Chemoinformatics-Supported Med Chem: Expectations, Pitfalls, and Success Stories

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Prestwick Chemical's Team

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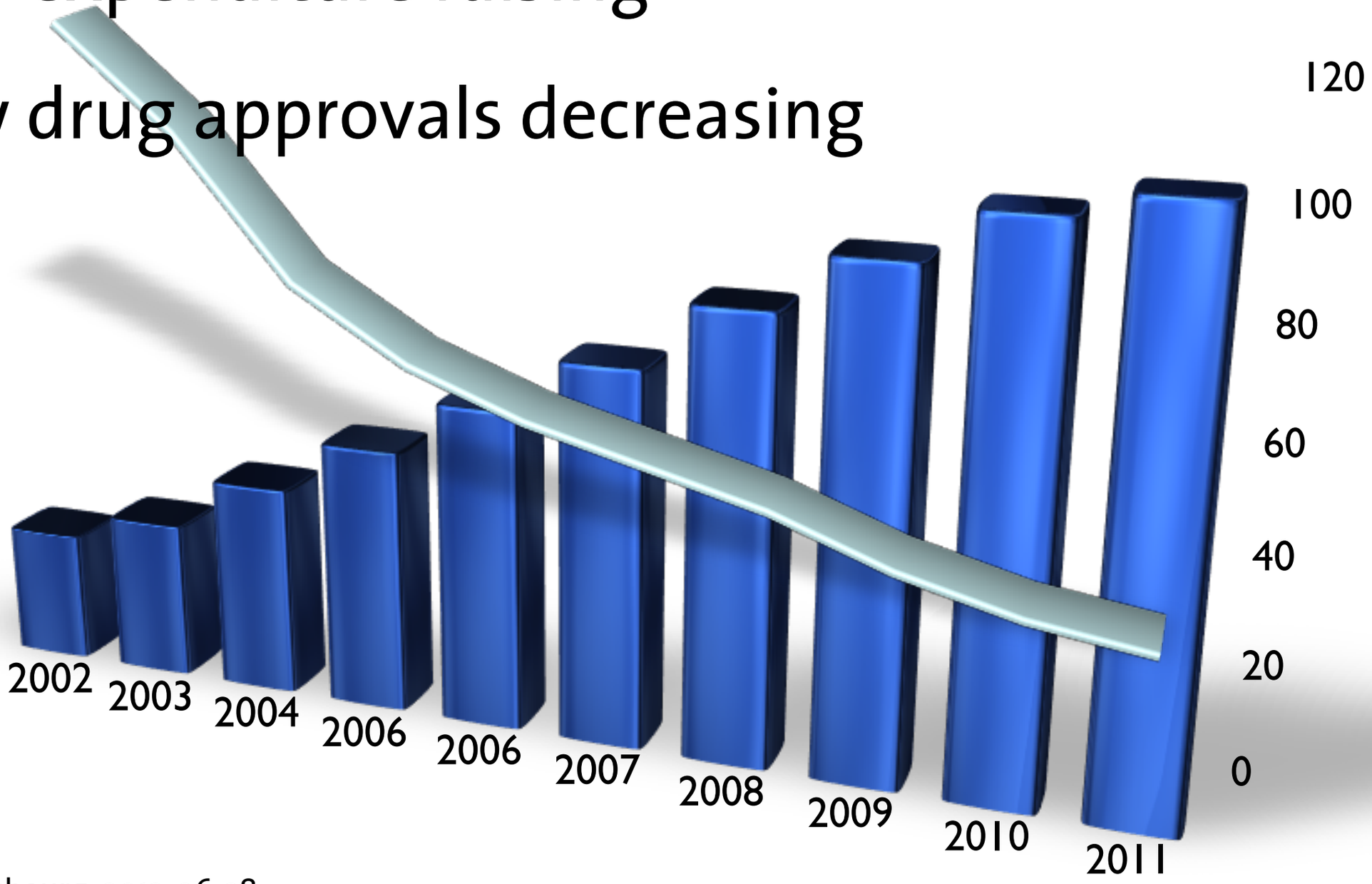
Dramatic Situation in Big Pharma ?

- R&D expenditure raising
- New drug approvals decreasing



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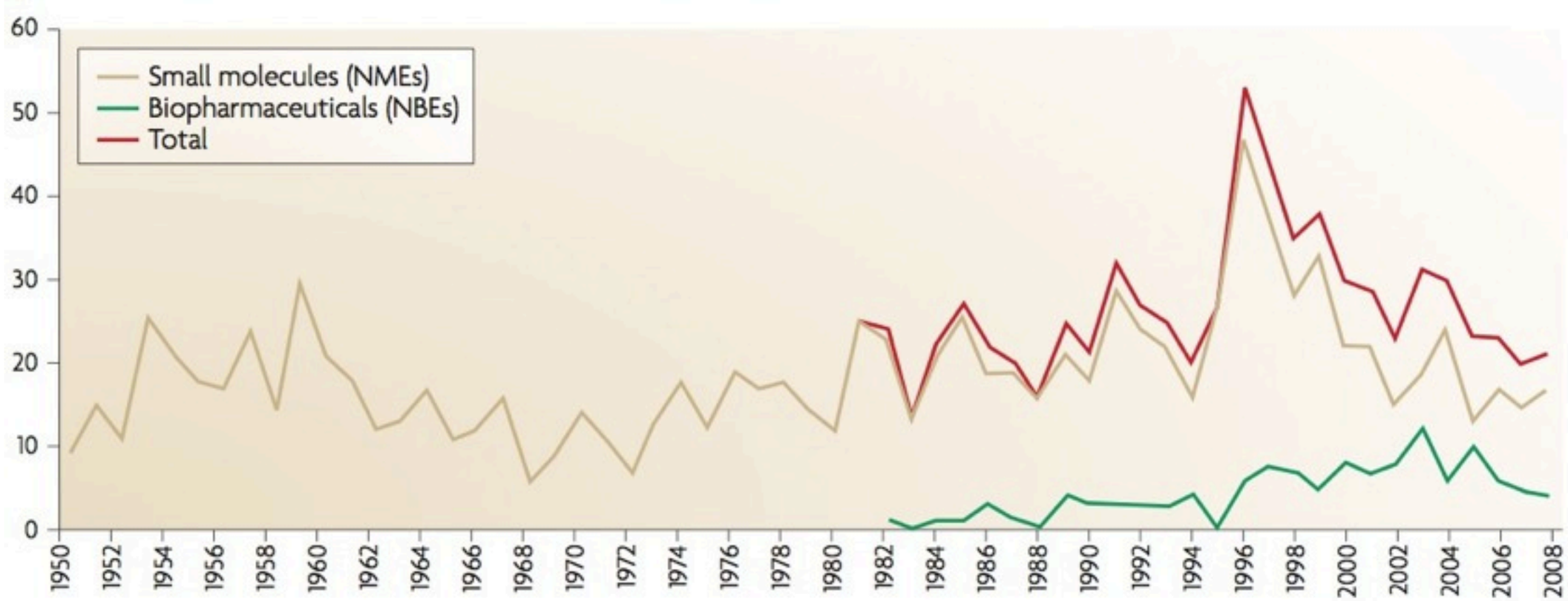
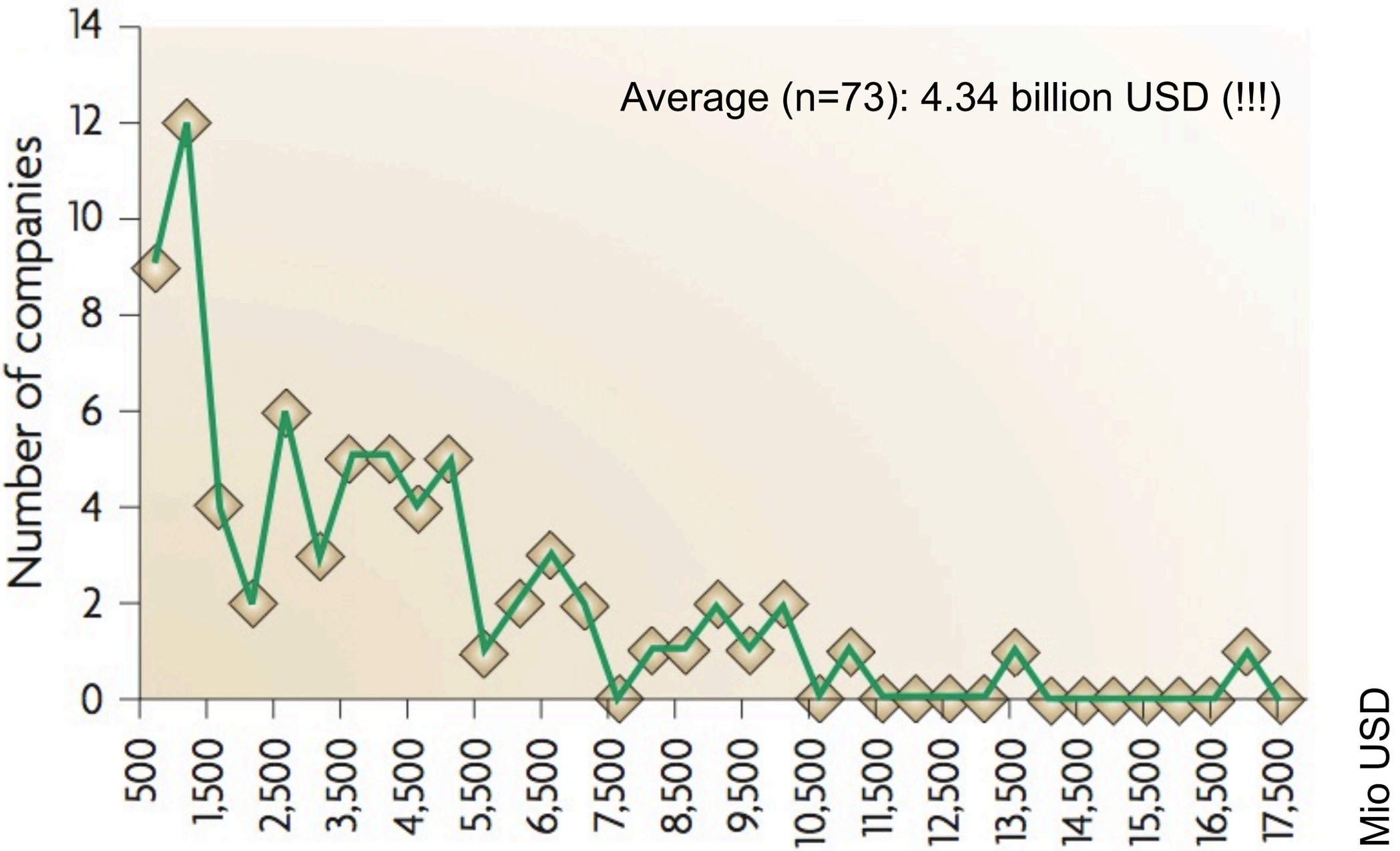
A True Productivity Problem ?

- New drugs approved since 1950 …
  - 1103 Small molecules
  - 119 Biologicals



Costs Per New Drug



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Nat. Rev. Drug Discov., 8, 959-968 (2009)

ANALYSIS

Lessons from 60 years of pharmaceutical innovation

Bernard Munos

Abstract | Despite unprecedented investment in pharmaceutical research and development (R&D), the number of new drugs approved by the US Food and Drug Administration (FDA) remains low. To help understand this conundrum, this article investigates the record of pharmaceutical innovation by analysing data on the companies that introduced the ~1,200 new drugs that have been approved by the FDA since 1950. This analysis shows that the new-drug output from pharmaceutical companies in this period has essentially been constant, and remains so despite the attempts to increase it. This suggests that, contrary to common perception, the new-drug output is not depressed, but may simply reflect the limitations of the current R&D model. The implications of these findings and options to achieve sustainability for the pharmaceutical industry are discussed.

