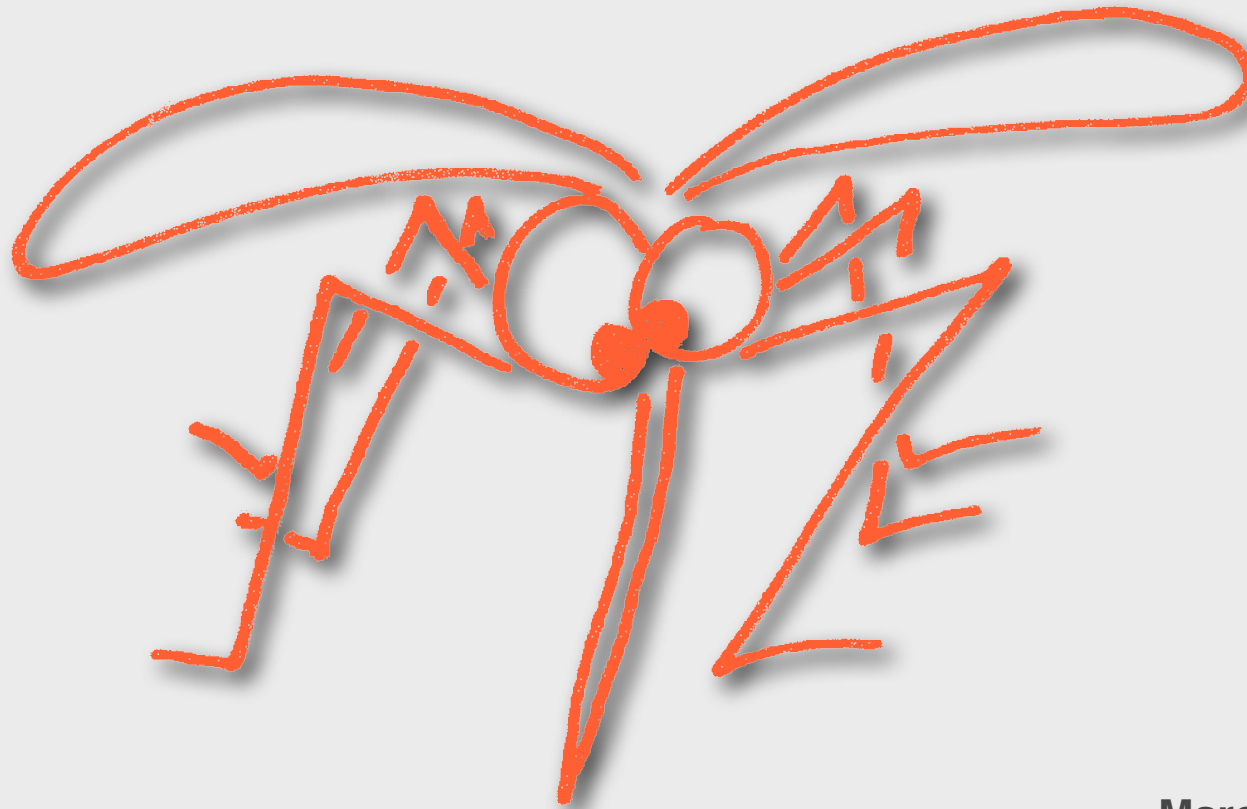


The Tropical Disease Initiative

An open source approach to drug development

www.tropicaldisease.org

www.thesynapticleap.org



Marc A. Marti-Renom

<http://salilab.org/~marcius>

Depts. of Biopharmaceutical Sciences and Pharmaceutical Chemistry
California Institute for Quantitative Biomedical Research
University of California at San Francisco

CM



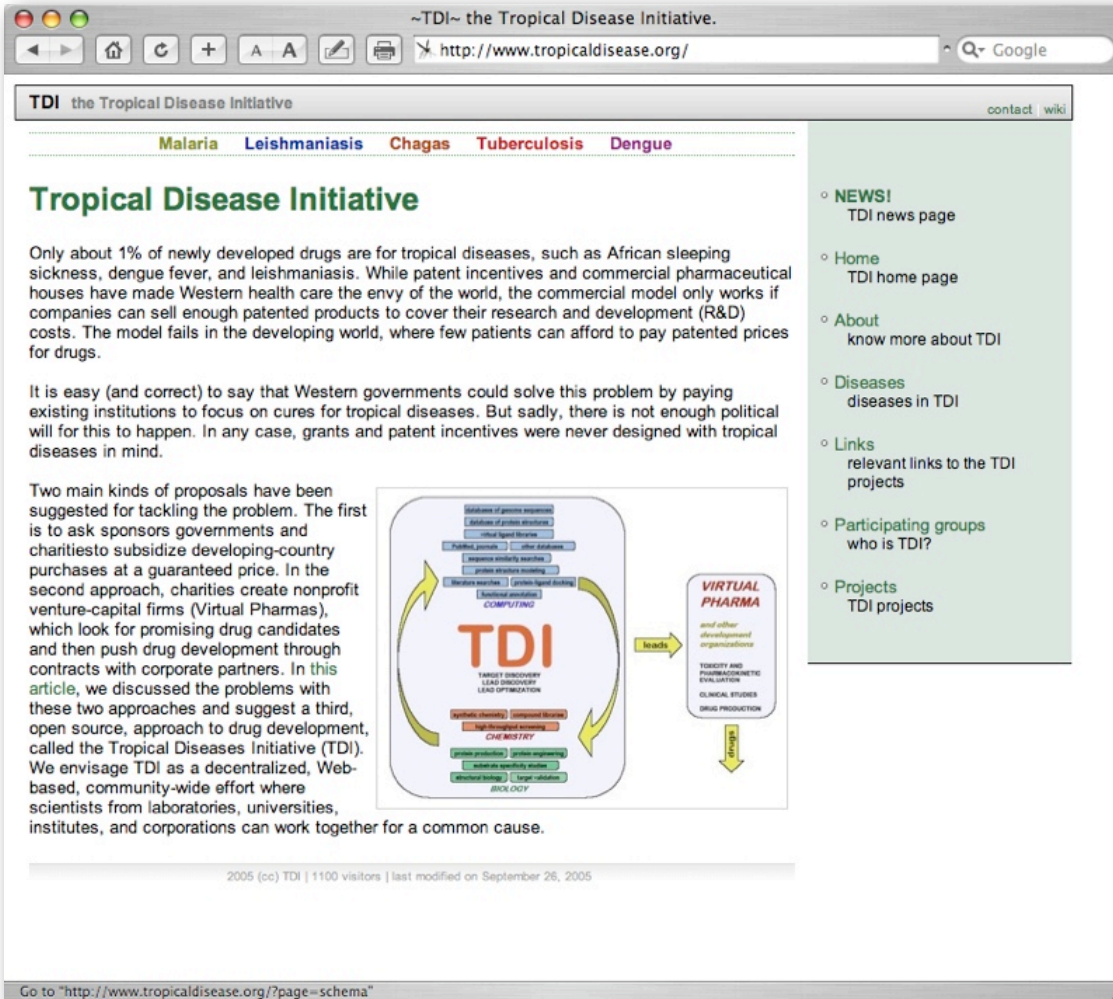
TDI

TDI

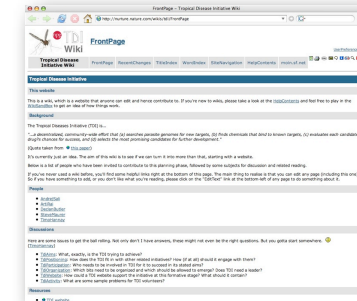
“20%”

TDI web site

<http://www.tropicaldisease.org>

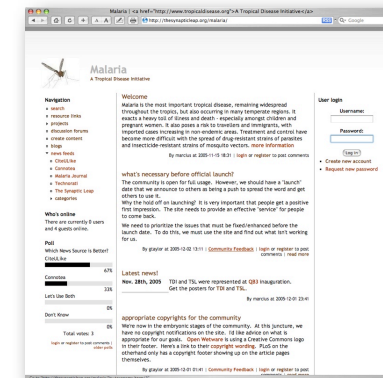


The screenshot shows the TDI website homepage. At the top, there is a navigation bar with links for Malaria, Leishmaniasis, Chagas, Tuberculosis, and Dengue. The main heading is "Tropical Disease Initiative". Below this, there is a paragraph explaining the initiative's goal: "Only about 1% of newly developed drugs are for tropical diseases, such as African sleeping sickness, dengue fever, and leishmaniasis. While patent incentives and commercial pharmaceutical houses have made Western health care the envy of the world, the commercial model only works if companies can sell enough patented products to cover their research and development (R&D) costs. The model fails in the developing world, where few patients can afford to pay patented prices for drugs." This is followed by another paragraph: "It is easy (and correct) to say that Western governments could solve this problem by paying existing institutions to focus on cures for tropical diseases. But sadly, there is not enough political will for this to happen. In any case, grants and patent incentives were never designed with tropical diseases in mind." A third paragraph states: "Two main kinds of proposals have been suggested for tackling the problem. The first is to ask sponsors governments and charities to subsidize developing-country purchases at a guaranteed price. In the second approach, charities create nonprofit venture-capital firms (Virtual Pharmas), which look for promising drug candidates and then push drug development through contracts with corporate partners. In this article, we discussed the problems with these two approaches and suggest a third, open source, approach to drug development, called the Tropical Diseases Initiative (TDI). We envisage TDI as a decentralized, Web-based, community-wide effort where scientists from laboratories, universities, institutes, and corporations can work together for a common cause." A central diagram shows the TDI process flow: "TROPICAL DISEASES INITIATIVE (TDI)" is at the center, with "COMPUTING" above and "CHEMISTRY" below. To the left, a circular flow includes "Genome analysis", "Target discovery", "Lead discovery", "Lead optimization", "Target validation", "Target identification", "Target validation", "Target identification", "Target validation", "Target identification". To the right, a box labeled "VIRTUAL PHARMA" contains "Target discovery", "Lead discovery", "Lead optimization", "Target validation", "Target identification". Below the diagram, it says "leads" and "drug". At the bottom, it says "2005 (cc) TDI | 1100 visitors | last modified on September 26, 2005".



The screenshot shows the TDI Wiki page. It features a navigation bar with links for Home, About, Diseases, Links, Participating groups, and Projects. The main content area is titled "Tropical Disease Initiative" and contains a list of links and information. The page is designed to be a central hub for community members to share and discuss research.

<http://nurture.nature.com/wikis/tidi/>



The screenshot shows the Malaria page on thesynapticleap.org. It features a navigation bar with links for Home, About, Diseases, Links, Participating groups, and Projects. The main content area is titled "Malaria" and contains a list of links and information. The page is designed to be a central hub for community members to share and discuss research.

<http://www.thesynapticleap.org>



The Synaptic Leap
Open Source Biomedical Research

<http://www.thesynapticleap.org>

Some time back...

14 Mar 2005

I think TDI is a unique and very interesting project. I would like so much to make something for it...

So, where are we going? What's happening? What can we do?

I still trust in open source drug discovery. :-))

Luca Brivio

t, if any, the bottlenecks are?

g ideas and potential avenues to explore,
n Action Plan!

9 Mar 2005

I'm a programmer, not
something to keep the
**If someone will tell me when
begin on, I'd be grateful.**

disease for underserved popu:
however, confused.
Regards,
Jacob Lester

GNU started with RM
Linux started with Lin
Thank you kindly,
Adam Huber

You need someone g
people start sending patches...

I know this is chicken-egg, but someone needs to point this out, since I haven't seen this brought up in the papers or the website.

