

The Tropical Disease Initiative

An open source approach to drug discovery

www.tropicaldisease.org



UCSF

Duke
UNIVERSITY

PRINCIPE FELIPE
CENTRO DE INVESTIGACION



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Bioinformatics Department

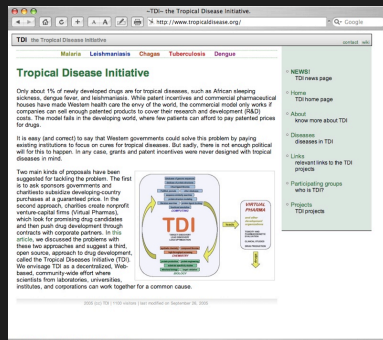
Prince Felipe Research Center (CIPF), Valencia, Spain



SG



TDI *a story*

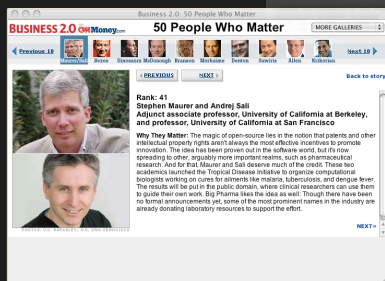


2004

.Steve Maurer (Berkeley) & Arti Rai (Duke)
.PLoS Medicine, Dec. 2004. Vol 1(3):e56

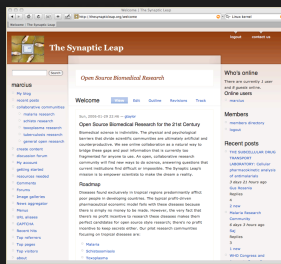
2005

.TDI web site <http://www.tropicaldisease.org>
.Ginger Taylor and The Synaptic Leap



2006

.Maurer & Sali are 41th in "50 Who Matter"
. <http://www.thesynapticleap.org>

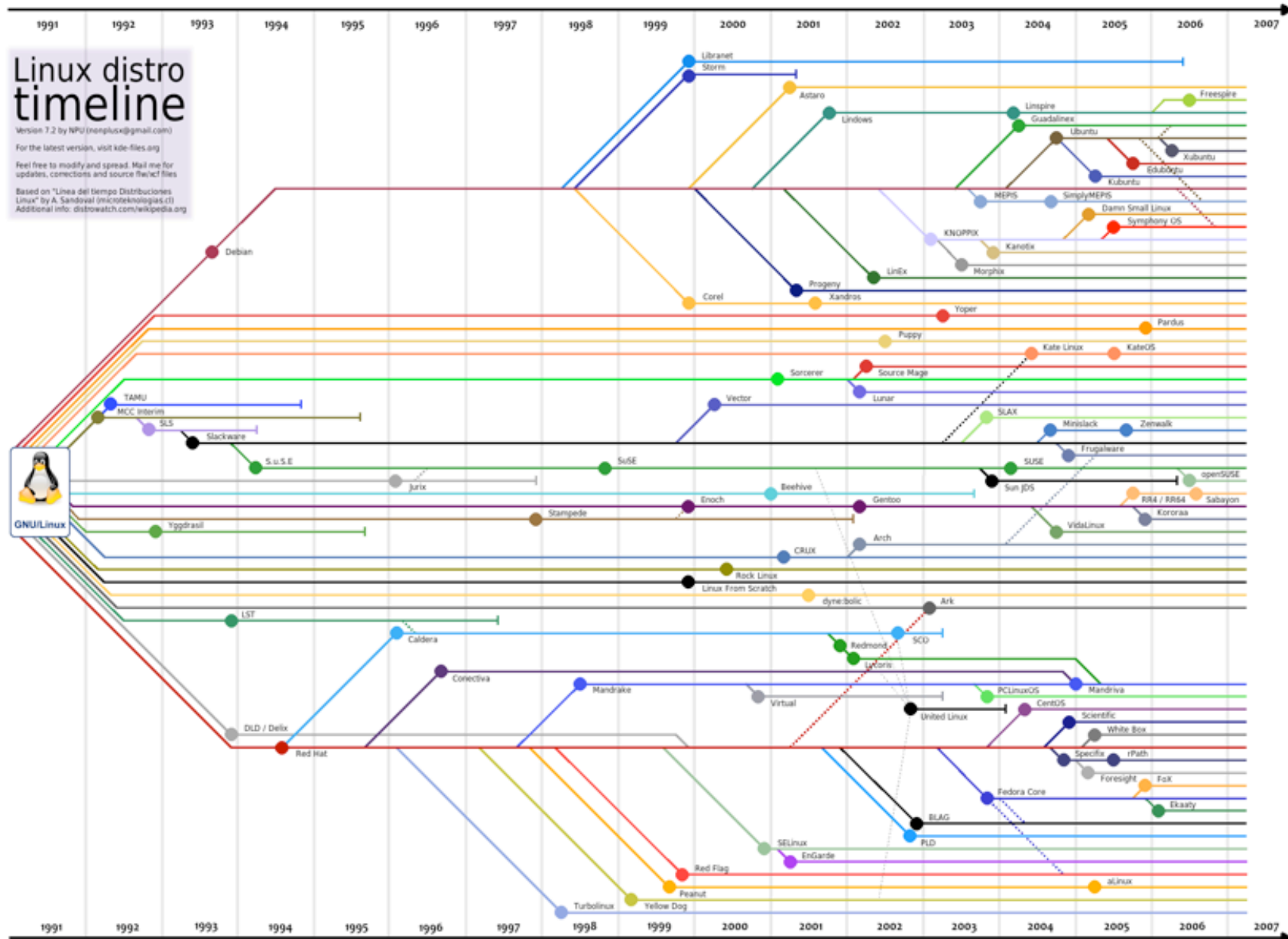


2007-2008

.KERNEL?

