

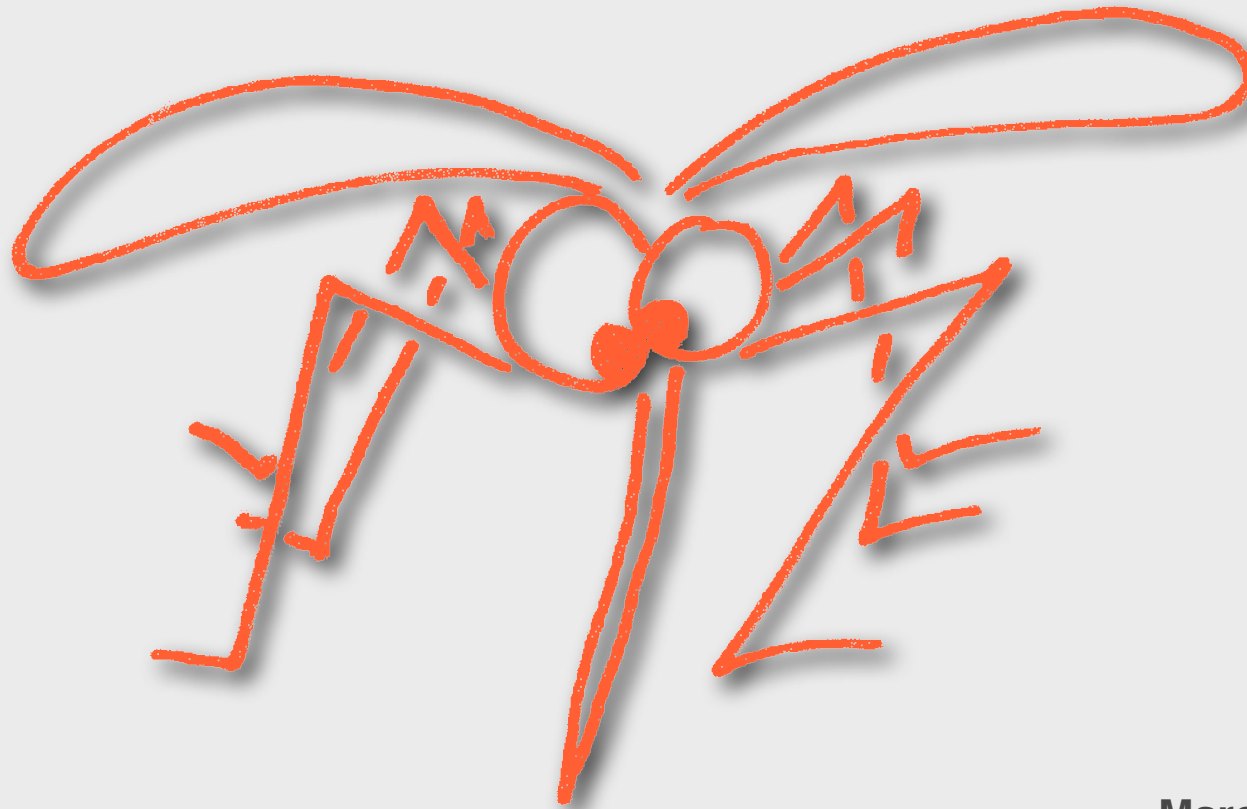
The Tropical Disease Initiative

An open source approach to drug development

www.tropicaldisease.org

www.thesynapticleap.org

not quite a scientific talk ;-)



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

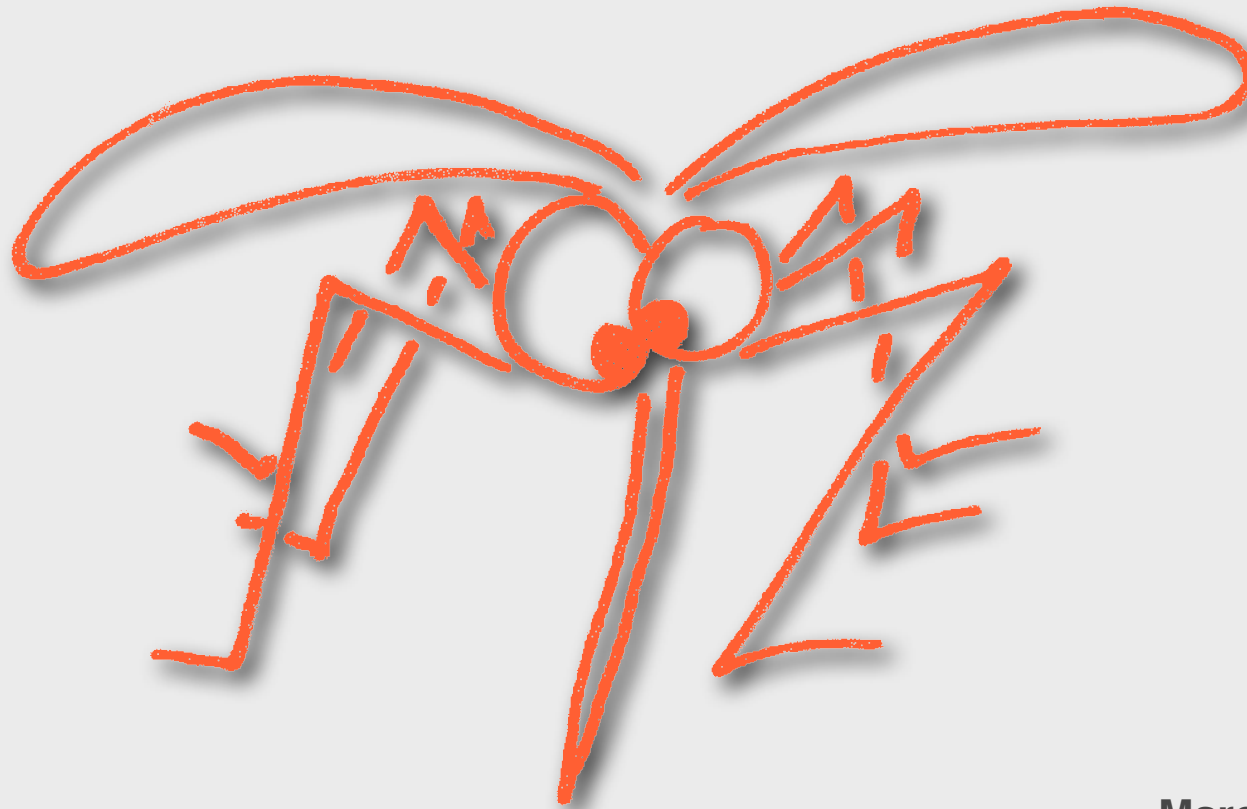
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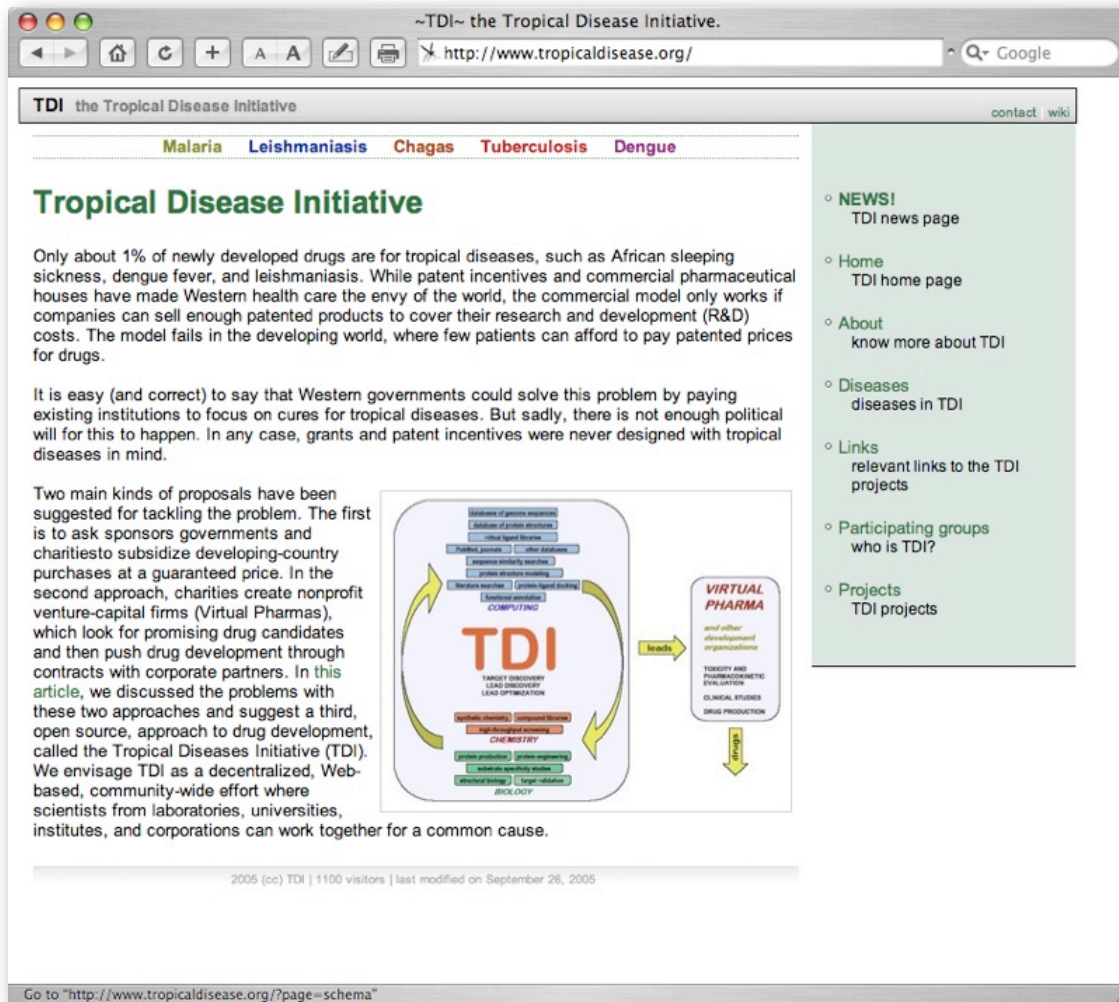
CM



