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

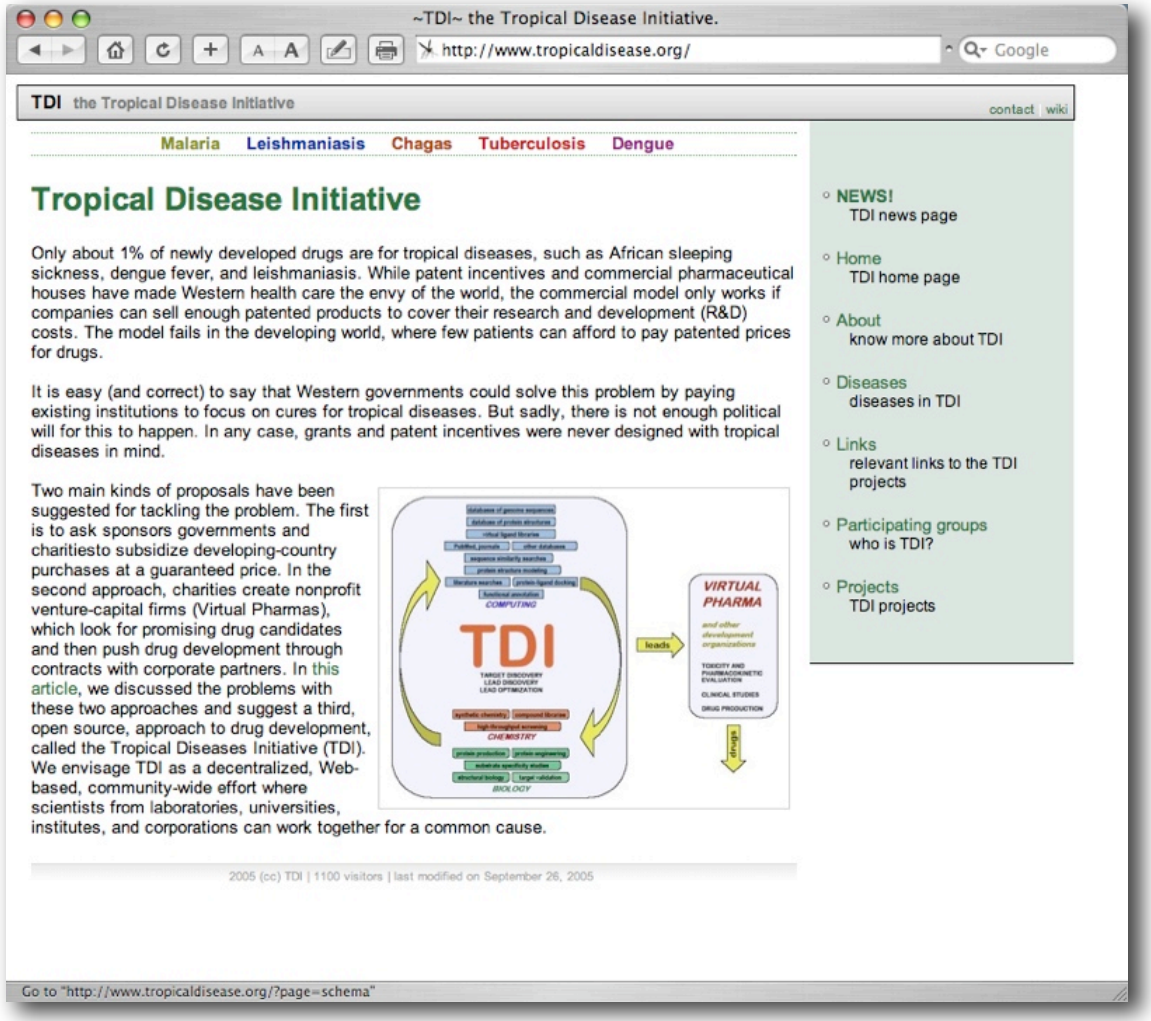
TDI

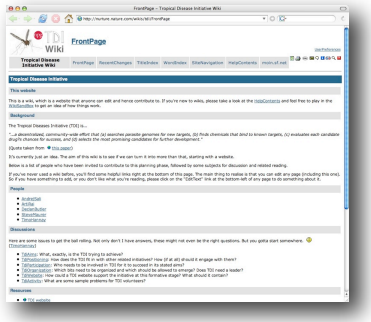
TDI

“20%”

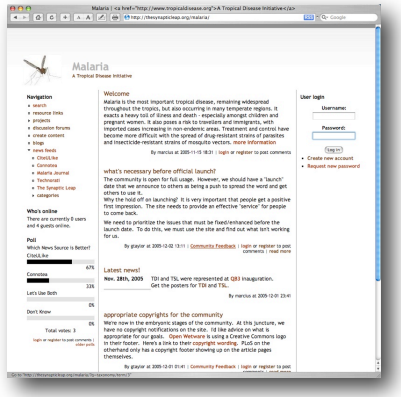
TDI web site

http://www.tropicaldisease.org





http://nurture.nature.com/wikis/tdi/



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!

disease for underserved popu
however, confused.
If someone will tell me wher
begin on, I'd be greatful.

Thank you kindly,
Adam Huber

Regards,
Jacob Lester

9 Mar 2005
I'm a programmer, not
something to keep the

GNU started with RM
Linux started with Li
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

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Stephen Mark Maurer

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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

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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 greatful.

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

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Daniel Amelang

19 Jan 2005

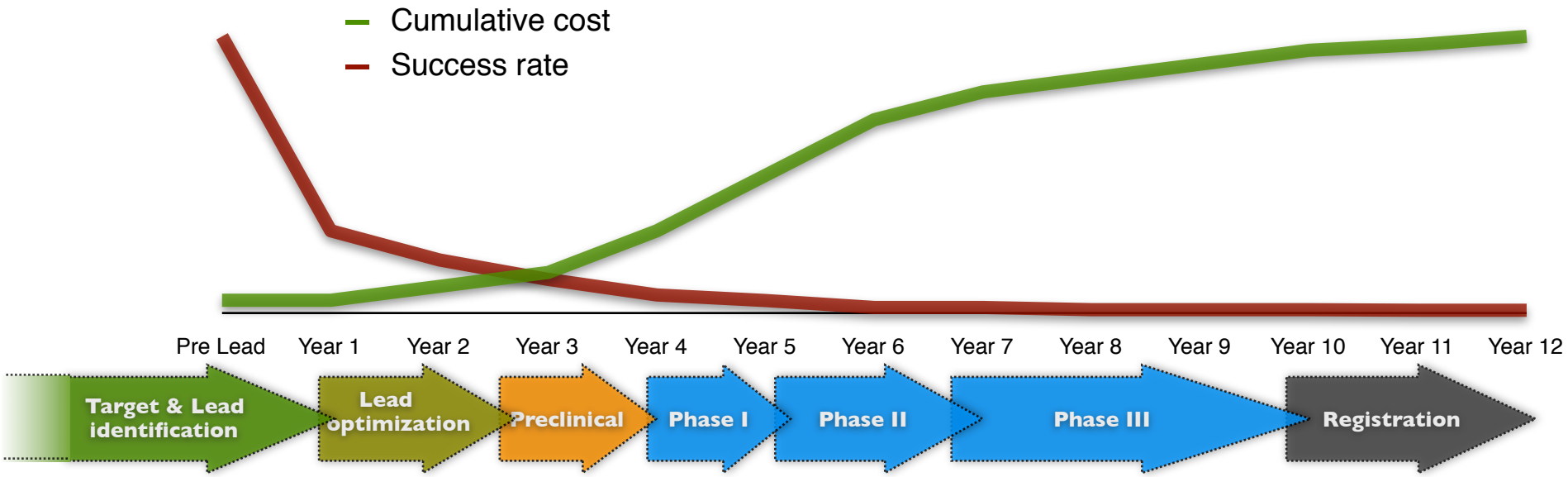
If we do the science well, I'm optimistic that the rest of TDI will fall into place.

