

# The Tropical Disease Initiative

*An open source approach to drug development*

[www.tropicaldisease.org](http://www.tropicaldisease.org)

[www.thesynapticleap.org/malaria/](http://www.thesynapticleap.org/malaria/)

not quite a scientific talk ;-)



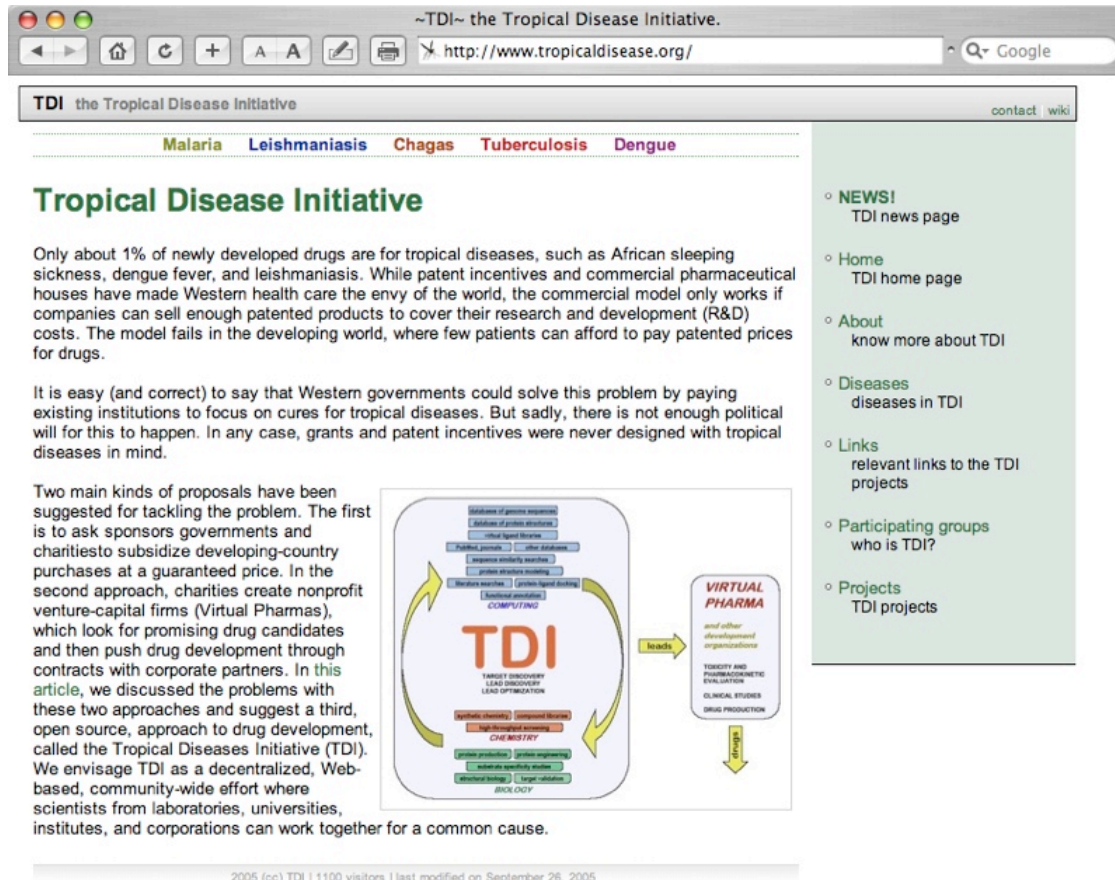
**Marc A. Marti-Renom**

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

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

# TDI web site

<http://www.tropicaldisease.org/>



The screenshot shows the TDI website homepage with a navigation bar for Malaria, Leishmaniasis, Chagas, Tuberculosis, and Dengue. The main content area features a 'Tropical Disease Initiative' header and a paragraph explaining the initiative's goal: to develop drugs for tropical diseases by leveraging Western health care and commercial pharmaceutical models. A sidebar on the right lists links such as 'NEWS!', 'Home', 'About', 'Diseases', 'Links', 'Participating groups', and 'Projects'. Below the screenshot is a diagram illustrating the TDI workflow, which involves a cycle of 'COMPUTING' (genomic, proteomic, metabolomic, transcriptomic, and clinical data) and 'BIOLOGY' (target discovery, lead optimization, and drug production) leading to 'VIRTUAL PHARMA' and 'DRUG PRODUCTION'.

