3DEXPERIENCE®

Accelerate Science-Led Innovation for Competitive Advantage

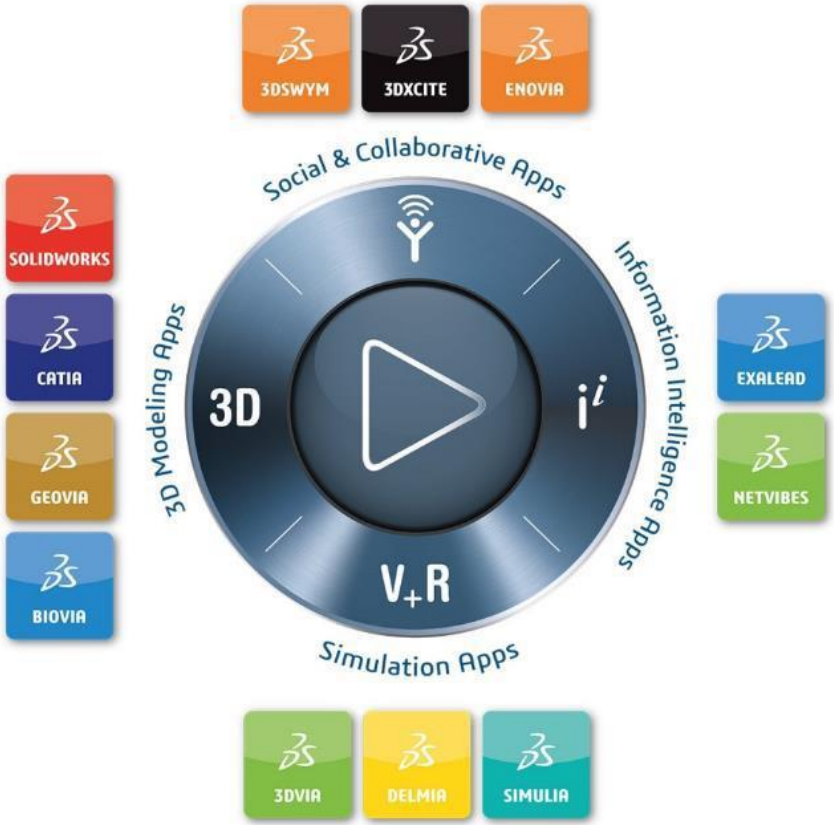
BIOVIA Discovery Studio

創源生技 分子視算中心

經理 陳冠文 (Gene)

創源生技 GGA

DASSAULT SYSTEMES | The 3DEXPERIENCE® Company



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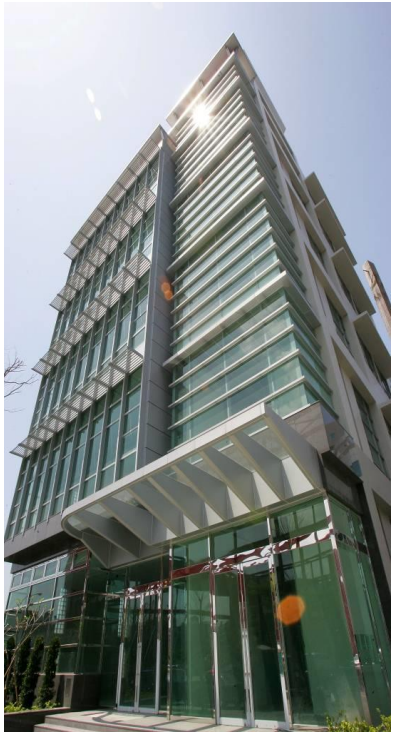


CEO: Christopher Tsai, Ph.D. 蔡政憲 博士

Established: Nov. 2008

Main Product & Service Areas:

1. Genetic Testing
2. Molecular Diagnosis
3. Scientific Informatics & Bio IT

IPO Date: September 17, 2012

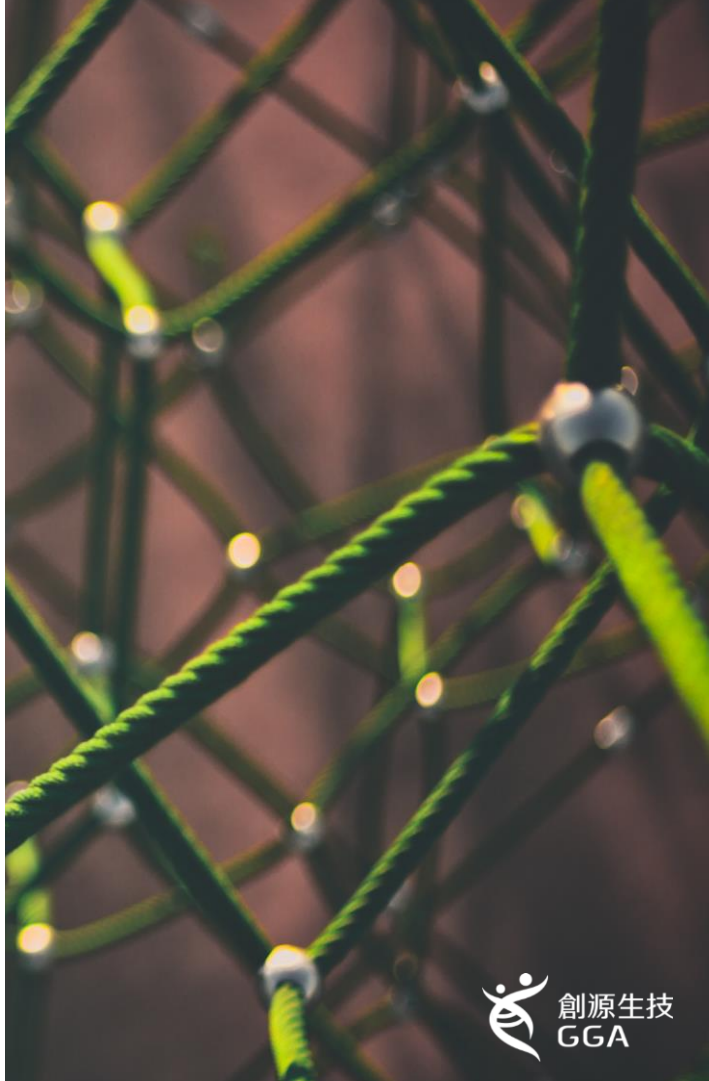
Stock Ticker: 4160 (Taiwan OTC)

代理品牌:

1. BIOVIA
2. ENOVIA
3. QIAGEN
4. EXTEDO
5. 其它

Our Vision

用科學的知識與技術，提昇台灣產業科技創新能量。



分子視算中心

Be Your Partner

我們是由物理、化工、生物、統計、資訊等超過十位不同領域的專家組成，具備多年產業經驗。

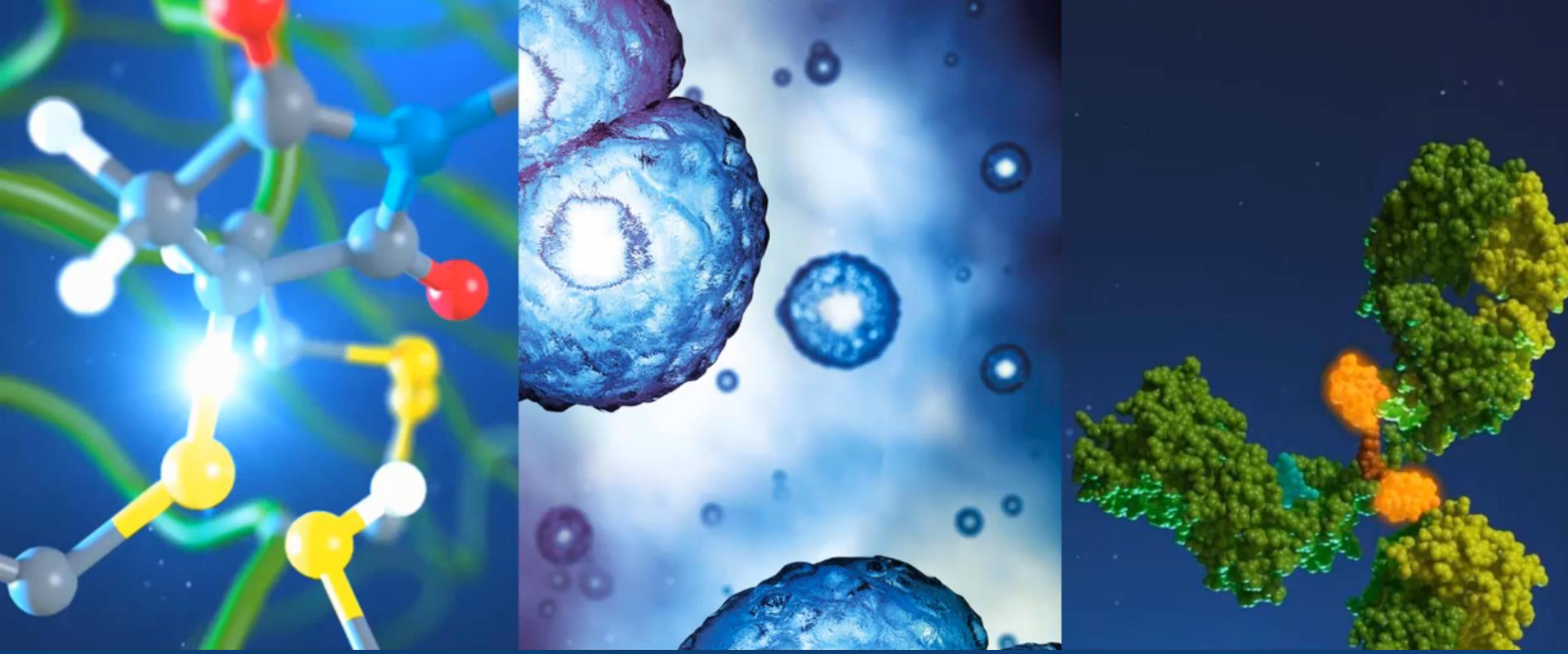
10+

我們服務全台灣超過四十所大專院校，每年舉辦超過100場以上教育訓練課程。

100+

我們擁有包含化學、材料、生物領域，超過百萬筆資料數據，並有實際處理分析案例。

1M+



Discovery Studio

Small Molecule and Biologics Lead Identification & Optimization

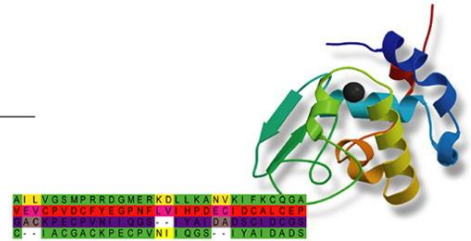
Best Validated Science – 30+ Years History

NAMD Scalable Molecular Dynamics

- Force-field simulations: CHARMm
- Force-field simulations: NAMD
- Protein homology modeling: MODELLER
- Protein-protein docking: ZDOCK
- Protein aggregation & viscosity: AggMap, SCM
- Pharmacophore: Catalyst
- And Many more novel, internally developed, peer reviewed scientific algorithms

Modeller

Program for Comparative Protein Structure Modelling by Satisfaction of Spatial Restraints



