Collaborative Virtual Organisation & Infrastructure for Anti-Malarial Drug Design

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Director of Communities & Research Activities
Douglas Connect, Switzerland

BioIT World Conference & Expo, Boston, USA
12-14 April 2011

Community of Practice starting point

innovationwell

echeminfo

We started with community development interactions, both virtual and face-to-face...

Knowledge Cafe Discussions

SAM

SYNERGY

Community of Practice starting point

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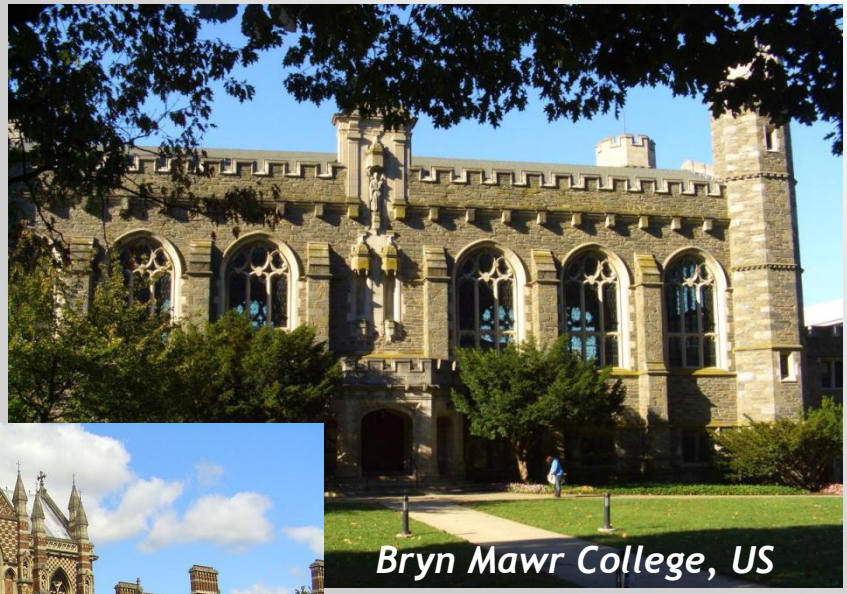
...and continued by holding workshops and InterAction Meetings in US and Europe


Bryn Mawr College, US


Oxford University, UK

Community of Practice starting point

echeminfo

Community of Practice for
Drug Discovery & Development

Latest Advances in Drug Discovery & Planning Methods

Advanced Training Workshop

Oxford University, June 25-29, 2007

Interactive pragmatic workshops with leading experts and industry practitioners...

- Protein Target & Ligand Modelling
- Virtual Screening & Docking
- Structure-based Drug Design
- Pharmacophore Models
- Focused Library Design
- ADME, QSAR & Predictive Toxicology

Study problems in detail using leading-edge

Community of Practice starting point

Community and workshop interactions created a valuable environment and network from which to build collaborations

Caprivi Delta, Namibia

While on a start-up conservation field trip in a remote region of Namibia, we visited many local villages -- meet your ‘future patients’ for malaria treatment.

Malaria is a common infection in this region which has many wetlands and a strong wet season.

Caprivi Delta, Namibia

Families and village communities form a critical part of the social fabric in this region.

Unfortunately a high HIV infection rate is having devastating impact on such communities.

Infections go untreated and many children lose their parents.

Caprivi Delta, Namibia

Educational context: visiting a local school

Education requires healthy families and children

Caprivi Delta, Namibia

The next generation of a community... who grow up with malaria and little medical care

Caprivi Delta, Namibia

A family we interviewed with proudly showed us their material possessions.

The current cost of our anti-malarials for just two weeks would exceed their entire annual income.

Health, Conservation and Sustainable Development

We can work on biodiversity conservation (rhino rescue work shown).

But we need a healthy, educated community involvement for it to be sustainable.

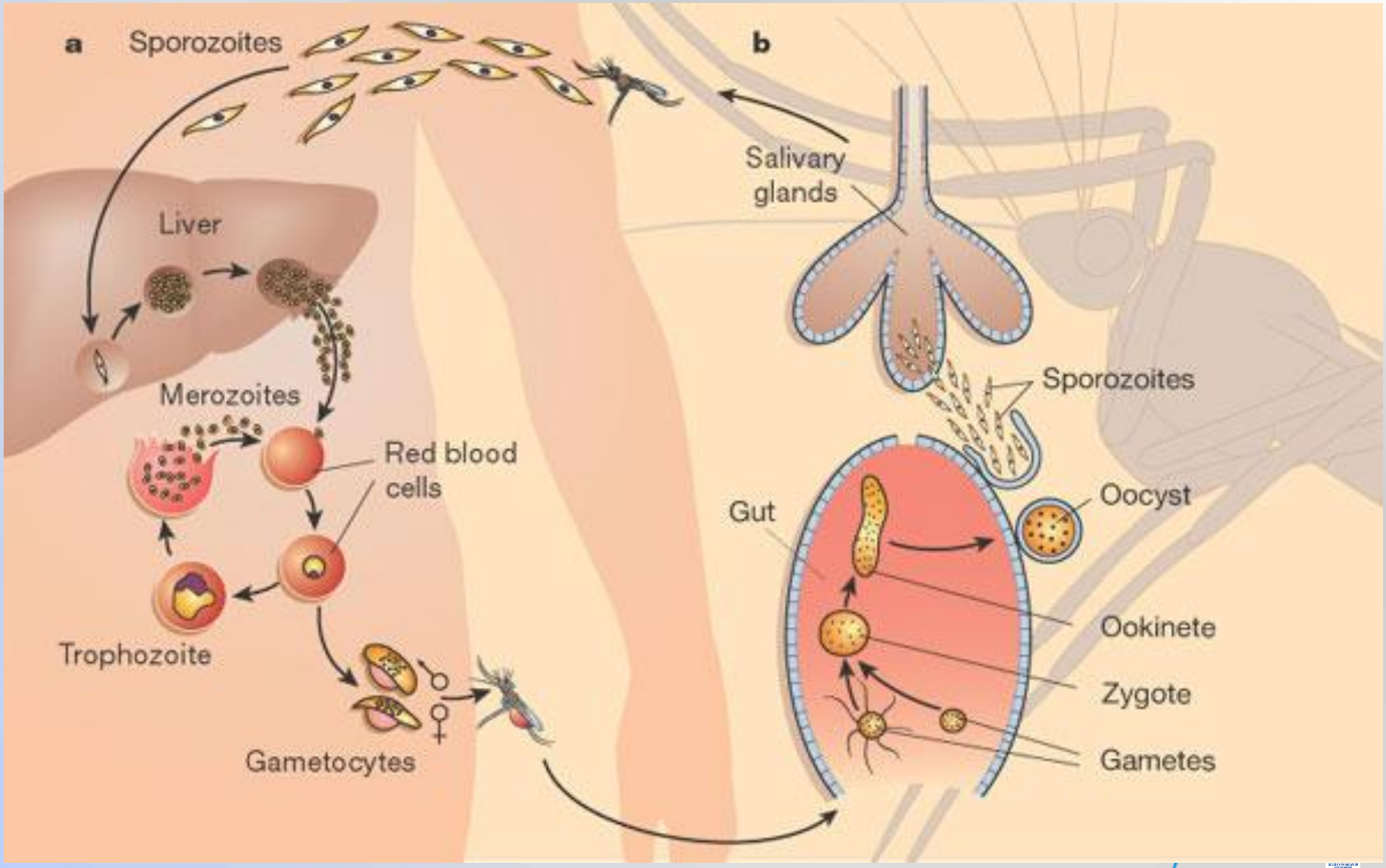
Criminal groups exploit these communities and region for poaching.

Health, Conservation and Sustainable Development

A breeding and reintroduction project fleeing the chaos in Zimbabwe.

And another neglected disease: Bovine TB, is threatening lions' genetic strength and survival (e.g., prides in Southern Kruger Park).

The (complicated) Plasmodium Life Cycle

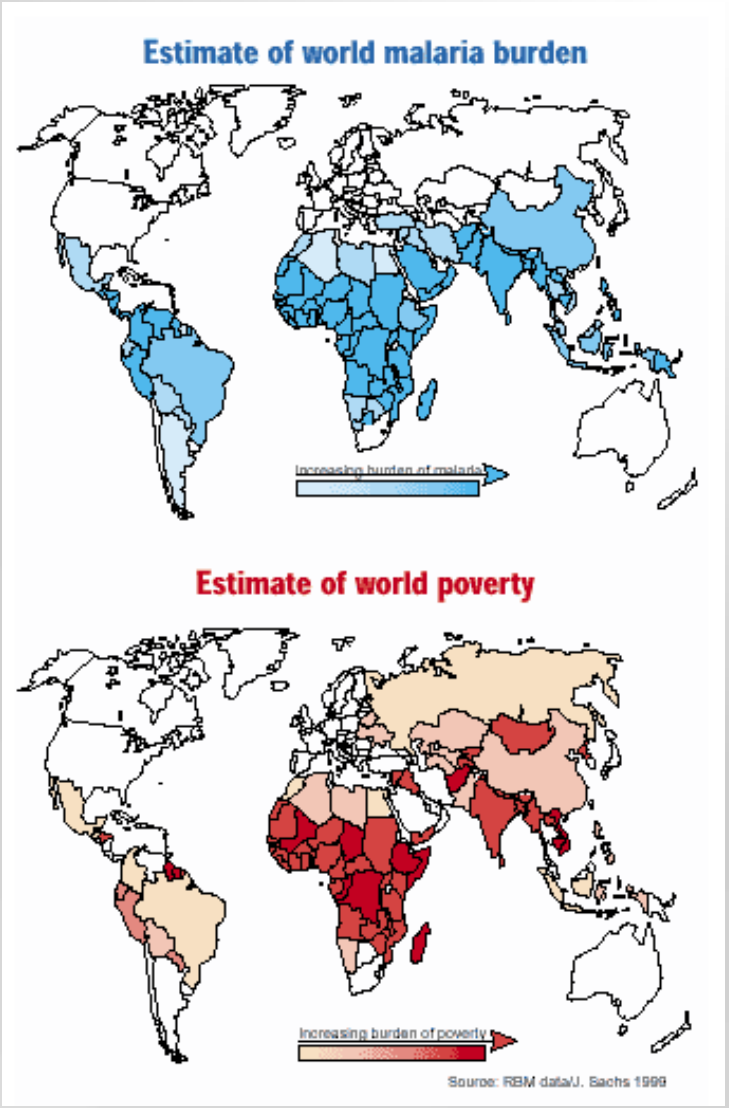


Malaria Treatment: Lack of Investment

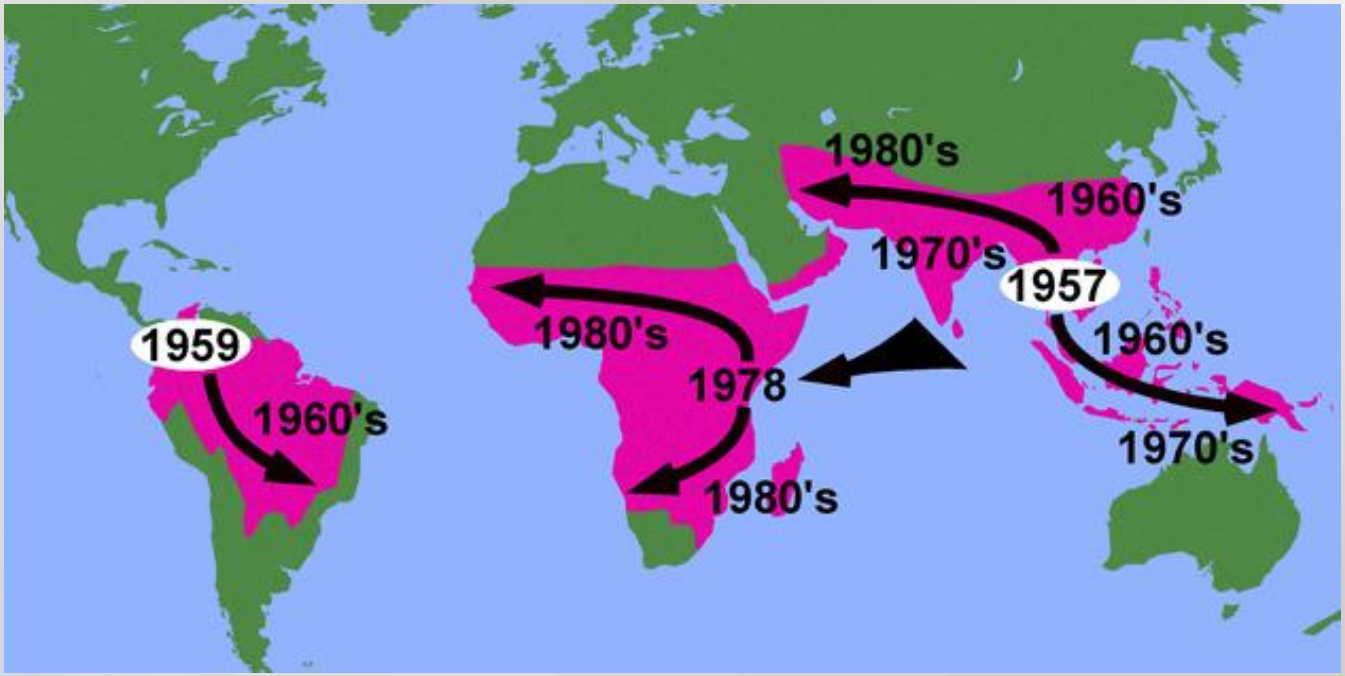
- 2.5 billion people at risk
- 500 M cases yearly
- 1-3 M deaths yearly
- Many child fatalities
- Brain Damage, Impaired Development
- Few drugs, no vaccine
- Impact on Education, Community, Income, Conservation, Sustainability

