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"Seeing all the topics covered in this 2015 Drug Design and Delivery Symposium in a different light helps me to re-think my project in all aspects, which leads often to a better approach to reach our goals."

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Mikel Ghelfi, PhD,
Brock University

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Upcoming ACS Webinars®

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Thursday, August 6, 2015

"Hot Topics in Patent Law: Non-Obviousness of Chemical and Pharmaceutical Patents"

Justin Hasford, Partner at Finnegan Henderson Farabow Garrett & Dunner

David Harwell, Assistant Manager, ACS Industry Member Programs

Thursday, August 27, 2015

"Choices and Trends in Solid Dosage Form Section:

Salt, Cocrystal, Prodrug or Amorphous?"

Scott Trzaska, Principal Scientist, J-Star Research

Ronald Smith, Distinguished Scientist in Pharmaceutical Sciences, Merck Research

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2015 Drug Design & Delivery Symposium

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Module 1: Improving Drug Design Efficiency and Efficacy		
Jan 29	Designing Better Drug Candidates	*Dr. Paul Leeson*
Feb 26	Strategies to Improve Solubility of Drug Candidates	*Dr. Michael Walker*
Module 2: Activity/Potency Screening for Drug Lead & Candidate Optimization		
Mar 19	Fragment-Based Drug Design Strategies	*Dr. Dan Erlanson*
April 30	Screening Strategies	*Dr. David Swinney*
May 28	PAINS (Pan-Assay Interference Compounds)	*Dr. Jonathan Baell*
June 25	Positron Emission Tomography (PET) Labeling in Drug Discovery & Development	*Dr. Lei Zhang*
July 30	X-Ray Crystallography in Drug Discovery	*Dr. Jon Mason & Dr. Miles Congreve*
Module 3: Enabling Drug Discovery		
Aug 27	Choices and Trends in Solid Dosage Form Section	*Dr. Scott Trzaska & Dr. Ron Smith*
Sept 24	Delivery Options to Support Dose Escalation in Preclinical Toxicology and Pharmacodynamic Activity Studies	*Dr. Evan Thackaberry*
Module 4: Pharmacokinetics		
Oct 29	Pharmacokinetic Considerations in Drug Design and Development	*Dr. Punit Marathe*
Nov 19	Prodrugs in Drug Discovery	*Dr. John Higgins*

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"2015 Drug Design and Delivery Symposium: X-ray Crystallography in Drug Discovery"

Gregory Petsko
Professor of Neurology and Neuroscience, Director, Alzheimer's Disease Research Institute, Weill Cornell Medical College

Miles Congreve
VP of Chemistry, Heptares Therapeutics

Jonathan Mason
Senior Research Fellow CADD, Heptares Therapeutics

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HEPTARES therapeutics

"X-ray Crystallography in Drug Discovery"

Miles Congreve and Jon Mason

ACS Webinar July 2015

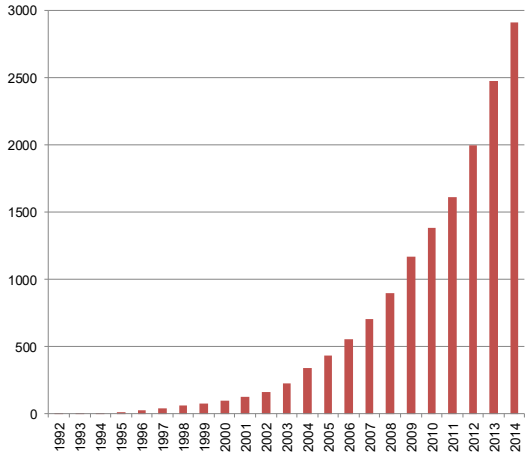
Interactive Audience Question

When was the first new protein-ligand X-ray structure published in the Journal of Medicinal Chemistry (i.e. PDB coordinates deposited)?

- ○ 1970's
- ○ 1980's
- ○ 1990's
- ○ 2000's

Answer - 1992

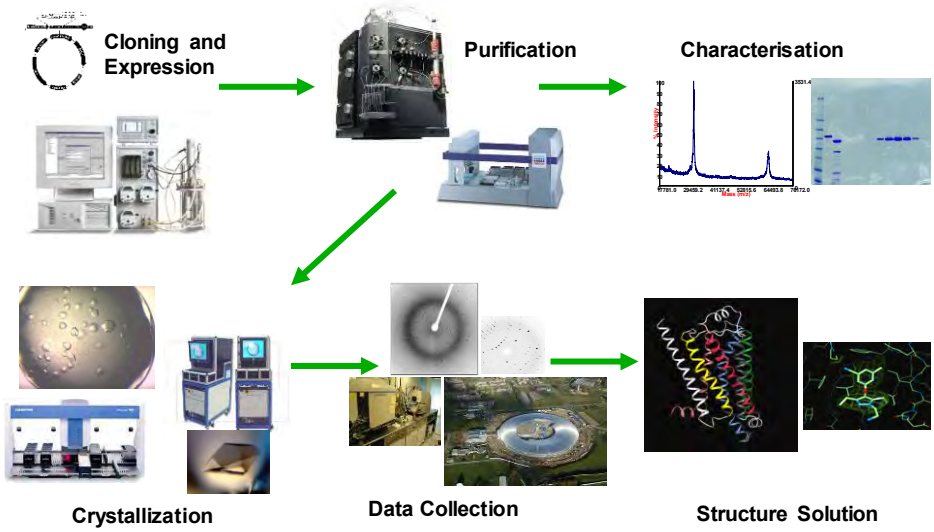
- Plot shows total number of PDB submissions in JMC increasing over time
- Implies the active use of SBDD in support of med chem projects developed slowly through the 1990s but is now very well established in medicinal chemistry best practice with >400 PDB submissions in JMC papers in 2014



Structure-Based Drug Design (SBDD)

- **Protein structure revolutionizes med chem design**
  - Atomic level optimisation of H-bonding and fitting to a protein site
  - Efficient process leading to better druglike properties
- **Many cases where ligands – even quite similar ones – bind in different ways giving complex SAR**
  - Ligand-receptor structures enable rational design avoiding wasted synthesis
- **Allows for discovery of new binding sites and new protein conformations which can be understood both in terms of compound binding and biologically**
  - Active vs inactive conformations
  - Allostery, both positive and negative modulators

Structure Determination Process:



