Suggested project topics

The following are possible phylogenetics projects for teams of 1 or 2 people. Normally, only one team will work on each project, unless there is a natural way to split the project into separate sub-projects. For example, several teams could work on a project to study nitrogen fixation genes, each analyzing a different gene that encodes a component of the nitrogenase enzyme. Topics will be assigned on a first-come-first-serve basis. Let me know once you choose a topic to make sure it is still available. I can also help you find a project partner.

- Email me your proposed project topic and team members by **October 17th**.
- Your one page project plan is due **October 24th.**

Evolution of yeast scaffolding proteins, FAR1 and STE5

STE5 and **FAR1** are scaffolding proteins with similar structural organization and related, but distinct roles in the mating pathway in Baker's yeast, *Saccharomyces cerevisiae.* The human pathogen, *Candida albicans,* has two analogous proteins, as do other closely related yeast species in the Saccharomycotina. More distantly related fungi have only one Ste5/Far1-like scaffolding protein. This raises the intriguing question of whether the mating pathway functions performed by two scaffolding proteins in Baker's yeast are all carried out by a single protein in those species. A recent study by Cote[1] and colleagues provides a thoughtful analysis of the evolution of fungal mating pathway scaffolding proteins, but includes no phylogenetic analysis. Their study is based on simple counting arguments that can lead to incorrect conclusions. Your phylogenetic analysis of FAR1 and STE5 has the potential to either confirm their results or offer a new hypothesis for the evolution of this pathway.

This could be a project for a multiperson team or two separate projects.

Mysteries of Yeast metabolism: DLD2, YMR027W, YOR283W

DLD2 is annotated as a lactate dehydrogenase, but we think it could also be the missing D-2-hydroxyglutarate dehydrogenase in yeast. 2-hydroxyglutarate is the metabolite of the moment, as it has been linked to cancer. Interestingly, forms of 2-hydroxyglutarate that are capable of permeating the cell appear to drive cell growth and regulate the differentiation of stem cells. The gene that catalyzes this reaction in humans is D2HGDH. Mutation of this gene causes a rare but serious disease marked by the accumulation of D-2-hydroxyglutarate with complications affecting both muscles and neurons.

[1] Evolutionary Reshaping of Fungal Mating Pathway Scaffold Proteins. Côte P, Sulea T, Dignard D, Wu C, Whiteway M. MBio. 2011 Jan 11;2(1):e00230-10. doi: 10.1128/mBio.00230-10.

We understand very little about yeast proteins YMR027W and YOR283W. Dr. Caudy at the University of Toronto has preliminary evidence that **YMR027W** breaks down fructose-1-phosphate. This is surprising because there is no known role for fructose-1-phosphate in the central metabolic pathways of yeast, which have been the targets of scientific scrutiny for more than 50 years. **YOR283W** is a member of a large and functionally diverse family of phosphatases, many of which are medically or agriculturally important. Although YOR283W has been shown to have broad substrate specificity in a test tube, nothing is known about its functional role in the cell. More information about the evolutionary history and conservation of these proteins could shed provide clues to their function and guide future experiments in the laboratory.

Phylogenetic analysis of any one of these genes would make a suitable project.

Coevolution of Bhlhb5 and Prdm8, two proteins involved in itching

Got an itch to align some proteins? Scratch it with this project! In a recent publication[2] it was shown that mice lacking either Bhlhb5 or Prdm8 develop a similar phenotype of incessant scratching. Bhlhb5, an activating transcription factor, is repressed by Prdm8. Similarly, Zfp488, a phylogenetically close relative of Prdm8, represses an Olig transcription factor that is a phylogenetically close relative of Bhlhb5. These phylogenetic relationships may help to explain the origins of Prdm8/Bhlhb5 and the itch response. In this project we'd like to try to identify homologs and orthologs of these protein pairs to expand on research explaining itch in humans and other organisms.

Opine synthesis genes in bacteria

Crown gall and hairy root tumors in plants are caused by pathogenic bacteria from the genus Agrobacterium. Agrobacteria trick the plant into synthesizing compounds called *opines,* which act as nitrogen and energy sources for the bacterium. Agrobacteria carry opine synthesis genes which they insert into the host plant genome during the infectious process. These genes have promoters recognizable by the plant's transcriptional machinery. Agrobacteria also have opine catabolism genes, with bacterial promoters, that allow them to extract energy from opines made by the plant. Hong[3] and colleagues have proposed that the opine biosynthesis and catabolism enzymes are encoded by homologous genes that arose via an ancient duplication. They suggest that the co-evolution of this gene family was a driving force in Agrobacterium's transition from plant symbiont to plant pathogen. Your phylogenetic analysis of opine biosynthesis and catabolism genes could help to confirm or refute this hypothesis.

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[2] Bhlhb5 and Prdm8 Form a Repressor Complex Involved in Neuronal Circuit Assembly. Ross *et al*. Neuron. 2012 Jan 26;73(2):292-303.

[3] A T-DNA gene required for agropine biosynthesis by transformed plants is functionally and evolutionarily related to a Ti plasmid gene required for catabolism of agropine by *Agrobacterium.* Hong *et al*. J. Bacteriol. *179*:4831-4840, 1997.

Does horizontal transfer of virulence genes in Neisseria contribute to pathogenicity?

The low cost and high throughput of next generation sequencing is revolutionizing our understanding of prokaryotic genome plasticity. Within a single species, gene content varies substantially from genome to genome. Horizontal transfer between individuals in the same or in closely related species is much higher than previously thought. This is leading to an ecological view of pathogenesis. According to this perspective, virulence of a pathogen is modulated by the genetic makeup and organization of other bacteria in its environment. Further, it has been proposed that non-virulent, commensal species may harbor genes that contribute to virulence when transferred to a virulent strain. In order to investigate this hypothesis, Marri and colleagues[4] characterized the distribution of gene families associated with virulence in a collection of commensal and pathogenic *Neisseria* genomes. These families include iron utilization genes (Fig. 4) and genes encoding the Type IV pilus (Fig. S1). The hypothesis that these genes are horizontally transferred can be tested by comparing their phylogenies with the phylogeny of the species tree. Disagreement between the trees indicates horizontal transfer and can further predict between which species these transfers arose. An analysis of one to three genes, for example genes acting in the same pathway, would make a good course project.

[4] Marri *et al., Genome Sequencing Reveals Widespread Virulence Gene Exchange among Human Neisseria Species,* PLoS ONE, 5(7): e11835