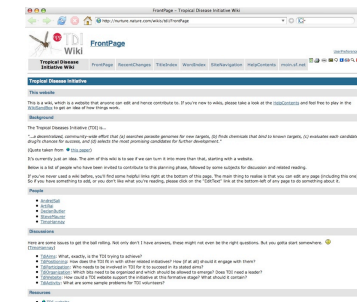
Only about 1% of newly developed drugs are for tropical diseases, such as African sleeping sickness, dengue fever, and leishmaniasis. While patent incentives and commercial pharmaceutical houses have made Western health care the envy of the world, the commercial model only works if companies can sell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



# 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

Stephen Mark Maurer

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

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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, but I'd like to do something to keep the 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**  
Thank you kindly,  
Adam Huber

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10 Feb 2005

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Hello,

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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.

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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 :)

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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...**

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Daniel Amelang

19 Jan 2005

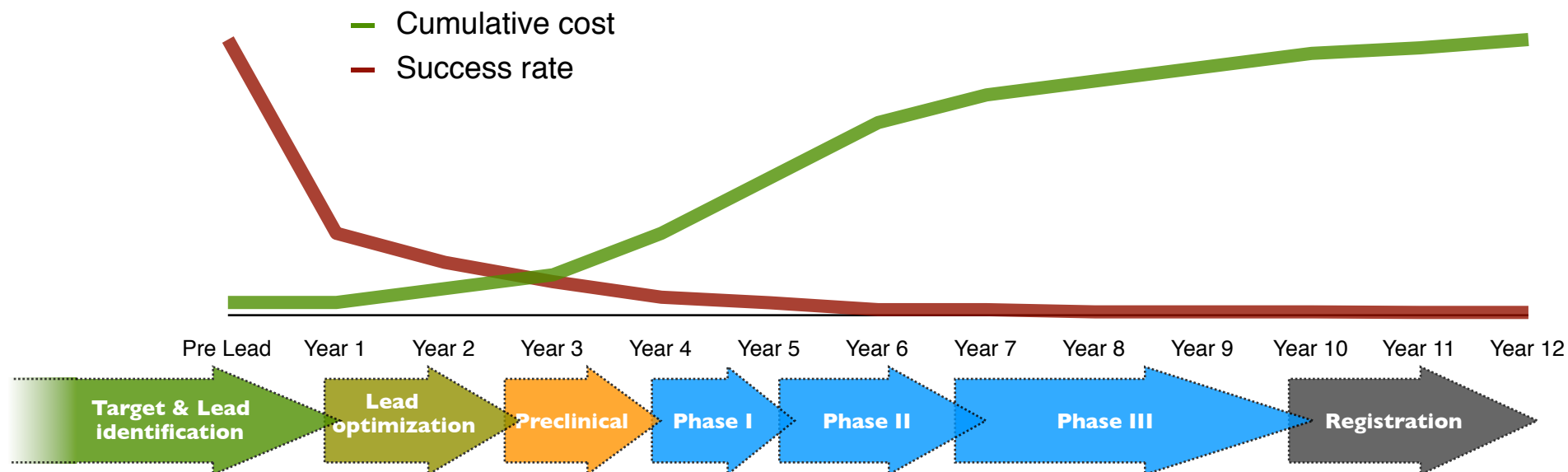
**If we do the science well, I'm optimistic that the rest of TDI will fall into place.**

Stephen Mark Maurer

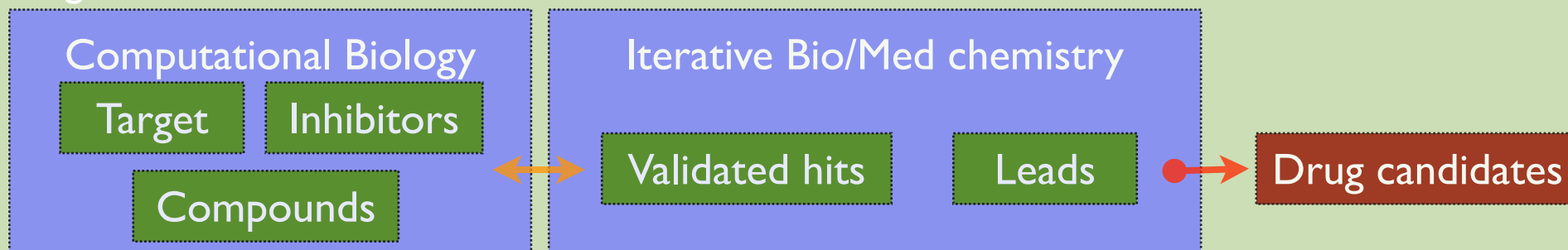
# Action plan @ Tropical Disease Initiative