New molecular entity (NME). A medication containing an active ingredient that has not been previously approved for marketing in any form in the United States. NME is conventionally used to refer only to small-molecule drugs, but in this article the term includes biologics as a shorthand for both types of

From 1950 to 2008, the US Food and Drug Administration (FDA) approved 1,222 new drugs (new molecular entities (NMEs) or new biologics). However, although the level of investment in pharmaceutical research and development (R&D) has increased dramatically during this period — to US$50 billion per year at present[1] — the number of new drugs that are approved annually is no greater now than it was 50 years ago. Indeed, in 2008, only 21 new drugs were approved for marketing in the United States,

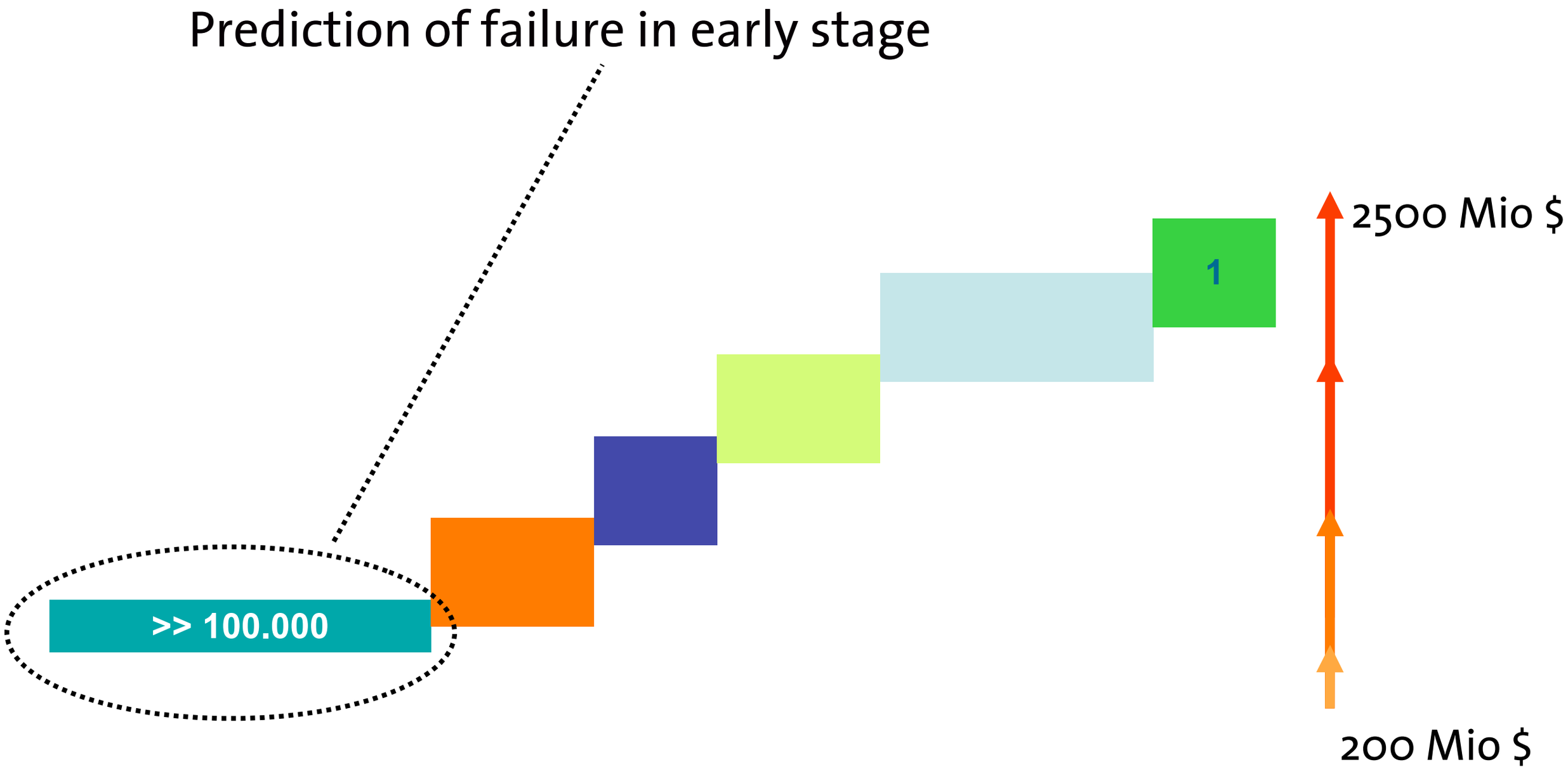
research organizations if they are to escape the increasing pressures created by linear new-drug output and rapidly rising R&D costs.

Rate of new drug introduction

Of the 1,222 NMEs that have been approved since 1950, 1,103 are small molecules and 119 are biologics. FIGURE 1a shows the timeline of these approvals. Although at first glance there are no obvious patterns, on closer obser-

T.

Efficiency Deficit ...



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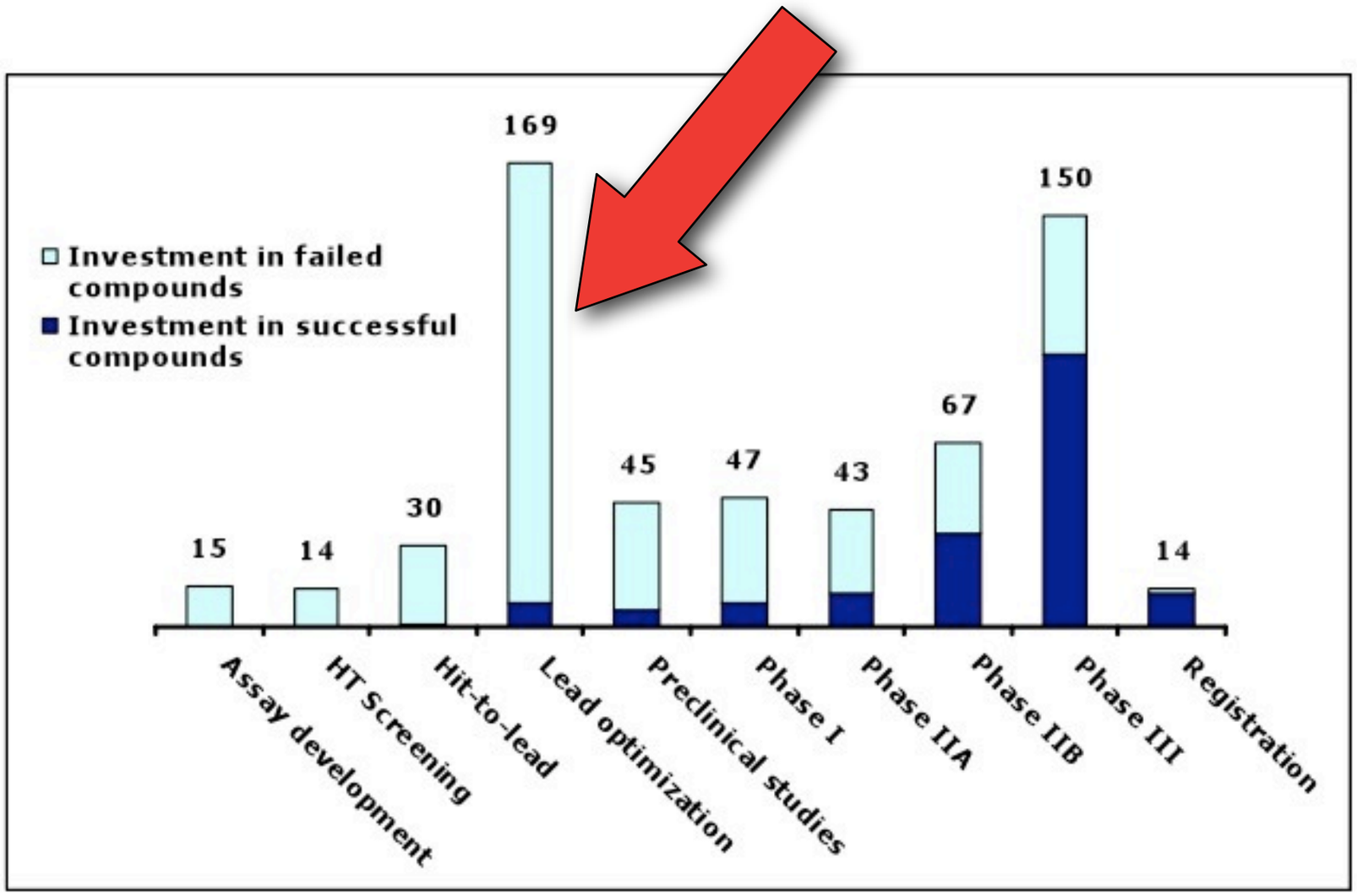
Costs Attributed To Drug Discovery



Investment per phase of drug discovery and development for one successful drug (USD millions)

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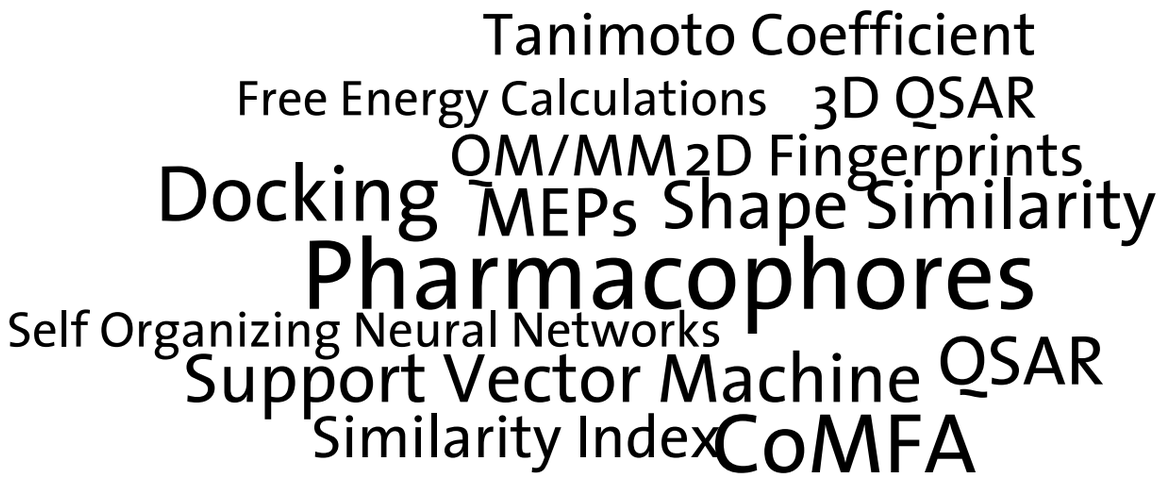
G.M. Milne, Jr., Annual Reports in Medicinal Chemistry, 2003, 38, 383-396

What are we talking about today?

- Examples of chemoinformatics methods
- Application in medicinal chemistry for early drug discovery research
- Focus on
  - Hit identification by virtual screening
  - Decision support for med chem optimization
  - Liability prediction for later development

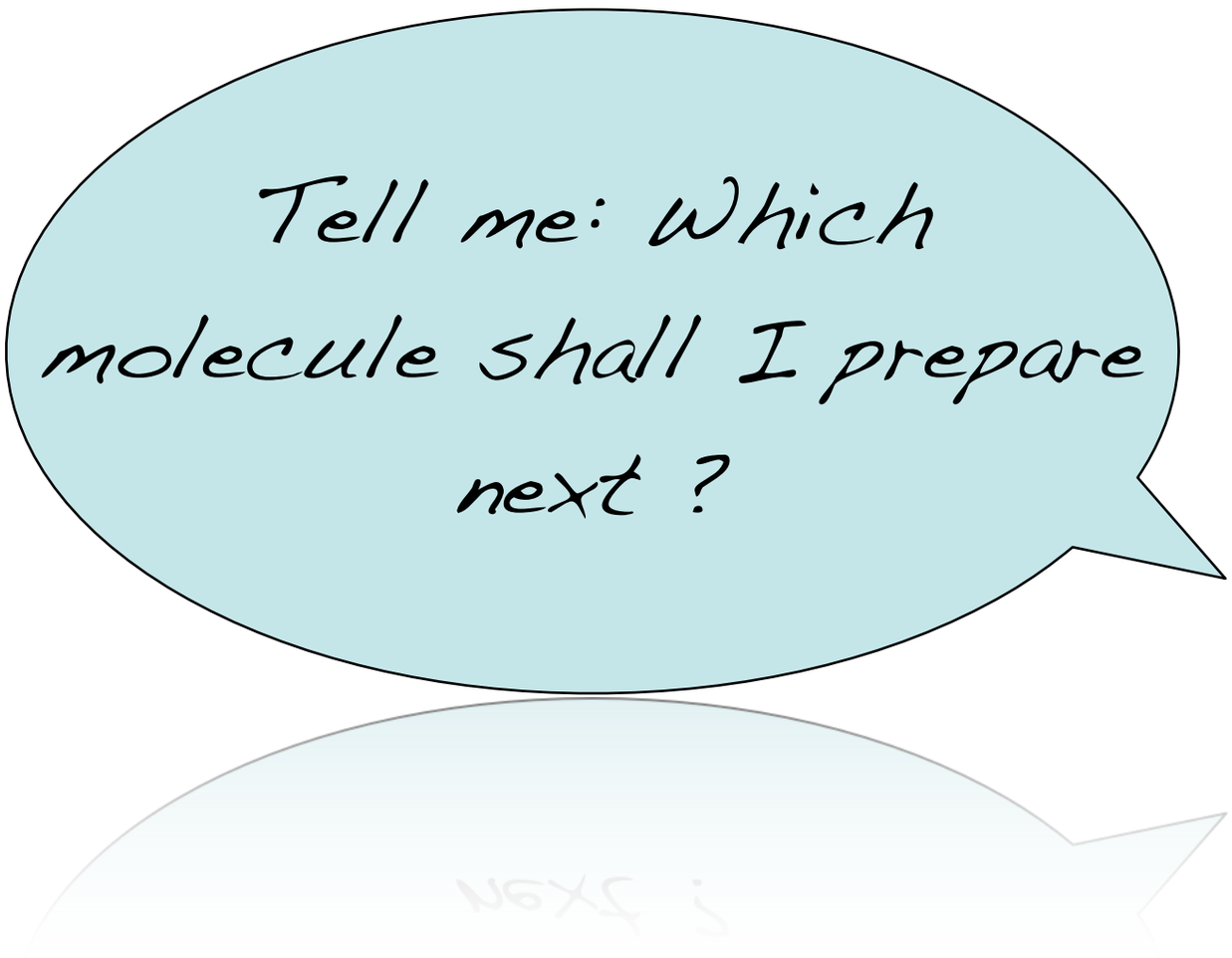
What Do We Need ?