And you might consider merging into the bios.net effort mentioned already. Together, you just might reach the critical mass for things to take off. Consider this like when people jumped off the HURD project to come together and make linux work.

Daniel Amelang

mistic that the

Stephen Mark Maurer

Some time back...

14 Mar 2005

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So, where are we going? What's happening?

I still trust in open source drug discovery. :-))

Luca Brivio

16 Feb 2005

Hi,

It would be interesting to know what, if any, the bottlenecks are?

The Wiki site contains many interesting ideas and potential avenues to explore, but from what I can see it is **lacking an Action Plan!**

Regards,
Jacob Lester

9 Mar 2005

I'm a programmer, not a biologist. I'd like to do something to help with disease for underserved populations, however, confused. **If someone will tell me where to begin on, I'd be grateful.**

GNU started with RM
Linux started with Lin

You need someone good
people start sending patches...

I know this is chicken-egg, but someone needs to point this out, since I haven't seen this brought up in the papers or the website.

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Stephen Mark Maurer

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Some time back...

14 Mar 2005

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So, where are we?

I still trust in open source.

Luca Brivio

16 Feb 2005

Hi,

10 Feb 2005

Hello,

My name is Adam Huber and I am a medical student at UNSW in Sydney Australia. I am interested in beginning research focused on tropical and infectious disease for underserved populations (A mission that seemingly matches TDI). I am, however, confused.

If someone will tell me where to sign up and give me some research topics to begin on, I'd be grateful.

Thank you kindly,

Adam Huber

9 Mar 2005

I'm a programmer, not a researcher. I'd like to do something to keep the project alive.

GNU started with RM and Linux started with Linus.

You need someone good to get the project started. I'd like to see if people start sending patches...

I know this is chicken-egg, but someone needs to point this out, since I haven't seen this brought up in the papers or the website.

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Daniel Amelang

What are the bottlenecks are?

What are the initial avenues to explore,

Optimistic that the

Stephen Mark Maurer

Some time back...

14 Mar 2005

I think TDI is a unique and very interesting project. I think there's something for it...

So, where are we?

I still trust in open

Luca Brivio

16 Feb 2005

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I'm a programmer, not a bioinformatician, but I stumbled across your site and thought I'd say something to keep the list active :)

GNU started with RMS. He gave us programming/administration tools to play with.

Linux started with Linus. He released an operating system for us to play with.

You need someone great in the field to release something for everyone to 'play with'. Then people start sending patches...

I know this is chicken-egg, but someone needs to point this out, since I haven't seen this brought up in the papers or the website.

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I know this is chicken-egg, but someone in the papers or the website.

And you might consider merging into the reach the critical mass for things to take a project to come together and make linux

Daniel Amelang

19 Jan 2005

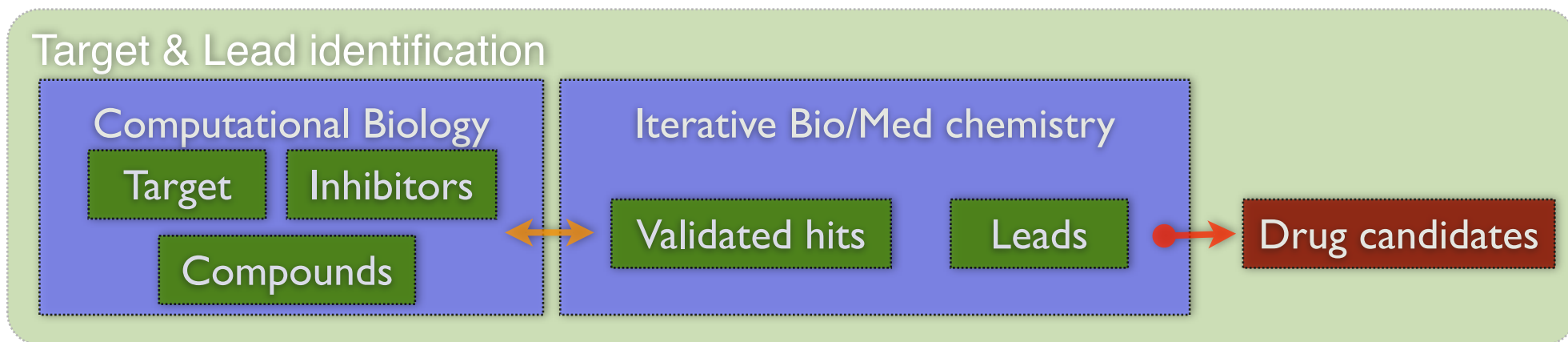
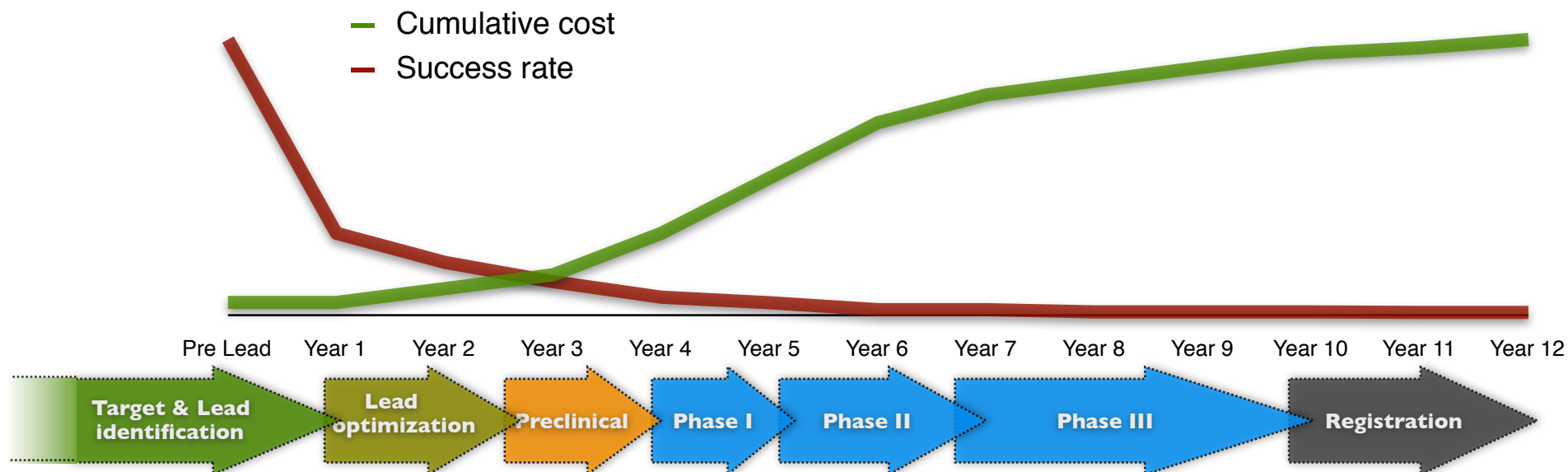
If we do the science well, I'm optimistic that the rest of TDI will fall into place.

Stephen Mark Maurer

Action plan @ Tropical Disease Initiative

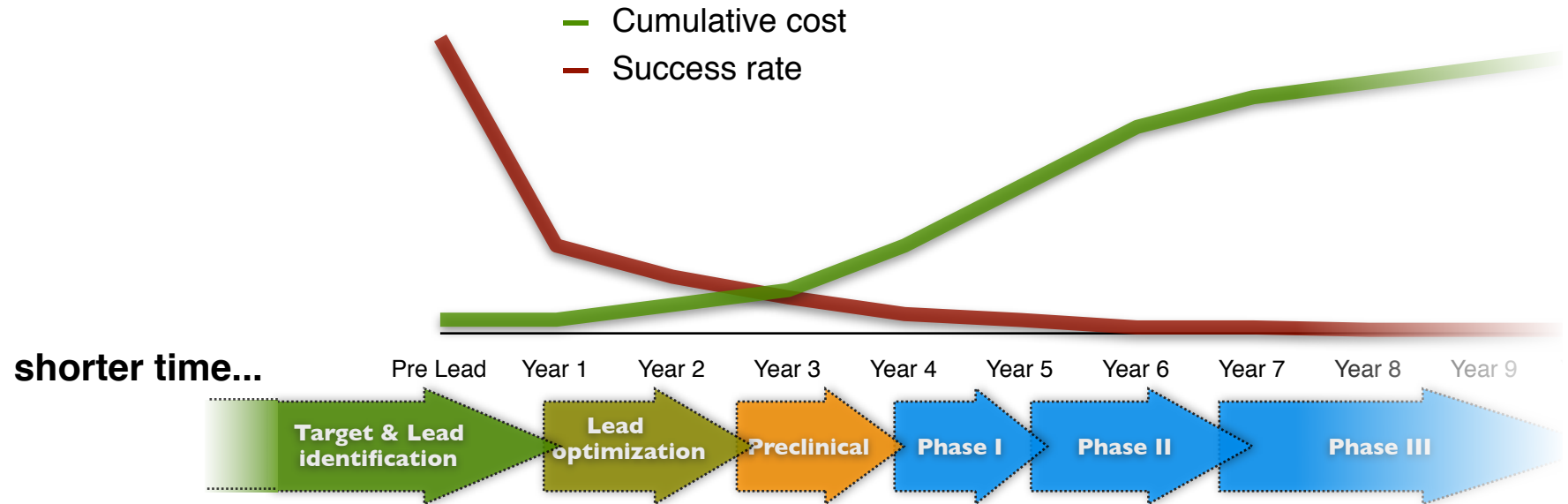
- * TDI and drug discovery
- * What CB can do?
- * What CB has done?
- * Projects in TDI/TSL

Drug Discovery pipeline



Adapted from: - Nwaka & Ridley. (2003) *Nature Reviews. Drug Discovery*. 2:919
- Austin, Brady, Insel & collins. (2004) *Science*. 306:1138

