

The Tropical Disease Initiative

An open source approach to drug development

www.tropicaldisease.org

www.thesynapticleap.org



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

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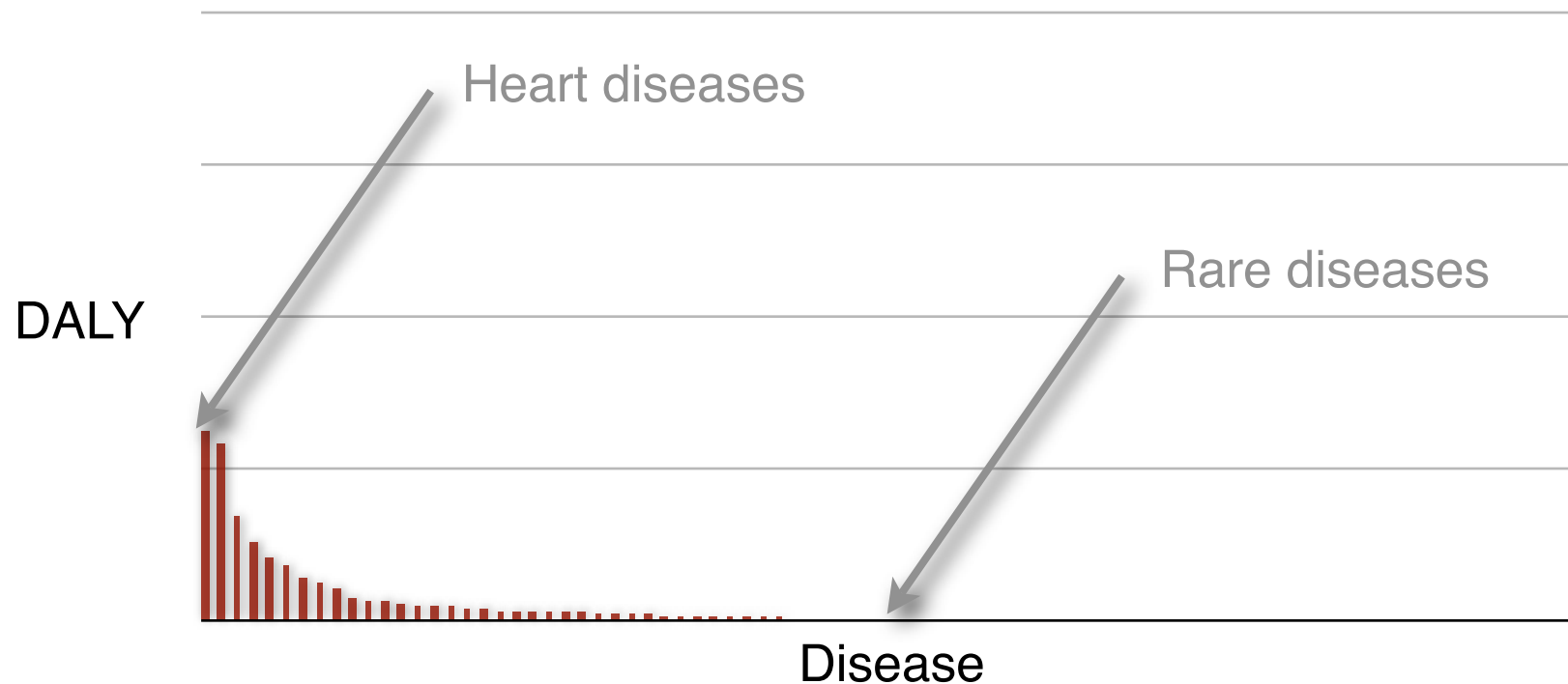
SG