Open Source

Why we need “a kernel”?



Is it possible?...

1. *In silico* drug discovery

2. Chemistry

3. Stem cell lines

NEXT STEPS

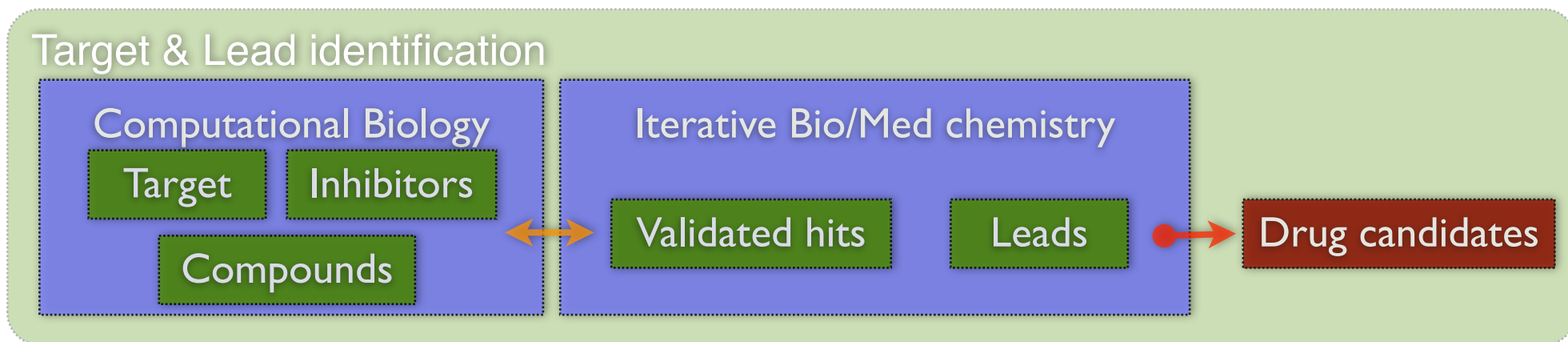
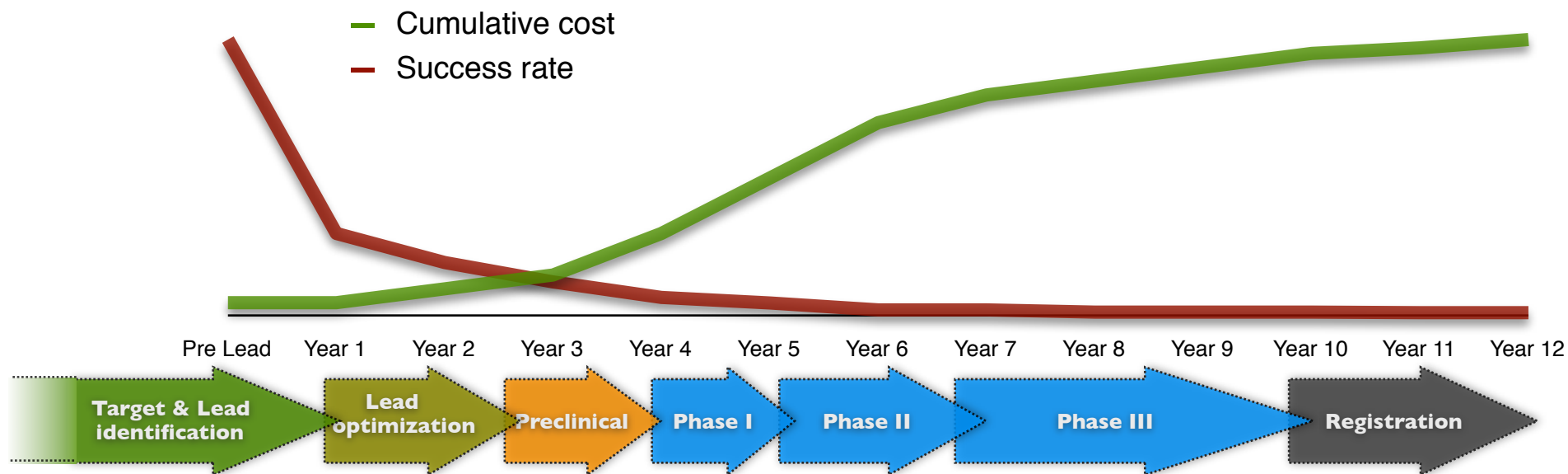
4. Phase IV Trials

