



Collaborative Virtual Organisation & Infrastructure for Anti-Malarial Drug Design

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Director of Communities & Research Activities

Douglas Connect, Switzerland

Bio-IT World Europe Conference, Hannover, Germany

11-13 October 2011



Community of Practice starting point

innovationwell

echeminfo

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

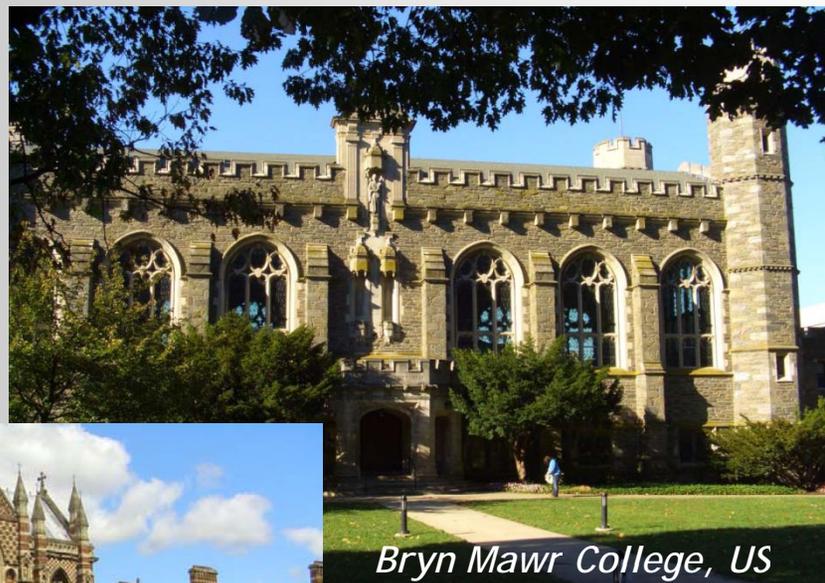


Knowledge Cafe Discussions

Community of Practice starting point



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



Community of Practice starting point



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



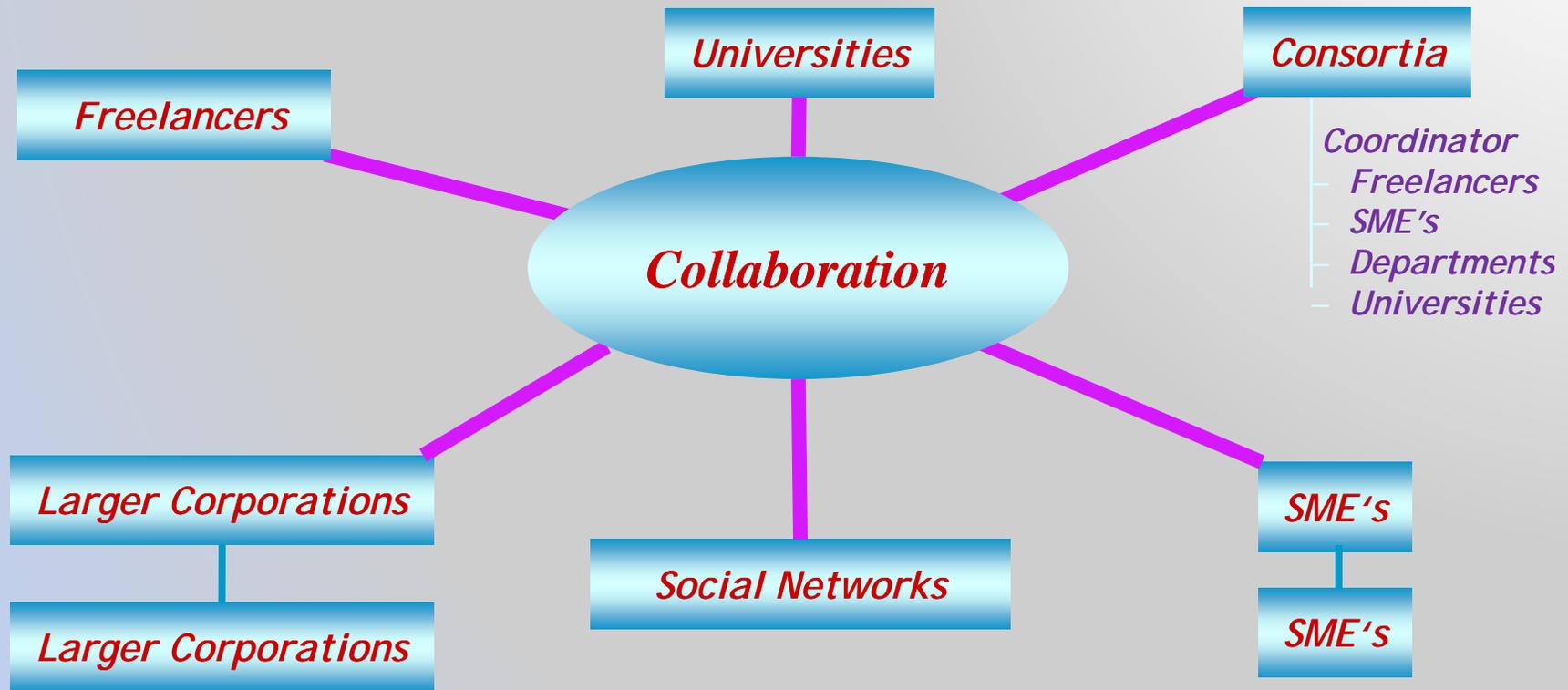
Study problems in detail using leading-edge
software. Discuss practical examples and methods.

Community of Practice starting point

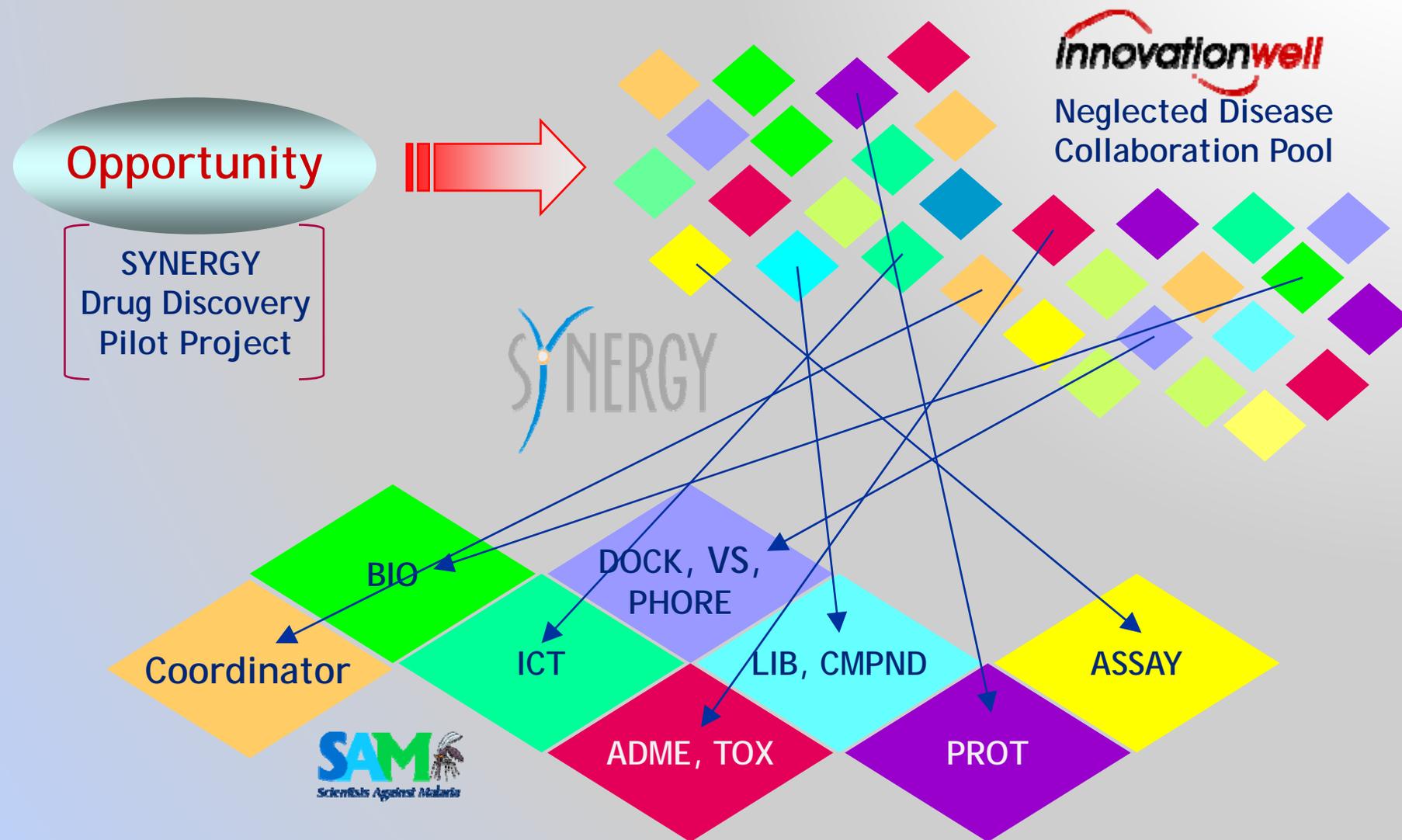
Community and workshop interactions created a valuable environment and network from which to build collaborations



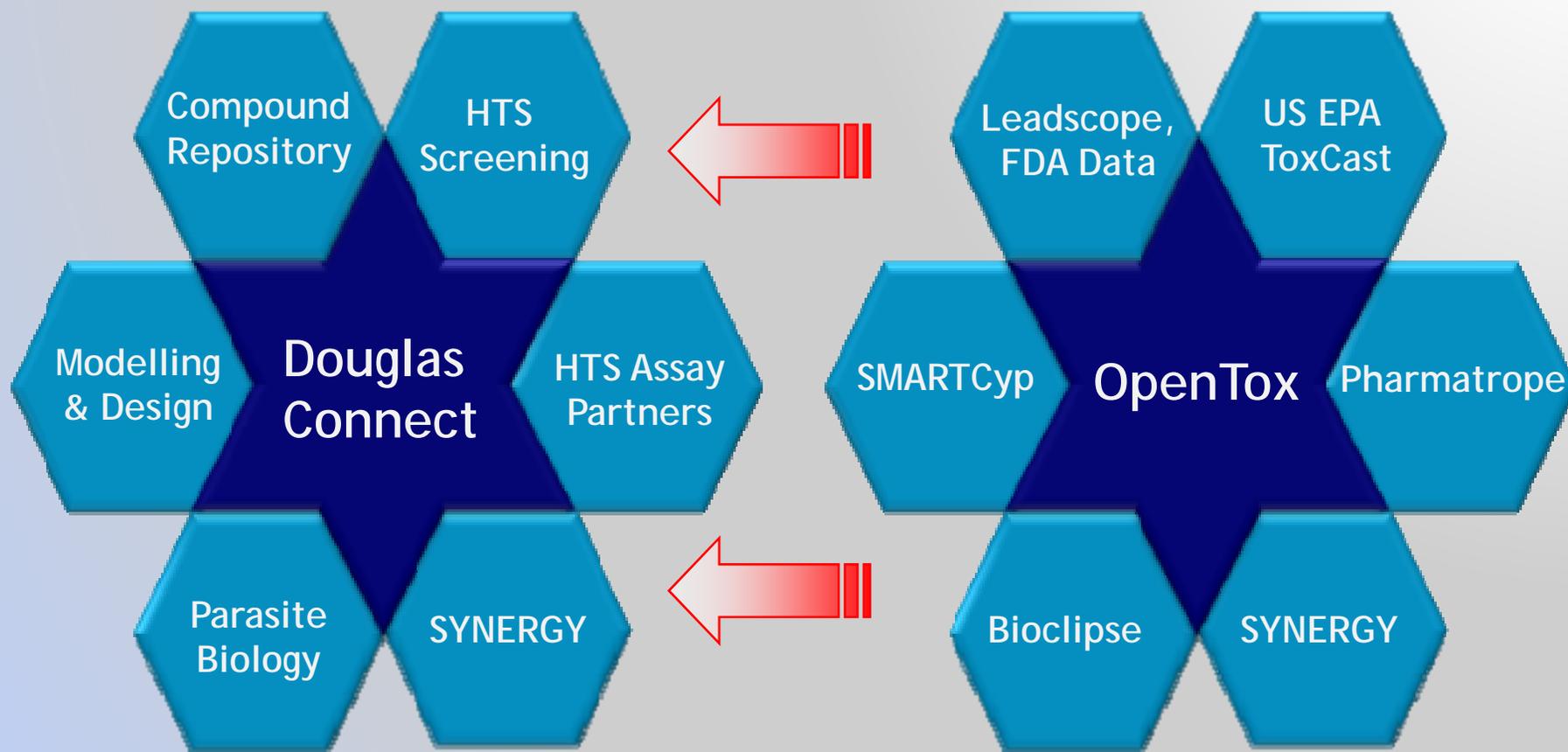
Emerging Multilateral Collaboration Landscape



Formation of VO from Collaboration Pool



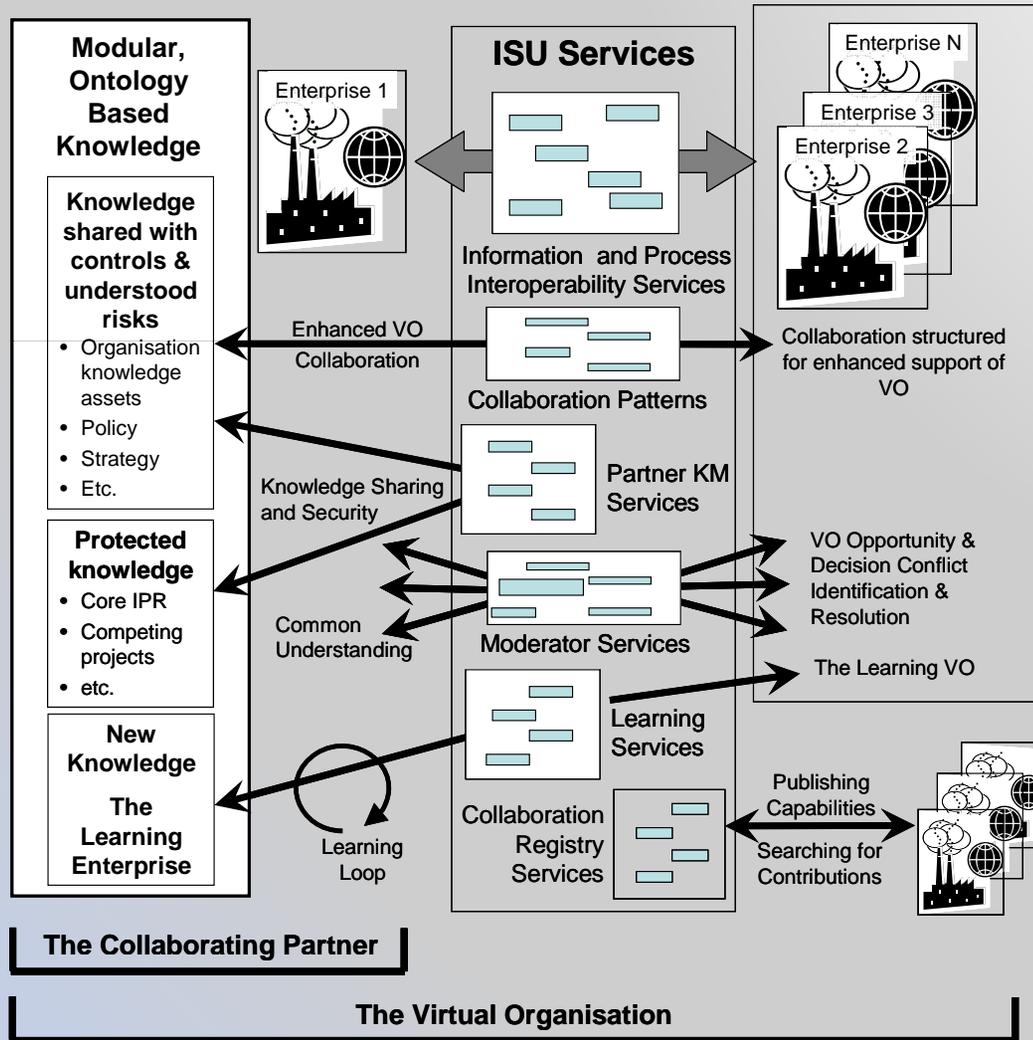
Virtual Organization Operational Pilots



Scientists Against Malaria VO

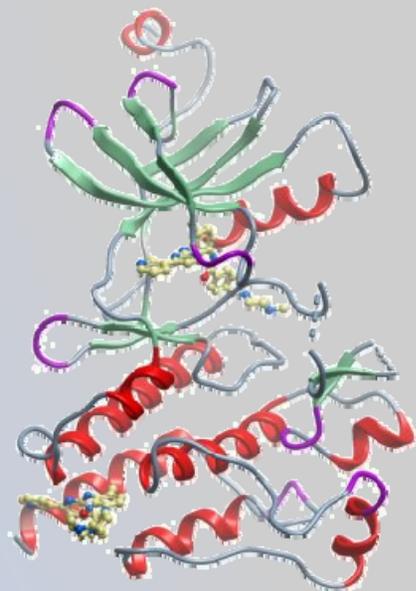
Predictive Toxicology VO

SYNERGY Collaboration Services



Operational Pilot 1 - Collaborative Drug Discovery

Target Protein Structure

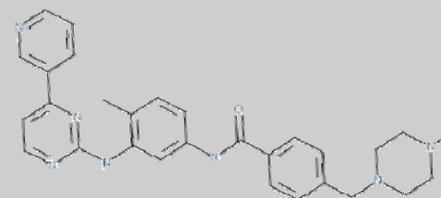


VO
→

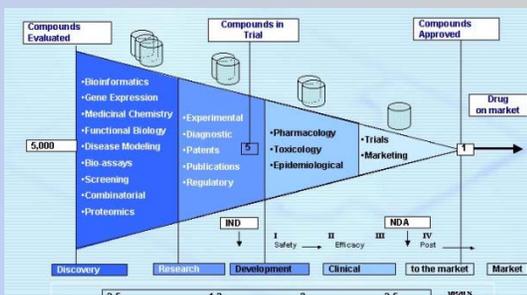
- Drug Design Techniques
- Molecular Modelling
- Virtual Screening
- Biological Assays
- Synthesis or Acquisition
- Testing

