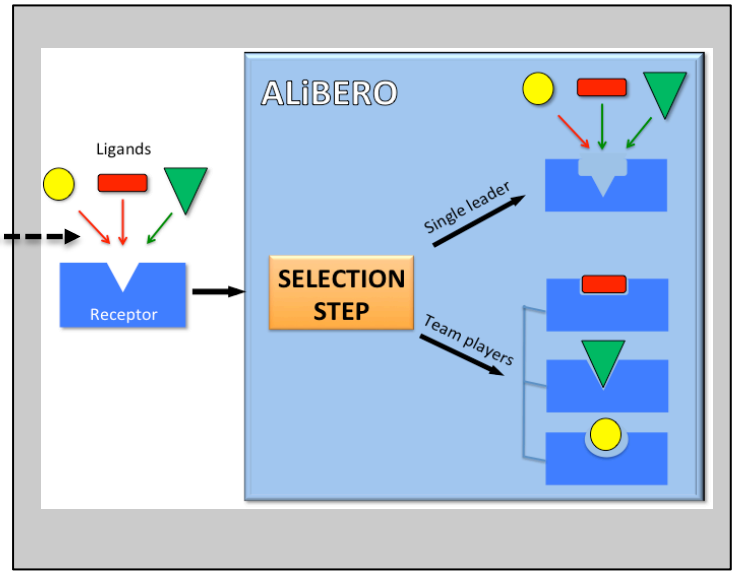
Bottegoni et al. 2009 **"4D docking: a fast and accurate account of discrete receptor flexibility .."**, *JMC*

Husby, Bottegoni, Kufareva, Abagyan, Cavalli**. Structure-based predictions of activity cliffs**. *J Chem Inf Model*. 2015

Ligand Guided Model Building

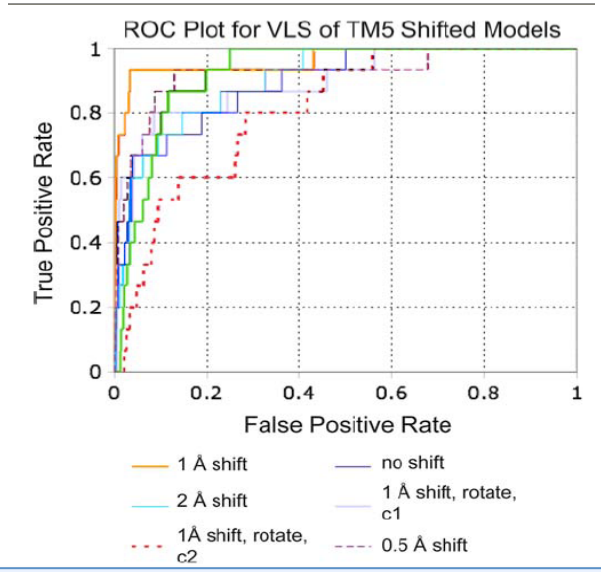


- ALibero
- Extension of _dockScan

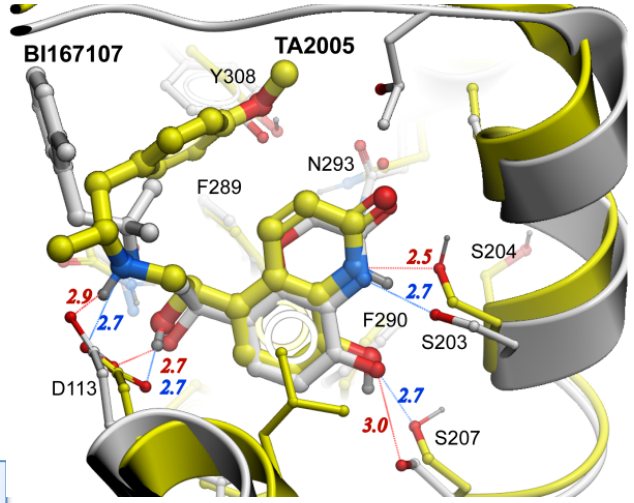


Bisson, Cheltsov et al. 2006, PNAS
Katritch et al. 2008, 2011, ++ **GPCR agonist binding revealed by modeling**..,
Rueda et al. **ALiBERO: Evolving a team of complementary pocket conformations rather than a single leader** (2012) *J Chem Inf Mod*

Prospective Prediction of Agonist-Bound Pocket and Agonist Binding by ICM LGM Model 2007-09, X-ray 2011



β_2AR agonists comparison 4 years later



100% identical contacts for ligand core
$Rmsd_{LIG\_CORE}$=0.5 Å,
$RMSD_{pocket}$ = 0.9Å

- Reynolds, Katritch, Abagyan**, Identifying conformational changes of the *b*2 adrenoceptor that enable accurate prediction of ligand/receptor interactions and screening for GPCR modulators**, *JCAMD*, 2009
- Katritch, Reynolds, Cherezov, Hanson, Roth, Yeager, Abagyan. **Analysis of full and partial agonists binding to beta(2)-adrenergic receptor suggests a role of transmembrane helix V in agonist-specific conformational changes** *J Mol Recognit*. 2009 Apr 7;22(4):307-318
- Katritch V, Abagyan**. GPCR agonist binding revealed by modeling and crystallography** , *Trends PharmacolSci*, 2011 Sep 6
- Warne, et al., Schertler G, Tate C, **The structural basis for agonist and partial agonist action on a β_1 adrenergic receptor**, *Nature*, 2011.

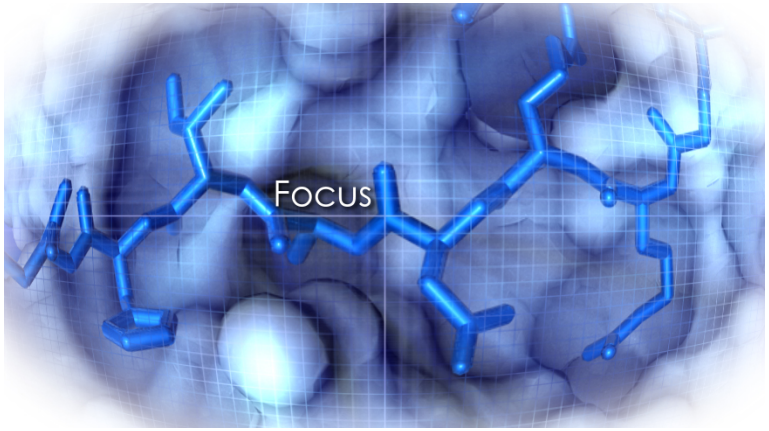
JOURNAL OF CHEMICAL INFORMATION AND MODELING

Article

pubs.acs.org/jcim

FOCUS — Development of a Global Communication and Modeling Platform for Applied and Computational Medicinal Chemists

Nikolaus Stiefl,*[,†] Peter Gedeck,[‡] Donovan Chin,[§] Peter Hunt,[∥] Mika Lindvall,[⊥] Katrin Spiegel,[∥] Clayton Springer,[§] Scott Biller,[§] Christoph Buenemann,[#] Takanori Kanazawa,[▽] Mitsunori Kato,[§,▽] Richard Lewis,[†] Eric Martin,[⊥] Valery Polyakov,[⊥] Ruben Tommasi,[§] John van Drie,[§] Brian Vash,[§] Lewis Whitehead,[§] Yongjin Xu,[⊥] Ruben Abagyan,[○] Eugene Raush,[○] and Max Totrov[○]

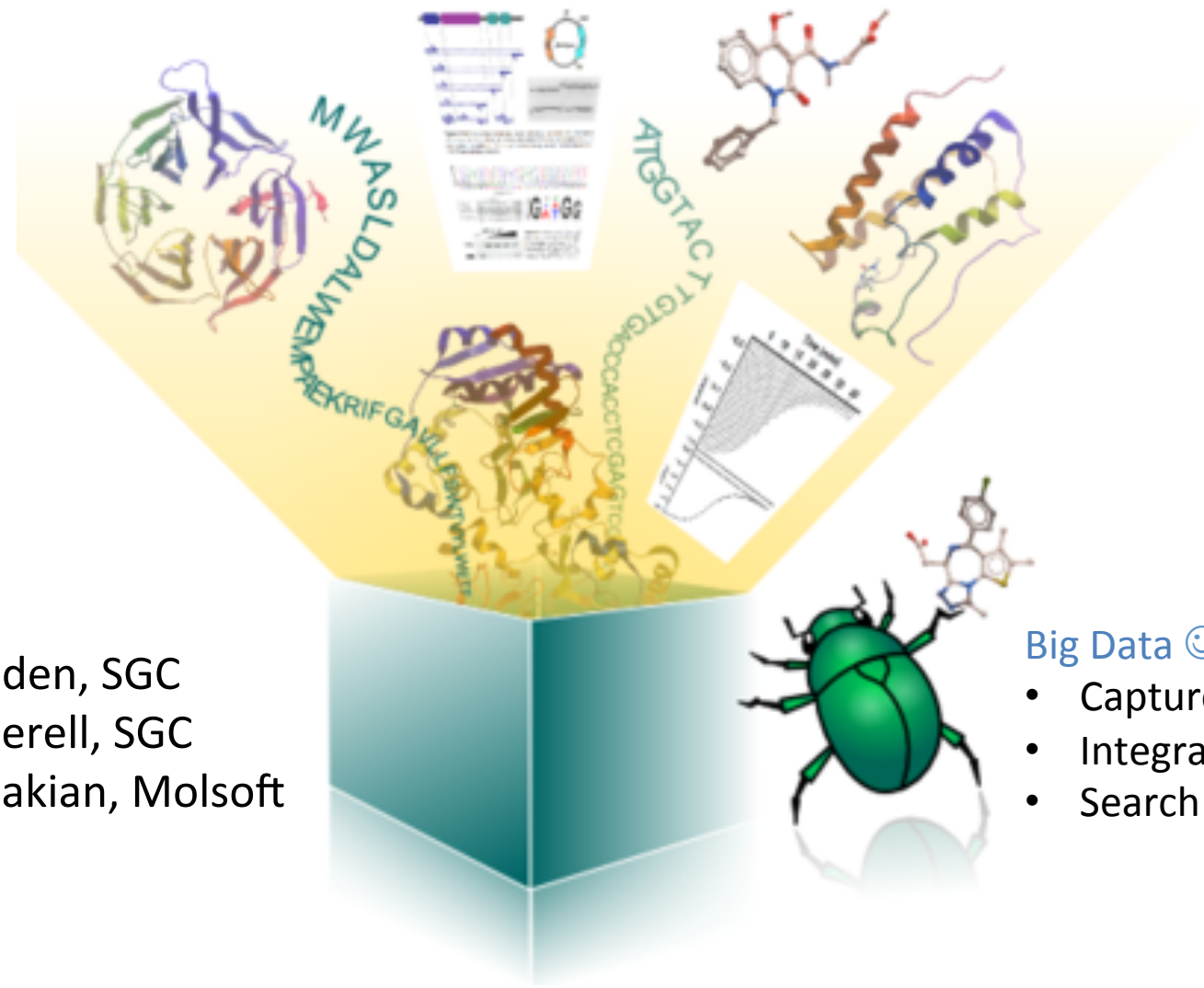


NOVARTIS

specifically Kenji Namoto, David Wayne Hughes, Paul Butler, Gregory Landrum, Sandra Mueller, Joerg Muehlbacher, Finton Sirockin, Simona Cotesta, Marc Litherland, Rajeshri Karki, Yipin Lu, Robert Pulz, Catherine Leblanc, Sabina Pecchi, Gabriel Gamber, Jay Knowles, Michael Dechantstreiter, and Thomas Dice. We also thank Jose Duca for supporting the project during the last three years. On the Molsoft side, we thank Andrew Orry, Crystal Crawford, Levon Budagyan, Polo Lam, Irina Kufareva, and Elena Arnauto y

Stiefl et al. JCIM, 2015

Scarab



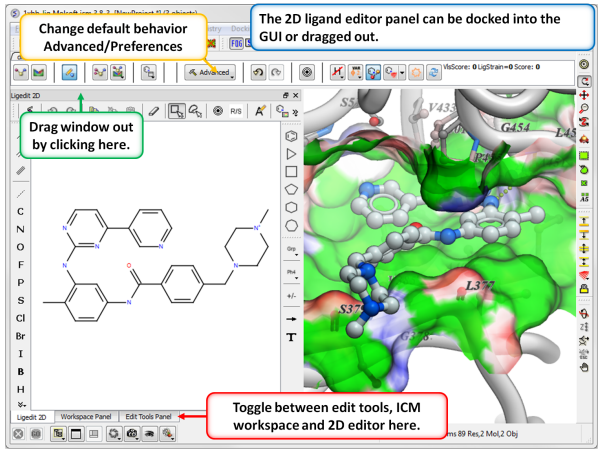
Brian Marsden, SGC
David Damerell, SGC
Arman Sahakian, Molsoft

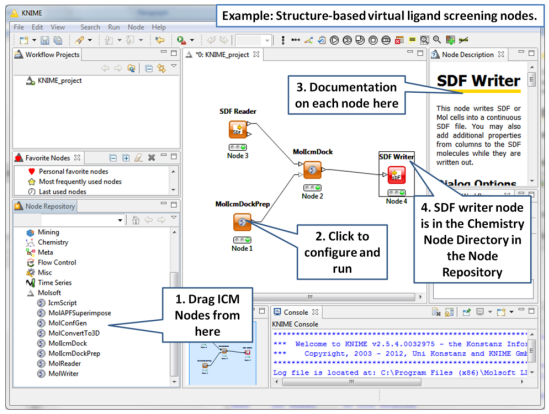
Big Data ☺ :

- Capture and Create
- Integrate
- Search and retrieve

Three in One

- Workstation GUI Client (eg ICM-pro, Focus, Scarab)
- ICM based backend units (models, screens, homology)
- Mobile or Web dissemination





Microsoft Windows

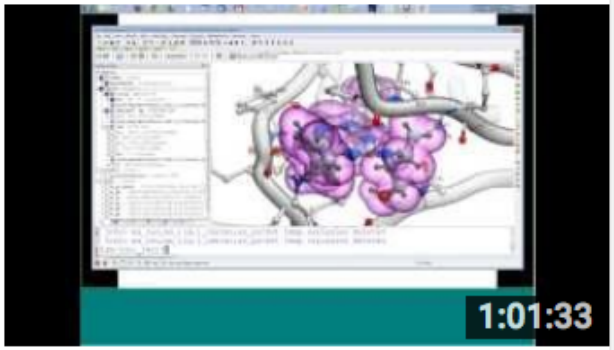
Linux

iPhone

iPad

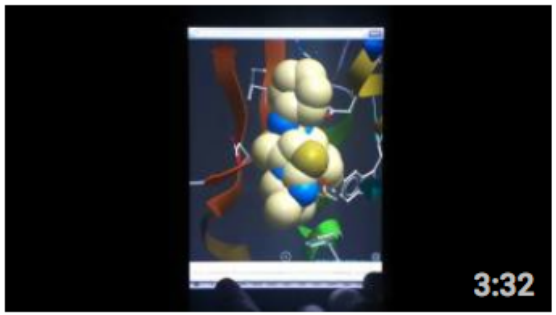
amazon

Training Videos



MolSoft Webinar: Ligand Design using ICM 3D Interactive Ligand…

1,695 views • 2 years ago



iMolview

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MolSoft Molecules in Silico

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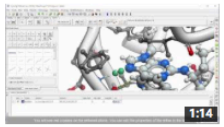
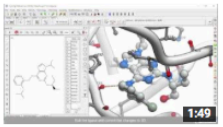


ICM 3D Ligand Editor: Distance Restraints and Tethers in Docking

17 views • 3 weeks ago



Ligand Editor - Ligand editing in 2D and commit changes to 3D.

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Explicit / Hybrid Docking: Fully flexible side-chains in the ICM…

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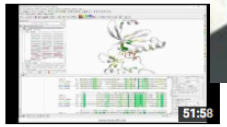

Webinar: Linking Protein Structure, Sequences and…

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Webinar: Molecular Graphics, Movies, and Fully Interactive 3…

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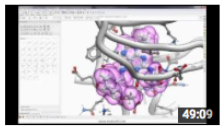

Webinar: Ligand Design using the ICM 3D Fully Interactive Ligand…

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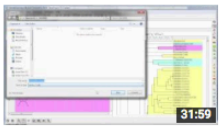

ICM Chemist Webinar - July 2015

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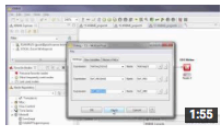
Install MolSoft ICM Nodes for KNIME

88 views • 11 months ago



MolSoft MolCalcProp in KNIME

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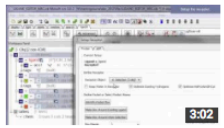

4D Docking in the Ligand Editor.

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ICM Molecular Editor Tutorial

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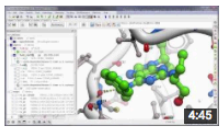

MolSoft - Fully Interactive 3D Ligand Editor v3.8

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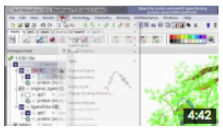

How to re-dock a ligand using MolSoft's ICM-Pro desktop…

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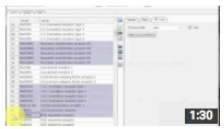

Introducing MolScreen from MolSoft.

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Covalent Docking Tutorial in ICM-Pro

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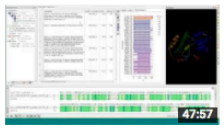

Protein Structure Modeling and Analysis Webinar

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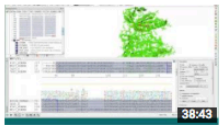

Linking Protein Sequence to 3D Structure using the ICM…

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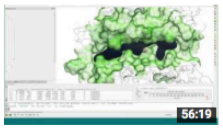

Introducing ICM version 3.8

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Molecular Graphics, Movies, and Fully Interactive 3D Documents…

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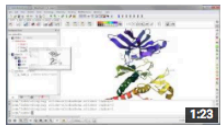

How to make a movie from a series of slides.

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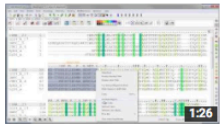

Alignment Annotation in ICM

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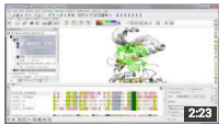
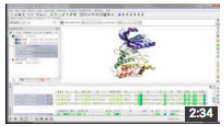


Highlighting Sequence Identity in the Ligand Binding Pocket usin…

140 views • 1 year ago

Editing an Alignment in ICM

80 views • 1 year ago



Making Sequence Alignments in ICM - Linking Sequence and…

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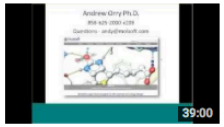
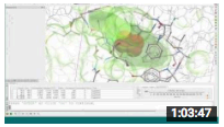
How to dock to two molecules.

