Fungal phylogenomics: Getting lost in the moldy forest

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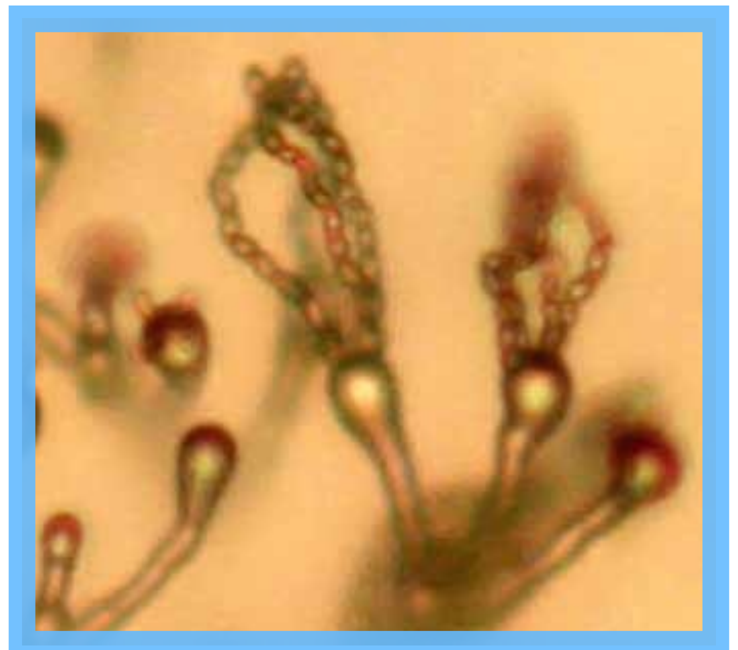
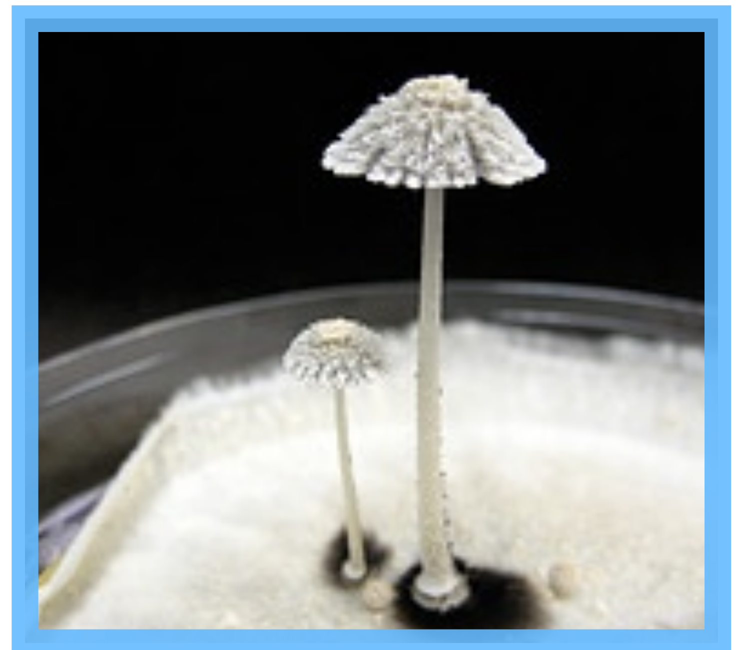
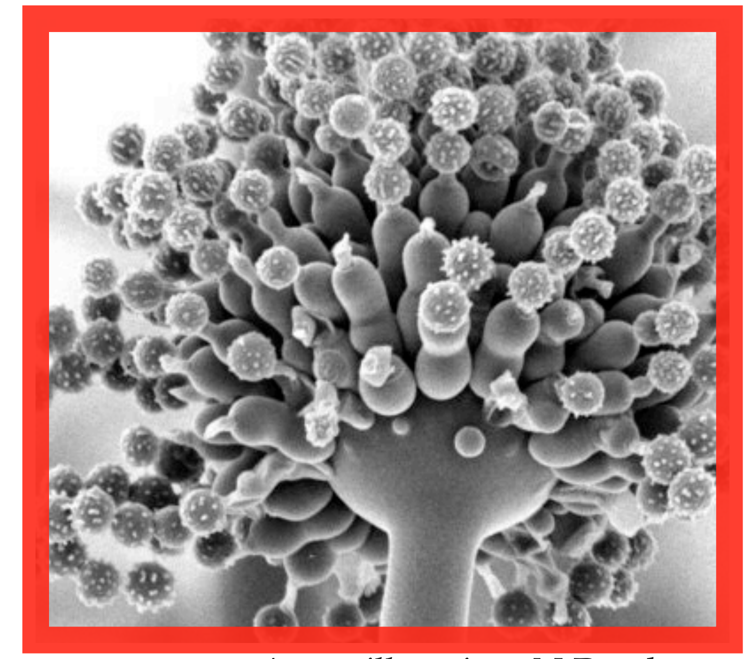
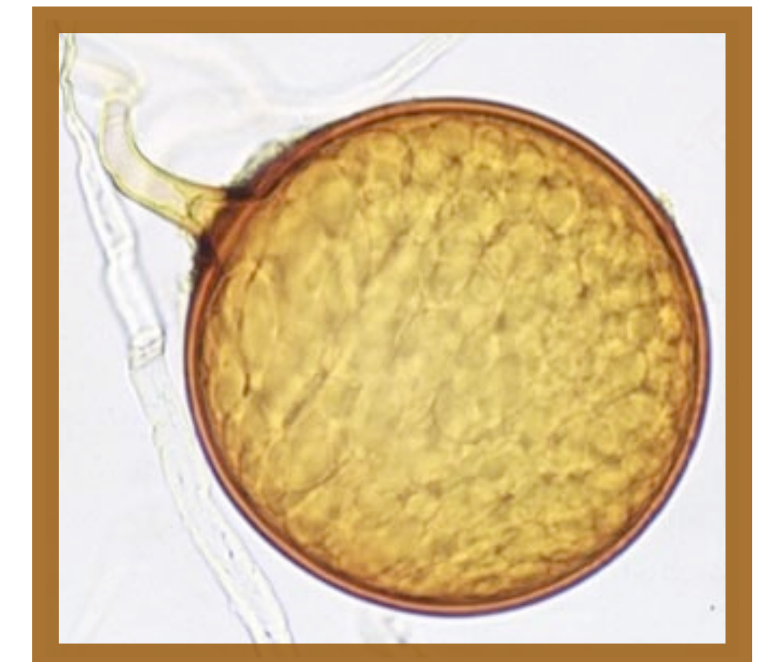
http://lab.stajich.org
http://fungalgenomes.org/blog
http://fungiDB.org
twitter{stajichlab,hyphaltip,fungalgenomes,fungidb}

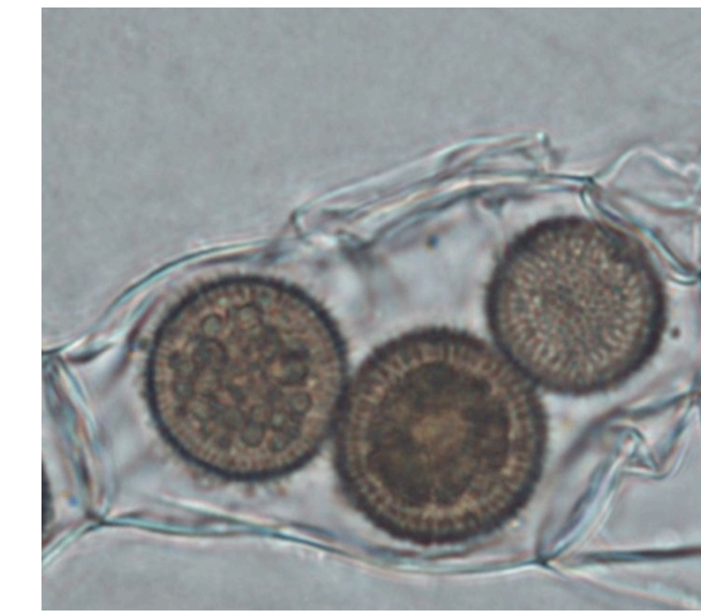
Fungi have diverse forms, ecology, and associations


Cryptococcus neoformans X. Lin

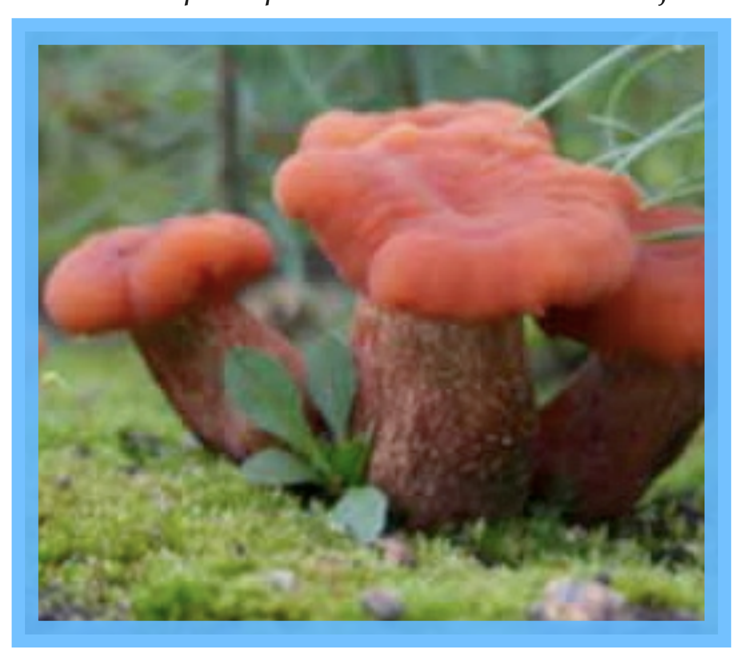

Coprinopsis cinerea Ellison & Stajich

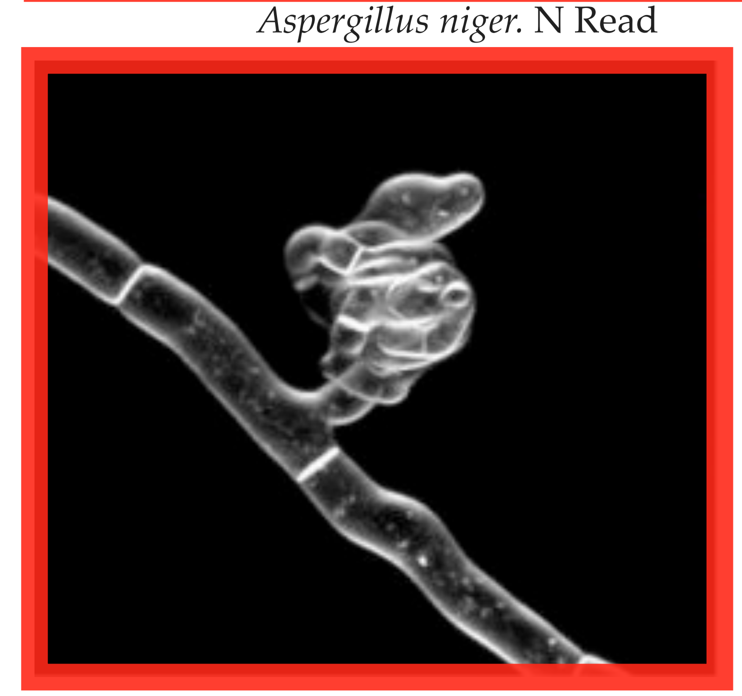

Aspergillus niger. N Read

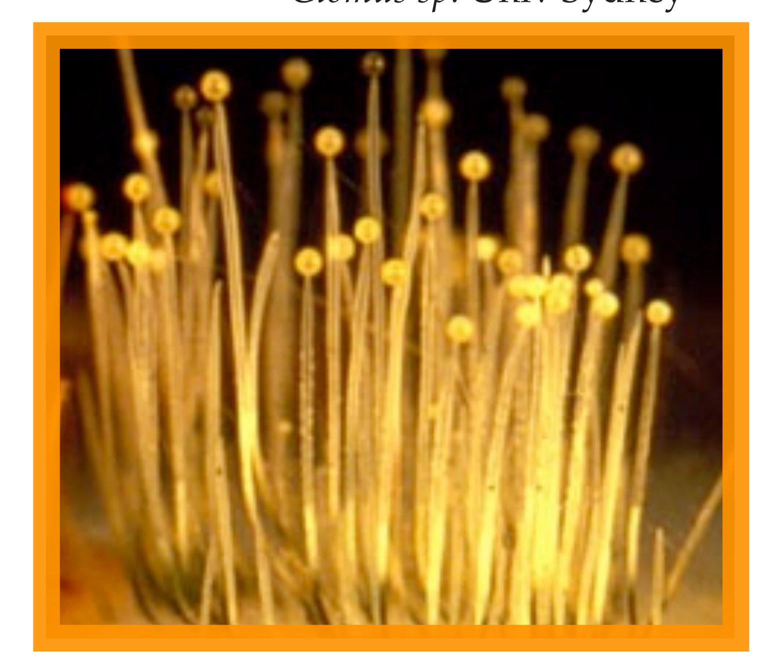

Glomus sp. Univ Sydney

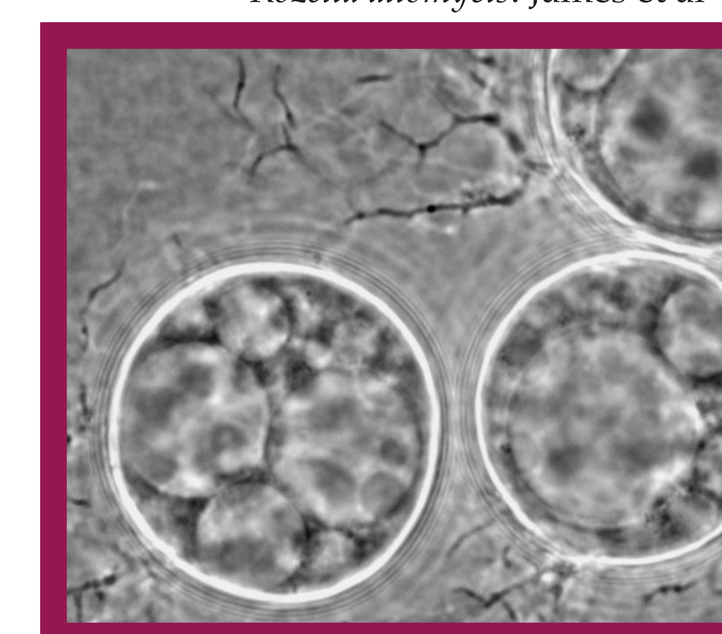

Rozella allomycis. James et al


Puccinia graminis J. F. Hennen


Laccaria bicolor Martin *et al.*

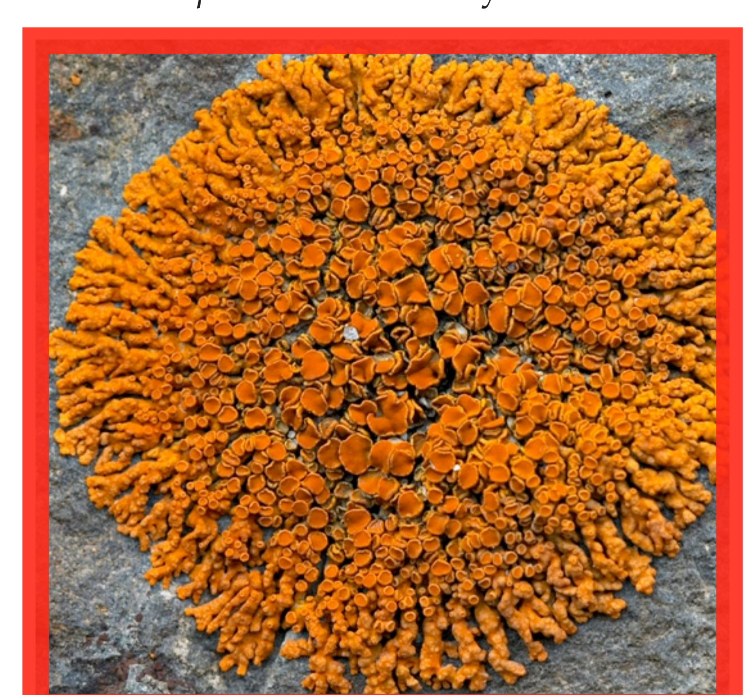

Neurospora crassa. Hickey & Reed

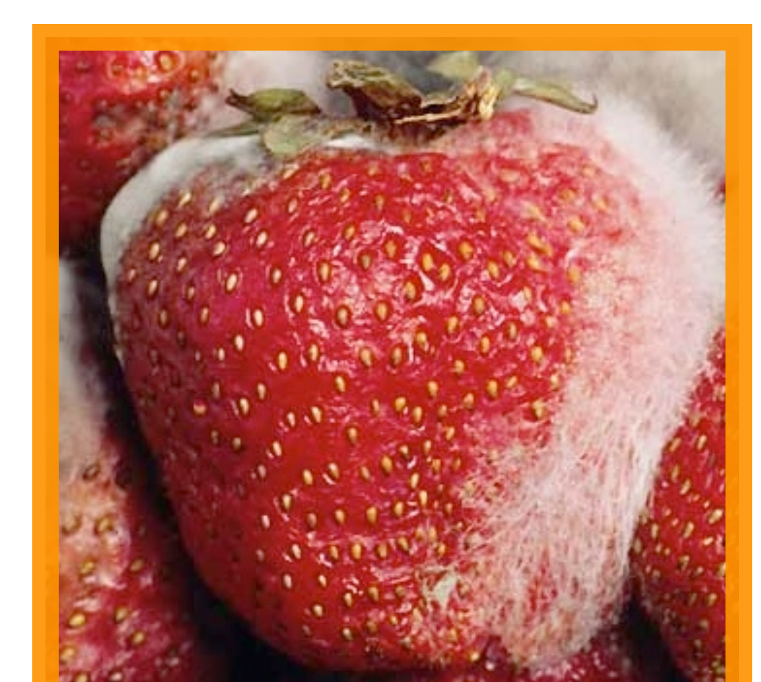

Phycomyces blakesleansus T. Ootaki

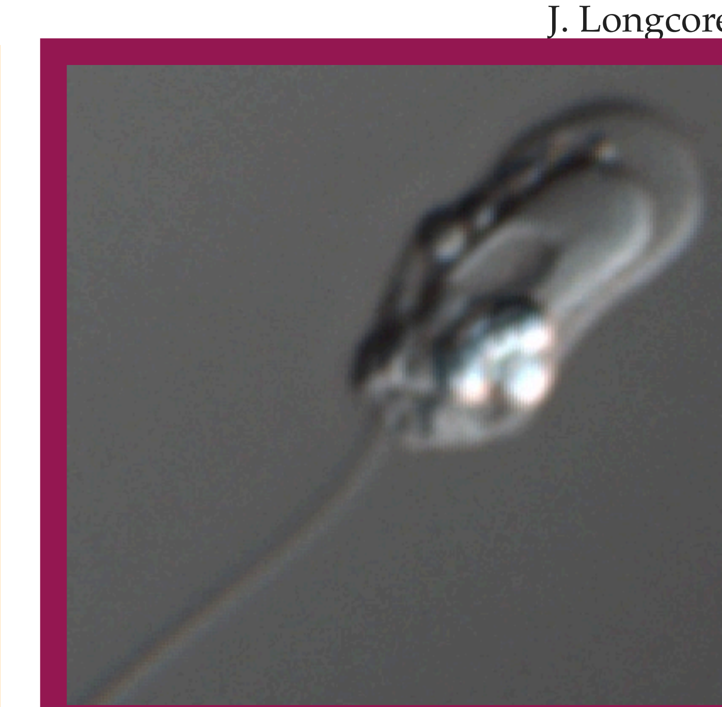

Batrachochytrium dendrobatidis J. Longcore


Ustilago maydis Kai Hirdes


Amanita phalloides. M Wood


Xanthoria elegans. Botany POtD


Rhizopus stolonifera.


