Research at Genentech

Michael Varney, Ph.D.
Vice President, Small Molecule Drug Discovery
Agenda

- Genentech Overview
- Research at Genentech
- Small Molecule Drug Discovery at Genentech
- Project Update
Pharmaceutical Business has Some Difficult Realities

QuickTime™ and a TIFF (LZW) decompressor are needed to see this picture.
Biotech is based on Genetic Engineering, Pharma is based on Chemical Engineering

**Biotech**
- DNA
- Copy of desired protein

Employees:
- Biologists
- Physicians

**Pharma**
- Chemical compound
- High Throughput Screen

Employees
- Chemists
- Chemical Engineers
Both Pharma and Biotech have Created Beneficial Drugs

**Biotech**

- Human Insulin
- Growth Hormone
- Factor VII
- Factor VIII
- Monoclonal Antibodies
  - Rituxan
  - Avastin
  - Synagis

**Pharmaceutical**

- Antibiotics
- Analgesics
- β Blockers
- Statins
- Anti-HIV
- Aspirin

Both have been successful!

- **Infectious disease**
- **Diabetes**
- **Heart Disease**
- **Cancers**
What are Biotech Medicines?

- Biotech medicines use the human body’s own natural defense mechanisms—cells, genes, proteins, enzymes and antibodies—to fight disease. By harnessing natural mechanisms, scientists can find more accurate ways to solve medical problems while producing fewer side effects and unintended consequences for the individual patient.

- Drug discovery involves systematically identifying which protein is causing a problem in the body, and then identifying and engineering a protein or related molecule to correct the problem.

- Recombinant DNA technology is the technology at the foundation of biotechnology and Genentech.
The Growth of Biotechnology

• A short but exciting history…
  Since Genentech founded the biotech industry 32 years ago, it has accelerated at a dizzying pace. At the close of 2005, there were 1,415 biotechnology companies in the United States, of which 329 were publicly held.

• Providing treatments that work today…
  Biotechnology has created more than 200 new therapies and vaccines, including products to treat cancer, diabetes, HIV/AIDS and autoimmune disorders.

• And a promise of an even greater tomorrow…
  There are more than 400 biotech drug products and vaccines currently in clinical trials targeting more than 200 diseases, including various cancers, Alzheimer's disease, heart disease, diabetes, multiple sclerosis, AIDS and arthritis.

*Reference: Biotechnology Industry Organization (www.bio.org), 2007*
Genentech was founded in 1976 by venture capitalist Robert A. Swanson and biochemist Dr. Herbert W. Boyer. In the early 1970s, Boyer and geneticist Stanley Cohen pioneered a new scientific field called recombinant DNA technology.

Though Swanson and Boyer faced skepticism from both the academic and business communities, they forged ahead with their idea. Within a few short years, they successfully demonstrated the viability of using recombinant DNA technology to develop products with practical applications and, in so doing, launched a whole new industry.
Our mission is to be the leading biotechnology company, using human genetic information to discover, develop, manufacture and commercialize biotherapeutics that address significant unmet medical needs.

We commit ourselves to high standards of integrity in contributing to the best interests of patients, the medical profession, our employees and our communities; and to seeking significant returns to our stockholders based on the continual pursuit of scientific and operational excellence.
Genentech: A History of Firsts

- Genentech was the first biotech company.
- Genentech was the first to produce a human protein and the first to clone human insulin using recombinant DNA technology.
- Genentech was the first biotech IPO.
- Recombinant human insulin, developed by Genentech and licensed to Eli Lilly, was the first biotech product on the market.
- Genentech’s growth hormone medicine was the first recombinant biotech drug manufactured and marketed by a biotechnology company.
- Rituxan was the first therapeutic antibody approved for cancer in the United States.
- Herceptin was the first therapeutic antibody approved for metastatic breast cancer.
- Xolair is the first humanized therapeutic antibody for the treatment of asthma and the first approved therapy designed to target the antibody IgE, a key underlying cause of the symptoms of allergy related asthma.
- Avastin was the first anti-angiogenesis therapy approved for treating cancer patients.
- Tarceva was the only drug in the EGFR class to demonstrate in a Phase III clinical trial an increase in survival in advanced non-small cell lung cancer patients.
- Lucentis was the first treatment to improve vision in up to 40 percent of patients with wet age-related macular degeneration.
Genentech Today