174 views • 1 year ago



MolSoft Webinar: Ligand Based Lead Discovery using Atomic…

488 views • 2 years ago

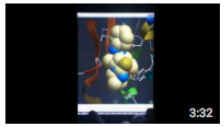


Webinar: Structure Based Lead Discovery using ICM Virtual…

1,213 views • 2 years ago

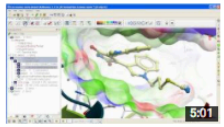
MolSoft Webinar: Ligand Design using ICM 3D Interactive Ligan…

1,695 views • 2 years ago



iMolview

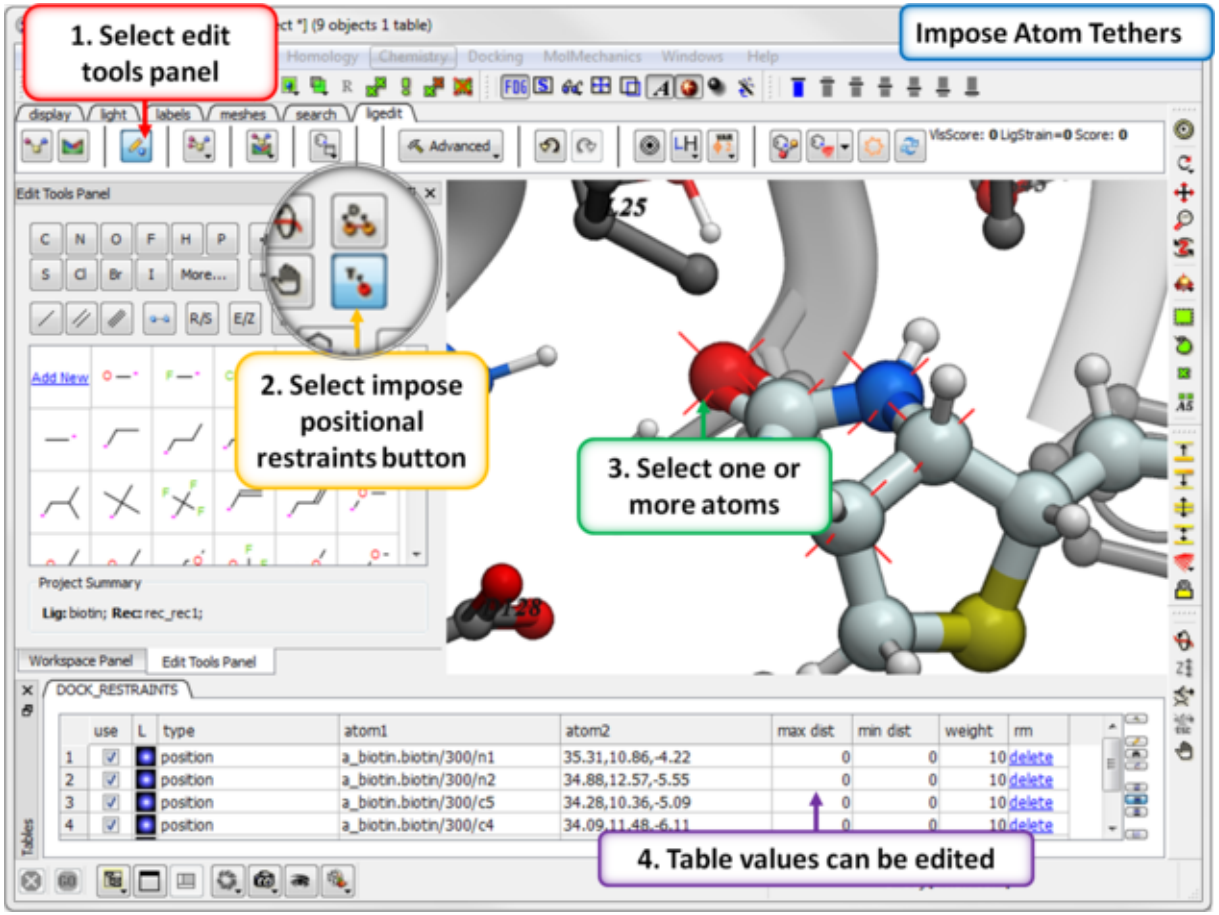
3,743 views • 4 years ago

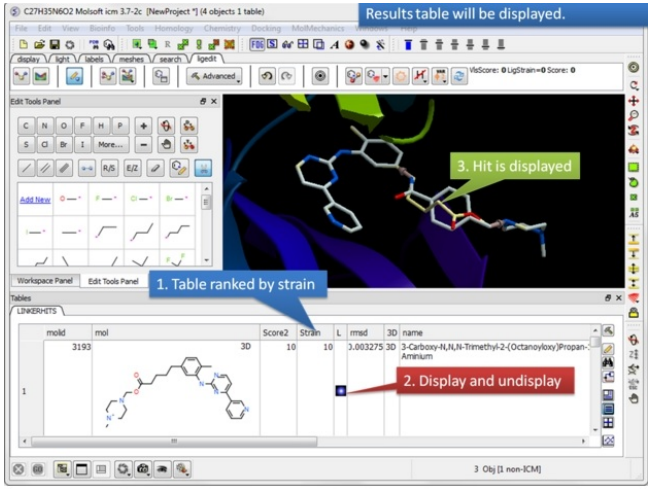


ICM-Browser & ActiveICM

698 views • 4 years ago

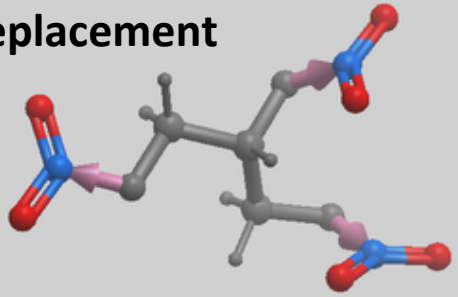
Ligand Editor





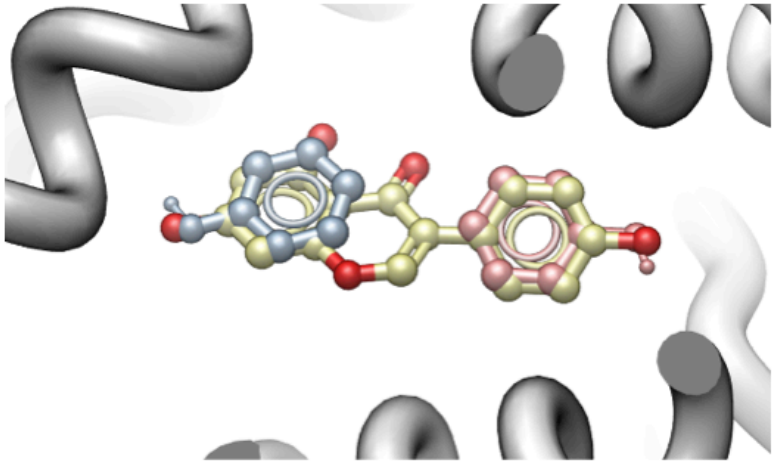
Fragment Linking

Three Point Core Replacement

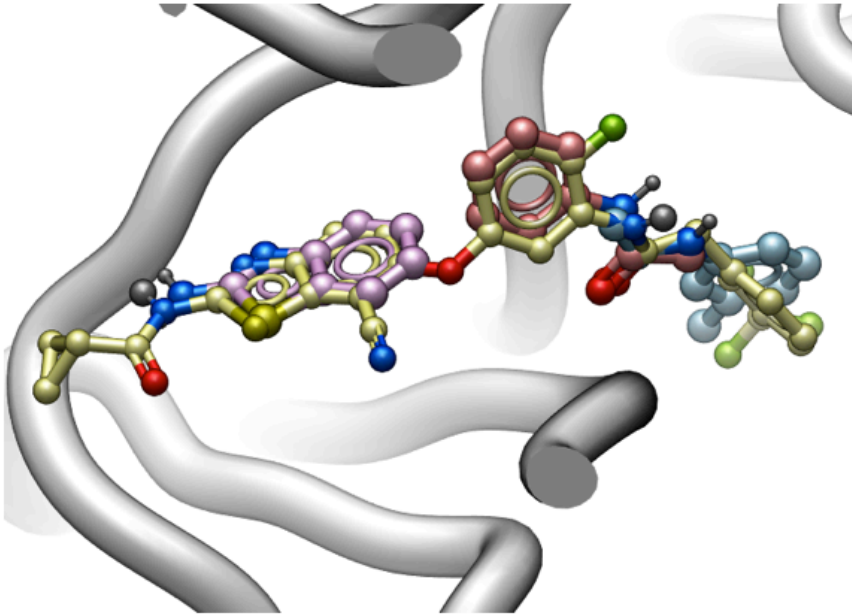


Computational Fragment Screen:

Examples of high-confidence fragment poses versus real ligands



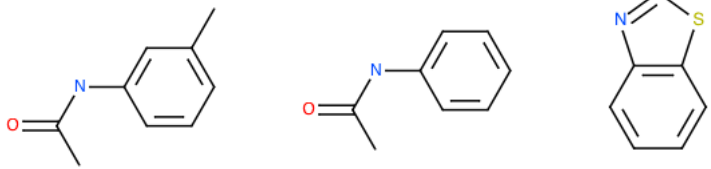
Bluish white -18.8 Red -22.7
p = 0.055 p = 0.011



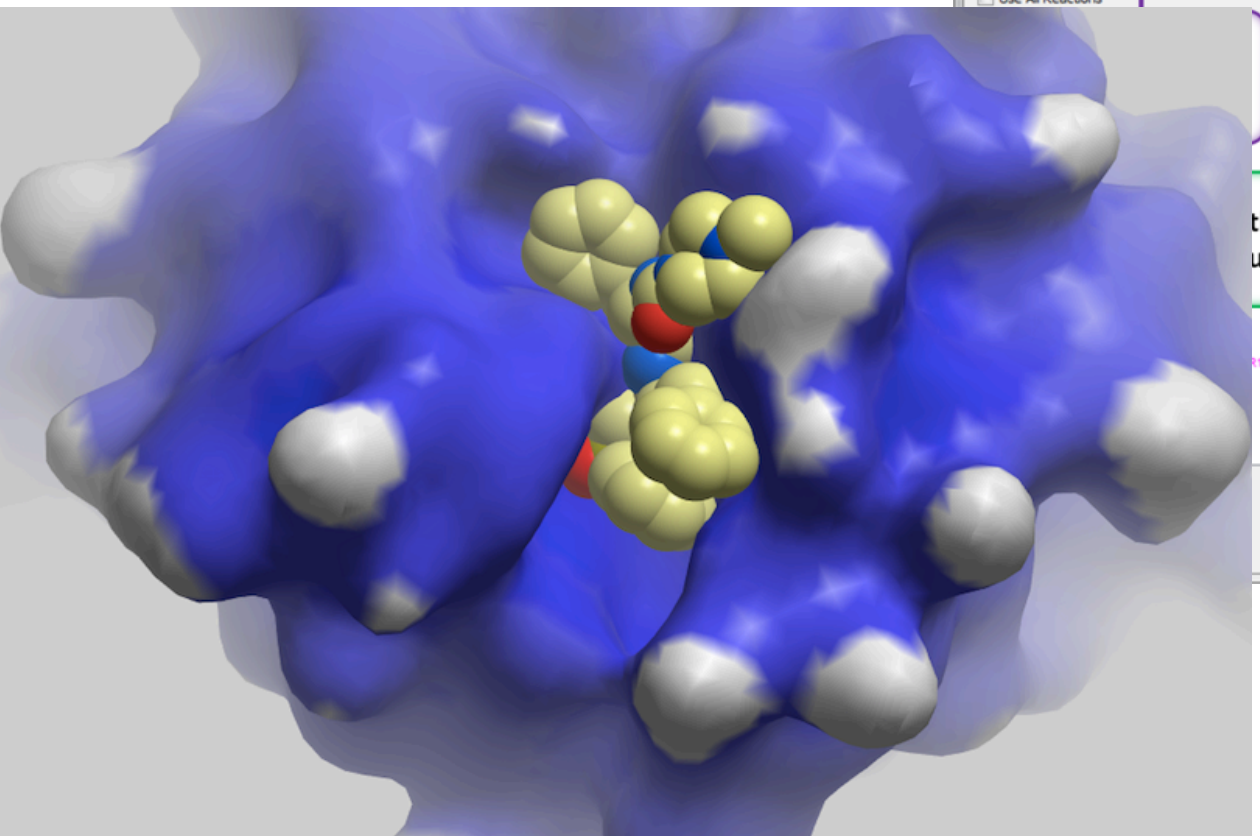
Bluish white Purple Red
p = 0.2 p = 0.047 p = <0.005

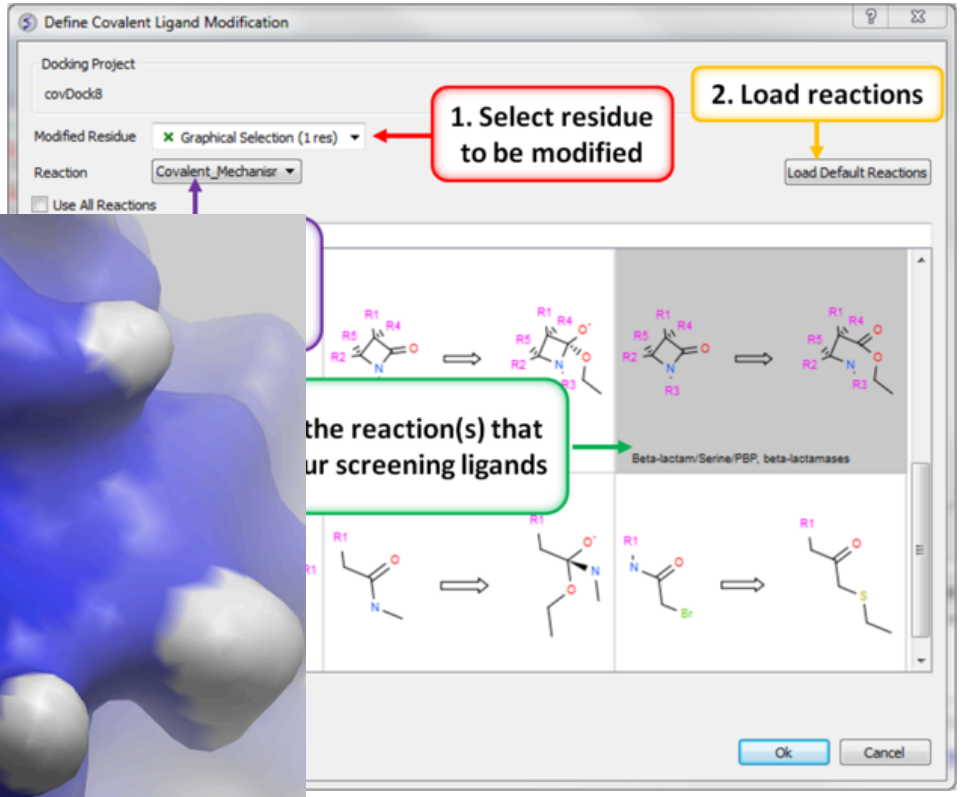
Phenol fragments in PDB 1QKM (ER)

PDB 4KSP (b-RAF kinase)



Covalent Inhibitors: screening & design

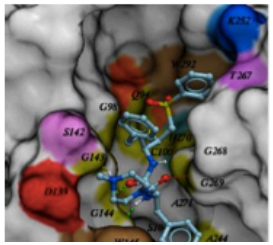
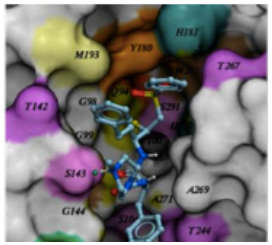
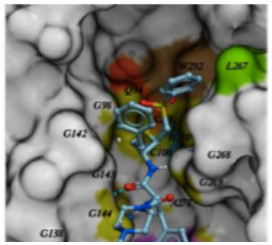
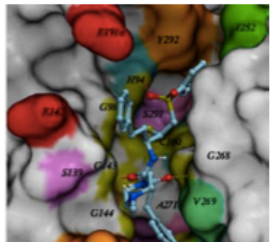


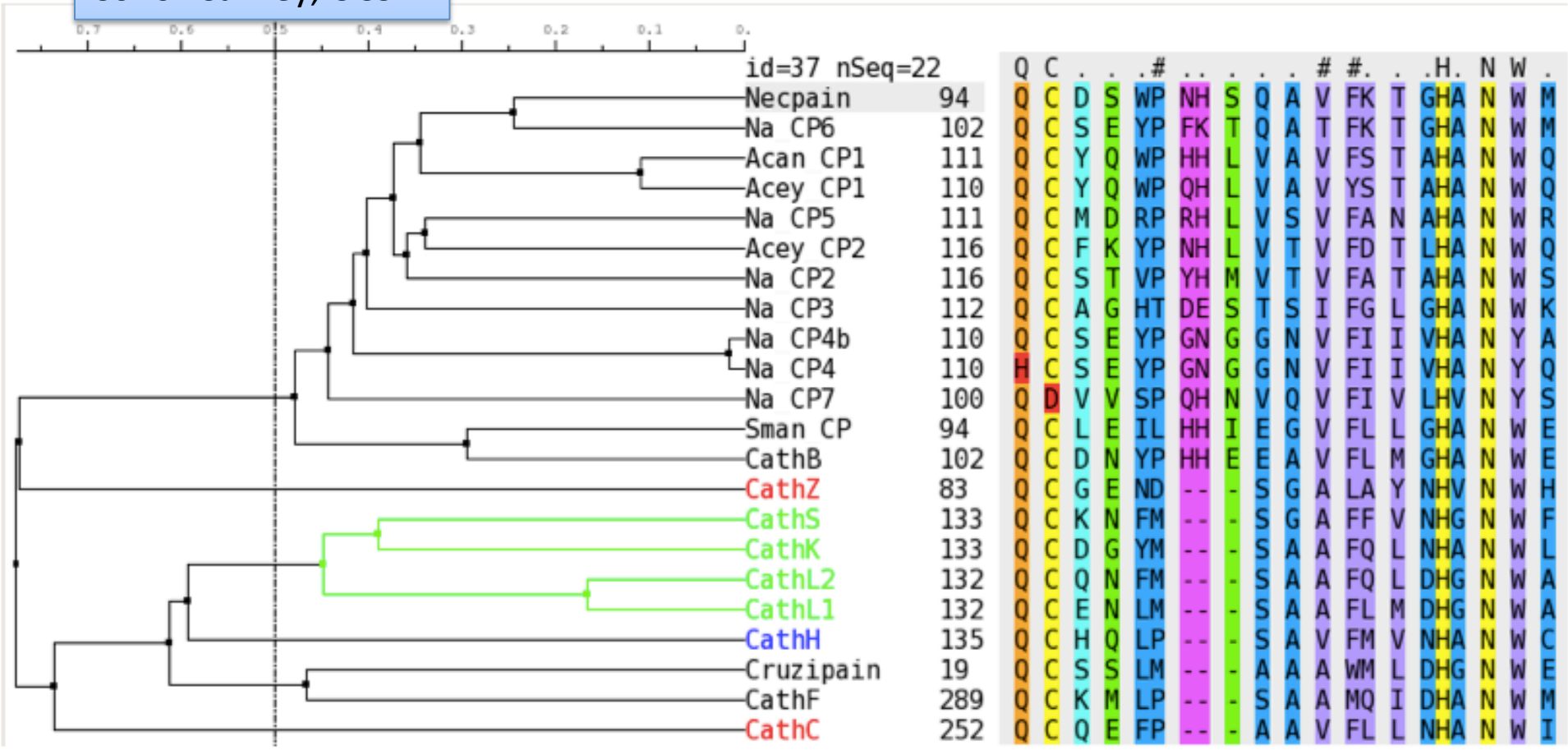


Protease with a covalent inhibitor screened by ICM

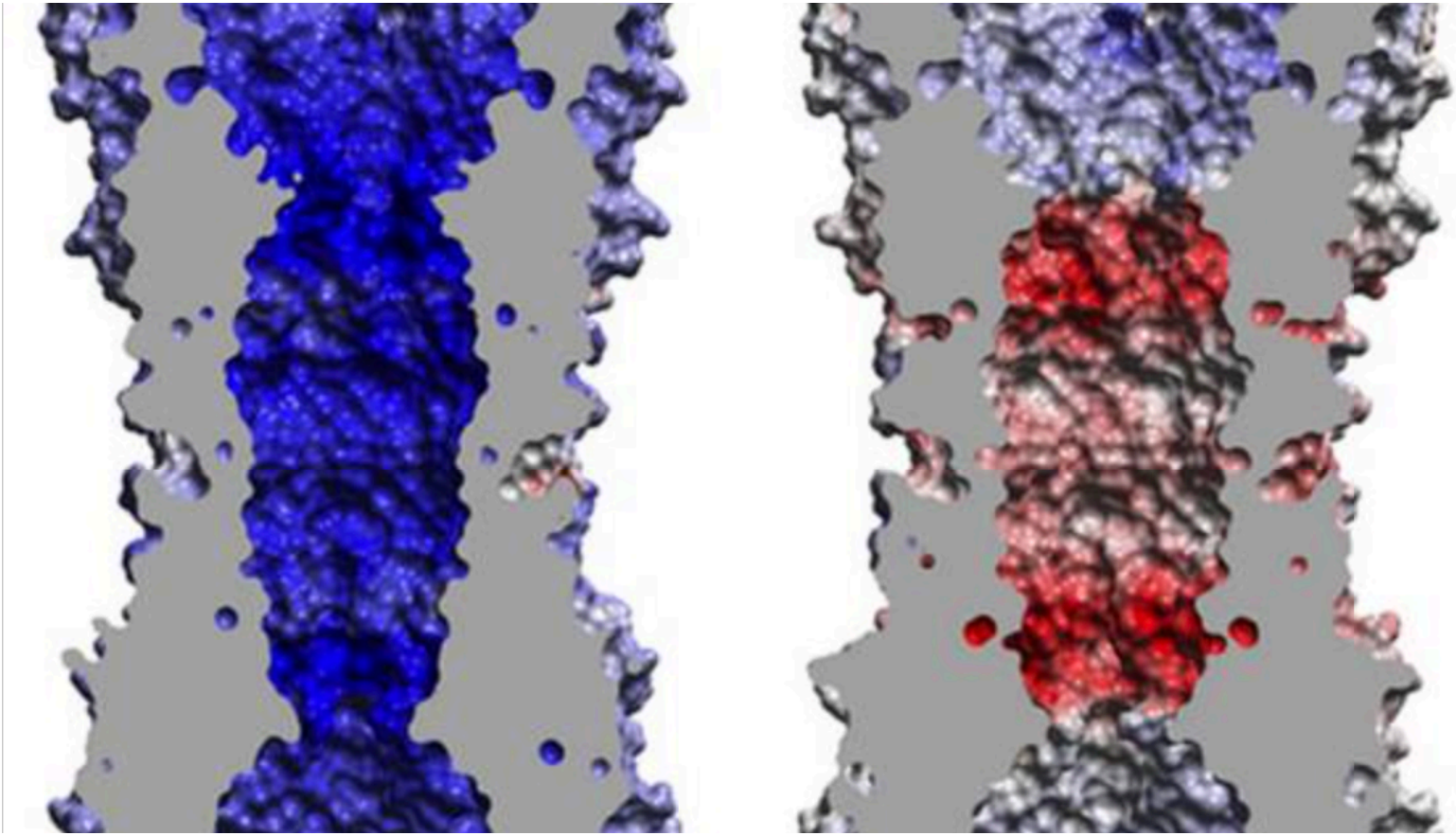
From Pocket Analysis to 3D Models
Cys-proteases from parasitic worms