5. Phase I to III Trials

AMBITIOUS GOALS

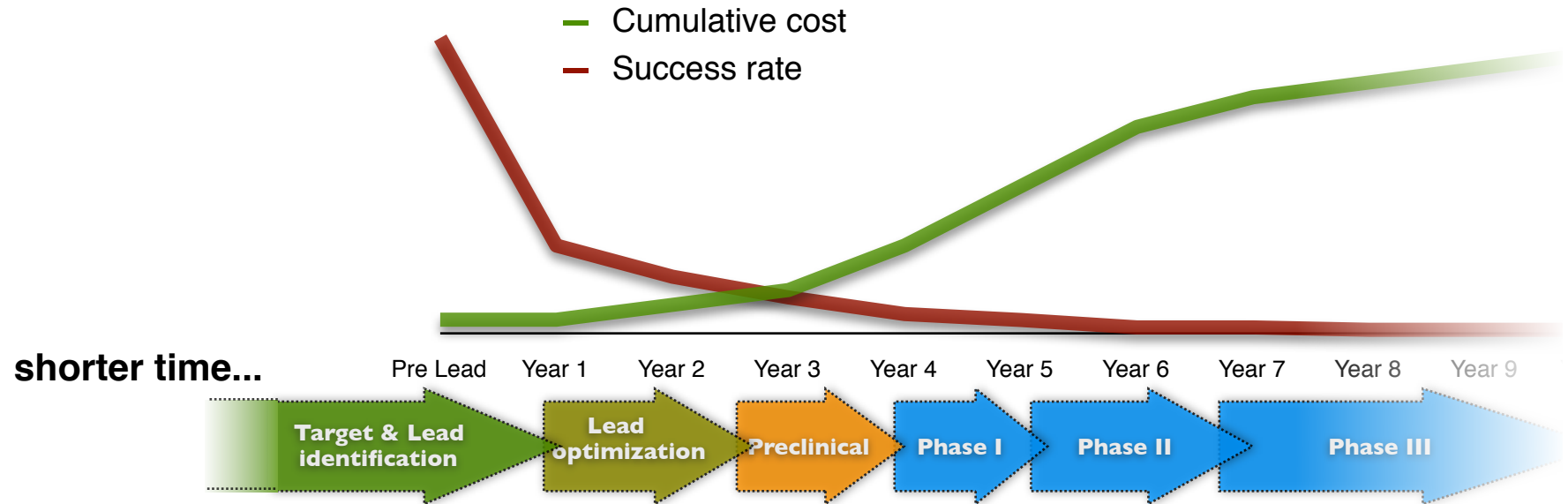
Maurer, Stephen M., "Open Source Drug Discovery: Finding a Niche (or Maybe Several)" (April 1, 2007).

Drug Discovery pipeline



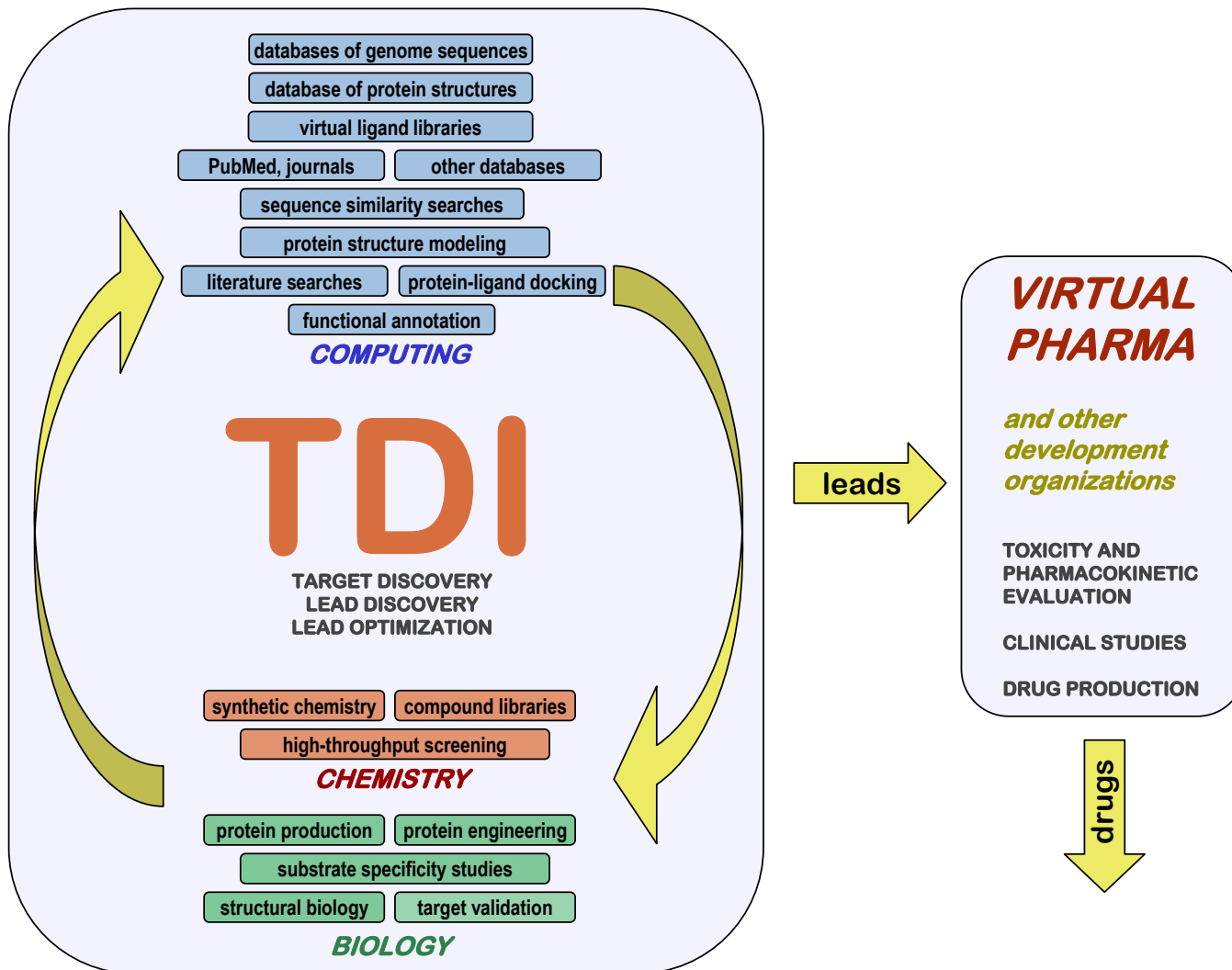
Adapted from: - Nwaka & Ridley. (2003) *Nature Reviews. Drug Discovery*. 2:919
 - Austin, Brady, Insel & Collins. (2004) *Science*. 306:1138

