Venture Ideas, EPFL

K. Besseghir, 4.11.2011
Overview of the development of a new drug

- **Lead selection**
- **First in man**
- **Clinical proof of concept**
- **Launch: marketing and sales**
- **Target Identification: Basic research**

**Time (years)**
- Preclinical Proof of concept: 9-13
- Marketing Authorization request: 20

**Cumulative Costs (M$)**
- 50
- 150
- 1’200

© Debiopharm Group 2011
Attrition in drug development

Phase transition probability:

- 0.008% of patents
- 0.1% of preclinical screenings
- 0.9% after preclinical evaluation
- 6% of projects reaching phase I
- 8% of projects reaching phase II
- 29% of projects reaching phase III
- 61% of projects undergoing NDA procedure

Debiopharm field of activity

Debiopharm: the business model

The basic principles

1. « The best way to find innovative molecules is not to do research »;
2. A high level of plasticity can be achieved by delegating sales and marketing to a partner;
3. A high level of reactivity can be achieved by subcontracting a large proportion of drug development activities;
4. Financial independence allows decisions centered exclusively on long-term drug development goals.
Debiopharm: the business model

In practical:

• No internal preclinical research,
• No sales,
• Concentration on drug development,
• Revenues come from royalties and milestones,

This concept has been since incorporated under the acronym NRDO (No Research Development Only).
Debiopharm: general aspects

Debiopharm is a family owned company:

- Founded in 1979 by Dr Mauvernay;
- Headquartered in Lausanne;
- Manufacturing facility in Martigny;
- Total headcount 350 employees;
- Financially independent.
Four strategic priorities

:: Pharmaceutical development of molecules
:: Production & redesign of molecules
:: Companion diagnostics & personalized medicine
:: Access to medicines in emerging economies

Debiopharm Group
Business Model: Bridging Discovery to Market

Discovery → DEBIOPHARM GROUP™ → Market

Academic institutions
Biotech
Start-up
Pharma

Fully funded drug development & innovation

from molecule → value added → to drug approval

© Debiopharm Group 2011
Main Partners

**Licensors**

- **USA**
  - Curis, Mercury Therapeutics, MSM Protein Technologies, Tulane University, Yale University, Ascenta Therapeutics
- **France**: Pharmaleads, TcLand
- **India**: Aurigene
- **Japan**: Nagoya University

**Licensees**

- **World wide**: Sanofi, Novartis
- **Latin America**: Pfizer, Aché, Tecnofarma
- **India**: Dr. Reddy’s Laboratories
- **Europe**: Ferring, Ipsen
- **USA**: Watson
- **Japan**: Yakult
Tools used in drug development:
1. Initial evaluation of a new molecule: novelty / medical need

We evaluate over 1’000 projects per year

Proof of concept ✗
Proof of relevance
## Development of drugs: targets

### Global burden of diseases (WHO)

<table>
<thead>
<tr>
<th>Year</th>
<th>Disease Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>Low respiratory tract infections</td>
</tr>
<tr>
<td></td>
<td>Diarrheas</td>
</tr>
<tr>
<td></td>
<td>Perinatal diseases</td>
</tr>
<tr>
<td></td>
<td>Unipolar depressions</td>
</tr>
<tr>
<td></td>
<td>Cardiovascular diseases</td>
</tr>
<tr>
<td>2020</td>
<td>Cardiovascular diseases</td>
</tr>
<tr>
<td></td>
<td>Unipolar depressions</td>
</tr>
<tr>
<td></td>
<td>Traffic accidents</td>
</tr>
<tr>
<td></td>
<td>Cerebrovascular accidents</td>
</tr>
<tr>
<td></td>
<td>Chronic pulmonary obstructions</td>
</tr>
</tbody>
</table>
Tools used in drug development:
2. Continuous risk analysis as a decision tool (1/2)

Sources:
Stage-related success rates: average across 9 publications, 1995-2005

Compounded success rate
Tools used in drug development:
2. Continuous risk analysis as a decision tool (2/2)

Predictibility of preclinical models?
Tools used in drug development:
3. Project Management (1/2)

(example of PERT chart)
Tools used in drug development:
3. Project Management (2/2)
Regulatory constraints in drug development: declining number of new approvals

By August 2011, the FDA had approved 26 new drugs for year 2011

Bethan Hughes Nature Reviews Drug Discovery 9, 89-92 2010
Phase transition probabilities in clinical development

Figure 3  Phase transition probabilities and clinical approval success probabilities by type of compound, for self-originated compounds first tested in humans from 1993 to 2004. BLA, biologics license application; NDA, new drug application.