Blastocadiela simplex Stajich & Taylor

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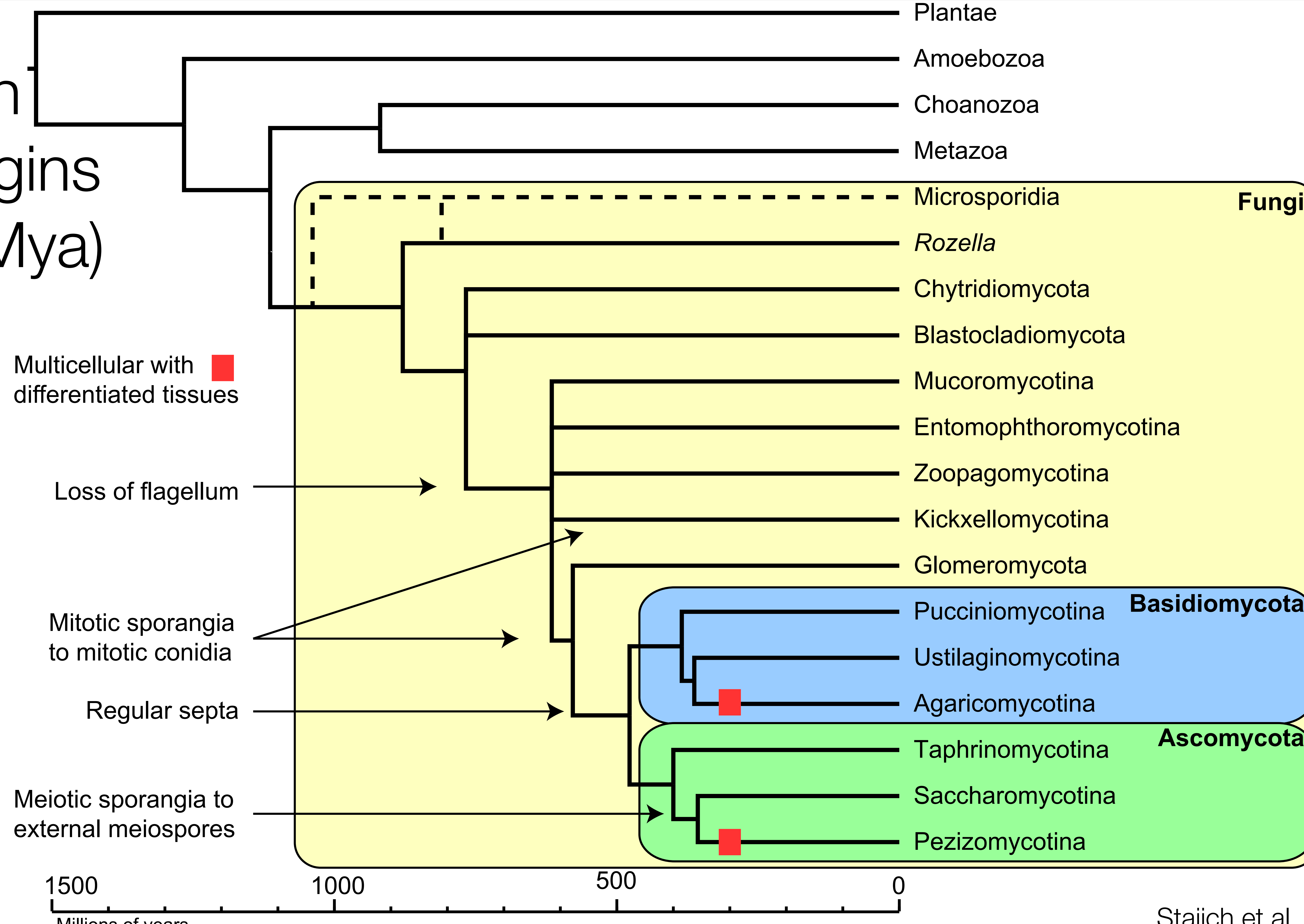
Fungi are an old group of organisms

(Eutherian mammal origins ~ 150-180 Mya)

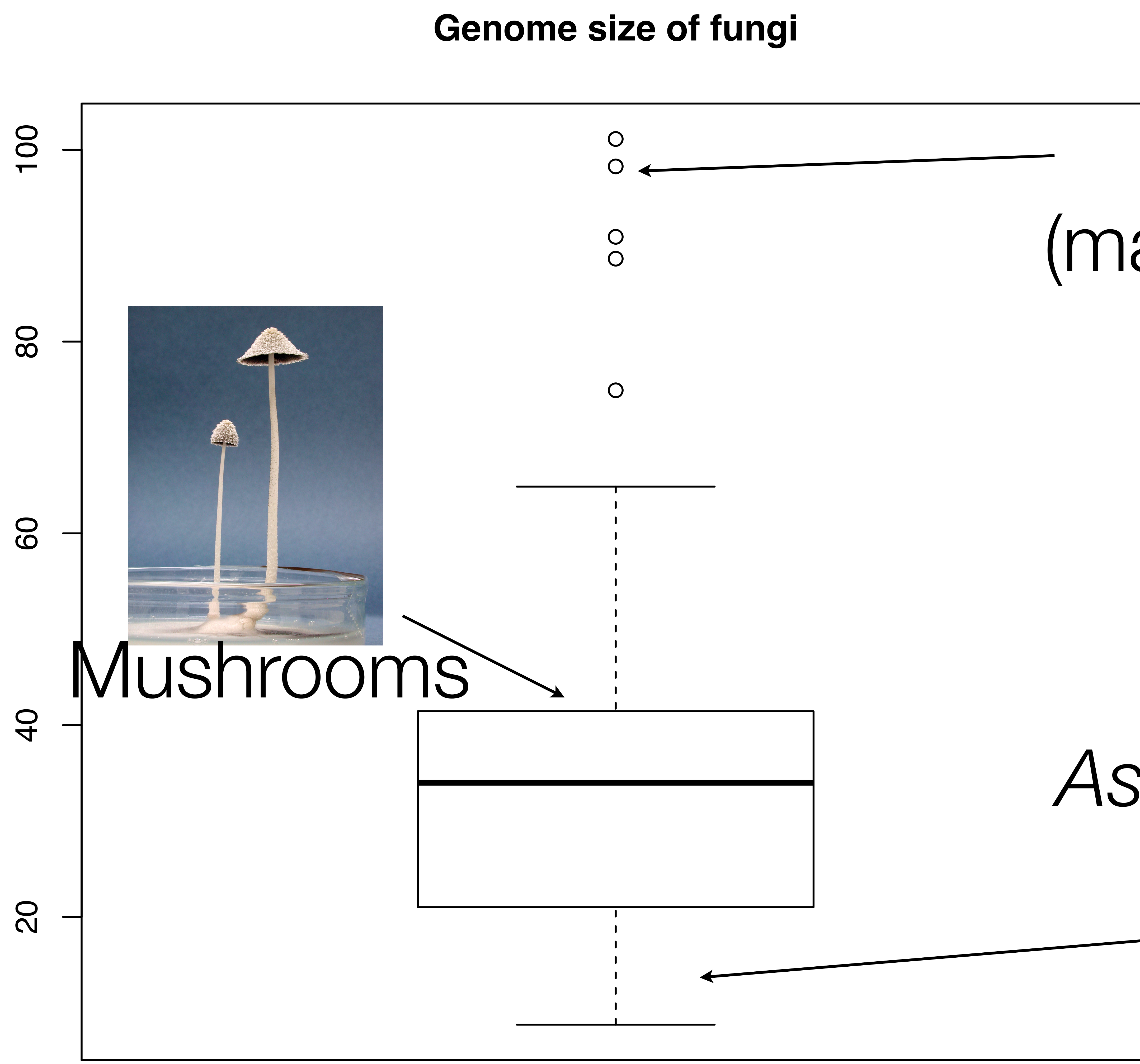


Stajich et al. Current Biol 2009

Awash in Fungal Genomes

- Mid-2011: Genomes from 150+ species sequenced and ~400 more in progress/pipeline
- Several multi-strain resequencing projects (*Neurospora* - Ellison PNAS 2011), Saccharomyces (Liti Nature 2009), *Coccidoides* (Neafsey Genome Res 2010) and many in progress/proposed.
- Many of sequenced genomes were focused around plant, animal pathogens, and some specific evolutionary questions.
- Now are starting to fill out the tree more to capture the diversity of kingdom and also for studies of molecular evolution among many related species.
- Also efforts targeting specific questions - pathogens and their relatives; wood rotting fungi; flagellated and non-flagellated forms; extremophiles; comparison of growth forms (e.g. yeast forms from phylogenetically very different species)

Genome sizes of fungi are 8Mb-100Mb = easy(ish) to sequence

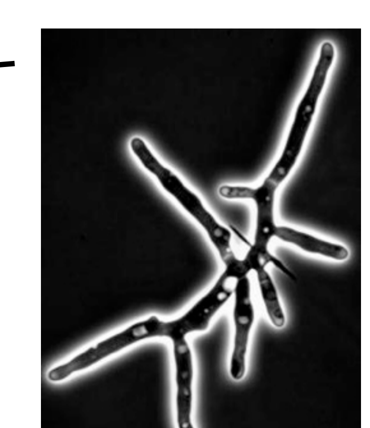


Melampsora, *Blumeria*, *Puccinia*
(many Transposable elements)

Francis Martin
Flickr:/fmartin1954/2338045504/

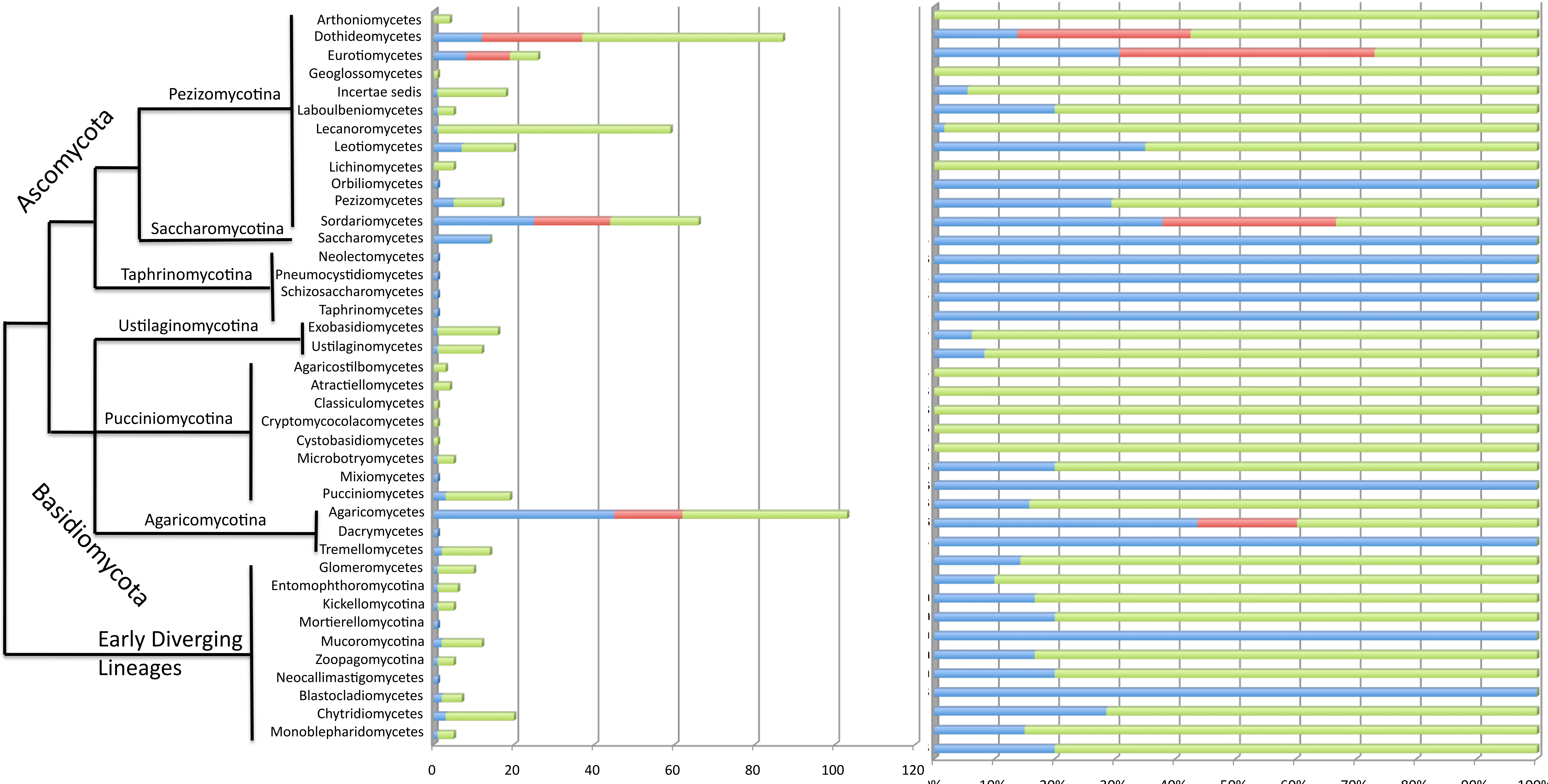
http://en.wikipedia.org/wiki/File:Barleypowderymildew.jpg

Ashbya, Malassezia, *Candida*
other yeasts



http://www.biologie.uni-osnabrueck.de/Genetik/index.php?menuid=12

Need to cover more of the phylogenetic diversity: 1000 Fungal genomes project



Blue = completed or in progress, Red= proposed for Tier One sampling, Green = remaining unsampled families

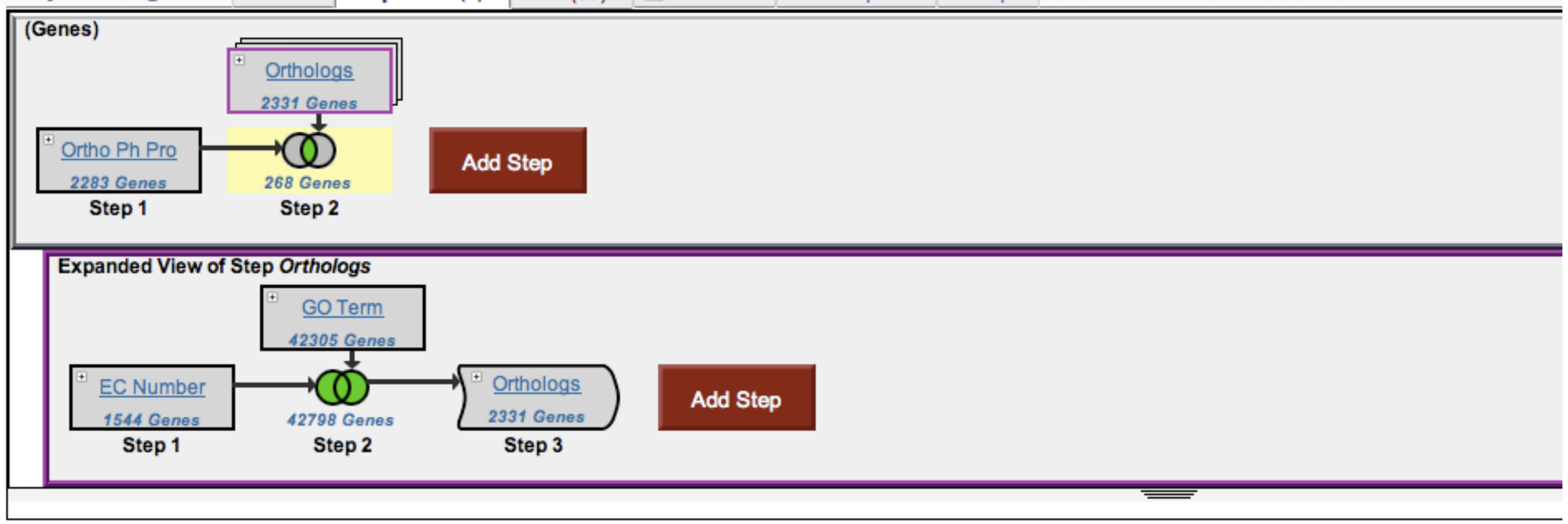
Numbers or Percent of Families in each clade and their current or proposed genome sampling

Tools to access this data

- Genome databases at sequencing centers and NCBI
- Comprehensive and integrated systems are not as well developed in Fungi, but some examples of excellent tools highlighted at http://tools.fungalgenomes.org/
- Ensembl Fungi, MicrobesOnline, JGI's Mycocosm, Comparative Fungal Genomics, and some targeted to specific clades e.g. *Saccharomyces* (SGD), *Aspergillus* (AspGD), *Candida* (CGD)
- We have launched FungiDB - http://fungidb.org to support integrating functional genomics data for data mining as well as standard 'Gene' pages for genes.

Searching with FungiDB:
A strategy for drug targets

My Strategies: New | Opened (1) | All (83) | Basket | Examples | Help



Filter results by species *(results removed by the filter will not be combined into the next step.)*

All Results	Ortholog Groups	Eurotiomycetes								Sordariomycetes					Saccharomycotina		Basidiomycota		Rhizopus oryzae
		A.cla	A.fla	A.fum	A.nid	A.nig	A.ter	C.imm H538.4	C.imm RS	F.gra	F.oxy	G.mon	M.ory	N.cra	C.alb	S.cer	C.neo	P.gra	
268	249	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	268	0	0

Cryptococcus Drug target? - step 2 - 268 Genes

First 1 2 3 4 5 Next Last Advanced Paging

Gene	Genomic Location	Weight	Predicted GO Function	Predicted GO Process
CneoH99__CNAG_07830	CneoH99__Chr_2.4: 1,052,305 - 1,054,670 (-)	20	DNA binding, zinc ion binding	transcription
CneoH99__CNAG_07632	CneoH99__Chr_2.6: 473,070 - 476,242 (+)	20	pyridoxal phosphate binding, transaminase activity	biosynthetic process, cellular amino acid metabolic process
CneoH99__CNAG_07589	CneoH99__Chr_2.11: 160,029 - 161,779 (-)	20	binding, catalytic activity, oxidoreductase activity, zinc ion binding	metabolic process, oxidation reduction
CneoH99__CNAG_07441	CneoH99__Chr_2.5: 1,287,517 - 1,288,271 (-)	20	4-alpha-hydroxytetrahydrobiopterin dehydratase activity	tetrahydrobiopterin biosynthetic process
CneoH99__CNAG_07011	CneoH99__Chr_2.12: 762,209 - 764,308 (+)	20	DNA binding, zinc ion binding	transcription
CneoH99__CNAG_06868	CneoH99__Chr_2.5: 29,970 - 32,039 (-)	20	phosphopyruvate hydratase activity	glycolysis
CneoH99__CNAG_06719	CneoH99__Chr_2.2: 235,880 - 239,543 (+)	20	DNA binding, zinc ion binding	transcription

C.neoformans genes with
- no hits in other eukaryotes (excepting fungi), bacteria
- has S.cerevisiae orthologs that have EC terms

OR orthologs in other fungi with GO metabolic terms associated

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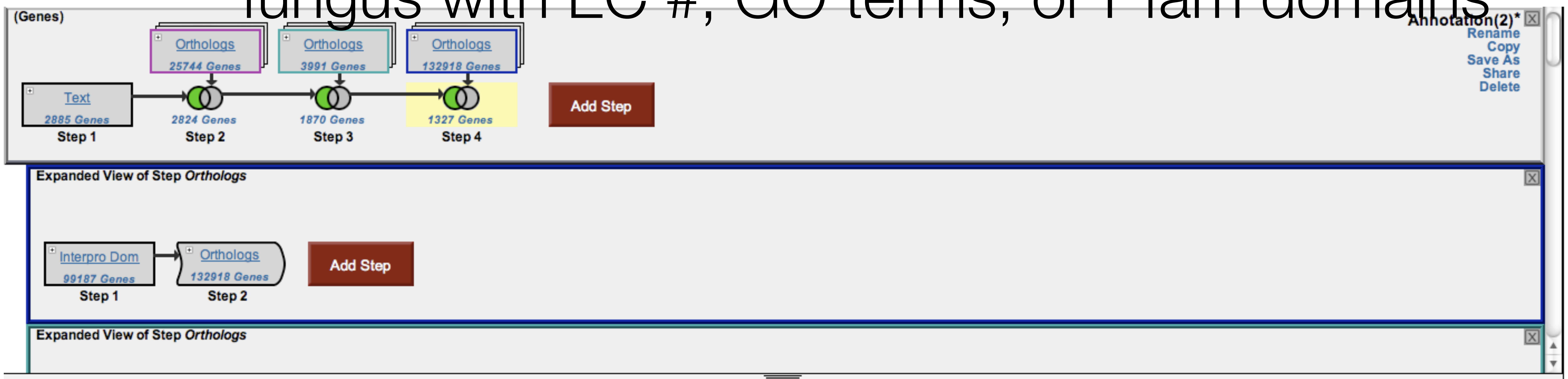
Searching with FungiDB:
A strategy for reannotation

2885 *C.neoformans* genes with desc “"conserved hypothetical protein” but 1327 can be assigned name from ortholog in any fungus with EC #, GO terms, or Pfam domains



Filter results by species *(results removed by the filter will not be combined into the next step.)*

All Results	Ortholog Groups	*Eurotiomycetes*								*Sordariomycetes*					*Saccharomycotina*		*Basidiomycota*		*Rhizopus oryzae*
		A.cla	*A.fla*	*A.fum*	*A.nid*	*A.nig*	*A.ter*	*C.imm* H538.4	*C.imm* RS	*F.gra*	*F.oxy*	*G.mon*	*M.ory*	*N.cra*	*C.alb*	*S.cer*	*C.neo*	*P.gra*	
1327	1229	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1327	0	0

Annotation(2) - step 4 - 1327 Genes

Add 1327 Genes to Basket | Download 1327 Genes

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

Gene	Genomic Location	Weight	Predicted GO Function	Predicted GO Process	Ortholog Group	SignalP Peptide
CneoH99__CNAG_07913	CneoH99__Chr_2.12: 637,812 - 638,653 (+)	10	N/A	N/A	OG5_226248	N/A
CneoH99__CNAG_07912	CneoH99__Chr_2.12: 636,724 - 637,155 (+)	10	N/A	N/A	OG5_226247	N/A
CneoH99__CNAG_07898	CneoH99__Chr_2.12: 191,256 - 192,798 (+)	10	N/A	N/A	OG5_226246	N/A
CneoH99__CNAG_07890	CneoH99__Chr_2.14: 796,716 - 797,600 (+)	10	N/A	N/A	OG5_226245	HMM: MSISKSPSLDLCLATLHELLHPSPILSLLLSALDLSAHFQLFAQQLSSDAALVSAL, NN: MSISKSPSLDLCLATLHELLHPSPILSLLLSAL...
CneoH99__CNAG_07883	CneoH99__Chr_2.14: 482,566 - 484,632 (-)	10	N/A	N/A	OG5_226244	N/A