Kevin Widmer, Basel,
Masterarbeit, 2016
Collaboration with
Conor Caffrey, UCSD



Boundary Element (REBEL) electrostatics

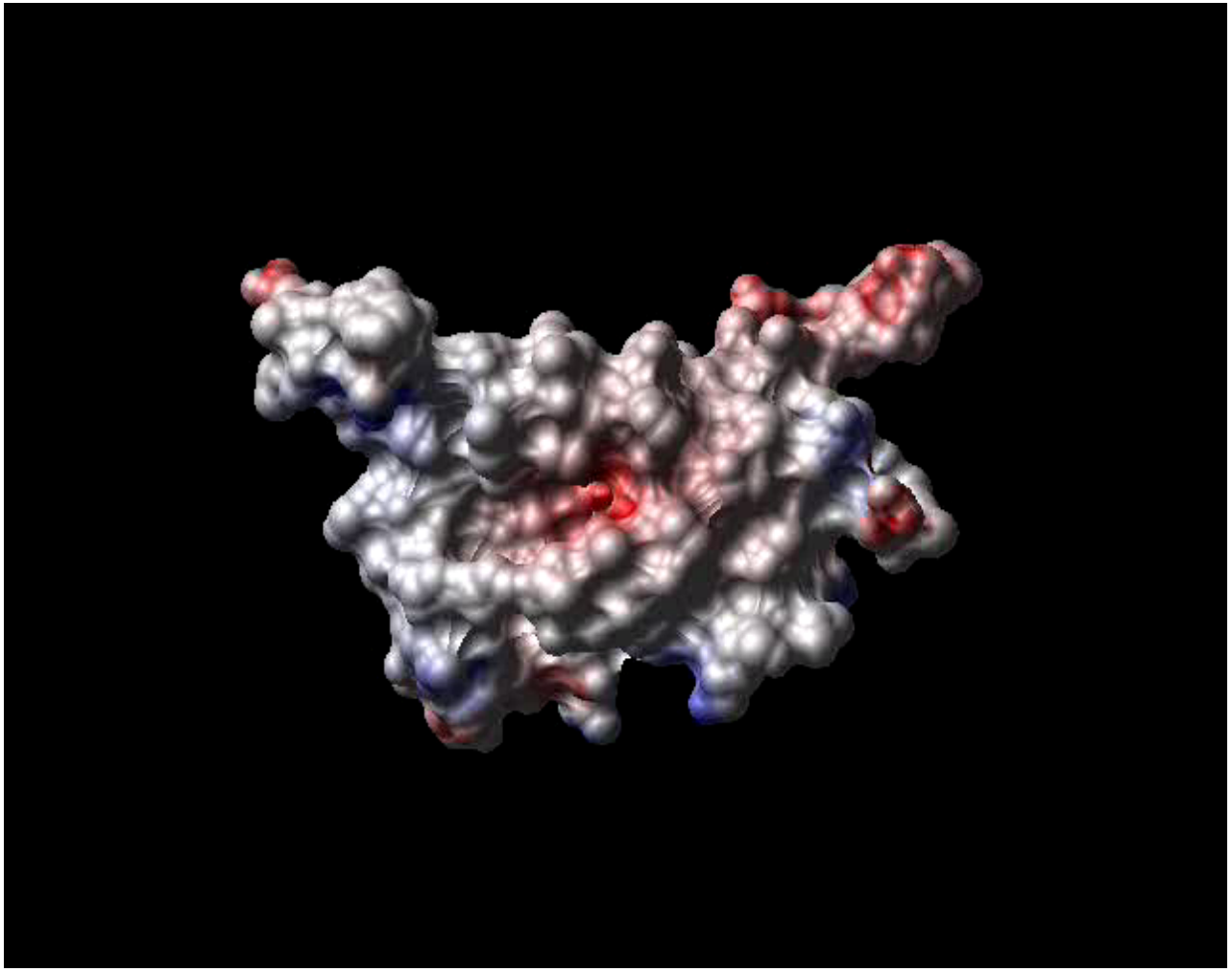


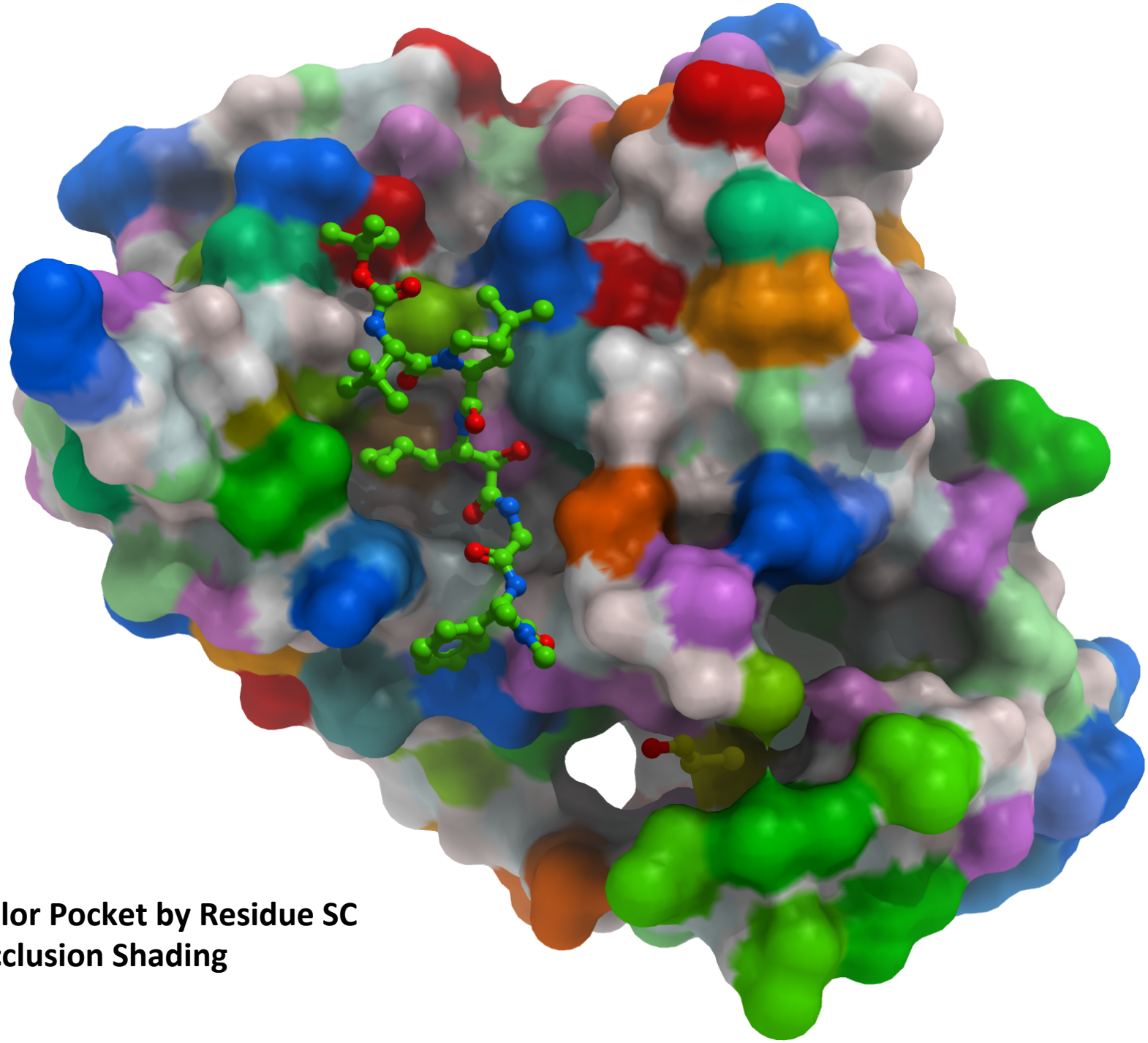
Bennet at al. **An electrostatic mechanism for Ca2+-mediated regulation of gap junction channels.** *Nature Comm*, 2016

Totrov, Abagyan. **Rapid boundary element solvation electrostatics calculations in folding simulations: successful folding of a 23-residue peptide.** *Biopolymers*. 2001;60(2):124-33

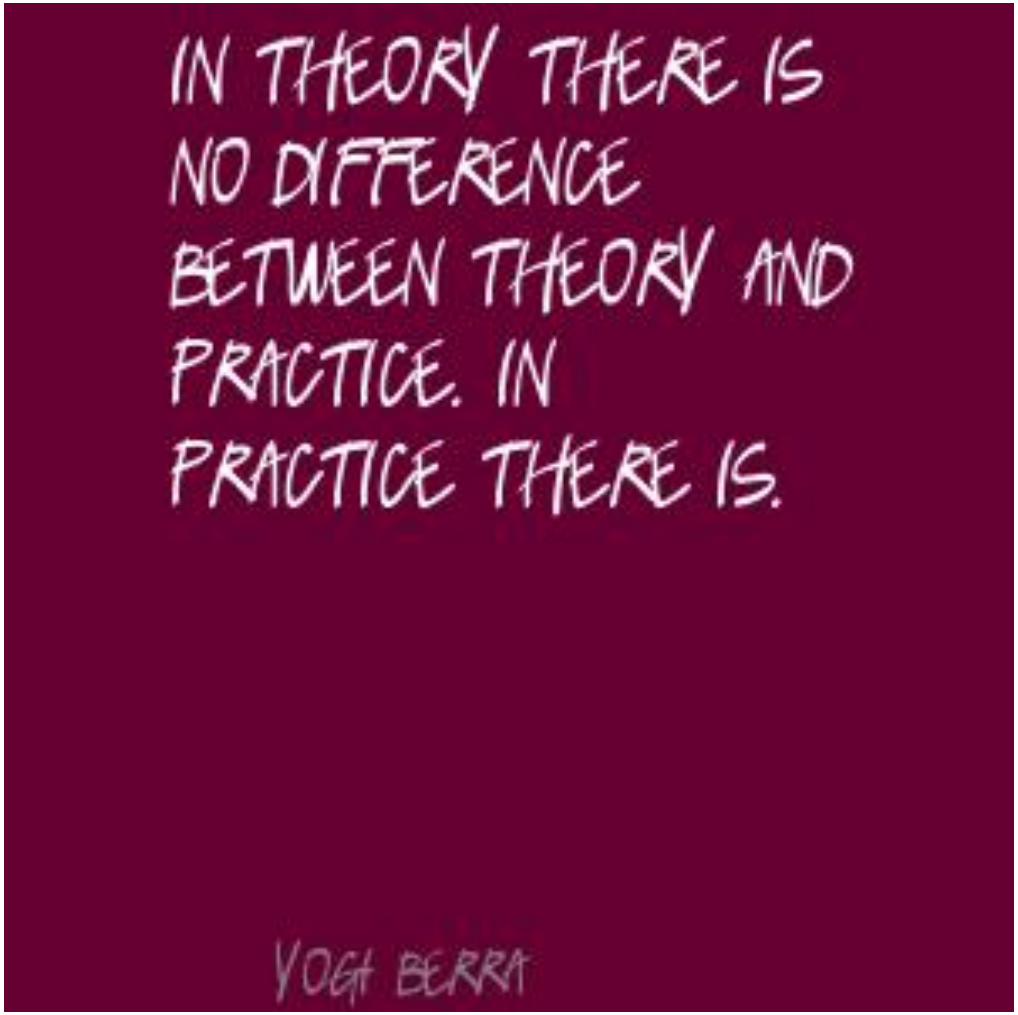
ICM pocket Finder

Jianghong An, Maxim Totrov, R. Abagyan. (2005) *Pocketome: Comprehensive Identification& Classification of Ligand Binding Envelopes, Mol. Cell Proteomics*

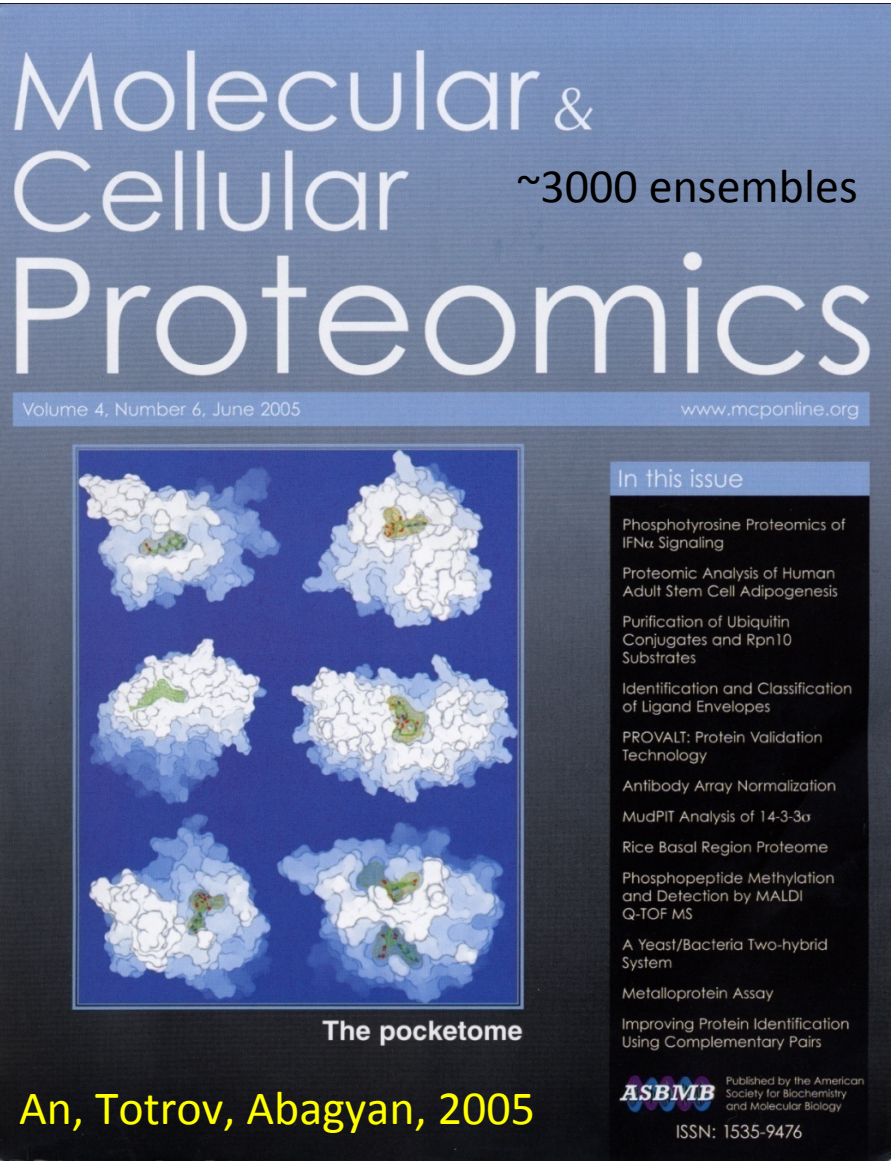




- **Color Pocket by Residue SC**
- **Occlusion Shading**


IN THEORY THERE IS
NO DIFFERENCE
BETWEEN THEORY AND
PRACTICE. IN
PRACTICE THERE IS.
YOGI BERRA

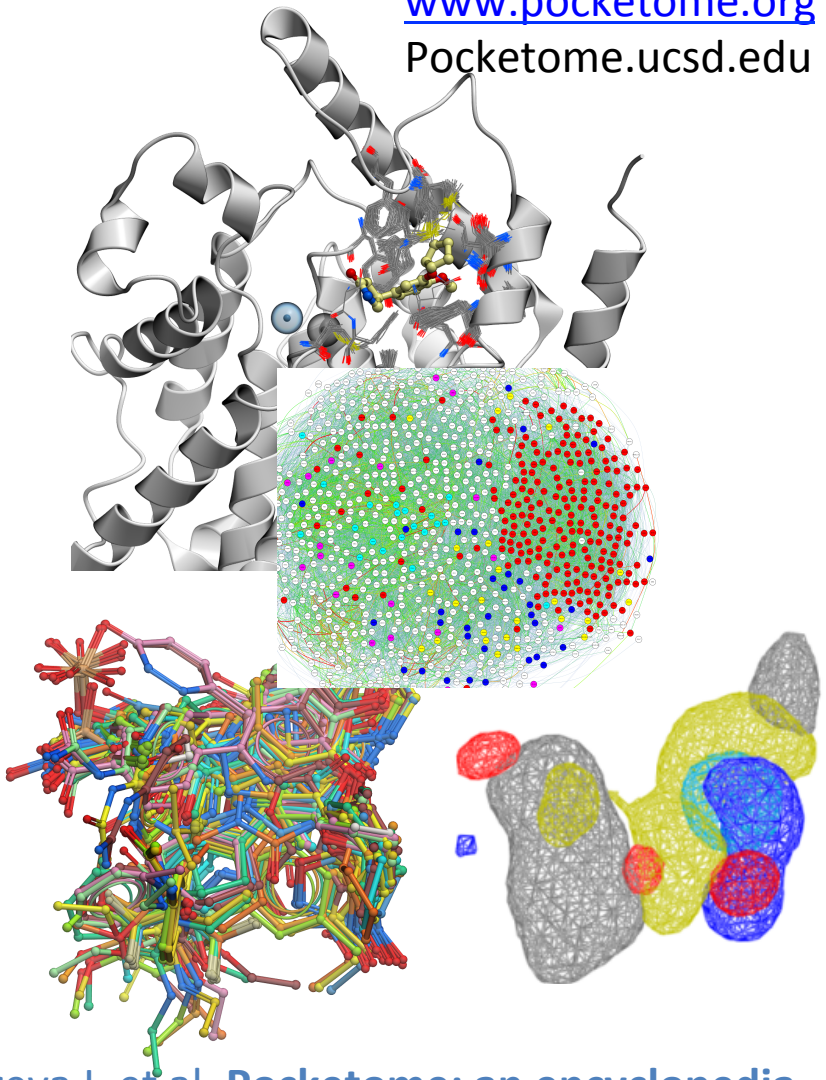
Docking to the Pocketome



An, Totrov, Abagyan, 2005

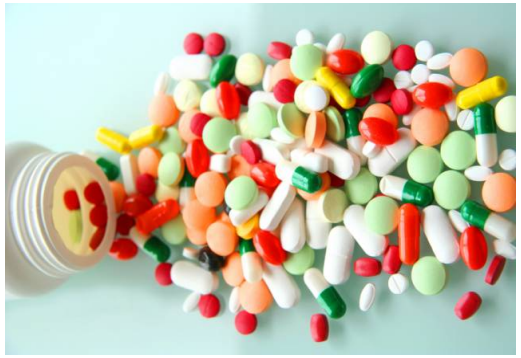
www.pocketome.org

Pocketome.ucsd.edu

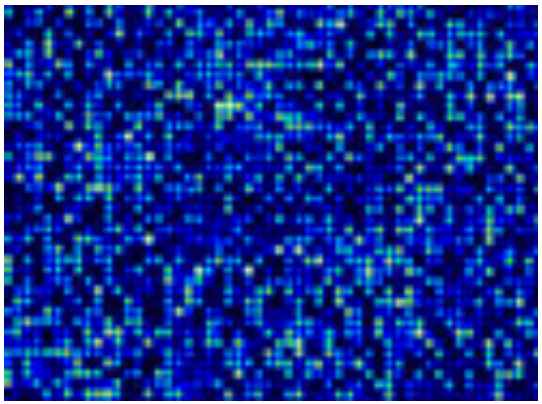


Kufareva I, et al. **Pocketome: an encyclopedia of binding sites in 4D**. *Nucleic Acids Res*. 2012

