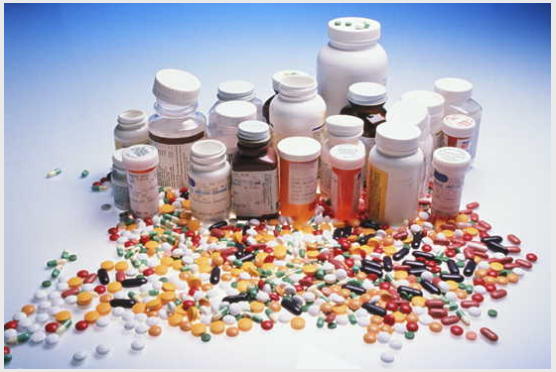
Shape Signatures:

Next-Generation Drug Discovery Tool



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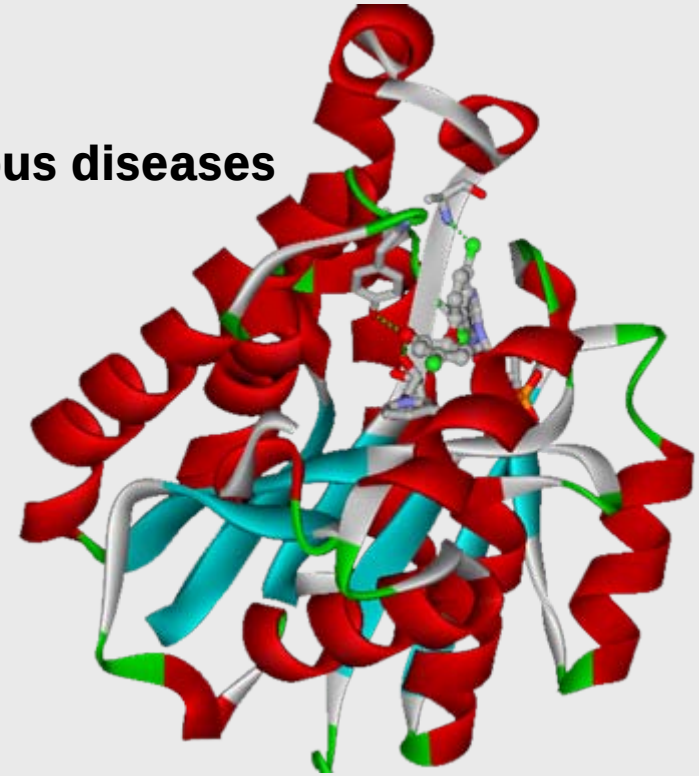
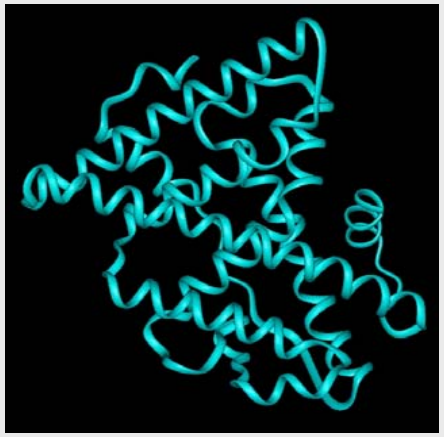
Overview of Technologies

- **Computational Tools**
  - **Rational (Computer-Aided) Drug Design**
  - **Predictive Toxicology**
- **Small Molecules**
  - **Therapeutic Areas: pain, cancer, infectious diseases**
- **Materials and Polymers**
  - **Biomaterials**
  - **Drug Delivery**

