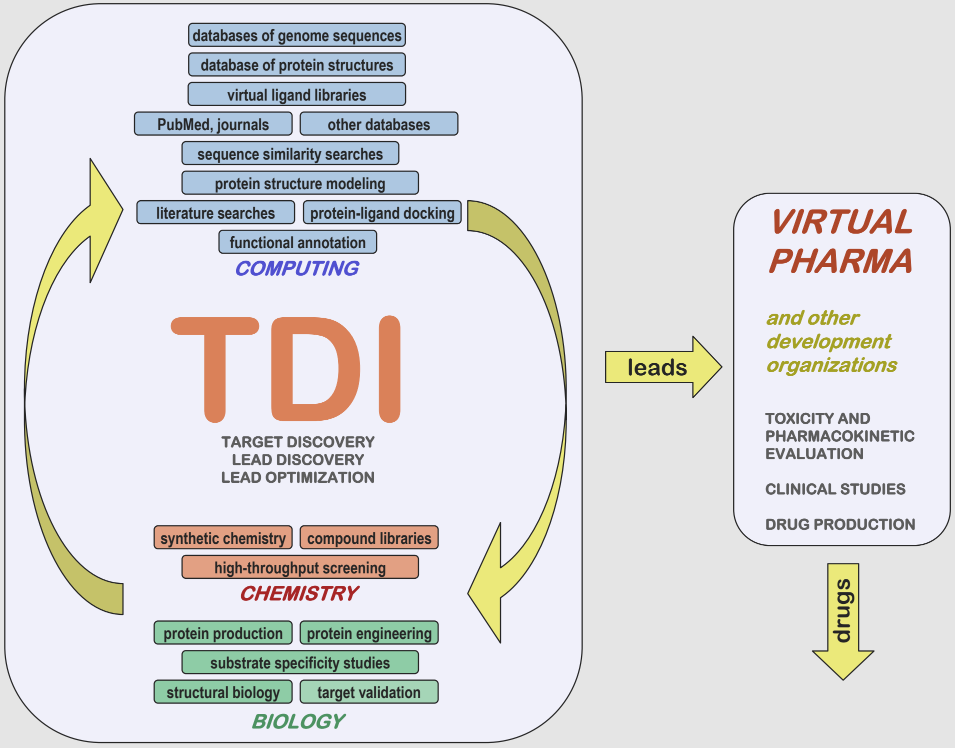
# A “kernel” for the Tropical Disease Initiative
## *An open source approach to drug discovery*


databases of genome sequences
database of protein structures
virtual ligand libraries
PubMed, journals
other databases
sequence similarity searches
protein structure modeling
literature searches
protein-ligand docking
functional annotation
*COMPUTING*

TDI
TARGET DISCOVERY
LEAD DISCOVERY
LEAD OPTIMIZATION

synthetic chemistry
compound libraries
high-throughput screening
*CHEMISTRY*

protein production
protein engineering
substrate specificity studies
structural biology
target validation
*BIOLOGY*

leads

*VIRTUAL PHARMA*

*and other development organizations*

TOXICITY AND PHARMACOKINETIC EVALUATION

CLINICAL STUDIES

DRUG PRODUCTION

drugs

**Marc A. Marti-Renom**
http://sgu.bioinfo.cipf.es

Structural Genomics Unit
Bioinformatics Department
Prince Felipe Resarch Center (CIPF), Valencia, Spain

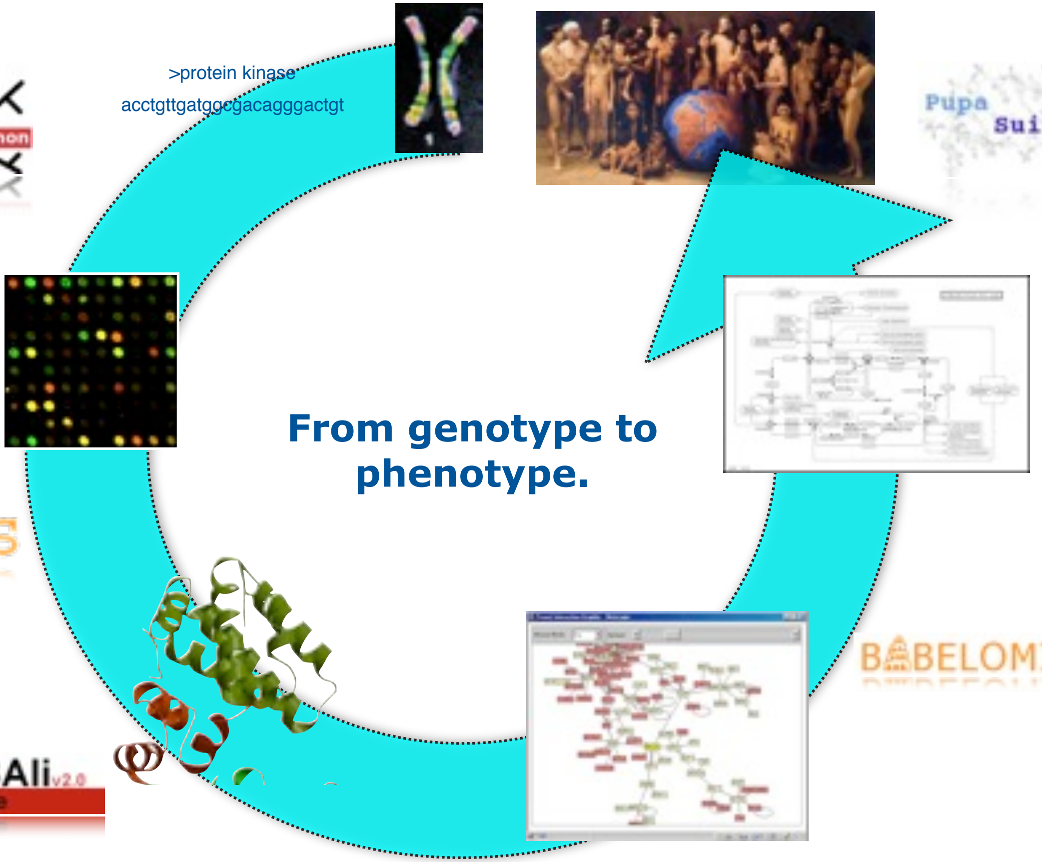
# Bioinformatics and Genomics Department (CIPF)

http://bioinfo.cipf.es

**Functional Genomics**
Dr. Joaquín Dopazo

**Comparative Genomics**
Dr. Hernán Dopazo

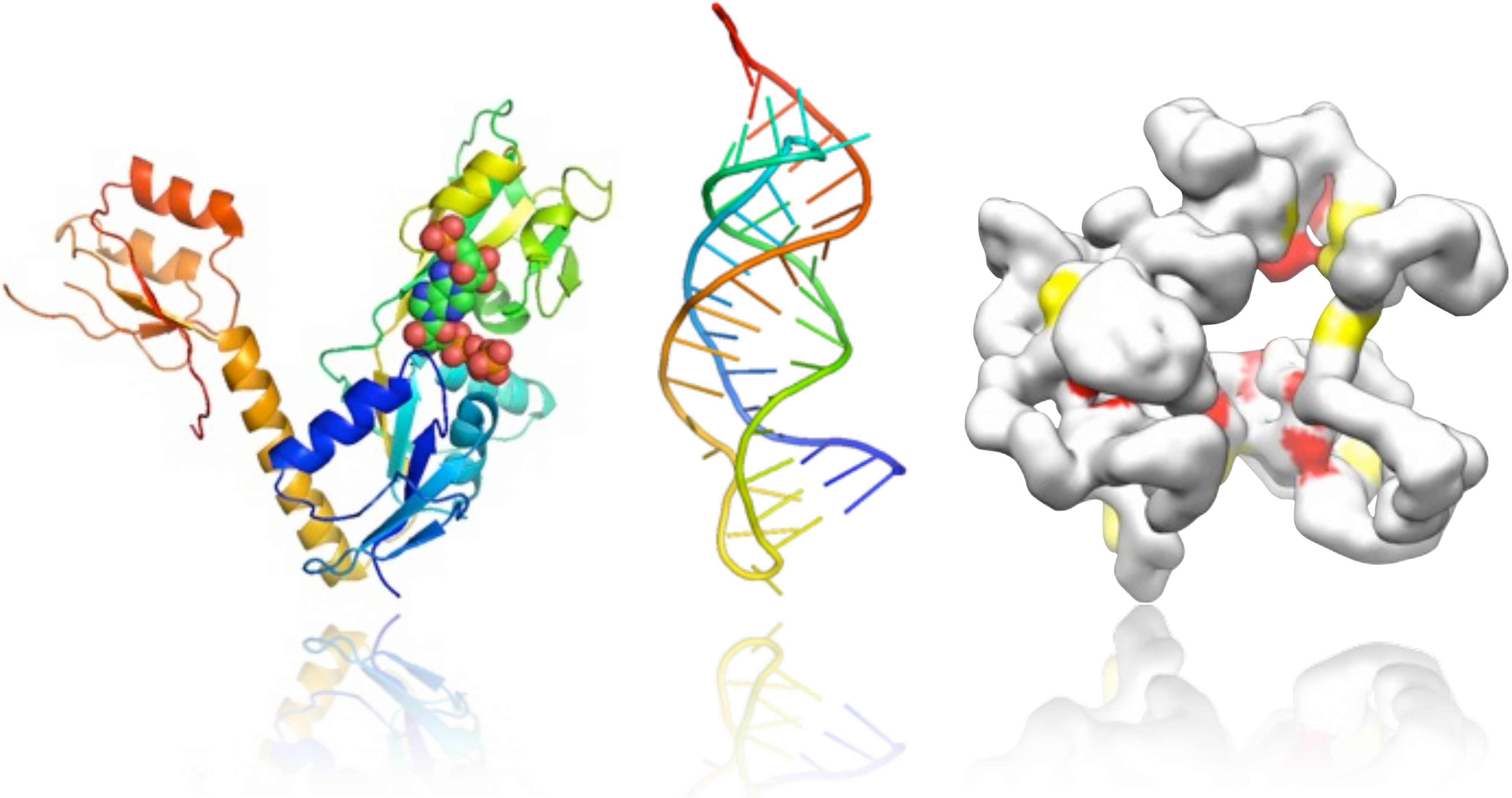
**Structural Genomics**
Dr. Marc A. Marti-Renom



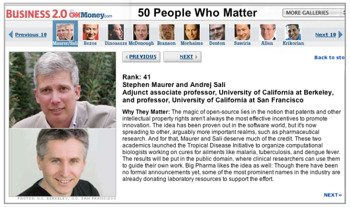
**From genotype to phenotype.**

# Structural Genomics Unit

*Bioinformatics Department, CIPF*



# TDI *a story*



**Rank: 41**
**Stephen Maurer and Andrej Sali**
**Adjunct associate professor, University of California at Berkeley, and professor, University of California at San Francisco**

**Why They Matter:** The magic of open-source lies in the notion that patents and other intellectual property rights aren't always the most effective incentives to promote innovation. The idea has been proven out in the software world, but it's now spreading to other, arguably more important realms, such as pharmaceutical research. And for that, Maurer and Sali deserve much of the credit. These two academics launched the Tropical Disease Initiative to organize computational biologists working on cures for ailments like malaria, tuberculosis, and dengue fever. The results will be put in the public domain, where clinical researchers can use them to guide their own work. Big Pharma likes the idea as well: Though there have been no formal announcements yet, some of the most prominent names in the industry are already donating laboratory resources to support the effort.