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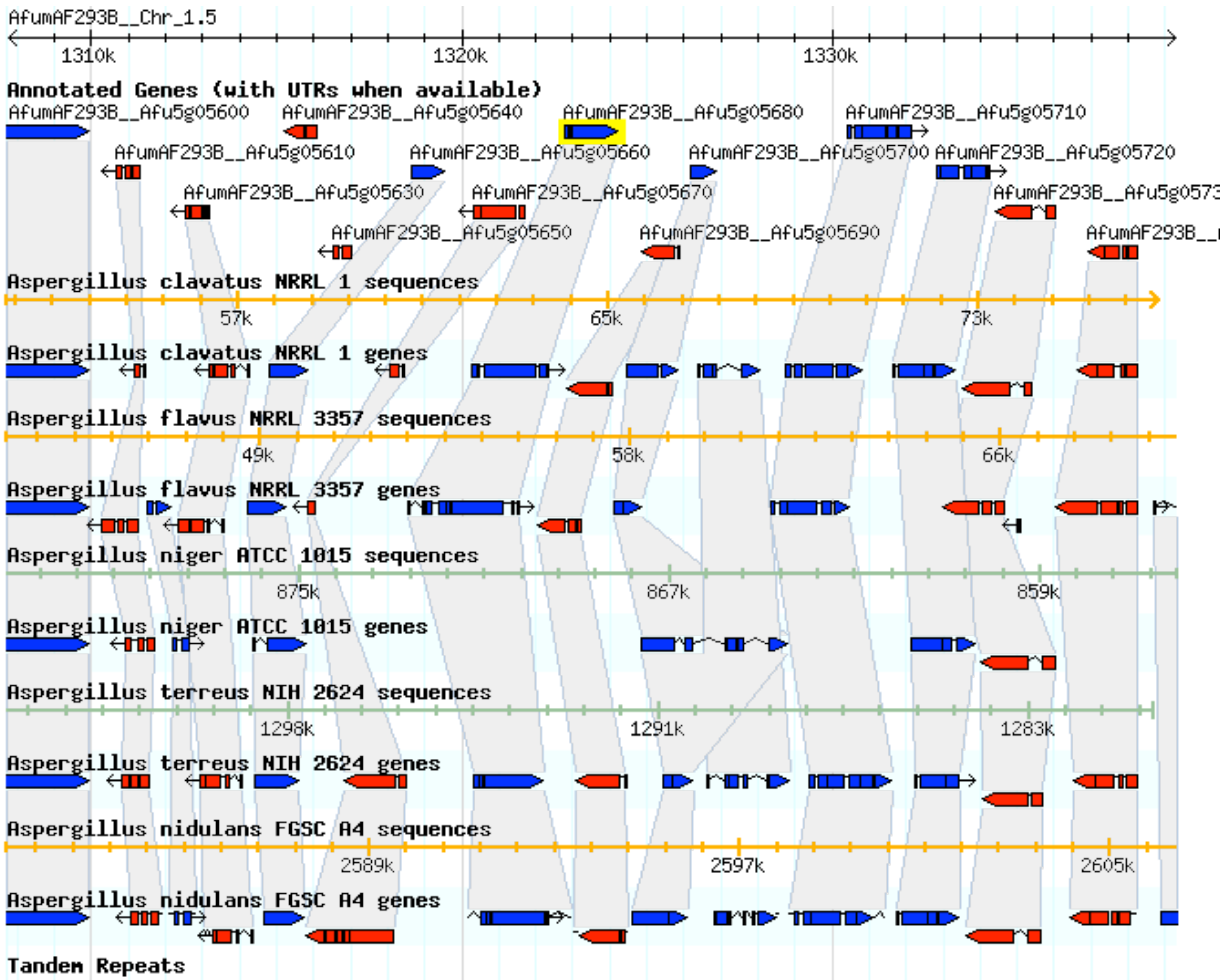
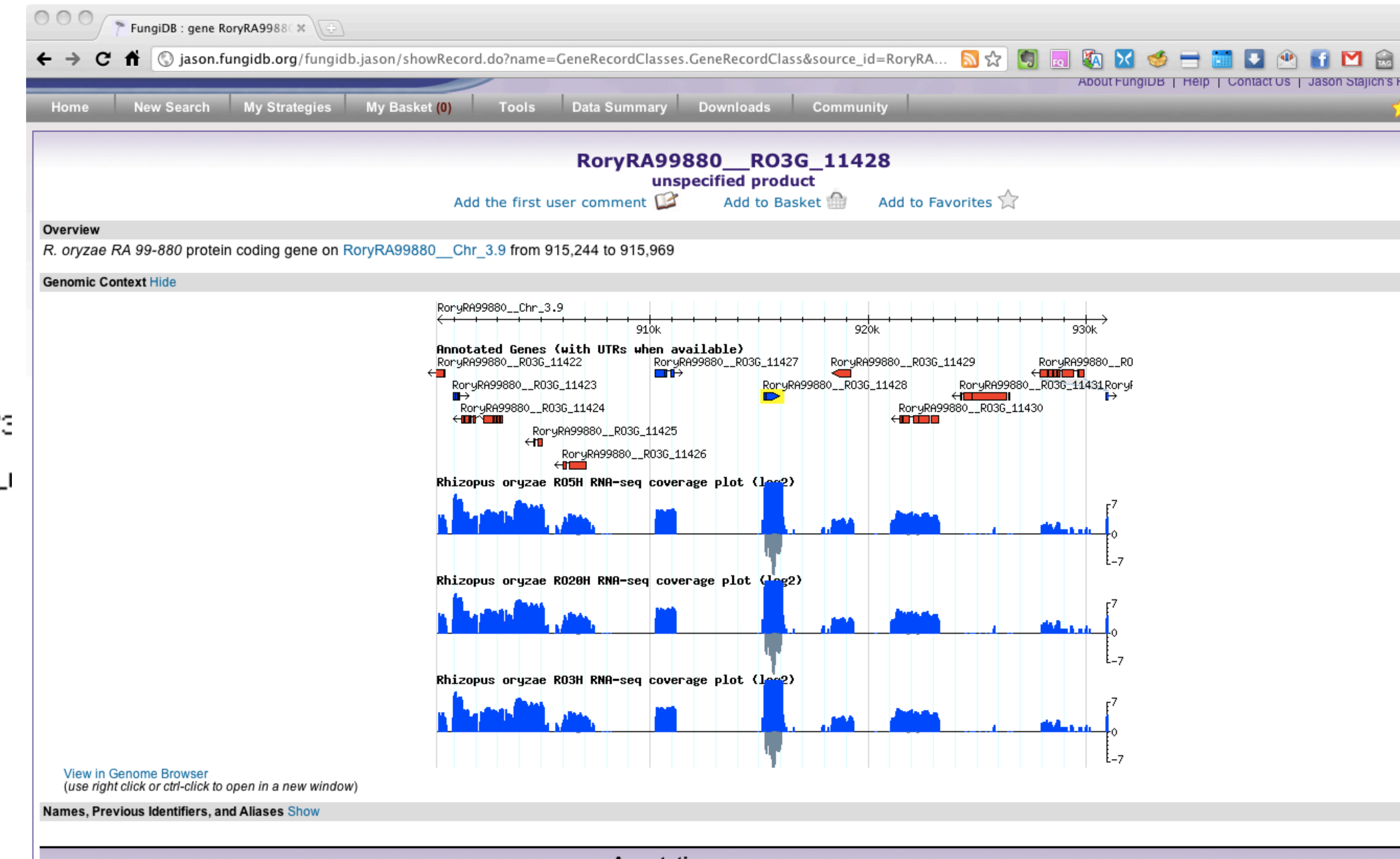
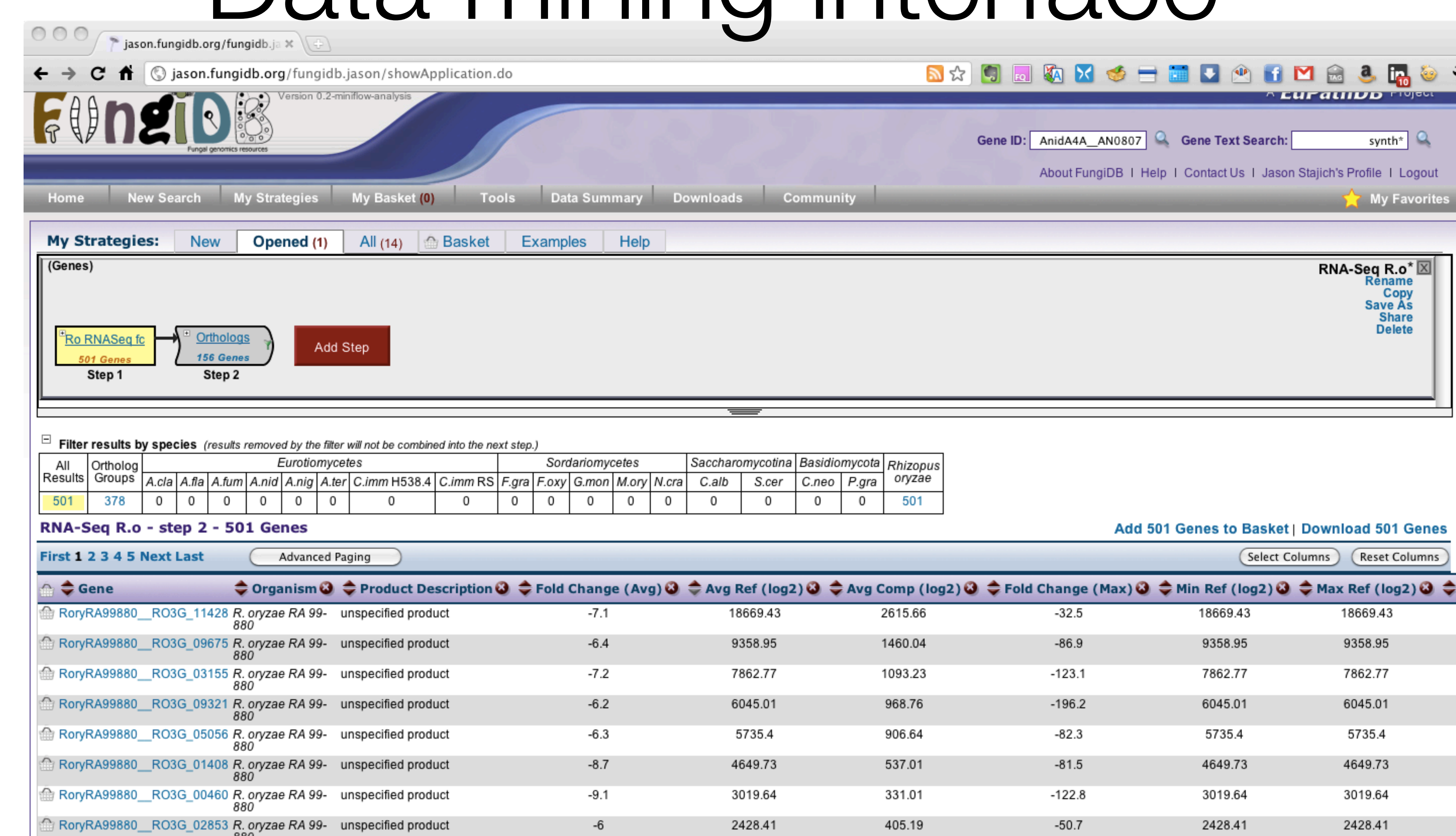
Gene page and genome browser

Synteny Views





Data mining interface



Using comparative genomics towards understand pathogen evolution

- How do traits like pathogenecity evolve?
- Can comparative genomics indicate meaningful differences that can lead to understanding the basis for pathogenesis?
- Contrasting genomes of pathogens with non-pathogens can suggest recent genomic changes that might be testable in the lab
- Gene duplication is thought to be important source for evolutionary innovation - What role might gene family size change play in adaptation?

Models for comparing gene family size changes

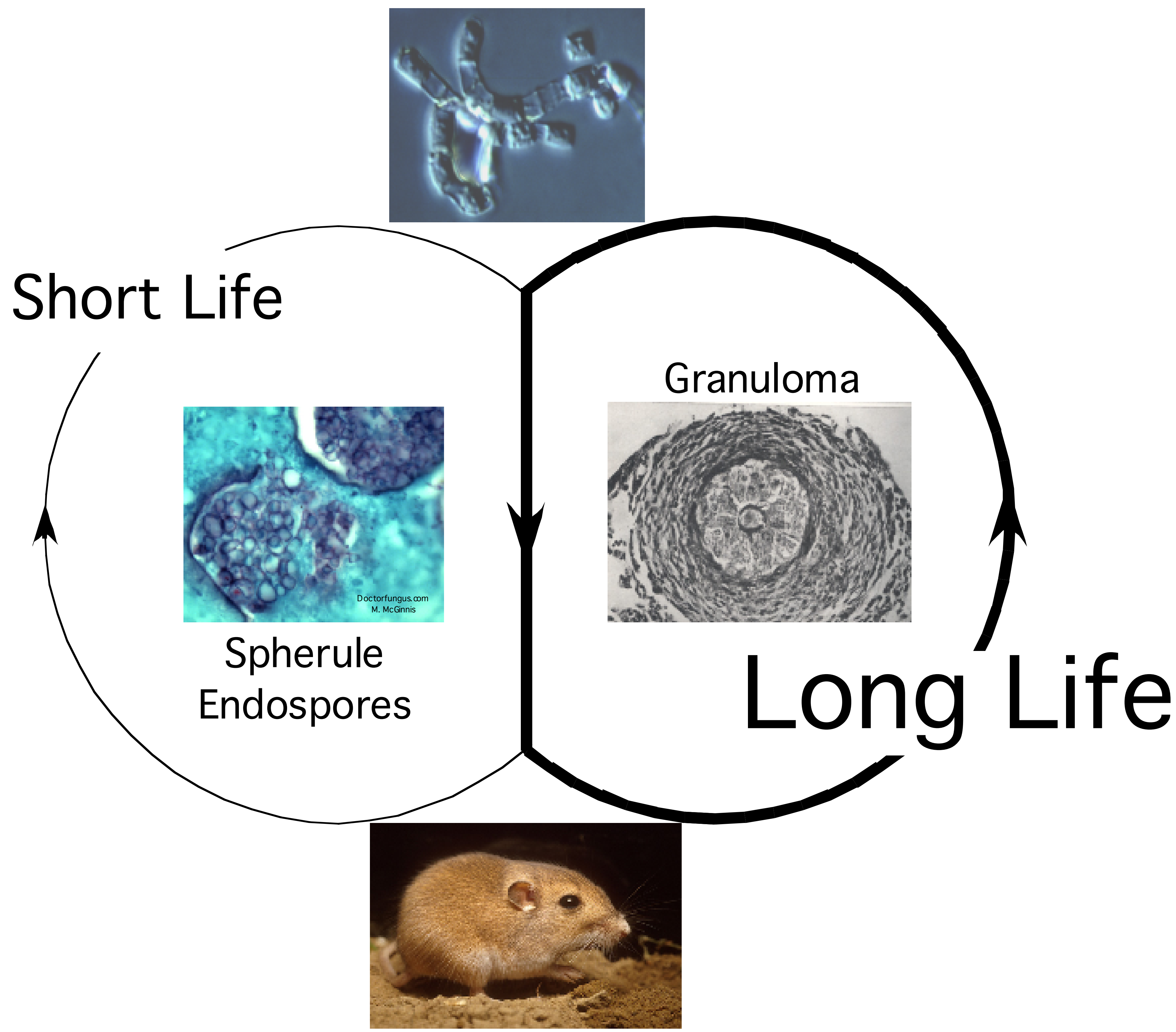
- A model for gene family size change that incorporates the birth-death process of gene families which follow a power law distribution (Hahn et al, Genome Res 2005)

- Implemented in a program called CAFE to find unexpectedly large lineage or clade-specific changes in gene family sizes (Hahn Lab @Indiana Univ) (De Bie et al, Bioinformatics 2006)

- Can screen genome family sizes across multiple species to find expectedly large changes (based on counts) which can be verified using gene tree-species tree reconciliation approaches like Notung (Chen, Durand, Farach-Colton, J Comp Bio 2000)

Coccidioides

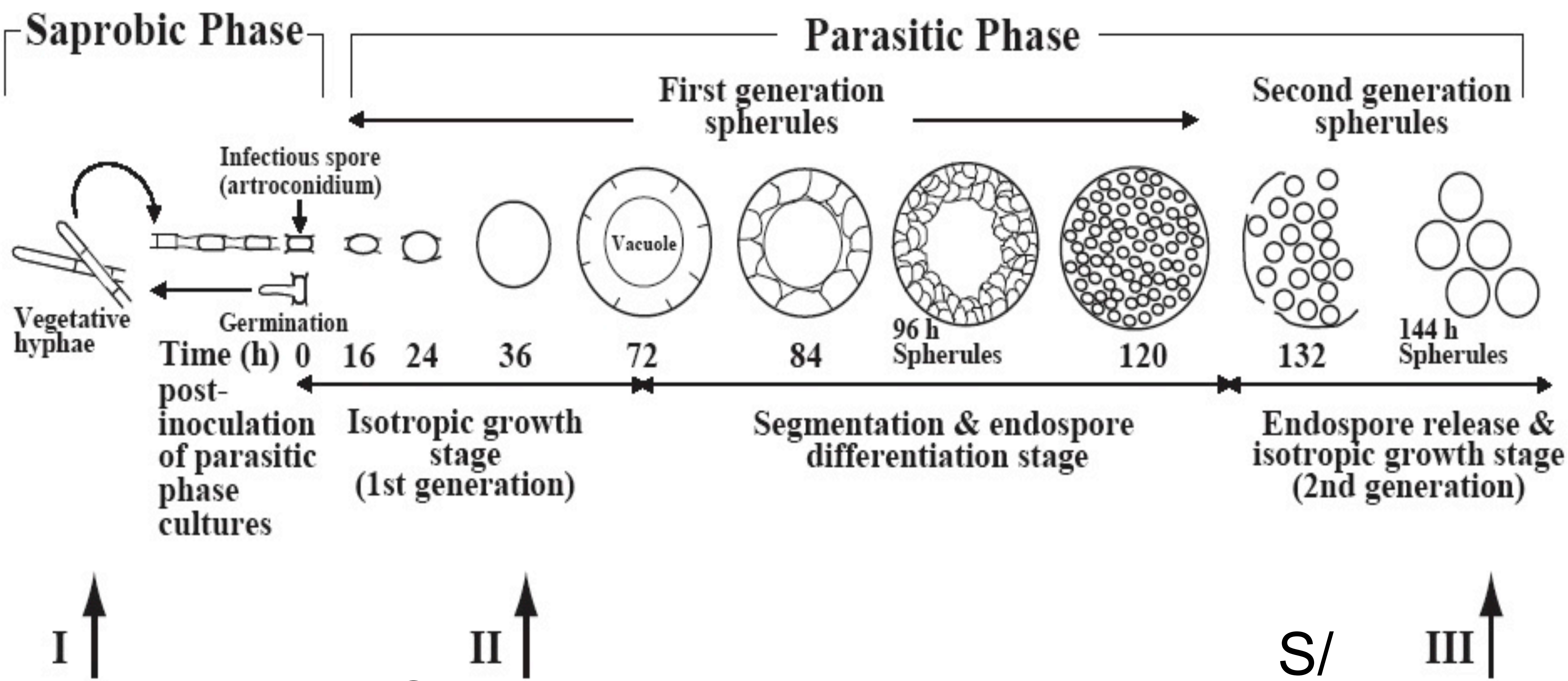
- Fungal pathogen genomics: Gene families and appetite differences



Human pathogen *Coccidioides*

- Coccidioides (Valley fever) - 2 species *C. immitis* and *C. posadasii*
  - Is a primary human pathogen - infects healthy people (most human pathogenic fungi are opportunistic)
  - Endemic in US Southwest, Mexico
  - Requires laboratory BSL3 and is a Select Agent
  - Genomes of 2 species (Sharpton et al Genome Res 2009) and then 18 strains (Neafsey et al Genome Res 2010)
- Comparative analyses of *Coccidoides* spp