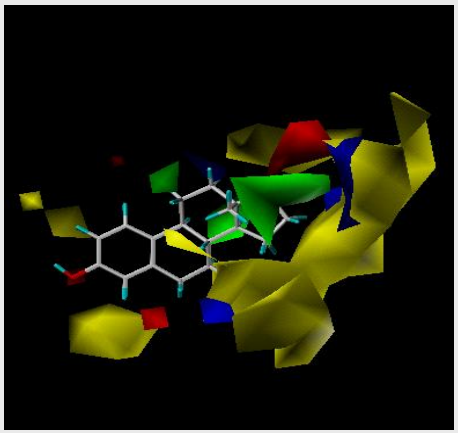


Synergistic Informatics Approaches

Receptor-based Approaches

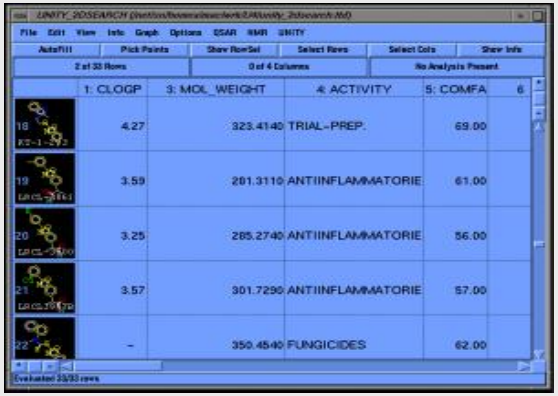


Ligand-based Approaches

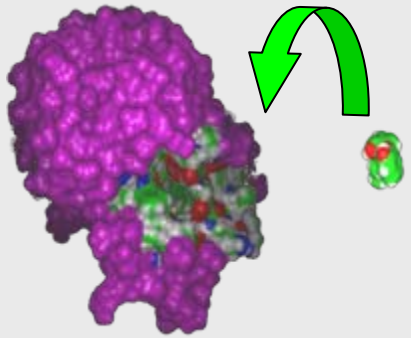


Drug Discovery

Predictive Toxicology



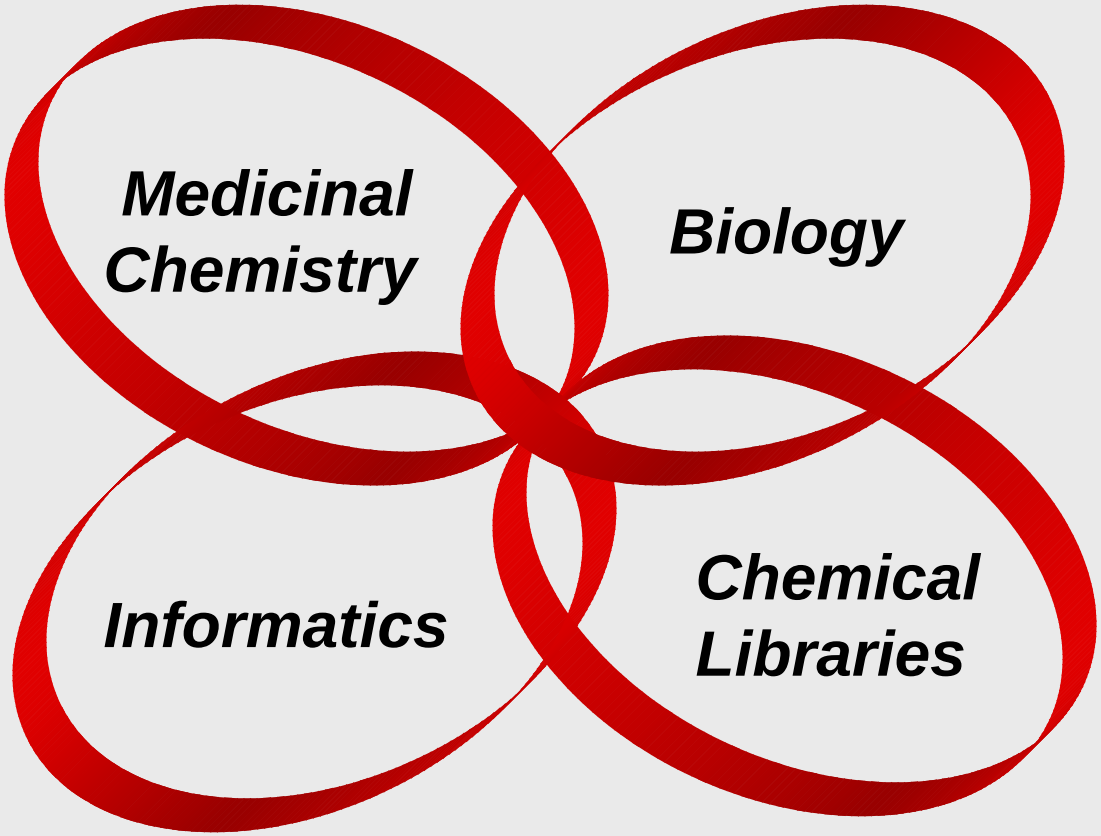
	1: CLOGP	3: MOL_WEIGHT	4: ACTIVITY	5: COMFA
18	4.27	323.4140	TRIAL-PREP.	69.00
19	3.59	281.3110	ANTIINFLAMMATORIE	61.00
20	3.25	285.2740	ANTIINFLAMMATORIE	56.00
21	3.57	301.7290	ANTIINFLAMMATORIE	57.00
22	-	350.4540	FUNGICIDES	62.00