- Reliable decision support tools
- Easy to use, easy to understand
- Need for speed
- Solid science behind



Expectations: The Medicinal Chemist

- Answer the most important question !



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Expectations: The Biologist

- Answer the most important question !

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The Chemoinformatician …

- Wants to find the right answers to all the questions …
- Wants to help the medicinal chemist by designing great molecules …
- Wants to explain biological data based on oversimplified models …

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Ultimate Goal - Predict Everything

- Molecular properties
  - physicochemical data
  - affinity to target(s)
- Effects of molecules
  - on cells
  - on organs
  - on the entire organism
  - ...

The Chemoinformatician ...

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Just Try To Avoid The Pitfalls …

- There is no “one-model-fits-all” paradigm
- Local models can only explain local phenomena
- Let’s have a closer look …

– Virtual screening pitfalls*

* T. Scior et al., J. Chem. Inf. Model. 2012, 52, 867−881

Some Pitfalls - In Detail

- Concerning erroneous assumptions
- Concerning data design & content
- Relating to the choice of software
- Concerning conformational sampling and molecular flexibility (target & ligand)

* T. Scior et al., J. Chem. Inf. Model. 2012, 52, 867−881

VS Pitfalls (1) - Wrong Assumptions

- Expectation: Identify high affinity compounds
- Stringency of queries
- Binding pose prediction
- The role of water in mediating interactions
- Subjectivity of compound selection
- …

* T. Scior et al., J. Chem. Inf. Model. 2012, 52, 867−881

VS Pitfalls (2) - Data Design & Content

- (Non)comparability of benchmark data
- (Non)comparability of performance metrics
- Hit rate in benchmark data sets
- ‘Bad’ molecules (reactive / aggregants)
- Inactives (‘decoy’) selection

* T. Scior et al., J. Chem. Inf. Model. 2012, 52, 867−881

VS Pitfalls (3) - Choice Of Software

- I/O errors & format incompatibilities
- Molecular structure preparation
- Pharmacophore feature definition
- Fingerprint selection & algorithms used
- Partial charges
- Single predictors / ensemble prediction

* T. Scior et al., J. Chem. Inf. Model. 2012, 52, 867−881

VS Pitfalls (4) - Flexibility (!!!)

- Conformational coverage
- Bio-active conformation
- Conformer comparison
- Conformer energy
- Target flexibility
- …

* T. Scior et al., J. Chem. Inf. Model. 2012, 52, 867−881

Let’s be more positive …

… and have a look at real life situations and related success stories …

Pharmacophores @ Prestwick

- Medicinal chemists want to understand what is driving the affinity - do not like a black box !!!
- Quickly elucidate ligand-target interactions
- Pharmacophores are versatile tools for
  - Identification of starting points by virtual screening
  - Understanding structure-activity relationships
  - Supporting the molecular design process
    - Achieving better target selectivity
    - Avoiding unwanted off-target effects

Our Initial Aim, 15 Years Ago ...

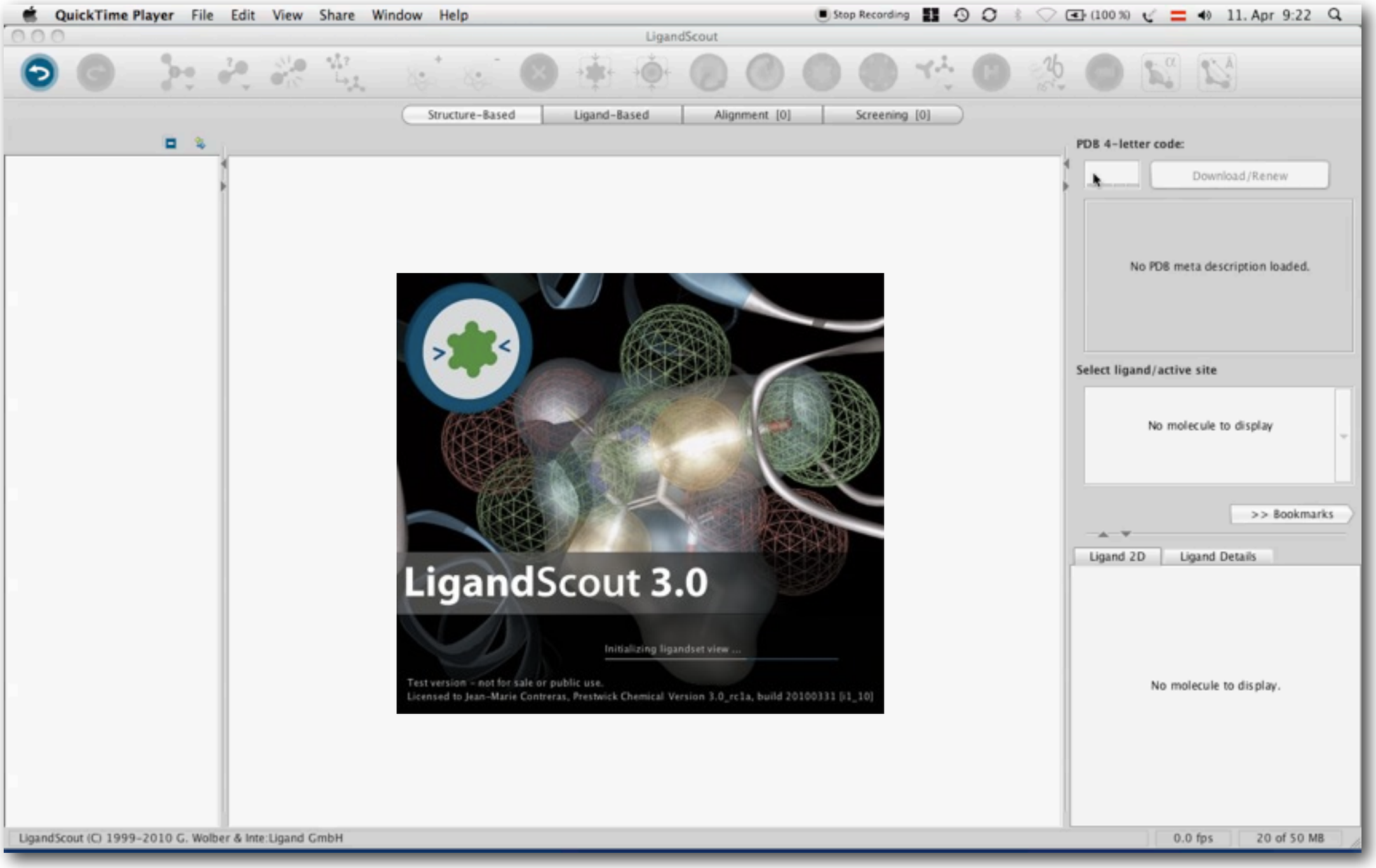
- Create a database of pharmacophore models for activity profiling of small organic molecules
- Need for a method for rapid and reliable model generation & validation
- Developed software prototypes @ IBK university
- Creation of spin-off company Inte:Ligand

EuroQSAR 2004: LigandScout 1.0

- Detect ligand and clean-up the binding site in the protein (all amino acids within 7Å default distance from the ligand)
- Interpret hybridization status and bond types in the ligand
- Perform chemical feature recognition for the ligand (H-bond donor, H-bond acceptor, positive ionizable, negative ionizable, hydrophobic, aromatic ring, metal ion coordination)
- Search for corresponding chemical features of the protein
- Add interaction features to the model only if a corresponding feature pair is found in the complex
- Add excluded volume spheres for opposite hydrophobic features

G. Wolber, T. Langer: J. Chem. Inf. Model. 45 , 160-169 (2005)

EuroQSAR 2010: LigandScout 3.0



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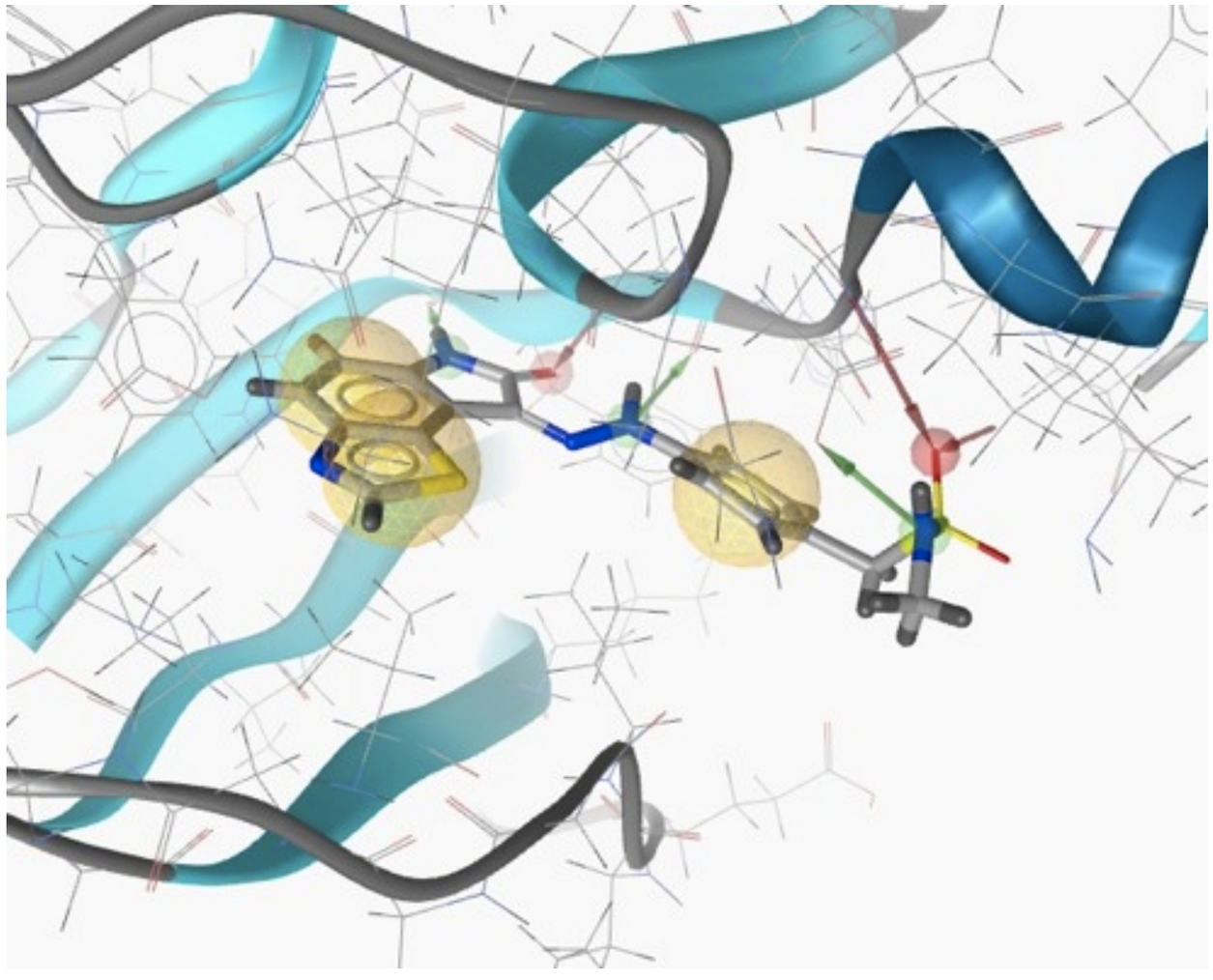
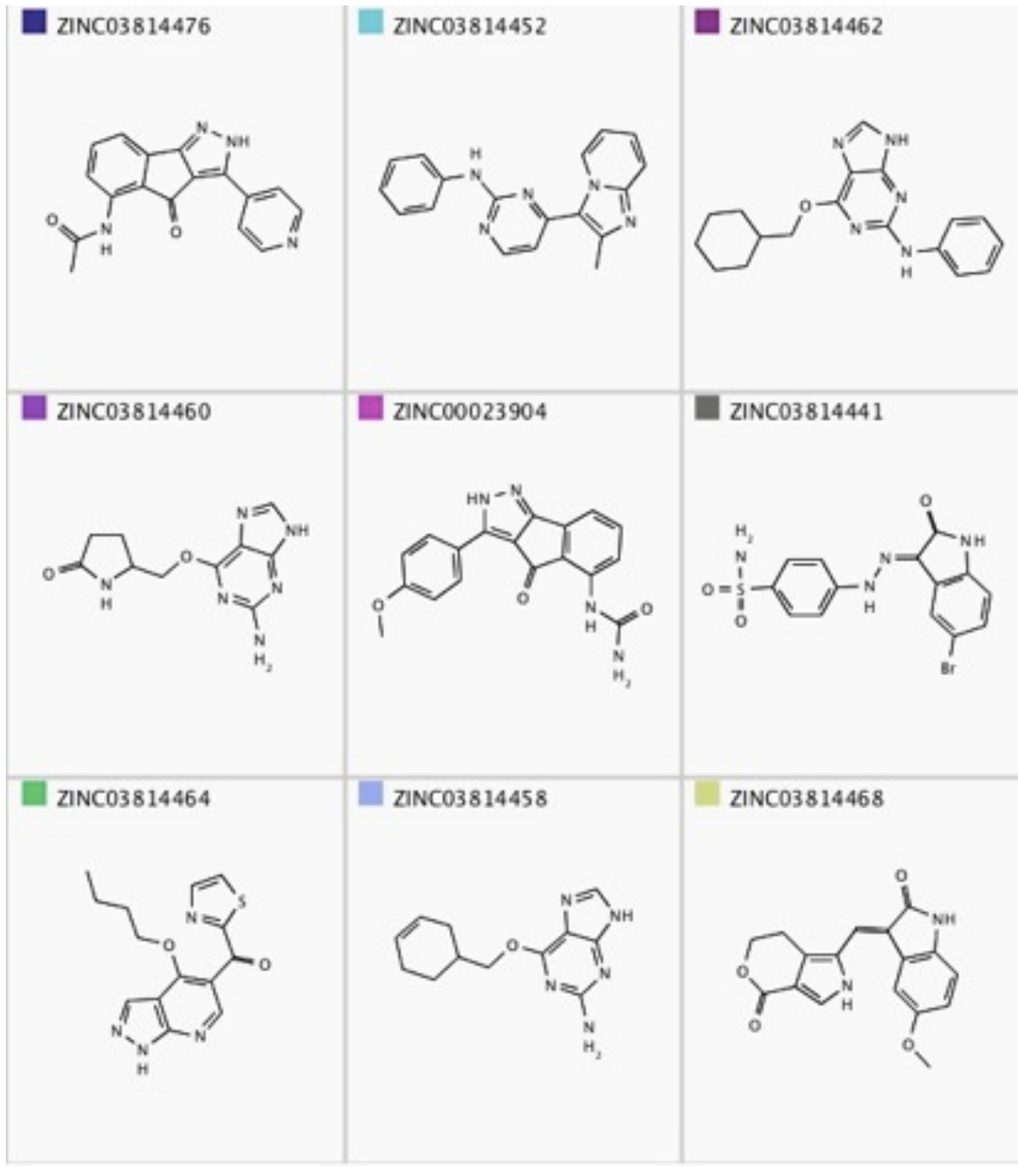
inte:ligand
Your partner for in-silico drug discovery.