TDI

TDI web site

<http://www.tropicaldisease.org>



The screenshot shows the TDI website homepage. At the top, there's a navigation bar with links for Malaria, Leishmaniasis, Chagas, Tuberculosis, and Dengue. Below this is the main heading "Tropical Disease Initiative". The text describes the initiative's goal: to develop drugs for tropical diseases by leveraging Western health care and commercial pharmaceutical models. It mentions that only about 1% of newly developed drugs are for tropical diseases. The text also discusses the challenges of drug development in the developing world and the role of the TDI. A diagram on the right side of the page illustrates the TDI workflow, showing the integration of genomics, proteomics, and chemistry to identify drug targets and develop drugs. The diagram is titled "TDI" and "VIRTUAL PHARMA".

~TDI~ the Tropical Disease Initiative.

http://www.tropicaldisease.org/

TDI the Tropical Disease Initiative

contact wiki

Malaria Leishmaniasis Chagas Tuberculosis Dengue

Tropical Disease Initiative

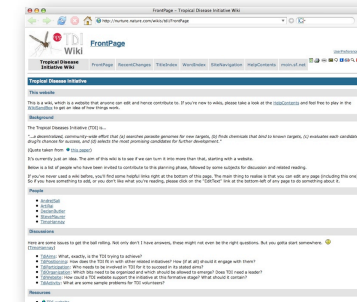
Only about 1% of newly developed drugs are for tropical diseases, such as African sleeping sickness, dengue fever, and leishmaniasis. While patent incentives and commercial pharmaceutical houses have made Western health care the envy of the world, the commercial model only works if companies can sell 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.

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.

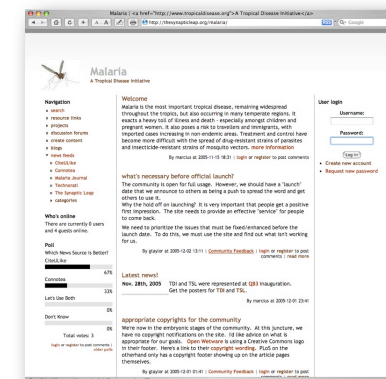
Two main kinds of proposals have been suggested for tackling the problem. The first is to ask sponsors governments and charities to subsidize developing-country purchases at a guaranteed price. In the second approach, charities create nonprofit venture-capital firms (Virtual Pharmas), which look for 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.

2005 (cc) TDI | 1100 visitors | last modified on September 26, 2005

Go to "http://www.tropicaldisease.org/?page=schema"



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



<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
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...

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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 need something to keep the project alive. **If someone will tell me where to begin on, I'd be grateful.**

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

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I still trust in open

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.

9 Mar 2005

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9 Mar 2005

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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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Daniel Amelang

19 Jan 2005

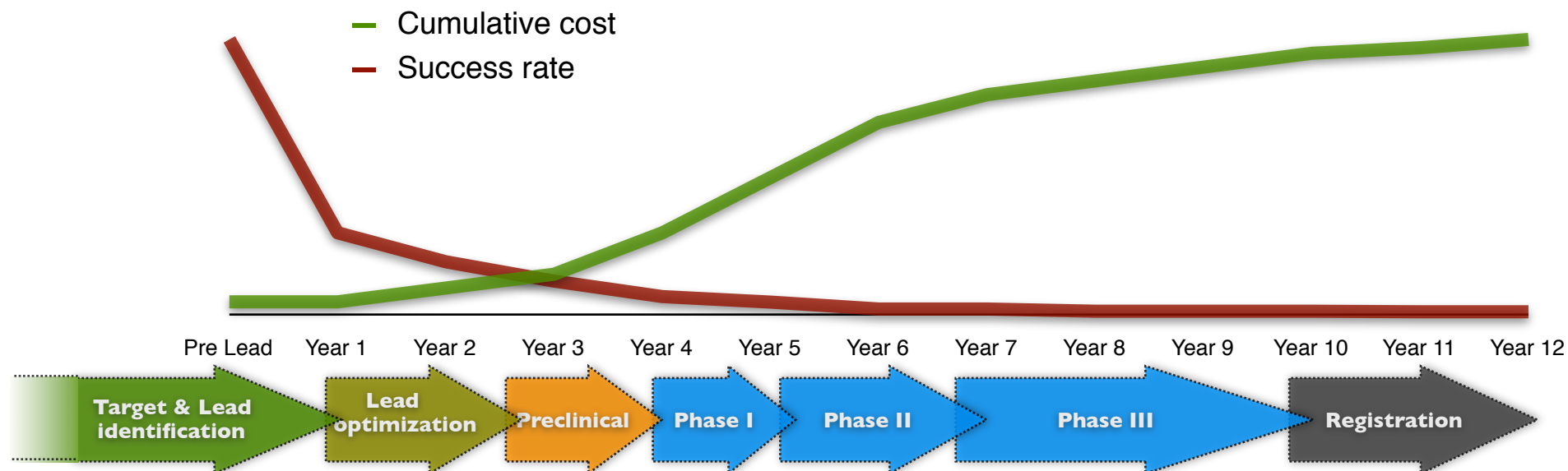
If we do the science well, I'm optimistic that the rest of TDI will fall into place.