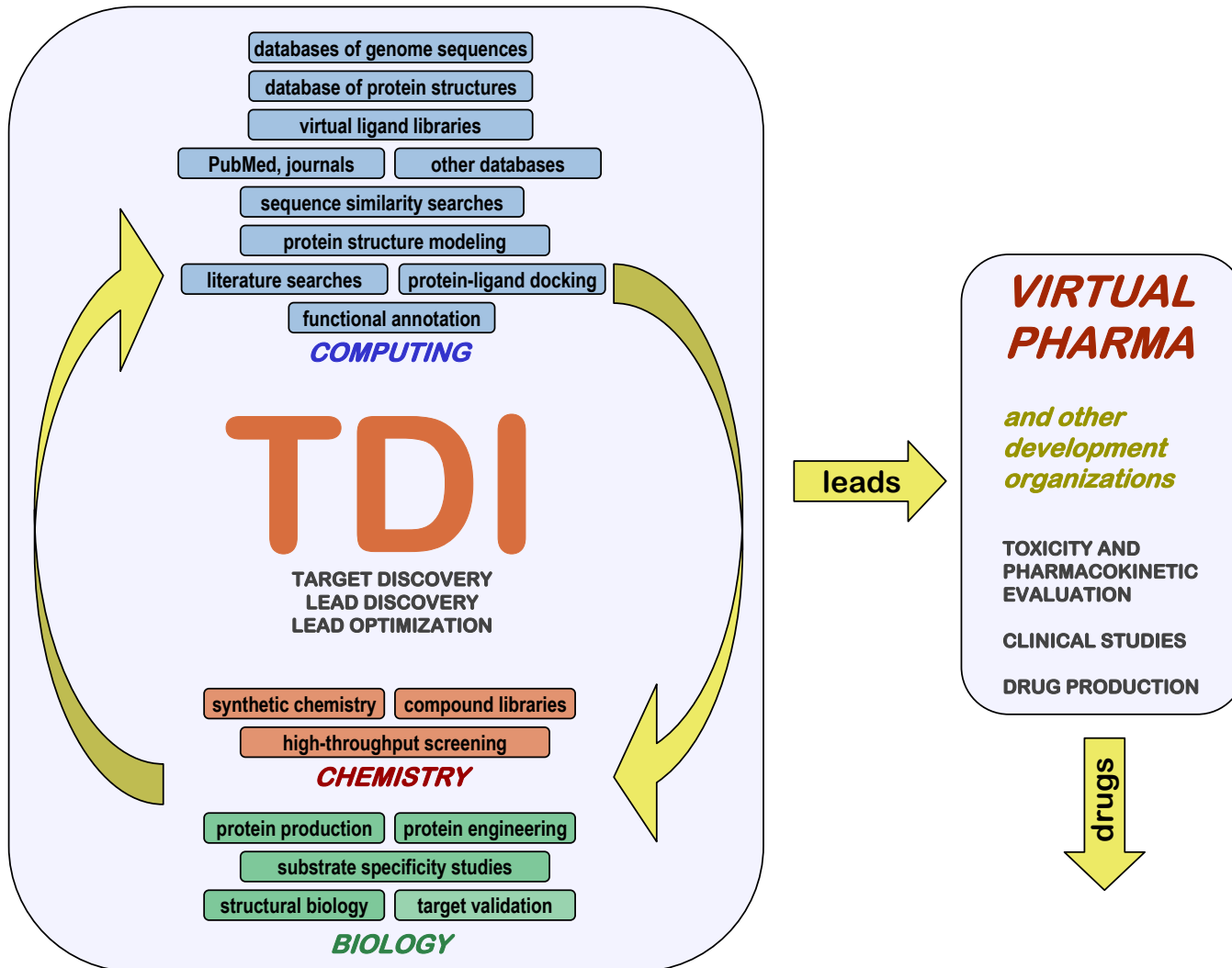
Drug Discovery pipeline



- + Completeness of genome projects (Malaria)
- + New and more complete biological databases
- + New software and computers (cheaper and faster)
- + Internet == more people == less cost

- Computational Biology **alone** is not enough
- TDI needs chemistry and biology! (**How?**)

TDI flowchart



Name	Type ^a	World Wide Web address ^b
DATABASES		
CATH	S	http://www.biochem.ucl.ac.uk/bsm/cath/
DBAli	S	http://www.salilab.org/DBAli/
GenBank	S	http://www.ncbi.nlm.nih.gov/Genbank/GenbankSearch.html
GeneCensus	S	http://bioinfo.mbb.yale.edu/genome
MODBASE	S	http://salilab.org/modbase/
MSD	S	http://www.rcsb.org/databases.html
NCBI	S	http://www.ncbi.nlm.nih.gov/
PDB	S	http://www.rcsb.org/pdb/
PSI	S	http://www.nigms.nih.gov/psi/
Sacch3D	S	http://genome-www.stanford.edu/Sacch3D/
SCOP	S	http://scop.mrc-lmb.cam.ac.uk/scop/
TIGR	S	http://www.tigr.org/tdb/mdb/mdbcomplete.html
TrEMBL	S	http://srs.ebi.ac.uk/
FOLD ASSIGNMENT		
123D	S	http://123d.ncifcrf.gov/
3D-PSSM	S	http://www.sbg.bio.ic.ac.uk/~3dpssm/
BIOINBGU	S	http://www.cs.bgu.ac.il/~bioinbgu/
BLAST	S	http://www.ncbi.nlm.nih.gov/BLAST/
DALI	S	http://www2.ebi.ac.uk/dali/
FASS	S	http://bioinformatics.burnham-inst.org/FFAS/index.html
FastA	S	http://www.ebi.ac.uk/fasta3/
FRSVR	S	http://fold.doe-mbi.ucla.edu/
FUGUE	S	http://www.cryst.bioc.cam.ac.uk/~fugue/
LOOPP	S	http://ser-loopp.tc.cornell.edu/cbsu/loopp.htm
PDB-Blast/FASS	S	http://bioinformatics.ljcrf.edu/pdb_blast/
RHD_PITTS	S	http://www.predictprotein.org/

What can CB do?

Available computational biology resources for TDI

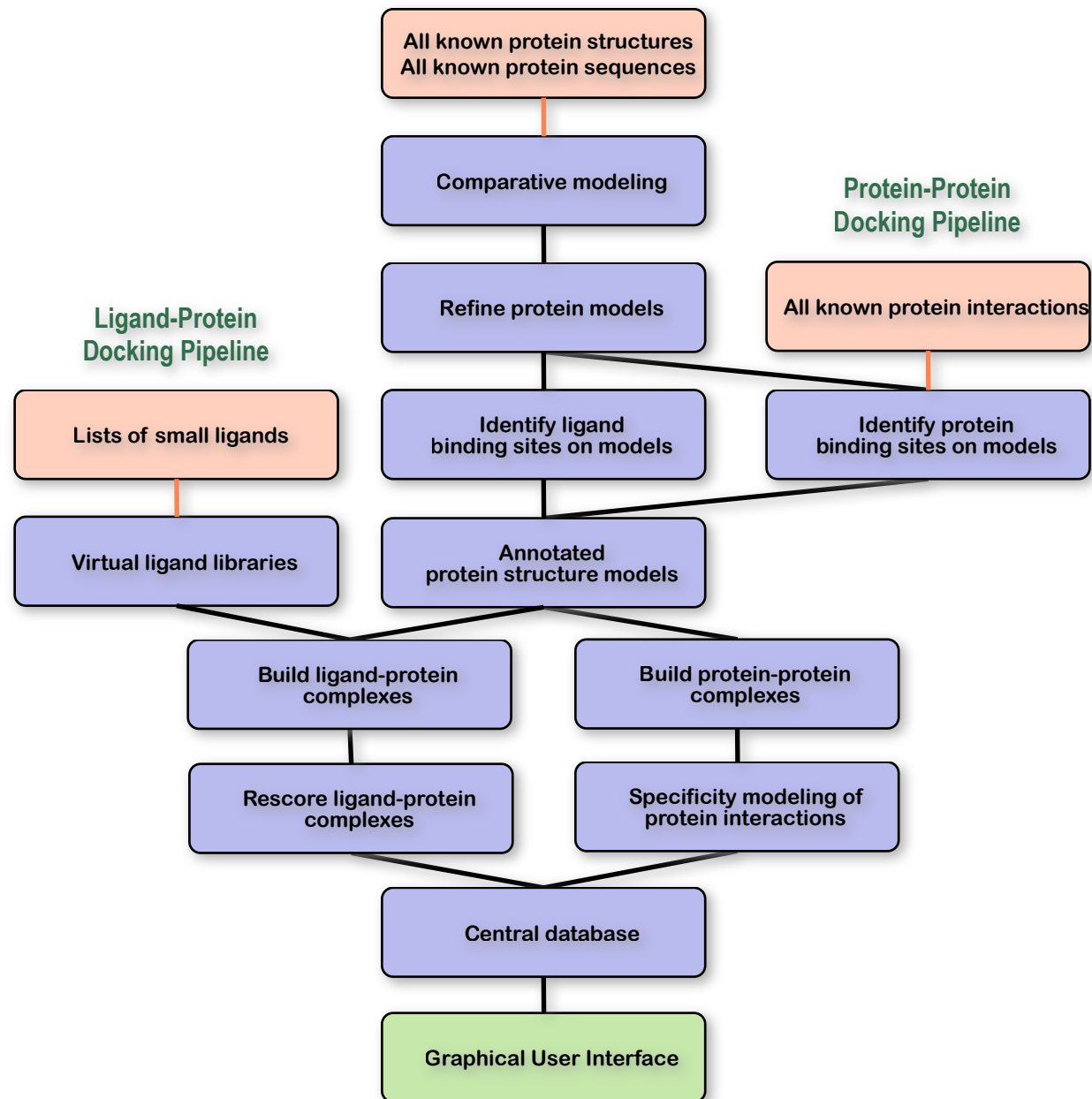
Protein-Ligand Universe

Center for Computational Proteomics Research (CCPR)

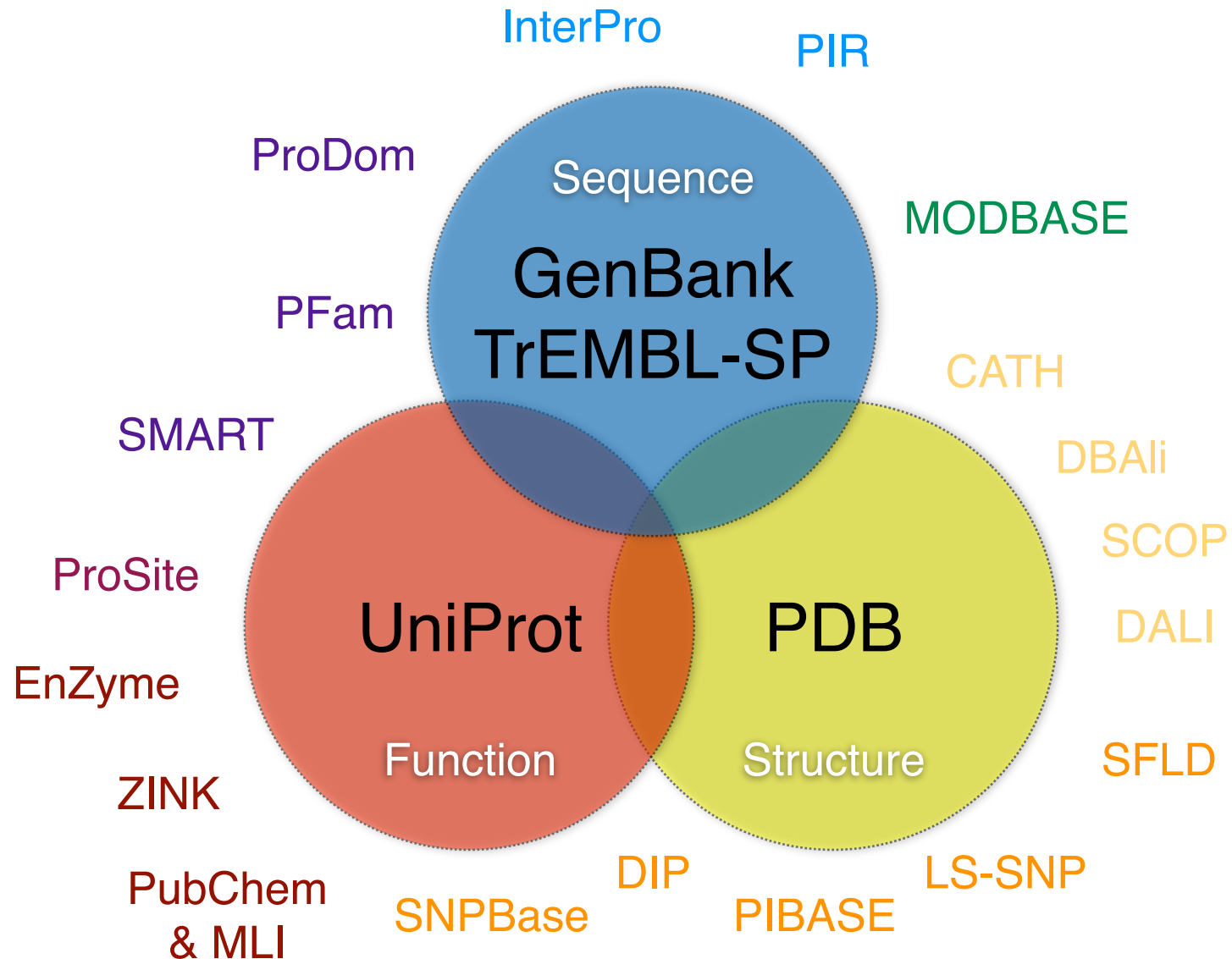
The California Institute for Quantitative Biomedical Research