- Approximately 11,000 employees
- $11.7 billion in total operating revenues (2007)
- World leader in biotech manufacturing, with more FDA-approved manufacturing capacity for the production of biotech medicines than any other company
- Largest single-site biotechnology research facility in the world, ~550,000 square feet of research space for 900 scientists
- Four primary sites (South San Francisco, Vacaville and Oceanside, California and Hillsboro, Oregon)
- Portfolio:
  - Therapies for breast cancer, colon cancer, lung cancer, non-Hodgkin's lymphoma, age-related macular degeneration, rheumatoid arthritis, allergic asthma, psoriasis, cystic fibrosis, heart attack, stroke, and growth hormone deficiency
  - Four cancer medicines that have been shown to extend survival
  - More than 100 projects in clinical development
Campus View
Genentech has since launched many successful drugs
Medicine development consists of four critical stages:

**Research**
The wellspring of potential products.

**Development**
The bridge from basic science to patient benefit.

**Commercialization**
Educating the medical community about our therapies.

**Manufacturing**
A complex process where Genentech leads.
A World-Class Research Organization

Genentech scientists:
- are allowed discretionary research time
- consistently publish important papers in peer-reviewed journals
- have secured approximately 6,900 current, non-expired patents worldwide, with 6,000 patent applications pending worldwide
- have received national awards and recognition for their work

In 2005, Marc Tessier-Lavigne, Senior Vice President of Research at Genentech, was elected member of the National Academy of Sciences in recognition of 20 years of outstanding scientific contributions.
In 2006, Napoleone Ferrara, Genentech Fellow, was also elected to the Academy.
Executive Vice President of Research Richard Scheller has been a member since 2000.

Ferrara also received the American Association of Cancer Research's annual Bruce F. Cain Memorial Award in 2005 and the 2006 General Motors Cancer Research Award.
Positioned for future growth

- We have a broad and robust pipeline of more than 100 projects, with a focus on oncology, immunological diseases and disorders of tissue growth and repair.

- We are dedicated to putting our therapies through tough clinical testing in order to demonstrate their potential power as therapeutics.

- We are a leader in targeted therapies and are looking into the possibility of combining targeted therapies. We are in a unique position to leverage our own pipeline due to the versatility of several of our molecules.

- In 2007, we added eight new molecular entities (NMEs) into clinical development.
Strong Top-Line Performance

Total Operating Revenues

- Contract Revenues
- Royalties
- Total Product Sales

Total Operating Revenues ($ in millions)

- 2000: $1,514
- 2001: $2,044
- 2002: $2,584
- 2003: $3,300
- 2004: $4,621
- 2005: $6,633
- 2006: $9,284
- 2007: $11,718 (non-GAAP)
Horizon 2010 Goals

Long-term strategy for growth

• Our Vision
  Utilize the science of biotechnology to become a leader in revolutionizing the treatment of patients with cancer, immunological diseases and angiogenic disorders

• Our Goals
  - To bring at least 20 new molecules into clinical development
  - To bring at least 15 major new products or indications onto the market
  - To become the number one U.S. oncology company in sales
  - To achieve an average compound annual non-GAAP EPS growth rate of 25 percent
  - To achieve cumulative free cash flow of $12 billion
Our People

The key to our success

• Starting with the founders, Genentech executives recognized that the company’s success depended on its ability to recruit and retain highly qualified and motivated people in all areas of the company.