SBDD – Methods 1

- **Analysis of the binding site to identify binding "hotspots"**
  - Lipophilic, H-bonding, ionic interactions.
    e.g. GRID software for energetic survey [Molecular Discovery]
  - Water networks and relative energies, e.g. WaterMap & WaterFLAP
- **Finding Hits 1: Structure-based virtual screening**
  - e.g. Glide software from Schrödinger
  - 1000's to millions of compounds ranked (docking score)
  - Top ranked compounds visualised in 3D in protein binding site together with surface, hotspots, waters etc. [e.g. Vida (OpenEye)]
- **Finding Hits 2: *De novo* design – from scratch or more usually now from a fragment hit**

SBDD – Methods 2

- **Optimizing Hits → Leads**
  - From a crystal structure ideally or from a high confidence docking
  - Use binding hotpots together with surface/shape, waters (with relative energies)
  - Many structures have water-mediated interactions (some polar ligands bind with no direct polar interactions, only lipophilic)
- **Methods**
  - Can use "manual" (visualization in 3D) and/or automated methods to elaborate hit structures
  - New idea structures are re-docked into protein structures
  - Effective SBDD often involves 3D "brainstorming" sessions
  - Important to evaluate the ligand conformational energy as well as the fit to the protein site (poorly handled by a lot of software…)

SBDD – Methods 3

- **Many examples of successful design that target the "unhappy" waters in the binding site**
  - Important to consider both the displacement of waters and the resulting perturbation on the new network
  - SBDD enables better design by considering the protein structure, the ligand and the water network; all 3 are needed!
- **New methods becoming available to calculate free energy of ligand binding in a realistic timeframe** (e.g. 1 day on a GPU)
  - FEP (free energy perturbation) e.g. FEP/REST from Schrödinger
  - Uses molecular dynamics (MD) simulations:
    Recent improvements in force fields and much faster simulation times using GPUs enables MD to be used as a standard approach

SBDD – Methods 4

- **Moving beyond potency: Selectivity**
  - Selectivity rationally designed using structure or homology model of the other target(s)
  - Classical approach uses size – to fit desired target, pierce surface of other target(s) and use property complementarity / differences
  - Other options enabled in SBDD, such as reducing size to trap an "unhappy" water in off-target structure also possible
- **Moving beyond potency: Kinetics**
  - Prediction of off-rates now becoming possible, considering water network (trapping of "unhappy" waters) and using molecular dynamics simulations [and approaches to speed up, e.g. adiabatic biased metadynamics]

What SBDD Can Do …

When: Whenever possible and as early as possible to help guide decision making

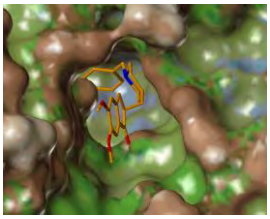
- Focuses synthetic efforts on targets to complement receptor
- Facilitates rapid improvements in potency / LE
- Directs the optimization of selectivity
- Guides attempts to remove undesirable structural groups
- Speeds the tuning of physicochemical properties
- Judges when exhausted possibilities in a series
- Probes new protein interactions
- Allows the circumvention of existing IP
- Directs the design of structural "chimeras"

Target Tractability and Druggability

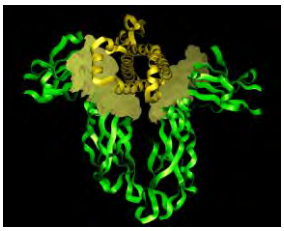
- **The apo structure of a protein can reveal much about the potential for small molecules to be identified as inhibitors or activators**
  - Shape of cavity
  - Polarity / electrostatics - lipophilicity
- **Detailed computational analysis of the characteristics of a binding site can be carried out using 'probes' to give a more objective description of druggability and 'hot spots' for small molecules**
  - Lipophilic/Hydrophobic
  - H-bond donor and acceptor
  - Water networks and energy
  - Halogen

Druggability Assessment using Structural Biology

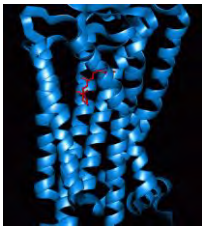
A beautiful binding site:
aricept bound to acetyl cholinesterase



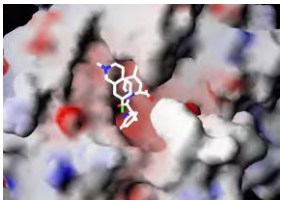
An ugly site:
HGH bound to receptor



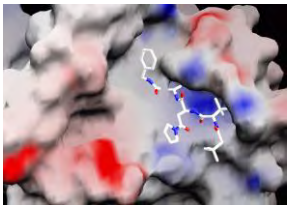
A beautiful site:
aminergic GPCR



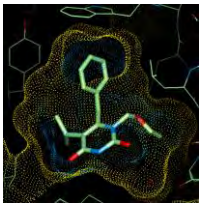
A beautiful serine protease site:
Thrombin



An ugly serine protease site:
CMV protease



A beautiful site:
HIV RT



Water – The 3rd Key Dimension

Why Water?

- Water molecules play an essential role in the structure and function of biological systems
- Displacement of waters from a binding site is a key component of ligand binding, with significant binding energy, and thus potency, often from the entropic gain of the displacement

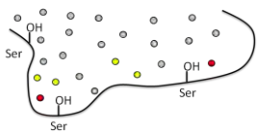
But all waters are not equal…

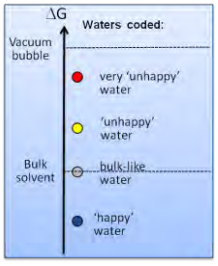
- Burying an ”unhappy” water *[i.e. entropically and/or enthalpically worse than bulk sovent]* may affect both potency and kinetics
- Pertubation of the remaining waters will also affect binding ±

Now possible to calculate water network for apo or liganded structures
(good correspondance with experimental water positions) and estimate relative energy to bulk solvent (→ concept of ”unhappy” and ”happy” waters)

Mason *et al. In Silico Pharmacology* 2013, 1:23 http://www.in-silico-pharmacology.com/content/1/1/23 & refs therein