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

**2005**
.TDI web site `http://TropicalDisease.org`
.Ginger Taylor and The Synaptic Leap

**2006**
.Maurer and Sali 41th in “50 Who Matter”
.TSL web site `http://TheSynapticLeap.org`

**2008**
.TDI kernel `http://TropicalDisease.org/kernel`

# Initial feed-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

---

**f any, the bottlenecks are?**
deas and potential avenues to explore,
**ction Plan!**

Regards,
Jacob Lester

---

I am interested in beginning rese
disease for underserved populat
however, confused.
**If someone will tell me where t**
**begin on, I'd be greatful.**

Thank you kindly,
Adam Huber

---

**9 Mar 2005**
I'm a programmer, not a
keep the list active :)

**GNU started with RMS**
**Linux started with Linu**
**You need someone gre**
**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

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**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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together and make linux work.

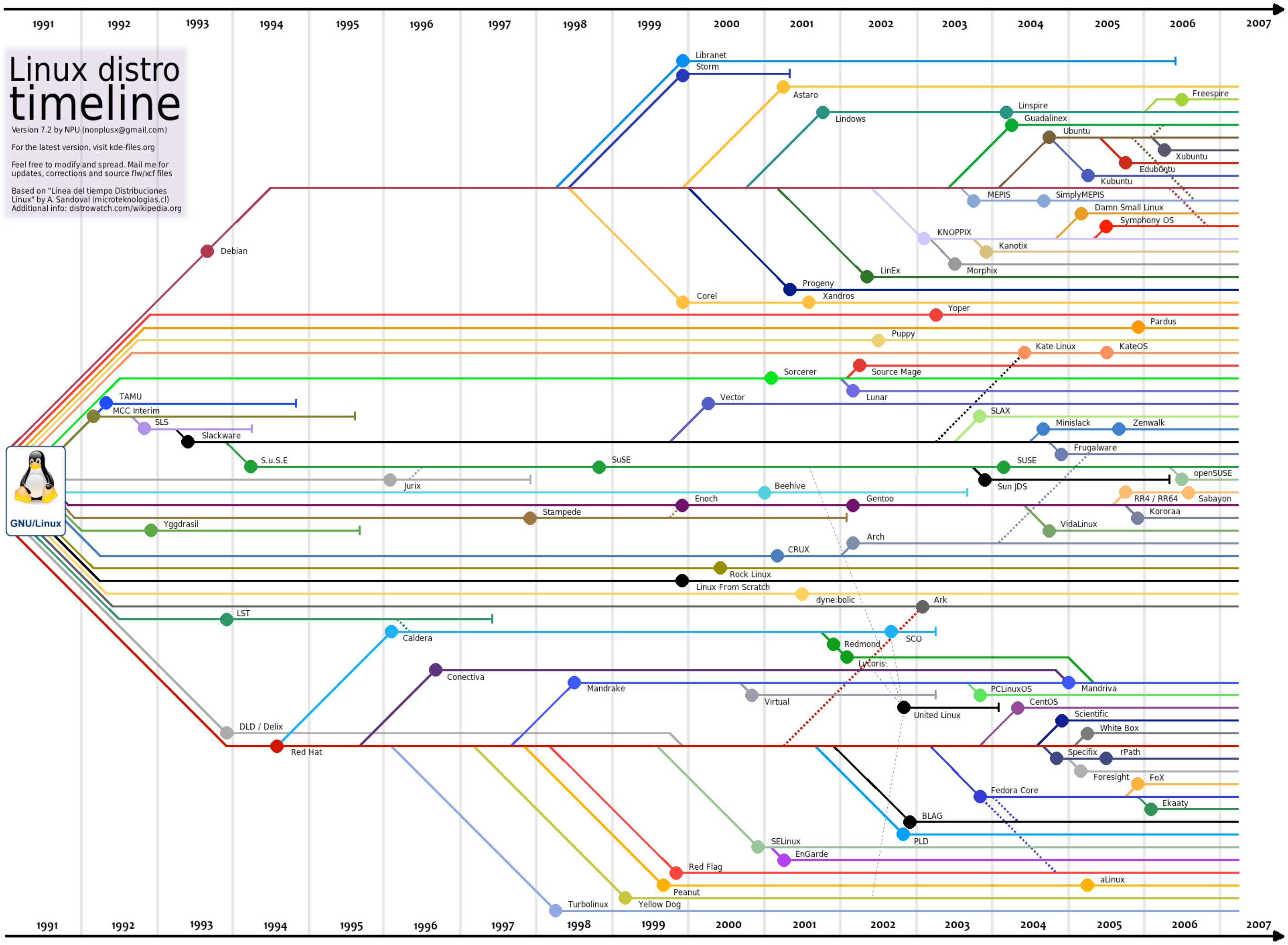
Daniel Amelang

## 19 Jan 2005

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

Stephen Mark Maurer

# Open Source without a Kernel?



# Is it possible? ...

**1. In silico drug discovery**
2. Chemistry
3. Stem cell lines

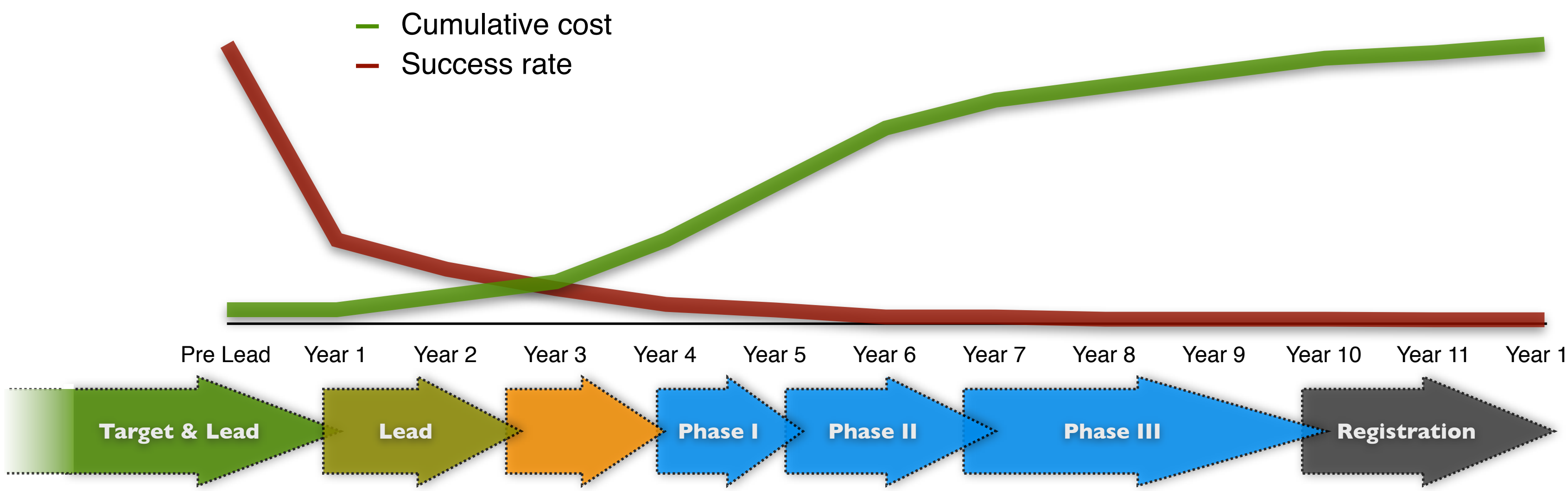
**NEXT STEPS**

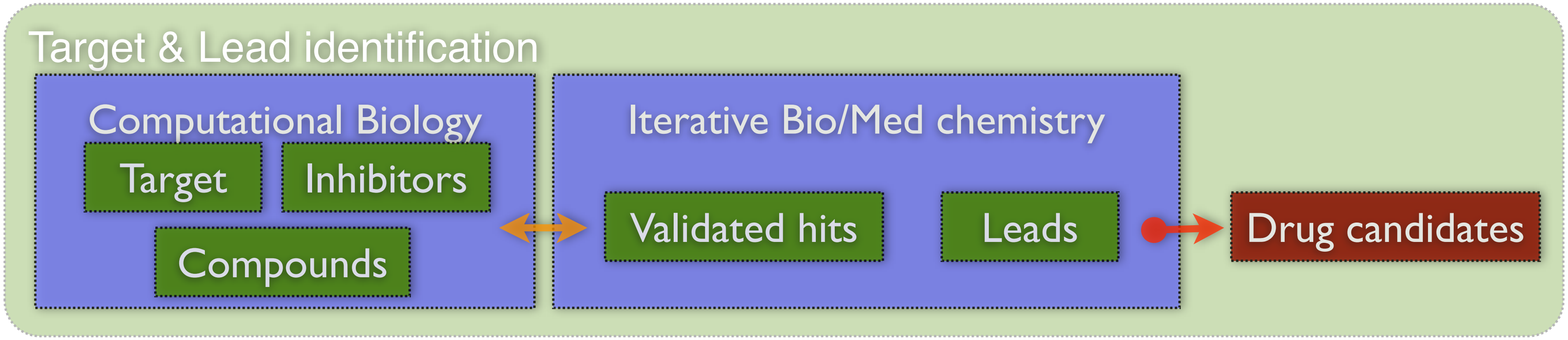
4. Phase I to III trials
5. Phase IV trials