Human pathogen *Coccidioides* Life cycle

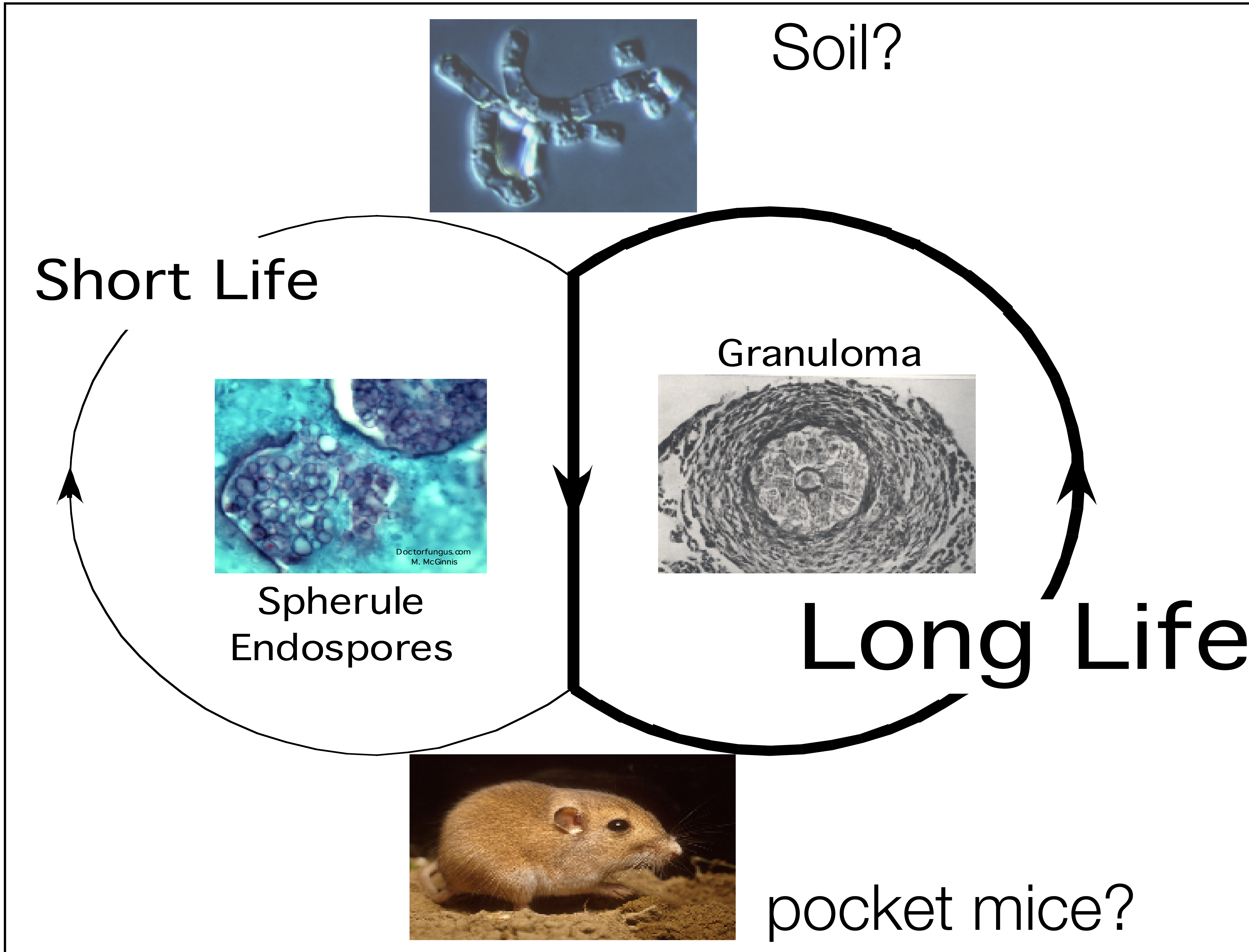


Hypha

Spherule

S/ Endospores

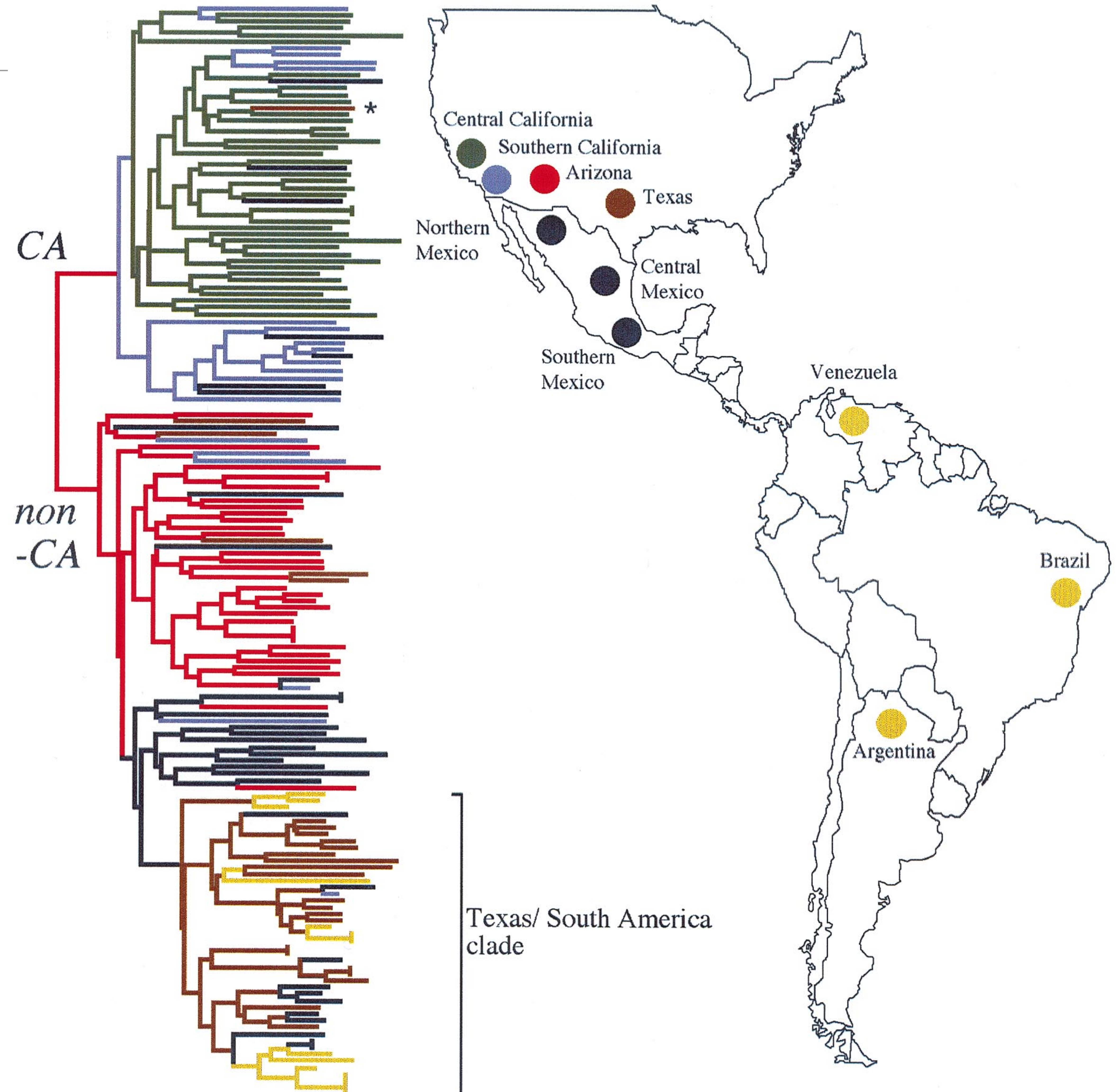
Coccidioides ecology



Two species of *Coccidioides* are allopatric

C.immitis

C.posadasii



Fisher et al, 2000

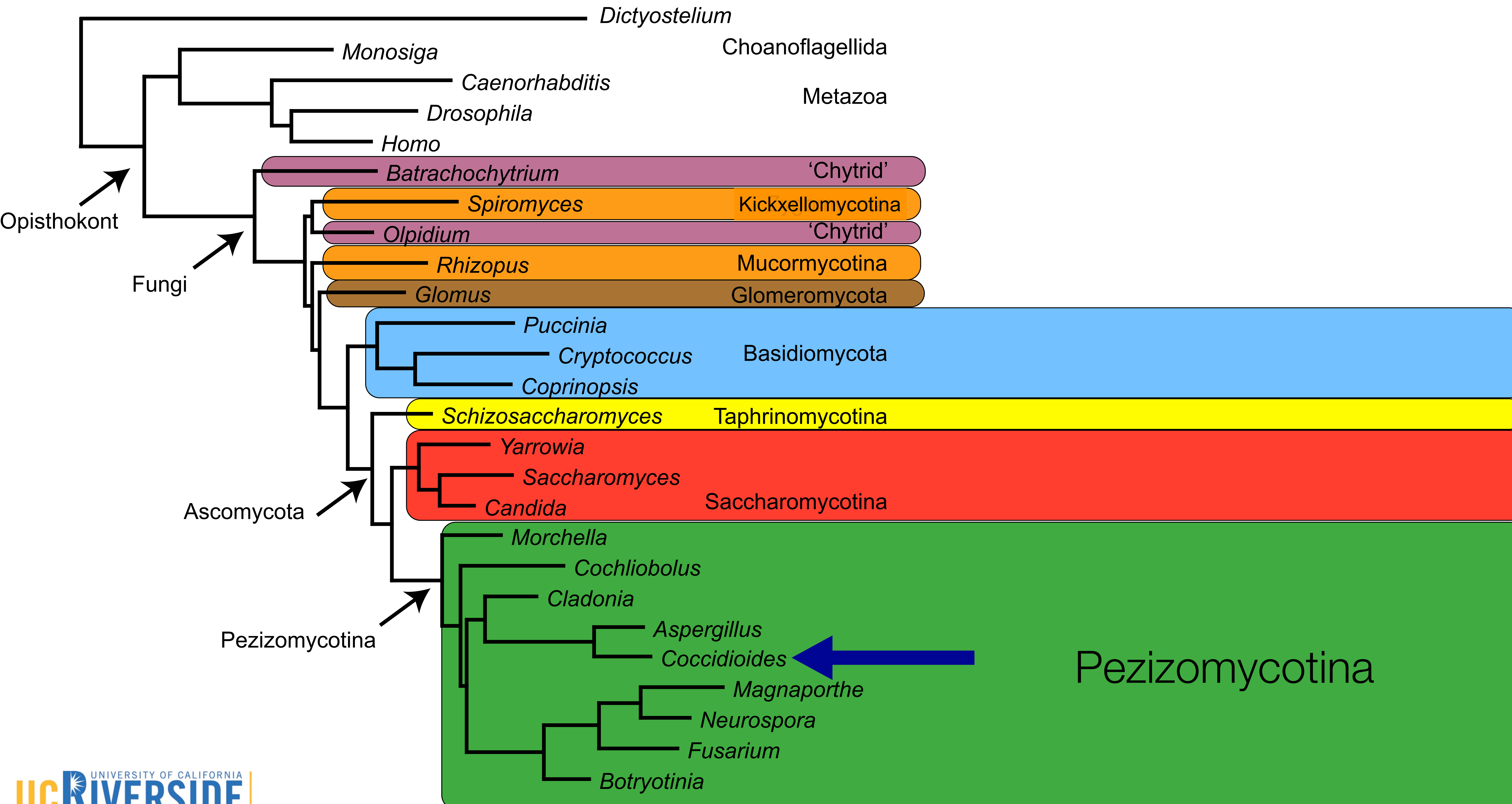
Studying the evolution of a pathogen

- Comparing sequences from two *Coccidioides* species, closely related outgroup, and more distant ougroups species:
- Evidence for recent positive selection
- What gene family differences can be identified that distinguish phenotypic groups (mammalian pathogens from non-pathogens)
- Evidence for recent introgression which contains candidate genes for pathogenesis

Gene family changes

- Another mechanism for adaptation may be changes in copy number of a gene family
    - Gene duplication is a source of novelty allowing for changes in the function of one copy if the other maintains original function
    - Expansions of copy number may also be an easy way to get more protein for a particular process
- How important is copy number change in adaptation?

Genome samples from fungi



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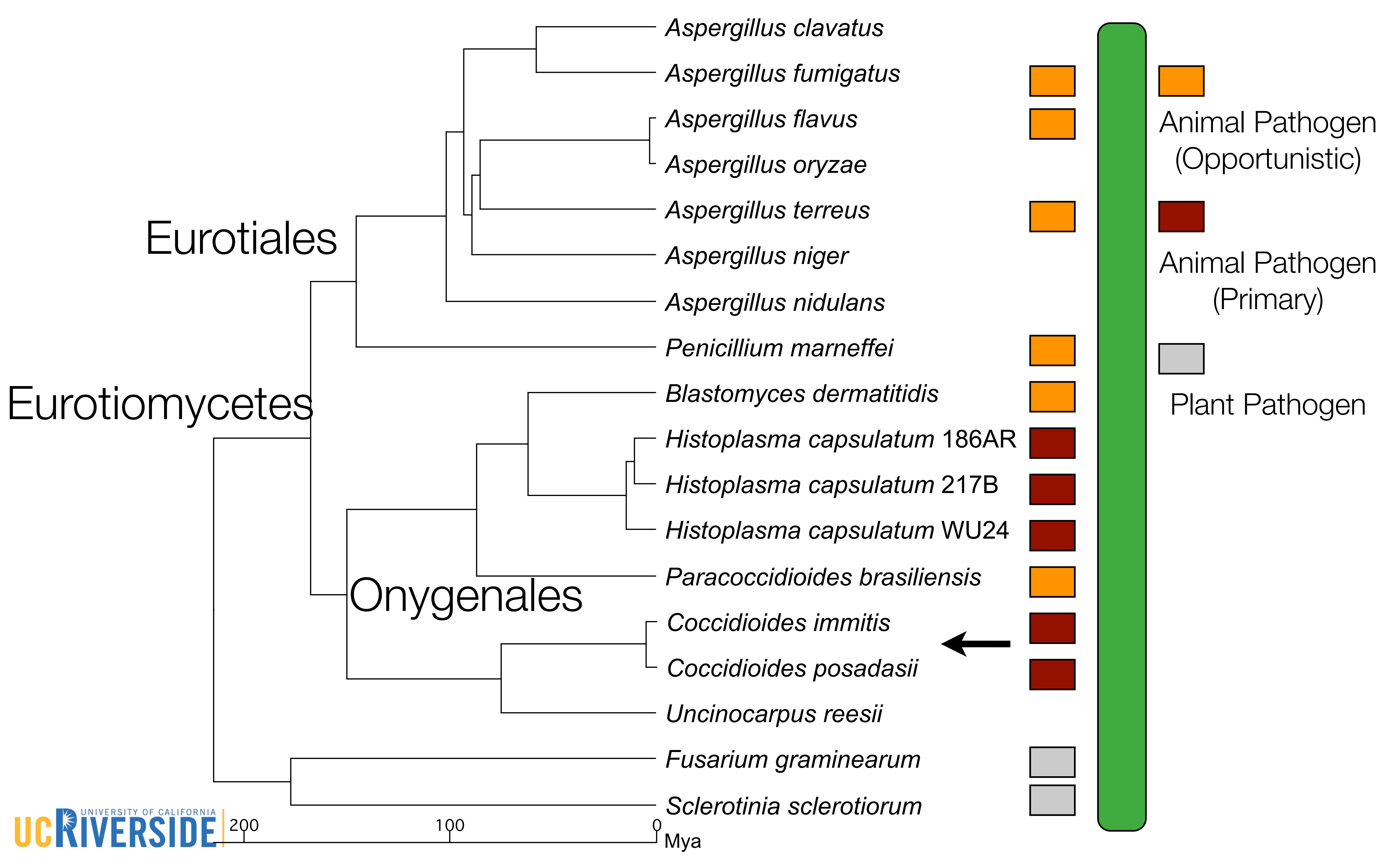
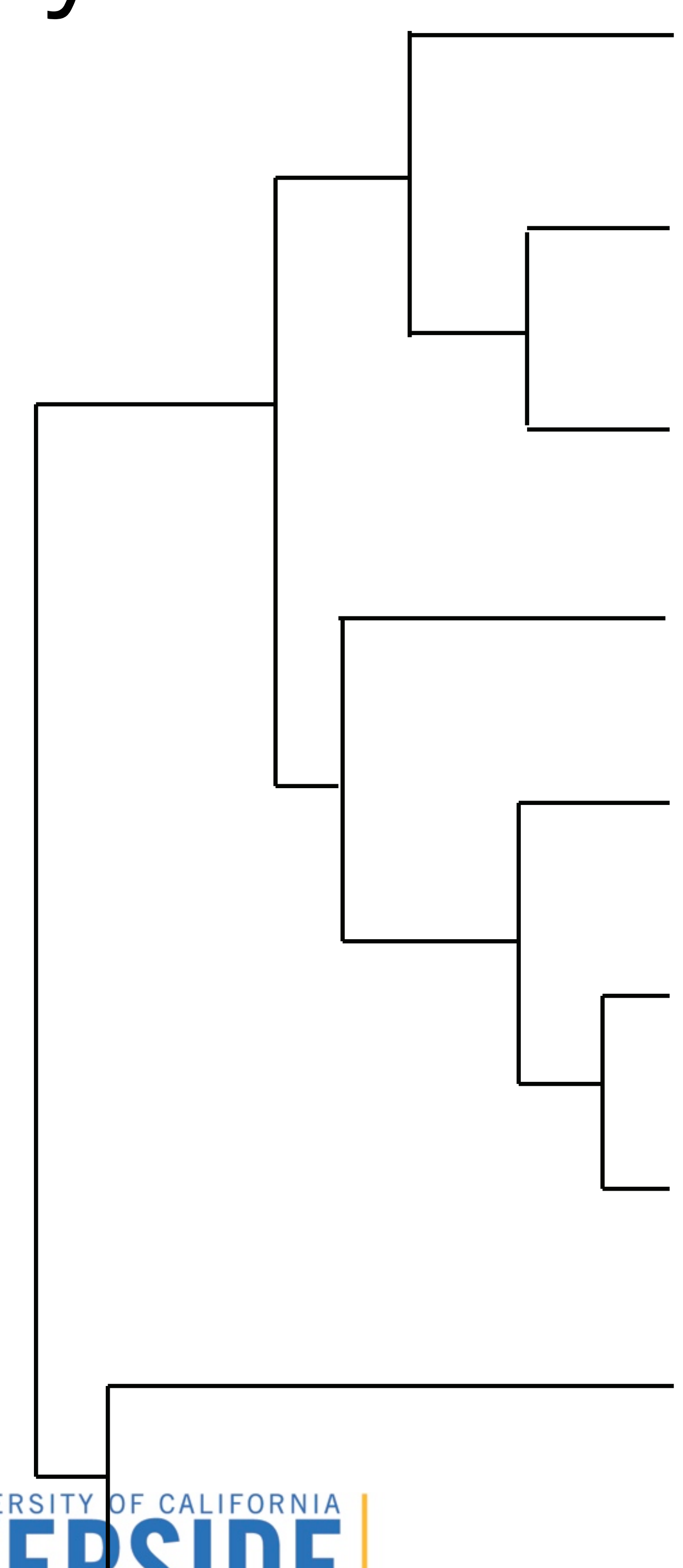

Aspergillus clavatus
Aspergillus fumigatus
Aspergillus flavus
Aspergillus oryzae
Aspergillus terreus
Aspergillus niger
Aspergillus nidulans
Penicillium marneffei
Blastomyces dermatitidis
Histoplasma capsulatum 186AR
Histoplasma capsulatum 217B
Histoplasma capsulatum WU24
Paracoccidioides brasiliensis
Coccidioides immitis
Coccidioides posadasii
Uncinocarpus reesii
Fusarium graminearum
Sclerotinia sclerotiorum
Eurotiales
Eurotiomycetes
Onygenales
200
100
0
Mya
Animal Pathogen (Opportunistic)
Animal Pathogen (Primary)
Plant Pathogen

Few protein domains for eating plant material in animal pathogens

Loss of plant saprophytic enzymes



	CBM_1	Tannase	Pec_lyase_C	NPP1	Cutinase	Cellulase	Subtilisin_N	Peptidase_S8	Peptidase_M35	Peptidase_M36	APH
Anid	6	6	6	2	4	13	2	3	3	0	9
Afum	17	5	5	2	5	10	2	5	2	1	9
Ater	15	6	6	2	8	13	2	6	2	1	29
Hcap	**0**	**0**	**0**	**0**	**2**	**2**	2	6	1	0	20
Uree	**0**	**0**	**0**	**0**	**1**	**2**	15	19	4	2	33
Cimm	**0**	**0**	**0**	**0**	**1**	**1**	13	16	7	2	38
Cpos	**0**	**0**	**0**	**0**	**1**	**1**	14	16	7	2	32
Ncra	18	1	1	4	3	6	3	6	2	0	6
Fgra	12	7	9	9	12	8	11	24	1	1	15

Animal Pathogen (Opportunistic)

Animal Pathogen (Primary)

Plant Pathogen

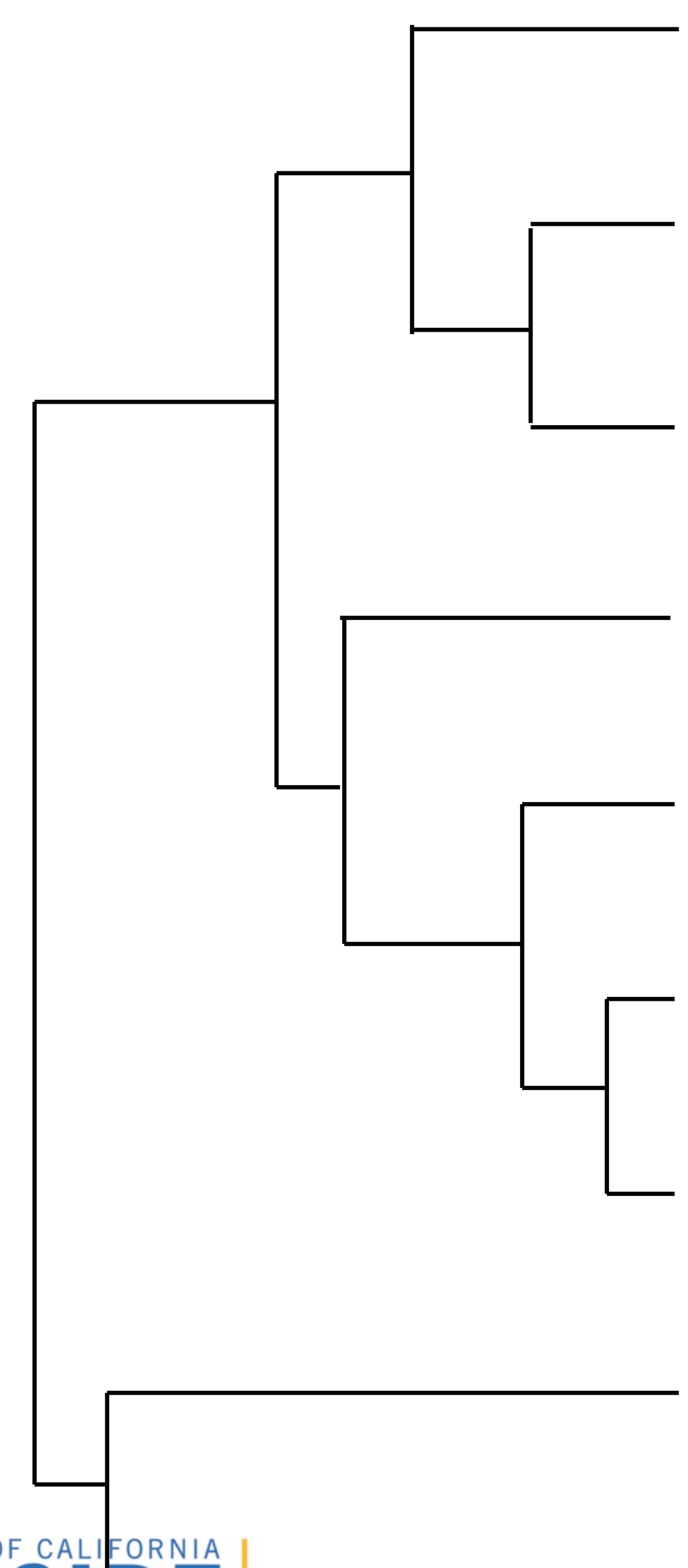
Sharpton, Stajich, et al, Genome Res. 2009

Domains for eating animal material?

