Scientific Excellence Transforming Medical Treatment

Genentech Research and Early Development as an Experiment in R&D Productivity

Karl Mahler - Head of Investor Relations
Sean Bohen - Senior Vice President, Genentech Early Development
R&D productivity of Pharma industry

Output relatively flat, while R&D costs have increased

Notes: R&D spend figures may not include overhead components as reported in company annual reports

Excellence in science leveraged to reduce attrition

- Understanding of disease biology
- Leveraging Personalized Healthcare - stratify patient population early on
- Rigorous decision making – transition only most promising projects

Industry success rate 2005-2009

<table>
<thead>
<tr>
<th>Probability of success</th>
<th>Research</th>
<th>Phase 0</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Registration</th>
<th>Launch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Industry: 4%</td>
<td>64%</td>
<td>48%</td>
<td>25%</td>
<td>67%</td>
<td>83%</td>
<td>8</td>
<td>4%</td>
</tr>
<tr>
<td>Roche: 9%</td>
<td></td>
<td></td>
<td></td>
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</table>

R&D allocation: qualitative and quantitative factors

Research & Early Development
- Top down
  - Annual budget allocation
  - Number of phase II transitions

Late Stage Development
- Project driven
  - Unmet medical need
  - Market potential
  - Efficient development
  - Probability of technical success
Personalized Healthcare: benefit for all

Benefit from patient stratification

Today
- Reduced Patient pool
- Price increase /stability

Future
- Time to market
- Faster penetration
- Lower development costs
- Increased market share
Genentech’s legacy

Founded in 1976 by professor Herb Boyer and entrepreneur Bob Swanson based on the idea of using recombinant DNA technology to create therapeutic proteins – *novel and unproven technology at the time*

“I also wanted to bring in scientists that were outstanding and have them have an opportunity to establish their own reputation, get their own recognition. So we tried to set up an atmosphere which would take the best from industry and the best from the academic community, and put them together” – Herb Boyer, Boyer oral history, 1994, 87

**Genentech** – Genetic engineering technology
Cultivating Scientific Excellence: awards and recognitions

- Vishva Dixit, M.D.
  - American Academy of Arts & Sciences membership, 2011

- Napoleon Ferrara, Ph.D.
  - Dr. Paul Janssen Award for Biomedical Research, 2011

- Richard Scheller, Ph.D.
  - Kavil Prize in Neuroscience, 2010

- Art Levinson, Ph.D.
  - Foti Award, 2011
  - Apple Chairman of the board, 2011

- Ira Mellman, Ph.D.
  - National Academy of Sciences Membership, 2011

- Robert Gentleman, Ph.D.
  - American Statistical Association, Statistical computing and graphics award, 2010
Scientific expertise to translate research data into development plans appropriate for each NME

<table>
<thead>
<tr>
<th>Education</th>
<th>Disease Expertise</th>
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<tbody>
<tr>
<td>23 Oncologists</td>
<td>23 Oncologists or Heme/Onc</td>
</tr>
<tr>
<td>1 Pulmonologist</td>
<td></td>
</tr>
<tr>
<td>1 Rheumatologist</td>
<td></td>
</tr>
<tr>
<td>18 MD, PhD</td>
<td>2 Cardiologists</td>
</tr>
<tr>
<td>1 MD, MPH, MS</td>
<td>2 Allergy/Immunology</td>
</tr>
<tr>
<td>1 MD, MS</td>
<td>2 Infectious Disease</td>
</tr>
<tr>
<td>17 MD</td>
<td>2 Neurologist</td>
</tr>
<tr>
<td>12 PhD</td>
<td>1 Ophthalmologist</td>
</tr>
<tr>
<td></td>
<td>1 Psychiatrist</td>
</tr>
<tr>
<td></td>
<td>1 Endocrinologist</td>
</tr>
<tr>
<td></td>
<td>1 Clinical Pharmacologist</td>
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</table>

**Development Sciences:** 130 doctorates and 34 Masters degrees in a group of 370 people
Genentech publications and patents: an external measure of Scientific Excellence

Genentech publications

12 papers were published in Cell, Science and Nature in 2011

US patents issued to Genentech in the last 10 years

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Research Review Committee (RRC)
- Sponsor: Richard Scheller, Ph.D.
- Alternate Chairs:
  - Andy Chan, M.D., Ph.D.
  - Ira Mellman, Ph.D.

Early Stage Portfolio Committee (ESPC)
- Sponsor: Richard Scheller, Ph.D.
- Alternate Chairs:
  - Sean Bohen, M.D., Ph.D.
  - Mike Varney, Ph.D.

Decision Points
- ESR Go
- LSR Go
- ED Ready
- ED Go
- Phase 1 Go
- Phase 2 Go
- LIP ready

Phase
- Discovery Research
- Early Stage Research
- Late Stage Research
- Early Development
- Phase 1
- Phase 2
- Phase 3

Governance
- RRC
- ESPC
- LSPC / CEC

Scientific review
- RRC
- ESPC
- DRC
- Late Stage DRC

Diagnostics
- Formulate diagnostic hypothesis
- Test diagnostic hypothesis
- Stratify/validate
Our approach to drug development

Understanding disease biology is key

Homogeneous diseases

• Defined underlying molecular defects manifesting in a unique set of symptoms
  • *Example:* Erivedge in Basal Cell Carcinoma (BCC)

Heterogeneous diseases

• The majority of diseases caused by multiple defects that manifest as similar clinical syndromes. Currently, we classify and attempt to treat them as a single, homogeneous disease
  • *Example:* Lebrikizumab in Asthma

*We strive to characterize the dominant causal factors in subsets of a heterogeneous disease and tailor the treatment to this well-defined subset*
Our approach to drug development