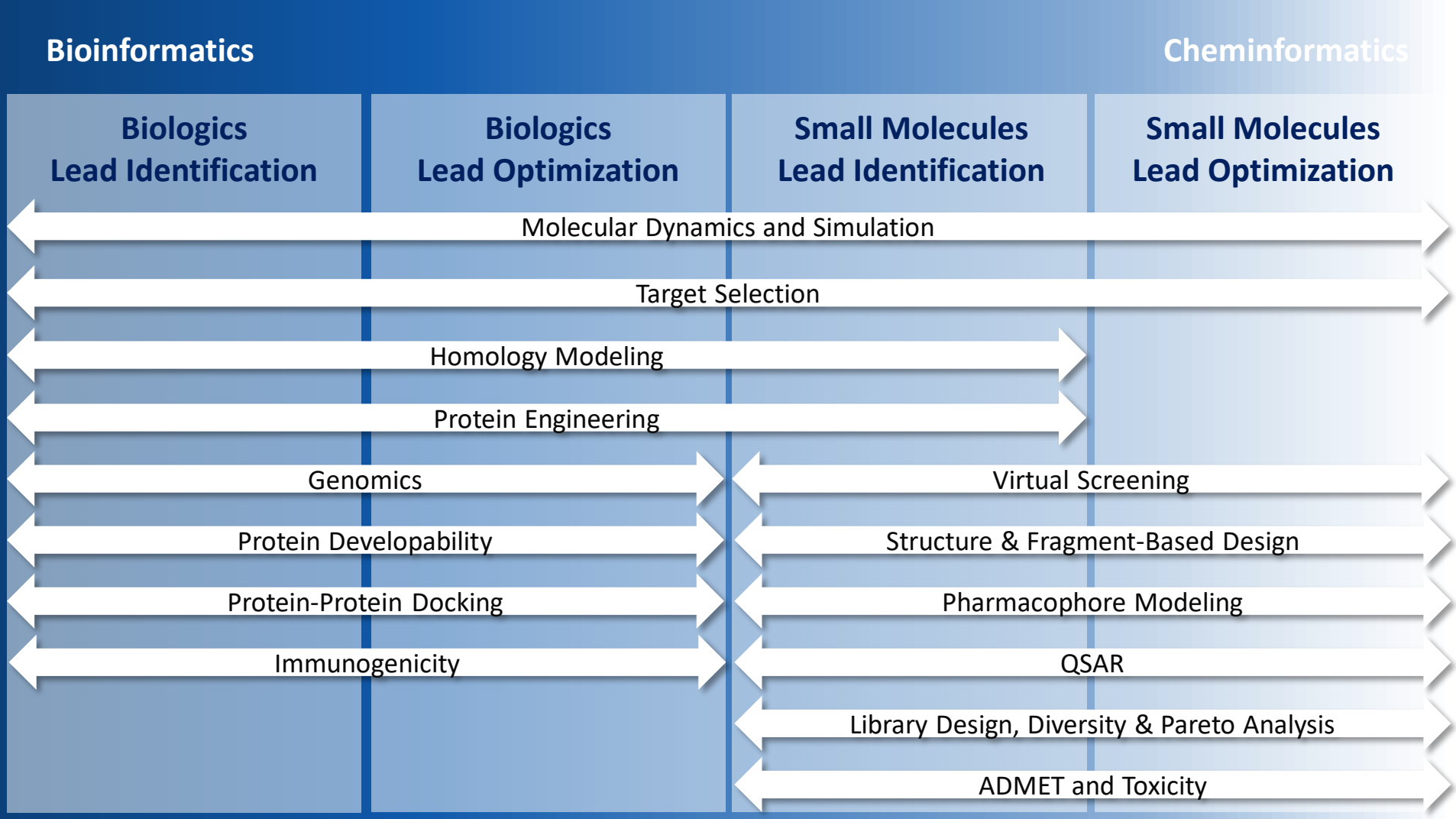
UCSF University of California n Francisco

Massachusetts Institute of Technology

accelrys®

UMASS MEDICAL SCHOOL

VE RI TAS HARVARD


Bioinformatics
Cheminformatics
Biologics
Lead Identification
Biologics
Lead Optimization
Small Molecules
Lead Identification
Small Molecules
Lead Optimization
Molecular Dynamics and Simulation
Target Selection
Homology Modeling
Protein Engineering
Genomics
Protein Developability
Protein-Protein Docking
Immunogenicity
Virtual Screening
Structure & Fragment-Based Design
Pharmacophore Modeling
QSAR
Library Design, Diversity & Pareto Analysis
ADMET and Toxicity

Bioinformatics

Cheminformatics

Biologics Lead Identification

- Antibody Modeling Cascade
- Full-length antibody automation
- Antibody framework automation
- Bispecific antibody modeling
- Antibody humanization
- Canonical loop types
- Enhanced CDR de novo loop modeling
- Protein Aggregation
- Developability Indices
- Disulfide bond predictor
- Post translational modification sequence motif annotations
- Biophysical property calculators
- Protein property predictions
- Protein stability analysis using residue scanning
- Binding affinity analysis using residue scanning

Biologics Lead Optimization

Small Molecules Lead Identification

- Small Molecules affinity modeling
  - Rank ligand binding using MM-GBSA
  - Accurately predict relative ligand binding energy (FEP)
- Fragment-based design (FBDD) toolkit
  - Grow: Enumerate in sity
  - Replace: Scaffold-hop in sity
- New Pharmacophore tools:
  - Receptor-ligand complexes
  - Ligand-based
- Enhanced Pharmacophore Validation
- Ligand profiling database
- Find Activity Cliffs using MMPs
- Activity cliffs visualizations
- New library design tools for novel ligand generation
- Receptor pocket surface visualizations
- 2D ligand interaction diagram
- Refactored non-bond interaction monitors
  - Favorable, Unfavorable and Unsatisfied
- Non-bond MD trajectory heat map

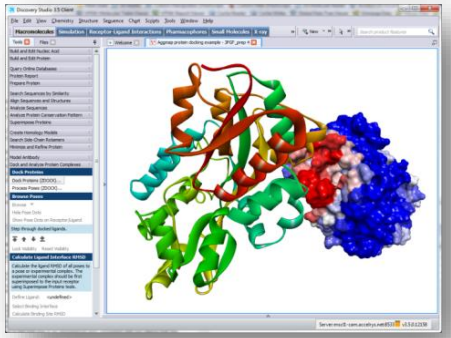
Small Molecules Lead Optimization

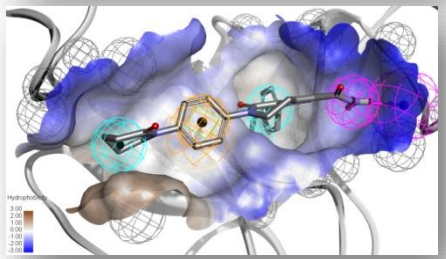
Bioinformatics **Cheminformatics**

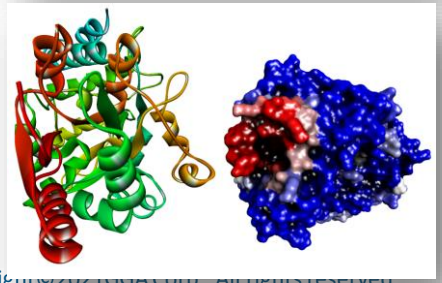
Biologics Lead Identification	Biologics Lead Optimization	Small Molecules Lead Identification	Small Molecules Lead Optimization
• Faster robust MD simulations • Enhanced MD analysis tools • Improved simulations workflow • Faster & more robust explicit solvation builder • Steered Molecular Dynamics (SMD) • Ligand conformer generation improved by order of magnitude • C36FF and CGenFF Forcefield typing		• Improved scaling performance in DMol3 • Topkat models published as OECD QMRFs • 3D printing of molecular models • Storyboard • WebGL 3D visualizer • Anaglyph Stereo • 64-bit Windows Client • Enhanced memory management	

What is Discovery Studio?

- 3D *in silico* modeling and simulation environment
  - Almost 30 years of peer-review validated science
  - Built on the industry standard BIOVIA Foundation (formerly **Accelrys Enterprise Platform**)
- Used in the design of therapeutic drug molecules
  - Small molecule drug design
  - Macromolecule drug design
  - Specialist biologics solutions since 2010