Stephen Mark Maurer

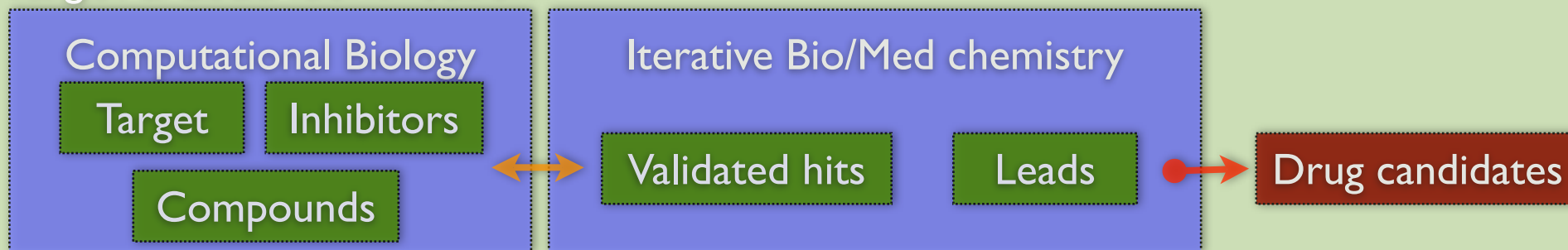
Action plan @ Tropical Disease Initiative

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

Drug Discovery pipeline

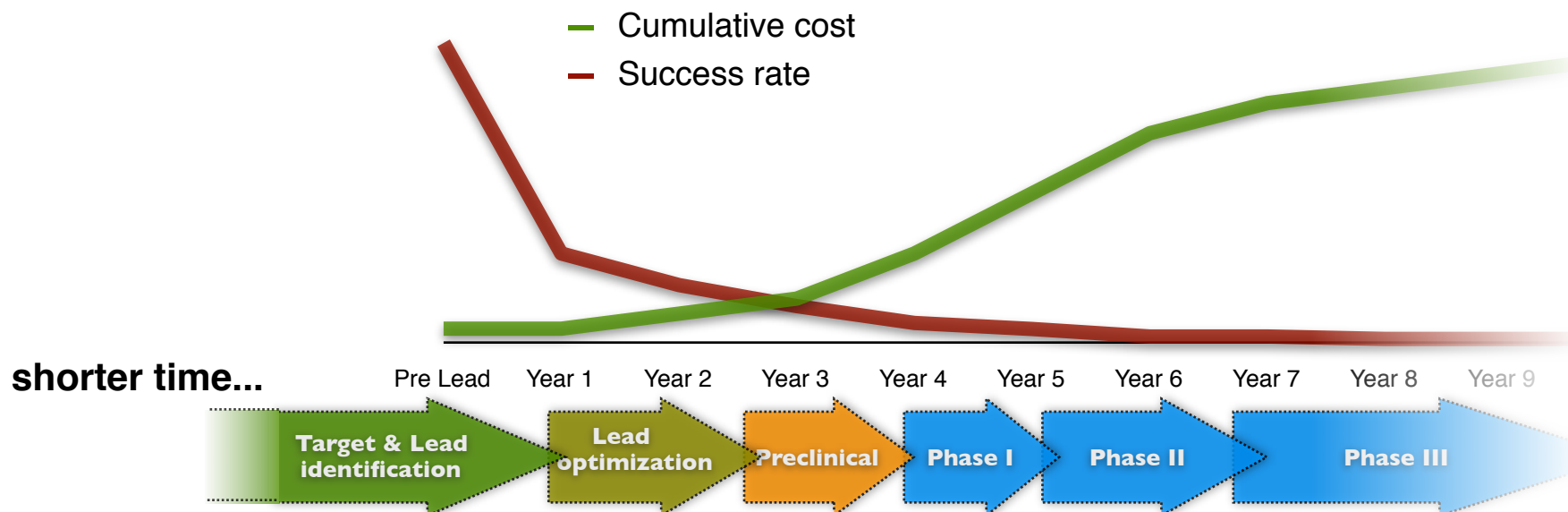


Target & Lead identification



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

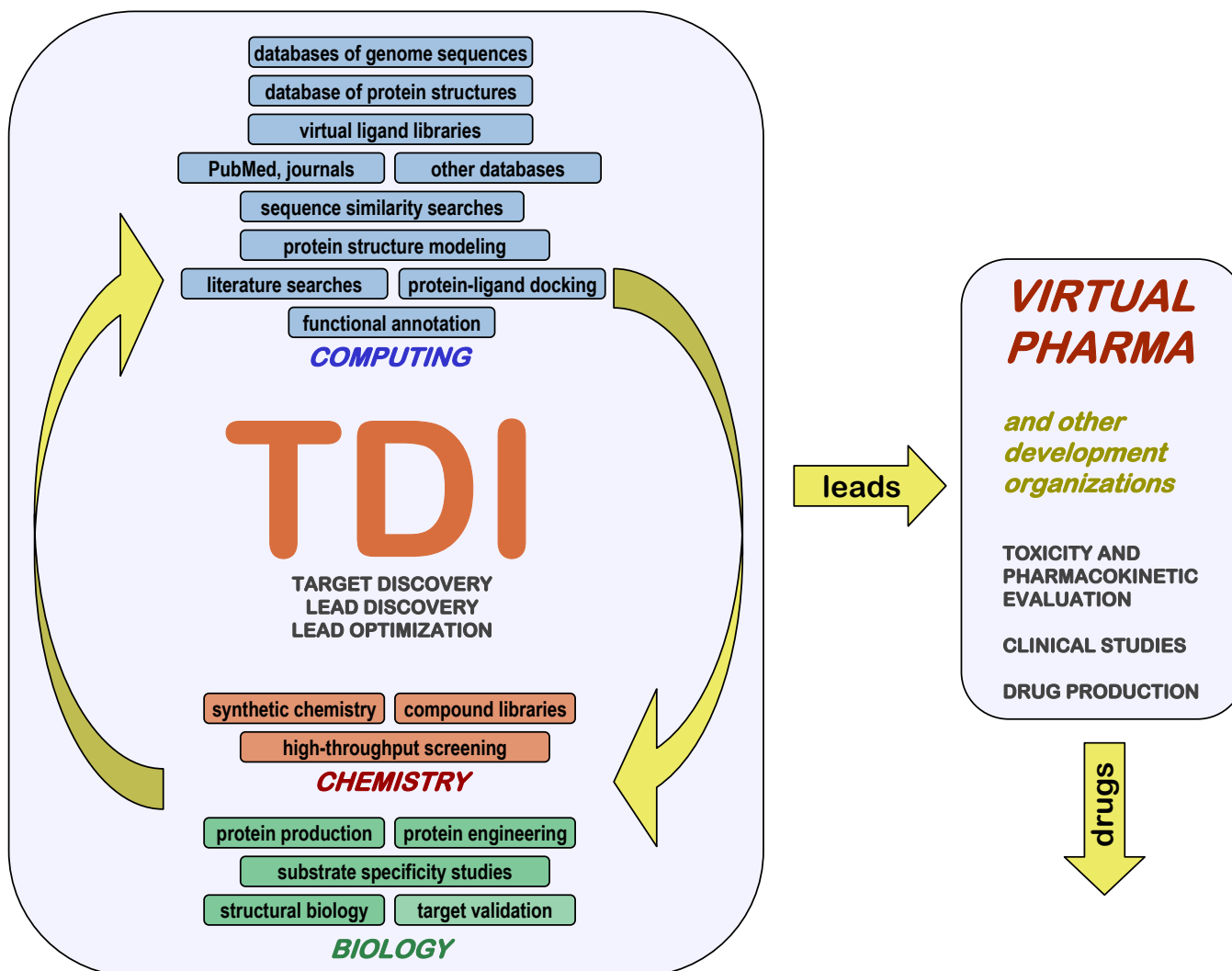
Drug Discovery pipeline



- + 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/
PHD, J. NITS	S	http://www.predictorprotein.org/

What can CB do?