Develop best in disease treatments

• Decisions are guided by a “Best in Disease” Target Product Profile

• Design early clinical studies with ambitious endpoints – efficacy can often be assessed early with a high bar

• For the heterogeneous diseases, Phase 2 studies are designed to show remarkable efficacy in a target subpopulation – this sometimes requires larger trials

• Technical review of new internal and external data occurs throughout the development process to identify potential issues, reassess probability of success, and modify the development strategy as appropriate
Homogeneous disease – Basal Cell Carcinoma

**Cause:** 90% of all BCCs have abnormal hedgehog pathway signaling

**Baseline**

**Week 8**

**Week 16 - no BCC on biopsy**

**Week 20**
Heterogeneous disease - Asthma

- Bronchoscope
- Trachea
- Left primary bronchus

- Bronchoalveolar lavage cell counts
- Histology
- Transcriptome of epithelial brushings
- Transcriptome of bronchial biopsies
Identification of two distinct asthma subgroups

IL-13 induced genes in epithelial brushings

May be responsive to lebrikizumab (anti-IL13)

May **NOT** be responsive to lebrikizumab (anti-IL13)
Subpopulation of patients derives significantly better benefit from treatment

Results of the proof-of-concept Phase 2 study*

<table>
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<tr>
<th></th>
<th>Relative Mean FEV1 change at week 12</th>
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<tr>
<td></td>
<td>Total ITT population</td>
</tr>
<tr>
<td>Placebo</td>
<td>4.3%</td>
</tr>
<tr>
<td>Lebrikizumab</td>
<td>9.8%</td>
</tr>
<tr>
<td>Difference</td>
<td>5.5% (p=0.02)</td>
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*Corren et al. NEJM, 2011

Incorporation of the diagnostic hypothesis doubled the number of projects transitioning to the late stage development in the past 3 years
75% of gRED molecules are being developed with companion diagnostics (CDx)

**Early Development**

- NME 1
- NME 2
- NME 3
- NME 4
- NME 5

**Phase 1**

- AKT Inhibitor (GDC-0068)
- Anti-PD-L1 MAb
- Anti-HER3/EGFR DAF
- MEK Inhibitor (GDC-0623)
- MEK Inhibitor (GDC-0973)
- Bcl-2 Inhibitor (GDC-0199)
- ChK1 Inhibitor (GDC-0425)
- PI3K Inhibitor (GDC-0032)
- NME 6
- Anti-CD22 vcMMAE ADC
- NME 7 ADC
- NME 8 ADC
- NME 9 ADC
- NME 10 ADC
- NME 11 ADC
- NME 12 ADC
- NME 13 ADC
- Anti-IL-17 MAb

**Phase 2**

- Anti-EGFL7
- PI3K Inhibitor (GDC-0941)
- PI3K/mTOR (GDC-0980)
- Rontalizumab (Anti-INF alpha)
- Anti-LT alpha
- Anti-M1 prime
- Etrolizumab (rhuMAb beta 7)
- Anti-factor D
- Crenezumab (Anti-Abeta)
- Anti-oxLDL

**Status as of March 31, 2012**

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ADCs: New generation of anti-cancer drugs building on T-DM1

**Antibody targeted to tumor antigen**

**Linker stable in circulation**

**Very potent Chemotherapeutic drug**

**Greater therapeutic window**

<table>
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<tr>
<th>Chemo</th>
<th>ADCs</th>
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**Phase 2 study TDM4450g: T-DM1 vs. Herceptin + docetaxel in HER2+ breast cancer**

* T-DM1 significantly improves PFS

<table>
<thead>
<tr>
<th>Median PFS, mos</th>
<th>Hazard ratio</th>
<th>Log-rank P value</th>
</tr>
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<tbody>
<tr>
<td>T+D</td>
<td>9.2</td>
<td>0.594</td>
</tr>
<tr>
<td>T-DM1</td>
<td>14.2</td>
<td></td>
</tr>
</tbody>
</table>

**Proportion progression-free**

**Duration of objective response (months)**

**Phase 3 study EMILIA: T-DM1 vs. Xeloda + lapatinib in HER2+ breast cancer**

- First randomized Phase 3 trial to demonstrate efficacy of T-DM1 in significantly extending PFS in breast cancer
- Data submitted for presentation at ASCO 2012
- Provides a proof-of concept for our extensive ADC portfolio

## gRED Development Portfolio: 35 molecules from Early Development to Phase 2

### Early Development
- NME 1
- NME 2
- NME 3
- NME 4
- NME 5

### Phase 1
- AKT Inhibitor (GDC-0068)
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- Crenezumab (Anti-Abeta)
- Anti-oxLDL

### Status as of March 31, 2012

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• 60 year old woman with platinum-resistant ovarian cancer who progressed through 7 prior therapies was given our novel antibody drug conjugate

• Confirmed partial response after four cycles with an overall 51% reduction in target lesions including the disappearance of some masses

• No treatment related adverse events have been reported for this patient. She continues to be able to work, now in the middle of cycle 10
Antibody drug conjugate (NME ADC)

Evidence of activity in ovarian cancer

Predose

Post cycle 2 dose

Predose

Post cycle 2 dose
• gRED continues to operate on the founding principles of Genentech – maintain an environment where talented researchers and physicians create innovative medicines, guided by science

• We invest in understanding the heterogeneity and underlying causes of disease to target treatments to the appropriate patients

• We set a high bar for moving forward in development and assess efficacy early

• By incorporating a diagnostic hypothesis early in development, we increase the success rate

• We have expanded beyond oncology and are exploring new technologies (ADCs, bispecific antibodies, DAFs) and treatment regimens (novel combinations) to bring more effective treatments to patients
Genentech
A Member of the Roche Group