Example Binding Site Analyses - GPCRs

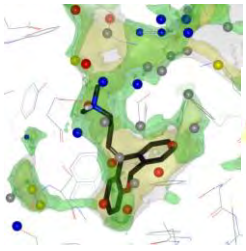




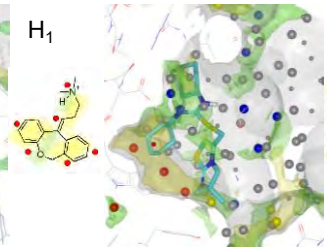
GRID C1= hot-spot (lipophilic)

GRID OH2 hot-spot (hydrophilic)

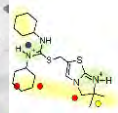
GRID CH3 pocket shape

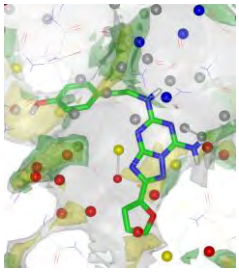


H_1

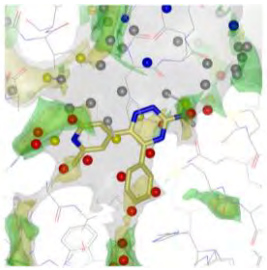


CXCR4





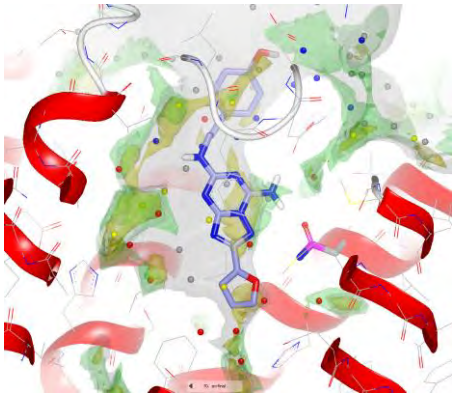
A_{2A}



New insights from structural biology into the druggability of G protein-coupled receptors. Mason, Bortolato, Congreve, Marshall. Trends Pharmacol Sci. 2012;33(5):249-60.

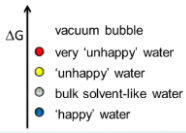
Improving Druggability by SBDD approaches

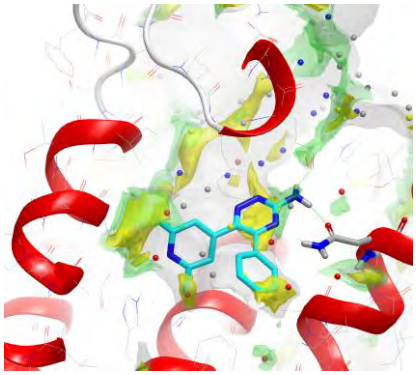
'Old' SAR can be challenged after structures become available



ZM241385

Existing A_{2A} antagonist bound in an non-ideal way: displacing "happy" waters and leaving "unhappy" ones





Triazine 4g

Alternative more efficient pharmacophore driven by SBDD (virtual screening & optimization)

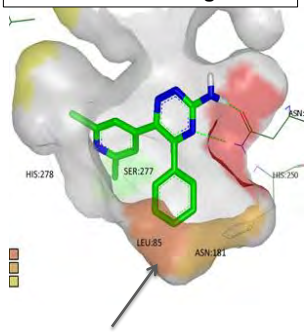
Impact of SBDD on Med Chem Projects

- **SBDD driven SAR is usually more efficient than empirical approaches unless a target is highly tractable**
  - Rationally introducing new substituents to fit the site; e.g. 'magic methyl'
  - Adding new polar interactions to satisfy polar regions of the site or water networks
  - Displacing buried (high energy) waters
  - Trapping out the biologically active conformation in a low energy conformation of the molecule
  - Rational design of subtype specificity

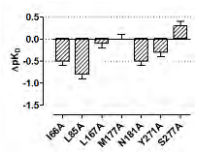
- **At the very least SBDD will rationalise why a project is challenging**
  - SAR 'cliffs'
  - Requirements for specific functional groups
  - Requirements for larger compounds to span a larger binding site with separated 'hotspots'

A_{2A} Antagonist SBDD Example

Site Directed Mutagenesis



BPM reveals
novel binding mode: ligand sits
deep in 'ribose pocket'

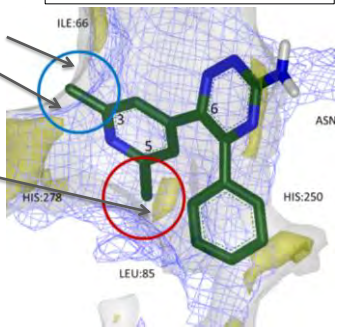


GRID hotspots & surfaces

A_{2A}R pocket boundary

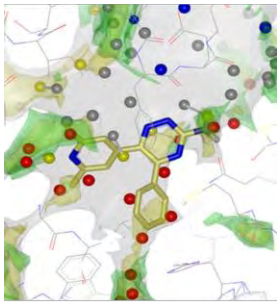
A_1R pocket boundary

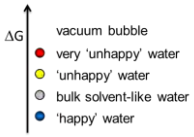
lipophilic hotspots in yellow (C1 probe)



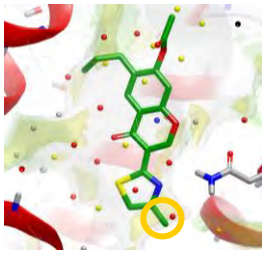
3,5-disubstitution increases affinity & selectivity

Water network energetics



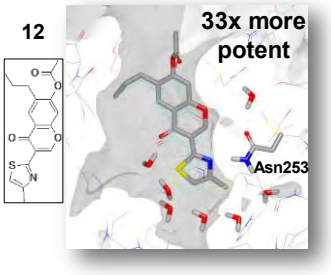


A_{2A} Chromone 'Magic Methyl' Effect

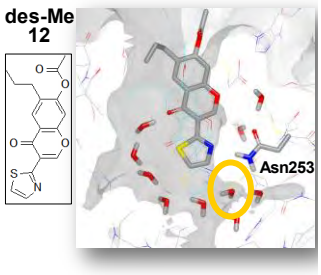


Methyl on thiazole displaces 'unhappy' water (WaterFLAP and WaterMap)