# Drug Discovery pipeline

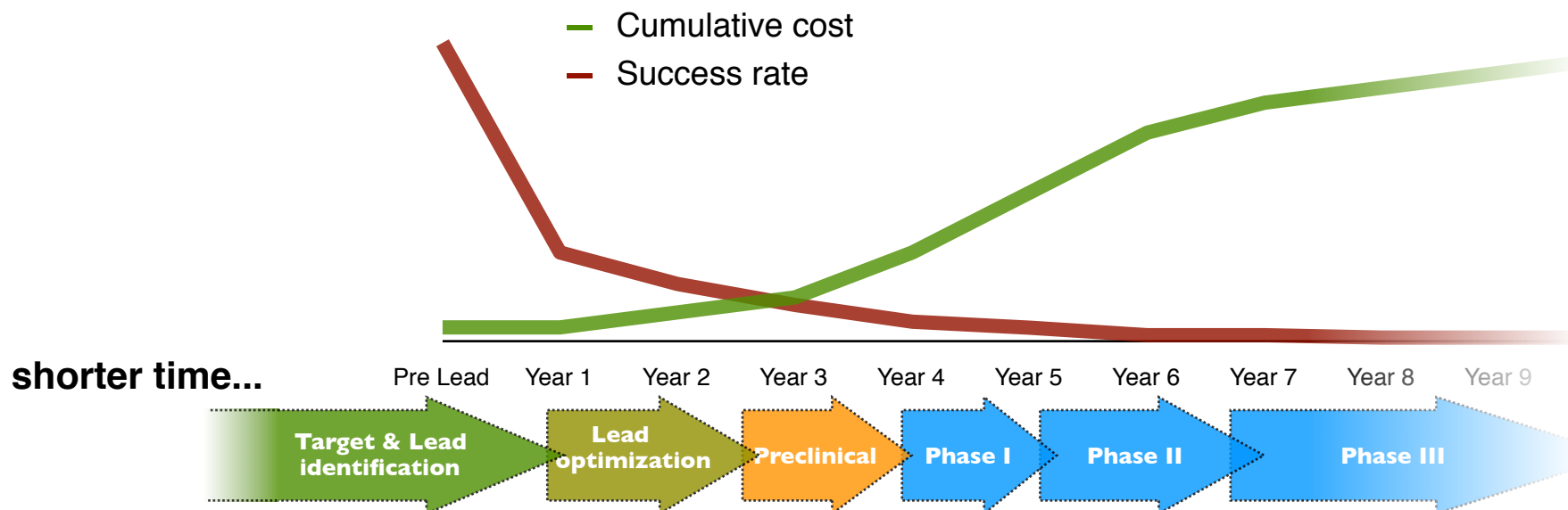


## Target & Lead identification



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 projects

PROJECT I

**Gene Cards**

PROJECT II

**Structure Prediction**

PROJECT III

**Target Selection for Structural Genomics**

PROJECT IV

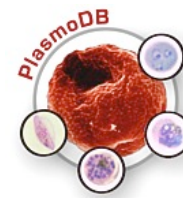
**Gene Annotation**

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**

http://dev.thesynapticleap.org/malaria/?q=genecard&target=NP\_702320

**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

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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

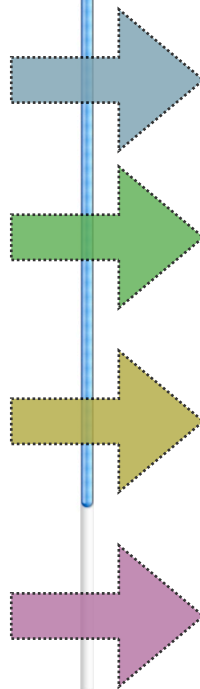
Sequence Identity: 34.00%  
PSI-Blast e-value: 4e-62  
Model Coverage: 38.3%  
Model Score: 1.00

