The challenges facing Japanese bioventures

日本のバイオベンチャーの課題と今後の展開

Fuminori Yoshida

The 9th Kitasato University - Harvard School of Public Health Symposium
The quality of wine is a reflection of the vineyard...
Many Variables Influencing Biotech Ventures

New Technologies
- Genomics
- Proteomics
- Physiomics
- Bioinformatics

Stock Market Volatility

Government Funding

IPO Window
2009

Biotech Ventures

Medical Needs

Big Pharma Companies Seeking Alliances
“NIH received US$10billion as part of Obama’s economic stimulus package”

NIH Director, Francis Collins, was recently quoted as saying...

“The support of biomedical research is a value that is almost unmatched in terms of economic returns, in terms of its improvement in human health... a trend that continues and which can be traced in large part to NIH-funded research.”

“This is an area where Public-Private partnership is going to be crucial. By investing in Public-Private partnerships for therapeutics, the NIH funding essentially de-risks a project to the point where even if the market is not particularly large, it becomes more attractive for a pharmaceutical company or biotech company to pick up a particular product along the way toward a clinical trial and run with it.”
Number of Japanese biotechs has been on the increase, but now...

Source: Japan Bioindustry Association
Why such a huge divide between US and Japan biotech?

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<td></td>
</tr>
<tr>
<td>1. AMGEN</td>
<td>60.1</td>
<td></td>
<td>12,430</td>
<td>14,268</td>
<td>14,771</td>
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<td>3. CELGENE</td>
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<td>537</td>
<td>899</td>
<td>1,406</td>
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<td>4. GENZYMЕ</td>
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<td>2,734</td>
<td>3,187</td>
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<td>4,605</td>
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<td>5. BIOGEN IDEC</td>
<td>14.8</td>
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<td>2,422</td>
<td>2,683</td>
<td>3,172</td>
<td>4,097</td>
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<table>
<thead>
<tr>
<th>JAPAN TOP 5 BIOTECHS</th>
<th>(US$ BIL)</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
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</thead>
<tbody>
<tr>
<td>1. ONCOTHERAPY SCIENCE</td>
<td>.4</td>
<td>16</td>
<td>8</td>
<td>20</td>
<td>33</td>
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<tr>
<td>2. ANGES MG</td>
<td>.2</td>
<td>24</td>
<td>29</td>
<td>17</td>
<td>9</td>
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<tr>
<td>3. SOSEI</td>
<td>.2</td>
<td>4</td>
<td>7</td>
<td>7</td>
<td>1</td>
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<tr>
<td>4. JAPAN TISSUE ENGINEERING</td>
<td>.1</td>
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<td>1</td>
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<td>1</td>
</tr>
<tr>
<td>5. MEDICINOVA</td>
<td>.1</td>
<td>.8</td>
<td>.3</td>
<td>--</td>
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</tr>
</tbody>
</table>

* Figures from FORM10-K annual reports filed with US Securities and Exchange Commission when available
## Top 10 Biotech Drugs in 2008

<table>
<thead>
<tr>
<th>Drug name (maker)</th>
<th>Indication</th>
<th>Revenue for 2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Enbrel (Amgen)</td>
<td>Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis</td>
<td>$5,962M</td>
</tr>
<tr>
<td>2 Rituxan (Genentech)</td>
<td>Non-Hodgkin's lymphoma, rheumatoid arthritis</td>
<td>$5,082M</td>
</tr>
<tr>
<td>3 Humira (Abbott)</td>
<td>Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis</td>
<td>$4,521M</td>
</tr>
<tr>
<td>4 Avastin (Genentech)</td>
<td>Colorectal cancer, non-small-cell lung cancer</td>
<td>$4,479M</td>
</tr>
<tr>
<td>5 Herceptin (Genentech)</td>
<td>Breast cancer</td>
<td>$4,394M</td>
</tr>
<tr>
<td>6 Remicade (J&amp;J)</td>
<td>Crohn's disease, ankylosing spondylitis, arthritis, ulcerative colitis, rheumatoid arthritis, plaque psoriasis</td>
<td>$3,748M</td>
</tr>
<tr>
<td>7 Gleevec (Novartis)</td>
<td>Chronic myelogenous leukemia, gastro-intestinal stromal tumors</td>
<td>$3,700M</td>
</tr>
<tr>
<td>8 Neulasta (Amgen)</td>
<td>Infection associated with chemotherapy-induced neutropenia</td>
<td>$3,318M</td>
</tr>
<tr>
<td>9 Lantus (Sanofi-Aventis)</td>
<td>Types I and II diabetes</td>
<td>$3,159M</td>
</tr>
<tr>
<td>10 Aranesp (Amgen)</td>
<td>Anemia</td>
<td>$3,137M</td>
</tr>
</tbody>
</table>

*Source: BioWorld research from company press releases and SEC filings.*
## R&D Expense Imbalance