12



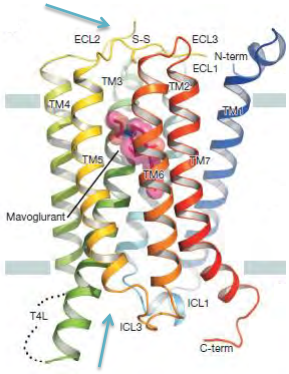
des-Me 12

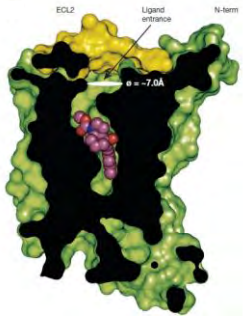


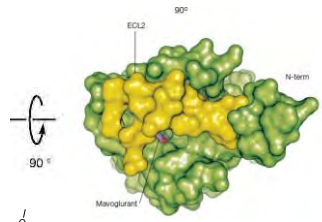
- A 33 fold potency increase is obtained by adding a methyl to the A_{2A} chromone ligand des-Me 12. WaterFLAP & WaterMap predicted an "unhappy" water would be displaced.
- 100ps MD simulation shows ligand 12 stable with methyl group anchored in pocket bounded by Met177 & Leu249 but the des-Me ligand moves up as water fills the vacuum created
- This results in a more "unhappy" water filling the even more lipophilic region and a weakened key binding interaction between N of thiazole with Asn253
  - 33 fold reduction in affinity

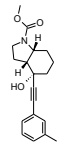
$mGlu_5$ Receptor: SAR 'cliffs'

ECL2 spans top of the receptor
Disulphide bond between TM3-ECL2









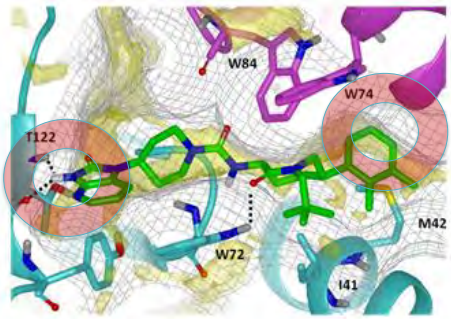
TM5 more 'inwards' than family A & B

Requirement for linker and 'tight' SAR Explained by the X-ray data and because of 'induced fit' Nature of pocket

Closed entrance consistent with native ligand binding to orthosteric site in ECD explains low MW (~300) of compounds binding to this region

CGRP Antagonists

Structure Rationalises Requirement for High Molecular Weight



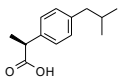
- Inhibitors must span both the CLR (N-terminal domain of the protein) and the RAMP1 (accessory protein) in order to inhibit CGRP selectively
- Not possible to design low MWT inhibitors (<350 MWT)
- Difficult to design orally available drugs with Lipinski complaint properties
- Entirely rationalised by the X-ray structures now available

Impact of SBDD Methods on Druglike Properties

- **Fragment based drug discovery was discussed in another ACS Webinar**
  - Session 3 "Fragment-Based Drug Design Strategies"
    http://www.acs.org/content/acs/en/acs-webinars/drug-discovery/fragment-drug.html
  - FBDD generally uses SBDD to optimise the fragment hits into lead compounds
  - The idea of Ligand Efficiency as a metric grew out of FBDD to help medicinal chemists compare fragments with larger hit compounds
  - Ligand Lipophilicity Efficiency (LLE or LipE) was developed to take account of lipophilicity not just size
- **These important ideas help us to focus our attention not just on potency but also on properties associated with oral drugs**
  - Efficient atom by atom optimisation
  - Introducing polar groups to pick up new interactions, not just driving potency by increasing lipophilic contacts

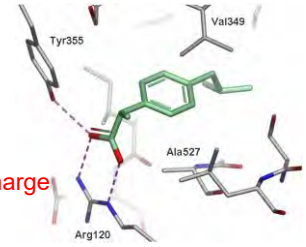
Example Fragment-Protein Complexes

Cyclooxygenase-1 (1EQG)



MW = 206
IC_{50} = 2.6 μM
LE = 0.51

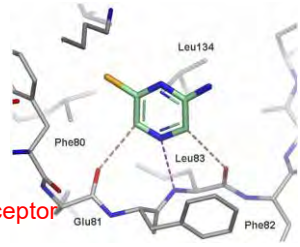
Charge-Charge



CDK2 (1WCC)

MW = 130
IC_{50} = 350 μM
LE = 0.59

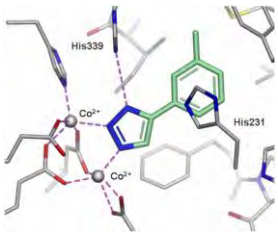
H-bond
Donor-Acceptor



Methionine Aminopeptidase 2 (2ADU)

MW = 159
IC_{50} = 0.018 μM
LE = 0.88

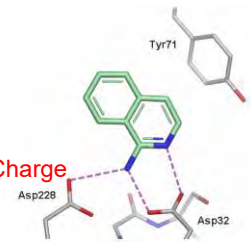
Metal
Complex



β-Secretase / BACE (2OHK)

MW = 144
IC_{50} ~ 2000 μM
LE ~ 0.33

Charge-Charge



Fragment Evolution

AT13387 / HSP90 Phase 2 for Cancer

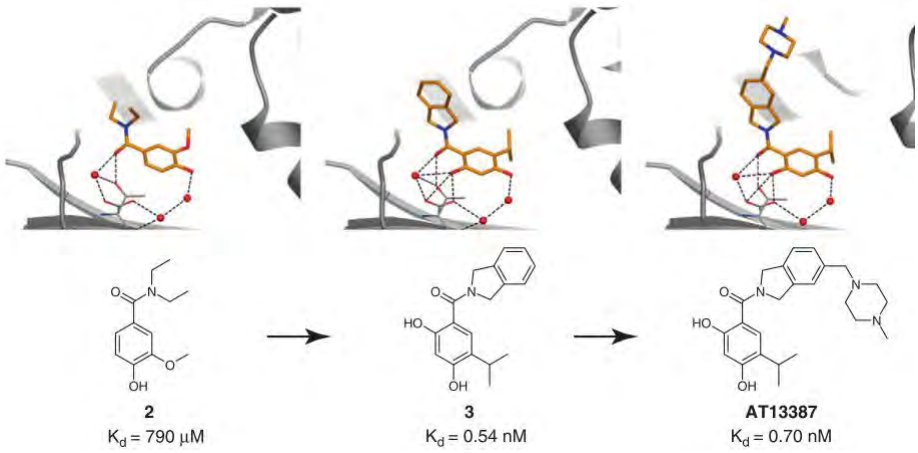


Figure taken from: Murray, C. W. et al., Trends Pharmacol. Sci., 2012, 33, 224-232
Woodhead, A. J. et al., J. Med. Chem., 2010, 53, 5956-5969