**AMBITIOUS GOALS**

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

# Drug Discovery pipeline





Target & Lead identification

Computational Biology

Target

Inhibitors

Compounds

Iterative Bio/Med chemistry

Validated hits

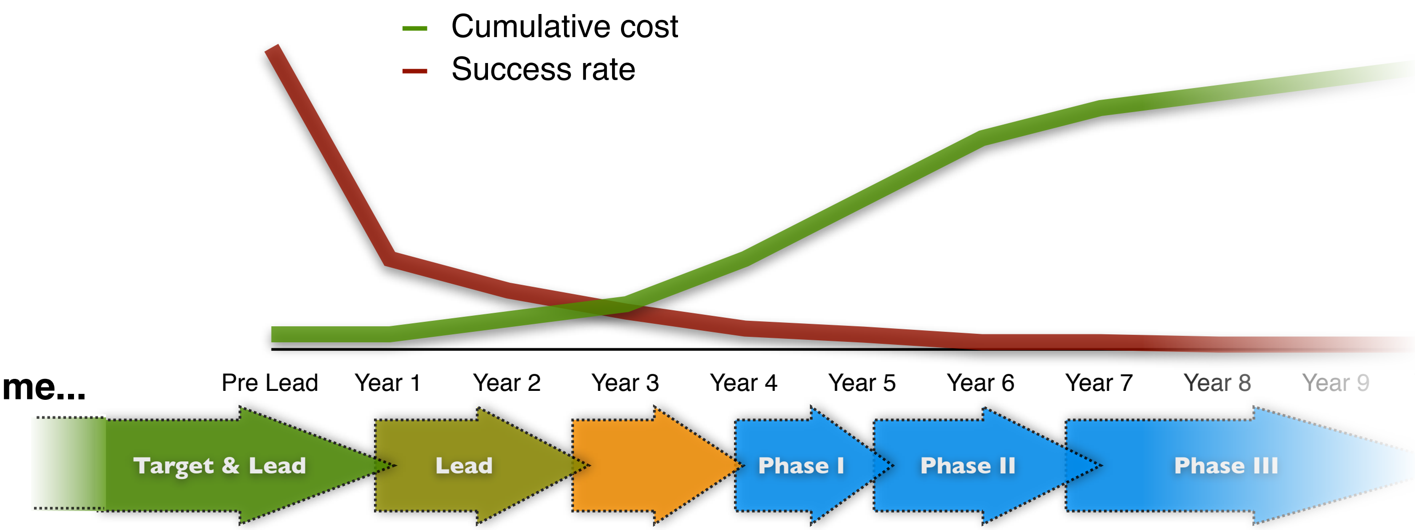
Leads

Drug candidates

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

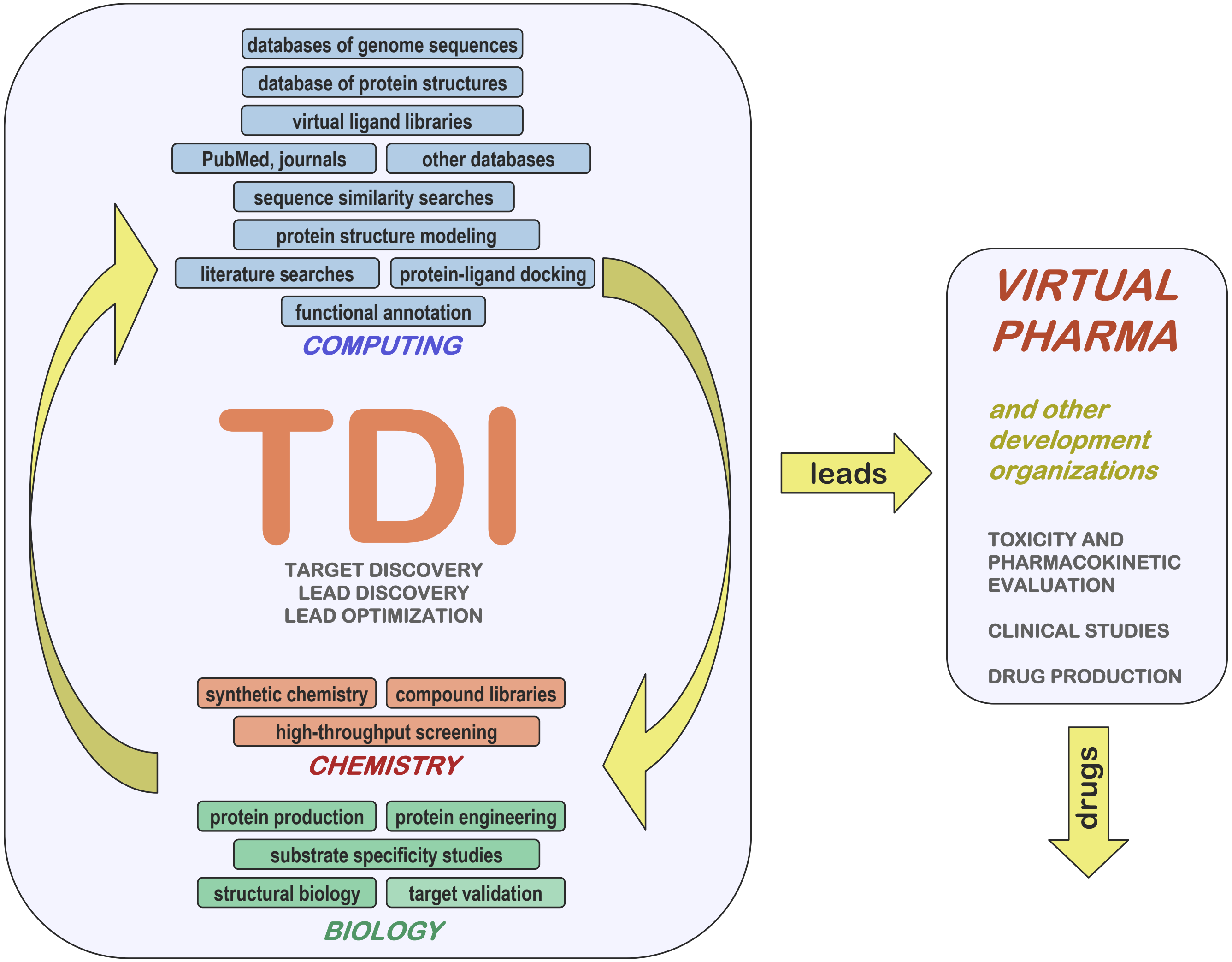
# Drug Discovery pipeline

**shorter time...**



+ 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



databases of genome sequences
database of protein structures
virtual ligand libraries
PubMed, journals
other databases
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protein structure modeling
literature searches
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functional annotation

***COMPUTING***

**TDI**

**TARGET DISCOVERY**
**LEAD DISCOVERY**
**LEAD OPTIMIZATION**

synthetic chemistry
compound libraries
high-throughput screening

***CHEMISTRY***

protein production
protein engineering
substrate specificity studies
structural biology
target validation

***BIOLOGY***

leads

***VIRTUAL PHARMA***

*and other development organizations*

**TOXICITY AND PHARMACOKINETIC EVALUATION**

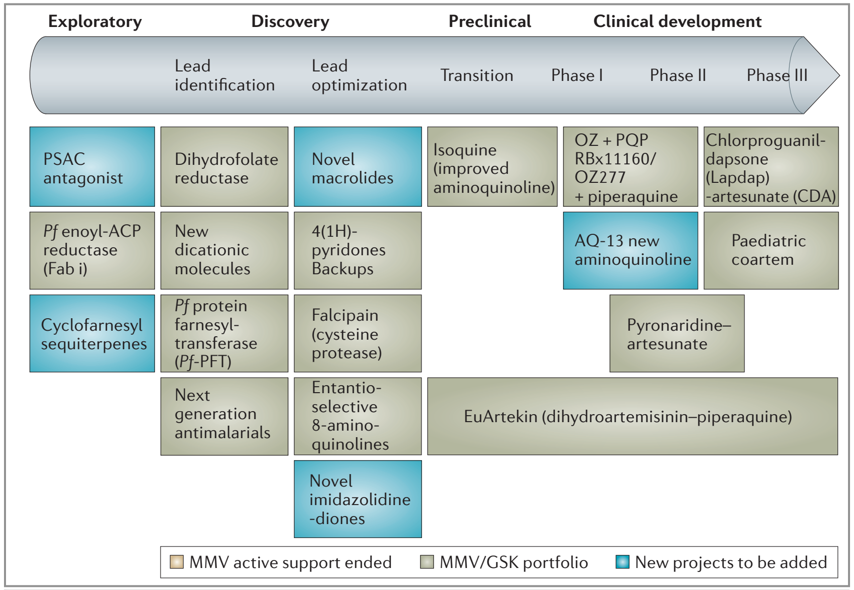
**CLINICAL STUDIES**

**DRUG PRODUCTION**

drugs

# Non-Profit organizations

*Open-Source + Out-Source = low cost business model*



**Exploratory** | **Discovery** | **Preclinical** | **Clinical development**

Lead identification | Lead optimization | Transition | Phase I | Phase II | Phase III

PSAC antagonist

*Pf* enoyl-ACP reductase (Fab i)

Cyclofarnesyl sequiterpenes

Dihydrofolate reductase

New dicationic molecules

*Pf* protein farnesyl-transferase (*Pf*-PFT)

Next generation antimalarials

Novel macrolides

4(1H)-pyridones Backups

Falcipain (cysteine protease)

Entantio-selective 8-amino-quinolines

Novel imidazolidine -diones

Isoquine (improved aminoquinoline)

OZ + PQP RBx11160/ OZ277 + piperaquine

AQ-13 new aminoquinoline

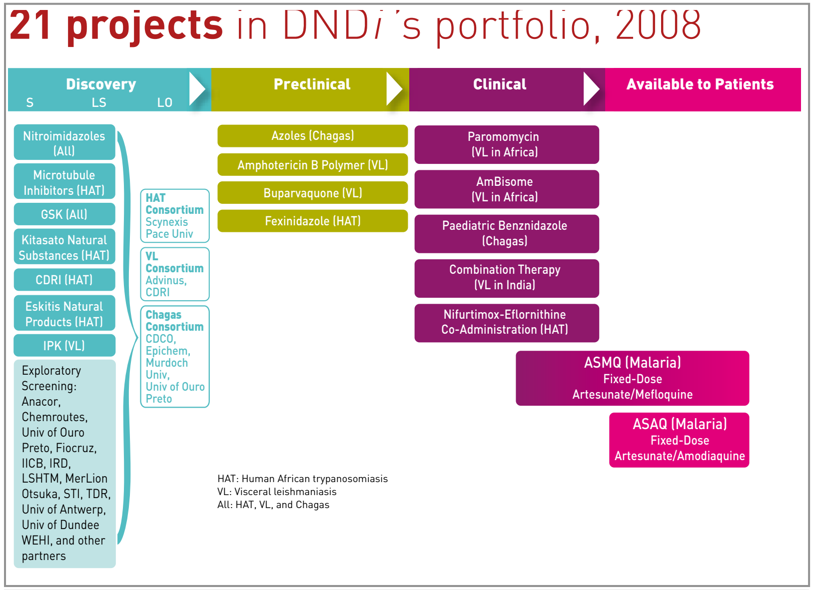
Pyronaridine–artesunate

Chlorproguanil-dapsone (Lapdap) -artesunate (CDA)

Paediatric coartem

EuArtekin (dihydroartemisinin–piperaquine)

☐ MMV active support ended ▨ MMV/GSK portfolio 🟦 New projects to be added



**21 projects** in DNDi´s portfolio, 2008

**Discovery** (S | LS | LO) | **Preclinical** | **Clinical** | **Available to Patients**

Nitroimidazoles (All)

Microtubule Inhibitors (HAT)

GSK (All)

Kitasato Natural Substances (HAT)

CDRI (HAT)

Eskitis Natural Products (HAT)

IPK (VL)

Exploratory Screening: Anacor, Chemroutes, Univ of Ouro Preto, Fiocruz, IICB, IRD, LSHTM, MerLion Otsuka, STI, TDR, Univ of Antwerp, Univ of Dundee WEHI, and other partners

**HAT Consortium** Scynexis Pace Univ

**VL Consortium** Advinus, CDRI

**Chagas Consortium** CDCO, Epichem, Murdoch Univ, Univ of Ouro Preto

Azoles (Chagas)

Amphotericin B Polymer (VL)

Buparvaquone (VL)

Fexinidazole (HAT)

Paromomycin (VL in Africa)

AmBisome (VL in Africa)

Paediatric Benznidazole (Chagas)

Combination Therapy (VL in India)

Nifurtimox-Eflornithine Co-Administration (HAT)

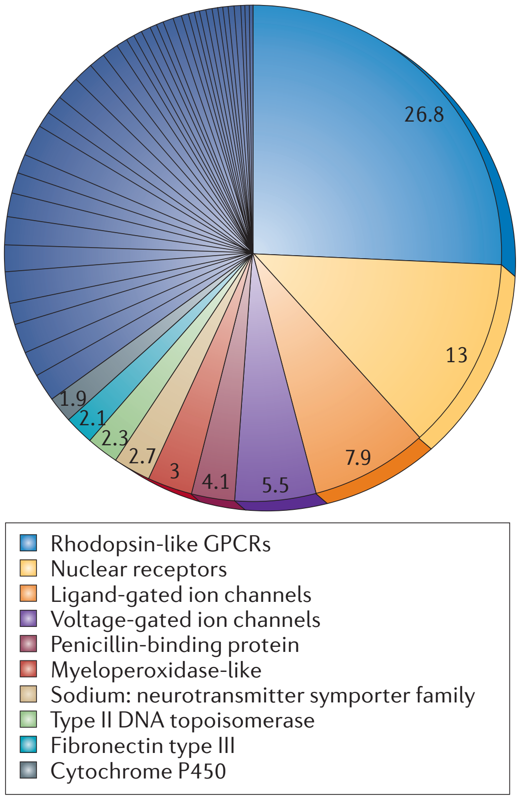
ASMQ (Malaria) Fixed-Dose Artesunate/Mefloquine