↓
Output result

Drug Leads

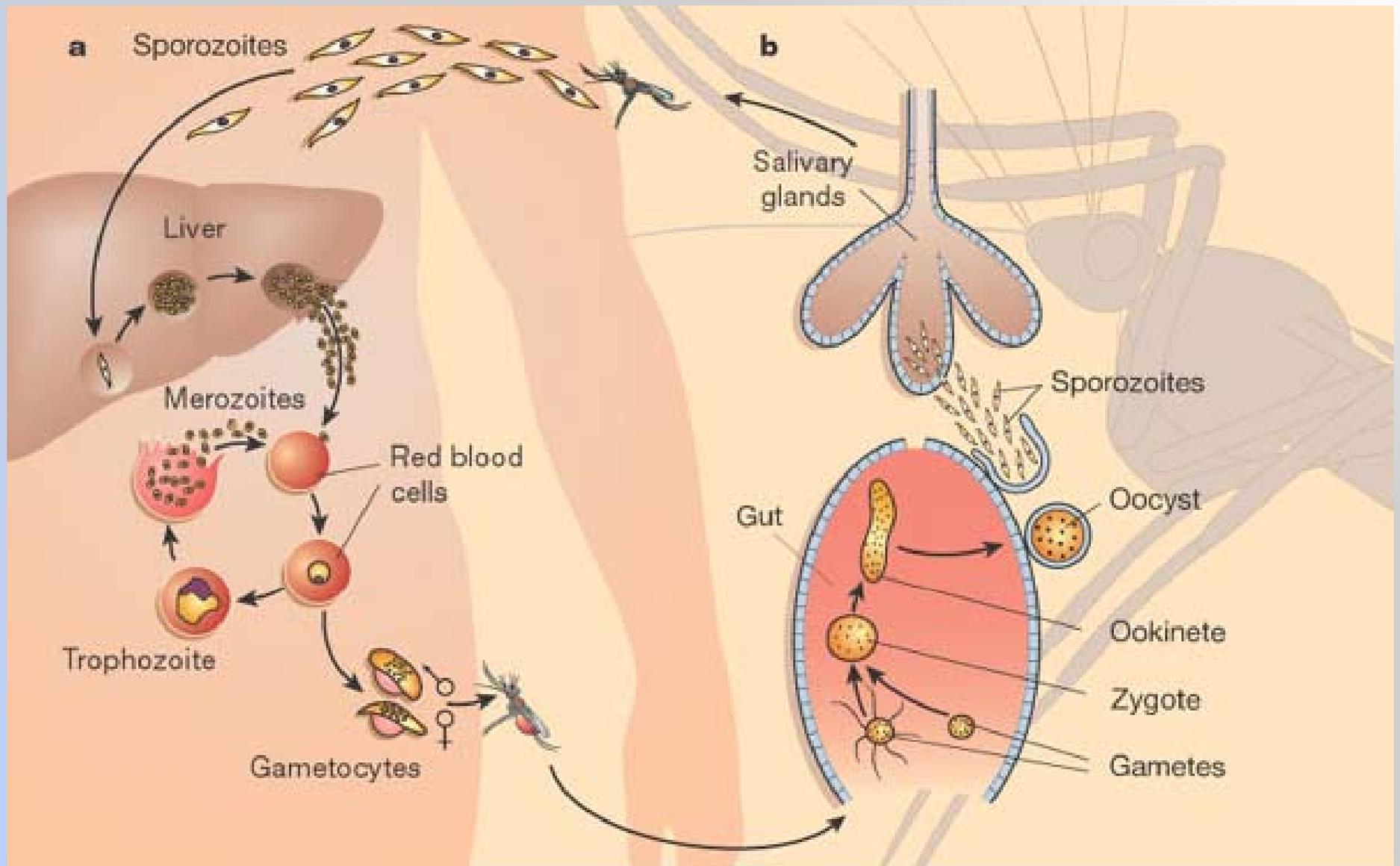


Drivers
→



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

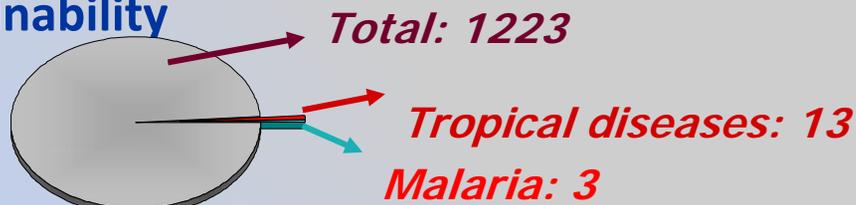
The (complicated) Plasmodium Life Cycle



Malaria Treatment: Lack of Investment

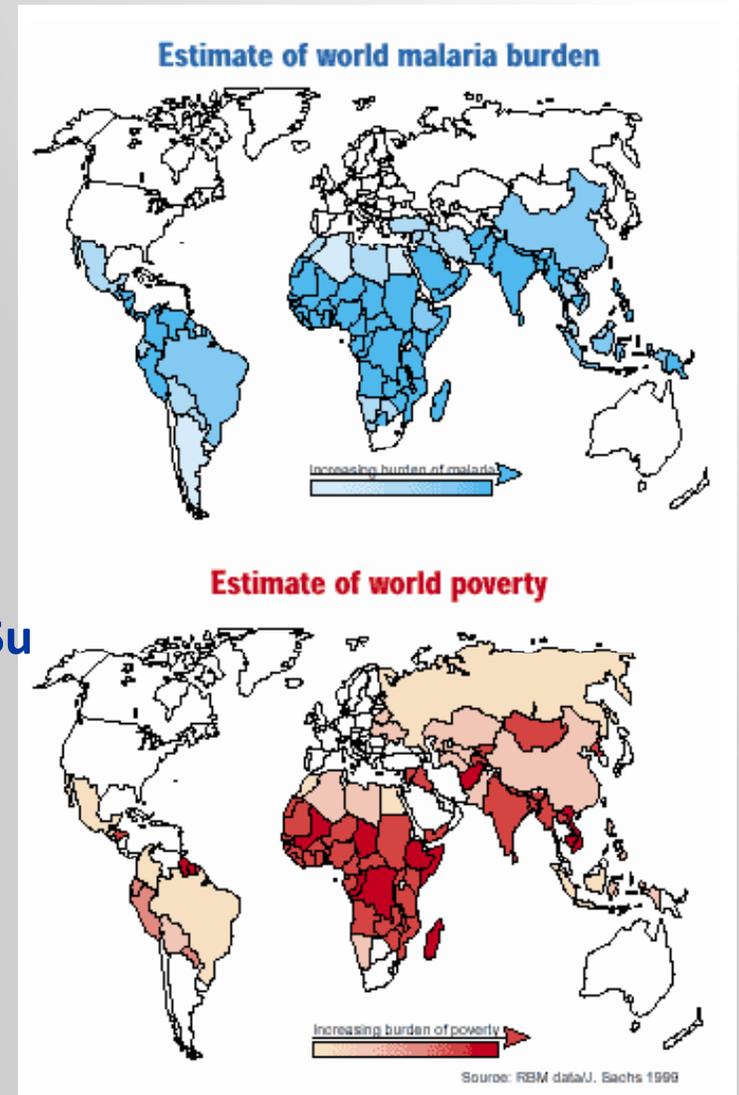
- 2.5 billion people at risk
- 500 M cases yearly
- ca. 1 M deaths yearly
- Many child fatalities
- Brain Damage, Impaired Development
- Few drugs, no vaccine yet
- Impact on

Education, Community, Income, Conservation, Sustainability

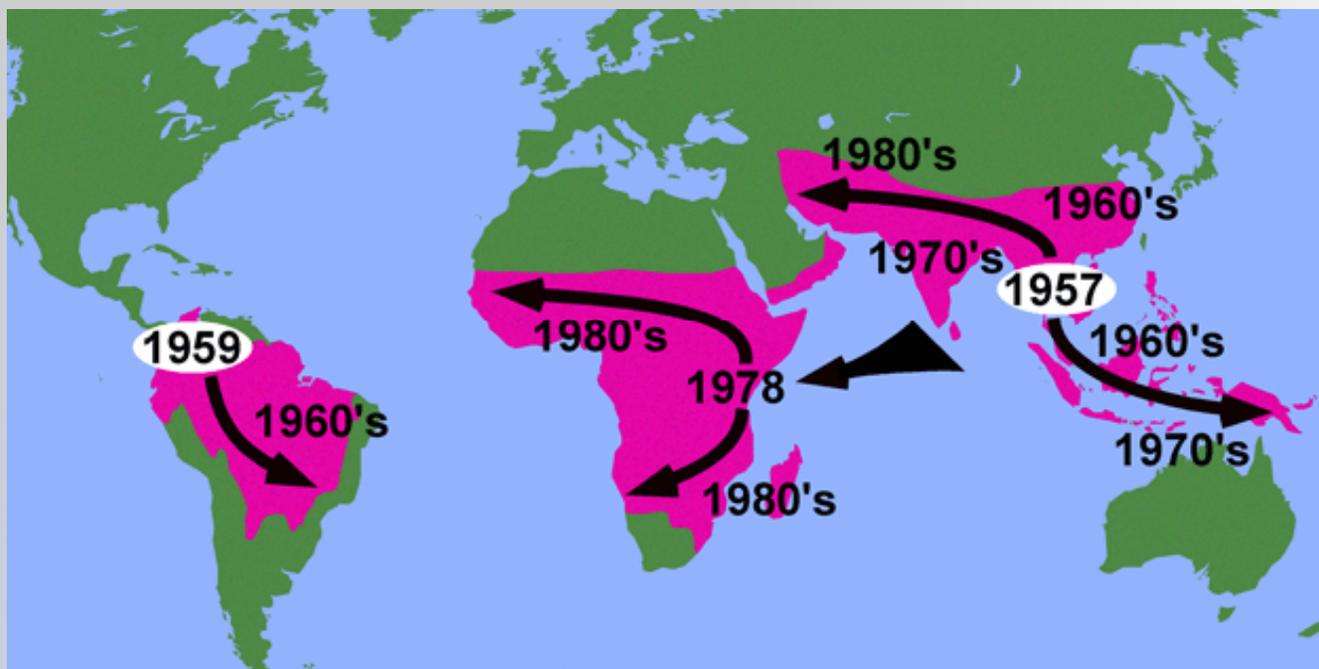


*Drug development outcome,
last quarter of the XXth century*

Greenwood & Mutabingwa, Nature 415:670-672



Drug Resistance is a challenge



Emergence and spread of chloroquine resistance

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** (Pharmatropé)
- **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



Plasmodium Life Cycle & Kinome

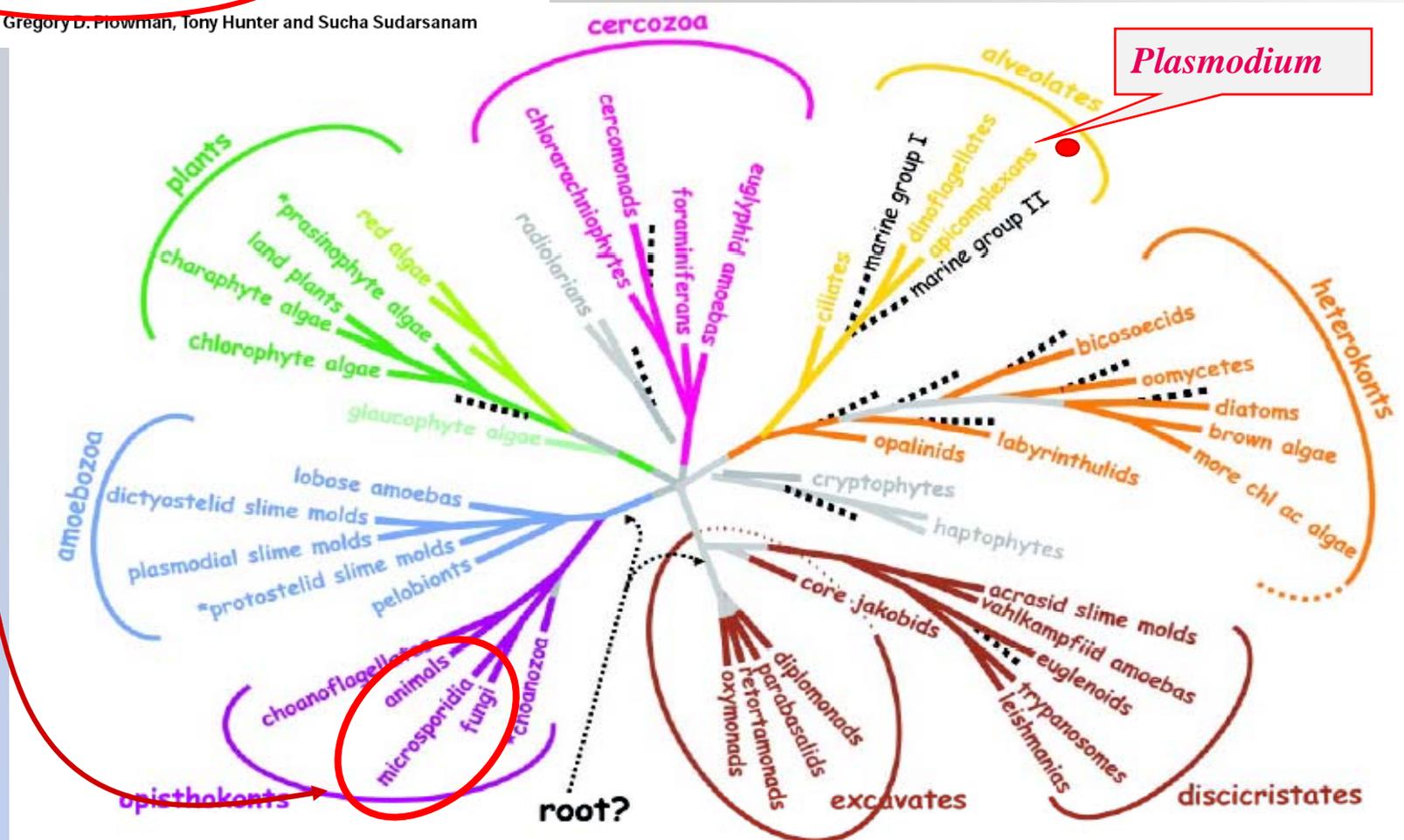
514

Review

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

Evolution of protein kinase signaling from yeast to man

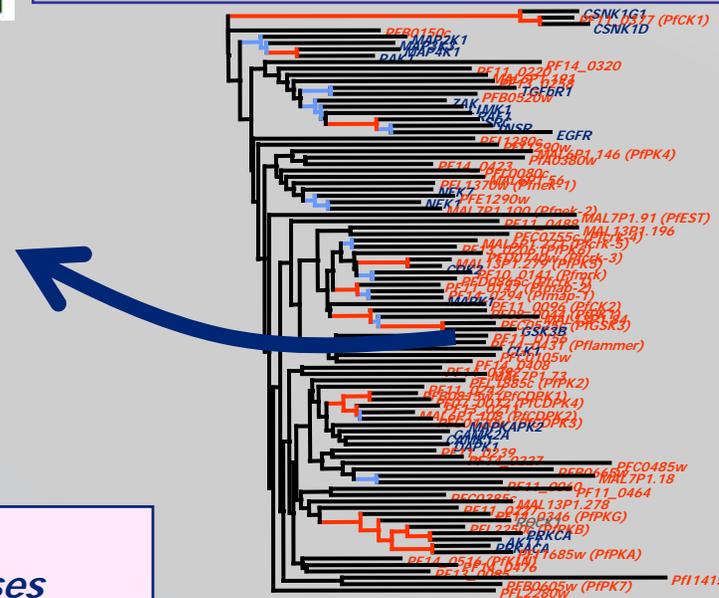
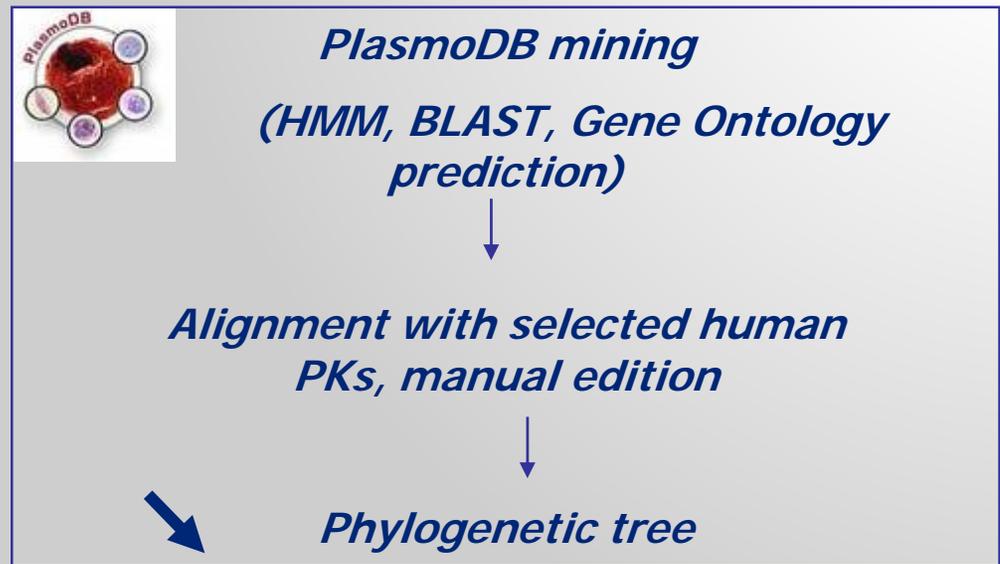
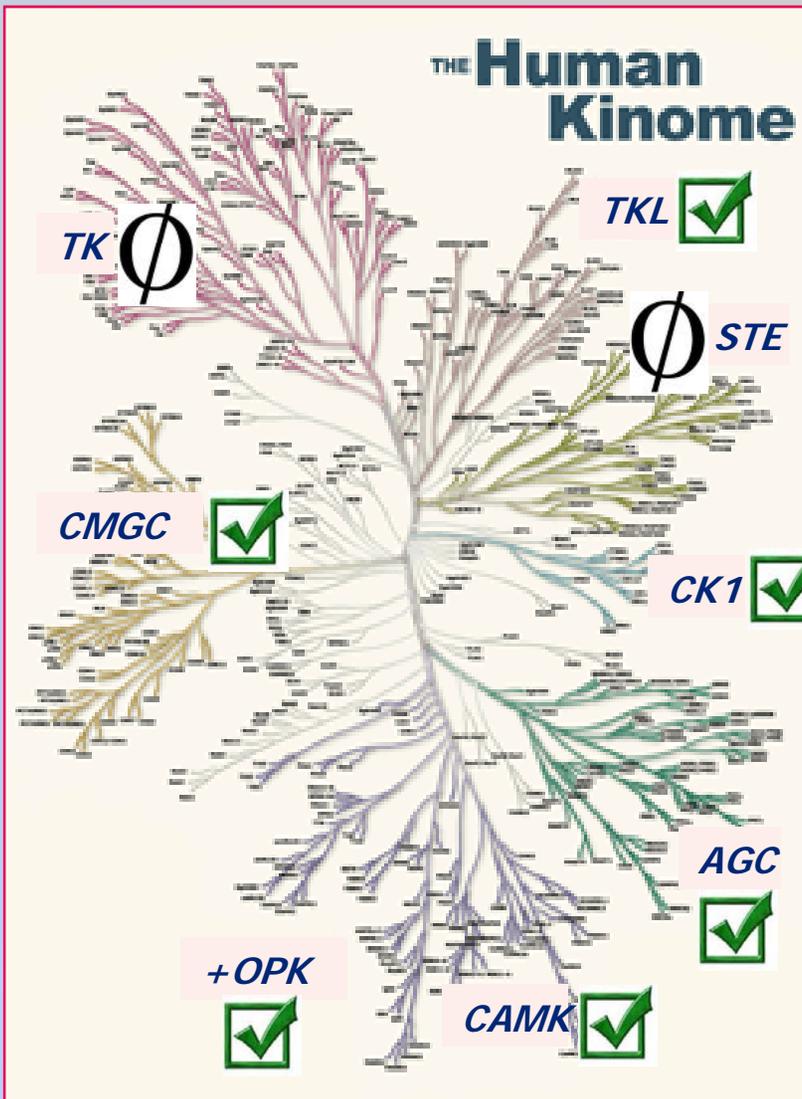
Gerard Manning, Gregory D. Prowman, Tony Hunter and Sucha Sudarsanam