Careful optimisation with a focus on Ligand Efficiency and extensive use of protein-ligand complexes to guide medicinal chemistry

Fragment Derived Launched Drug

Vemurafenib / B-Raf Kinase / Melanoma

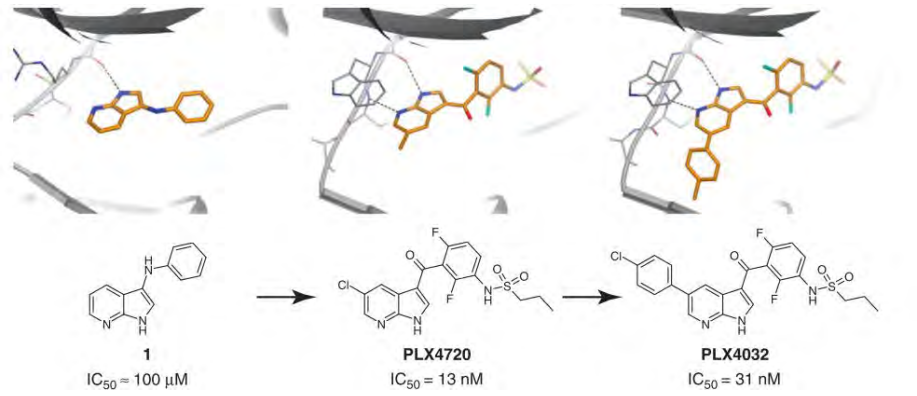
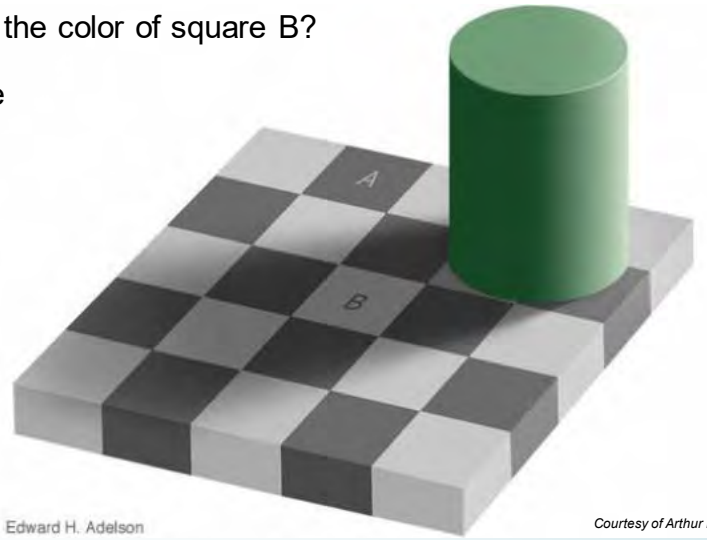


Figure taken from: Murray, C. W. et al., Trends Pharmacol. Sci., 2012, 33, 224-232
Bollag, G. et al., Nature, 2010, 467, 596-599

Interactive Audience Question

What is the color of square B?

- White
- Black

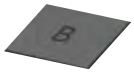


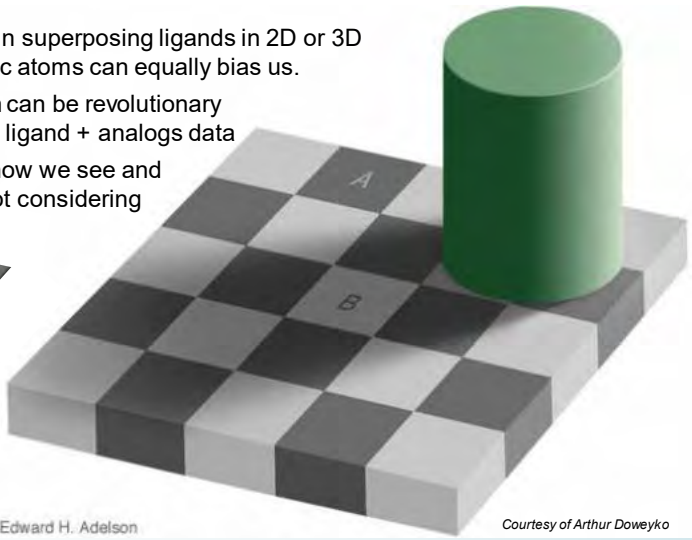
Edward H. Adelson

Courtesy of Arthur Doweyko

Answer: Black!

- Brain biased by previous experience – checkerboard, shadow effect
- Previous experience in superposing ligands in 2D or 3D using pharmacophoric atoms can equally bias us.
- Structural information can be revolutionary - previously biased by ligand + analogs data
- Beware of biases in how we see and "force-fit" data and not considering water mediation





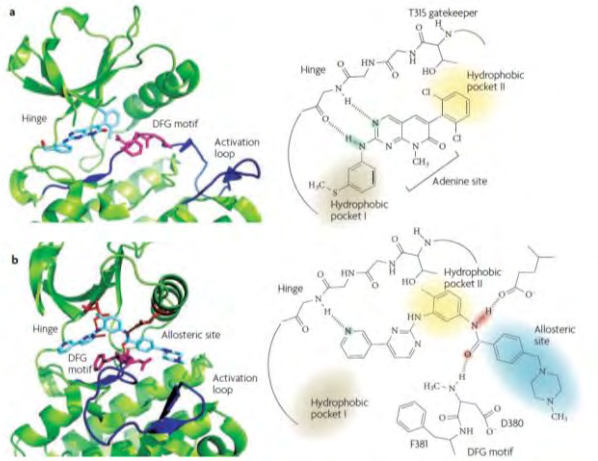
Edward H. Adelson

Courtesy of Arthur Doweyko

Understanding Binding Modes

- Oftentimes in drug discovery the binding mode of different compounds can help interpret the SAR and enables rational design using the protein structure
- In extreme cases quite similar compounds can very in their binding modes significantly
  - Binding mode 'flips' of the ligand
  - Significant conformational changes in the protein opening up new sub-pockets
- In further cases new chemical series can be identified that bind to completely new binding sites outside of the enzyme catalytic site or receptor orthosteric site
  - Phenotypic screens
  - Fragment screening or other biophysical screens
- Allosteric binders may offer better opportunities for optimisation than e.g. peptide substrate binding sites or receptor agonist binding pockets
- They may also have different pharmacology
  - Negative, silent and positive allosteric modulators
  - Different binding kinetic properties, or bind to a different protein conformation

