

Shape Signatures:
Next-Generation Drug Discovery Tool



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Overview of Technologies

➤ Computational Tools

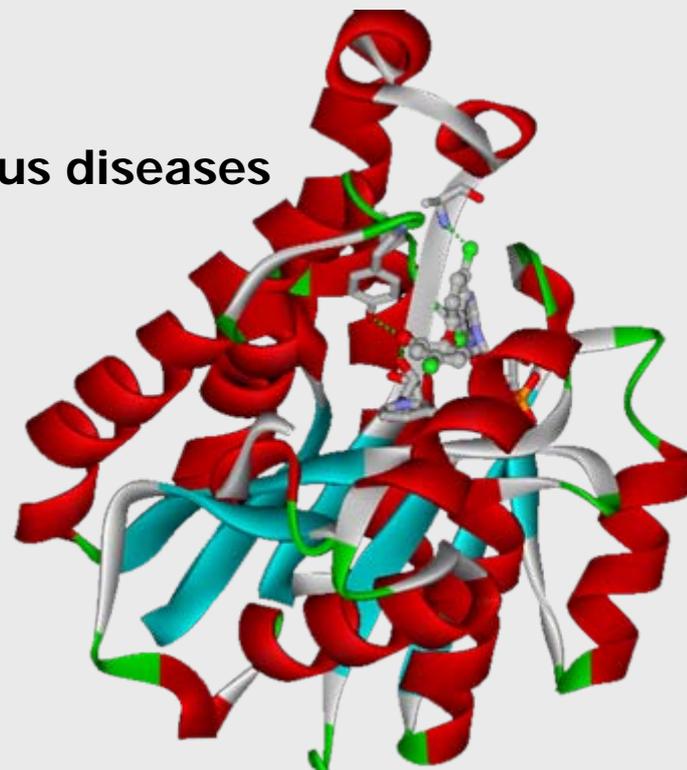
- Rational (Computer-Aided) Drug Design
- Predictive Toxicology

➤ Small Molecules

- Therapeutic Areas: pain, cancer, infectious diseases

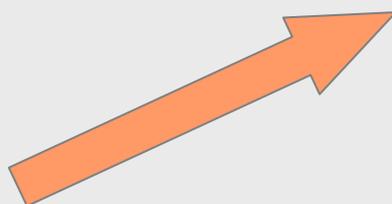
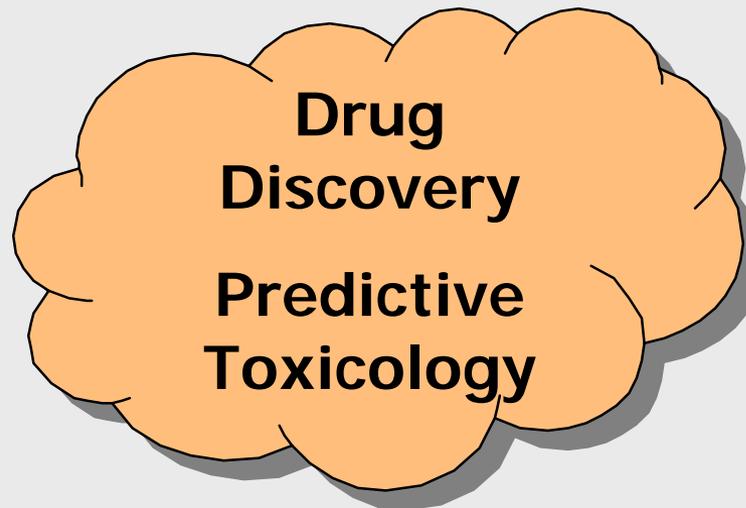
➤ Materials and Polymers

- Biomaterials
- Drug Delivery

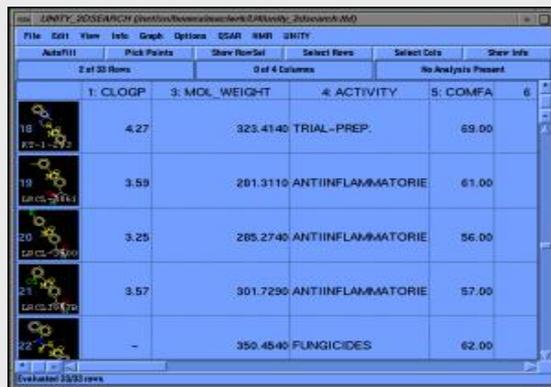
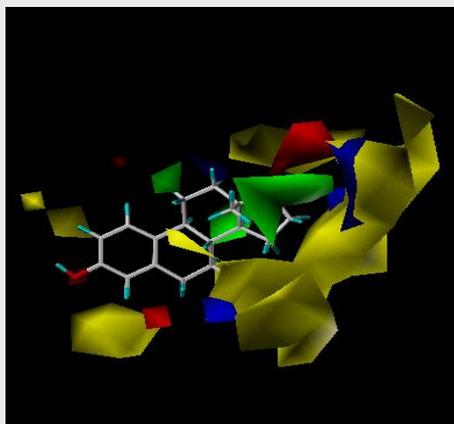