TDI

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*

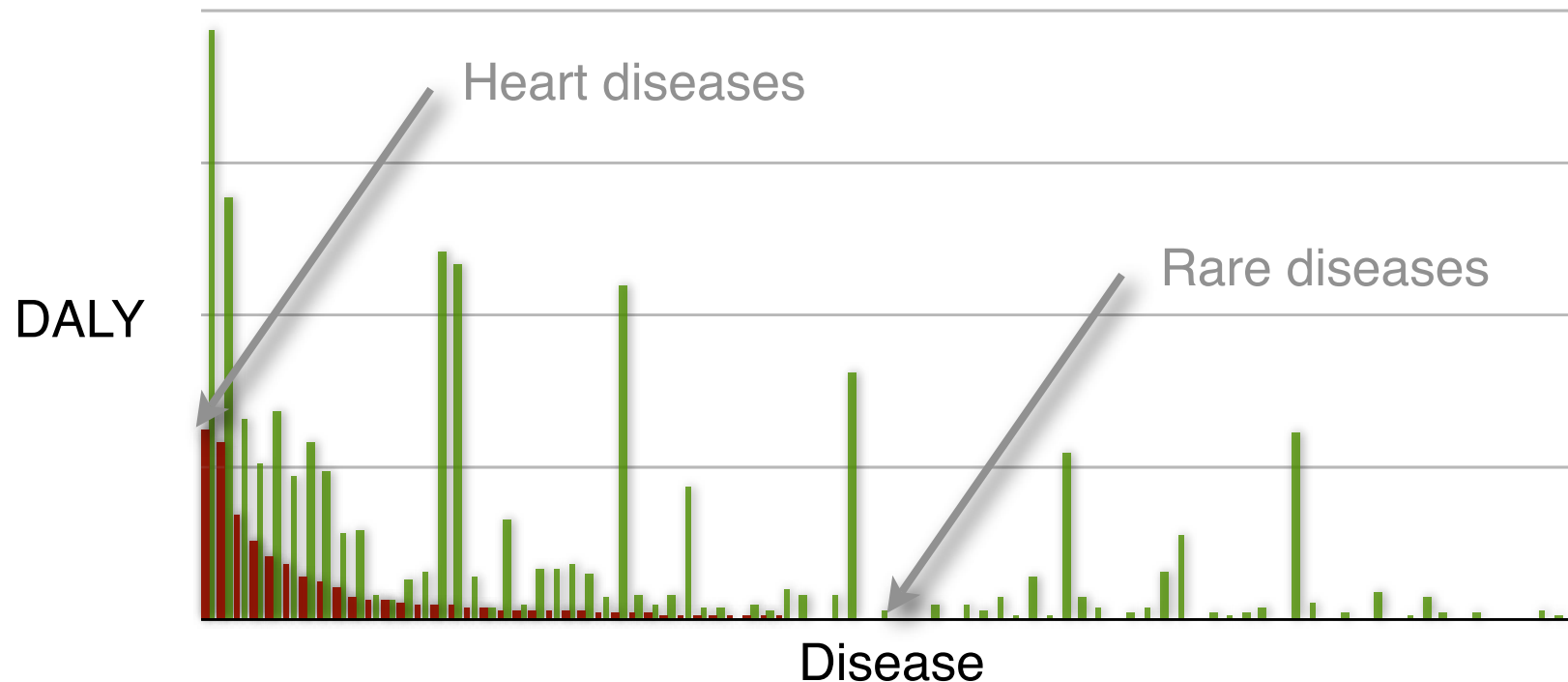
DALY - Disability adjusted life years

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
Syphilis.....4,200
Chagas Disease*667
Leishmaniasis*2,090
Poliomyelitis.....151
Tetanus.....7,074
Diphtheria.....185
Trichuriasis.....1,006
Lymphatic filariasis* ..5,777

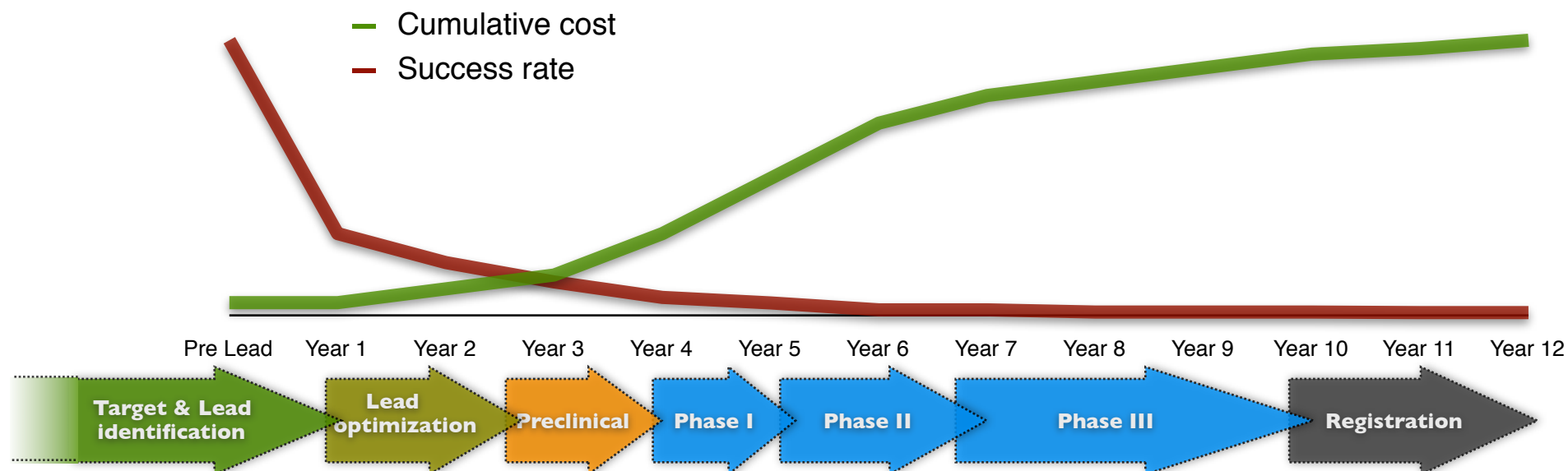
Ascariasis.....1,817
Leprosy*199
Schistosomiasis*1,702
Japanese encephalitis...709
Dengue*616
Hookworm disease.....59
Trachoma.....2,329
Trypanosomiasis*1,525
Onchocerciasis*484

