Genomics for the development of new control tools for schistosomiasis

Guilherme Oliveira, Alexandria, Egypt - 2014

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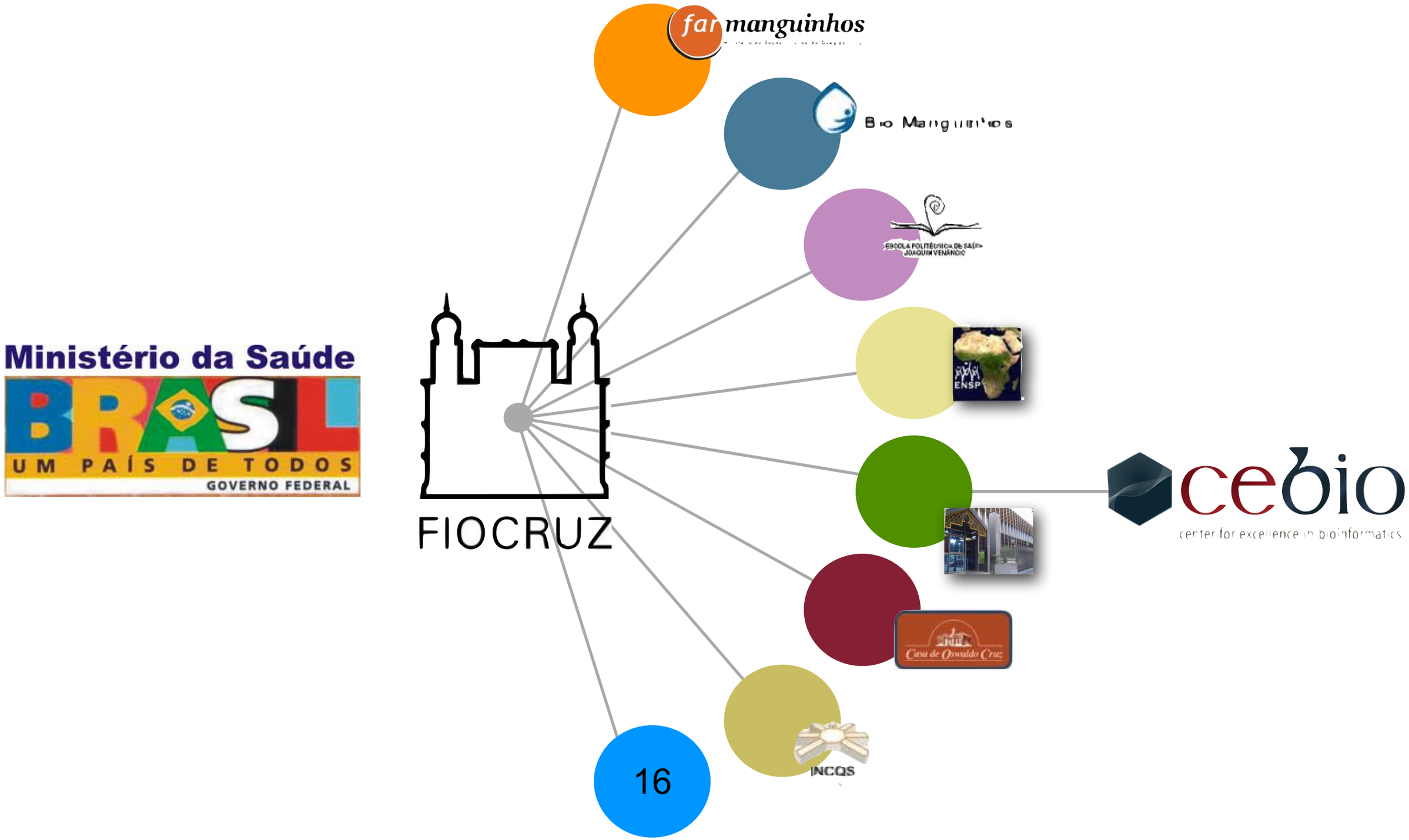
FIOCRUZ


farmanguinhos
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Ministério da Saúde
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cebio
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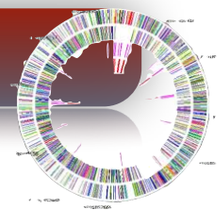
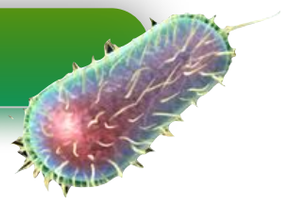
Genomics and Bioinformatics



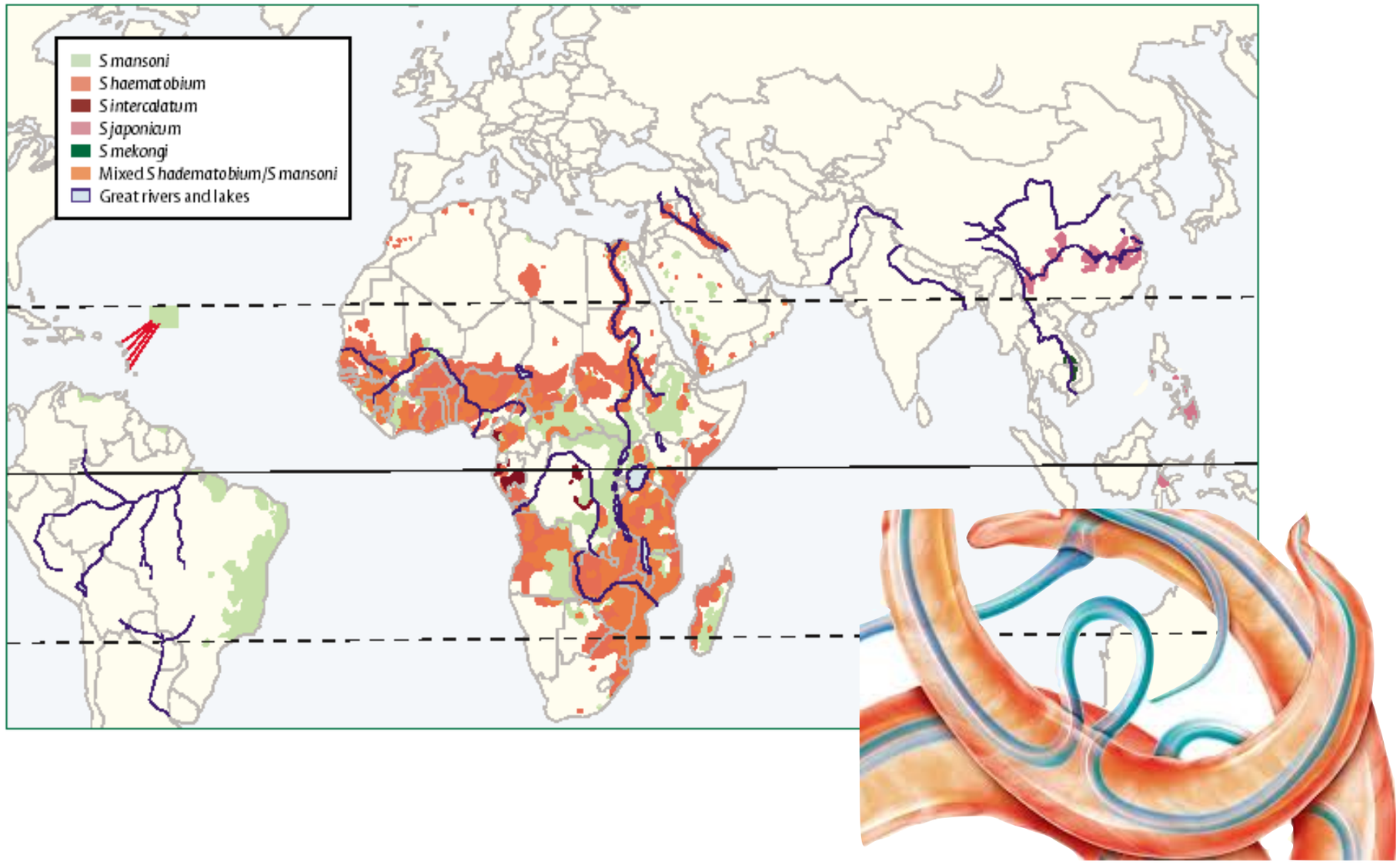
Academic projects
R&D with industry

Biotecnology

Synthetic Biology

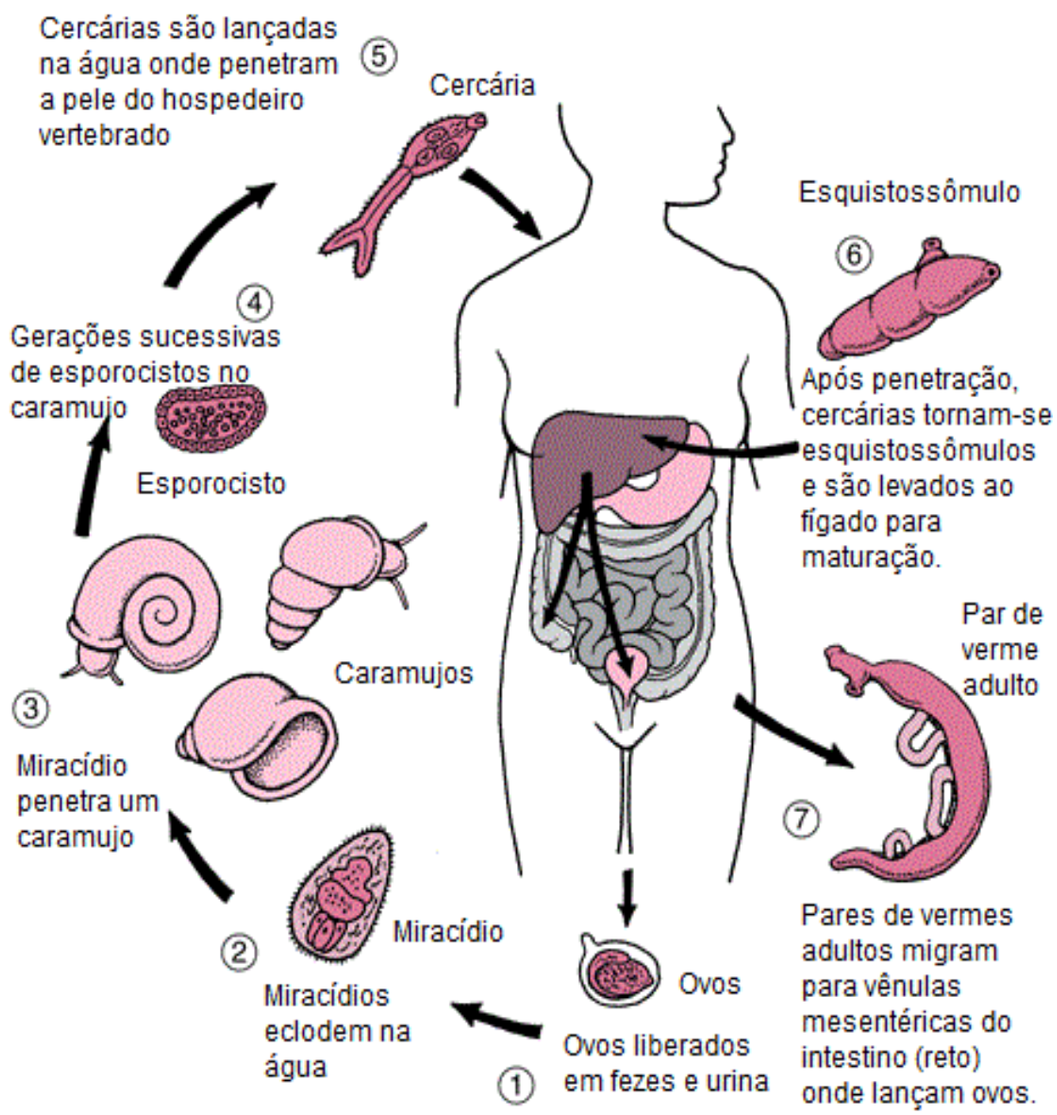


Schistosomiasis

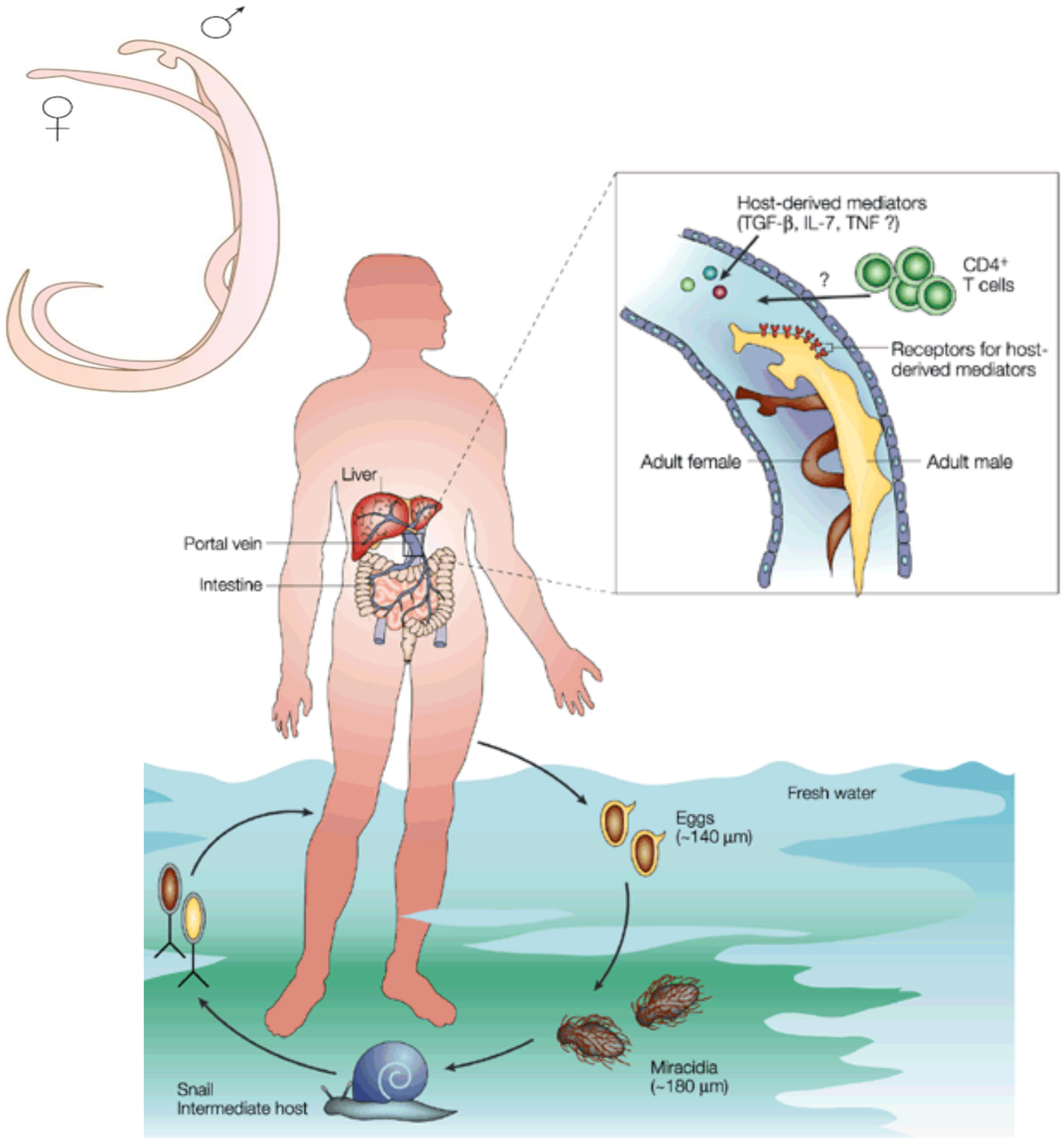


- ✓ 200 million infected
- ✓ Over 200 thousand deaths/year

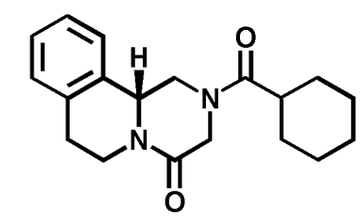
The *Schistosoma mansoni*



Schistosomiasis



Control

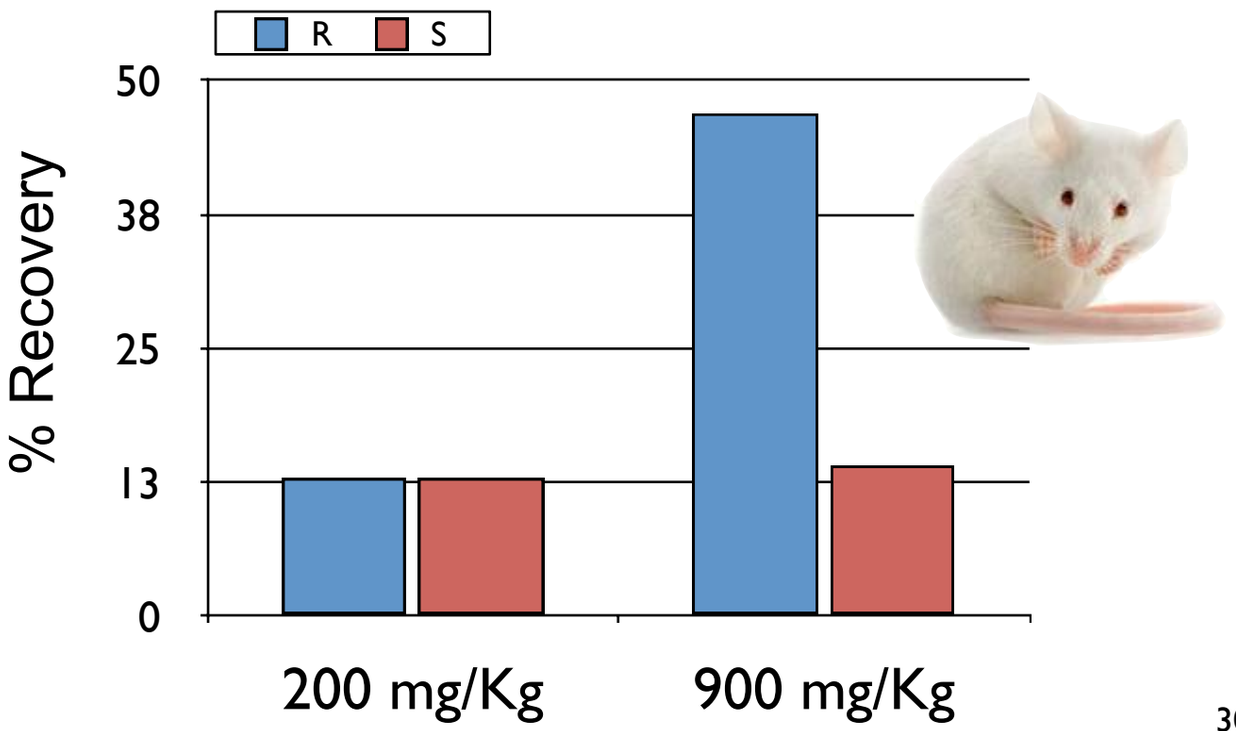


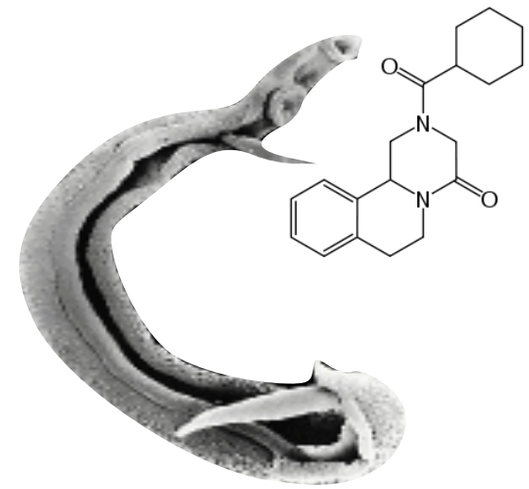
1, Praziquantel (PZQ)

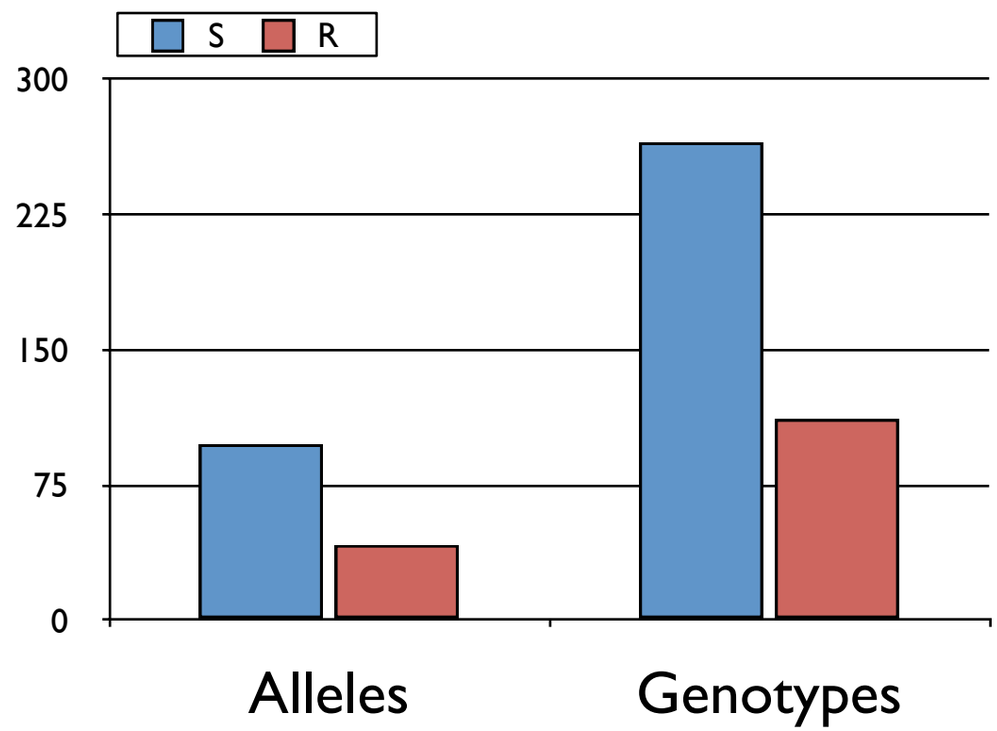
- No vaccine
- One drug
- Resistance?