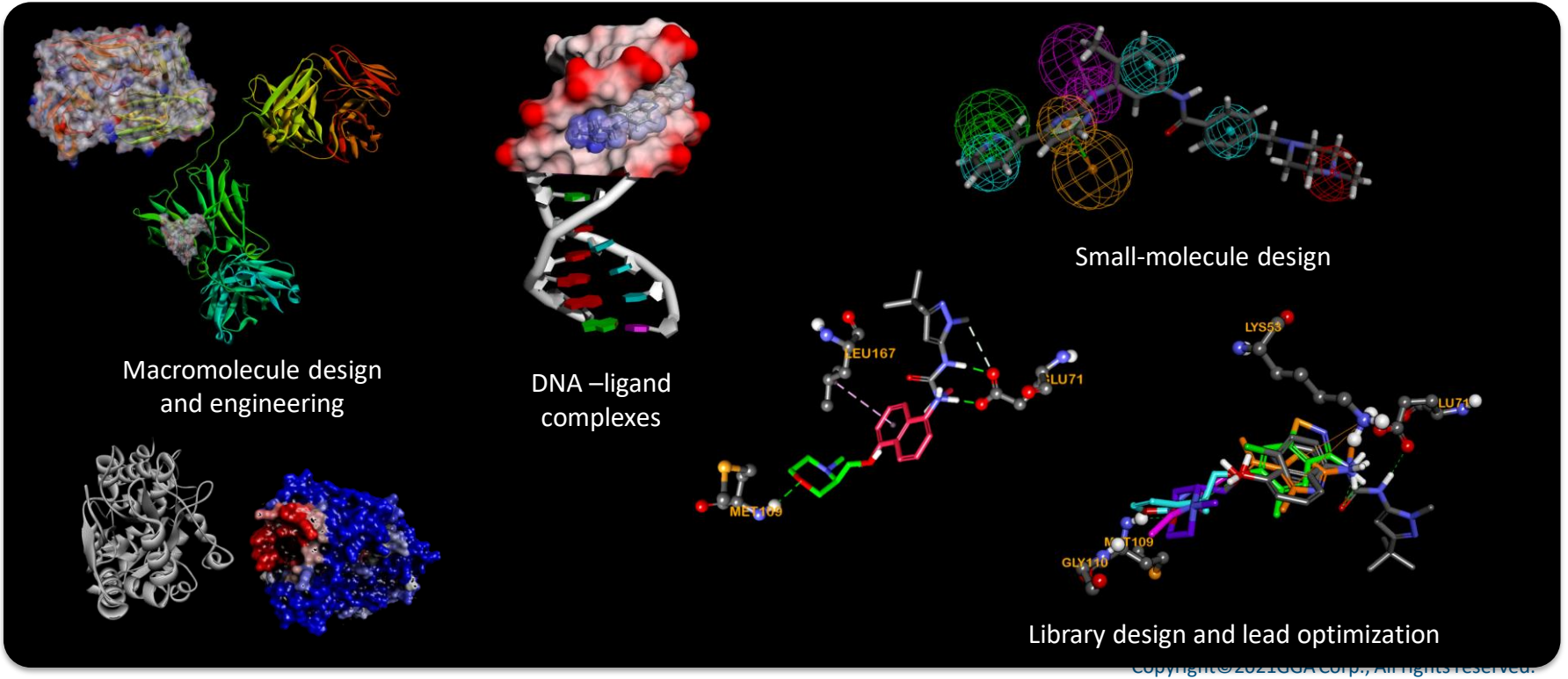




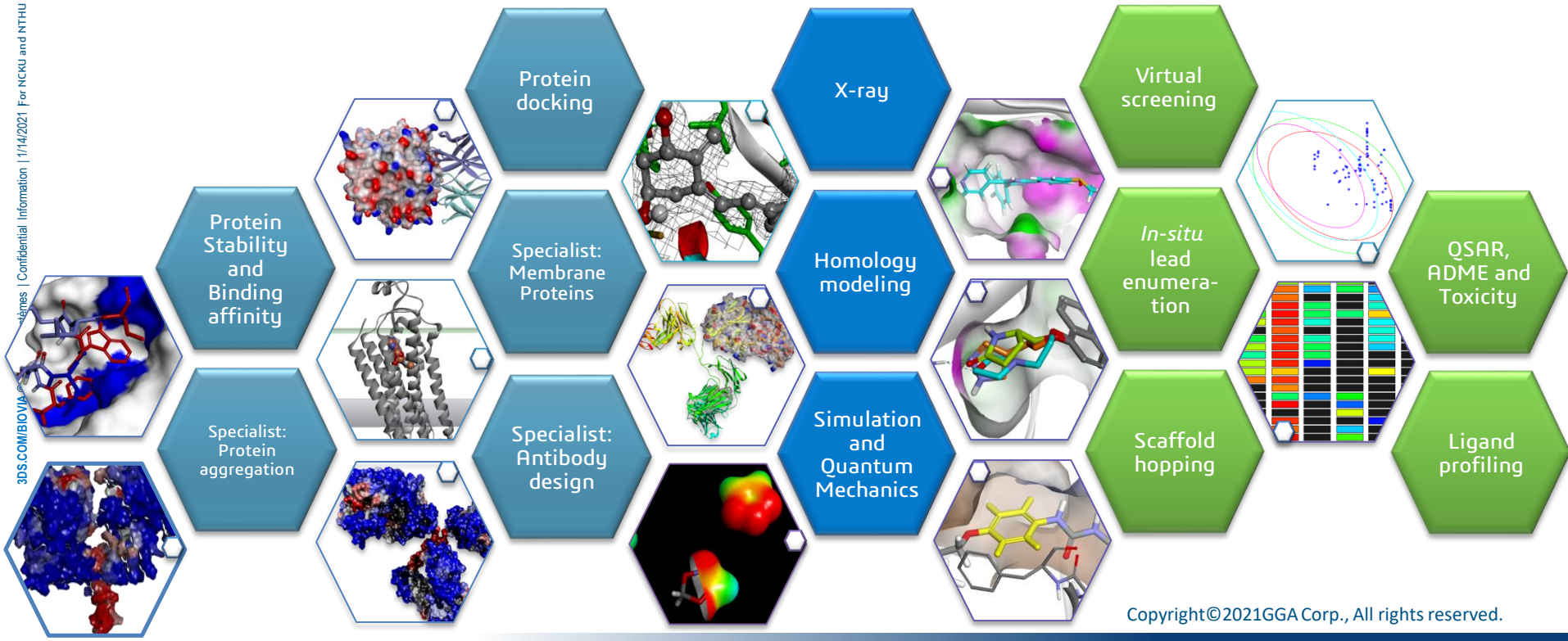


Discovery Studio

- It is an interactive 3D modeling environment



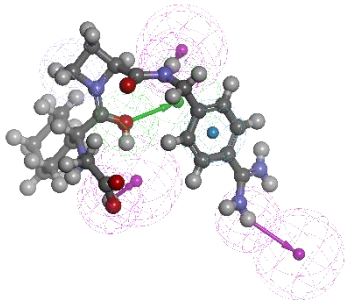
Discovery Studio: A Comprehensive Portfolio



Discovery Studio 2021 – Delivering Science

Pharmacophore

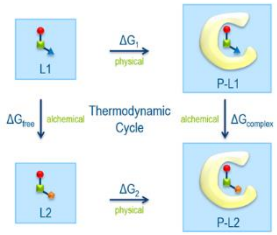
Pharmacophore features (Non-bond)

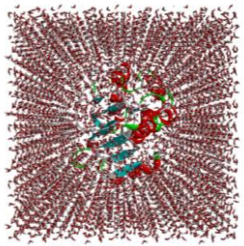


新增12種非鍵結之藥效基團特徵

Drug Design

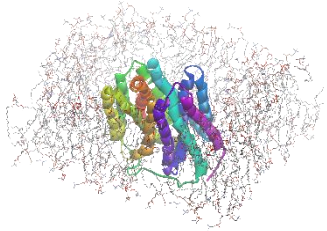
CHARMm Relative FEP Calculations



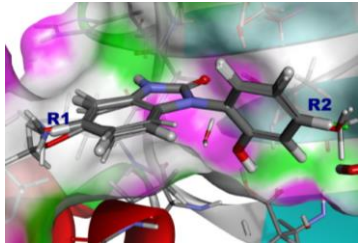


Simulation

Improve Solvate with Explicit Membrane and Dynamics

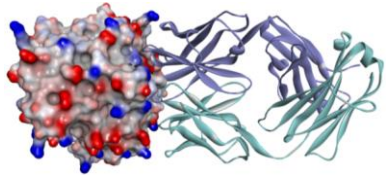


MSLD Bias Optimization and Production

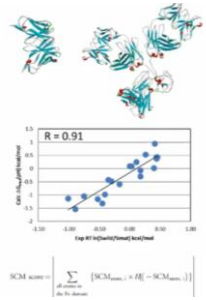


Protein Modeling

Improve Dock Proteins(ZDOCK)

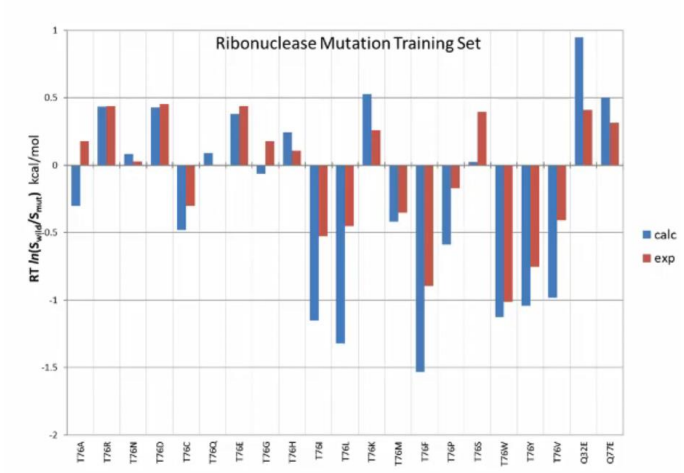


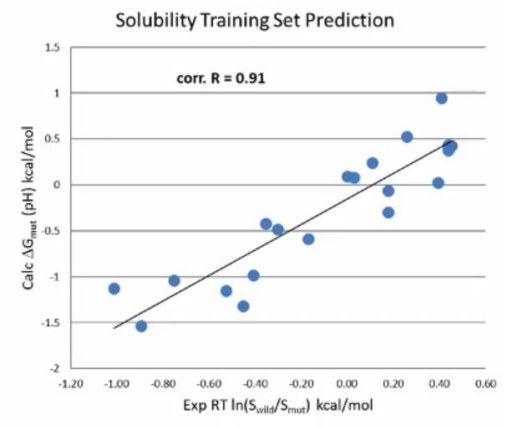
Protein Formulatioon Propeties



Biotherapeutics Formulation: Protein Solubility

- Structure-based protein solubility prediction algorithm, developed with globular protein experimental data and tested with antibody solubility data
  - Solubility score includes hydrophobic surface patches properties and electrostatic interactions (molecular charge and dipole moment)
  - New protocol predicts the protein solubility (and other properties) of biotherapeutics for lead identification and optimization





Solubility data from j Mol Bio. 2007, 366, 449-460

Biotherapeutics Formulation: Antibody Viscosity

- Traditionally, monoclonal antibodies (mAbs) are formulated at low concentrations (e.g.,20g/L) for intravenous administration in hospitals
- Recently, high-concentration and low-volume (<1.5mL) formulations have been developed (e.g., 150 mg/mL) for sub-cutaneous self-administrered delivery to improve patient compliance, ease of administration and to save on treatment costs
- High concentration antibody solutions can become highly viscous, leading to challenges in manufacturing, storage and administration
- In-licensed MIT spatial charge map (SCM) algorism for viscosity prediction
  - Extensively validated at 3 different pharma (MedImmune, Novatis, Pfizer)

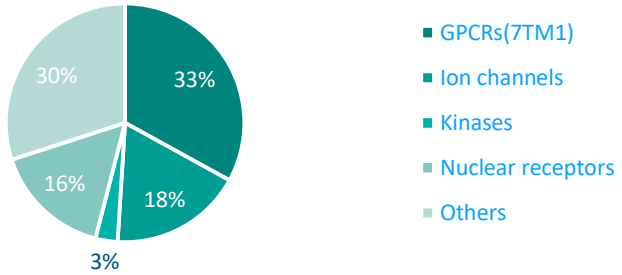
Formulation Properties Calculated at pH 6.0

Index	Details	Structures	Net Charge	pI (Isoelectric Point)	pH of Maximum Stability	Dipole Moment (Debye)	Solubility Score	Developability Index (All)	Developability Index (Fv)	Viscosity Score
1	mab1	mab1	1.26	7.52	4	301.5	0.87	56.37	56.37	649.2
2	mab2	mab2	1.74	7.59	4	243.04	-1.6	65.17	65.17	551.96
3	mab3	mab3	2.11	7.16	4	228.85	-0.43	64.86	64.86	743.87
4	mab4	mab4	-0.75	5.56	4	290.7	2.28	51.36	51.36	744.52
5	mab5	mab5	1.86	7.17	7.8	166.54	2.52	53.14	53.14	594.08
6	mab6	mab6	-0.62	5.57	3.8	344.46	-1.94	65.61	65.61	760.47
7	mab7	mab7	1.43	7.65	4	337.28	1.91	53.62	53.62	660.81
8	mab8	mab8	-1.01	5.46	3.8	245.21	0.3	57.48	57.48	753.38
9	mab9	mab9	-1.45	5.3	3.8	99.41	1.72	53.71	53.71	708.16

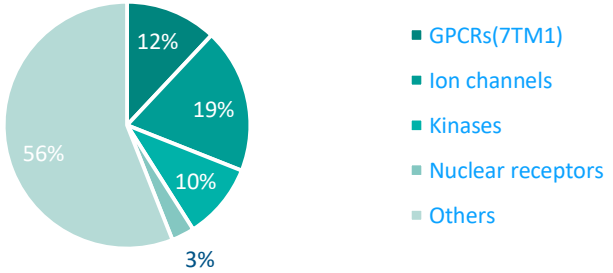
Explicit Membrane-Based MD Simulations

- Membrane proteins account for approximately 1/3 of the human proteome and account for ~60% of pharmaceutical targets+
- These membrane proteins include a large number of signaling receptors, transporters, ion channels and enzymes that are vital to cellular regulation, metabolism and homeostasis, and are high-priority, pharmaceutically relevant research
- CHARMm has the best and most consistent set of lipid parameters, including sterols, unusual bacterial, mitochondrial, and endosomal lipids, and a consistent set of protein parameters, to model complex membranes and protein membrane interactions+

Proportion of human protein drug targets in major families



Proportion of small-molecule drugs that target major families



Nat Rev Drug Discov. 2006, *5*, 993-6
Chem Rev. 2019, *119*, 6184-6226

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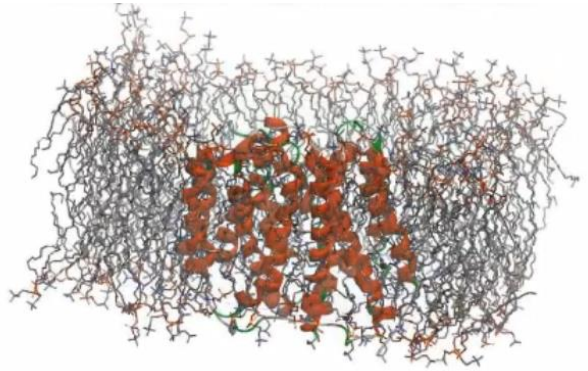