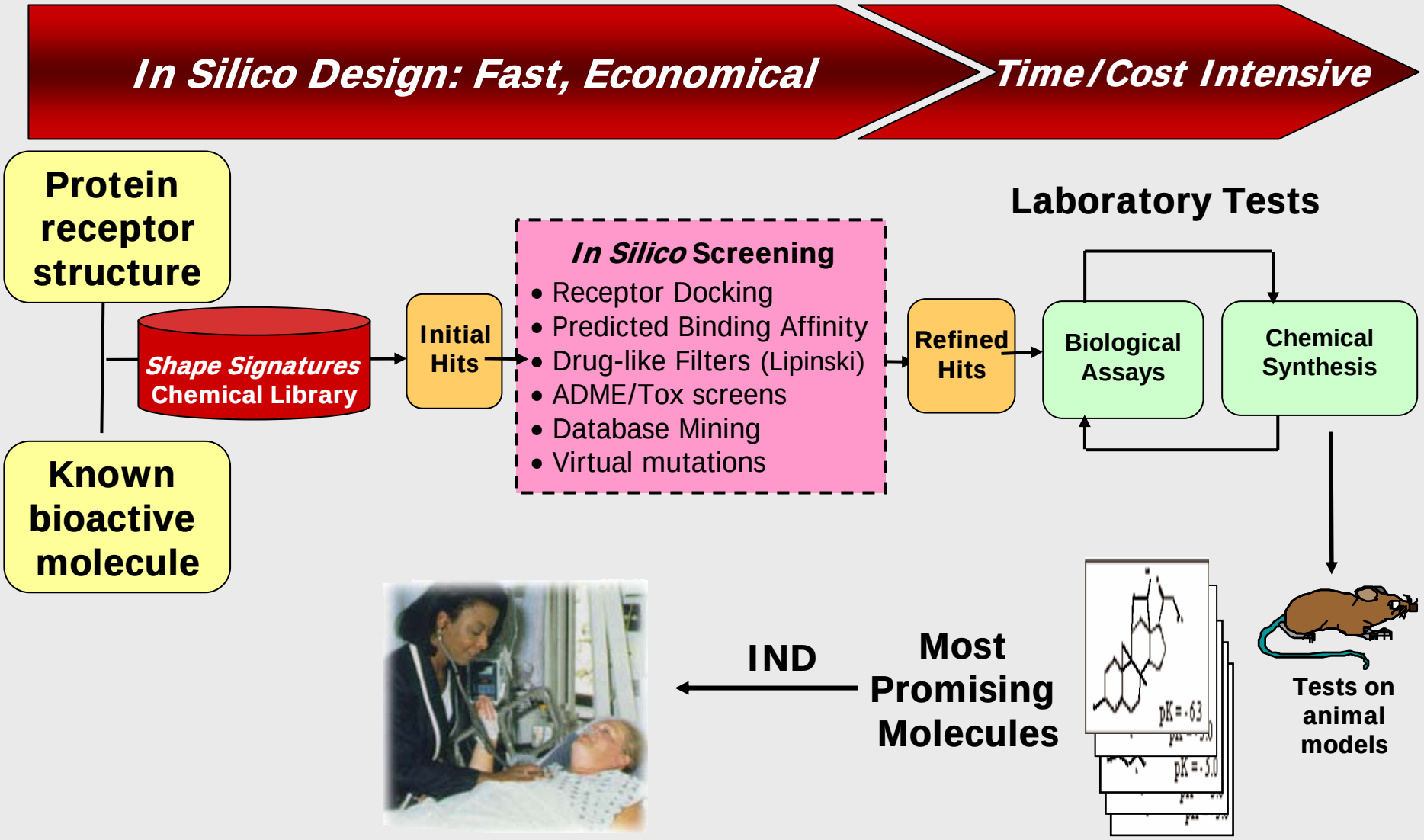
Database Mining, Pattern Recognition

Drug Discovery Paradigm

Seamless Integration of Critical Technologies

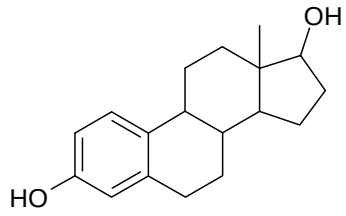


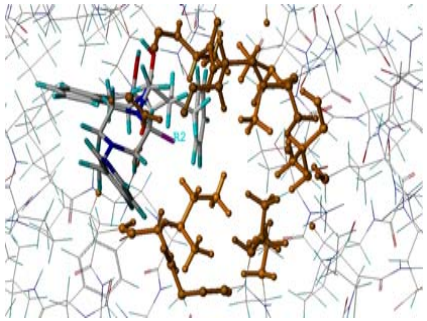
Our Integrated Discovery Platform



Shape Signatures

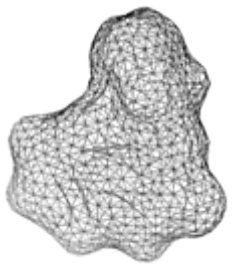
START

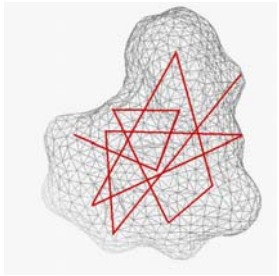


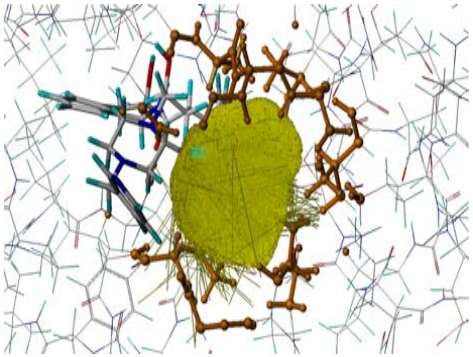


Small molecule or Protein binding pocket

PROCESSING



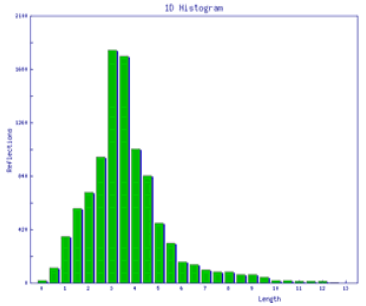




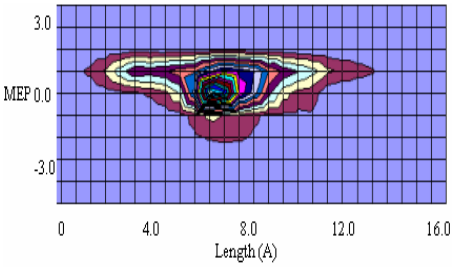
Ray tracing to generate the raw data

OUTPUT

Shape (1D)



Shape + Charge (2D)

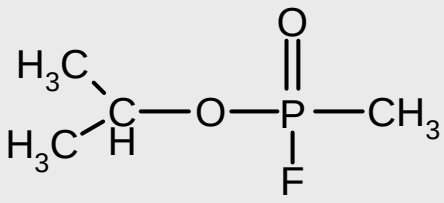


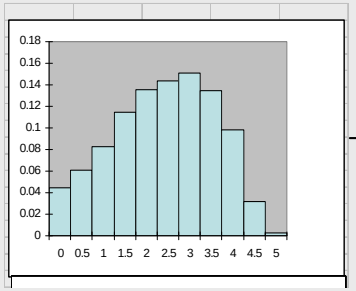
1D and 2D Shape Signatures

Shape Signatures Technology

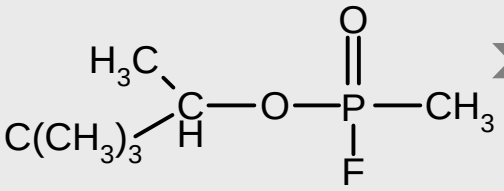
molecules are compared by subtracting their histograms