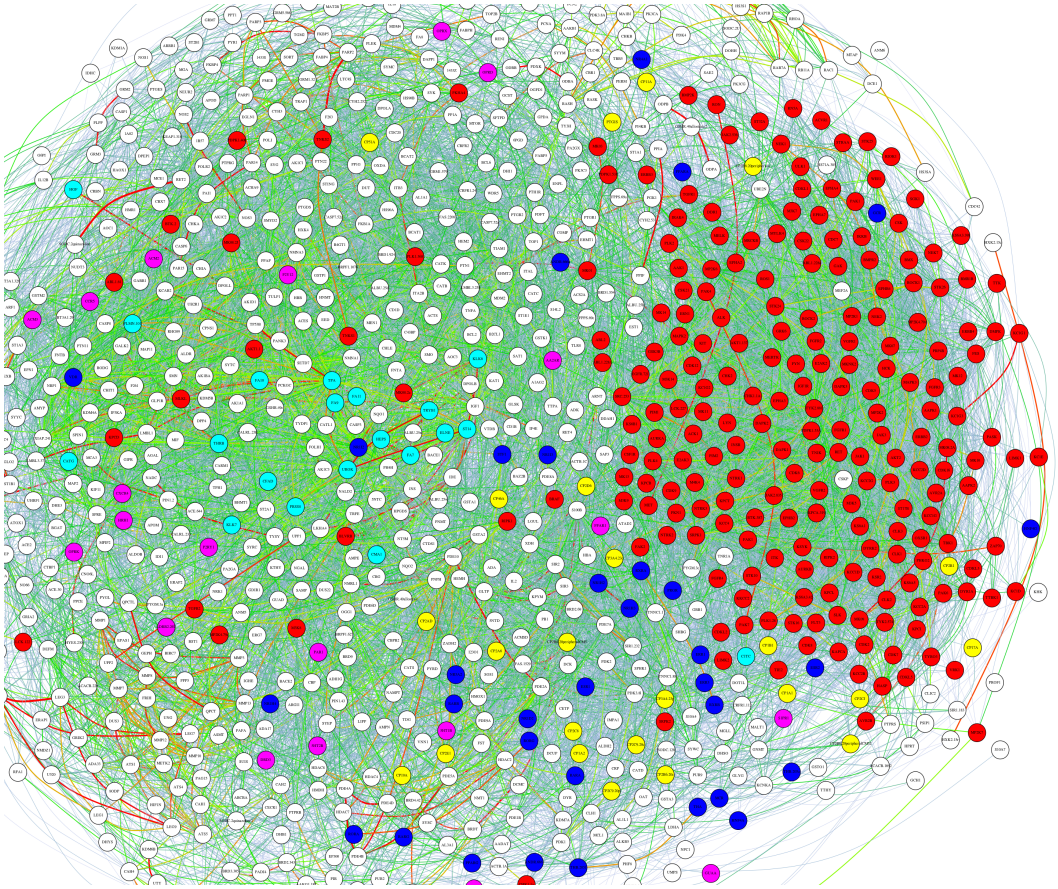
Drugs



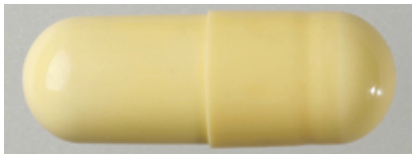
Profiles of relevant Patient Cells



MULTIPLE Drug Targets (the **Pocketome**)

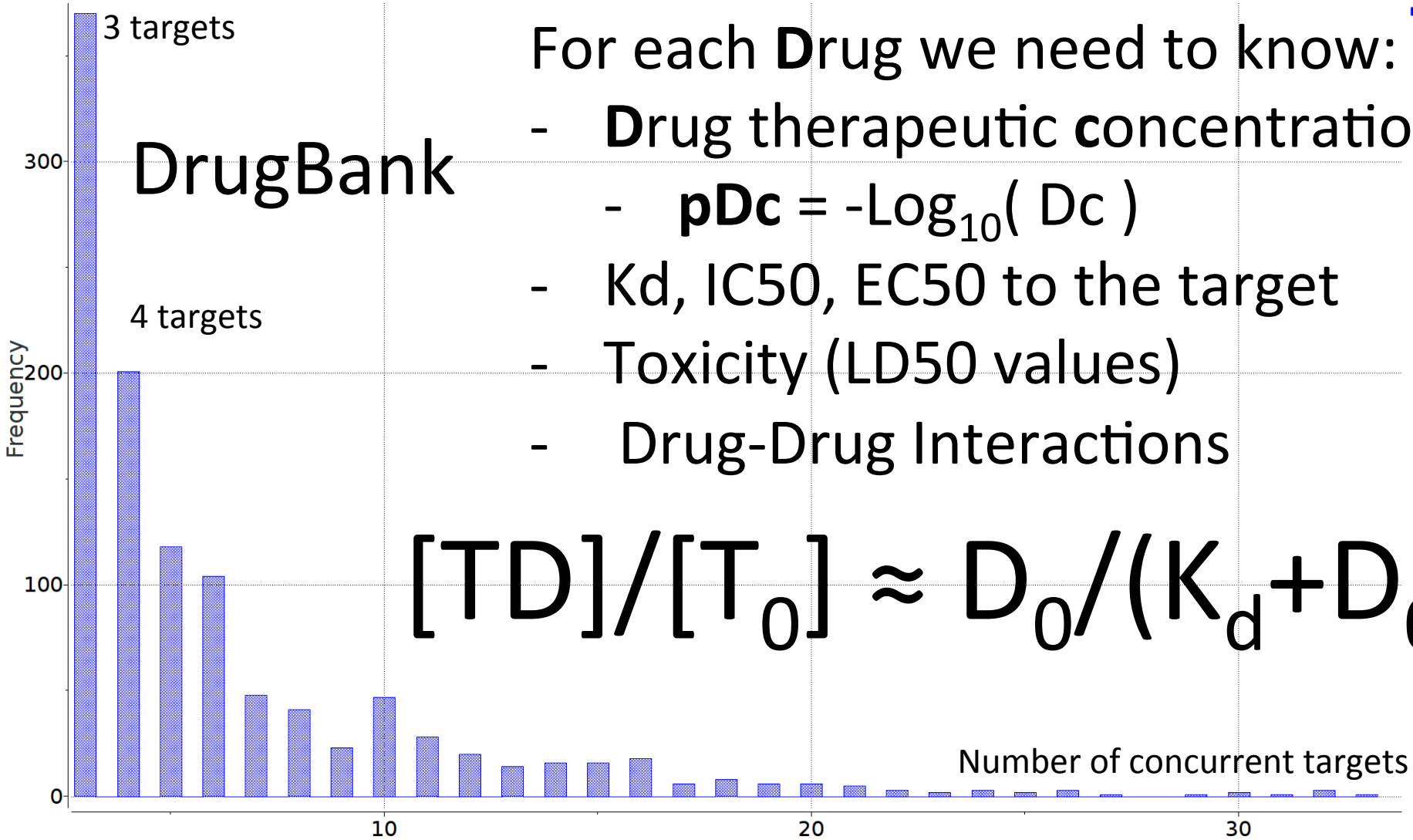


Optimal Match with one or few drugs



Substantial Multi-target Pharmacology

Targets of Drugs are under-Discovered and the binding is under-Quantified



DrugBank

For each **D**rug we need to know:

- **D**rug therapeutic **c**oncentration
  - **pDc** = $-\text{Log}_{10}(\text{Dc})$
- Kd, IC50, EC50 to the target
- Toxicity (LD50 values)
- Drug-Drug Interactions

$$[TD]/[T_0] \approx D_0/(K_d+D_0)$$

Chembl Database

- Example: Acitivites of **Bosutinib** above the **trough drug levels** + a margin to achive > 75% inhibition
- pDc+0.5

chembl_Bosutinib | Bosutinib_targets

	1	2	3	4
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4	uniprot_id LCK_HUMAN fullname Tyrosine-protein kinase Lck pAct 9.23	uniprot_id ERBB3_HUMAN fullname Receptor tyrosine-protein kin pAct 9.11	uniprot_id SRC_HUMAN fullname Proto-oncogene tyrosine-pro pAct 9	uniprot_id FGR_HUMAN fullname Tyrosine-protein kinase Fgr pAct 8.96
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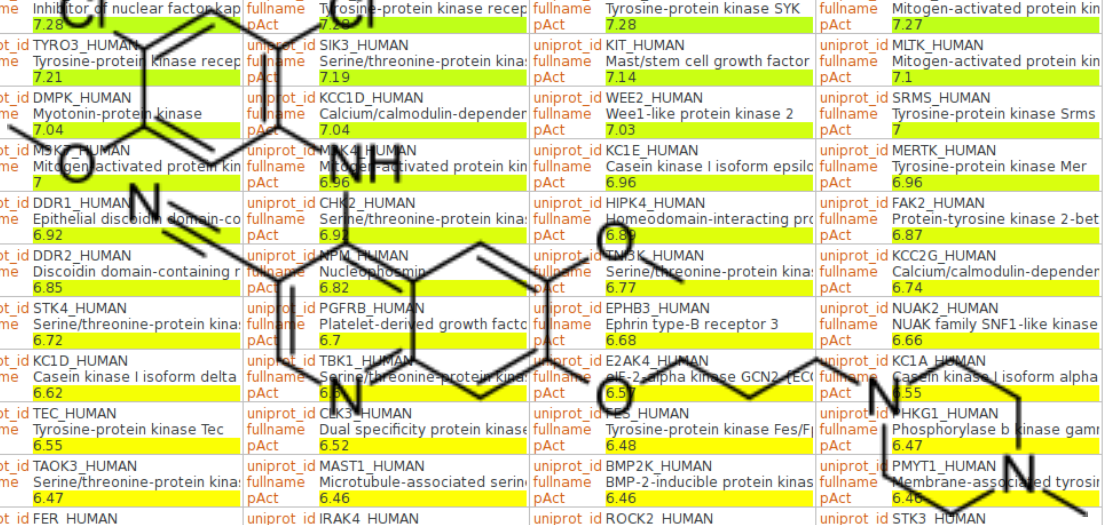


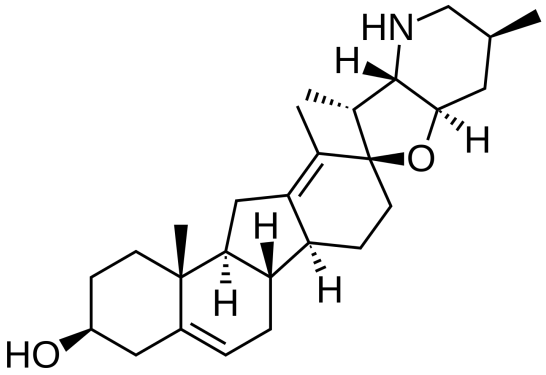
Multi-target pharmacology: friend of foe?

Discovery of *Useful* Additional Activities of Existing Drugs

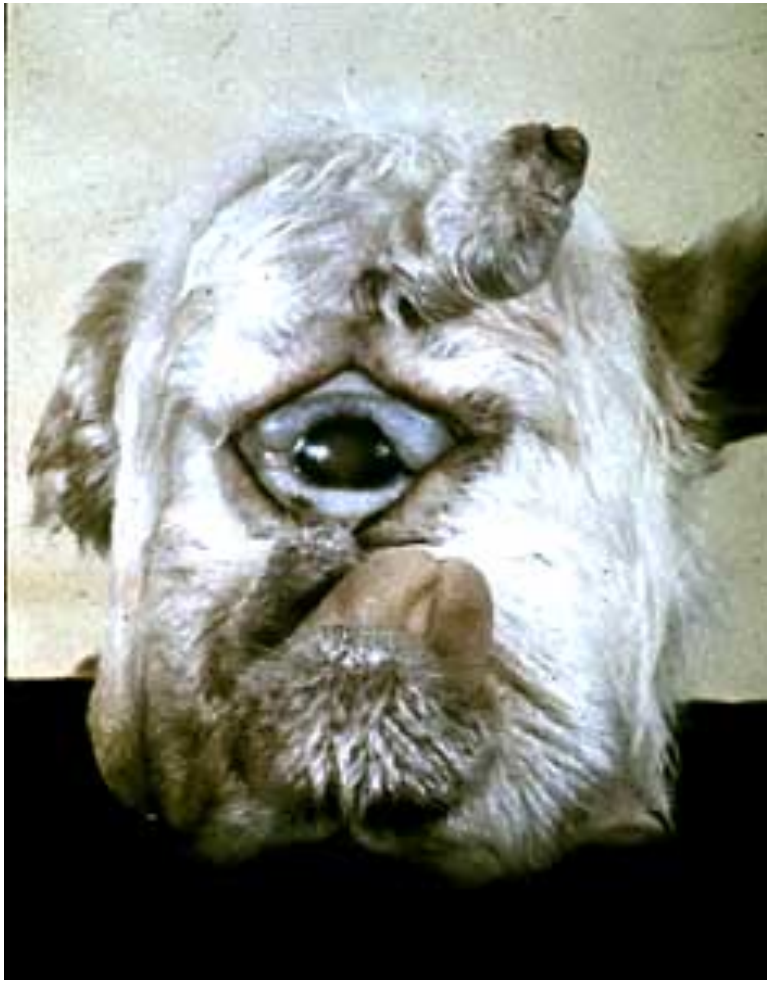
MTP opportunities

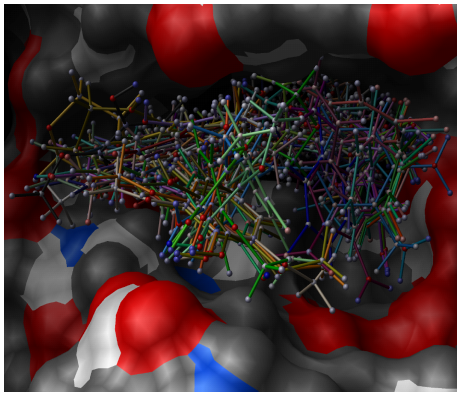
- Better drugs for a specific target
- Additional targets for specific drugs
- Targets for a drug with unknown mechanism of action

Dysregulated Hedgehog Pathway. Smoothened Receptor



Cyclopamine: teratogen from Corn Lily.
Hh-pathway: embryonic development, differentiation, cancer





Converting Pocket Ensembles with Co-crystallized Ligands into Docking/Binding Models

From **Score** to **pKd or ΔG**?

- Target specific Score shifts
- Re-trained docking Score
- Full pKd training on docked poses

2008, Kufareva et al., *JMC*, Profiling Kinases
2010, Park et al. *JCAMD*, 17 Nuclear Receptors
2014, Chen et al., *FMC*, 37 Pocket/Ligand Ensembles
2016, Lam et al., (MolScreen), >3000 Models

- Screening for a real multi-target profile of drugs
- Repurposing drugs or reviving abandoned candidates
- Predicting targets of hits from phenotypic assays
- Predicting adverse effects of drugs and environmental chemicals, additives and metabolites

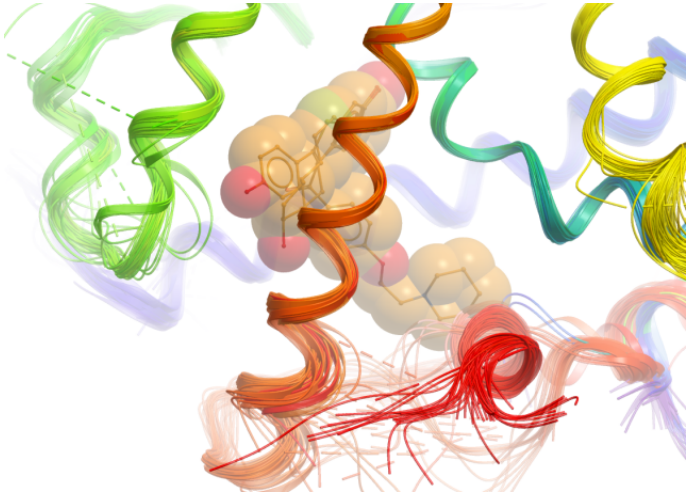
$$\Delta G_l \approx \sum_i \sum_k \omega_i^k E_i^{kl}$$

Pocket Selection: Rueda, et al. 2012, Alibero, *JCIM*
Bottegoni G, Rocchia W, Rueda M, Abagyan R, Cavalli A. **Systematic exploitation of multiple receptor conformations for virtual ligand screening.** *PLoS One.* 2011

Pocketome-derived **Target Screen**: Docking-Model Types and Outputs

DPC: Docking to Pocket, (343)

- Multi-conformational, 4D
- Template assisted, DP
- Selection, *single* cluster
- Pose + Class plus Activity (pIC50)



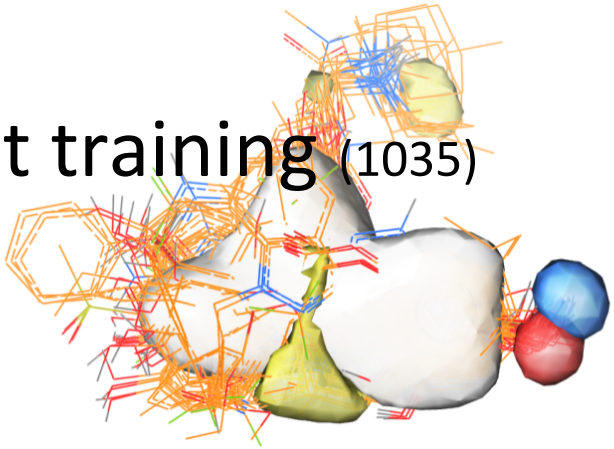
DFZ: Docking to Ligand (504)

Fields, Z-Score (normalized docking Score)