Drug development outcome, last quarter of the XXth century

Greenwood & Mutabingwa, Nature 415:670-672

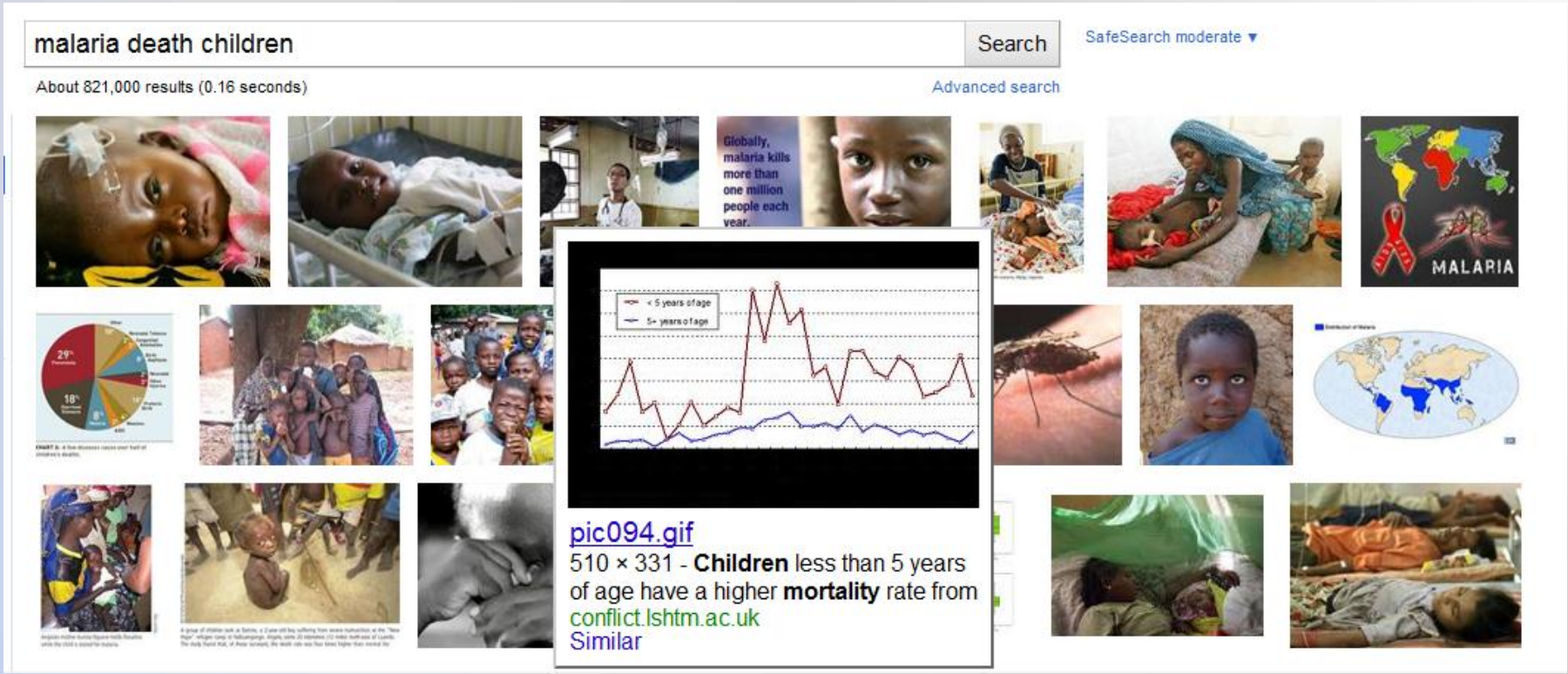


Drug Resistance is a challenge

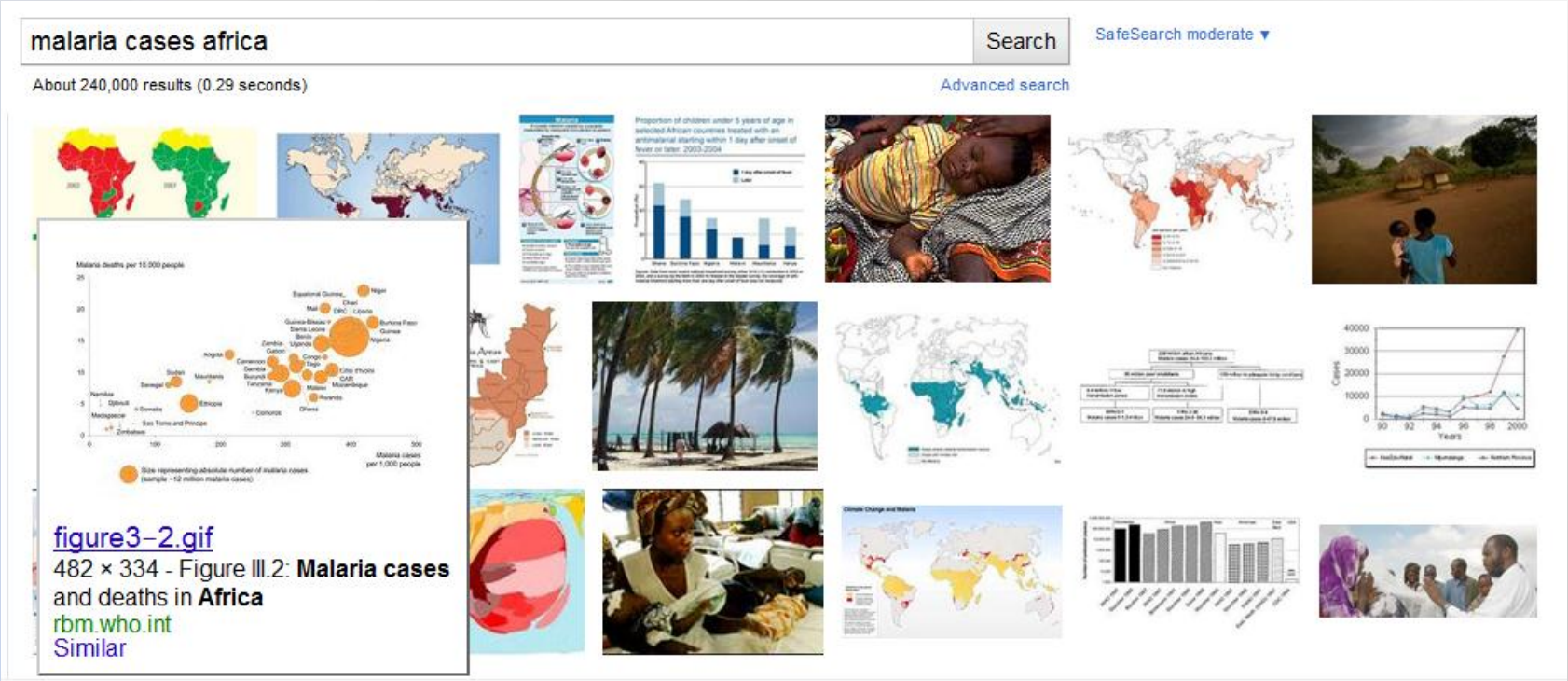


Emergence and spread of chloroquine resistance

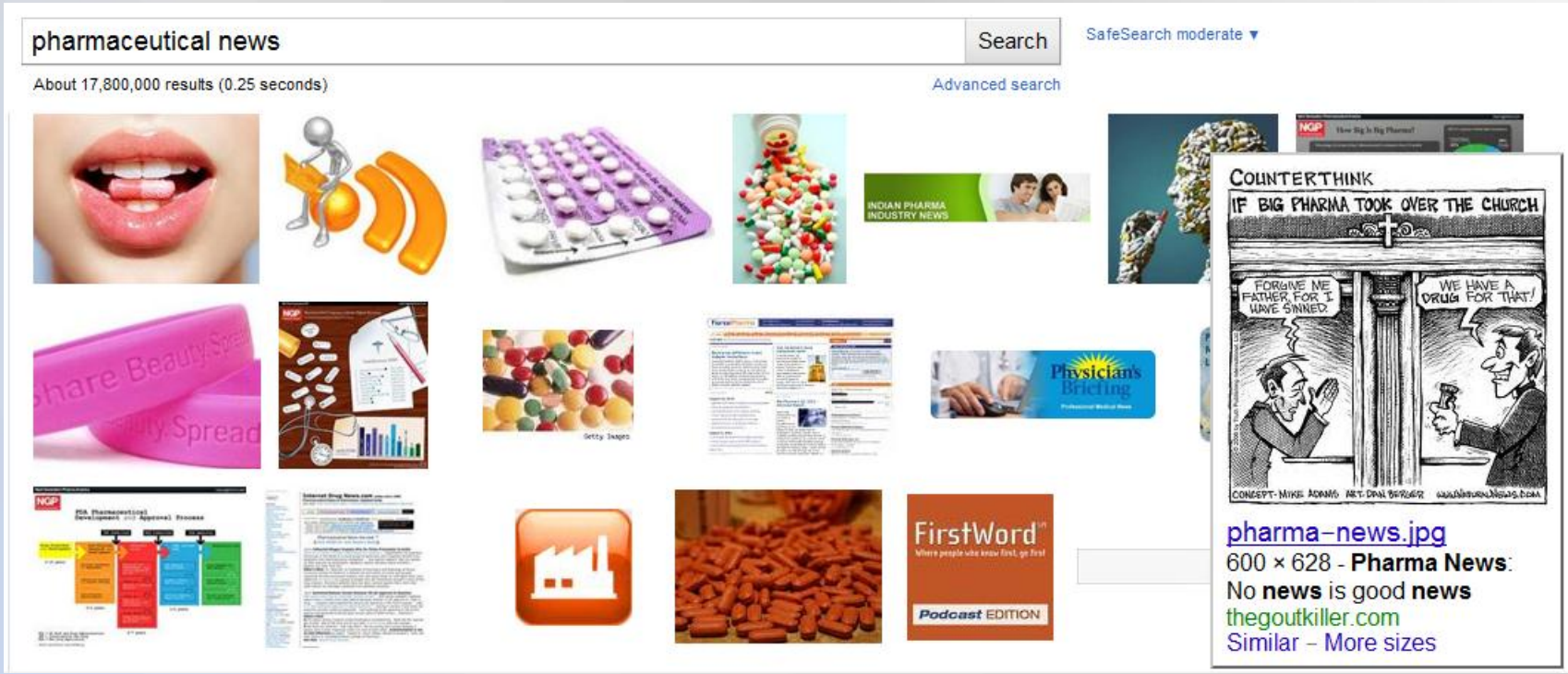
Malaria, Death, Children



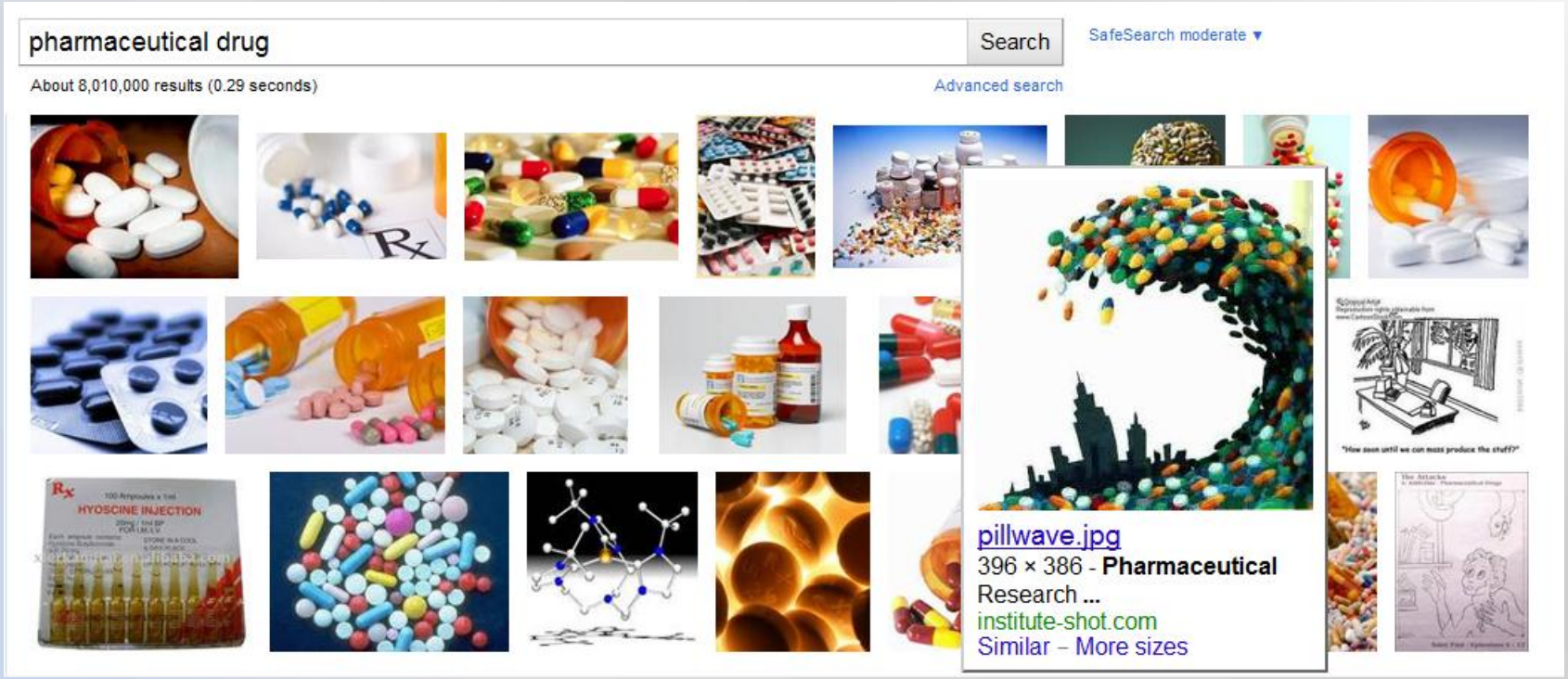
Malaria, Cases, Africa



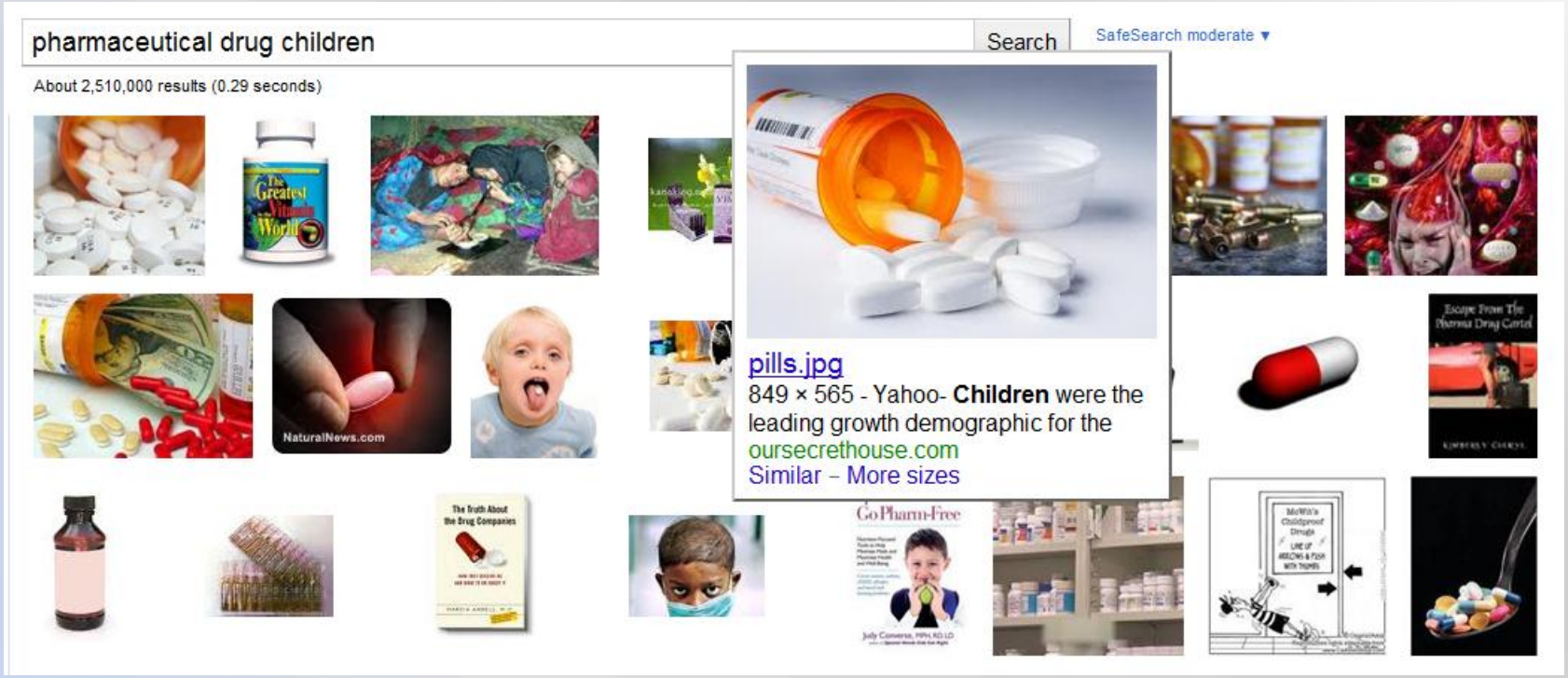
Pharmaceutical, News



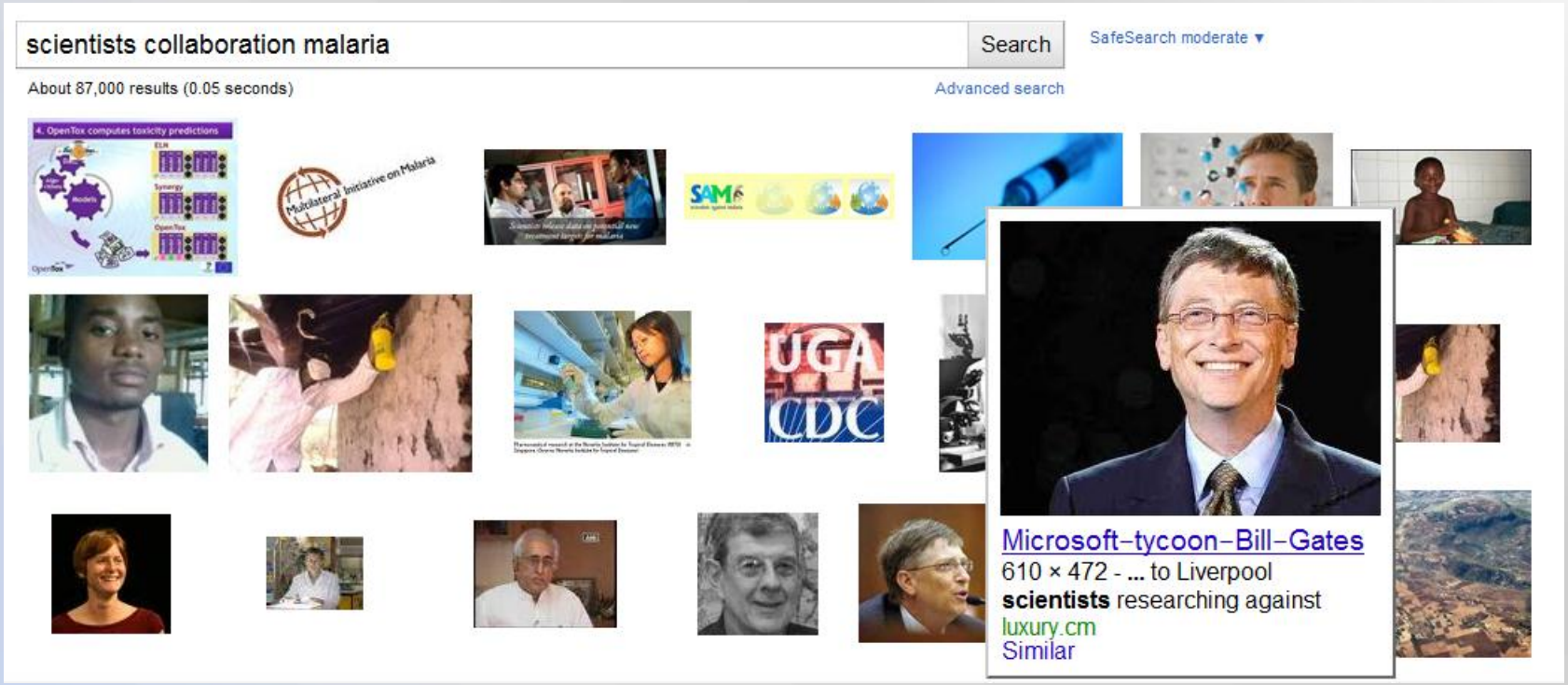
Pharmaceutical, Drug



Pharmaceutical, Drug, Children

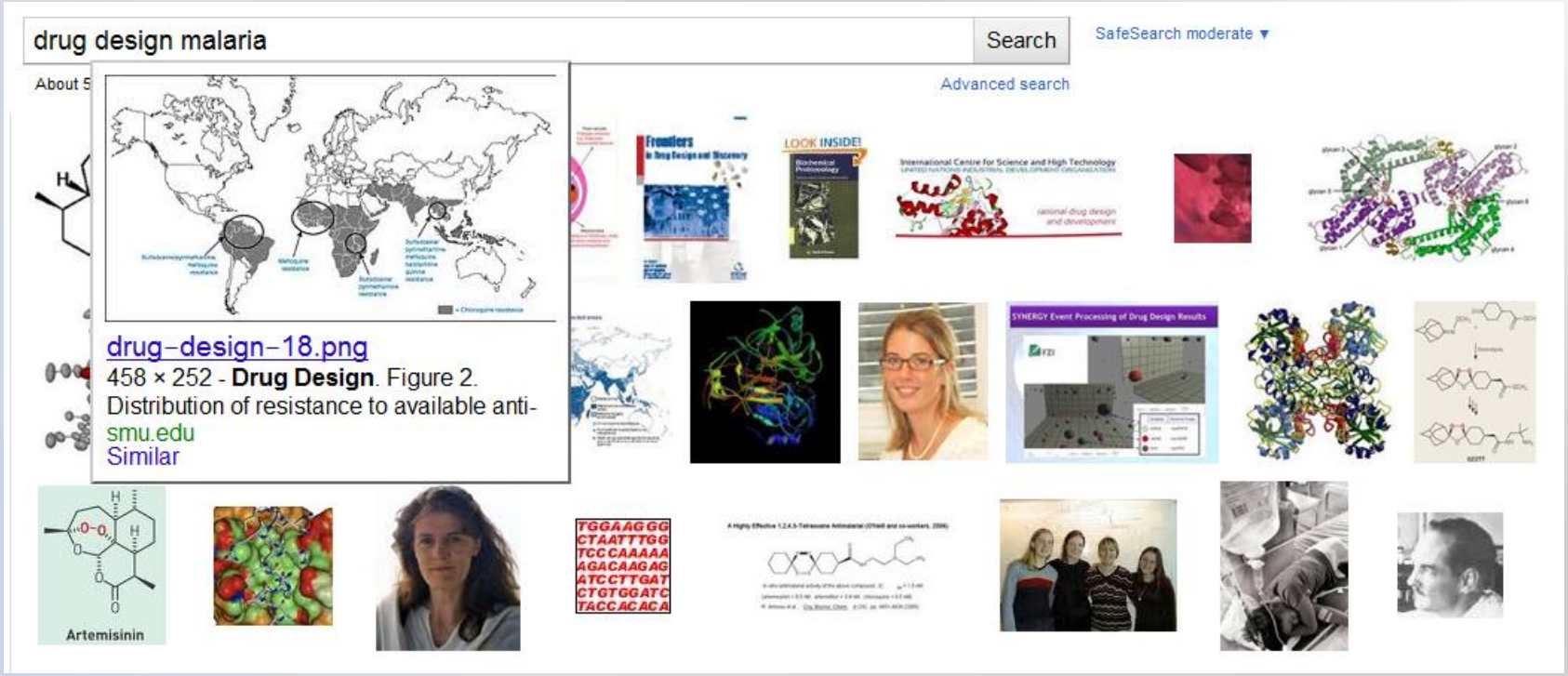


Scientists, Collaboration, Malaria

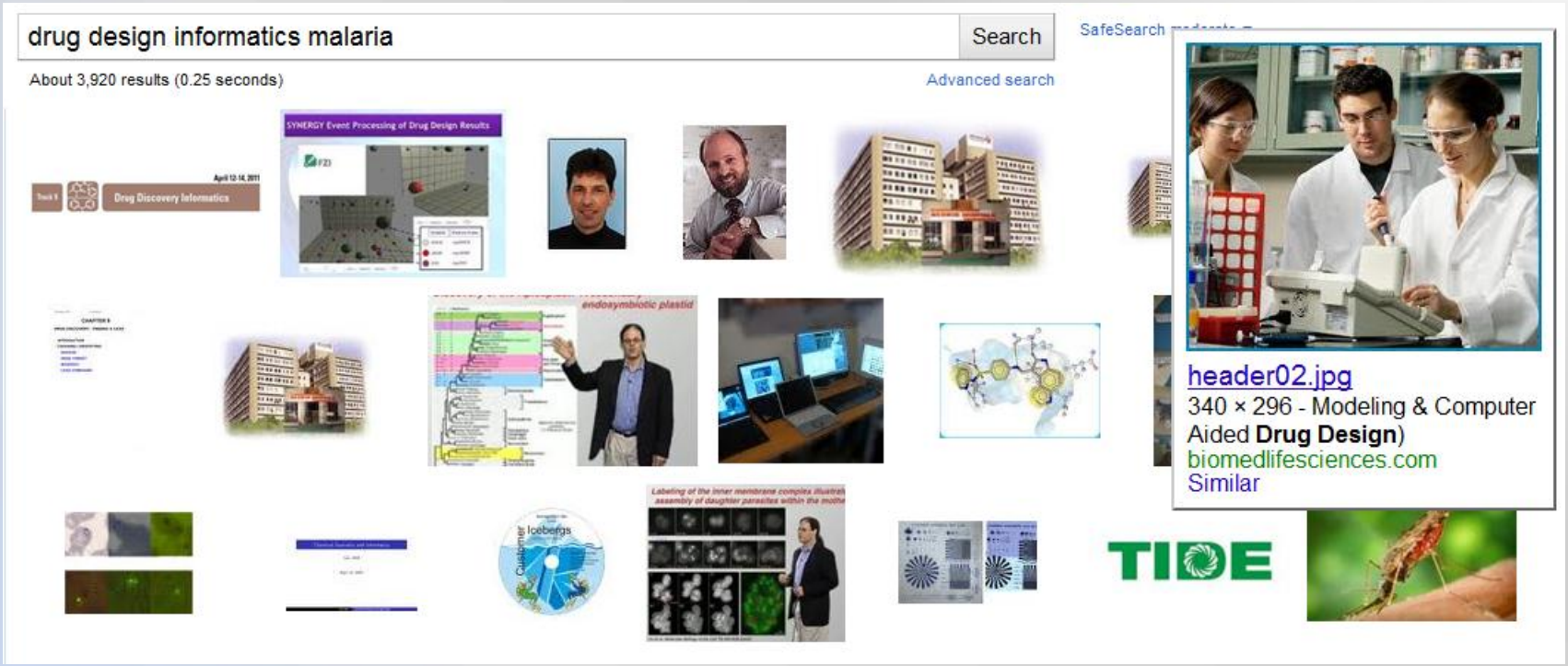


Scientists, Collaboration, Malaria

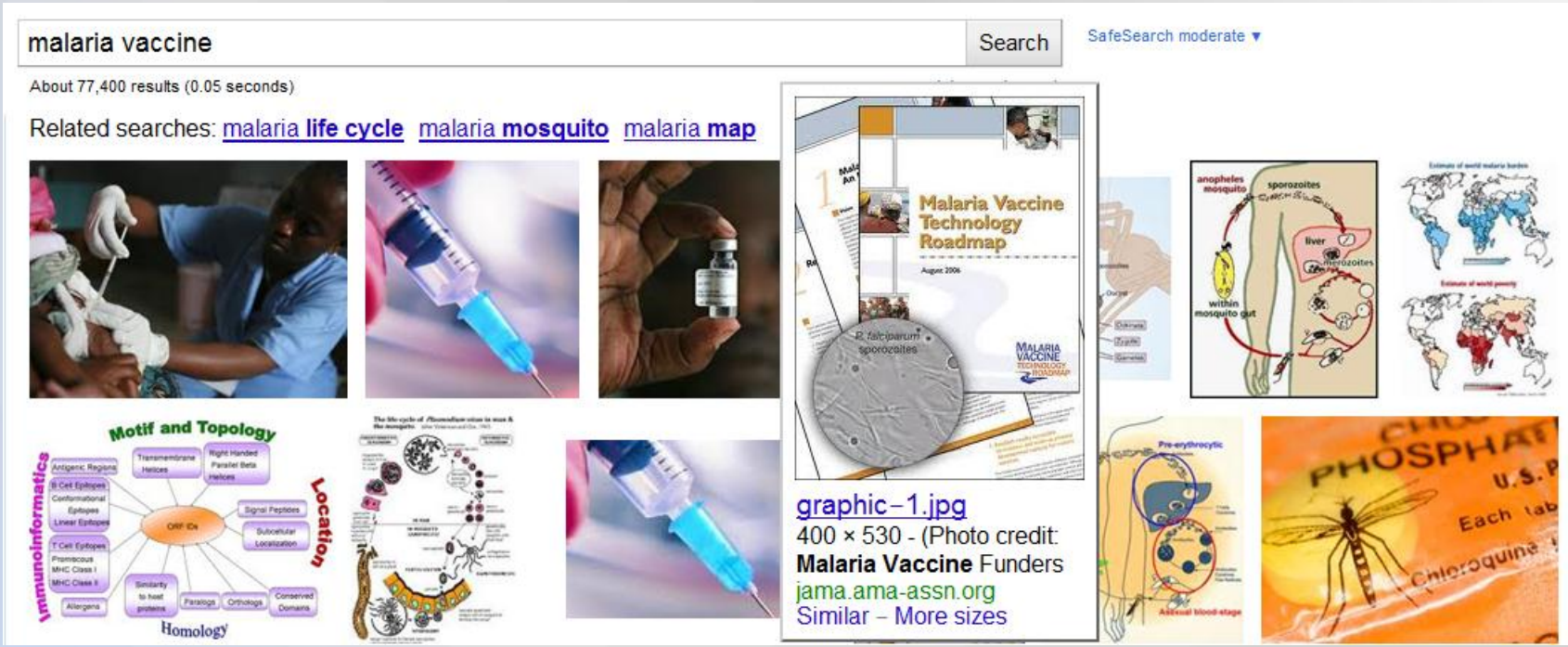
Drug, Design, Malaria



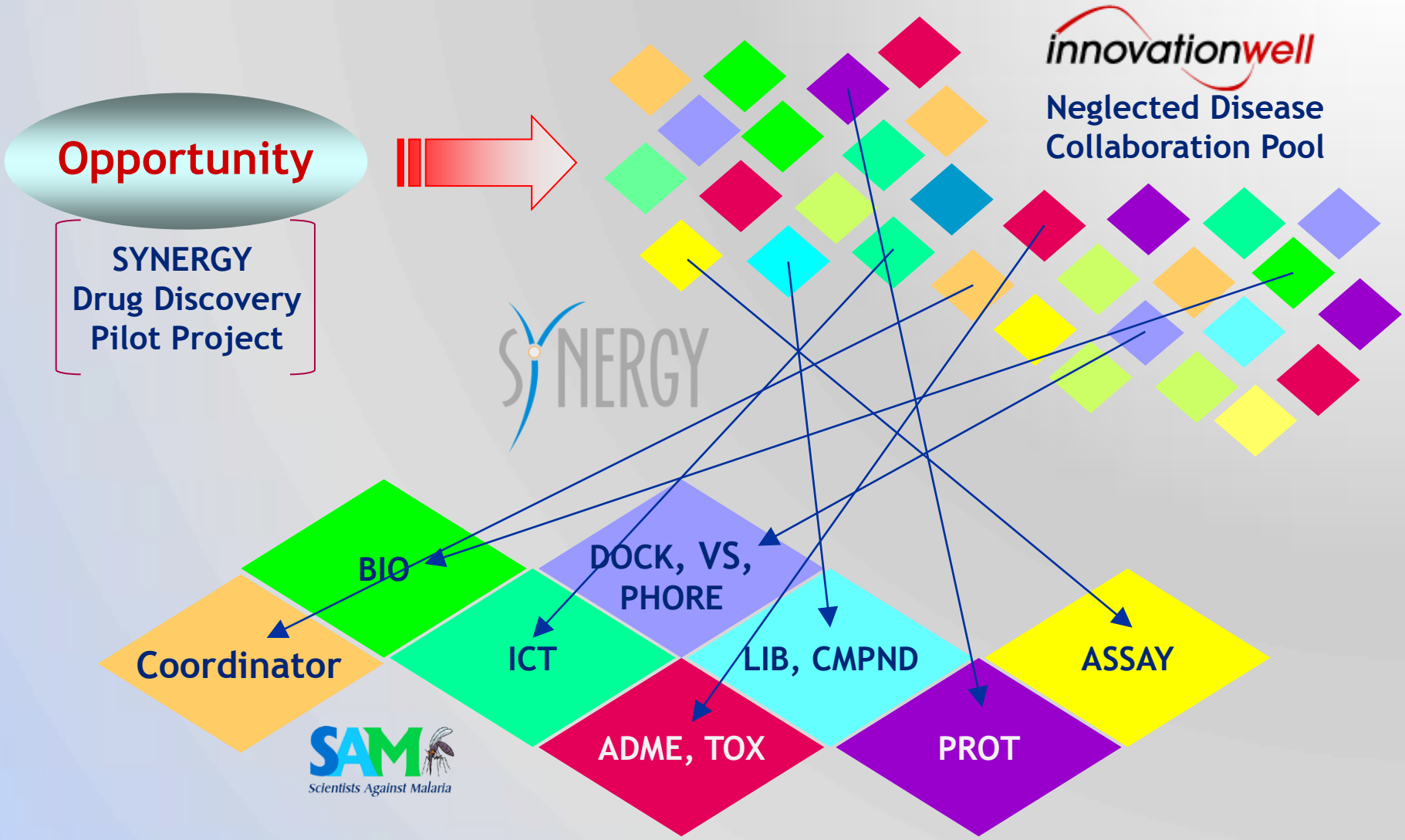