Bridging Gaps

Structure-based



Ligand-based



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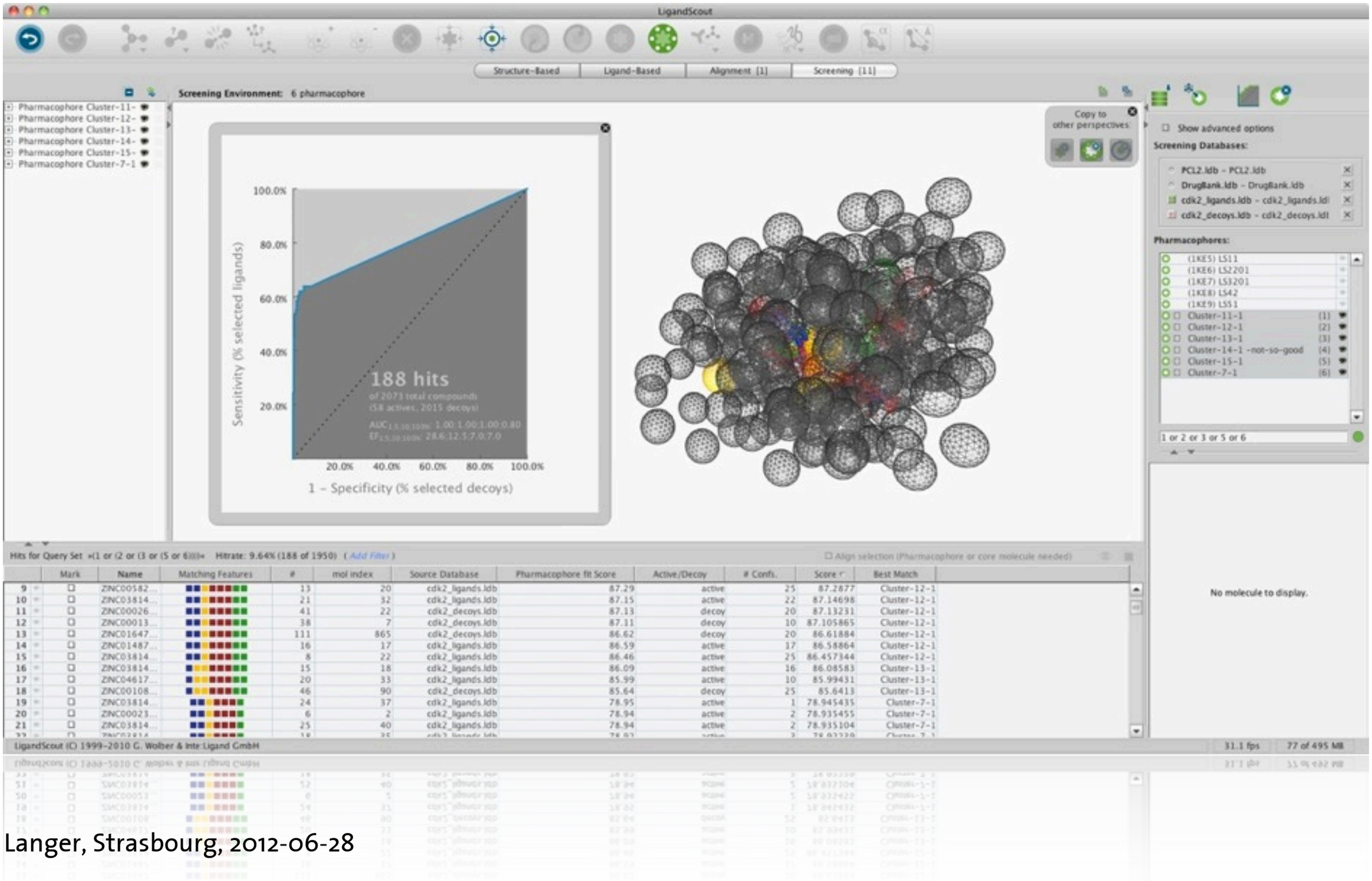
Example: CDK2 DUD Set



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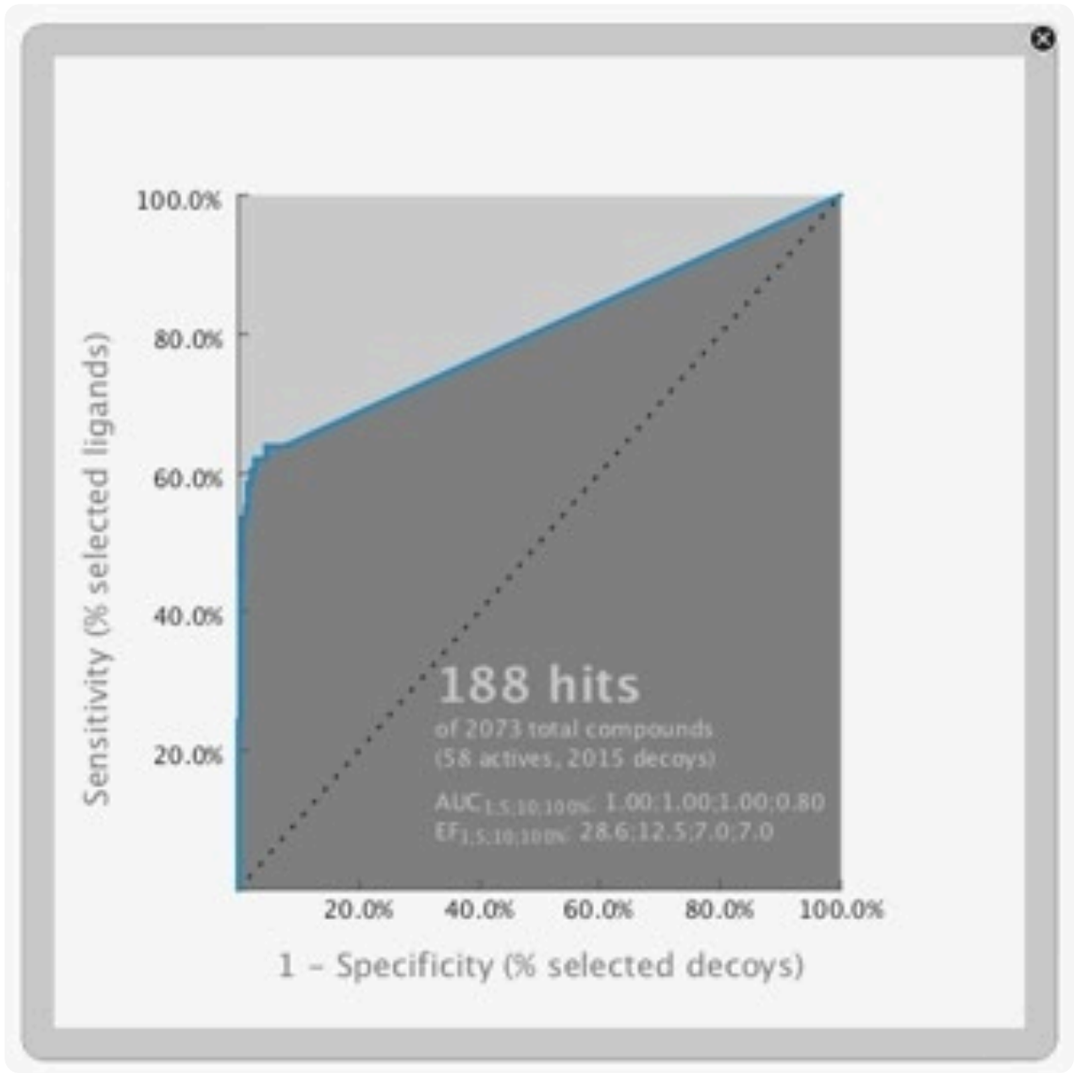
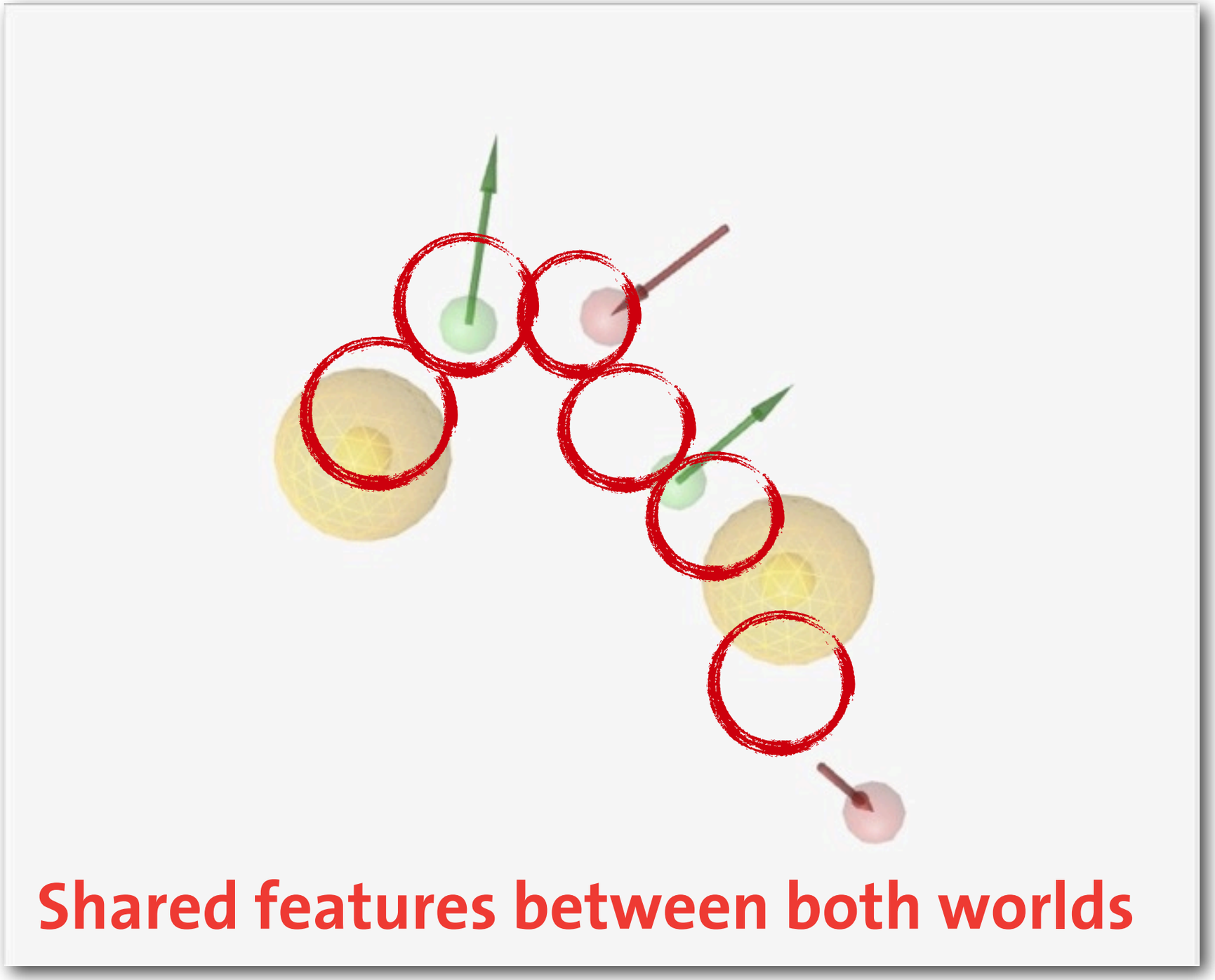
Example: CDK2 DUD Set