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

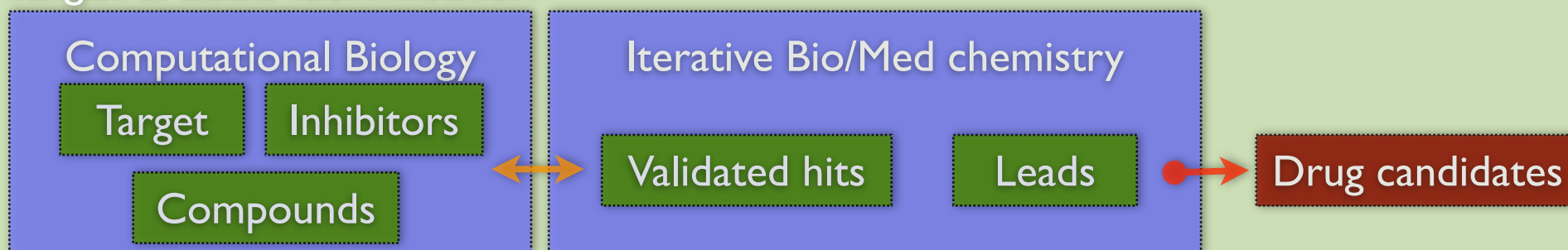
DALY - Disability adjusted life year in 1000's.