Kinase 'DFG In' and 'DFG Out' Binding Modes

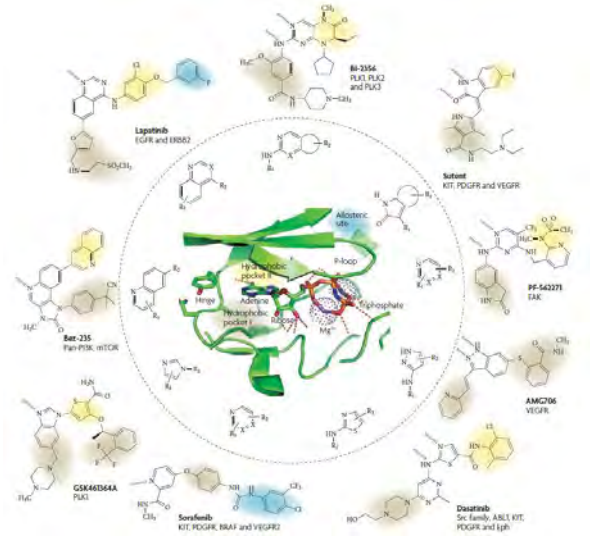


From *Nature Reviews Cancer* 9, 28-39 (January 2009) | doi:10.1038/nrc2559

a ABL1 in complex with the type 1 ATP-competitive inhibitor PD166326 (Protein Data Bank (PDB) ID 1OPK) Shown here is the DFG-in conformation of the activation loop (dark blue).

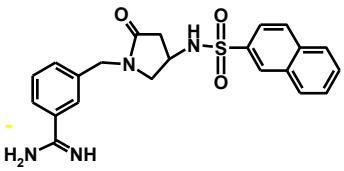
b The DFG-out conformation of the activation loop of ABL1 (dark blue) with the type 2 inhibitor imatinib (PDB ID 1IEP) The allosteric pocket exposed in the DFG-out conformation is indicated by the blue shaded area (right).

Kinase Inhibitors Bind in Multiple Ligand and Protein Conformations Enabling Design of Selectivity

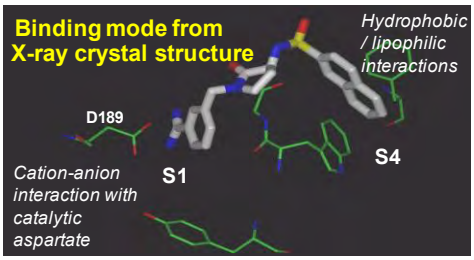


From *Nature Reviews Cancer* 9, 28-39 (January 2009) | doi:10.1038/nrc2559

Q – How will this modified Factor Xa inhibitor bind?



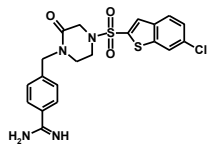
The napthalene group of this Factor Xa ligand is changed to a chlorobenzothiaphene



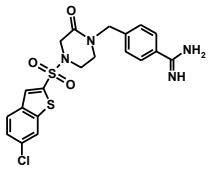
Will it bind?

A. In a similar fashion
B. Not bind
C. Flip, putting the benzamidine in the S4 pocket ?

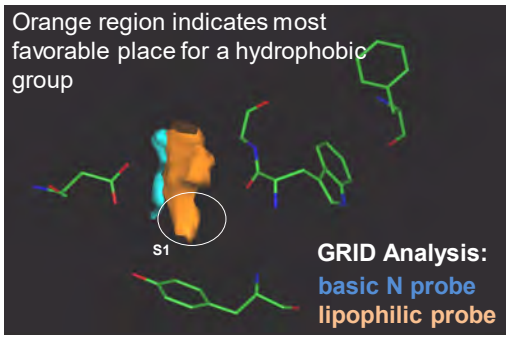
A

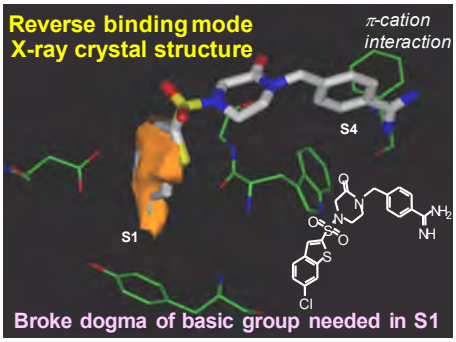


C



Answer: C - Reversed binding mode



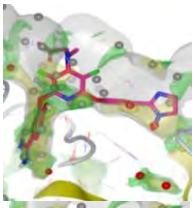


- **Could we have predicted this?**
  - Yes: docking found both modes but wasn't believed…
  - Yes: lipophilic hotspot
  - Yes: new water network energy calculations show an "unhappy" (high energy relative to bulk solvent) water where Cl goes

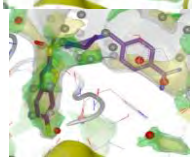
Importance of Lipophilic Regions and "Unhappy" Waters

Factor Xa

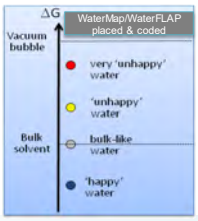
The myth: Basic S1 for serine proteases (factor Xa)

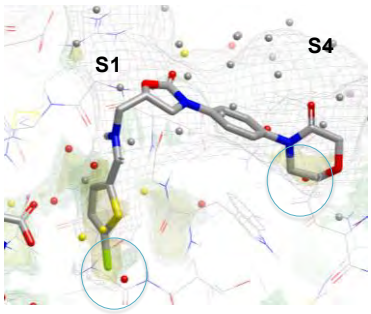


The structure that broke the myth



GRID Map contoured at:
C1= (lipophilic) probe:
Yellow -2.5 kcal/mol
Water (H-bonding) probe:
Green -6.0 kcal/mol
Surface defined by CH3 probe:
Grey 1.0 kcal/mol