Animal Pathogen (Opportunistic)

Animal Pathogen (Primary)

Plant Pathogen



	CBM_1	Tannase	Pec_lyase_C	NPP1	Cutinase	Cellulase	Subtilisin_N	Peptidase_S8	Peptidase_M35	Peptidase_M36	APH
Anid	6	6	6	2	4	13	2	3	3	0	9
Afum	17	5	5	2	5	10	2	5	2	1	9
Ater	15	6	6	2	8	13	2	6	2	1	29
Hcap	0	0	0	0	2	2	2	6	1	0	20
Uree	0	0	0	0	1	2	**15**	**19**	**4**	**2**	**33**
Cimm	0	0	0	0	1	1	**13**	**16**	**7**	**2**	**38**
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Ncra	18	1	1	4	3	6	3	6	2	0	6
Fgra	12	7	9	9	12	8	11	24	1	1	15

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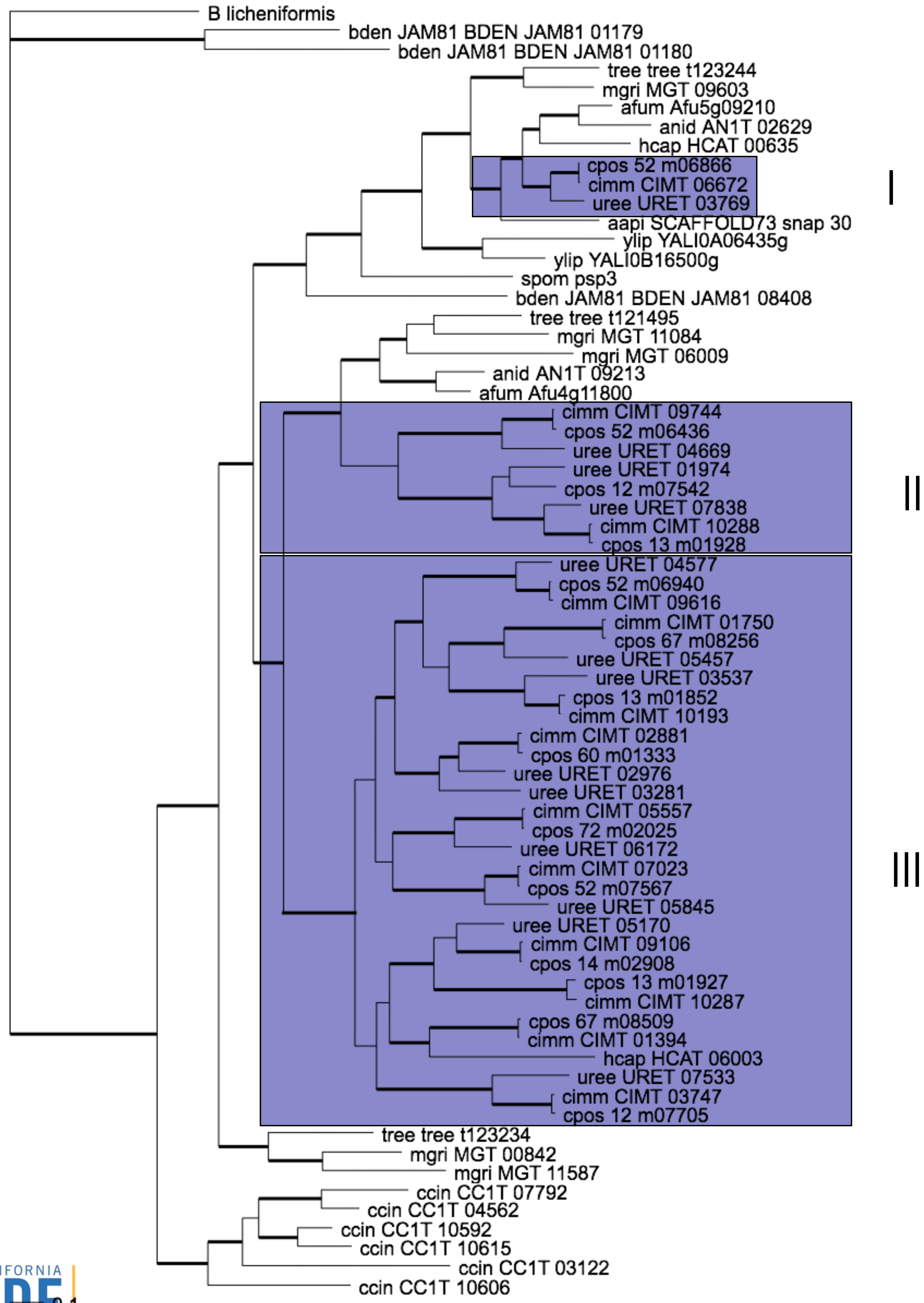
Sharpton, Stajich, et al, Genome Res. 2009

Keratinases in Onygenales

- Onygenales are Keratinophilic
- Domains: Peptidase S8, Subtilisin domains
- Large expansion of putative keratinases in Onygenales

Peptidase S8 expansion in Onygenales

14 copies in *Coccidioides*
1 in *Histoplasma*



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Peptidase S8 expansion in Onygenales

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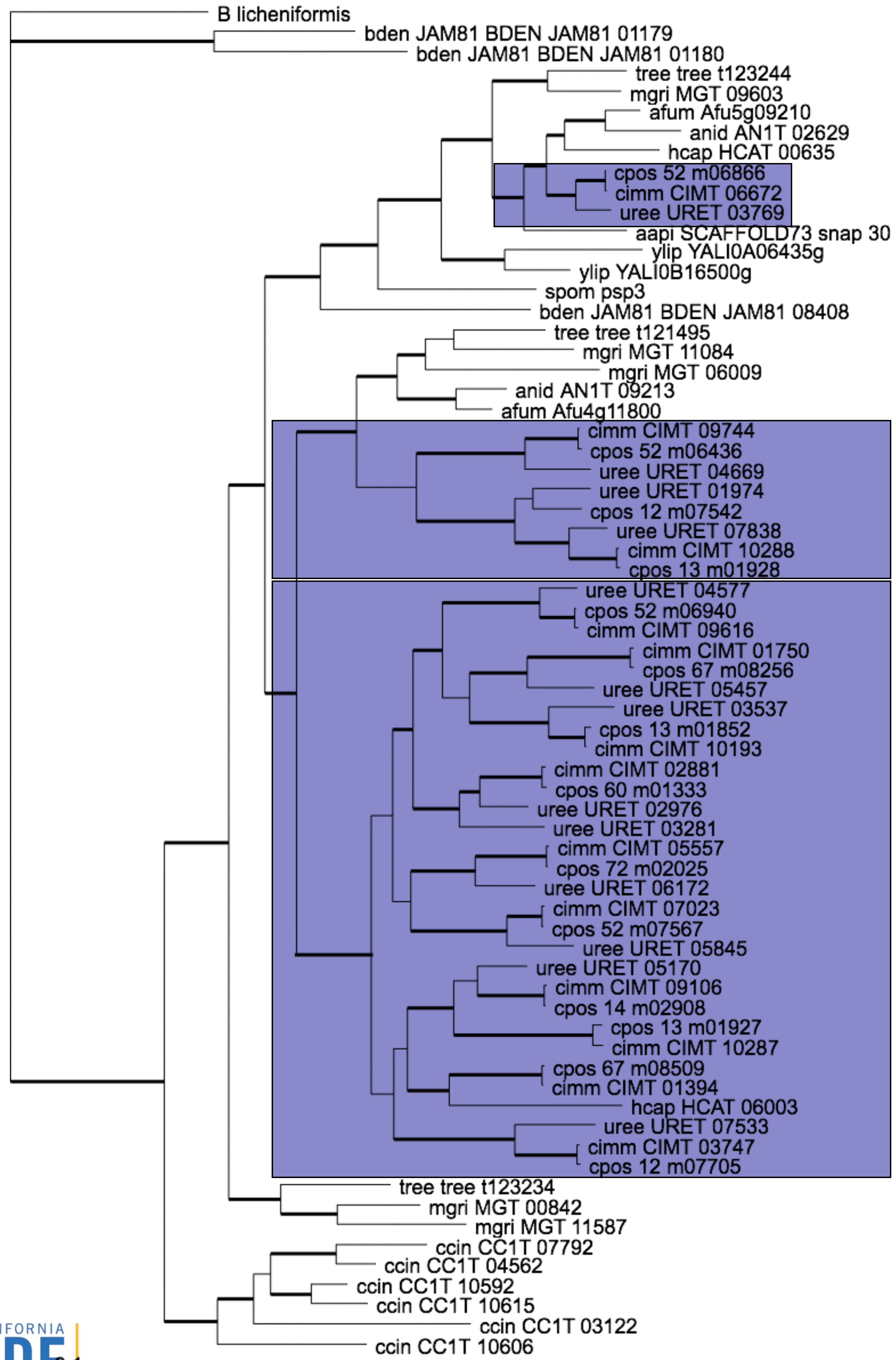

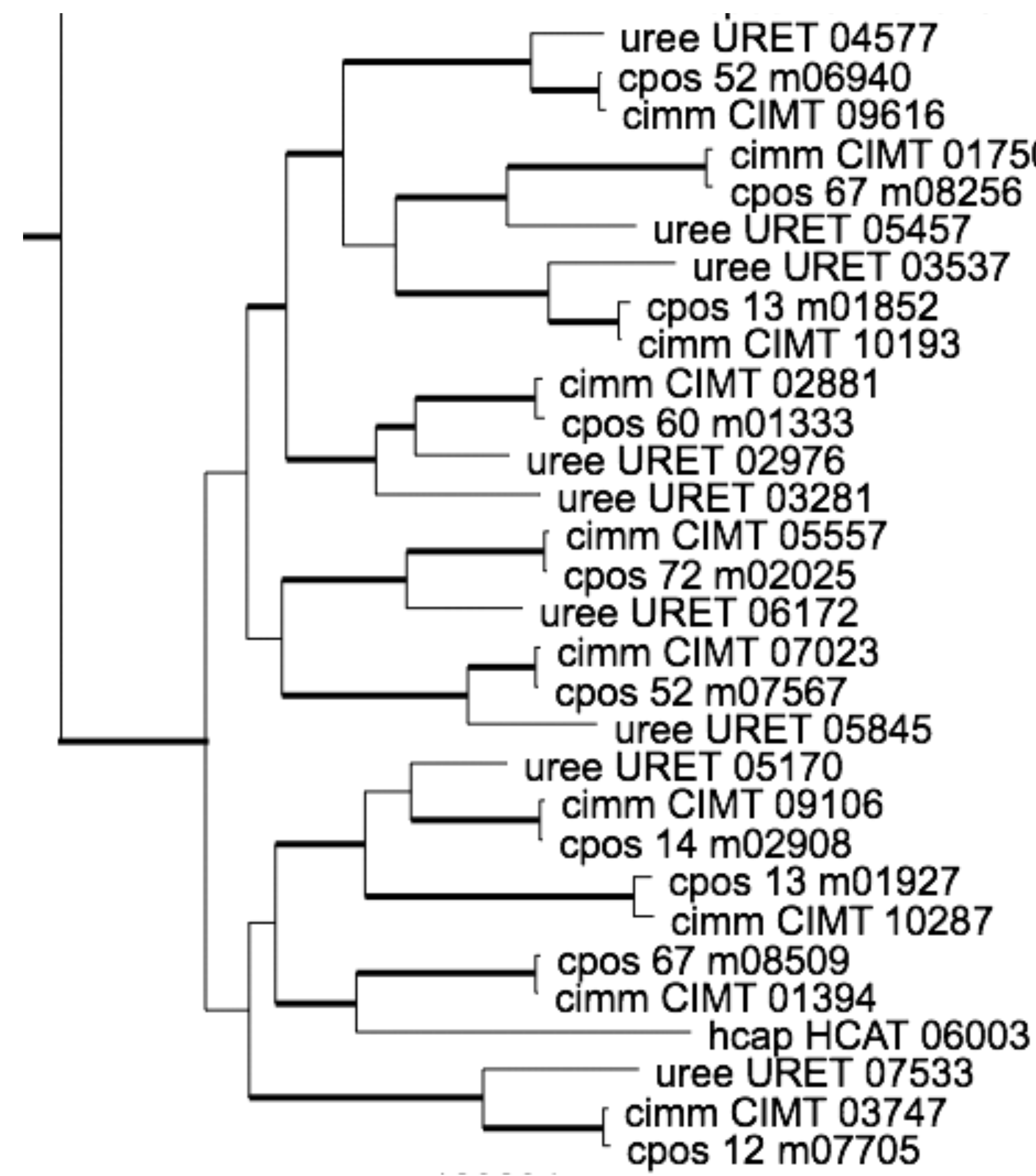

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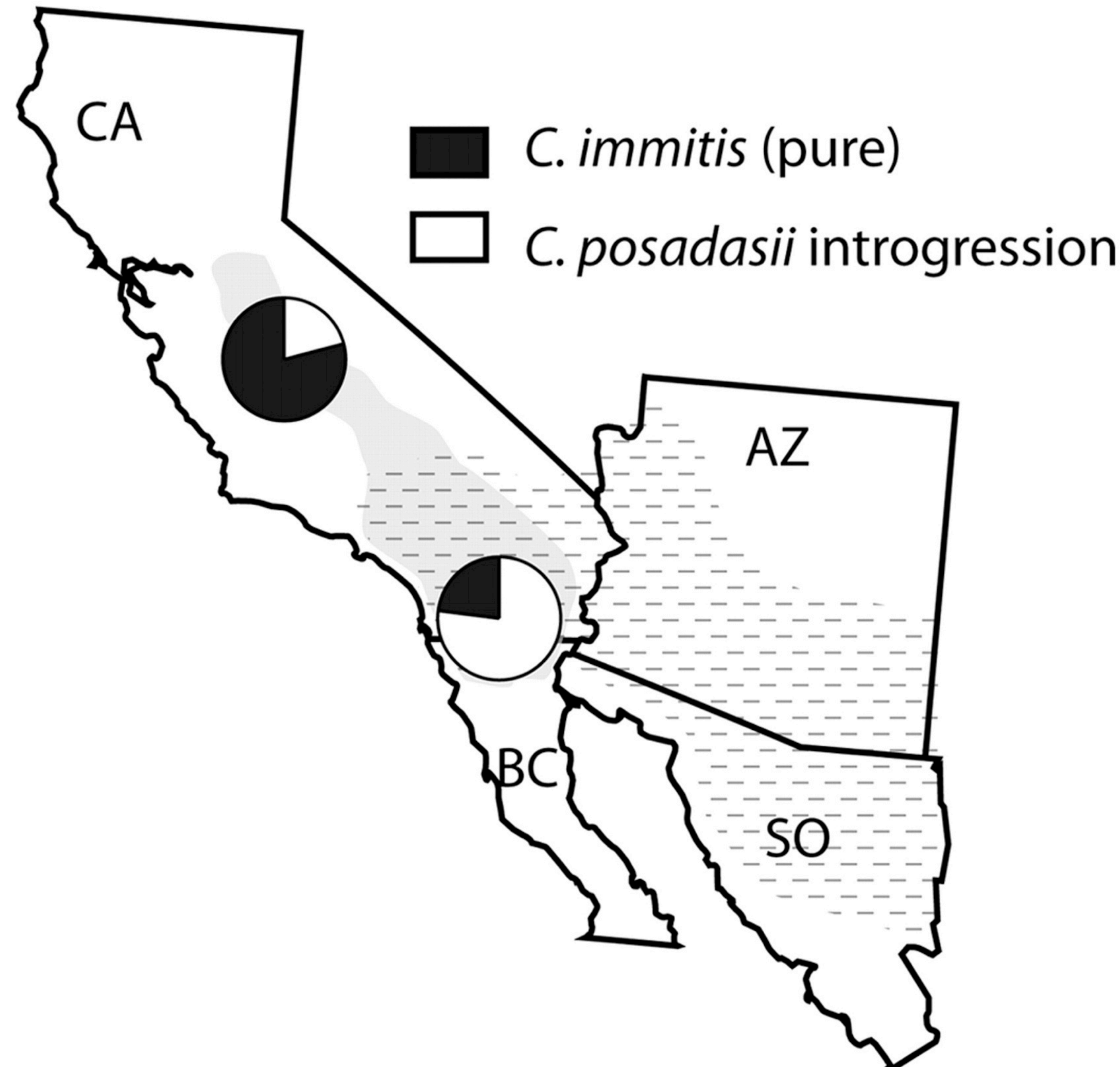
Population genomics

- Revealed no loci with evidence for balancing selection - so little evidence for long standing host-pathogen battle as in *Plasmodium*.
- Sliding window F_{ST} analysis revealed some regions of reduced divergence and followup revealed a regions of recent intergression. Directionality looks to be mostly from Cp and into Ci.
- One gene implicated in pathogenesis, MEP4, is found in introgressed region



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Towards identifying genes underlying adaptation

Sharpton et al. Genome Res 2009
Neafsey et al, Genome Res 2010

Towards identifying genes underlying adaptation

- Coccidioides is found in desert soil and associated with animals - perhaps has a long term animal association without inducing response from the host.

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Neafsey et al, Genome Res 2010

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- Expansion of only a few gene families, seem to be involved in metabolism - none are *Coccidioides* specific though.

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- Loss of genes involved in plant product metabolism suggests nutritional shift in Onygenales from relatives in Eurotiales
- Expansion of only a few gene families, seem to be involved in metabolism - none are *Coccidioides* specific though.
- From population genetics analysis - failed to find regions under balancing selection suggesting there is not a long-term arms race between host and pathogen.

Sharpton et al. Genome Res 2009
Neafsey et al, Genome Res 2010

Towards identifying genes underlying adaptation

- Coccidioides is found in desert soil and associated with animals - perhaps has a long term animal association without inducing response from the host.
- Loss of genes involved in plant product metabolism suggests nutritional shift in Onygenales from relatives in Eurotiales
- Expansion of only a few gene families, seem to be involved in metabolism - none are *Coccidioides* specific though.
- From population genetics analysis - failed to find regions under balancing selection suggesting there is not a long-term arms race between host and pathogen.
- Evidence for introgression between the species and perhaps imported novel alleles that are important for adaptation in both species to their animal hosts.

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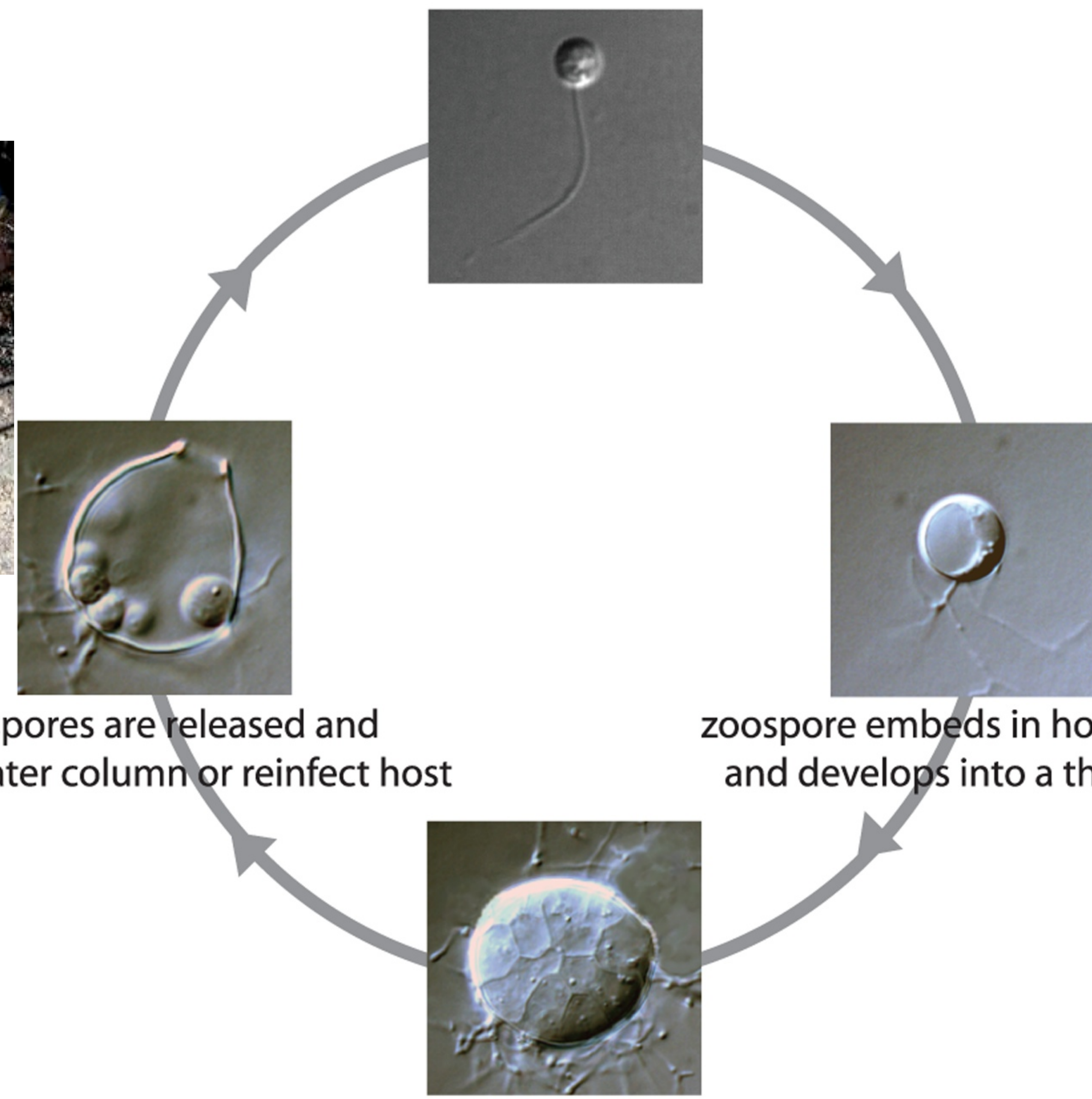
Sharpton et al. Genome Res 2009
Neafsey et al, Genome Res 2010