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

Drug Discovery pipeline

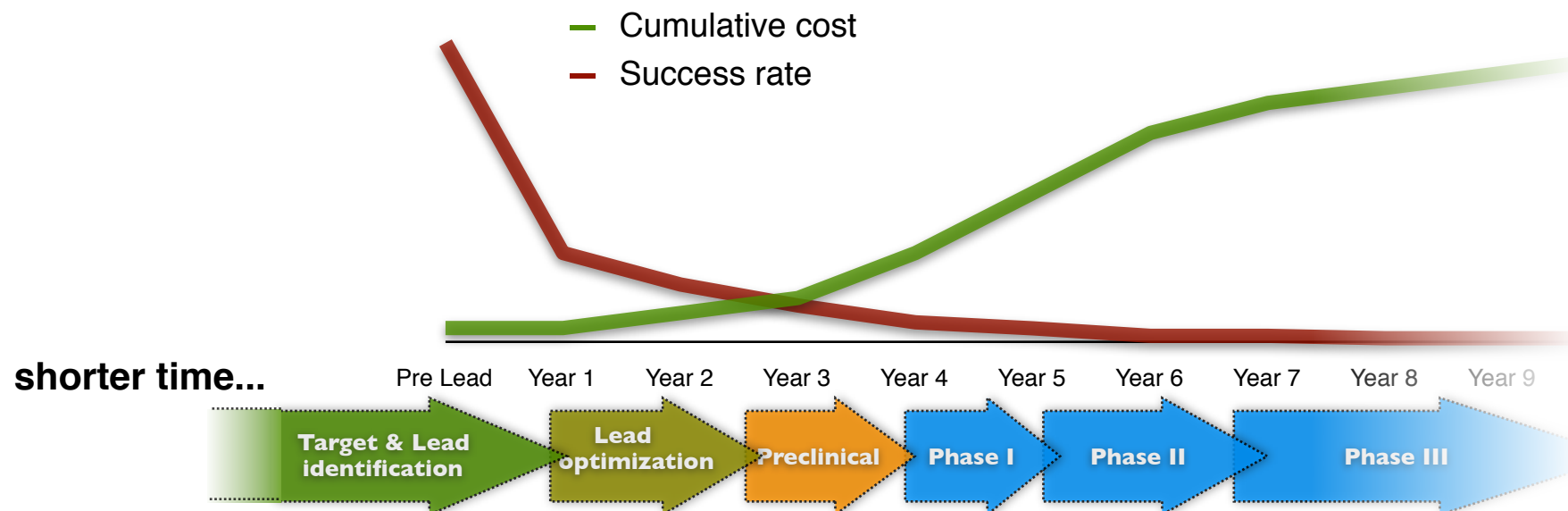


Target & Lead identification



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

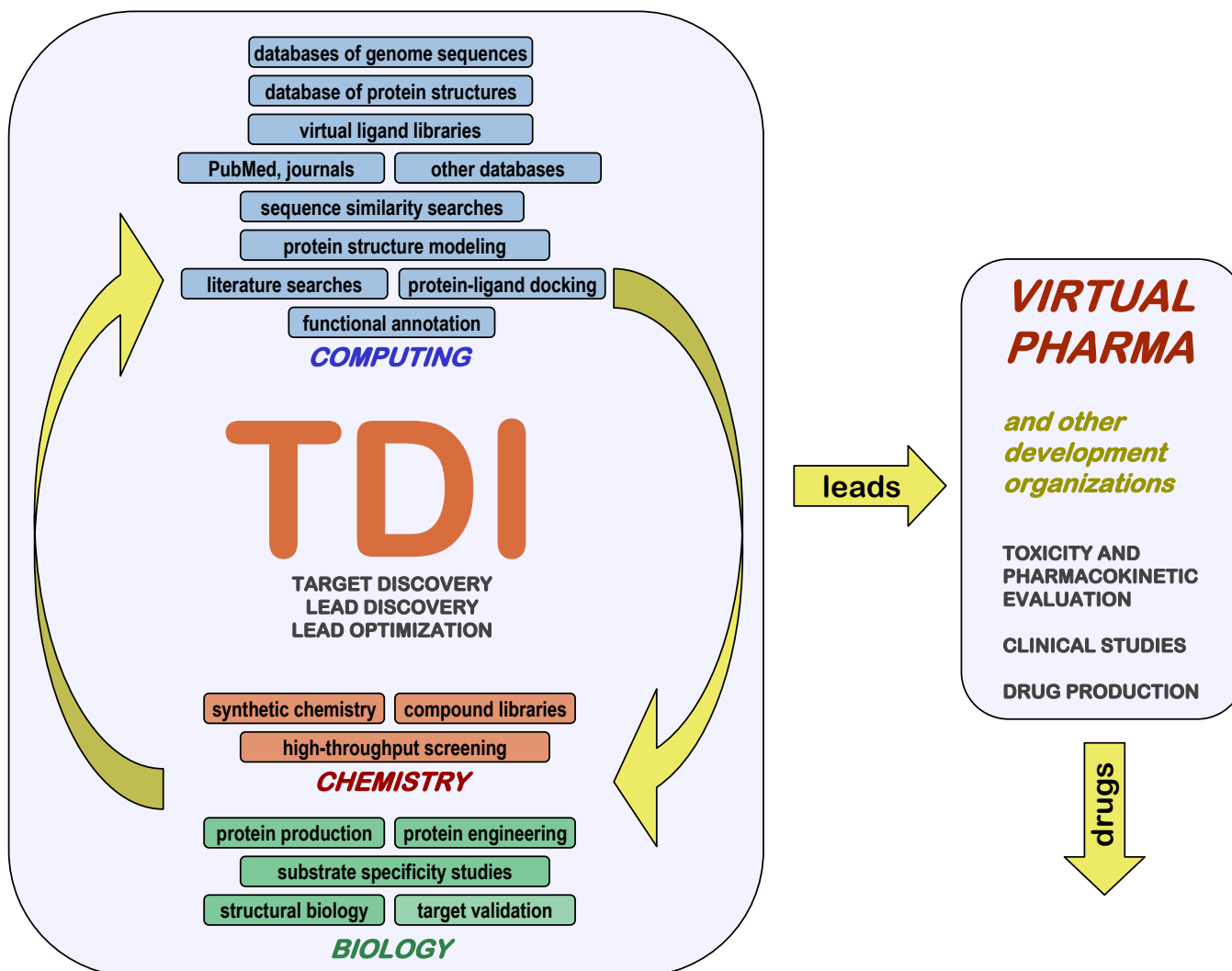
Drug Discovery pipeline



- + Completeness of genome projects (eg, 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?**)

