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GENOMICS AT GENENTECH

Developing innovative therapies through expertise in biology

Genomics: An Overview

In the years to come, molecular biologists will reflect on the date June 26, 2000 as a milestone in genetics just as today's scientists think of Watson & Crick's deciphering of the double-helix structure of DNA in 1953. June 26, 2000 will be known as the day scientists announced the sequencing and assembling of the first rough draft – about 99 percent – of the genetic code that makes up the human genome.

While the race to sequence the entire human genome has been underway since 1990, a parallel effort has been occurring within companies such as Genentech to utilize genomic tools as a means to expedite the process of identifying genes and proteins that may have therapeutic potential.

The following pages discuss Genentech's unique position within the biotechnology industry to apply genomics to powerful drug discovery and foundation development. Genentech's genomics efforts have enabled the company to:

- Accelerate the time to discover and develop novel targeted therapies
- Build an extensive portfolio of marketed and pipeline protein therapeutics
- Further the understanding of diseases at the molecular level
- File over 1,200 patent applications on potentially novel, full-length DNA sequences with data on the biological activity or utility of the encoded proteins. (We believe we were the first to file on 800 significant proteins as part of the 1,200 patent applications.)

Genentech's genomics program is built on biology. Scientists at Genentech have been utilizing genomic-like technologies for the past 27 years with goals that have not changed – finding genes and proteins with therapeutic value, filling

unmet medical needs and improving patients' lives. This strategy has yielded 15 products based on Genentech science currently on the market, as well as a robust pipeline with approximately 20 new products and indications.

Genentech's ability to utilize genomics tools to accelerate drug discovery is the result of:

- Twenty-seven years of experience developing protein-based therapeutics
- A focused approach to understanding the biology of the genes and proteins involved in disease
- Integration of innovative technologies developed at Genentech and accessed through external collaborations
- Scientists with diverse backgrounds and experience striving toward a common goal
- A multi-disciplinary approach to identifying and validating novel protein drug targets

By capitalizing on Genentech's expertise in biology and the increasing speed of genomics research and discovery, the company plans to advance up to four new drug candidates into clinical development every year for the next three years and more than four into preclinical development annually.

Over the past decade, genomics has become a major research tool at the company, with the majority of Genentech's recent efforts focused in three key areas: oncology, immunological disease, and vascular biology. Genomics has not only played a role in the discovery of new drugs but has also enabled Genentech to provide both prognostic and therapeutic information that will change the practice of medicine. Genentech expects that within the next five to 10 years, its entire drug pipeline will have been influenced to some extent by its genomics technologies.

The Science Behind Genomics

At its core, genomics starts with deoxyribonucleic acid (or DNA) organized into structures called chromosomes. The DNA necessary to carry out all of life's activities is present in the nucleus of every human cell.

DNA is made up of the four nucleotides (A, Adenine; C, Cytosine; G, Guanine; and T, Thymine) that are arranged in a specific order and provide the cell with instructions on what functions to complete. Knowledge of how these four letters are strung together to form genes that encode functional proteins and how these proteins are expressed and interact with each other is essential to discovering new medicines to improve patients' lives.

Making a protein, the body's workhorse

Tens of thousands of genes are encoded by the human genome. Less than 10 percent of the entire human genome is comprised of genes. The rest of the genome encompasses what is commonly known as “junk DNA,” or DNA that does not serve a yet-identified purpose. Genes carry the necessary information to produce the proteins that perform all of the necessary functions within the body. To create a protein, messenger RNA (mRNA) – a copy of one DNA strand of a gene – is sent out of the cell's nucleus and into the cytoplasm, where the protein is synthesized by ribosomes that recognize and link together specific amino acid chains that make up a protein.

Unlike DNA, which is fairly stagnant in its three-dimensional structure, proteins are dynamic molecules with the ability to adapt to various environmental and physiological factors. This flexibility allows a protein to transmit information from one biochemical pathway to another. Changes to the shape of a protein can activate, inactivate, or affect the function of a protein. Although these properties make the study of proteins complex and difficult, Genentech scientists have vast experience in this arena.

Here is a look at this process at its most simplistic level:

DNA → gene → mRNA → protein → network/pathways of interacting proteins → organism biology

Information gathered at any one of these levels can play an important role in identifying areas of scientific interest. Many companies and research institutions are focused on a specific step of this process, for instance sequencing DNA and selling databases or identifying different mRNA expression levels through microarray (chip) technology.