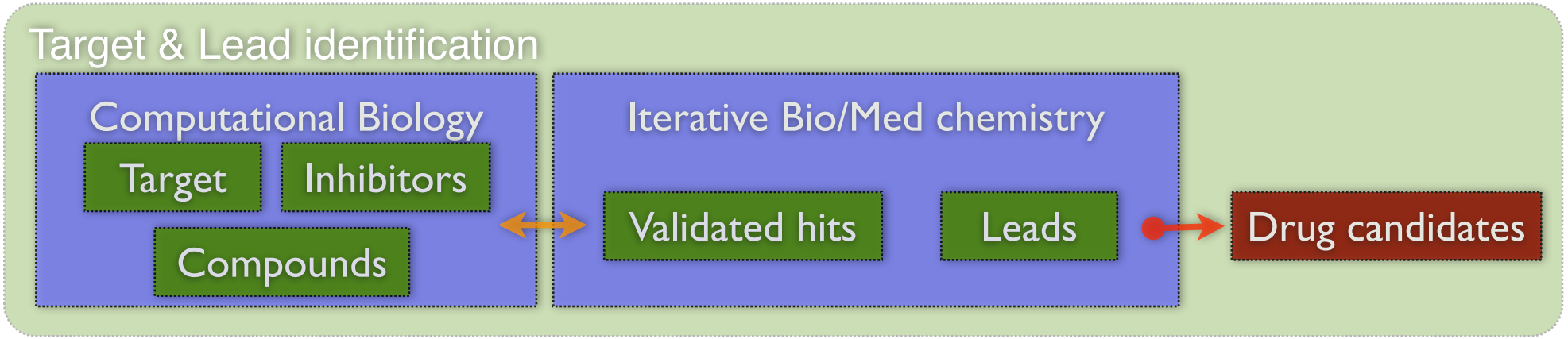
Stephen Mark Maurer

Action plan @ Tropical Disease Initiative

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

Drug Discovery pipeline





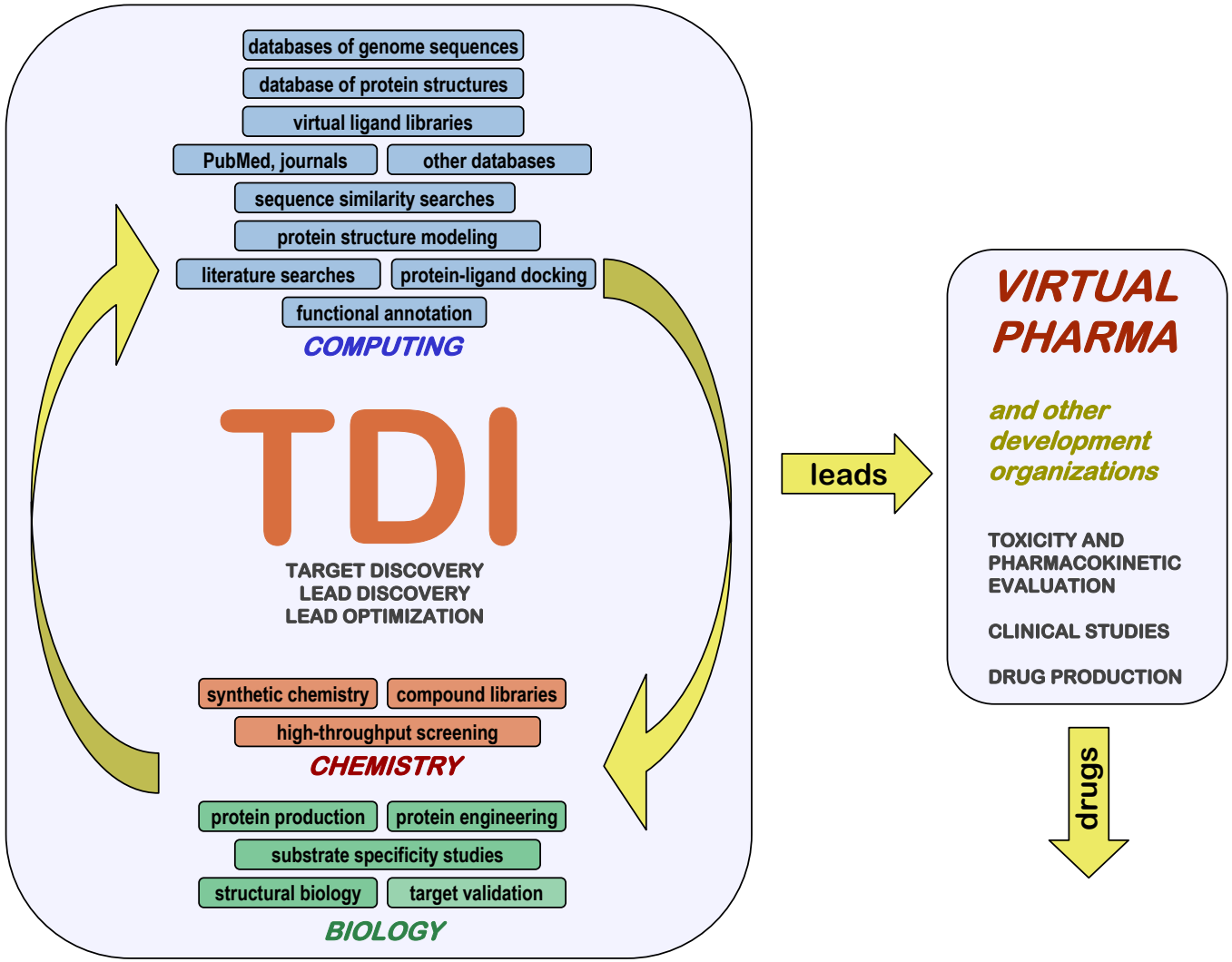
Adapted from: - Nwaka & Ridley. (2003) *Nature Reviews. Drug Discovery.* **2**:919
- Austin, Brady, Insel & collins. (2004) *Science*. **306**:1138

Drug Discovery pipeline

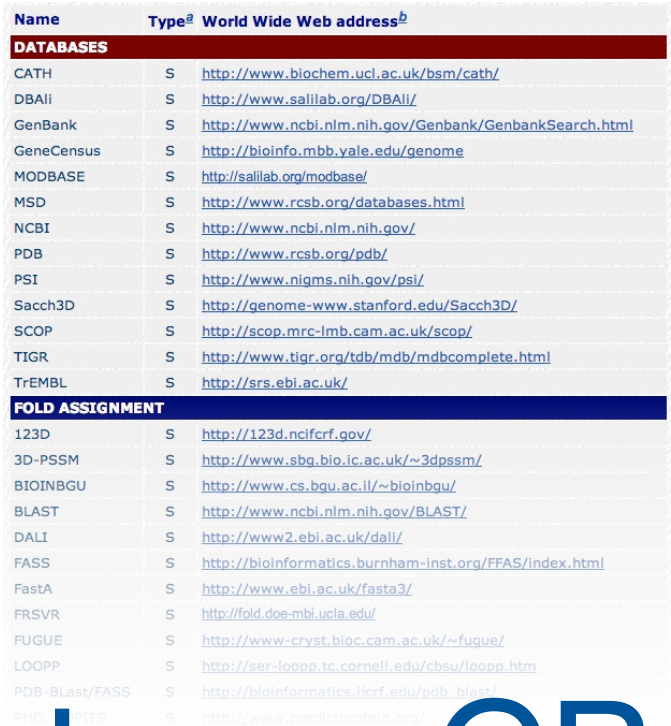
+ Completeness of genome projects (Malaria)
+ New and more complete biological databases
+ New software and computers (cheaper and faster)
+ Internet == more people == less cost

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

TDI flowchart



http://salilab.org/bioinformatics_resources.shtml



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/
PHDpsi/PROTS	S	http://www.predictprotein.org/

What can CB do?

Available computational biology resources for TDI

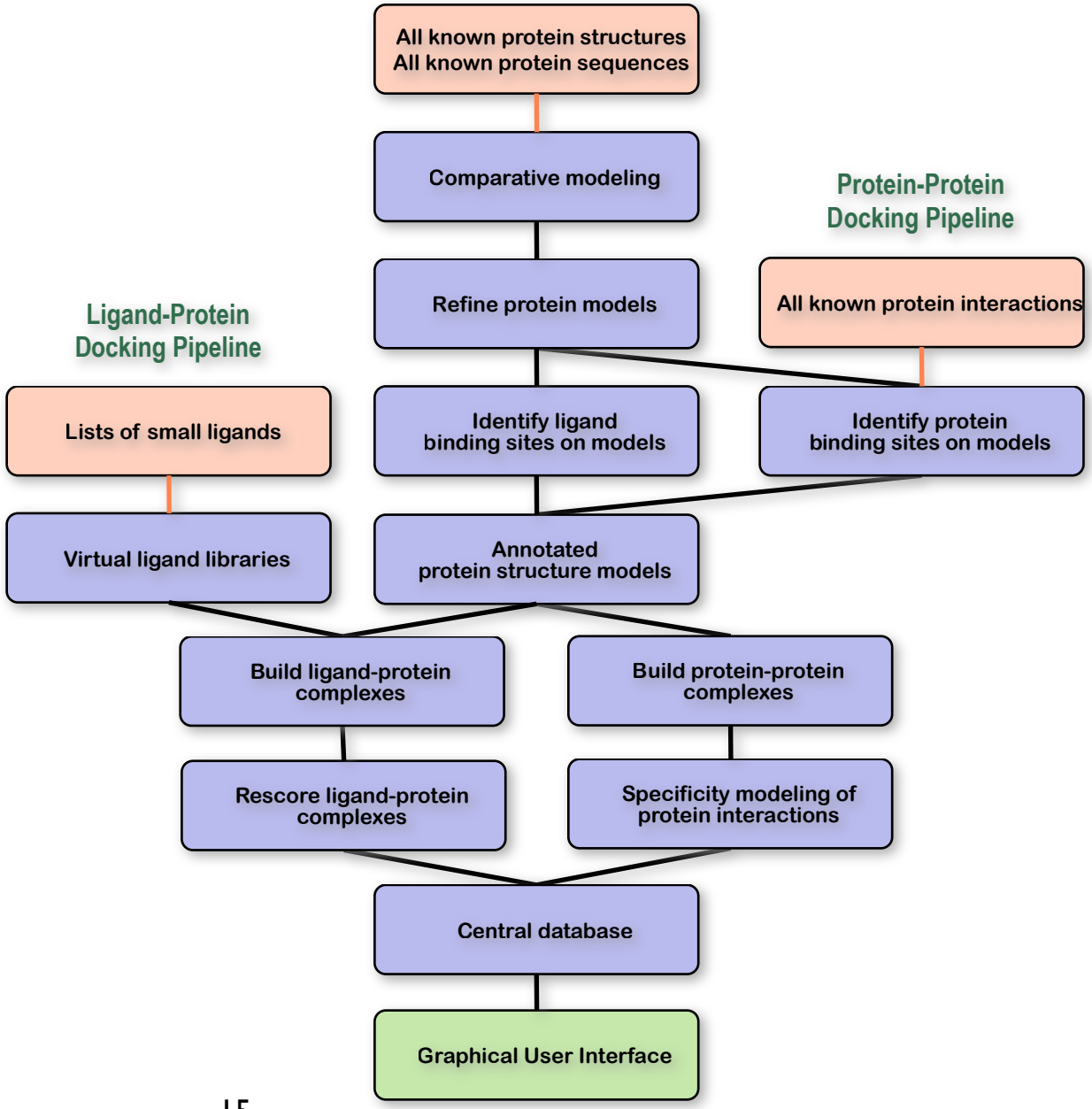
Protein-Ligand Universe

Center for Computational Proteomics Research (CCPR)