Synergistic Informatics Approaches

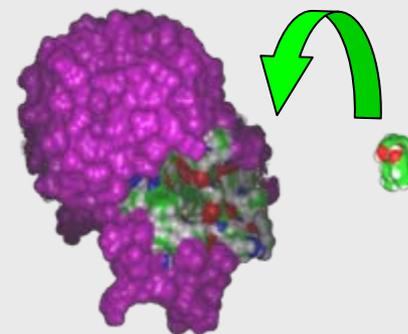
Receptor-based Approaches



Ligand-based Approaches



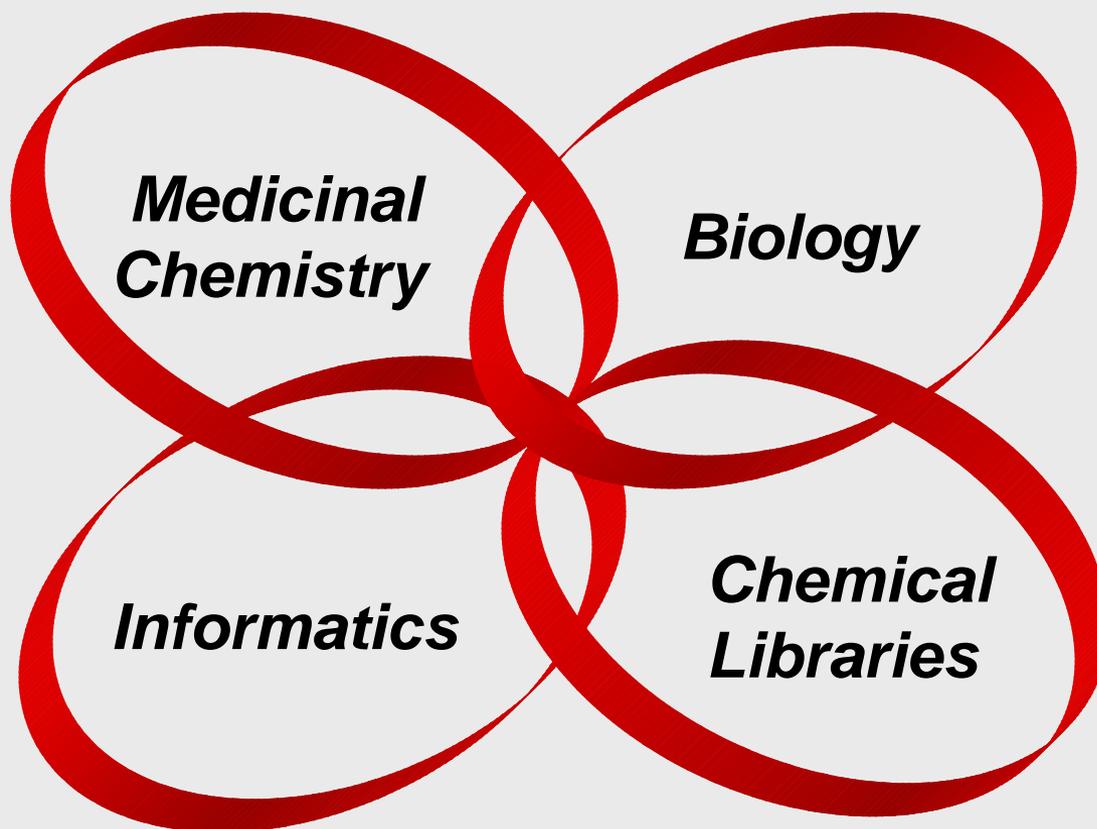
1: CLOGP	3: MDL_WEIGHT	4: ACTIVITY	5: COMFA
18 	4.27	323.4140 TRIAL-PREP.	69.00
19 	3.59	201.3110 ANTIINFLAMMATORIE	61.00
20 	3.25	285.2740 ANTIINFLAMMATORIE	56.00
21 	3.57	301.7290 ANTIINFLAMMATORIE	57.00
22 	-	350.4540 FUNGICIDES	62.00



Database Mining,
Pattern Recognition

Drug Discovery Paradigm

Seamless Integration of Critical Technologies



Our Integrated Discovery Platform

In Silico Design: Fast, Economical

Time/Cost Intensive

Protein
receptor
structure

Shape Signatures
Chemical Library

Initial
Hits

In Silico Screening

- Receptor Docking
- Predicted Binding Affinity
- Drug-like Filters (Lipinski)
- ADME/Tox screens
- Database Mining
- Virtual mutations

Refined
Hits

Laboratory Tests

Biological
Assays

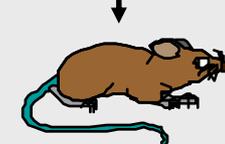
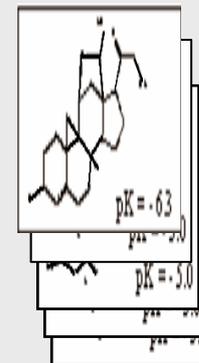
Chemical
Synthesis