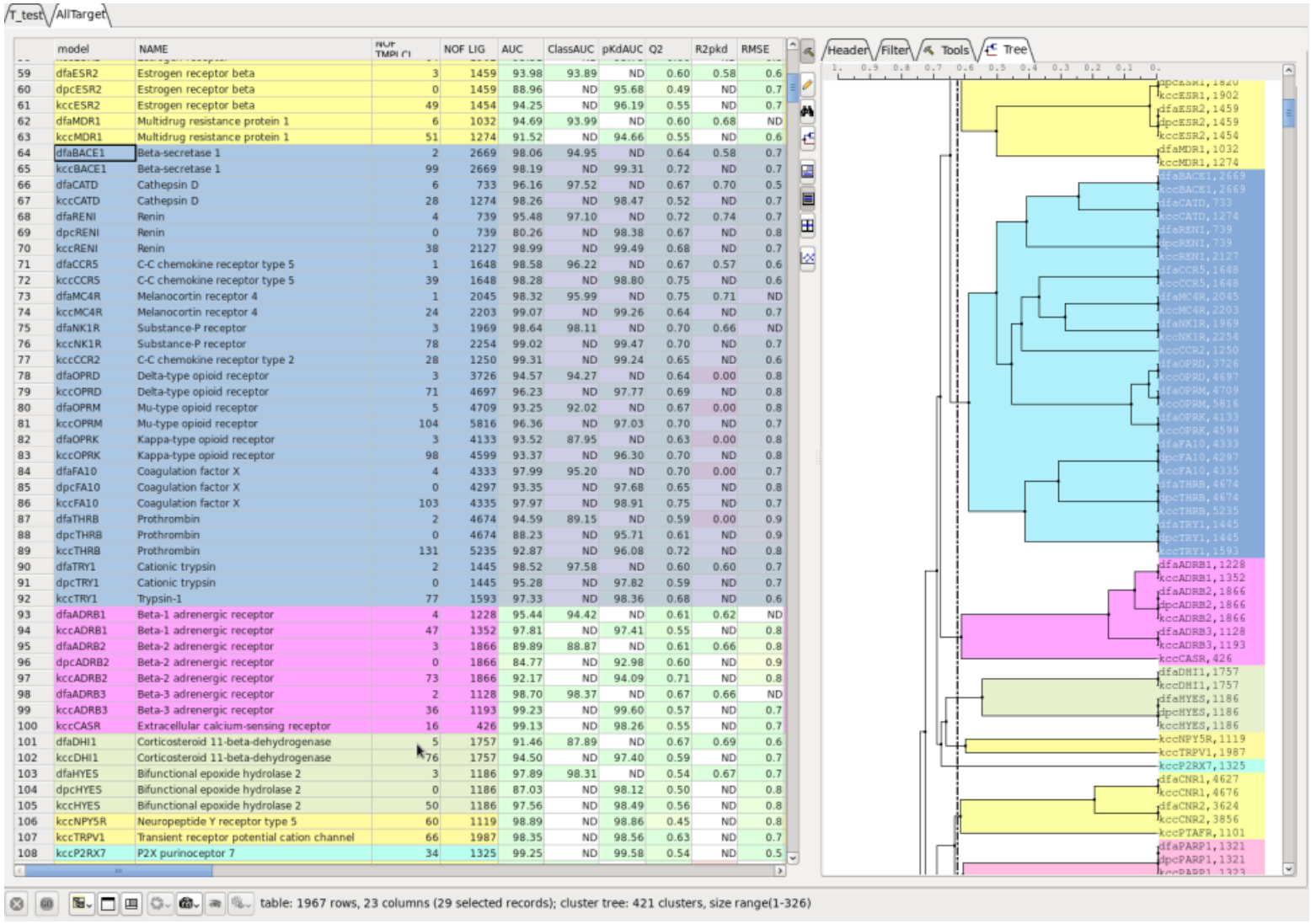
KCC: 2D Random Forest: (1139)

DFA: Docking to Ligand Fields+Act training (1035)

- Pocket driven or APF-Superposition
- *Multiple* Clusters
- Pose + Activity (pP, pIC50)



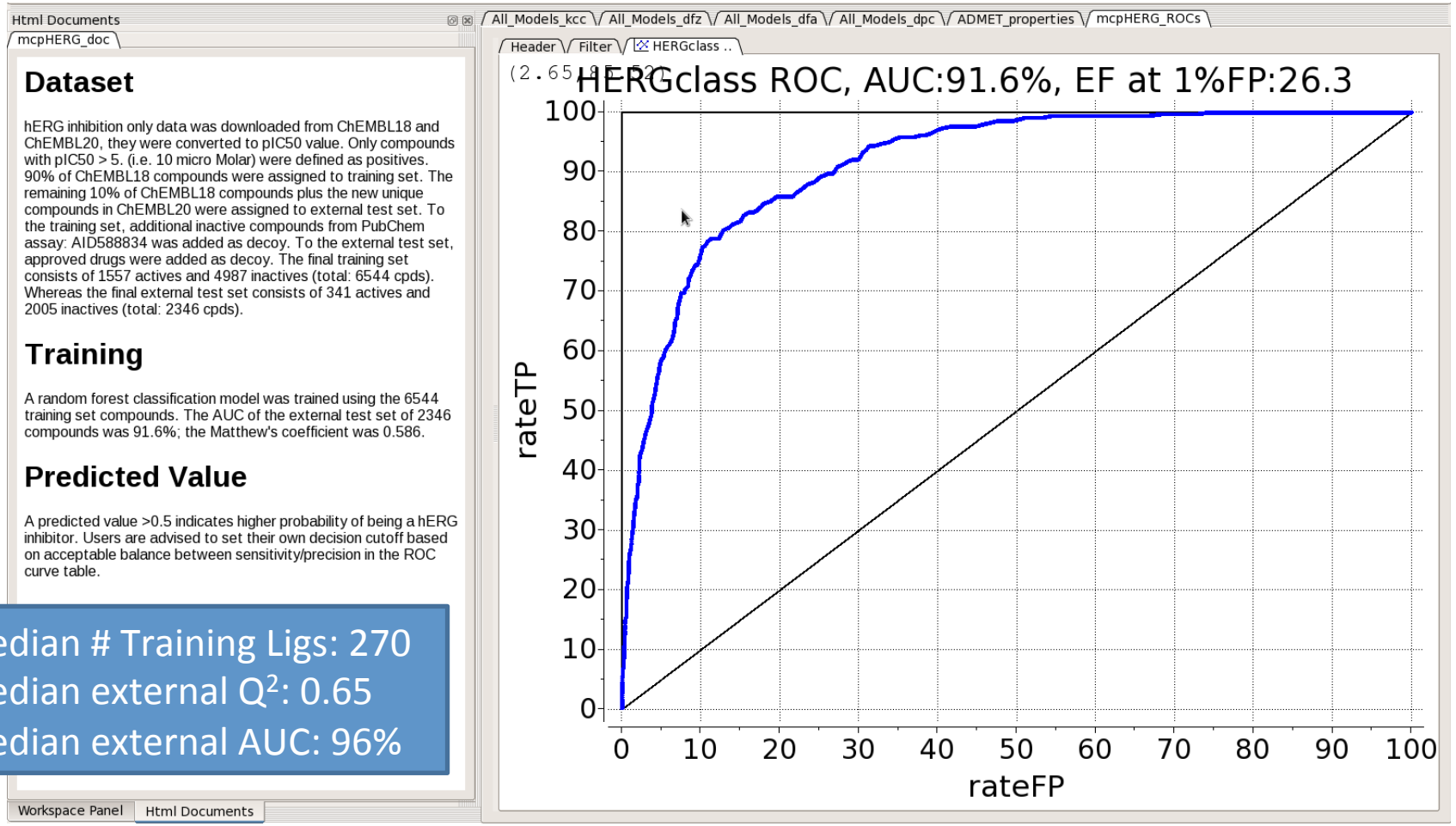
~3000 MolScreen Models clustered



	model	NAME	NOF TMPLCL	NOF LIG	AUC	ClassAUC	pKdAUC	Q2	R2pkd	RMSE
59	dfaESR2	Estrogen receptor beta	3	1459	93.98	93.89	ND	0.60	0.58	0.6
60	dpcESR2	Estrogen receptor beta	0	1459	88.96	ND	95.68	0.49	ND	0.7
61	kccESR2	Estrogen receptor beta	49	1454	94.25	ND	96.19	0.55	ND	0.7
62	dfaMDR1	Multidrug resistance protein 1	6	1032	94.69	93.99	ND	0.60	0.68	ND
63	kccMDR1	Multidrug resistance protein 1	51	1274	91.52	ND	94.66	0.55	ND	0.6
64	dfaBACE1	Beta-secretase 1	2	2669	98.06	94.95	ND	0.64	0.58	0.7
65	kccBACE1	Beta-secretase 1	99	2669	98.19	ND	99.31	0.72	ND	0.7
66	dfaCATD	Cathepsin D	6	733	96.16	97.52	ND	0.67	0.70	0.5
67	kccCATD	Cathepsin D	28	1274	98.26	ND	98.47	0.52	ND	0.7
68	dfaRENI	Renin	4	739	95.48	97.10	ND	0.72	0.74	0.7
69	dpcRENI	Renin	0	739	80.26	ND	98.38	0.67	ND	0.8
70	kccRENI	Renin	38	2127	98.99	ND	99.49	0.68	ND	0.7
71	dfaCCR5	C-C chemokine receptor type 5	1	1648	98.58	96.22	ND	0.67	0.57	0.6
72	kccCCR5	C-C chemokine receptor type 5	39	1648	98.28	ND	98.80	0.75	ND	0.6
73	dfaMC4R	Melanocortin receptor 4	1	2045	98.32	95.99	ND	0.75	0.71	ND
74	kccMC4R	Melanocortin receptor 4	24	2203	99.07	ND	99.26	0.64	ND	0.7
75	dfaNK1R	Substance-P receptor	3	1969	98.64	98.11	ND	0.70	0.66	ND
76	kccNK1R	Substance-P receptor	78	2254	99.02	ND	99.47	0.70	ND	0.7
77	kccCCR2	C-C chemokine receptor type 2	28	1250	99.31	ND	99.24	0.65	ND	0.6
78	dfaOPRD	Delta-type opioid receptor	3	3726	94.57	94.27	ND	0.64	0.00	0.8
79	kccOPRD	Delta-type opioid receptor	71	4697	96.23	ND	97.77	0.69	ND	0.8
80	dfaOPRM	Mu-type opioid receptor	5	4709	93.25	92.02	ND	0.67	0.00	0.8
81	kccOPRM	Mu-type opioid receptor	104	5816	96.36	ND	97.03	0.70	ND	0.7
82	dfaOPRK	Kappa-type opioid receptor	3	4133	93.52	87.95	ND	0.63	0.00	0.8
83	kccOPRK	Kappa-type opioid receptor	98	4599	93.37	ND	96.30	0.70	ND	0.8
84	dfaFA10	Coagulation factor X	4	4333	97.99	95.20	ND	0.70	0.00	0.7
85	dpcFA10	Coagulation factor X	0	4297	93.35	ND	97.68	0.65	ND	0.8
86	kccFA10	Coagulation factor X	103	4335	97.97	ND	98.91	0.75	ND	0.7
87	dfaTHRB	Prothrombin	2	4674	94.59	89.15	ND	0.59	0.00	0.9
88	dpcTHRB	Prothrombin	0	4674	88.23	ND	95.71	0.61	ND	0.9
89	kccTHRB	Prothrombin	131	5235	92.87	ND	96.08	0.72	ND	0.8
90	dfaTRY1	Cationic trypsin	2	1445	98.52	97.58	ND	0.60	0.60	0.7
91	dpcTRY1	Cationic trypsin	0	1445	95.28	ND	97.82	0.59	ND	0.7
92	kccTRY1	Trypsin-1	77	1593	97.33	ND	98.36	0.68	ND	0.6
93	dfaADRB1	Beta-1 adrenergic receptor	4	1228	95.44	94.42	ND	0.61	0.62	ND
94	kccADRB1	Beta-1 adrenergic receptor	47	1352	97.81	ND	97.41	0.55	ND	0.8
95	dfaADRB2	Beta-2 adrenergic receptor	3	1866	89.89	88.87	ND	0.61	0.66	0.8
96	dpcADRB2	Beta-2 adrenergic receptor	0	1866	84.77	ND	92.98	0.60	ND	0.9
97	kccADRB2	Beta-2 adrenergic receptor	73	1866	92.17	ND	94.09	0.71	ND	0.8
98	dfaADRB3	Beta-3 adrenergic receptor	2	1128	98.70	98.37	ND	0.67	0.66	ND
99	kccADRB3	Beta-3 adrenergic receptor	36	1193	99.23	ND	99.60	0.57	ND	0.7
100	kccCASR	Extracellular calcium-sensing receptor	16	426	99.13	ND	98.26	0.55	ND	0.7
101	dfaDHI1	Corticosteroid 11-beta-dehydrogenase	5	1757	91.46	87.89	ND	0.67	0.69	0.6
102	kccDHI1	Corticosteroid 11-beta-dehydrogenase	76	1757	94.50	ND	97.40	0.59	ND	0.7
103	dfaHYES	Bifunctional epoxide hydrolase 2	3	1186	97.89	98.31	ND	0.54	0.67	0.7
104	dpcHYES	Bifunctional epoxide hydrolase 2	0	1186	87.03	ND	98.12	0.50	ND	0.8
105	kccHYES	Bifunctional epoxide hydrolase 2	50	1186	97.56	ND	98.49	0.56	ND	0.8
106	kccNPY5R	Neuropeptide Y receptor type 5	60	1119	98.89	ND	98.86	0.45	ND	0.8
107	kccTRPV1	Transient receptor potential cation channel	66	1987	98.35	ND	98.56	0.63	ND	0.7
108	kccP2RX7	P2X purinoceptor 7	34	1325	99.25	ND	99.58	0.54	ND	0.5

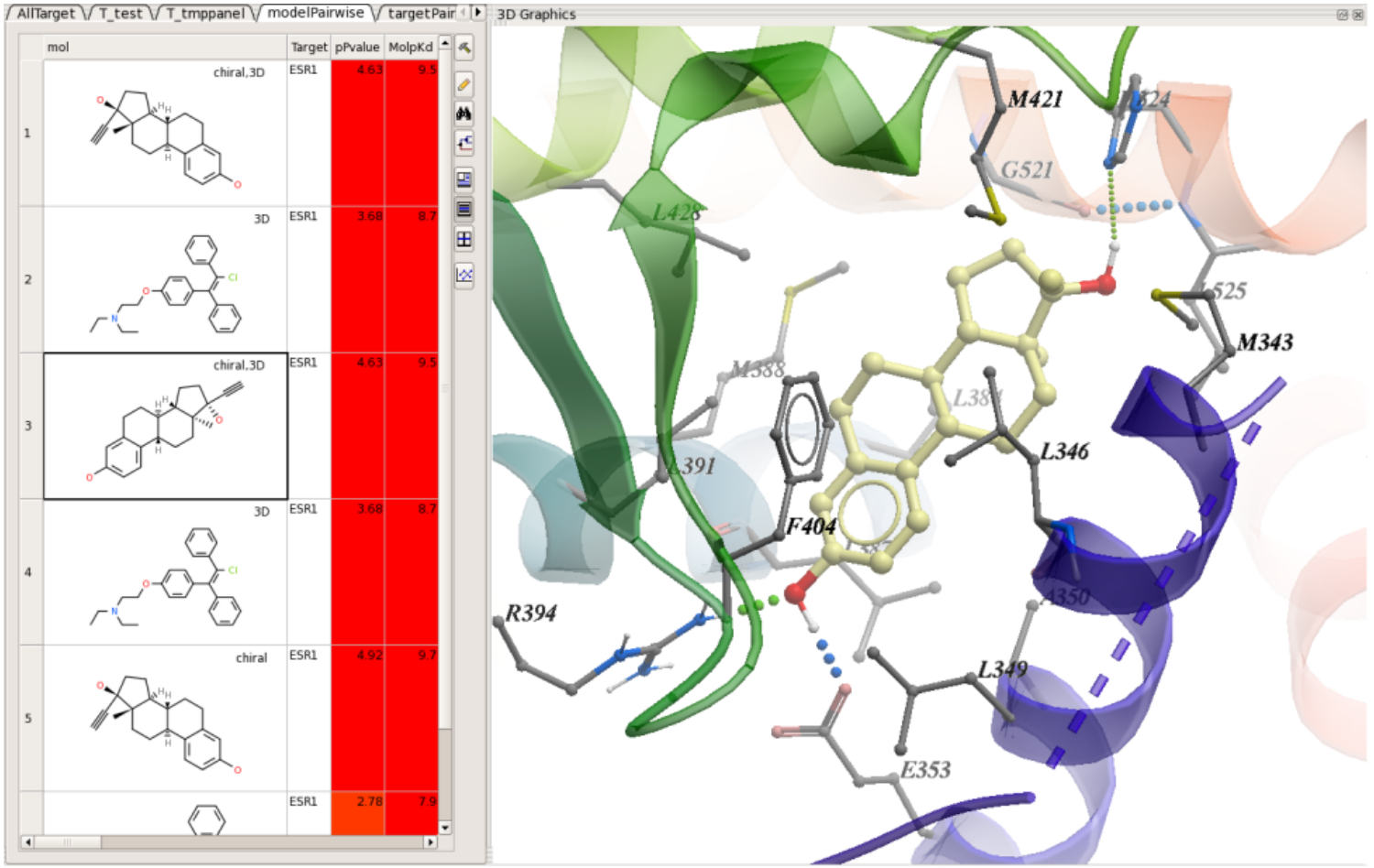
Individual models: performance and training details

- Load Panel -> Check Model Performance:



Median # Training Ligs: 270
Median external Q^2: 0.65
Median external AUC: 96%

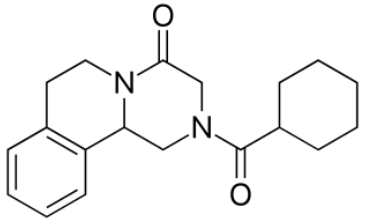
Best Docking Pose to go with c-pKd

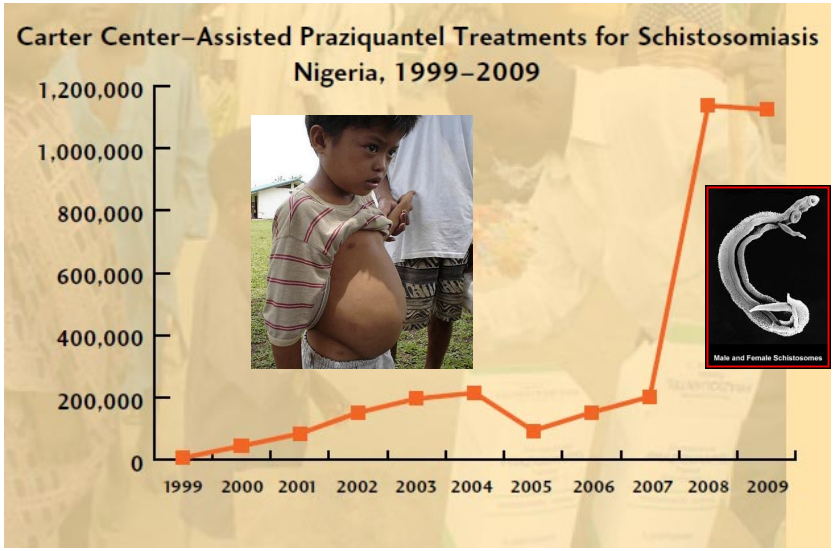


- dfa, dpc, dfz models are based on docking
- pKd prediction based on random forest training if 3D methods fail or are not accurate enough

Discovering MOA with the Pocketome
Parasitic flatworms and **Praziquantel**

- *Schistosomiasis*: 200-400M
  - Some develop CNS symptoms
- *Hydatid* disease (Echinococcus)
- *Cysticercosis*: brain/muscle by eggs and larvae of the pork tapeworm





- Praziquantel against tapeworms and flukes (schisto: single dose)
- PZQ is extremely well tolerated. But .. The **MOA is unknown** and resistance is imminent