Drug Design, Informatics, Malaria



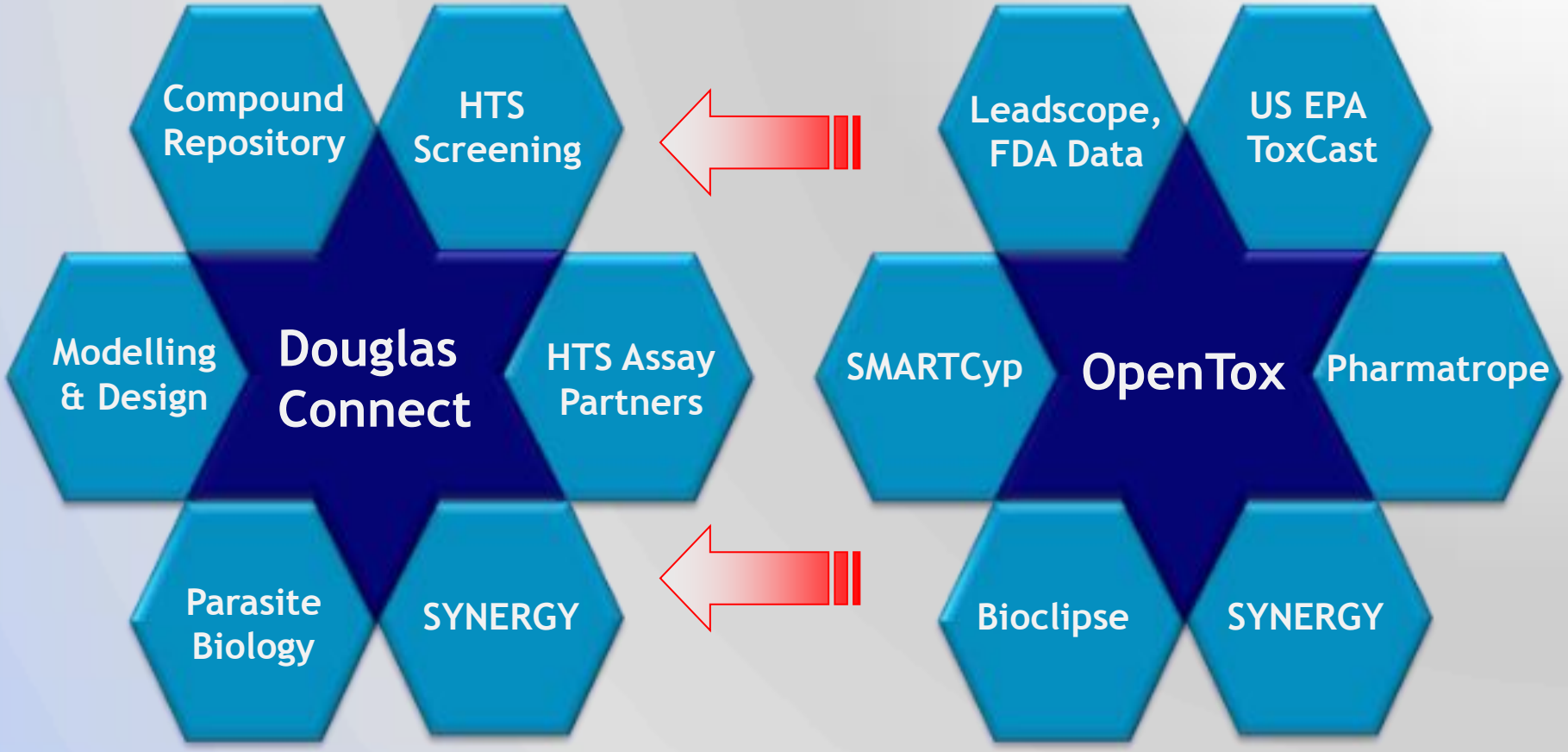
Malaria, Vaccine



Formation of VO from Collaboration Pool



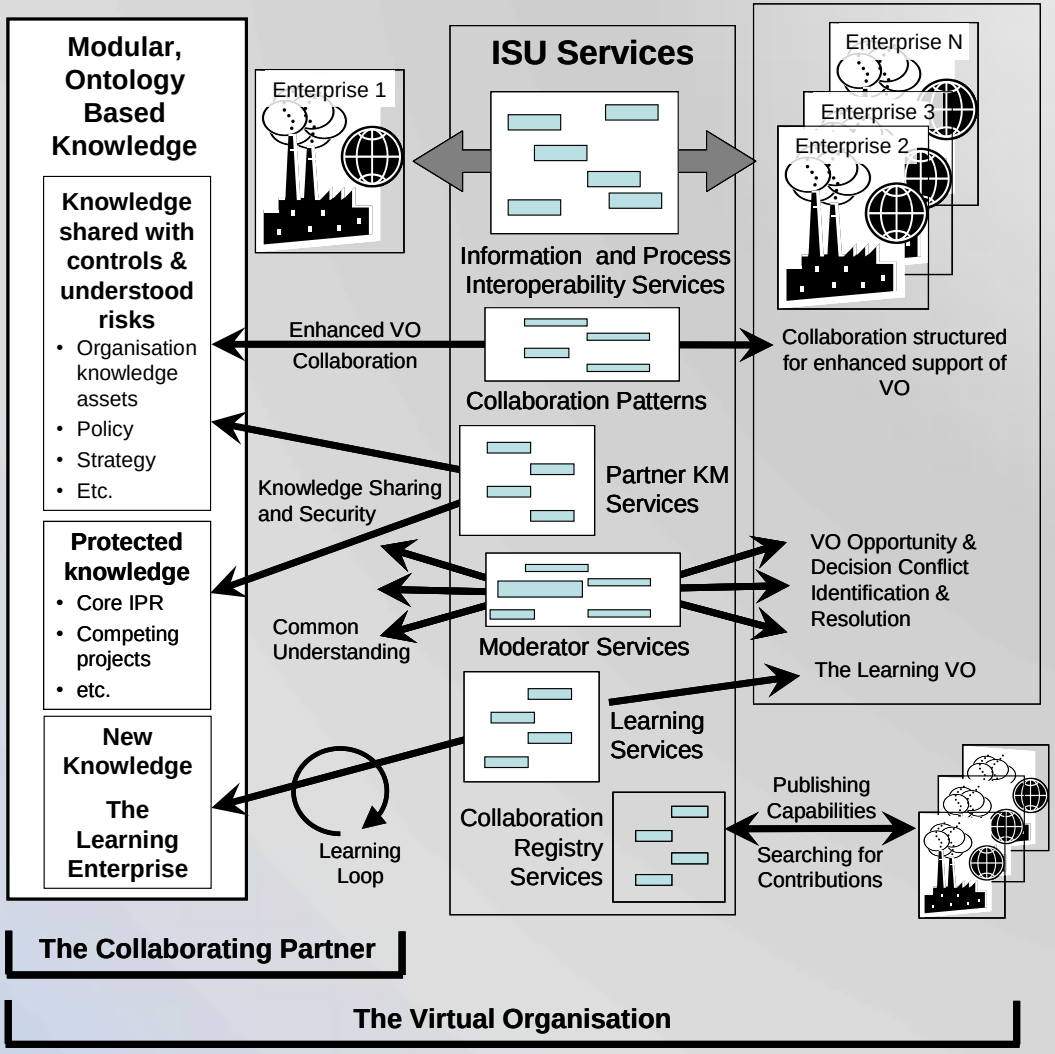
Virtual Organization Operational Pilots



Scientists Against Malaria VO

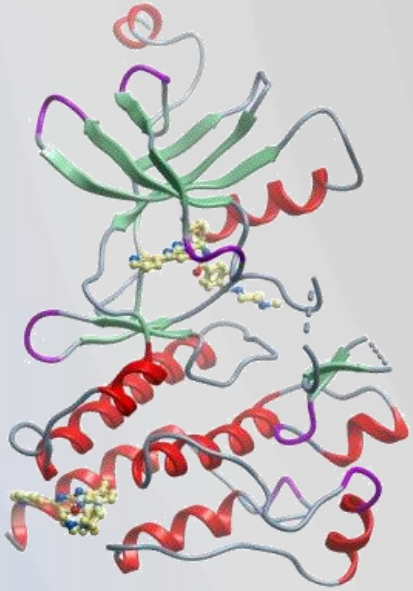
Predictive Toxicology VO

SYNERGY Collaboration Services



Operational Pilot 1 - Collaborative Drug Discovery

Target Protein Structure

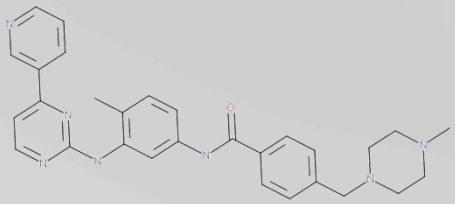


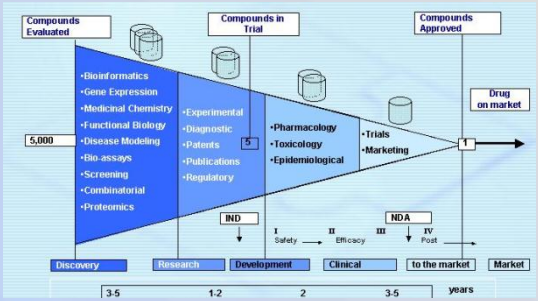
VO

- Drug Design Techniques
- Molecular Modelling
- Virtual Screening
- Biological Assays
- Synthesis or Acquisition
- Testing

Output result

Drug Leads





Drivers

- *Pharmaceutical Industry pressures on R&D environment*
- *Progressing innovation and discoveries for Neglected Diseases*