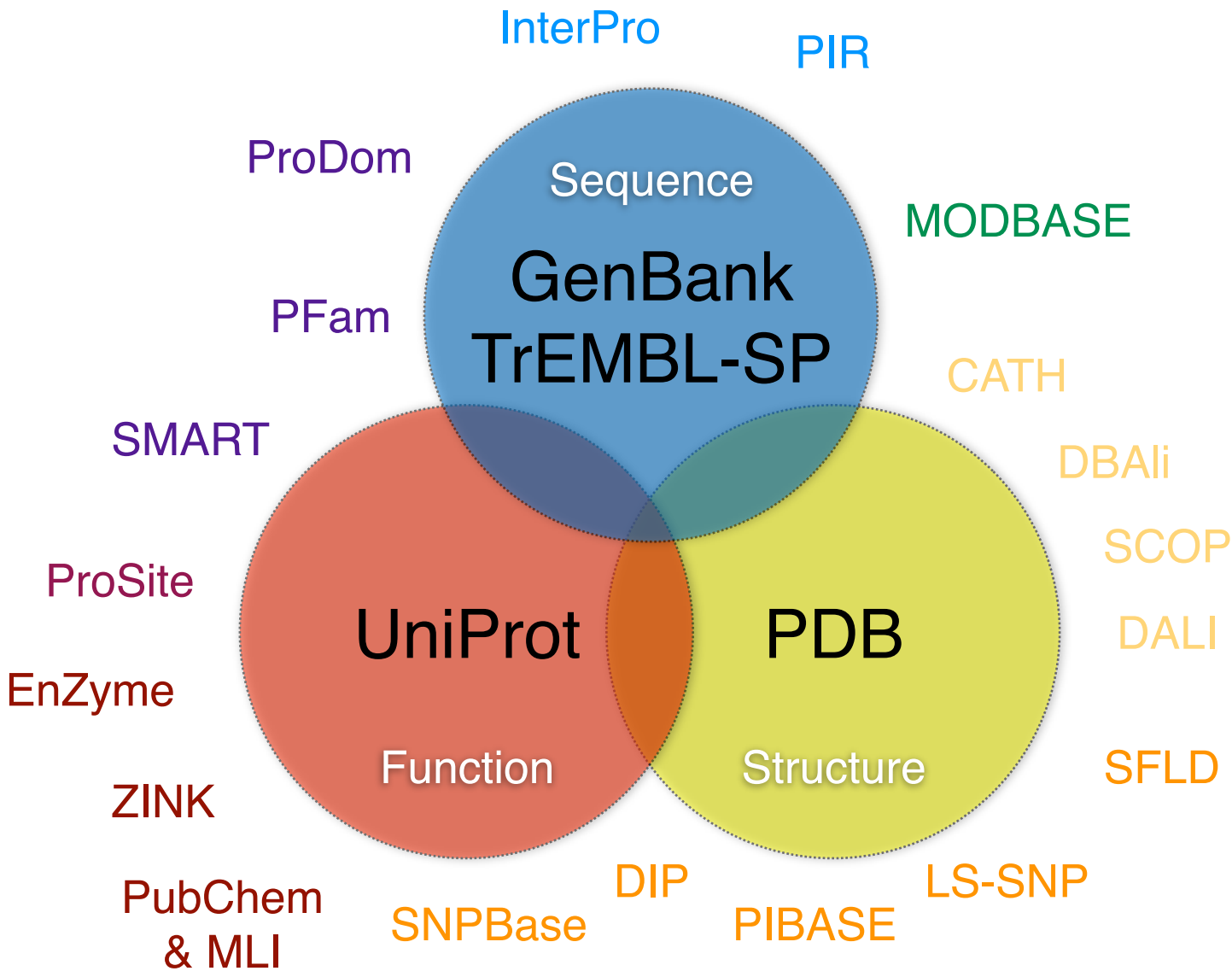
The California Institute for Quantitative Biomedical Research

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


InterPro
PIR
ProDom
Sequence
MODBASE
GenBank
TrEMBL-SP
PFam
CATH
SMART
DBAli
SCOP
ProSite
UniProt
PDB
DALI
EnZyme
Function
Structure
SFLD
ZINK
DIP
LS-SNP
PubChem
& MLI
SNPBase
PIBASE