ASAQ (Malaria) Fixed-Dose Artesunate/Amodiaquine

HAT: Human African trypanosomiasis
VL: Visceral leishmaniasis
All: HAT, VL, and Chagas

*Munos (2006) Nature Reviews. Drug Discovery.*

# Number of (new) targets?



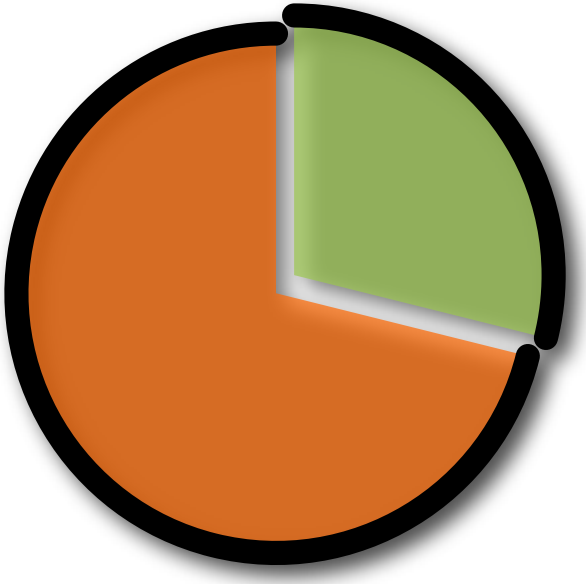
"... of 361 new molecular entities approved by the FDA between 1989 and 2000, 76% targeted a precedented drugged domain and only 6% targeted a previously undrugged domain ..."

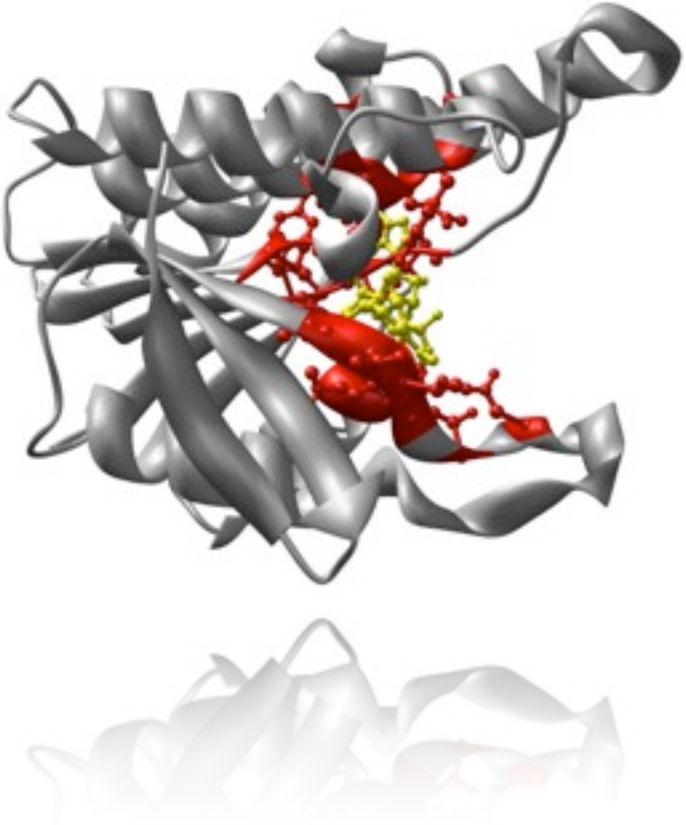
| Class of drug target | Species | Number of molecular targets |
|---|---|---|
| Targets of approved drugs | Pathogen and human | 324 |
| Human genome targets of approved drugs | Human | 266 |
| Targets of approved small-molecule drugs | Pathogen and human | 248 |
| Targets of approved small-molecule 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 are the targets from tropical diseases?**

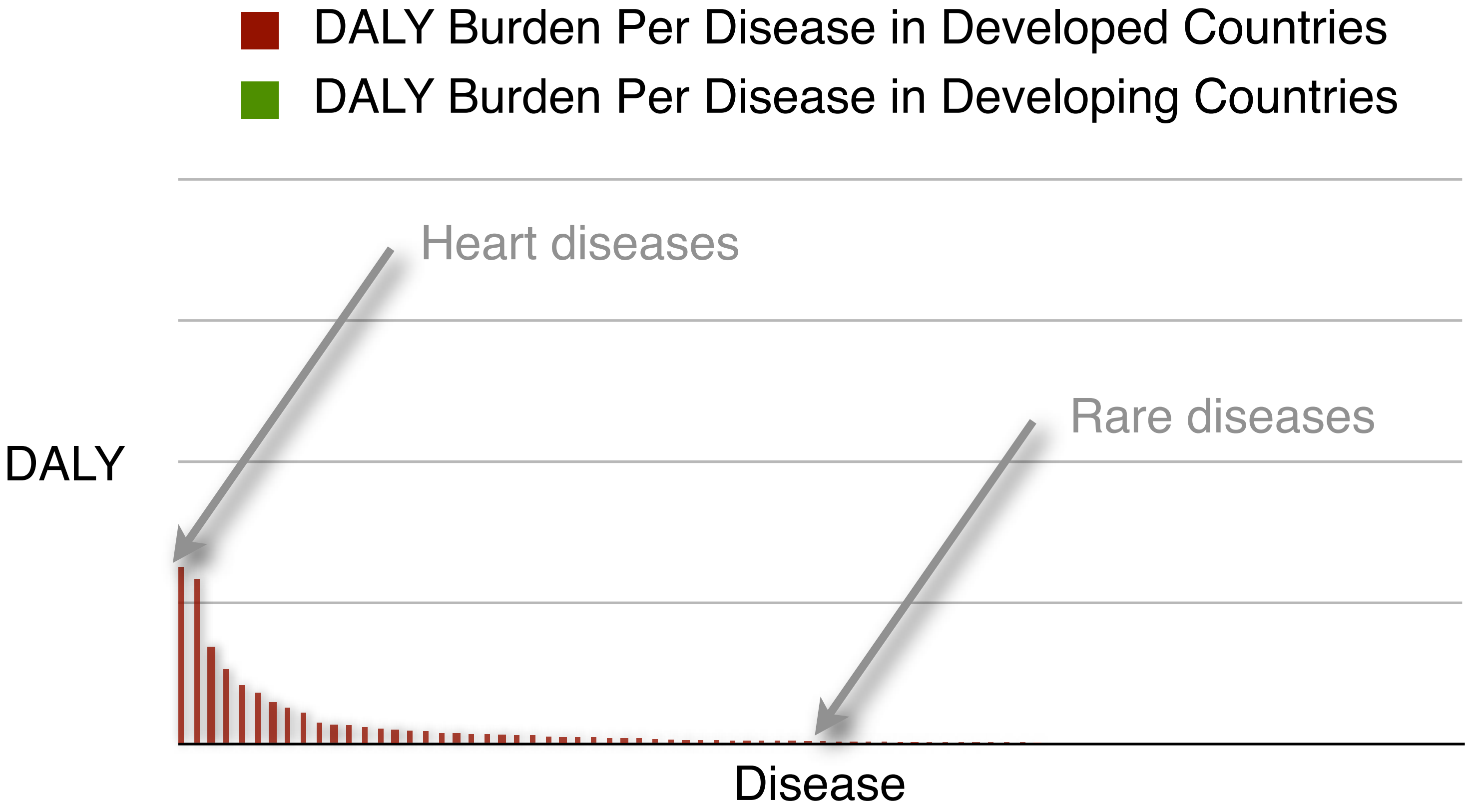
*Overington et al. How many drug targets are there?. Nature reviews Drug discovery (2006) vol. 5 (12) pp. 993-6*

# Predicting binding sites in protein structure models.





# Need is High in the Tail



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

DALY - Disability adjusted life years

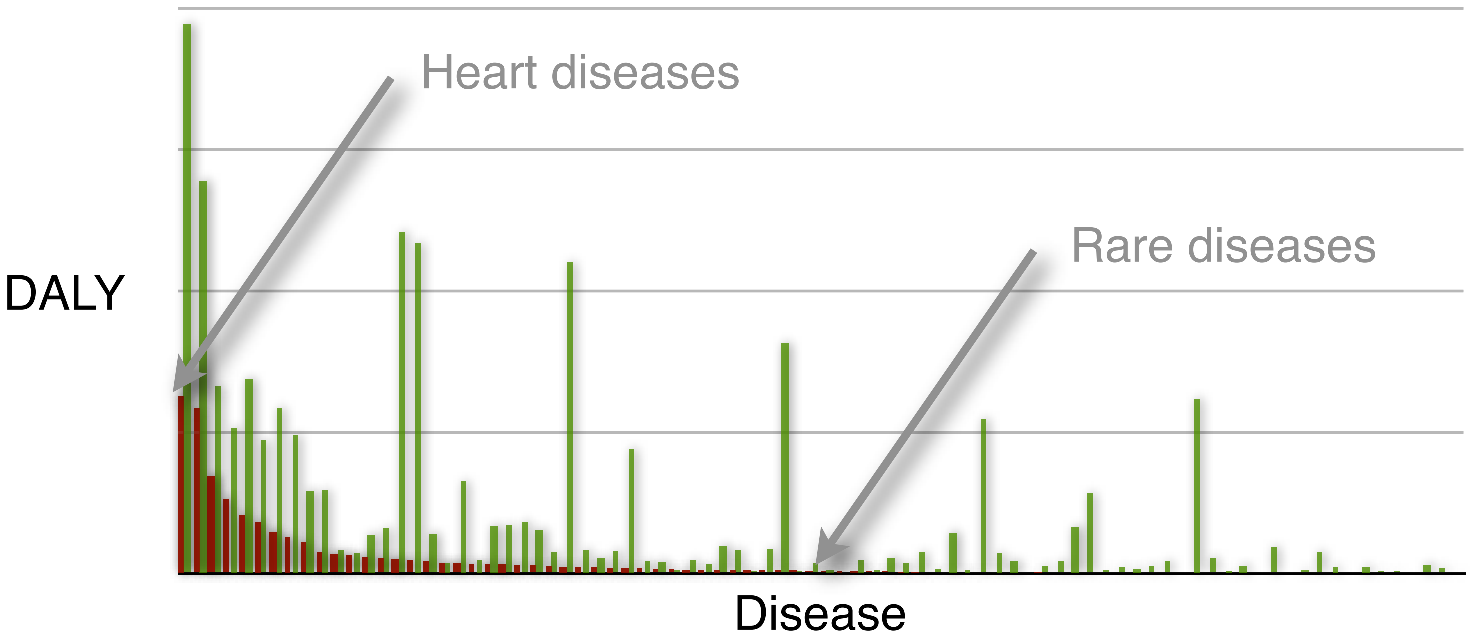
DALY is not a perfect measure of market size, but is certainly a good measure for importance.

