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14. ABSTRACT

The overall objective of this project was to rapidly find molecular reagents to interfere or bind to every gene product in the Saccharomyces cerevisiae through the development of new screening and data analytical technologies. Two experimental approaches were taken. Ron Davis developed the haploinsufficiency profiling (HIP) technology wherein two libraries of yeast were constructed one containing strains missing one copy the other strains missing both copies of every gene in yeast (that could be knock out). In place of its missing gene, each strain was engineered with a DNA bar code to identify it. Affymetrix chips were used to measure the relative populations of each strain under different chemical perturbations. Roger Brent worked on build protein aptamers to bind gene products. Arkin's role was in the development of analyses for the Haploinsufficiency data.

15. SUBJECT TERMS

haploinsuffciency, yeast, affymetrix chips

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a. REPORT	b. ABSTRACT	c. THIS PAGE			Adam P. Arkin
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Grant #:N00014-99-F-0458
Principal Investigator: Adam P. Arkin
Institution: E.O. Lawrence Berkeley National Laboratory
Grant Title: Instant Cell Analysis & BioSPICE
Award Period: 1 September 1999 - 31 December 2001

Objective: The overall objective of this project was to rapidly find molecular reagents to interfere or bind to every gene product in the Saccharomyces cerevisiae through the development of new screening and data analytical technologies.

Approach: Two experimental approaches were taken. Ron Davis developed the haploinsufficiency profiling (HIP) technology wherein two libraries of yeast were constructed one containing strains missing one copy the other strains missing both copies of every gene in yeast (that could be knock out). In place of its missing gene, each strain was engineered with a DNA bar code to identify it. Affymetrix chips were used to measure the relative populations of each strain under different chemical perturbations. Roger Brent worked on build protein aptamers to bind gene products. Arkin's role was in the development of analyses for the Haploinsufficiency data.

Accomplishments: Our role on the project was to aid in the quality analysis and quality control of the HIP pipeline and to develop the databases and analyses for this data. During the course of this project we developed the database and the initial analyses that led to proof of the quality and reproducibility of the method at moderate scale screening[1]. We discovered a number of interesting facts:The gene necessary for surviving a perturbation to the environment were not represented by the set of genes that changed gene expression (adding a caveat to the power gene expression microarray techniques) and that we are able to determine accurately the molecular target and gross mechanism of action of each of the drugs or environmental exposures the cell is subjected to. The success of the project during this grant was parlayed into a larger NIH grant in which we have screened hundreds of small molecules for the effects on the population—the database is now large, the analyses of the data are very sophisticated leading to very robust prediction of molecular targets and we have developed new algorithms for classification of genes and chemical perturbants that allow deduction of

orthogonal perturbation sets and prediction of the effects of new chemicals[2, 3].

Conclusions: HIP profiling technology is an effective method for rapidly screening large chemical libraries to infer the action of each molecule on the proteins of yeast and the attendant mechanisms of action. We were able not only to correctly identify the known target of a number of antifungals but discover the mechanisms of less characterized members of the library and discover the pleiotropic effects that make some drugs less specific than others.

Significance: Apart from developing and hardening a entirely new technology for screening the activity of new molecules and identifying their protein targets—this method is now being adapted to screen for new classes of druggable proteins for use in human therapeutics and for deducing networks of interaction in the yeast cell.

Patent Information: No patents have been filed related to this research

Award Information: TR100, Time Magazine Top Innovator

Publication and Abstracts:

1. Giaever, G., et al., *Functional profiling of the Saccharomyces cerevisiae genome*. Nature, 2002. 418(6896): p. 387-91.
2. Giaever, G., et al., *Chemogenomic profiling: identifying the functional interactions of small molecules in yeast*. Proc Natl Acad Sci U S A, 2004. 101(3): p. 793-8.
3. Flaherty, P., et al., *A Latent Variable Model for Chemogenomic Profiling*. Bioinformatics, 2004. Accepted Conditionally.

Numerous talks were given during the period of which this topic was a portion. A full list of invited talks during this project period is available upon request.