Patsy Babbitt, Fred
Cohen, Ken Dill, Tom
Ferrin, John Irwin, Matt
Jacobson, Tack Kuntz,
Marc A. Marti-Renom,
Andrej Sali, Brian
Shoichet, Chris Voigt

<http://www.ccpr.ucsf.edu/>



Databases



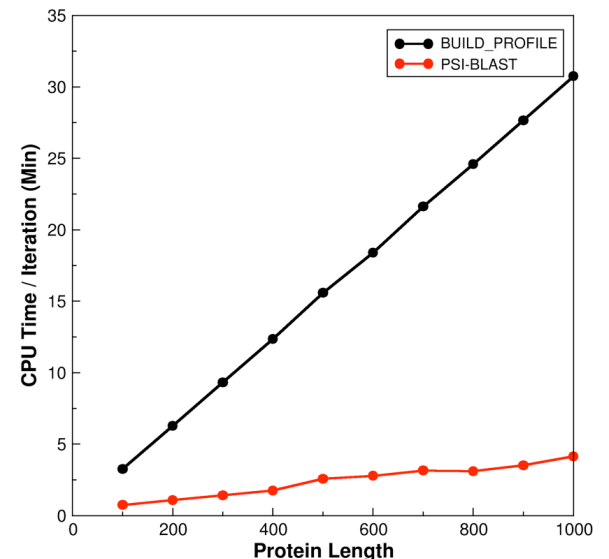
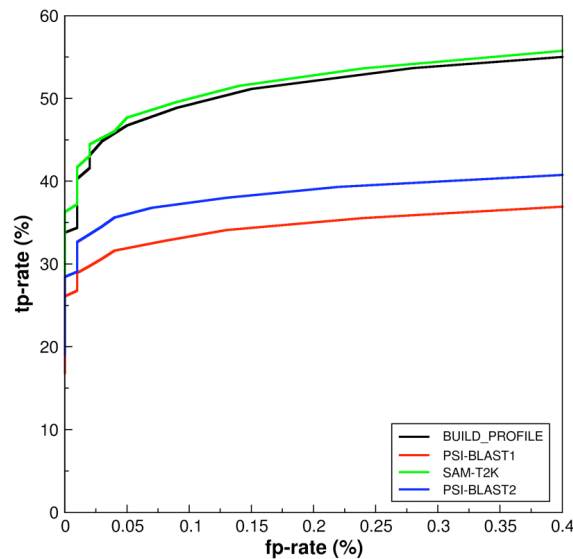
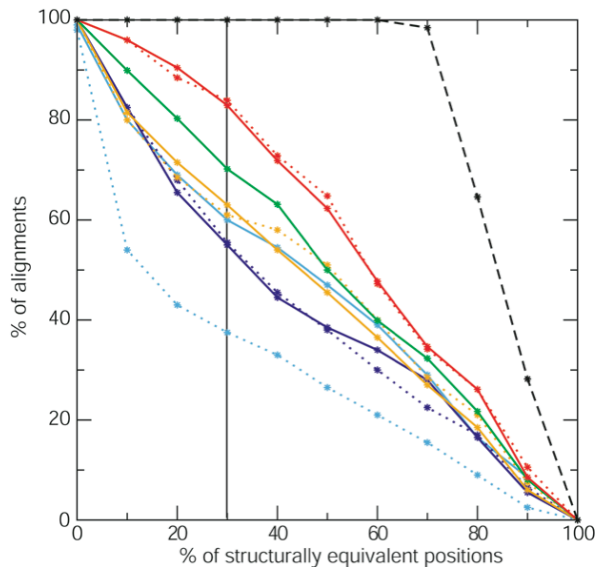
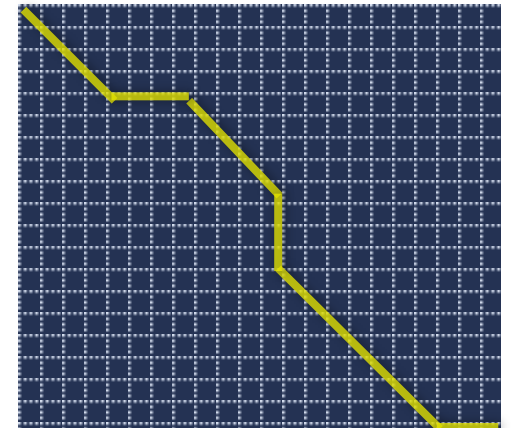
Sequence search

Profile based homology detection

Sequence A: **AGHLAHTRCELKLP**TCRGNMSSRFC
 Sequence B: **AGHLRHTRRCLRLP**TAGNARFC

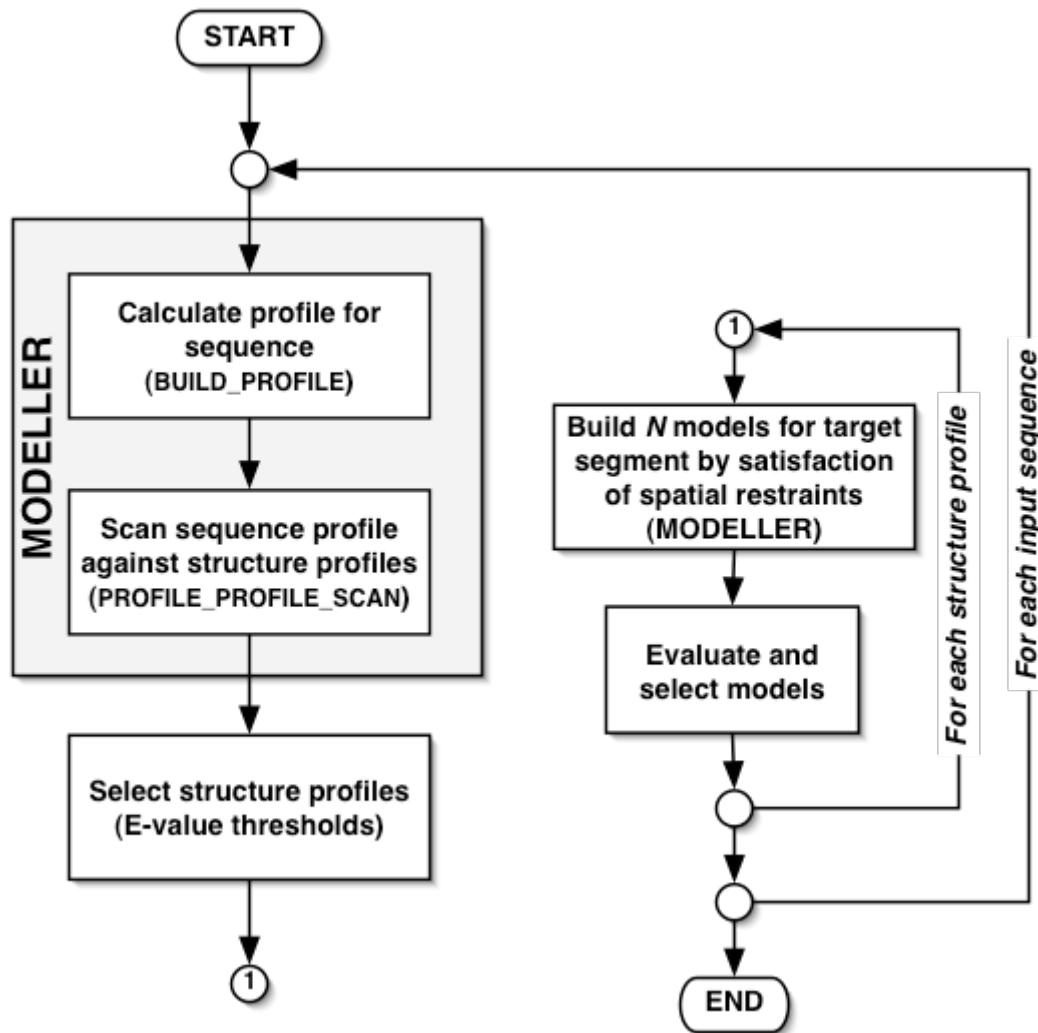
AGHLRHTRRCLRLPTAGNARFC
 AGHLRHTRRCLRLPTA---RFC
 AGHLRATRRCCLRLTTAGNAR--
 AGHLRHALAIIRLPTAGNAR--
 AGHL---AACLRRLPTAGNARFC

AGCATHTRCELK-----
 AGHLAHPILELKLPTC---MSSRFC
 AGCGTHPILELK-----SSRFC
 AGHLAHTRCELKLP TCRGNMSSRFC



Protein Structure Modeling

ModPipe & ModWeb



Mod Web

Your e-mail address	<input type="text"/>
A name for the run (optional)	<input type="text"/>
MODELLER Access Key	<input type="text"/>
Input	
Enter the 4-letter PDB code of the structure <input type="text"/>	
or upload a file containing the structure (PDB format only)	
<input type="button" value="Choose File"/>	no file selected
Output	
You will receive an e-mail informing you how to access the models in ModBase.	
<input type="button" value="CALCULATE MODELS"/> <input type="button" value="RESET"/>	
Advanced Options	
Maximum number of iterations for PSSM	<input type="text" value="10"/>
E-value cutoff for inclusion in PSSM	<input type="text" value="0.0005"/>
E-value cutoff for IMPALA search	<input type="text" value="1"/>
Hit Selection :	<input type="radio"/> soft <input type="radio"/> normal <input checked="" type="radio"/> strict

<http://www.salilab.org/modweb/>

Eswar et.al., (2003) Nucl.Acids.Res. 31(13)

Protein Structure Modeling

Large-Scale prediction

Sequences	3,094,524
Modeled sequences	1,084,750
Models	2,978,447
ModWeb datasets	1,506
ModWeb Models	387,403

Protein Structure Modeling

MODBASE (<http://www.salilab.org/modbase/>)

Search Page

Model Details

Sequence Overview

	<input type="checkbox"/>	Q8G8A6	hypothetical protein	Pseudomonas aeruginosa	3738
	<input type="checkbox"/>	Q8G9W1	hypothetical protein	Escherichia coli	1140
	<input type="checkbox"/>	Q8CY62	hypothetical protein spr1965	Streptococcus pneumoniae , Streptococcus pneumoniae R6	1038

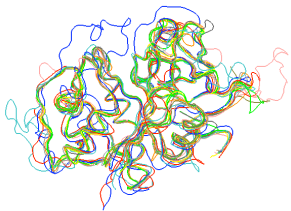
Model Overview

	<input type="checkbox"/>	Q8G8C7	hypothetical protein	Pseudomonas aeruginosa	4996	2089-2158	70	37.00	7e-14	1.00	1dnyA	8-78
	<input type="checkbox"/>	Q8G8C7	hypothetical protein	Pseudomonas aeruginosa	4996	492-1017	526	36.00	1e-82	1.00	1amuA	19-529
	<input type="checkbox"/>	Q8G9W1	hypothetical protein	Escherichia coli	1140	349-1135	787	35.00	0	1.00	1r9dA	6-783