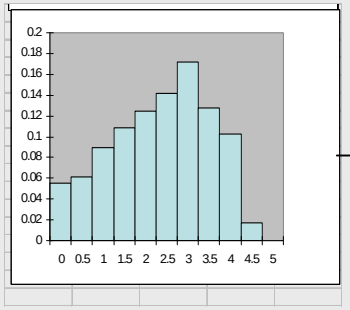
Sarin





Soman





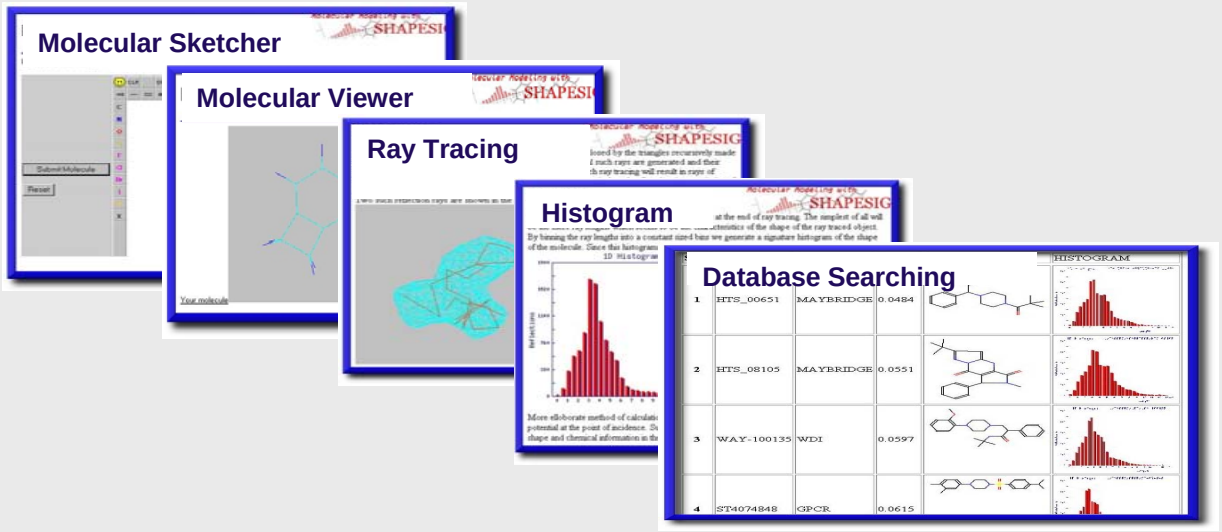
***Diff* = 0.022**

Small *Diff* value means that two molecules have similar biorelevant properties

Shape Signatures
Chemical Library

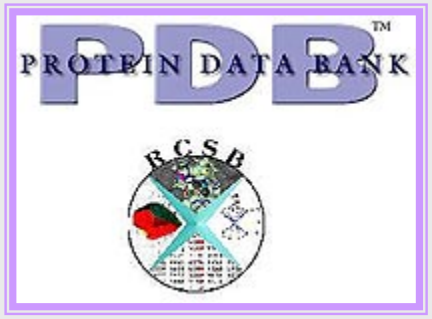
3+ million compounds

Shape Signatures Software Tool & Chemical Databases



Searchable *Shape Signatures* Databases

- 3+ million vendor available drug-like compounds
- Directed libraries for kinases, NRs, GPCRs
- Thematic libraries for indoles, pyrimidines, triazoles, etc
- 40,000 Natural Products
- 5,000 ligands extracted from Protein Data Bank (PDB)



Extract Ligands

~35K high quality crystal structures
(resolution < 2.5 Å)

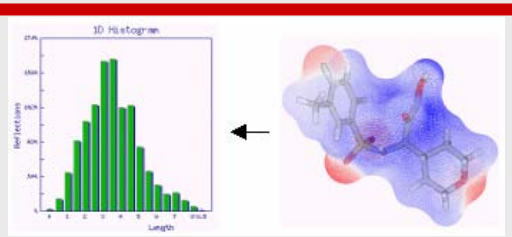
Preliminary Ligand Database

Remove metal ions, salts, redundant structures

Filter

Final Ligand Database

Convert to ShapeSig



PDB-extracted Shape Signature Database
~5,000 ligands

2D or 3D structure

Query Molecule

List of Hits With high similarity to query

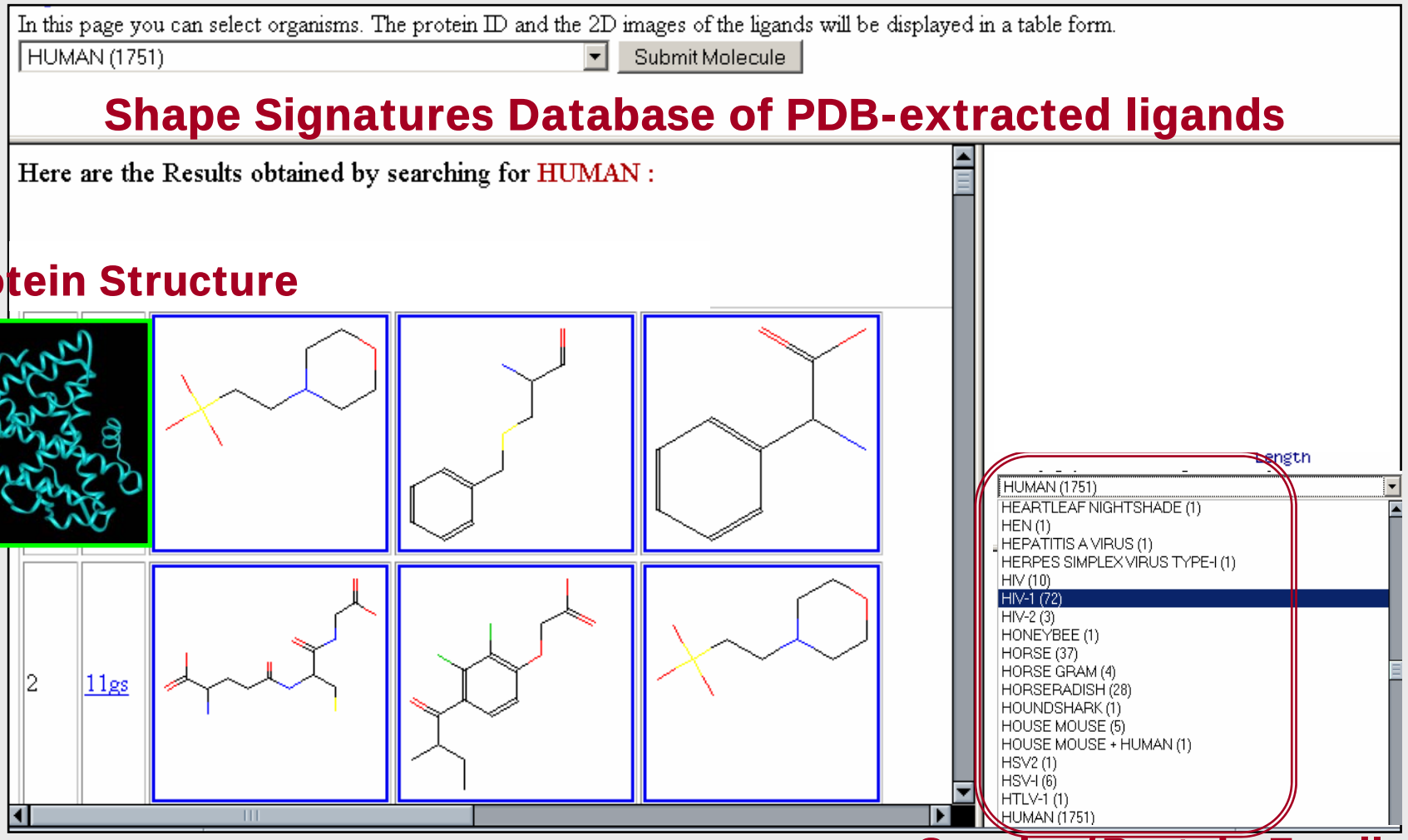
- drug-like features (Lipinski)
- parent protein ID, structure, link
- protein functionality
- pathway info