Sequence search

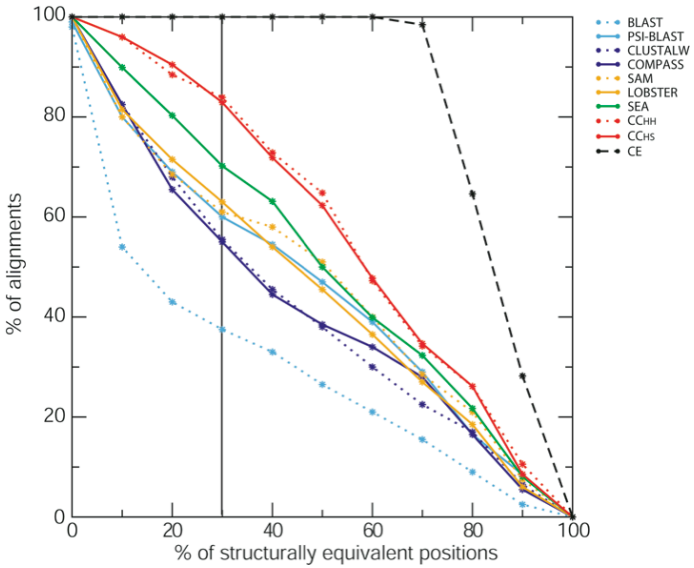
Profile based homology detection

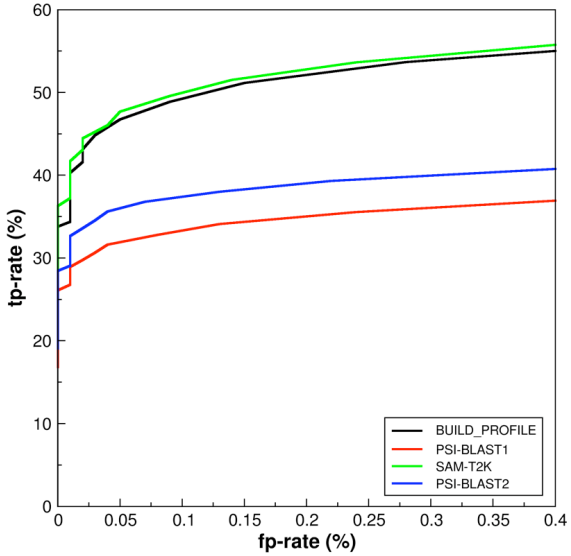
Sequence A: AGHLAHTRCELKLPTCRGNMSSRFC

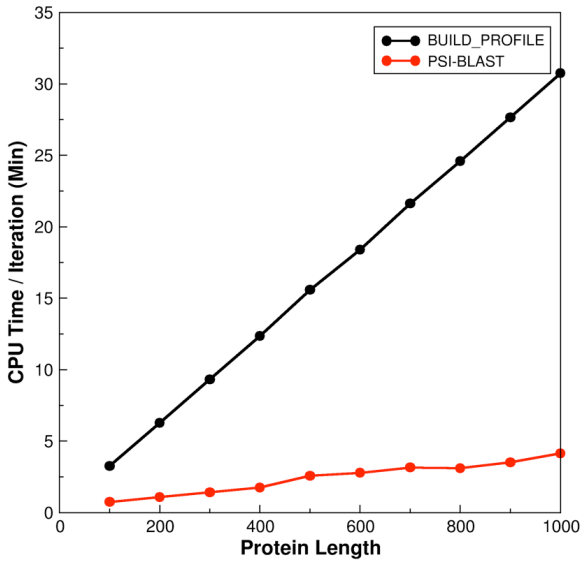
Sequence B: AGHLRHTRRCLRLPTAGNARFC

AGCATHTRCELK----------
AGHLAHPILELKLPTC---MSSRFC
AGCGTHPILELK--------SSRFC
AGHLAHTRCELKLPTCRGNMSSRFC

AGHLRHTRRCLRLPTAGNARFC
AGHLRHTRRCLRLPTA---RFC
AGHLRATRCCLRLTTAGNAR--
AGHLRHALAILRLPTAGNAR--
AGHL---AACLRLPTAGNARFC



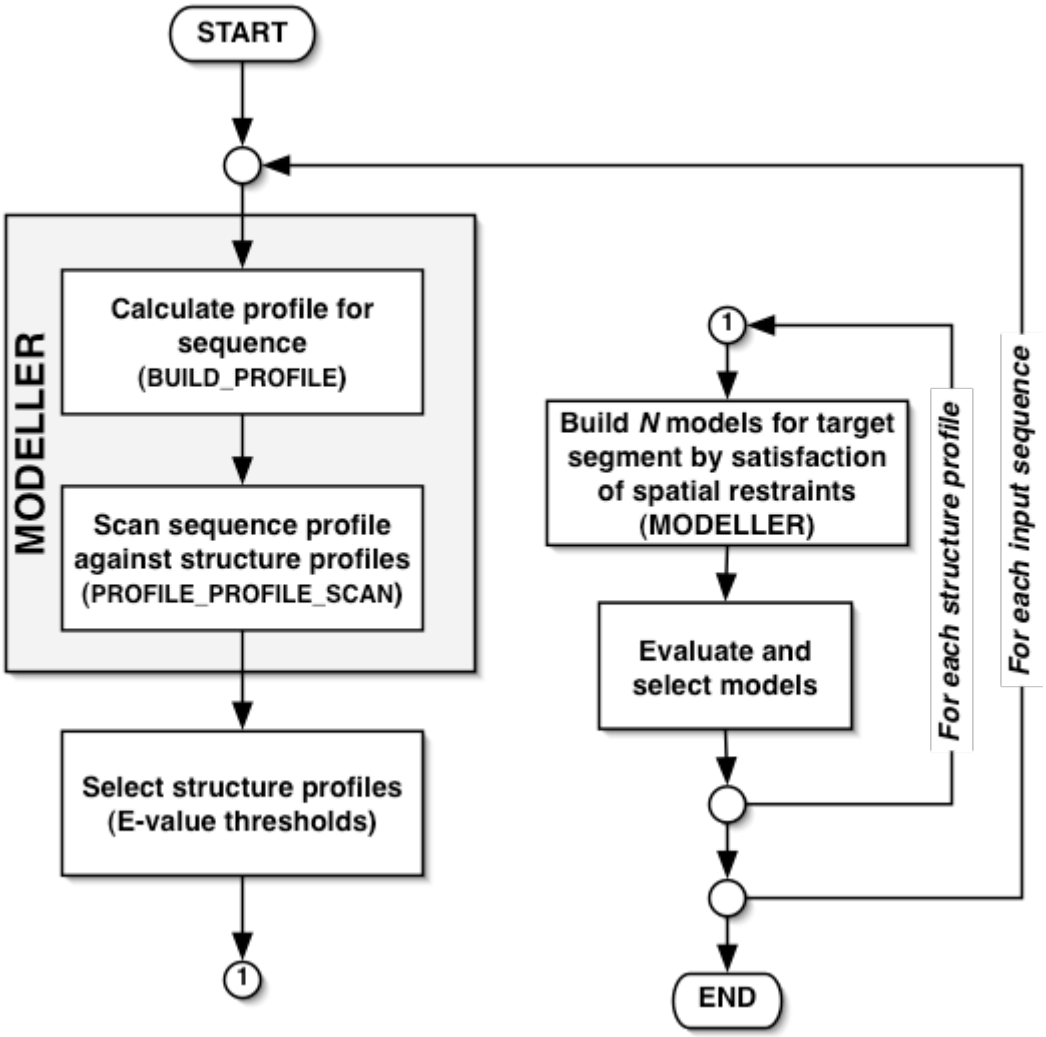


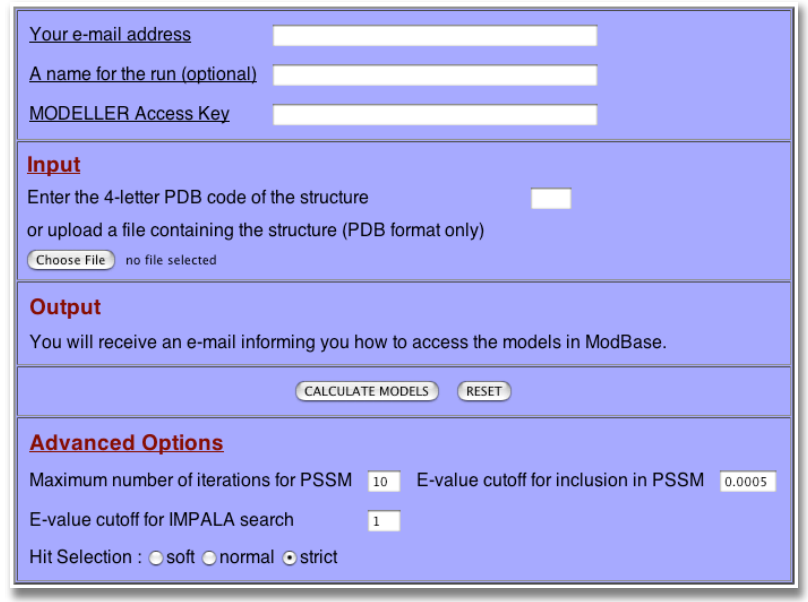


Marti-Renom etal. (2004) Prot. Sci. **13**:1071

Protein Structure Modeling

ModPipe & ModWeb





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

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

Protein Structure Modeling

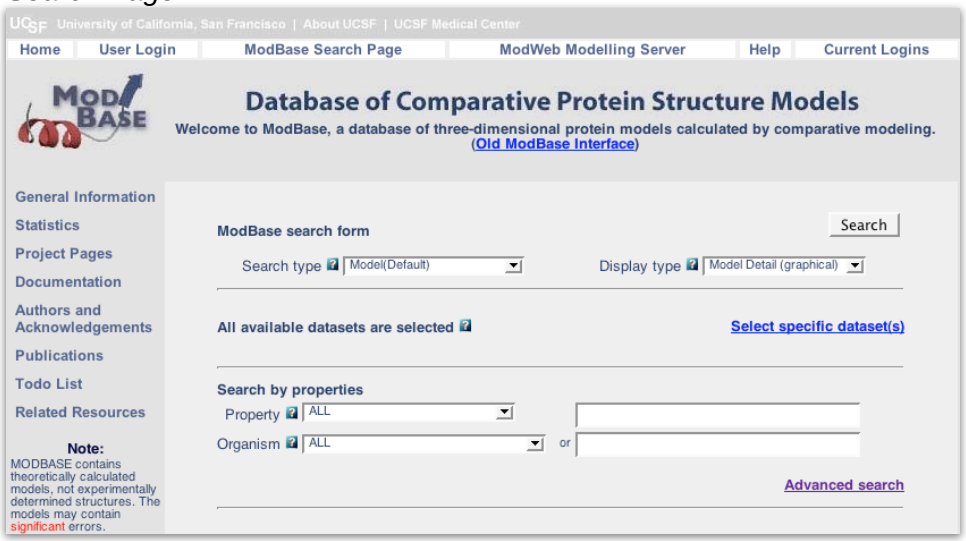
Large-Scale prediction

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

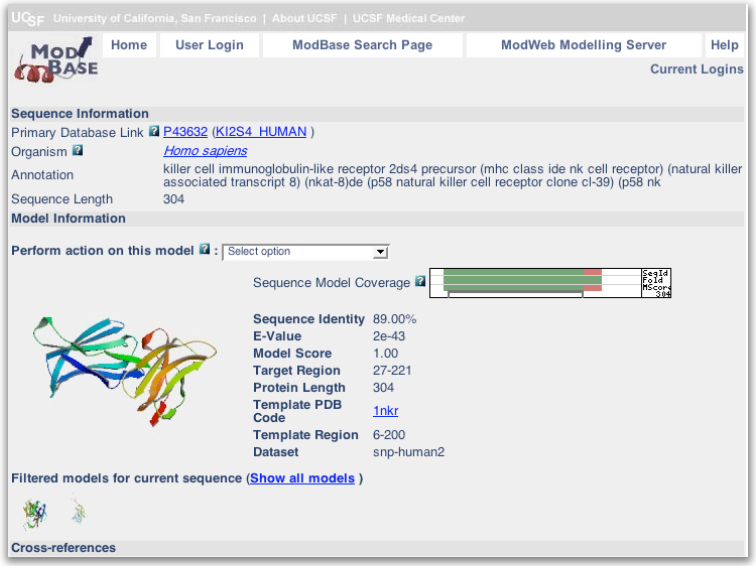
Protein Structure Modeling

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

Search Page

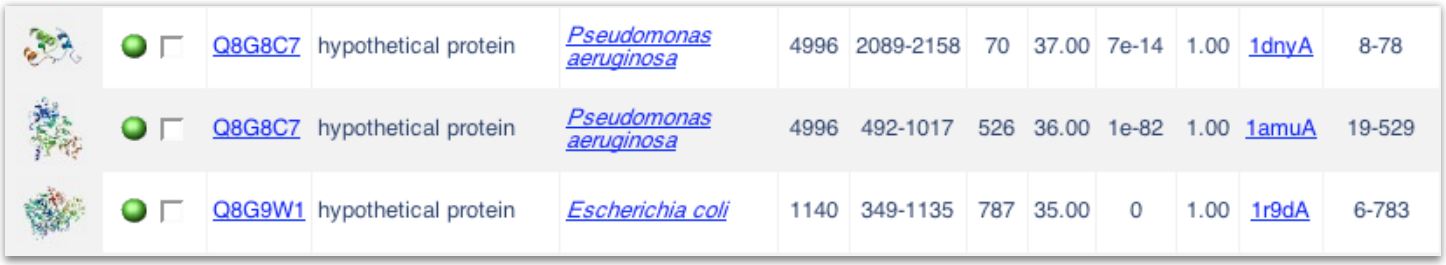