However, it is the integration of many different technologies and know-how at all four of these levels, coupled with an intense focus on understanding the biology of how each one of these parts interacts with the entire disease process, that best describes how Genentech utilizes its genomics capabilities to identify novel drug targets with therapeutic potential.

Genomics as Drug Discovery Tool

Unlike some biotechnology companies that have focused on a few genomic research technologies, Genentech has developed an integrated foundation to provide its researchers with access to the most advanced technologies and biological information necessary to make important decisions about potential drug candidates. This integrated platform brings together:

- Public and private databases
- Bioinformatics capabilities such as Genentech's own Secreted Protein Discovery Initiative
- Proprietary microarray technology built by Genentech scientists with external DNA chip technology
- Cell-based assays, knock-outs, transgenic animal models and antibody technology to validate potential drug targets

Most importantly, genomics at Genentech is about people. While Genentech's genomics capabilities have allowed an acceleration in the speed at which information about a specific gene or protein can be found, the backbone of Genentech's research efforts is the people – the molecular biologists, pathologists, and computer scientists who work together to achieve a common goal. Tools are only as useful as the person using them. Based on 27 years of experience developing biotherapeutics, Genentech scientists have acquired the ability to know the right questions to ask and how best to seek the answers they need.

The drug discovery process

Mining the databases

Drug discovery at Genentech begins with information – information on specific genes and their related proteins. Genomics has significantly increased Genentech's ability to provide individual scientists with the information necessary to understand disease at the molecular level.

The hunt for new information starts with Genentech's bioinformatics program and Secreted Protein Discovery Initiative (SPDI), an initiative started in 1996 and completed in 2001 that generated a database of genes cloned, proteins made and assay results produced by Genentech. In order to conduct the initiative and create this database, Genentech scientists took advantage of the vast amounts of genomic information available through GenBank, the Human Genome Project's worldwide database, and through a collaboration with Incyte Genomics to access its Expressed Sequence Tag (EST) subscription database.

Genentech's proprietary SPDI program

The scientists in SPDI focused on identifying the thousands of secreted proteins from the human genome. The impetus behind SPDI was the premise that secreted proteins – transmembrane receptors that transfer information inside cells, and ligands, molecules that activate receptors on the surface of cells – are the proteins with the highest likelihood of becoming therapeutics. Over the

years, secreted proteins have proven to be the most successful drugs to come from biotechnology research, including insulin, which was first made by DNA technology at Genentech. Secreted proteins can become drugs themselves, such as tissue plasminogen activator (t-PA), or can be used as target antigens or receptors (HER2) for an antibody therapy such as Herceptin® (Trastuzumab).

To identify secreted proteins, which make up about 10 to 15 percent of known proteins, scientists in Genentech's bioinformatics group designed sophisticated computer algorithms that recognize a specific signal sequence of nucleotides common to genes that code for secreted proteins. Each night the bioinformatics group (about 20 people) would download the new sequence information from the GenBank system and run its algorithms with this information to seek out new genes. From signal sequences that were identified, Genentech scientists physically cloned the full-length gene. Often a protein was developed and evaluated against known proteins to see whether it was related to a specific family of proteins. This process gave scientists clues as to the protein's potential function and therapeutic utility.

Another example of the power of SPDI was the sequencing information obtained from model organisms. When the complete genome of *C. elegans* (round worm) was sequenced in 1998, scientists at Genentech ran the sequence information against their SPDI algorithms to identify potential secreted proteins from the 19,000 genes of *C. elegans*. Within a month, scientists had identified potentially new secreted proteins and searched the genomic databases for human homologs, or genes with a similar sequence, to determine whether they were unique. This strategy can be used on all model organisms as their sequences become available.

The SPDI program cast a wide net that provided Genentech's world-class molecular biologists with the raw genetic data needed to identify novel drug targets and therapies. As part of SPDI, Genentech identified and sequenced more than 1,000 genes that encode secreted proteins, with a majority of these having their full-length sequence cloned. In large part due to SPDI, Genentech has filed more patents on novel secreted proteins than any other biotechnology company and established a strong intellectual property position.

The art of the assay

With its biology expertise, Genentech has created a vast library of assays for scientists to access in order to determine the function of a protein and find answers to other important questions. In their most simple form, assays provide information to the scientist on how a protein *changes* a biological system and how the protein affects change. From here, a scientist can begin to understand the potential applications of the protein.