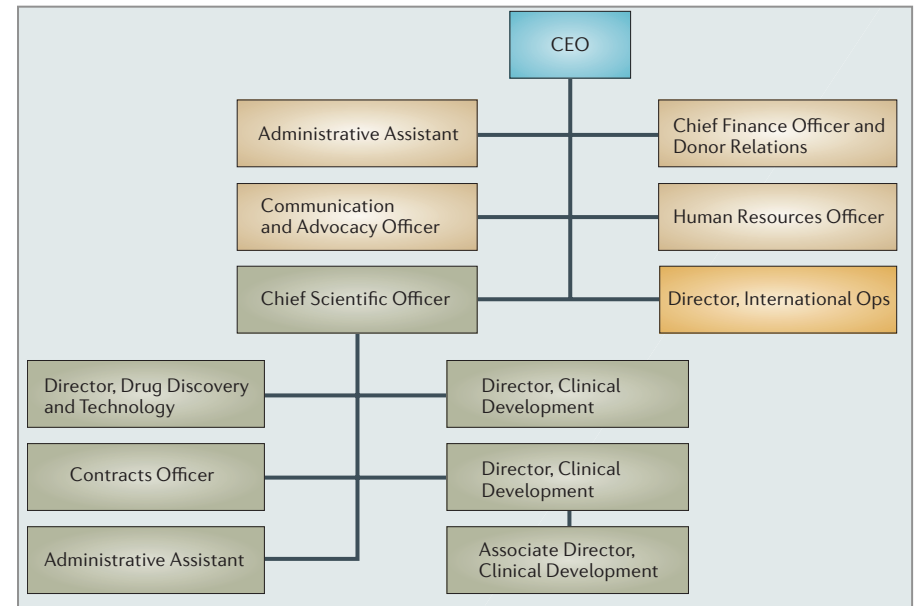
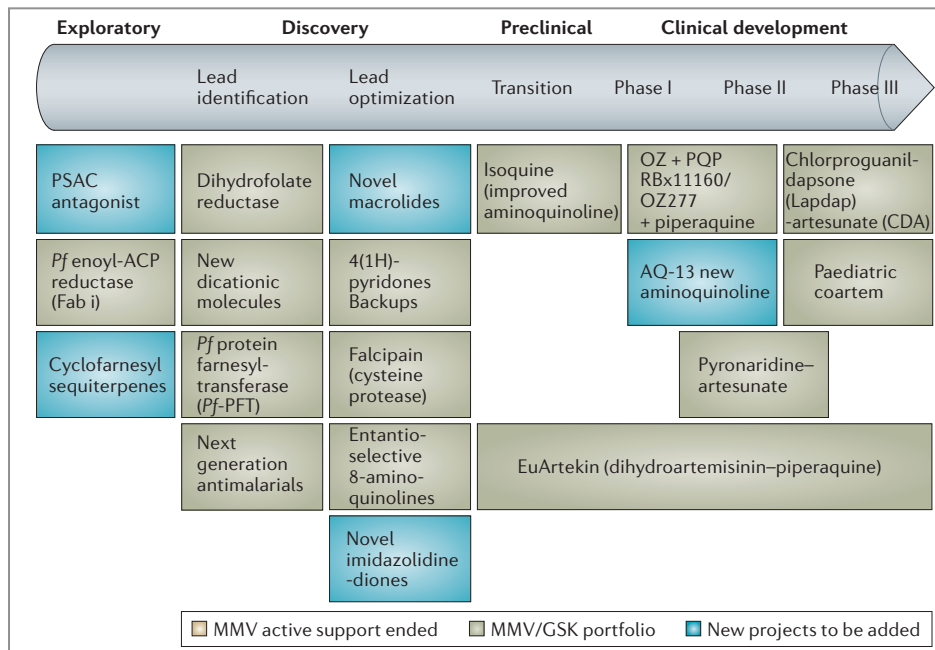
TDI flowchart