Known
bioactive
molecule



IND

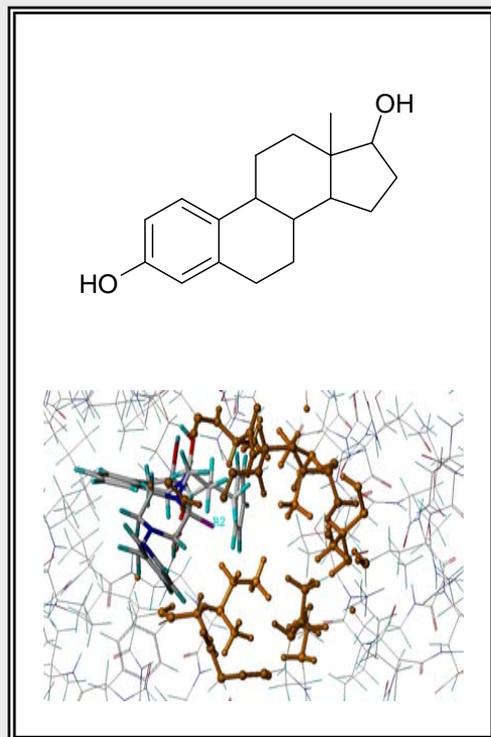
Most
Promising
Molecules



Tests on
animal
models

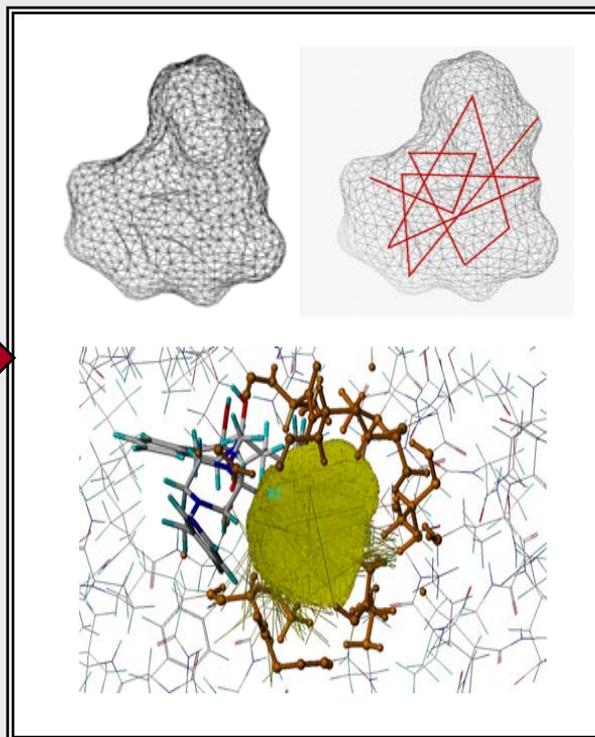
Shape Signatures

START



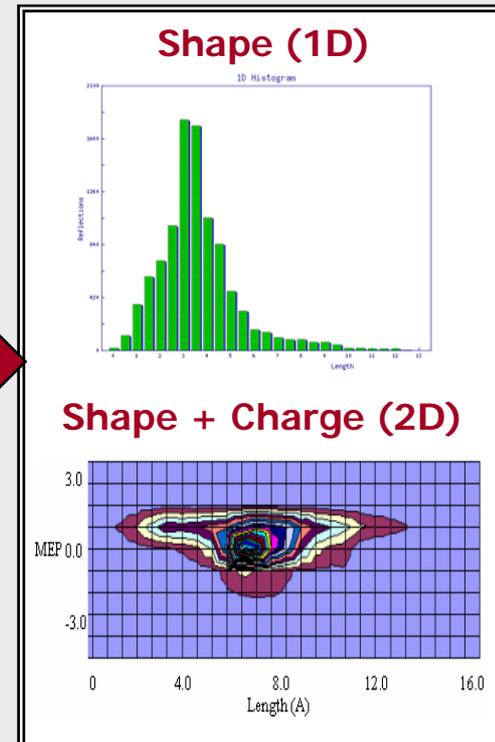
Small molecule or
Protein binding pocket

PROCESSING



Ray tracing to
generate the raw data

OUTPUT

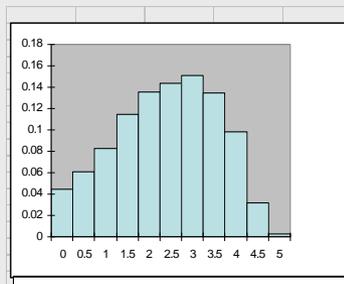
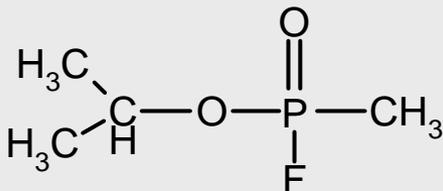