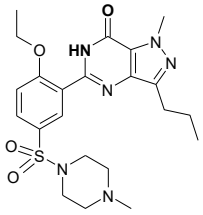


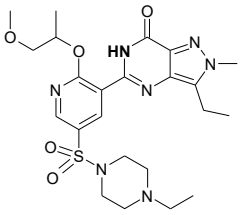


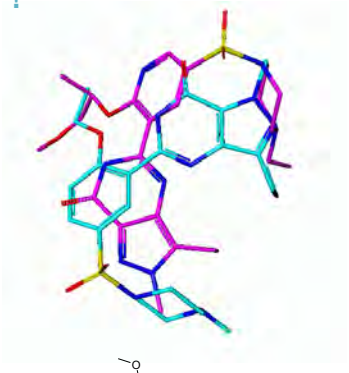
The clinical candidate

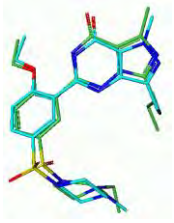
Protein-ligand Structures Show That Ligands Within a "Series" Often "Flip" Binding Modes, Enabling New Design Possibilities – When Identified !

PDE5 inhibitors



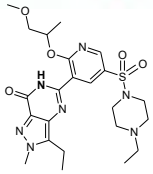






Binds completely different
- 2D structure alignment gives wrong ideas

→ Traditional ligand based approach / QSAR would not work

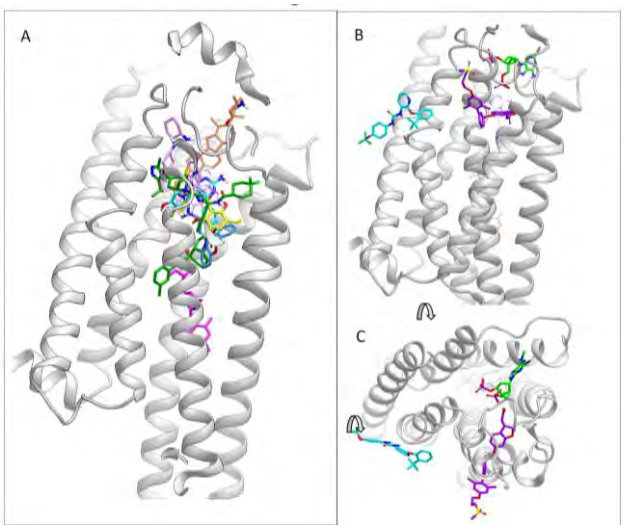


other not !:

- Some analogs bind in a similar way

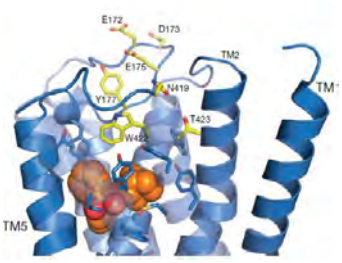
Finding New Binding Sites

- GPCRs are showing a remarkable diversity of binding sites
  - Ligands deep inside the centre of the receptor
  - On the outside of the receptor
  - Cutting into the receptor from the outside
- Creates a range of opportunities to discover drugs, even when the natural ligand is e.g. a peptide hormone

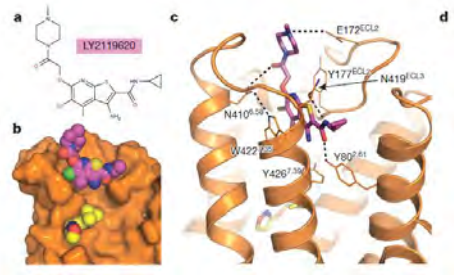


Allosteric Binders

- M_2 PAM – helps to understand pharmacology



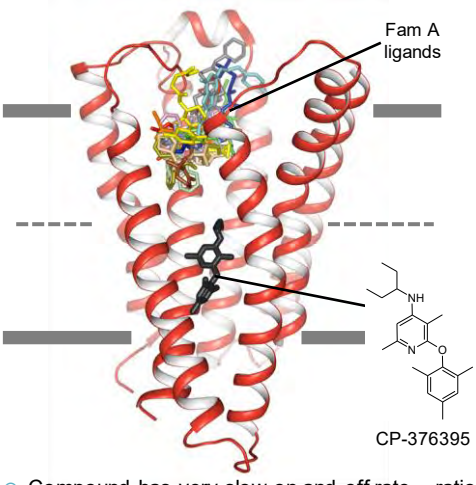
Antagonist binding site
Haga et al Nature 482, 547–551



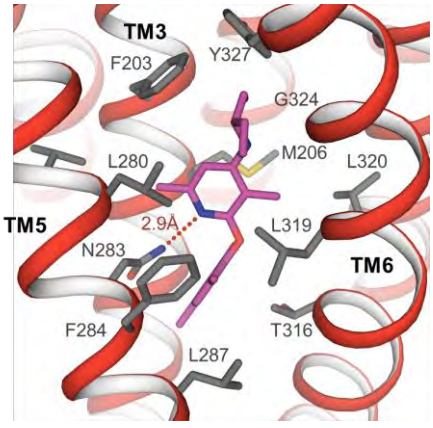
Agonist and PAM binding site
Kruse et al Nature 504, 101–106

- Positive allosteric modulator binds to a site that is contiguous to the orthosteric site (which may be a pre-engagement site for the agonist)
- Acts to slow down the off-rate of the agonist, increasing its agonist effect *in vivo*

CRF-1 Receptor Allosteric Antagonist

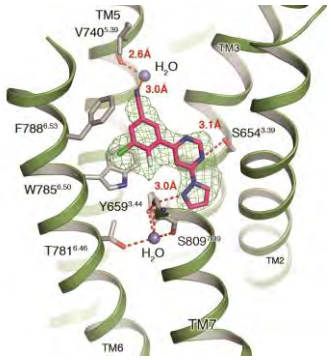


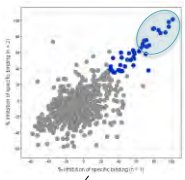
CP-376395



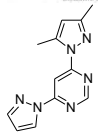
- Compound has very slow on and off rate – rationalised by the structure
- A significant change in kinetic parameters might suggest a compound is binding to a different or induced fit pocket