Medicines for Malaria Venture

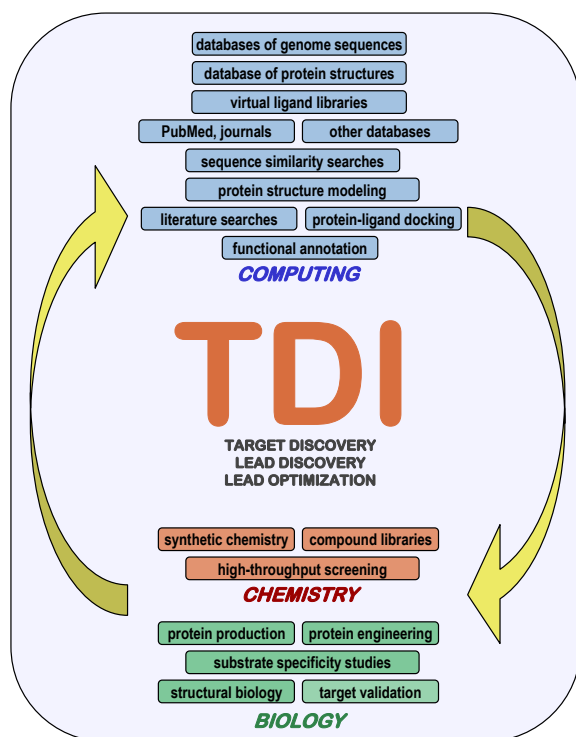
a virtual pharma

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



From: - Munos (2006) *Nature Reviews. Drug Discovery*.

Do we have the toolbox?



***VIRTUAL
PHARMA***

*and other
development
organizations*

**TOXICITY AND
PHARMACOKINETIC
EVALUATION**

CLINICAL STUDIES

DRUG PRODUCTION

TDI web site projects

Collaboration tools

Gene Cards

Structure Prediction

Target Selection for Structural Genomics

Gene Annotation

Gene Basket

Database of annotated chemical compounds



The Synaptic Leap

Open Source Biomedical Research

<http://www.thesynapticleap.org>

Ginger Taylor



Collaborative Drug
Discovery

Barry Bunin

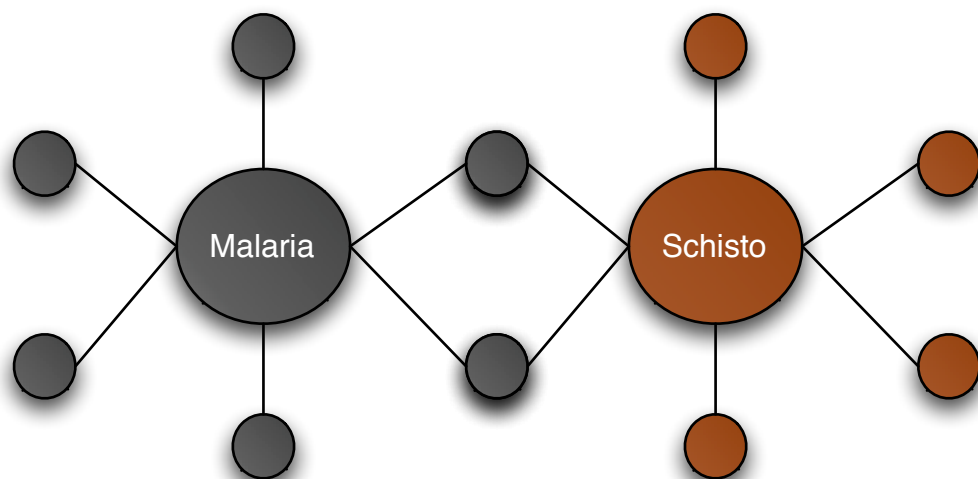
The Synaptic Leap

- Non-profit organization
- Original volunteers have commercial portal application background
- Significant science partner Tropical Disease Initiative

<http://www.thesynapticleap.org>



Malaria & Schisto Communities



Useful Chemistry

XML

B

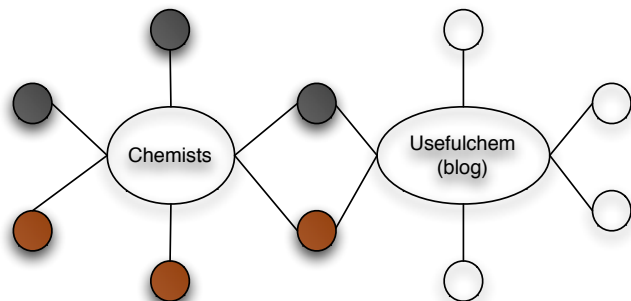
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UsefulChem molecules

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UsefulChem Experiments

An attempt at open source science in chemistry. Post specific problems in chemistry that need to be solved. Post specific partial solutions to these problems. Or execute a suggested step. NOTE: ANYTHING POSTED HERE IS MADE PUBLIC IMMEDIATELY AND DONATED TO THE PUBLIC DOMAIN . ANYONE MAY USE, EVEN FOR COMMERCIAL PURPOSES, AS LONG AS ATTRIBUTION IS MADE TO THE RELEVANT POSTS IN THIS BLOG