<table>
<thead>
<tr>
<th>TOP 5 BIOTECHS</th>
<th>MARKET CAP (US$ BIL)</th>
<th>R&amp;D EXPENSES (US$ MIL)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2005</td>
</tr>
<tr>
<td><strong>US</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. AMGEN</td>
<td>60.1</td>
<td>2,314</td>
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<tr>
<td>2. GILEAD SCIENCES</td>
<td>42.3</td>
<td>278</td>
</tr>
<tr>
<td>3. CELGENE</td>
<td>23.7</td>
<td>191</td>
</tr>
<tr>
<td>4. GENZYME</td>
<td>15.1</td>
<td>503</td>
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<td>5. BIOGEN IDEC</td>
<td>14.8</td>
<td>748</td>
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<tr>
<td><strong>JAPAN</strong></td>
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<td></td>
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<tr>
<td>1. ONCOTHERAPY SCIENCE</td>
<td>.4</td>
<td>11</td>
</tr>
<tr>
<td>2. ANGES MG</td>
<td>.2</td>
<td>38</td>
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<td>3. SOSEI</td>
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<td>4. JAPAN TISSUE ENGINEERING</td>
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<tr>
<td>5. MEDICINOVA</td>
<td>.1</td>
<td>23</td>
</tr>
</tbody>
</table>
Amgen’s early 9-yr drought in capital

**Total Revenues/Income (1980~2001)**

($US in millions)
Epogen®: 1st product launch in Amgen’s 9th year
Cephalon also experienced an early 11-yr drought in capital

Total Revenues/Income (1987~2008)

($US in millions)
Provigil®: 1st product launch in Cephalon’s 11th year
3 key success factors

- **Funding** --- Amgen raised US$350million, and Cephalon $300million by 1st product launch

- **People** --- more than 600 people were employed at Amgen, and 280 people at Cephalon by the time of 1st product launch

- **Product** --- Epogen and Provigil proved to be the cornerstone of each company’s success
From ‘Scientific Discovery’ to ‘Patient Care’
Surviving the ‘Valley of Death’
Funding gap creates challenges for Japanese bioventures

Total VC Investment in biotech: US vs. Japan

($US in billions)

Source: Japan, only annual new investment data available from Venture Enterprise Center; US, findings from the MoneyTreeTM Report, quarterly survey produced by PricewaterhouseCoopers and the National Venture Capital Association (data provided by Thomson Reuters)
Japan NDA review period shows some sign of improvement, but still behind US

<table>
<thead>
<tr>
<th>Drug Category</th>
<th>Median NDA Review Times (months)</th>
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<tbody>
<tr>
<td></td>
<td>Japan</td>
</tr>
<tr>
<td>Standard</td>
<td></td>
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<tr>
<td></td>
<td>--</td>
</tr>
<tr>
<td>Priority</td>
<td></td>
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</table>

* CDER Approval Times for Priority and Standard NMEs and New BLAs; CY 2006 filed figures include applications received in the last 60 days of the calendar year pending filing decision.
Japan Lags Behind Global Market

► 93 Oncology NCEs launched globally 1995 - 2006
► 23 out of these 93 Oncology NCEs launched in Japan
► Average 2.7 yr delay in Japan launches

SOURCE: IMS JAPAN REVIEW 2007 – MARKET TRENDS AND GROWTH DYNAMICS
SymBio’s Mission Statement

“SymBio Pharmaceuticals aspires to be a leading specialty pharmaceutical company in the Asia Pacific Rim, dedicated to addressing underserved medical needs in the areas of oncology, hematology and autoimmune disease.”
Patients are suffering due to this ‘Disease Divide’

Gap is widening…

**THE WALL STREET JOURNAL.**

**Japan’s ‘Cancer Refugees’ Demand More Options**

**Limited Menu**

*Patients Decry System That’s Frugal, Universal But Restricts Choices*

By Peter Landers

TOKYO—With the prime minister looking on, a legislator named Takashi Yamamoto stood before Japan’s parliament last May and told his colleagues that he had cancer. Then he denounced the nation’s standard of cancer care.

“Even when there are treatments, people are being told they will never get better,” he said. “These abandoned cancer refugees are roaming the Japanese archipelago.”

The speech galvanized the parliament, which had been dawdling over a bill that called for more cancer specialists and a permanent role for patients in policy making. Within four weeks, the bill became law.

It was a signal victory for a spreading movement in Japan among patients who want American-style care and drugs for cancer. But the idea of becoming more like the U.S. raises alarms among policy makers. In Japan, the government guarantees that everyone has health-insurance coverage and it pays most of the bills. Masashiro Nakajima, until recently director general of the Health Bureau at the Ministry of Health, Labor and Welfare, says Japan already offers excellent cancer care. With a huge national debt and corporations worried about higher taxes, Japan can’t afford to throw money into treatments and training that offer little hope of significantly extending lifespans, he says.

