Lunch Seminar Abstract, Union Biometrica, Inc.

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Seminar is in conjunction with the Drug Discovery Technology 2003 Conference.
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Use of the COPAS Biosort in a hi-throughput screen for genes that regulate lifespan.

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The roundworm *C. elegans* has proven to be a powerful tool to investigate the genetic mechanisms of lifespan regulation. A number of single-gene mutations have been identified that confer substantial lifespan extension. For instance, loss of function of the insulin/IGF-1 like receptor (*daf-2*), or downstream components of this pathway, can double the worm's lifespan. Despite this success much remains unknown. Indeed there are several pathways for which few if any components have been found – particularly caloric restriction and mitochondrial lesions, both of which extend lifespan through unknown mechanisms. The search for novel genes that regulate aging is extremely time consuming, and existing screens are not sufficiently sensitive to reliably identify candidates with modest lifespan phenotypes. We are now attempting to address both of these issues by coupling an RNAi feeding screen with a high throughput phenotype analysis employing the COPAS Biosort. Stress response loci have been identified that are upregulated in genetic backgrounds that produce lifespan extension. We have created a green fluorescent protein (GFP) transcriptional reporter for one of these genes. By growing these animals in liquid cultures containing individual clones from the RNAi library (a library of approximately 17,000 clones created by the Ahringer laboratory) and then passing these animals through the COPAS Biosort, we hope to identify negative regulators of stress response genes. We will then test these candidates to see if they play a role in lifespan regulation. A manual direct screen for lifespan mutants that was recently completed in our lab took two people more than eight months to complete. By contrast, this mechanized screen will take one person roughly six weeks to complete, and will yield quantitative data on each worm in the overall sample of ~1,000,000 worms.