Resistance

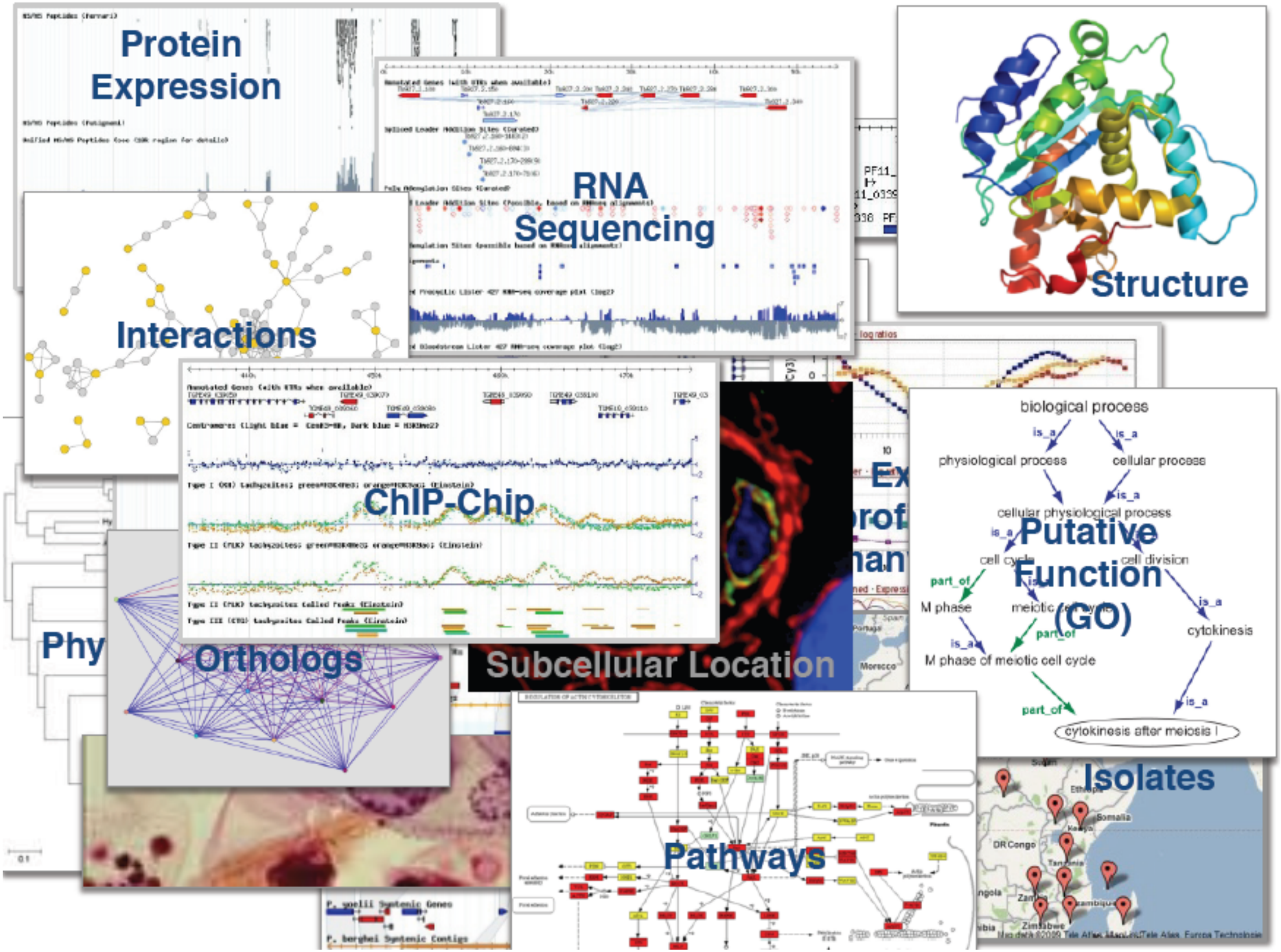
Coeli *et al.*, PLoS NTD, 2013







Genomics


Protein Expression
RNA Sequencing
Structure
Interactions
ChIP-Chip
Putative Function (GO)
biological process
physiological process
cellular process
cellular physiological process
cell cycle
cell division
M phase
cytokinesis
M phase of meiotic cell cycle
cytokinesis after meiosis I
Orthologs
Subcellular Location
Pathways
Isolates

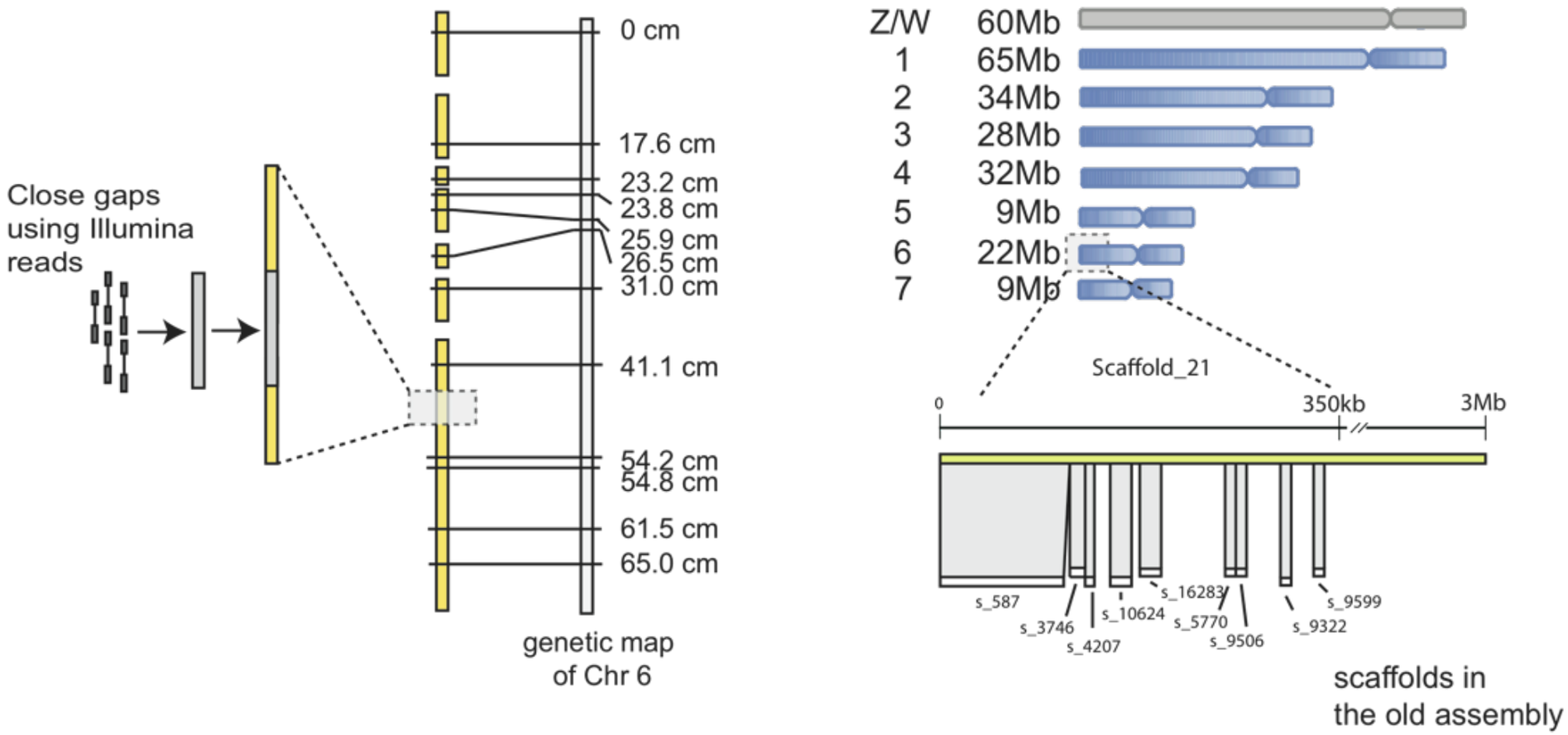
Making use of the genome

Berriman *et al*., Nature, 2009
Protasio *et al.*, PLoS NTD, 2012
Young *et al.*, Nature Genetics 2012

Genomic features	***S. mansoni***	***S. haematobium***	***S. japonicum***
Sequencing Methods	WGS	WGA	WGS
Genome size (Mb)	381	385	403
Repetitive elements (%)	45	47,2	40,1
GC content (%)	34,7	34,3	33.5
% coding genome	4,72	4,43	4,32
Number of predicted genes	10.852	13.073	13.469
Gene lenght (average)	13.397	11.952	10.003
Exon number per gene (average)	6,2	5,4	5,3
Exons lenght (average)	218	246	223
Intron lenght (average)	2.331	2.442	2.058

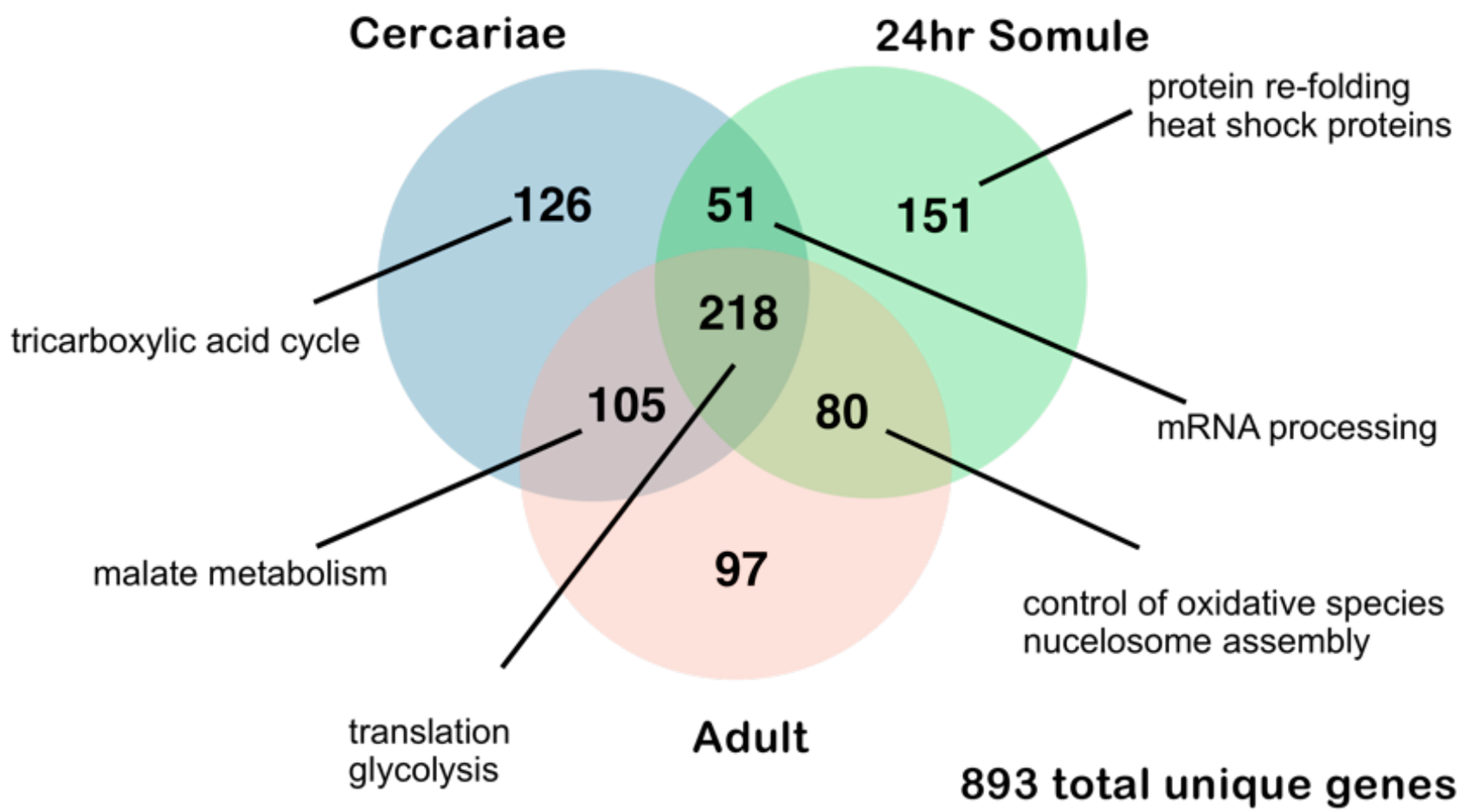
Making use of the genome

Berriman *et al*., Nature, 2009
Protasio *et al.*, PLoS NTD, 2012
Young *et al.*, Nature Genetics 2012



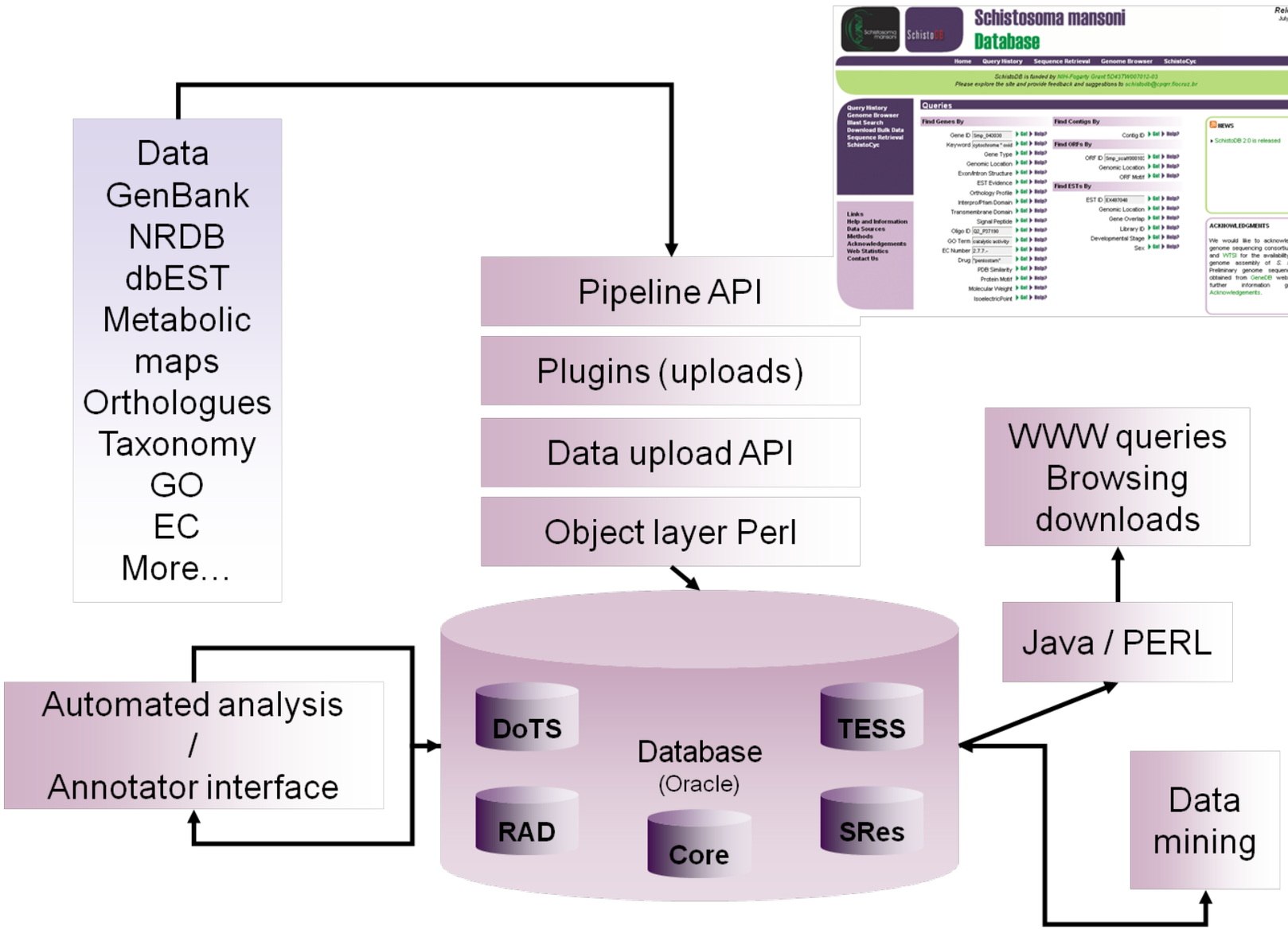
Making use of the genome

Berriman *et al*., Nature, 2009
Protasio *et al.*, PLoS NTD, 2012
Young *et al.*, Nature Genetics 2012



Data integraton: SchistoDB

Zerlotini *et al.*, NAR, 2009
Zerlotini *et al.*, NAR 2012



SchistoDB 3.0

FIOCRUZ
CPqRR / FIOCRUZ
FIOCRUZ MINAS
Centro de Pesquisas René Rachou
Genomics and Computational Biology Group

SchistoDB Version 3.0 15 Aug 11
Schistosoma Genomic Resources
A EuPathDB Project

Gene ID: Smp_089330 Gene Text Search: synth*

About SchistoDB | Help | Contact Us | Login | Register

Home | New Search | My Strategies | My Basket (0) | Tools | Data Summary | Downloads | Community | My Favorites

Data Summary

News

- **15 August 2011** SchistoDB 3.0 is released of three species, Schistosoma mansoni, S. japonicum, S. haematobium with new EST, RNA-Seq, Mass Spec. and Assemblies Data.

All SchistoDB News

Community Resources

Web Tutorials

Information and Help
expand for 9 new items

Identify Genes by:

Expand All | Collapse All
- Text, IDs, Species
- Genomic Position
- Gene Attributes
- Protein Attributes
- Protein Features
- Similarity/Pattern
- Transcript Expression
- Cellular Location
- Putative Function
- Evolution

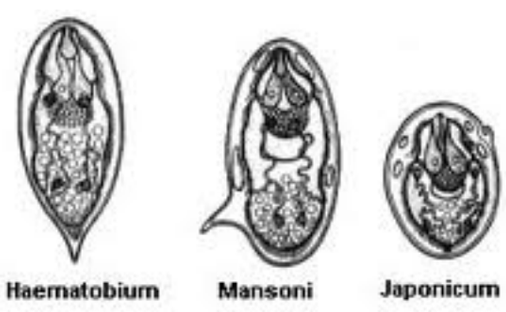
Identify Other Data Type:

Expand All | Collapse All
- Genomic Sequences
- Genomic Segments (DNA Motif)
- ESTs
- ORFs

Tools:

BLAST
Identify Sequence Similarities
Sequence Retrieval
Retrieve Specific Sequences using IDs and coordinates
PubMed and Entrez
View the Latest Pubmed and Entrez Results
Genome Browser
View Sequences and Features in the genome browser
Searches via Web Services
Learn about web service access to our data

www.schistodb.net



SchistoDB 3.0

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Identify Genes based on Predicted Signal Peptide

Organism: *Schistosoma japonicum*, *Schistosoma mansoni*

Advanced Parameters

Minimum SignalP-NN Conclusion Score: 3
Minimum SignalP-NN D-Score: 0.5
Minimum SignalP-HMM Signal Probability: 0.5
Matches any or all advanced parameters: any

Give this search a weight: 10
Optionally give this search a "weight" (for example 10, 200, -50, integer only).
In a search strategy, unions and intersects will sum the weights, giving higher scores to items found in multiple searches.

Give this search a name

Get Answer

Run a new Search for
Transform by Orthology
Add contents of Basket
Add existing Strategy
Filter by assigned Weight

Add Step

Add Step 2 : Transmembrane Domain Count

Minimum Number of Transmembrane Domains: 2
Maximum Number of Transmembrane Domains: 4
Organism: *Schistosoma japonicum*, *Schistosoma mansoni*

Give this search a weight: 10
Optionally give this search a "weight" (for example 10, 200, -50, integer only).
In a search strategy, unions and intersects will sum the weights, giving higher scores to items found in multiple searches.

Give this search a name

Combine Genes in Step 1 with Genes in Step 2:

1 Intersect 2 | 1 Minus 2
1 Union 2 | 2 Minus 1
1 Relative to 2 , using genomic colocation

Run Step

Description: Find genes with at least a given number of transmembrane domains.

Transmembrane domains were predicted using TMHMM2.

Close

My Strategies: New | Opened (1) | All (1) | Basket | Examples | Help

(Genes)

Signal Pep — 2874 Genes — Step 1
Transmb Dom — 1533 Genes — 504 Genes — Step 2
EST Evidence — 5228 Genes — 88 Genes — Step 3

Add Step

Signal Pep* Rename Copy Save As Share Delete

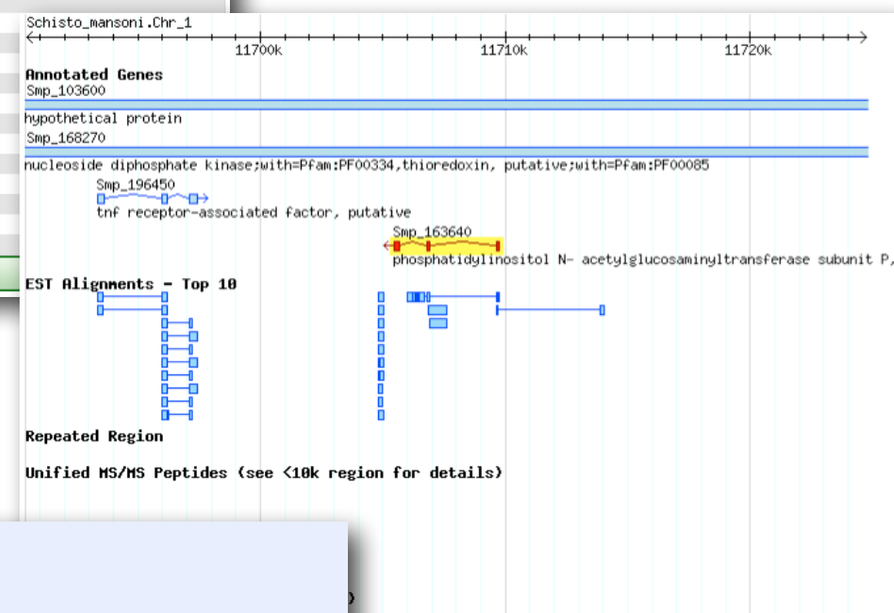
SchistoDB 3.0

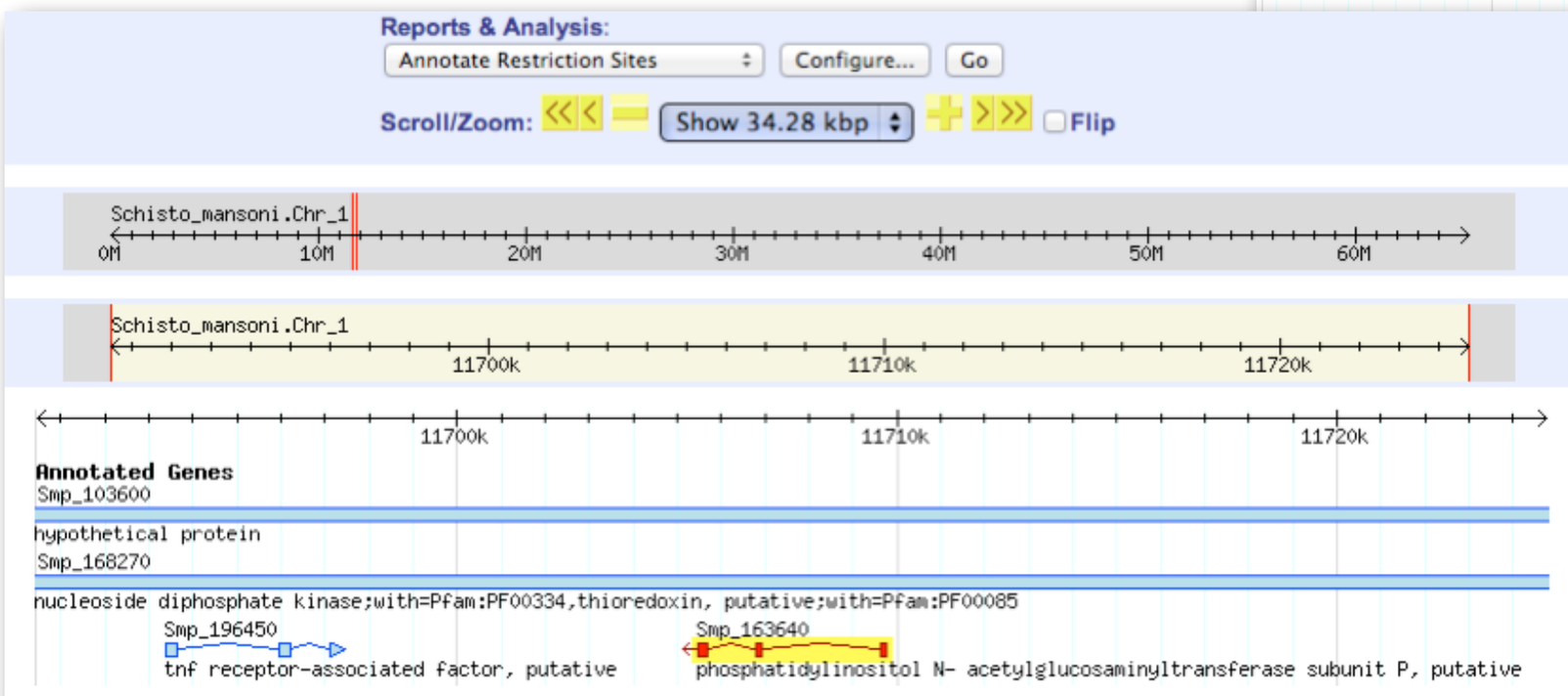
Signal Pep - step 3 - 88 Genes — Add 88 Genes to Basket | Download 88 Genes