• Because of our emphasis on finding and keeping the right people, the company is populated by employees who are highly intelligent, entrepreneurial, and driven by a desire to develop novel medicines that help patients.
Employer of Choice

2007 and 2008 List Placements

**FORTUNE**
In 2008, named on the magazine’s annual list of the “100 Best Companies to Work For” - tenth consecutive year on the list

**Working Mother**
In 2007, named one of the "100 Best Companies for Working Mothers" for 15th time

**Science Magazine**
In 2007, named a “top employer in the biotech, biopharma, pharma and related industries” for the sixth year in a row

**San Francisco Business Times**
In 2007, ranked Genentech #1 on its list of the “Best Places to Work in the Bay Area” - third consecutive year on the list
Largest Single Biotech Research Facility (560,000 sq ft)

Research ~ 1100 FTEs

2002-2006
Research Vision

- To be one of the world’s top biomedical research organizations

- To keep the Genentech product pipeline filled with high value therapeutic candidates

- Diverse approaches to modern biology including genetics, transgenic and knock-out technology, animal models of disease, cell biology, biochemistry, in vivo physiology, imaging and bioinformatics

- Balance of early discovery, basic science, and translational research

- Commitment to fundamental understanding of the mechanism of action of our therapeutics and diagnostics to select patients that may benefit
Genentech R & D focus

- Immunology 30%: Xolair Raptiva
- Oncology 50%: Rituxan Herceptin Avastin Tarceva
- Angiogenesis 20%: Lucentis
- Neuroscience Growing:
A Multi-Pronged Approach to Treating Disease

Diverse Therapeutic Platforms

• Antibodies
• Proteins
• Antibody Drug conjugates (ADCs)
• Small Molecules

Diverse Therapeutic Target Types

• External Receptors
• Internal Enzymes
• Secreted Proteins
• Internal Signaling
## Excellence in Genentech Research

#### 1. Innovative Leader In The Industry

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<tr>
<th>Rank</th>
<th>Employer</th>
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<td>1</td>
<td>Genentech</td>
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<tr>
<td>2</td>
<td>Monsanto Company</td>
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<tr>
<td>3</td>
<td>Amgen</td>
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#### 2. Treats Employees With Respect

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<td>Johnson &amp; Johnson</td>
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<tr>
<td>3*</td>
<td>Amgen / Boehringer Ingelheim / Genzyme Corp.</td>
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#### 3. Clear Vision Toward The Future

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#### 4. Work And Personal Values Are Aligned

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#### 5. Loyal Employees

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#### 6. Does Important Quality Research

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Research Leadership Team

**Richard H. Scheller, Ph.D.**
Executive Vice President, Research

**Marc Tessier-Lavigne, Ph.D.**
Senior Vice President, Research
Drug Discovery

**Andy C. Chan, M.D., Ph.D**
Senior Vice President
Immunology & Antibody Engineering

**Vishva Dixit, M.D.**
Vice President
Early Discovery Research

**Michael D. Varney, Ph.D.**
Vice President
Small Molecule Drug Discovery
Small Molecule Drug Discovery
at Genentech
What the Heck is a Small Molecule Anyway?

- A Small Molecule is a compound (chemical) with a molecular weight of roughly 300-600
- Size wise, it is 100-1000 times smaller than an antibody
- A Small Molecule can be delivered through many routes, including orally
- Small Molecules widen target opportunity space because they can hit targets both inside and outside of cells
Synergistic Value of Small Molecules

- Expands available target space, Small Molecules can be developed to attack both intracellular and extracellular targets (50% of cancer targets are intracellular)

- Small molecules complement Genentech’s antibody rich portfolio

- Can be used in scientifically rational combinations to create dominant positions against given tumor types

- Expands the treatment opportunity (Small Molecules can be delivered orally, IV or subcutaneously allowing for many dosing options both within and outside the hospital)
To identify new drug candidates to move forward into Early Clinical Development