*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.*

# Need is High in the Tail

🟥 DALY Burden Per Disease in Developed Countries

🟩 DALY Burden Per Disease in Developing Countries



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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 |
| Poliomyelitise | 151 |
| Hookworm disease | 59 |

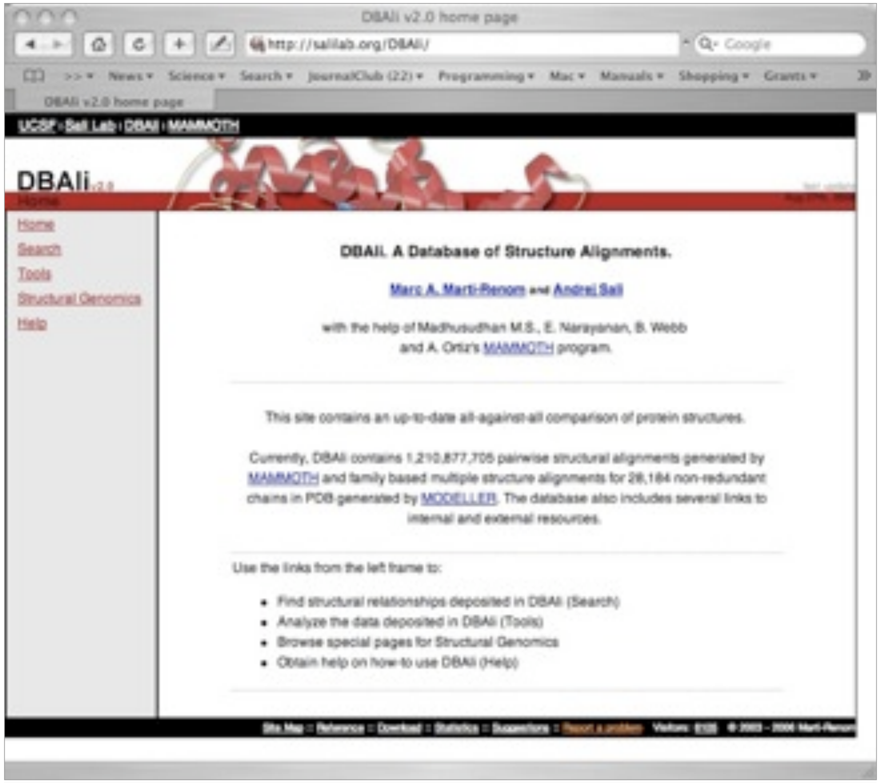
Disease data taken from WHO, *World Health Report 2004*

DALY - Disability adjusted life year in 1000’s.

* Officially listed in the WHO Tropical Disease Research disease portfolio.

# DBAli$_{v2.0}$ database

`http://www.dbali.org`



**DBAli. A Database of Structure Alignments.**

Marc A. Marti-Renom and Andrej Sali

with the help of Madhusudhan M.S., E. Narayanan, B. Webb
and A. Ortiz's MAMMOTH program.

This site contains an up-to-date all-against-all comparison of protein structures.

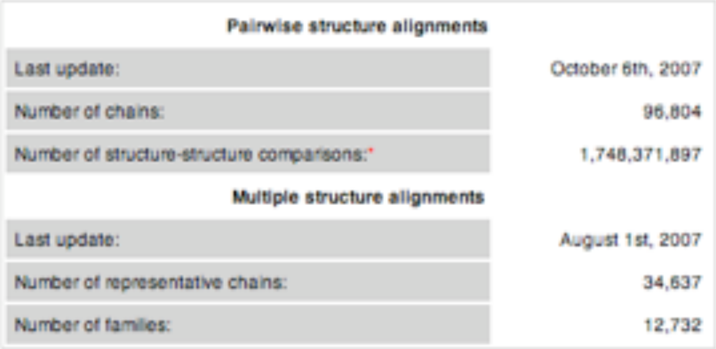
Currently, DBAli contains 1,210,877,705 pairwise structural alignments generated by MAMMOTH and family based multiple structure alignments for 28,184 non-redundant chains in PDB generated by MODELLER. The database also includes several links to internal and external resources.

Use the links from the left frame to:

- Find structural relationships deposited in DBAli (Search)
- Analyze the data deposited in DBAli (Tools)
- Browse special pages for Structural Genomics
- Obtain help on how to use DBAli (Help)

- ✓ Fully-automatic
- ✓ Data is kept up-to-date with PDB releases
- ✓ Tools for "on the fly" classification of families.
- ✓ Easy to navigate
- ✓ Provides tools for structure analysis

Does not provide a stable classification similar to that of CATH or SCOP



| Pairwise structure alignments | |
|---|---|
| Last update: | October 6th, 2007 |
| Number of chains: | 96,804 |
| Number of structure-structure comparisons:* | 1,748,371,897 |
| **Multiple structure alignments** | |
| Last update: | August 1st, 2007 |
| Number of representative chains: | 34,637 |
| Number of families: | 12,732 |

Uses MAMMOTH for similarity detection

- ✓ VERY FAST!!!
- ✓ Good scoring system with significance

*Ortiz AR, (2002) Protein Sci. 11 pp2606*

*Marti-Renom et al. 2001. Bioinformatics. 17, 746*

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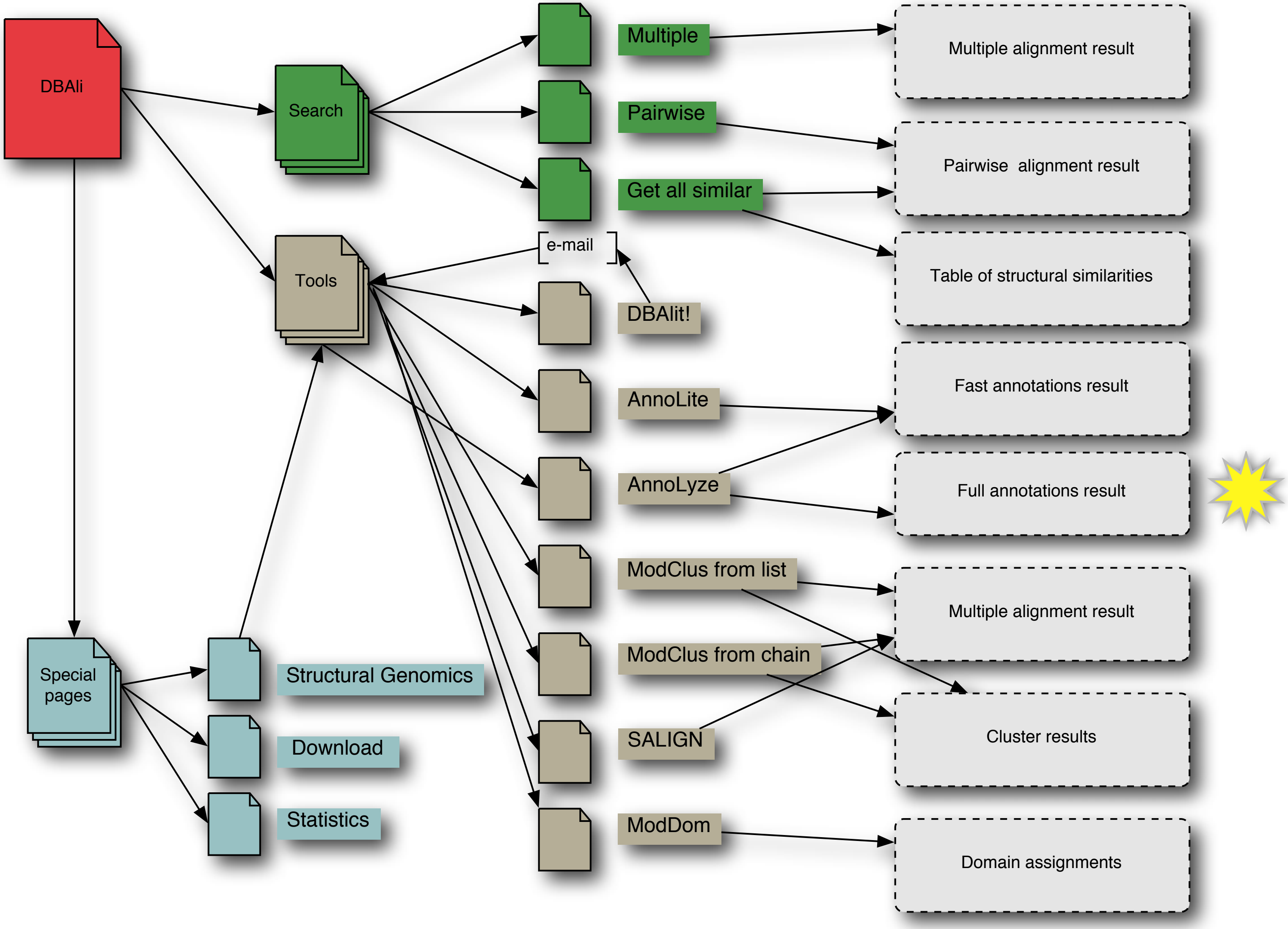
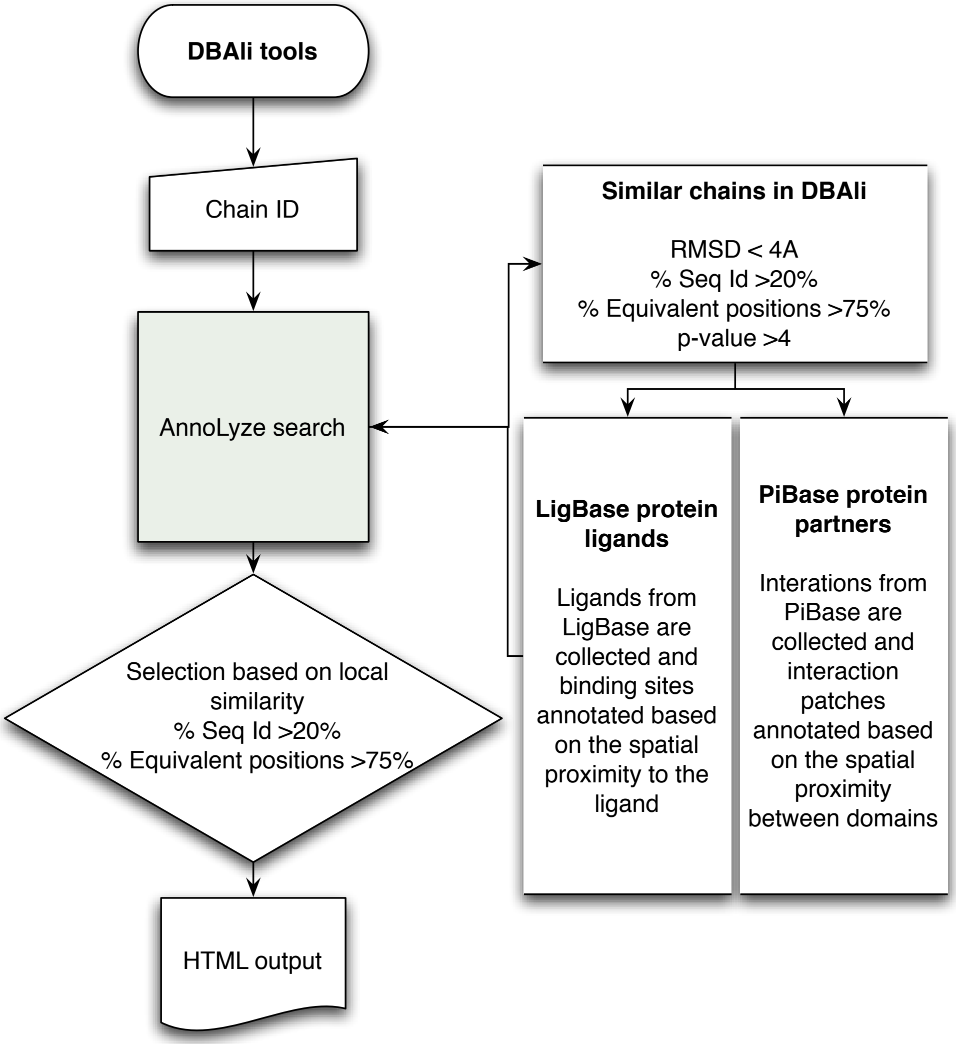
http://www.dbali.org