First 1 2 3 4 5 Next Last — Advanced Paging — Select Columns — Reset Columns

Gene	Genomic Location	Product Description
Smp_163640	Schisto_mansoni.Chr_1: 11,705,469 - 11,709,753 (-)	phosphatidylinositol N- acetylglucosaminyltransferase subunit P, putative
Smp_035020.1	Schisto_mansoni.Chr_1: 14,957,585 - 14,973,848 (+)	cd151-related
Smp_035020.2	Schisto_mansoni.Chr_1: 14,957,585 - 14,973,848 (+)	cd151-related
Smp_196620	Schisto_mansoni.Chr_1: 27,599,514 - 27,610,703 (+)	hypothetical protein
Smp_173390	Schisto_mansoni.Chr_1: 29,445,949 - 29,491,437 (+)	ribosomal protein L5, putative
Smp_006040	Schisto_mansoni.Chr_1: 37,885,529 - 37,901,591 (-)	hypothetical protein
Smp_160780	Schisto_mansoni.Chr_1: 43,784,334 - 43,825,817 (+)	voltage-gated potassium channel, putative;with=UniProt:P17971
Smp_006840	Schisto_mansoni.Chr_1: 45,375,672 - 45,383,319 (+)	hypothetical protein
Smp_148100	Schisto_mansoni.Chr_1: 47,030,493 - 47,041,923 (-)	prokaryotic DNA topoisomerase, putative
Smp_152050	Schisto_mansoni.Chr_1: 62,230,587 - 62,253,610 (+)	tetraspanin 18, isoform 1 , putative
Smp_137360	Schisto_mansoni.Chr_1.unplaced.SC_0010: 9,400 - 18,507 (+)	hypothetical protein
Smp_019340	Schisto_mansoni.Chr_1.unplaced.SC_0010: 1,456,136 - 1,462,238 (+)	transmembrane 4 superfamily member, putative;with=UniProt:Q9QY33
Smp_000070	Schisto_mansoni.Chr_1.unplaced.SC_0010: 2,736,439 - 2,739,738 (-)	1-acyl-sn-glycerol-3-phosphate o-acyltransferase;with=UniProt:A0JMM2
Smp_170400	Schisto_mansoni.Chr_2: 1,400,122 - 1,422,471 (-)	nicalin (M28 family);with=UniProt:Q6NZ07
Smp_180920	Schisto_mansoni.Chr_2: 4,169,006 - 4,169,518 (+)	hypothetical protein
Smp_102480	Schisto_mansoni.Chr_2: 6,912,568 - 6,917,891 (+)	hypothetical protein
Smp_099670	Schisto_mansoni.Chr_2: 10,137,407 - 10,139,361 (+)	hypothetical protein
Smp_113200	Schisto_mansoni.Chr_2: 12,007,017 - 12,017,969 (-)	hypothetical protein
Smp_157390	Schisto_mansoni.Chr_2: 21,850,167 - 21,891,732 (+)	lipoma hmgic fusion partner-like protein
Smp_173150	Schisto_mansoni.Chr_2: 25,522,146 - 25,524,700 (-)	cd63 antigen-like;with=UniProt:P08962

First 1 2 3 4 5 Next Last — Advanced Paging





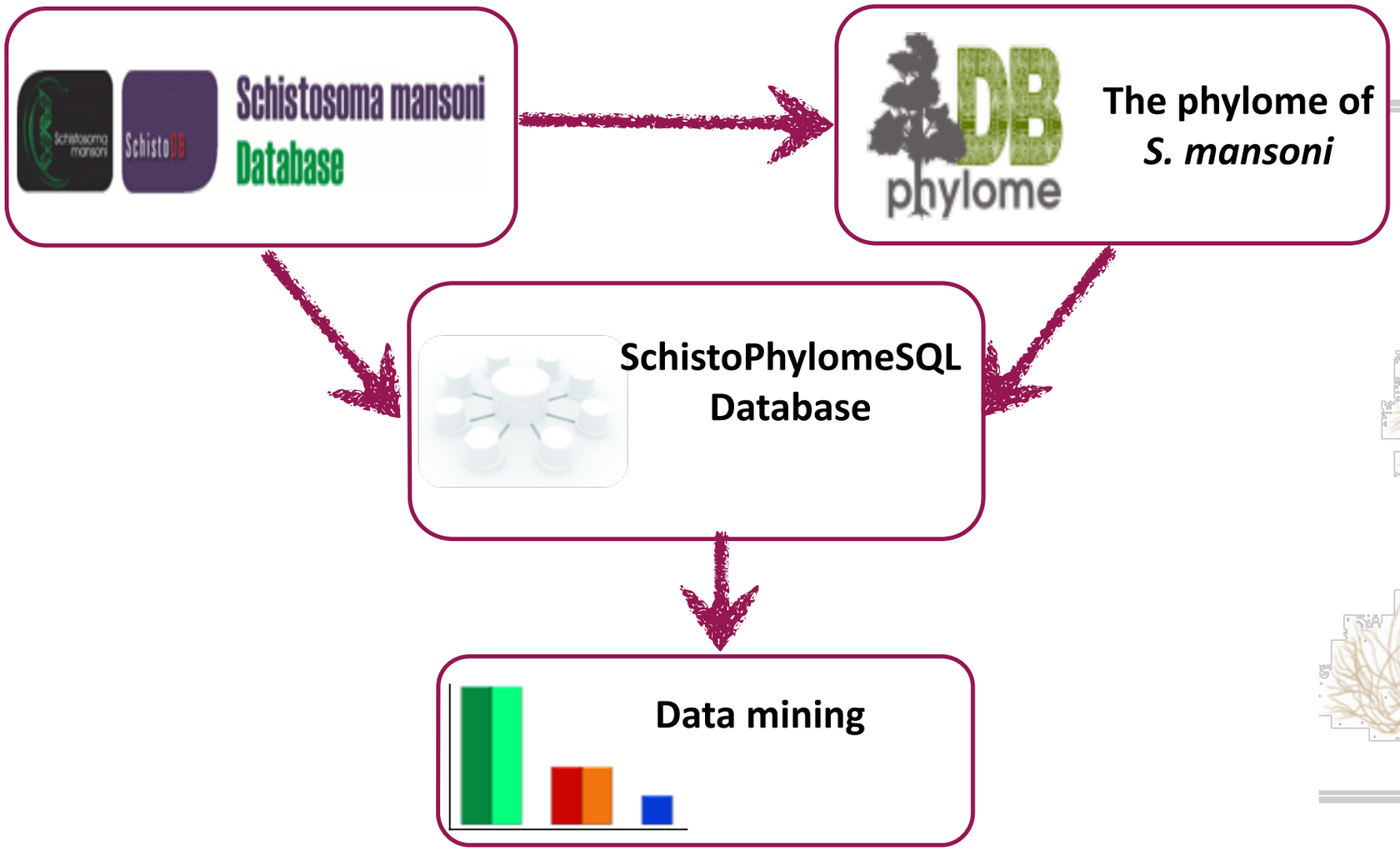
SchistoDB access

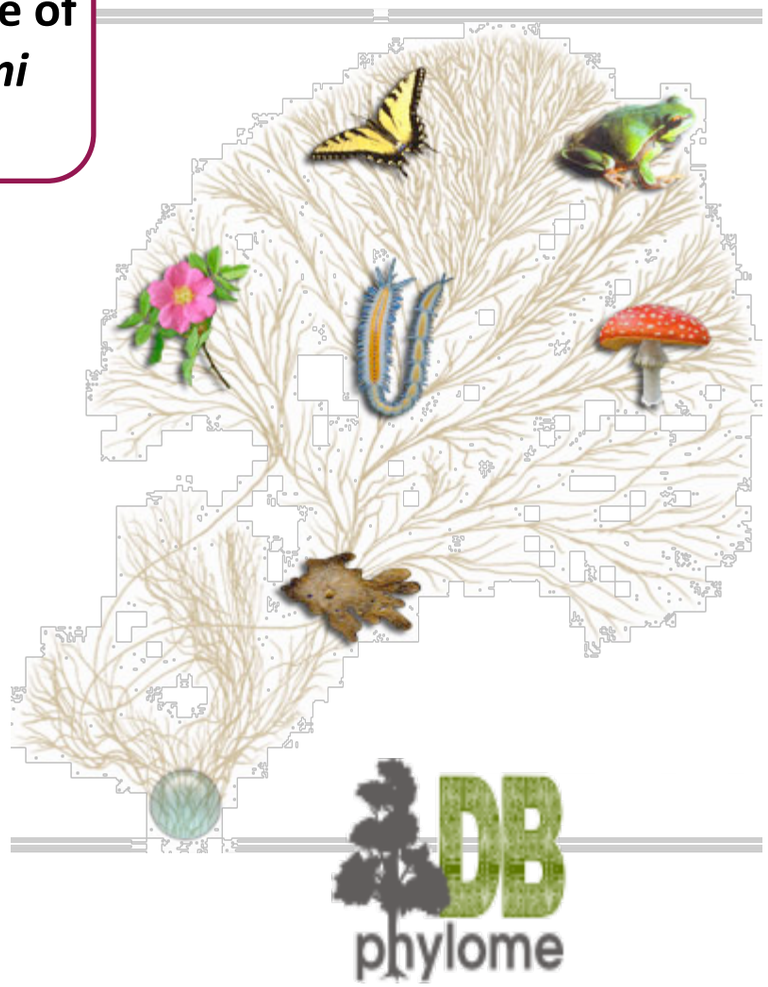
180,000 visits

Gene annotation

Silva *et al.*, BMC Genomics, 2012

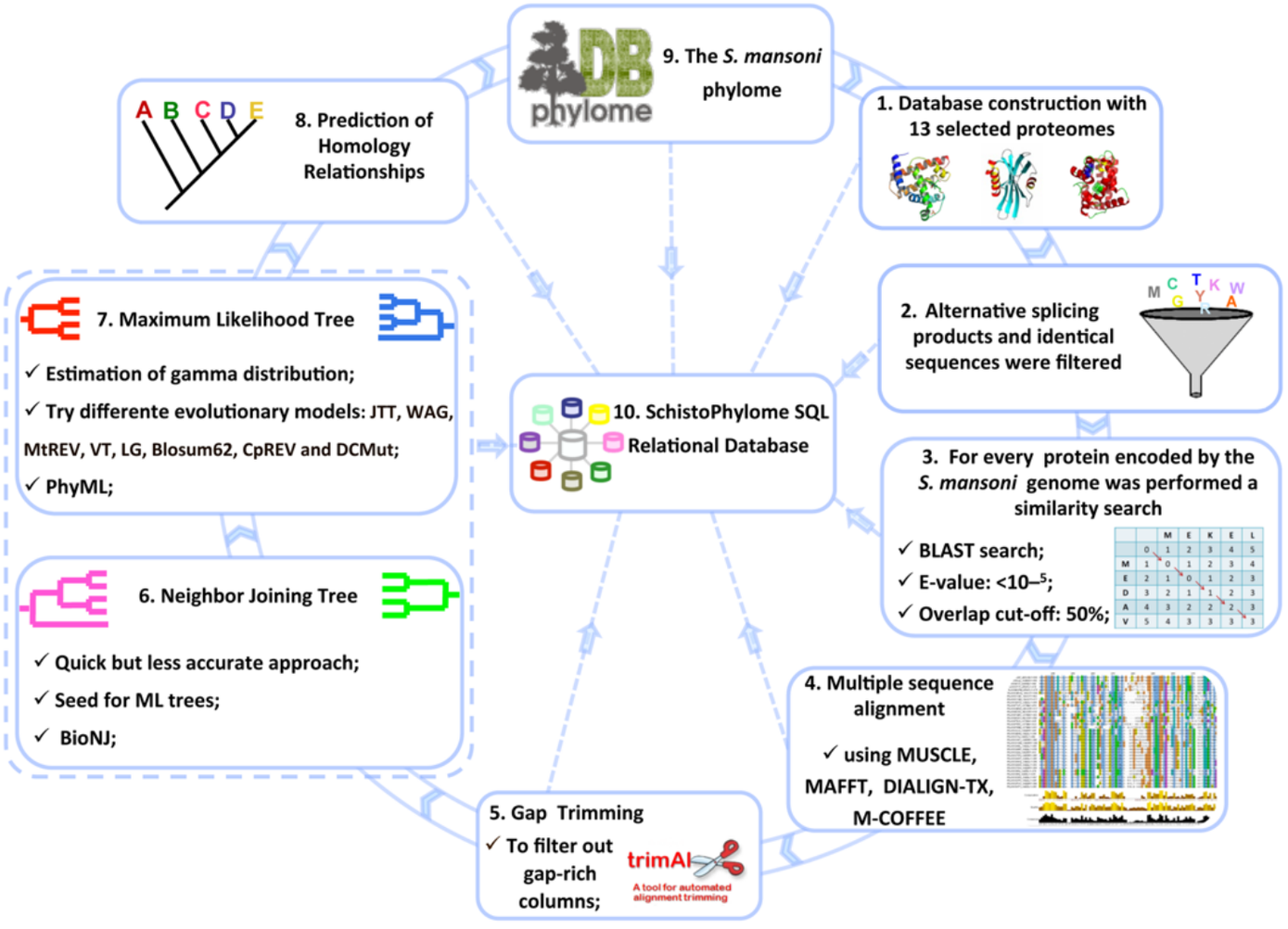
- >40% without annotation
- similarity based annotation





Gene annotation

Silva *et al.*, PLoS NTD, 2012.



Gene annotation

Silva *et al.*, PLoS NTD, 2012.

- 11,763 *S. mansoni* proteins
- 7,964 phylogenetic trees
- 70% of the proteome
- 3,038 unknowns
- Expansions
  - Tetraspanins, Fucosyltransferases
  - Venom allergen-like proteins tegumental-allergen-like proteins (SmTAL), leishmanolysins
  - elastases

PHOG

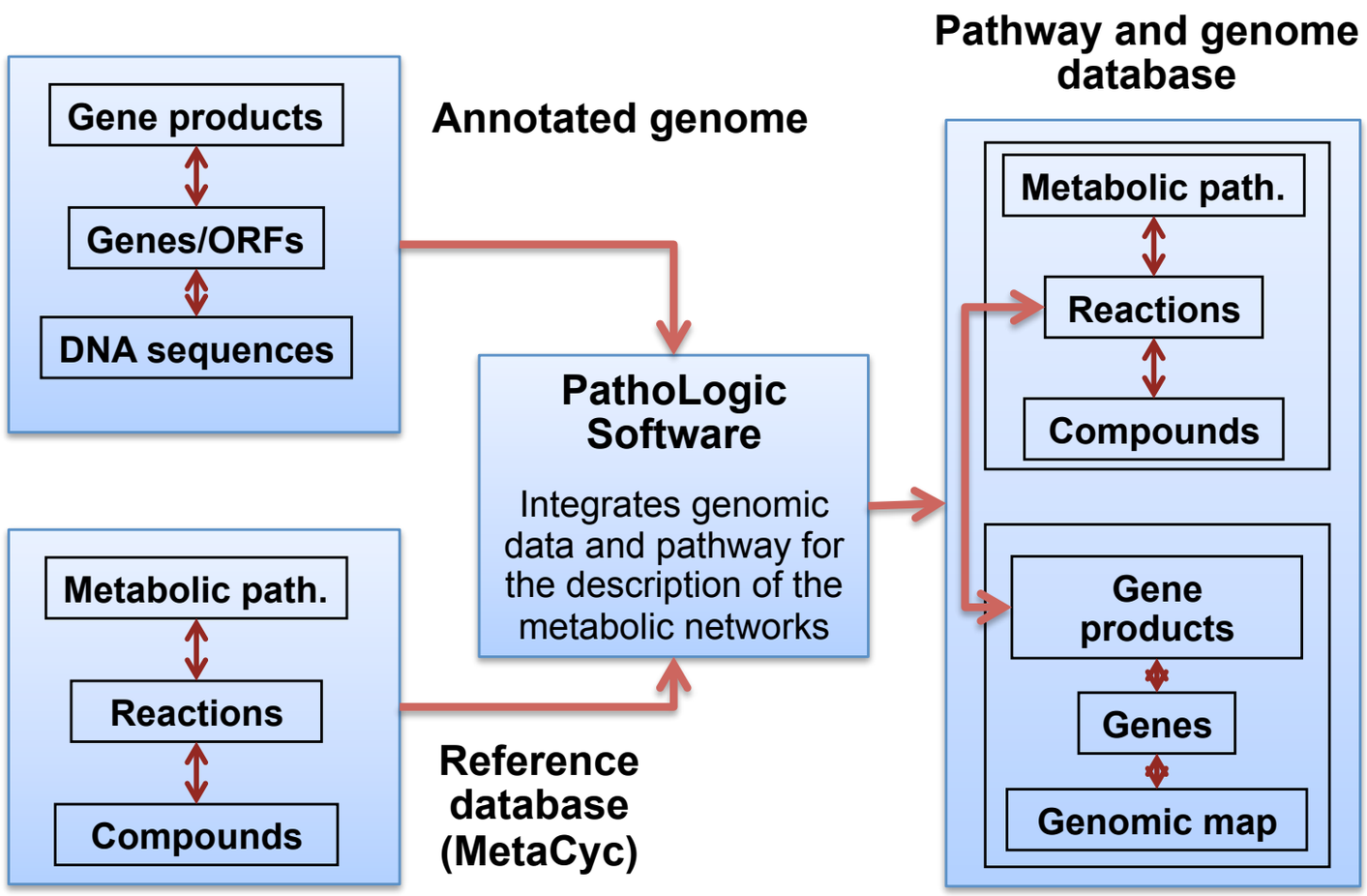
PhyloFacts Orthology Group

Target identification

- Metabolic pathways
- The kinome
- HMEs
- Antigen characterization

Metabolic pathways

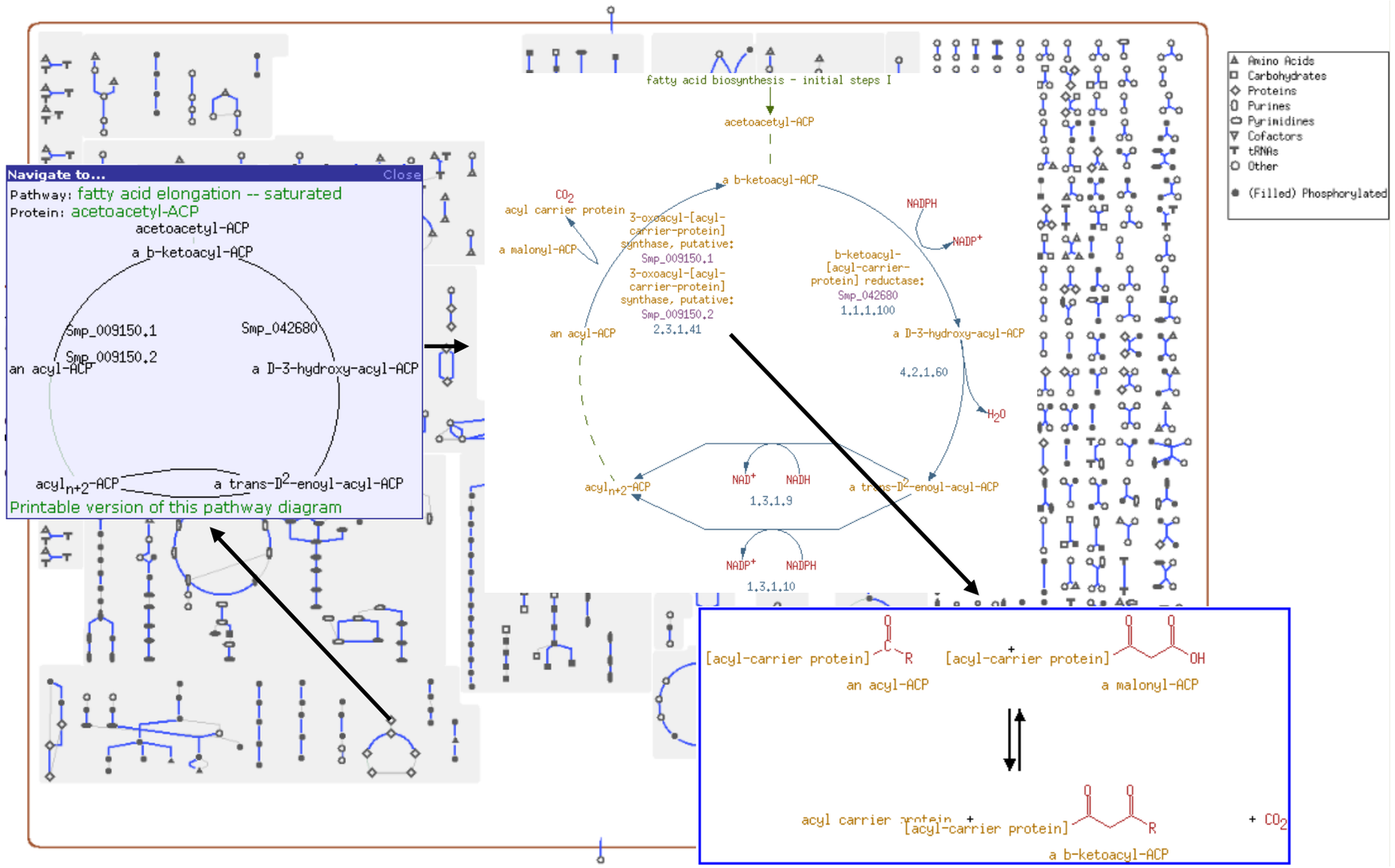
Berriman *et al.*, Nature 2009
Zerlotini et al., NAR, 2009