Available computational biology resources for TDI

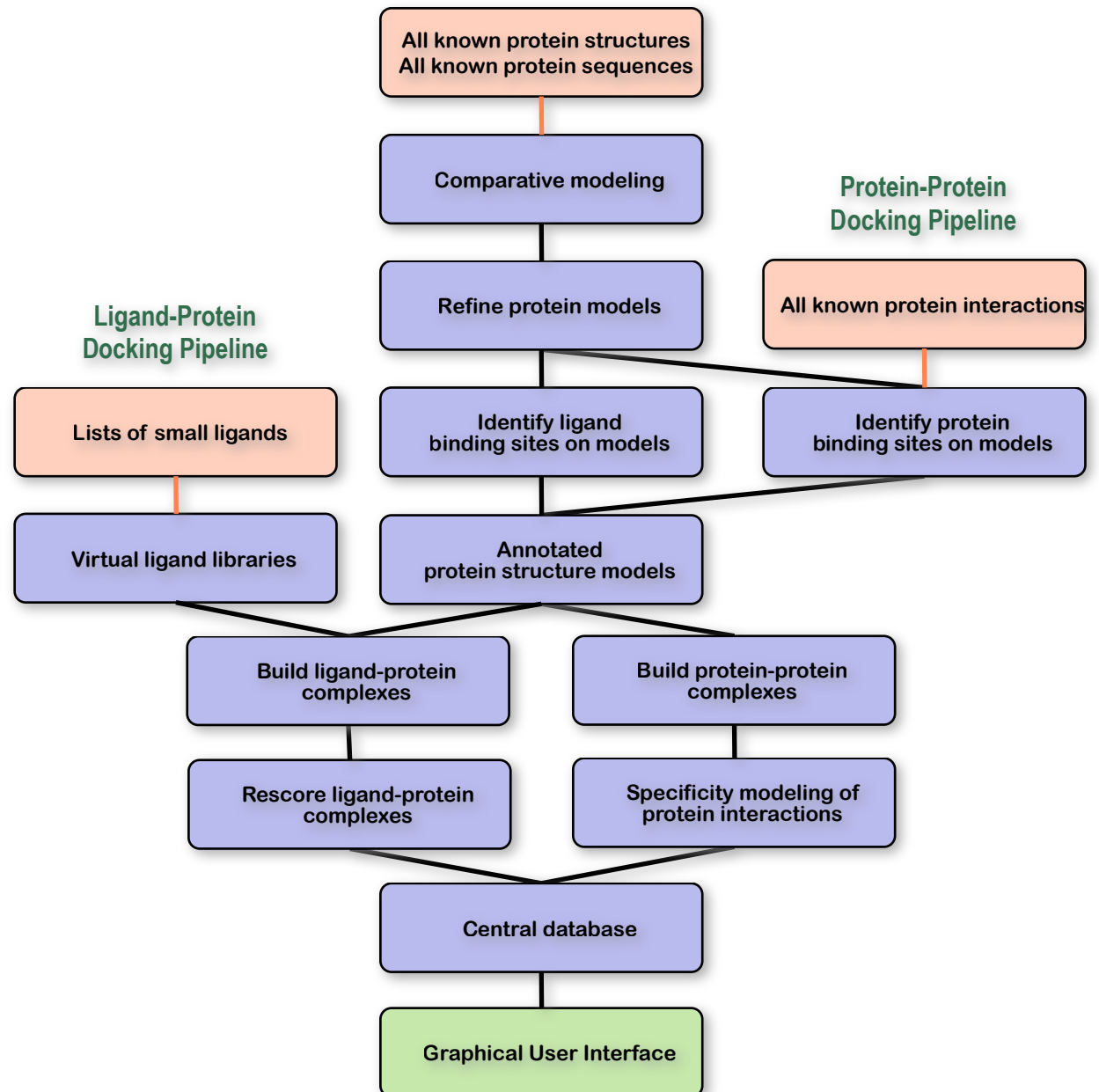
Protein-Ligand Universe

Center for Computational Proteomics Research (CCPR)

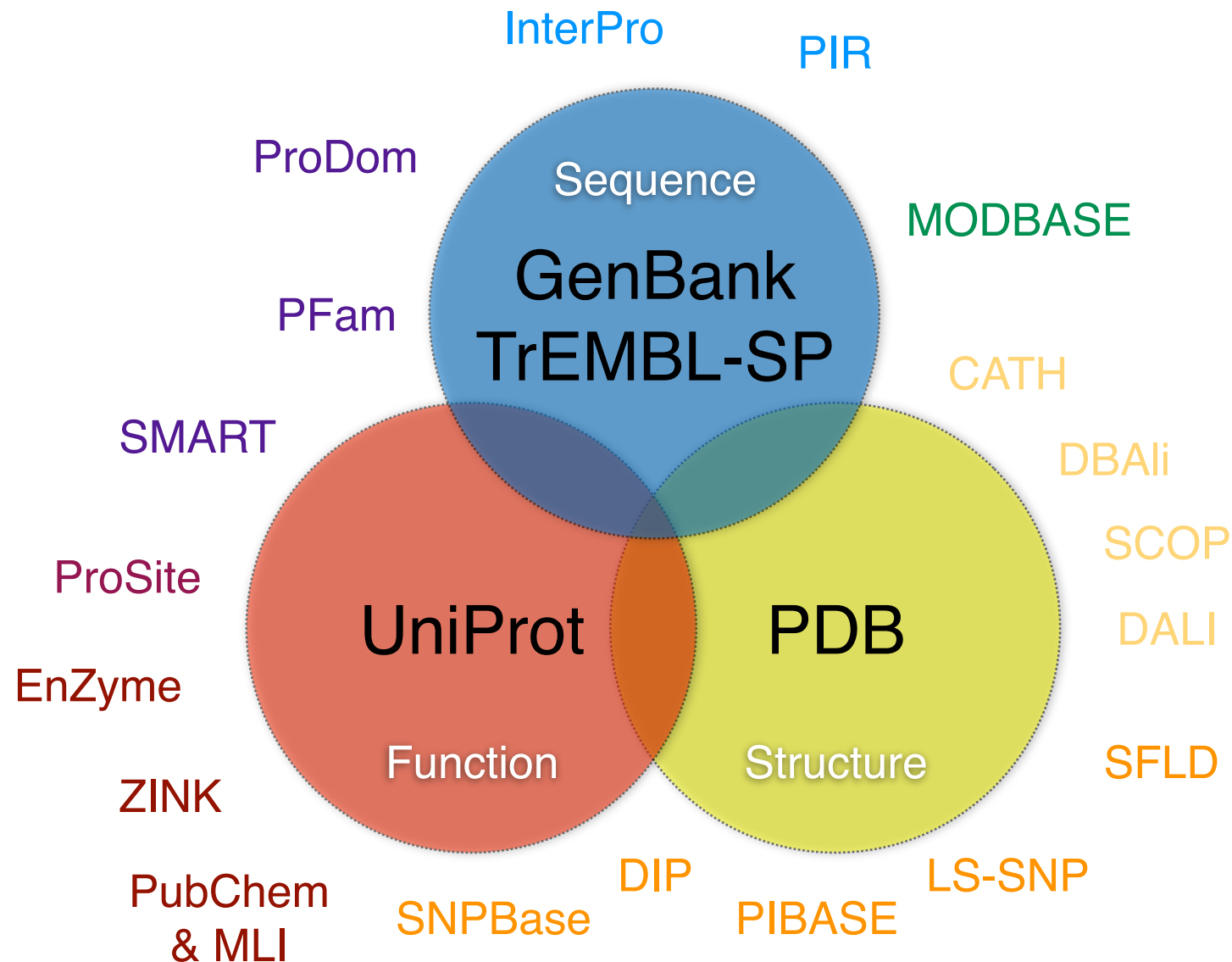
The California Institute for Quantitative Biomedical Research