Baldauf, Science, 2003

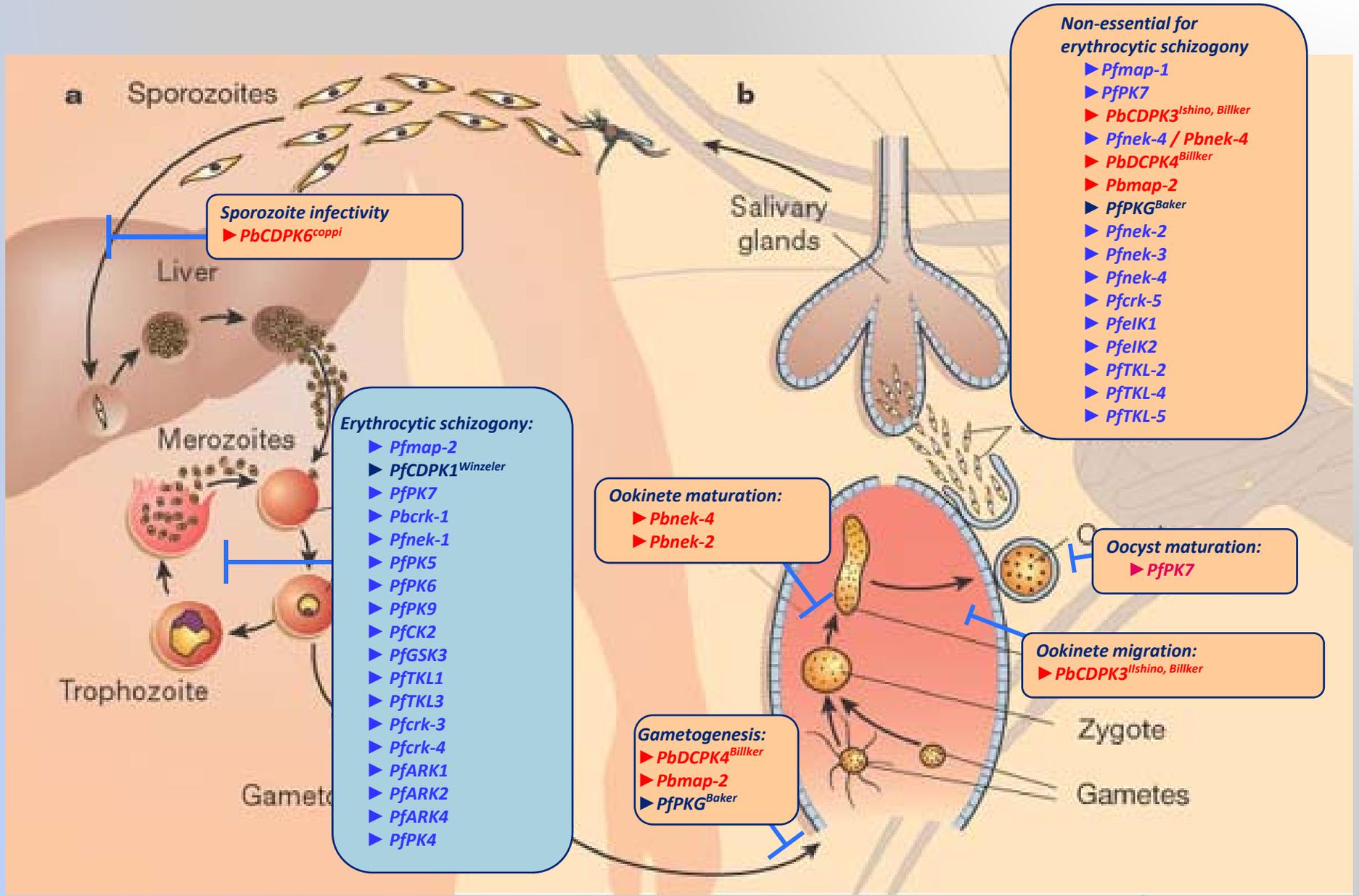


Plasmodium Life Cycle & Kinome

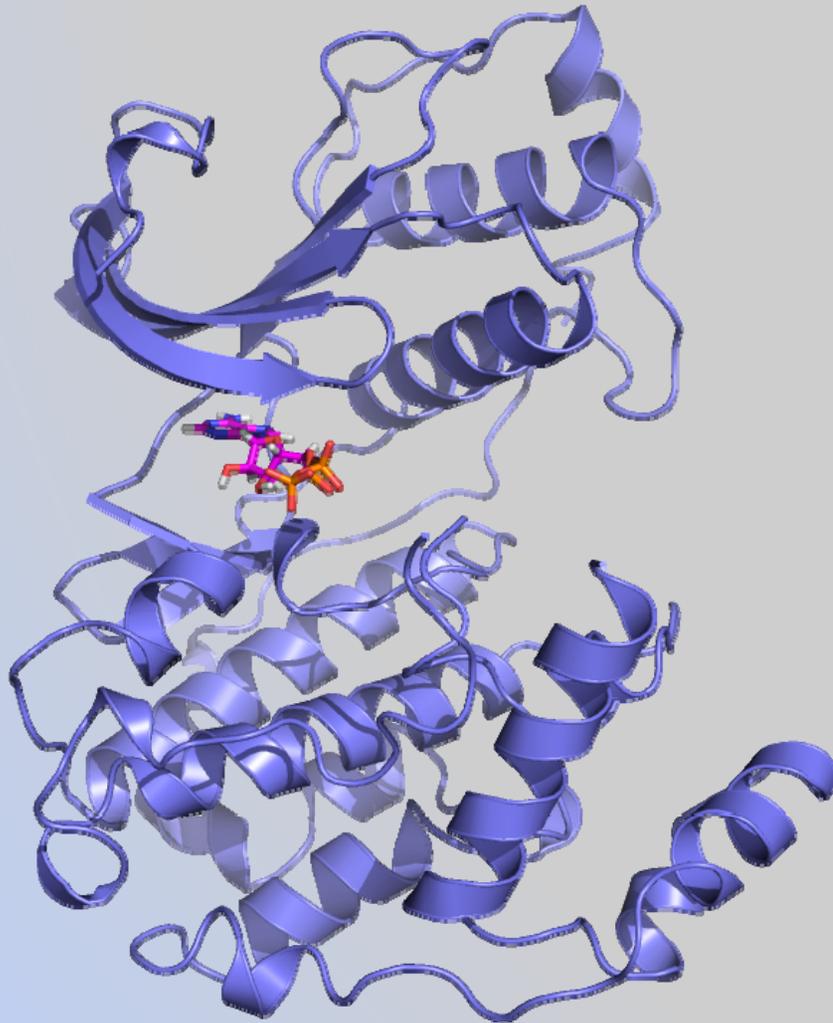


- 518 protein kinases (2% of genes)
- Involved in essentially all cellular processes (30% of the proteome is phosphorylated)

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  -----AAAAAAGPEMVRGQVFDVGPRTNLSYIGEGAYGMVCSAYDNLNKRVAIRK
1cm8A  -----RSGFYRQEVTKTA---WEVRAVYRDLQPV-----AVCSAVDGRTGAKVAIKK
pfmap2 DNISKNCNIVEKKNKSKEEKINIKEAI IKNVKVPDNYEIKHLIGRGSYGYVYLAYDKNANKNVAIKK
_consrvd                *  *                               *  *  *          *  *  *

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

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

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

1golA  NRPIFPKG-----HYLDQLNHILGILGSPSQEDLNCCIINLKARNYLLSLPHKNKVP
1cm8A  GKTLFKGS-----DHLQDLKEIMKVTGTPPAEFVQRLQSDAKNYMKGLPELEKGD
pfmap2 RFPLFPSSCFPLSPDHNSKKVHEKSNRDLNIIFNVIIGTPPEEDLKCITKQEVIKYIKLFPTRDGID
_consrvd  *  *                               *  *  *  *  *  *          *  *

