Role of academic research and spin-off (start-up) companies in drug development and pharma/biotech industry

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Why pharma industry is a leading one?

„The desire to take medicine is perhaps the greatest feature which distinguishes man from animals.”

Sir William Osler
(1849-1919, founder of the John Hopkins Hospital)

• Science for curiosity?
• Science for the benefit of the society?
  - results useful for pharma/biotech industry
No limits of drug development: what can be a medicine?

1. Small molecules

2. Macromolecules (mostly biologics)

   - Gene therapy medicinal products:
     - recombinant nucleic acid for the regulation, repair, substitution, addition or delation of a specific gene sequence
   - Cell / tissue therapy medicinal products:
     - consist of manipulated cells or tissues

4. The Combination of the above with medical devices
No limits of drug development: What can be a medicine?

„DNA nano spider” : A molecular nanorobot dubbed a 'spider' and labeled with green dyes moves along a DNA track to its red-labeled goal (Lund et al, Nature, 2010)

„When using appropriately designed DNA origami, the molecular spiders autonomously carry out sequences of actions such as 'start', 'follow', 'turn' and 'stop’“
Magnetic nanoparticles provide physical guidance to direct more efficient nerve regeneration

Riggio et al, Nanomedicine, 2014
No limits of drug development
A drug-device combination for targeted release of drugs

- Magnetic Membrane
- Aperture
- Drug Reservoir
- Drug
- Deflected Membrane
- Applied Magnetic Field
- Released Drug
- Drug Formulation

Actuation
Drug development and pharma industry:

Takes 8-12 years and roughly $1bn to market

Patent protection: only for 25 years
## Drug development and pharma industry: total cost of drug development

<table>
<thead>
<tr>
<th>Company</th>
<th>drugs approved</th>
<th>R&amp;D Spending/Per Drug ($Bil)</th>
<th>Total R&amp;D Spending 1997-2011 ($Bil)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AstraZeneca</td>
<td>5</td>
<td>11,8</td>
<td>58,9</td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
<td>10</td>
<td>8,2</td>
<td>81,7</td>
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<tr>
<td>Sanofi</td>
<td>8</td>
<td>7,9</td>
<td>63,3</td>
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<tr>
<td>Roche Holding AG</td>
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<td>7,8</td>
<td>85,8</td>
</tr>
<tr>
<td>Pfizer Inc.</td>
<td>14</td>
<td>7,7</td>
<td>108,2</td>
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<tr>
<td>Johnson &amp; Johnson</td>
<td>15</td>
<td>5,9</td>
<td>88,3</td>
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<tr>
<td>Eli Lilly &amp; Co.</td>
<td>11</td>
<td>4,6</td>
<td>50,3</td>
</tr>
<tr>
<td>Abbott Laboratories</td>
<td>8</td>
<td>4,5</td>
<td>36,0</td>
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<tr>
<td>Merck &amp; Co Inc</td>
<td>16</td>
<td>4,2</td>
<td>67,4</td>
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<tr>
<td>Bristol-Myers Squib</td>
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<td>45,7</td>
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<tr>
<td>Novartis AG</td>
<td>21</td>
<td>4,0</td>
<td>83,6</td>
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<tr>
<td>Amgen Inc.</td>
<td>9</td>
<td>3,7</td>
<td>33,2</td>
</tr>
</tbody>
</table>

Forbes 2012: „At $12 billion per drug, inventing medicines is a pretty unsustainable business”

„At $3.7 billion, you might just be able to make money”

„the main expense is failure”

Sources: Forbes; InnoThink Center For Research In Biomedical Innovation; Thomson Reuters Fundamentals via FactSet Research Systems, 2012
Drug development is risky:
Success rate is extremely low (but better than lottery)

High risk of development: efficacy, safety, and affordability

Drug development for rare diseases (orphan disease) - financing problems
Figure 1 | **Novel approvals since 1993.** New molecular entities (NMEs) and Biologics License Applications (BLAs) approved.
The productivity of pharma/biotech industry - declining

Productivity of the pharma industry

Finding the true cost of a new drug is complex and controversial...

Cost of a new drug in US$ (billions)*

Data: USFDA, PhRMA

* New drug cost and R&D spend could be 30% higher if non-PhRMA members are included
How to move forward?