Metabolic pathways

Berriman *et al.*, Nature 2009
Zerlotini et al., NAR, 2009

SchistoCyc

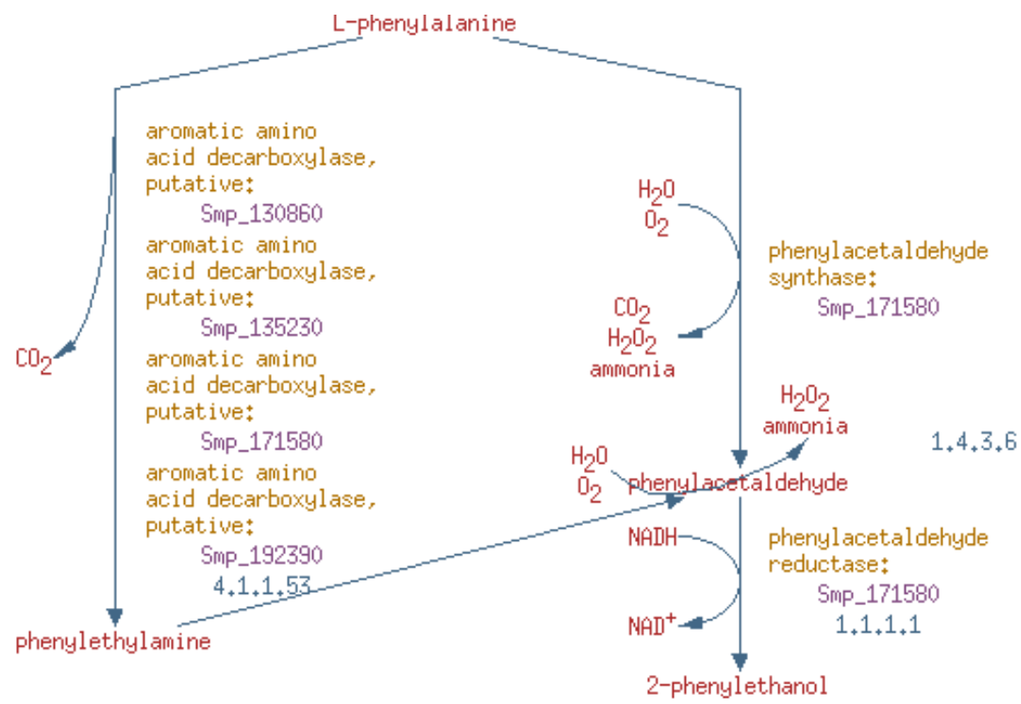


SchistoDB.net

Metabolic pathways

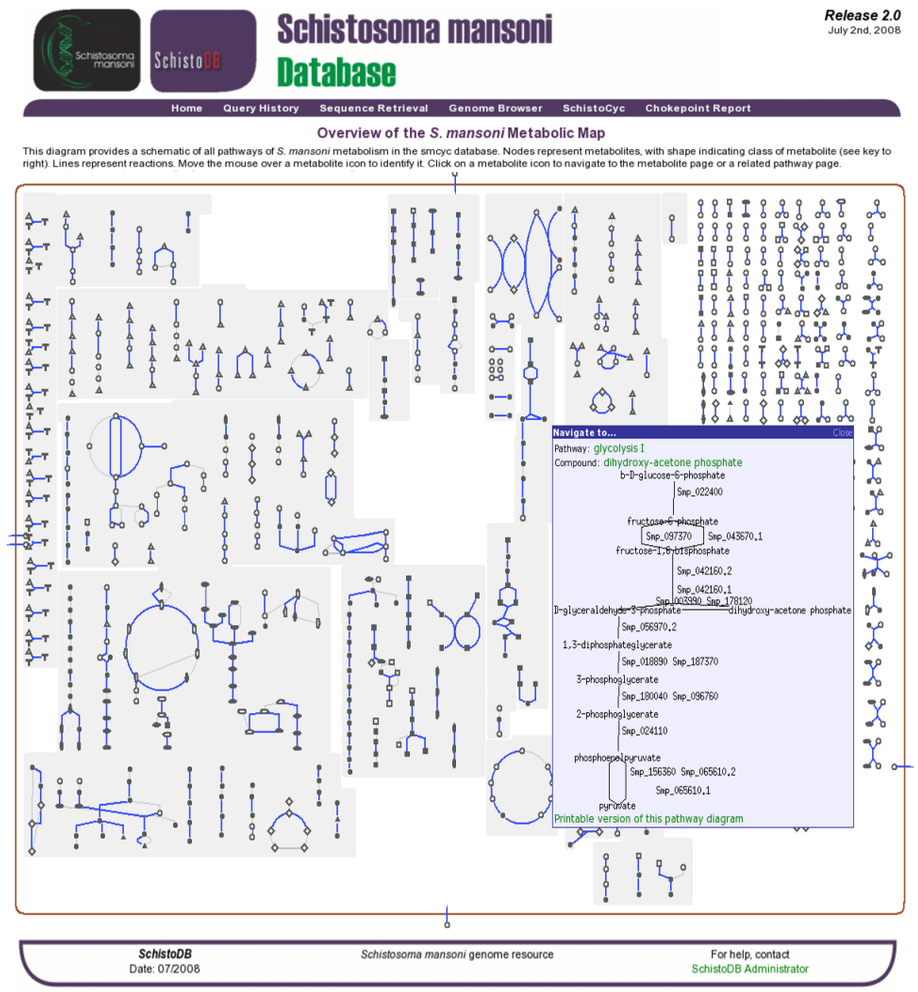
Berriman *et al.*, Nature 2009
Zerlotini et al., NAR, 2009

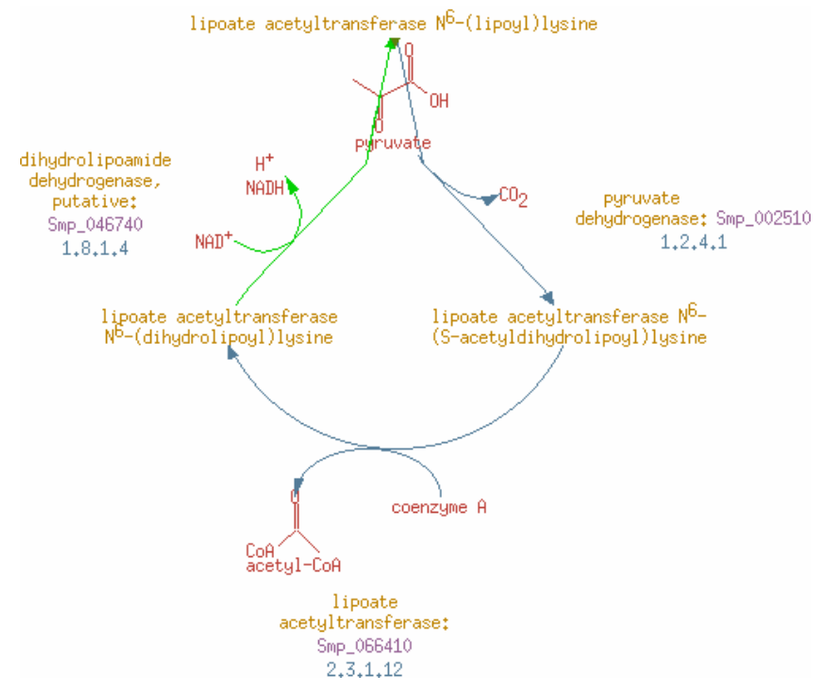
Asparagine biosynthesis III
Betacyanin biosynthesis (via dopamine)
Chorismate biosynthesis
De novo biosynthesis of pyrimidine deoxyribonucleotides
Degradation to 2-amino-3-carboxymuconate semialdehyde
Fatty acid biosynthesis initial stps I
Folate transformations
Formy lTHF biosynthesis I
Glutamate biosynthesis I
Glutamine degradation II
Glycine cleavage complex
Glycogen biosynthesis II (from UDP-D-Glucose)
Polyglutamylation
Lipoate biosynthesis and incorporation I
Mannosyl-chito-dolichol biosynthesys dolichyl-diphosphooligosaccharide biosynthesisc
Phenylethanol biosynthesis
UDP-N-acetyl-D-glucosamine biosynthesis I



Responsible for floral scent in roses!
Used in insects for chemical communication.
Cancer treatment.

Chokepoint analysis





Chokepoint analysis

Chokepoint Reactions

Generated on 5/28/2008 - 2:57:40

This report contains a list of reactions that either consume an unique substrate or produce an unique product, chokepoints.
The list of reactions was obtained using the SRI Pathway Tools software.
In house scripts generated this web report, where the reactions are grouped by the pathway.
The reactions are also linked to their coding genes and to drugs.
The genes contain % similarity to PDB structures and OrthoMCL orthology information.
The drugs and the EC number of their targets were obtained from Kegg Drug Database.

+ **Pathway**: formylTHF biosynthesis I		Reactions: 2	Drugs: 13	SchistoCyc Pathway
+ **Pathway**: superpathway of cholesterol biosynthesis		Reactions: 8	Drugs: 12	SchistoCyc Pathway
+ **Pathway**: mevalonate pathway		Reactions: 6	Drugs: 12	SchistoCyc Pathway
+ **Pathway**: catecholamine biosynthesis		Reactions: 2	Drugs: 5	SchistoCyc Pathway
+ **Reaction**: RXN66-221	4.1.1.28	Genes: 1	Drugs: 4	SchistoCyc Reaction
Genes				
Smp_135230		1js3:49%	OrthoMCL (*Hsa*)	SchistoDB Gene
Drug				
D03082 - Benserazide (USAN)				Kegg Drug
D01653 - Benserazide hydrochloride (JP15)				Kegg Drug
D00558 - Carbidopa (JP15/USP)				Kegg Drug
D00253 - Carbidopa hydrate - levodopa mixt				Kegg Drug
+ **Reaction**: Dopamine-β-monooxygenase	1.14.17.1	Genes: 1	Drugs: 1	SchistoCyc Reaction
+ **Pathway**: de novo biosynthesis of pyrimidine ribonucleotides		Reactions: 6	Drugs: 3	SchistoCyc Pathway
+ **Pathway**: *de novo* biosynthesis of uridine-5'-monophosphate		Reactions: 6	Drugs: 3	SchistoCyc Pathway
+ **Pathway**: tRNA charging pathway		Reactions: 2	Drugs: 2	SchistoCyc Pathway
+ **Pathway**: phenylethanol biosynthesis		Reactions: 2	Drugs: 1	SchistoCyc Pathway
+ **Pathway**: dolichyl-diphosphooligosaccharide biosynthesis		Reactions: 9	Drugs: 0	SchistoCyc Pathway
+ **Pathway**: phospholipid biosynthesis II		Reactions: 6	Drugs: 0	SchistoCyc Pathway
+ **Pathway**: purine nucleotides *de novo* biosynthesis II		Reactions: 5	Drugs: 0	SchistoCyc Pathway
+ **Pathway**: TCA cycle variation III (eukaryotic)		Reactions: 5	Drugs: 0	SchistoCyc Pathway
+ **Pathway**: de novo biosynthesis of pyrimidine deoxyribonucleotides		Reactions: 5	Drugs: 0	SchistoCyc Pathway

Drug repositioning

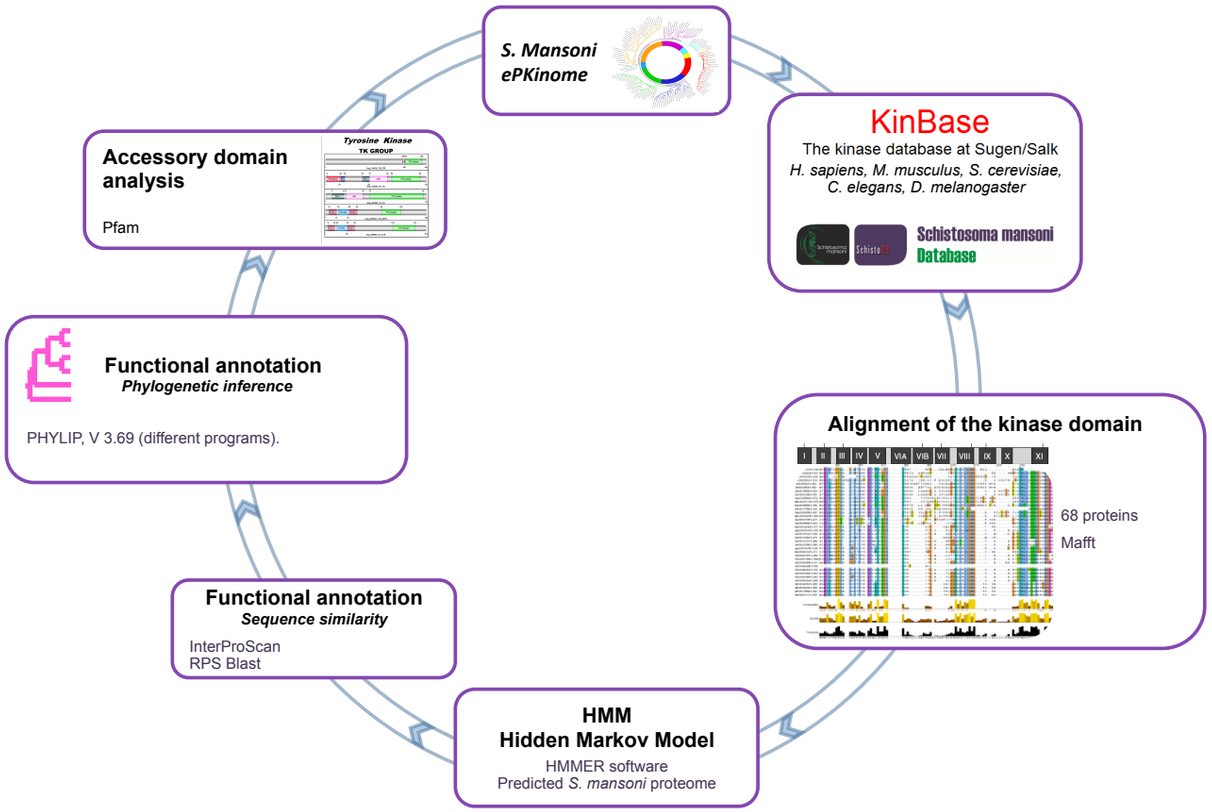
Classification	Number	% total
Genes	13.302	0,0456
Enzymes	112	0,0084
Targets (literature)	4	0,0003
Targets (EC #)	8	0,0006

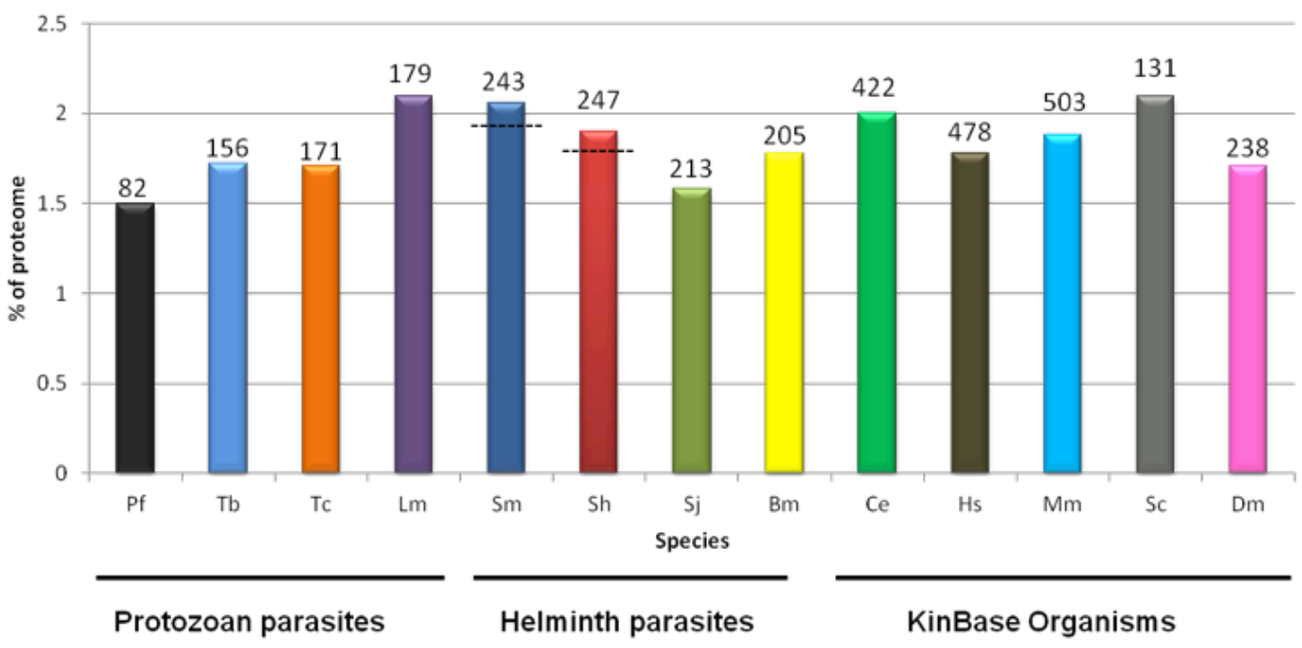
- Fosfofrutoquinase
- HMG-CoA Redutase
- L-Dopa descarboxilase
- Quinureninase

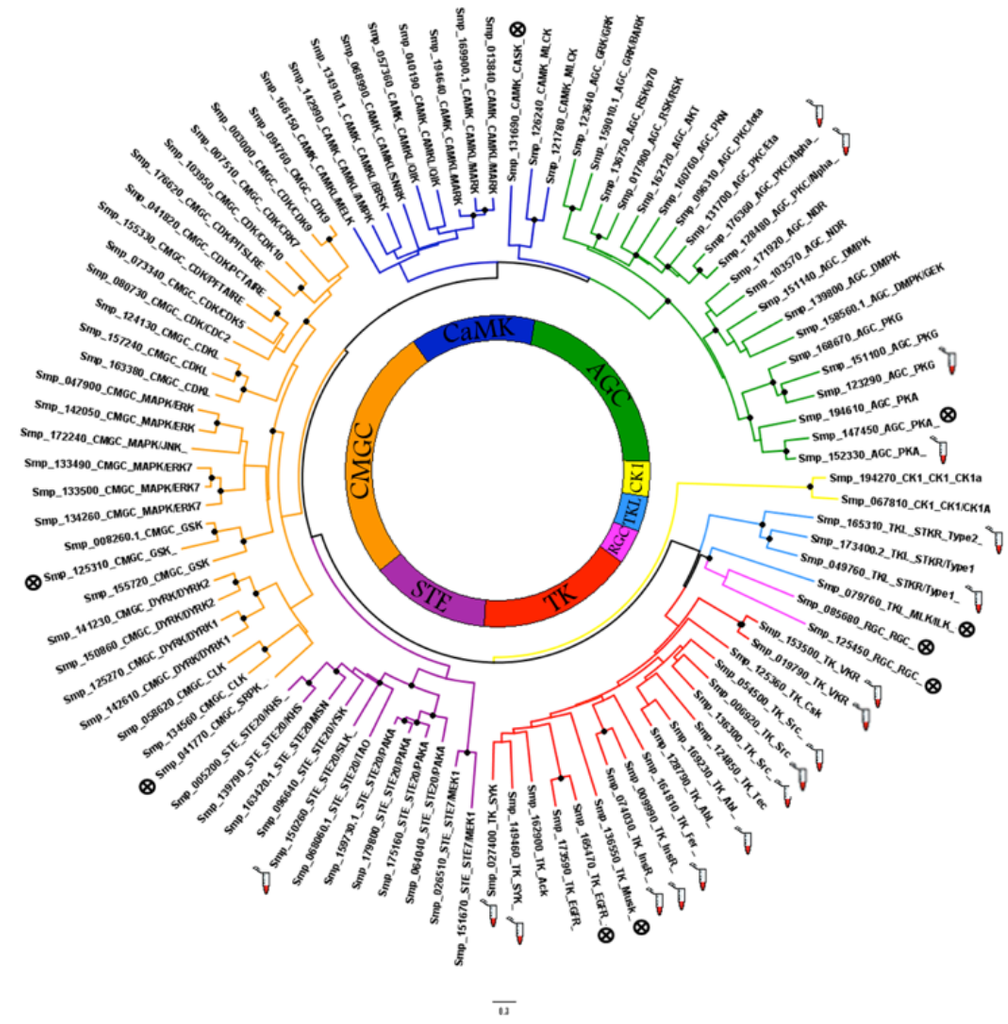
Compound	Dose mg/Kg	% reduction
Alopurinol	300	30,50
Metotrexate	20	35,67
Pravastatine	65	10,35
Trimetropime	25	0,23
PZQ	200	35%
Control	0	0

The ePKinome

Andrade *et al.*, BMC Genomics 2011
Avelar *et al.* J. Signal Trans. 2011







ePKinome

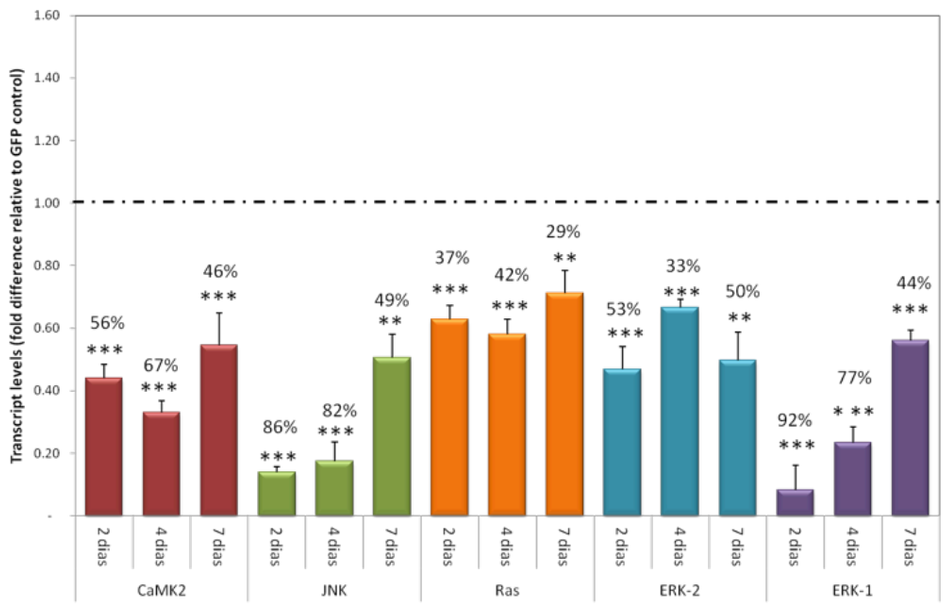
Andrade *et al*., BMC Genomics 2011
LoVerde *et al.* Curr Op Microbiol, 2009
Andrade *et al*., PLoS NTD, submitted

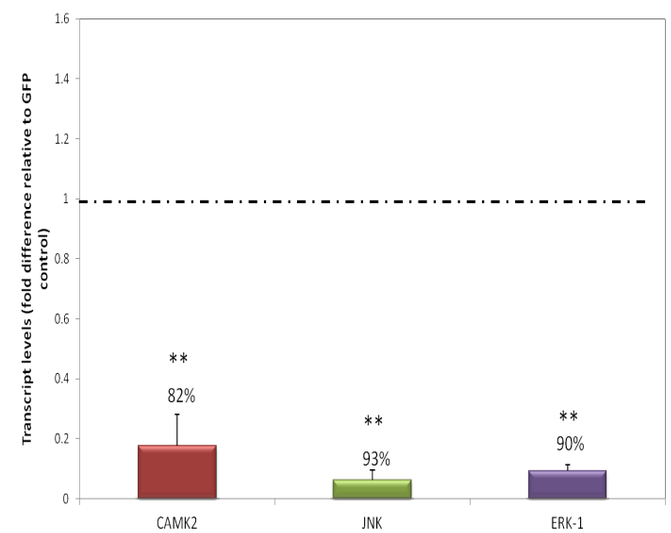
After phylogenetic analysis		
Changes	**Genes**	**% ePKinome**
Group	14	5,55%
Family	18	7,14%
Subfamily added	61	24,20%
Previously unknown	11	3,96%
Total	**104**	**40,85%**