Model Details



Sequence Overview

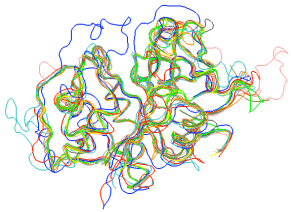
Model Overview



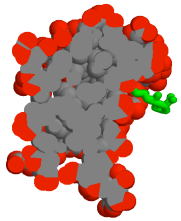
Functional Annotation

Localization of binding sites

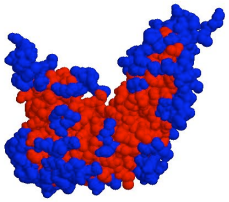
Structure conservation



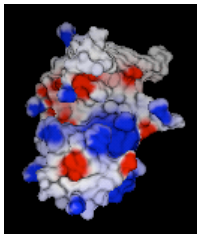
Solvent accessibility



Surface geometry



Electrostatics



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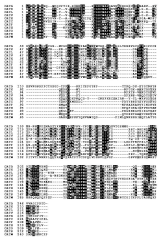
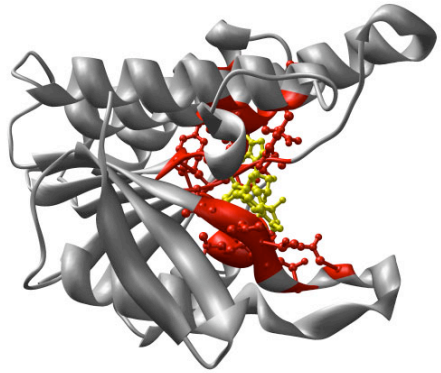
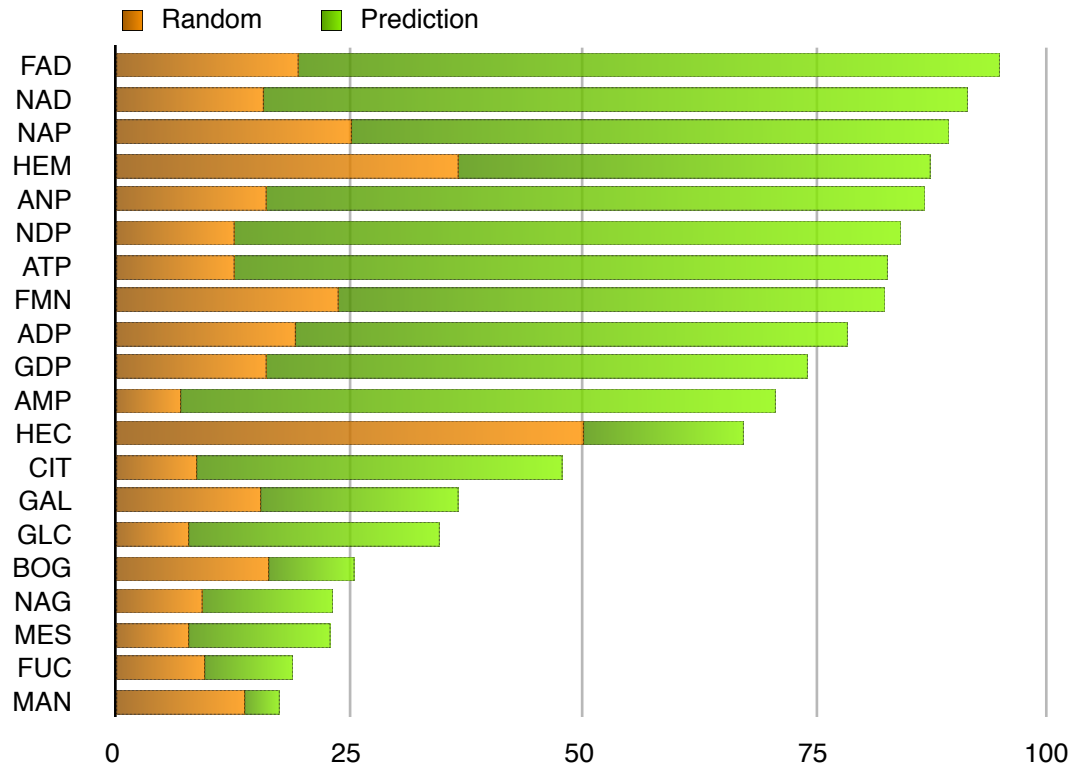


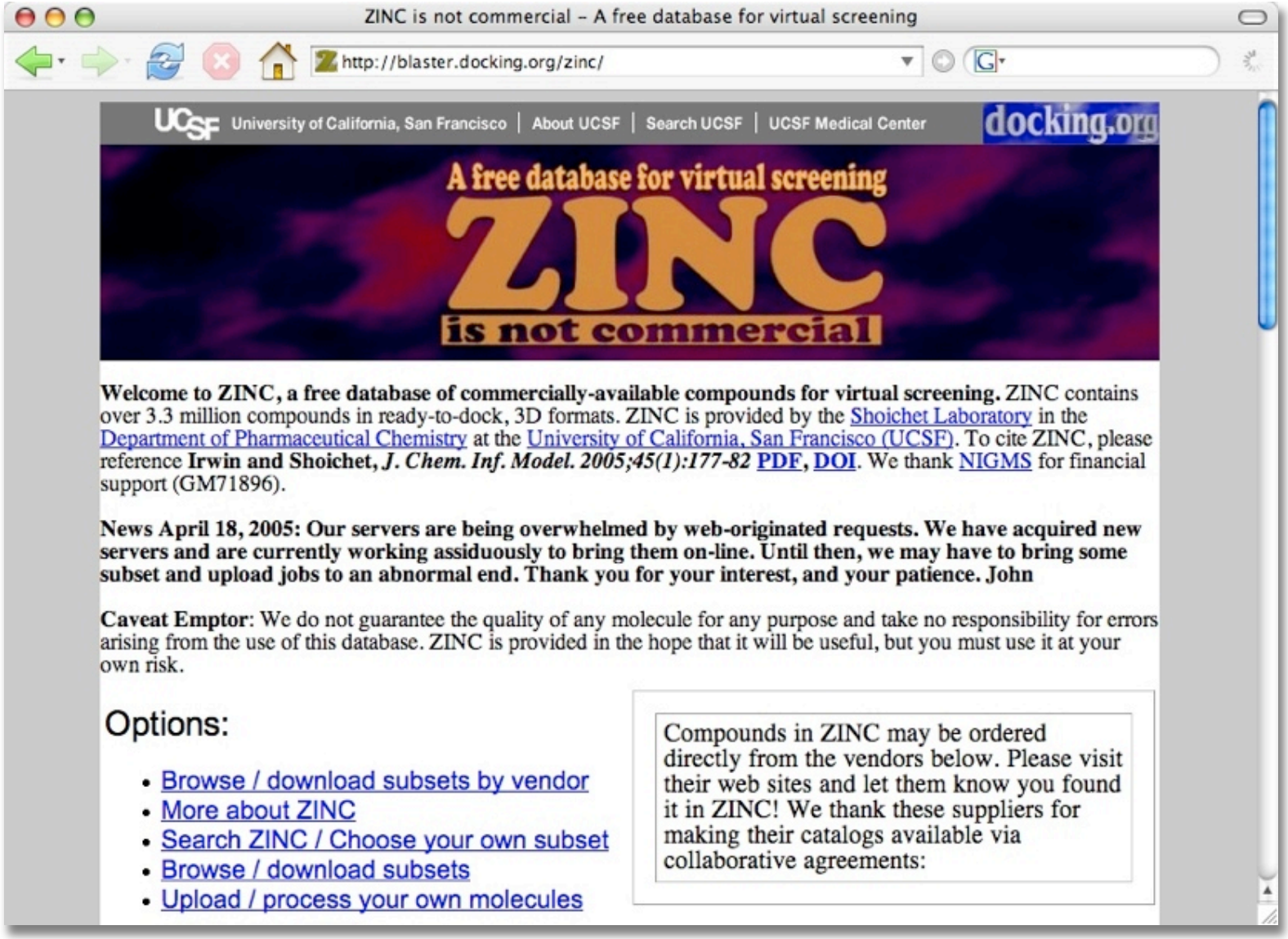




Rossi, Marti-Renom and Sali (2005) Submitted for publication

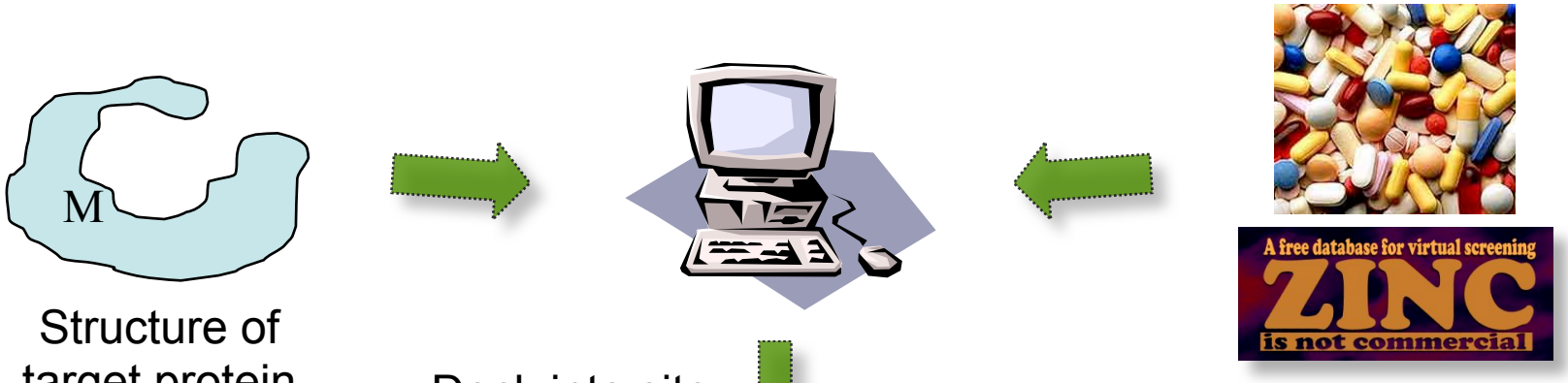
Virtual ligand libraries

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



Irwin and Shoichet, J. Chem. Inf. Model. 2005;45(1):177-82

Protein-Ligand Docking



Docking .vs. HTS

Target: reductase TB
Library: Merk chemical

IC_{50} < 100μM hit rate

HTS	Dock
0.2%	~6%

Paiva et al. (2001) Biochem. Biophys. Acta. ***1545****:67-77*
Shoichet, McGovern,Wei, Irwin (2002) Curr Opin Chem Biol. ***6****:439-46*