Praziquantel target screen

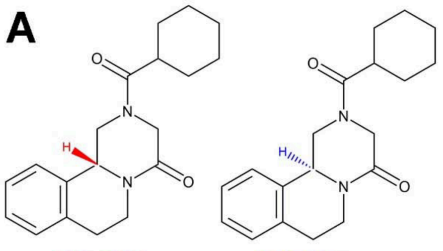
Collaboration with
Pauline Cupid, Brian Roth
Charles Cunningham,
Jonathan Marchant
Nature Comm. (submitted)

Docking PZQ-R/S to 343 4D pockets

Target	Code	pPvalue	Mol_pKd	pKd_Error	Drug
5-hydroxytryptamine receptor 2B	5HT2B	1.99	6.99	1.44	(*R*)-PZQ
5-hydroxytryptamine receptor 2B	5HT2B	1.91	6.89	1.44	(*S*)-PZQ
Muscarinic acetylcholine receptor M2	ACM2	1.48	6.33	1.24	(*R*)-PZQ
Muscarinic acetylcholine receptor M3	ACM3	1.18	5.88	1.20	(*R*)-PZQ
Kappa-type opioid receptor	OPRK	1.13	5.81	1.28	(*S*)-PZQ
D(3) dopamine receptor	DRD3	1.12	5.80	1.28	(*R*)-PZQ
Muscarinic acetylcholine receptor M3	ACM3	0.81	5.26	1.20	(*S*)-PZQ
Kappa-type opioid receptor	OPRK	0.79	5.22	1.28	(*R*)-PZQ
Delta-type opioid receptor	OPRD	0.78	5.20	1.23	(*S*)-PZQ
Muscarinic acetylcholine receptor M2	ACM2	0.76	5.16	1.24	(*S*)-PZQ
Adenosine receptor A2a	AA2AR	0.45	4.25	1.26	(*R*)-PZQ
Adenosine receptor A2a	AA2AR	0.48	3.54	1.26	(*S*)-PZQ
Delta-type opioid receptor	OPRD	0.39	3.44	1.23	(*R*)-PZQ
Beta-2 adrenergic receptor	ADRB2	0.82	2.41	1.27	(*R*)-PZQ
Beta-2 adrenergic receptor	ADRB2	0.23	ND	ND	(*S*)-PZQ
D(3) dopamine receptor	DRD3	0.05	ND	ND	(*S*)-PZQ
Corticotropin-releasing factor receptor 1	CRFR1	0.55	ND	ND	(*S*)-PZQ
Corticotropin-releasing factor receptor 1	CRFR1	0.68	ND	ND	(*R*)-PZQ

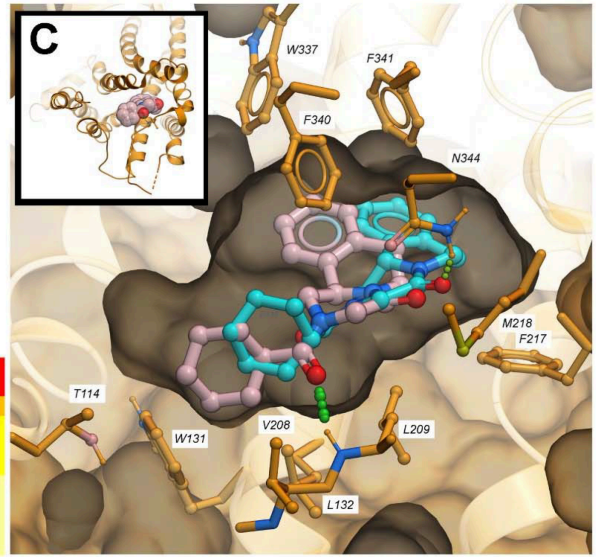
Figure 1

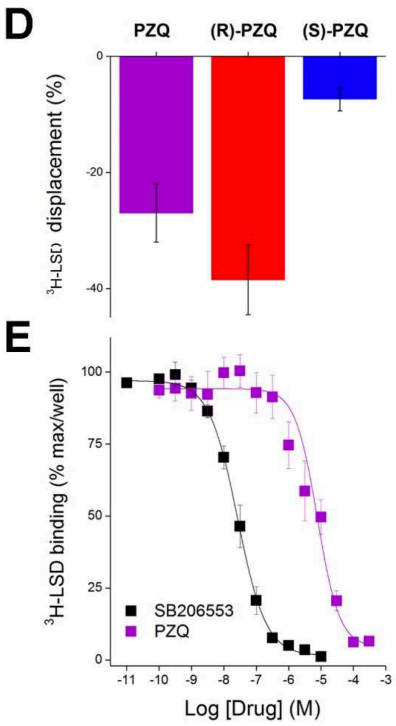
Predicting a human target of the schistosomal drug Praziquantel

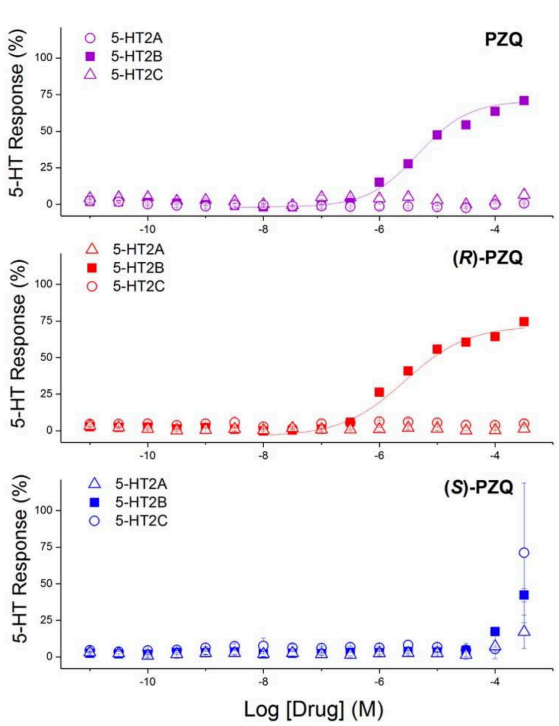


B

		pPvalue	pKd
5-hydroxytryptamine receptor 2B	(R)-PZQ	1.99	6.99
5-hydroxytryptamine receptor 2B	(S)-PZQ	1.91	6.89
Muscarinic acetylcholine receptor M2	(R)-PZQ	1.48	6.33
Muscarinic acetylcholine receptor M3	(R)-PZQ	1.18	5.88
Kappa-type opioid receptor	(S)-PZQ	1.13	5.81
D(3) dopamine receptor	(R)-PZQ	1.12	5.8
Muscarinic acetylcholine receptor M3	(S)-PZQ	0.81	5.26
Kappa-type opioid receptor	(R)-PZQ	0.79	5.22
Delta-type opioid receptor	(S)-PZQ	0.78	5.2
Muscarinic acetylcholine receptor M2	(S)-PZQ	0.76	5.16







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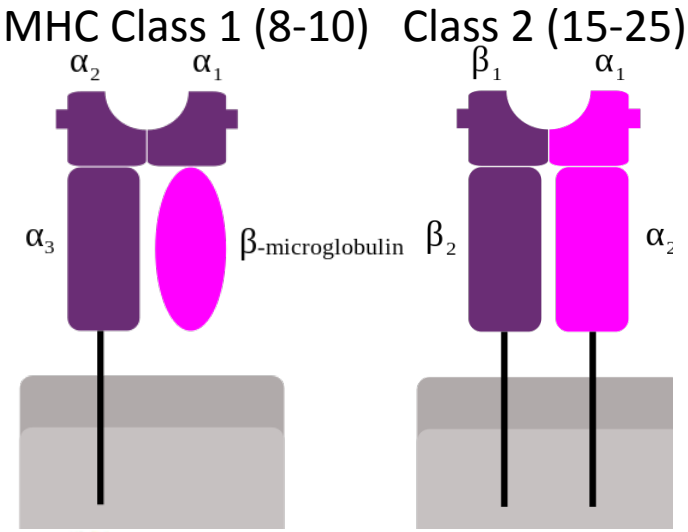
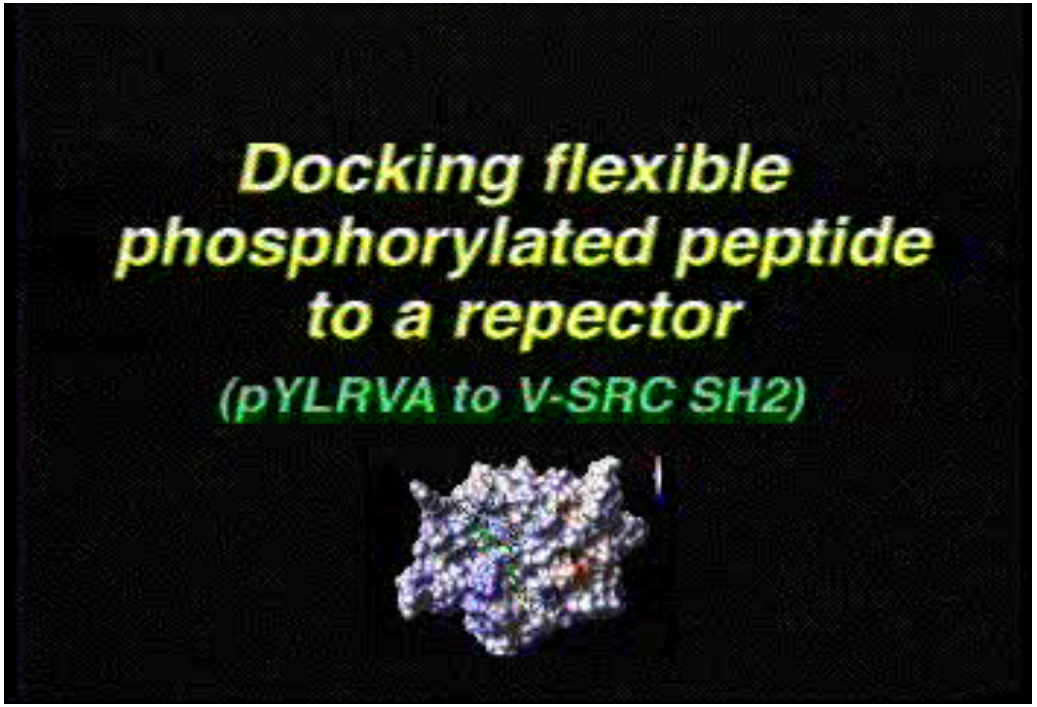
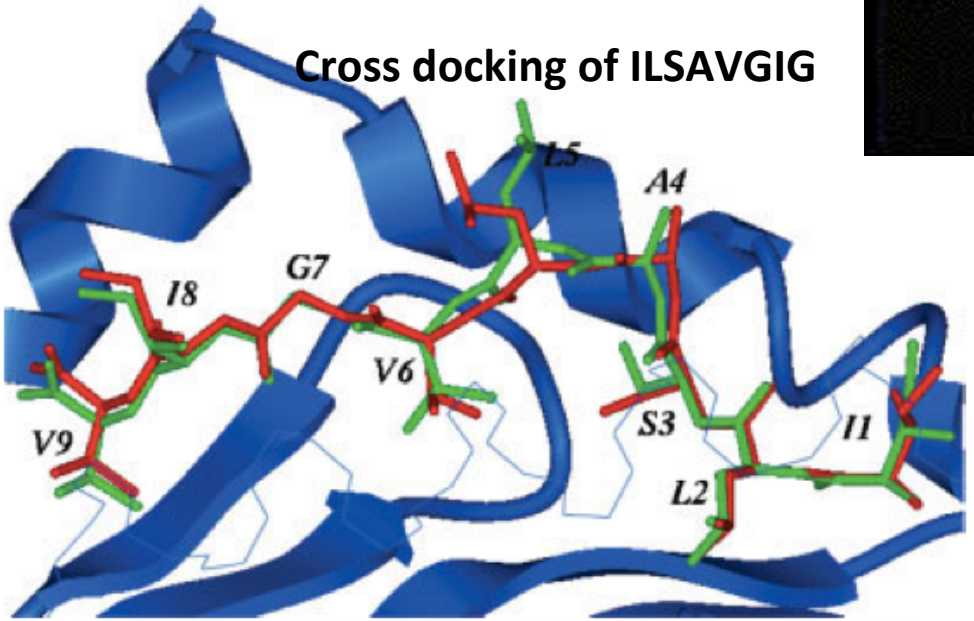


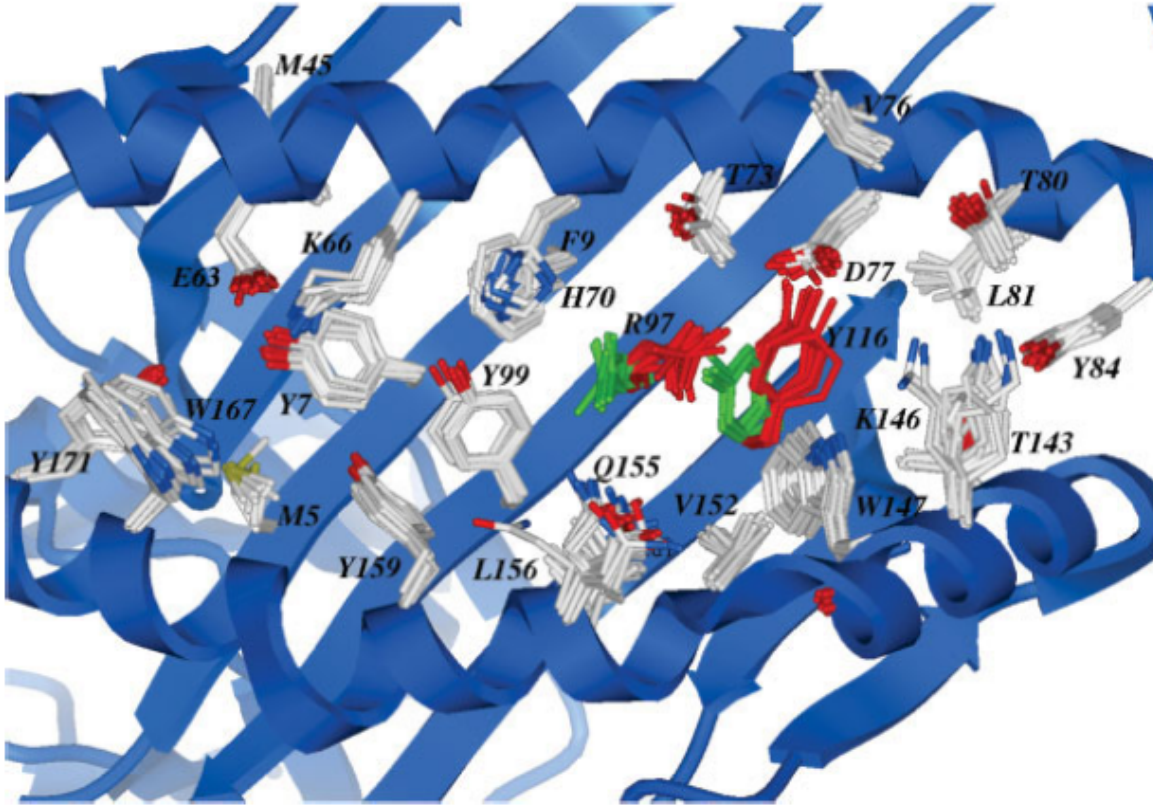




Ab Initio Prediction of Peptide-MHC Binding Geometry for Diverse Class I MHC Allotypes (4D docking)
Bordner, Abagyan, *Proteins*, 2006

Peptide docking

MHC 1 peptide cross-docking: multiple pocket conformations



HLA-A *0201 peptide binding pocket

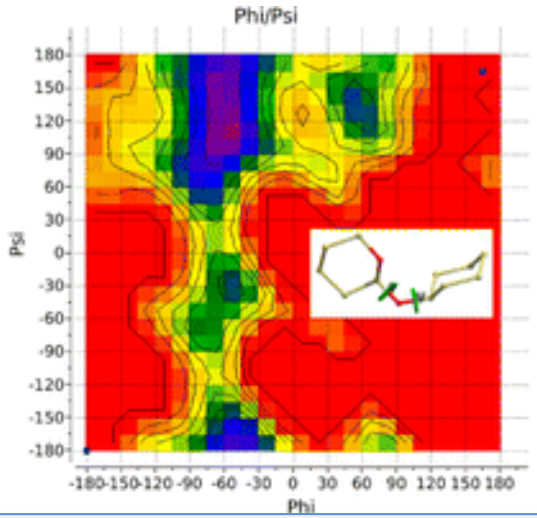
- Grids from 2 alternative conformations
- Full BB & SC Sampling until convergence
- N- and C- terminal Hbonds as d.restraints
- Atomic refinement

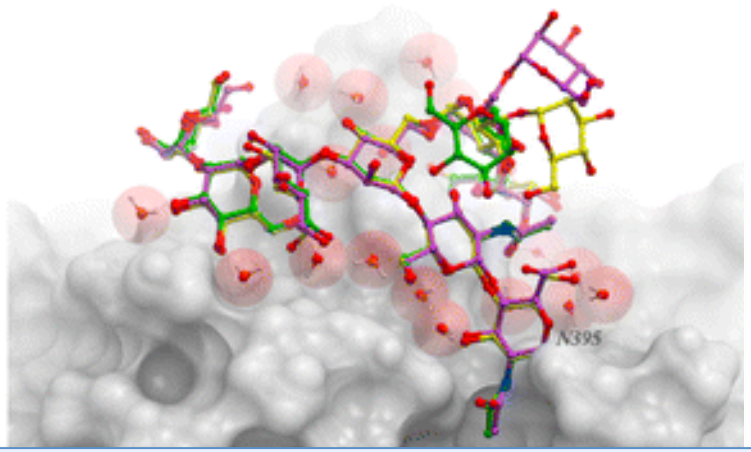
Bordner AJ, Abagyan R
Ab initio prediction of peptide-MHC binding geometry for diverse class I MHC allotypes.
Proteins, 2006 May 15, 63, 512-26

Better ICM Force Field: ICMFF

- First ideas : ICFF *Seva Katrich et al. 2003*
- Current QM-based ICMFF:
  - Softer flexibility model, 3-param VW, ε=2, better combination rules, torsion profiles, .:

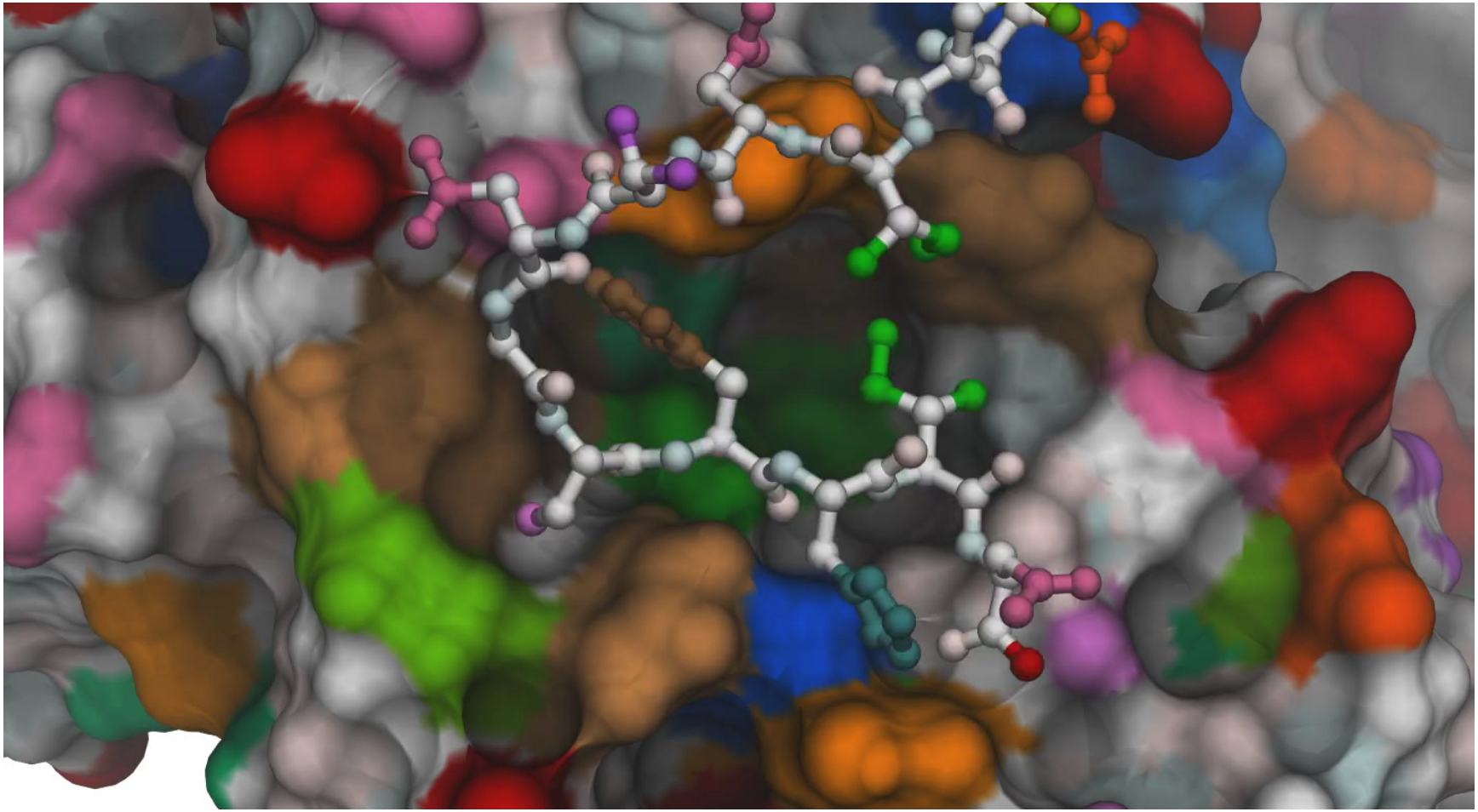
ICM Scripts:
- _loopmodel
- _dockScan
- _mutant*
- _protDesign