Regulatory constraints in drug development: soaring costs of R&D

Figure 2 New drug approvals (dots), represented on the left vertical axis, and pharmaceutical R&D expenditures (shaded area), represented on the right vertical axis, in the United States from 1963 to 2008. R&D expenditures are presented in terms of constant 2008 dollar value. The trend line is a 3-year moving average. The source of drug approval data is the Tufts Center for the Study of Drug Development (CSDD). The source of R&D expenditure data is the Pharmaceutical Research and Manufacturers of America; Industry Profile 2009; conversion of actual expenses to constant dollars was performed by Tufts CSDD.

Quoted by Kaitin KI. Clin.Pharmacol. Ther. 87:356-361
Debiopharm Group’s achievements

- Two products in 5 formulations commercialized worldwide
  - Triptorelin: LH-RH analog, treatment of prostate cancer (Decapeptyl® / Trelstar® / Pamorelin® Moapar Salvacyl®) in 1-month, 3-month and 5-month formulations.
  - Oxaliplatin: first line treatment of colon cancer (Eloxatin® / Elplat® / Dacotin® / Dacplat®)
Clinical effects of cyclosporin in HIV infected patients
Preliminary observations

 ➔ The effect of cyclosporine on the progression of human immunodeficiency virus type 1 infection transmitted by transplantation--data on four cases and review of the literature.


 ➔ Two women and two men were infected with the human immunodeficiency virus type 1 (HIV-1) transmitted by renal transplantation from i.v. drug-addicted donors in 1984. …

 ➔ … We evaluated the case reports of 53 patients with HIV-infection caused by an infected transplant or by blood transfusions during or shortly after transplantation. The cumulative incidence of AIDS was significantly lower in 40 transplant patients with an immunosuppressive regimen including cyclosporine than in 13 transplant patients receiving immunosuppressive treatment without cyclosporine (5-year cumulative risk of AIDS: 31% versus 90%, P = 0.001).
Preclinical evaluation of the first non immunosuppressive cyclosporin in AIDS

Inhibition of Human Immunodeficiency Virus Type 1 Replication by SDZ NIM 811, a Nonimmunosuppressive Cyclosporine Analog

BRIGITTE ROSENWIRTH,1* ANDREAS BILICH,1 ROELF DATEMA,1 PETER DONATSCH,2 FRANZ HAMMERSCHMID,1 RICHARD HARRISON,1 PETER HIESTAND,2 HERBERT JAKSCH1 PETER MAYER,1 PETER PEICHL,1 VALERIE QUESNIAUX,2 FRANZ SCHATZ,1 HENK JAN SCHUURMAN,2 RENE TRABER,2 ROLAND WENGER,2 BARBARA WOLFF,1 GERHARD ZENKE,2 AND MAURO ZURINI2

1997 – 1999: Synthesis of more than 100 compounds, and selection of Debio025
Debio025 activity against HIV

• Excellent preclinical activity of Debio025 against HIV confirmed in various models
• Little toxicity in preclinical models
• Oral bioavailability of 60%
• Half-life of 120h

BUT

• Very deceiving activity against HIV in patients (less than 1 log decrease in viremia)!
Debio 025 shows potent anti–HCV effect in HIV/HCV Patients Coinfected with Hepatitis C and Human Immunodeficiency Virus

Mean maximal HCV RNA decrease of $3.6 \log_{10}$ copies/mL

Flisiak et al Hepatology. 2008;47(3):817-26
© Debiopharm Group 2011
Hepatitis C: a public health problem

⇒ 170 millions patients infected around the world
Press Release, 9 February 2010

« Novartis has gained from Debiopharm exclusive rights to develop and market Debio 025 (alisporivir), a potential first-in-class antiviral agent currently in Phase IIb development for the treatment of hepatitis C. «
Présidence et Membres du Comité de Direction

R.-Y. Mauvernay  T. Mauvernay  K. Besseghir
P. Kairouz  A. McAllister  H. Ibrahim  R. Bär
J.-M. Dumont  J.-L. Béjot  C. Deuscher  A. Maret