Resources for Gene Discovery

Hunting for disease genes is not a specific goal of the DOE Human Genome Program. However, DOE-supported libraries sent to researchers worldwide have facilitated gene hunts by many research teams. DOE libraries have played a role in the discovery of genes for cystic fibrosis, the most common lethal inherited disease in Caucasians; Huntington's disease, a progressive lethal neurological disorder; Batten's disease, the most prevalent neurodegenerative childhood disease; two forms of dwarfism; Fanconi anemia, a rare disease characterized by skeletal abnormalities and a predisposition to cancer; myotonic dystrophy, the most common adult form of muscular dystrophy; a rare inherited form of breast cancer; and polycystic kidney disease, which affects an estimated 500,000 people in the United States at a healthcare cost of over $1 billion per year.

The team led by Fa-Ten Kao (Eleanor Roosevelt Institute) has microdissected several chromosomes and made derivative clone libraries broadly available to disease-gene hunters. This resource played a critical role in isolating the gene responsible for some 15% of colon cancers.

Of Mice and Humans: The Value of Comparative Analyses

A remaining challenge is to recognize and discriminate all the functional constituents of a gene, particularly regulatory components not represented within cDNAs, and to predict what each gene may actually do in human biology. Comparing human and mouse sequences is an exceptionally powerful way to identify homologous genes and regulatory elements that have been substantially conserved during evolution.

Researchers led by Leroy Hood (University of Washington, Seattle) have analyzed more than 1 million bases of sequence from T-cell receptor (TCR)

To IMAGE the Human Gene Map

Since 1993, the Integrated Molecular Analysis of Gene Expression (IMAGE) Consortium has played a major role in the development of a human gene map. Founding members of the IMAGE Consortium are Bento Soares (Columbia University, now at University of Iowa), Gregory Lennon (LLNL), Mihael Polymeropoulos (National Institutes of Health's National Institute of Mental Health), and Charles Auffrey (Généthon, in France). Because cDNA molecules represent coding (expressed-gene) areas of the genome, sets of cloned cDNAs are a valuable resource to the gene-mapping community. The cDNA libraries representing different tissues have many members in common. Thus, good coordination among participating laboratories can minimize redundant work. The international IMAGE Consortium laboratories fulfill this role by developing and arraying cDNA clones for worldwide use. *[http://www-bio.llnl.gov/bbrp/image/image.html]*

From the IMAGE cDNA clones, researchers at the Washington University (St. Louis) Sequencing Center determine ESTs with support from Merck, Inc. The data, which are used in gene localization, are then entered into public databases. More than 10,000 chromosomal assignments have been entered into Genome Database (*http://www.gdb.org*). Including replica copies, over 3 million clones have been distributed, probably representing about 50,000 distinct human genes.

The IMAGE infrastructure is being used in two additional programs. At LLNL, the IMAGE laboratory arrays mouse cDNA libraries produced by Soares for the Washington University Mouse EST project (*http://genome.wustl.edu/est/mouse_esthmpg.html*) with sequencing sponsored by the Howard Hughes Medical Institute. Additional clone libraries are being used in a collaborative sequencing project sponsored by the NIH National Cancer Institute as part of the Cancer Genome Anatomy Project to identify and fully sequence genes implicated in major cancers (*http://www.ncbi.nlm.nih.gov/ncicgap*).