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/>

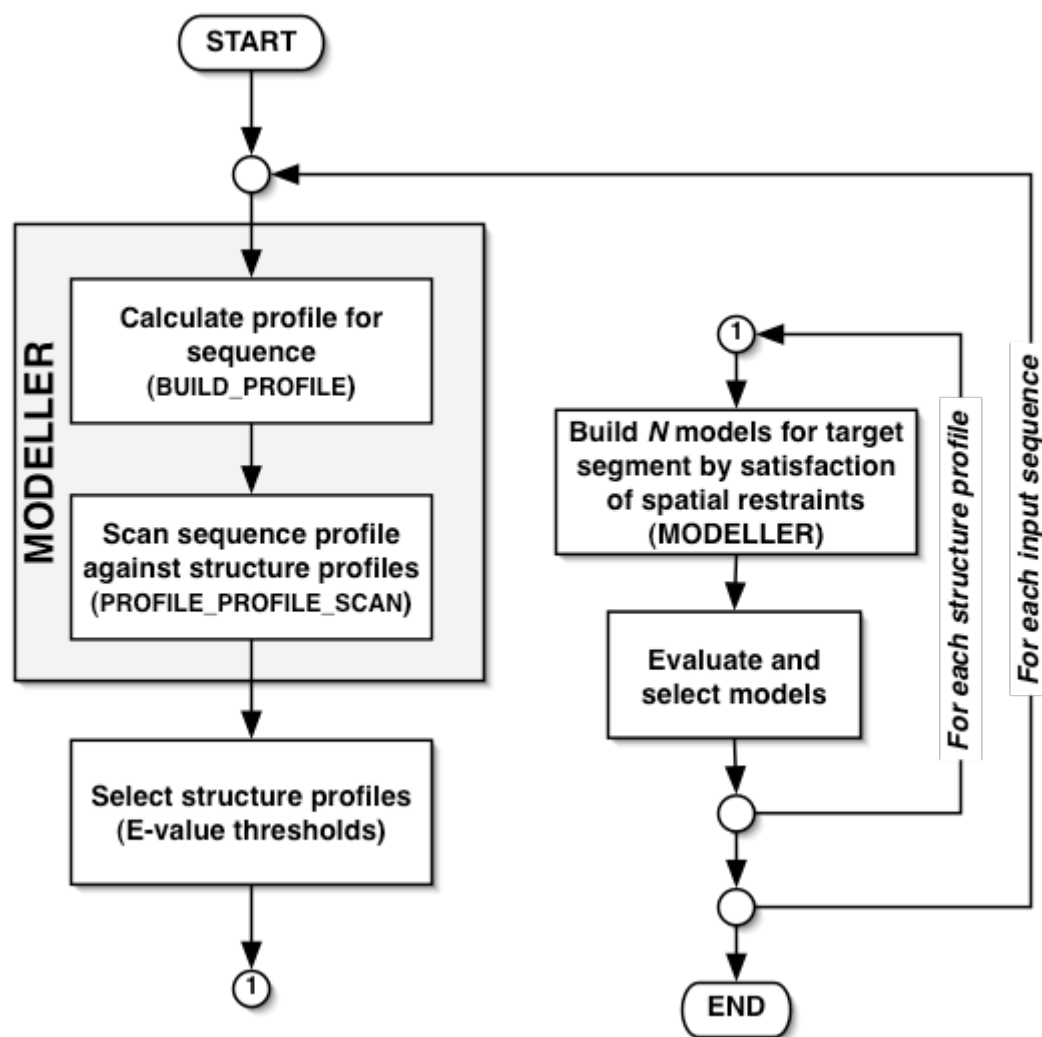


Databases



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

UCSF University of California, San Francisco | About UCSF | UCSF Medical Center

Home User Login ModBase Search Page ModWeb Modelling Server Help Current Logins

MODBASE

Database of Comparative Protein Structure Models

Welcome to ModBase, a database of three-dimensional protein models calculated by comparative modeling. ([Old ModBase Interface](#))

General Information
 Statistics
 Project Pages
 Documentation
 Authors and Acknowledgements
 Publications
 Todo List
 Related Resources

Note:
 MODBASE contains theoretically calculated models, not experimentally determined structures. The models may contain significant errors.

ModBase search form

Search type Display type

All available datasets are selected

Search by properties

Property

Organism or

[Advanced search](#)

Model Details

UCSF University of California, San Francisco | About UCSF | UCSF Medical Center

Home User Login ModBase Search Page ModWeb Modelling Server Help Current Logins

MODBASE

Sequence Information

Primary Database Link [P43632 \(K12S4_HUMAN\)](#)

Organism [Homo sapiens](#)

Annotation killer cell immunoglobulin-like receptor 2ds4 precursor (mhc class ide nk cell receptor) (natural killer associated transcript 8) (nk-8) (p58 natural killer cell receptor clone cl-39) (p58 nk)

Sequence Length 304

Model Information

Perform action on this model

Sequence Model Coverage

Sequence Identity 89.00%

E-Value 2e-43

Model Score 1.00

Target Region 27-221

Protein Length 304

Template PDB Code [1nkr](#)

Template Region 6-200

Dataset snp-human2

Filtered models for current sequence ([Show all models](#))

Cross-references

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

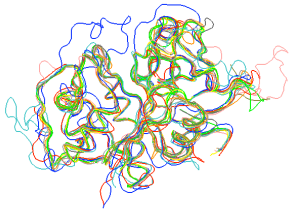
Model Overview

	<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

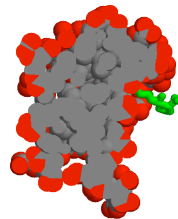
Functional Annotation

Localization of binding sites

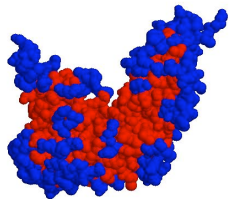
Structure conservation



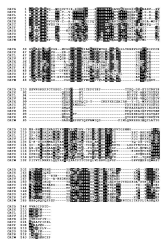
Solvent accessibility



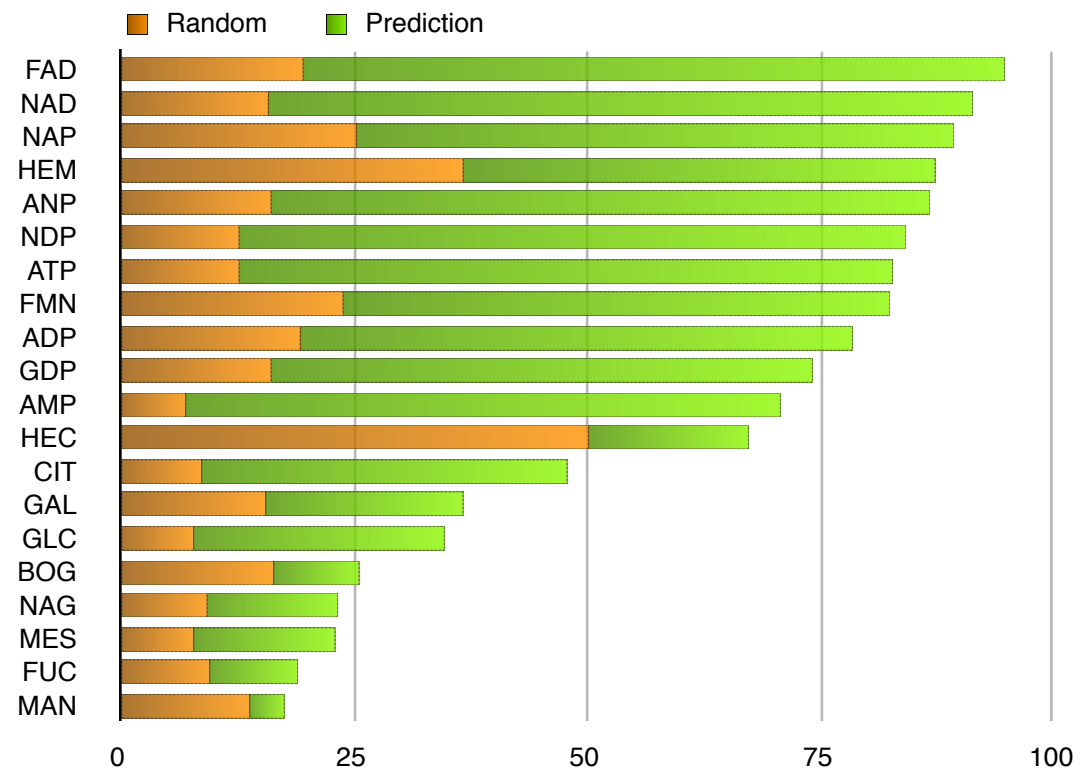
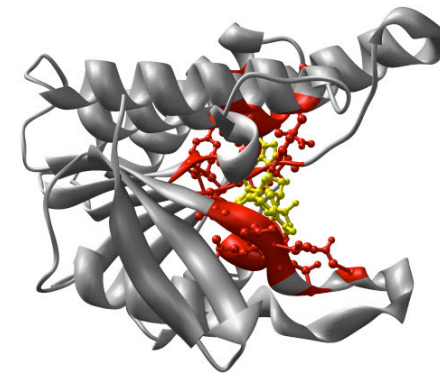
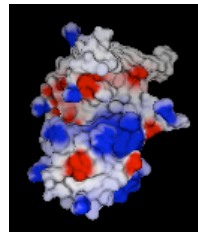
Surface geometry