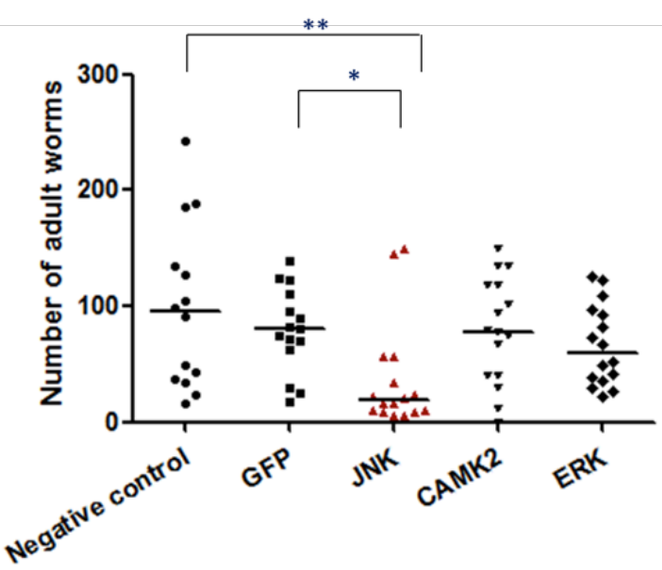
Group	*S. mansoni*	*C. elegans*	*Brugi malayi*	*C. elegans RNAi phenotype*
CaMK				
	Smp_053560	C44C8.6_Ce e K08F8.1	-	Embryonic Lethal
AGC				
	Smp_123640	F19C6.1_Ce	-	Embryonic lethal, maternal sterile, organism morphology variant.
	Smp_136750	Y47D3A.16_Ce	Bm1_44635	Larval lethal, fertility reduced
	Smp_158560	K08B12.5_Ce	Bm1_02320	Body morphology defect, slow growth
	Smp_096310	pkc-3_Ce_A	Bm1_03335	Embryonic lethal, sterile, body morphology defect
TK				
	Smp_139480	vab-1_Ce_T	Bm1_03410	Embryonic lethal, body morphology defect
STE				
	Smp_026510, Smp_151670	mek-2_Ce	-	Embryonic lethal, sterile, reduced brood size, exploted through vulva, slow growth
	Smp_096640	gck_1_Ce	-	cortical dynamics defective early embryonic, maternal sterile
	Smp_163420	mig_15_Ce	Bm1_32540	Abnormal cell migration, protruding vulva, developmental delay
	Smp_068060	kin_18_Ce	Bm1_55590	Embryonic lethal, body morphology defect, slow growth, sterile, larval lethal, dumpy
	Smp_131800	Y59A8B.23_CE	Bm1_11845	More depolarized oocytes
	Smp_150260	C04A11.3_Ce	Bm1_26435	Slow growth, larval lethal late L3/L4
TKL				
	Smp_079760	pat4_Ce_TK	Bm1_20815	Embryonic lethal, body morphology defect, larval lethal, sterile, paralyzed, uncoordinated movement, paralyzed
	Smp_176990	lin45_Ce_T	Bm1_40290	Sterile, osmotic integrity problems
CMGC				
	Smp_068960	F22D6.5_Ce	Bm1_12230	Embryonic lethal, slow growth, sterile progeny, uncoordinateed movement
	Smp_041770	spk_1_Ce	-	Embryonic lethal, larval lethal, maternal sterile
	Smp_172700	cdk_4_Ce	-	Locomotion variant, larval lethal, sterile progeny
	Smp_133020	pmk-1_Ce, pmk-2_Ce	-	Apoptosis increased, sterile progeny, reduced brood size, embryonic lethal
	Smp_134260, Smp_133490, Smp_133500	C05D10.2	-	Reduced brood size, embryonic lethal
	Smp_080730	cdk_1_Ce	-	embryonic lethal, sterile progeny
	Smp_155720, Smp_125310, Smp_008260.1	Y18D10A.5_Ce, C44H4.6_Ce	-	Larval lethal, slow growth, embryonic lethal
	Smp_156990	F39H11.3_Ce	Bm1_33825	Sterile
	Smp_176620	B0495.2_Ce, ZC504.3_Ce	Bm1_17240	Embryonic lethal
	Smp_003000	H25P06.2_Ce	-	Embryonic lethal, slow growth, uncoordinated movement
	Smp_150040	Cdk_7_Ce	Bm1_14135	Embryonic lethal
	Smp_140700, Smp_074080	lit_1_Ce	Bm1_130	Embryonic lethal, larval lethal
	Smp_141230	mbk_2_Ce	Bm1_38345	Embryonic lethal, sterile progeny

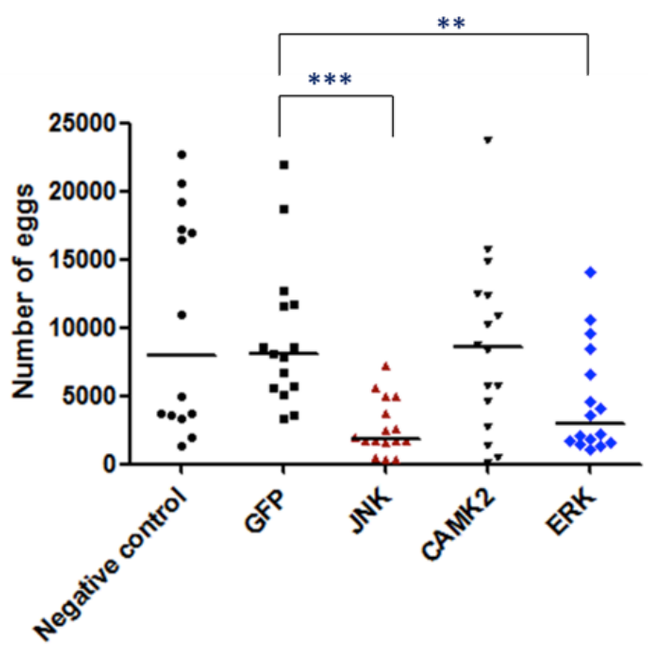
Embryonic Lethal!

JNK and ERK

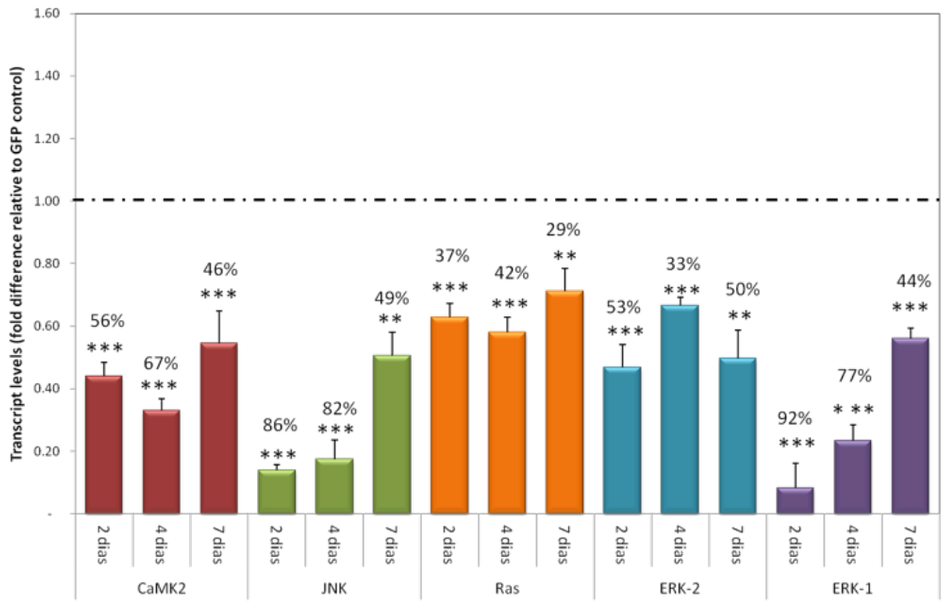

Transcript levels (fold difference relative to GFP control)
1.60
1.40
1.20
1.00
0.80
0.60
0.40
0.20
-
56% ***
67% ***
46% ***
86% ***
82% ***
49% **
37% ***
42% ***
29% **
53% ***
33% ***
50% **
92% ***
77% * **
44% ***
2 dias
4 dias
7 dias
CaMK2
JNK
Ras
ERK-2
ERK-1


Transcript levels (fold difference relative to GFP control)
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
** 82%
** 93%
** 90%
CAMK2
JNK
ERK-1


Number of adult worms
300
200
100
0
**
*
Negative control
GFP
JNK
CAMK2
ERK

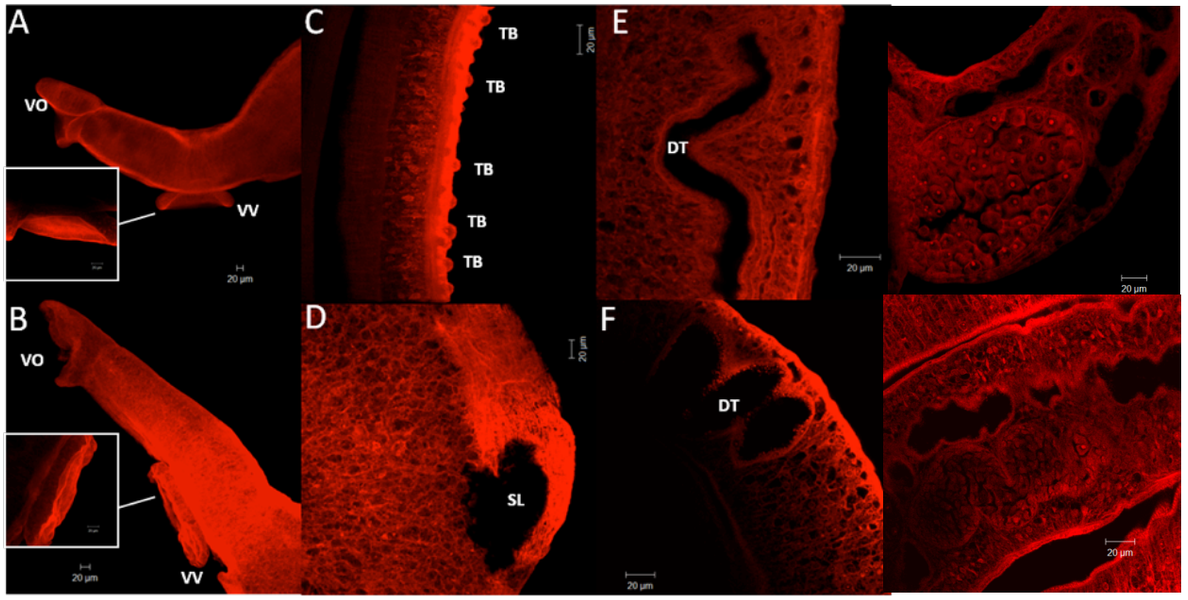

Number of eggs
25000
20000
15000
10000
5000
0
***
**
Negative control
GFP
JNK
CAMK2
ERK