Home » collaborative communities » schisto research » current projects » Enantioselective Synthesis of Praziquantel

Aza-Henry Route to PZQ

view

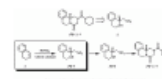
edit

revisions

track

Aza-Henry route to PZQ

We have designed a new synthesis of PZQ based on a catalytic, asymmetric aza-Henry reaction (Scheme 1). The key step is the generation of the new stereogenic centre in **4**. From here, the reduction to **5** should be facile with e.g. samarium iodide.¹ From **5**, the two steps to PZQ are known from the original report.²



Aza-Henry route to PZQ

The catalytic, asymmetric Henry reaction has recently been the

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Aza-Henry route to PZQ



Collaboration tools

Caution!

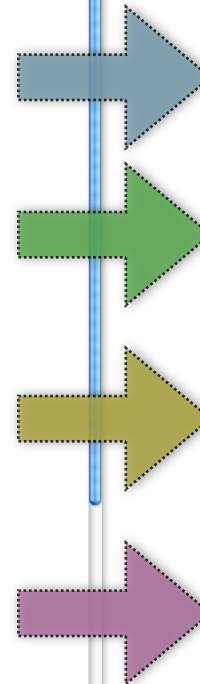
The following does not exist
and is *STILL* not funded.

Gene Board

collecting gene information

The screenshot shows the 'Gene Card | Development Site' interface. The main content area displays a 'Gene Card' for 'NP_702320 - serine/threonine kinase-1'. The card is divided into several sections: 'Literature' (listing 1 PubMed entry), 'Annotation' (listing 8 external links), 'Structure' (stating no PDB entries are available), and 'Function' (listing 27 GO terms). The left sidebar contains a 'User login' section, a 'Navigation' menu, and a 'Who's online' section. The bottom of the sidebar features a poll titled 'Which News Source is Better?' and a 'Total votes: 2' section.

- 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

Target Annotation

Gene Wiki

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
• 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
[login or register to post comments](#) | [older polls](#)

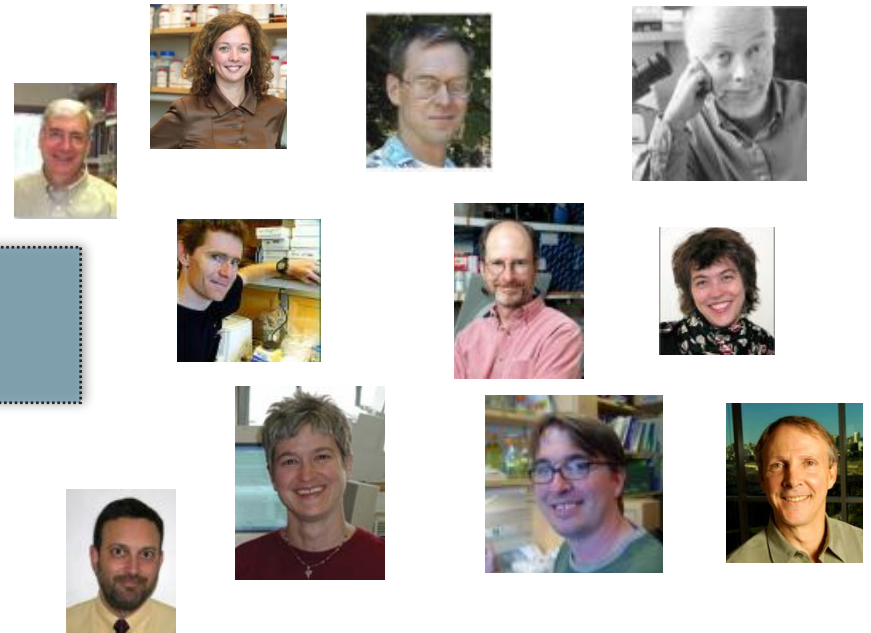
Home
Gene Card
NP_702320 - serine/threonine kinase-1.

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, J.T., James, K., Eisen, J.A., Rutherford, K., Salzberg, S.L., Craig, A., Kyes, S., Chan, M.-S., Nene, V., Shallom, S.J., Suh, B., Peterson, J., Angiuoli, S., Peres, 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 Barrell, 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
PlasmaDB entry id: chr14_glm_487
PlasmaDB entry id: chr14_phat_425
PlasmaDB 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:0000166 nucleotide binding
GO:0003824 catalytic activity
GO:0004872 protein kinase activity
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 an association between the article and any of the genes in his/her basket.