Nat Rev Drug Discov. 2006, *5*, 993-6
Chem Rev. 2019, *119*, 6184-6226

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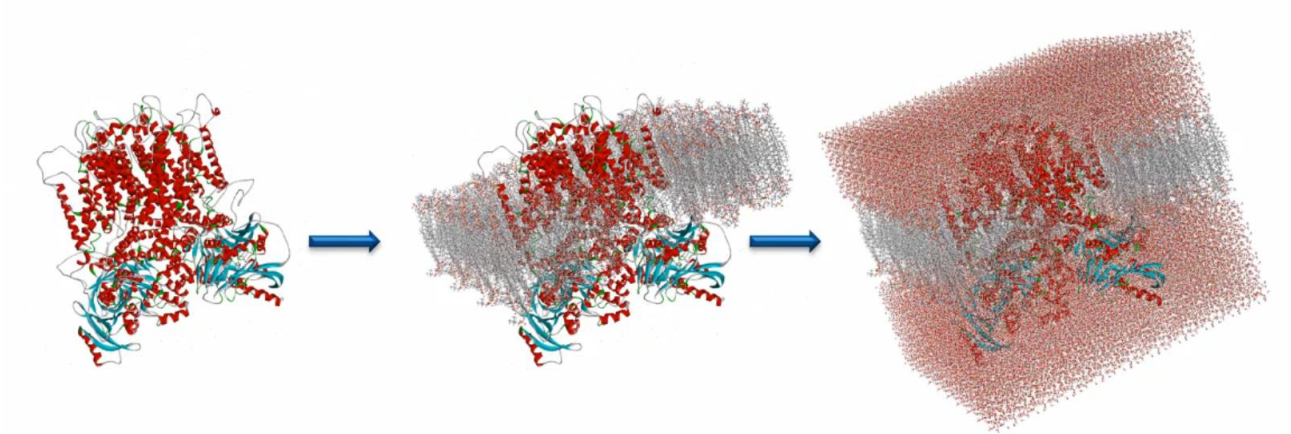
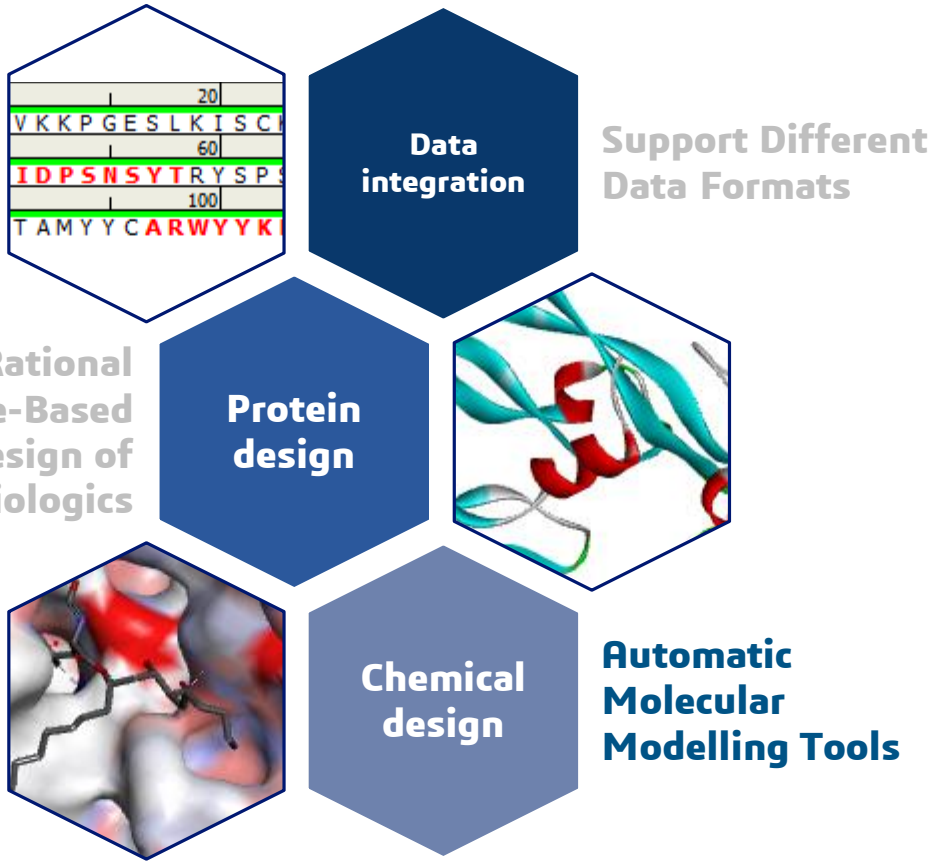
Explicit Membrane-Based MD Simulations

- New protocol adds an explicit bilayer of lipids, water and counterions to a transmembrane protein and allows the option to equilibrate the system, prior to further simulation
- Supports a number of prepared equilibrated homologenous membranes, as well as complex custom membranes (e.g. http://www,charm-gui.org)
  - POPC, POPE, DPPC, DMPC, and DLPC





Chemical design tool includes:

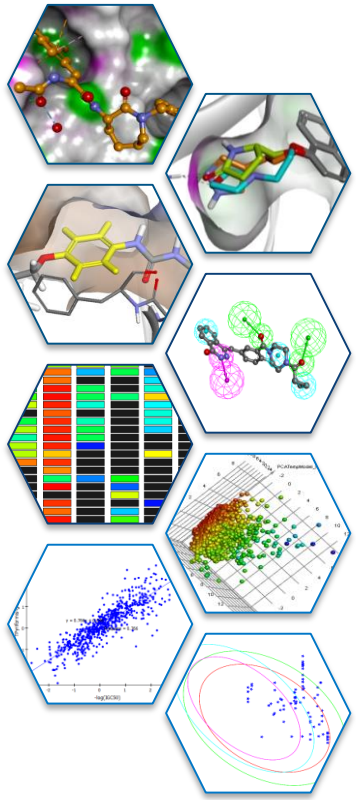
1. Structure-based design tools
2. Ligand-based design tools
3. Fragment-based design tools
4. Library design tools
5. ADMET and Toxicity prediction tools

Benefit

1. Explore the drug mechanism
2. Reduce the cost and failure rate
3. Target fishing
4. Lead optimization

Science and Functionality Highlights

- Structure-based design
  - Docking
  - Fragment-based design
  - Scoring/Prioritisation
  - Refinement/ Filtering/Analysis
- Pharmacophore modelling
  - Ligand-based
  - Structure-based
  - Ligand Profiling
- Library Design and Analysis
- ADMET and Toxicology
- Structure Activity Relationships



Rationale Small Drug Design

Scales

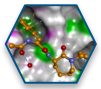
10^3~10^7 Molecules from Library

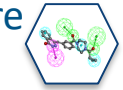
10^0~10^2 Molecules As Leads

10^2~10^3 Molecules as Novel Derivatives

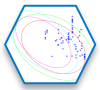
10^0~10^2 Molecules Pass ADMET and Toxicity Screening

Library Design and Analysis 

Structure-based design 

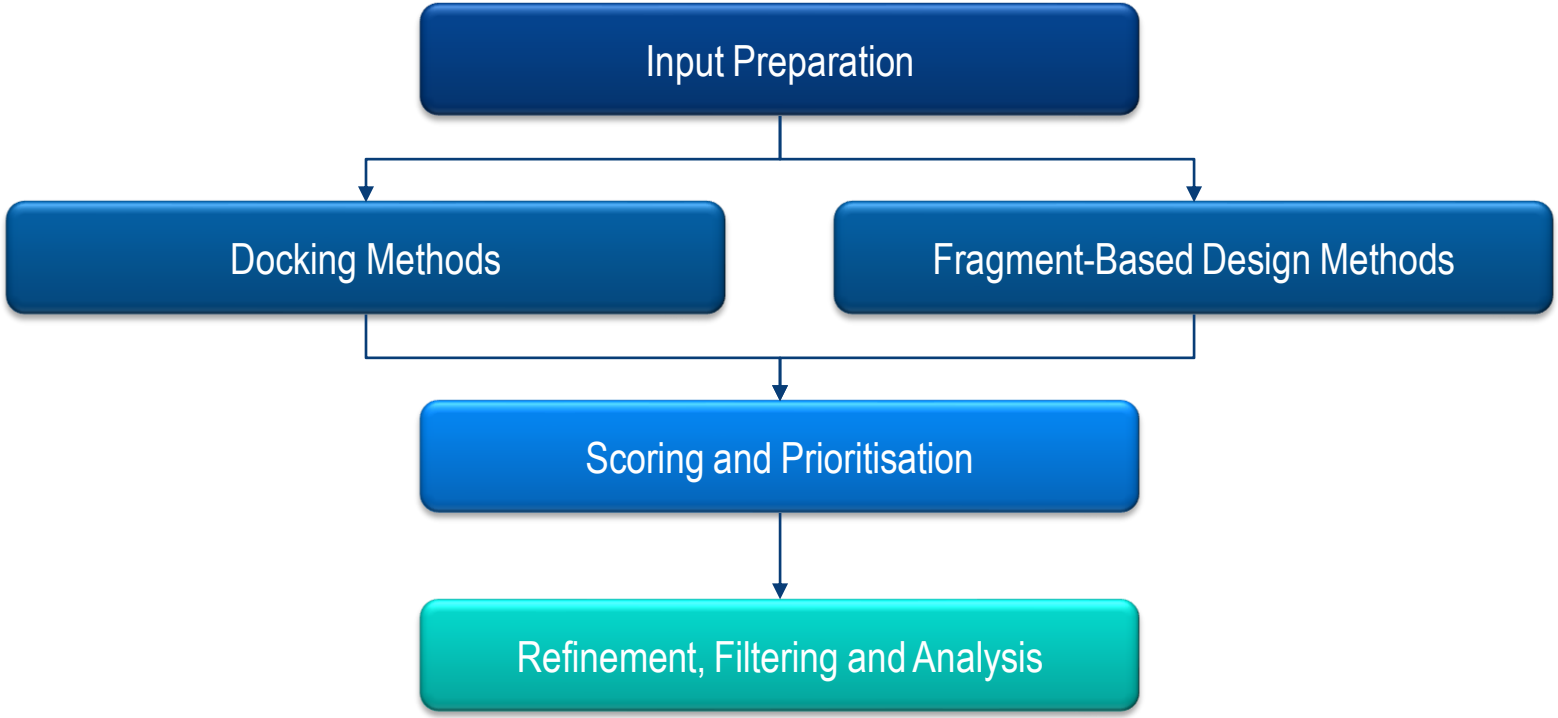
Pharmacophore modeling 

Fragment-based design 

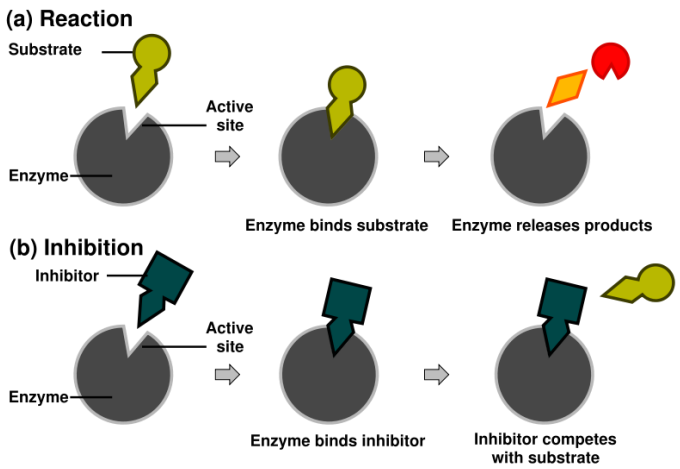
ADMET and Toxicity Analysis 

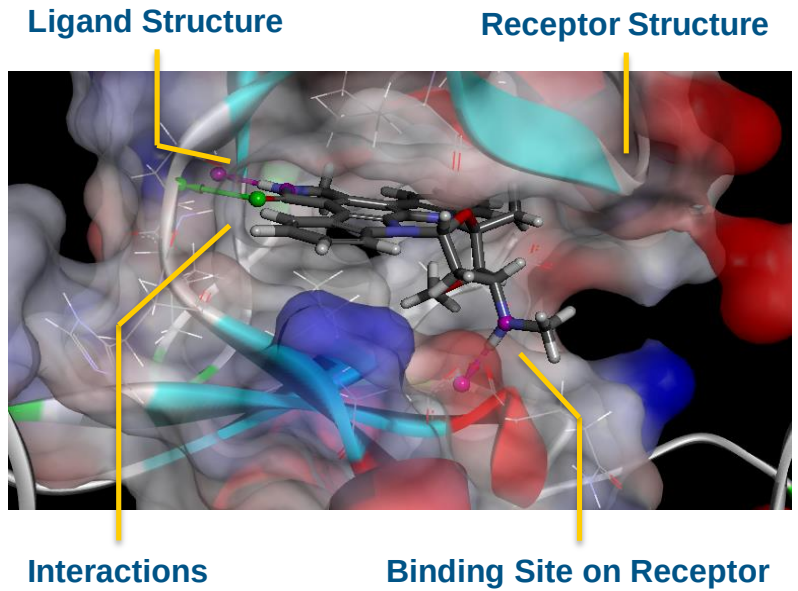
What if the hit has multiple targets? (Side effects)

Structure-Based Design: Overview



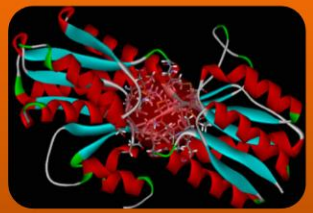
Docking & Scoring – Structure-Based Design