*Marti-Renom et al. BMC Bioinformatics (2007) Volume 8. Suppl S4*

# Method



**DBAli tools**

Chain ID

AnnoLyze search

Selection based on local similarity
% Seq Id >20%
% Equivalent positions >75%

HTML output

**Similar chains in DBAli**

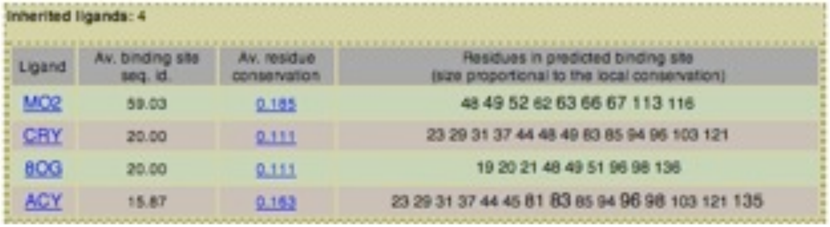
RMSD < 4A
% Seq Id >20%
% Equivalent positions >75%
p-value >4

**LigBase protein ligands**

Ligands from LigBase are collected and binding sites annotated based on the spatial proximity to the ligand

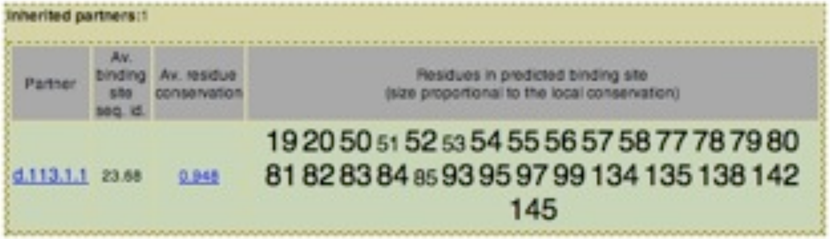
**PiBase protein partners**

Interations from PiBase are collected and interaction patches annotated based on the spatial proximity between domains



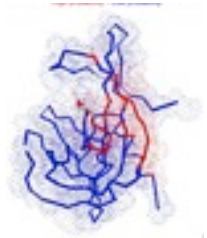
Inherited ligands: 4

| Ligand | Av. binding site seq. id. | Av. residue conservation | Residues in predicted binding site (size proportional to the local conservation) |
|---|---|---|---|
| MO2 | 59.03 | 0.185 | 48 49 52 62 63 66 67 113 116 |
| CRY | 20.00 | 0.111 | 23 29 31 37 44 48 49 83 85 94 96 103 121 |
| 8OG | 20.00 | 0.111 | 19 20 21 48 49 51 96 98 136 |
| ACY | 15.87 | 0.163 | 23 29 31 37 44 45 81 83 85 94 96 98 103 121 135 |



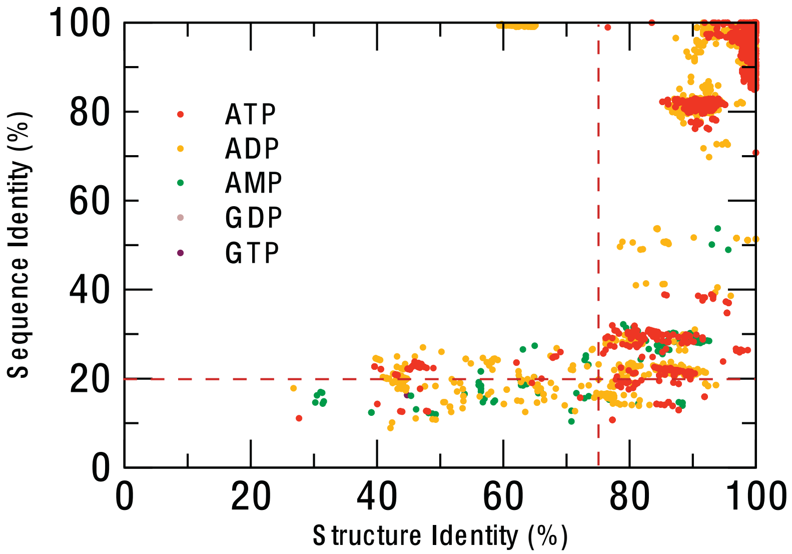
Inherited partners:1

| Partner | Av. binding site seq. id. | Av. residue conservation | Residues in predicted binding site (size proportional to the local conservation) |
|---|---|---|---|
| d.113.1.1 | 23.68 | 0.948 | 19 20 50 51 52 53 54 55 56 57 58 77 78 79 80 81 82 83 84 85 93 95 97 99 134 135 138 142 145 |

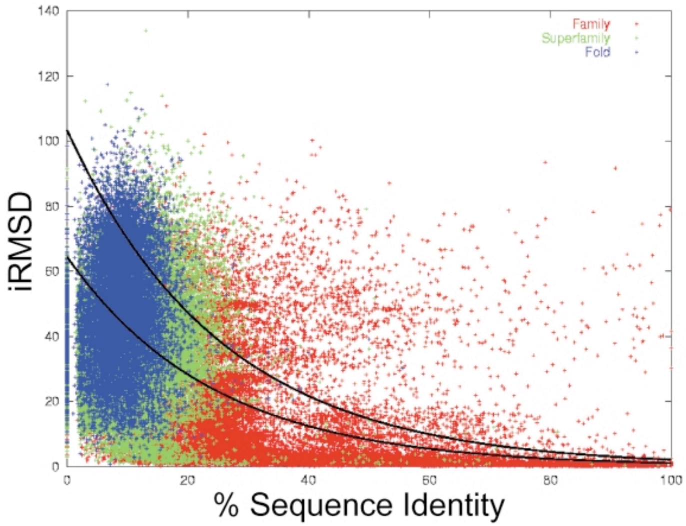


# Scoring function

## Ligands



## Partners



Aloy *et al.* (2003) J.Mol.Biol. 332(5):989-98.

# Benchmark

| | Number of chains |
|---|---|
| Initial set* | 78,167 |
| LigBase** | 30,126 |
| Non-redundant set*** | 4,948 (8,846 ligands) |

*all PDB chains larger than 30 aminoacids in length (8th of August, 2006)
**annotated with at least one ligand in the LigBase database
***not two chains can be structurally aligned within 3A, superimposing more than 75% of their Cα atoms, result in a sequence alignment with more than 30% identity, and have a length difference inferior to 50aa

| | Number of chains |
|---|---|
| Initial set* | 78,167 |
| πBase** | 30,425 |
| Non-redundant set*** | 4,613 (11,641 partnerships) |

*all PDB chains larger than 30 aminoacids in length (8th of August, 2006)
**annotated with at least one partner in the πBase database
***not two chains can be structurally aligned within 3A, superimposing more than 75% of their Cα atoms, result in a sequence alignment with more than 30% identity, and have a length difference inferior to 50aa

# Sensitivity .vs. Precision

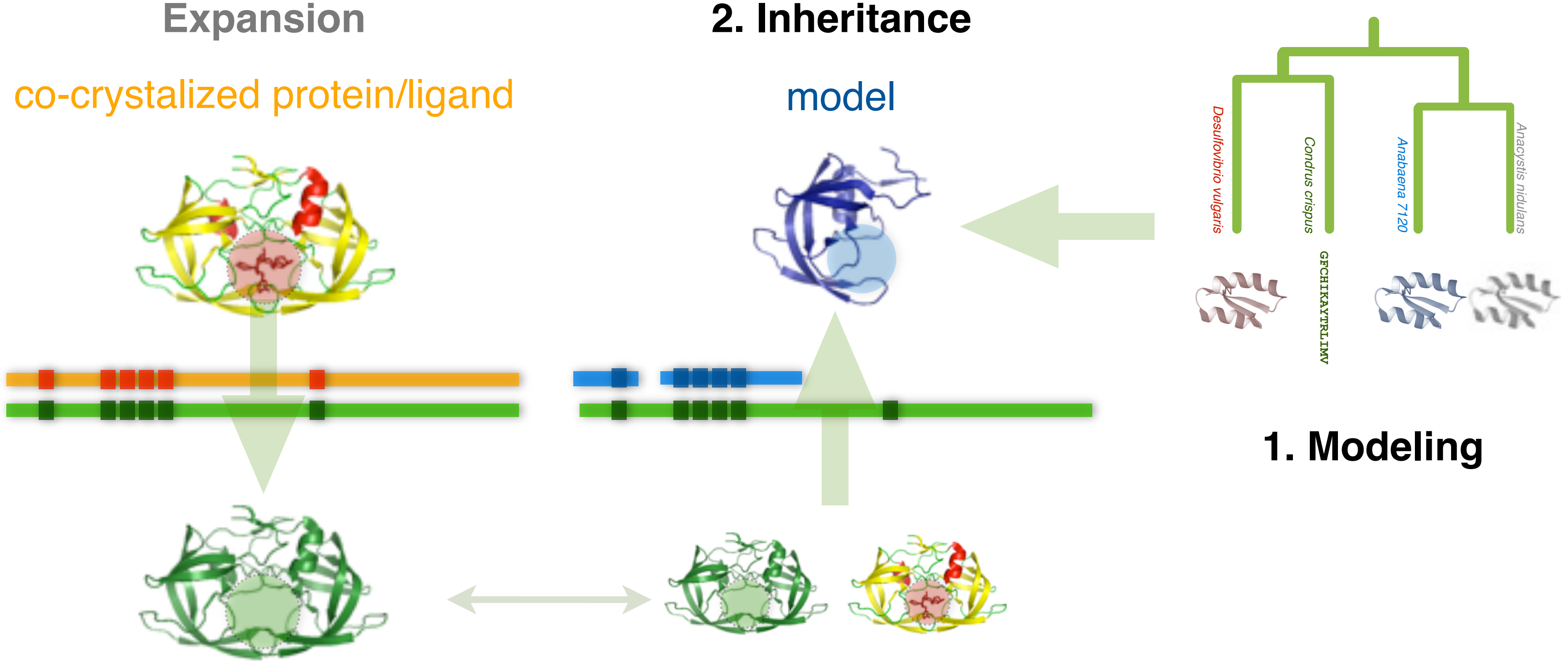
| | Optimal cut-off | Sensitivity (%)<br>Recall or TPR | Precision (%) |
|---|---|---|---|
| **Ligands** | 30% | 71.9 | 13.7 |

$\text{Sensitivity} = \frac{TP}{TP + FN}$ $\text{Precision} = \frac{TP}{TP + FP}$