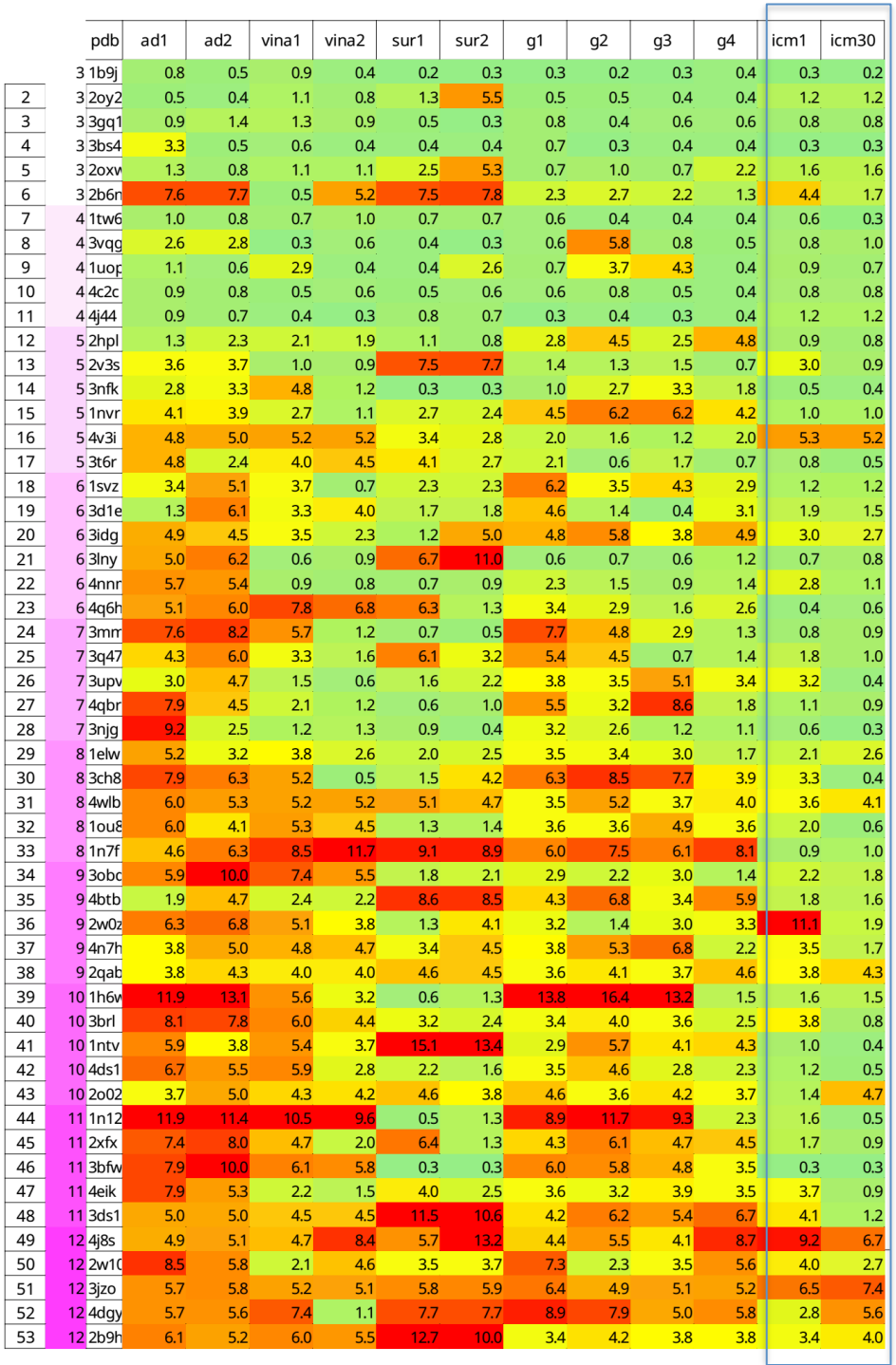


Arnautova, Abagyan, Totrov. RNA; 2015 (glycoproteins) and 2011 (loops, peptides). **All-Atom Internal Coordinate Mechanics(ICM) Force Field for Hexopyranoses and Glycoproteins**. *J Chem Theory Comput*. 2015

Difficult: 12-residue peptide docking



Performance: 1.5 hours on 1 CPU



		pdb	ad1	ad2	vina1	vina2	sur1	sur2	g1	g2	g3	g4	icm1	icm30
	3	1b9j	0.8	0.5	0.9	0.4	0.2	0.3	0.3	0.2	0.3	0.4	0.3	0.2
2	3	2oy2	0.5	0.4	1.1	0.8	1.3	5.5	0.5	0.5	0.4	0.4	1.2	1.2
3	3	3gq1	0.9	1.4	1.3	0.9	0.5	0.3	0.8	0.4	0.6	0.6	0.8	0.8
4	3	3bs4	3.3	0.5	0.6	0.4	0.4	0.4	0.7	0.3	0.4	0.4	0.3	0.3
5	3	2oxv	1.3	0.8	1.1	1.1	2.5	5.3	0.7	1.0	0.7	2.2	1.6	1.6
6	3	2b6n	7.6	7.7	0.5	5.2	7.5	7.8	2.3	2.7	2.2	1.3	4.4	1.7
7	4	1tw6	1.0	0.8	0.7	1.0	0.7	0.7	0.6	0.4	0.4	0.4	0.6	0.3
8	4	3vqg	2.6	2.8	0.3	0.6	0.4	0.3	0.6	5.8	0.8	0.5	0.8	1.0
9	4	1uop	1.1	0.6	2.9	0.4	0.4	2.6	0.7	3.7	4.3	0.4	0.9	0.7
10	4	4c2c	0.9	0.8	0.5	0.6	0.5	0.6	0.6	0.8	0.5	0.4	0.8	0.8
11	4	4j44	0.9	0.7	0.4	0.3	0.8	0.7	0.3	0.4	0.3	0.4	1.2	1.2
12	5	2hpl	1.3	2.3	2.1	1.9	1.1	0.8	2.8	4.5	2.5	4.8	0.9	0.8
13	5	2v3s	3.6	3.7	1.0	0.9	7.5	7.7	1.4	1.3	1.5	0.7	3.0	0.9
14	5	3nfk	2.8	3.3	4.8	1.2	0.3	0.3	1.0	2.7	3.3	1.8	0.5	0.4
15	5	1nvr	4.1	3.9	2.7	1.1	2.7	2.4	4.5	6.2	6.2	4.2	1.0	1.0
16	5	4v3i	4.8	5.0	5.2	5.2	3.4	2.8	2.0	1.6	1.2	2.0	5.3	5.2
17	5	3t6r	4.8	2.4	4.0	4.5	4.1	2.7	2.1	0.6	1.7	0.7	0.8	0.5
18	6	1svz	3.4	5.1	3.7	0.7	2.3	2.3	6.2	3.5	4.3	2.9	1.2	1.2
19	6	3d1e	1.3	6.1	3.3	4.0	1.7	1.8	4.6	1.4	0.4	3.1	1.9	1.5
20	6	3idg	4.9	4.5	3.5	2.3	1.2	5.0	4.8	5.8	3.8	4.9	3.0	2.7
21	6	3lny	5.0	6.2	0.6	0.9	6.7	11.0	0.6	0.7	0.6	1.2	0.7	0.8
22	6	4nnr	5.7	5.4	0.9	0.8	0.7	0.9	2.3	1.5	0.9	1.4	2.8	1.1
23	6	4q6h	5.1	6.0	7.8	6.8	6.3	1.3	3.4	2.9	1.6	2.6	0.4	0.6
24	7	3mm	7.6	8.2	5.7	1.2	0.7	0.5	7.7	4.8	2.9	1.3	0.8	0.9
25	7	3q47	4.3	6.0	3.3	1.6	6.1	3.2	5.4	4.5	0.7	1.4	1.8	1.0
26	7	3upv	3.0	4.7	1.5	0.6	1.6	2.2	3.8	3.5	5.1	3.4	3.2	0.4
27	7	4qbr	7.9	4.5	2.1	1.2	0.6	1.0	5.5	3.2	8.6	1.8	1.1	0.9
28	7	3njg	9.2	2.5	1.2	1.3	0.9	0.4	3.2	2.6	1.2	1.1	0.6	0.3
29	8	1elw	5.2	3.2	3.8	2.6	2.0	2.5	3.5	3.4	3.0	1.7	2.1	2.6
30	8	3ch8	7.9	6.3	5.2	0.5	1.5	4.2	6.3	8.5	7.7	3.9	3.3	0.4
31	8	4wlb	6.0	5.3	5.2	5.2	5.1	4.7	3.5	5.2	3.7	4.0	3.6	4.1
32	8	1ou8	6.0	4.1	5.3	4.5	1.3	1.4	3.6	3.6	4.9	3.6	2.0	0.6
33	8	1n7f	4.6	6.3	8.5	11.7	9.1	8.9	6.0	7.5	6.1	8.1	0.9	1.0
34	9	3obc	5.9	10.0	7.4	5.5	1.8	2.1	2.9	2.2	3.0	1.4	2.2	1.8
35	9	4btb	1.9	4.7	2.4	2.2	8.6	8.5	4.3	6.8	3.4	5.9	1.8	1.6
36	9	2w0z	6.3	6.8	5.1	3.8	1.3	4.1	3.2	1.4	3.0	3.3	11.1	1.9
37	9	4n7h	3.8	5.0	4.8	4.7	3.4	4.5	3.8	5.3	6.8	2.2	3.5	1.7
38	9	2qab	3.8	4.3	4.0	4.0	4.6	4.5	3.6	4.1	3.7	4.6	3.8	4.3
39	10	1h6w	11.9	13.1	5.6	3.2	0.6	1.3	13.8	16.4	13.2	1.5	1.6	1.5
40	10	3brl	8.1	7.8	6.0	4.4	3.2	2.4	3.4	4.0	3.6	2.5	3.8	0.8
41	10	1ntv	5.9	3.8	5.4	3.7	15.1	13.4	2.9	5.7	4.1	4.3	1.0	0.4
42	10	4ds1	6.7	5.5	5.9	2.8	2.2	1.6	3.5	4.6	2.8	2.3	1.2	0.5
43	10	2o02	3.7	5.0	4.3	4.2	4.6	3.8	4.6	3.6	4.2	3.7	1.4	4.7
44	11	1n12	11.9	11.4	10.5	9.6	0.5	1.3	8.9	11.7	9.3	2.3	1.6	0.5
45	11	2xfx	7.4	8.0	4.7	2.0	6.4	1.3	4.3	6.1	4.7	4.5	1.7	0.9
46	11	3bfw	7.9	10.0	6.1	5.8	0.3	0.3	6.0	5.8	4.8	3.5	0.3	0.3
47	11	4eik	7.9	5.3	2.2	1.5	4.0	2.5	3.6	3.2	3.9	3.5	3.7	0.9
48	11	3ds1	5.0	5.0	4.5	4.5	11.5	10.6	4.2	6.2	5.4	6.7	4.1	1.2
49	12	4j8s	4.9	5.1	4.7	8.4	5.7	13.2	4.4	5.5	4.1	8.7	9.2	6.7
50	12	2w1(	8.5	5.8	2.1	4.6	3.5	3.7	7.3	2.3	3.5	5.6	4.0	2.7
51	12	3jzo	5.7	5.8	5.2	5.1	5.8	5.9	6.4	4.9	5.1	5.2	6.5	7.4
52	12	4dgy	5.7	5.6	7.4	1.1	7.7	7.7	8.9	7.9	5.0	5.8	2.8	5.6
53	12	2b9h	6.1	5.2	6.0	5.5	12.7	10.0	3.4	4.2	3.8	3.8	3.4	4.0

Peptide docking benchmark performance

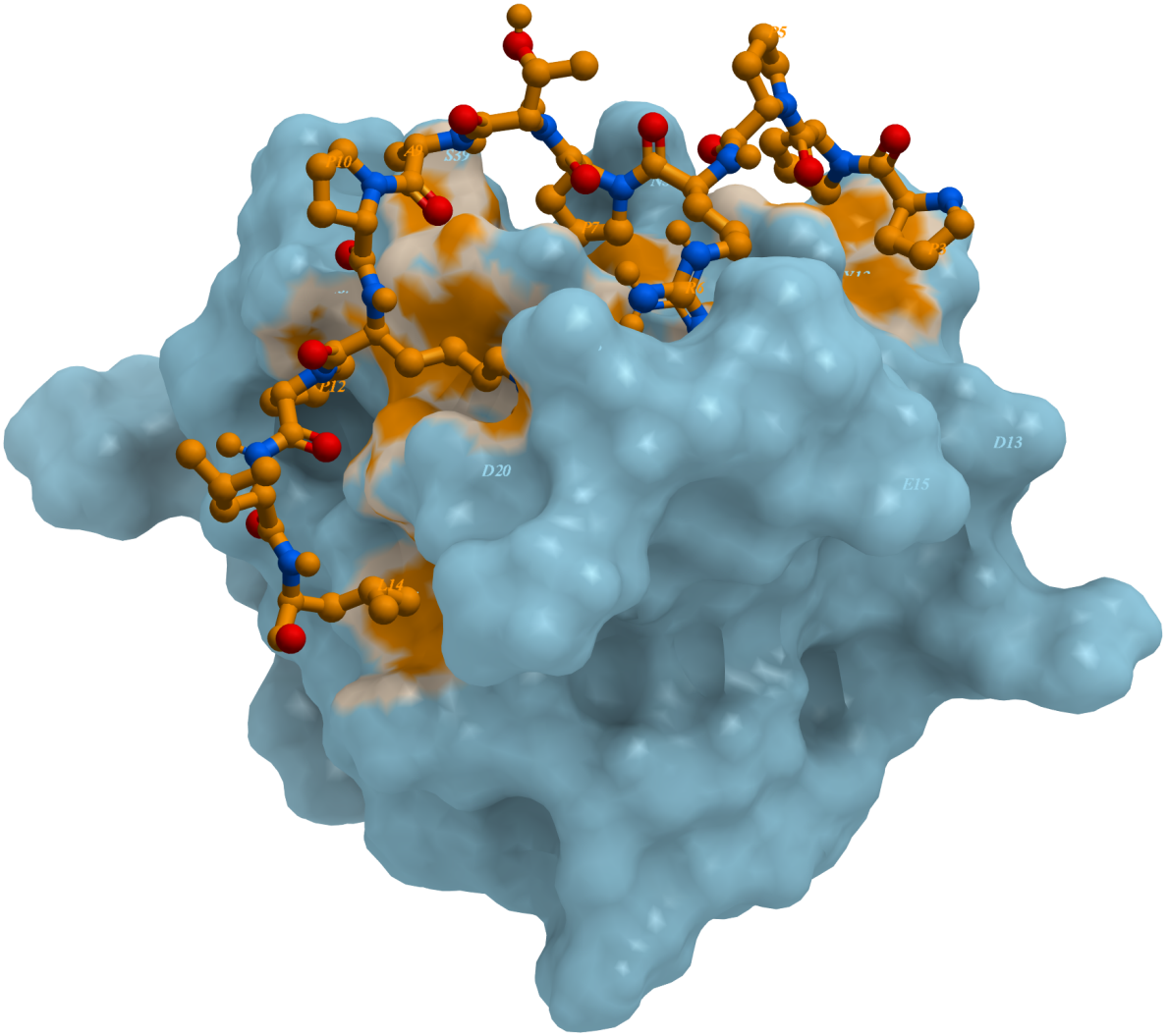
#correct out of 53

- **AutoDock: 12** /53
- **Vina: 28** /53
- **Surflex: 29** /53
- **GOLD: 28** /53
- **ICM: 42** /53

LEADS-PEP: A Benchmark Data Set for Assessment of Peptide Docking Performance
Alexander S Hauser and Björn Windshügel
J. Chem. Inf. Model., 2016, 56 (1), pp 188–200

Ilatovskiy, Abagyan, 2017 (in preparation)

Peptide Docking example: 12-aminoacid peptide 2w10



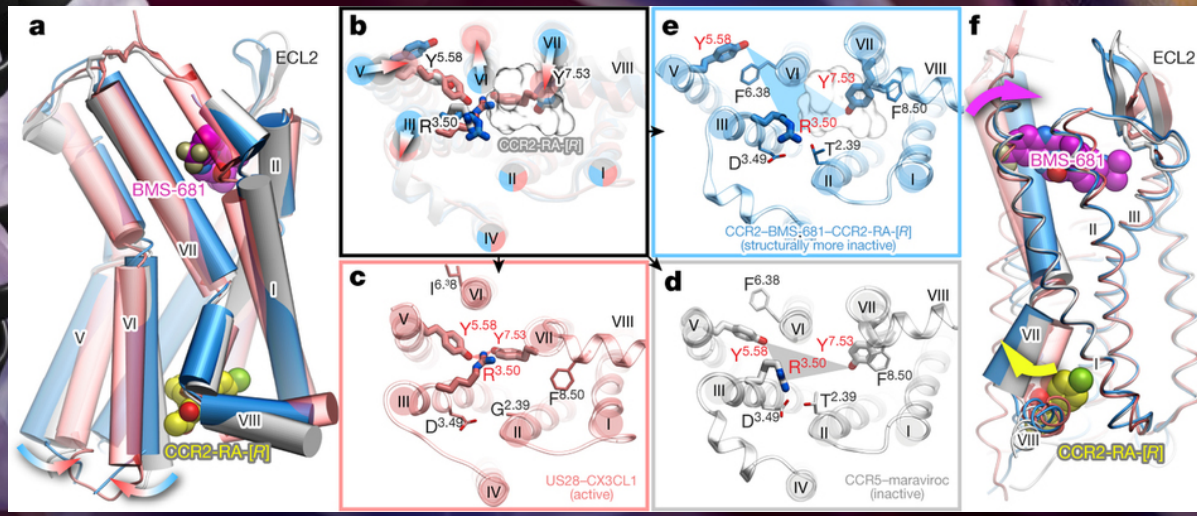
Chemokine

CXCR4

Qin L, Kufareva I, Holden LG, Wang C, Zheng Y, Zhao C, Fenalti G, Wu H, Han GW, Cherezov V, Abagyan R, Stevens RC, Handel TM
Structural biology. Crystal structure of the chemokine receptor CXCR4 in complex with a viral chemokine.
Science, 2015