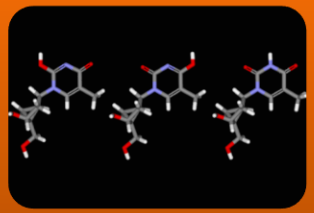
SBD: Input Preparation

Proteins



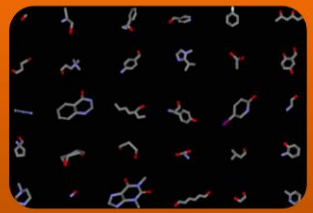
- Standardise atom names
- Insert missing atoms in residues
- Remove alternate conformations
- Insert missing loops
- Optimize short & medium size loops
- Calculate pK and protonate

Ligands



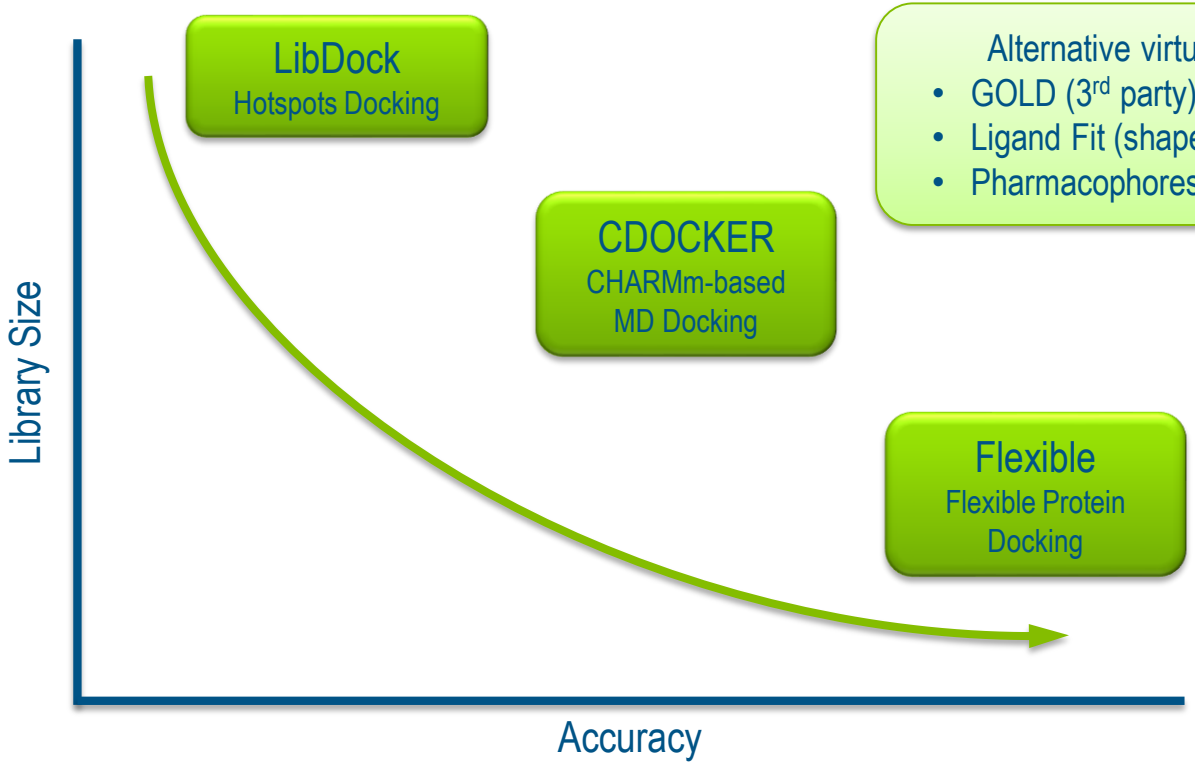
- Add hydrogens
- Calculate 3D coordinates
- Enumerate ionization states
- Ionize functional groups
- Generate tautomers and isomers
- Remove duplicates
- Fix bad valencies
- Standardize charges for common groups
- Retain largest fragment

Fragments



- Generate fragments using RECAP* rules
- Rule of Three filters

SBD: Docking and Virtual Screening



Alternative virtual screening methods available

- GOLD (3rd party)
- Ligand Fit (shape-based)
- Pharmacophores: Structure Based & Receptor-Ligand

SBD: Fragment-Based Design Methods

Probing the Binding Site

Adding Fragments

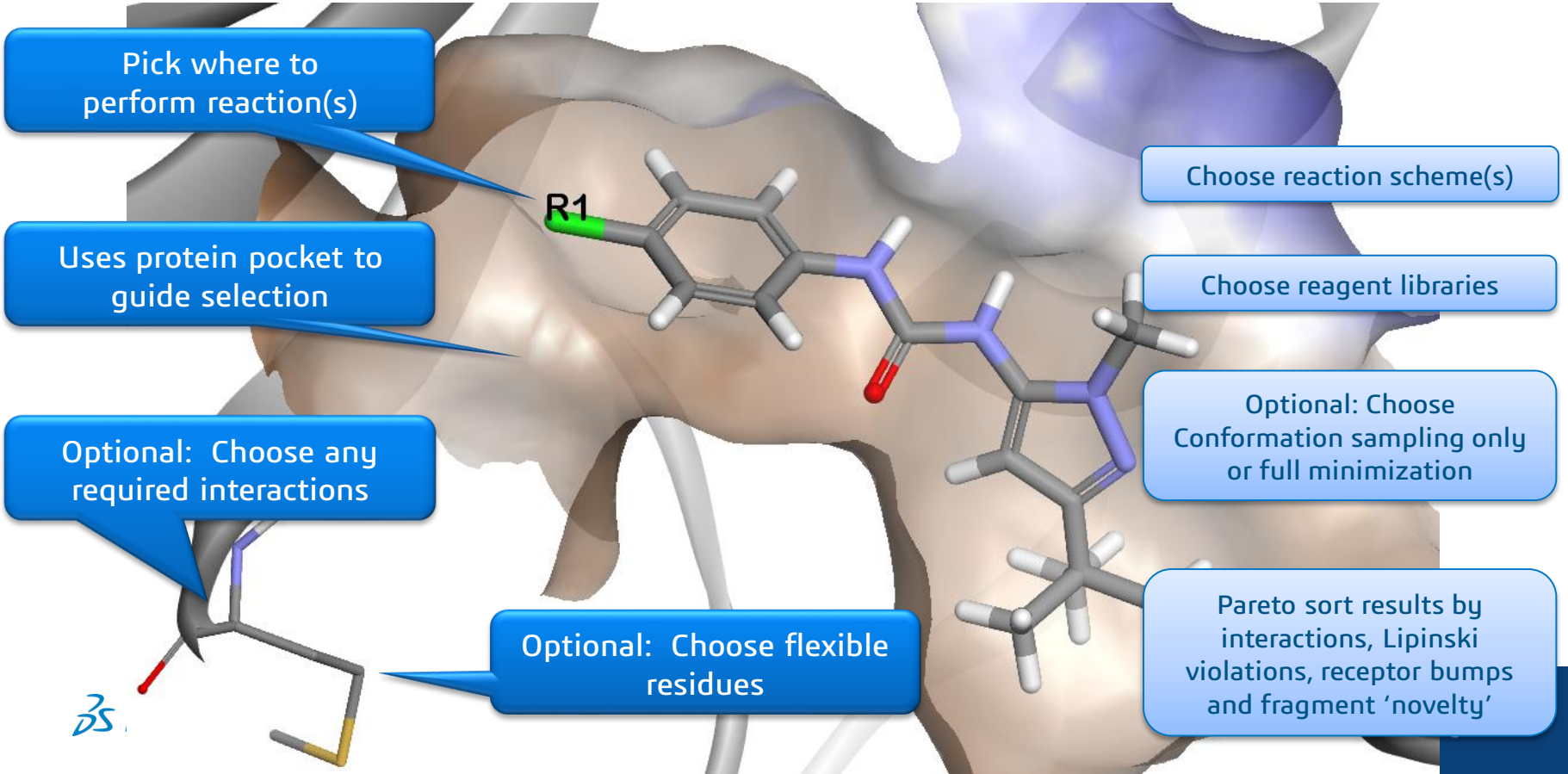
Modifying Scaffolds

Alternative fragment-based methods available
- Fragment Based Pharmacophores

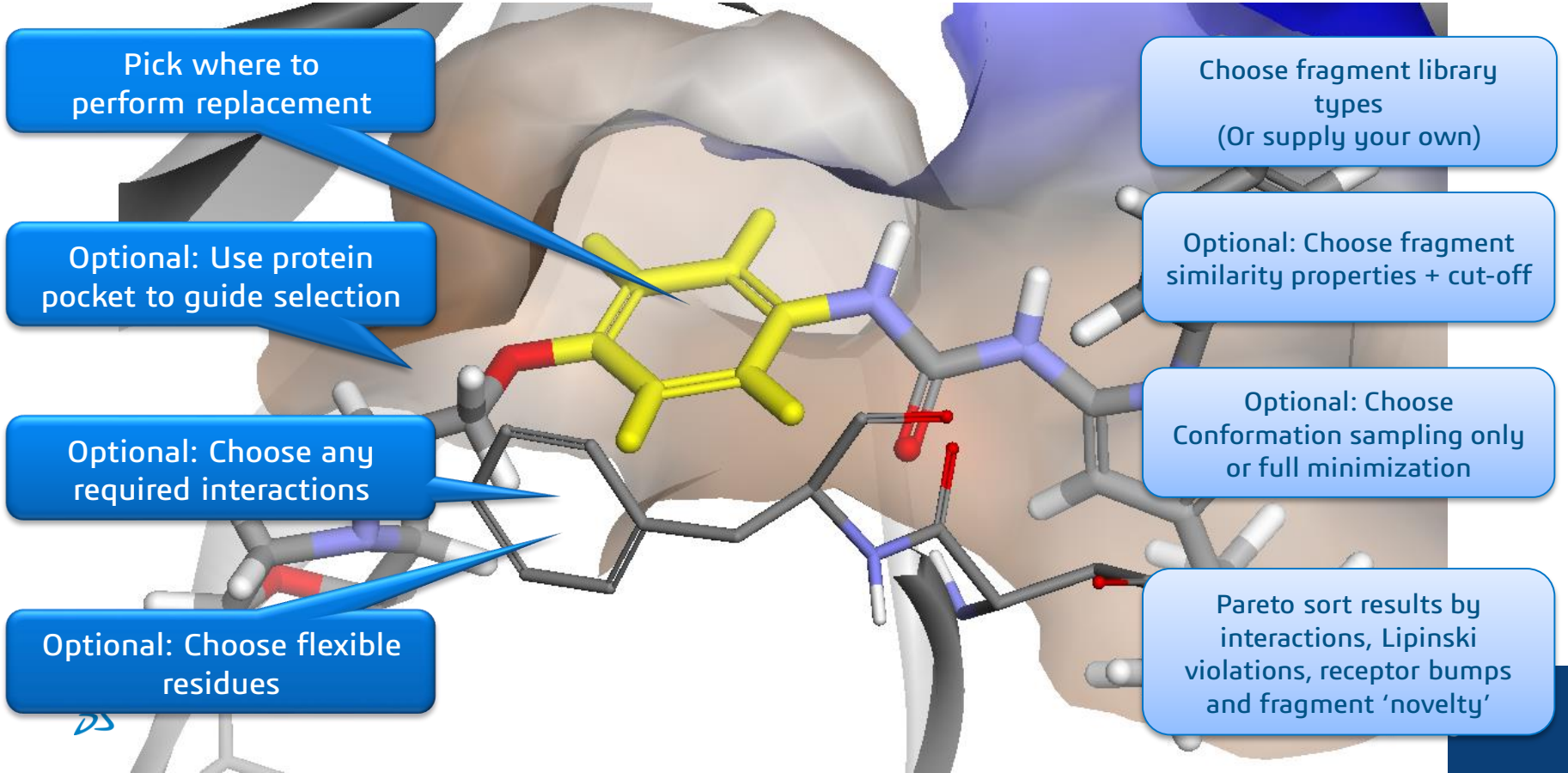
SBD: Fragment-Based Design Methods

- GROW
  - Reaction-based in situ ligand enumeration
  - E.g., Amide synthesis, Esterification, Hiyama, Kuyama, Negishi, Stille, Suzuki, Williamson Ether
  - Pre-filtered sets of reagents selected from ACD
- REPLACE
  - Fragment based in situ isostere replacement
  - E.g., scaffold-hopping, R-group replacement
  - Pre-filtered set of 1.5M fragments generated from SCD

GROW: Reaction-based *in-situ* Ligand Optimization

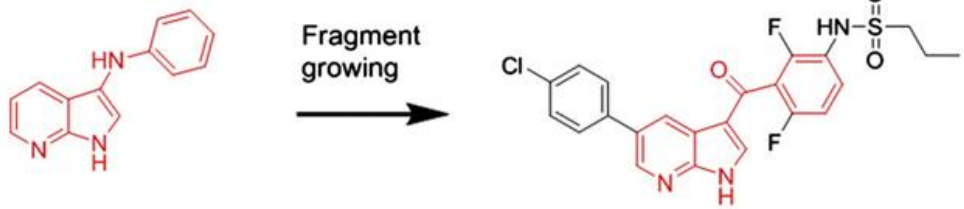


REPLACE: Fragment Based *In-Situ* Substitution



Fragment-based design of the BRAF inhibitor vemurafenib.