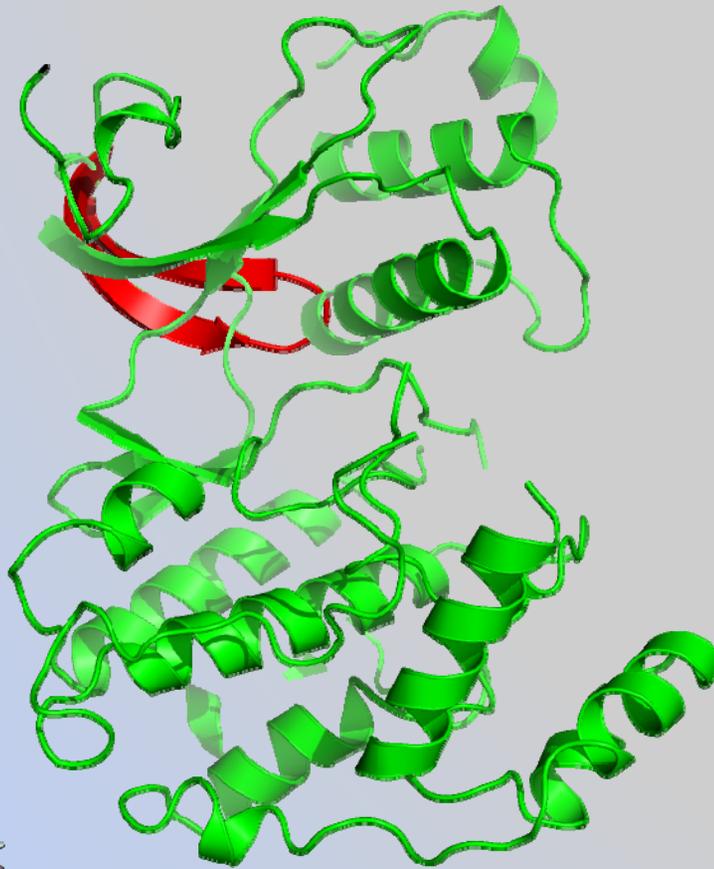
1golA  WNRLFPNADSKALDLLDKMLTFNPHKRIEVEQALAHPYLEQYYDPSDEPIAEAPFKFDMEL-DDLPKE
1cm8A  FASILTNASPLAVNLLKMLVLDAAEQRVTAGAALAHPYFESLH-----QVQKYDDS-----RTL D
pfmap2 LSKKYSSISKEGIDLLESMLRFNAQKRITIDKALSHPHYLKDV RKENLENFSTEKIIILPFDDWMVLSET
_consrvd                **  **      *      **  **  **
```



PfMAP2 modelling

Three template pdbs selected:

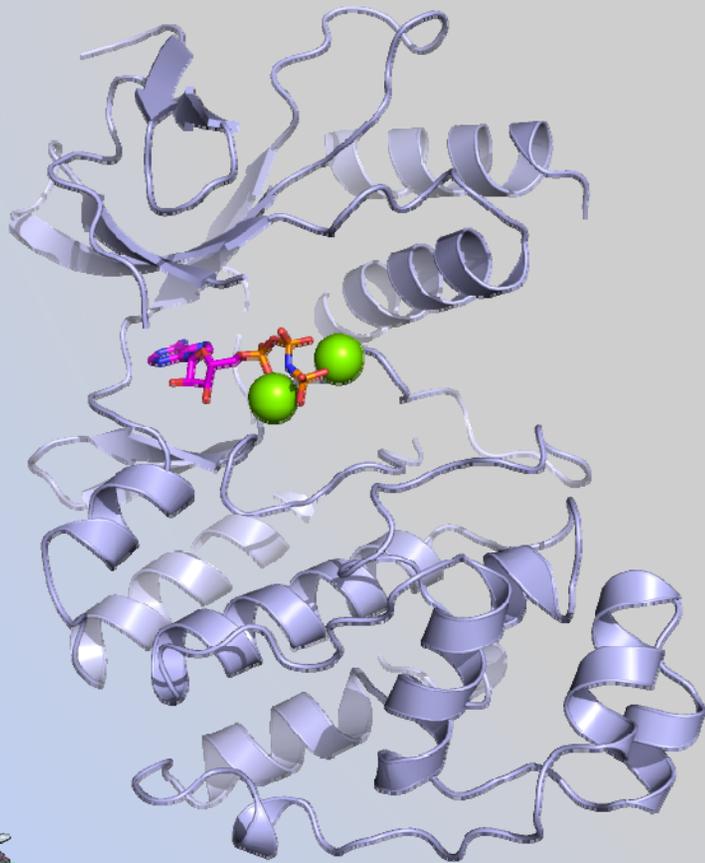
3N9X_PRE-RELEASE.pdb



PfMAP2 modelling

Three template pdbs selected:

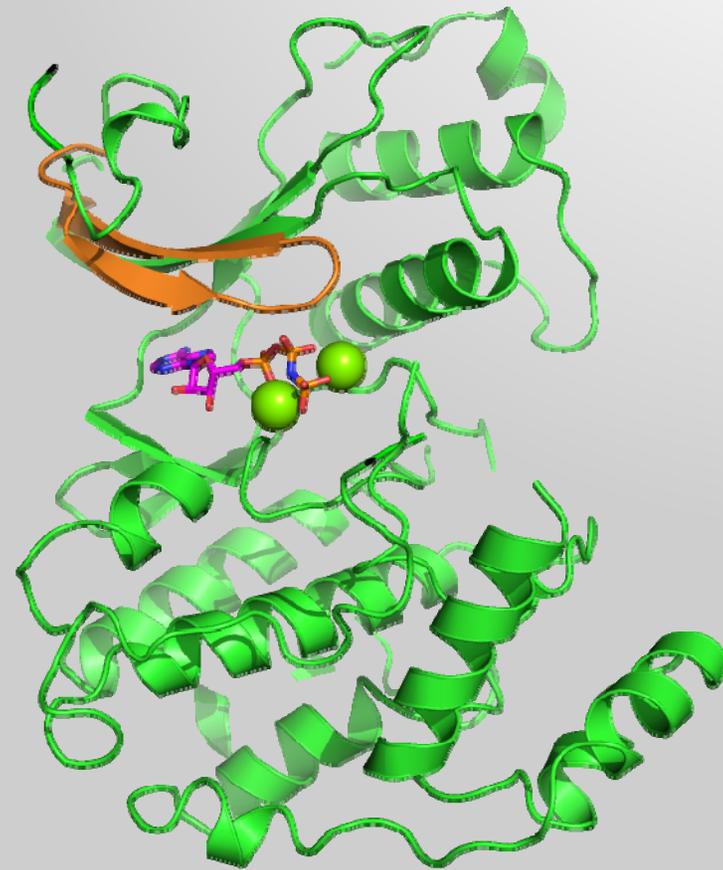
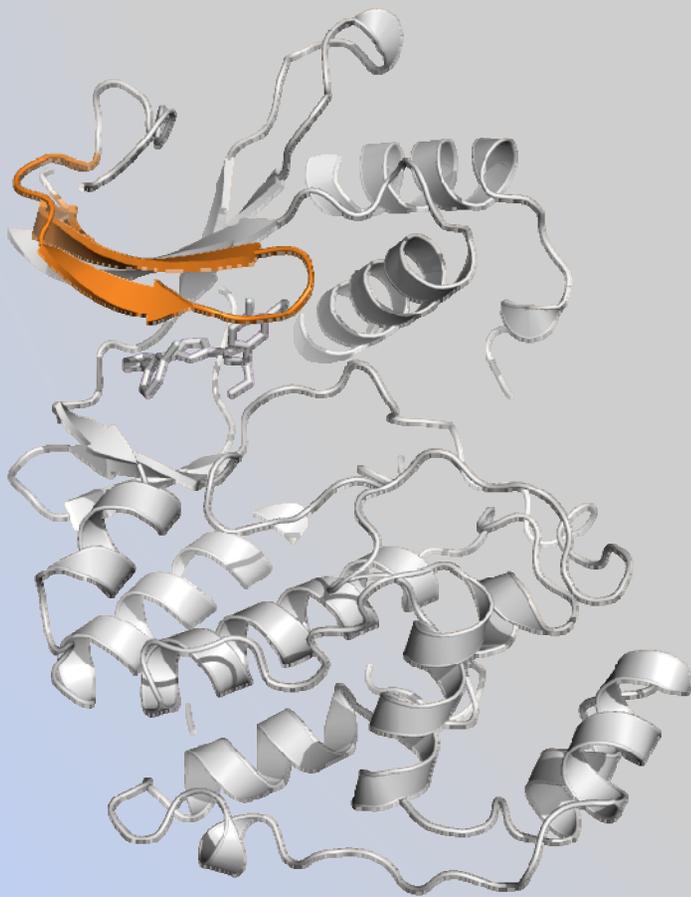
1CM8.pdb



PfMAP2 modelling

Three template pdbs selected:

2OJJ.pdb



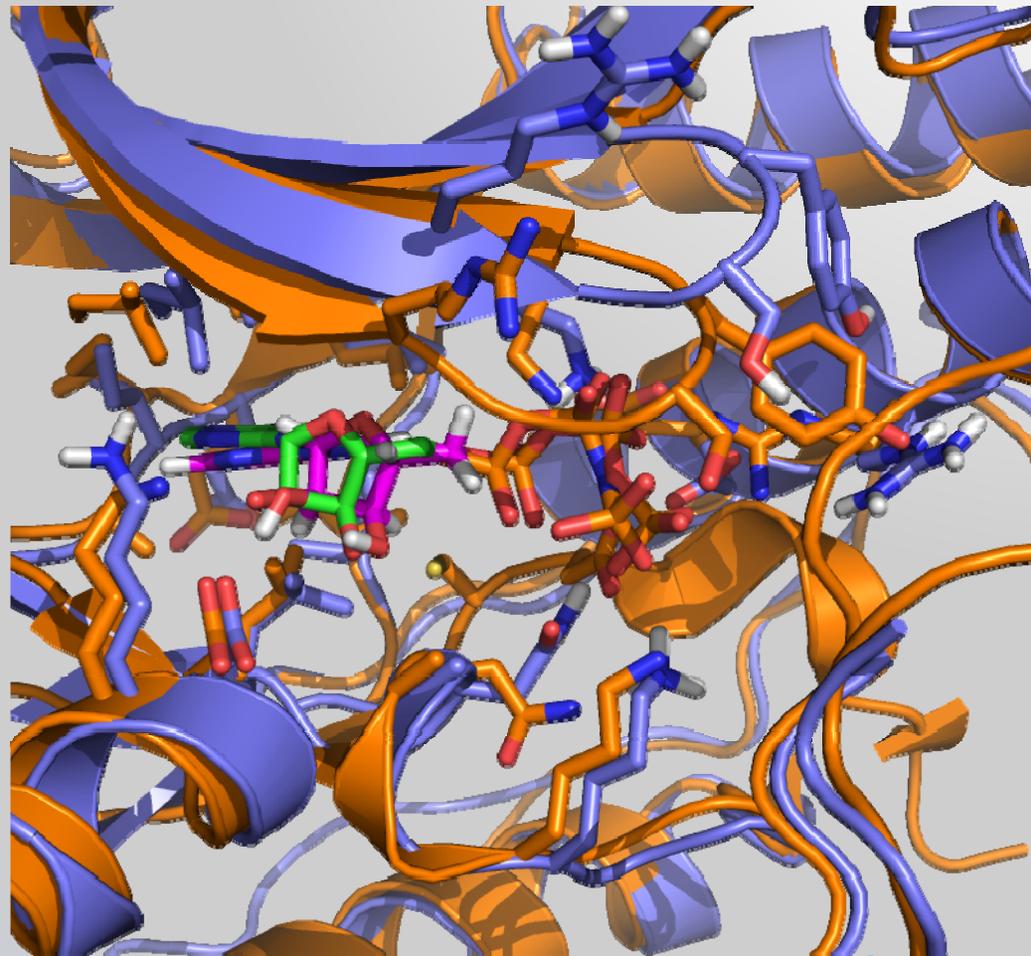
PfMAP2 Crystal Structure Model Comparison

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

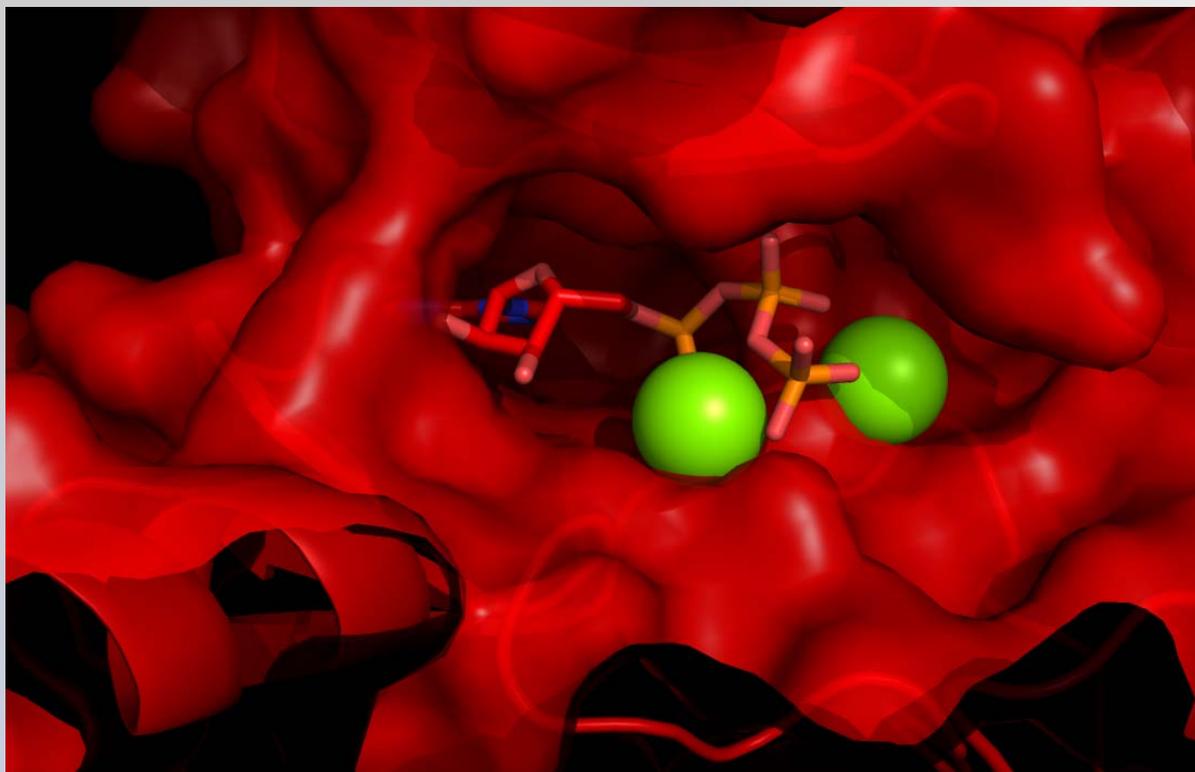
Overall, our model was quite accurate

Conformation of ATP was modelled well

Binding pocket residues were mostly ok

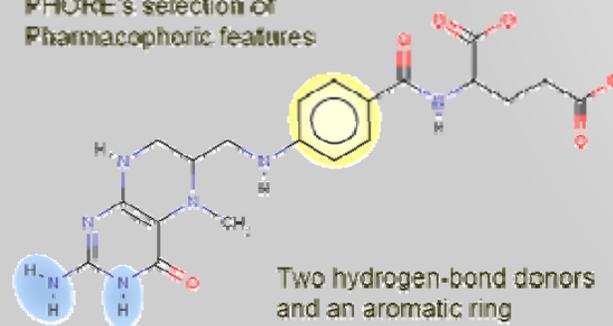


Binding Pocket

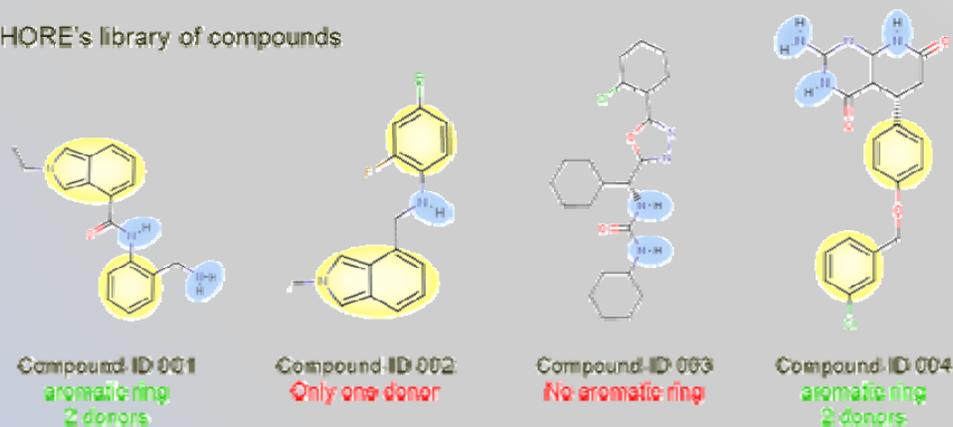


Pharmacophore-based Screening

PHORE's selection of
Pharmacophoric features



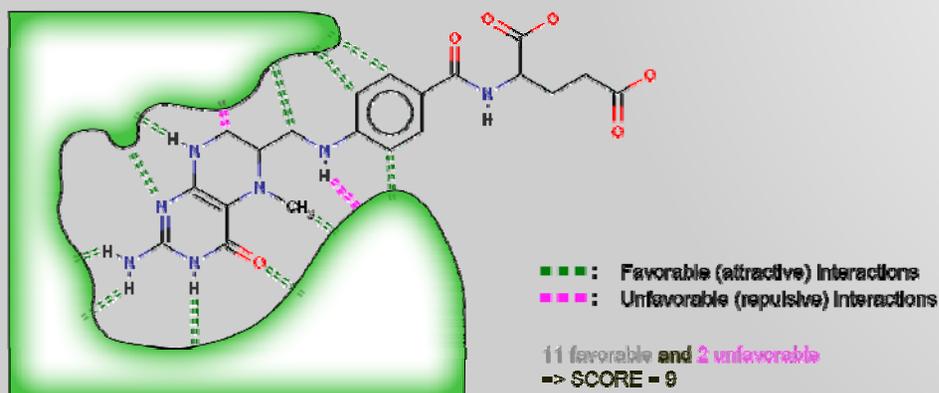
PHORE's library of compounds



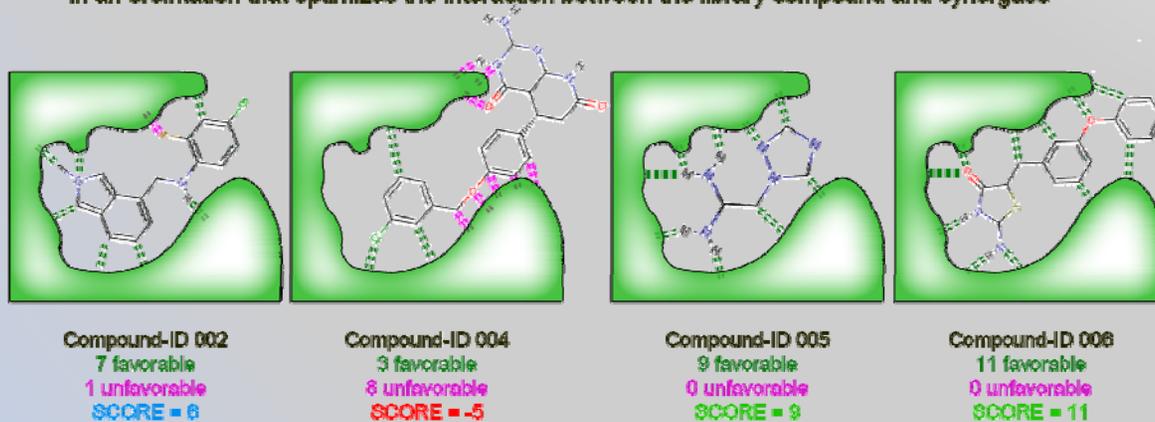
PHORE's activity hits prediction: compound-IDs 001 and 004

Dock Screening Prediction

γ -synergine bound to synergase (schematic depiction)

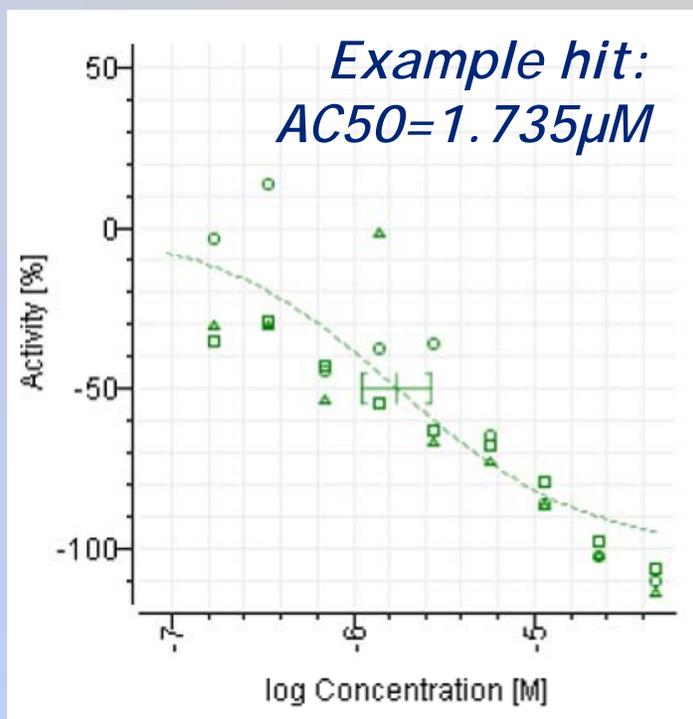
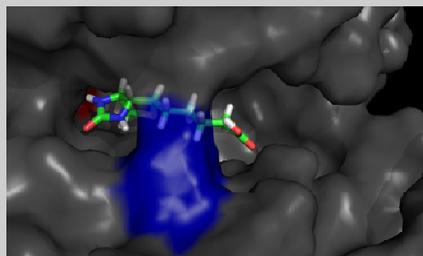
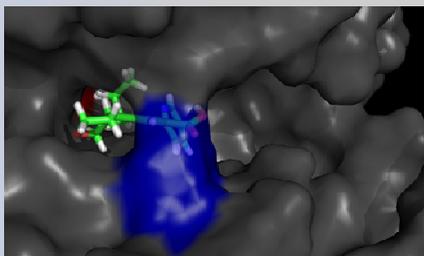


Each member of DOCK's library of compounds is placed in the binding pocket of synergase in an orientation that optimizes the interaction between the library compound and synergase



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

Preliminary Results



Pharmacophore Search

- Found 696 fits in library of >300,000 compounds
- Evaluated energies by free energy simulations

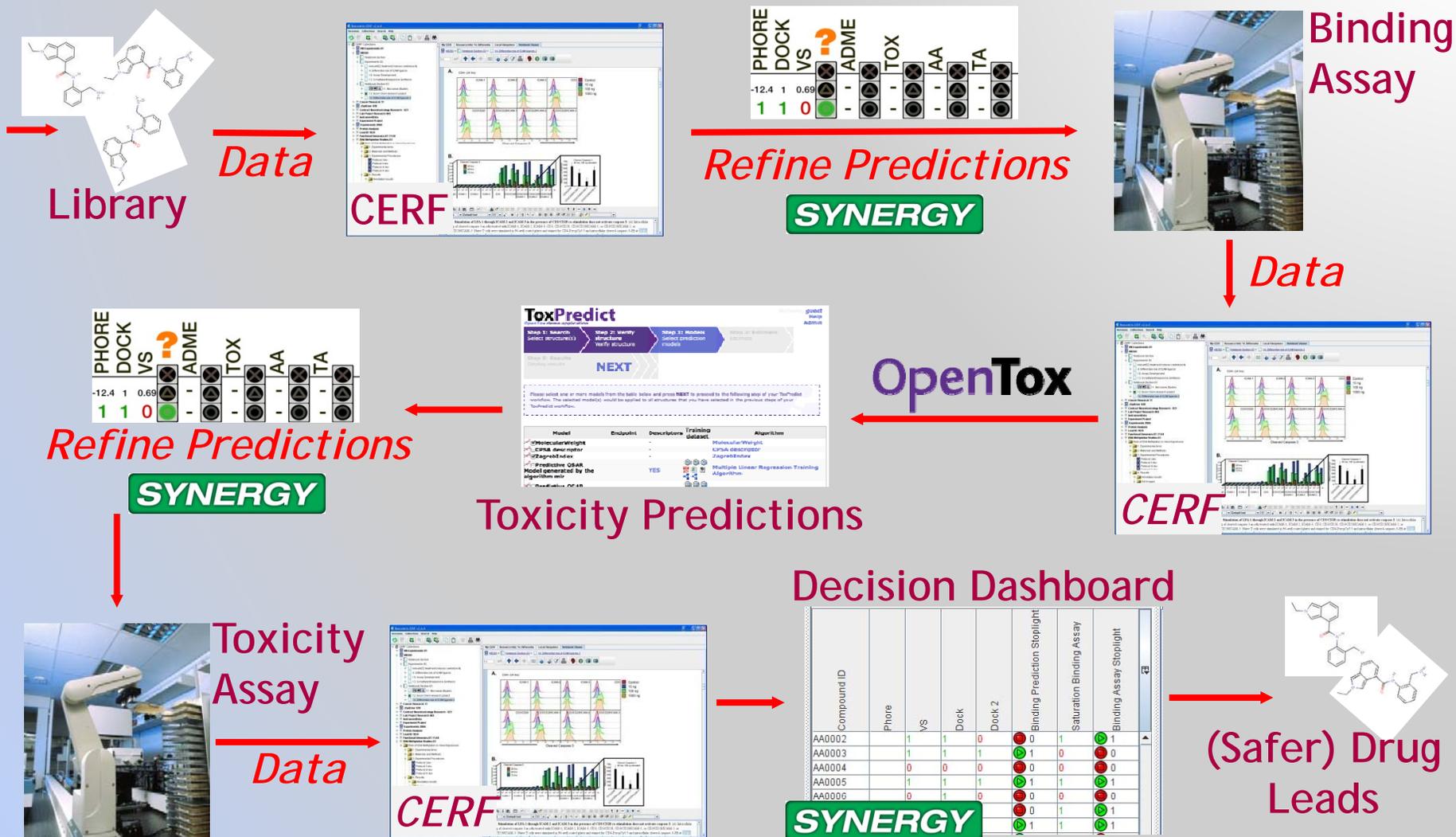
Docking predictions

- 996 compounds predicted as consensus between three docking screens (AutoDock, Vina, Glide)

Binding Assay

- Assay required Development & Optimisation Time
- Several micromolar hits with dose-response curves obtained from initial screenings.

SAM Workflow



Data Entry & Analysis

The screenshot shows the Rescentris CERF v2.6.0 interface. On the left is a 'CERF Collections' tree with folders like 'NB-Experiments-01', 'Cancer Research 11', and 'DNA Methylation Studies-03'. A red arrow points to 'Contract Neurotoxicology Research - 003' with the text 'Controlled Vocabularies'. The main window shows a 'Notebook Viewer' for '14. Differential role of ICAM ligands-2'. It contains two panels: Panel A shows flow cytometry histograms for CD4+ (24 hrs) cells, comparing Control (red), 10 ng (blue), 100 ng (green), and 1000 ng (orange) of ICAM-1, ICAM-2, ICAM-3, and CD3. Panel B shows a bar chart of 'Cleaved Caspase 3' median fluorescence at 24, 48, and 72 hours for various conditions. A red arrow points to the bar chart with the text 'Collaborative Electronic Research Framework (CERF)'. The bottom of the window has a text area with a figure caption.

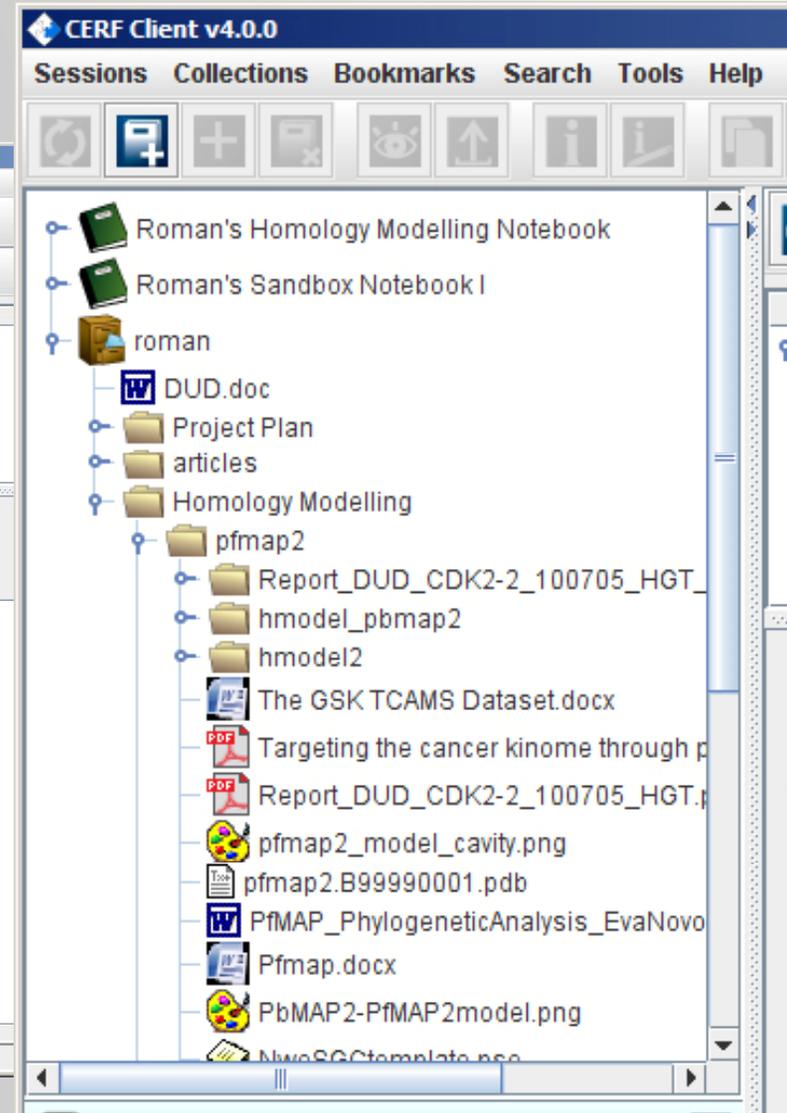
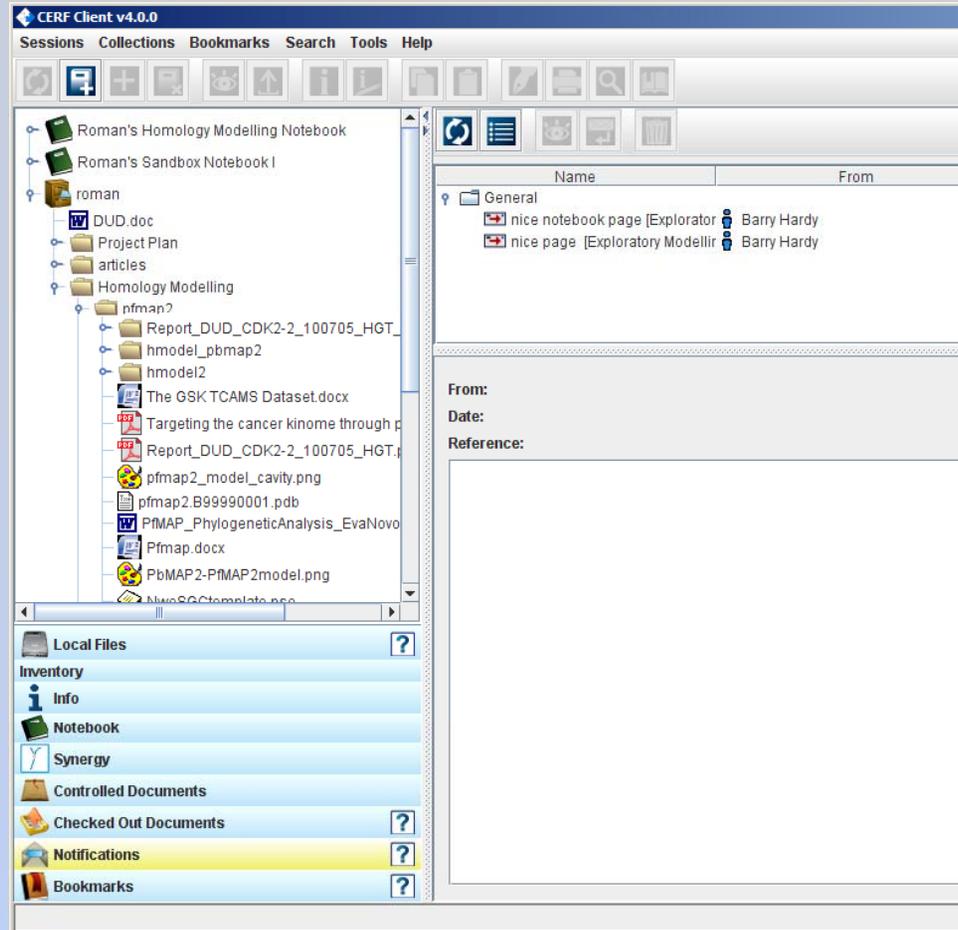
Controlled Vocabularies

Visualisation

Collaborative Electronic Research Framework (CERF)

Fig. 1. Stimulation of LFA-1 through ICAM-2 and ICAM-3 in the presence of CD3/CD28 co-stimulation does not activate caspase-3. (A) Intracellular staining of cleaved-caspase 3 in cells treated with ICAM-1, ICAM-2, ICAM-3, CD3, CD3/CD28, CD3/CD28/ICAM-1, or CD3/CD28/ICAM-2, or CD3/CD28/ICAM-3. Naive T cells were stimulated in 96-well coated plates and stained for CD4-PerpCy5.5 and intracellular cleaved-caspase-3-PE at 24 hrs.

File cabinets to store data etc