“If we keep going like this, Japan is going to be crushed under medical expenses,” says Dr. Nakajima, a surgeon who used to treat cancer patients before joining the ministry. Referring to the demand for more specialists, he says: “America did too much of this and that’s why their medical costs have grown.”

The debate in Japan raises the question of where nations should draw the line when modern medicine offers almost unlimited ways to spend money. In the U.S., both private insurers and

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**Disease Divide**

Cancer is Japan’s No. 1 cause of death, while the U.S. cancer death rate is declining. Cancer deaths per 100,000 people:

- **U.S.**
- **Japan**

Sources: Ministry of Health, Labor and Welfare (Japan); Centers for Disease Control and Prevention (U.S.)

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Patients in underserved therapeutic areas need our help
What is Innovation?

Medical Need Oriented

SymBio

Patient-centered Innovation

Technology-centered Innovation

Technology Oriented
Reducing development risk by in-licensing drug candidates with POC established

<table>
<thead>
<tr>
<th>Stage</th>
<th>Number of Compounds</th>
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<tr>
<td>SCREENING</td>
<td>10,000</td>
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<tr>
<td></td>
<td>5,000</td>
</tr>
<tr>
<td></td>
<td>1,000</td>
</tr>
<tr>
<td>PHARMACOLOGY</td>
<td>500</td>
</tr>
<tr>
<td></td>
<td>50</td>
</tr>
<tr>
<td>PRE-CLINICAL</td>
<td>20</td>
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<tr>
<td>CLINICAL</td>
<td>13</td>
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<td></td>
<td>5</td>
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<tr>
<td>MARKETPLACE</td>
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SymBio

IND
NDA
### Where we are today...

<table>
<thead>
<tr>
<th>Product</th>
<th>Lead Indication</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Pivotal</th>
<th>NDA Filing</th>
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<tbody>
<tr>
<td>Bendamustine</td>
<td>Indolent L-NHL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2009 (Oct)</td>
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<tr>
<td>(SyB L-0501)</td>
<td>Aggressive NHL</td>
<td></td>
<td></td>
<td></td>
<td>Initiate Q1 2010</td>
<td></td>
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<tr>
<td></td>
<td>Multiple Myeloma</td>
<td></td>
<td></td>
<td></td>
<td>Initiate Q4 2009</td>
<td></td>
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<tr>
<td>Anti-emeric Patch</td>
<td>CINV</td>
<td></td>
<td></td>
<td></td>
<td>Initiate Q2 2010</td>
<td></td>
</tr>
<tr>
<td>(SyB D-0701)</td>
<td></td>
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<tr>
<td>Hsp32 Inhibitor</td>
<td>Imatinib - resistant CML</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(SyB - 0702)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Initiate Q1 2013</td>
<td></td>
</tr>
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</table>

* In-licensing of 4th drug candidate planned in Q1 2010
Bringing together talent and expertise
• despite being small, we offer big pharma capabilities in oncology
Establishing strategic alliances is a lifeline for biotech companies
NDA for our 1\textsuperscript{st} drug candidate to be filed soon…

Bendamustine Pivotal P2 study efficacy data

<table>
<thead>
<tr>
<th>NHL</th>
<th>Pts</th>
<th>Efficacy</th>
<th>ORR%</th>
<th>CR%</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>CR(u)</td>
<td>PR</td>
<td>SD</td>
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<tr>
<td>Indolent NHL</td>
<td>58</td>
<td>38</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>MCL</td>
<td>11</td>
<td>7</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>69</td>
<td>46</td>
<td>17</td>
<td>6</td>
</tr>
</tbody>
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SymBio attracting capital for development

@100yen/$

US$ Mil

Equity finance
Partnership revenues

A
B
C
D

B+Bex

10
20
7
18
55
9
64
10
89
5
10
10
Issues to be addressed

1. **Where to focus?**
   - Biotech companies need to address high unmet medical needs

2. **How to overcome a long, deep and protracted ‘Valley of Death’?**
   - Joint effort in the creation of Public-Private partnerships
   - Increase in government funding for translational medicine through matching funds
   - Increase in supply of capital to bioventures in clinical stage with funding via VCs, IPO listings, and public market

3. **How to improve overall development and registration efficiency?**
   - More available regulatory options for shorter and clearer registration pathways, such as SPAs, Fast Track & Orphan Drug designation, rolling NDAs and 505-(b)(2) submissions
Furthermore…

4. How to encourage the development of drugs for rare disease with high unmet medical needs?
   • Public-Private partnerships are essential
   • Incentives for innovation must be put into place

5. How to improve the mobilization of quality talent?
   • Willingness to leave big pharma to join bioventures
   • Using one’s experience and expertise for the ‘betterment of society’

6. Risk-taking!
   • “Nothing Ventured, Nothing Gained”
Thank you!