VEuPathDB

Eukaryotic Pathogen, Vector & Host Informatics Resources

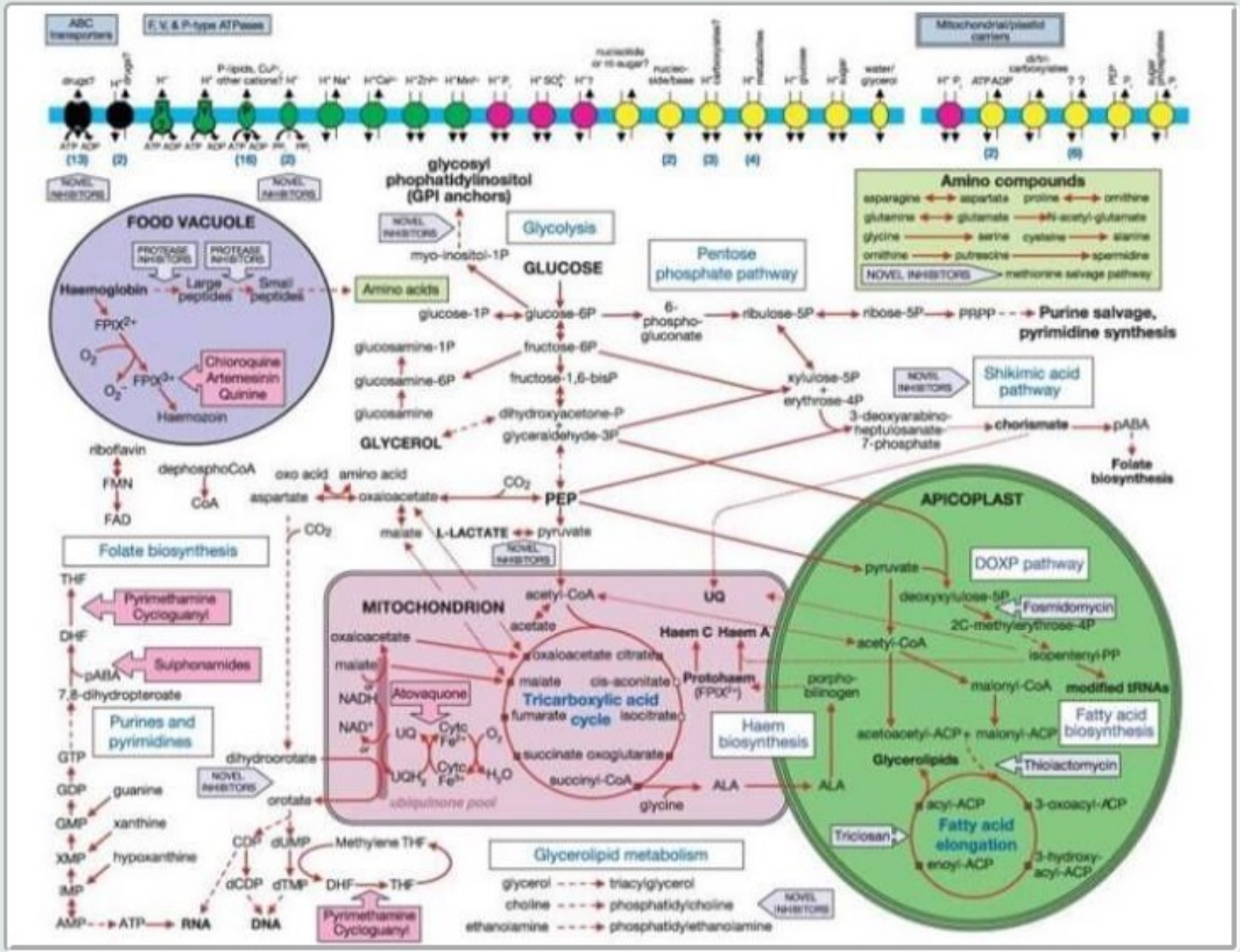
Metabolic Pathways

Jessie Kissinger

June 10, 2021

Today's module ties many tools together

- VEuPathDB maps gene products to pathways using EC numbers
- VEuPathDB imports pathways from sources like KEGG and MetaCyc
- You have multiple ways to search and interact with pathways
- You can transformation compounds into pathways or the genes in those pathways
- You can paint pathways with orthology, transcriptomics, eQTLs & proteomics
- You can locate gene products involved in pathways to cellular compartments
- You can examine how compounds/metabolites change during experiments