Scientists Against Malaria Founding Partners

- **Barry Hardy** & **Roman Affentranger** (Douglas Connect)
- **Alessandro Contini** (University of Milan)
- **Hugo Gutierrez de Teran** (Public Galician Foundation of Genomic Medicine)
- **Jeffrey Wiseman & Matt Clark** (Pharmatrope)
- **Jeff Spitzner** (Rescentris)
- **Ruben Papoian**, **William Seibel** & **Sandra Nelson** (Univ. of Cincinnati Drug Discovery Center)
- **Sharon Bryant** (Inte:Ligand)
- **Andrew Wilks** & **Isabelle Lucet** (Monash University)
- **Christian Doerig** Coordinator of the FP7 MALSIG project on signalling in Malarial parasites
- **Matteo Dal Peraro** (EPFL, Lausanne)

www.scientistsagainstmalaria.net

SAM

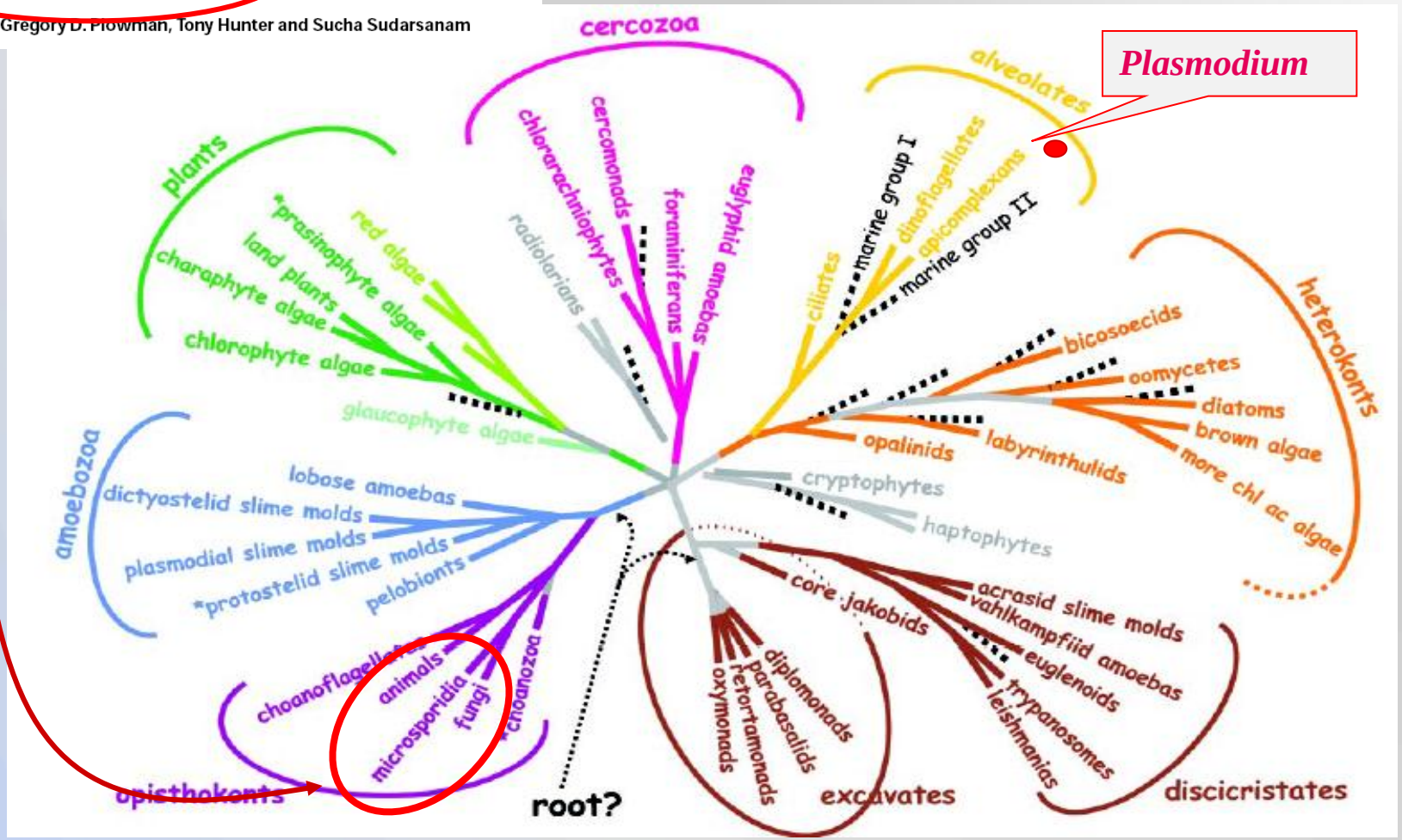
SYNERGY

Plasmodium Life Cycle & Kinome

514 Review TRENDS in Biochemical Sciences Vol.27 No.10 October 2002

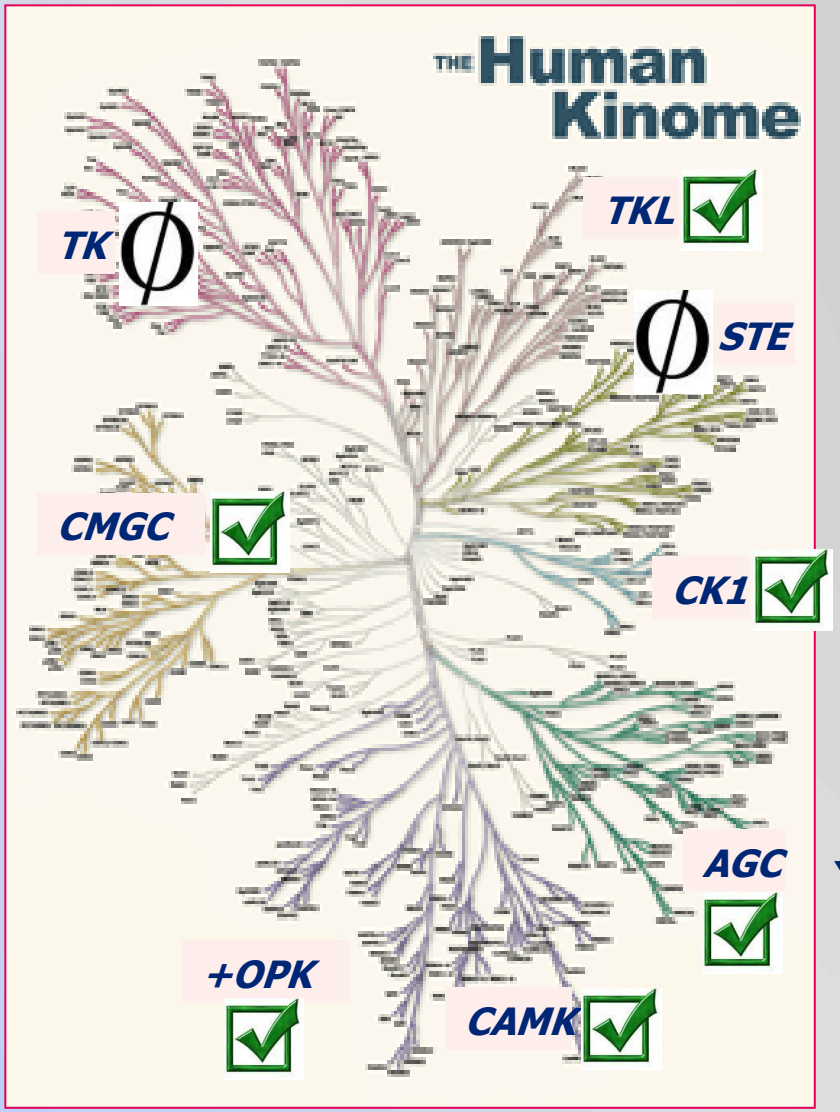
Evolution of protein kinase signaling from yeast to man

Gerard Manning, Gregory D. Plowman, Tony Hunter and Sucha Sudarsanam



Baldauf, Science, 2003

Plasmodium Life Cycle & Kinome



PlasmoDB mining

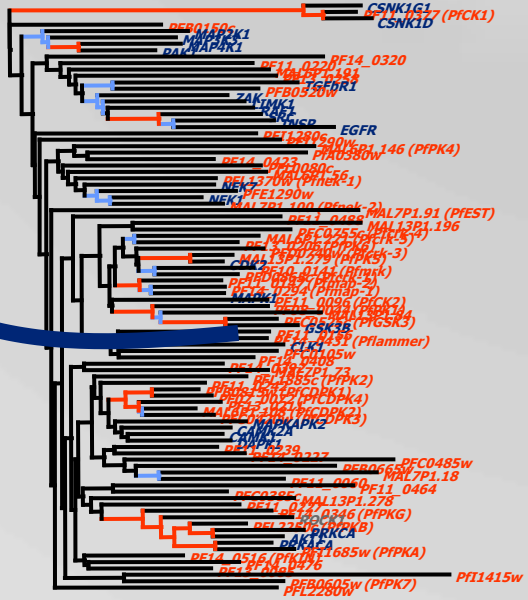
(HMM, BLAST, Gene Ontology prediction)

↓

Alignment with selected human PKs, manual edition

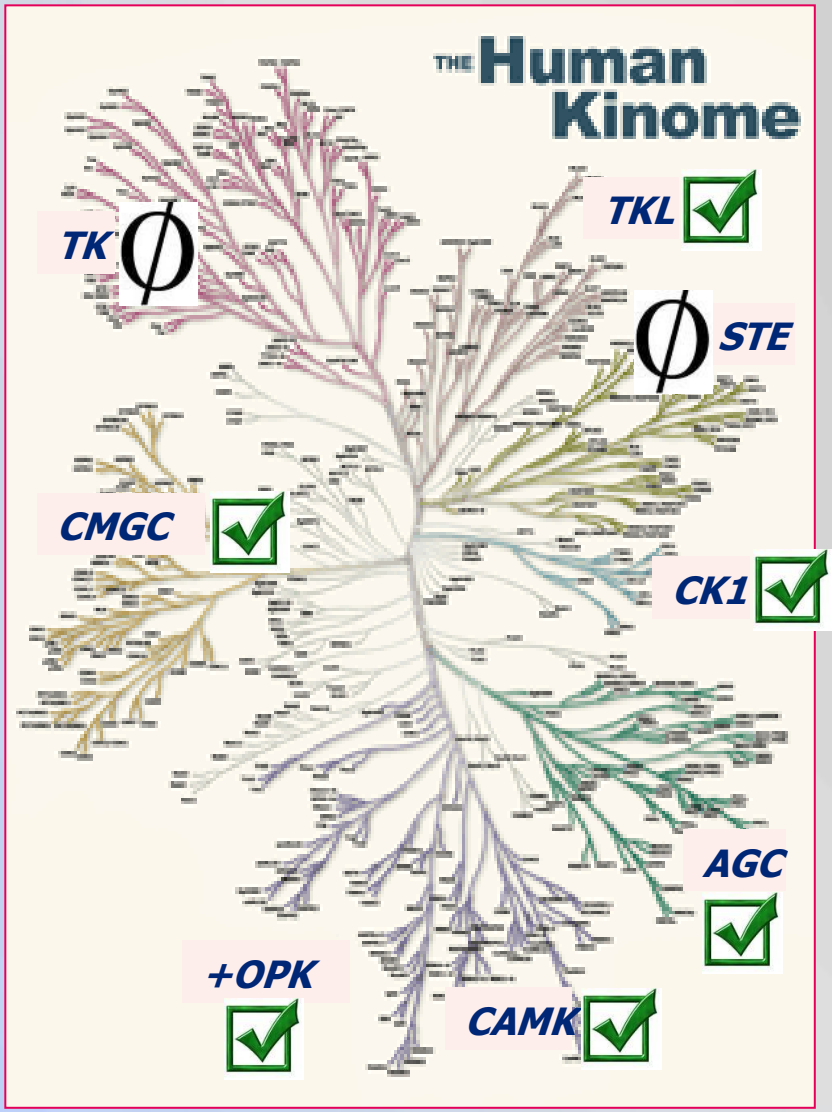
↓

Phylogenetic tree



- **518 protein kinases (2% of genes)**
- **Involved in essentially all cellular processes (30% of the proteome is phosphorylated)**

Plasmodium Life Cycle & Kinome



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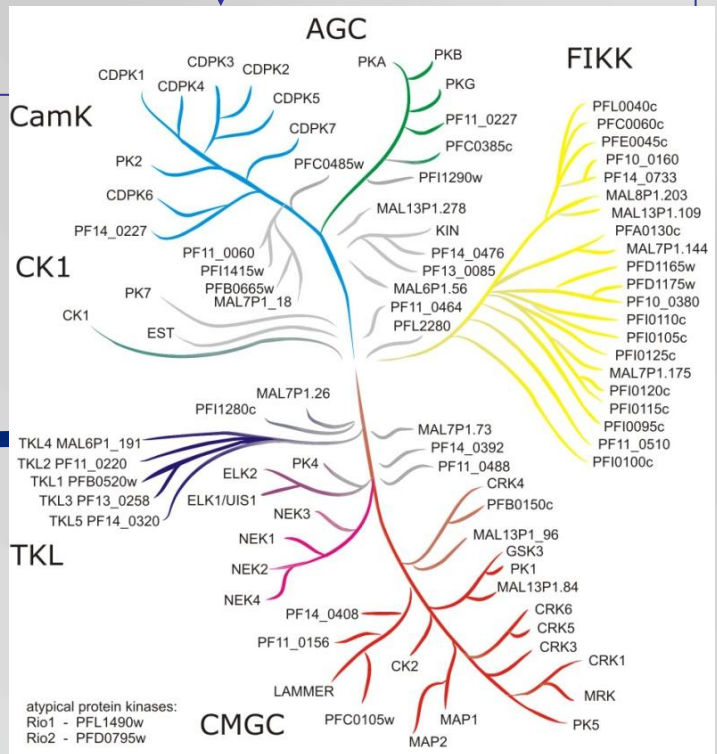

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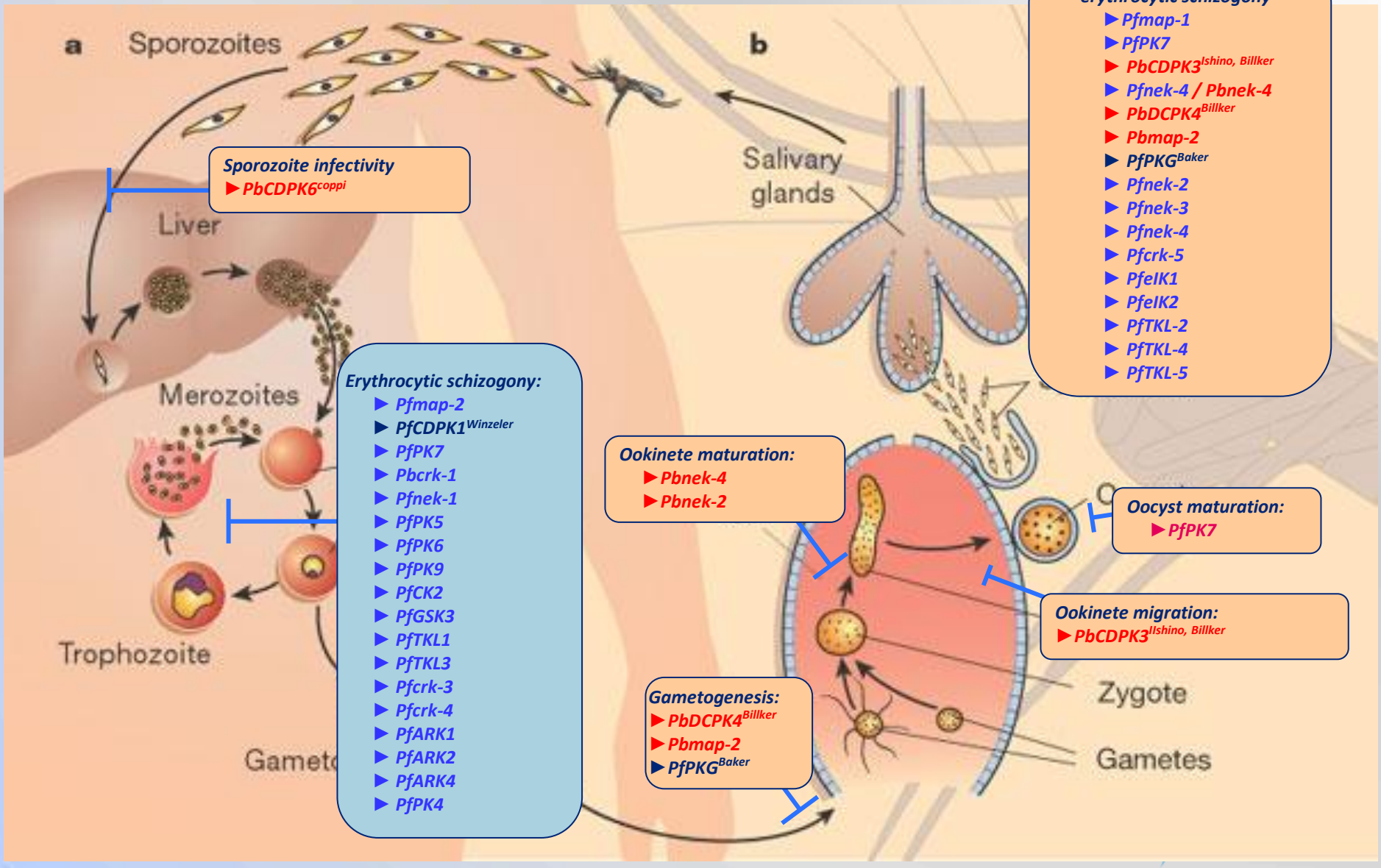
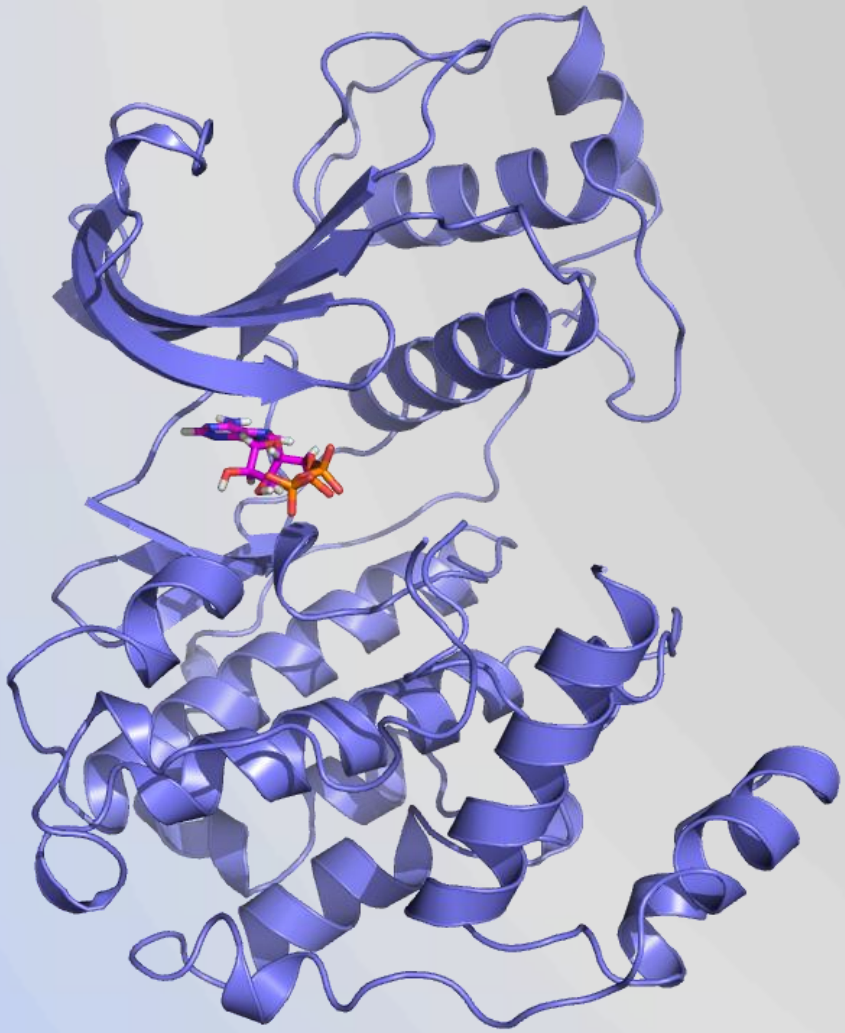
Plasmodium Life Cycle & Kinome



Target Model



- Starting point – no protein structure, no known ligand/inhibitor
- Initial model of PfMAP2 Kinase Protein built based on existing knowledge
- Library of Potential Inhibitors created (ca. 1.2 M structures)
- Virtual screening runs carried out at computing centres in Italy, Spain and USA
- Protein expressed in Monash, Australia and shipped to screening centre at Univ. Cincinnati where assays were developed and run