Potential Drug Leads

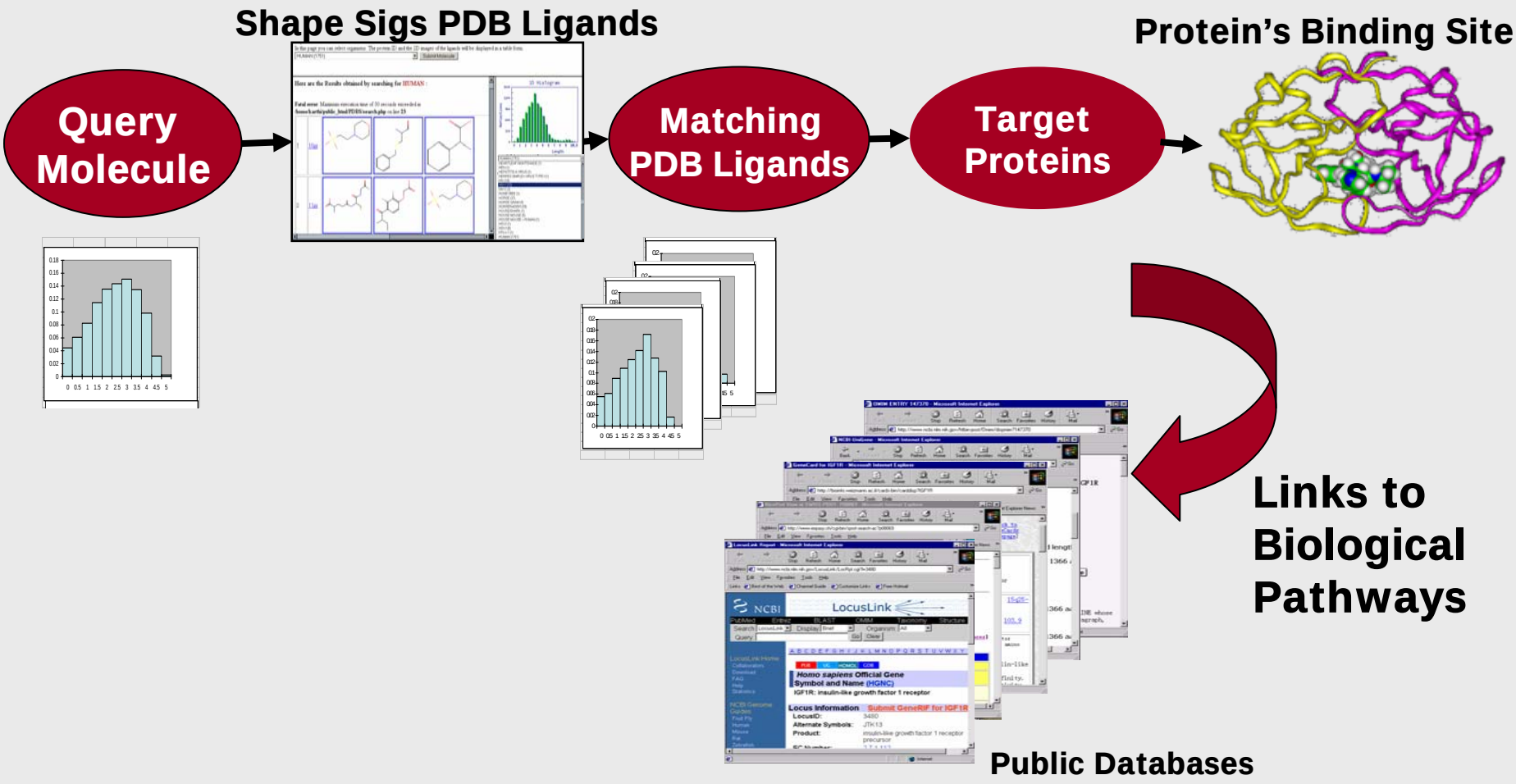
PDB-extracted Ligands

Novel Discovery Platform

Protein Data Bank (PDB): World Repository of 35,000 Protein Crystal Structures

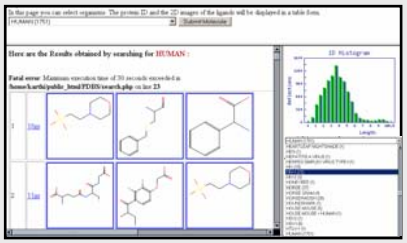


Molecules → Target Protein → Mechanism

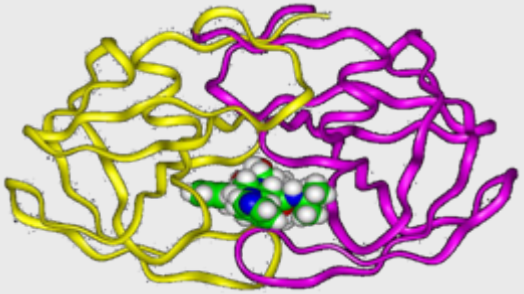


Medical Countermeasures

Novel Molecules for Detection, Diagnosis, Prevention, and Treatment of CWAs & BWAs