Drug Discovery pipeline



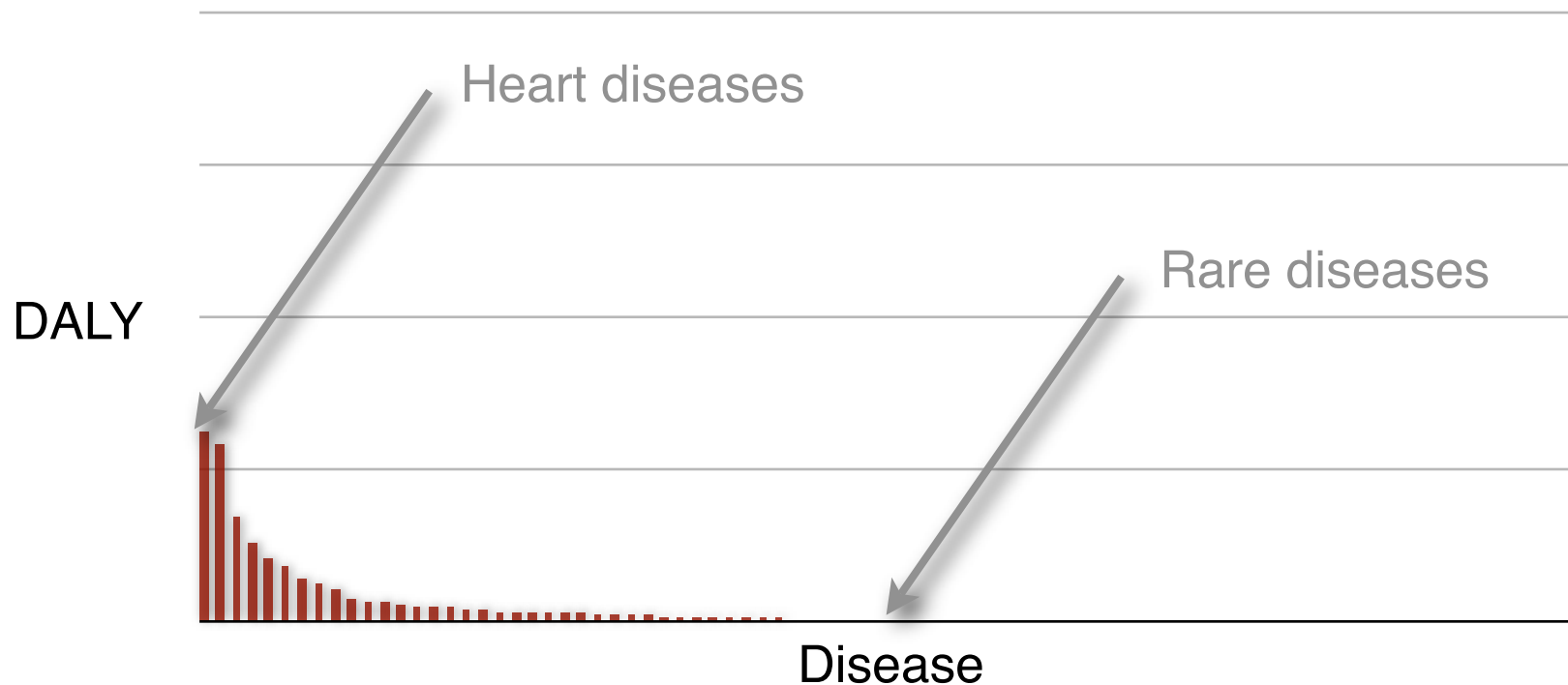
- + Completeness of genome projects (eg, Malaria)
- + New and more complete biological databases
- + New software and computers (cheaper and faster)
- + Internet == more people == less cost

TDI flowchart



Need is High in the Tail

- DALY Burden Per Disease in Developed Countries
- DALY Burden Per Disease in Developing Countries