A *Plasmodium* metabolic map

https://mpmp.huji.ac.il/

Metabolic pathways and drug development

Target Identification

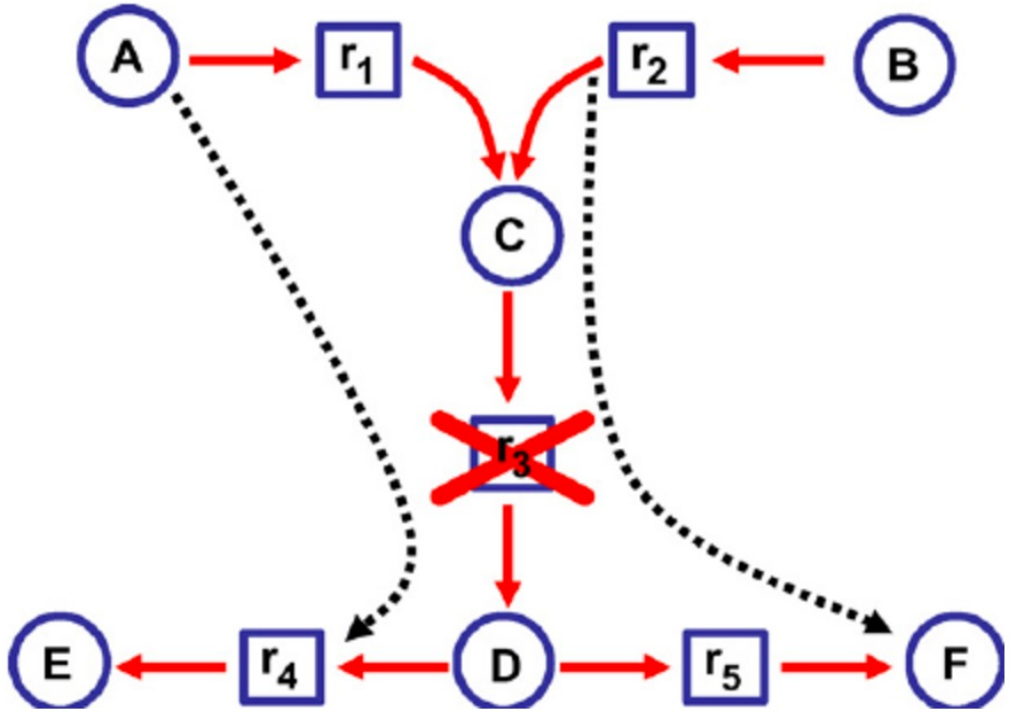
- Rational Drug Design – begin with a known druggable target in another organism (an ortholog)
- Predict targets in pathogen or organism of interest (and not the host). Is the pathway conserved?

Target Validation

- When target or mechanism of drug action are unknown
- Transcriptomics
- Metabolomics
- Targeted knock-outs/phenotype
- Studies of resistance

Identification of pathway choke points

- Identification of an essential reaction in an organism. Proof of essentiality via analysis of KO data are critical
- Depends on identification of all genes in pathway
- Success depends on having a drug, getting it in, having organism not pump it out, or bypass with import of reaction intermediates and the compound not being toxic to the host.