1D and 2D
Shape Signatures

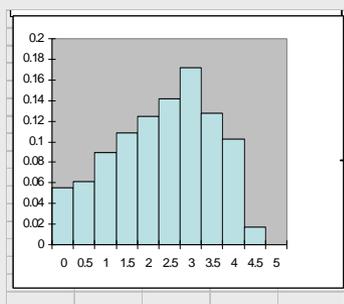
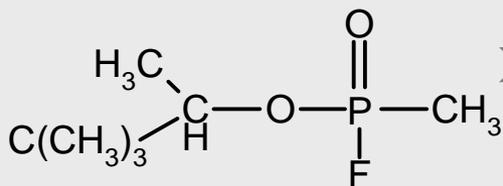
Shape Signatures Technology

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

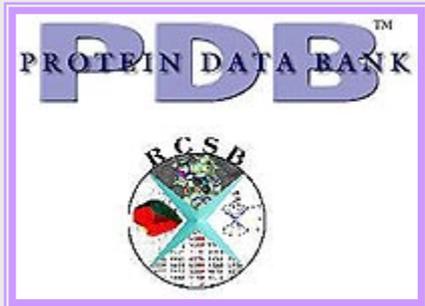
The image displays five overlapping screenshots of the Shape Signatures software tool. From left to right, they are: Molecular Sketcher, Molecular Viewer, Ray Tracing, Histogram, and Database Searching. Each screenshot shows a different stage of the process, from molecule input to final search results.

Database Searching

Rank	HTS ID	Library	Score	Chemical Structure	Histogram
1	HTS_00651	MAYBRIDGE	0.0484	<chem>CC1=CC=C(C=C1)C2=CC=CC=C2</chem>	
2	HTS_08105	MAYBRIDGE	0.0551	<chem>CC1=CC=C(C=C1)C2=CC=CC=C2</chem>	
3	WAY-100135	WDI	0.0597	<chem>CC1=CC=C(C=C1)C2=CC=CC=C2</chem>	
4	STM074848	GPCR	0.0615	<chem>CC1=CC=C(C=C1)C2=CC=CC=C2</chem>	

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)

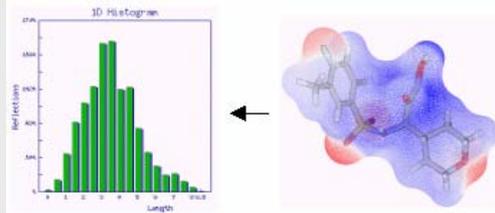
**Preliminary
Ligand Database**

Remove metal ions,
salts, redundant
structures

Filter

**Final Ligand
Database**

Convert to ShapeSig



**PDB-extracted
Shape Signature
Database**
~5,000 ligands

**List of Hits
With high
similarity
to query**

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

Potential Drug Leads

2D or 3D
structure

**Query
Molecule**

PDB-extracted Ligands

Novel Discovery Platform

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

In this page you can select organisms. The protein ID and the 2D images of the ligands will be displayed in a table form.

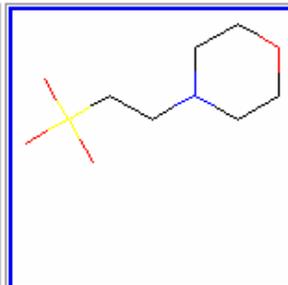
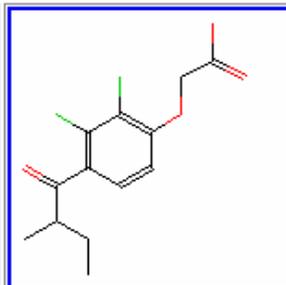
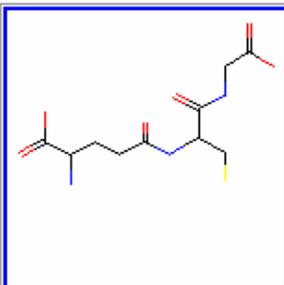
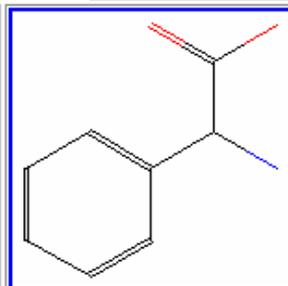
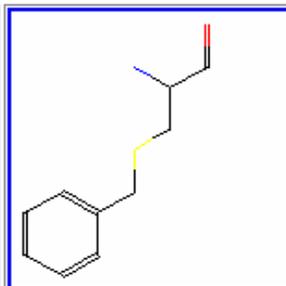
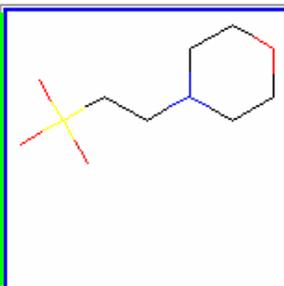
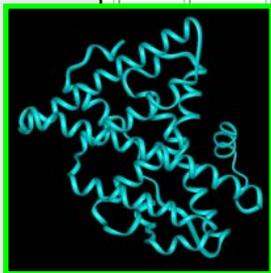
HUMAN (1751)

