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GENSCAN: A Powerful Tool for Gene Prediction

by Laura Roundy

Will it ever be possible to uncover the mystery of cancer? Will we ever understand the biochemistry behind genius or mental illness? Will it ever be possible to control toxic waste? These may seem like impossible problems to solve, but scientists working in genome research are making a detailed map of the genetic landscape that could provide the raw material for finding solutions.

The complete set of instructions for making an organism is called its genome. A genome contains the master blueprint for all cellular structures and determines, among other things, how the organism looks, how well its body metabolizes food or fights infection, and sometimes, how it behaves. In 1990, The Human Genome Project (HGP) was launched by the US Department of Energy and the National Institutes of Health to identify and map the human genome. This knowledge could revolutionize biological research and medicine into the 21st century and beyond. New ways to diagnose, treat, and prevent genetic disorders are the ultimate goals of genome researchers. An understanding of the basic blueprints of biology could also lead to benefits in the fields of agriculture, health care, energy, and the environment.

The HGP hopes to map the full human genome by the end of 2003. However, only about 5% of the human genome is known to include the protein-coding sequences (exons) of genes. The other 95% or so consists of intron sequences and other noncoding regions. Biologists are primarily interested in the information contained in the protein-coding sequences of genes. Locating and identifying these sequences from the rest of the genome is a huge hurdle that must be overcome before these advances in medicine and biology can be realized. That's why gene prediction programs like GENSCAN are so vital.

GENSCAN is a powerful software tool for extracting biologically important information from bulk human/vertebrate or plant genomic DNA. The software was developed by Dr. Christopher Burge in the research group of Dr. Samuel Karlin in the Department of Mathematics at Stanford. Dr.

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The Ins and Outs of Patenting at Stanford's OTL

by Stefani Yee

For most people, patents are associated with inventions. Researchers who walk into OTL, enthusiastic and excited about their new discoveries, often assume we will automatically file patent applications on their inventions as soon as possible. While it is true that patents are often an integral part of the licensing process, the decisions to file, when to file, and what kind of application to file must be made carefully. OTL spends approximately 2 million dollars a year on patent expenses; however, we only file patent applications on 1 out of every 3 invention disclosures we receive.

To better explain the role patents have in the licensing process, let's use the hypothetical situation of Professor Ivan Hoe. Professor Hoe has invented Weedestroy, a new weedwhacker that uses a laser to destroy weeds at their roots. Once treated with Weedestroy, weeds never grow back. The OTL Associate who is assigned Professor Hoe's invention reviews the disclosure and notes that Professor Hoe plans to discuss Weedestroy at the 1999 Weed Symposium next month. In addition, an abstract of the presentation will be published in the Symposium Proceedings. Professor Hoe is very enthusiastic about filing a patent application on Weedestroy, which he believes will revolutionize gardening and generate thousands of dollars in licensing income.

After doing some searching on the Internet, looking through trade journals, and talking with a patent agent, the Associate decides Weedestroy is probably patentable. However, she is unsure the gardening market needs or wants such a device. She makes a few calls to contacts within the gardening industry who tell her it's an interesting idea and probably commercially useful. Typically, OTL likes to be fairly certain that an invention can be licensed before filing a patent.

Soon the Weed Symposium rolls around. The Associate decides to file a provisional patent application, which contains a specification describing the invention but no claims. A provisional is less expensive than a regular patent application and is not examined by the US Patent and Trademark Office (USPTO). However, the provisional does secure the

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Editor
Kirsten Leute

Office of Technology Licensing (OTL)
Stanford University
900 Welch Road
Suite 350
Palo Alto, CA 94304
Campus M/C: 1850
Ph. (650) 723-0651
Fax (650) 725-7295
"http://www.stanford.edu/group/OTL/"

Director
Katharine Ku

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To learn about a specific technology or to disclose one of your own, contact us at the above address.

Ins and Outs of Patenting...

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filing/priority date before the Symposium and gives the Associate one year to decide whether to file a regular patent application. The Associate also wants to secure the priority date because unlike the US, which allows inventors to file patent applications for up to one year after commercialization or publication of an invention, the rest of the world requires inventors to file patent applications before such commercialization or publication. Should Weedestroy be marketable in non-US markets, the Associate wants to be able to file foreign patent applications.

With the priority date secure, the Associate is able to spend more time researching potential Weedestroy markets. She initially finds that regular hoes have saturated the market. However, Professor Hoe, who has been furiously thinking of new applications for Weedestroy, suggests she contact companies that make gardening implements for the physically disabled. He says people who cannot bend over to pull weeds will embrace Weedestroy. The Associate calls the chief technical officer (CTO) of Weedease, which is just such a company. The CTO loves the idea of Weedestroy and licenses it exclusively right away.