Courtesy of John Irwin, UCSF http://www.docking.org

Protein-Ligand Docking

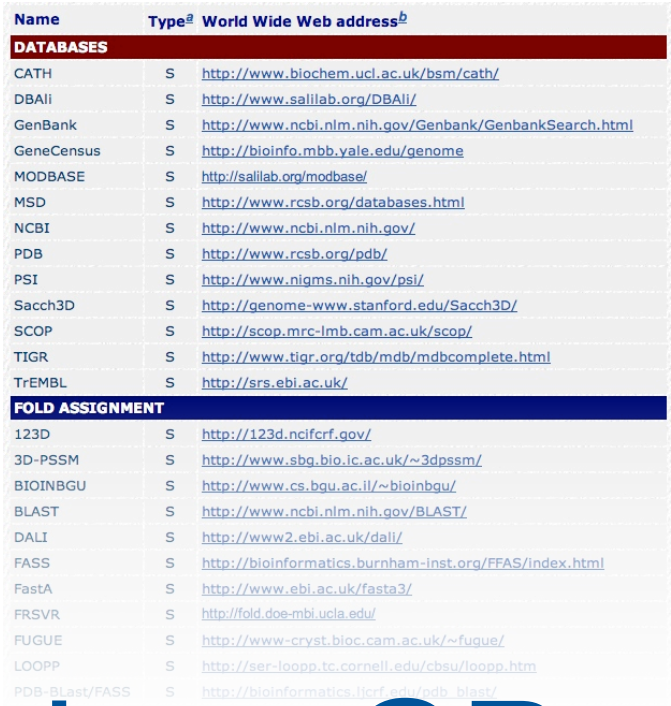
Successfully applied

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_2picolinate 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.).

Shoichet, McGovern,Wei, Irwin (2002) Curr Opin Chem Biol. ***6****:439-46*

http://salilab.org/bioinformatics_resources.shtml



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/PROFTS	S	http://www.predictprotein.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".

HIV Proteinase structure

X-ray analysis of HIV-1 proteinase at 2.7 A 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."

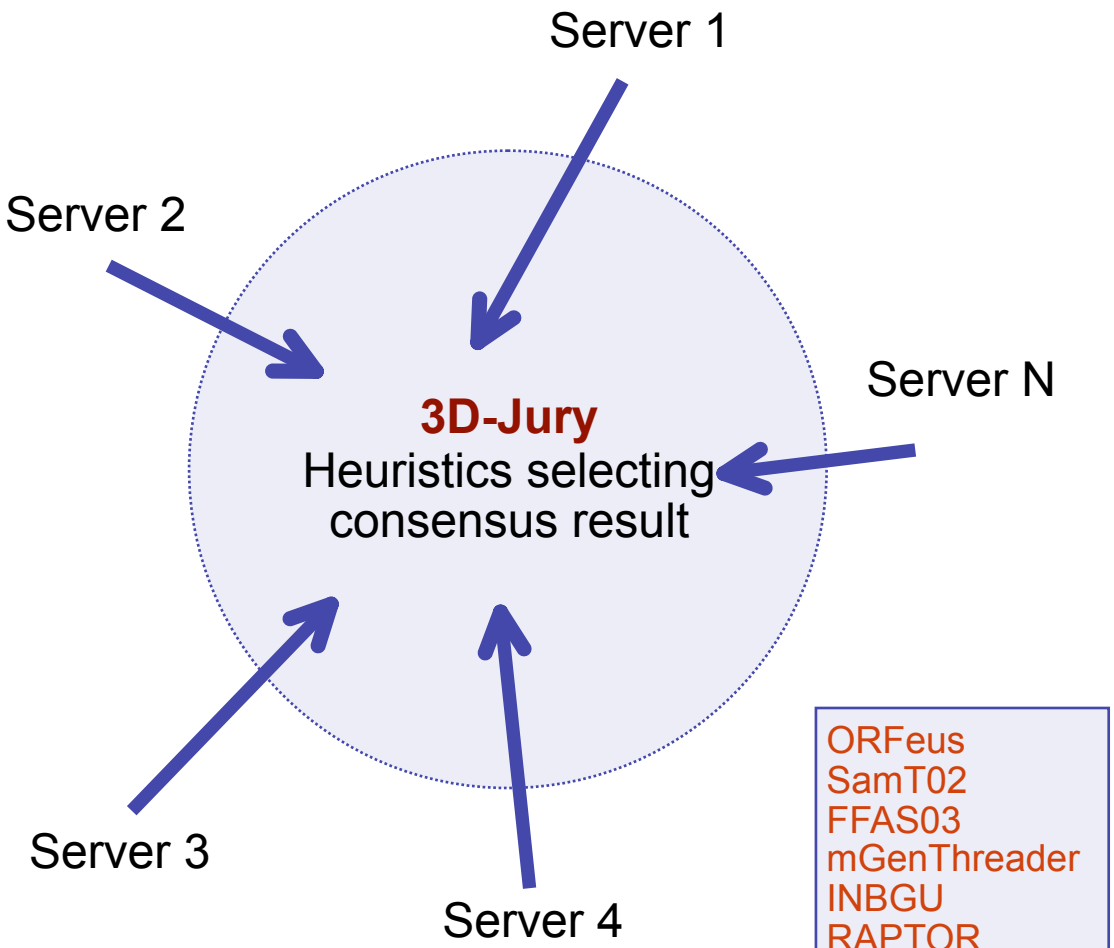
The 3-D structure of HIV-1 proteinase and the design of antiviral agents for the treatment of AIDS.

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

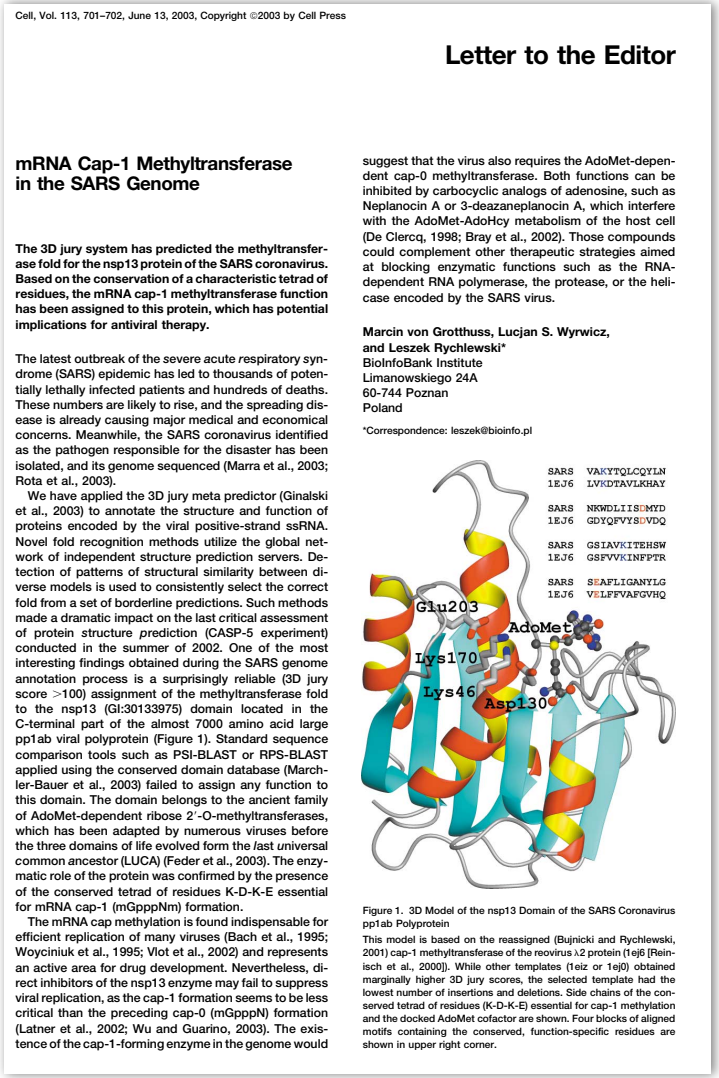
"Analogies between the structures of HIV-1 proteinase and the mammalian enzyme renin have given **important clues** concerning the design of specific inhibitors that have antiviral activity."

Examples

mRNA Cap-1 Methyltransferase in SARS (2003)



ORFeus
SamT02
FFAS03
mGenThreader
INBGU
RAPTOR
FUGUE-2
3D-PSSM



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 form 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 (mGpppNm) formation.

The mRNA cap methylation is found indispensable for efficient replication of many viruses (Bach et al., 1995; Woyciniuk 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 (mGpppN) 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.