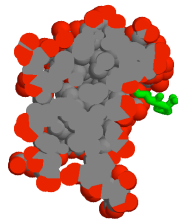
Functional Annotation

Localization of binding sites

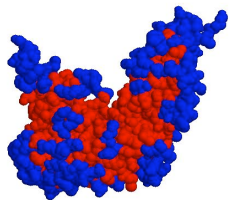
Structure conservation



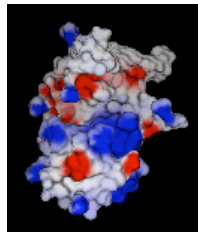
Solvent accessibility



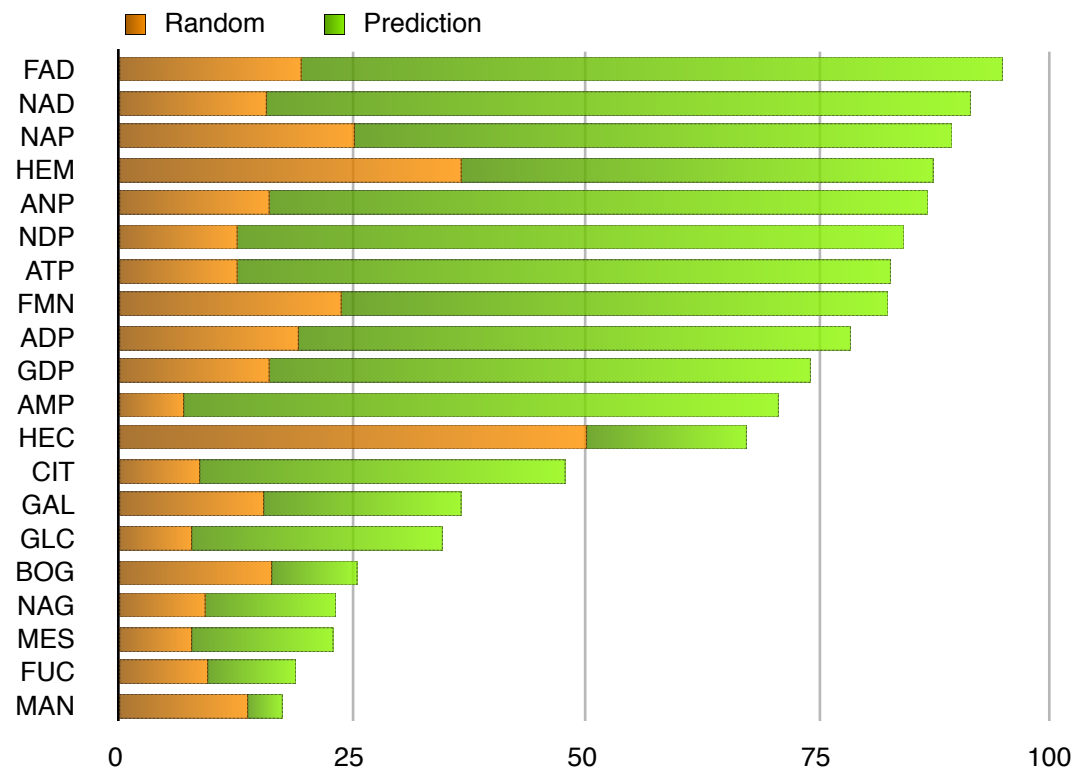
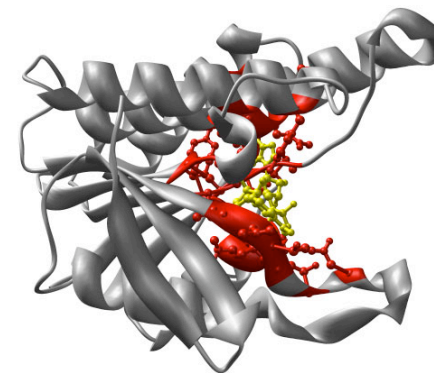
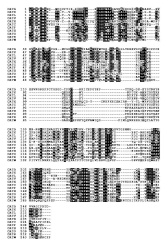
Surface geometry



Electrostatics

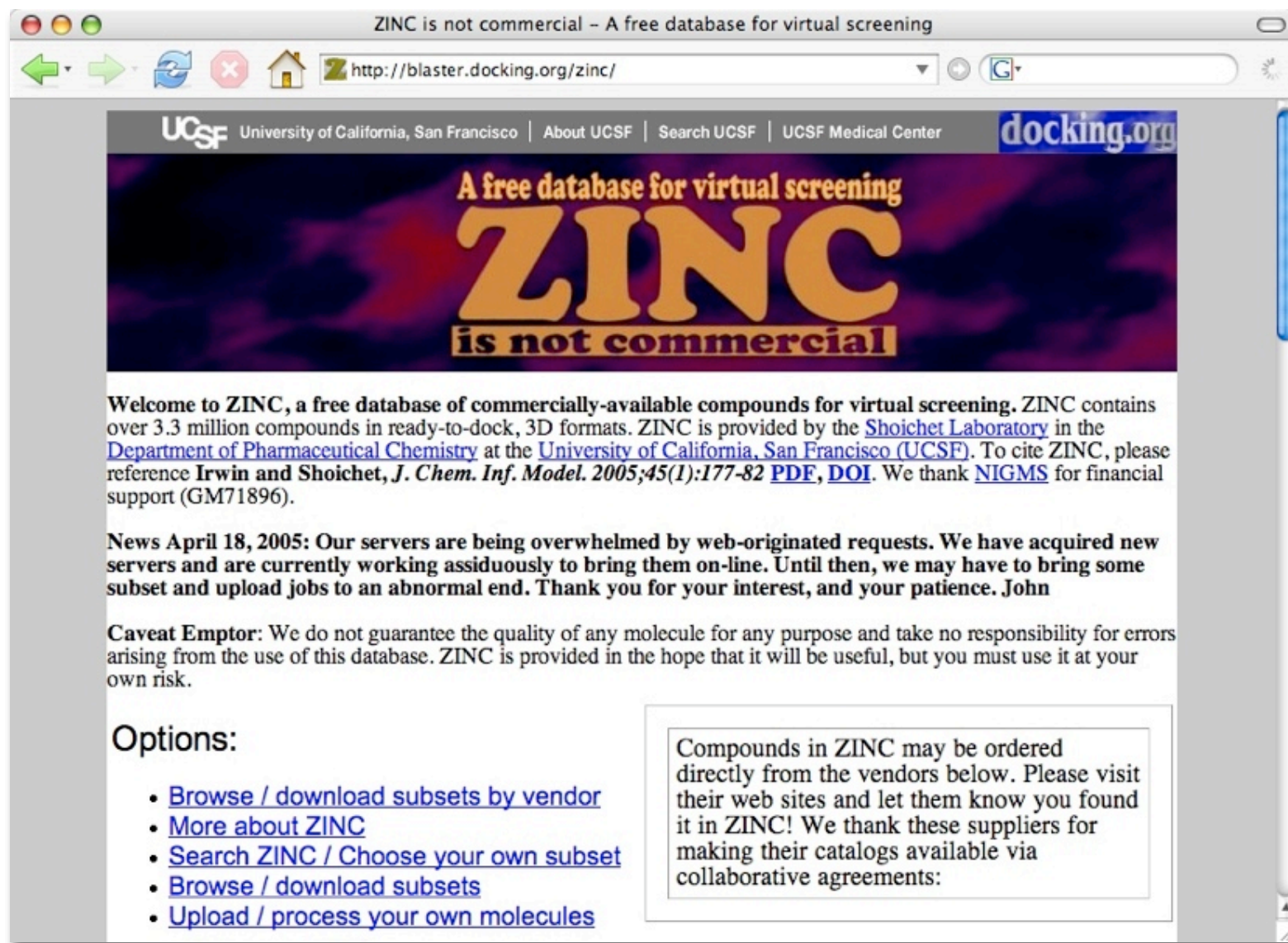


Sequence conservation



Virtual ligand libraries

ZINK (<http://blaster.docking.org/zinc/>)



The screenshot shows a web browser window with the title "ZINC is not commercial - A free database for virtual screening". The address bar contains the URL "http://blaster.docking.org/zinc/". The page header includes the UCSF logo and navigation links: "University of California, San Francisco | About UCSF | Search UCSF | UCSF Medical Center". A "docking.org" logo is also present in the top right. The main content area features a large banner with the text "A free database for virtual screening ZINC is not commercial". Below the banner, the text reads: "Welcome to ZINC, a free database of commercially-available compounds for virtual screening. ZINC contains over 3.3 million compounds in ready-to-dock, 3D formats. ZINC is provided by the Shoichet Laboratory in the Department of Pharmaceutical Chemistry at the University of California, San Francisco (UCSF). To cite ZINC, please reference Irwin and Shoichet, *J. Chem. Inf. Model.* 2005;45(1):177-82 PDF, DOI. We thank NIGMS for financial support (GM71896)."

News April 18, 2005: Our servers are being overwhelmed by web-originated requests. We have acquired new servers and are currently working assiduously to bring them on-line. Until then, we may have to bring some subset and upload jobs to an abnormal end. Thank you for your interest, and your patience. John

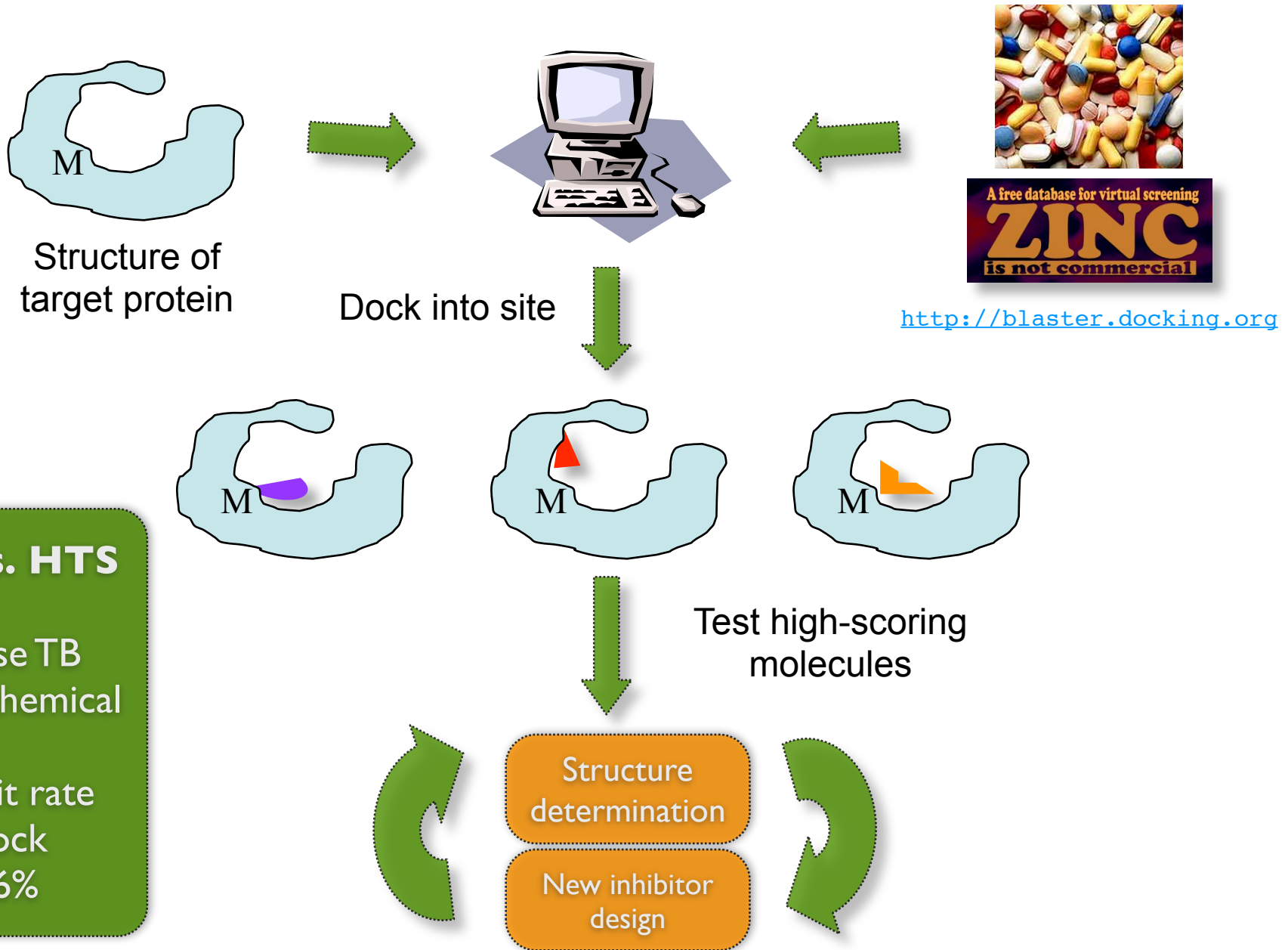
Caveat Emptor: We do not guarantee the quality of any molecule for any purpose and take no responsibility for errors arising from the use of this database. ZINC is provided in the hope that it will be useful, but you must use it at your own risk.