Weedease has a small, but growing market in the US. It also has manufacturing plants in Ireland and Australia, where there are Weedease retail stores. In addition, the CTO's brother regularly imports Weedease products into Tunisia, where he runs a chain of discount bazaars. Weedease wants patent coverage in all countries where it will be making, using, or selling Weedestroy.

Before the one year anniversary date of the provisional patent application filing, the Associate files a regular US patent application and a Patent Cooperation Treaty (PCT) application. The PCT application allows her to then file patent applications in Ireland and Australia, both of which belong to the PCT. Since Tunisia is not a member of the PCT, the Associate will have to file in that country separately. Foreign filings are very expensive and the Associate estimates she will spend around $25,000 for patent coverage in Ireland, Australia, and Tunisia. Luckily, Weedease has agreed to reimburse OTL for all foreign patent expenses.

As the months roll by, Weedease sells increasing numbers of Weedestroys and generates income for Stanford and Professor Hoe. About two years after filing the regular US patent application, the US PTO sends a letter announcing the patent has been allowed and will issue. Professor Hoe is overjoyed at the news and his inventive spirit begins to stir anew. A few weeks later he meets with the Associate to show her an improved Weedestroy, the Weedestroy Plus. The Weedestroy Plus contains a specific wavelength of light that not only zaps the roots of weeds, but also reduces the entire weed to compost instantaneously. The Associate contacts Weedease, which immediately wants to license Weedestroy Plus. Accordingly, OTL files a continuation-in-part (CIP) application. The CIP is filed during the lifetime of the earlier application and repeats some or all of the earlier application, while adding new information not contained in the earlier application. When the CIP application issues, no one else can legally make, use, or sell the Weedestroy Plus without taking a license.

Happily for Weedease, Professor Hoe, and Stanford, Weedestroy Plus is a hit not only among physically challenged gardeners, but all gardeners, due to its ability to instantaneously compost. Weedestroy Plus becomes one of the most visible licensed products from Stanford and receives glowing reviews from every gardening magazine.

This abbreviated description of a hypothetical invention and licensing process shows one example of how patents are used in the licensing process. As you can see, the patentability of an invention alone does not control OTL's decision to file a patent application. The nature of the invention, the market, and the response we get from potential licensees are all factors that must be considered when deciding if, when, and how to obtain patent protection for an invention. Should you have any questions about patents and your invention, please contact OTL at 650-723-0651 or visit our website at http://www.stanford.edu/group/OTL. ♣

A Sampling of Licenses Granted by OTL in the Last Quarter

Docket(s)	Title(s)	Uses	Licensee(s)	License Type
S79-066	"Mouse Hybridomas"	Biological Material	BioGenex Lab.	Non-exclusive
S89-011	"Protege-II"	Knowledge Acquisition Soft.	Greenstone	Non-exclusive
S95-115	"Cy7-APC"	Fluorescent Probe	Caltag, BD-Pharmingen	Non-exclusive
S96-125	"Detection of Molec. Interactions"	Screening Assay	Tropix	Field Exclusive
S97-009,etc	"Cavity Ring-Down Spectroscopy"	Minute Amount Measuring	Informed Diagnostics	Exclusive
S97-083	"EMOTIF/IDENTIFY/SCAN"	Protein Identification	Scios	Non-exclusive
S97-118	"Lymphocyte Progenitors"	Immunotherapy	Systemix, Inc.	Excl. Option
S97-161	"Bi-Axial Texturing"	Superconductivity	Elec. Power Research Inst.	Exclusive
S97-180	"Endoskeletal Hand"	Artificial Hand	Hosmer Dorrance Corp.	Exclusive
S97-500	"Sondius-XG™"	Sound Synthesis	Korg Research & Devel.	Non-exclusive
S98-142	"Catheter Sys. for Cardiac Delivery"	Drug Delivery	TherOx	Excl. Option

OTL Celebrates Licensed Products and $61 Million

On October 14, 1998, OTL threw a party to honor many inventions that have made it to the market place and to commemorate reaching over $61 Million in total income for fiscal year 1997-1998.

Each commercialized product had its own display that was viewed by the many guests who joined the celebration. These exhibits are now on display at the OTL office. Please come by and see our new museum of Stanford inventions that have been incorporated into commercial products. We hope to continually add to this museum in the coming years.

Dave Bloom(l) and Francisco Sandejas, two of the inventors of "Deformable Grating Modulator," Stanford Docket S91-126. This technology was commercialized by Silicon Light Machines and is displayed on the table.