- Less risky ways to develop new drugs
- Increasing success of innovations
The less risky ways of drug development

(a) High risk
   High reward
   High cost

   Primary care
   Novel NMEs
   NBEs
   Follow on NMEs
   Advanced therapy products

(b) Mid risk
   Mid reward
   Mid cost

   Drug repositioning
   Biosimilars
   Orphan drugs
   Drugs for rare, neglected Ind
   Life extension - Indications

(c) Low risk
   Low reward
   Low cost

   Branded combinations
   LCM
   Generics, super generics
   Drug-device

Drug „repositioning”: new indications for old drugs (little preclinical development - jump into phase II clinical trials)

**Phase I**
- New indication at the same dose range
- Human tolerance (HT)
- Pharmako-kinetics (PK)

**Phase II**
- New indication

**Phase III**
- New indication

**Phase IV**
- Observational studies
- Postmarketing controlling studies
- Prospective, randomized, comparative trials

**Quality of life and pharmaco-economical studies**

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Increase the success of innovations: modern drug development is a cooperative effort

- **Academic institutions**: basic science and new technologies („omics”, nanotech, in silico models, etc)
- **Small innovative R&D companies** („small biotech”, spin-offs)
- **R&D service companies**: assays, animal studies, organizing clinical studies, patent lawyers, etc
- **Large pharma companies**: development, financing
- **Investors**: business angels, FFF, venture capitalists, investments funds
- **Government regulatory authorities**
- **Health care insurance** (government, private)
- **Hospitals**
- **Doctors**
Increasing the success rate of innovations: „translational medicine” - „biomarkers”

**Non-clinical R&D:**
- Translational models (comorbidities, comedications)
- Biomarkers
- Large animals

**Clinical phases:**
- "Phase 0"
- Phase I
- Phase II
- Phase III

**Learning phase**

**Confirmation phase**

**Feedback Optimization**
Materials of human origin
Source of innovation (FDA approved drugs)

<table>
<thead>
<tr>
<th>Year</th>
<th>Source of Innovation</th>
<th>Registration</th>
<th>Current Owner</th>
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<tr>
<td>2013</td>
<td>Source of Innovation</td>
<td>59%</td>
<td>7%</td>
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<tr>
<td></td>
<td>Registration</td>
<td>22%</td>
<td>15%</td>
</tr>
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<td></td>
<td>Current Owner</td>
<td>22%</td>
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<td>Source of Innovation</td>
<td>59%</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>Registration</td>
<td>31%</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td>Current Owner</td>
<td>18%</td>
<td>13%</td>
</tr>
</tbody>
</table>

top 20 big pharma
medium pharma
small pharma/biotech
other (e.g. academia)

Source: IMSHealth analytics
Innovation in drug development: role of academic research and spin-off (start-up) companies

Innovation process: from basic research to marketed product

- Basic research
  - Academic institution
    - Basic science financing (government, charity, etc)
  - IP protection and technology transfer of early stage projects
  - Applied research
  - Industrial development
  - Product on the market
  - Spin-offs - start-ups
    (SME - small medium enterprise)
    - Financing
      - private
      - public

- Big pharma
Management difficulties at academic institutions and start-up companies

Early stage R&D company manager

“Hard qualities”
- Business missions, financial goals
- Strict quality control, project goals (e.g. ISO, GLP, GCP)

“Soft qualities”
- Business missions, financial goals
- Balanced management
- Science values
- Customs, “genious professor” behaviour, creativity

Company output

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Role of the academic sector in pharma industry:
- discovery research
- development of basics of novel technologies
- protecting intellectual property and transfer of technology to industry
- special R&D services? – administrative and structural challenges?
- clinical development

Role of spin-off companies in pharma/biotech industry:
- create and utilise intellectual property
- further progress of early stage projects to be visible for big pharma and investors
- tech transfer to big pharma / or growing to become mid size or big pharma
- R&D services (e.g. non-clinical and clinical CRO, SMO, Phase 1 units, consultancy, regulatory, medical writing, etc.)
Protection of your intellectual property: patent and publish

„Research that is not carried out under quality control and not documented is not done”

Protecting your know-how (keeping secrets)
- no confidentiality, no business with pharma/biotech industry
- idea and data can be stolen? – data sharing?

Patenting
- only publication? – your idea will never get to the market
- future benefit for you and your institution (more chance than lottery :-)

Publishing
Productivity in publications: Central-Eastern EU is among leaders... is it good?