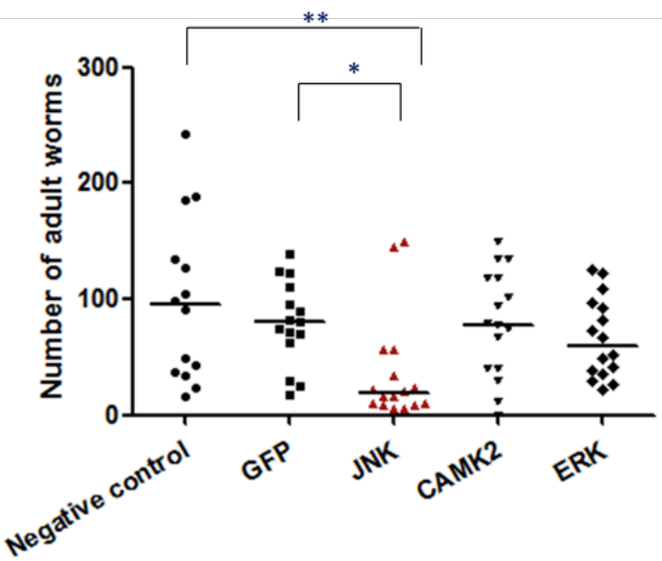
JNK and ERK

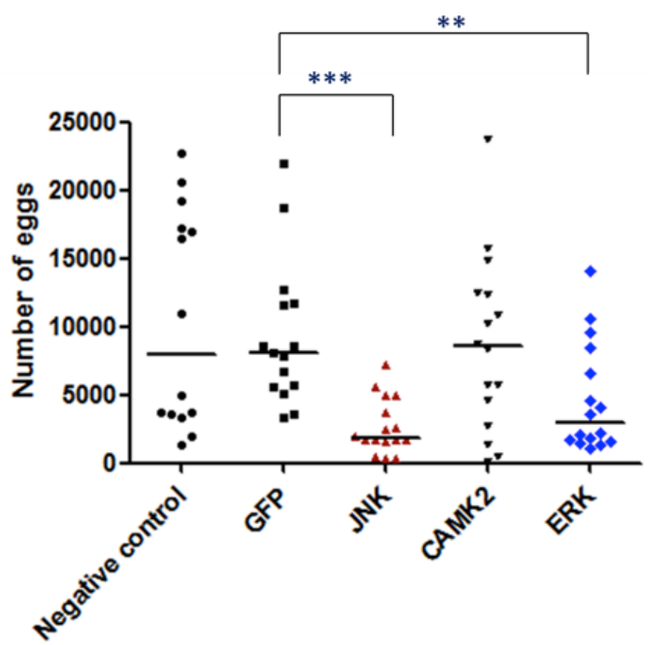


Control

RNAi JNK

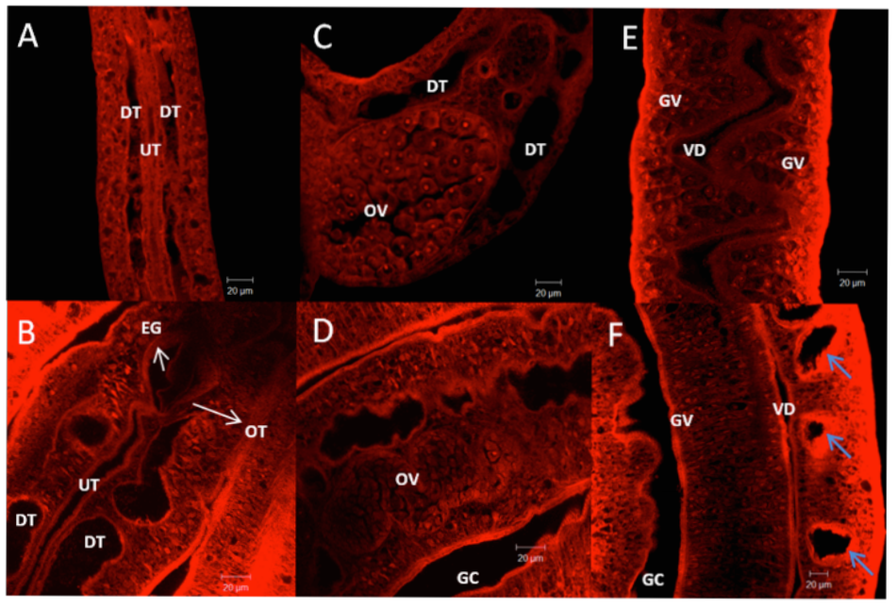






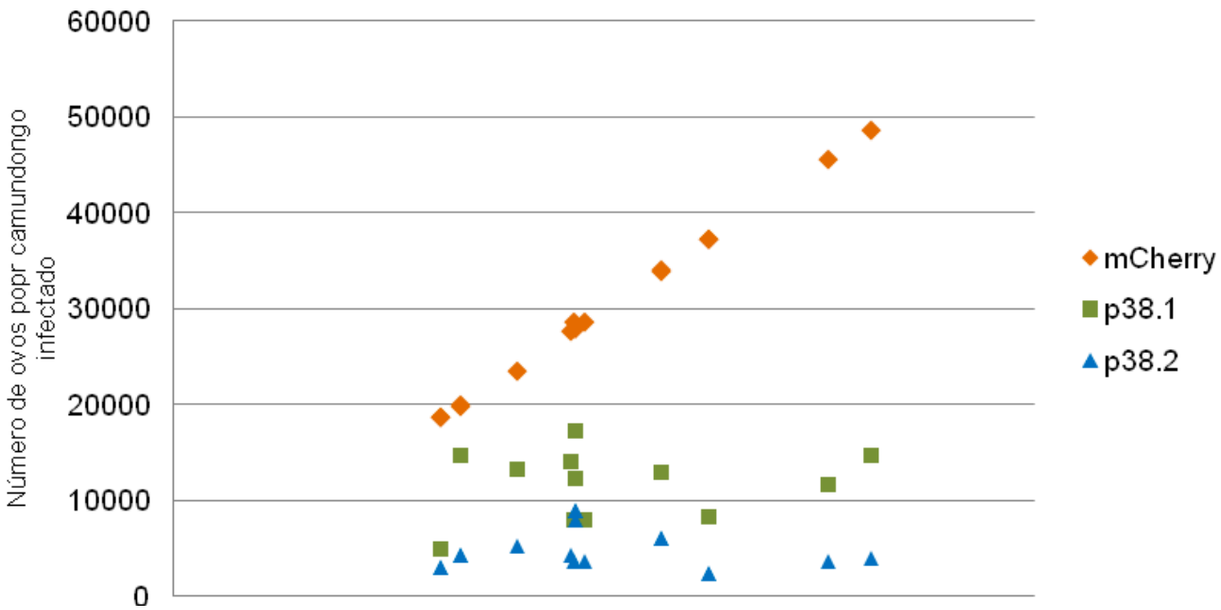
Control

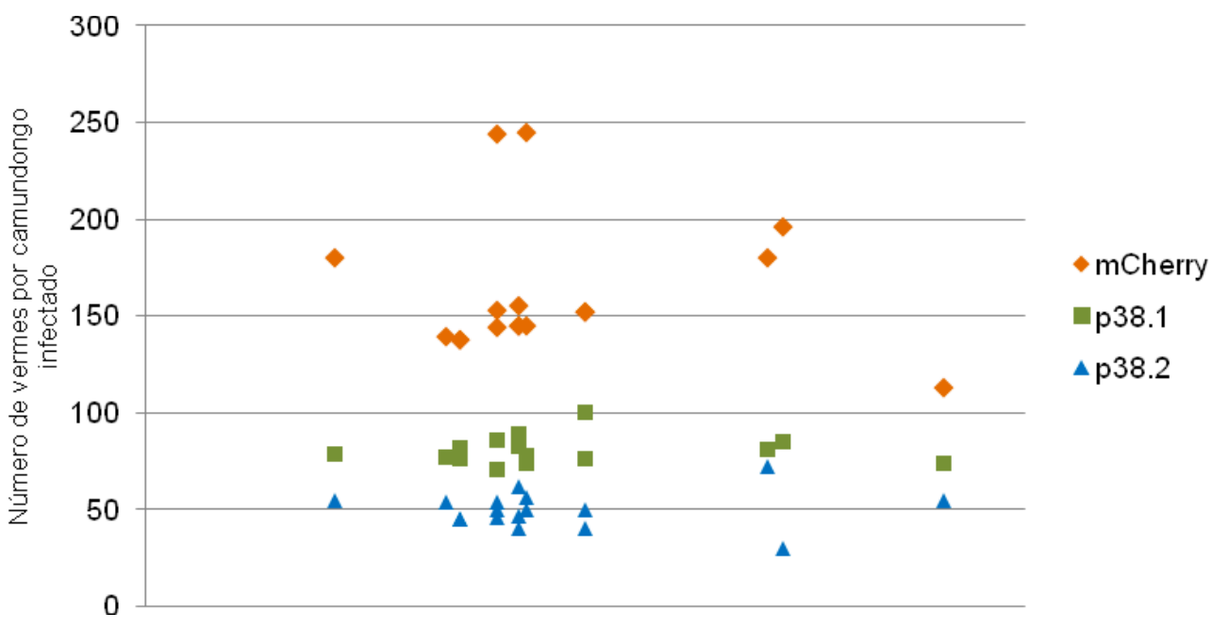
RNAi ERK



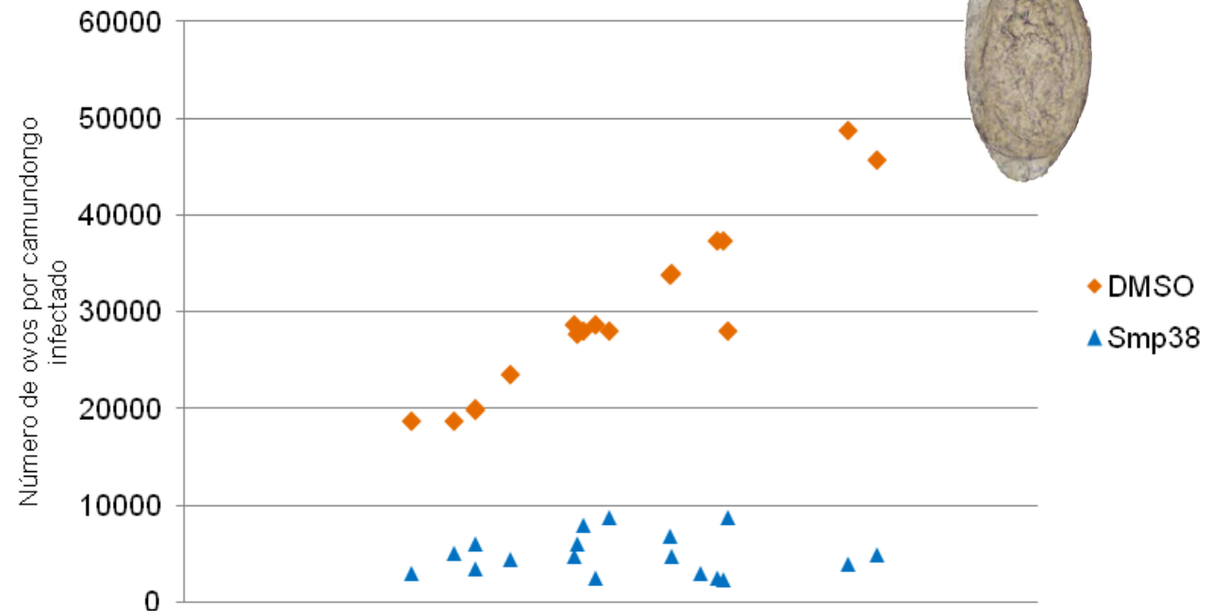
p38

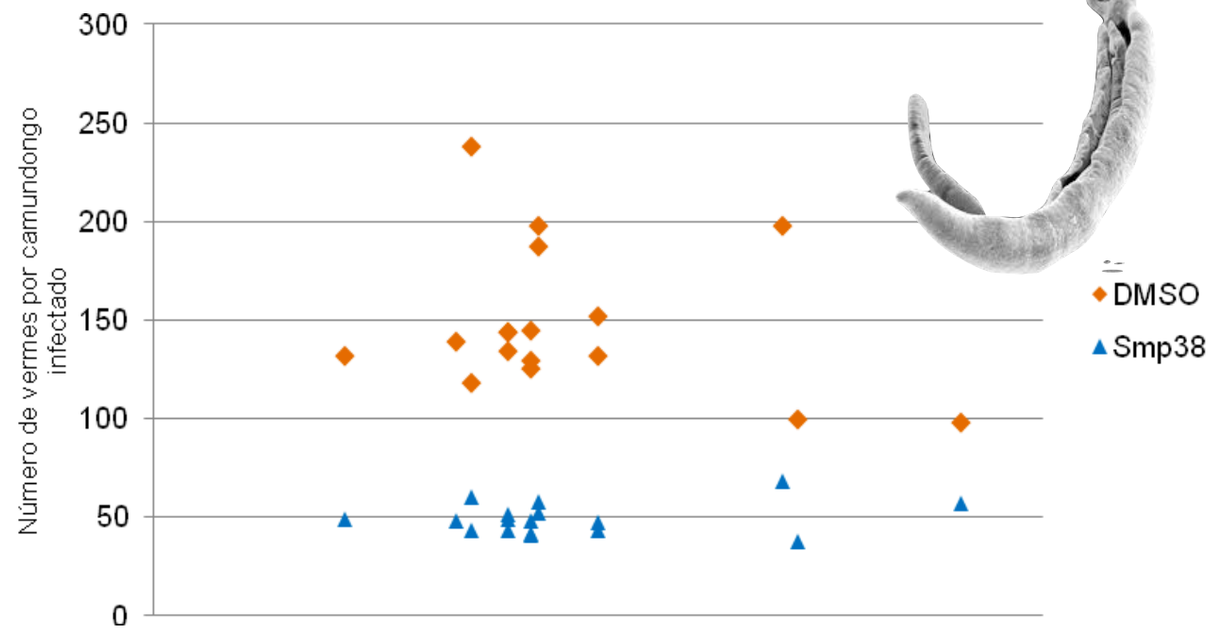
Knockdown

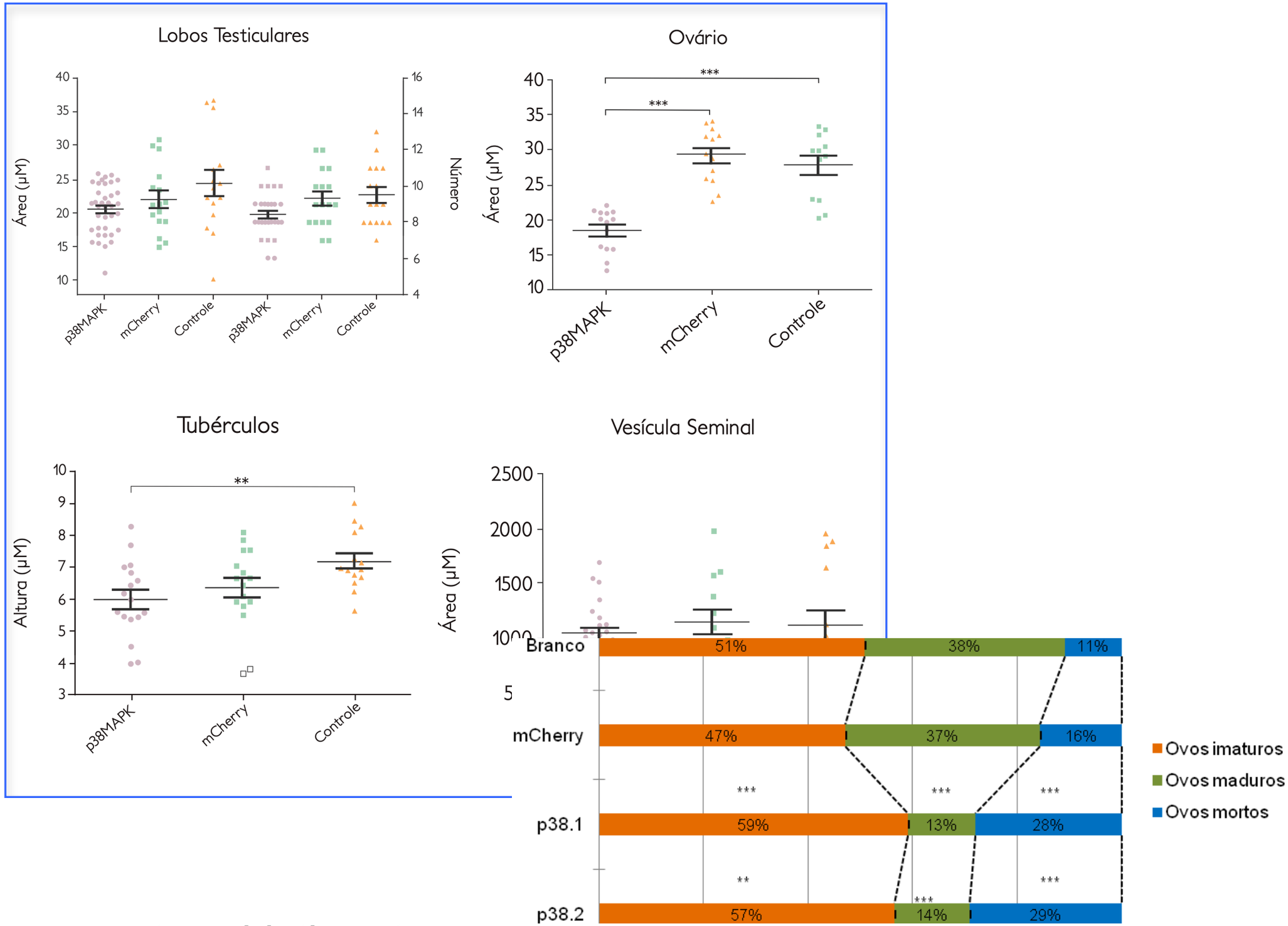




SB 203580



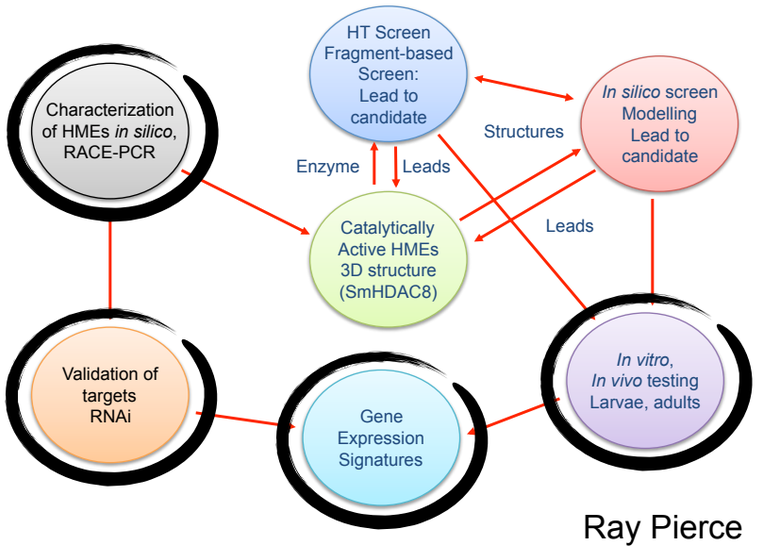




Regulation of response to oxidative stress

The SETtReND project

Pierce *et al.*, Curr Pharm Des 2012

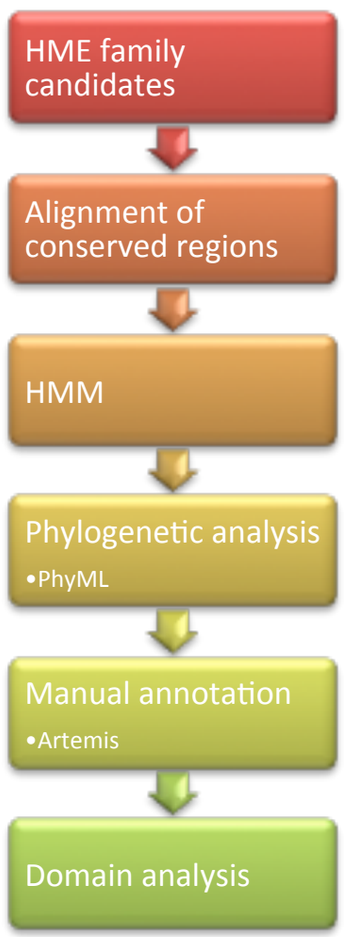


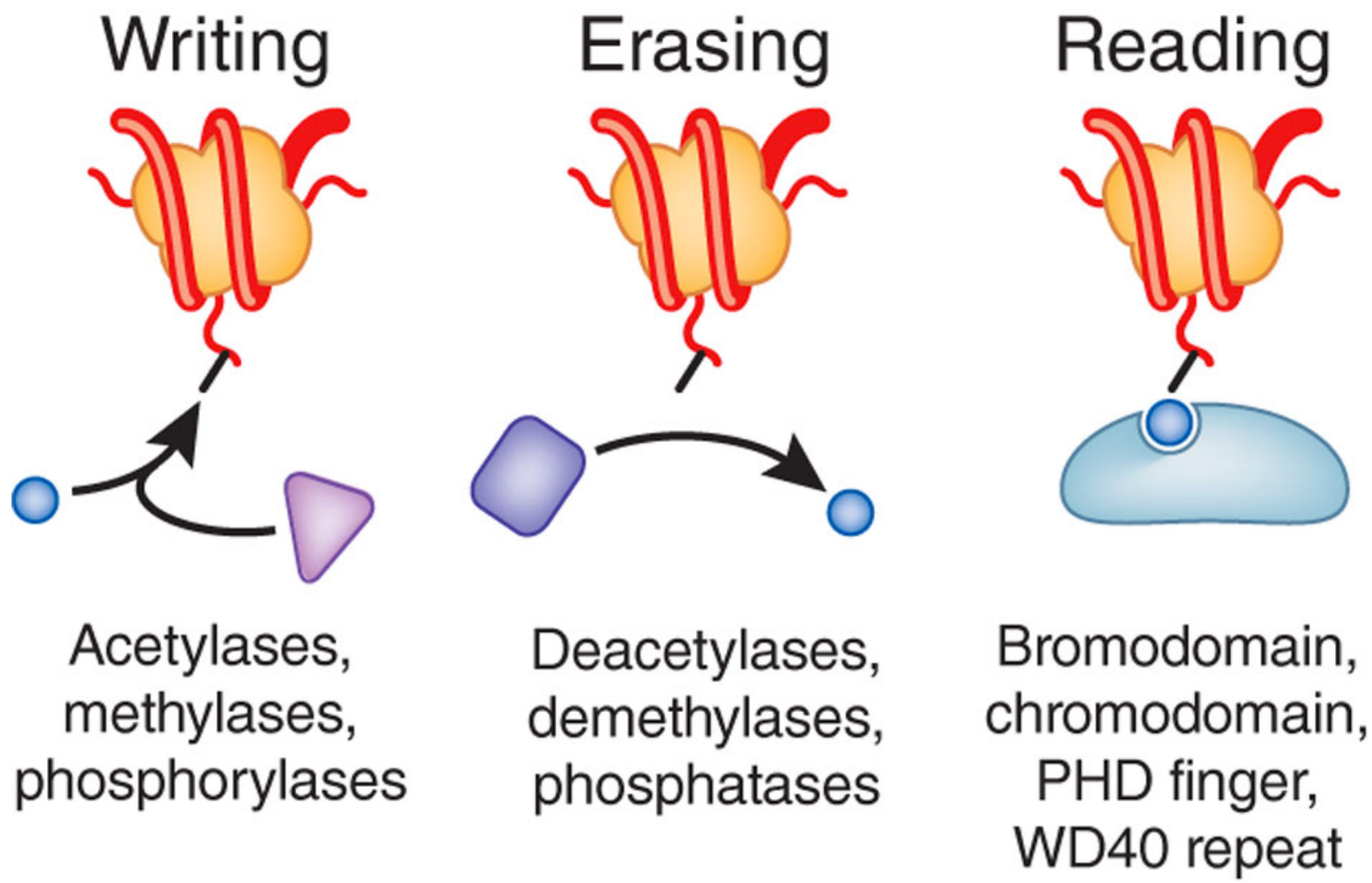
Ray Pierce

- Identify HMEs
- RNAi
- Test inhibitors

SEtTReND

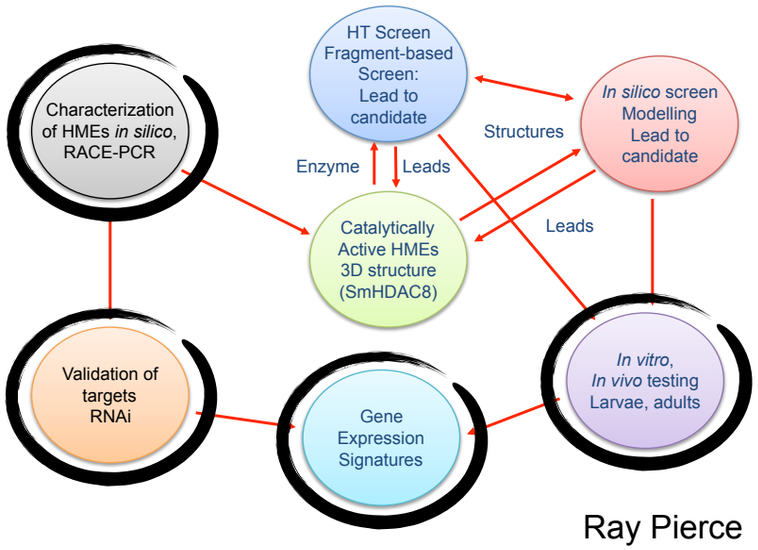
http://settrend.cebio.org





The SETtReND project

Pierce *et al.*, Curr Pharm Des 2012



Ray Pierce

- Identify HMEs
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SEtTReND

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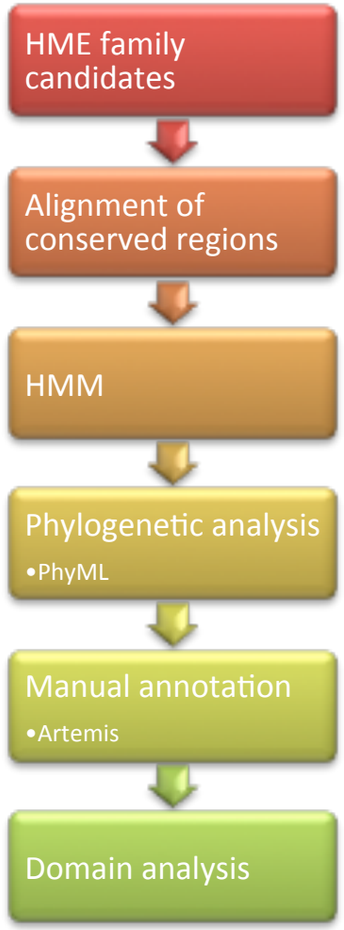
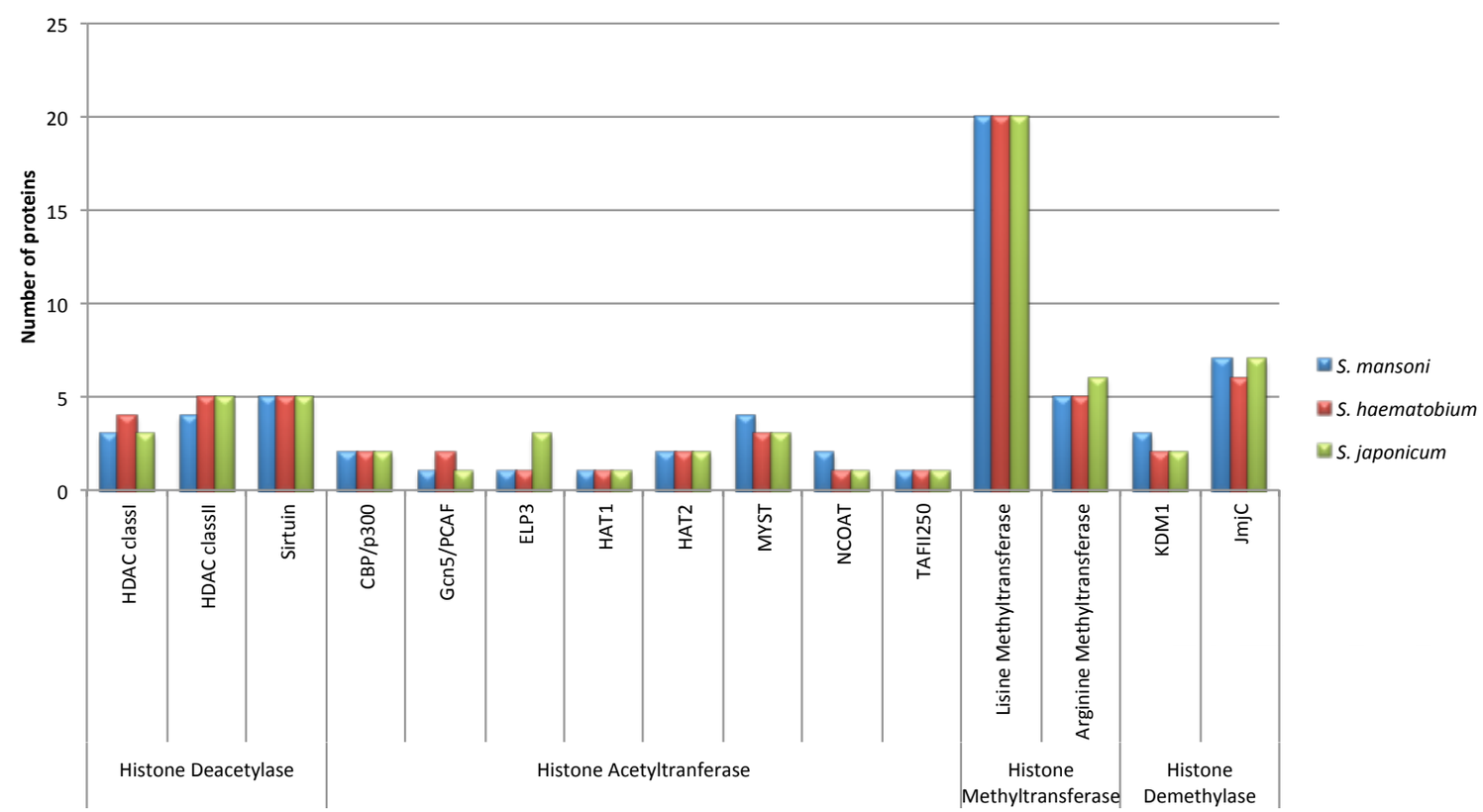
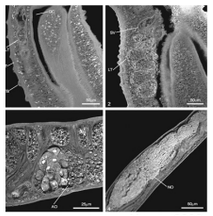