GENSCAN...

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Karlin's research group is focused on the development of mathematical and computational techniques and tools for the analysis of DNA and protein sequences. Dr. Karlin is widely known for his development of "score statistics," the theory behind the BLAST program for comparing a DNA or protein sequence against a sequence database. Other computer programs for analysis of biomolecular sequences according to new statistical methods are under continuous development (visit their web page at http://gnomic.stanford.edu/).

The GENSCAN program takes as input a raw, unannotated genomic sequence of virtually any length and outputs a set of predicted gene locations, describing the precise intron/exon organization of the gene and the predicted amino acid sequence of the encoded protein. Unlike most other gene prediction programs, GENSCAN can predict the location of multiple genes per sequence. GENSCAN is based on models of biological signals such as splice sites, promoters, and translation initiation sites, not homology information. Therefore, it provides information that is independent of and complementary to that provided by standard database similarity searching methods such as BLAST.

Identifying novel genes in human genomic DNA is the most important application of GENSCAN. However, researchers and companies are using GENSCAN for many other applications. For example, the software can be used to help find disease genes and to identify potential peptide drugs and drug targets. GENSCAN can also be used to analyze mRNA sequence data to predict open reading frames and the presence of artifacts such as included introns. Researchers working in agricultural genomics can use the software to find genes in plant genomes such as *Arabidopsis* and maize. Plant genes have potential applications such as genetic engineering of crops to increase food production or to make them more drought or disease resistant.

Dr. Burge has created a web site where an individual genomic sequence can be entered. The output is a list of one or more predicted genes within that sequence. Researchers are welcome to access the GENSCAN web server at http://CCR-081.mit.edu/GENSCAN.html. Many companies—from large pharmaceuticals to small biotech start-ups—have taken site licenses to GENSCAN.

Dr. Burge is continuing his research in bioinformatics as a postdoctoral fellow at M.I.T. He is currently working on computational approaches to the study of pre-mRNA splicing and intron evolution in the research group of Dr. Philip Sharp at the Center for Cancer Research. Dr. Sharp and Dr. Richard Roberts first discovered introns in 1977 and the Sharp laboratory has been studying RNA splicing and related problems ever since. RNA splicing is the process by which introns are removed from the RNA copy of a gene before protein synthesis.

As the focus of the human genome project shifts from mapping to large-scale sequencing, the need for efficient methods for identifying genes in anonymous genomic DNA sequences will increase. Gene identification tools such as GENSCAN are filling that need. Identifying these genes and characterizing their functions will be an important step toward unraveling the manifold mysteries of life.

Companies may obtain a site license to the software by contacting Linda Chao at (650) 725-9408 or linda@otlmail.stanford.edu. ♣

Technology Spotlight: Track 'n Find

Could it be possible to never lose your keys or glasses again? An ingenious device called Track'n Find could make this a reality.

The Track'n Find was created to be compact, convenient and easy to use. It consists of a master unit to lead you to your lost item and satellite units that you attach to often misplaced items. The master unit has an LCD display with an arrow-shaped bar graph that visually indicates to the user the strength of the response signal received from the satellite unit. This points you in the direction of your lost object along with an audible signal that increases in noise level and rapidity as you move closer to your object (similar to a Geiger counter).

Mery and Bryan Clausen, Sr., with their first prototype of the Track'n Find

The satellite units come in two types. A larger unit can be worn by people or animals either on a belt or on a wrist like a wrist watch. The smaller units are passive strips intended to attach to smaller items. These passive strips have no power source and simply re-rediate the radio frequency sent out by the master unit.

The principles behind the Track'n Find are relatively simple. The master unit sends out a radio frequency signal with an identity code that is picked up by the selected satellite unit or passive strip. The satellite unit transmits a signal back to the master unit. The strength of the signal is indicated on the LCD display.

Track'n Find has many intended uses including a simple version to be used as a high tech toy, and an enhanced version for general use.

Track'n Find was granted U.S. patent No. 5,771,002 on June 23, 1998. The inventors have built a prototype that can find up to six different frequently missing items, but the actual commercial product could search out many more.

OTL is looking for a company to bring this product to market. For more information or to discuss a license for Track'n Find, please contact Jon Sandelin at jon@otlmail.stanford.edu or (650) 725-9404.

Inventors: William C. Creek, Marvin J. Wahl, Bryan L. Clausen, Sr., Mery Clausen, Bryan Clausen, Jr.

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Office of Technology Licensing
Stanford University
900 Welch Road, Suite 350
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