Candidates come from Projects

Therefore the Project is the Central Focus of the Organization
Discovery Collaborations are Key to Success

Project as Central Focus

- Medicinal Chemistry
- In vivo Pharmacology
- Protein Structure Production
- Early Leads
- SM Pharmaceutical Sciences
- Safety Assessment
- Biochemical Pharmacology
- DMPK
Early Development Collaborations are Key to Success

- Diagnostics Biomarkers
- Regulatory
- Early Clinical
- Project Management
- SM Pharmaceutical Sciences
- Safety Assessment
- External Contracting
- DMPK

Project as Central Focus
SM Drug Discovery is an Elaborate Sorting Exercise

Target Selection → Cloning and Expression → Target Characterization and Assay Development

← Lead Optimization

Pre-Candidates → Initial Data & Initial “Hits” → High Throughput Screening

← Preclinical Workup → ED Candidate
Optimization in Drug Discovery

Potency

Selectivity

PK

Solubility

The Needle in the Haystack
Four Modes in the Practice of Medicinal Chemistry

• “Conventional” Medicinal Chemistry
• Structure-Based Drug Design
• Combinatorial Chemistry
• Computational Property Prediction
Genentech - Small Molecule Discovery Capabilities and Expertise

- Highly experienced leadership team with a track record of success (over 100 years of Small Molecule experience on Leadership Team)
- Integrated internal Discovery organization of >200 internal scientists
  - Chemistry
  - Biochemical Pharmacology (UHTS, project assay support)
  - DMPK (PK/PD, ADME)
  - Pharmaceutical Sciences (formulation, process development)
  - Translational Biology groups (partnership)
  - Protein Engineering/Structural Biology (partnership)
- Highly collaborative
- Growing rapidly, very successful in hiring top-talent
- Support 200 additional external scientists (collaborations and CROs)
### Genentech - Small Molecule Discovery Collaborators and CROs

- Array Biopharma
- Argenta Discovery
- Piramed Pharma
- CGI Pharmaceuticals Inc.
- The WEHI Institute
- Abbott
- WUXI
Life and Death of a Cancer Cell

Signals for life and growth (survival/proliferation)

Signals for death (apoptosis)

Cell cycle machine

Cell death machine

Global regulators (gene, protein)

Signaling
PI3-Kinase in collaboration with Piramed
PI3K Pathway Commonly Perturbed in Cancer

PI3K p110a oncogenic mutations in:
- 28% Breast
- 30% Colon
- 35% Liver
- <8% Ovarian, Brain, Gastric, Lung

p110a amplified in 30% Ovarian

PTEN mutant/loss in:
- Glioblastoma, melanoma, prostate, endometrial, breast, head and neck, ovarian, lung, hepatocellular, thyroid

Potential for first-in-class inhibitor
Collaboration with Piramed
Structure-Based Design Enabled

PI3K Structure with Inhibitor Bound
PI3Kinase Ligand Binding Pocket
Prostate Orthotopic Model: Western Blot PD Marker in Tumors

2 hr

4 hr

6 hr

control

Drug

pAKT

AKT

control

Drug

pAKT

AKT

control

Drug

pAKT

AKT
PI3-Kinase Inhibitors Slowed the Growth of Prostate Tumors in Mice

![Graph showing the effect of PI3-Kinase inhibitors on tumor growth in mice.](image)
PI3Kinase Inhibitors Regress Established Breast Tumors in Mice via Oral Dosing

![Graph showing mean tumor volume over days post treatment for different doses.]

- **Vehicle**
- **Dose 1**
- **Dose 2**

Days Post Treatment:
-5 0 5 10 15 20

Mean Tumor Volume (mm³):
- 100 200 300 400 500 600
Genentech Research Summary

- Unparalleled basic and translational research
- Cutting-edge technology and biology
- Strong capabilities in oncology and immunology
- Experience, capabilities and critical mass in Small Molecule R&D