Template Spreadsheets to Document Computations

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

	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		pffmap2.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		pffmap2.ali			
15		Script	Input	Output		
16	Reference Files (inputs and outputs) - attach as links		build_profile.py		pffmap2.ali	
17					build_profile.prf	
18					build_profile.log	
19			get_pdb.sh		pdb-list.dat	
20			salign.py		get_pdb.sh	
21					salign.log.gz	
22					pffmap2-salign-templates.tree	
23					pffmap2-salign-templates.pap	
24					pffmap2-salign-templates.ali	

Sheet 1

Event-driven Collaboration Dashboard

CERF Client v4.0.0 - Logged in to Enterprise as jspitzner

Sessions Collections Bookmarks Search Tools Help

Project: Project-1001 Subject: Subject-1001 Compound Set: All Compound Sets Refresh Show Filters New Project New Subject New Compound Set New Compound Add Result

Results 1 to 100 of 197

Compound ID	Phase	NS	Dock	Dock 2	Binding Prediction Stoplight	QSPAR ADME	QSPR ADME	ADME Prediction Stoplight	Binding + ADME Prediction Stoplight	Logic Based Tox	Unlabeled Free Energy Tox	Toxicology Prediction Stoplight	Binding + ADME + Tox Prediction Stoplight	Saturation Binding Assay	Protein-DNA Binding Assay	Binding Assay Stoplight	In Vitro Toxicology Assay	In Vivo Toxicology Assay	Toxicology Assay Stoplight	Binding + Tox Assay Stoplight	Final Stoplight	
UC0000353		0	0					0.0	-6.0999999													
UC0000862		1	1					-10.47	-10.8													
UC0000864		1	1					-10.2	-10.9													
UC0000884		1	1					-9.1400003	-10.6													
UC0000885		1	1					-9.1400003	-10.5													
UC0000886		1	1					-9.41	-10.6													
UC0000921		1	1					-10.91	-9.1000004													
UC0001349		1	1					-9.9799995	-11.2													
UC0001350		1	1					-9.96	-11.2													
UC0001500		1	1					-9.3299999	-9.3999996													
UC0001501		1	1					-9.5699997	-9.6000004													
UC0001623		1	1					-9.4899998	-9.1000004													
UC0001624		1	1					-9.4899998	-9.1000004													
UC0001699		1	1					-12.2	-10.9													
UC0001700		1	1					-9.9899998	-9.8000002													
UC0001702		1	1					-13.37	-9.6000004													
UC0001703		1	1					-10.61	-10.7													
UC0001743		1	1					-9.29	-9.1000004													
UC0001775		1	1					-9.7700005	-9.1000004													
UC0001875		1	1					-9.84	-9.2													
UC0001987		1	1					-9.7700005	-9.1999998													
UC0002838		1	1					-9.1999998	-9.8999996													
UC0002854		1	1					-10.09	-10.0													
UC0003266		1	1					-9.4799995	-9.8000002													
UC0003454		1	1					-9.1899996	-10.0													
UC0003835		1	1					-9.1000004	-9.8000002													
UC0003867		1	1					-10.25	-9.3999996													
UC0003923		1	1					-9.7200003	-9.8000002													
UC0003941		1	1					-10.52	-9.3000002													
UC0003973		1	1					-9.3100004	-9.1999998													

Previous Next Results per page: 100

Aggregate Resource

Project Subject Compound Set Compound

Title: Project-1001

Status ?

Edit Status: Versionable
Owner: jspitzner
My Role: Notebook Creator
Closed: No
Checked Out: No
Visibility: Shared
Id: 26203 (Federation: 43214, Server: 801)

Metadata ?

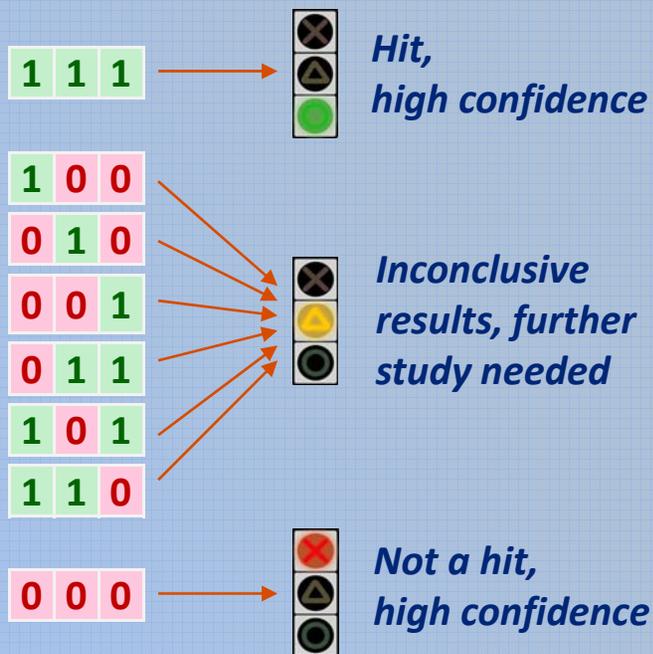
Title: Project-1001
Submission/Modification
Resource Type: Drug Design Project
Creation Date: Oct 21, 2010 2:57:10 PM
Last Update: Oct 21, 2010 2:57:10 PM
Contributor: Jeff Spitzner

Relations and Annotations ?

Comment Tag Browse Tags

Resolving Inconclusives

Recommendation Rules:



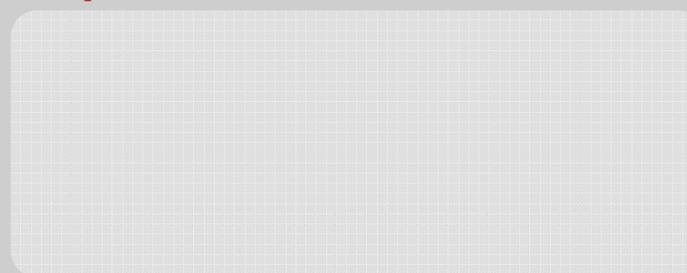
ELN



Synergy



OpenTox



Resolving Inconclusives



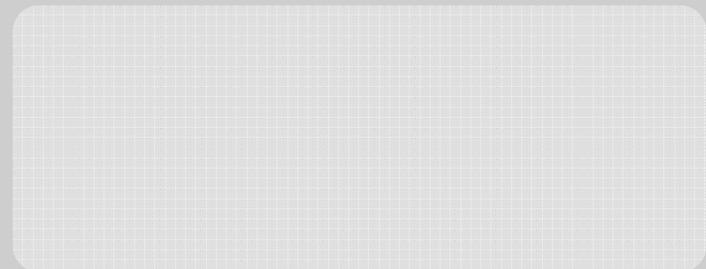
ELN

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

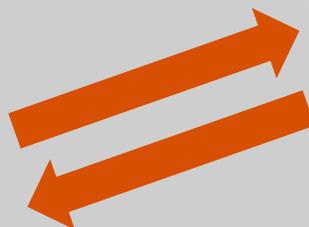
Synergy