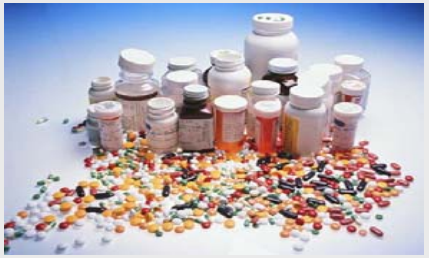


Searchable Molecular Libraries

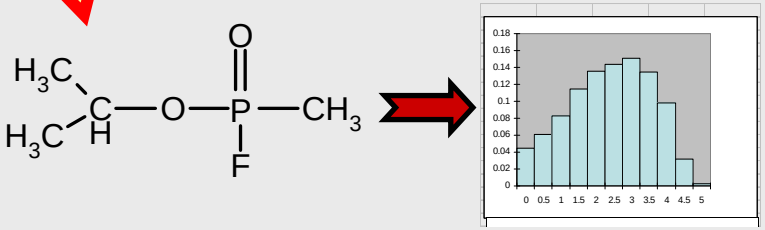


Automated Drug Design

Shape Signatures



New Drug Candidates



CWA/BWA Target Mapping

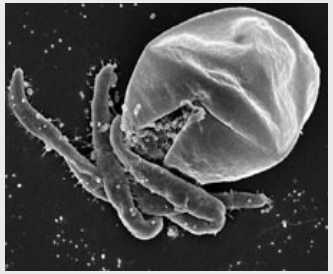
Broad Applicability

- Therapeutics and Prophylactics
- Diagnostic Agents
- Medical Countermeasures
- Agricultural Goods
- Veterinary Medicine
- Drug Delivery Systems

Case Study

Shape Signatures for Discovery of Novel Anti-parasitic Agents

Intracellular Parasitic Diseases



- Cause acute & chronic GI distress (diarrhea) in humans and animals; life threatening; endemic
- Serious threat to warfighter stationed in endemic regions
- Examples: malaria, toxoplasmosis*, cryptosporidiosis*, cyclosporiasis*, many others

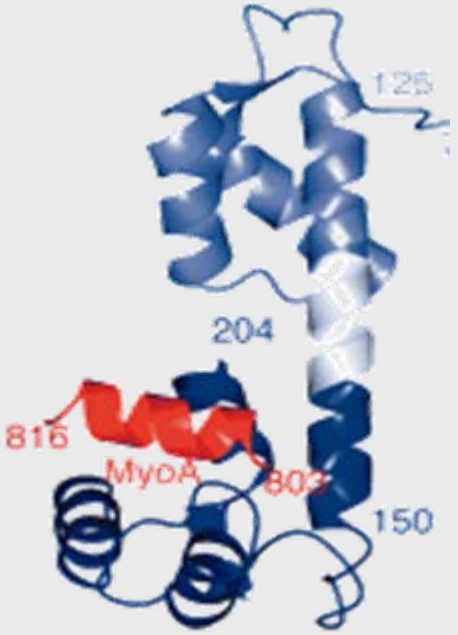
*** NIAID Biodefense Category B pathogens**

- Highly contagious & infectious; direct contact, insects, waterborne; resistant to disinfectants (bleach)
- No vaccines, and drugs are either non-existent, inadequate, or induce parasite resistance

Infectious Parasitic Diseases

Our Solution

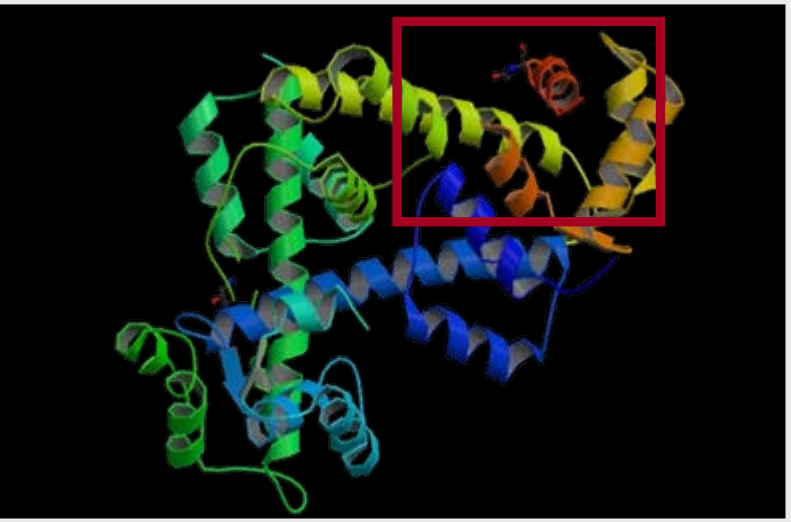
- Holy Grail: Block parasite invasion of host
- Invasion of host cells by parasite <u>requires</u> interaction of two proteins (Myosin A and MTIP)
- This interaction is unique to, and universal among, <u>all</u> of these parasites
- Myosin-MTIP Inhibitors
  - ✓ broad-spectrum activity against all species
  - ✓ high specificity for parasite over host
  - ✓ parasitic resistance virtually impossible
  - ✓ applicable for prophylaxis and therapy



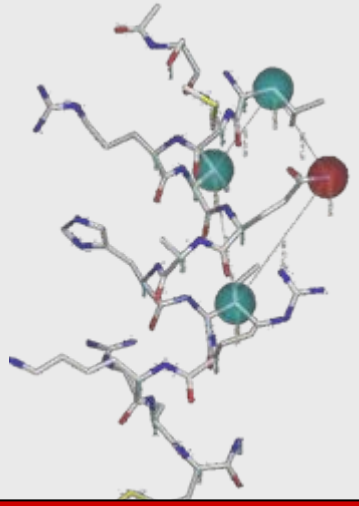
X-ray Crystal Structure of MTIP-MyoA Complex

Bosch J et al; *PNAS* (2006)