First fragment-based drug (Zelboraf) approved in 2011!



4

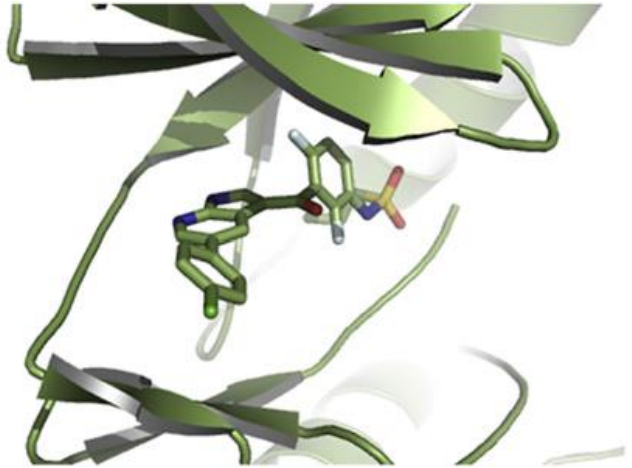
Unselective, weakly potent fragment hit (IC_{50} > 100μM)

PIM-1 IC_{50} ~ 100μM

5 (Vemurafenib)

BRAF (V600E) IC_{50} = 31nM
High degree of selectivity against other kinases

PIM-1 IC_{50} > 100μM



Swen Hoelder, Paul A. Clarke, Paul Workman, 2012

SBD: Scoring and Prioritisation

Literature Scoring Functions
LigScore 1 & 2
PLP 1 & 2
PMF & PMF04
Jain
Ludi 1, 2 , & 3

Docking Functions
LibDockScore
CDOCKER Energy
CDOCKER Interaction Energy

Energy-Based Functions
Binding Energies (MM-PBSA & MM-GBSA)
Interaction Energies (CHARMm and QM/MM)

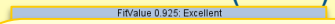
Additional Functions
Ligand Efficiency
Pharmacophore Fit Values
GoldScore (P450), ChemScore (P450), ASP & CHEMPLP *

* Only available with GOLD from the CCDC

Consensus scoring, and *pareto* sorting and optimisation are available for working with multiple functions

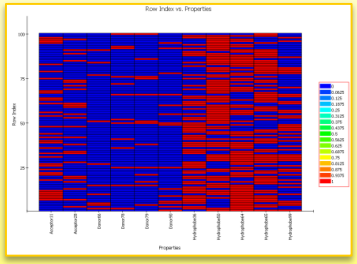
SBD: Refinement, Filtering and Analysis

Receiver Operating Characteristic (ROC)



Hit Rate Plots

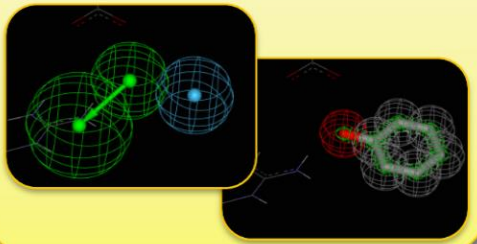
Heat Maps



RMSD
(Heavy Atom, All Atom)

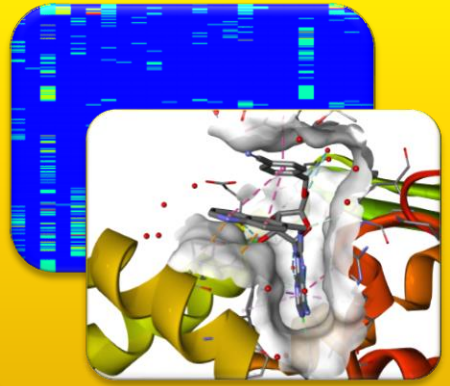
Minimisation
(*In Situ* CHARMm, or QM/MM)

Filter Poses
(Pharmacophore)

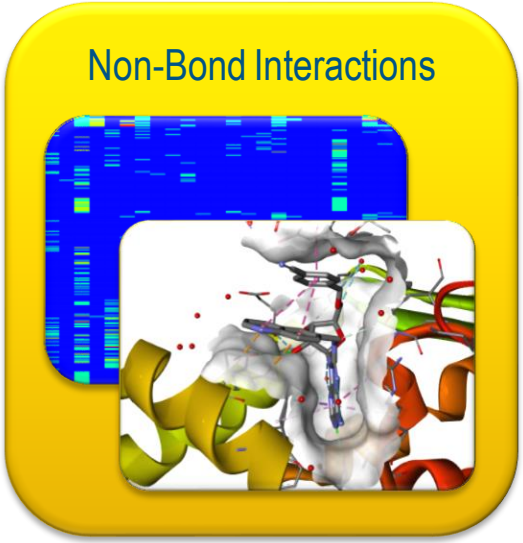


Analyze Ligand Poses
(Molecule, Chain, Residue, Atom)

Non-Bond Interactions



SBD: Non-Bond Interaction Monitors



Comprehensive perception of non-bond interaction monitors
Quick analysis of protein-ligand interactions with simple visualization control and ability to modify interaction perception

- **Favorable**
  (*See below*)
- **Unfavorable**
  - Steric Bumps
  - Charge Repulsion
  - Acceptor-Acceptor Clashes
  - Donor-Donor Clashes
- **Unsatisfied**
  - Hydrogen bond donor
  - Hydrogen bond acceptor
  - Charged atoms

- Hydrogen Bond
  - Conventional Hydrogen Bond
  - Carbon Hydrogen Bond
  - Pi Donor Hydrogen Bond
  - Water Mediated Hydrogen Bond
  - Water Hydrogen Bond
  - Salt Bridge
- Hydrophobic
  - Pi-Pi Stacked
  - Pi-Pi T-Shaped
  - Amide-Pi Stacked
  - Alkyl
  - Pi-Sigma
  - Pi-Alkyl
- Halogen
  - Halogen (Fluorine)
  - Halogen (Cl, Br, I)
- Charge
  - Attractive Charges
  - Salt Bridge
  - Pi-Cation
  - Pi-Anion
- Other
  - Metal-Acceptor
  - Pi-Sulfur
  - Sulfur-X
  - Pi-Lone Pair

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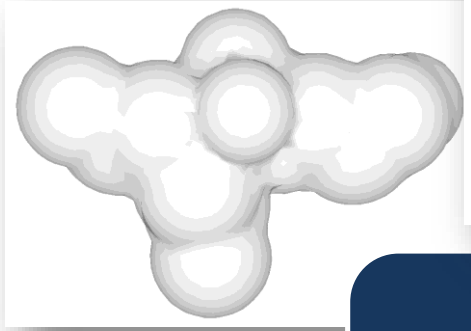
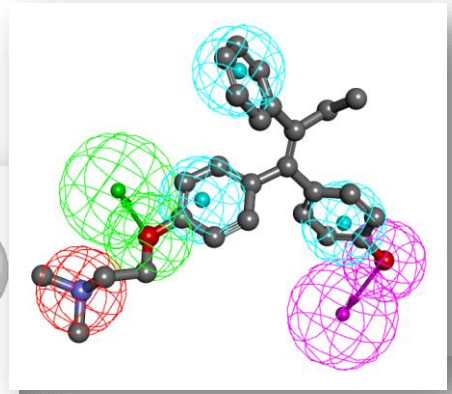
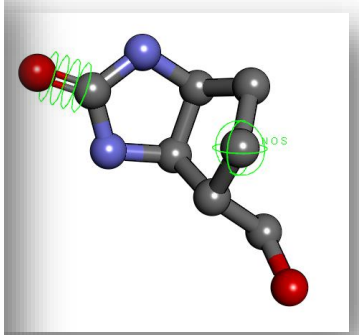
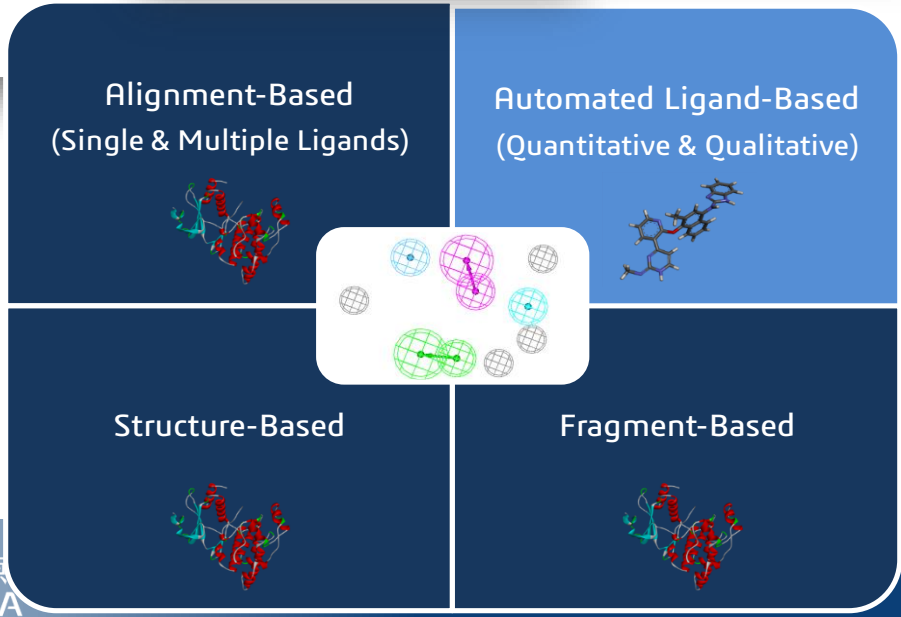
Pharmacophore Modelling

- 2D and 3D
  - SMARTS
  - Fragment-based
  - Feature-based
  - Shape
  - Combination
- Customisable pharmacophore features
- Automatic and manual generation
- Ligand-based and structure-based



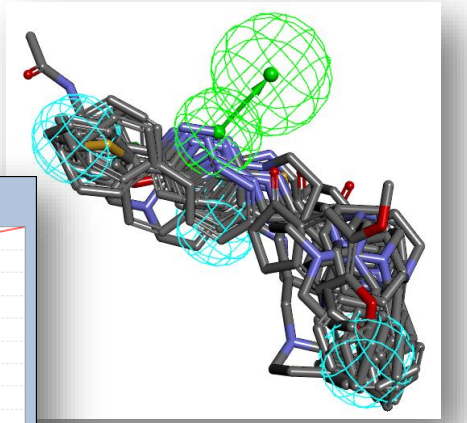


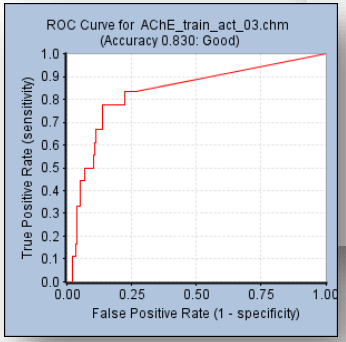


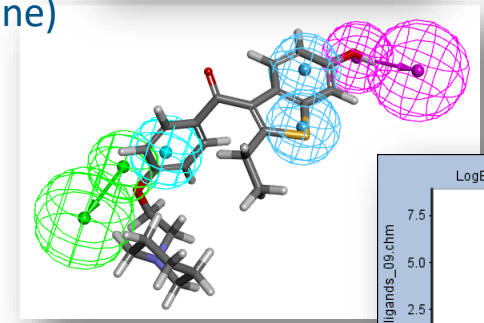


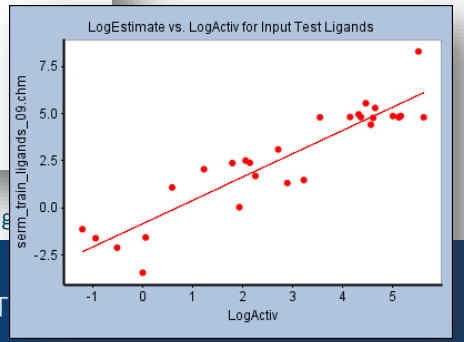
Ligand-Based Pharmacophores

- Automatic
  - Qualitative
    - Common features (HipHop / HipHopRefine)
    - Finds features shared by a set of similarly active ligands
  - Quantitative
    - SAR predicative (HypoGen / HypoGenRefine)
    - Finds features that relate to activity
  - Bioactive ligand conformation
- Manual
  - Alignment