Options:

- [Browse / download subsets by vendor](#)
- [More about ZINC](#)
- [Search ZINC / Choose your own subset](#)
- [Browse / download subsets](#)
- [Upload / process your own molecules](#)

Compounds in ZINC may be ordered directly from the vendors below. Please visit their web sites and let them know you found it in ZINC! We thank these suppliers for making their catalogs available via collaborative agreements:

Protein-Ligand Docking



Docking .vs. HTS

Target: reductase TB
Library: Merk chemical

$IC_{50} < 100\mu M$ hit rate

HTS	Dock
0.2%	~6%

Protein-Ligand Docking

Successfully applied

Target	Best hit IC ₅₀ (μM)	Docking program	Structure solved?
Aldose reductase	4.3	Adam & Eve	No
CDK4	44	Legend	Yes
Matriptase	0.9	DOCK	No
Bcl-2	10.4	DOCK	No
Adenovirus protease	3.1	EUDOC	No
AmpC	26 ^a	DOCK3.5.54	Yes
Retinoic acid receptor	2	ICM	No
TH receptor	1.5	ICM	No
TGT	8.3	LUDI/ FlexX	Yes
Carbonic anhydrase	0.0008	FlexX	Yes
HPRTase	2.2 ^a	DOCK3.5.54	No
Lysozyme cavity site	56 ^b	DOCK3.5.54	Yes
H ₂ picolinate reductase	7.2	FLOG	No
PTP-1B	0.5	DOCK3.5.54	No
Edema Factor	25 ^a	DOCK3.5.54	No
CDK2	0.08	DOCK4	No

Some recent docking successes (a. K_i. b. K_d).

Name	Type ^a	World Wide Web address ^b
DATABASES		
CATH	S	http://www.biochem.ucl.ac.uk/bsm/cath/
DBAli	S	http://www.salilab.org/DBAli/
GenBank	S	http://www.ncbi.nlm.nih.gov/Genbank/GenbankSearch.html
GeneCensus	S	http://bioinfo.mbb.yale.edu/genome
MODBASE	S	http://salilab.org/modbase/
MSD	S	http://www.rcsb.org/databases.html
NCBI	S	http://www.ncbi.nlm.nih.gov/
PDB	S	http://www.rcsb.org/pdb/
PSI	S	http://www.nigms.nih.gov/psi/
Sacch3D	S	http://genome-www.stanford.edu/Sacch3D/
SCOP	S	http://scop.mrc-lmb.cam.ac.uk/scop/
TIGR	S	http://www.tigr.org/tdb/mdb/mdbcomplete.html
TrEMBL	S	http://srs.ebi.ac.uk/
FOLD ASSIGNMENT		
123D	S	http://123d.ncifcrf.gov/
3D-PSSM	S	http://www.sbg.bio.ic.ac.uk/~3dpssm/
BIOINBGU	S	http://www.cs.bgu.ac.il/~bioinbgu/
BLAST	S	http://www.ncbi.nlm.nih.gov/BLAST/
DALI	S	http://www2.ebi.ac.uk/dali/
FASS	S	http://bioinformatics.burnham-inst.org/FFAS/index.html
FastA	S	http://www.ebi.ac.uk/fasta3/
FRSVR	S	http://fold.doe-mbi.ucla.edu/
FUGUE	S	http://www.cryst.bioc.cam.ac.uk/~fugue/
LOOPP	S	http://ser-loopp.tc.cornell.edu/cbsu/loopp.htm
PDB-Blast/FASS	S	http://bioinformatics.licrf.edu/pdb_blast/
PREDICTOR	S	http://www.predictor.com/

What has CB done?

Success stories in structure-based drug design...

Examples

HIV Proteinase inhibitors (1989)

Knowledge-based protein modelling and design.

Blundell T, et al Eur J Biochem. 1988 15:513

“A systematic technique for protein modelling that is applicable to the design of drugs, peptide vaccines and novel proteins is described. We have modelled an analogous protein, HIV viral proteinase on the basis of aspartic proteinases”.

X-ray analysis of HIV-1 proteinase at 2.7 Å resolution confirms structural homology among retroviral enzymes.

Lapatto et al Nature. 1989 Nov 16;342(6247):299-302.

“Knowledge of the tertiary structure of the proteinase from human immunodeficiency virus HIV-1 is important to the design of inhibitors that might possess antiviral activity and thus be useful in the treatment of AIDS. The conserved Asp-Thr/Ser-Gly sequence in retroviral proteinases suggests that they exist as dimers similar to the ancestor proposed for the pepsins.”



HIV Proteinase structure

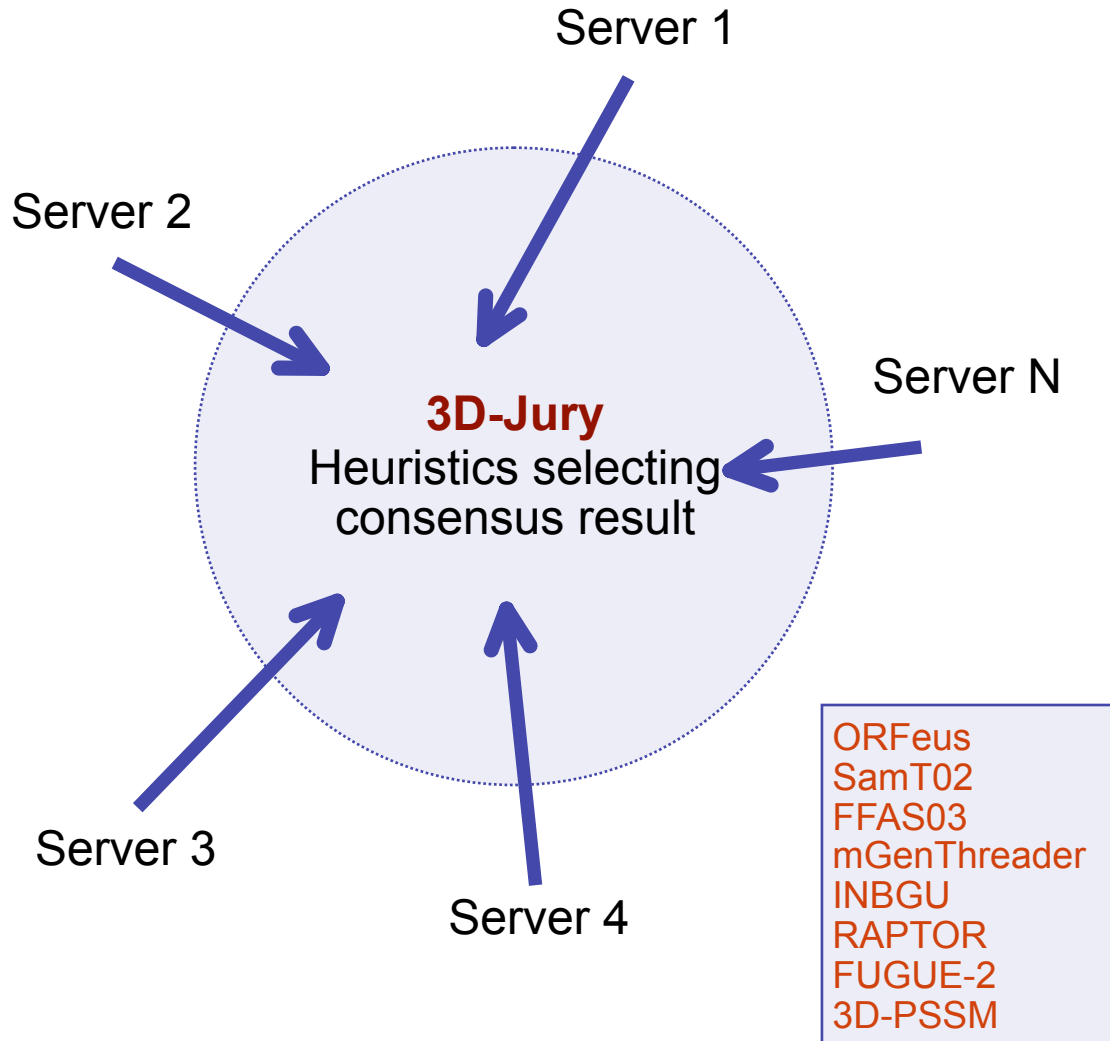
The 3-D structure of HIV-1 proteinase and the design of antiviral agents for the treatment of AIDS.

Blundell et al Trends Biochem Sci. 1990 Nov;15(11):425-30.

“Analogies between the structures of HIV-1 proteinase and the mammalian enzyme renin have given **important clues** concerning the design of specific inhibitors that have antiviral activity.”

Examples

mRNA Cap-1 Methyltransferase in SARS (2003)



Cell, Vol. 113, 701–702, June 13, 2003, Copyright ©2003 by Cell Press

Letter to the Editor

mRNA Cap-1 Methyltransferase in the SARS Genome

The 3D jury system has predicted the methyltransferase fold for the nsp13 protein of the SARS coronavirus. Based on the conservation of a characteristic tetrad of residues, the mRNA cap-1 methyltransferase function has been assigned to this protein, which has potential implications for antiviral therapy.

The latest outbreak of the severe acute respiratory syndrome (SARS) epidemic has led to thousands of potentially lethally infected patients and hundreds of deaths. These numbers are likely to rise, and the spreading disease is already causing major medical and economical concerns. Meanwhile, the SARS coronavirus identified as the pathogen responsible for the disaster has been isolated, and its genome sequenced (Marra et al., 2003; Rota et al., 2003).