**~90-95% of residues correctly predicted**

*Marti-Renom et al. BMC Bioinformatics (2007) Volume 8. Suppl S4*

# Comparative docking



Expansion

co-crystalized protein/ligand

**2. Inheritance**

model

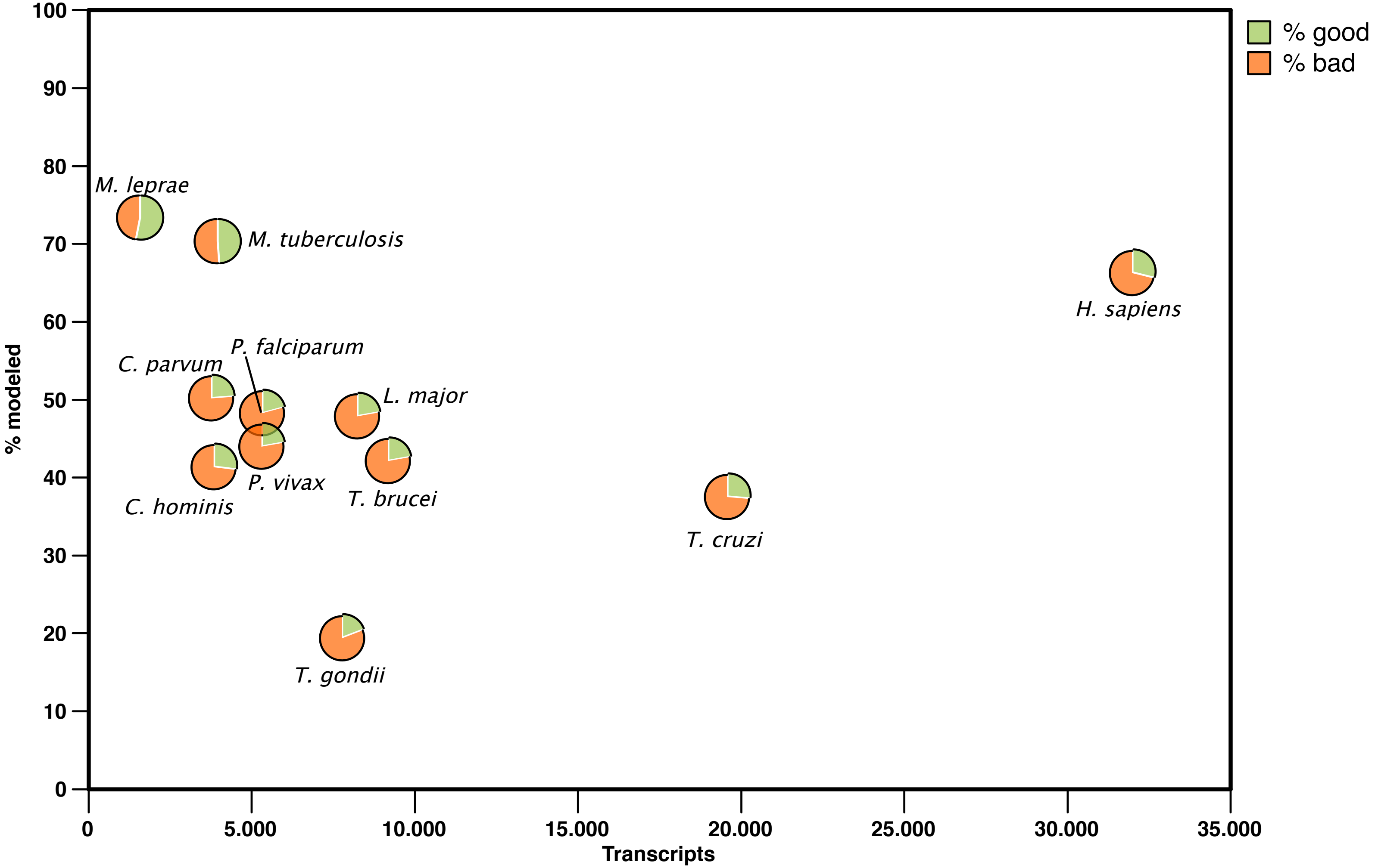
**1. Modeling**

crystalized
protein

template

# Modeling Genomes

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



*A good model has MPQS of 1.0 or higher*

# Summary table

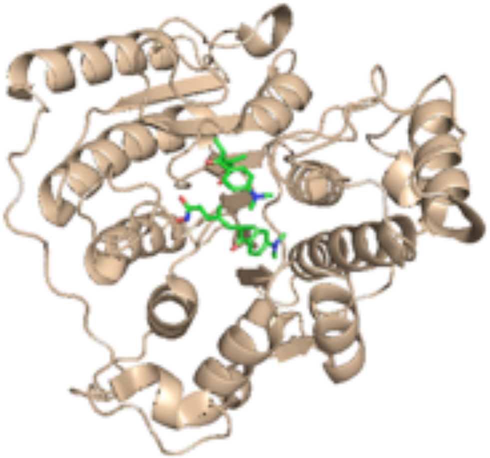
## models with inherited ligands

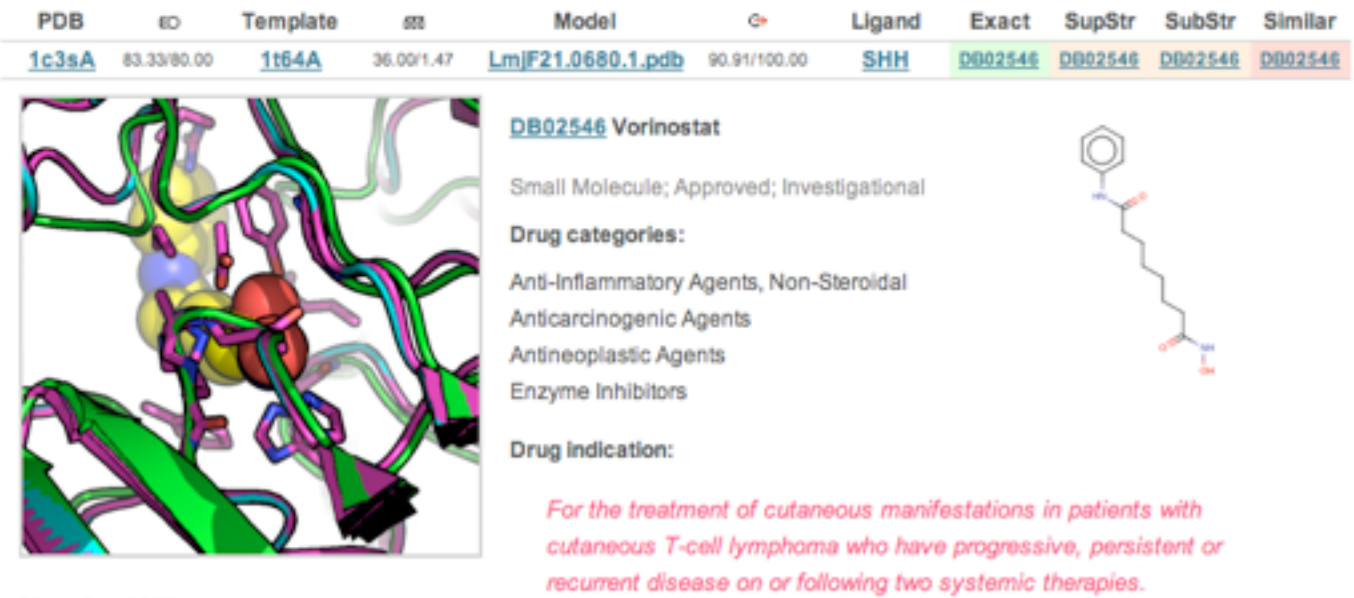
**29,271 targets with good models, 297 inherited a ligand/substance similar to a known drug in DrugBank**

| | Transcripts | Modeled targets | Selected models | Inherited ligands | Similar to a drug | Drugs |
|---|---|---|---|---|---|---|
| ***C. hominis*** | 3,886 | 1,614 | 666 | 197 | 20 | 13 |
| ***C. parvum*** | 3,806 | 1,918 | 742 | 232 | 24 | 13 |
| ***L. major*** | 8,274 | 3,975 | 1,409 | 478 | 43 | 20 |
| ***M. leprae*** | 1,605 | 1,178 | 893 | 310 | 25 | 6 |
| ***M. tuberculosis*** | 3,991 | 2,808 | 1,608 | 365 | 30 | 10 |
| ***P. falciparum*** | 5,363 | 2,599 | 818 | 284 | 28 | 13 |
| ***P. vivax*** | 5,342 | 2,359 | 822 | 268 | 24 | 13 |
| ***T. brucei*** | 7,793 | 1,530 | 300 | 138 | 13 | 6 |
| ***T. cruzi*** | 19,607 | 7,390 | 3,070 | 769 | 51 | 28 |
| ***T. gondii*** | 9,210 | 3,900 | 1,386 | 458 | 39 | 21 |
| **TOTAL** | **68,877** | **29,271** | **11,714** | **3,499** | **297** | **143** |

# *L. major* Histone deacetylase 2 + Vorinostat

***Template 1t64A a human HDAC8 protein.***





| PDB | | Template | | Model | | Ligand | Exact | SupStr | SubStr | Similar |
|---|---|---|---|---|---|---|---|---|---|---|
| 1c3sA | 83.33/80.00 | 1t64A | 36.00/1.47 | LmjF21.0680.1.pdb | 90.91/100.00 | SHH | DB02546 | DB02546 | DB02546 | DB02546 |

**DB02546 Vorinostat**

Small Molecule; Approved; Investigational

**Drug categories:**

Anti-Inflammatory Agents, Non-Steroidal

Anticarcinogenic Agents

Antineoplastic Agents

Enzyme Inhibitors

**Drug Indication:**

*For the treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma who have progressive, persistent or recurrent disease on or following two systemic therapies.*

# *L. major* Histone deacetylase 2 + Vorinostat

## *Literature*

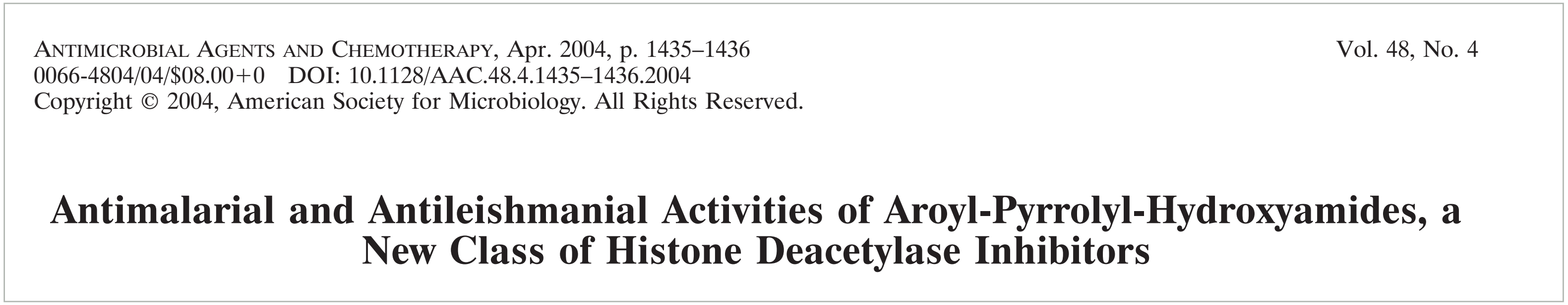
*Proc. Natl. Acad. Sci. USA*
Vol. 93, pp. 13143–13147, November 1996
Medical Sciences