RNAi

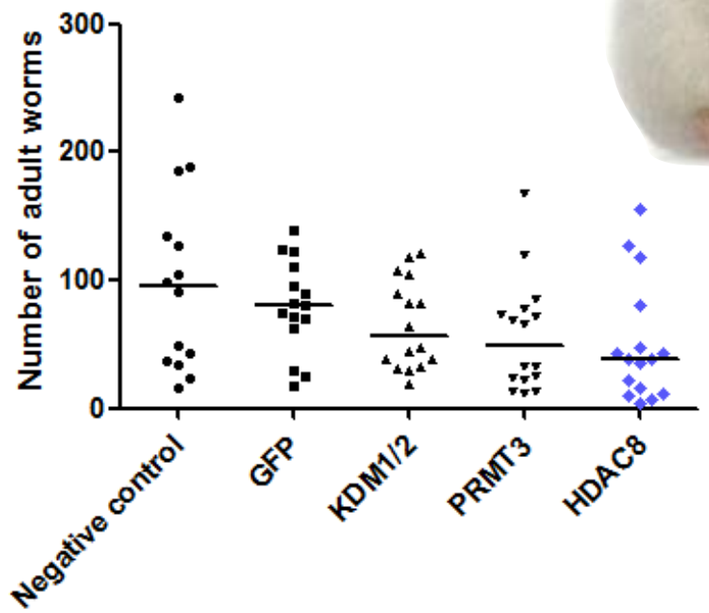
Marek *et al.*, PLoS Pathogens 2013

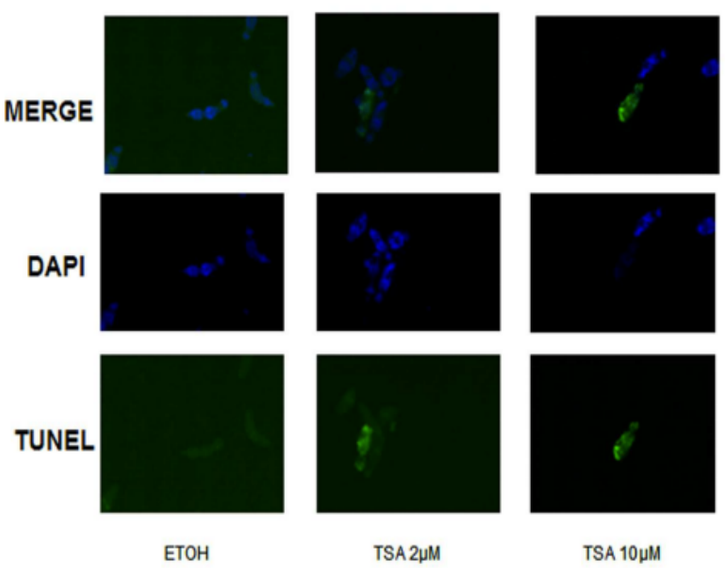
In vitro transformation

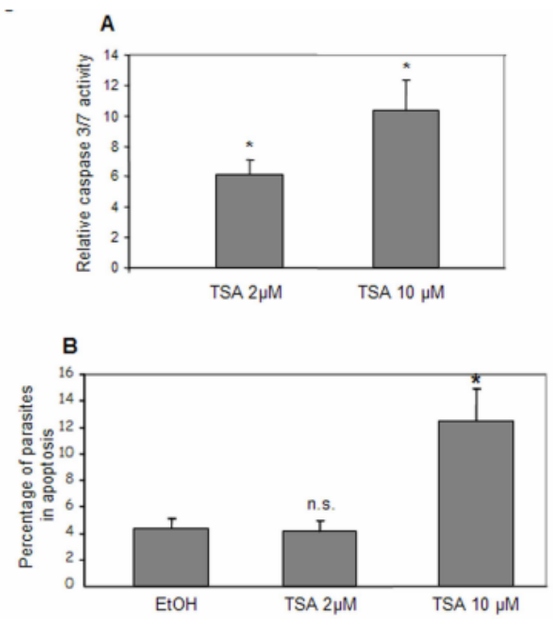


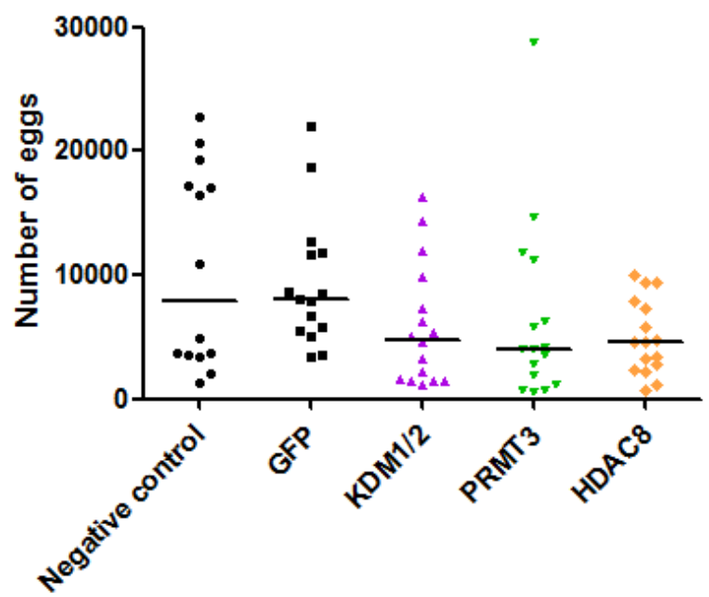
Neves, 2003

qPCR



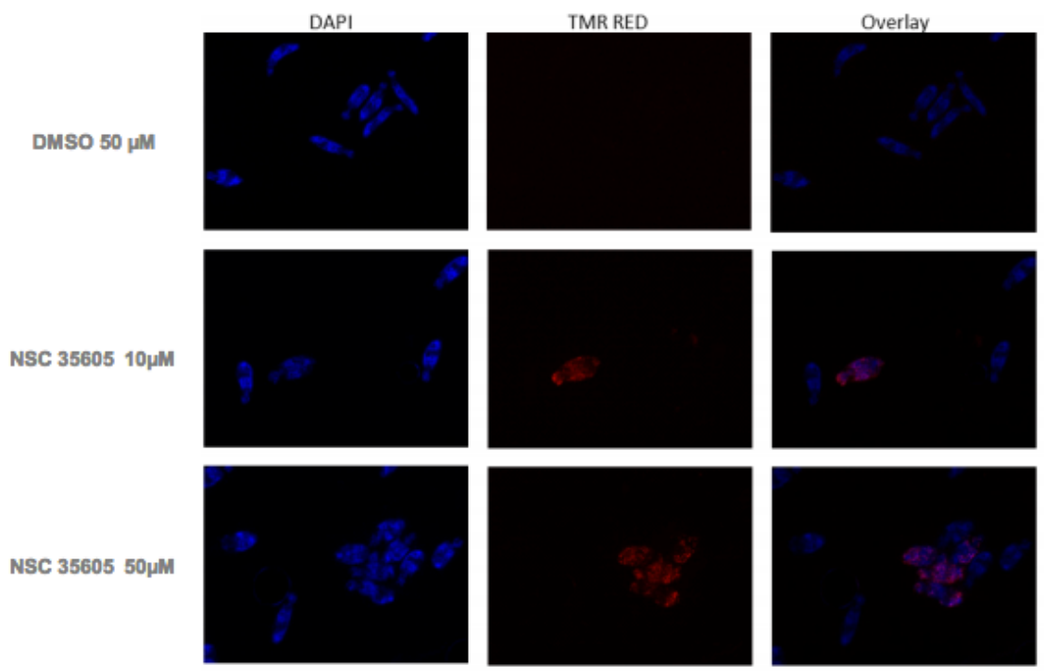


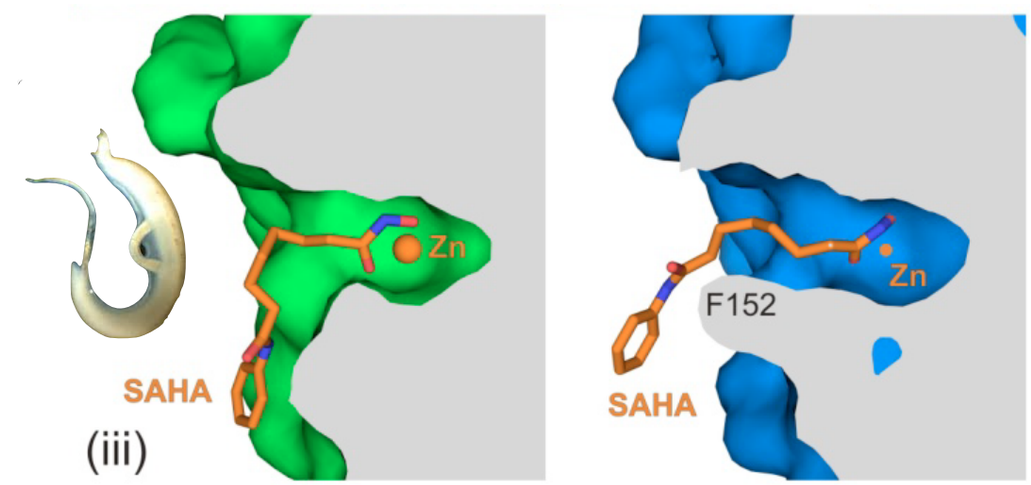


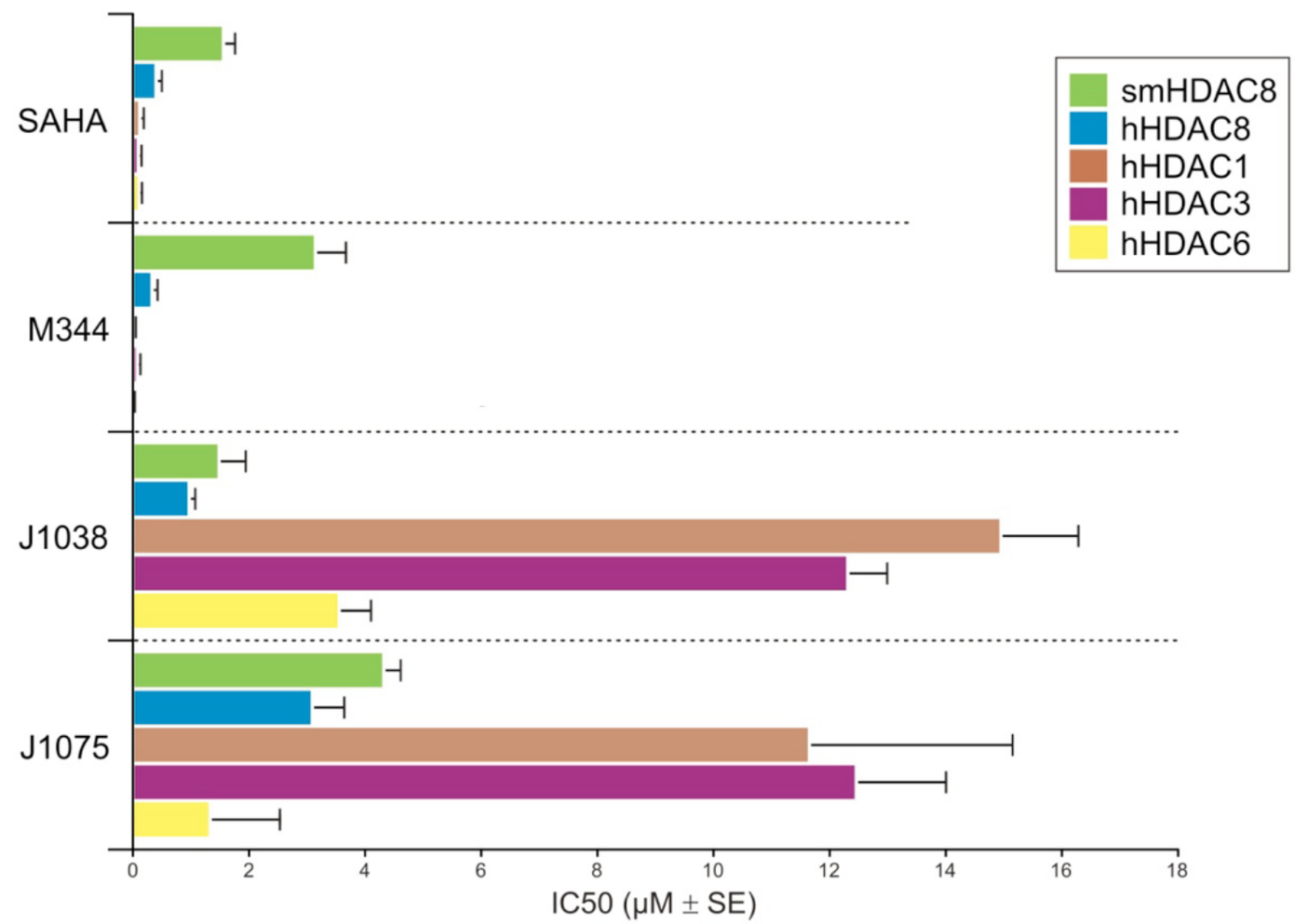


New compounds

Marek *et al.*, PLoS Pathogens 2013

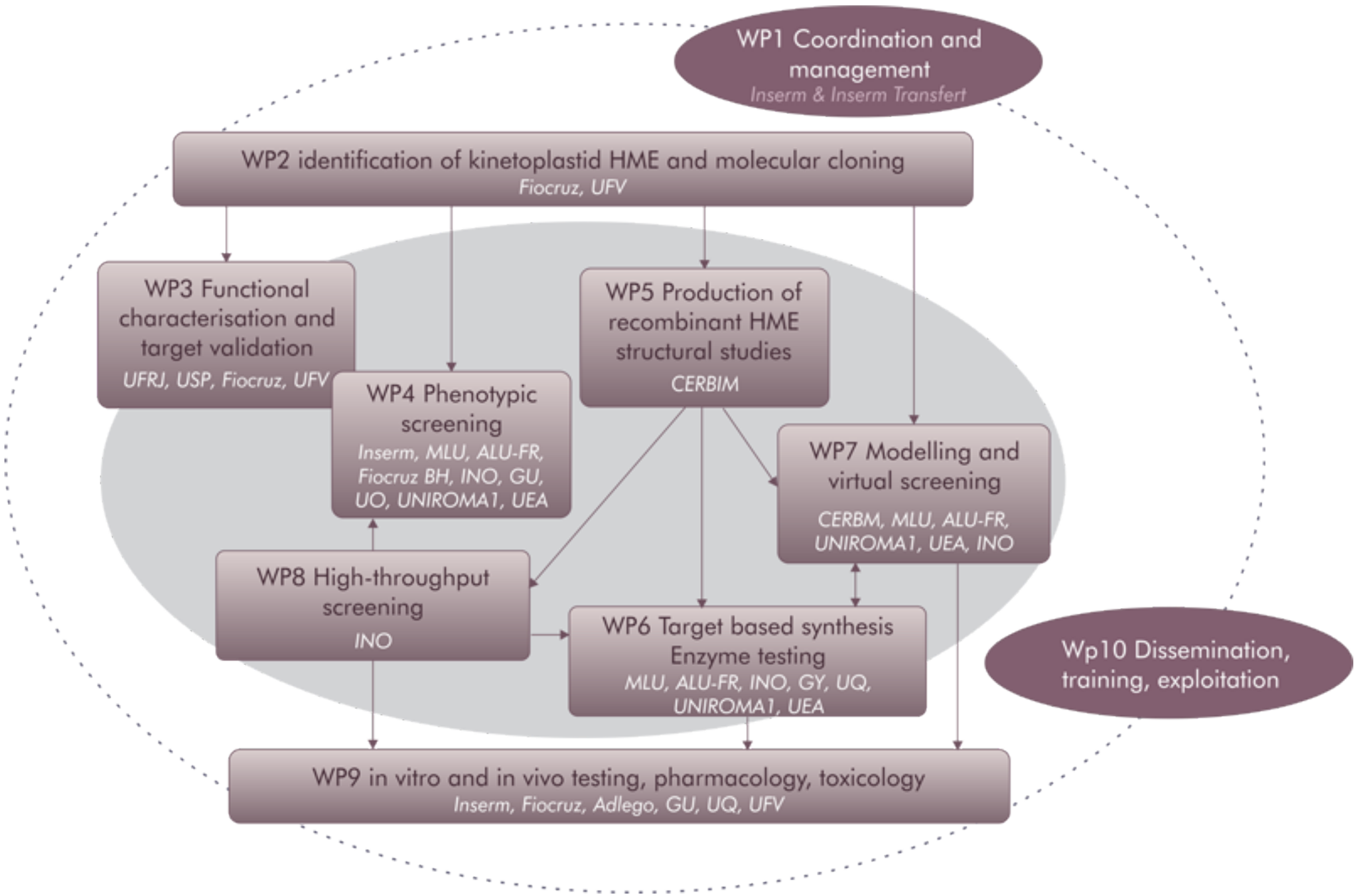


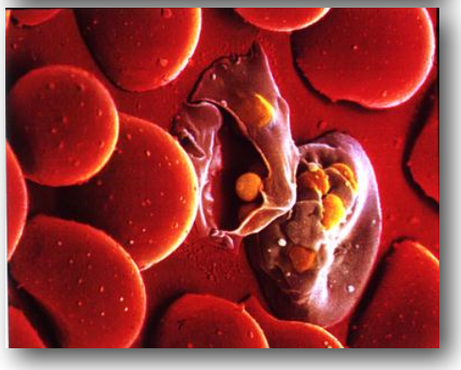




A-PARADDISE

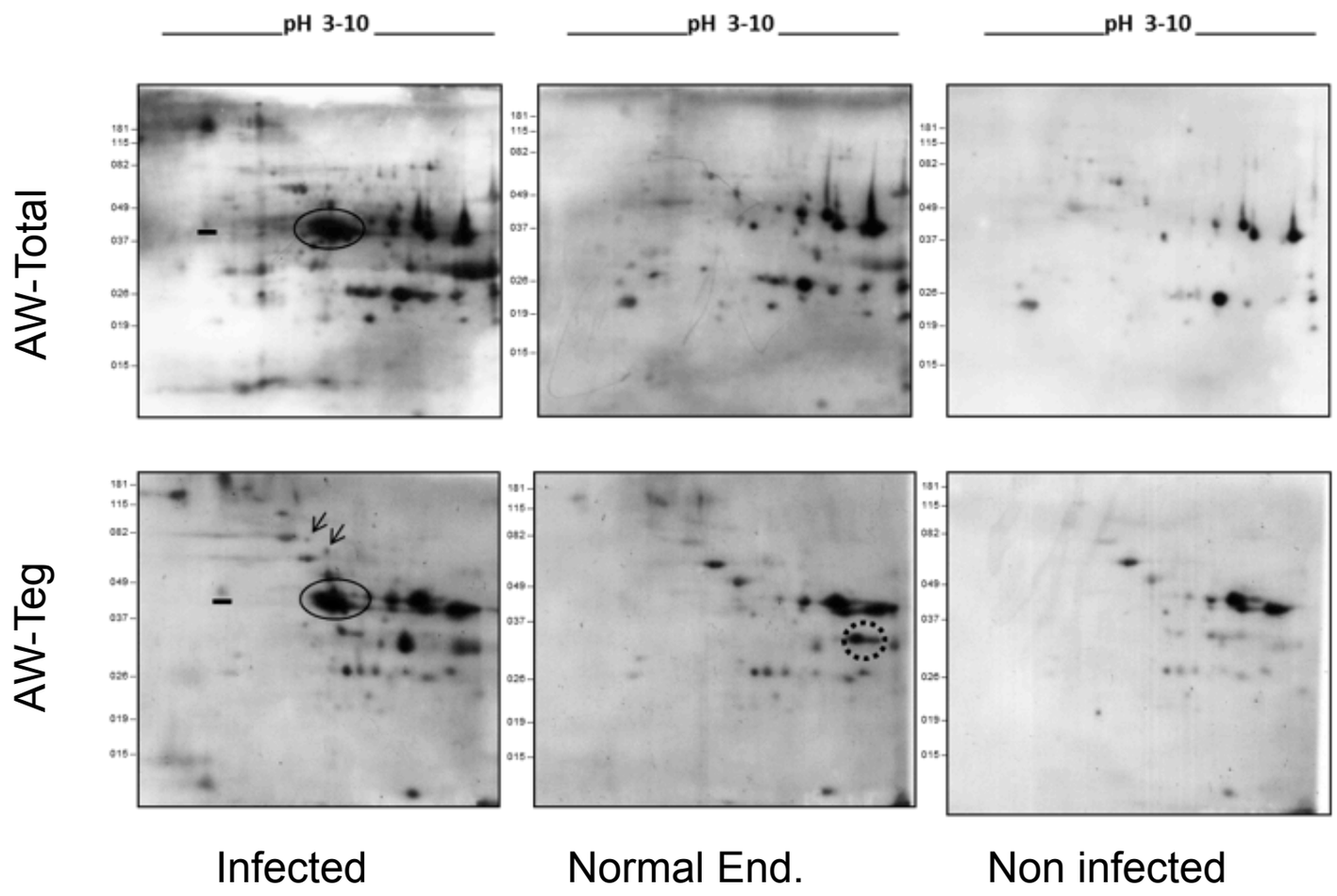
A-PARADDISE
Anti-Parasitic Drug Discovery in Epigenetics