Sequence conservation

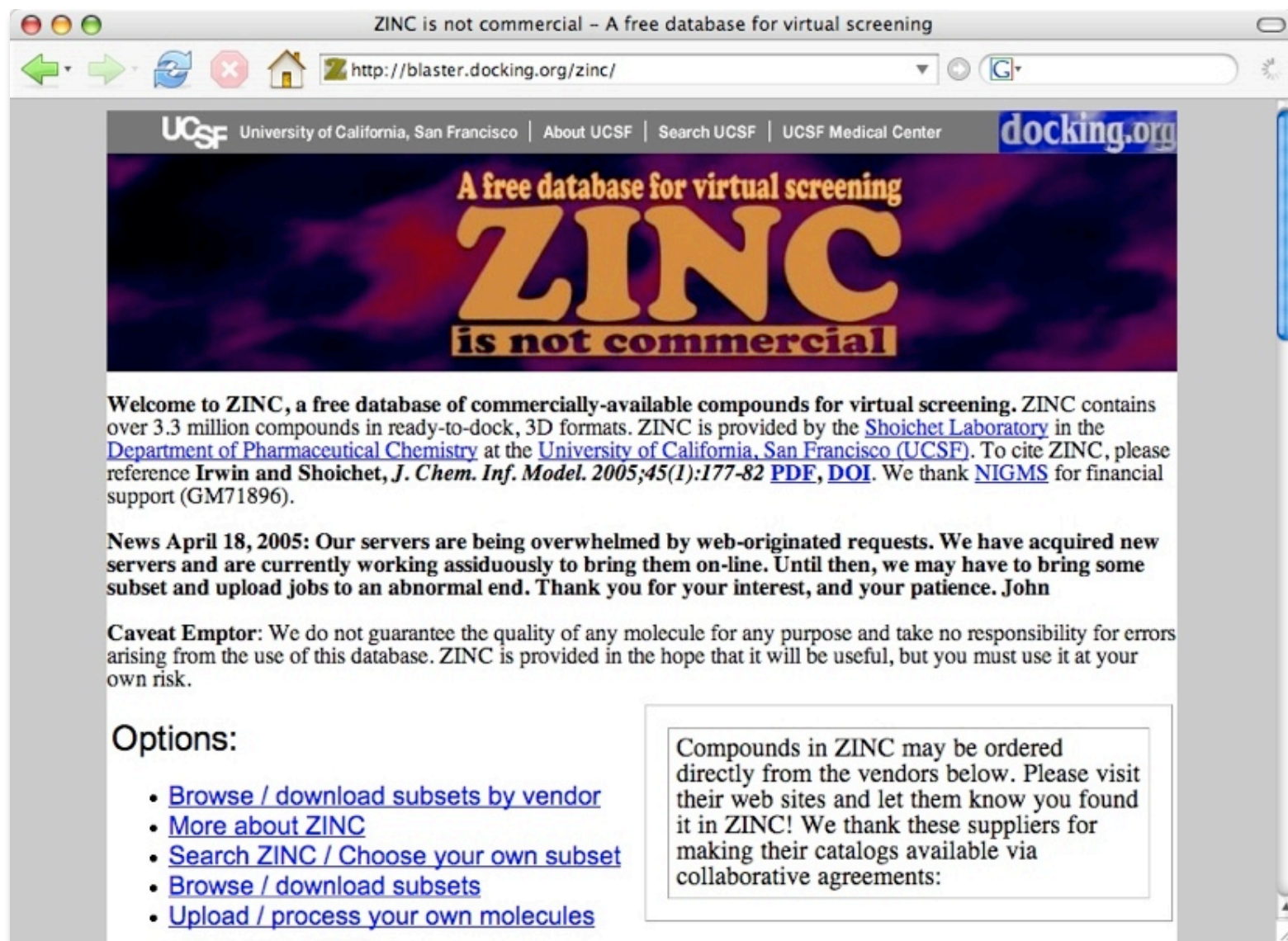


Electrostatics



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 shows 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. The main banner features the text "A free database for virtual screening" above the large "ZINC" logo, with "is not commercial" written below it. The main text area contains a welcome message, a news update from April 18, 2005, a caveat, and a list of options. A side box contains information about ordering compounds.

UCSF University of California, San Francisco | About UCSF | Search UCSF | UCSF Medical Center **docking.org**

A free database for virtual screening
ZINC
is not commercial

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

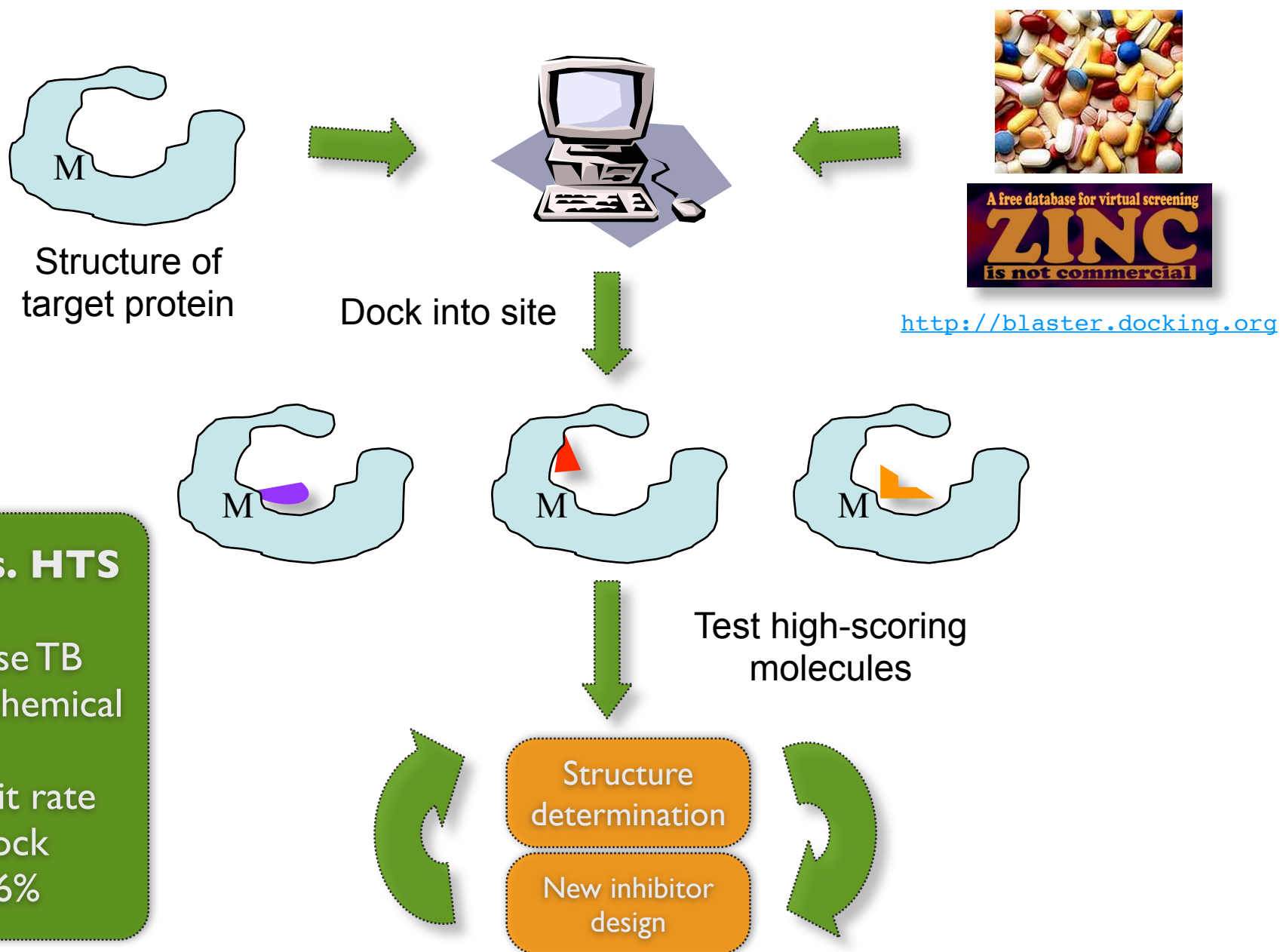
Caveat Emptor: We do not guarantee the quality of any molecule for any purpose and take no responsibility for errors arising from the use of this database. ZINC is provided in the hope that it will be useful, but you must use it at your own risk.