We have applied the 3D jury meta predictor (Ginalski et al., 2003) to annotate the structure and function of proteins encoded by the viral positive-strand ssRNA. Novel fold recognition methods utilize the global network of independent structure prediction servers. Detection of patterns of structural similarity between diverse models is used to consistently select the correct fold from a set of borderline predictions. Such methods made a dramatic impact on the last critical assessment of protein structure prediction (CASP-5 experiment) conducted in the summer of 2002. One of the most interesting findings obtained during the SARS genome annotation process is a surprisingly reliable (3D jury score >100) assignment of the methyltransferase fold to the nsp13 (GI:30133975) domain located in the C-terminal part of the almost 7000 amino acid large pp1ab viral polyprotein (Figure 1). Standard sequence comparison tools such as PSI-BLAST or RPS-BLAST applied using the conserved domain database (Marchler-Bauer et al., 2003) failed to assign any function to this domain. The domain belongs to the ancient family of AdoMet-dependent ribose 2'-O-methyltransferases, which has been adapted by numerous viruses before the three domains of life evolved from the last universal common ancestor (LUCA) (Feder et al., 2003). The enzymatic role of the protein was confirmed by the presence of the conserved tetrad of residues K-D-K-E essential for mRNA cap-1 (m⁵GpppNm) formation.

The mRNA cap methylation is found indispensable for efficient replication of many viruses (Bach et al., 1995; Wocyniuk et al., 1995; Vlot et al., 2002) and represents an active area for drug development. Nevertheless, direct inhibitors of the nsp13 enzyme may fail to suppress viral replication, as the cap-1 formation seems to be less critical than the preceding cap-0 (m⁷GpppN) formation (Latner et al., 2002; Wu and Guarino, 2003). The existence of the cap-1-forming enzyme in the genome would

suggest that the virus also requires the AdoMet-dependent cap-0 methyltransferase. Both functions can be inhibited by carbocyclic analogs of adenosine, such as Neplanocin A or 3-deazaneplanocin A, which interfere with the AdoMet-AdoHcy metabolism of the host cell (De Clercq, 1998; Bray et al., 2002). Those compounds could complement other therapeutic strategies aimed at blocking enzymatic functions such as the RNA-dependent RNA polymerase, the protease, or the helicase encoded by the SARS virus.

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BioInfoBank Institute
Limanowskiego 24A
60-744 Poznan
Poland

*Correspondence: leszek@bioinfo.pl

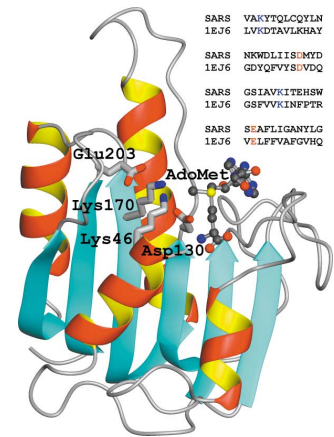


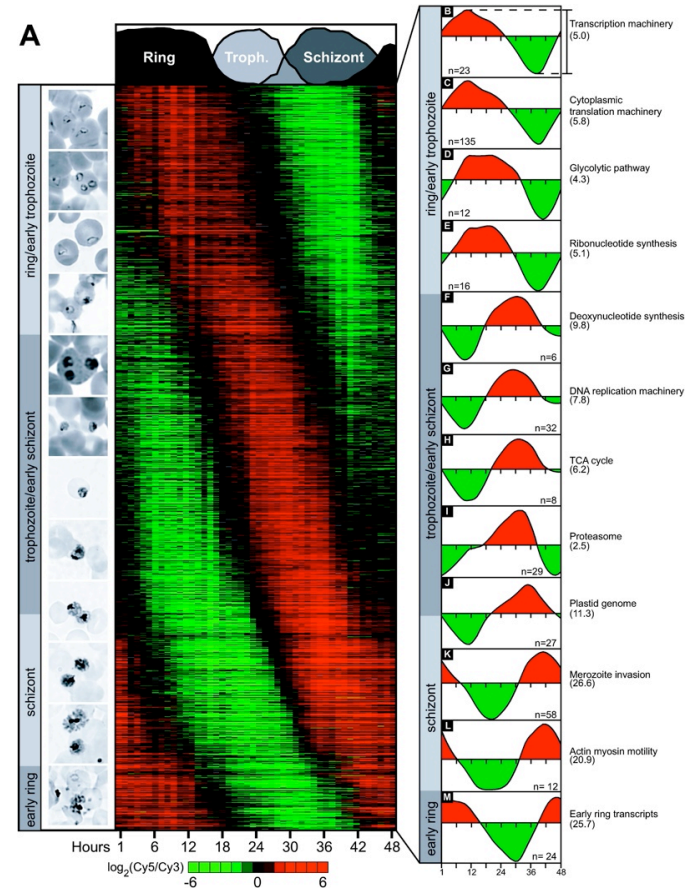
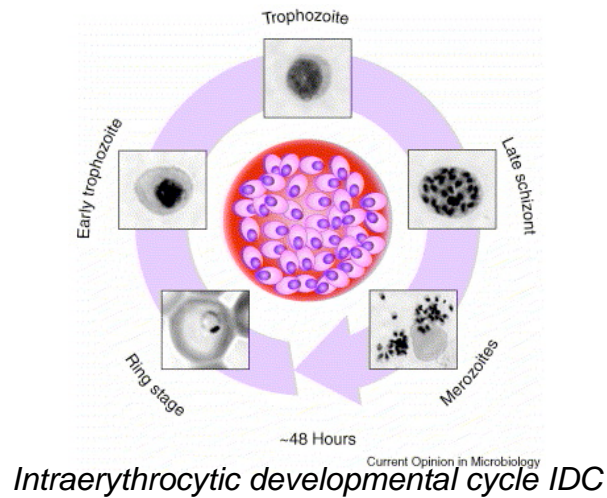
Figure 1. 3D Model of the nsp13 Domain of the SARS Coronavirus pp1ab Polyprotein
This model is based on the reassigned (Bujnicki and Rychlewski, 2001) cap-1 methyltransferase of the reovirus λ 2 protein [1q6] (Reinisch et al., 2000). While other templates (1eiz or 1e10) obtained marginally higher 3D jury scores, the selected template had the lowest number of insertions and deletions. Side chains of the conserved tetrad of residues (K-D-K-E) essential for cap-1 methylation and the docked AdoMet cofactor are shown. Four blocks of aligned motifs containing the conserved, function-specific residues are shown in upper right corner.

von Grotthuss M. et al. (2003) Cell 113 pp701

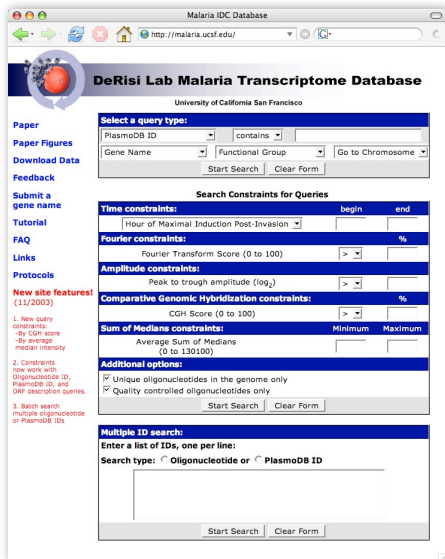
Ginalski K, et al. (2003) Bioinformatics 19 pp1015

Examples

Genomic research on Malaria (2003)



1. Periodic and continuum nature of the *P. falciparum* transcriptome (for at least 80% of the genes)
2. Potential for characterizing ~60% genes of unknown function



Bozdech et al. (2003). *PLoS Biology* 1(1):e5
 Llinas & DeRisi (2004). *Current Opinion in Microbiology* 7:382

Structure-based DD

in companies...



	cloning	Tissue distribution	Disease association	expression	1° assay	2° assay	screening	Hit optimisation	Lead optimisation
Nuclear Receptors	█	█	█	█	█	█	█	█	█
P450s	█	█	█	█	█	█	█	█	█
Ion-channels	█	█	█	█	█	█	█	█	█
Progesterin GPCRs	█	█	█	█	█	█	█	█	█
Metalloproteinases	█	█	█	█	█	█	█	█	█



	Preclinical	Phase I	Phase II	Phase III	Market
Viral Diseases					
Agenerase [®] HIV Infection	█	█	█	█	█
Lexiva [®] /Telzir [®] HIV Infection	█	█	█	█	█
VX-385 HIV Infection	█	█	█	█	█
merimepodib HCV Infection	█	█	█	█	█
VX-950 HCV Infection	█	█	█	█	█
Inflammation and Autoimmune Diseases					
VX-702 Rheumatoid Arthritis	█	█	█	█	█
VX-765 Psoriasis	█	█	█	█	█
pralnacasan Inflammatory Diseases	█	█	█	█	█
Cancer					
VX-680 Oncology	█	█	█	█	█
VX-322 Oncology	█	█	█	█	█
VX-944 Oncology	█	█	█	█	█
Other					
VX-409 Pain	█	█	█	█	█
VX-692 Bacterial Infection	█	█	█	█	█



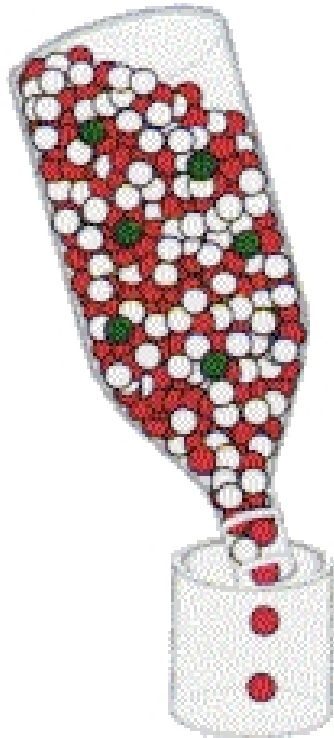
Predix' Clinical Development Programs

Indication	Target	Drug Discovery	Lead Optimization	Pre-Clinical	IND	Phase I	Phase II
PRX-00023 Anxiety/Depression	5-HT1A	█	█	█	█	Phase I Complete	1H
PRX-03140 Alzheimer's Disease	5-HT4	█	█	█	█	Phase I	1H
PRX-08066 Pulmonary Hypertension	5-HT2B	█	█	Pre-Clinical	█	█	Q2

█ February 2005 █ 2005 Anticipated Milestones



Our lead product candidate Troxatyl,™ is currently being evaluated in Phase I trials for the treatment of relapsed AML and various solid tumors.



TDI

bottle-neck...
“getting the tools to play with”

TDI projects

PROJECT I

Gene Cards

PROJECT II

Structure Prediction

PROJECT III

Target Selection for Structural Genomics

PROJECT IV

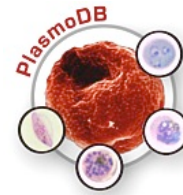
Gene Annotation

PROJECT V

Gene Basket

Gene Cards

collecting gene information



As of September 2005, the Malaria genome had 5,270 ORFs.

- NCBI at <http://www.ncbi.nlm.nih.gov/>
- BioMart at <http://www.biomart.org/>
- ModBase at <http://www.salilab.org/modbase>

Gene Card | Development Site

Development Site
Link to Malaria Site

User login
Username:
Password:

Navigation
 search
 resource links
 projects
 discussion forums
 create content
 blogs
 news feeds
 CiteULike
 Connotea
 Malaria Journal
 Technorati
 categories

Who's online
There are currently 0 users and 1 guest online.

Poll
Which News Source is Better?
CiteULike 50%
Connotea 50%
Let's Use Both 0%
Don't Know 0%
Total votes: 2
[login or register to post comments](#) | [older polls](#)

Home

Gene Card
NP_702320 - serine/threonine kinase-1.