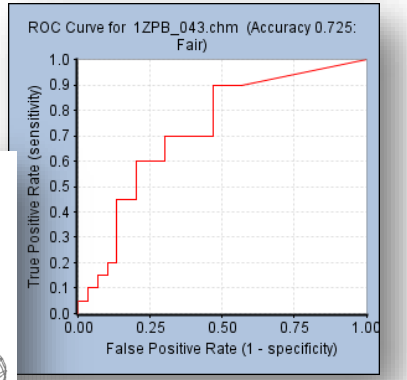


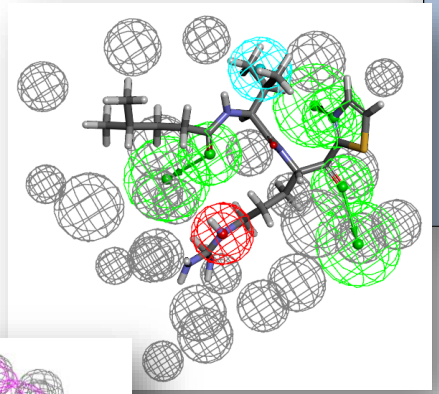


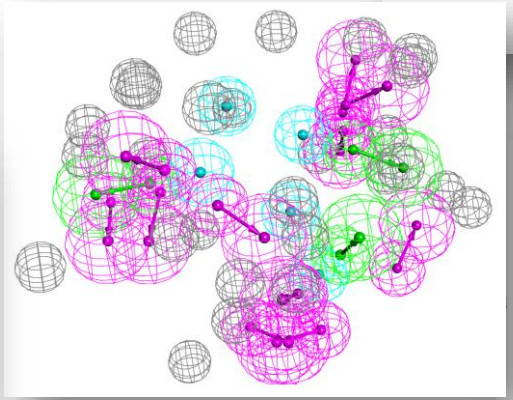


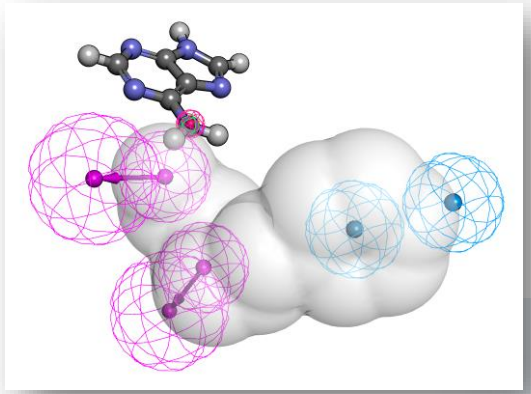
Structure-Based Pharmacophores

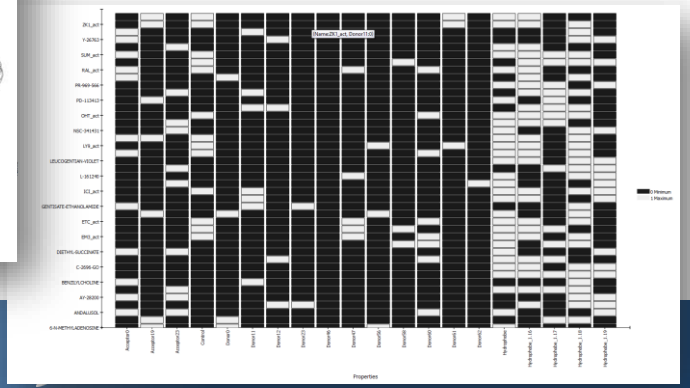
- Automatic
  - Receptor-Ligand complex
  - Interactions from a binding site
- Manual
  - Interaction map
  - Fragment-based





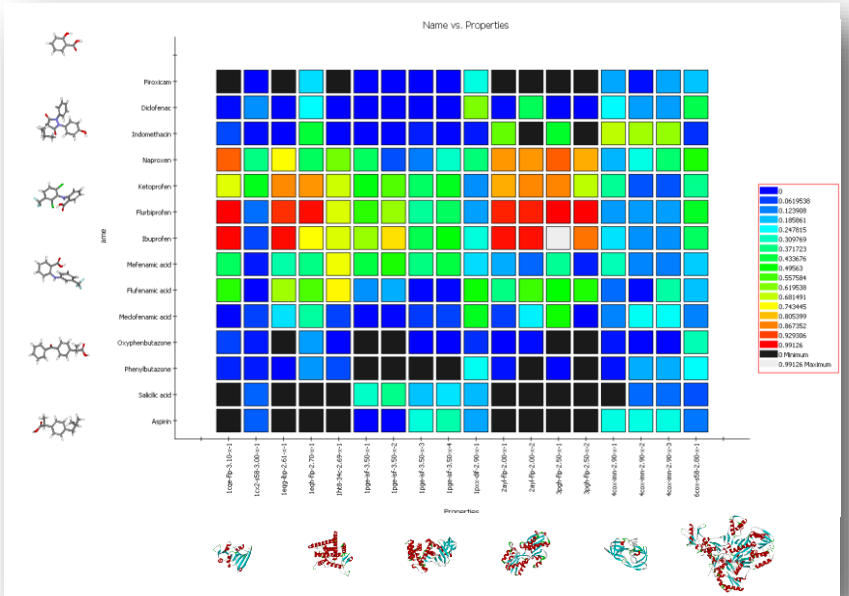






Ligand Profiling

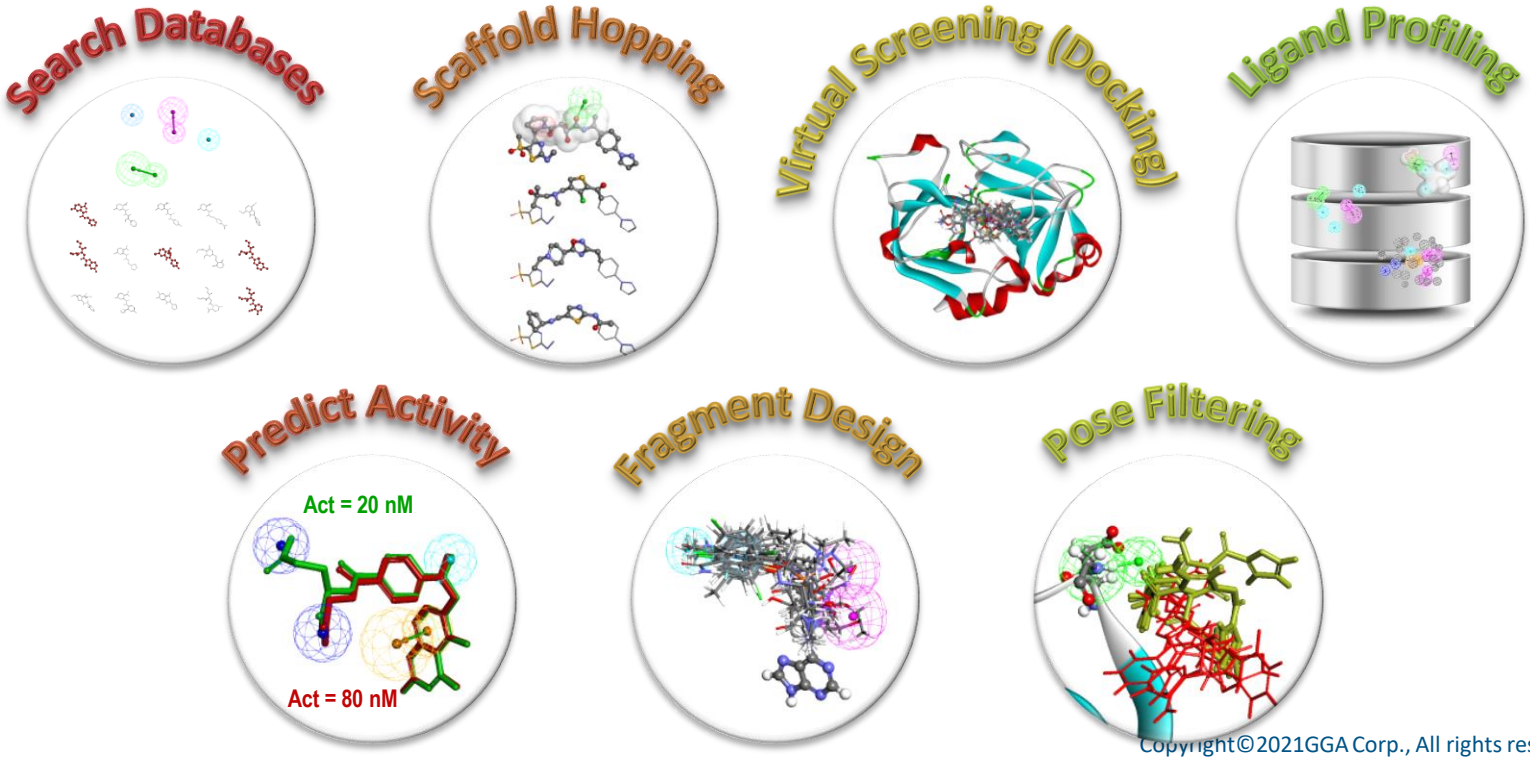
- Rapidly screen libraries of ligands against multiple pharmacophores
  - Predicting protein-drug off-targets (side effects)
  - Repositioning/repurposing existing drugs
  - In silico target fishing



- PharmaDB
  - Validated in collaboration with Prof. Rognan at University of Strasbourg*
  - Derived from the scPDB (http://bioinfo-pharma.u-strasbg.fr/scPDB)
  - 16034 validated models
  - Classified using Kyoto Encyclopedia of Genes and Genomes (KEGG)-BRITE

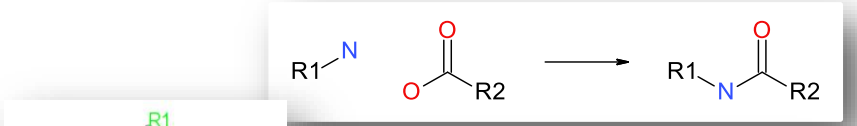
* Kellenberger *et al*, *J Chem Info Model*, **2006**, 46, 717-727

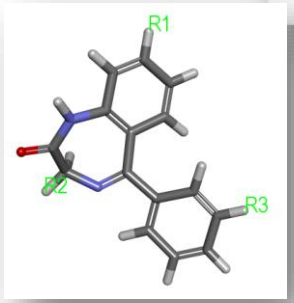
Pharmacophores Applications

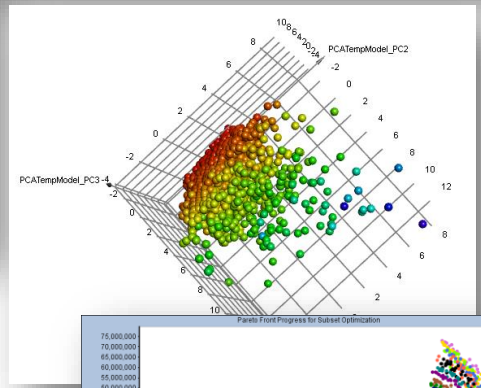


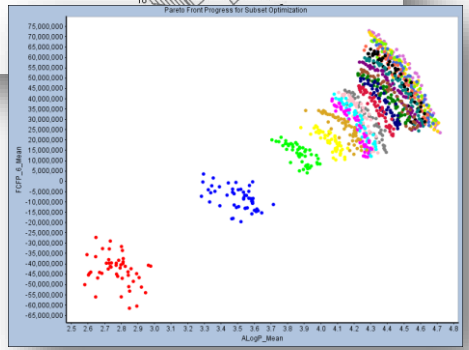
Library Design and Analysis

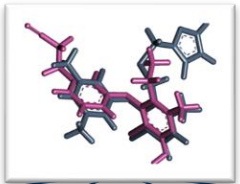
- Library enumeration
  - Reaction-based
  - Markush-based
- Diversity selection
- Clustering
- Similarity selection
- Multi-objective pareto optimization
- Novel ligand generation
  - BREED
- DS Application Edition (Pipeline Pilot)