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



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-crysl.bioc.cam.ac.uk/~fugue/
LOOPP	S	http://ser-loopp.tc.cornell.edu/cbsu/loopp.htm
PDB-Blast/FASS	S	http://bioinformatics.ticrf.edu/pdb_blast/
PHD, PPTTS	S	http://www.predictor.org/

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

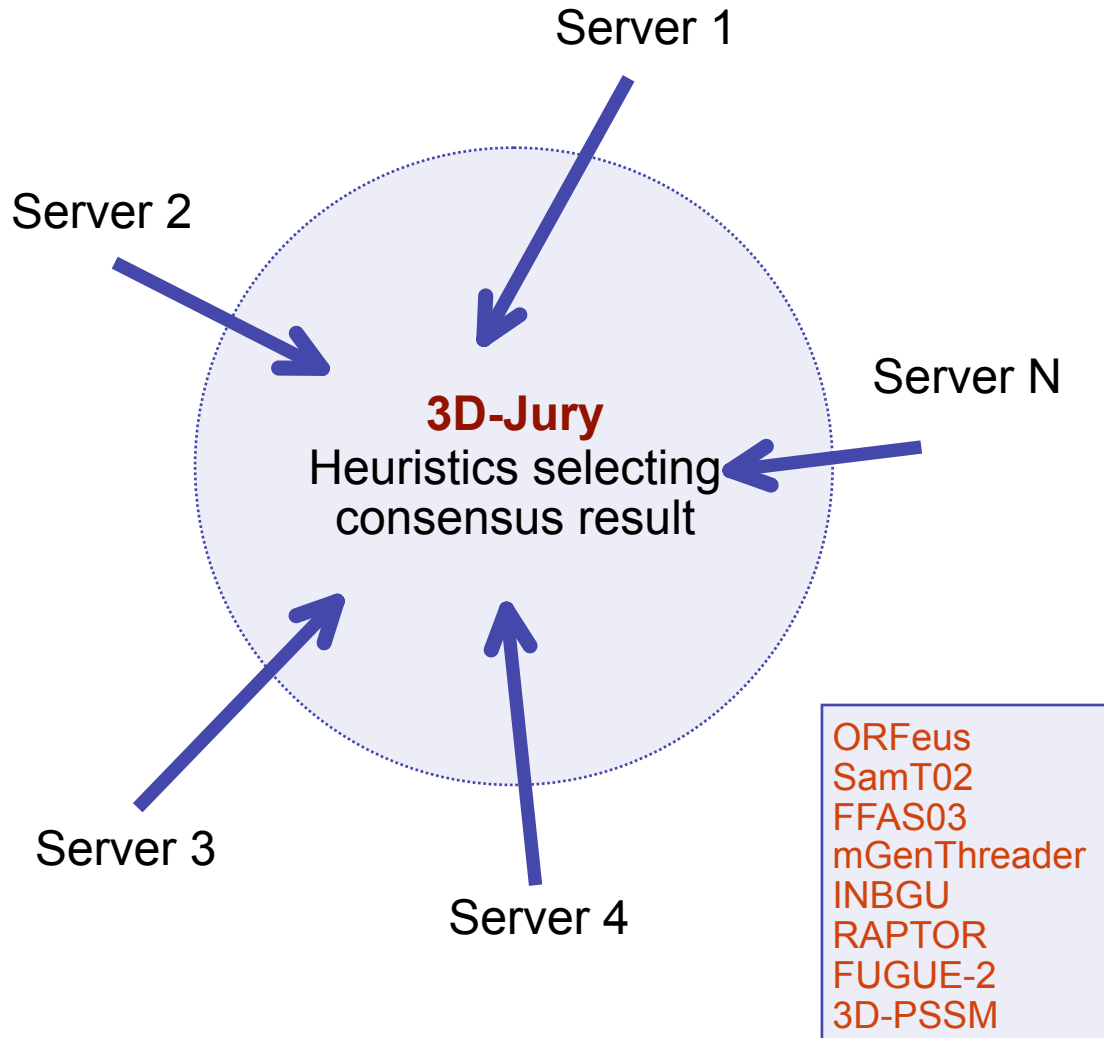
The 3-D structure of HIV-1 proteinase and the design of antiviral agents for the treatment of AIDS.

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 (mGpppN) formation.

The mRNA cap methylation is found indispensable for efficient replication of many viruses (Bach et al., 1995; Wocyniuk et al., 1995; Viot 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 (mGppN) 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 Poznań
Poland

*Correspondence: leszek@bioinfo.pl

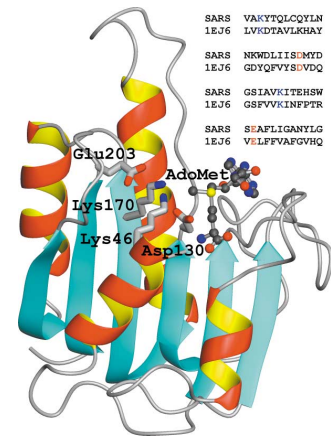


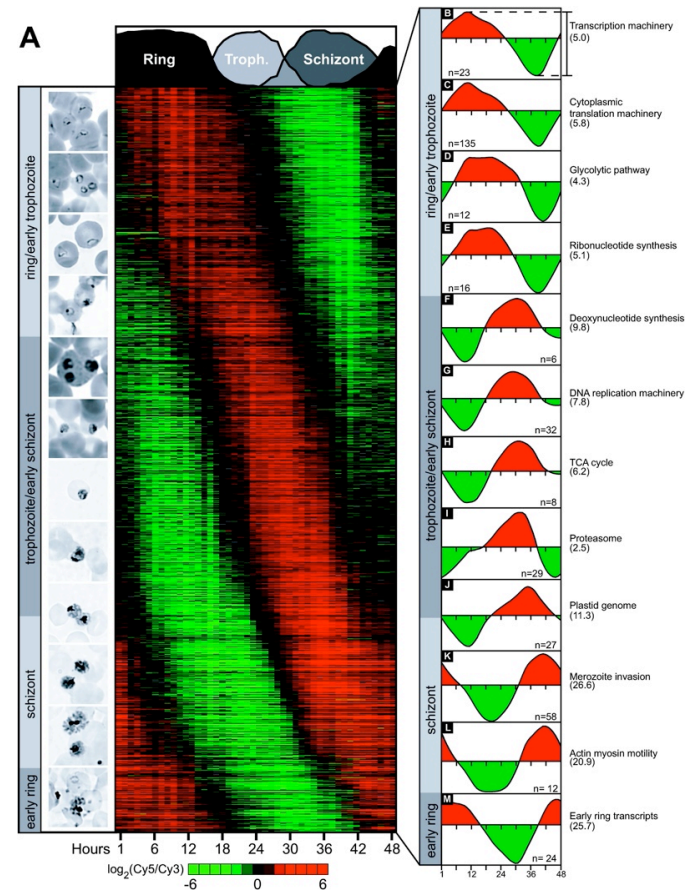
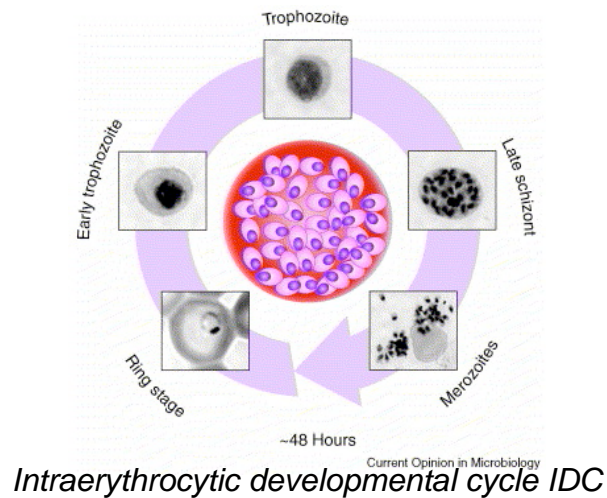
Figure 1. 3D Model of the nsp13 Domain of the SARS Coronavirus pp1ab Polyprotein
This model is based on the reassigned (Bujnicki and Rychlewski, 2001) cap-1 methyltransferase of the reovirus λ 2 protein [1qj6] (Reinisch et al., 2000). While other templates (1eiz or 1ej0) obtained marginally higher 3D 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