Submit Molecule

Shape Signatures Database of PDB-extracted ligands

Here are the Results obtained by searching for **HUMAN** :

Protein Structure

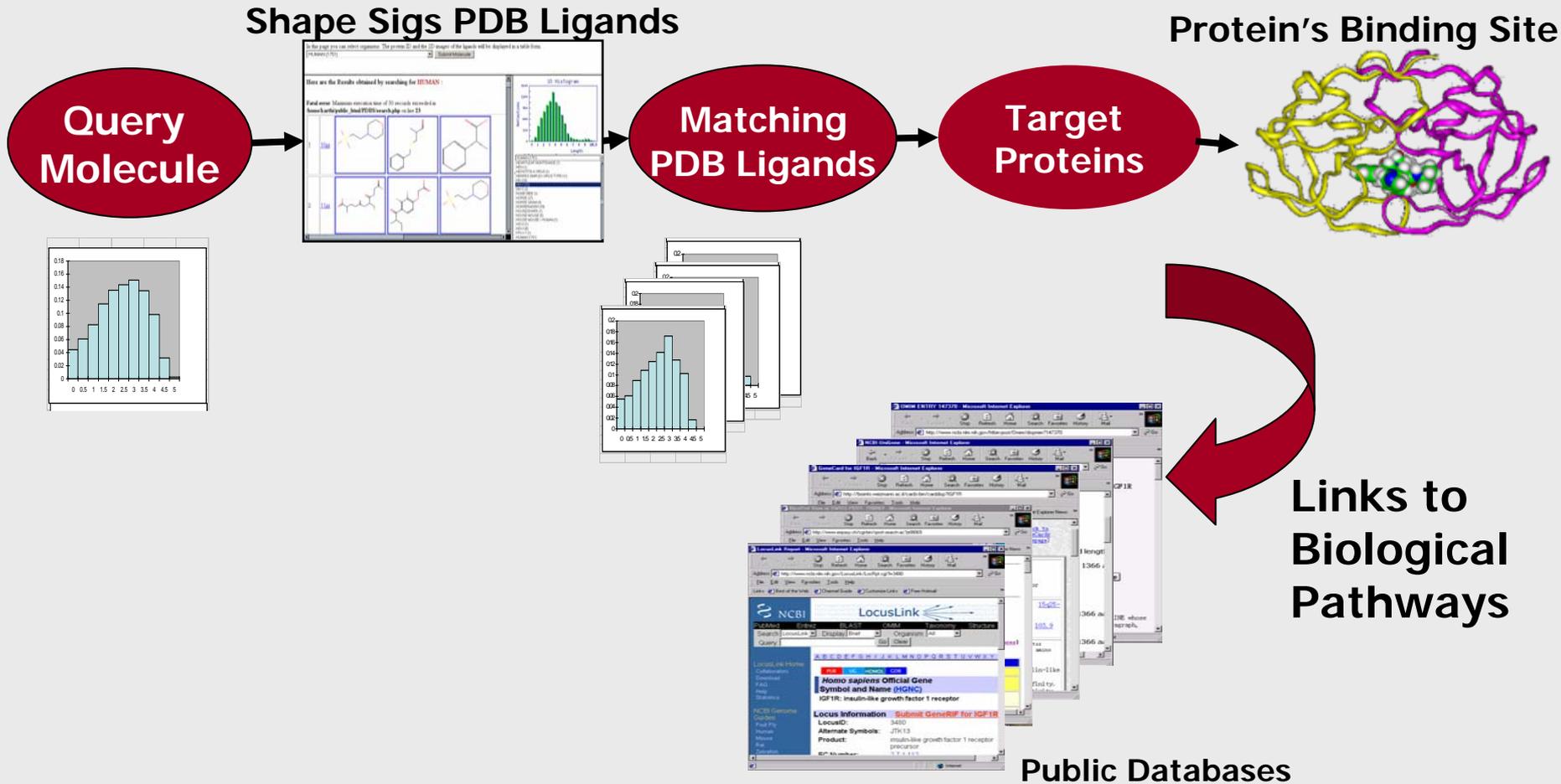


2

[11lgs](#)

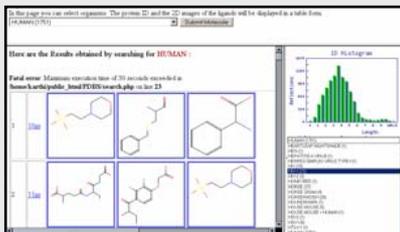
Species/Protein Family	Length
HUMAN (1751)	
HEARTLEAF NIGHTSHADE (1)	
HEN (1)	
HEPATITIS A VIRUS (1)	
HERPES SIMPLEX VIRUS TYPE-1 (1)	
HIV (10)	
HIV-1 (72)	
HIV-2 (3)	
HONEYBEE (1)	
HORSE (37)	
HORSE GRAM (4)	
HORSE RADISH (28)	
HOUND SHARK (1)	
HOUSE MOUSE (5)	
HOUSE MOUSE + HUMAN (1)	
HSV2 (1)	
HSV-1 (6)	
HTLV-1 (1)	
HUMAN (1751)	