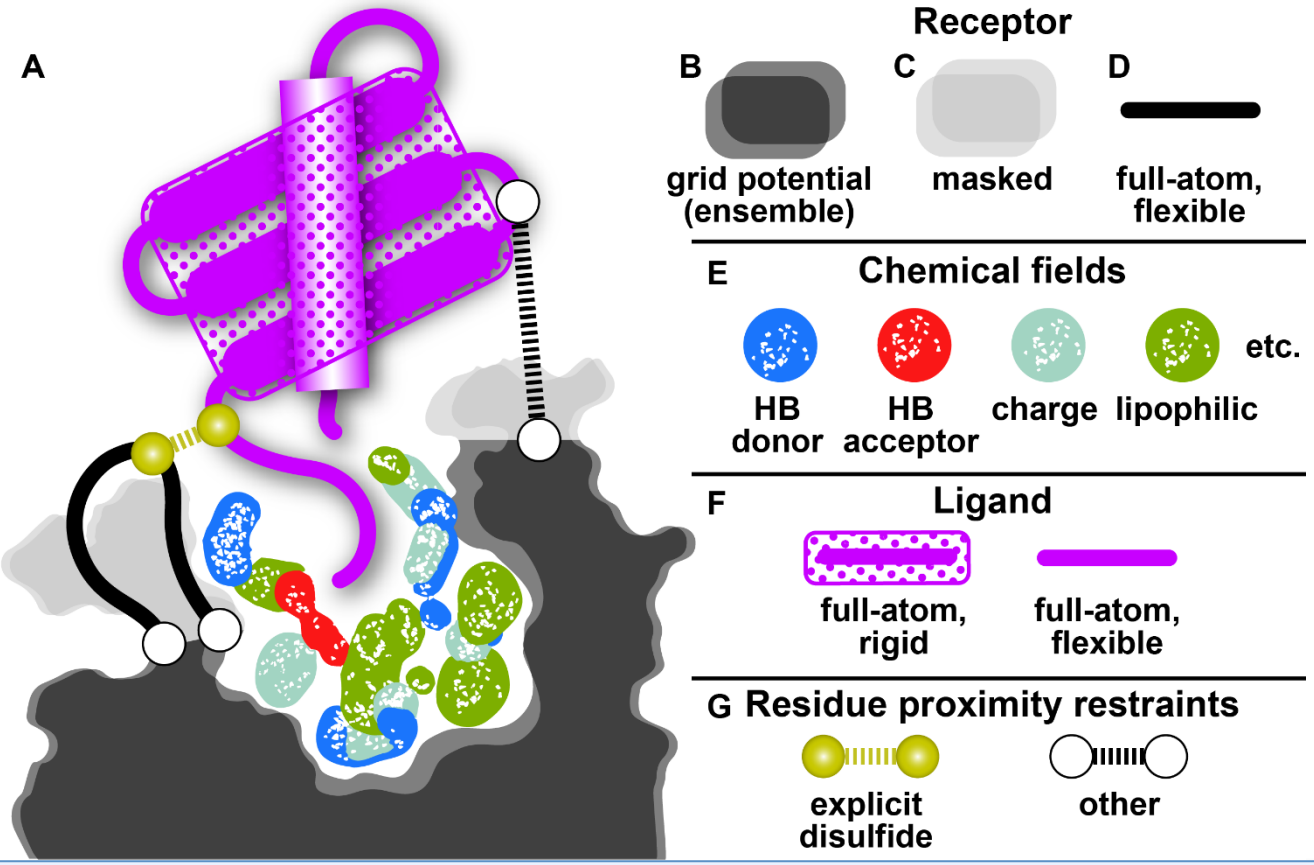
Structure of CC chemokine receptor 2 with orthosteric and allosteric antagonists.Zheng et al. *Nature* 2016

Structural basis of ligand interactions with atypical chemokine receptor 3.
Gustavsson et al. *Nat. Commun*. 2017



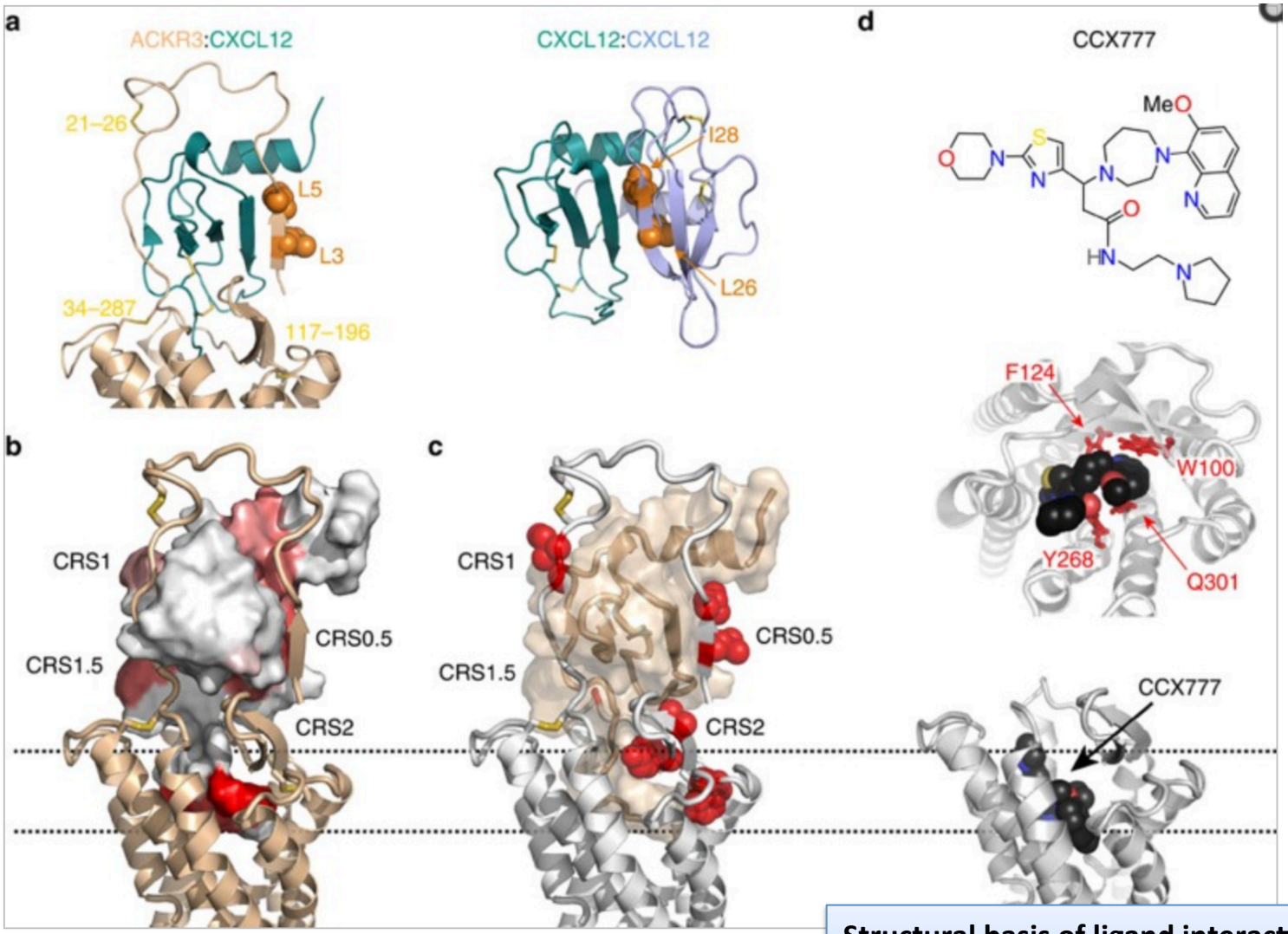
Hybrid modeling & docking protocols

- Stochastic optimization of a system in internal coordinates (ICM)
- Explicit Flexibility of tails, loops and sice chains, plus Masking
- Integrated *ambiguous* experimental restraints



Kufareva *et al.*, Stoichiometry and geometry of the CXCR4 complex with CXCL12: Molecular modeling and experimental validation. *PNAS* **2014**
Kufareva, Handel, Abagyan , Experiment-guided molecular modeling of protein-protein complexes involving GPCRs, *Meth Mol Biol* **2015**

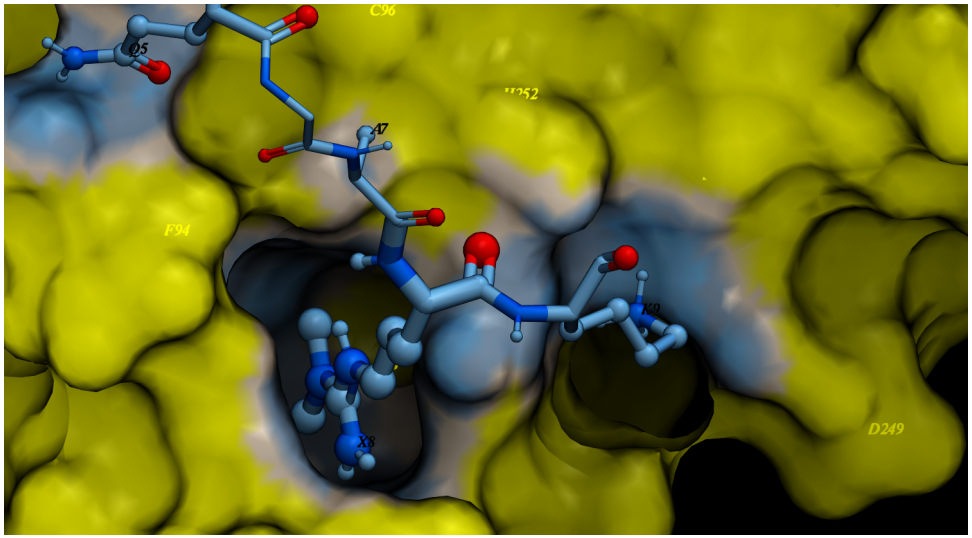
ACKR3-Nterm and CxCL12

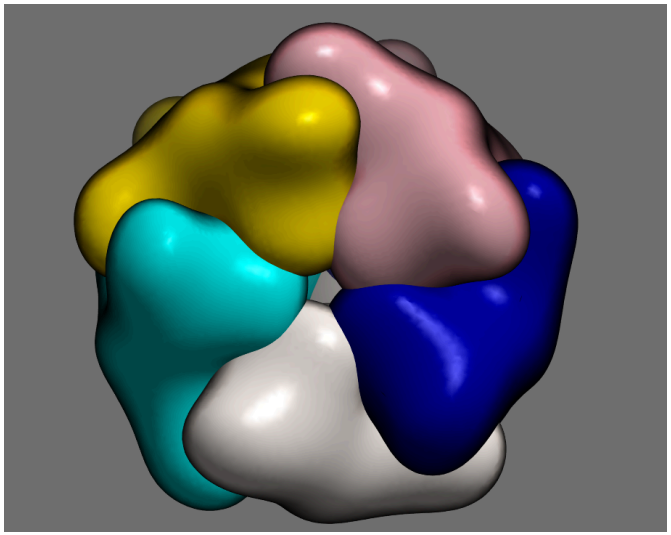


Structural basis of ligand interaction with atypical chemokine receptor 3. Gustavsson et al.**,**

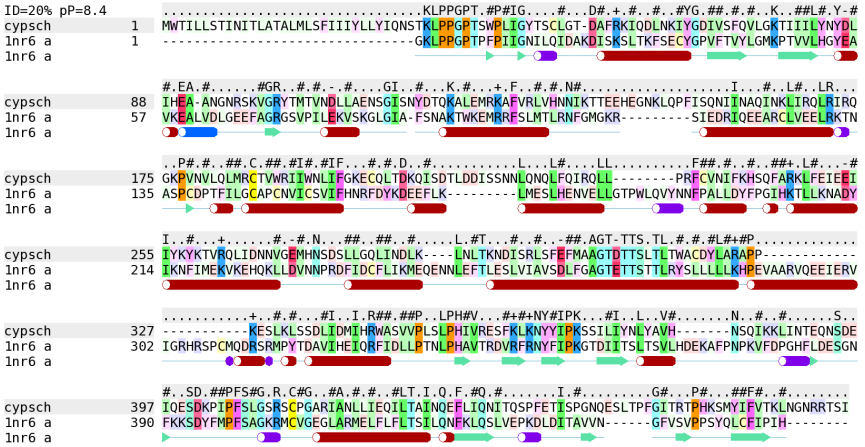
Nature Comm, **2017** (collaboration with Handel Lab)

Homology Modeling

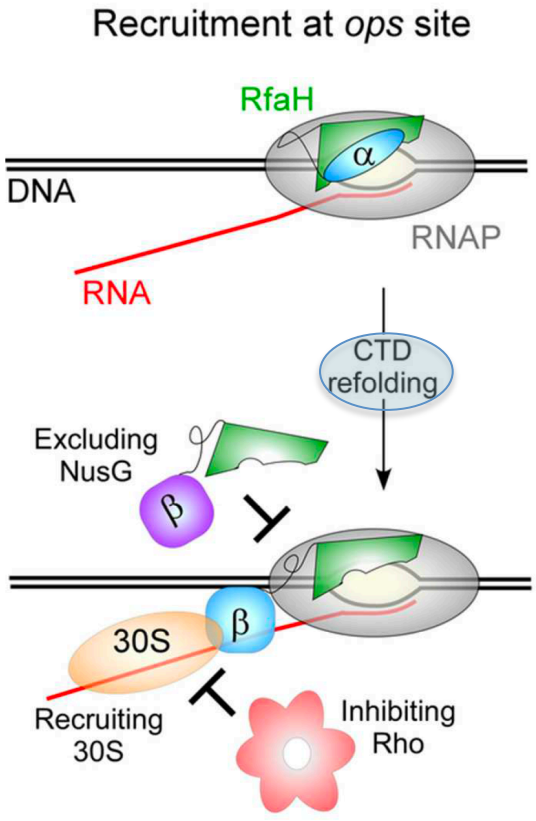


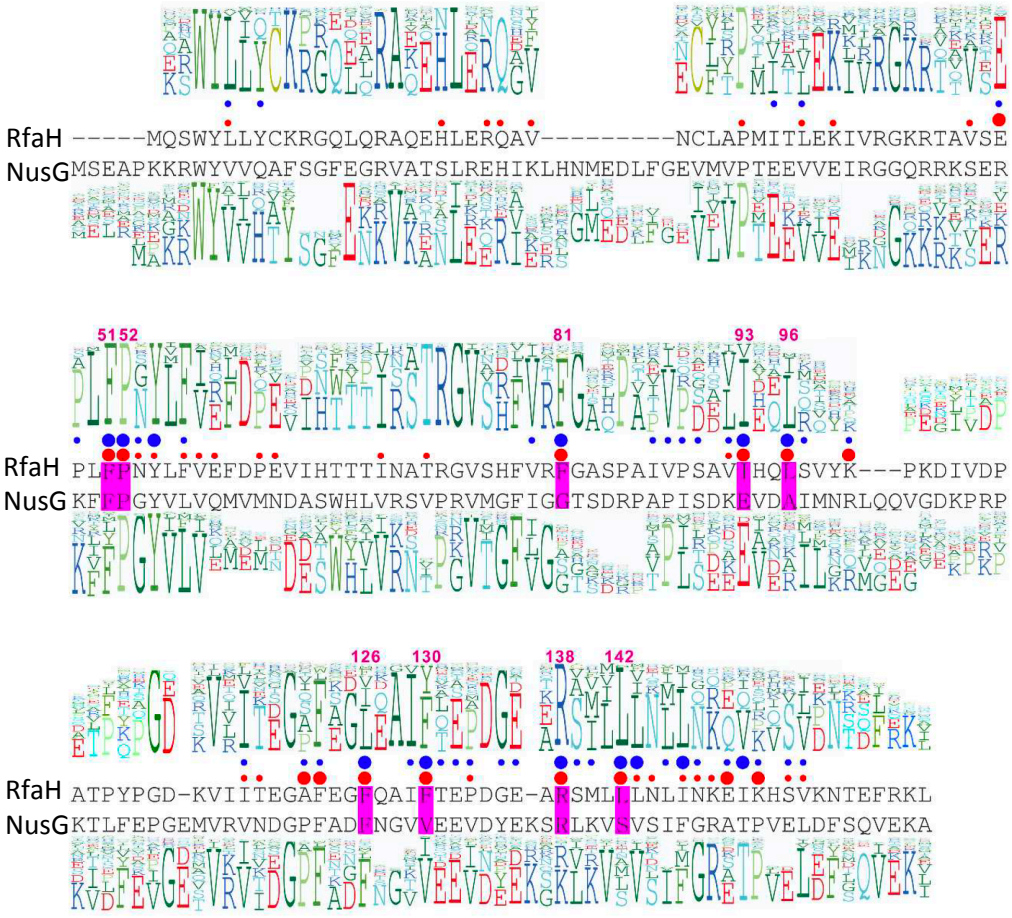


- Single mutations (geometry, stability, ppi, ligand binding)
- Search for template(s)
- Structural alignments/edits
- Including Ligand
- Loops & Ends
- Refinement



Bioinformatics & Modeling



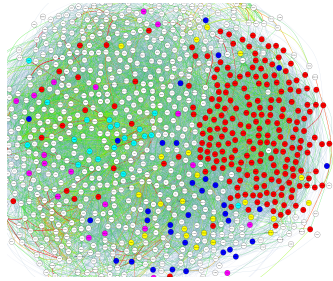


ICM modeling and bioinformatics:

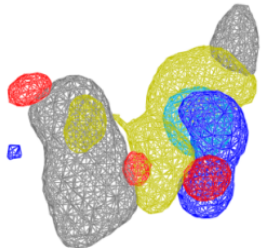
- Alignments of several hundreds sequences for RfaH and NusG
- Calculating Profiles/Logos, Sequence Entropy, Conservation
- Building 3D models of RfaH
- Calculating ΔΔG of mutations for conserved yet different sites
- Prioritizing experimental mutations

Da Shi, Dmitri Svetlov, Ruben Abagyan, and Irina Artsimovitch
Flipping states: a few key residues decide the winning conformation of the only universally conserved transcription factor
Nucleic Acid Research, 2017 (in press)

Conclusions



- Small drugs have **extensive multi-target-pharmacology**, it must and used in matching. We need to use the known and discover the missing.
- **The Pocketome** (~3000) pocket ensembles and superimposed ligand can be used for **Target Screening** via docking combined with machine learning.



- **Complex modeling challenges** can be guided by Internal Coordinate simulations and fuzzy experimental restraints.
- Recent **progress in predictive peptide docking** and scoring enables complex applications.
- **Drug-patient** data helps with targets discovery

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Kirti Kandhwal, *grad student, drug repurposing*
Tony Ngo, grad *student,* **Patricia Oto**, *undegrad*

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R01 on modeling & docking (active)
U01 on Chemokine Receptors (completed)

UCSD Collaborations

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Anjan Debnath, Larissa Podust, Jair L.de S.Neto, Conor Caffrey, Jim McKerrow, CDIPD
Tracy Handel lab, *U01, chemokine receptors*

Active Outside UCSD

GPCR structures and modulators

Nicola Smith, Bob Graham, Melbourne, AU
Ray Stevens lab, Seva Katritch USC, U54
Mark Yeager, UVa
Joel Linden's LJIAI, *Adenosine Receptors*
Pat Sexton, **Art Christopoulos, Katie Leach**
Larry Miller lab, Mayo, Arizona, A,B-GPCRs

Multi-target pharmacology

Charles Cunningham, UNM, Bryan Roth, UNC, Jonathan Marchant

Structure Based Drug Discovery

K.Y. Wong and PolyU team: FtsZ, glycosyltransferase, TNFa, b-lactamase,

RfaH and NusG

Dmitry Svetlov, Irina Artsimovich

4D docking and activity cliffs