**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

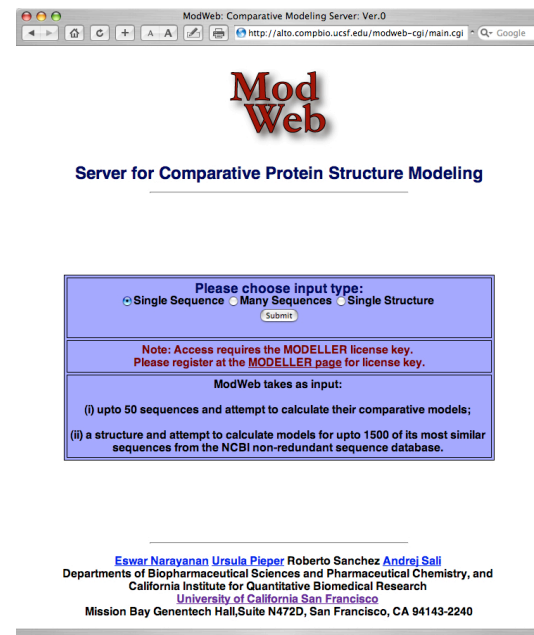
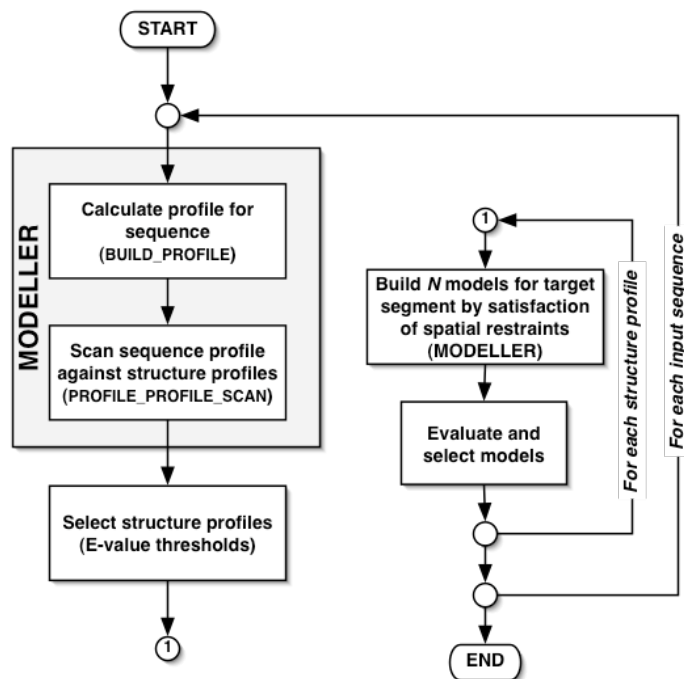
Annotation

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.

**Gene Card | Development Site**

Link to Malaria Site

**User login**

Username:

Password:

[Log in](#)

- [Create new account](#)
- [Request new password](#)

**Navigation**

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
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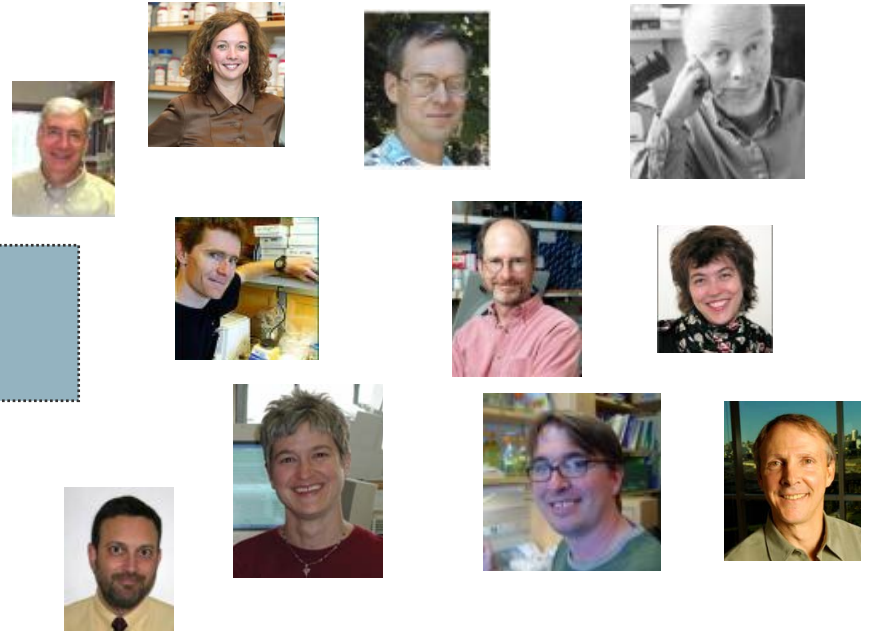
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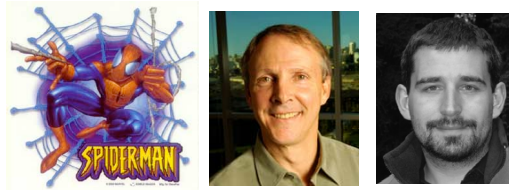
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GO:0004874 protein serine/threonine kinase activity  
GO:0005488 binding  
GO:0005524 ATP binding  
GO:0016301 kinase activity  
GO:0016740 transferase activity  
GO:0016772 transferase activity, transferring phosphorus-containing groups  
GO:0016773 phosphotransferase activity, alcohol group as acceptor  
GO:0017076 purine nucleotide binding  
GO: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.