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

OpenTox



Resolving Inconclusives



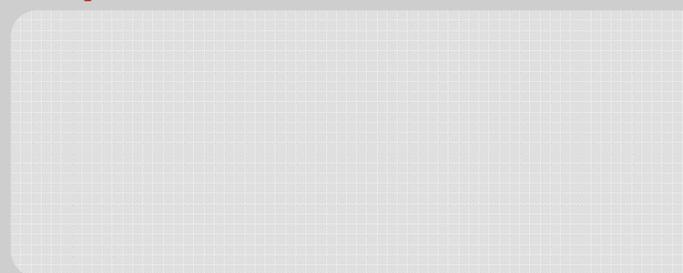
ELN

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

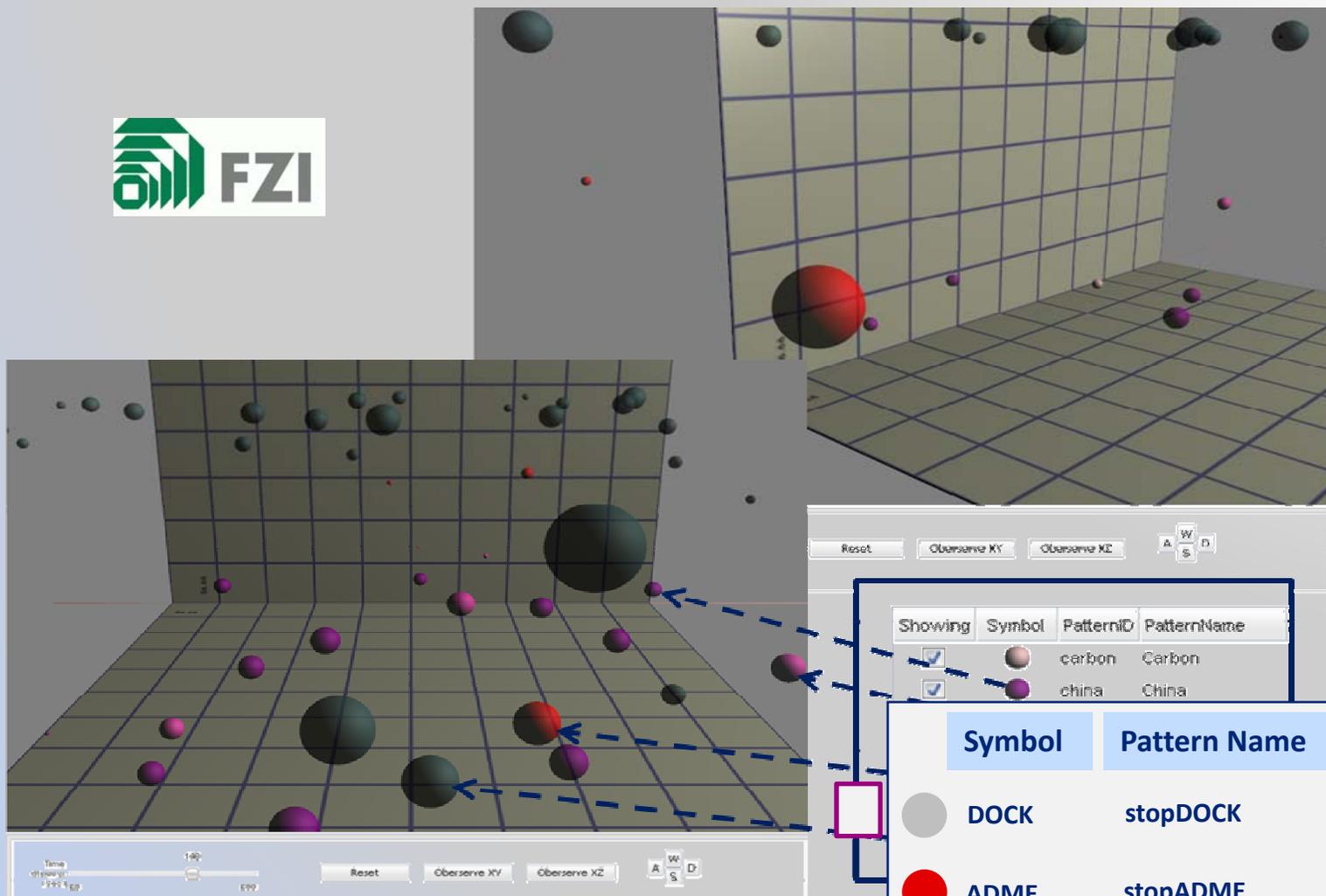
Synergy

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

OpenTox



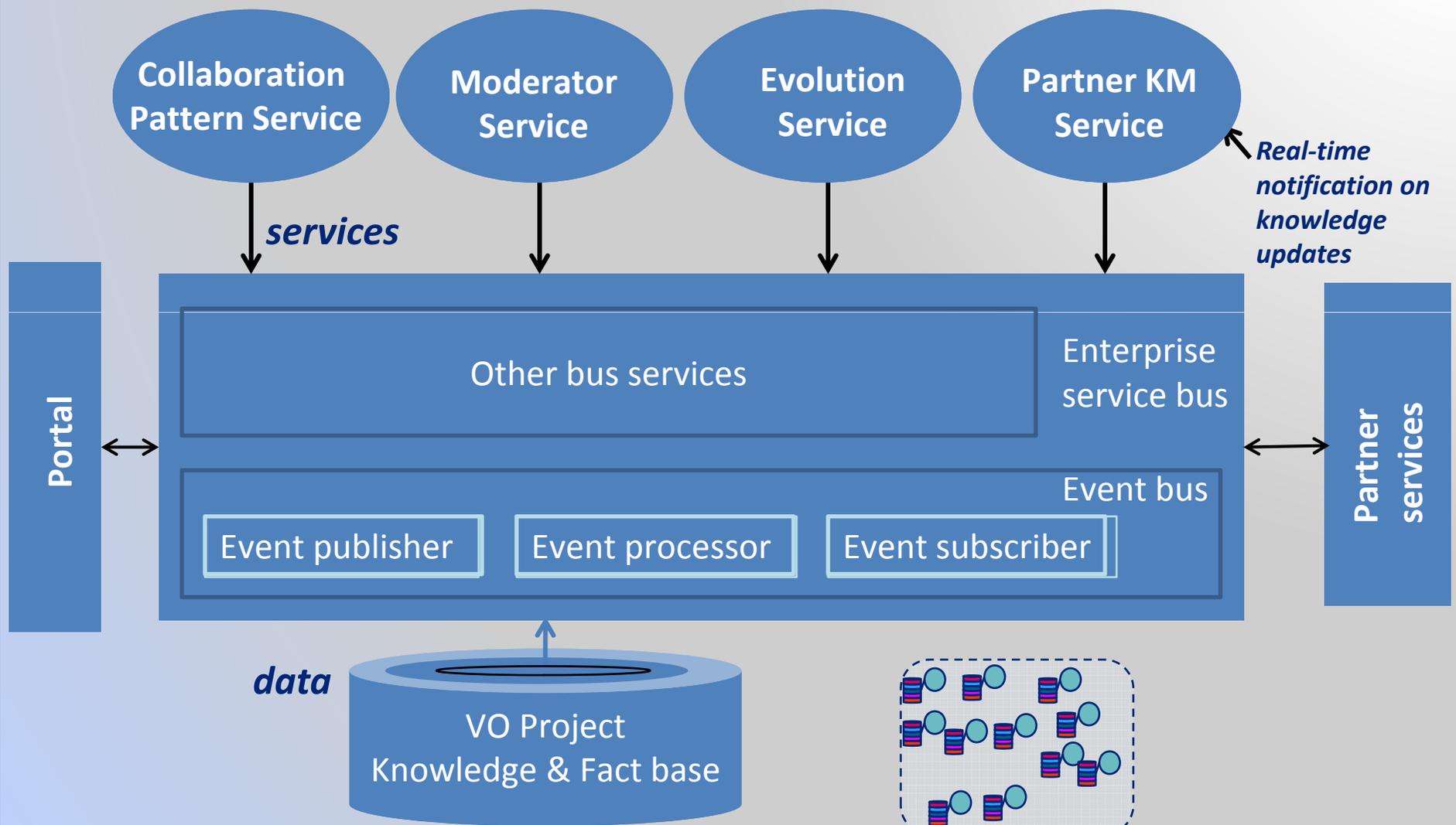
Complex Events Stream



Showing	Symbol	PatternID	PatternName
<input checked="" type="checkbox"/>		carbon	Carbon
<input checked="" type="checkbox"/>		china	China

Symbol	Pattern Name
	DOCK stopDOCK
	ADME stopADME
	TOX stopTOX

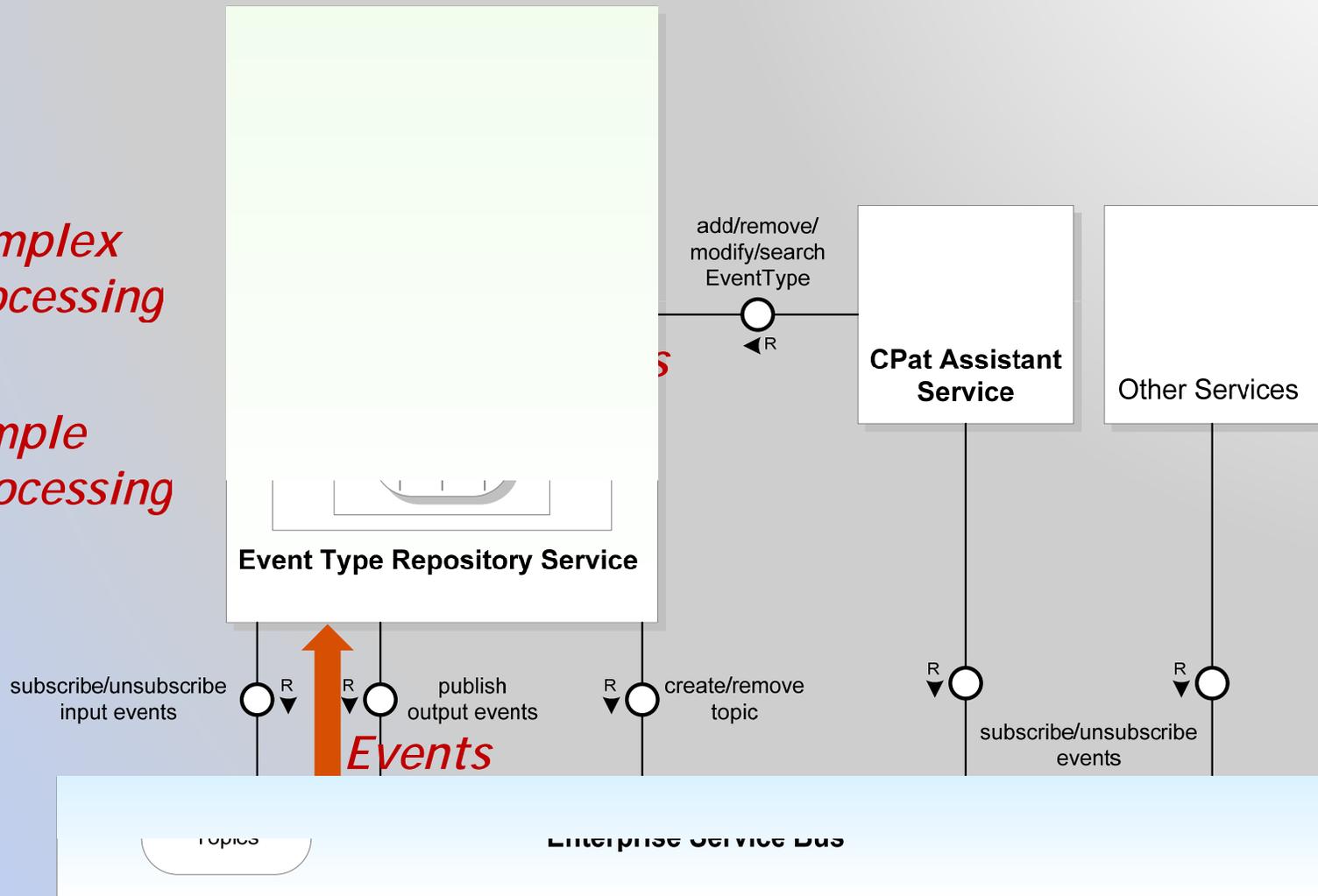
SYNERGY Service Support



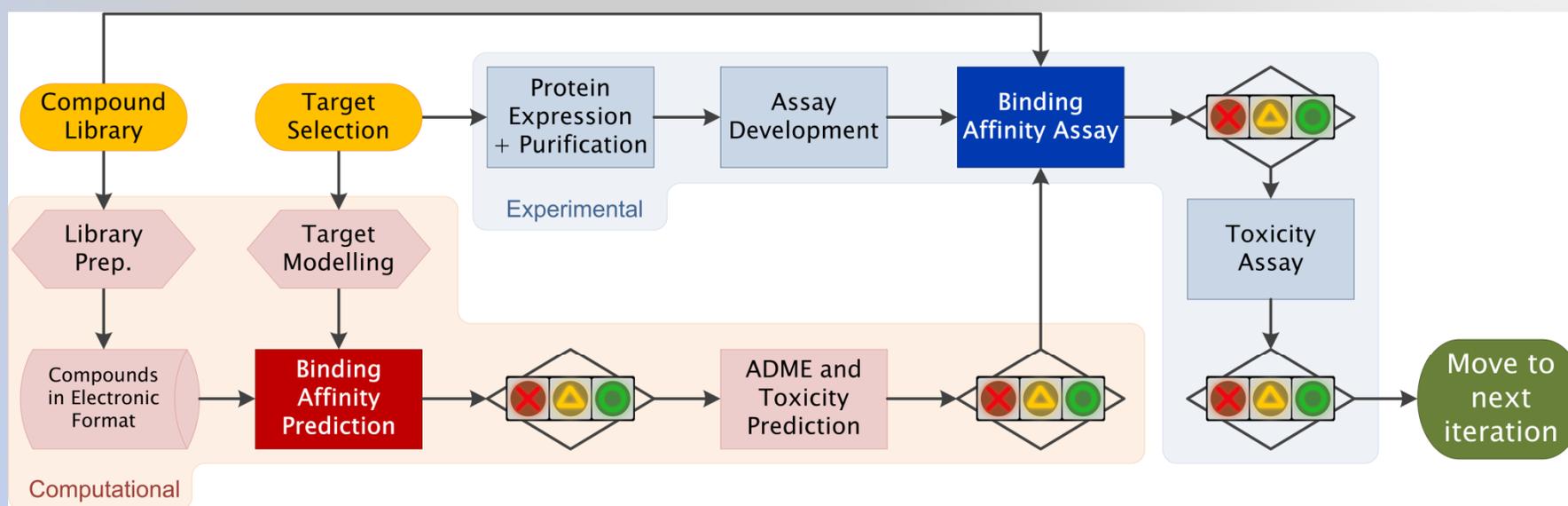
SYNERGY Complex Event Processing

Complex processing

Simple processing



Incorporation of Holistic Predictive ADME & Toxicity



Predictive toxicology model building



The screenshot shows the ToxPredict web application in a Mozilla Firefox browser. The page title is "ToxPredict" and it is described as an "OpenTox demo application". A progress bar at the top indicates five steps: Step 1: Search (Select structure(s)), Step 2: Verify structure (Verify structure), Step 3: Models (Select prediction models), Step 4: Estimate (Estimate), and Step 5: Results (Display results). A "NEXT" button is visible at the end of the progress bar. Below the progress bar is a table with the following columns: Endpoint, Model, Descriptors, Training dataset, and Algorithm.

Endpoint	Model	Descriptors	Training dataset	Algorithm
	<input checked="" type="checkbox"/> OpenTox model created with TUM's kNNregression model learning web service.	YES	http://opentox.informatik.tu-muenchen.de:8080/OpenTox-dev/algorithm/kNNregression	
Carcinogenicity	<input checked="" type="checkbox"/> ToxTree: Bonigni/Bossa rules for carcinogenicity and mutagenicity	-		ToxTree: Bonigni/Bossa rules for carcinogenicity and mutagenicity
Dissociation constant (pKa)	<input checked="" type="checkbox"/> pKa	-		pKa
Endpoints	<input checked="" type="checkbox"/> ToxTree: Structure Alerts for the in vivo micronucleus assay in rodents	-		ToxTree: Structure Alerts for the in vivo micronucleus assay in rodents
Endpoints	<input checked="" type="checkbox"/> ToxTree: Michael acceptors	-		ToxTree: Michael acceptors
Eye irritation/corrosion	<input checked="" type="checkbox"/> ToxTree: Eye irritation	-		ToxTree: Eye irritation
Human health effects	<input checked="" type="checkbox"/> ToxTree: Extended Cramer rules	-		ToxTree: Extended Cramer rules
Human health effects	<input checked="" type="checkbox"/> ToxTree: ILSI/Kroes decision tree for TTC	-		ToxTree: ILSI/Kroes decision tree for TTC
Skin irritation/corrosion	<input checked="" type="checkbox"/> ToxTree: Skin irritation	-		ToxTree: Skin irritation

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

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



www.opentox.org



Predictive toxicology model building



The screenshot shows the ToxPredict web application interface. On the left, there is a table with two columns: "Endpoint" and "Model". The table lists various toxicological endpoints and the models used for their prediction. On the right, there is a map of Europe with several green circular markers placed over different countries, indicating a distributed network of applications.

Endpoint	Model
	OpenTox model creation TUM's kNN regression machine learning web service.
Carcinogenicity	ToxTree: Benigni/Bo for carcinogenicity and mutagenicity
Dissociation constant (pKa)	pKa
Endpoints	ToxTree: Structure A the in vivo micronucleus rodents
Endpoints	ToxTree: Michael acc
Eye irritation/corrosion	ToxTree: Eye irritation
Human health effects	ToxTree: Extended C rules
Human health effects	ToxTree: ILSI/Kroes tree for TTC
Skin irritation /corrosion	ToxTree: Skin irritati