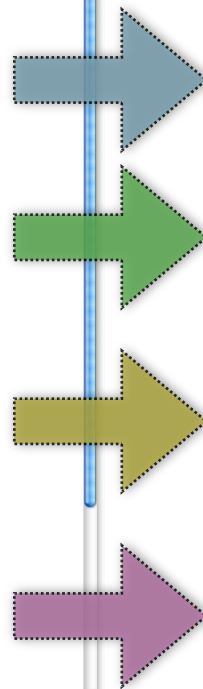
Literature
There are 1 pubmed entries:
Genome sequence of the human malaria parasite *Plasmodium falciparum*
Gardner,M.J., Hall,N., Fung,E., White,O., Berriman,M., Hyman,R.W., Carlton,J.M., Pain,A., Nelson,K.E., Bowman,S., Paulsen,I.T., James,K., Eisen,J.A., Rutherford,K., Salzberg,S.L., Craig,A., Kyte,S., Chan,M.-S., Nene,V., Shalim,S.J., Suh,B., Peterson,J., Angiuoli,S., Pertea,M., Allen,J., Selengku,J., Haft,D., Mather,M.W., Vaidya,A.B., Martin,D.M.A., Fairlamb,A.H., Fraunholz,M.J., Roos,D.S., Ralph,S.A., McFadden,G.I., Cummings,L.M., Subramanian,G.M., Mungall,C., Venter,J.C., Carucci,D.J., Hoffman,S.L., Newbold,C., Davis,R.W., Fraser,C.M. and Barrell,B. Nature 419 (6906), 498-511 (2002)

Annotation
There are 8 external links:
GenPept entry id: 23497502
GenPept entry id: 23509653
NCBI protein db entry id: AAN37044.1
PlasmoDB entry id: chr14_glm_487
PlasmoDB entry id: chr14_phat_425
PlasmoDB entry id: PF14_0431
TrEMBL entry id: Q8IL19
TrEMBL entry id: Q8IL19_PLAF7

Structure
Sorry, no PDB entries for this target..
There are 8 models in ModBase for this target:
Summary for the highest sequence identity model in ModBase

Sequence Identity: 34.00%
PSI-Blast e-value: 4e-62
Model Coverage: 38.3%
Model Score: 1.00

Function
There are 27 GO terms associated to this target:
GO Molecular Function terms
GO:000166 nucleotide binding
GO:0003824 catalytic activity
GO:0004672 protein kinase activity
GO:0004674 protein serine/threonine kinase activity
GO:0005488 binding
GO:0005524 ATP binding
GO:0016301 kinase activity
GO:0016740 transferase activity
GO:0016772 transferase activity, transferring phosphorus-containing groups
GO:0016773 phosphotransferase activity, alcohol group as acceptor
GO:0017076 purine nucleotide binding
GO:0030954 adenyly nucleotide binding



Literature

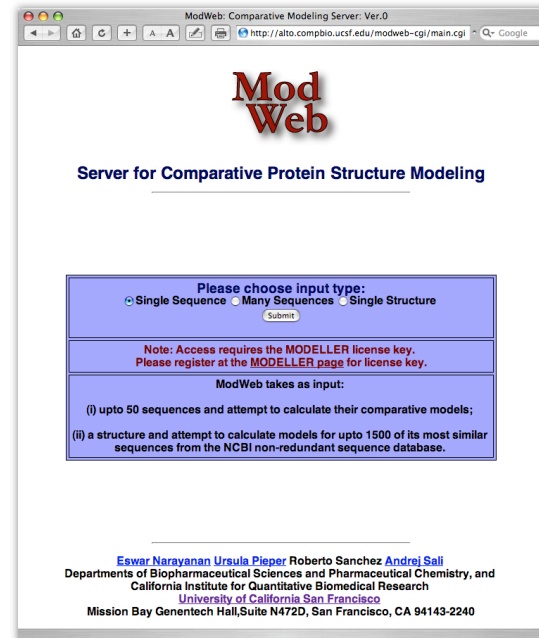
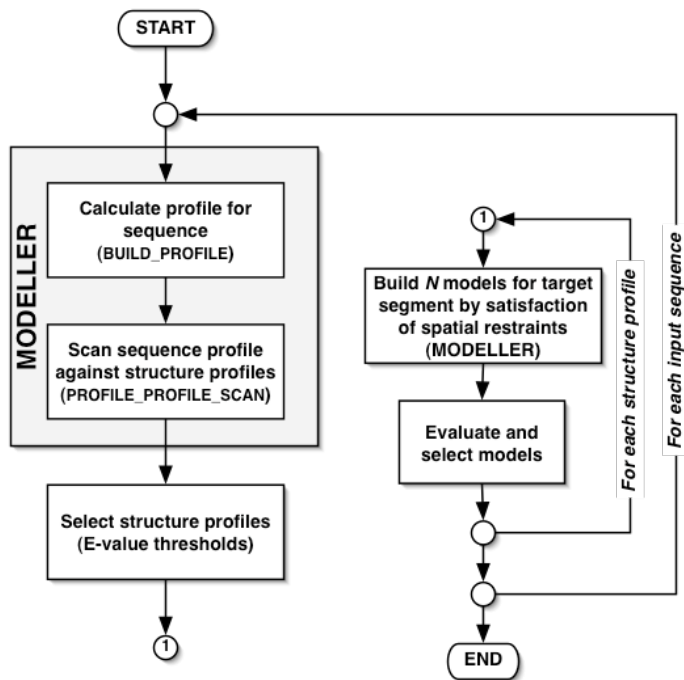
Annotation

Structure

Function

Protein Structure Modeling

structure my genes!



<http://www.salilab.org/modweb/>

Eswar et al., (2003) Nucl.Acids.Res. 31(13)

Sequences	5,270
Modeled sequences	3,321
Models	10,743

Target Selection for structural genomics

The aim of the project is to generate a list of target proteins, which structure may help the advance of drug discovery for malaria.

We intend to do so by allowing the community of researchers to collectively determine such a priority list.



Dr. Raymond Hui
University of Toronto and SGC

Target Annotation

what do you know about this gene?

The aim of the project is to provide tools to registered users to manually annotate malaria genes.

Development Site
Link to Malaria Site

User login
Username:
Password:

• Create new account
• Request new password

Navigation
□ search
□ resource links
□ projects
□ discussion forums
□ create content
□ blogs
□ news feeds
□ CiteULike
□ Connotea
□ Malaria Journal
□ Technorati
□ categories

Who's online
There are currently 0 users and 1 guest online.

Poll
Which News Source is Better?
CiteULike 50%
Connotea 50%
Let's Use Both 0%
Don't Know 0%
Total votes: 2
[login or register to post comments](#) | [older polls](#)

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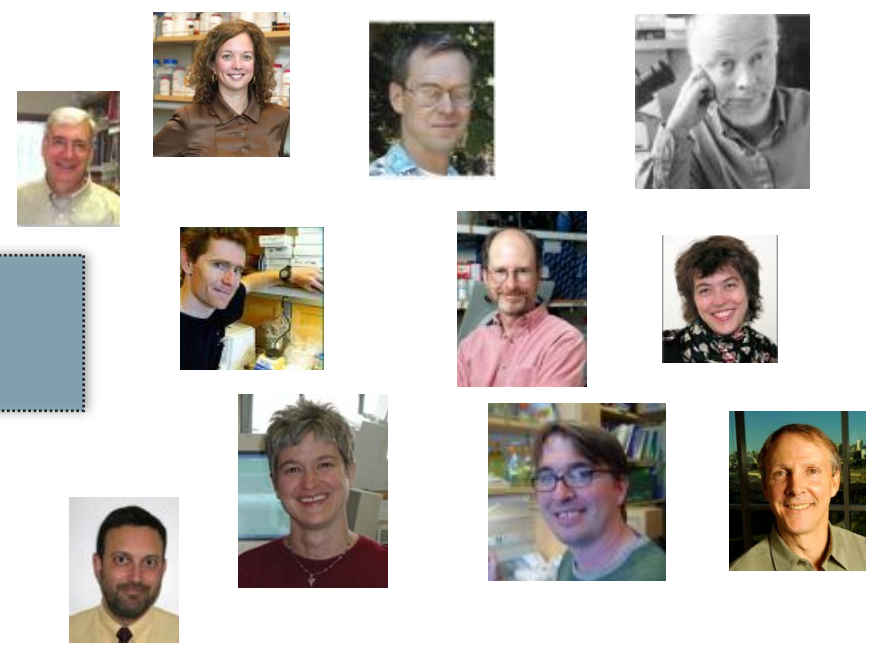
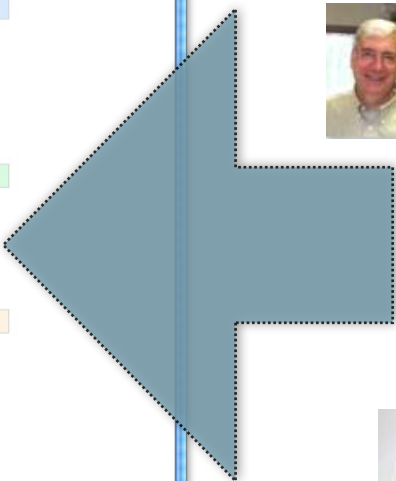
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GO:0005524 ATP binding
GO:0016301 kinase activity
GO:0016740 transferase activity
GO:0016772 transferase activity, transferring phosphorus-containing groups
GO:0016773 phosphotransferase activity, alcohol group as acceptor
GO:0017076 purine nucleotide binding
GO:0030554 adenylyl nucleotide binding



Gene Basket

add content to your genes... add genes to your content



TSL registered users will be able to save *gene cards* in their baskets and associate pieces of information to entries in the basket.

For example, a user may be browsing the literature at PubMed and find an interesting article, with just one click the system should be able to propose and association between the article and any of the genes in his/her basket.

As seen on: **YAHOO!** flickr^{BETA}



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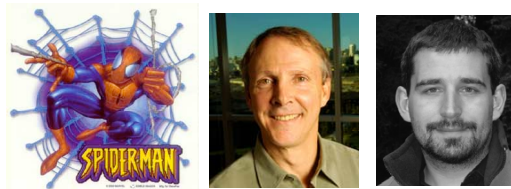
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As seen on: **YAHOO!** flickr^{BETA}



What can you do for TDI?

- Concept of “the power of us” to the (sometimes) very individualist BioMed research community
== **we need tools**
- Reach worldwide
== **we need exposure**
- Enhance collaborative research
== **we need to port existing tools**

What is in it for you?

- to be a part of **innovative** new approaches for research - "**the power of us**"
- to connect, work with other scientists interested in the same problems - **worldwide...**
- to develop **new** research tools
- GOOD KARMA!

5%

95%

Acknowledgments

Read more @

- PLoS Medicine, Dec. 2004. Vol 1(3) e56
- The Economist (June 10, 2004)

“At its best, academia is a market of ideas. But many scientists are reluctant to embrace the latest web tools that would allow them to communicate their ideas in new ways.”

Declan Butler (Nature, vol 438, p548)

“Put a description of your paper on a weblog, and something very different happens. People who are very far afield from your usual circle start thinking about the subject . They bring up interesting perspectives. ”

Paul Meyers (Nature, vol 438, p549)

<http://www.tropicaldisease.org>

<http://www.thesynapticleap.org>

The Sali Lab

Andrej Sali
Eswar Narayanan
Ursula Pieper

Tropical Disease Initiative

Stephen Maurer
Arti Rai
Andrej Sali
Thomas Kepler
Matt H. Todd

The Synaptic Leap

Ginger Taylor
Randy Akl
Chris Heller
Rich Manalang
Ken Pugsley

Wiki site at NPG

Timo Hannay
Declan Butler