Disease data taken from WHO, *World Health Report 2004*

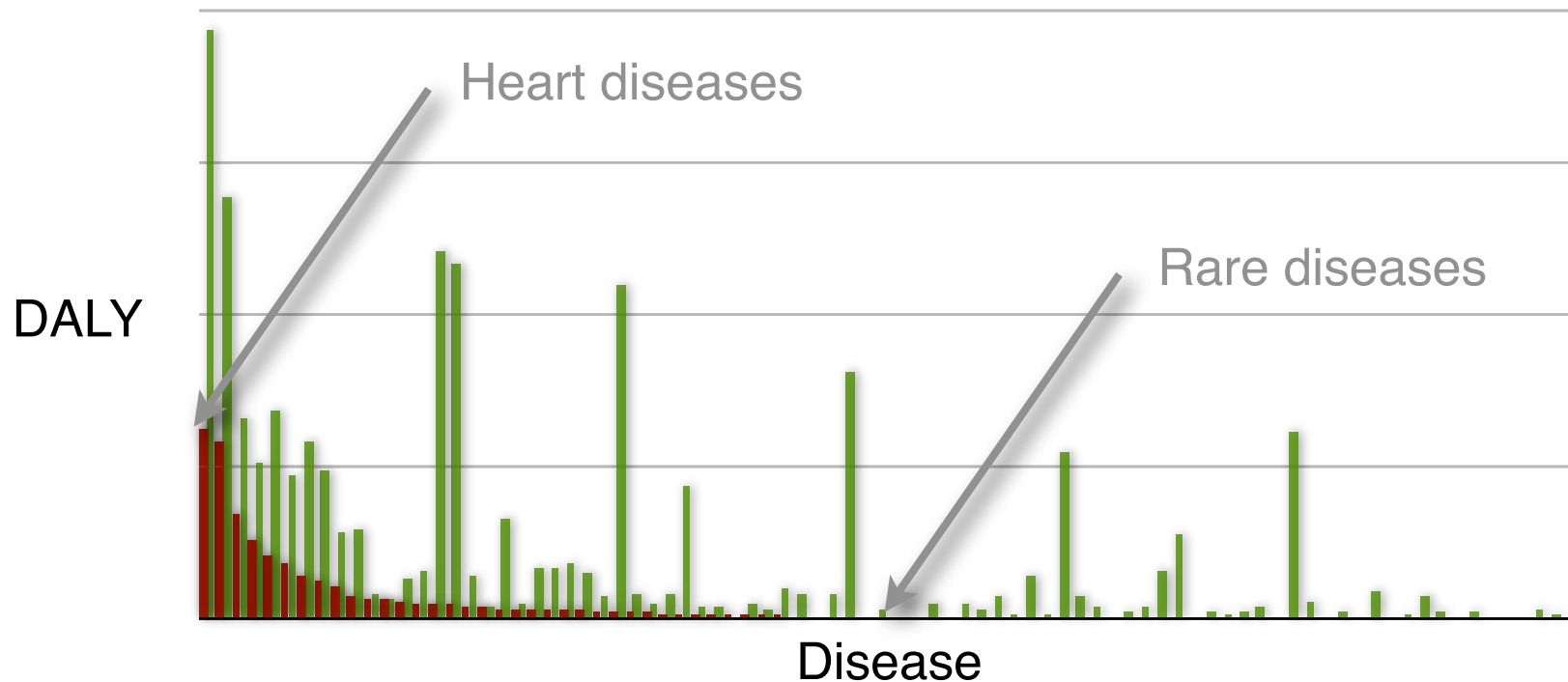
DALY - Disability adjusted life years

DALY is not a perfect measure of market size, but is certainly a good measure for importance.

DALYs for a disease are the sum of the years of life lost due to premature mortality (YLL) in the population and the years lost due to disability (YLD) for incident cases of the health condition. The DALY is a health gap measure that extends the concept of potential years of life lost due to premature death (PYLL) to include equivalent years of 'healthy' life lost in states of less than full health, broadly termed disability. One DALY represents the loss of one year of equivalent full health.

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“Unprofitable” Diseases and Global DALY (in 1000’s)

Malaria*	46,486
Tetanus	7,074
Lymphatic filariasis*	5,777
Syphilis	4,200
Trachoma	2,329
Leishmaniasis*	2,090
Ascariasis	1,817
Schistosomiasis*	1,702
Trypanosomiasis*	1,525

Trichuriasis	1,006
Japanese encephalitis	709
Chagas Disease*	667
Dengue*	616
Onchocerciasis*	484
Leprosy*	199
Diphtheria	185
Poliomyelitis	151
Hookworm disease	59