Simple but
application
methods a

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



Predictive toxicology model building



Models - Mozilla Firefox

http://apps.ideaconsult.net:8180/ToxPredict/user/4996263b-9d7c-4fec-8b68-15e38c29e7cd/A/step3

ToxPredict

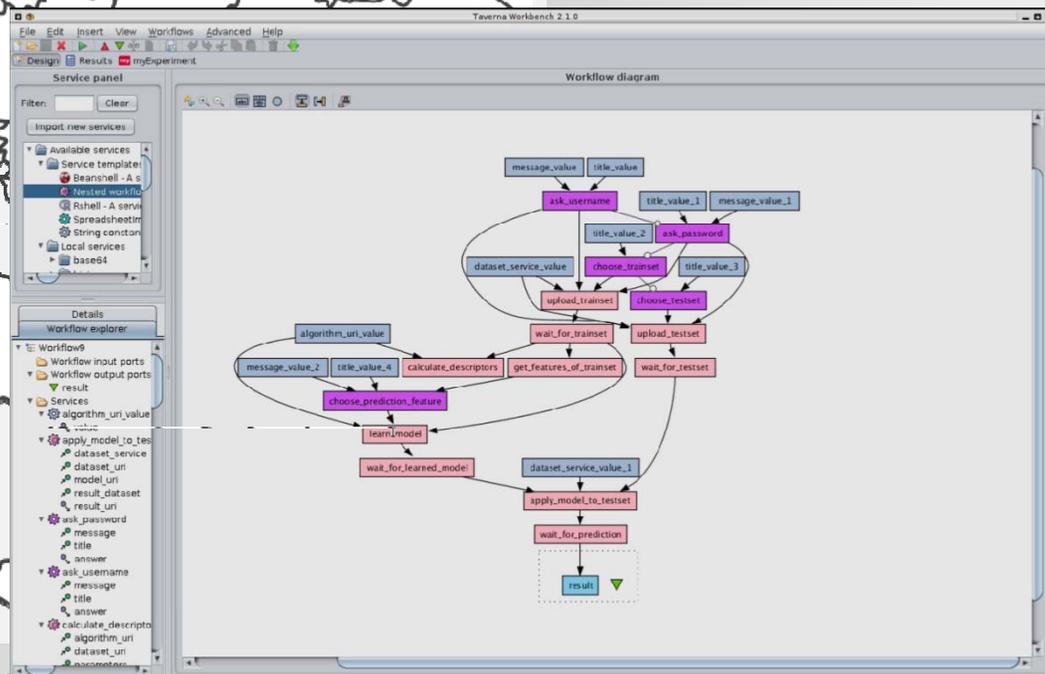
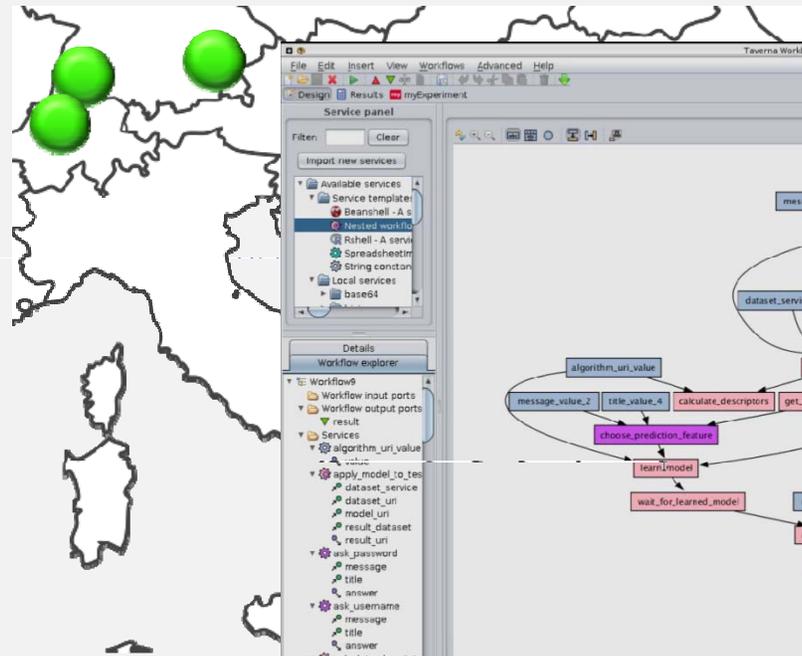
OpenTox demo application

Step 1: Search
Select structure(s)

Step 2: Verify structure
Verify structure

Endpoint	Model
	OpenTox model creation: TUM's kNN regression model learning web service.
Carcinogenicity	ToxTree: Bonigni/Bos for carcinogenicity and mutagenicity
Dissociation constant (pKa)	pKa
Endpoints	ToxTree: Structure Alerts in the in vivo micronucleus test in rodents
Endpoints	ToxTree: Michael acceptance
Eye irritation/corrosion	ToxTree: Eye irritation
Human health effects	ToxTree: Extended Cramer rules
Human health effects	ToxTree: ILSI/Kroes decision tree for TTC
Skin irritation/corrosion	ToxTree: Skin irritation

Done



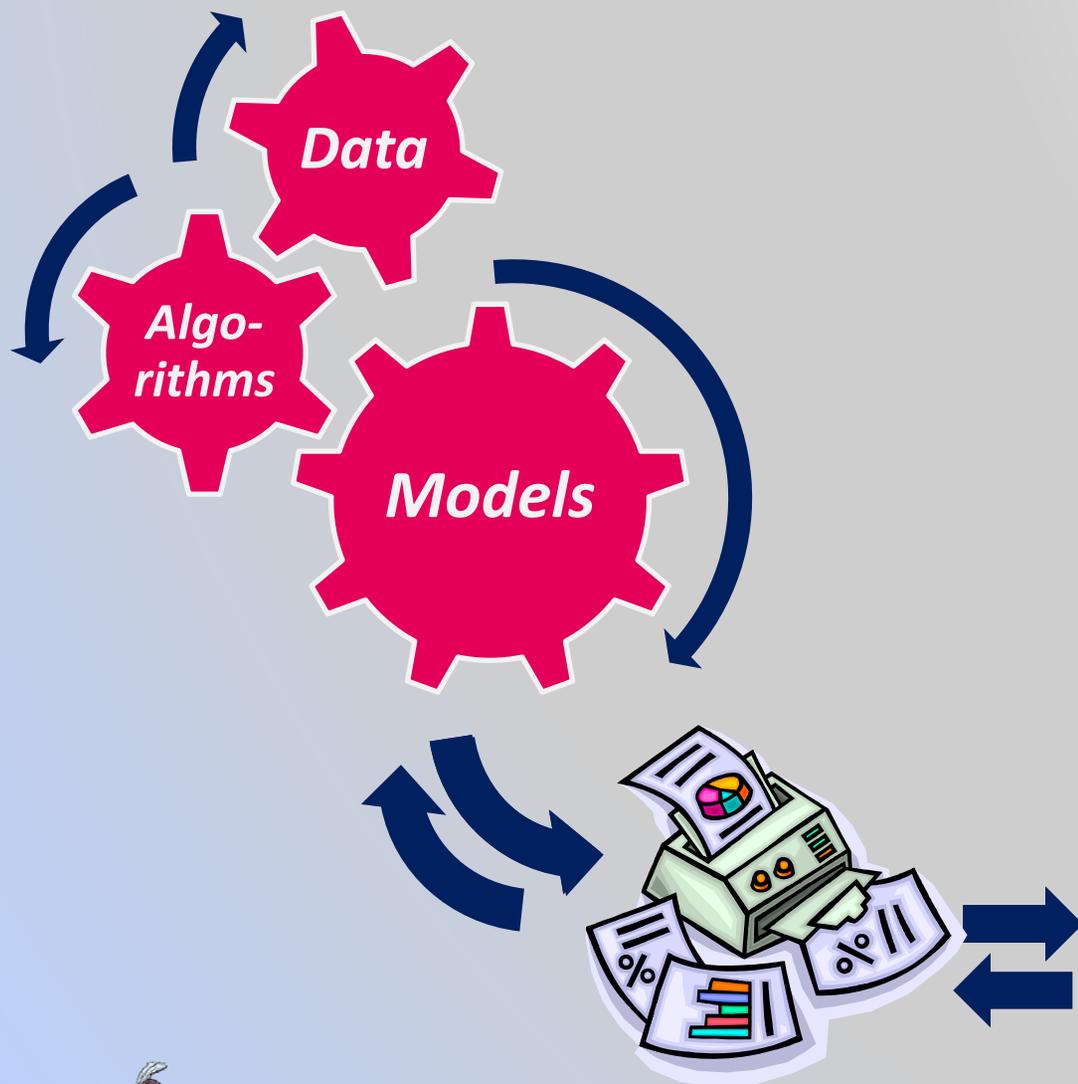
Simple building blocks for applications and methods and

Distributed and wide range of methods

Integration into workflow systems for computational biology (Taverna)



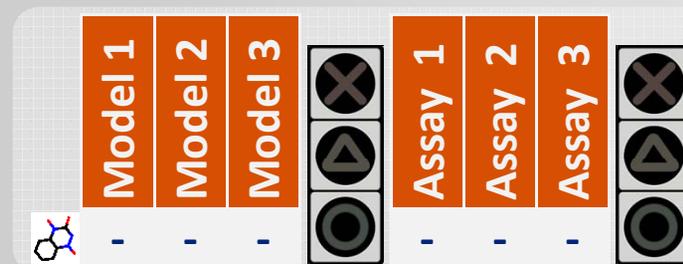
Predictive toxicology model building



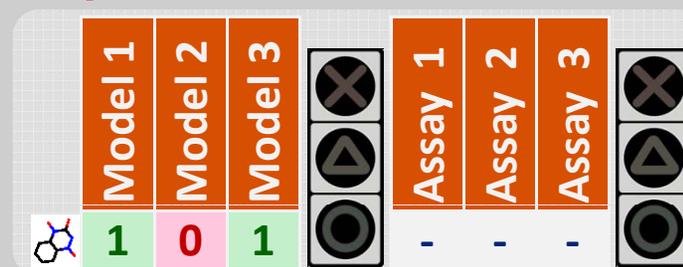
ELN



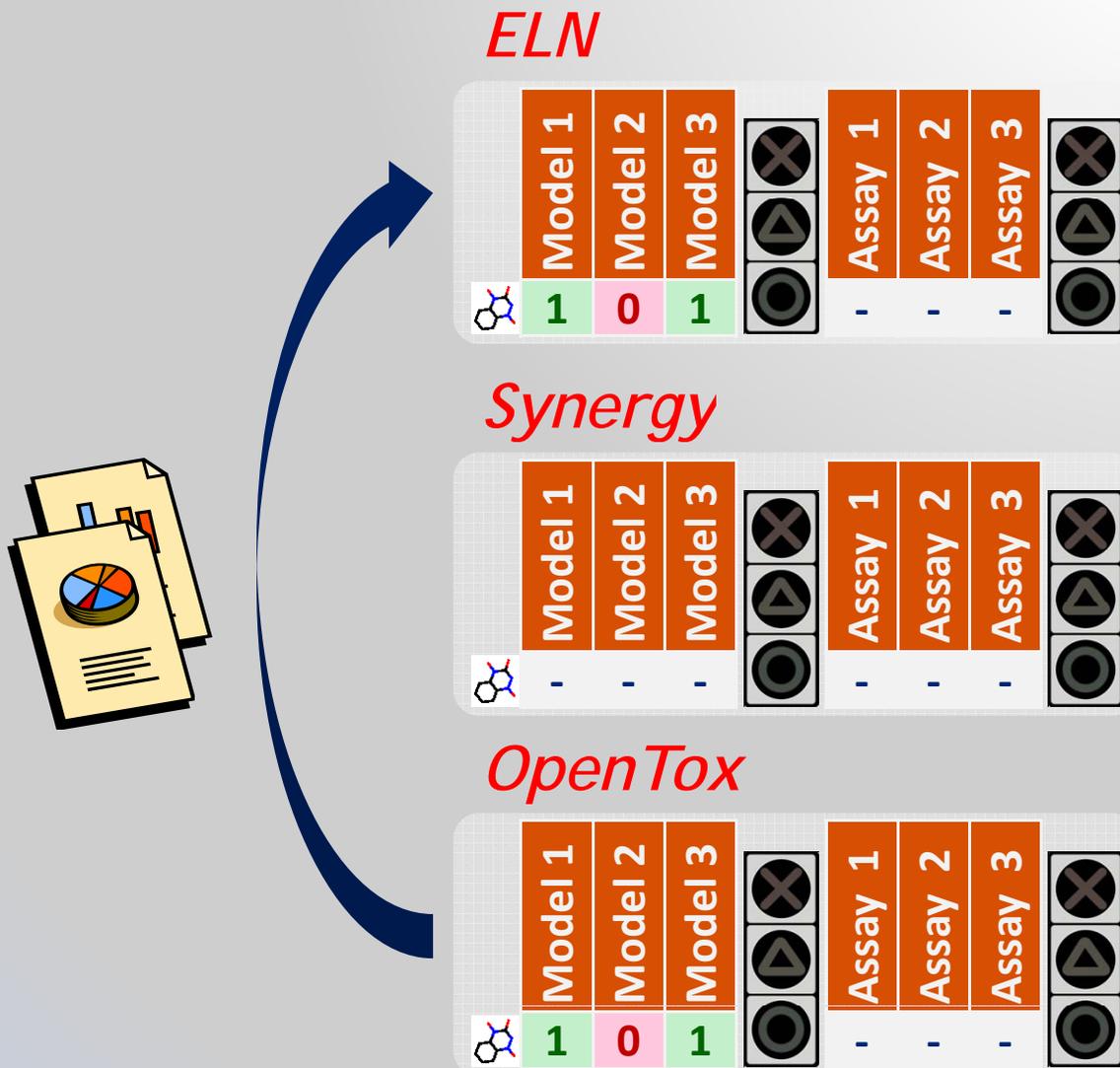
Synergy



OpenTox



Predictive toxicology model building



Bioclipse - OpenTox Interoperation

The screenshot displays the Bioclipse software interface. The main window shows a chemical structure of a complex polycyclic molecule with an epoxide ring highlighted in red. The word "Changed" is written in purple above the structure. The interface includes a menu bar (File, Edit, Window, Help), a toolbar, and several panels:

- Decision Support:** A tree view showing analysis results:
 - Ames Structural Alerts [1 pos]
 - Epoxide
 - Ames exact matches [no hits]
 - Ames nearest neighbour [3 pos, 1 neg]
 - 26761-45-5 [tanimoto=0.82]
 - 2461-18-9 [tanimoto=0.81]
 - 2461-15-6 [tanimoto=0.73]
 - 5926-90-9 [tanimoto=0.71]
 - OpenTox
 - Caco-2 Cell Permeability <http://www.n>
 - caco2 = -4.548099994659424
 - Lipinski Rule of Five
 - LipinskiFailures = 0.0
 - MolecularWeight
- Properties:** A table showing the classification and test results for the selected structure.

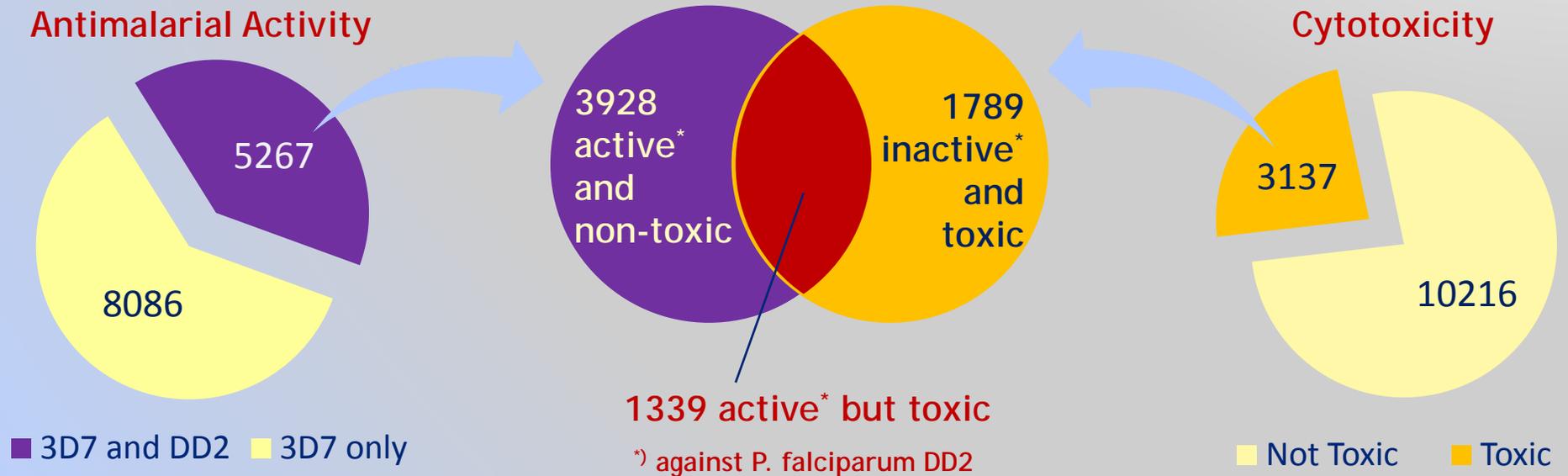
Property	Value
General	
Classification	POSITIVE
Matching atoms	22, 21, 23
Name	Epoxide
Test	Ames Structural Alerts

TCAMs Malaria Box - Predictive Toxicology Workflow Development & validation

“Malaria Box”*: A collection of chemical compounds active against (*i.e. inhibiting growth of*) the malaria parasite *Plasmodium falciparum*

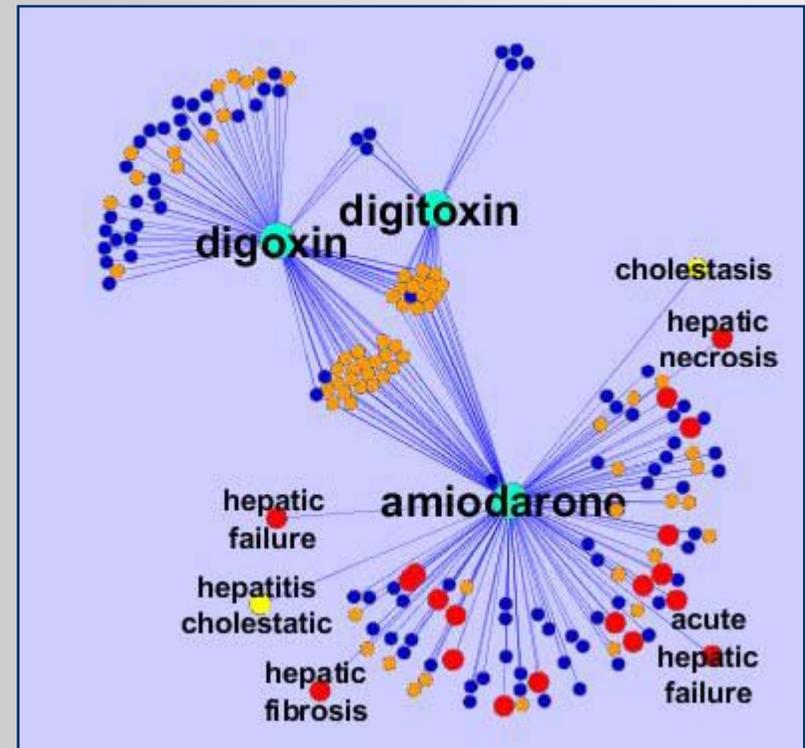
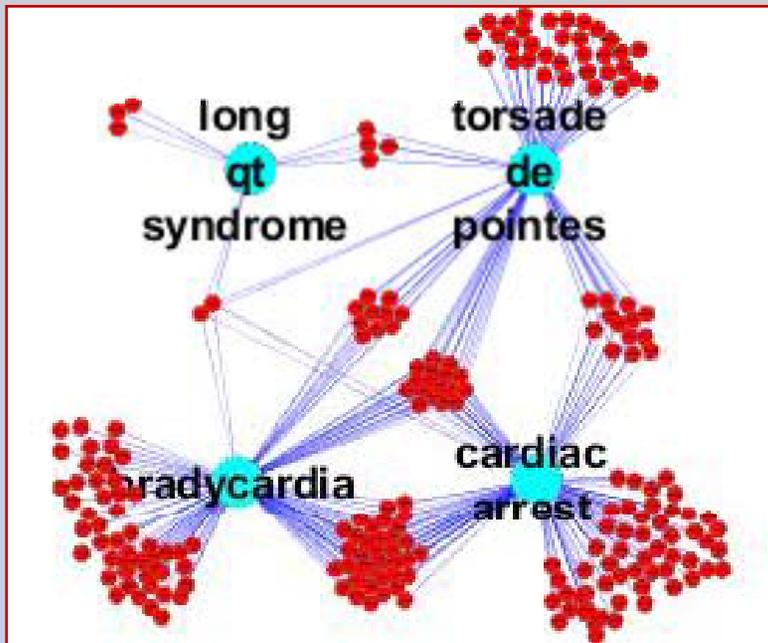
Data provided that is relevant for this project:

- Activity against (growth inhibition of) *P. falciparum* strain 3D7 (common strain)
- Activity against (growth inhibition of) *P. falciparum* strain DD2 (multi-drug resistant strain)
- Cytotoxicity against (growth inhibition of) human hepatocytes, HepG2 (hepatoma cells)



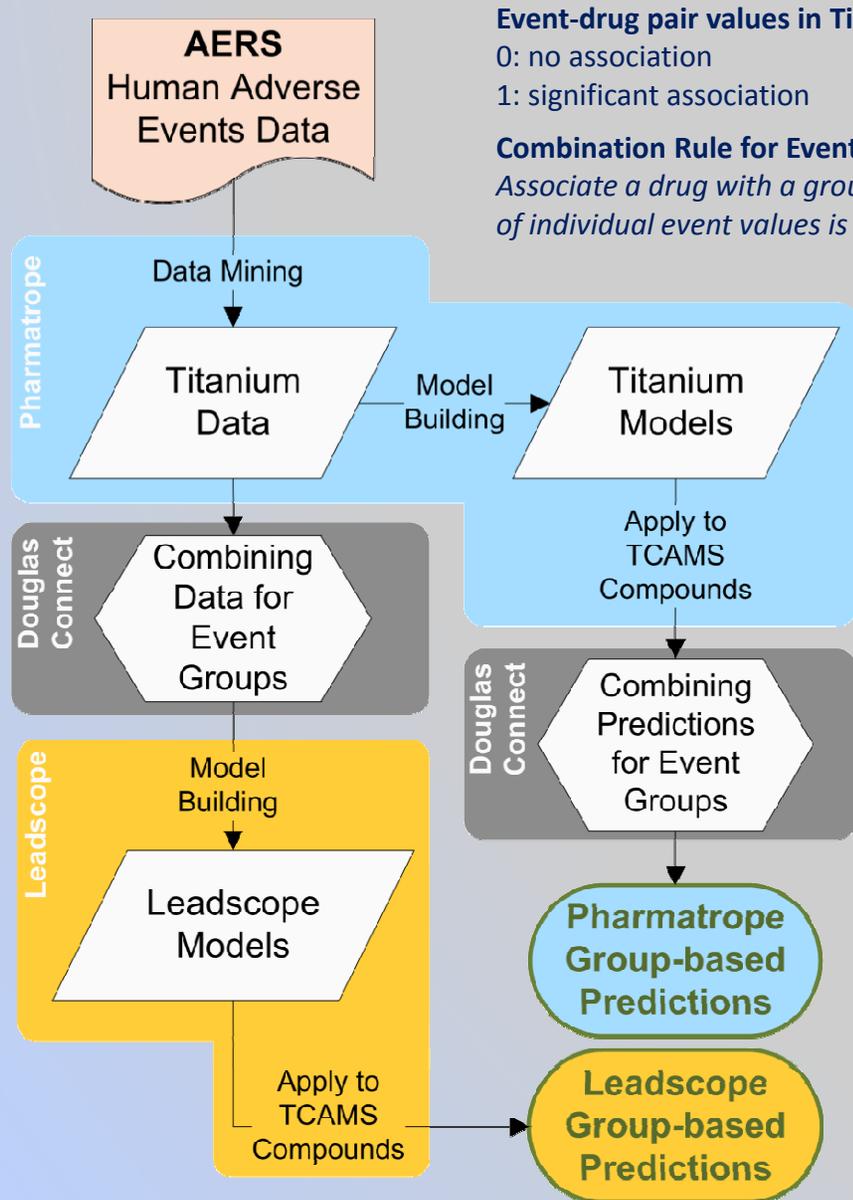
*Gamo et al., *Nature* **465**(7296), 305-10 (2010)

Mining Human Adverse Events



PHARMATROPE

Adverse Events Model Development



Event-drug pair values in Titanium Data:

- 0: no association
- 1: significant association

Combination Rule for Event Groups:

Associate a drug with a group if the sum of individual event values is non-zero

Event-drug pair values in Titanium Predictions:

- 0 : no association (0)
- 0.35-0.4 : non-significant association (0)
- > 0.4 : significant association (1)

Combination Rule for Event Groups:

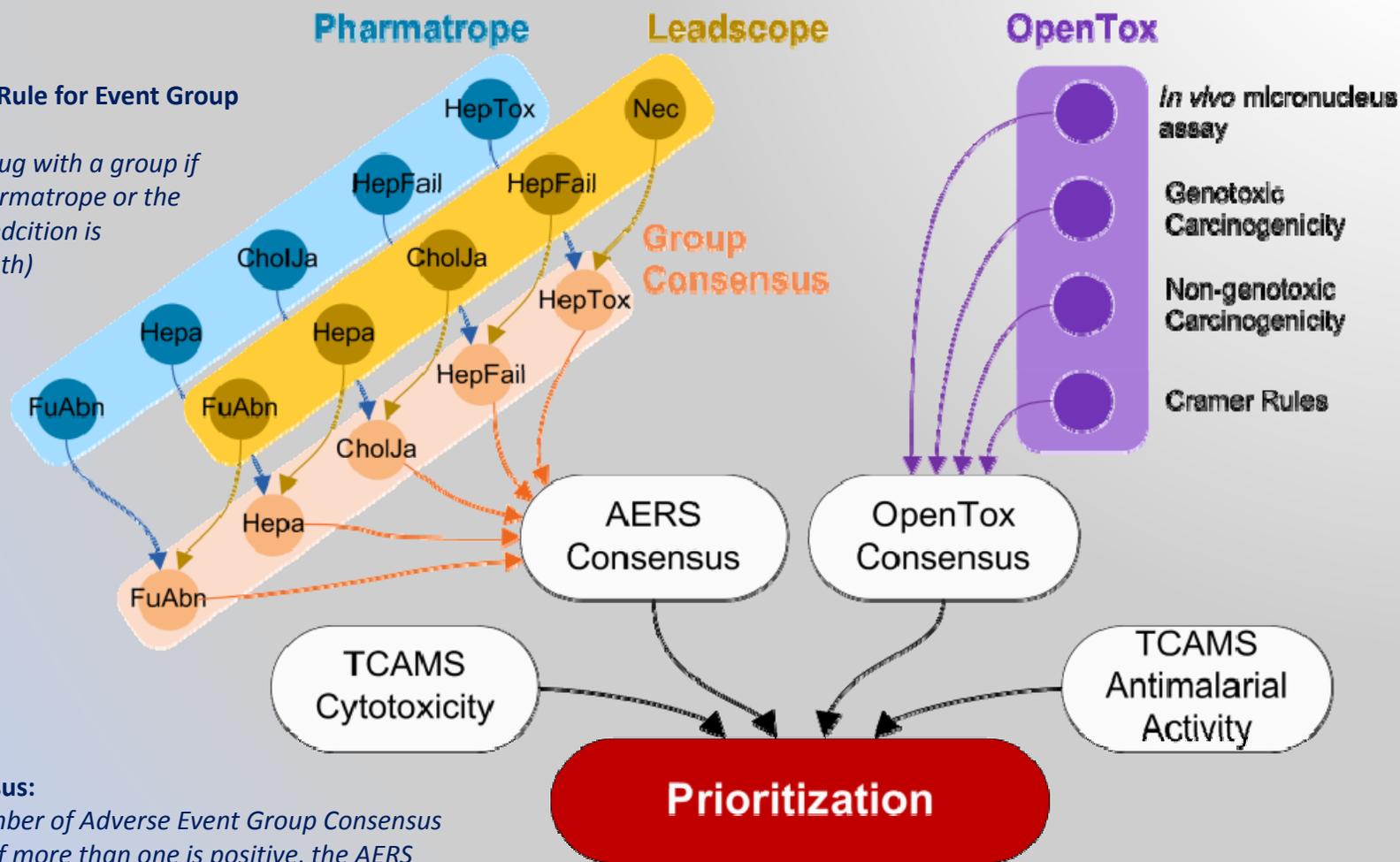