Marcin von Grotthuss, Lucjan S. Wyrwicz, and Leszek Rychlewski*
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

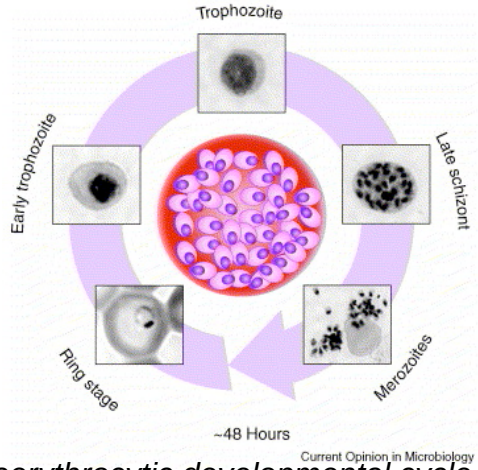
This model is based on the reassigned (Bujnicki and Rychlewski, 2001) cap-1 methyltransferase of the reovirus λ2 protein (1ej6 [Reinisch et al., 2000]). While other templates (1eiz or 1ej0) obtained marginally higher 3D jury scores, the selected template had the lowest number of insertions and deletions. 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** pp**701***

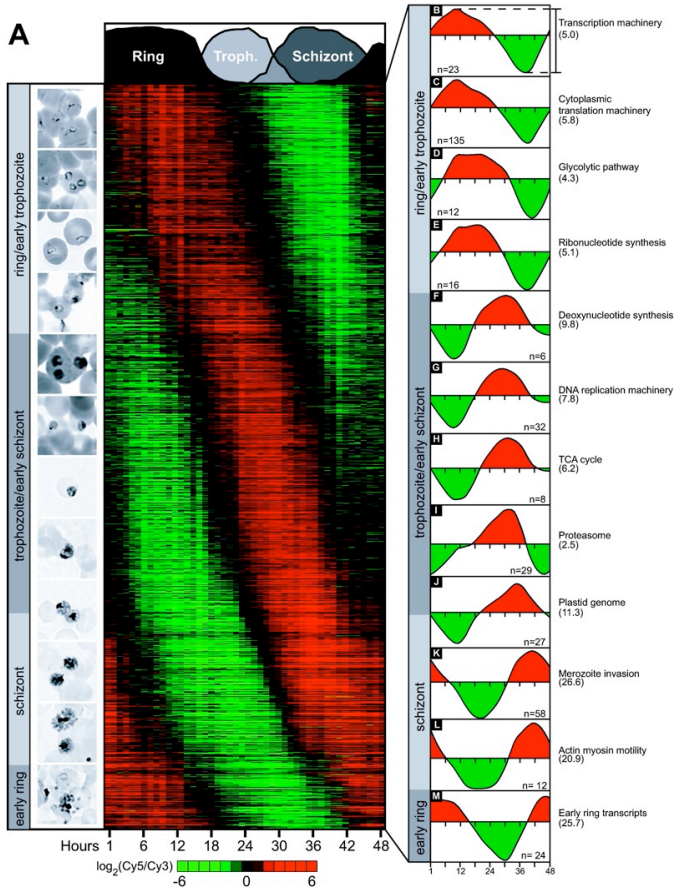
*Ginalski K, et al. (2003) Bioinformatics **19** pp**1015***

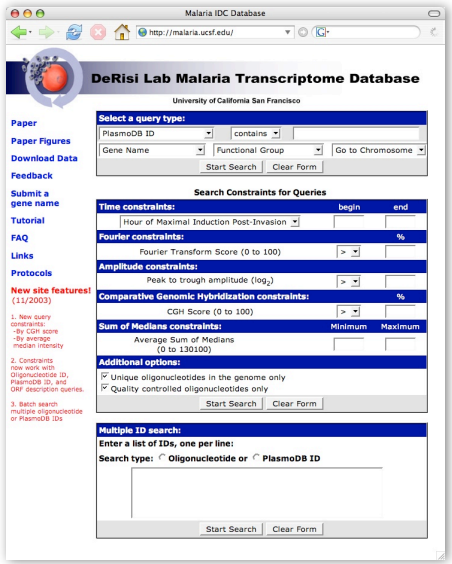
Examples

Genomic research on Malaria (2003)



Intraerythrocytic developmental cycle IDC





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...

inpharmatica

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

VERTEX

Viral Diseases	Preclinical	Phase I	Phase II	Phase III	Market
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 Pharmaceuticals

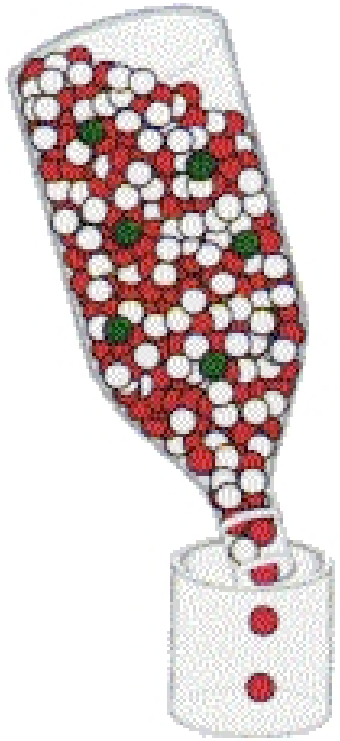
Predix' Clinical Development Programs

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

SGX

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

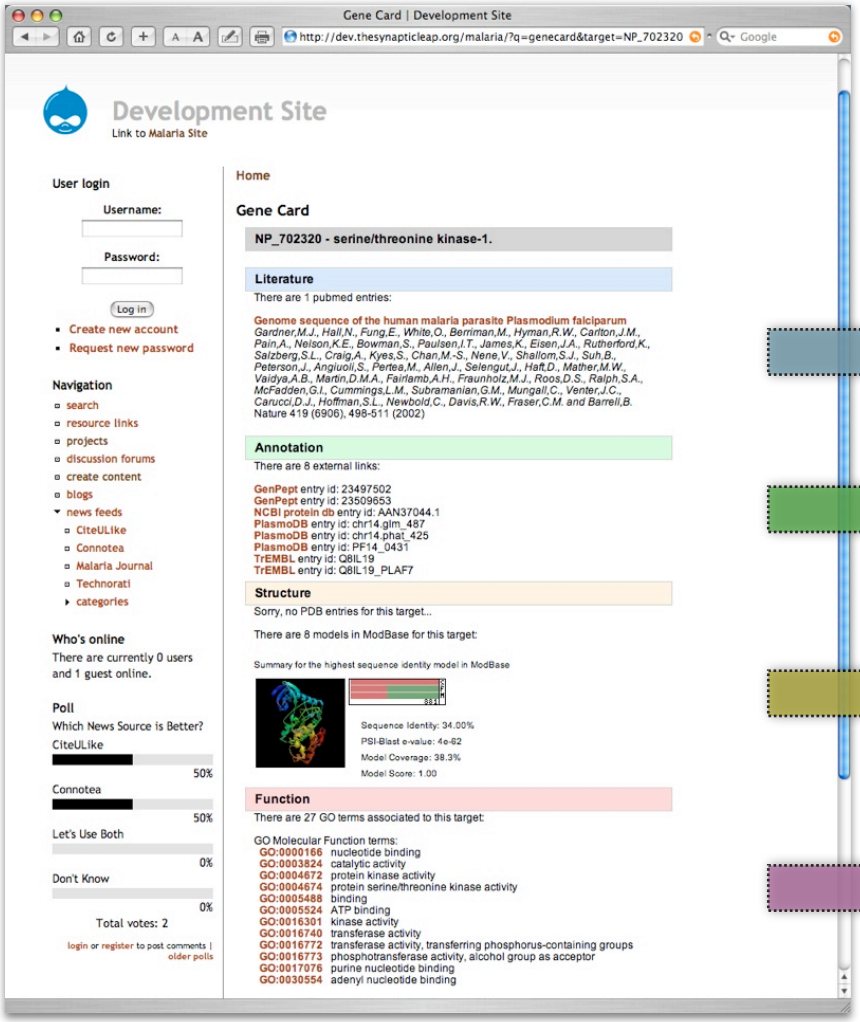
PROJECT I	**Gene Cards**
PROJECT II	**Structure Prediction**
PROJECT III	**Target Selection for Structural Genomics**
PROJECT IV	**Gene Annotation**
PROJECT V	**Gene Basket**

