

Brenda Andrews, Ph.D.
Wednesday, September 25, 3:00-3:45 p.m.

From phenotypes to pathways: Global exploration of cellular networks using yeast functional genomics

The entire landscape of eukaryotic genetic research has been transformed by our ability to rapidly sequence genomes – while we can now map genomes efficiently, we do not yet know how to interpret genome variation to predict inherited phenotypes. Emerging evidence suggests that we must account for genetic interactions in order to relate genotype to important phenotypes in any eukaryotic system. To systematically explore genetic interactions, our group developed a unique functional genomics platform called ‘synthetic genetic array’ (SGA) analysis that automates yeast genetics and enables the systematic construction of double mutants. We developed two powerful pipelines which combine SGA and automated microscopy for systematic and quantitative cell biological screens or phenomics. Our first pipeline uses SGA to introduce fluorescent markers of key cellular compartments, along with sensitizing mutations, into yeast mutant collections. We then perform live cell imaging on the mutant arrays using HTP confocal microscopy to quantitatively assess the abundance and localization of our fluorescent reporters, providing cell biological readouts of specific pathways and cellular structures in response to thousands of genetic perturbations. Our second pipeline exploits the yeast GFP collection, a unique resource consisting of thousands of strains with different genes uniquely tagged with GFP. This remarkable collection has been arguably underutilized for systematic analysis of the proteome, largely due to the challenges associated with analysis of large sets of cell biological data. We addressed this challenge by adopting a high-content screening approach to measure protein abundance and localization changes in an automated fashion on a genome scale. Our general approach, in particular our network analysis and visualization methods, are readily extensible to other systems.