Molecules → Target Protein → Mechanism

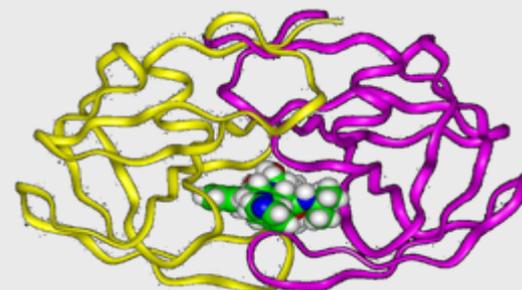


Medical Countermeasures

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



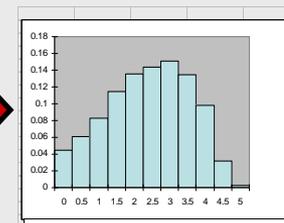
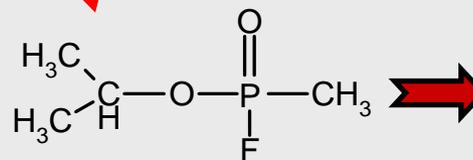
Searchable
Molecular Libraries



Automated
Drug Design



New Drug Candidates



CWA/BWA Target Mapping

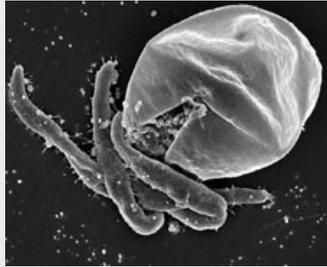
Broad Applicability

- 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

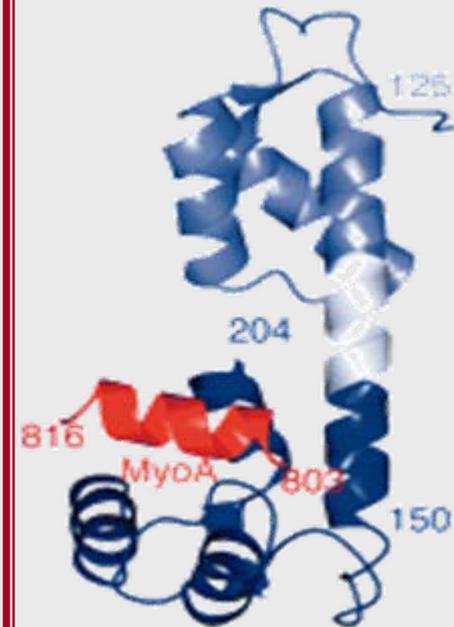
*** NIAID Biodefense Category B pathogens**

- 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

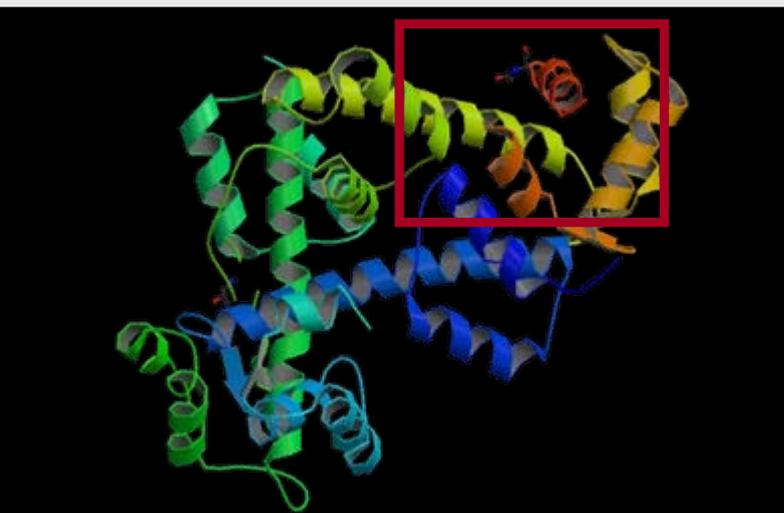
Our Solution

- Holy Grail: Block parasite invasion of host
- Invasion of host cells by parasite requires interaction of two proteins (Myosin A and MTIP)
- This interaction is unique to, and universal among, all 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

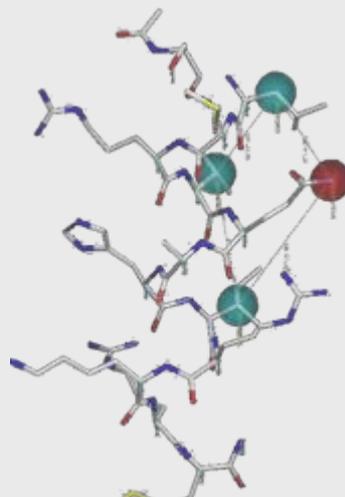


X-ray Crystal
Structure of MTIP-
MyoA Complex
Bosch J et al; *PNAS*
(2006)