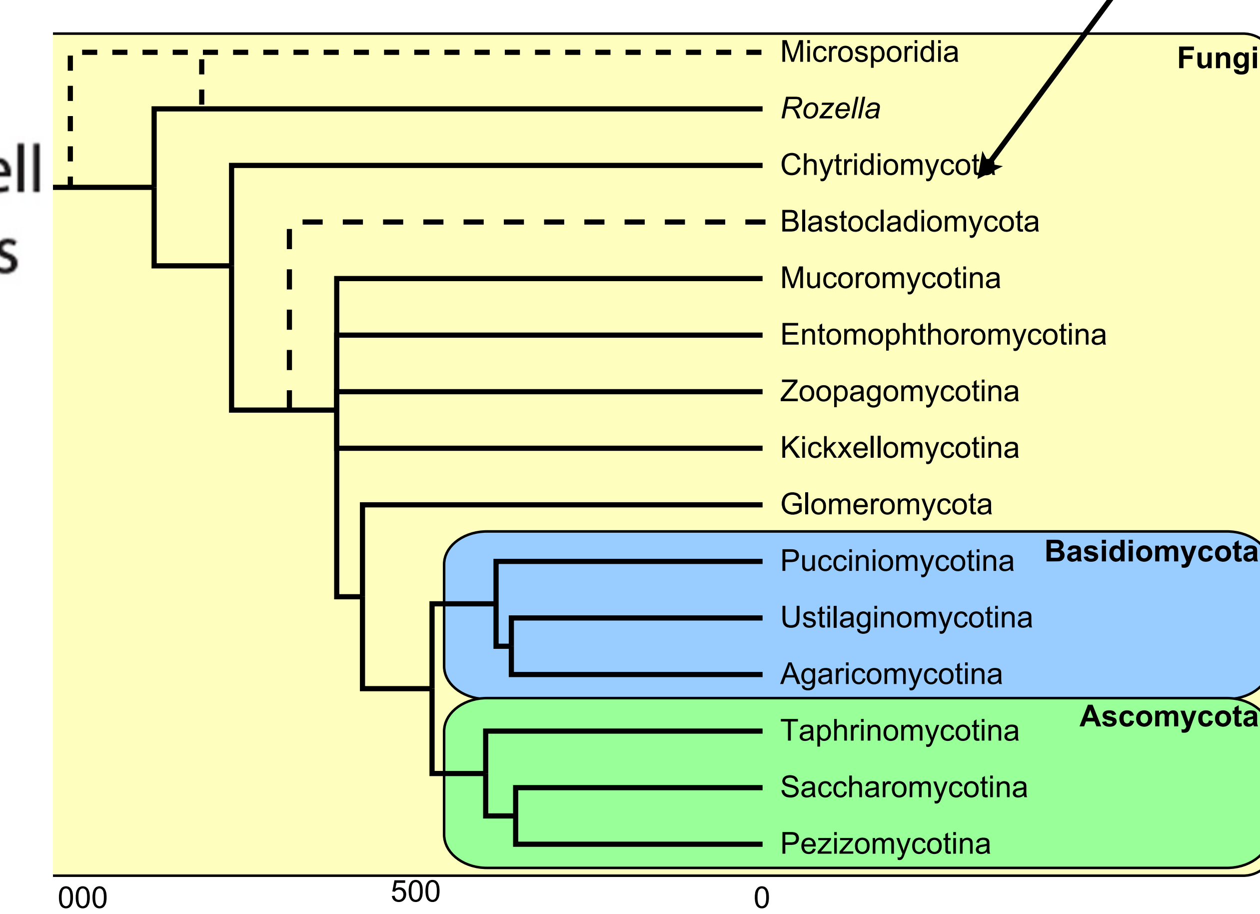
Batrachochytrium dendrobatidis (Bd)- a major cause of amphibian decline

http://cisr.ucr.edu/chytrid_fungus.html



Rosenblum et al PNAS 2008

Bd is a Chytrid fungus



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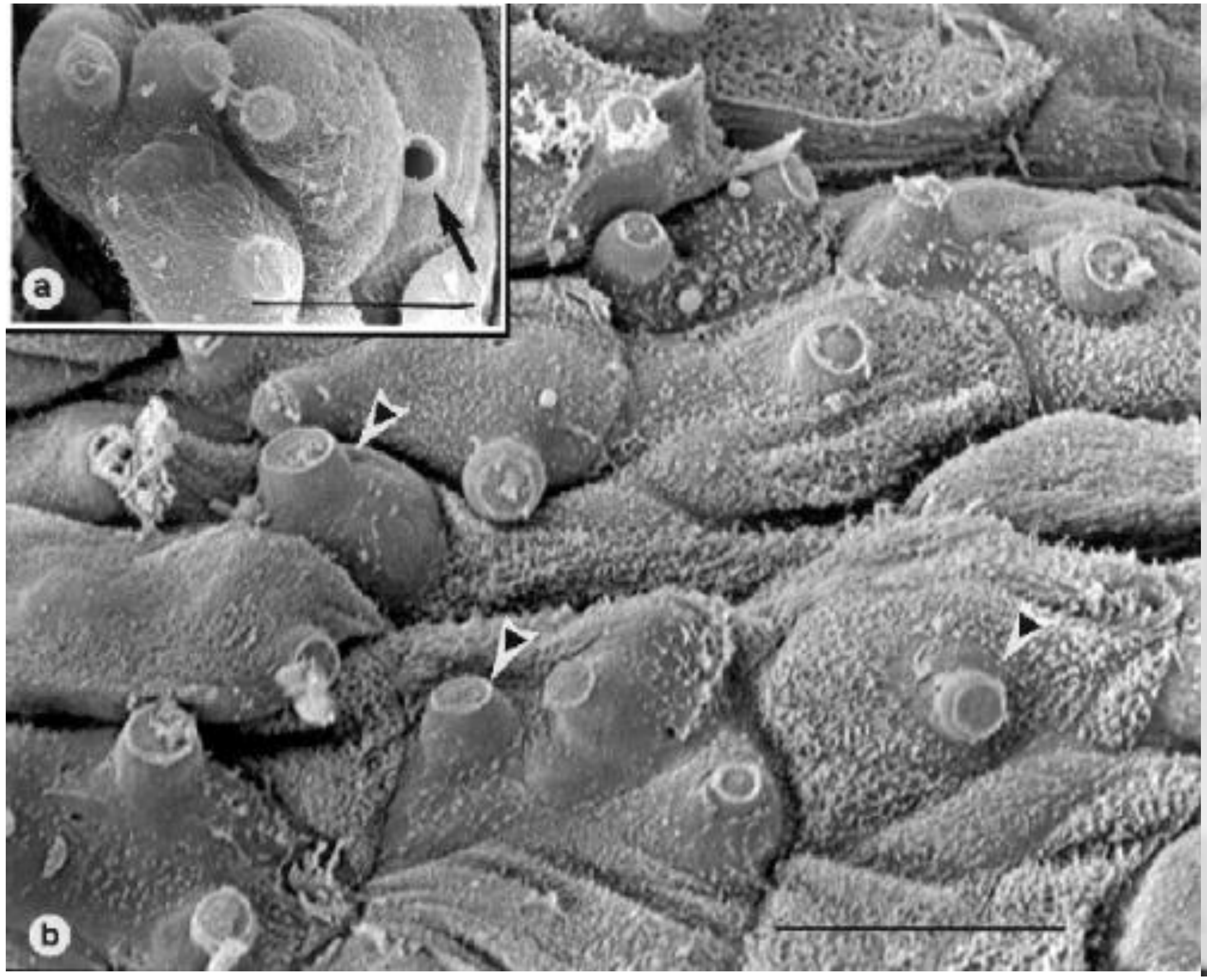
Bd genome sequence projects

- 2 strains sequenced at JGI and Broad; allow whole genome comparison between strains
- Found that genome is diploid, but with large regions with loss of heterozygocity (LOH)
- Identified gene family changes that might suggest mechanisms of pathogenecity
- Greater understanding of what the early fungus was like
- With collaborators we are sequencing 20 more strains for population genomics to better understand population dynamics, trace origin of diversity, and understand the LOH as independent or shared events.

Bd grows intercellularly

Formally described by Joyce Longcore (U Maine) (Mycologia 1999)



Rick Speare, Lee Berger, Alax Haytt
James Cook University, Townsville, Australia

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http://www.jcu.edu.au/school/phtm/PHTM/frogs/chpr1/fc13.htm

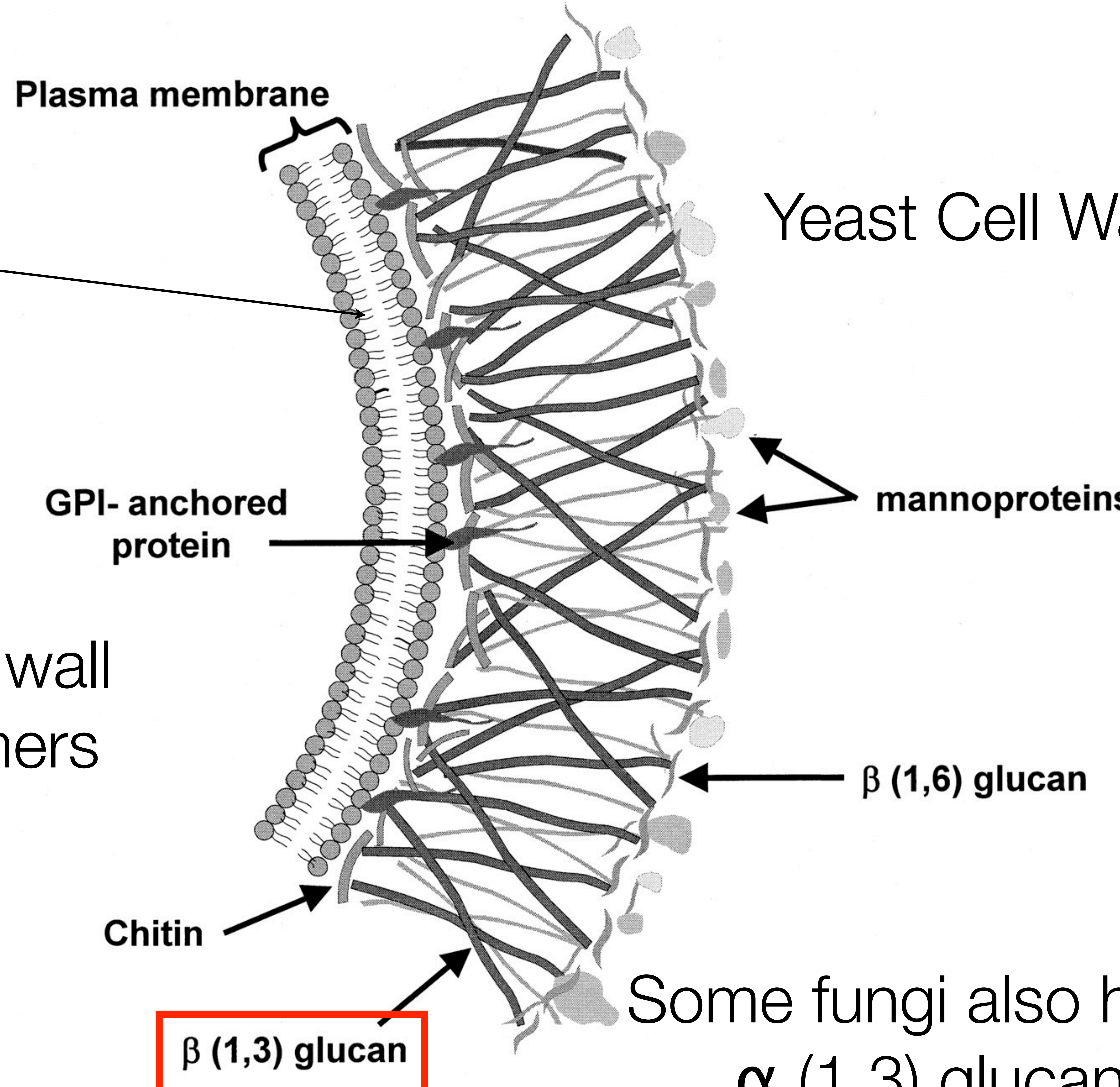
Phylogenomic profiling

- For each gene in the the target (*Bd*) genome, look to see which have homologs in other fungi, animals, plants
- Classify genes by its profile as to when it must have arisen based on identified homologs
- Also compare well-studied organisms (*S. cerevisiae*, *N. crassa*) to see which genes were missing
- For *Bd*/Chytrids several trends appeared
  - Missing: some cell wall genes, spindle-pole body
  - Present in *Bd* but not other non-chytrid fungi: Flagella, some signaling pathways, effector like proteins
  - Some expansions of gene families

Fungal cell wall evolution- a view from earliest branches

Ergosterol

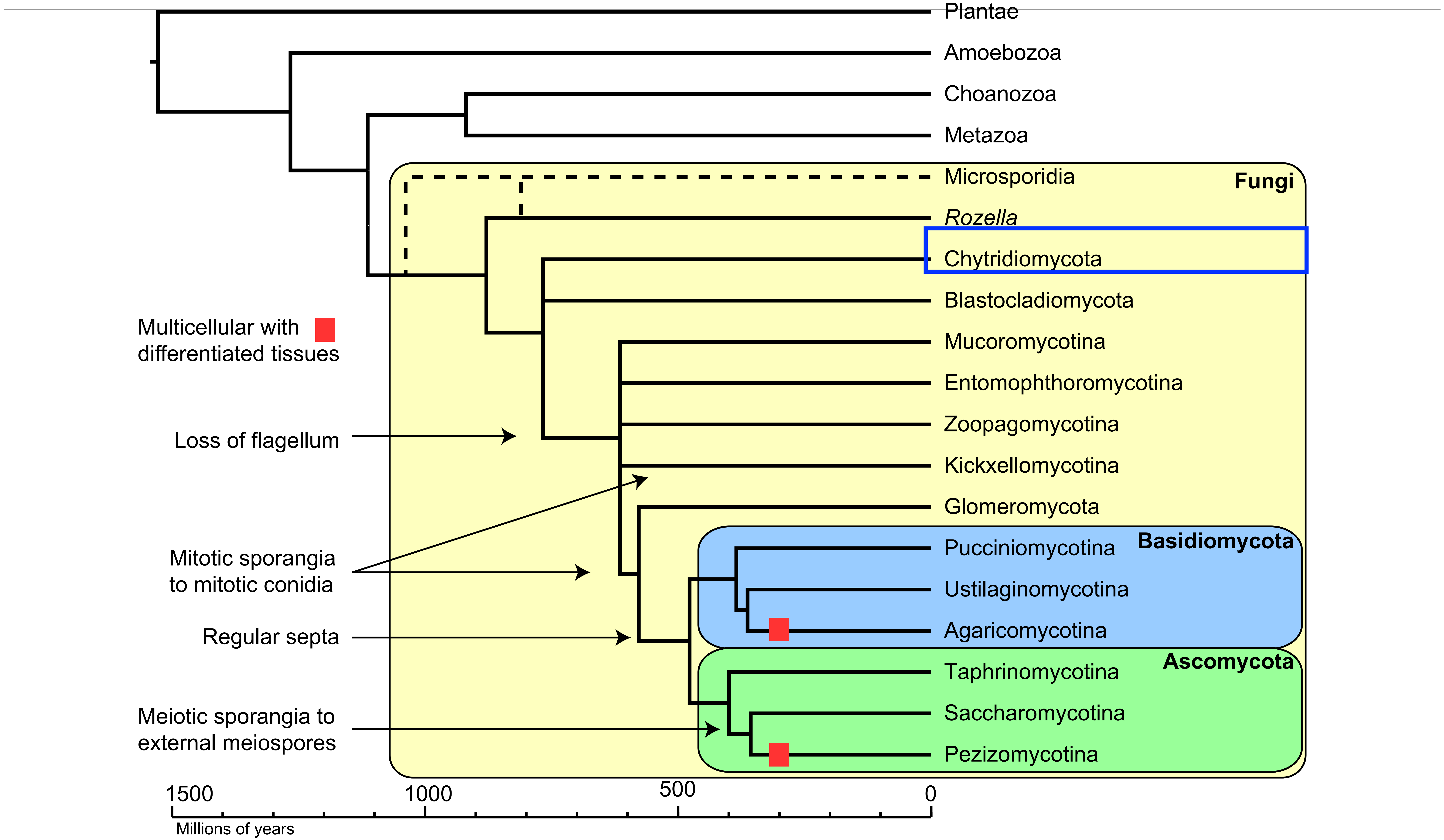
Yeast Cell Wall



What is the fungal cell wall made of? Sugar polymers

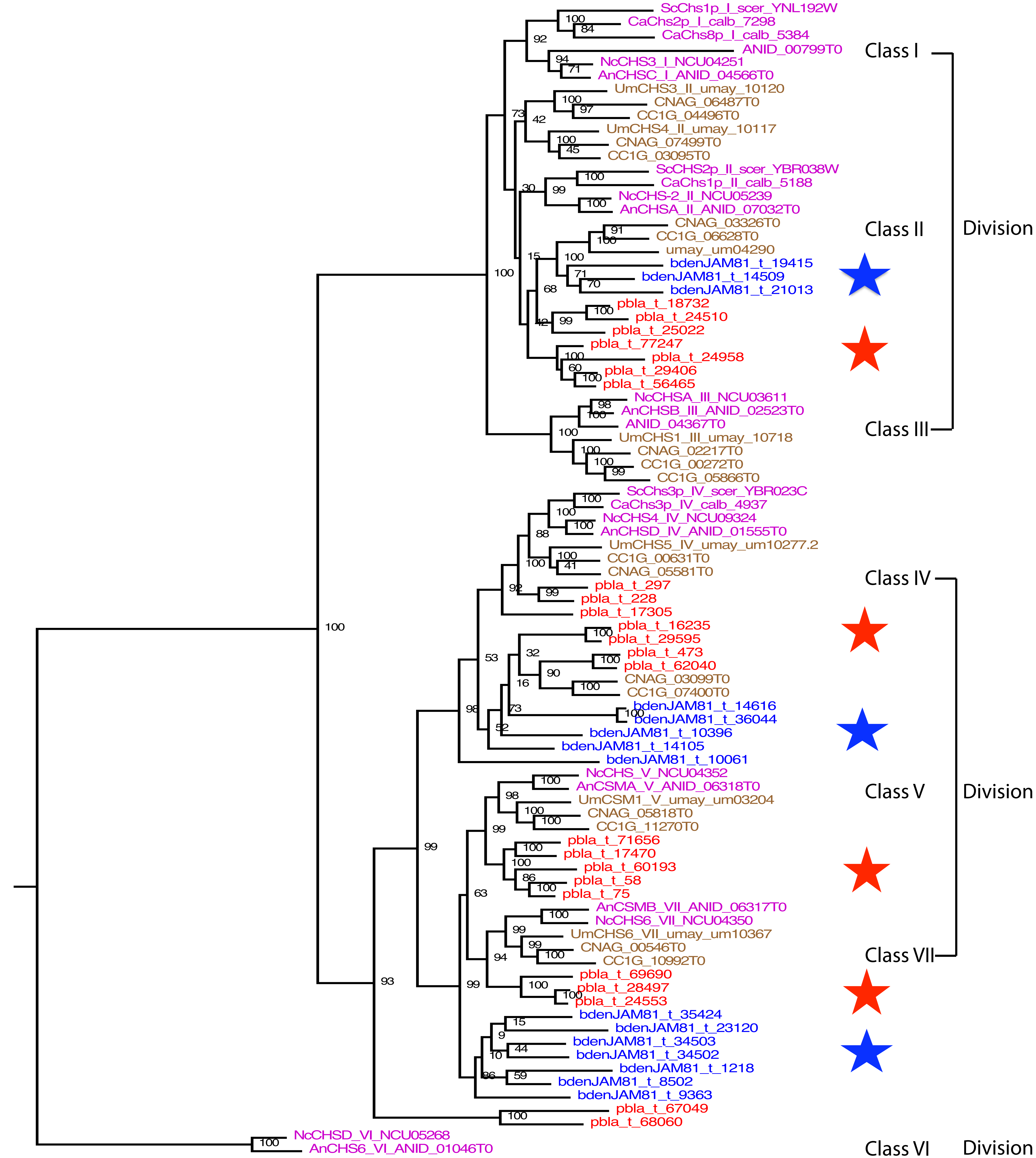
Some fungi also have α (1,3) glucan

Selitrennikoff CP, AEM 2001



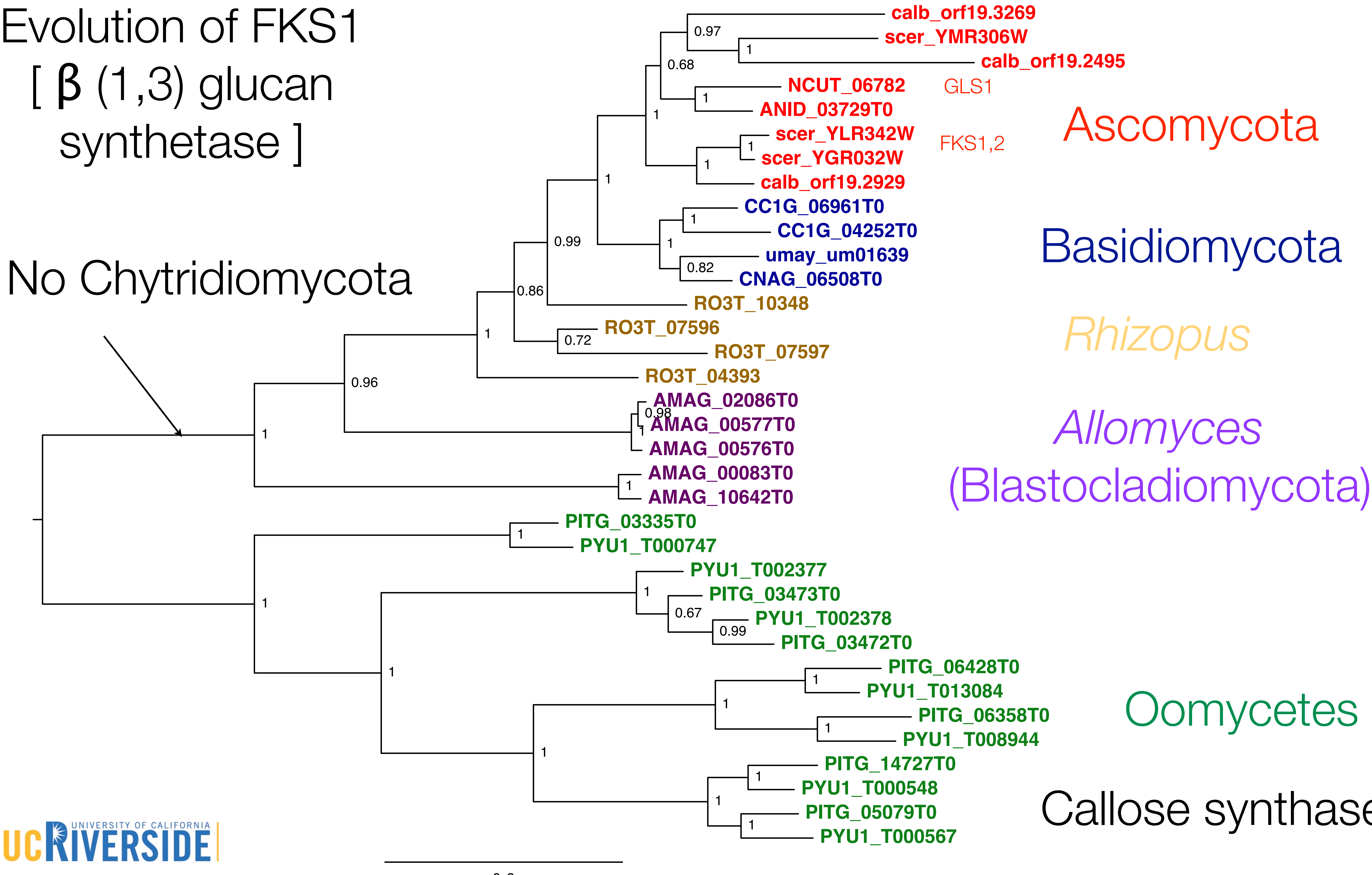
Plantae
Amoebozoa
Choanozoa
Metazoa
Microsporidia
Fungi
Rozella
Chytridiomycota
Blastocladiomycota
Mucoromycotina
Entomophthoromycotina
Zoopagomycotina
Kickxellomycotina
Glomeromycota
Pucciniomycotina
Basidiomycota
Ustilaginomycotina
Agaricomycotina
Taphrinomycotina
Ascomycota
Saccharomycotina
Pezizomycotina
Multicellular with differentiated tissues
Loss of flagellum
Mitotic sporangia to mitotic conidia
Regular septa
Meiotic sporangia to external meiospores
1500
1000
500
0
Millions of years

Chitin Synthase Gene Evolution



Evolution of β (1,3) glucan synthase

Evolution of FKS1 [β (1,3) glucan synthetase]



No 1,3 Beta-glucan?