Homology Modelling

Alignment of Pfmap-2 with 1GOL and 1CM8

```
 _aln.p   70        80        90       100       110       120       130
1golA     ----------------AAAAAAGPEMVRGQVFDVGPRYTNLSYIGEGAYGMVCSAYDNLNKVRVAIRK
1cm8A     ---------------RSGFYRQEVTKTA---WEVRAVYRDLQPV------AVCSAVDGRTGAKVAIKK
pfmap2    DNISKNCNIVEKKNNKSKEEKINIKEAIIKNVKVPDNYEIKHLIGRGSYGYVYLAYDKNANKNVAIKK
 _consrvd                                  *   *            *  * *      *** *

1golA     I-SPFEHQTYCQRTLREIKILLRFRHENIIGINDIIR-APTIEQMKDVYIVQDLMETDLYKLLKTQ-H
1cm8A     LYRPFQSELFAKRAYRELRLLKHMRHENVIGLLDVFTPDETLDDFTDFYLVMPFMGTDLGKLMKHE-K
pfmap2    VNRMFEDLIDCKRILREITILNRLKSDYIIRLHDLIIPEDLL-KFDELYIVLEIADSDLKKLFKTPIF
 _consrvd     *       *  **   *        *   *             * *      ** ** *

1golA     LSNDHICYFLYQILRGLKYIHSANVLHRDLKPSNLLLNTTCDLKICDFGLARVADP------------
1cm8A     LGEDRIQFLVYQMLKGLRYIHAAGIIHRDLKPGNLAVNEDCELKILDFGLARQADS------------
pfmap2    LTEQHVKTILYNLLLGEKFIHESGIIHRDLKPANCLLNQDCSVKICDFGLARTINSDKDIHIVNDLEE
 _consrvd *         *  * *   **     ****** *   *  *  ** ******

1golA     --DHDHTG--------FLTEYVATRWYRAPEIMLNSKGYTKSIDIWSVGCILAEMLS-----------
1cm8A     --EM.--------------G.VVTRWYRAPEVILNWMRYTQTVDIWSVGCIMAEMIT-----------
pfmap2    KEENEEPGPHNKNLKKQLTSHVVTRWYRAPELILLQENYTNSIDIWSTGCIFAELLNMMKSHINNPTN
 _consrvd                     * ********  *    **   **** *** **

1golA     NRPIFPGK-----------------HYLDQLNHILGILGSPSQEDLNCIINLKARNYLLSLPHKNKVP
1cm8A     GKTLFKGS-----------------DHLDQLKEIMKVTGTPPAEFVQRLQSDEAKNYMKGLPELEKKD
pfmap2    RFPLFPGSSCFPLSPDHNSKKVHEKSNRDQLNIIFNVIGTPPEEDLKCITKQEVIKYIKLFPTRDGID
 _consrvd     * *                     ***  *    * *  *           *    *

1golA     WNRLFPNADSKALDLLDKMLTFNPHKRIEVEQALAHPYLEQYYDPSDEPIAEAPFKFDMEL-DDLPKE
1cm8A     FASILTNASPLAVNLLEKMLVLDAEQRVTAGEALAHPYFESLH-------QVQKYDDS------RTLD
pfmap2    LSKKYSSISKEGIDLLESMLRFNAQKRITIDKALSHPYLKDVRKENLENFSTEKIILPFDDWMVLSET
 _consrvd               **  **      *     ** ***
```

PfMAP2 modelling

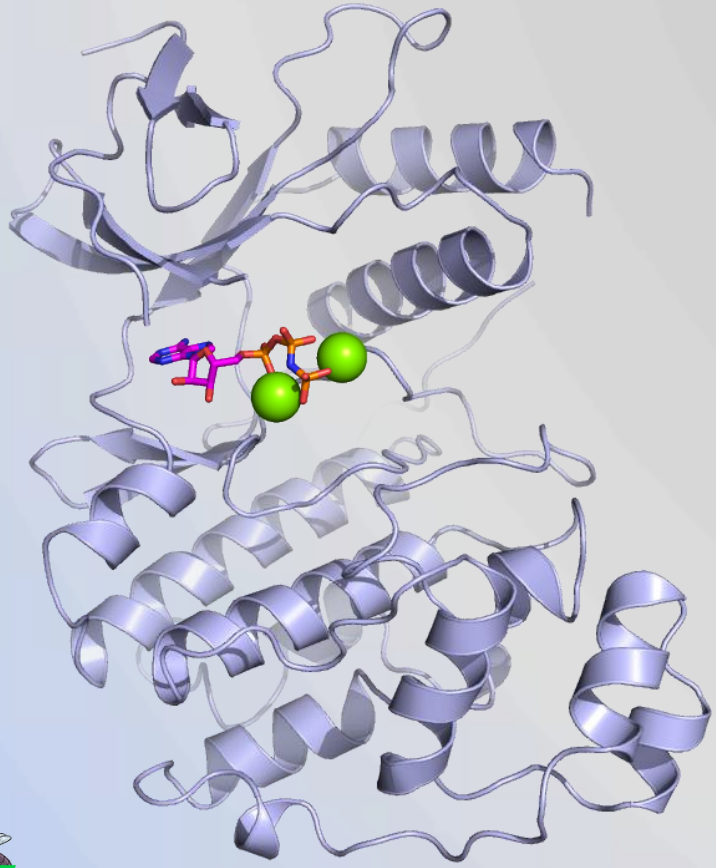
Three template pdbs selected:

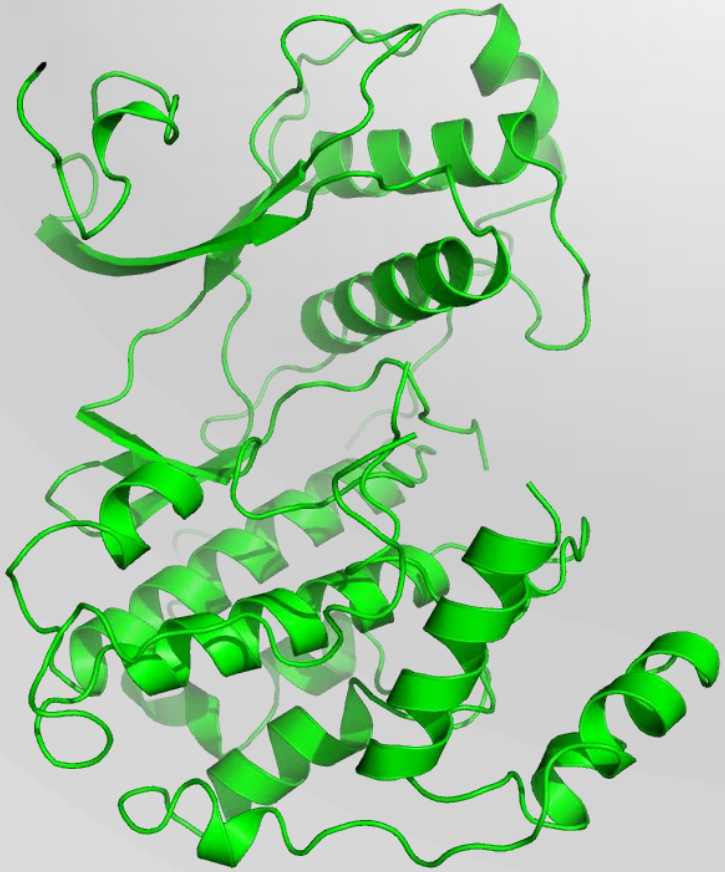
3N9X_PRE-RELEASE.pdb

PfMAP2 modelling

Three template pdbs selected:

1CM8.pdb

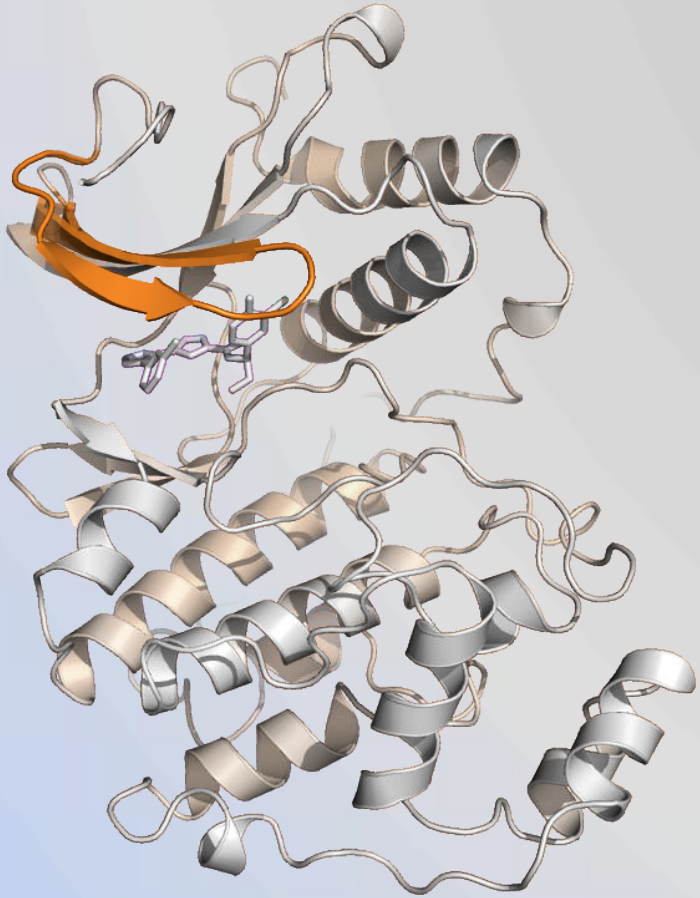


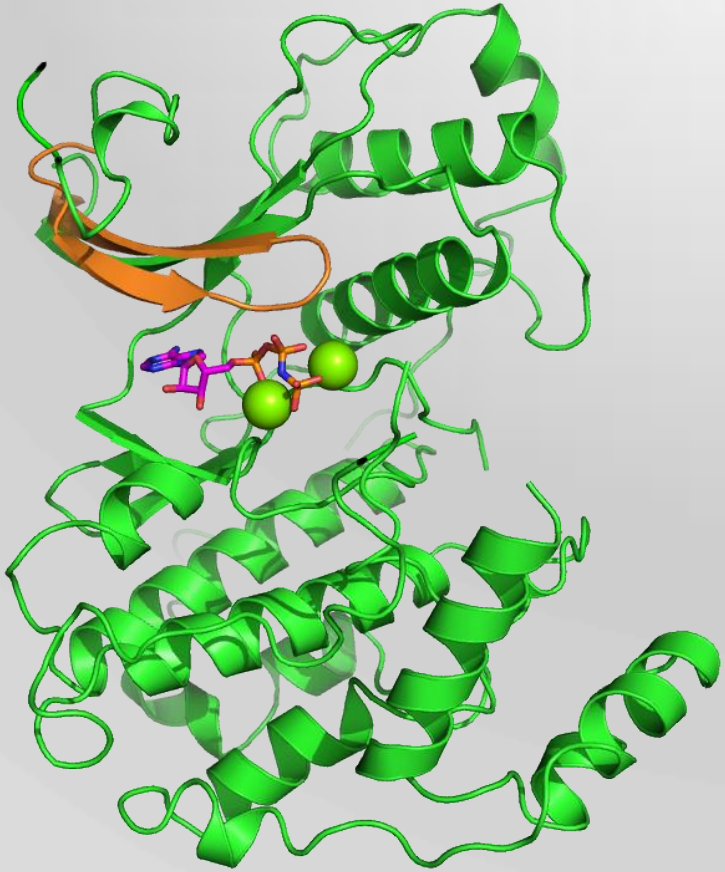


PfMAP2 modelling

Three template pdbs selected:

2OJJ.pdb





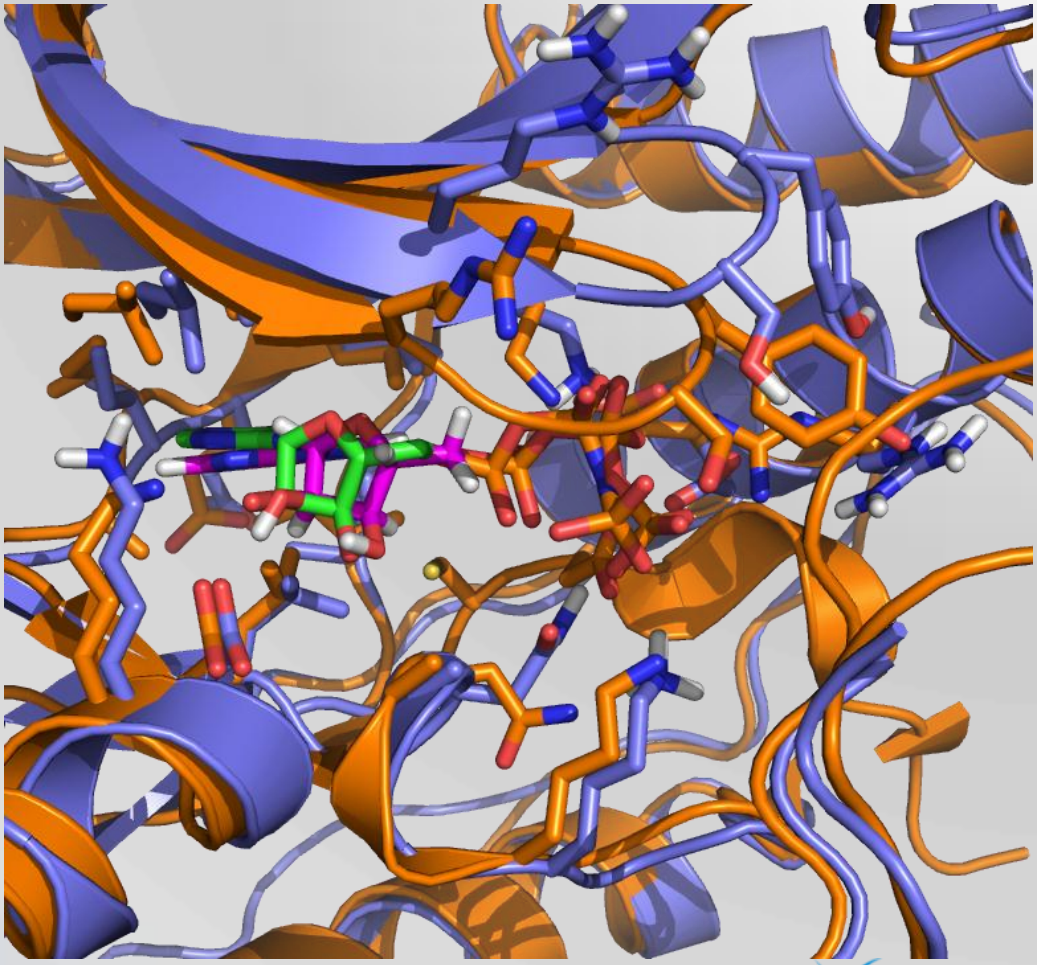
PfMAP2 Crystal Structure Model Comparison

3NIE.pdb protein structure by SGC was released August 11, 2010

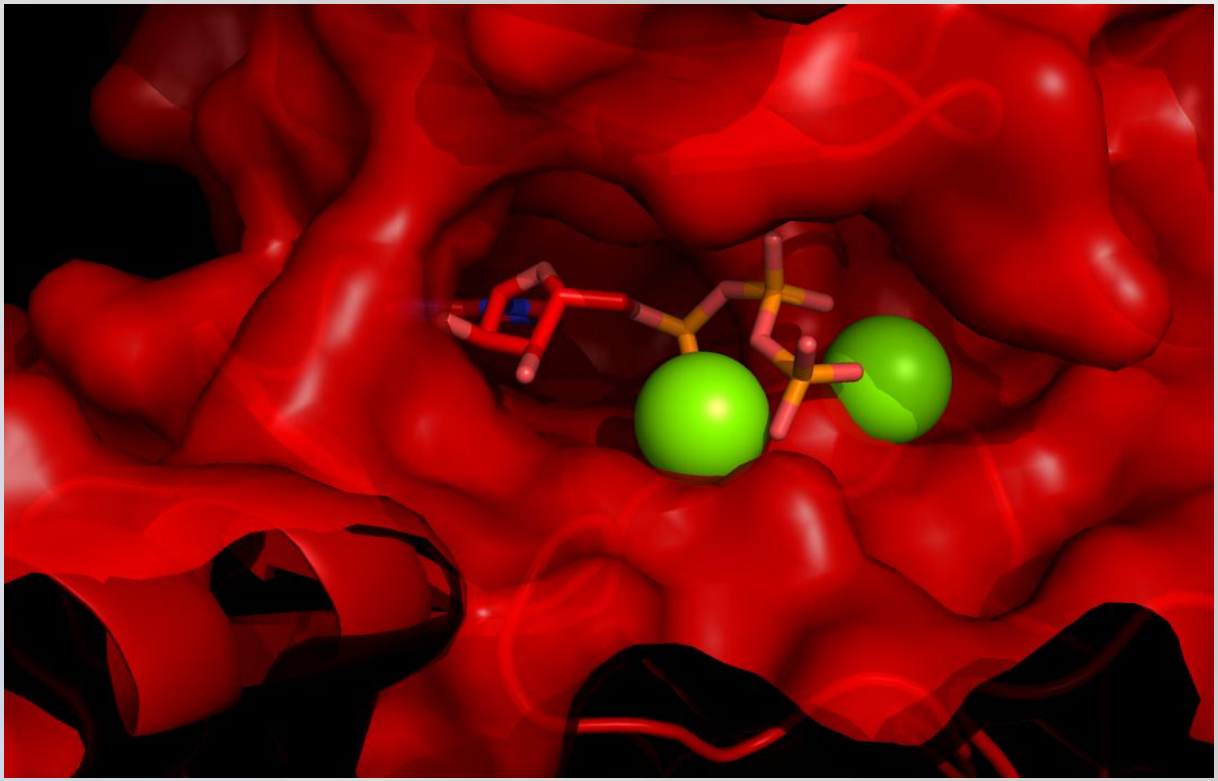
Overall, our model was quite accurate

Conformation of ATP was modelled well

Binding pocket residues were mostly ok

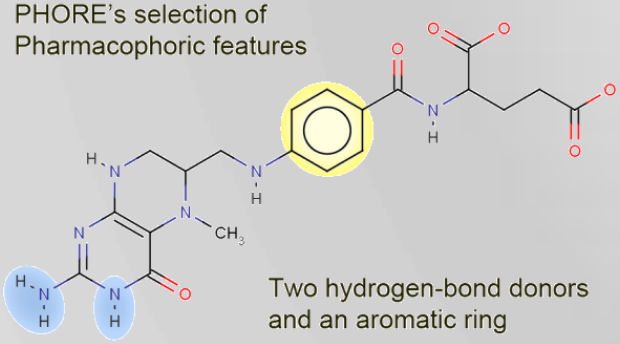


Binding Pocket



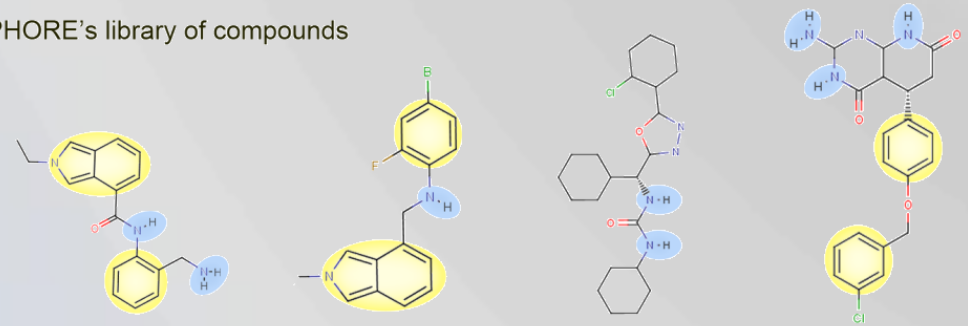
Pharmacophore-based Screening

PHORE's selection of
Pharmacophoric features



Two hydrogen-bond donors
and an aromatic ring

PHORE's library of compounds



Compound-ID 001
aromatic ring
2 donors

Compound-ID 002
Only one donor

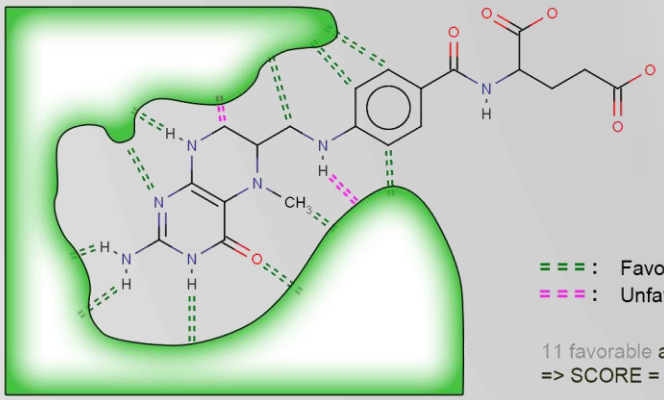
Compound-ID 003
No aromatic ring

Compound-ID 004
aromatic ring
2 donors

PHORE's activity hits prediction: compound-IDs 001 and 004

Dock Screening Prediction

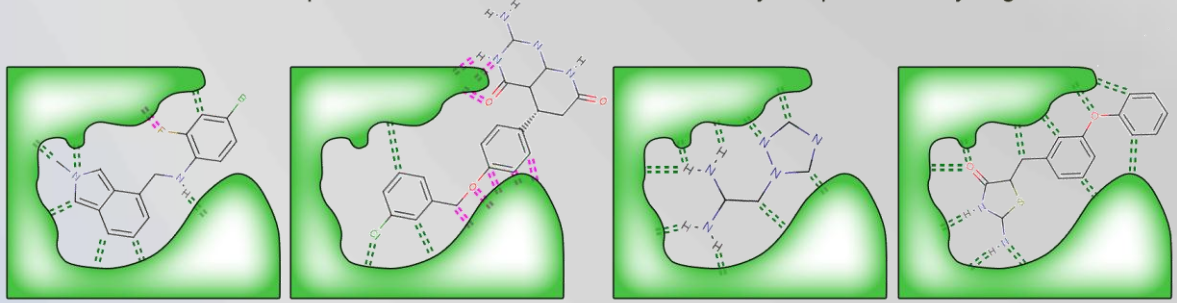
γ-synergine bound to synergase (schematic depiction)