Number of publications per 1 M USD R&D expenditure in universities and research institutes
(source: NSIOD, Institute for Scientific Information)

<table>
<thead>
<tr>
<th>Country</th>
<th>Productivity</th>
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<tbody>
<tr>
<td>Korea</td>
<td>21.8</td>
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<tr>
<td>USA</td>
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<tr>
<td>Poland</td>
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<tr>
<td>Czech Rep.</td>
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<td>Spain</td>
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<td>Hungary</td>
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</table>

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Where are Central-Eastern Europe?: the number of patent applications does not meet with publication productivity.
Responsibilities of universities in protecting the intellectual property

Deprenyl:
50 Years of Life Enhancement and Life Extension
By Leslie J. Farer

When the drug called deprenyl was first developed in the early 1960’s, the Hungarian doctor who synthesized it could hardly have foreseen its widespread therapeutic potential.

Over the past half century, deprenyl has gained recognition not only as a clinically proven antidepressant and Parkinson’s treatment, but also as a mental energizer, physical and cognitive performance booster, generalized mood lifter, sex enhancer, brain protector, and longevity tonic. The age-retarding and performance-enhancing effects of deprenyl have been clearly demonstrated in animal studies, and humans can benefit from these intriguing findings. The drug is not just beneficial in cases of neurodegenerative diseases; the general healthy but aging population can employ low-dose deprenyl to improve quality of life in their middle to late years, fend off physiological and cognitive decline, boost physical, sexual, and mental vigor, and promote longevity.

Deprenyl Preserves the Essential Neurotransmitter Dopamine

Deprenyl (also known by trade names Selegiline, Jumbex, and Eldepryl) exhibits a wide spectrum of pharmacological activity. The first one, for which it is most well-known, is inhibition of an enzyme that breaks down neurotransmitters such as dopamine. (1-5) Let’s take a quick look at the operation of the brain’s circuitry, which depends on the continuous regulation of neurotransmitter levels. In a healthy brain, this achieved by a fine balance between neurotransmitter manufacture from amino acids and breakdown by enzymes. Any disruption of either neurotransmitter synthesis or degradation (or both) can upset the brain’s delicate equilibrium, resulting in mood, psychiatric, or neurological disorders. Here we’re focused on neurotransmitter breakdown, specifically by MAO-B, a member of the monoamine oxidase family of enzymes that degrades dopamine (as well as other brain chemicals such as phenylethylamine (PEA)). Enzymatic degradation is a biochemical pathway necessary for the elimination of used neurotransmitters. MAO-B is essential to brain metabolism, but if its over-activity exceeds the rate of dopamine synthesis, the brain’s dopamine stores become depleted, with disastrous consequences. That’s

- discovered and developed at Semmelweis University, Budapest in the sixties

- on the market in 62 countries

- Direct benefit of the university?
An Interview with Joseph Knoll, M.D.
(adapted from Mavericks of Medicine)

Joseph Knoll, M.D., a Hungarian neurochemist and pharmacologist probably best known for developing the drug deprenyl (Selegiline), the first selective monoamine oxidase-B (MAC-B) inhibitor, has researched its properties for more than half a century.

Dr. Knoll’s recently published book, The Brain and Its Self: A Neurochemical Concept of Innate and Acquired Drives (Springer, 2005), summarizes his life’s research and his fascinating speculations about the relationship between brain activity and culture. Dr. Knoll describes how his experience as a Nazi concentration camp survivor helped inspire and motivate much of his scientific research. Although his parents were sent to the gas chamber when he was a teenager, Dr. Knoll survived because he spoke fluent German and was chosen to serve as the personal servant to the Chief of the SS guards. In 1945, after the war, Dr. Knoll returned to his native city of Budapest. He earned his M.D. from the University of Budapest in 1951, and later became a professor and the head of the Department of Pharmacology at the Semmelweis University of Medicine in Budapest.

In the early 1950s, Dr. Knoll helped to pioneer research into the physiological basis of innate and acquired drives in animals. Trying to make sense of his experience in the Nazi concentration camp, Dr. Knoll became interested in how animals acquire new drives. The research that resulted from Dr. Knoll’s interest in this subject centered around studying the brain changes in rats that had been trained to have an acquired drive for an unnatural object—a glass cylinder. This acquired drive—which urged the animals to search for and jump to, the rim of a thirty centimeter-high glass-cylinder, and then crawl inside—would often override the animals’ instinctive drives for food and sex.

Deprenyl Protects Cognitive Function via Several Distinct Mechanisms

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Take home messages

• no limits of drug development – you can be part of it
• confidentiality – think of patents – publish
• quality control system is essential (SOPs, strict documentation)
• think of being an entrepreneur – „start up” - create jobs
• collaborate with industry
  - access to novel technologies
  - better publications?
  - helps in financing your lab
  - my example – listed on highlycited.com 2014 – thanks to industry driven projects (at least 1/3 of my publications/citations)