- ROC Curve Analysis
  - 58 actives / 2015 decoys
  - 188 hits
  - Enrichment Factor: 28.6 (first 1% of screening)

Comparison - Structure & Ligand Based



Shared features between both worlds

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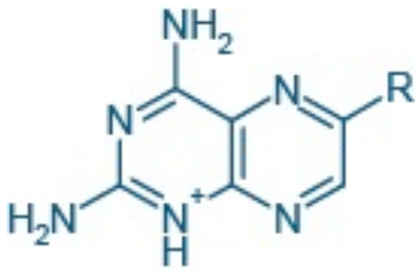
Pharmacophore Models for Rapid VS

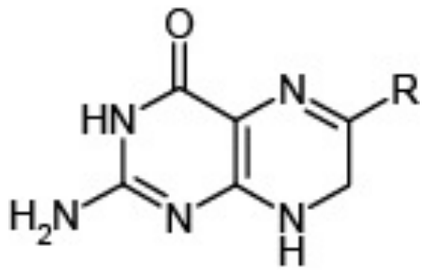
- The alignment problem
  - Which type of matching ?
  - How to define matching pairs of features ?
  - How to define a fast and accurate scoring function ?

- The solution
  - Pharmacophore elements-based matching
  - Adaptation of the hungarian matcher algorithm

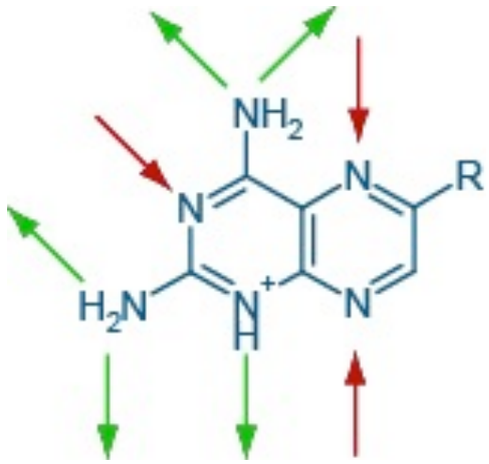
Alignment By Pharmacophore Points

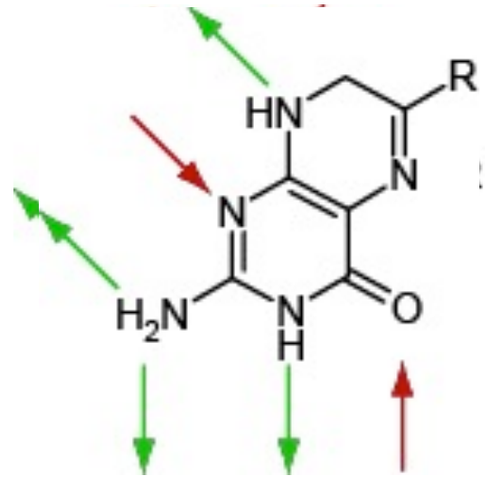


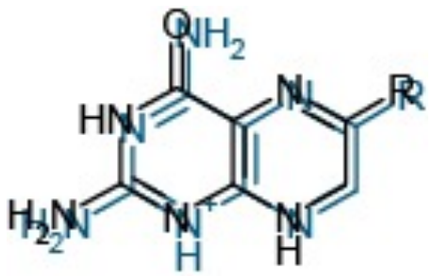
Methotrexate



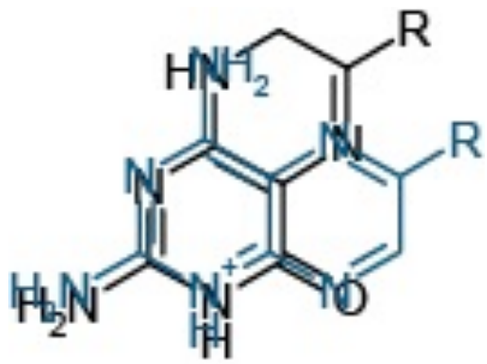
Dihydrofolate



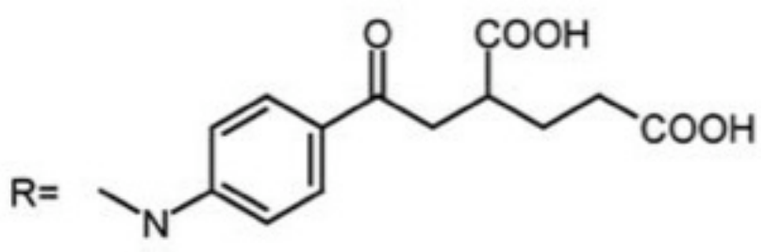




Wrong



Correct



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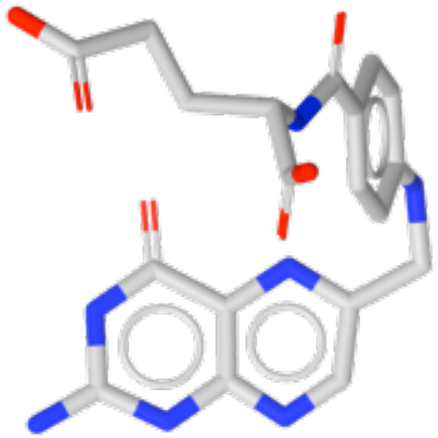
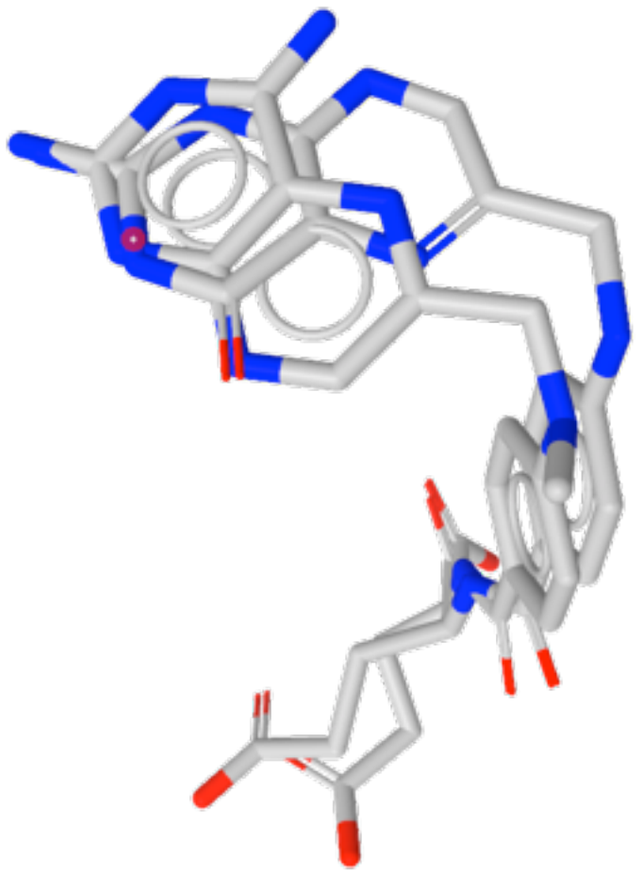
Bystroff, Oatley, Kraut: Biochemistry. (1990) 29, 3263-77

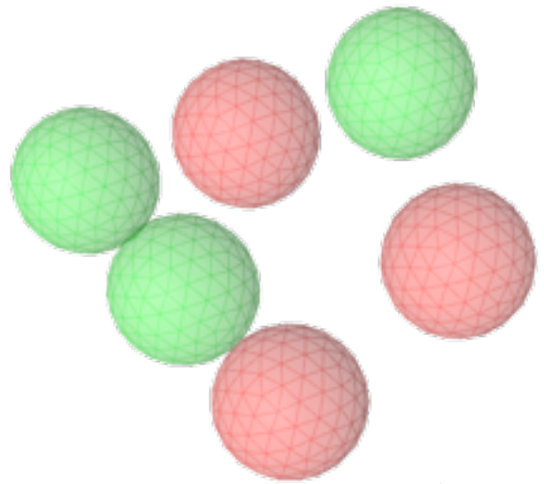
Böhm, Klebe, Kubinyi: Wirkstoffdesign (1999) p. 320f

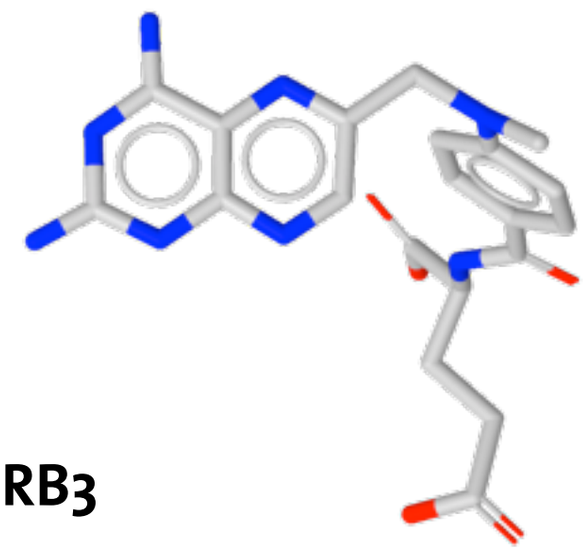
Alignment By Pharmacophore Points

1RX2









1RB3

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First Achievements

- Universal method for **accurate** feature-based pharmacophore model generation
- New pattern recognition-based alignment
- Highly **selective** models will retrieve low number of false positives / false negatives
- **High enrichment** factor can be obtained
- **Speed** allows for implementation of massive parallel screening