Disease data taken from WHO, *World Health Report 2004*

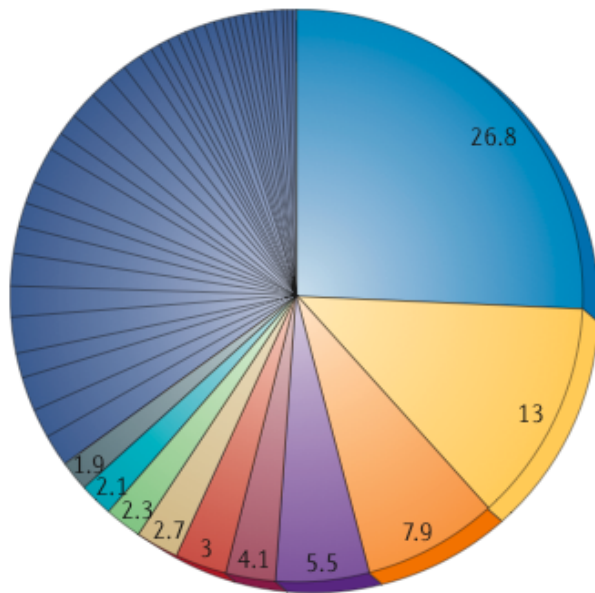
DALY - Disability adjusted life year in 1000’s.

* Officially listed in the WHO Tropical Disease Research [disease portfolio](#).

targets?

Overington, Al-Lazikani & Hopkins. (2006) *Nature Reviews. Drug Discovery*. 5:993

“... of 361 new molecular entities approved by the FDA between 1989 and 2000, 76% targeted a precedented drugged domain and only 6% targeted a previously undrugged domain ...”



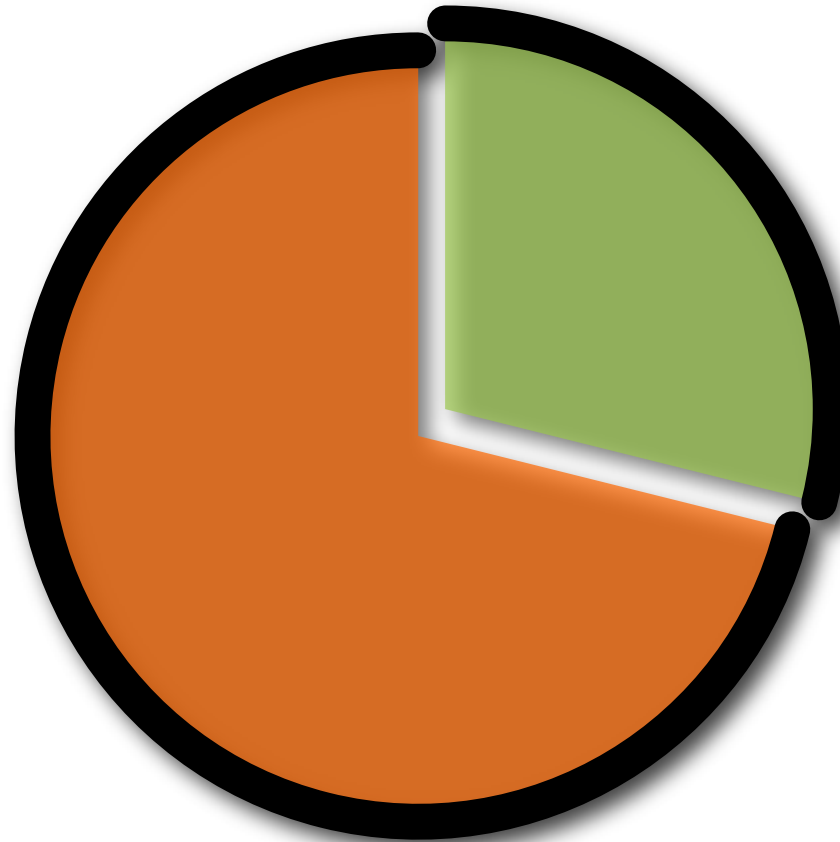
- Rhodopsin-like GPCRs
- Nuclear receptors
- Ligand-gated ion channels
- Voltage-gated ion channels
- Penicillin-binding protein
- Myeloperoxidase-like
- Sodium: neurotransmitter symporter family
- Type II DNA topoisomerase
- Fibronectin type III
- Cytochrome P450

Class of drug target	Species	Number of molecular targets
Targets of approved drugs	Pathogen and human	324
Human genome targets of approved drugs	Human	266
Targets of approved small-molecule drugs	Pathogen and human	248
Targets of approved small-molecule drugs	Human	207
Targets of approved oral small-molecule drugs	Pathogen and human	227
Targets of approved oral small-molecule drugs	Human	186
Targets of approved therapeutic antibodies	Human	15
Targets of approved biologicals	Pathogen and human	76

Where at the pathogens targets???!??!