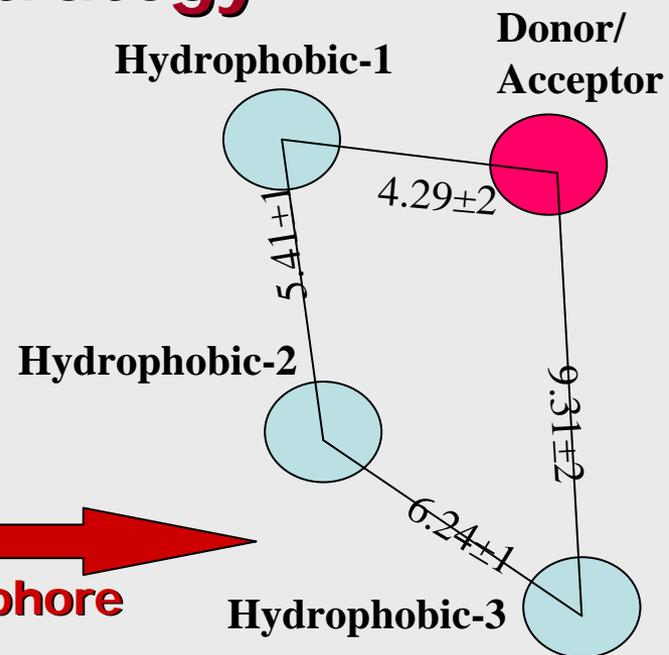
Computational Design Strategy



MTIP-Myosin A complex



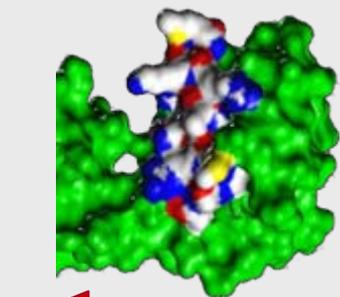
Extract Pharmacophore



**Screen
Shape Sigs
Library**

Shape Signatures
Chemical Library
3+ million compounds

Initial Hits



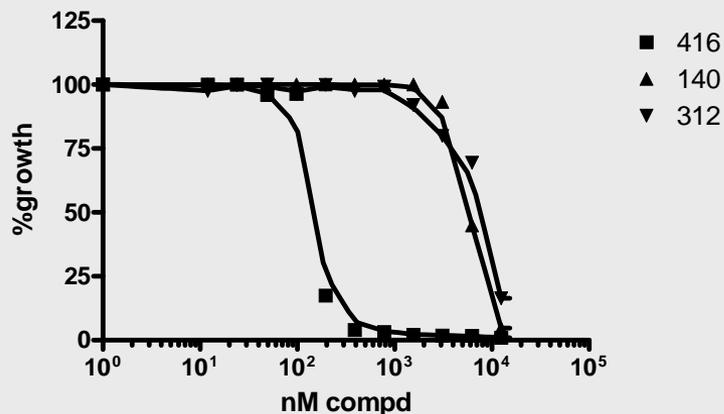
Docking of Hits

Priority List

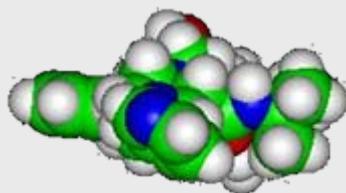
- 1 ...
- 2 ...
- 3 ...
- 4 ...
-

Family of MTIP-Myosin Inhibitors

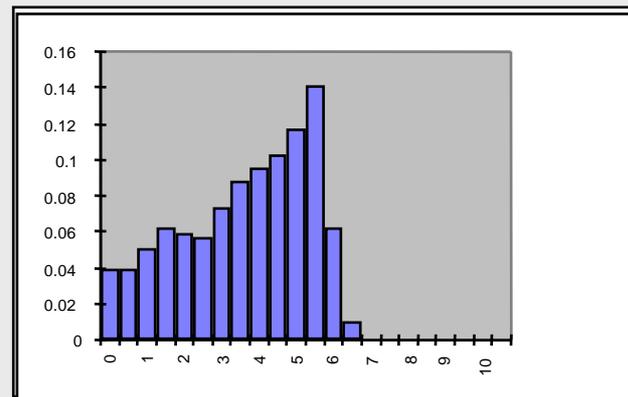
Transform of Data 1: Transformed data



SW416: IC₅₀ = 75 nM



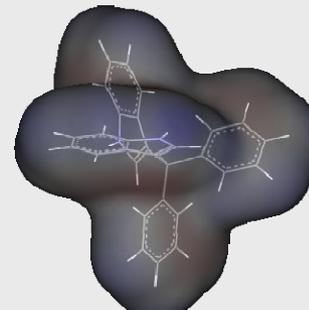
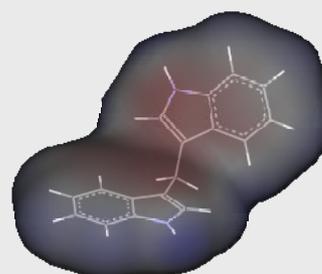
Convert to
Shape Signature