Assays come in many different forms, including:

- Cell-based tissue culture assays
- Microarray (chip) expression technology
- Knock-out animal models
- Transgenic animal models
- Antisense
- Antibodies

Evaluating a novel protein through a series of cell-based assays is in many instances the first step in determining the protein's function. Certain cell-based assays can be completed in a matter of days, helping to define the direction of later studies.

Rather than focusing on a specific disease area and "guessing" that a certain protein will have application in that area, all identified proteins are put through a series of approximately 30 cell-based screens. Each of these assays is designed to evaluate the protein for activity across numerous disease areas of interest to Genentech, including oncology, immunology, and others.

Using this system allows biology to indicate the right decision. Scientists may find that a protein may not have activity in cancer, but has significant involvement in cardiovascular disease or is active in both disease processes, which can lead to several different potential therapies.

Targets from chips: Tumor Antigen Project

Over the past few years, microarray technology, also known as DNA chips, has held great promise in expediting the identification and validation of novel drug targets by studying thousands of genes at the same time. At Genentech, the microarray program, also known as the Tumor Antigen Project, is focused primarily on identifying new protein targets in oncology, though the technology is applicable across all disease areas.

Importantly, the microarray program is an example of the power of integrating genomics information, molecular biology, in-house and external capabilities, innovation and people. Some examples include:

- Development of proprietary microarray technology
- Use of Affymetrix's DNA chip technology
- Use of known and novel genes identified through genomic databases and SPDI
- Collaboration with the Pathology department to provide appropriate tumor and normal samples

- Close work with antibody and oncology specialists to validate potential antigen targets

The Tumor Antigen Project seeks to analyze the expression levels of known and novel genes from both tumor cells and normal tissue. A gene that is identified as highly expressed in tumor cells but not normal cells may make a potential antigen target for a therapeutic antibody.

As an example of the progress being made, the HER2 protein that is overexpressed in a quarter to a third of all breast tumors would have been identified in a matter of days using microarray technology that was not available when HER2 was discovered in the late 1980s.

From Concept to Reality

For many, the race to map the human genome was the “end of the beginning.” The more crucial race of understanding how genes cause disease is seen as the first step towards the beginning of the end. While this is a fair analysis when looking across the entire industry, there are several clear examples of how genomics has changed and will continue to change the way medicine is practiced.

Herceptin

While Herceptin was not found using traditional genomics techniques, it has been heralded as an example of the types of drugs that genomics can yield. The FDA approved Herceptin in 1998 as a treatment for women with metastatic breast cancer who overexpress the HER2 protein. In the late 1980s, researchers at the University of California, Los Angeles discovered that HER2 was overexpressed in approximately 25 percent to 30 percent of breast tumors and, importantly, is associated with a more aggressive type of breast cancer and poor prognosis.

The HER2 protein was first cloned by Genentech scientists, and later a humanized antibody was developed at Genentech to specifically target this genetic abnormality in certain breast tumors while limiting adverse events.

While the development of Herceptin is a retrospective example of the utility of genomics, recent studies by scientists at Genentech have shown that the use of Herceptin in treating breast cancer patients is an example of pharmacogenomics as well. Pharmacogenomics is the ability to use genetic information to predict which patients are most likely to respond to a specific therapy.

Recent studies by scientists at Genentech have demonstrated the efficiency of utilizing a different test (fluorescence in situ hybridization or FISH) than the standard to identify patients for treatment with Herceptin. The FISH test

measures HER2 gene amplification rather than immunohistochemistry (IHC). In August 2002, Genentech received approval from the Food and Drug Administration to include information about the FISH breast cancer gene-detection test into the labeling of the product insert of Herceptin.

Getting the Best Molecules: From Discovery to Development

Genomics is about the parallel integration of people and technology. Researchers working in parallel with each other and analyzing novel genes and proteins as part of a larger network of information has given Genentech scientists the ability to ask tougher questions and obtain better answers than ever before in drug discovery.

Genomics has made a significant impact on the drug discovery process at Genentech. While Genentech's mission of finding novel proteins to treat unmet medical needs has not wavered during the past 27 years, genomics research has increased (and will continue to increase) the speed at which Genentech's scientists can gather information to make development decisions.

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