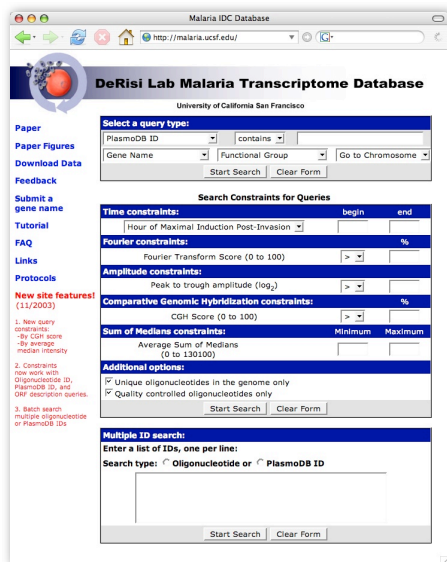
Ginalski K, et al. (2003) *Bioinformatics* 19 pp1015

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 ^o assay	2 ^o assay	screening	Hit optimisation	Lead optimisation
Nuclear Receptors									
P450s									
Ion-channels									
Progestin 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					



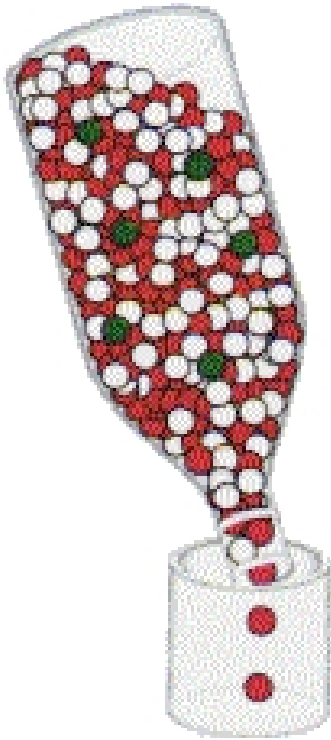
Predix' Clinical Development Programs

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>

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


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Connotea: 50%
Let's Use Both: 0%
Don't Know: 0%
Total votes: 2
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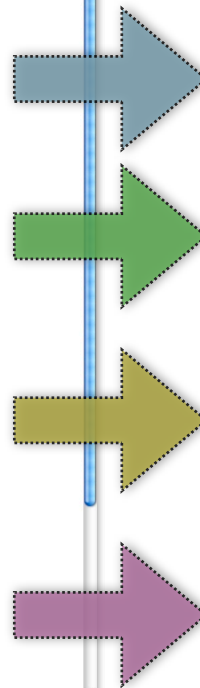
Home
Gene Card
NP_702320 - serine/threonine kinase-1.

Literature
There are 1 pubmed entries:
Genome sequence of the human malaria parasite *Plasmodium falciparum*
Gardner,M.J., Hall,N., Fung,E., White,O., Bertman,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., Shallow,S.J., Suh,B., Peterson,J., Angiuoli,S., Pertea,M., Allen,J., Selengut,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 Berrell,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

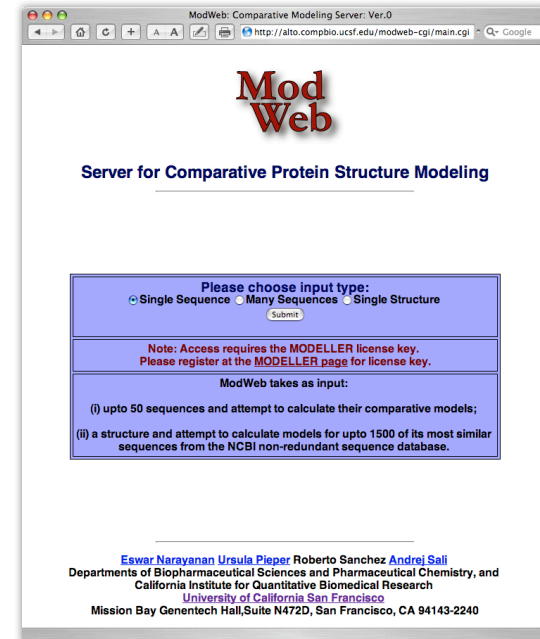
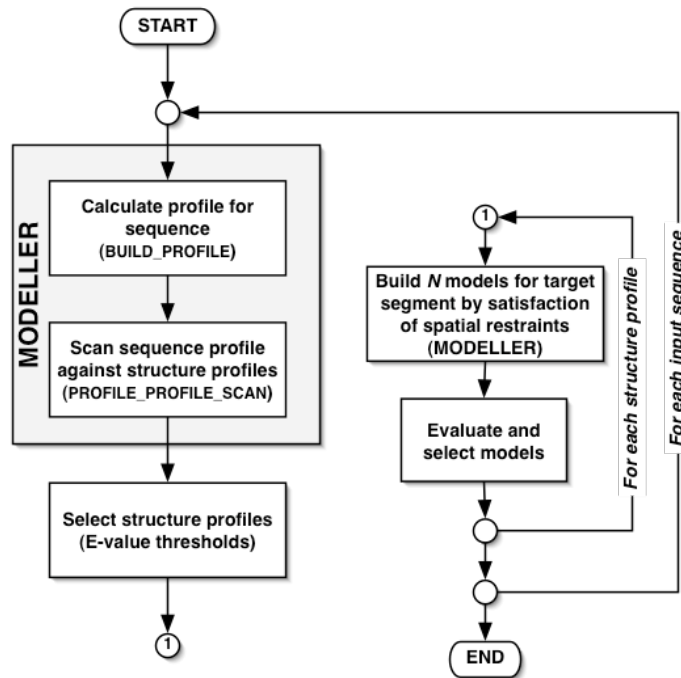
Annotation

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
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
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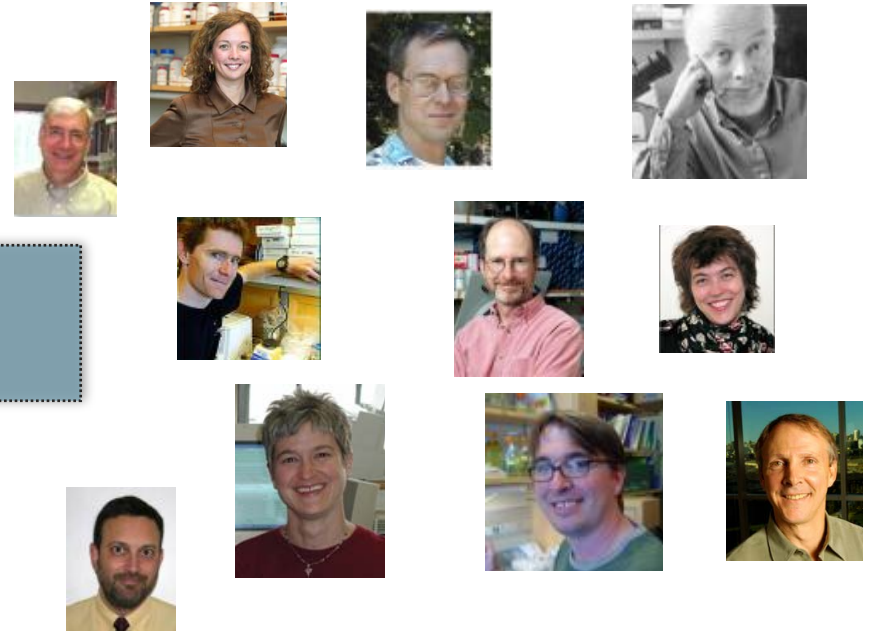
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 GO:0005488 binding
 GO:0005524 ATP binding
 GO:0016301 kinase activity
 GO:0016740 transferase activity
 GO:0016772 transferase activity, transferring phosphorus-containing groups
 GO:0016773 phosphotransferase activity, alcohol group as acceptor
 GO:0017076 purine nucleotide binding
 GO: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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<http://www.thesynapticleap.org>

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- to be a part of **innovative** new approaches for research - "**the power of us**"
- to connect, work with other scientists interested in the same disease - **worldwide...**
- to access to **new** research tools
- **free** collaborative site

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>

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Eswar Narayanan

Ursula Pieper

Tropical Disease Initiative

Stephen Maurer

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Andrej Sali

Thomas Kepler

Matt H. Todd

The Synaptic Leap

Ginger Taylor

Randy Akl

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Wiki site at NPG

Timo Hannay

Declan Butler