Family of Inhibitors

Drug-like
Filters

Shape Signatures
Chemical Library
3+ million compounds

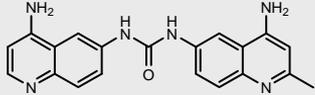
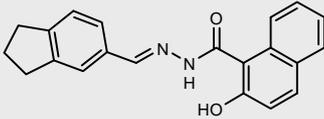
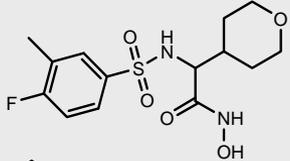
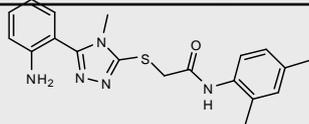
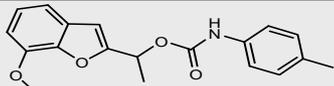
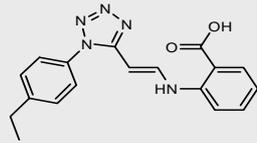


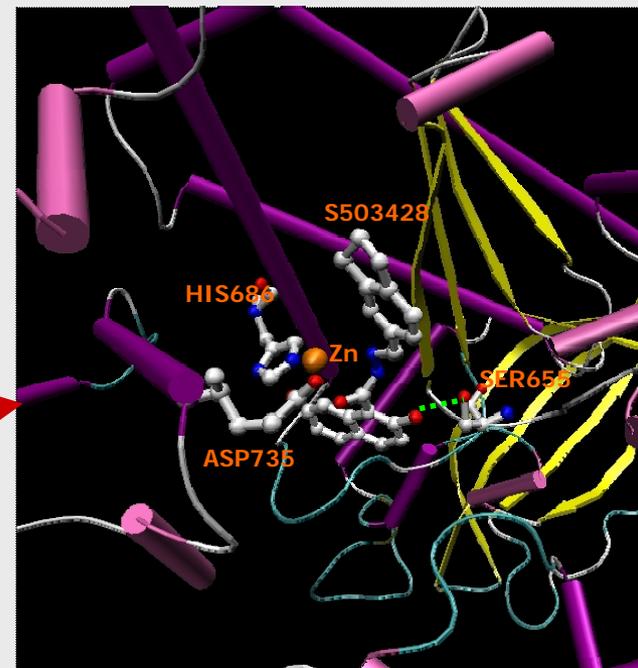
Summary

- 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 μ M)
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



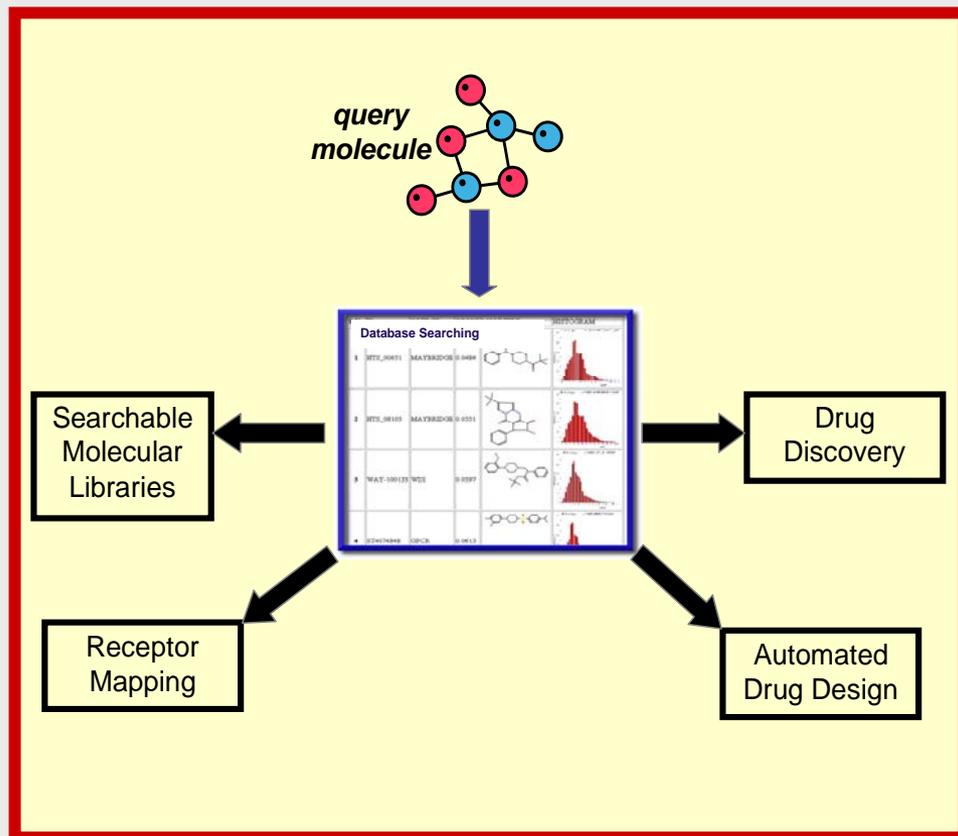
S503428 docked in the ligand binding pocket of anthrax LF

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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