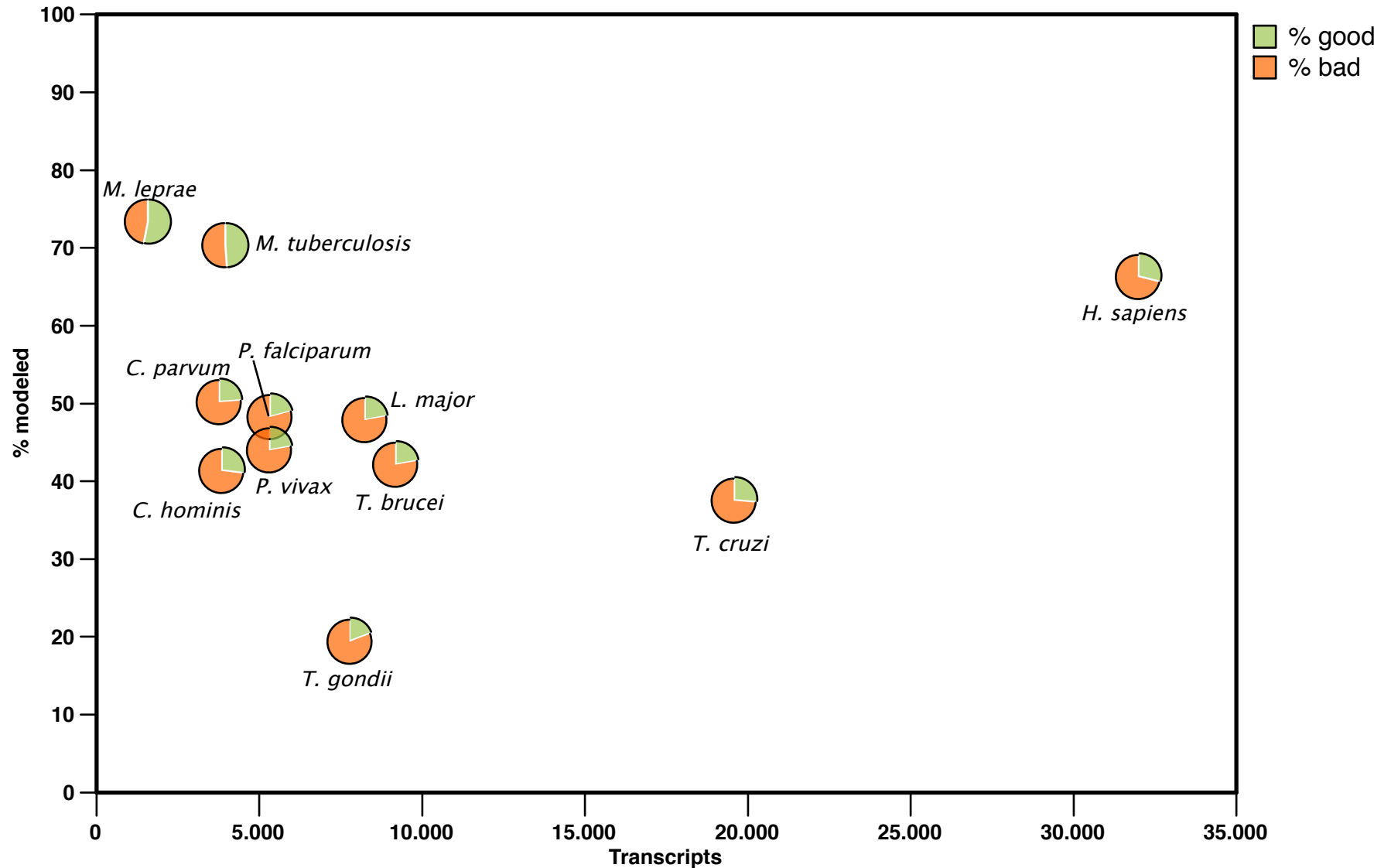
Predicting binding sites in protein structure models.

TDI's Kernel



Modeling Genomes

data from models generated by ModPipe (Eswar, Pieper & Sali)

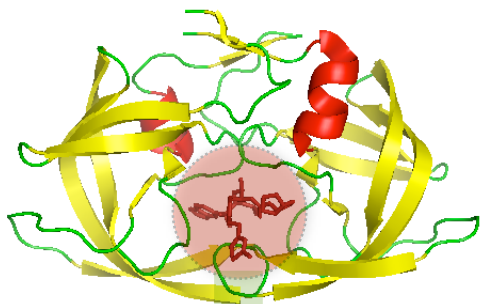


A good model has MPQS of 1.1 or higher

Comparative docking

1. Expansion

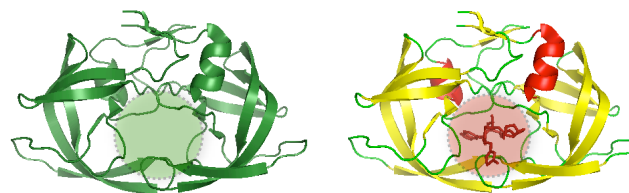
co-crystallized protein/ligand



crystallized protein

2. Inheritance

model



template

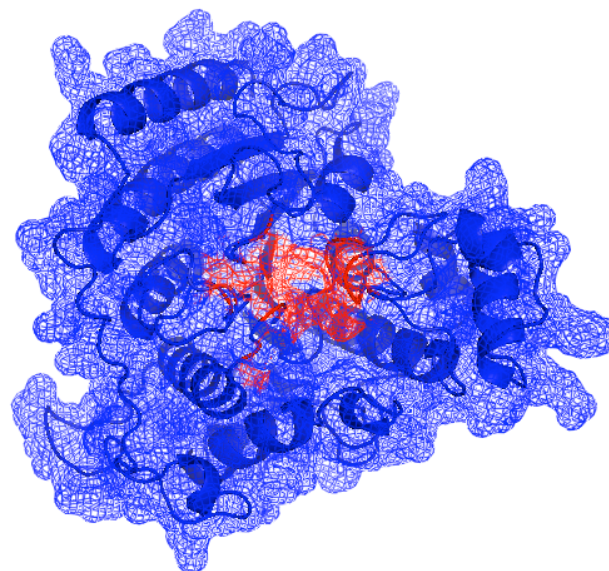
Models with inherited ligands

from 16,284 good models, 295 inherited a ligand/substance with at least a partial hit (exact SMILE) to a compound already approved by FDA and ready to be used from ZINC