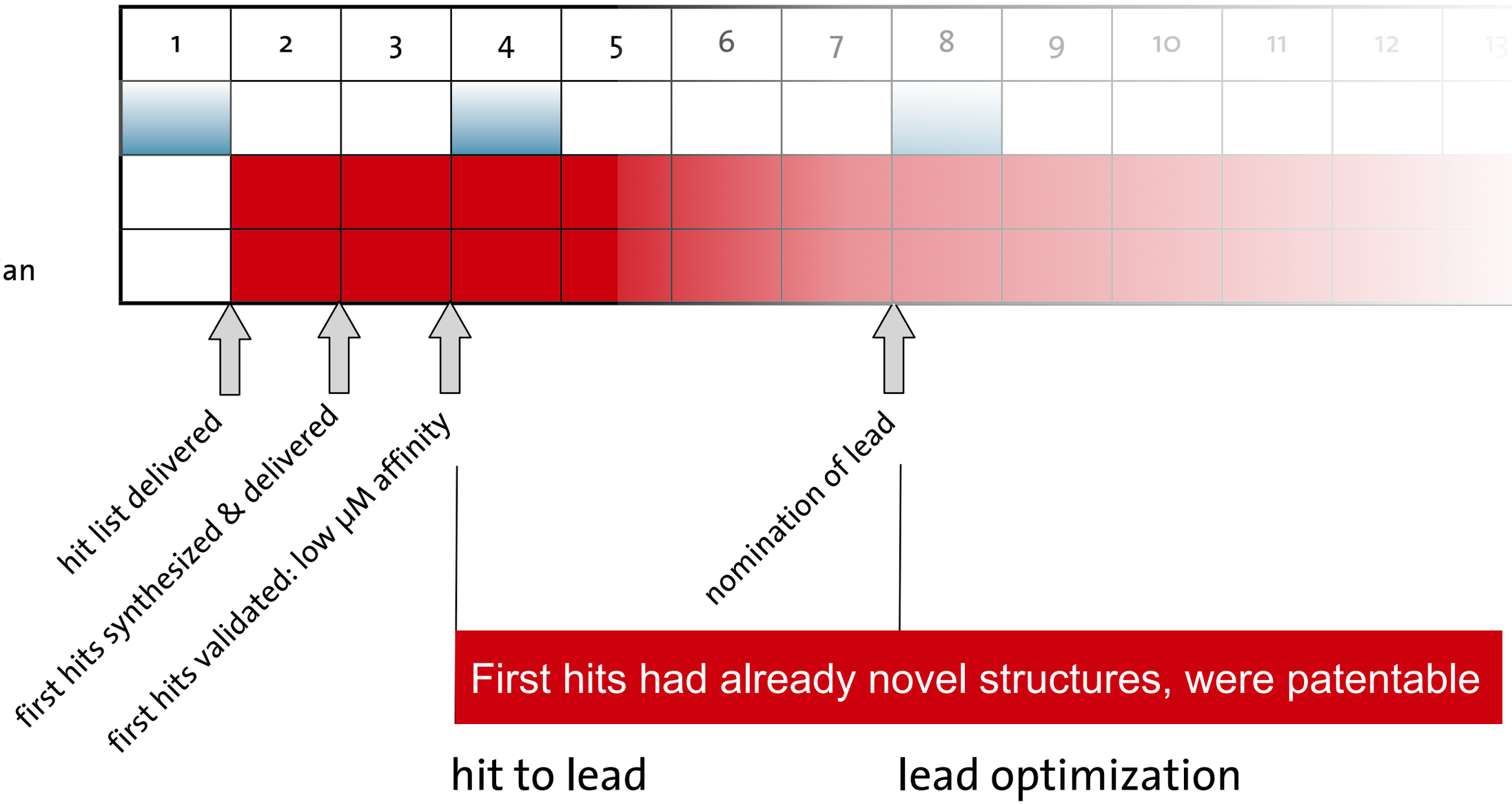
Use Cases / Success Stories

- Finding starting points for medicinal chemistry program: Hit identification by virtual screening
- Medicinal chemistry decision support in hit to lead and lead optimization
- Activity profile estimation by parallel screening
- Target fishing for natural products

Identification of Starting Points

- Real life example
- Target with known 3D structure (x-ray)
- Pharmacophore derived in direct approach
- Virtual library built ab-initio using a fragment-based approach (90k compounds)
- Screening delivers reasonable small number of hits (0.05% range)
- Synthesis and biological testing

Time Line & Results



PRESTWICK CHEMICAL
A medicinal chemistry company

Ligand Profiling: Proof of Principle

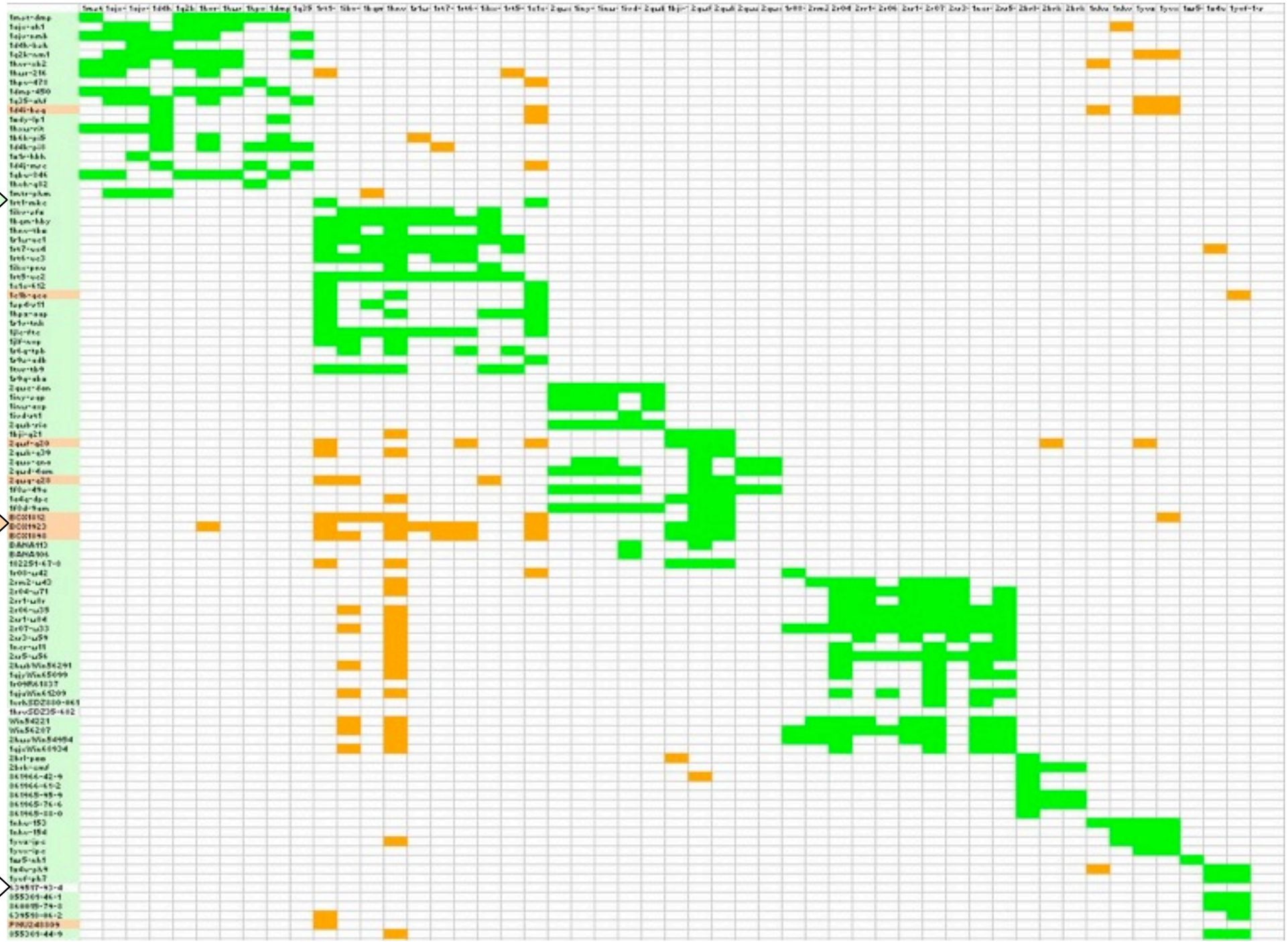
- First pharmacophore-based ligand profiling
- Case study: Five targets relevant in viral diseases
  - 10 pharmacophore models per target
- Investigation on 100 antiviral compounds
  - 20 compounds per target
- Target profile estimation by parallel screening

Ligand-directed Analysis

Ratio ≥ 1
90% of the compounds correctly predicted

Ratio < 1
8% more often predicted for one specific false target than for correct one

for 2% of the compounds no activity prediction possible



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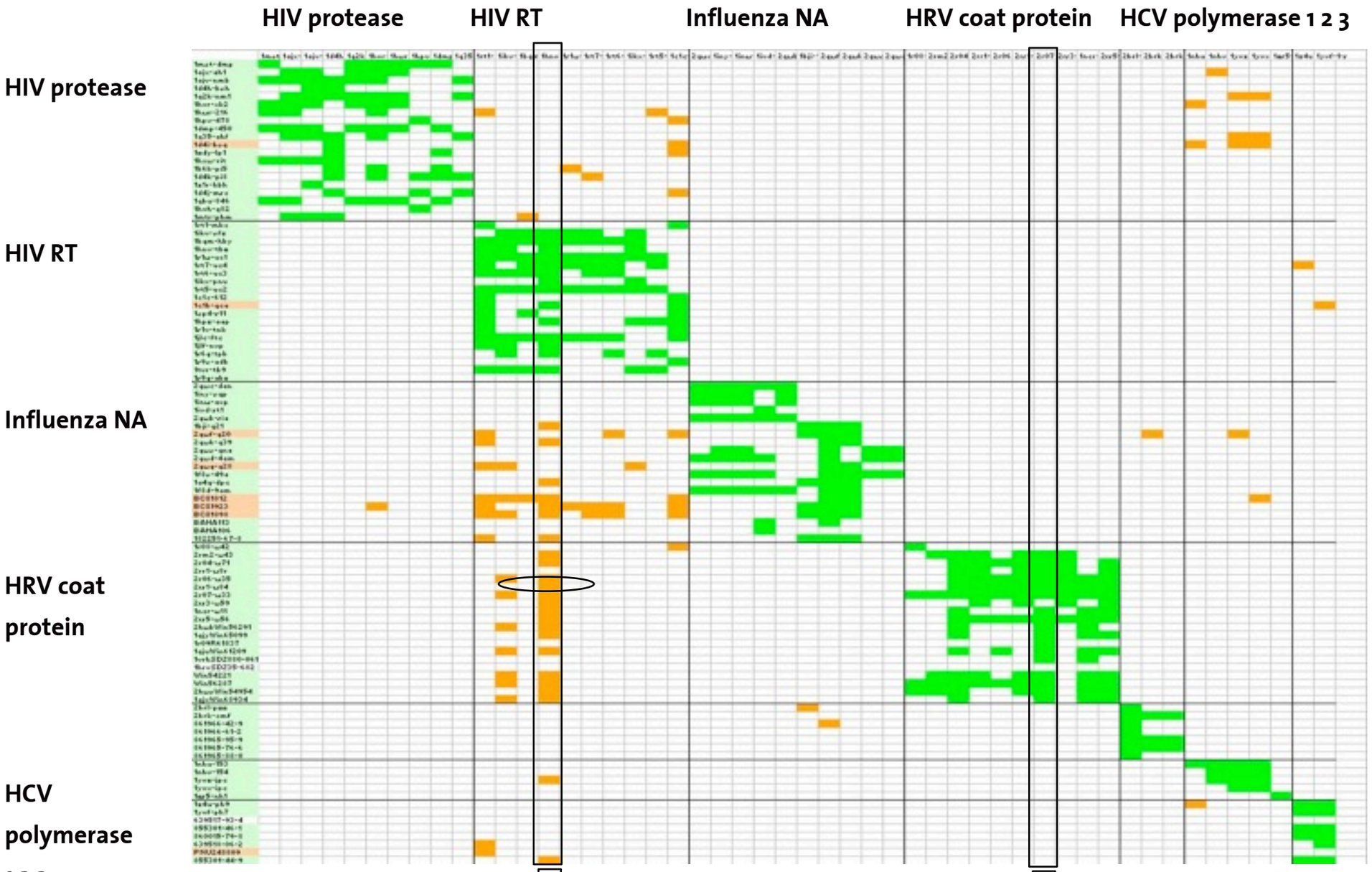
T. Steindl et al., J. Chem. Inf. Model., 46, 2146-2157 (2006)

Pharmacophore-directed Analysis



Model with low selectivity:
70% of actives (HIV RT), but 75% from one specific false target (HRV coat protein)
40% active and 60% inactive compounds in hit list

Model with high selectivity:
95% of actives (HRV coat protein),
0% inactive compounds in hit list