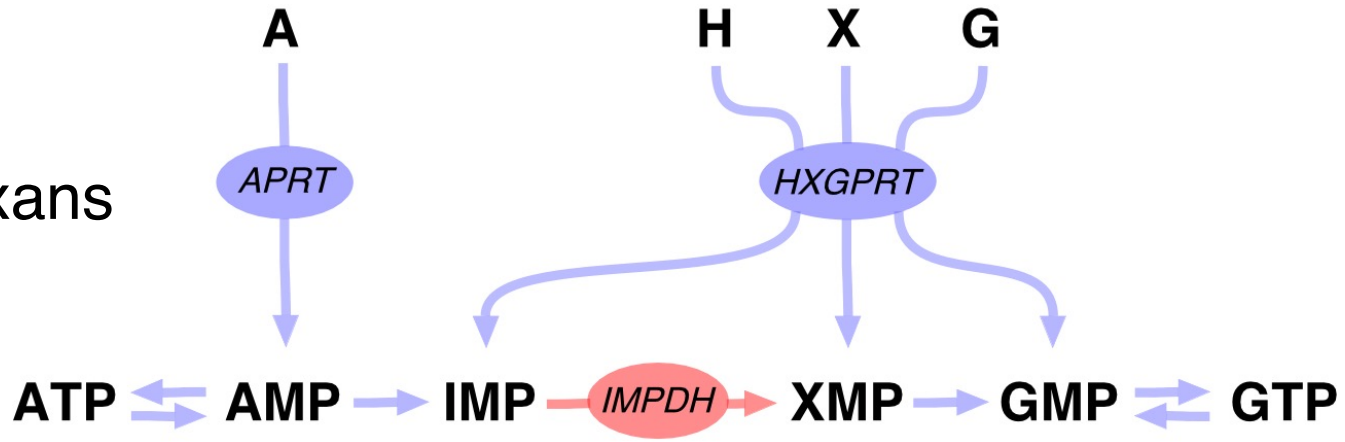


Estimating novel potential drug targets of *Plasmodium falciparum* by analysing the metabolic network of knock-out strains *in silico*

Journal of molecular epidemiology and evolutionary genetics in infectious diseases 9(3):351-8 · February 2008