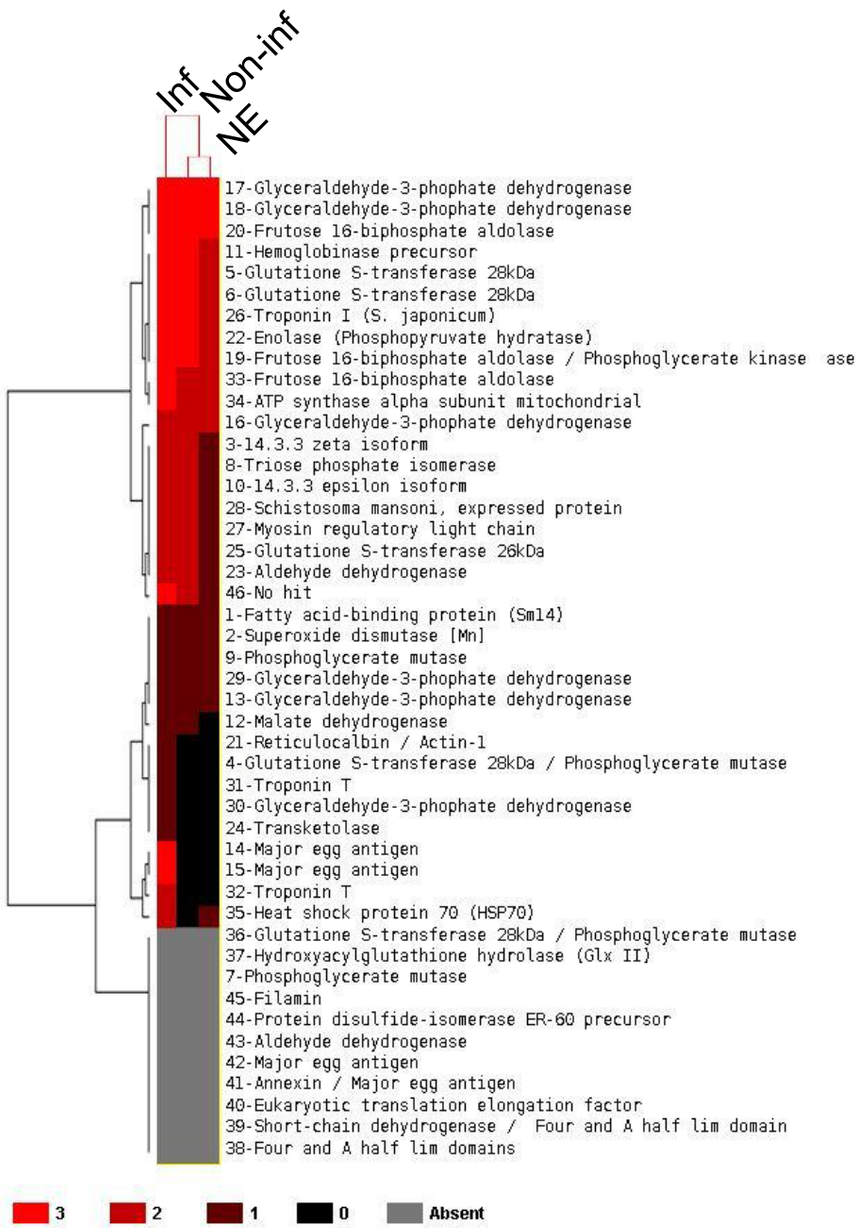
Antigen Search

Ribeiro PLoS NTD, 2014

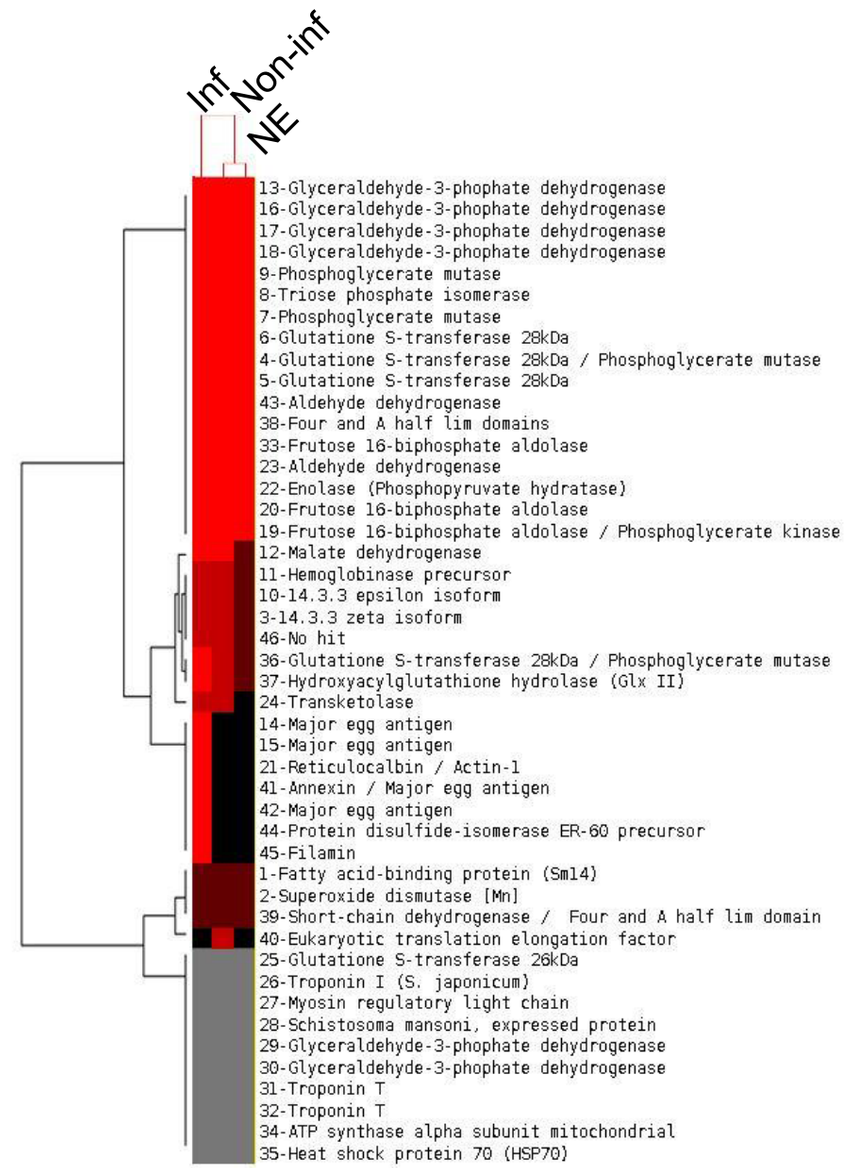


Antigen Search

Ribeiro PLoS NTD, 2014



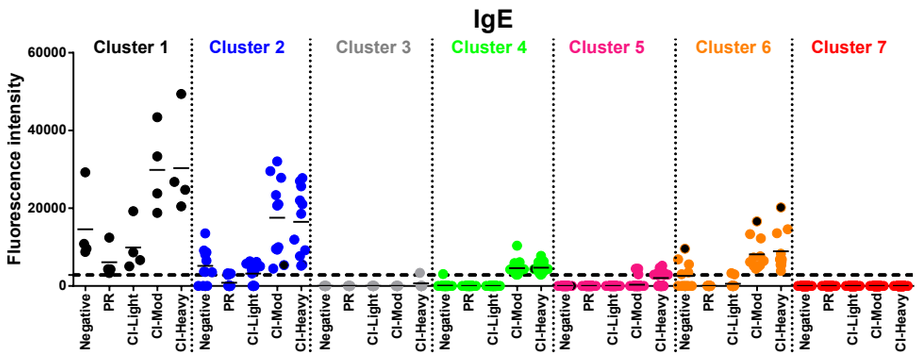
Total Adult Worm



Tegument

Antigen Search

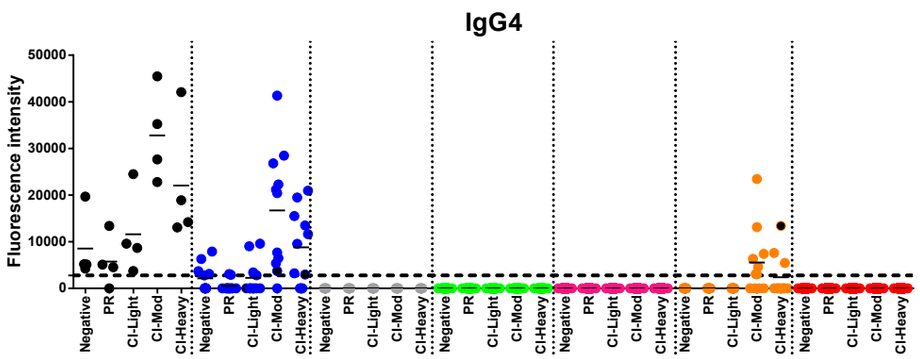
Gaze, PLoS Pathogens, 2014

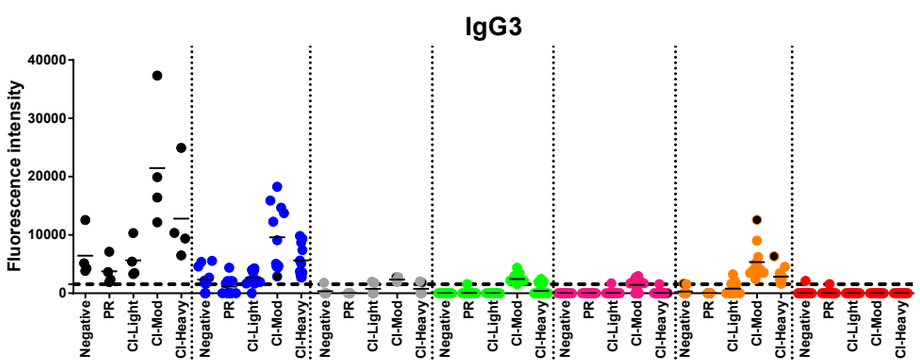


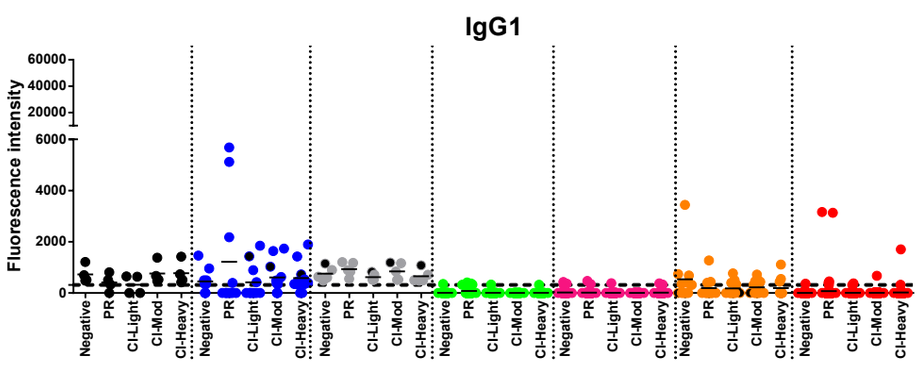
215 proteins

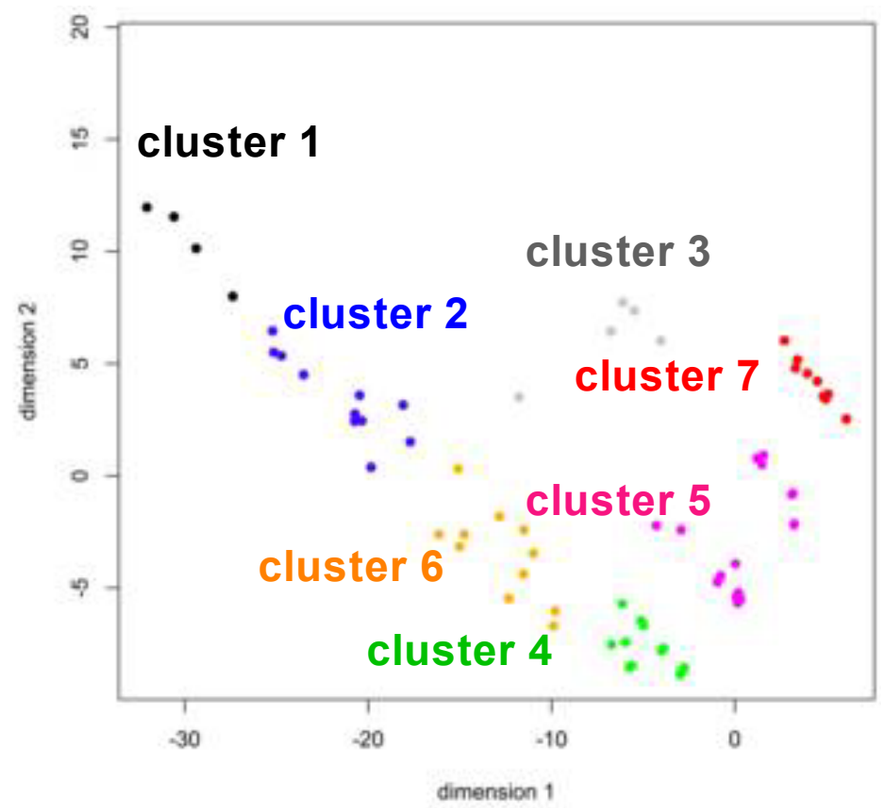
NI - BR / USA
CI - Low / Mod / High
PR

IgE / IgG4 /
IgG3 / IgG1



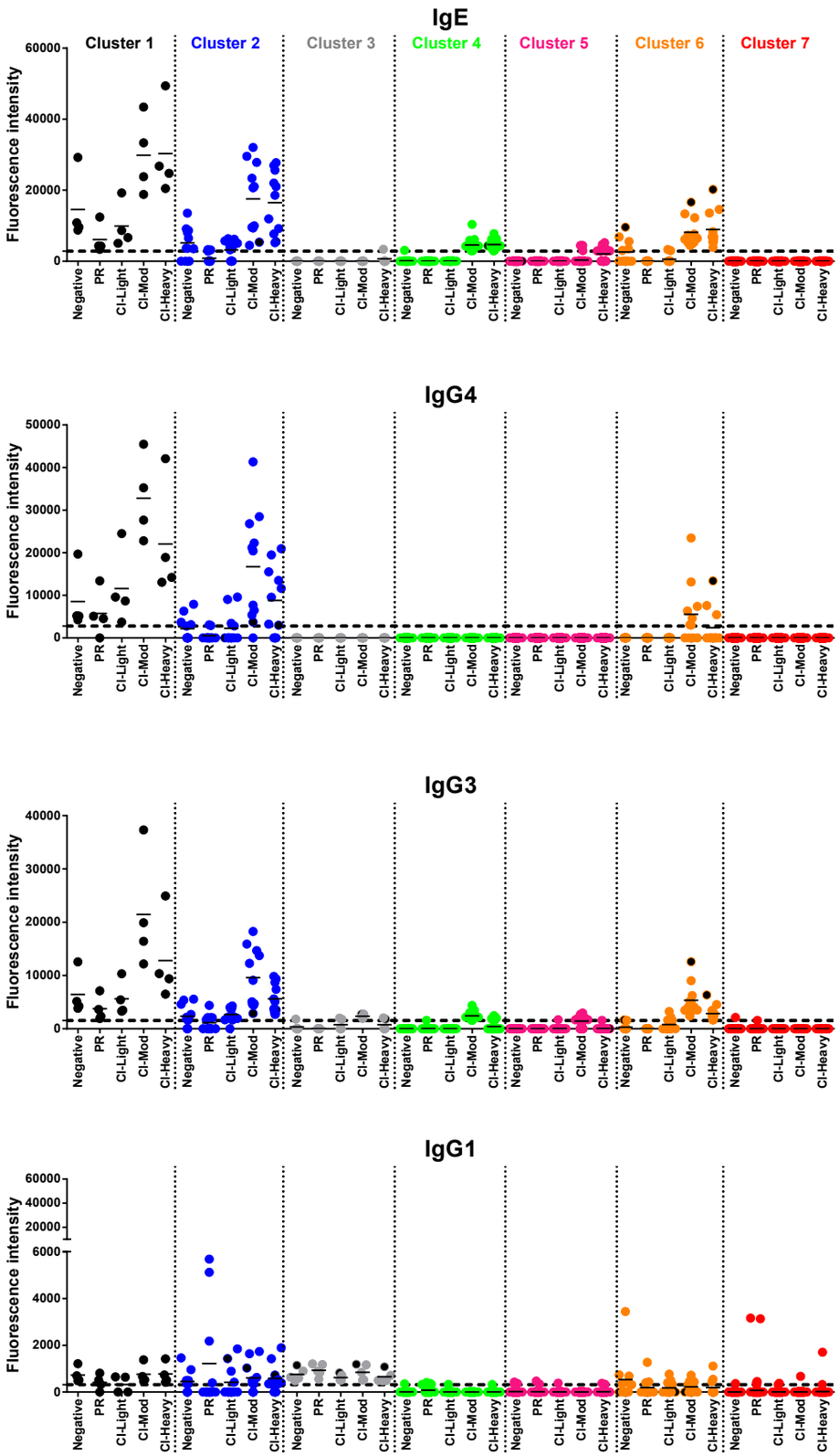






Antigen Search

Gaze, PLoS Pathogens, 2014

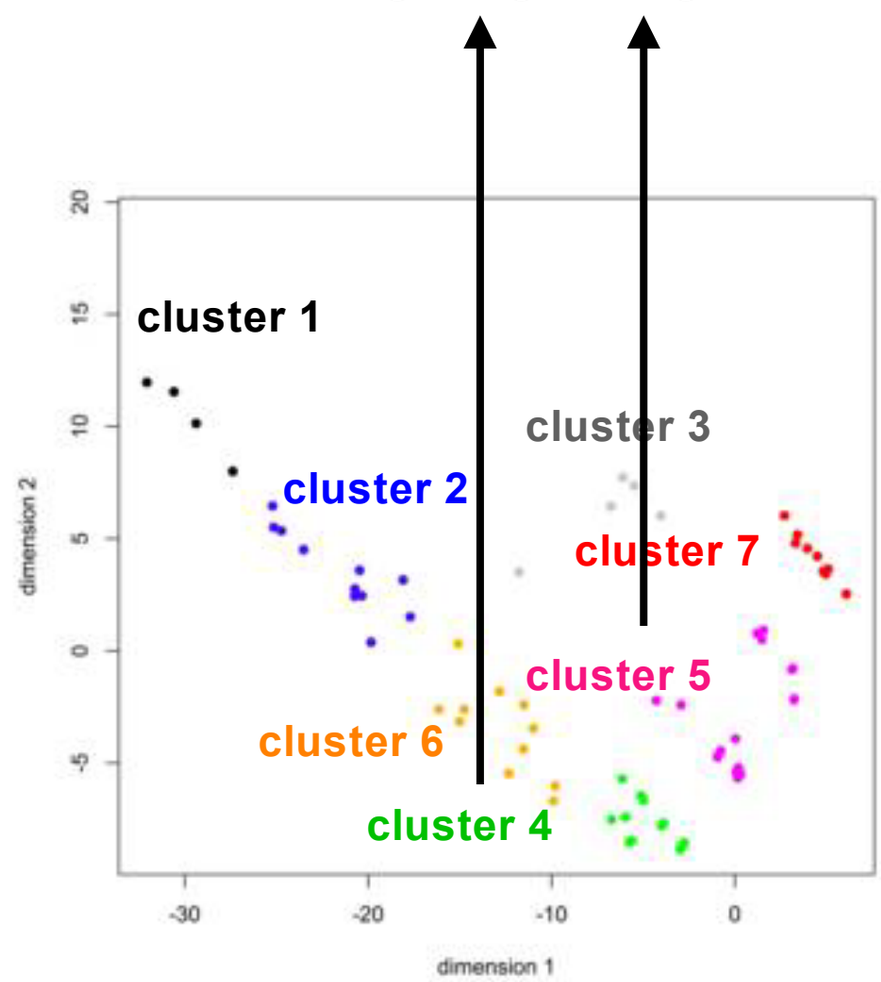


215 proteins

NI - BR / USA
CI - Low / Mod / High
PR

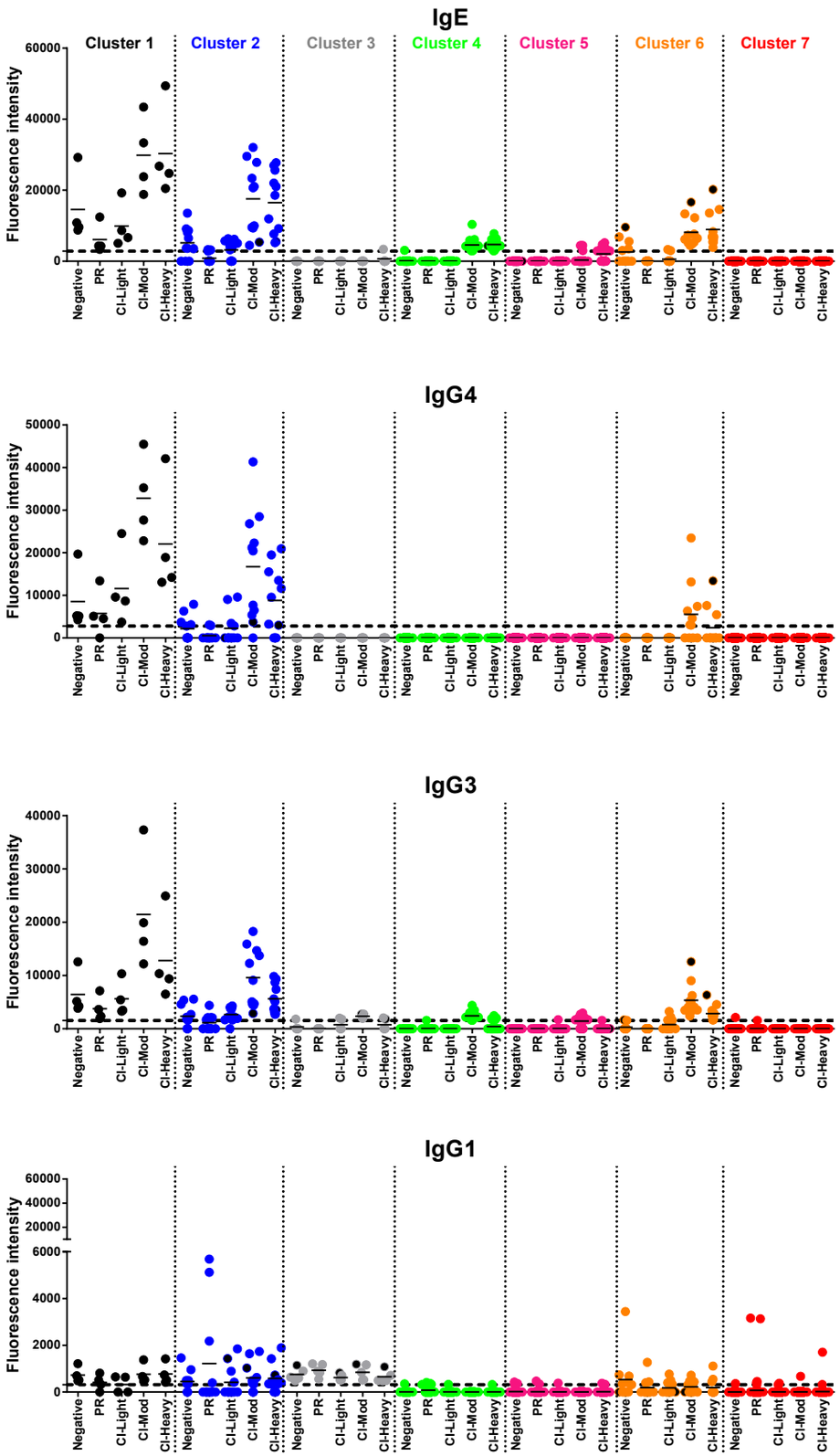
IgE / IgG4 / IgG3 / IgG1

IgE, IgG3, IgG1



Antigen Search

Gaze, PLoS Pathogens, 2014

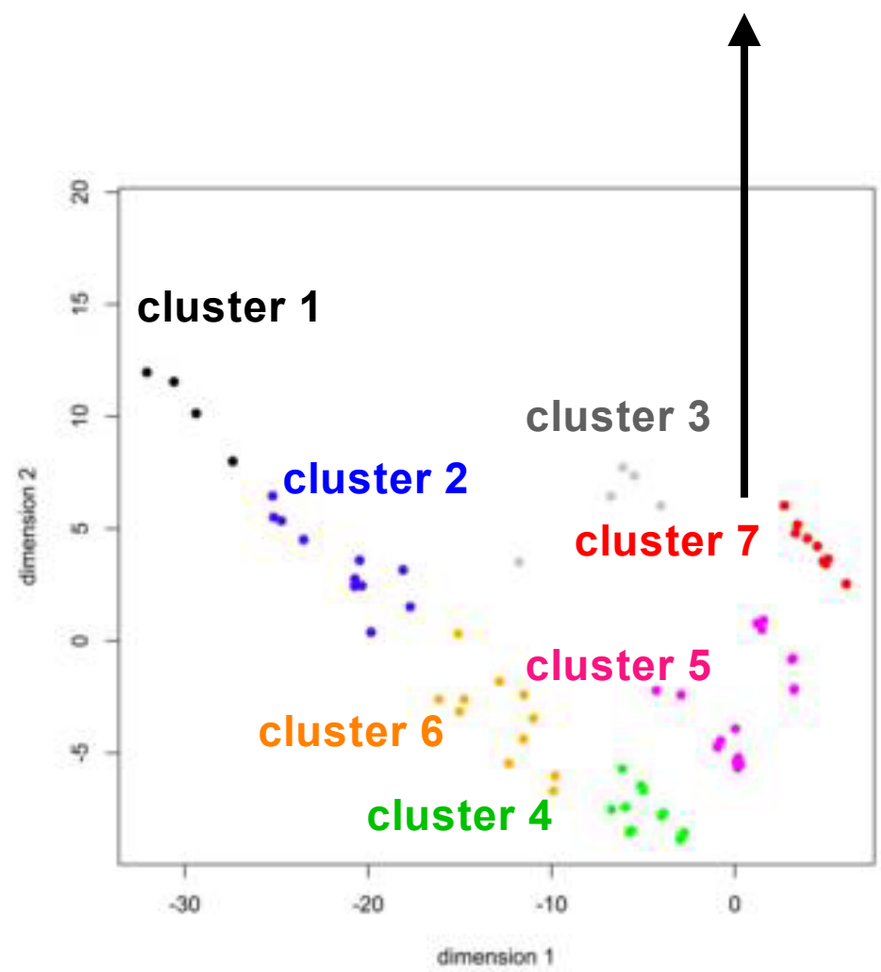


215 proteins

NI - BR / USA
CI - Low / Mod / High
PR

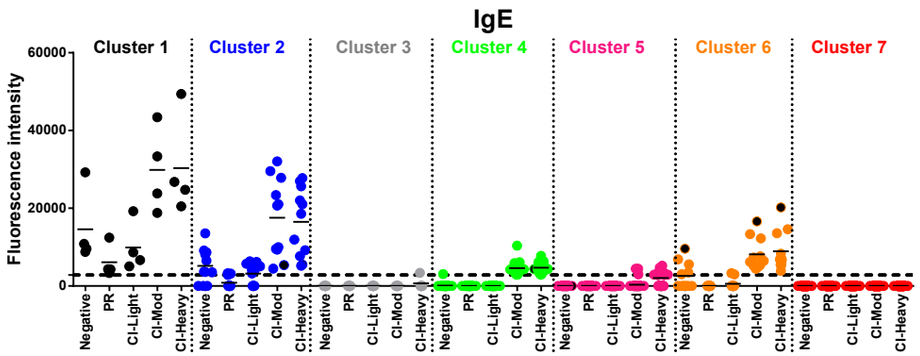
IgE / IgG4 / IgG3 / IgG1

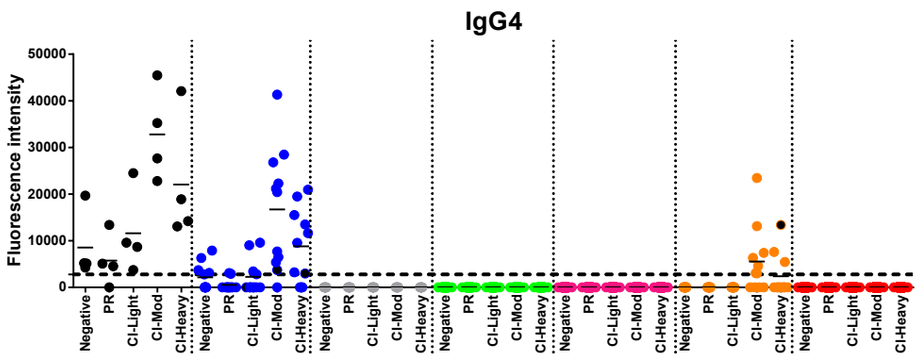
Non reactive Ag

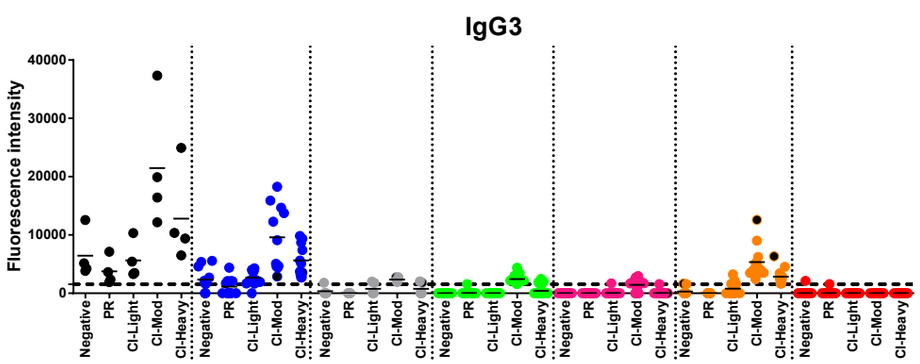


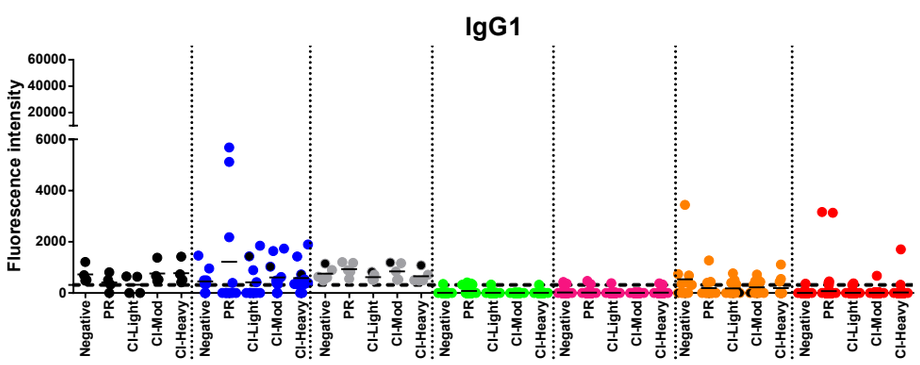
Antigen Search

Gaze, PLoS Pathogens, 2014





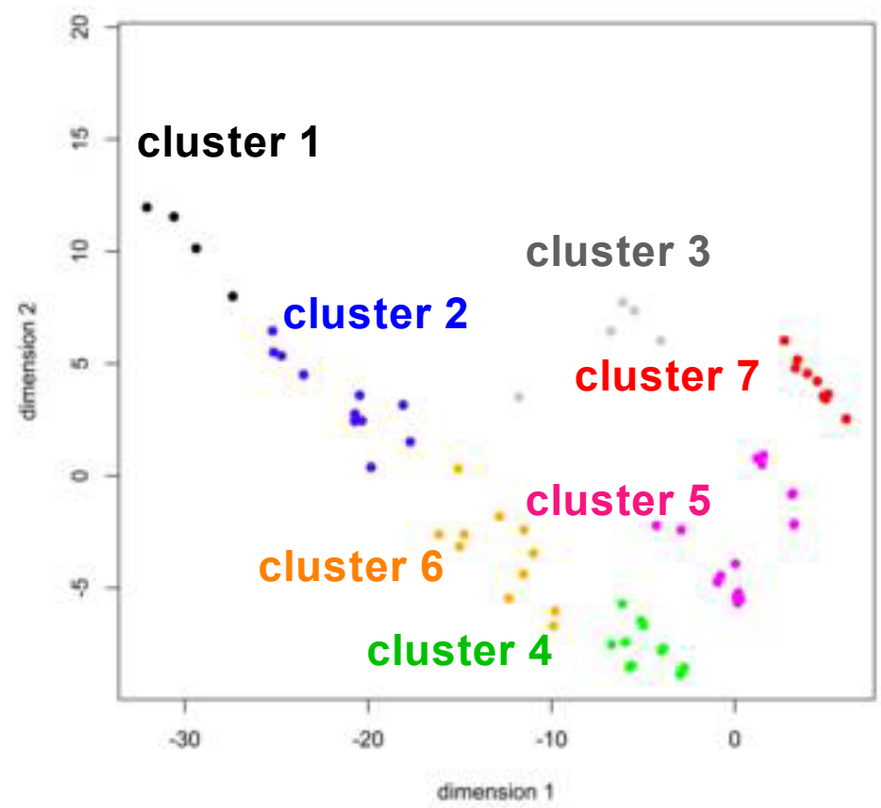




215 proteins

NI - BR / USA
CI - Low / Mod / High
PR

IgE / IgG4 /
IgG3 / IgG1



1,000 proteins
Deep exome sequencing (genetics/variability)

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A-PARADDISE
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THE ROYAL SOCIETY

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Thank you

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