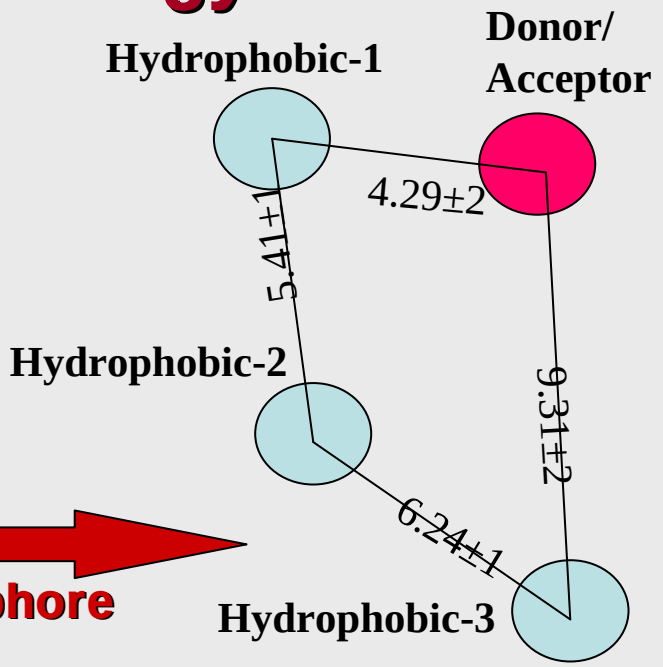
Computational Design Strategy



MTIP-Myosin A complex



Extract Pharmacophore

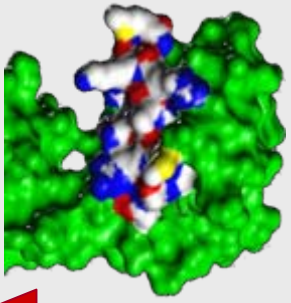


Screen Shape Sigs Library

Shape Signatures Chemical Library

3+ million compounds

Initial Hits

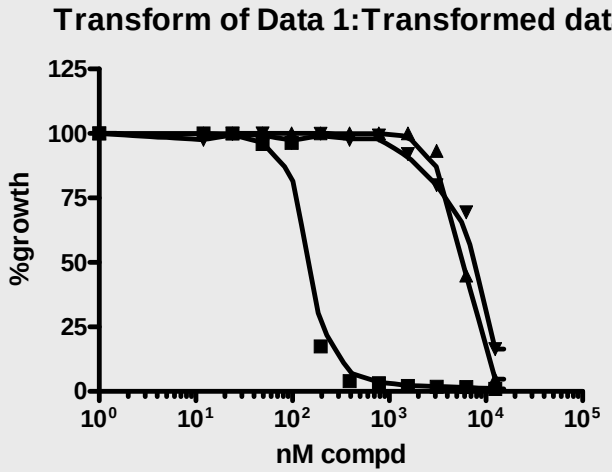


Docking of Hits

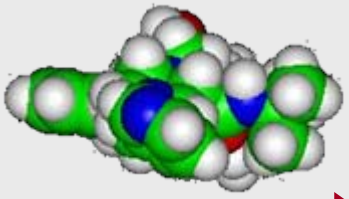
Priority List

1 ...
2 ...
3 ...
4 ...
.....

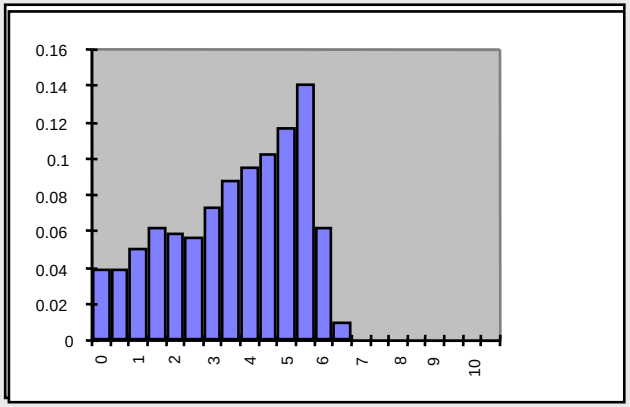
Family of MTIP-Myosin Inhibitors



SW416: IC_{50} = 75 nM



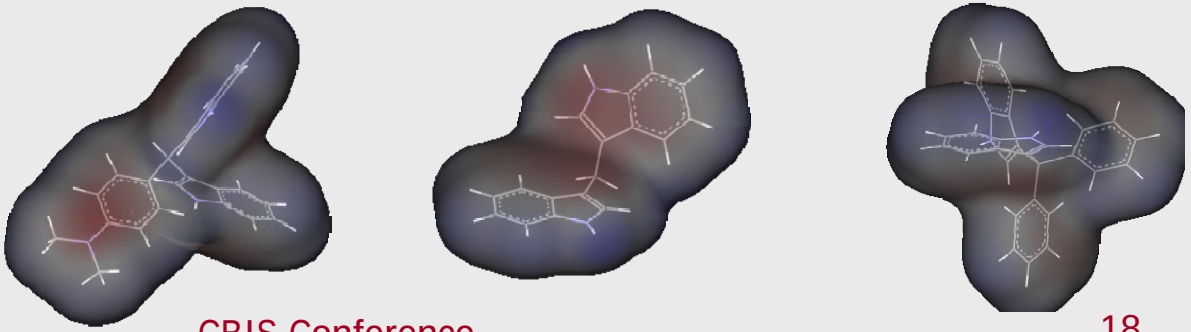
Convert to Shape Signature



Family of Inhibitors

Drug-like Filters

Shape Signatures
Chemical Library
3+ million compounds

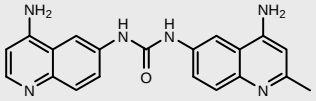
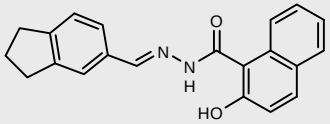
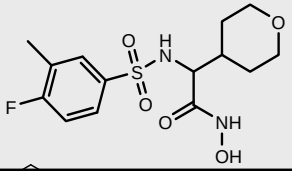
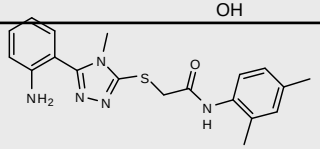
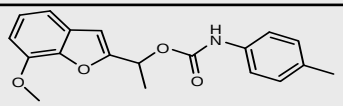
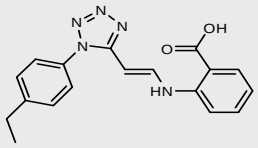