= = = : Favorable (attractive) interactions
= = = : Unfavorable (repulsive) interactions

11 favorable and 2 unfavorable
=> SCORE = 9

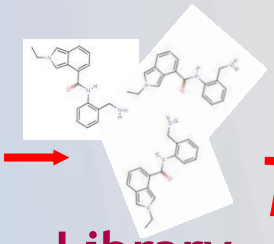
Each member of DOCK's library of compounds is placed in the binding pocket of synergase in an oreintation that optimizes the interaction between the library compound and synergase



Compound-ID 002	Compound-ID 004	Compound-ID 005	Compound-ID 006
7 favorable	3 favorable	9 favorable	11 favorable
1 unfavorable	8 unfavorable	0 unfavorable	0 unfavorable
SCORE = 6	SCORE = -5	SCORE = 9	SCORE = 11

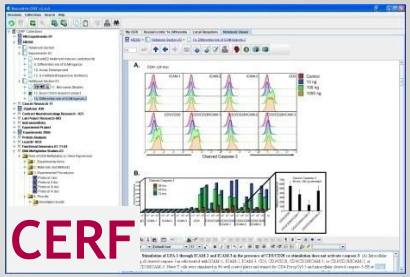
DOCK's activity hits prediction: compound-IDs 005 and 006

SAM Workflow

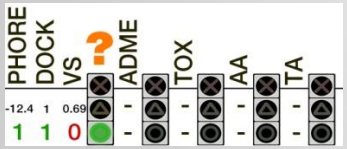


Library

Data

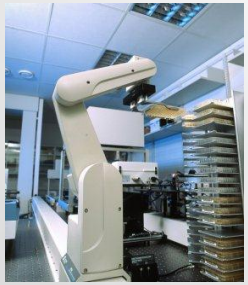


CERF



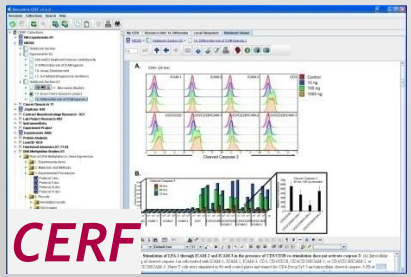
Refine Predictions

SYNERGY



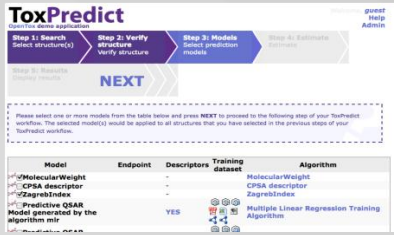
Binding Assay

Data



CERF

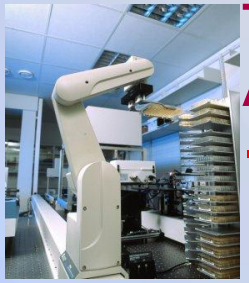
OpenTox



Toxicity Predictions

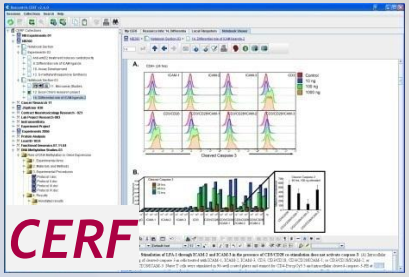
Refine Predictions

SYNERGY



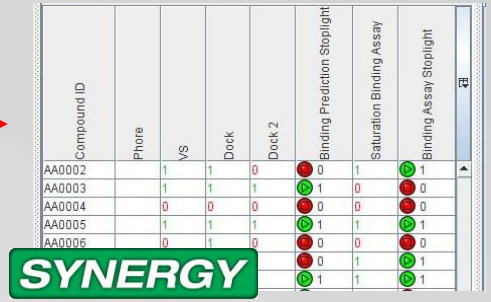
Toxicity Assay

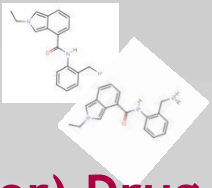
Data



CERF

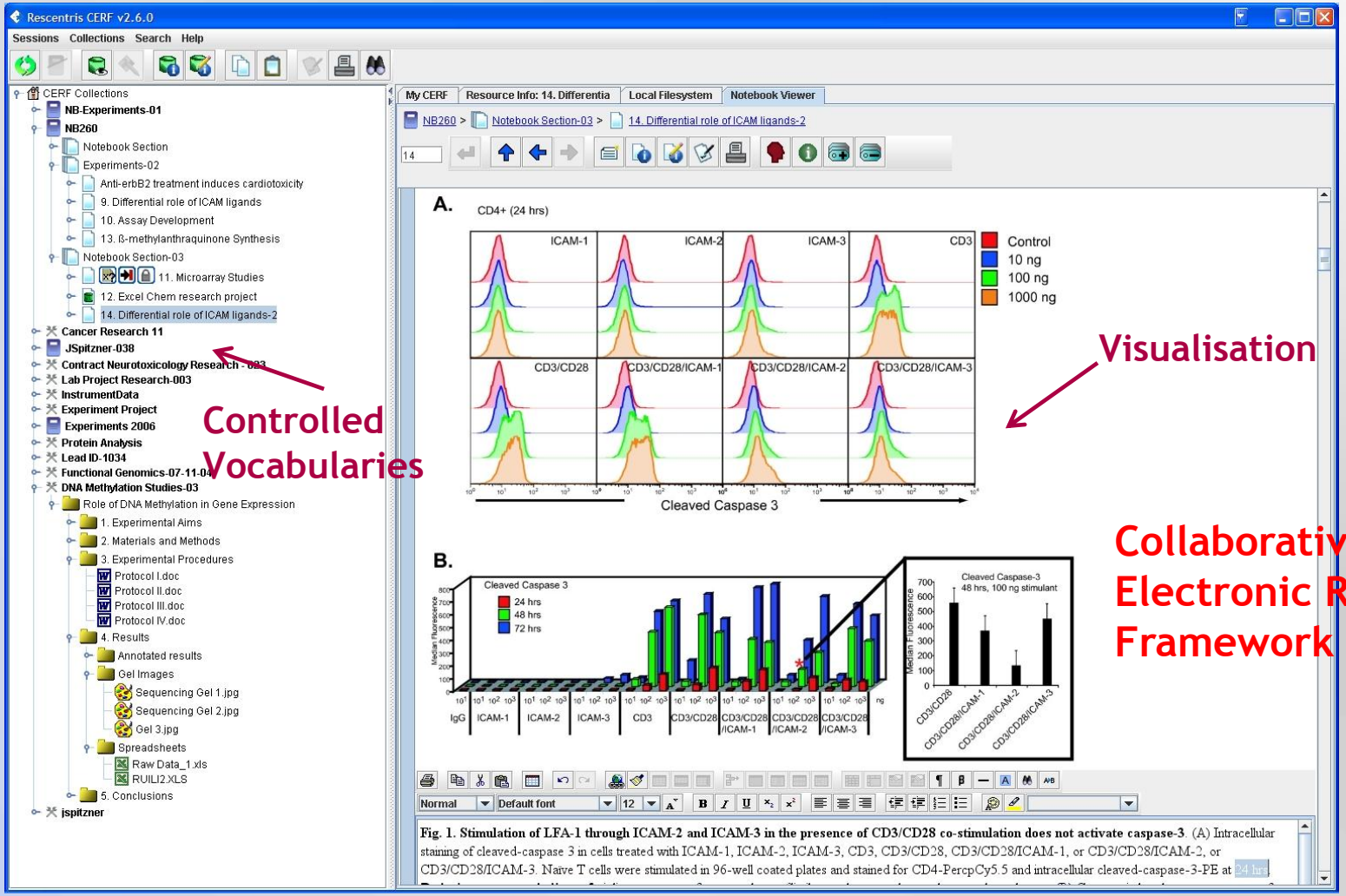
Decision Dashboard





(Safer) Drug Leads

Data Entry & Analysis



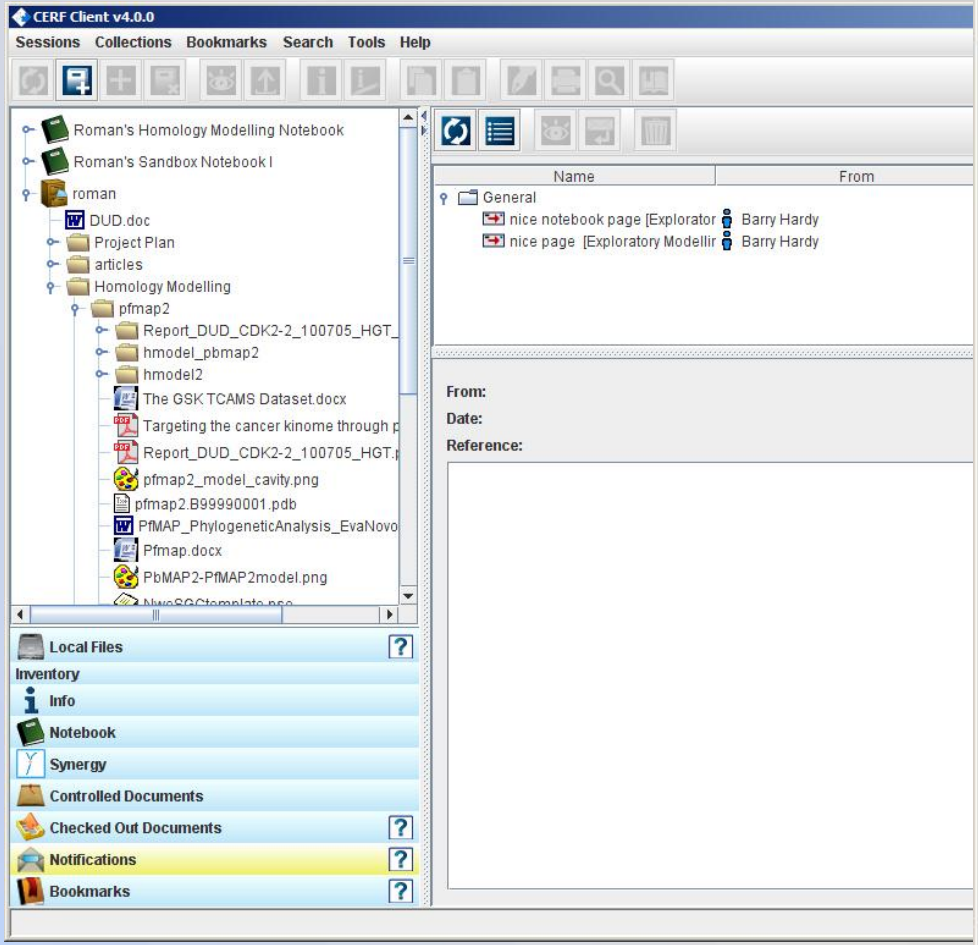
Controlled Vocabularies

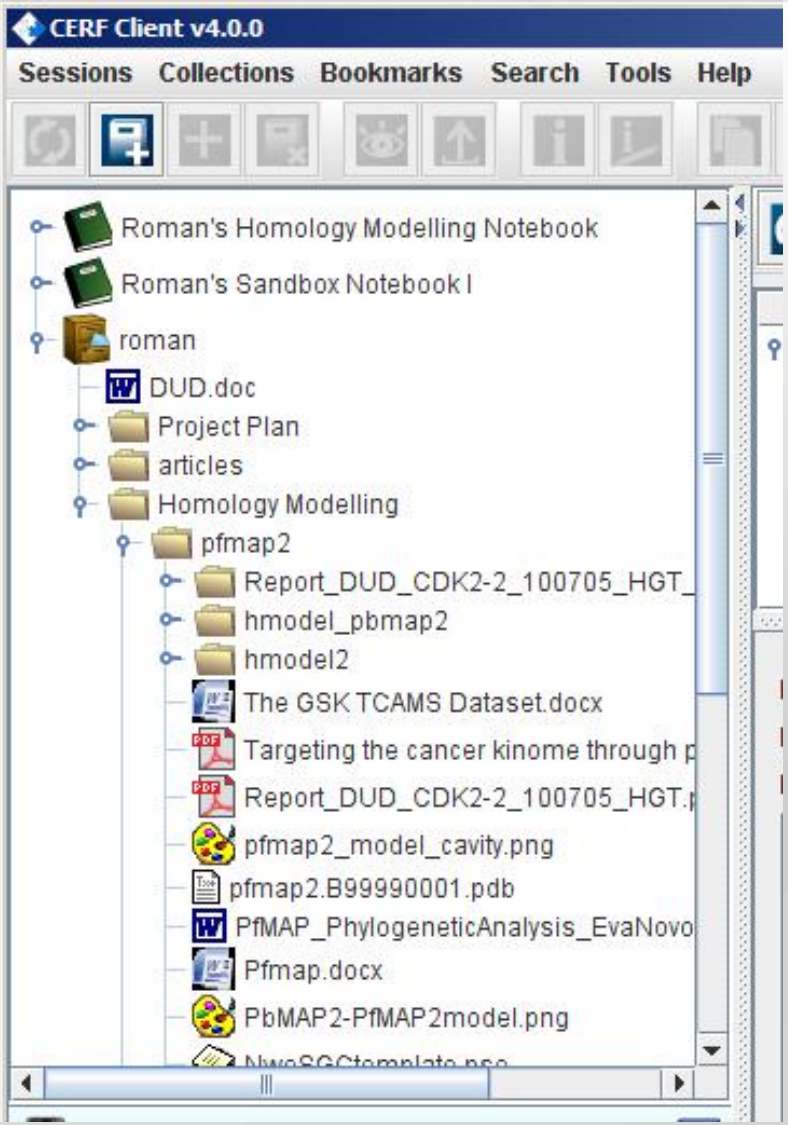
Visualisation

Collaborative Electronic Research Framework (CERF)

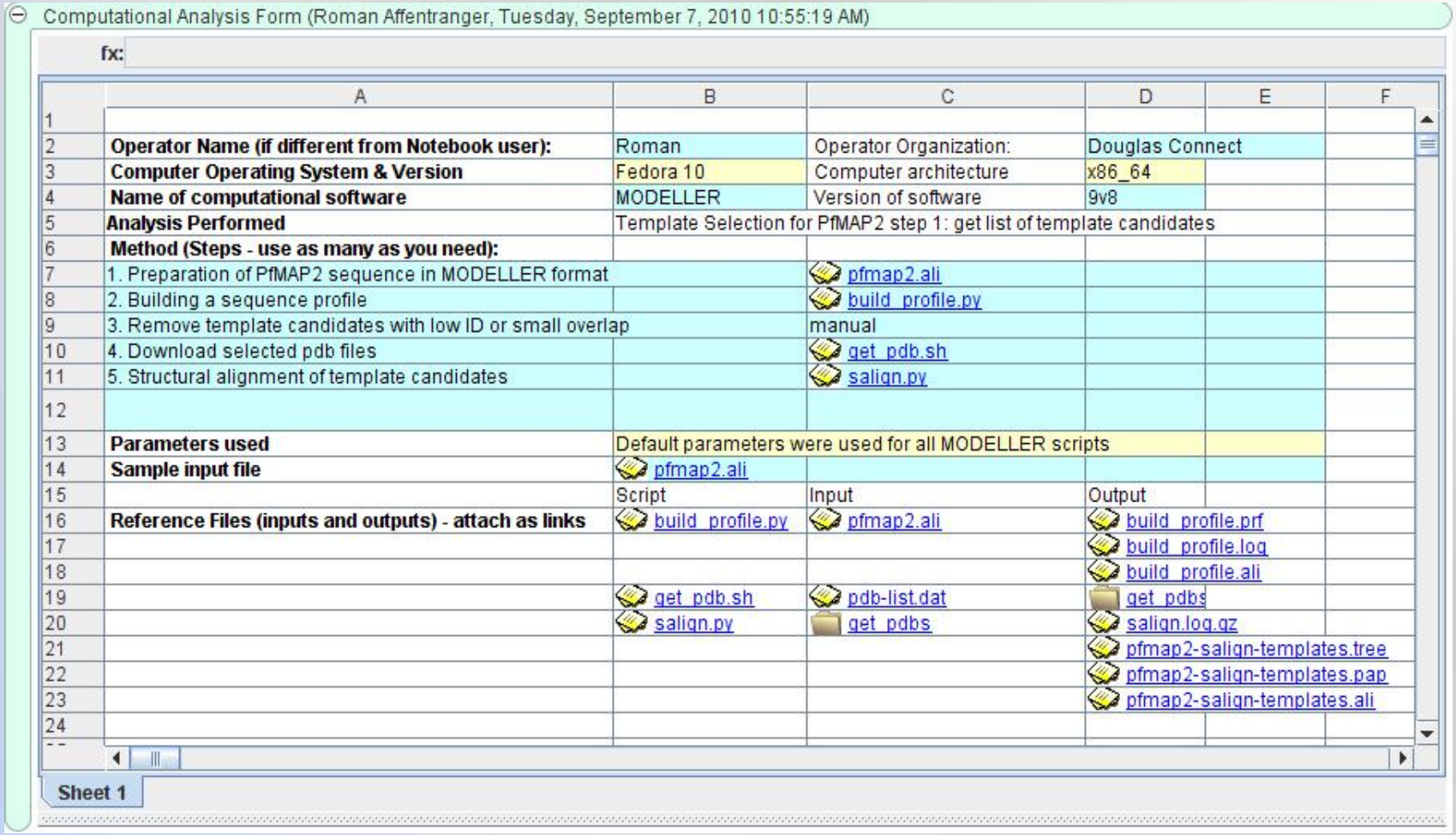
www.rescentris.com

File cabinets to store data etc





Template Spreadsheets to Document Computations



Computational Analysis Form (Roman Affentranger, Tuesday, September 7, 2010 10:55:19 AM)

fx:

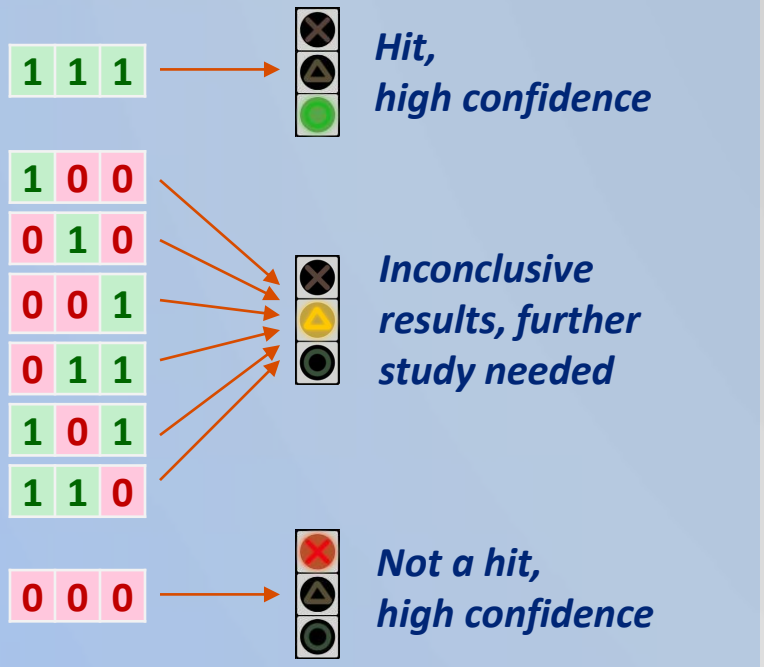
	A	B	C	D	E	F
1						
2	**Operator Name (if different from Notebook user):**	Roman	Operator Organization:	Douglas Connect		
3	**Computer Operating System & Version**	Fedora 10	Computer architecture	x86_64		
4	**Name of computational software**	MODELLER	Version of software	9v8		
5	**Analysis Performed**	Template Selection for PfMAP2 step 1: get list of template candidates				
6	**Method (Steps - use as many as you need):**					
7	1. Preparation of PfMAP2 sequence in MODELLER format		pfmap2.ali			
8	2. Building a sequence profile		build_profile.py			
9	3. Remove template candidates with low ID or small overlap		manual			
10	4. Download selected pdb files		get_pdb.sh			
11	5. Structural alignment of template candidates		salign.py			
12						
13	**Parameters used**	Default parameters were used for all MODELLER scripts				
14	**Sample input file**	pfmap2.ali				
15		Script	Input	Output		
16	**Reference Files (inputs and outputs) - attach as links**	build_profile.py	pfmap2.ali	build_profile.prf		
17				build_profile.log		
18				build_profile.ali		
19		get_pdb.sh	pdb-list.dat	get_pdbs		
20		salign.py	get_pdbs	salign.log.gz		
21				pfmap2-salign-templates.tree		
22				pfmap2-salign-templates.pap		
23				pfmap2-salign-templates.ali		
24						

Sheet 1

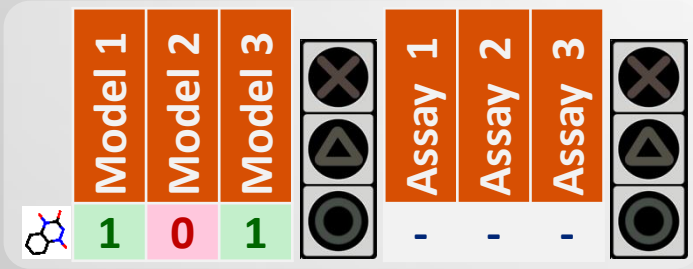
SAM ICT Architecture

Resolving Inconclusives

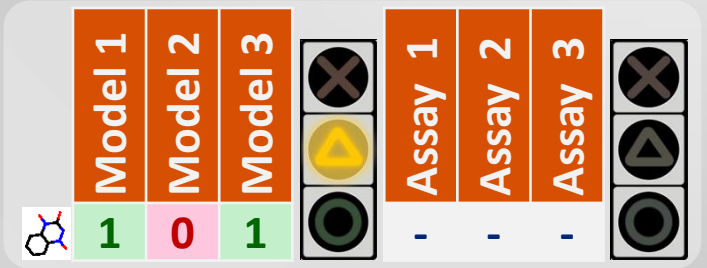
Recommendation Rules:



ELN

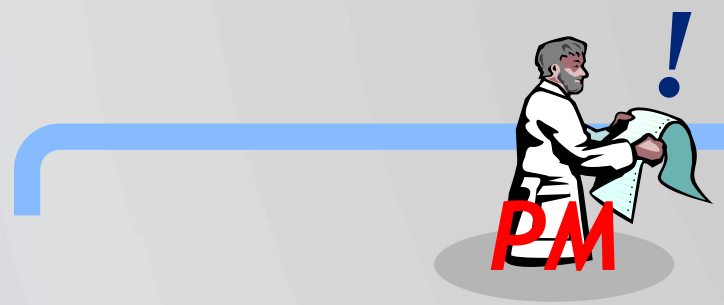


Synergy



OpenTox

Resolving Inconclusives



?

ELN

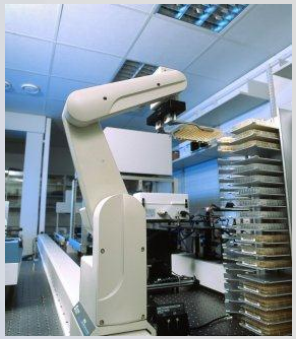
Model 1	Model 2	Model 3	Assay 1	Assay 2	Assay 3
1	0	1	-	-	-

Synergy

Model 1	Model 2	Model 3	Assay 1	Assay 2	Assay 3
1	0	1	-	-	-

OpenTox

Resolving Inconclusives



ELN

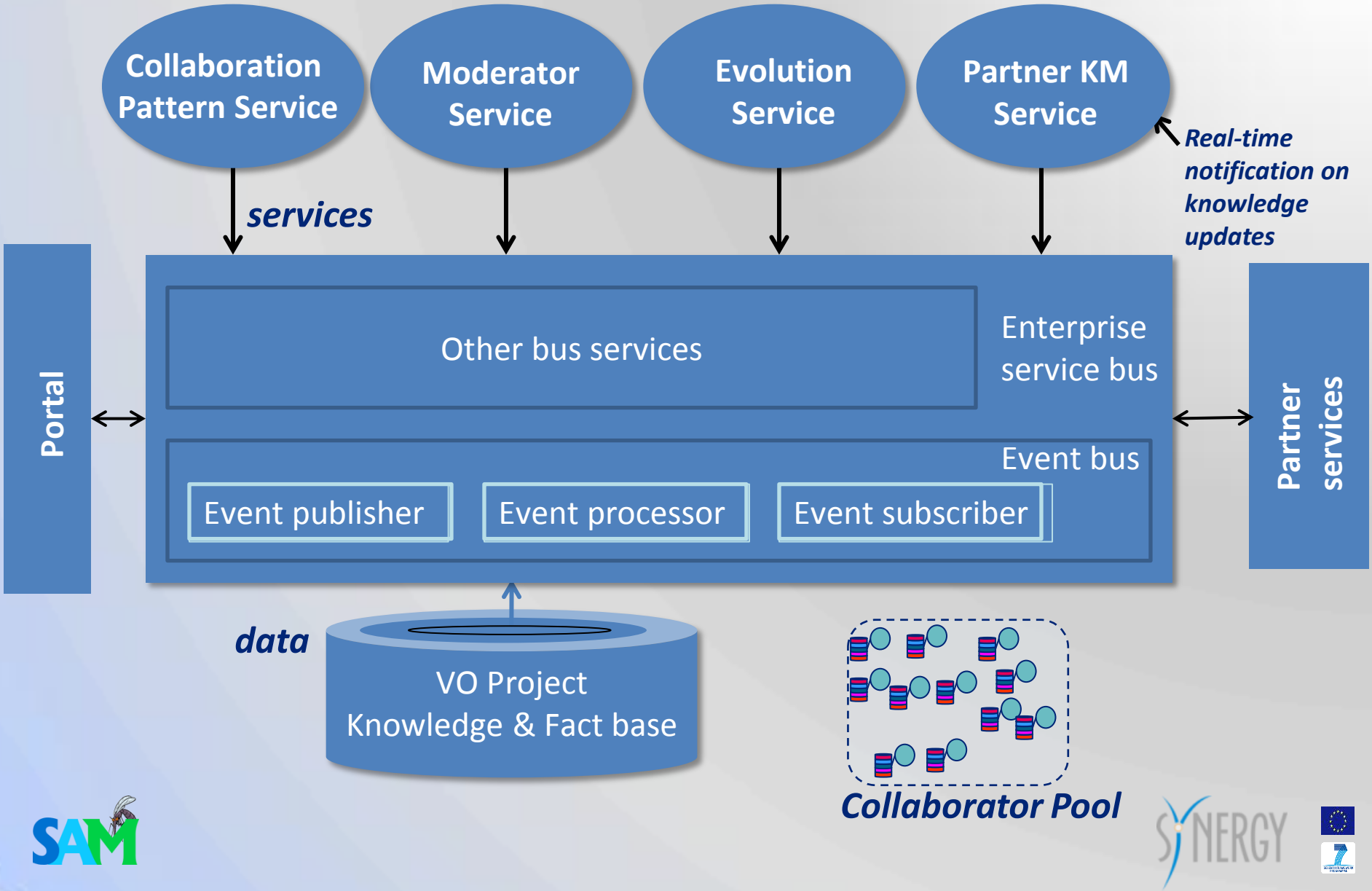
Model 1	Model 2	Model 3	Assay 1	Assay 2	Assay 3
1	0	1	-	1	1

Synergy

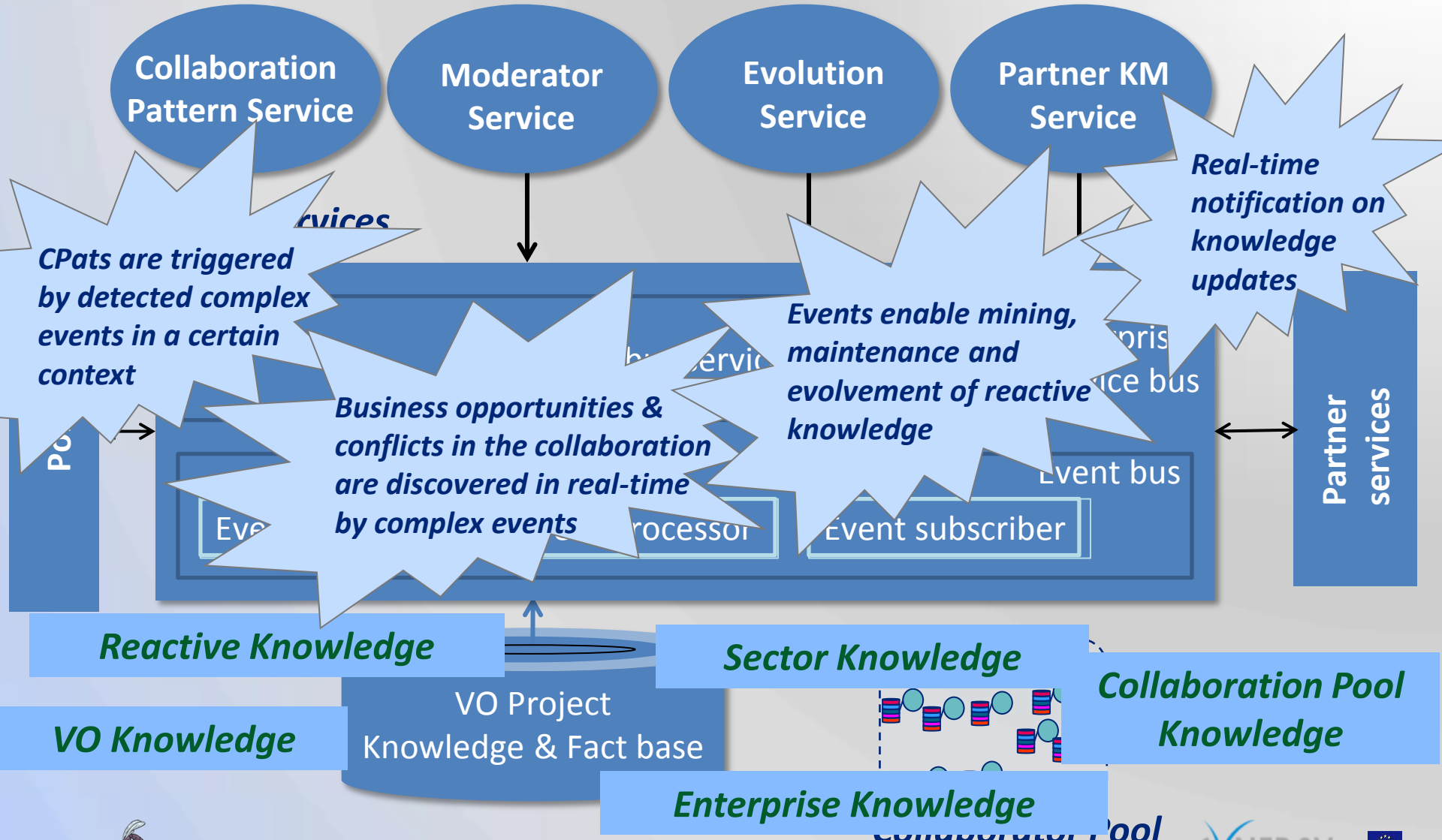
Model 1	Model 2	Model 3	Assay 1	Assay 2	Assay 3
1	0	1	-	-	-

OpenTox

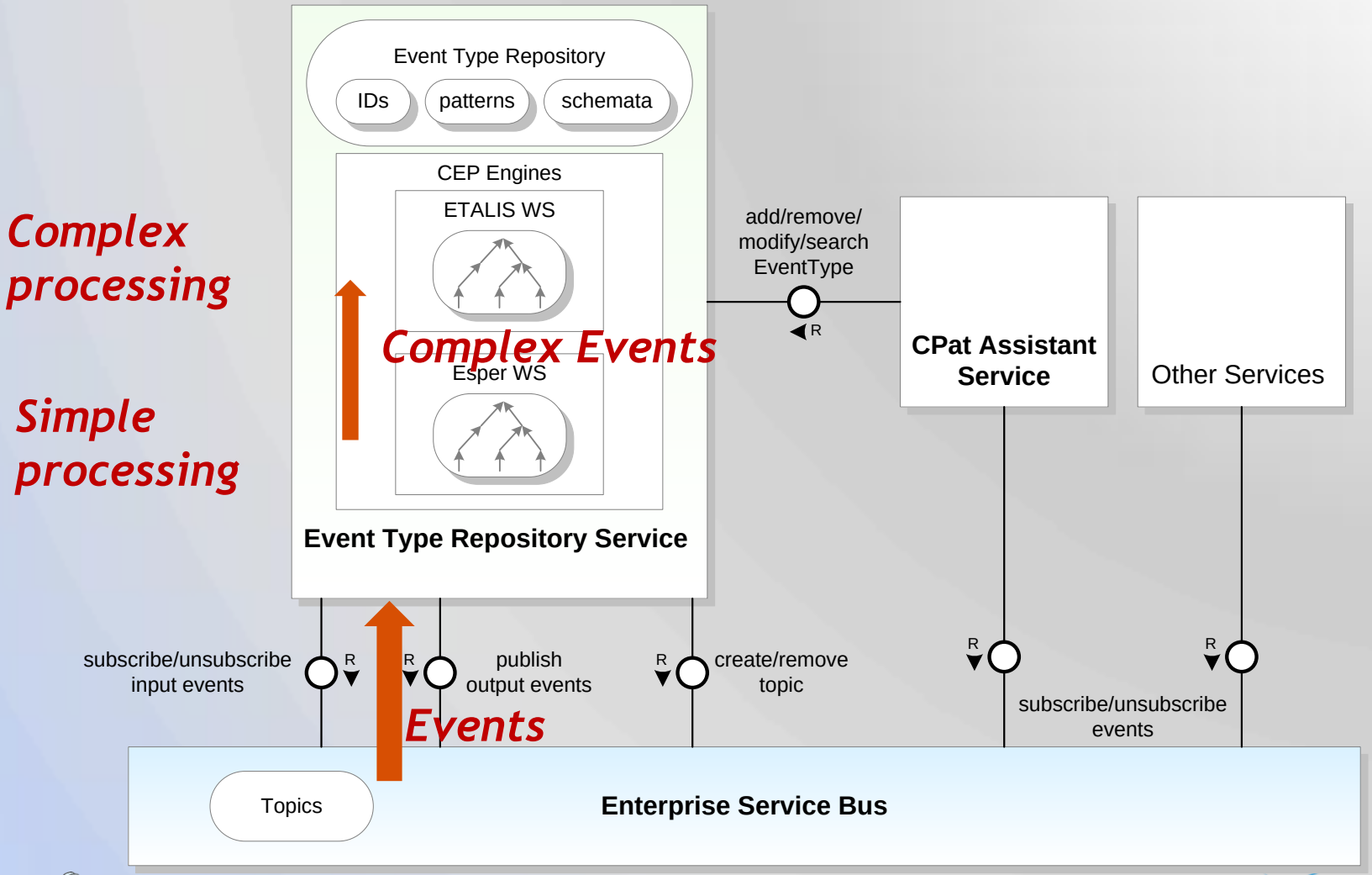
SYNERGY Service Support



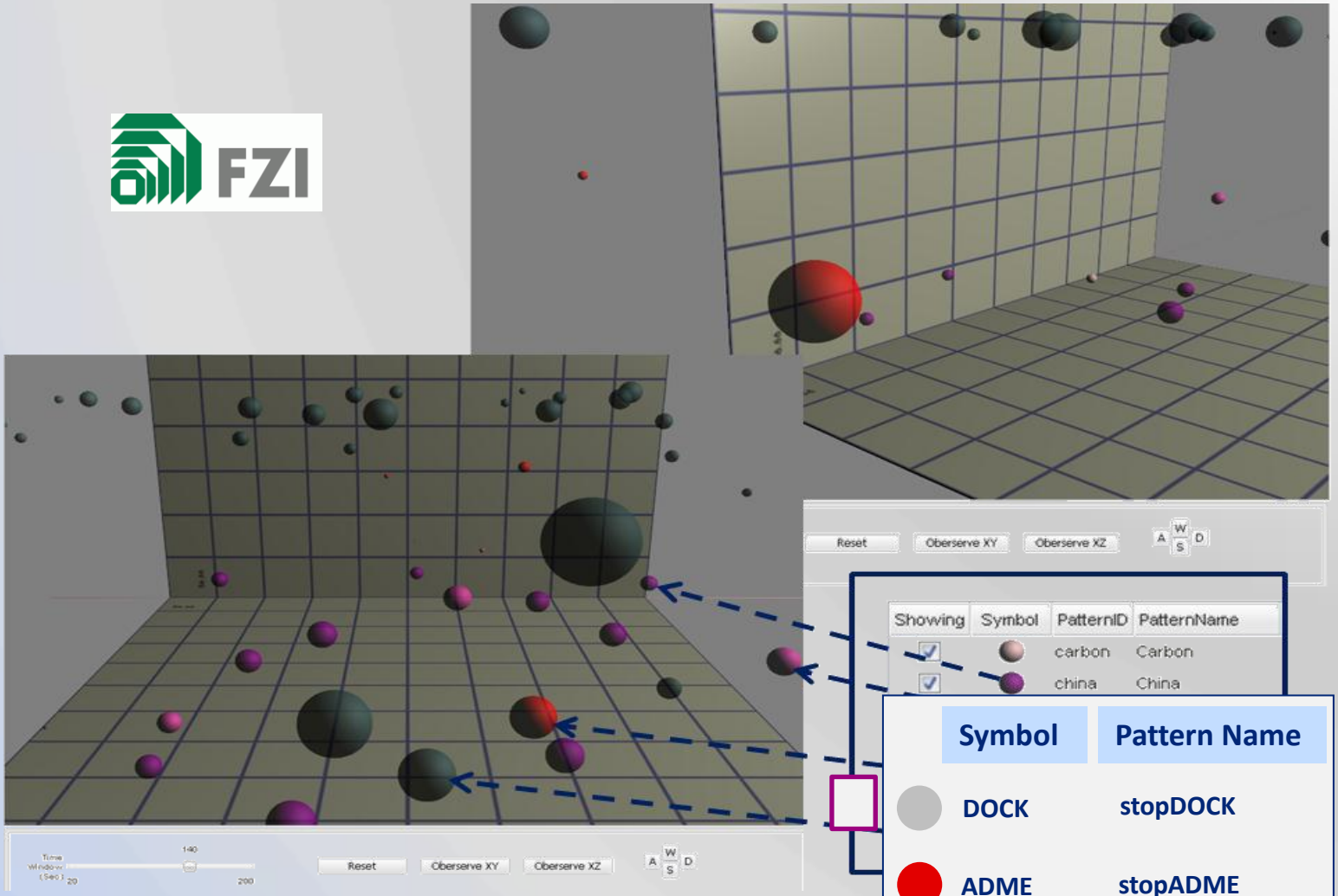
SYNERGY Service Support



SYNERGY Complex Event Processing

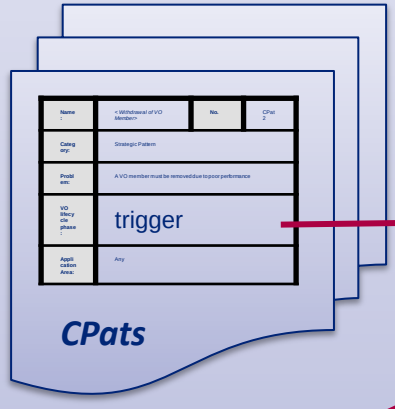


Complex Events Stream



Collaboration Patterns

How are the building blocks of communication (ie. events) identified?



events from trigger definitions

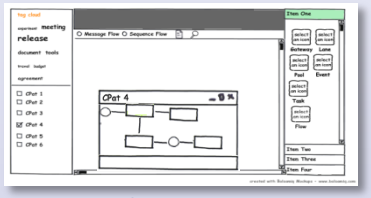
other communication primitives in SYNERGY

Where are they represented?