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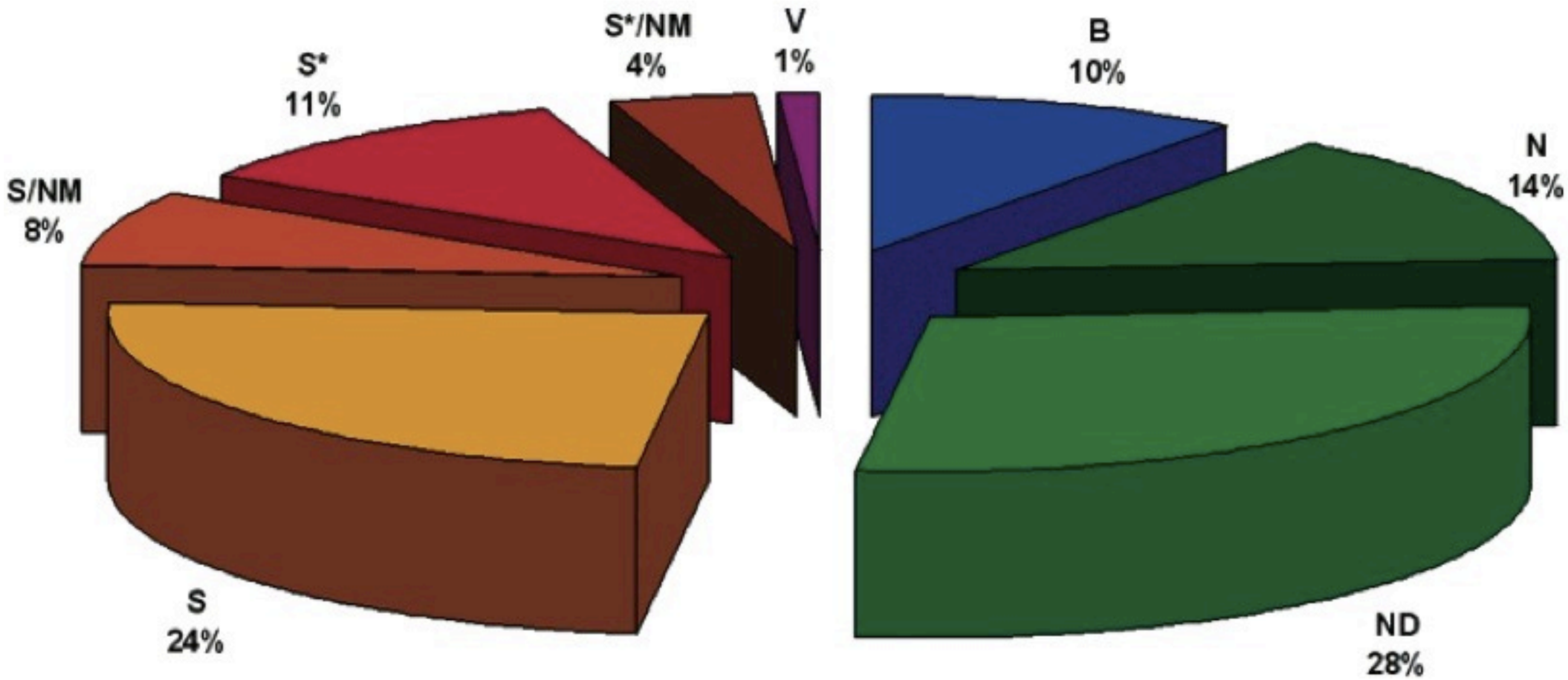
T. Steindl et al., J. Chem. Inf. Model., 46, 2146-2157 (2006)

Target Fishing With Natural Products



Small molecule new chemical entities organized by source/year (N =974).

David J. Newman, and Gordon M. Cragg, *J. Nat. Prod.*, 2007, **70**, 461-477

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Target Fishing With Natural Products

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Leoligin, the major lignan from Edelweiss, activates cholesteryl ester transfer protein

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ABSTRACT

Objective: Cholesteryl ester transfer protein (CETP) plays a central role in the metabolism of high-density lipoprotein particles. Therefore, we searched for new drugs that bind to CETP and modulate its activity.
Methods: A preliminary pharmacophore-based parallel screening approach indicated that leoligin, a major lignan of Edelweiss (*Leontopodium alpinum* Cass.), might bind to CETP. Therefore we incubated leoligin *ex vivo* at different concentrations with human ($n = 20$) and rabbit plasma ($n = 3$), and quantified the CETP activity by fluorimeter. Probucol served as positive control. Furthermore, we dosed CETP transgenic mice with leoligin and vehicle control by oral gavage for 7 days and measured subsequently the *in vivo* modulation of CETP activity ($n = 5$ for each treatment group).
Results: In vitro, leoligin significantly activated CETP in human plasma at 100 pM ($p = 0.023$) and 1 nM ($p = 0.042$), respectively, whereas leoligin concentrations of 1 mM inhibited CETP activity ($p = 0.012$). The observed CETP activation was not species specific, as it was similar in magnitude for rabbit CETP. *In vivo*, there was also a higher CETP activity after oral dosage of CETP transgenic mice with leoligin ($p = 0.015$). There was no short-term toxicity apparent in mice treated with leoligin.
Conclusion: CETP agonism by leoligin appears to be safe and effective, and may prove to be a useful modality to alter high-density lipoprotein metabolism.

K. Duwensee, et al.,
Atherosclerosis (2011) 219, 109-115

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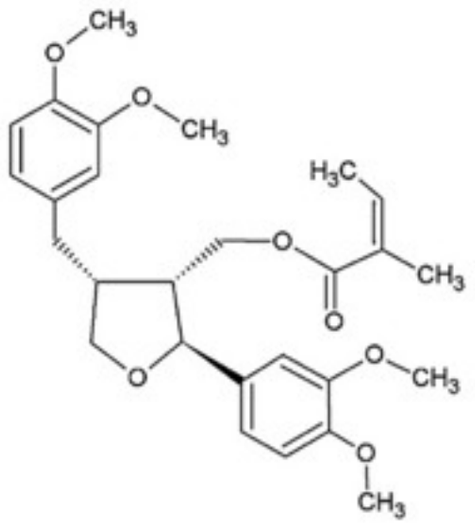
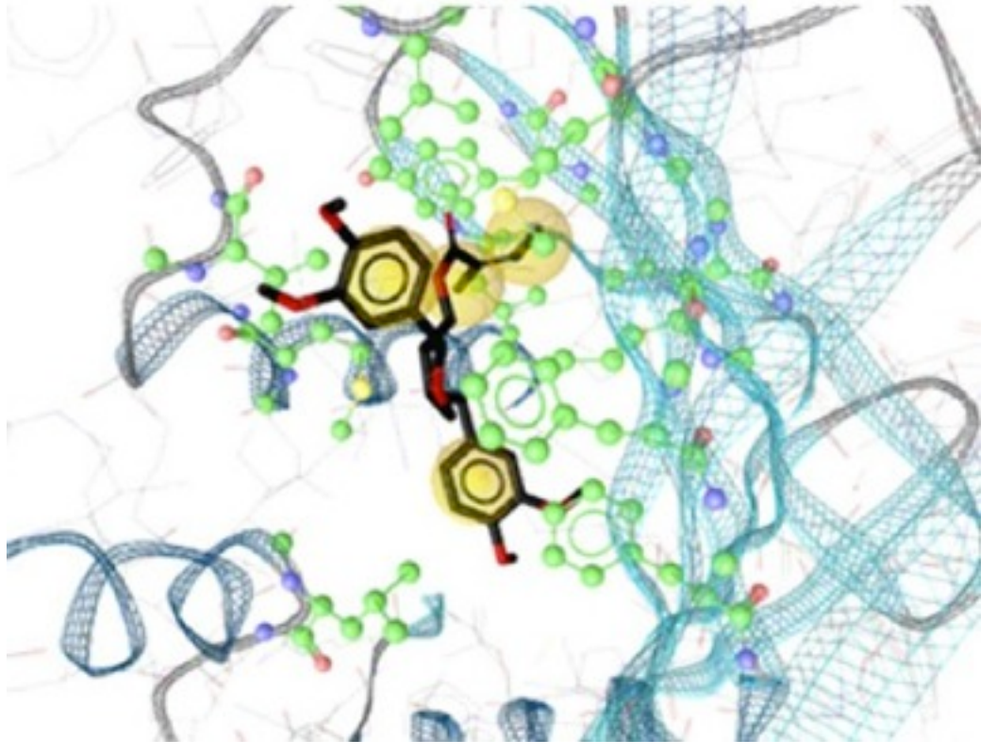
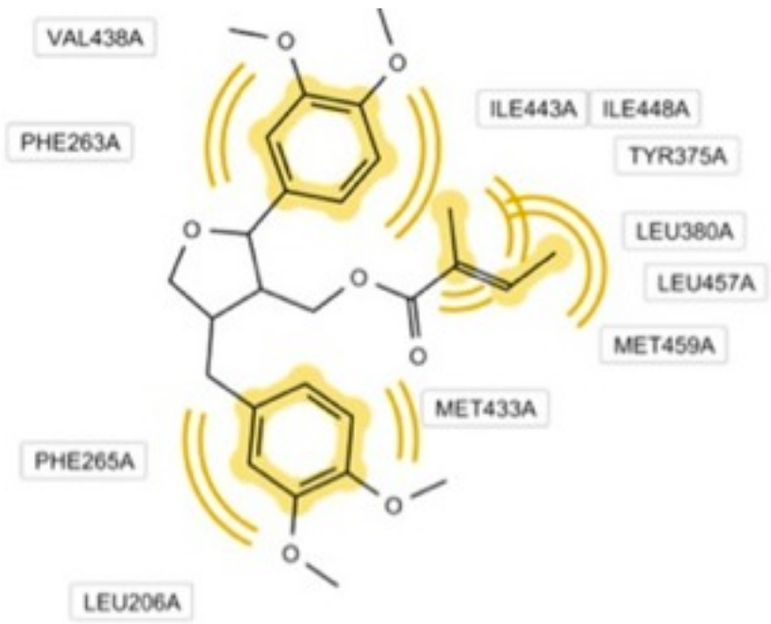
Pharmacophore Profiling of Leoligin





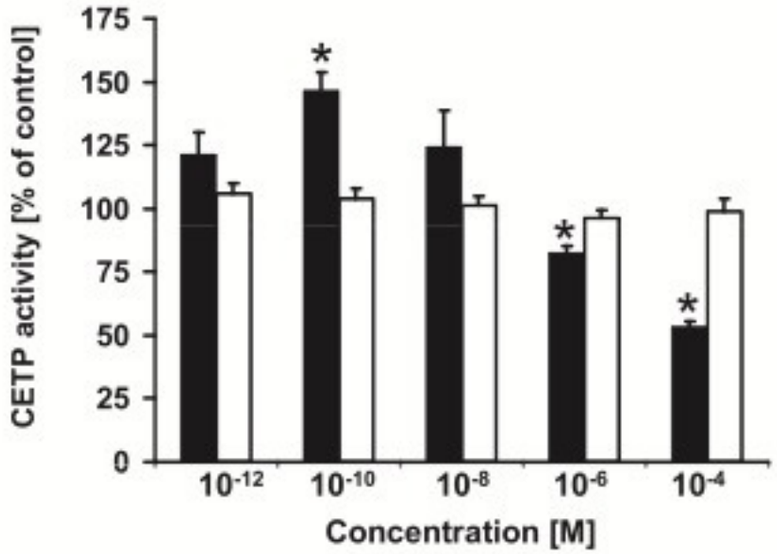


Leoligin matches the pharmacophore model encoding for the interaction site of cholesteryl ester transfer protein (CETP)

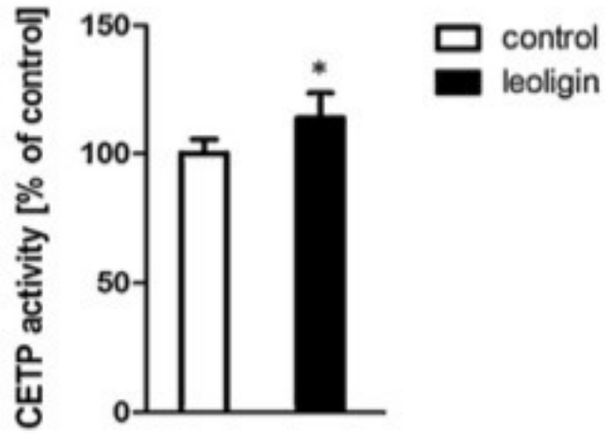
K. Duwensee, et al.,
Atherosclerosis (2011) 219, 109-115

T. Langer, Strasbourg, 2012-06-28

Biological Testing



Leoligin enhances the activity of human and rabbit CETP in vitro when applied in subnanomolar concentration (control Probucol)



Leoligin activates CETP in vivo (7 days test with CETP transgenic mice, leoligin dosed orally, 1 mg/kg)

K. Duwensee, et al.,
Atherosclerosis (2011) 219, 109-115

Summary ...

First published examples of applications of extensive parallel screening approach based on pharmacophores

- Multitude of pharmacophore models (up to several thousand ...)
- Large set of molecules (up to several million ...)

Results indicate

- Correct assignment of selectivity in most cases
- Independent of search algorithms used

Fast, scalable *in silico* activity profiling is now possible !

Recent Success Stories

Protein Protein Interfaces

Available online at www.sciencedirect.com
ScienceDirect
Current Opinion in Chemical Biology

ELSEVIER

Small molecular weight protein–protein interaction antagonists—an insurmountable challenge?

Alexander Dömling

Several years ago small molecular weight protein–protein interaction (PPI) antagonists were considered as the Mount Everest in drug discovery and generally regarded as too difficult to be targeted. However, recent industrial and academic research has produced a great number of new antagonists of diverse PPIs. This review structurally analyses small molecular weight PPI antagonists and their particular targets as well as tools to discover such compounds. Besides general discussions there will be a focus on the PPI p53/mdm2.