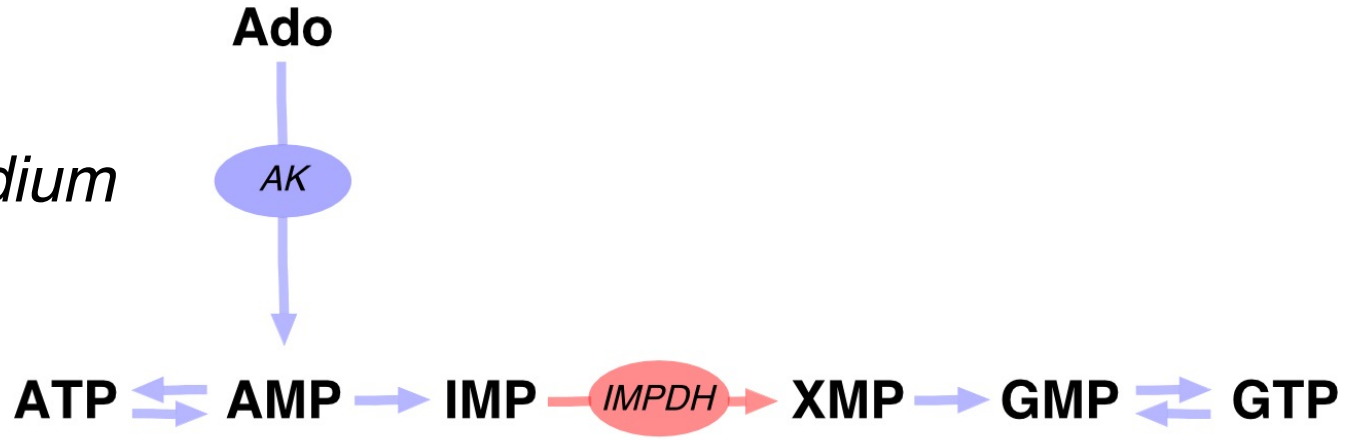
C. parvum lacks HXGPRT

Other Apicomplexans

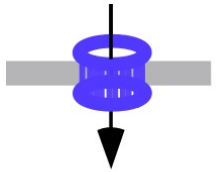


Doyle, P.S. et al., Exp. Parasitol. 89: 9-15

Cryptosporidium



Genomic analysis of *C. parvum* purine pathway



Adenosine

AMP

IMP

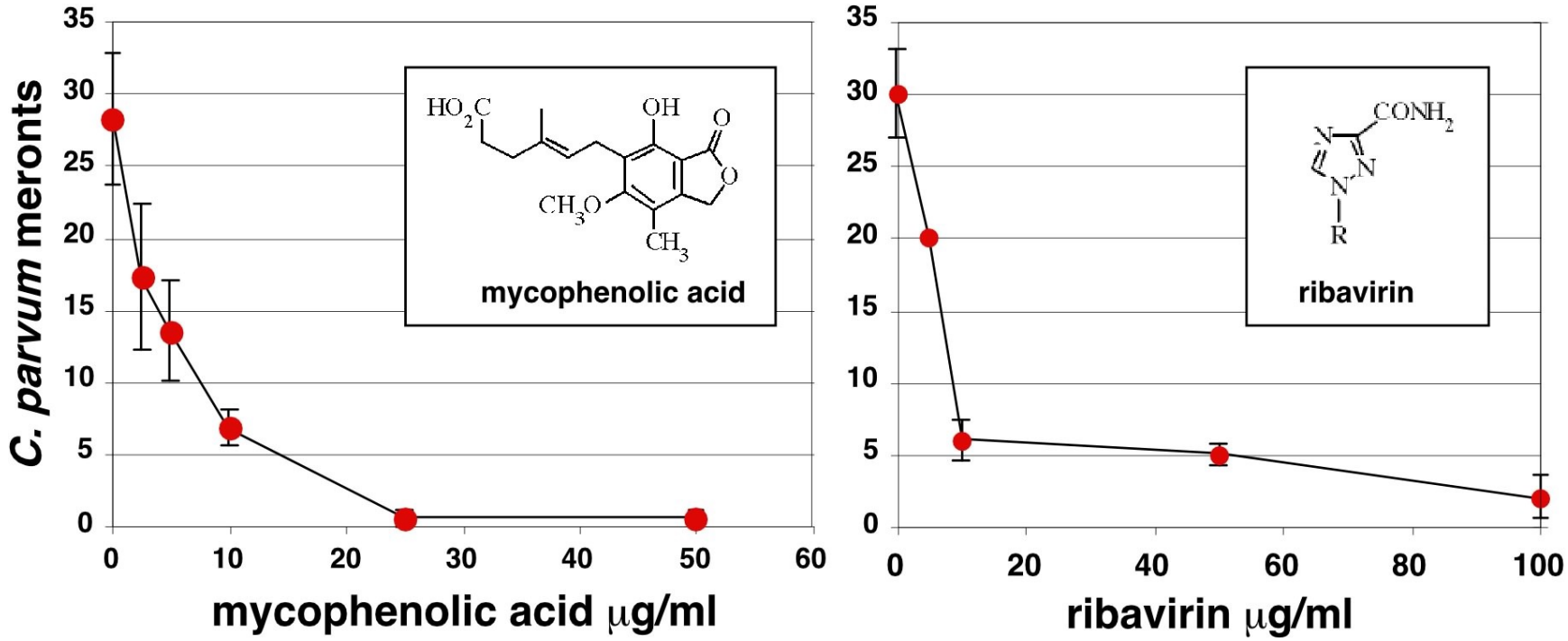
XMP

GMP

gene	Bovine gt	Human gt	GNBR & p-value
Transporter	CpIOWA_256	CpTypeIH_3002 & 3198	*T. gondii* AT, $2e^{-13}$
Adenosine Kinase	CpIOWA_274	CpTypeIH_3589	*T. gondii* AK, $2e^{-30}$
AMP Deaminase	CpIOWA_271	CpTypeIH_3695	*P. yoellii* AMPD, e^{-147}
IMP Dehydrogenase	CpIOWA_249	CpTypeIH_3432 & 3397	*H. pylori* IMPDH, e^{-102}
GMP Synthase	CpIOWA_221	CpTypeIH_2191	*H. sapiens* GMPS, $5e^{-68}$