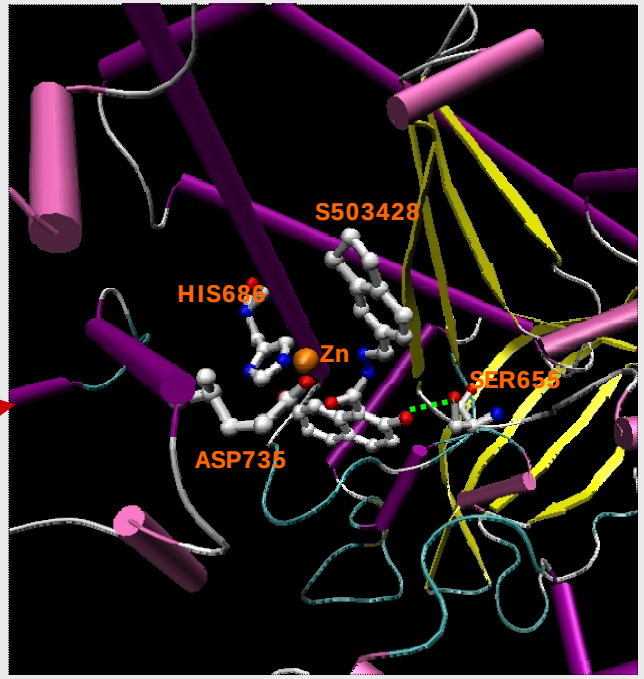
Summary

- Aided by *Shape Signatures*, we have discovered a family of potent MTIP-myosin inhibitors
- Exhibit low nM inhibitory activity against *P falciparum*, including multi-drug resistant strains
  - ✓ Block invasion of erythrocytes
  - ✓ Lethal to parasite
- Attractive drug-like properties: low MW, soluble, achiral, easy synthesis
- Non-toxic in mice (MTD > 100 mg/kg)
- Efficacy studies in mice indicate prophylactic and therapeutic activity
- *In vivo* studies vs other familial parasites are scheduled
  - ✓ *Toxoplasma*, *Cryptosporidium*, *Cyclospora*, *Babesia, Eimeria*
- May represent a breakthrough as broad-spectrum orally active prophylactic and therapeutic agents, with minimal chance of parasite resistance

For more details, visit: www.snowdonpharma.com

Shape Signatures: Discovery of Anthrax LF Inhibitors

ID	Structure	Source	Docking Score	% Inhibition (10 μM)
QUERY NSC 12155 (known inhibitor)		NIH-NCI	33	95
QUERY LFI (known inhibitor)		Merck	39	-
--		S503428	42	99
--		G626310	38	95
--		B788321	36	96
--		HT4369	36	94



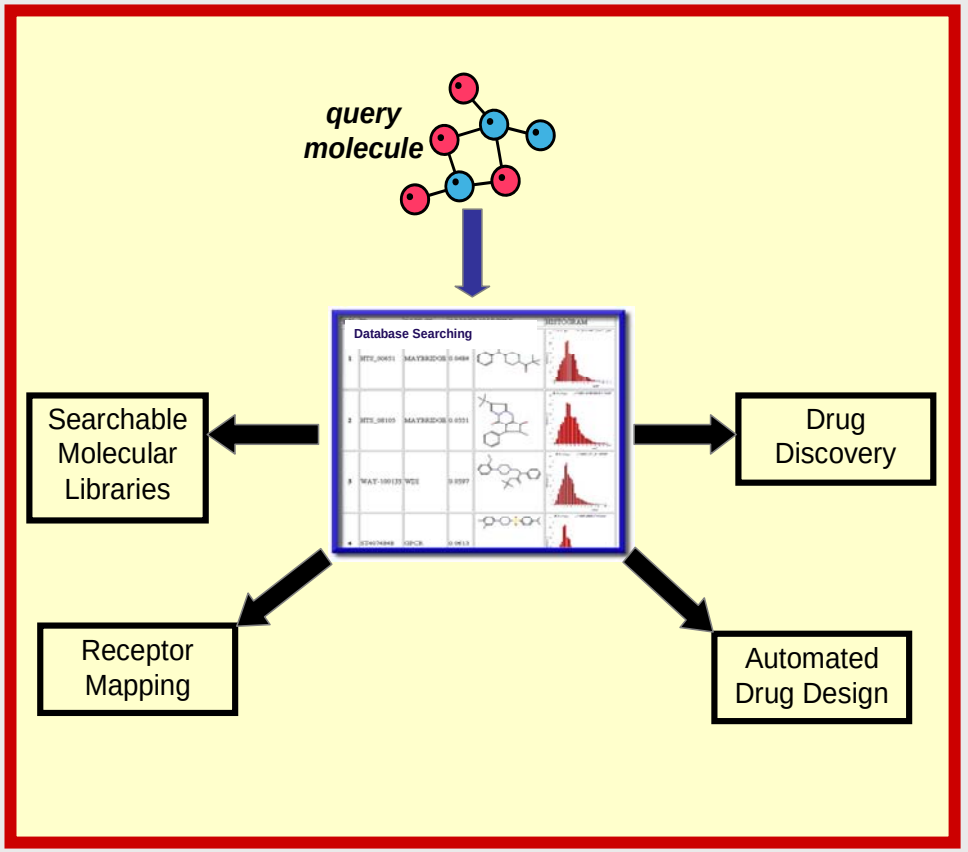
S503428 docked in the ligand binding pocket of anthrax LF

In Vitro Activity

Shape Signatures

- Innovative Drug Discovery Tool -

- Fast
  screens large databases in secs
- Extensible
  works with any kind or number of molecular species
- Innovative
  excels at scaffold hopping
- Powerful
  enables automated ligand design



Thank You!

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