$mGlu_5$ Negative Allosteric Modulator SBDD

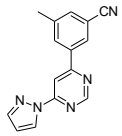




Screening of StaR receptor
by high concentration radioligand binding

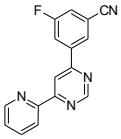


$mGlu_5$ pK_i 5.2
LE 0.40

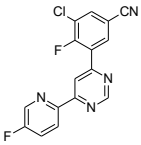


$mGlu_5$ pK_i 8.4
LE 0.57

- First example of FBDD for a family C GPCR
- Rapid fragment evolution
- Supported by X-ray data during the project lifetime
- Gave a preclinical candidate HTL14242



$mGlu_5$ pK_i 7.1
LE 0.46



$mGlu_5$ pK_i 9.1
LE 0.54

Congreve, M. et al., ACS Denver 2015, MEDI 256

HEPTARES therapeutics

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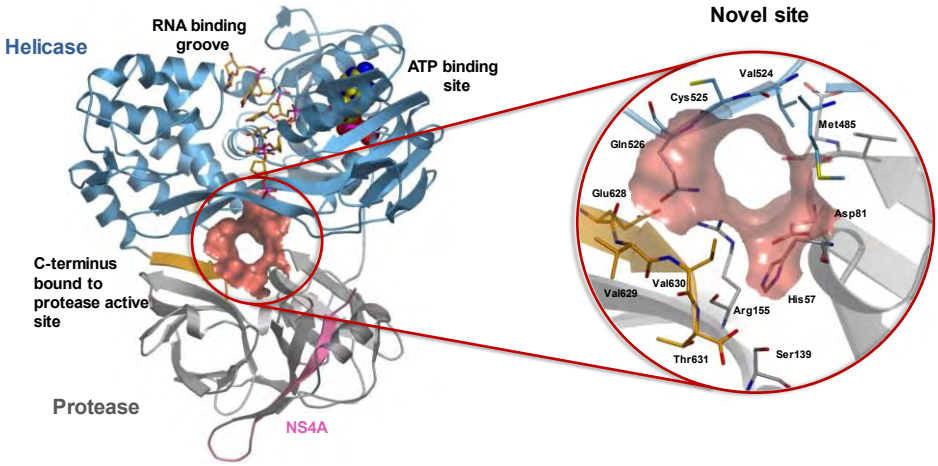
Discovering Inhibitors of HCV Protease Allosteric Binding Site



Saalau-Bethell *et al.* (2012), *Nature Chemical Biology*, 8(11), 920-925

Courtesy of Susanne Saalau-Bethell, Astex Pharmaceuticals

HEPTARES therapeutics

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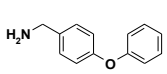
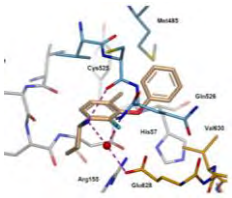
Discovering Inhibitors of HCV Protease Allosteric Binding Site

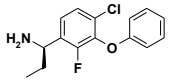
Fragment Hit (2)



Compound 2
FL IC_{50} ~ 500μM (LE = 0.30)
PD IC_{50} - Inactive
MW = 199

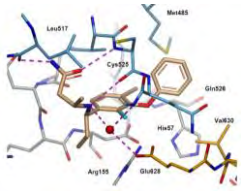
Optimised benzylamine (4)

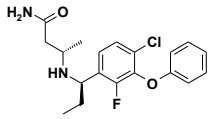




Compound 4
FL IC_{50} = 2.1μM (LE = 0.41)
Kd = 5.5μM
PD IC_{50} - Inactive at 1000μM
MW = 279.8

Lead (5)





Compound 5
FL IC_{50} = 0.10μM (LE = 0.38)
Kd = 0.06μM
PD IC_{50} - Inactive at 1000μM
MW = 364.9

FL = Full-length; PD = Isolated protease domain

Courtesy of Susanne Saalau-Bethell, Astex Pharmaceuticals

Understanding Biology and Proof of Mechanism

- Drugs developed from phenotypic screens, cell based assay or that are non-competitive with the substrate or agonist of a protein can cause concerns regarding their true mode of action
- Unusual biological behaviour makes people nervous
- Structural biology can help uncover the reasons for these behaviours and give confidence to move forward into clinical studies
  - Allosteric binders
  - PAMs and NAMs
  - Rationalizing slow off-rates
  - Covalent inhibitors
- Alternatively structural biology can retrospectively rationalise the mode of action of drugs allowing new generations of agents to be developed
  - Antiviral drug resistance
  - Resistance mutations in cancer
  - Anti-infective, CNS and cancer drug action

To Conclude
The Advocate vs. The Sceptic

Advocate	Sceptic
SBDD is much more efficient and elegant than empirical med chem and gives a much better chance of success	SBDD is expensive to implement and requires a high level of resources to support medicinal chemistry Tractable targets don't need SBDD
SBDD allows an atom by atom optimisation leading to better quality compounds	LE, LLE and multiparameter optimisation can also be applied using empirical approaches, ligand based design and QSAR
SBDD has led to success for difficult and intractable targets	Empirical med chem will get there in the end
SBDD is coupled with biophysics allowing fragment screening, identification of new binding sites, binding kinetics and proof of target engagement of ligands	Phenotypic screening has led to many new drugs and target engagement can be measured e.g. using receptor occupancy expts in tissue

Interactive Audience Question

What is your opinion of Structure-Based Drug Design (SBDD)?

- advocate
- sceptic/skeptic
- I'm still on the fence

SBDD Take Home Messages

- **Full FBDD/SBDD now possible for enzymes and GPCRs and can be game-changing** – *e.g. no single GPCR 'rhodopsin-like' binding site*
- **Waters are not optional – key missing 3rd dimension in many computational studies (need protein + ligand + water)**
  - key for selectivity & kinetics as well as potency
  - & protein structure-function
  - & *possible now to generate & score networks rapidly*
- **Many new target structures have "unexpected/predicted" elements**
  - binding position (orthosteric, allosteric) & mode
- **A single ligand complex structure is generally not sufficient**
  - e.g. Insights from multiple GPCR ligand structures, including water-mediated
  - *Polar molecules can bind with all polar interactions water-mediated*
  - → ☹ *Pharmacophore models*

HEPTARES therapeutics

X-ray Crystallography in Drug Discovery

Note Heptares literature and references (not always included in the presentation) are available from www.heptares.com

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