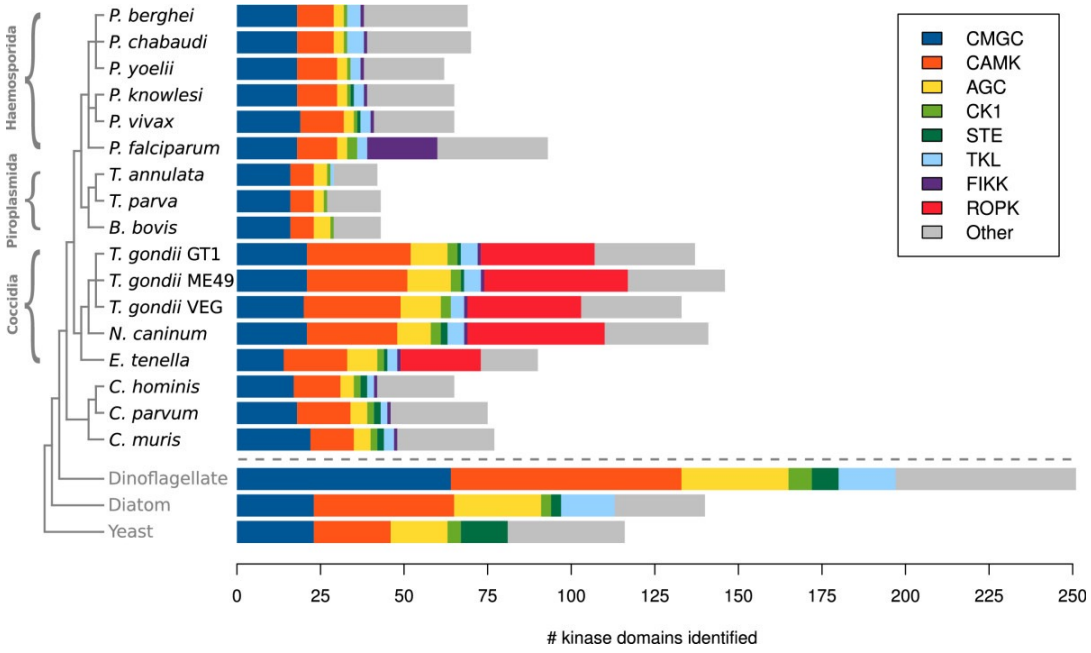
Striepen et al., PNAS 2002 99:6304

C. parvum is inhibited by drugs targeting IMPDH

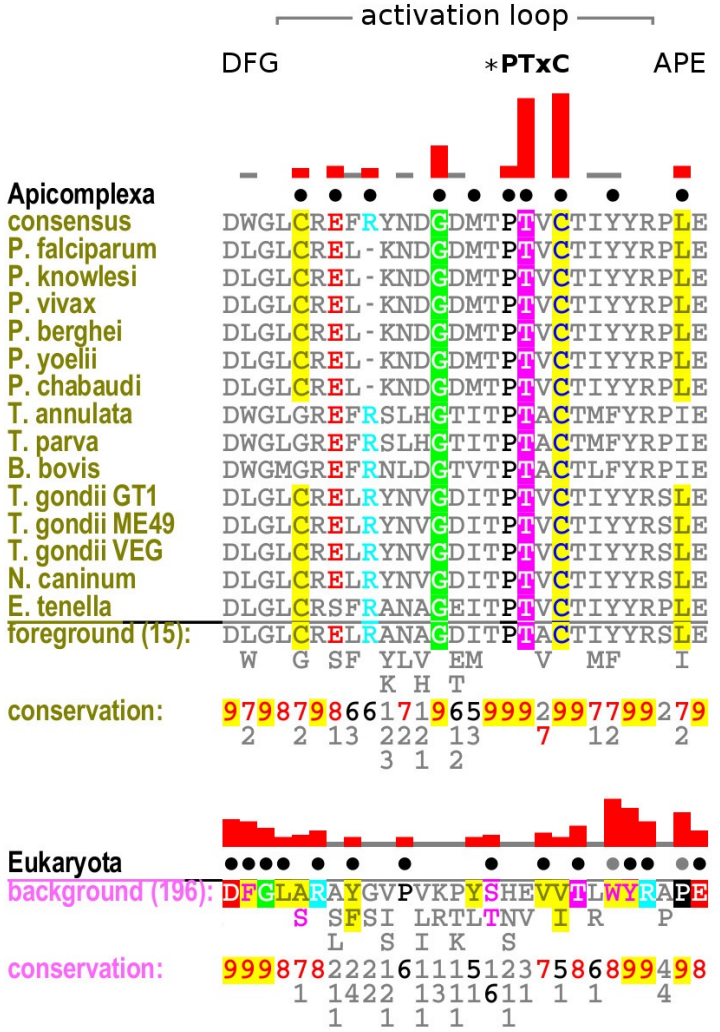


Striepen et al, 2004 PNAS 101(9): 3154-3159

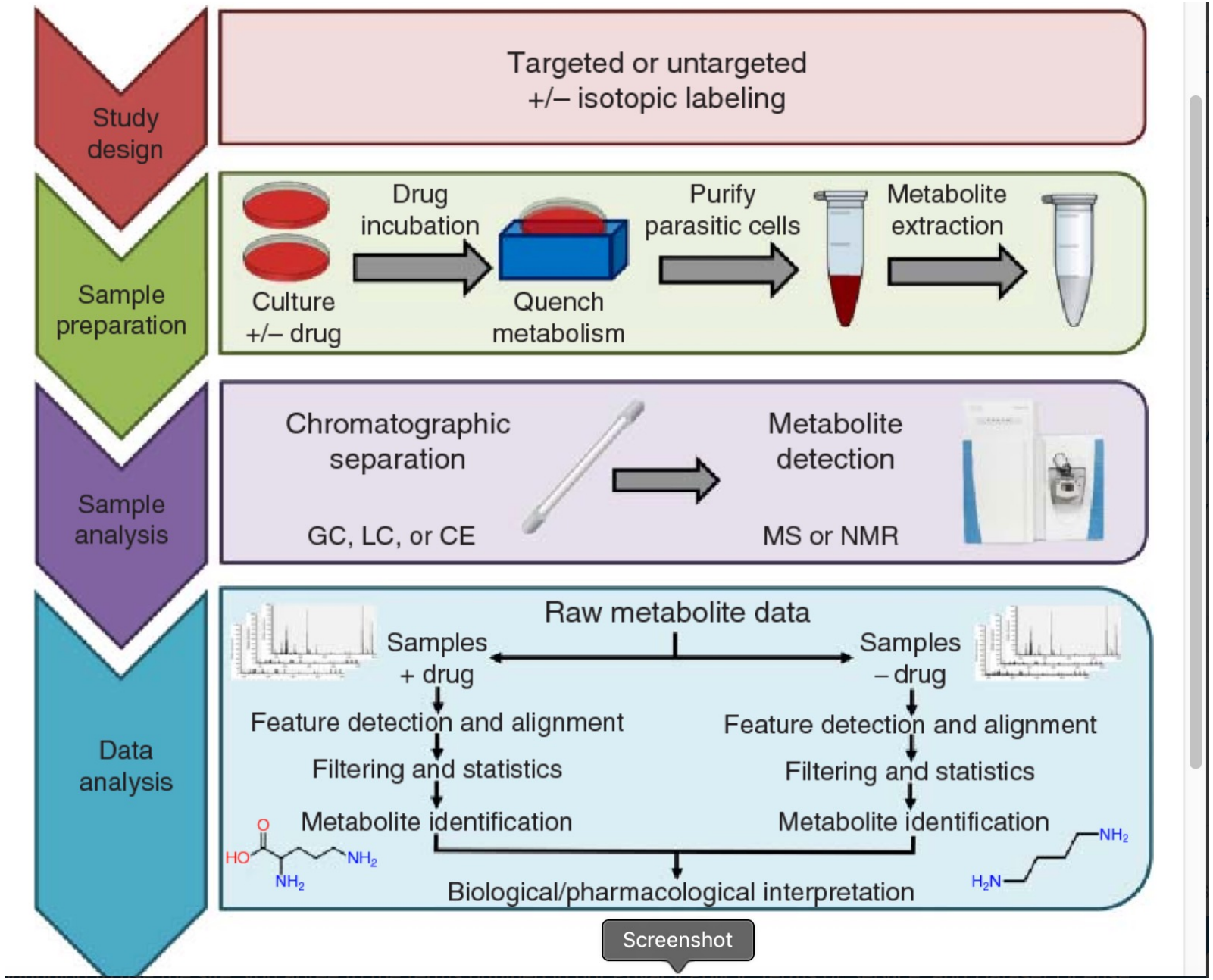
Evolution of protein function and families



BMC Evolutionary Biology 2011 **11**:321



Apicomplexan Protein Kinases



Metabolomics is a powerful window into drug effects

Complements transcriptomics

DOI:10.1002/9783527694082.ch14

Additional Useful resources:

- http://dgidb.genome.wustl.edu/
- http://VEuPathDB.org & http://HostDB.org
- http://orthomcl.org/orthomcl/
- http://www.membranetransport.org/
- http://www.genome.jp/kegg/pathway.html
- http://mpmp.huji.ac.il/ (*Plasmodium* only)
- Drugbank - https://go.drugbank.com/
  - https://go.drugbank.com/drugs/DB06697
- TTD (Therapeutic Target Database) - http://db.idrblab.net/ttd/
- chEMBL - https://www.ebi.ac.uk/chembl/
- Small Molecule Pathway Database - SMPDB - https://smpdb.ca/

In this module:

- We will learn about finding and exploring pathways
- Visualizing experimental gene expression data and orthologs in the context of a pathway
- Learn to search for specific metabolic compounds
- Learn to mine metabolomics data
- Learn how to transform compounds into the pathways and genes encoding the enzymes that act upon them