As seen on:  



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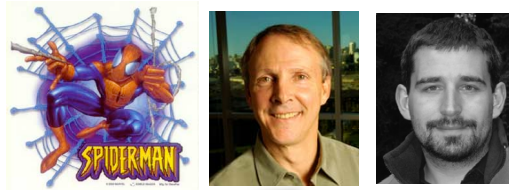
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As seen on: **YAHOO!** **flickr**^{BETA}



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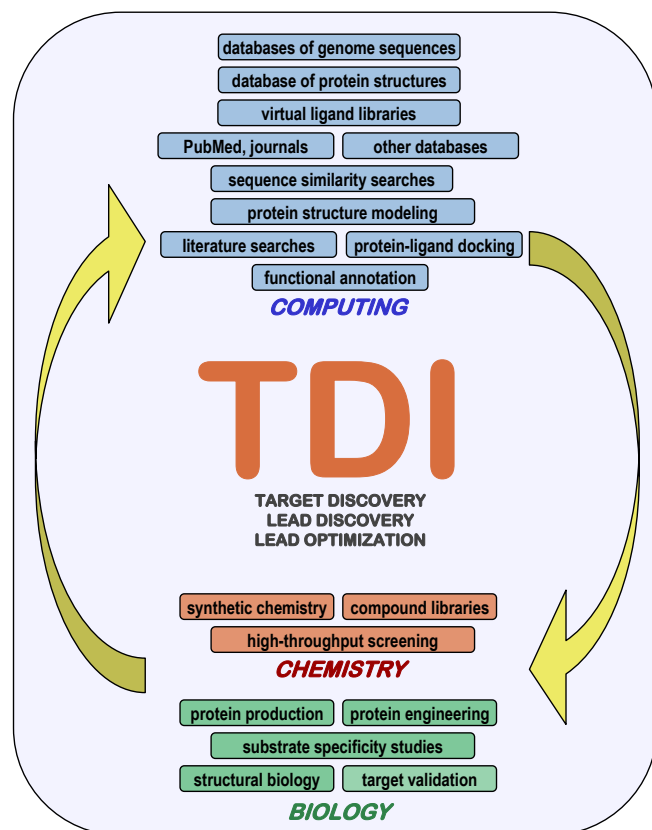


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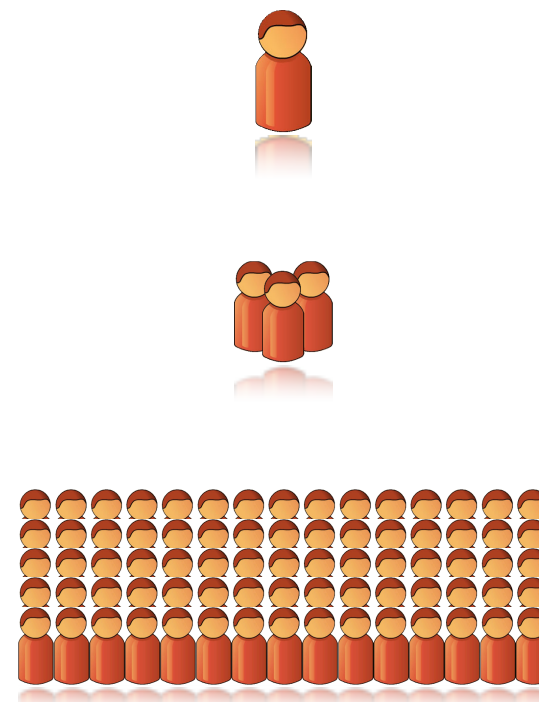
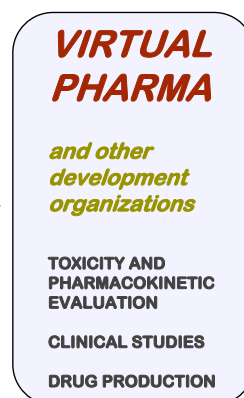
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As seen on: **YAHOO!** **flickr**^{BETA}





leads



Acknowledgments

Read more @

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

Tropical Disease Initiative

Barry Bunin (CDD)
Moses M. Hohman (CDD)
Thomas Kepler (Duke U)
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John P. Overington (Impharmatica Inc.)
Arti Rai (Duke U)
David Roos (U Penn)
Andrej Sali (UCSF)
Brian Schoichet (UCSF)

<http://bioinfo.cipf.es/sgu/>
<http://www.tropicaldisease.org>
<http://www.thesynapticleap.org>

"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)

The Synaptic Leap

Ginger Taylor (Founder)

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)



Wiki site at NPG

Timo Hannay
Declan Butler