	Transcripts	Good	Ligands	Lipinski	Lipinski+ZINC	FDA+ZINC
<i>C. hominis</i>	3,886	886	183	131	28	12 (10)
<i>C. parvum</i>	3,806	949	219	145	30	12 (10)
<i>L. major</i>	8,274	1,845	488	334	84	44 (34)
<i>M. leprae</i>	1,605	1,321	286	189	39	29 (25)
<i>M. tuberculosis</i>	3,991	2,887	404	285	71	44 (37)
<i>P. falciparum</i>	5,363	1,057	271	191	48	20 (16)
<i>P. vivax</i>	5,342	1,042	267	177	37	18 (15)
<i>T. brucei</i>	921	1,795	440	309	94	46 (36)
<i>T. cruzi</i>	19,607	3,915	730	493	127	62 (52)
<i>T. gondii</i>	7,793	587	174	124	28	8 (7)
TOTAL	60,588	16,284	3,462	2,378	586	295 (242)

L. major Histone deacetylase 2

	Formula	Name	Cov.	Seq. Id. (%)	Residues
TSN	C ₁₇ H ₂₂ N ₂ O ₃	Trichostatin A	100.00	90.9	90 131 132 140 141 167 169
SHH	C ₁₄ H ₂₀ N ₂ O ₃	Octadenoic acid hydroxyamide phenylamide	100.00	90.9	256 263 293 295



ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2004, p. 1435–1436
0066-4804/04/\$08.00+0 DOI: 10.1128/AAC.48.4.1435–1436.2004
Copyright © 2004, American Society for Microbiology. All Rights Reserved.

Vol. 48, No. 4

Antimalarial and Antileishmanial Activities of Aroyl-Pyrrolyl-Hydroxyamides, a New Class of Histone Deacetylase Inhibitors

TDI Models database

Is that the kernel? - Under what licensing?

The TDIModels server

http://sgu.bioinfo.cipf.es/services/TDIModels/

The TDIModels server

[SGU - HOME]
DBAI
Eva-CM
Omidios
SARA
TDIModels

TDIModels

Results for **Q7K6A1** [Q7K6A1 Histone deacetylase]
Number of models: 2

Model 1

This model has 2 predicted binding sites.

	Lipinski	ZINC	FDA	Coverage	Seq. Id.
<input checked="" type="checkbox"/> SHH	●	●	●	100.00	90.91
<input type="checkbox"/> TSN	●	●	●	100.00	90.91

SEQUENCE IDENTITY: 40.00
MODPIPE QUALITY SCORE: 1.43
TEMPLATE PDB: 1t64
TEMPLATE CHAIN: A
TARGET LENGTH: 449
TARGET BEGIN: 7
TARGET END: 373
[Download PDB file](#)

Model 2

This model has 2 predicted binding sites.

	Lipinski	ZINC	FDA	Coverage	Seq. Id.
<input type="checkbox"/> SHH	●	●	●	100.00	90.91
<input type="checkbox"/> TSN	●	●	●	100.00	90.91

SEQUENCE IDENTITY: 42.00
MODPIPE QUALITY SCORE: 1.45
TEMPLATE PDB: 1t64
TEMPLATE CHAIN: A
TARGET LENGTH: 449
TARGET BEGIN: 28
TARGET END: 373
[Download PDB file](#)

[<- new search](#)

HELP:

PLEASE NOTE. Our servers have been optimized for Firefox and Safari. If you are using Internet Explorer, the CSS may not be properly rendered.

To use TDIModels you need to:
- Enter a UNIPROT id or a Keyword of interest to find models.

Applet jmolApplet1 started

<http://sgu.bioinfo.cipf.es/services/TDIModels/>

Acknowledgments

Read more @

- PLoS Medicine, Dec. 2004. Vol 1(3):e56
- The Economist (June 10, 2004)
- Aust. J. Chem, 2006. Vol 59:291
- Steve Maurer

Tropical Disease Initiative

Thomas Kepler (Duke U)
Marc A. Marti-Renom (CIPF)
Stephen Maurer (Berkeley)
Arti Rai (Duke U)
Andrej Sali (UCSF)

The Synaptic Leap

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Jean-Claude Bradley (Chemistry)
Sebastian Jayaraj (Coder)
Thomas Kepler (Board)
Marc A. Marti-Renom (Advisor)
Stephen Maurer (Advisor)
Miguel Miychell (Tuberculosis)
Arti Rai (Board)
Saj Sajid (Malaria)
Matt H. Todd (Schisto)

“Volunteers can gain nothing from shading the truth”

Richard M. Titmuss (1972)

“THE GIFT RELATIONSHIP: FROM HUMAN BLOOD TO SOCIAL POLICY”

<http://sgu.bioinfo.cipf.es>

<http://www.salilab.org>

<http://www.tropicaldisease.org>

<http://www.thesynapticleap.org>