PROJECT I

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

Literature

Annotation

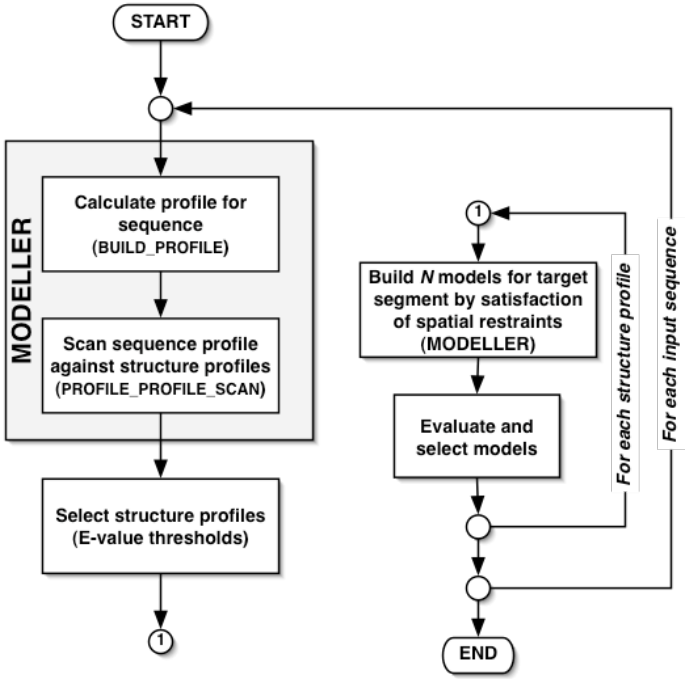
Structure

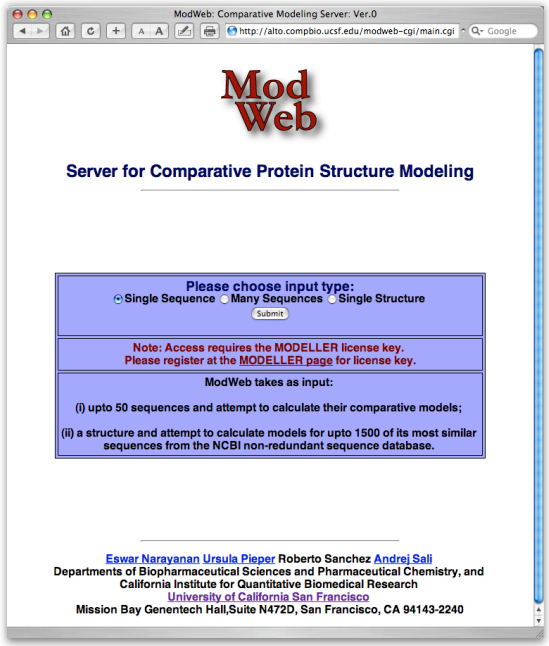
Function

PROJECT II

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

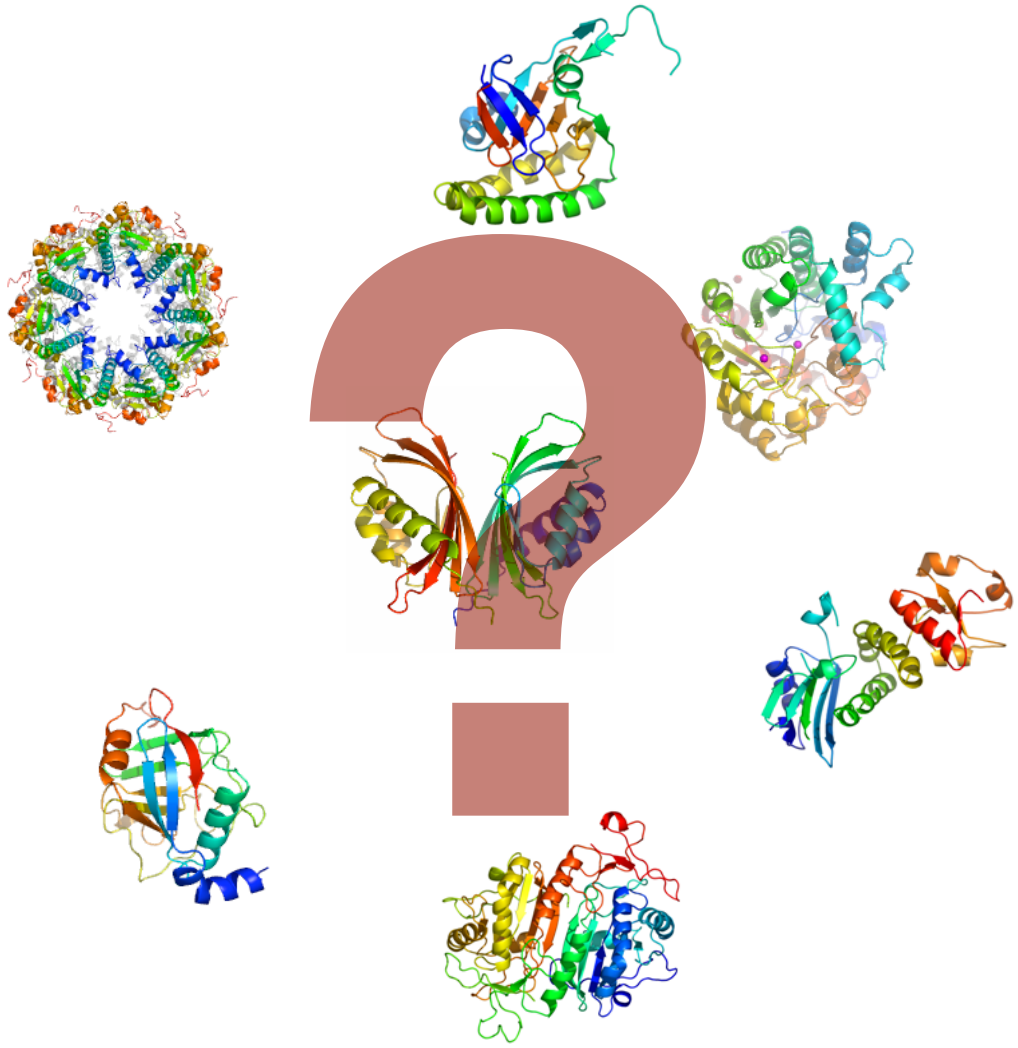
PROJECT III

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.

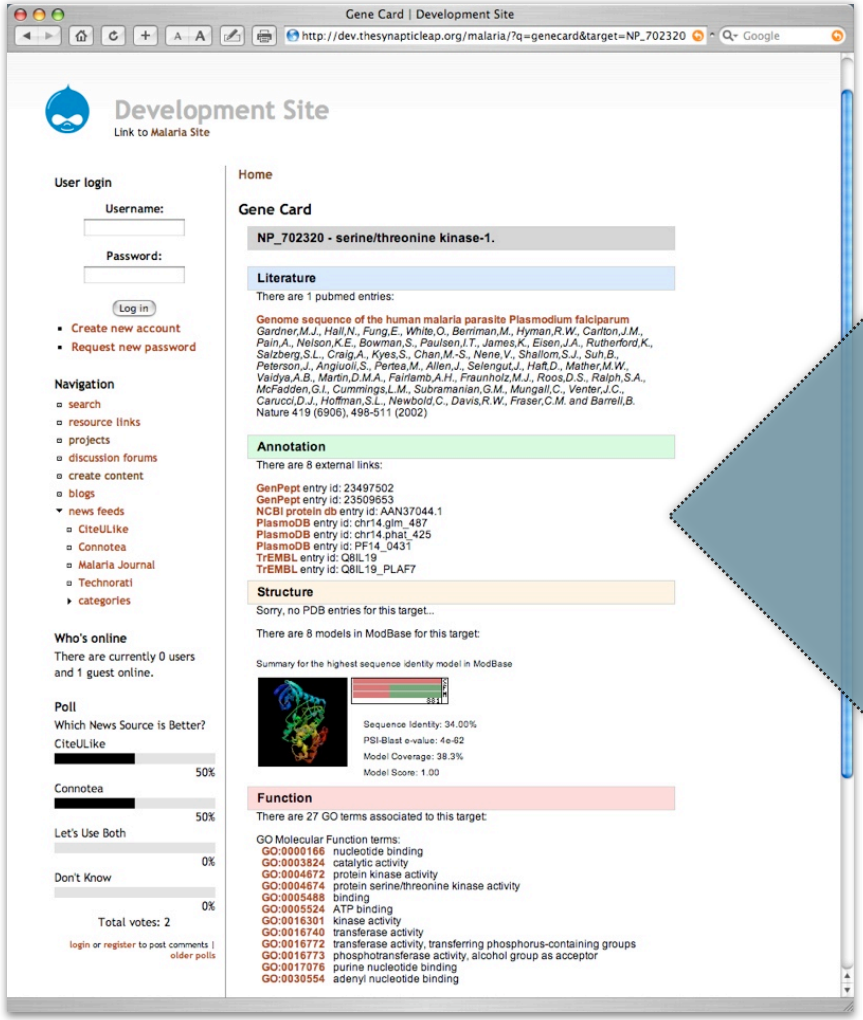


Dr. Raymond Hui
University of Toronto and SGC

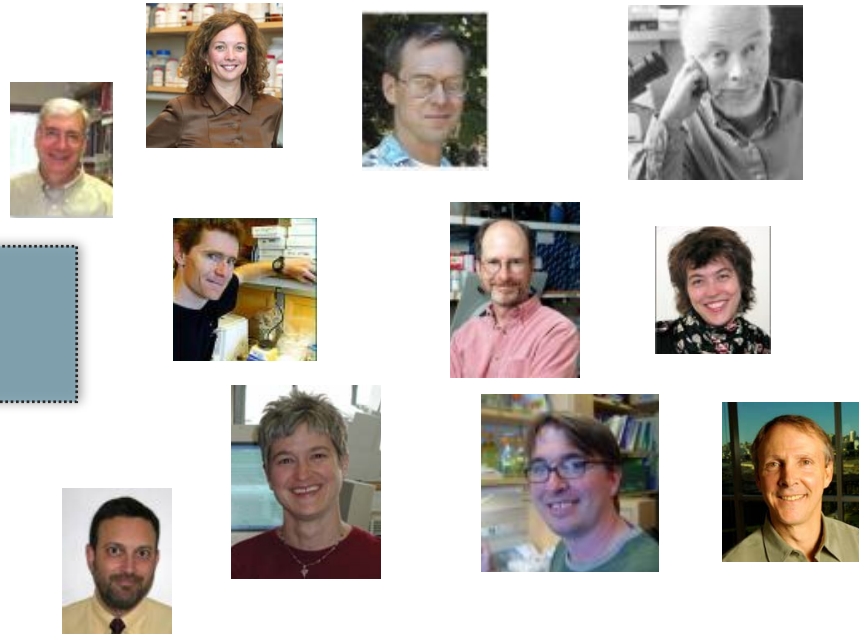
PROJECT IV

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.



PROJECT V

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 del.icio.us

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As seen on: YAHOO! flickr BETA del.icio.us

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