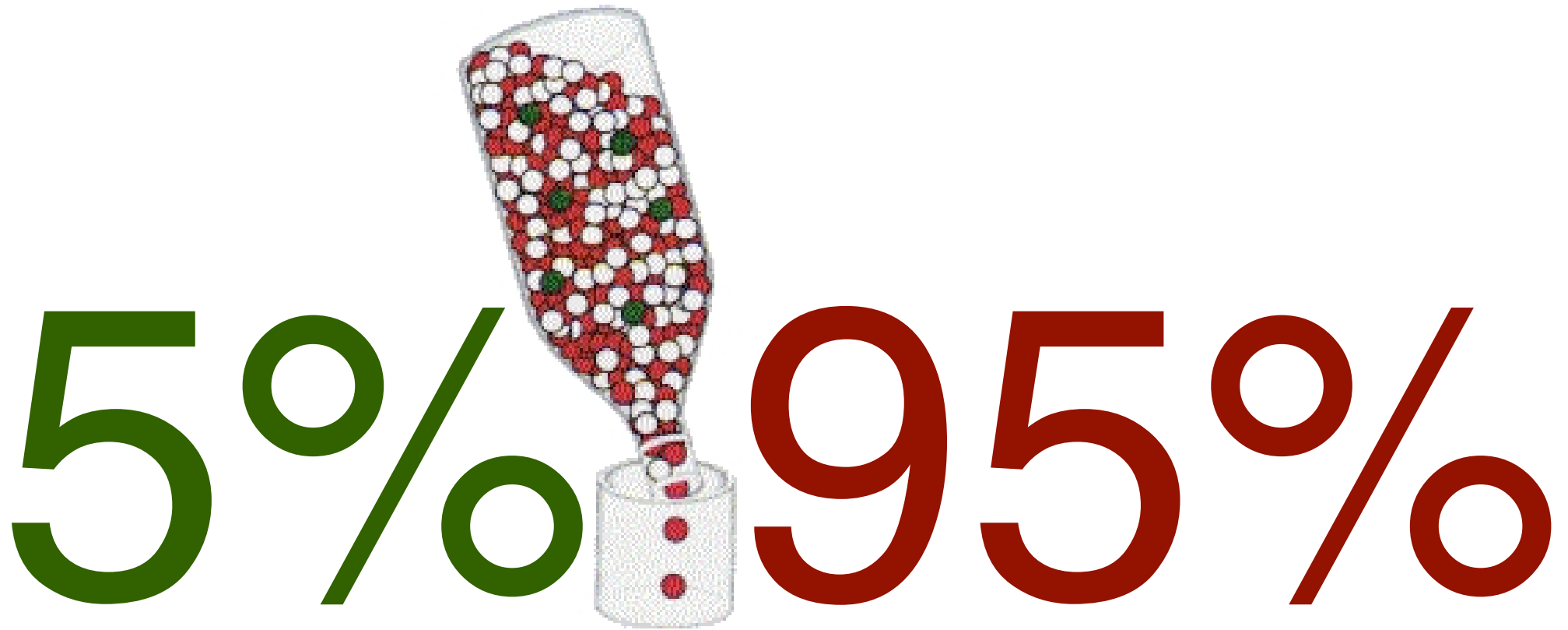
As seen on: **YAHOO!** **flickr**<sup>BETA</sup>





**YOURS!**  
send us suggestions

[tdi@tropicaldisease.org](mailto:tdi@tropicaldisease.org)



# What is in it for the 95%?

## 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 disease - **worldwide...**
- to access to **new** research tools
- **free** collaborative site

# 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/>

## The Sali Lab

Andrej Sali  
Eswar Narayanan  
Ursula Pieper

## Tropical Disease Initiative

Stephen Maurer  
Arti Rai  
Andrej Sali  
Thomas Kepler

## The Synaptic Leap

Ginger Taylor  
Randy Akl  
Chris Heller  
Rich Manalang  
Ken Pugsley

## Wiki site at NPG

Timo Hannay  
Declan Butler