IPRO 318

Searching for Novel Drug Targets

ILLINOIS INSTITUTE OF TECHNOLOGY

Background:

In the *post genome* era, rationale drug design based on structure-function relationship and protein–protein interaction is becoming the most exciting drug design venture. Finding novel drug targets is even more exhilarating. Although there has been a significant and rapid progress in the genome-and proteome-based high-throughput screening methods, the functions of a large portion of the genes in the human genome remain yet to be uncovered. Identifying the functions of all those proteins in a short time is unlikely. Thus, identifying new drug targets among the proteins with unknown function is the aim of this IPRO.

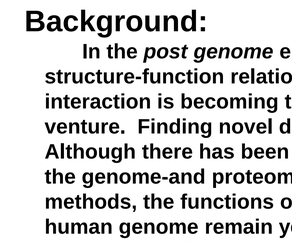
Methods:

Our approaches is shown by the flowchart at the center. Our team was divided into four groups. The effort of each group was largely focused on one the following tasks:

1. Construction of the three databases (see the flowchart), mainly by collecting information on gene-disease relations for the "disease" database, "filtering out" all the hypothetical human genes in the GenBank for the hypothetical gene database, and BLASTing those two databases against each other get construct a database to search for new drug targets. (For, results please visit our website.)
2. Studying the property of putative high value genes (genes which can serve as new drug target and generate economical profit for pharmaceutical companies) by molecular modeling, protein expression and structural determination. (For results, see the figures.)
3. Identifying interaction proteins for putative high value genes by two-hybrid screens. (For results, see the figures.)
4. Construction of a website with searchable database. (For results, please visit our website.)

Result:

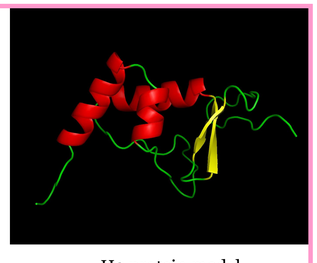
The color of a picture frame corresponds to a task in the flowchart highlighted with the same color.



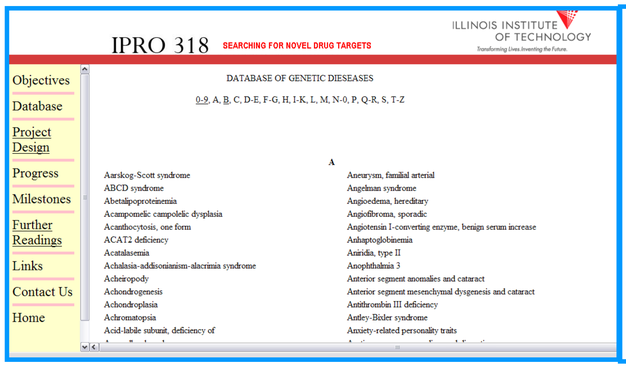
Two-Hybrid Screen for Interacting Protein (318H1)