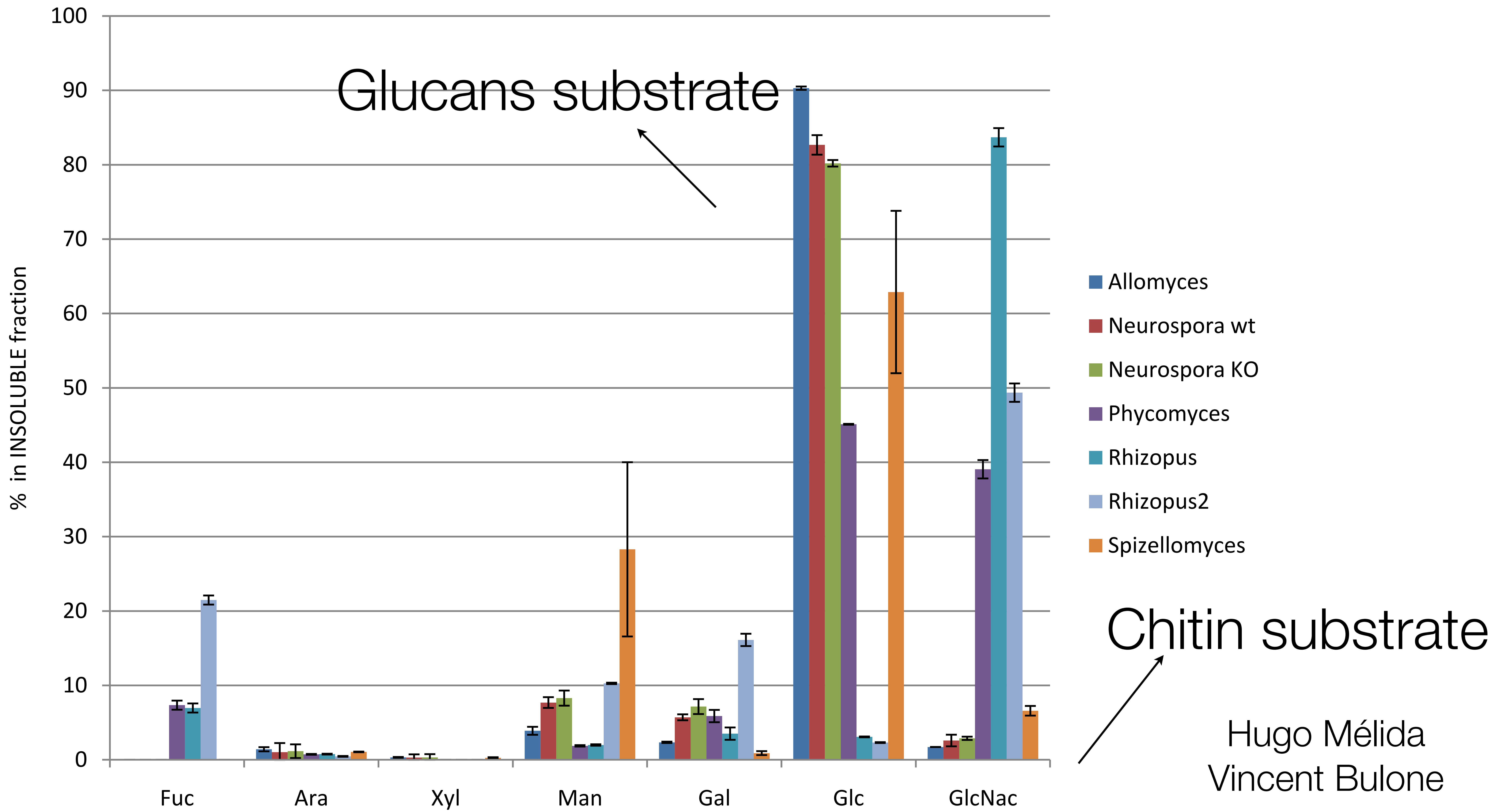
B. dendrobatidis cell wall biochemical analysis

β (1,3)-glucan	β(1,6)-glucan	α(1,3)-glucan	Cellulose β(1,4)-glucan	Chitin
X	**X**	**X**	✓	✓

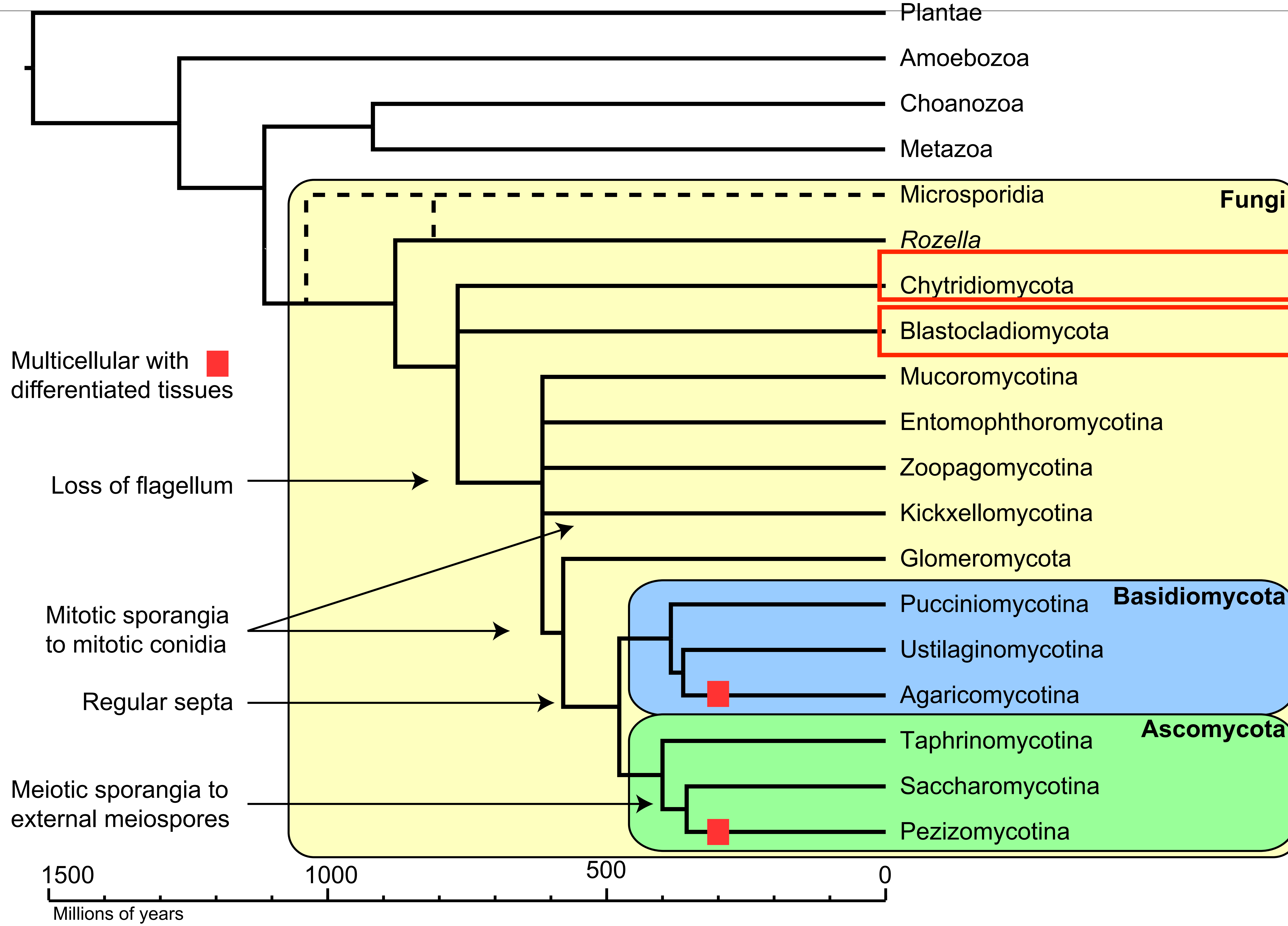
A putative cellulose synthase gene can be found in genome of *Bd* but also found in *N. crassa* and other Fungi

with JP Latgé, M. Fisher

Monosaccharide breakdown of several fungal cell walls



Hugo Mélida
Vincent Bulone



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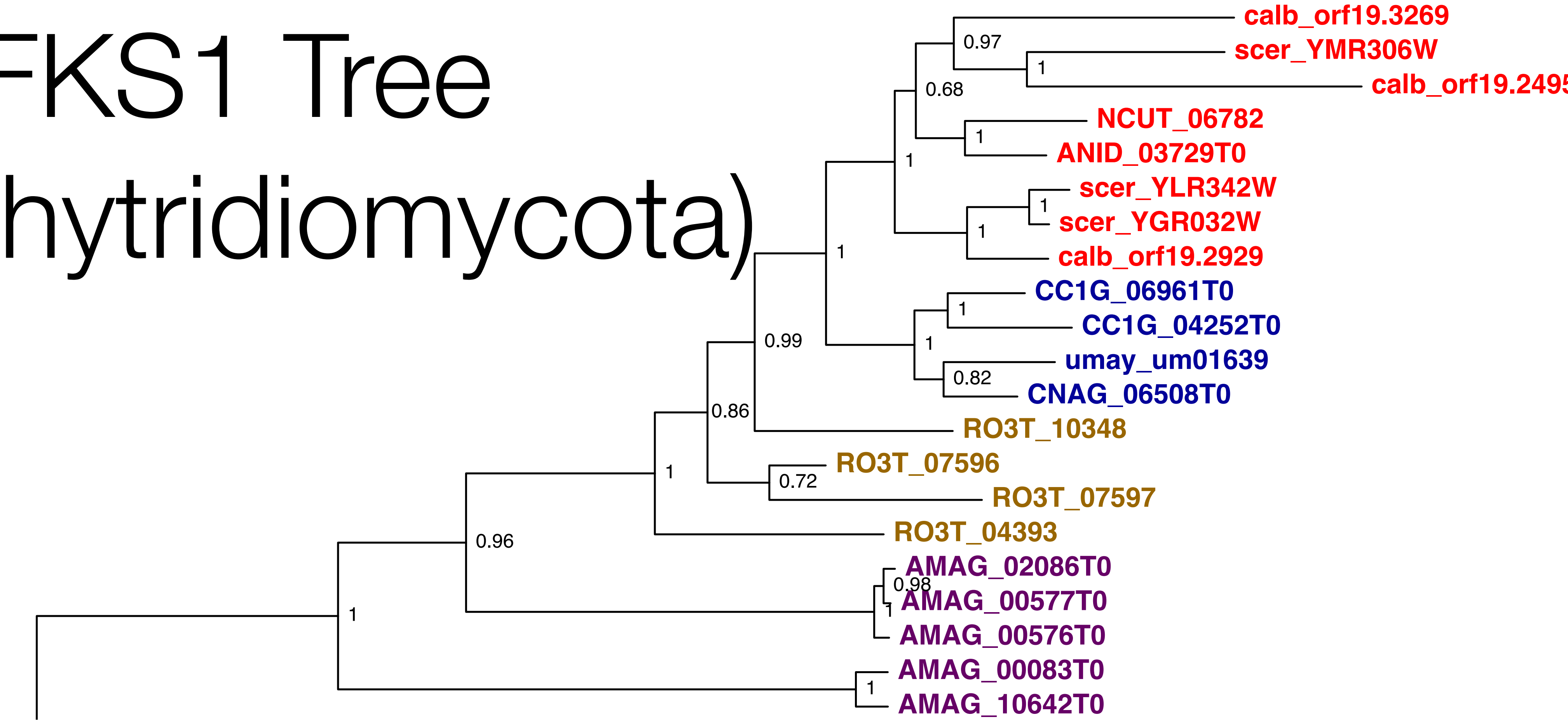
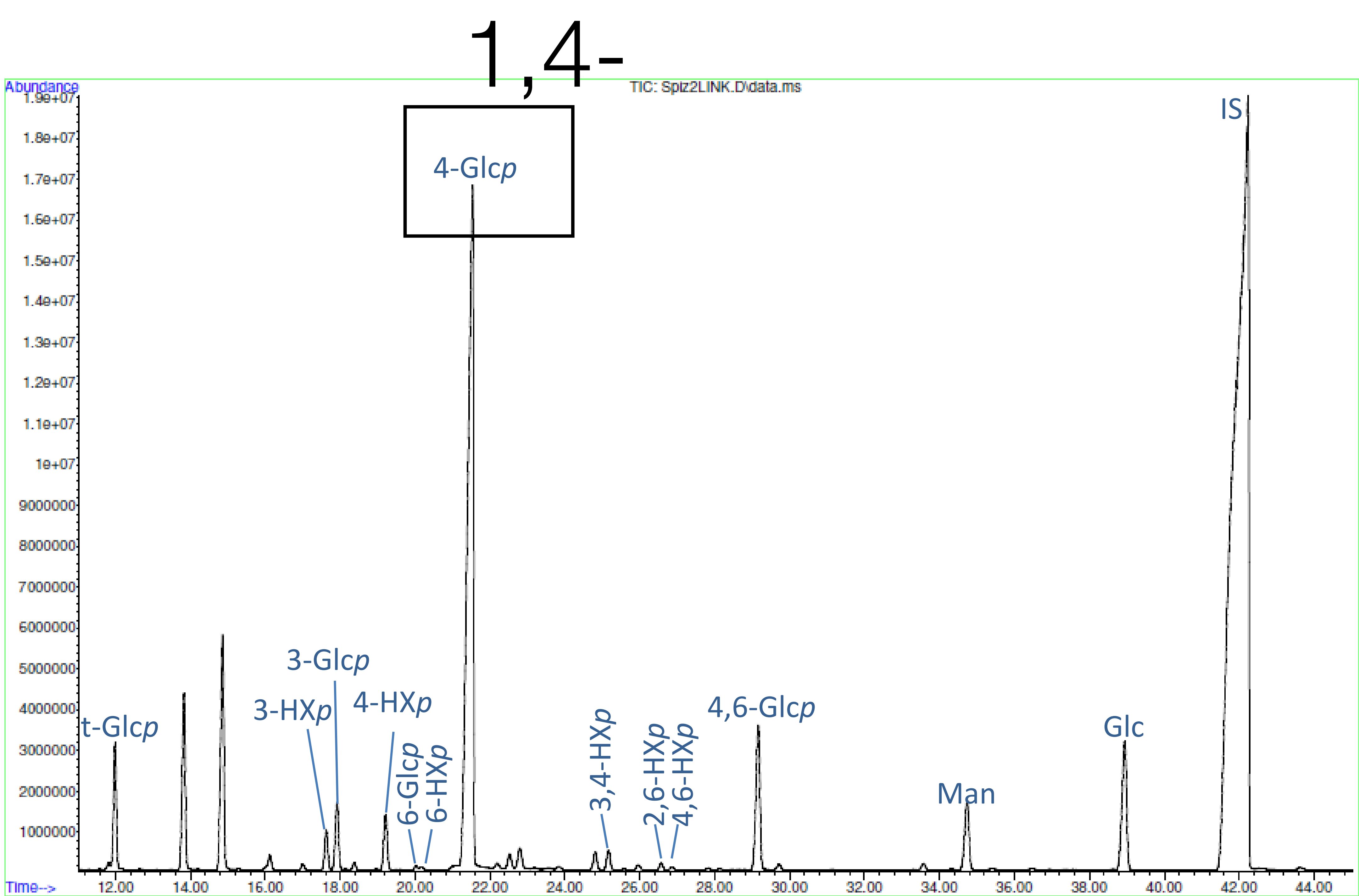
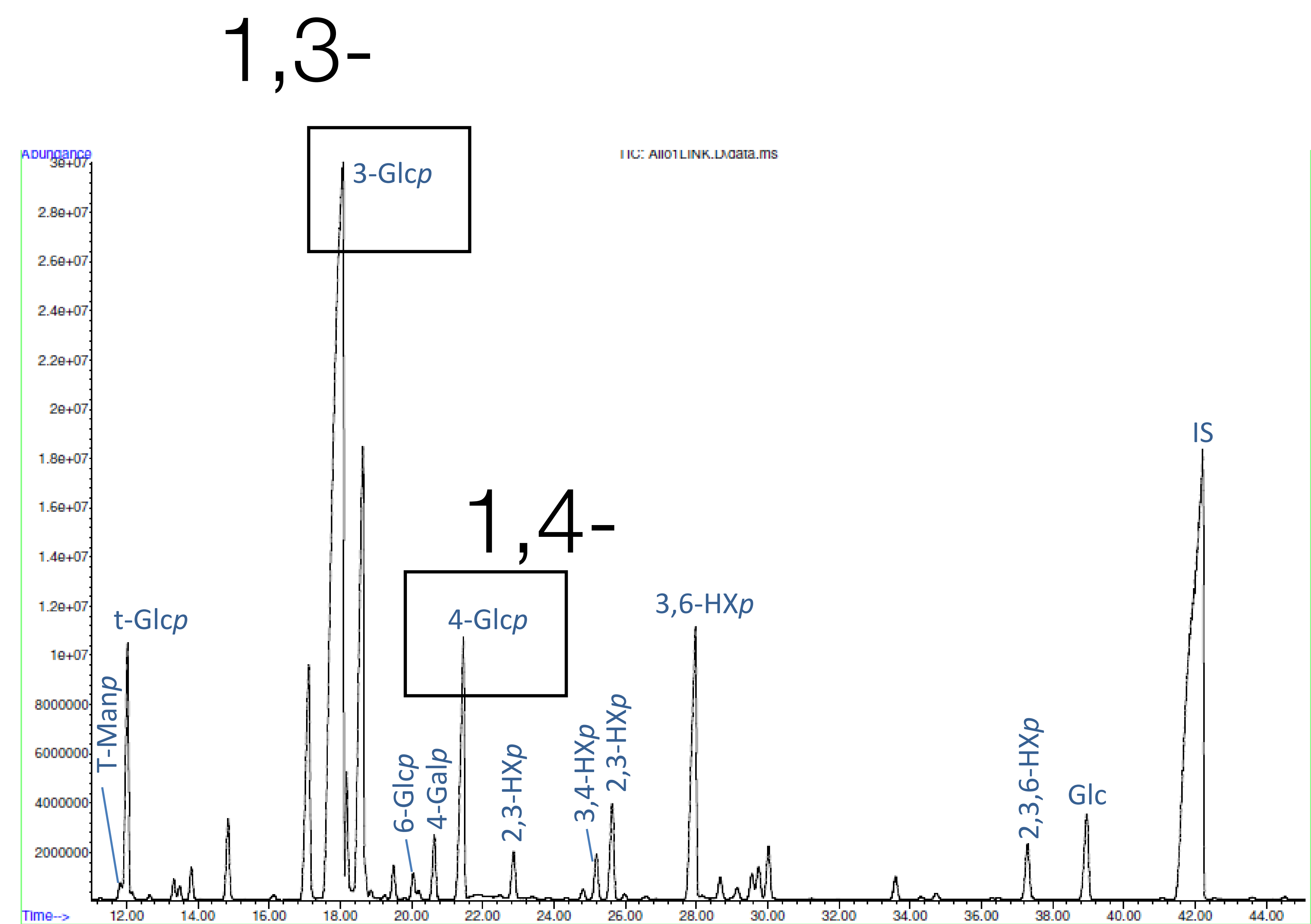
Saccharomycotina
Meiotic sporangia to external meiospores
Pezizomycotina
1500
1000
500
0
Millions of years

FKS1 Tree
(No Chytridiomycota)