Event Type Repository

1. Identifyer
2. Pattern
3. Schema

Where are they put to use?

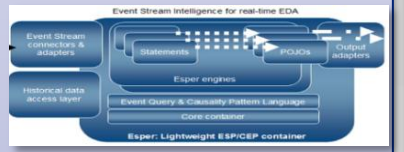


CPat Editor

pub/sub

PETALS

PEtALs ESB



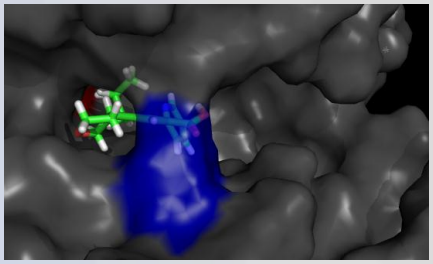
Esper CEP

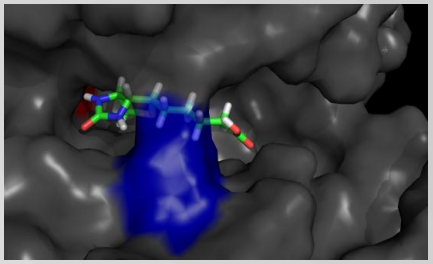
ETALIS iCEP

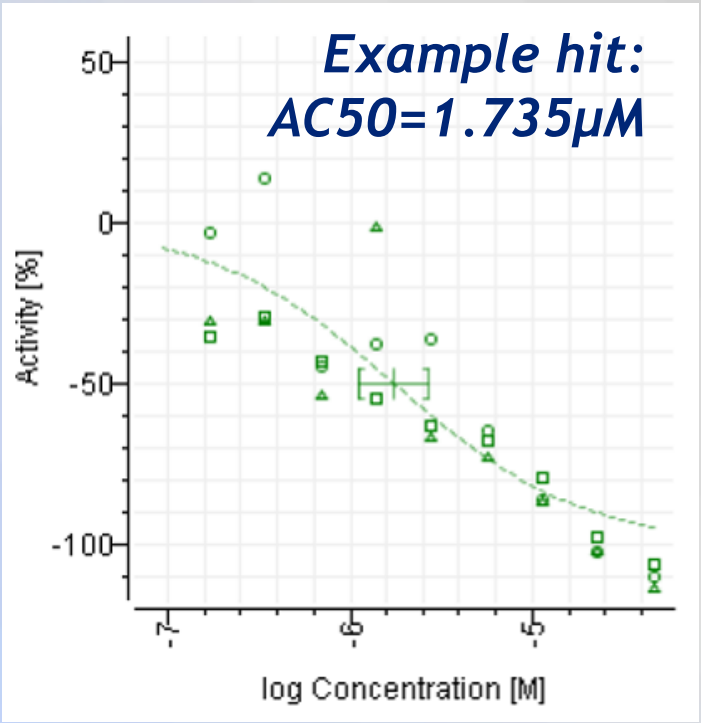
Who are the end consumers?

SYNERGY Services

Preliminary Results







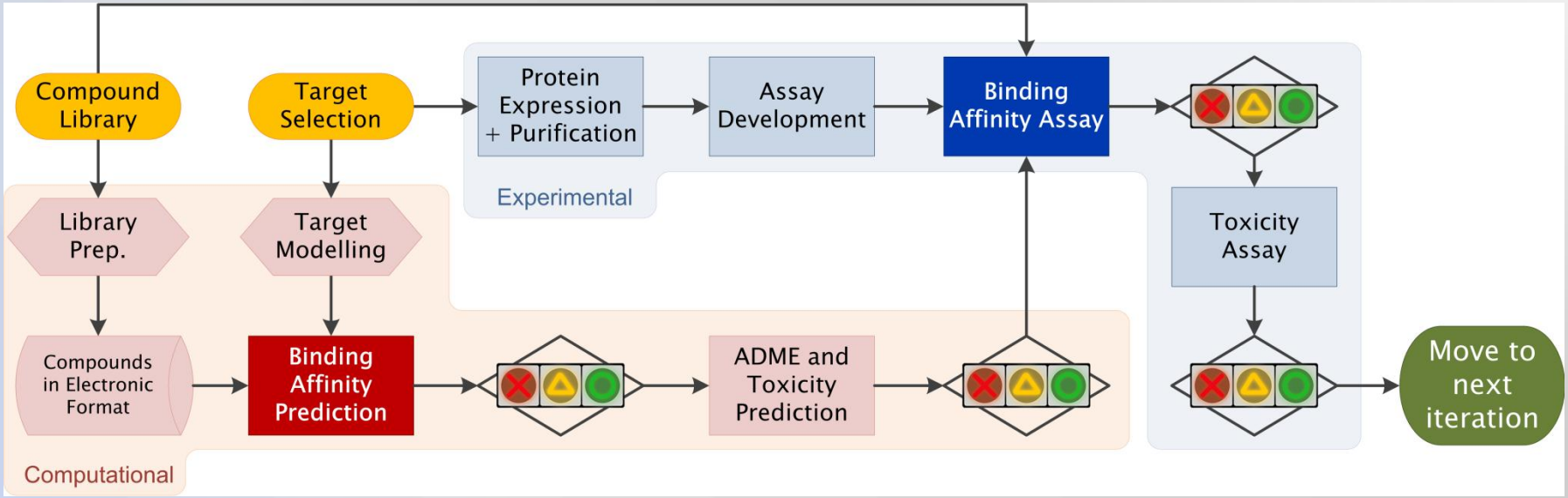
Pharmacophore Search

- Found 696 fits in library of >300,000 compounds
- Evaluated energies by free energy simulations
- Binding assays run for 588 compounds

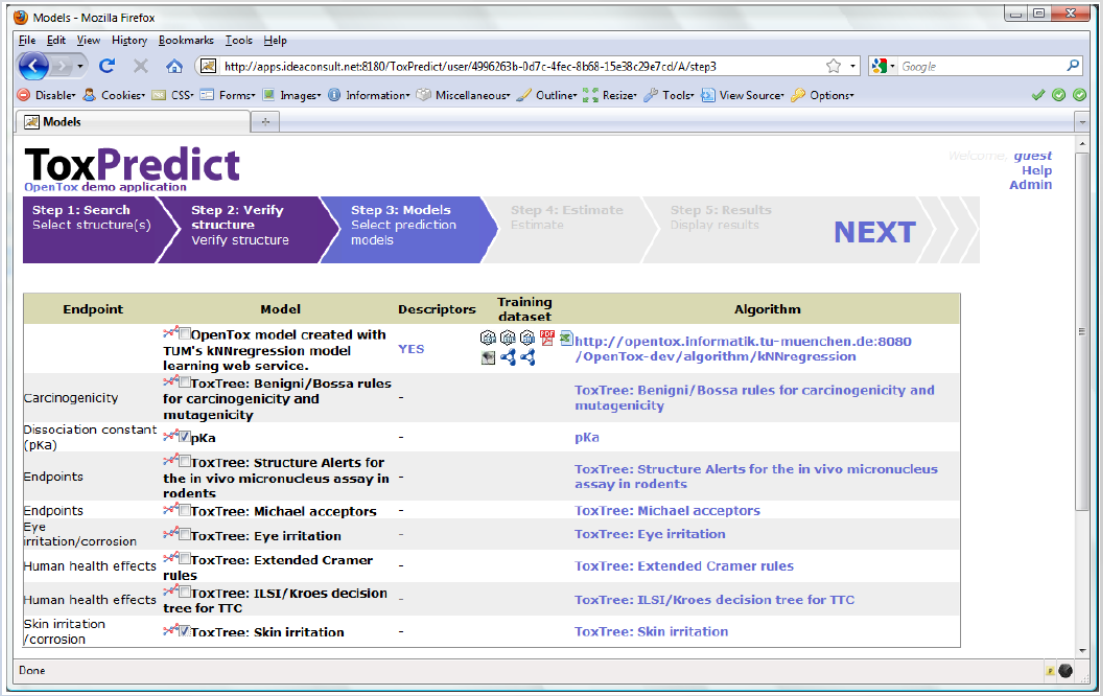
Docking predictions

- 996 compounds predicted as consensus between three docking screens (AutoDock, Vina, Glide)
- Binding assays are currently in progress

Incorporation of Holistic Predictive ADME & Toxicity



Predictive toxicology model building



Simple building of predictive toxicology applications based on well-established methods and databases

OpenTox

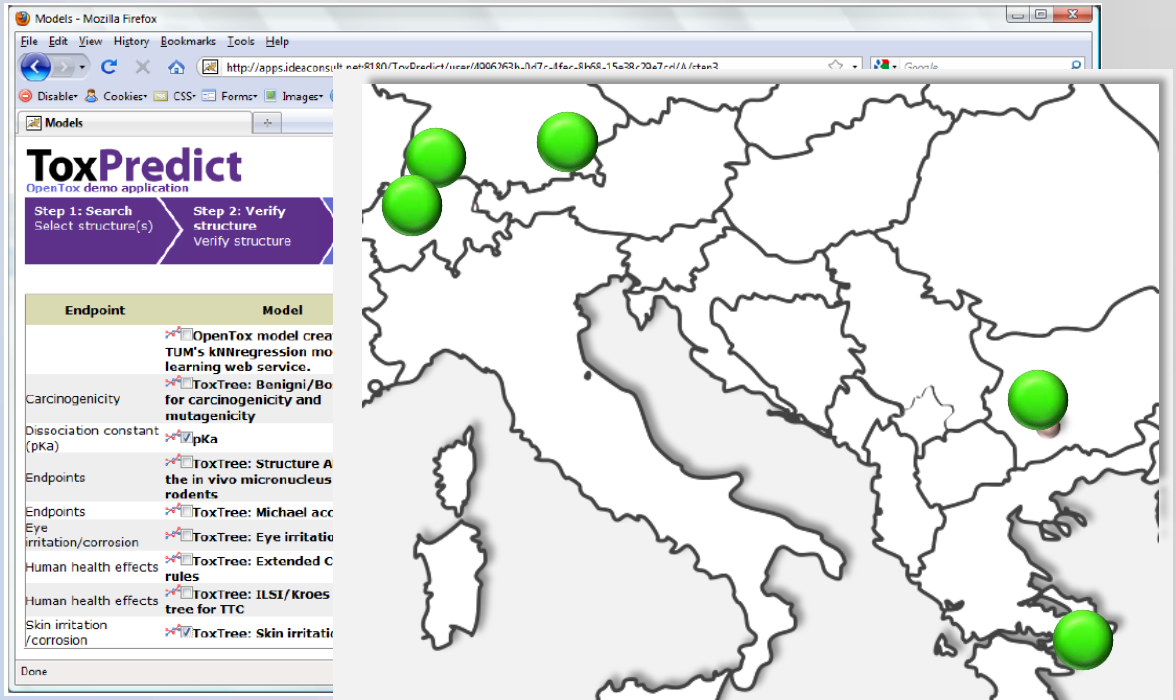
Applications and Models based on OpenTox Web Services will be applied holistically to drug design libraries to help guide decisions on chemistry directions and classes...

SAM

www.opentox.com

SYNERGY

Predictive toxicology model building



Simple bui

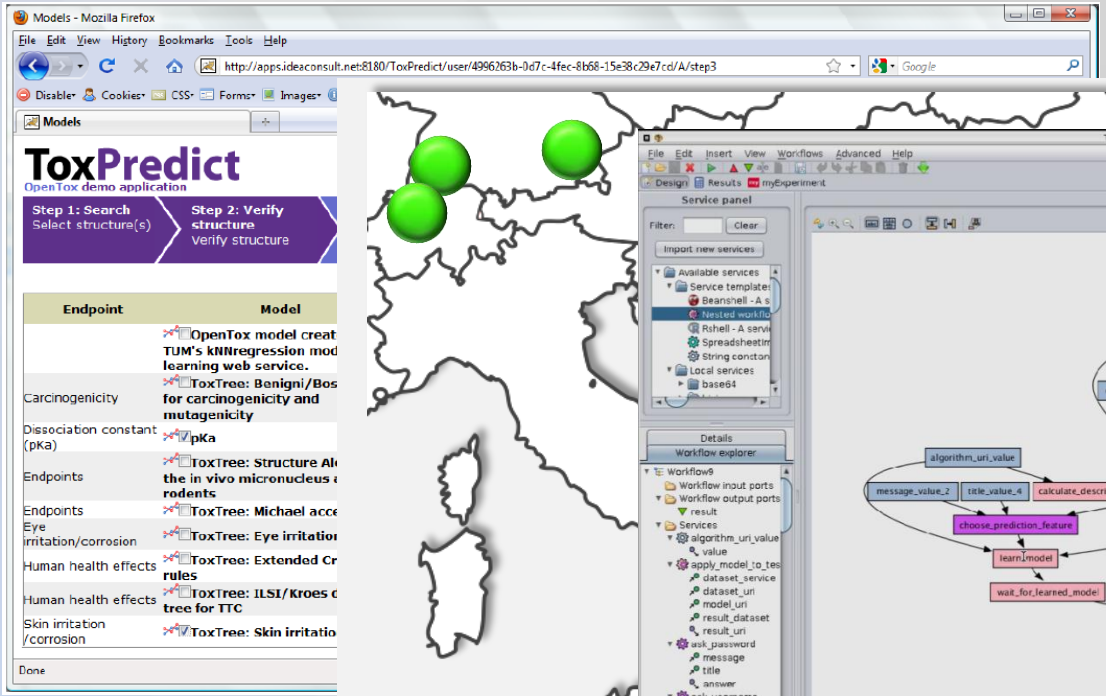
applicatio

methods a

Distributed applications, integrating wide range of data, models, prediction methods

Predictive toxicology model building

OpenTox



Simple buildi applications methods and

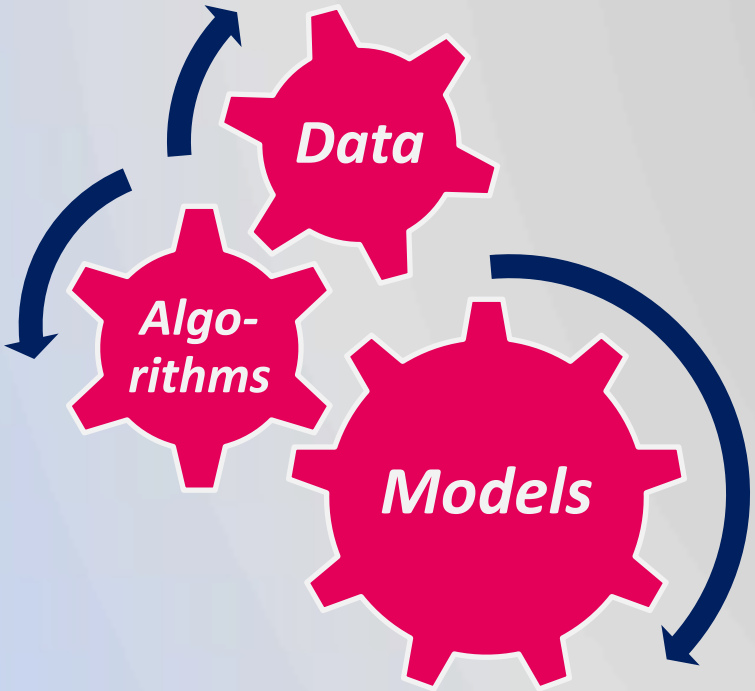
Distributed a wide range o methods

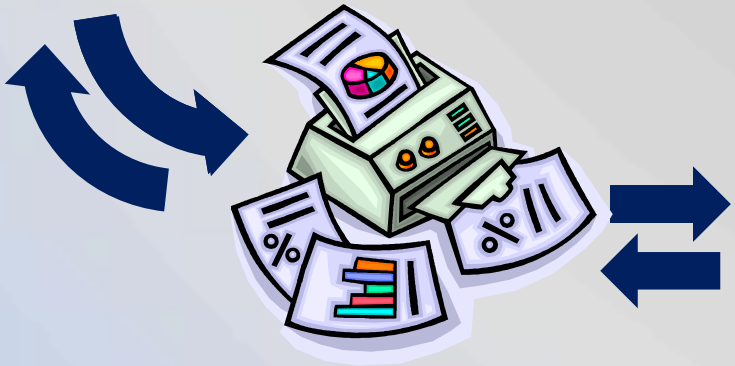
Integration into workflow systems for computational biology

SAM

SYNERGY

Predictive toxicology model building





ELN

	Model 1	Model 2	Model 3	Assay 1	Assay 2	Assay 3
	-	-	-	-	-	-

Synergy

	Model 1	Model 2	Model 3	Assay 1	Assay 2	Assay 3
	-	-	-	-	-	-

OpenTox

	Model 1	Model 2	Model 3	Assay 1	Assay 2	Assay 3
	1	0	1	-	-	-

Predictive toxicology model building

ELN

	Model 1	Model 2	Model 3	Assay 1	Assay 2	Assay 3
	1	0	1	-	-	-

Synergy

	Model 1	Model 2	Model 3	Assay 1	Assay 2	Assay 3
	-	-	-	-	-	-

OpenTox

	Model 1	Model 2	Model 3	Assay 1	Assay 2	Assay 3
	1	0	1	-	-	-




Current Realities (we can impact on):

1) Nearly half of the parents of these children in Namibia will die of AIDS
2) These children will be infected with malaria
3) They will not receive medical care or drugs for either of these diseases

If you would like to get involved in our Scientists Against Malaria work, please contact us!

barry.hardy -(at)- douglasconnect.com

www.scientistsagainstmalaria.net