Blue Colonies for UHXL on Dropout Plates Indicating Putative Interactors

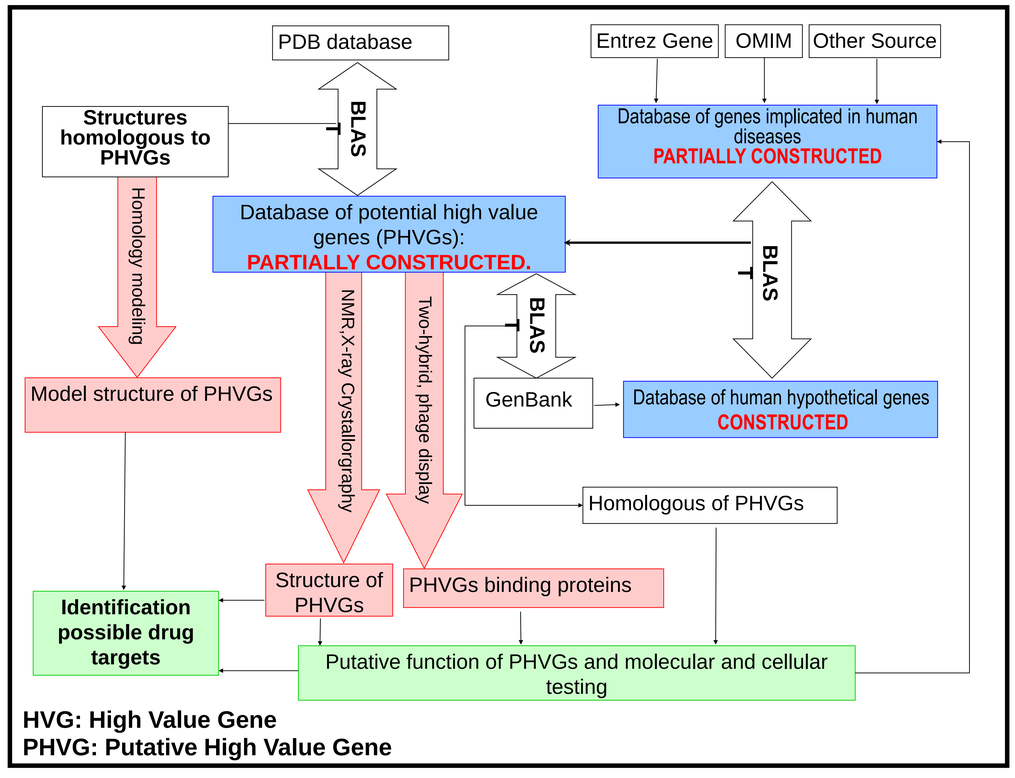
H2 protein model

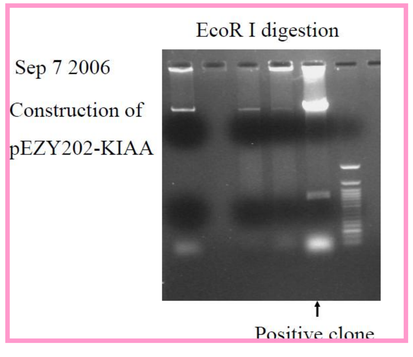


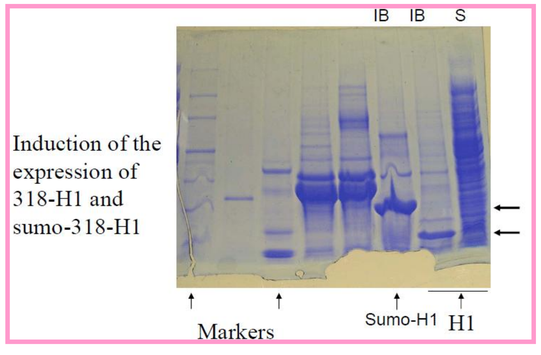
H3 protein model

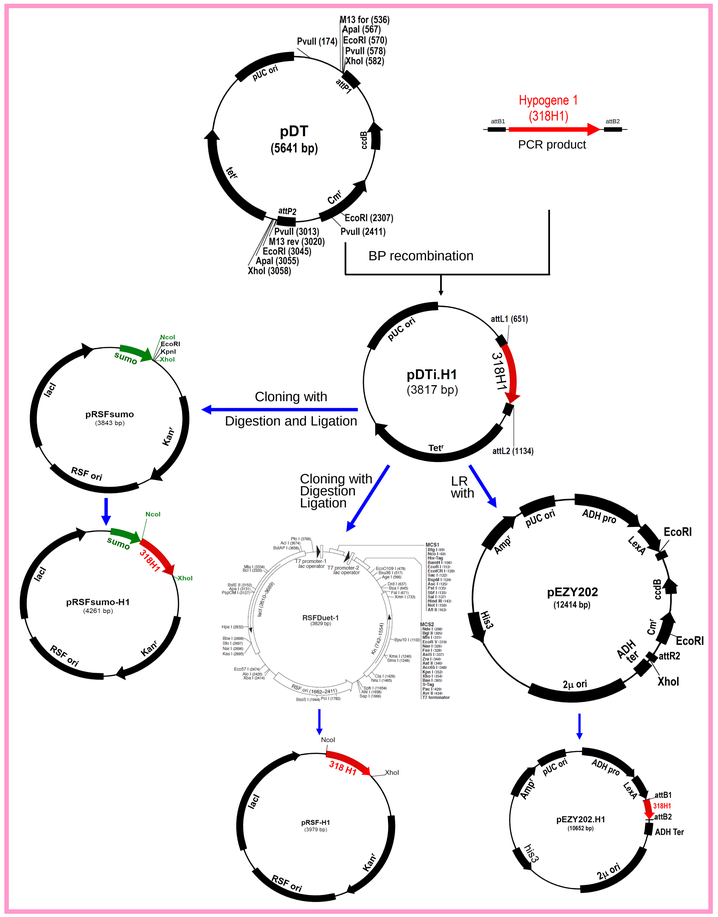


http://snx2.biol.iit.edu/ipro318/









Discussion:

A previous IPRO team built a disease gene database containing ~300 human genes which are involved in diseases. They also built a hypothetical gene database based on the GenBank database at that time and identified a number of putative genes for testing.

Our team has expanded the disease gene database to over 2000 genes. We also updated the hypothetical gene database based on the current GenBank. We have constructed a website for the databases. We started to work on four of the genes identified by our previous team. We temporarily named these gene Hypothetical gene 1, 2 , 3, and 4 (H1, H2, H3, and H4 also name KIAA). We have started working on the expression of those genes, identifying interactors of those genes.

The objective of this project is to discover possible drug targets for future reference. Future IPRO teams will be developing from the framework we established. Specifically, the databases still need to be expanded to cover more diseases. The website need to be more easy to search for disease information. For validation, in a later stage for putative novel drug targets which have passed the first round of validation, DNA microarray, proteomic techniques, and other molecular and cellular techniques will need to be used.

Reference:

- *NCBI Protein Database* www.ncbi.nlm.nih.gov/entrez/
- *Online Mendelian Inheritance in Man* www.ncbi.nlm.nih.gov/omim/
- *"Current Protocols in Molecular Biology" Chapters 13 & 20 from the Yeast Protocols Handbook – Clontech*