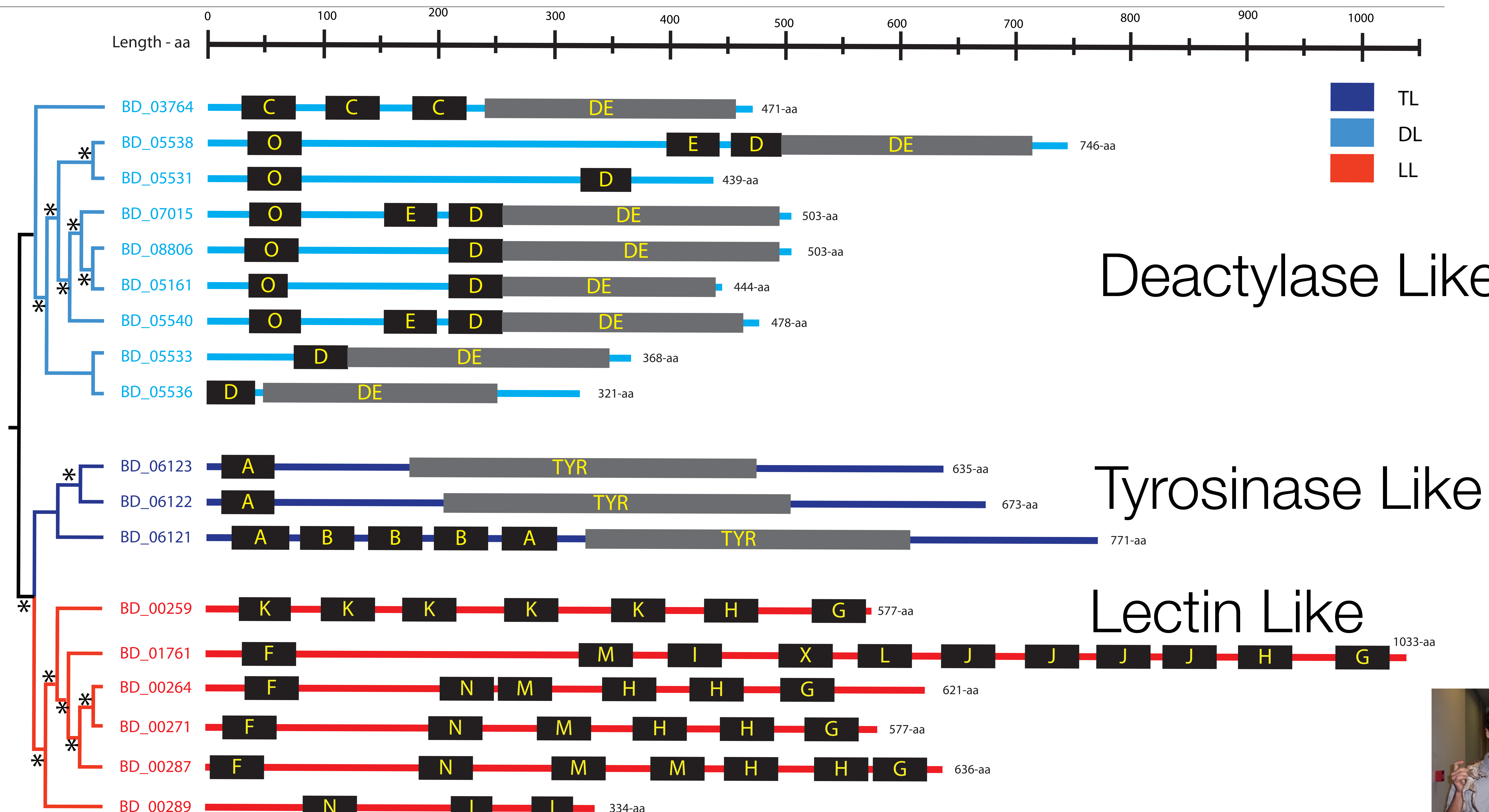


Spizellomyces



Allomyces

Expansion of CBM18 domain - Chitin binding gene family



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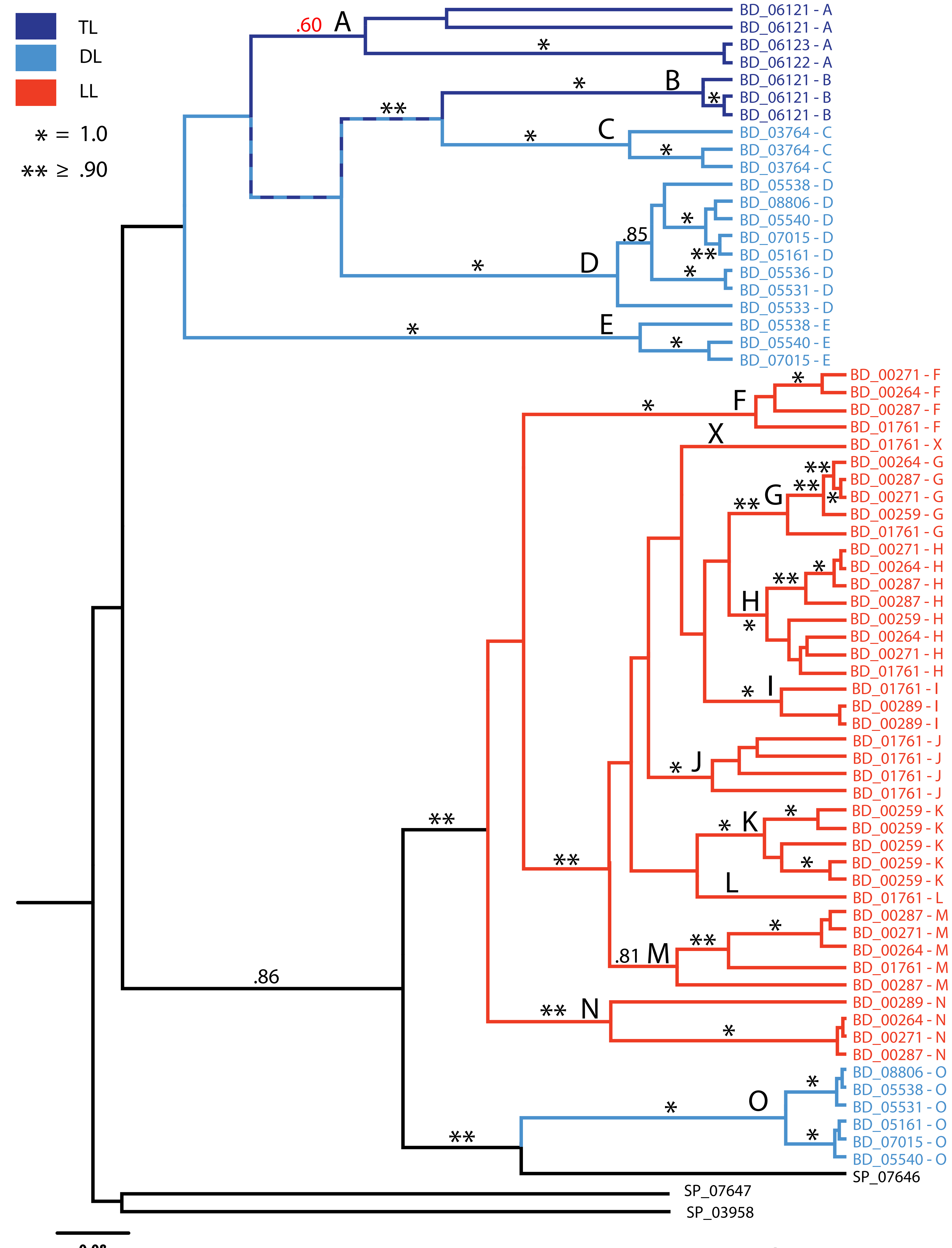
Abramyan & Stajich, submitted

Domain tree shows clade-specific grouping

Domains evolved from mostly tandem duplications with some intergene duplications.



Abramyan & Stajich, submitted

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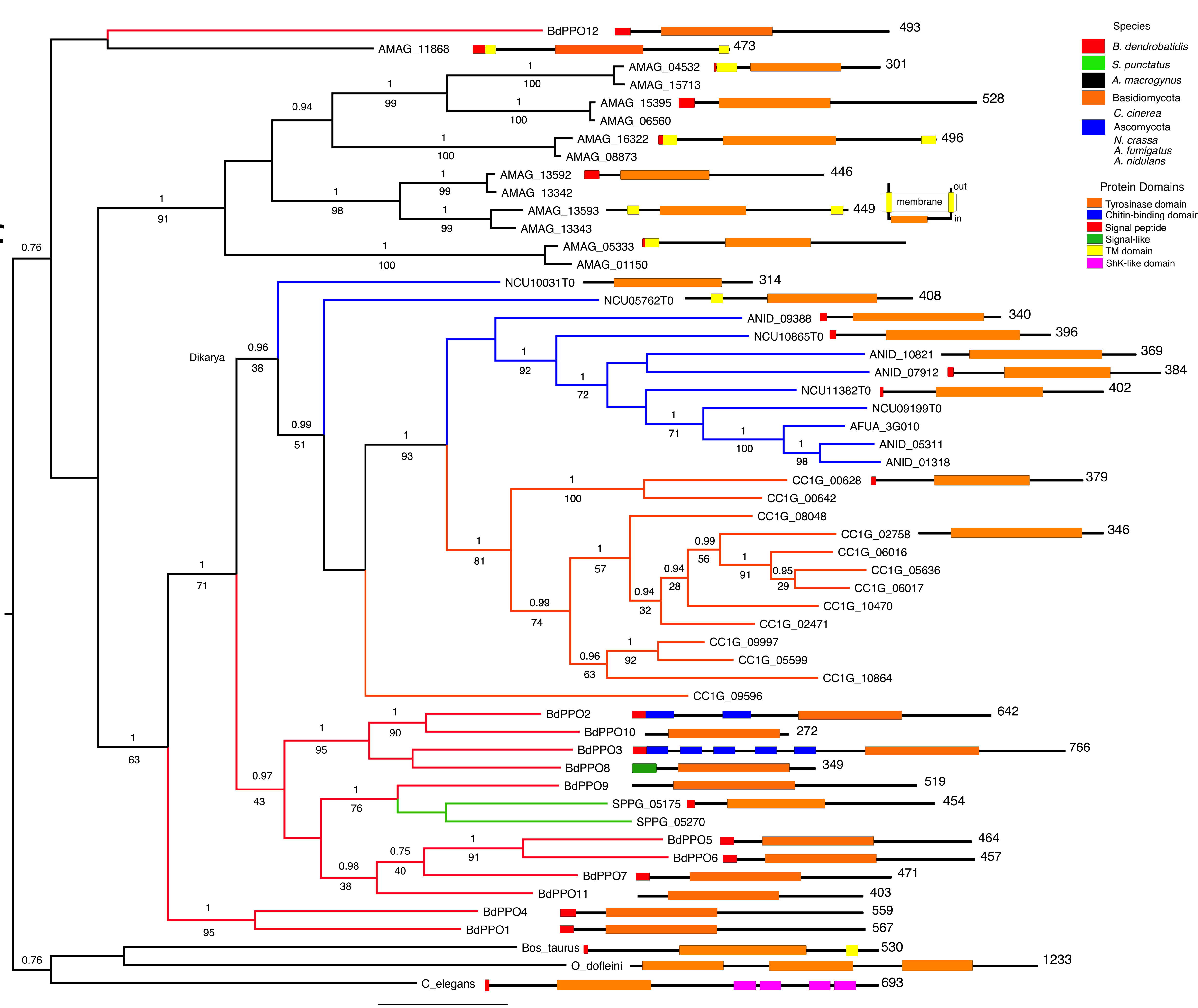
CBM18 expansion

- Largest copy number of CBM18 in all fungi, and most number of domains (11) in a single locus
- Evidence for positive selection among copies of the domains based on codon analyses
- CBM18 thought to bind chitin, could be involved in binding its own chitin to cloak the cells from the host immunity
- Could also bind chitin-related molecules in animals attach more firmly to the animal cells

Abramyan & Stajich, submitted

Tyrosinase expansions in *Bd* and other fungi

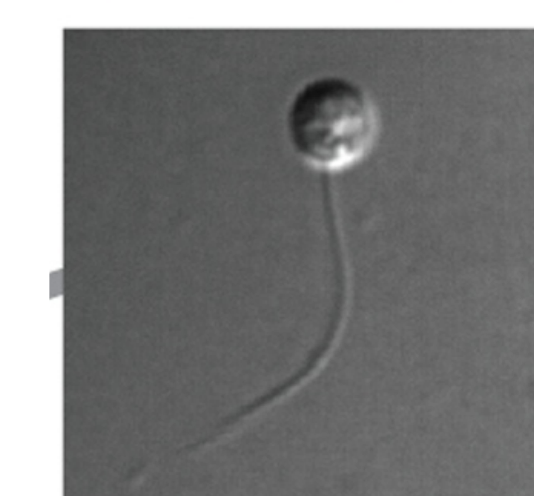
Synthesis of melanin, pigments and other polyphenols



Allomyces

H.Whistler via Liu et al BMC Evol Biol 2006

Hajime Muraguchi via Stajich et al PNAS 2010



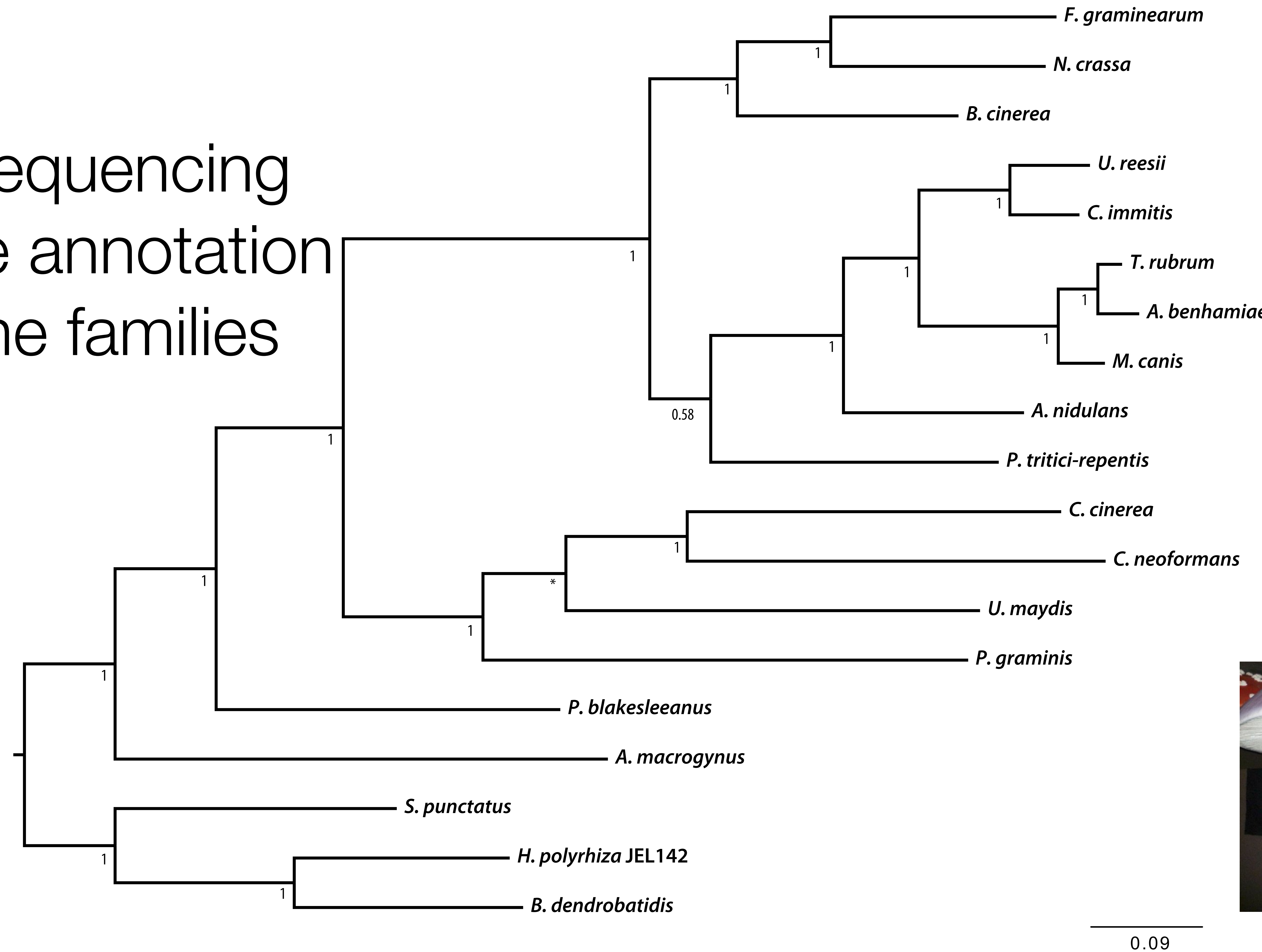
E.Medina

But are these changes important?

- Just observing big families in a genome is nice, but does it mean that changes are really related to recent adaptation?
    - The branches on some gene trees are short, indicating duplications are recent
- A better is to polarize the changes to the *Bd* branch by having a closer species than 50-100 Mya...
- So is there a species closer to *Bd* we can use? ...

Homolaphylictis polyrhiza JEL142 is a close(ish) relative

454 genome sequencing
MAKER genome annotation
OrthoMCL gene families



Joneson et al, Submitted

Contrasting some family sizes among the Chytrids

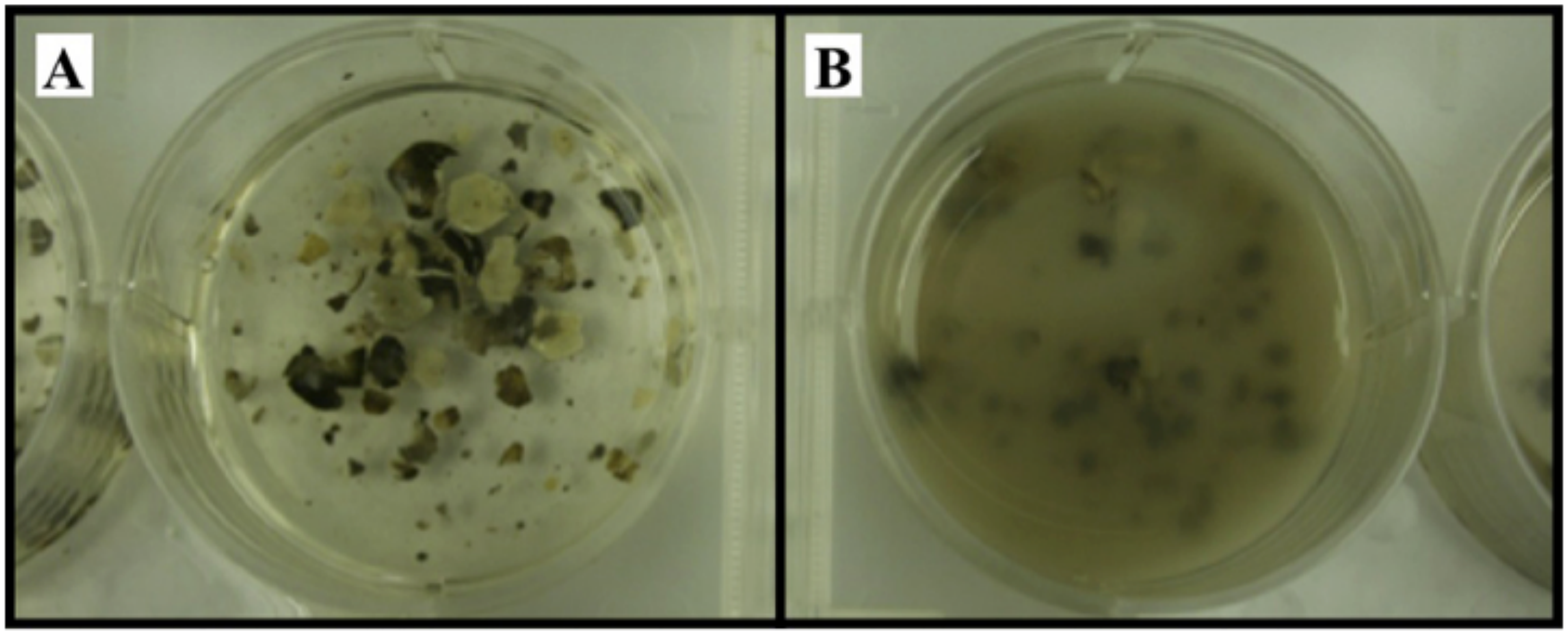
	M36	**S41**	Tyrosinase	**CBM18**
Allomyces	31	0	16	3
Spizellomyces	3	3	3	3
Hp	3-5	3	15	5
Bd	**38**	**32**	12	**14-16**
	Fungalysin	Serine protease		

Fungalysins - thought to be keratinases (break down keratin in an amphibian skin...)

Serine protease expansions in *Coccidoides* and relatives maybe related to breaking down on animal matter

Joneson et al, Submitted

H. polyrhiza won't grow on frog skin; doesn't cause mortality in frogs



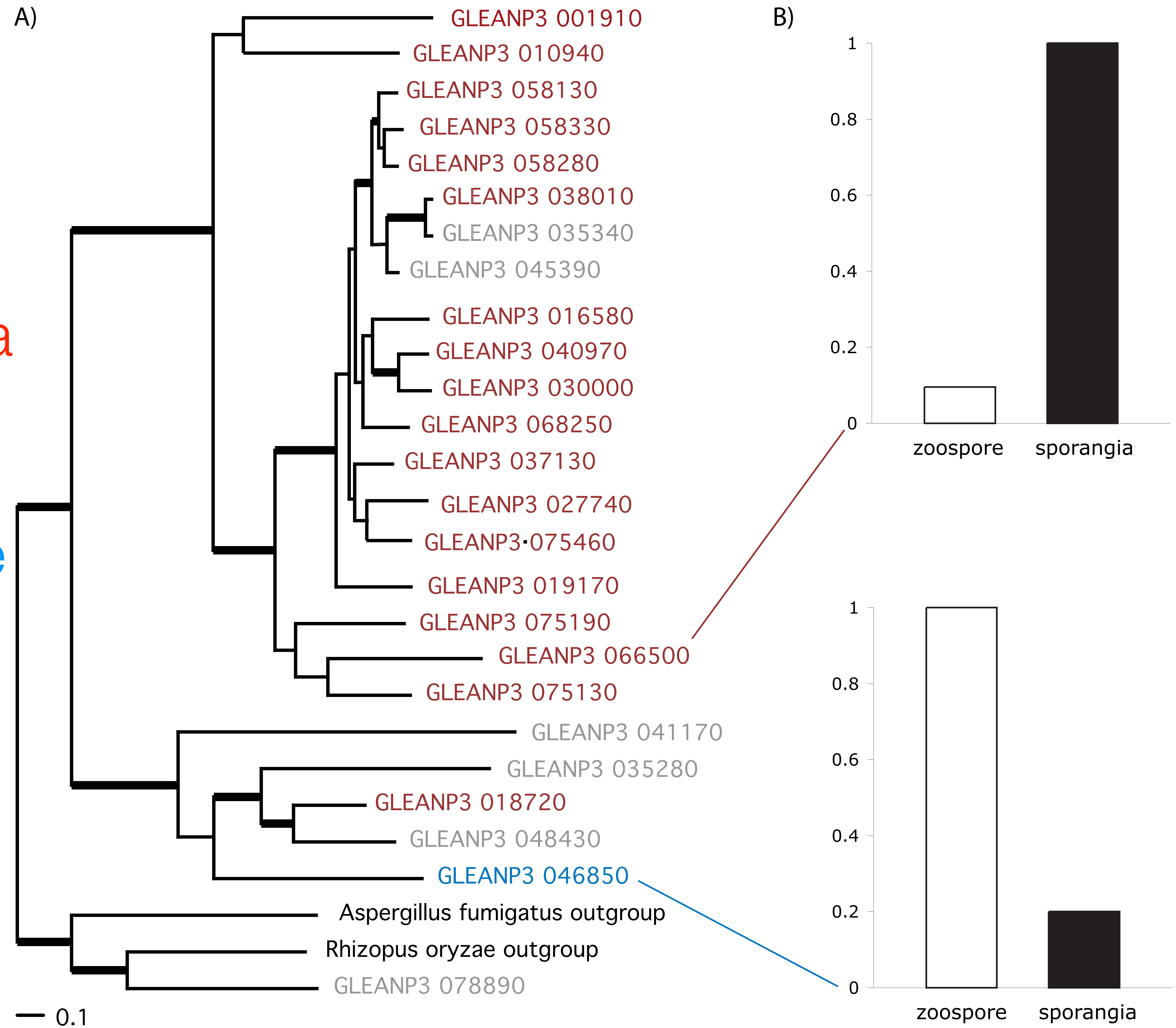
Hp- frog skin intact

Bd- frog skin degraded

Joneson et al, Submitted

Fungalysin M36

up in sporangia
no expression diff
up in zoospore



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Rosenblum et al PNAS 2008

Bd summary

- Comparisons to close species can polarize some differences in lineage specific expansions
    - Findings of M36, S41 expansions seem to be recent to *Bd* and could be a functional link to pathogenesis
    - Expansion of Tyronsinase from counts is less compelling, but gene tree analyses suggests recent expansions on *Bd-Hp* branch
    - Lack of FKS1 in early Chytridiomycota lineages suggests a more recent origin of this gene than origin of the Fungi and predicts timing of some changes in fungal cell wall composition
    - CBM18 expansion may be related to adhesion, future experiments to test this
- Future: We are employing a population genomic approach, resequencing 24 strains of *Bd* and hope to understand more about origins and variation in the genome from these data.

Summary

- Unraveling the evolution of pathogens can be tricky, more so when mode of pathogenesis is not obvious (e.g. not just a toxin gene)

- Comparative genomics at the scale of gene and gene families can suggest changes that may be important in adaptation of a species.

- Connecting these molecular changes to pathogenecity is still needed to understand the role these expansions may play - but provides rich experimental fodder for the laboratory.

Acknowledgements

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Annie Nguyen

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H. polyrhiza
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Joyce Longcore {U Maine}
Tim James {U Michigan}

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