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However, more and more scientists recognize the eigenvalue of protein interaction antagonization. The growing importance of PPIs as oncology targets was underlined by many talks and posters at the recent AACR-EORTC meeting in San Francisco. Covered examples included p53/mdm2/mdm4, Bcl family interactions, IAPs, c-Myc, SPRY2-Cb, ERCC1/XPF, FAK–protein interactions, orphan nuclear receptor COUP-TFI, Smad4-SKI, c-Src-SH3, Smad2/3/4, Rb/Raf-1, SDF-1/CXCR4, tissue factor/FVIIa, HOX/PBX and tubulin. In the following the small molecule antagonists of the p53/mdm2 interaction are discussed, as an example of a successfully targeted PPI.

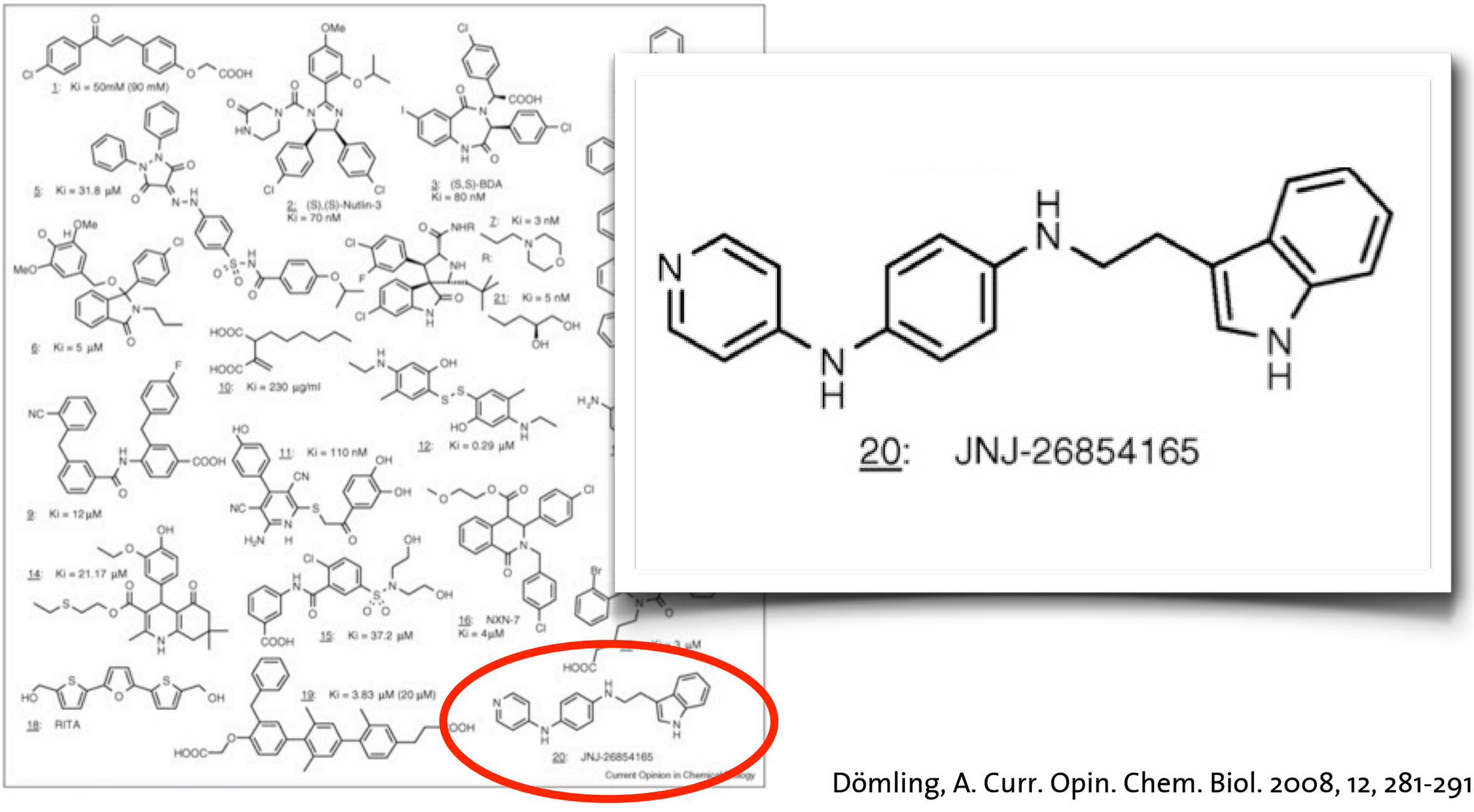
The p53/mdm2 case

Structure

T. Langer, Strasbourg, 2012-06-28

Dömling, A. Curr. Opin. Chem. Biol. 2008, 12, 281-291.

Described p53/mdm2 Inhibitors



Dömling, A. Curr. Opin. Chem. Biol. 2008, 12, 281-291.

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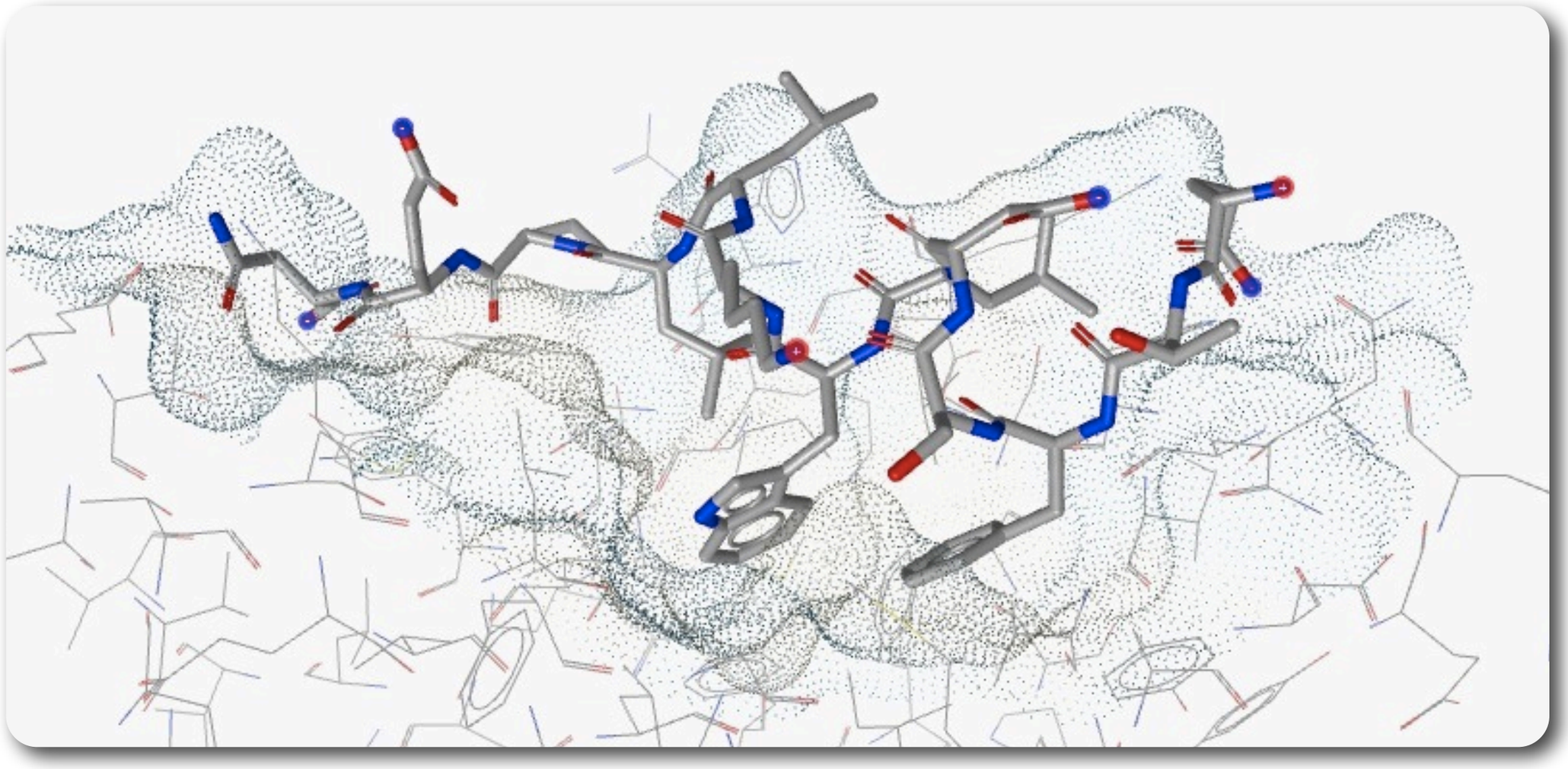
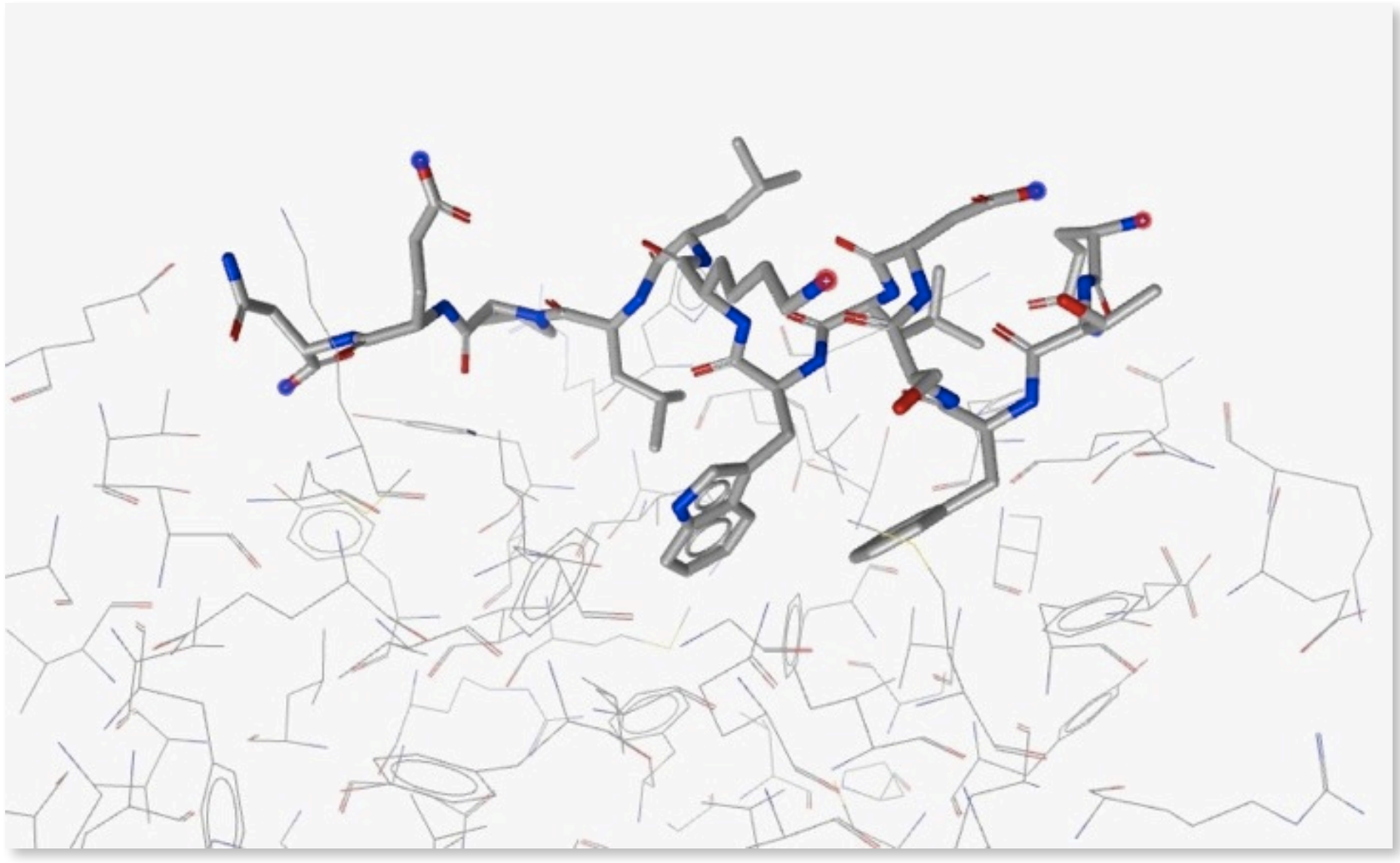
Structure-based Pharmacophore

- p53/mdm2 complex structure (PDB: 1YCR)



Comparison with JNJ-26854165



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Conclusions

- Smart medicinal chemistry, supported by cutting-edge chemoinformatics methods is a straight-forward and rapid method for the generation of promising new lead compounds
- Assessment of risks in later development stages becomes possible on a rational & transparent basis
- Translation into an academic research environment is feasible

Thank you for your attention

NEVER GIVE UP !!!

T. Langer, Strasbourg, 2012-06-28

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