**Apicidin: A novel antiprotozoal agent that inhibits parasite histone deacetylase**

**(cyclic tetrapeptide/Apicomplexa/antiparasitic/malaria/coccidiosis)**

SANDRA J. DARKIN-RATTRAY*†, ANNE M. GURNETT*, ROBERT W. MYERS*, PAULA M. DULSKI*, TAMI M. CRUMLEY*, JOHN J. ALLOCCO*, CHRISTINE CANNOVA*, PETER T. MEINKE‡, STEVEN L. COLLETTI‡, MARIA A. BEDNAREK‡, SHEO B. SINGH§, MICHAEL A. GOETZ§, ANNE W. DOMBROWSKI§, JON D. POLISHOOK§, AND DENNIS M. SCHMATZ*

Departments of *Parasite Biochemistry and Cell Biology, ‡Medicinal Chemistry, and §Natural Products Drug Discovery, Merck Research Laboratories, P.O. Box 2000, Rahway, NJ 07065

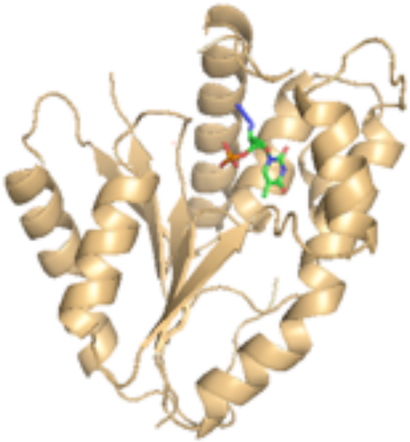


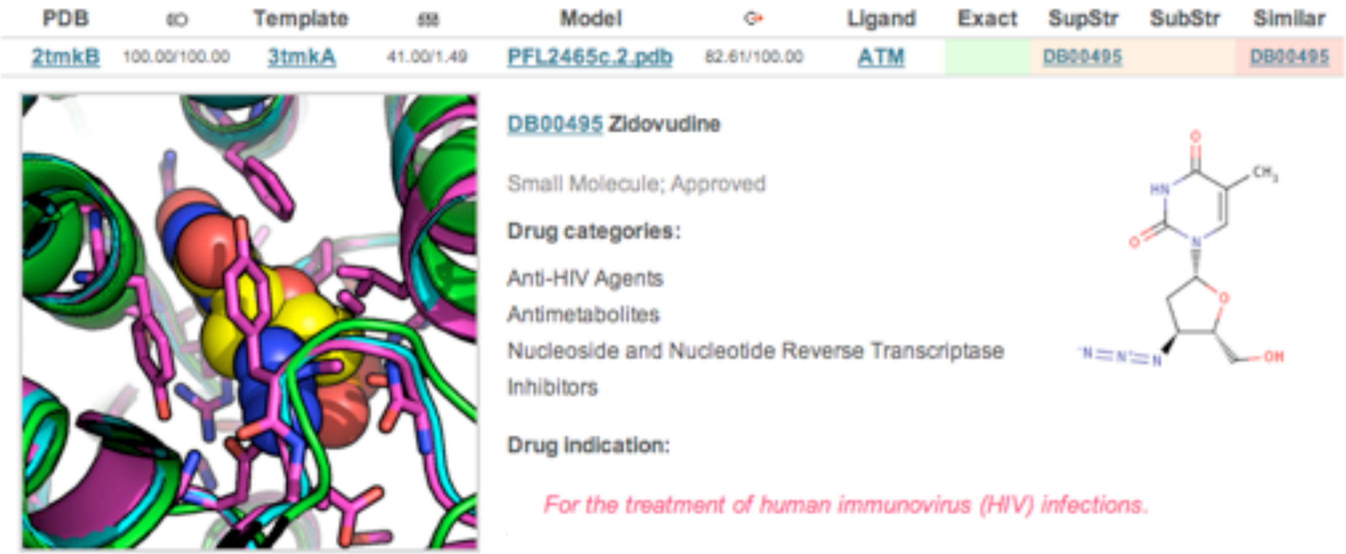
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2004, p. 1435–1436 Vol. 48, No. 4
0066-4804/04/$08.00+0 DOI: 10.1128/AAC.48.4.1435–1436.2004

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

# *P. falciparum* tymidylate kinase + zidovudine

## *Template 3tmkA a yeast tymidylate kinase.*





| PDB |  | Template |  | Model |  | Ligand | Exact | SupStr | SubStr | Similar |
|---|---|---|---|---|---|---|---|---|---|---|
| 2tmkB | 100.00/100.00 | 3tmkA | 41.00/1.49 | PFL2465c.2.pdb | 82.61/100.00 | ATM |  | DB00495 |  | DB00495 |

**DB00495 Zidovudine**

Small Molecule; Approved

**Drug categories:**

Anti-HIV Agents

Antimetabolites

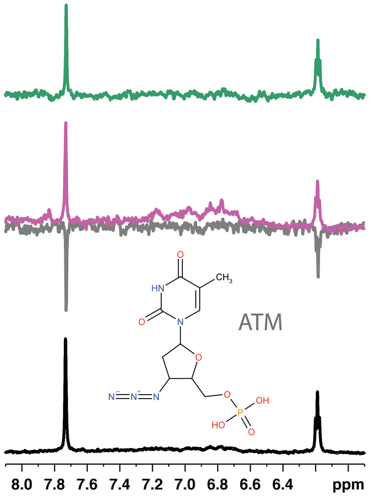
Nucleoside and Nucleotide Reverse Transcriptase Inhibitors

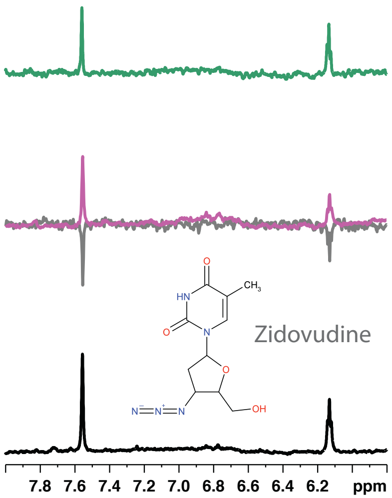
**Drug Indication:**

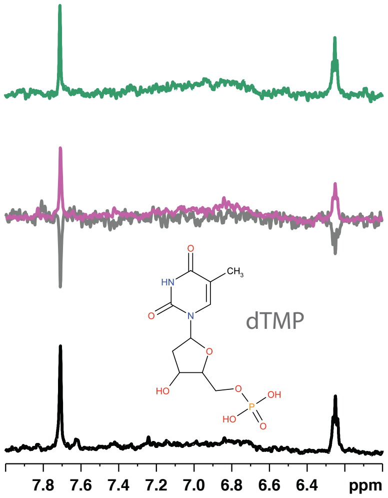
*For the treatment of human immunovirus (HIV) infections.*

# *P. falciparum* thymidylate kinase + zidovudine

*NMR Water-LOGSY and STD experiments*





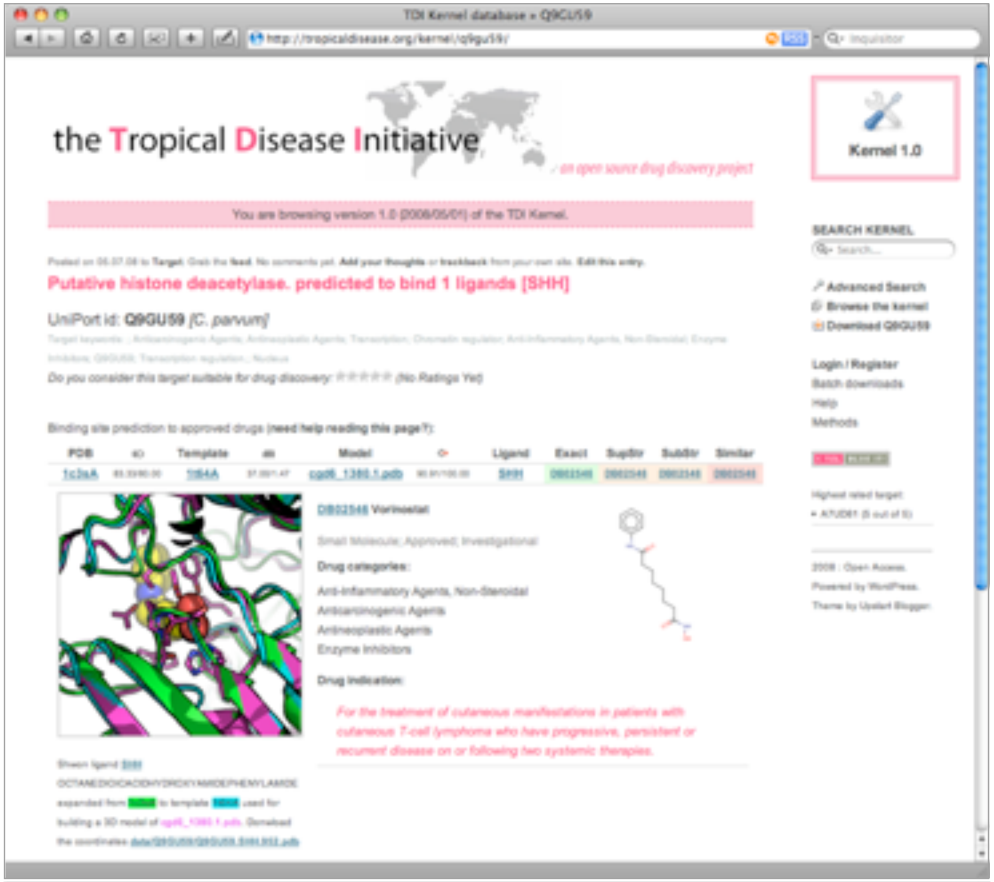


*Leticia Ortí, Rodrigo J. Carbajo, and Antonio Pineda-Lucena*

# TDI’s kernel

http://tropicaldisease.org/kernel

***Ortí et al . “A kernel for open source drug discovery in tropical diseases”. Submitted.***
***Ortí et al . “A Kernel for the Tropical Disease Initiative”. Submitted.***



TDI Kernel database » Q9GU59

http://tropicaldisease.org/kernel/q9gu59/

the Tropical Disease Initiative

an open source drug discovery project

You are browsing version 1.0 (2008/05/01) of the TDI Kernel.

**Putative histone deacetylase. predicted to bind 1 ligands [SHH]**

UniPort id: **Q9GU59** *[C. parvum]*

*Do you consider this target suitable for drug discovery:* ☆☆☆☆☆ *(No Ratings Yet)*

Binding site prediction to approved drugs (**need help reading this page?**):

DB02546 **Vorinostat**

Small Molecule; Approved; Investigational

**Drug categories:**

Anti-Inflammatory Agents, Non-Steroidal
Anticarcinogenic Agents
Antineoplastic Agents
Enzyme Inhibitors

**Drug indication:**

*For the treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma who have progressive, persistent or recurrent disease on or following two systemic therapies.*

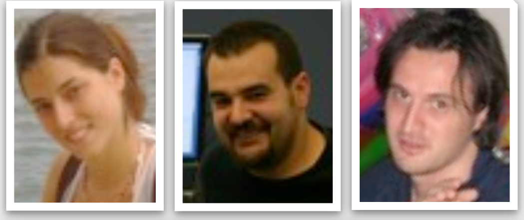
# TDI’s visitors...

http://tropicaldisease.org

http://tropicaldisease.org/kernel

# Acknowledgments

http://tropicaldisease.org
http://thesynapticleap.org



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