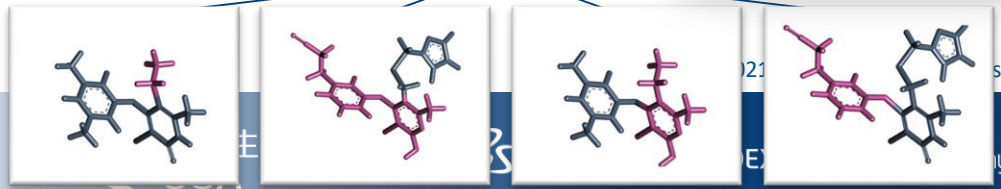












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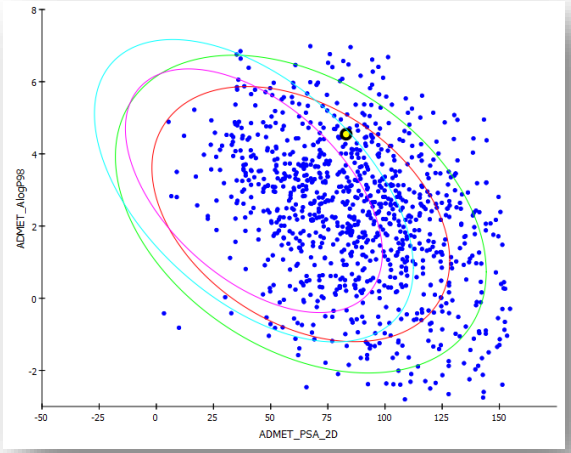
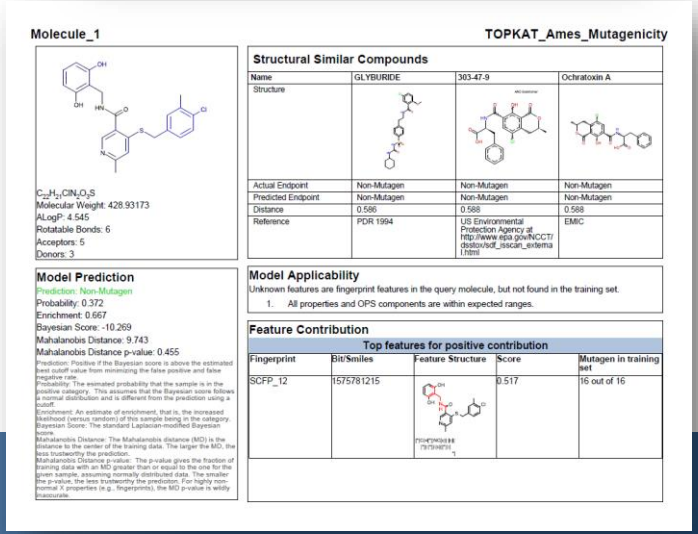
ADMET and Toxicology

- ADMET
  - Human intestinal absorption
  - Aqueous solubility
  - Blood brain barrier penetration
  - Plasma protein binding
  - CYP2D6 binding
  - Hepatotoxicity
  - Filter sets of small molecules for undesirable function groups based on published SMARTS rules
- Property calculation
  - 2D and 3D molecular properties
  - Semi-empirical and DFT

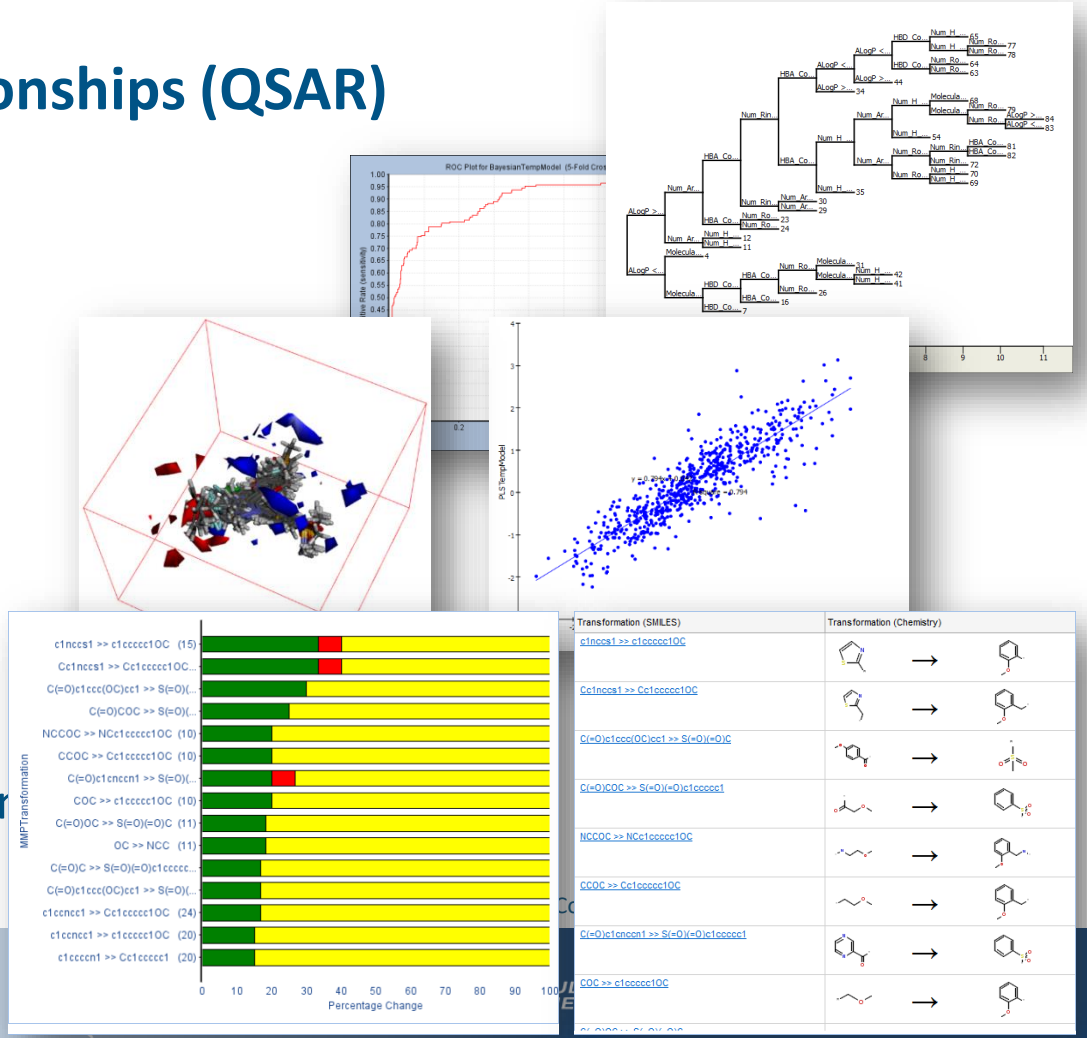
- Predictive Toxicology
  - Ames mutagenicity
  - Rodent carcinogenicity (NTP and FDA data)
  - Weight of evidence carcinogenicity
  - Carcinogenic potency TD50
  - Developmental toxicity potential
  - Rat oral LD50
  - Rat maximum tolerated dose
  - Rat inhalation toxicity LC50
  - Rat chronic LOAEL
  - Skin irritancy and sensitization
  - Eye irritancy
  - Aerobic biodegradability
  - Fathead minnow LC50
  - Daphnia magna EC50
  - Log P





Structure-Activity Relationships (QSAR)

- Categorical data
  - Bayesian
  - Recursive Partitioning
- Continuous data
  - Genetic Function Approximation
  - Partial Least Squares
  - Multiple Linear Regression
- 3D molecular field-based
- Matched Molecular Pairs (MMPs) transformations ar
  activity cliffs



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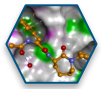
Rationale Small Drug Design

Library Design and Analysis

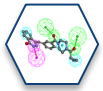
- Enumerate Library
- Pareto Optimization
- Find Similarities

- CDOCKER
- LibDock
- Flexible Dock

Structure-based design



Pharmacophore modeling



- Common Feature Pharmacophore (Hip Hop)
- 3D QSAR Pharmacophore (Hypogen)
- Structure-based Pharmacophore
- Ligand Profiler (Target Fishing)

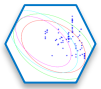
- Grow
- Replace
- MCSS

Fragment-based design

- MSLD
- FEP
- SMD

Simulation

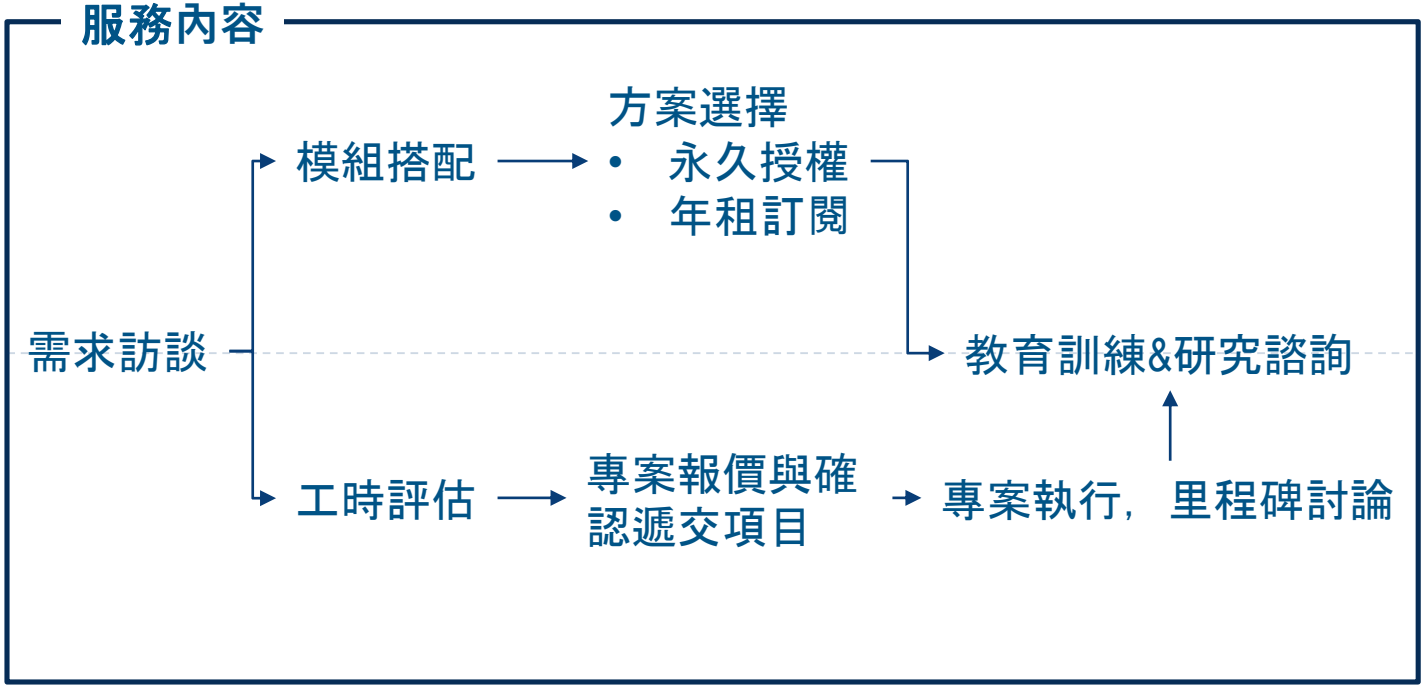
ADMET and Toxicity Analysis



合作方案介紹

軟體建置

委託服務



Q&A

創源生技
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