Associate a drug with a group if the sum of individual event values is larger of equal to 0.4.

Adverse Event Groups	Group Name
Hepatic function abnormal Liver disorder	FuAbn
Hepatic necrosis	Nec
Cytolytic hepatitis Hepatitis Hepatitis acute Hepatitis toxic	Hepa
Cholestasis Jaundice Hepatitis cholestatic jaundice cholestatic Yellow skin	CholJa
Hepatic failure Hepatitis fulminant Acute hepatic failure Hepatorenal failure	HepFail
Hepatotoxicity Hepatomegaly Hyperbilirubinaemia Hepatosplenomegaly	HepTox

Combining Predictions & Experimental Data

Combination Rule for Event Group Predictions:

Associate a drug with a group if either the Pharmatrope or the Leadscope prediction is positive (or both)



AERS Consensus:

Count the number of Adverse Event Group Consensus associations. If more than one is positive, the AERS Consensus is positive.

OpenTox Consensus:

Negative if both carcinogenicity and the micronucleus assay predictions are negative, OR if the Cramer Rule classification is Class I. Positive otherwise.

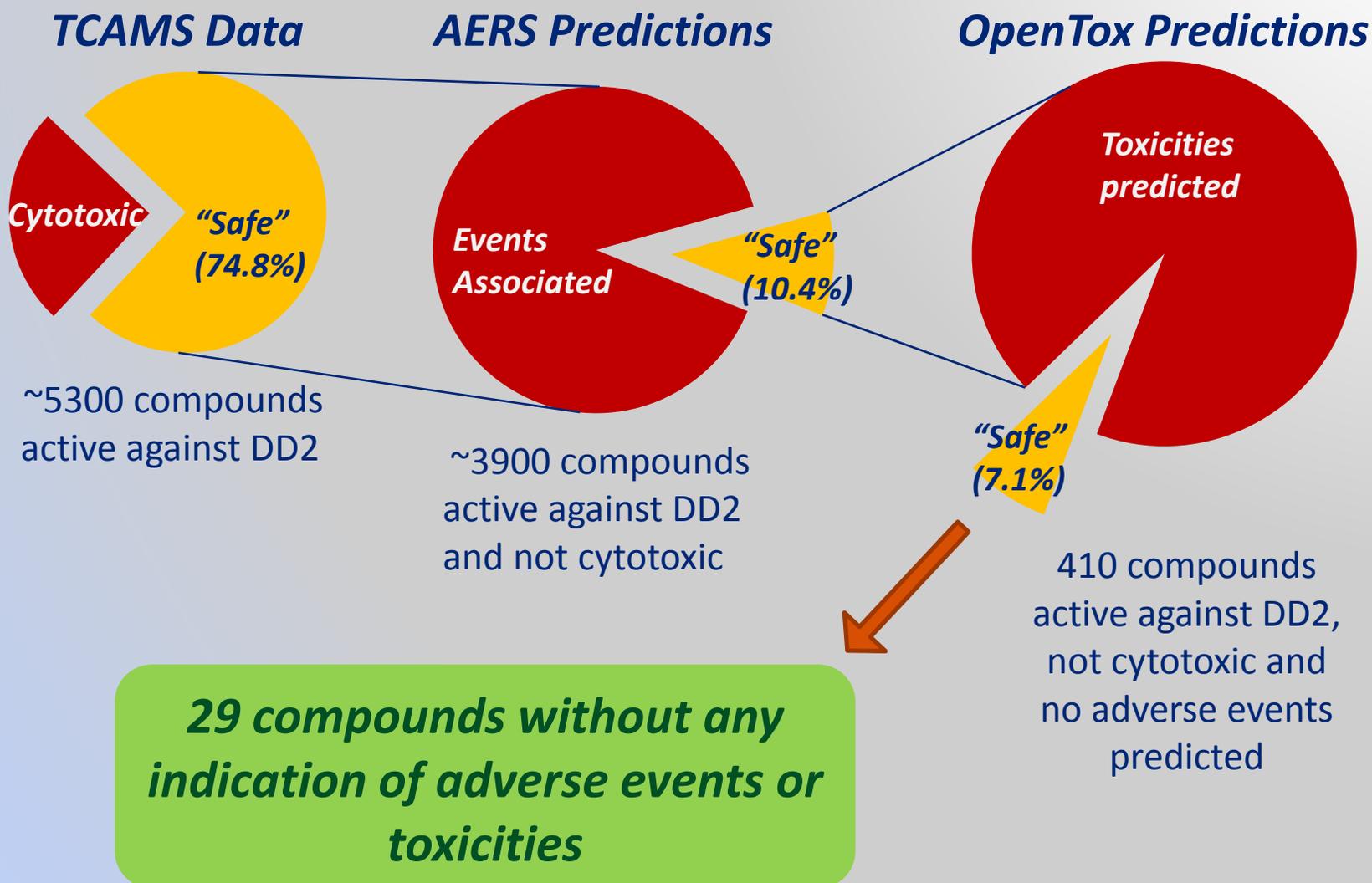
TCAMS Cytotoxicity:

Positive if > 30% growth inhibition at 10 μ M.

TCAMS Antimalarial Activity:

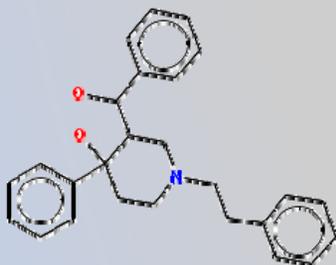
Positive if > 80% growth inhibition of *P. Falciparum* DD2 at 2 μ M.

Compound Prioritisation Filtering



Example Classified Compounds

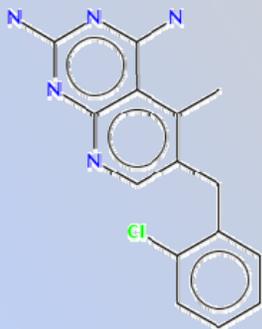
"Safe"



TCMDC-131287:

- No predicted association with adverse events (consistent)
- Negative for carcinogenicity and mutagenicity
- No inhibition of HepG2 growth
- Strong inhibition of *P. falciparum* DD2 growth

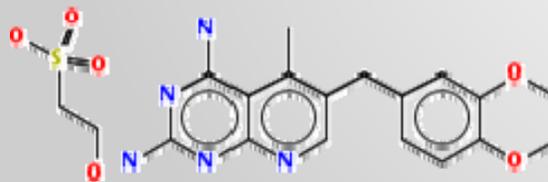
"Toxic"



TCMDC-137245:

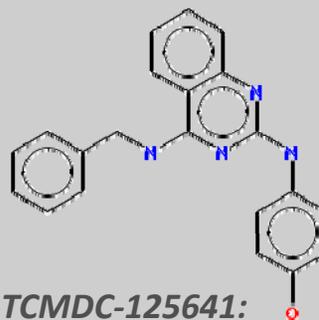
- Associated with 4 and 5 (out of 5) adverse events group by Pharmatropo and Leadscope, respectively
- Positive for carcinogenicity and mutagenicity, Cramer Class III
- 67% HepG2 inhibition (10 μ M)
- 91% *P. falciparum* DD2 growth inhibition (at 2 μ M)

Ambiguous, Further Data Required



TCMDC-138057:

- Predicted association with many adverse events groups
- Positive for carcinogenicity and mutagenicity
- Considered safe (Class I) with Cramer rules
- Inhibition of HepG2 growth could not be measured
- Strong inhibition of *P. falciparum* DD2 growth



TCMDC-125641:

- No adverse event association predicted with Pharmatropo models
- Strong association with all five adverse events groups predicted with the Leadscope models
- Negative for carcinogenicity and mutagenicity
- Intermediate inhibition of HepG2 growth (33% at 10 μ M)
- Strong inhibition of *P. falciparum* DD2 growth (100% at 2 μ M)

Future Directions

Collaborations

- Develop Malaria R&D project (e.g., chemistry, targets, libraries, Kinome Knowledge Base)
- Support New Collaborative Discovery Projects
- Multi-Project Resource Management
- Progress Collaborative Innovation in “Blue Ocean” areas
- Develop Collaboration Pool, Member Profiles & Legal/IP Templates

Collaboration Infrastructure

- Add Services in the Cloud Capability for data management, model building
- Integrated Omics Analysis, Biomarkers
- Weight of Evidence Methods and Workflows
- Support of hESC and iPSC protocols, assays, data
- Add Partners who can plugin value-add services, resources



Caprivi Delta, Namibia

Many High Risk areas for Malaria lack local resources (e.g., doctors, medicines, roads, nutrition, water etc.,).

Simple solutions (e.g., nets, needles) can have significant impact.

New innovation and bottom-of the pyramid business models are needed.



Caprivi Delta, Namibia



Current Realities (we can impact on):

- 1) Many of the parents of these children may die of AIDS
- 2) Many of these children will be infected with malaria
- 3) Many 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

