Nanobodies®: journey from research to commercial

UPIP-VAPI
VUB Campus Jette  April 2013

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Outline

From research to commercialization
  • The story of Ablynx

The Nanobody technology

Product pipeline and examples of clinical assets
  • anti-IL-6R to treat RA – strong efficacy and safety results in Phase II
  • anti-vWF (caplacizumab) to treat TTP
  • anti-RSV
Creating a Spin-Off Company: steps and issues involved

Commercialization via Start-up/Spin-Off Company

What do you need to create a Start-up/Spin-Off Company?

A BRIGHT IDEA

- An invention arises from university research
- A platform technology is built up
- If the technology (invention) is a platform on which could be built multiple commercial products, it can form basis for a new company
  - New business allows a researcher to be personally involved in the translation of its discoveries into products & services and see the correlation between hard work and financial reward
Creating a Spin-Off Company: steps and issues involved

- The Business Opportunity Document
  - A key marketing document that describes the business opportunity

- Development of Business Plan

- Protection and exploitation of Intellectual Property
  - Multi-layered approach (platform, drugs, formulation,…)
  - Life cycle management

- Finding investors

- Finding infrastructure

- Negotiation and legal support
In the beginning….

- Early ’90: discovery of camelid heavy-chain only antibodies at ALBI (VUB)
- Further characterization and development of the $V_H$ platform technology
- In 1996: ALBI joins VIB
- Intensive collaboration between VIB headquarters and ALBI (VIB6) to validate the technology for potential spin-off
- Generation of IP
- Development of Business Plan
- Patent Portfolio (University/VIB)
- In 2001: ABLYNX established
- In 2002: ABLYNX incorporated (completed first financing round)
- Nanobody technology
Rapid evolution from platform to product based company

Discovery platform
- No partners
- €5M seed financing
- No products
- 10 staff
- Platform building

Discovery and early development
- 3 partners
- €70M private equity
- €85M IPO (NYSE)
- 11 R&D projects
- 1 Nanobody in clinic
- 144 staff
- Platform upscaling

Discovery and later development
- 4 partners
- > €200M equity funding
- €160M in cash from partners
- ~ 25 R&D projects
- >700 people treated
- 7 Nanobody products in clinic
- 2 clinical POC (RA)
- < 250 staff
- Commercial production

End 2001 | End 2002 | End 2007 | Today
Nanobodies – demonstrated track record

1st inhaled Nanobody successfully completes Phase I safety study

>750 patients and subjects have received Nanobodies

Two clinical POCs in RA

Clinical grade material produced up to 2,500L scale

Nanobodies have been tested in 18 countries, 4 continents
### Three-pronged approach to balancing risk and reward

<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>Boehringer Ingelheim, Novartis and Merck &amp; Co</strong></td>
<td><strong>Merck Serono – Ablynx</strong></td>
<td><strong>Ablynx</strong></td>
</tr>
<tr>
<td>• 11 active programmes</td>
<td>• 5 active programmes in inflammation, immunology and oncology</td>
<td>• TNFα (ozoralizumab) – Ph II*</td>
</tr>
<tr>
<td>• €113 million in cash received since 2005</td>
<td>• First Phase I expected in 2013</td>
<td>• vWF (caplacizumab) – Ph II</td>
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<tr>
<td>• BI is current shareholder (4.9%)</td>
<td>• €47 million in cash received since 2008</td>
<td>• IL-6R (ALX-0061) – Ph II</td>
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<td><img src="image1" alt="Boehringer Ingelheim" /> <img src="image2" alt="Novartis" /> <img src="image3" alt="Merck &amp; Co., Inc." /></td>
<td><img src="image4" alt="Merck Serono" /></td>
<td>• RANKL (ALX-0141) – Ph I</td>
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<td><img src="image4" alt="Merck Serono" /></td>
<td>• RSV (ALX-0171) – Ph I</td>
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</table>

Balancing risk and reward

€160M in non-dilutive cash from collaborators received to date

* No investment in clinical trials made to date by Ablynx
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Ablynx’s Nanobodies – proven single variable domain approach

*Camelidae* family has both forms

**Conventional antibody**
- Heavy and light chains
- Both chains required for antigen binding and stability
- Large size and relatively low formatting flexibility
- Administered through injection

**Heavy-chain antibody**
- Only heavy chains
- Full antigen binding capacity and very stable

**Ablynx’s Nanobody®**
- Small (1/10 size of a mAb)
- Flexible formatting
- Highly potent, robust and stable
- Broad target applicability
- Multiple administration routes
- Ease of manufacture
- Speed of discovery
Nanobody discovery process – the power of evolution

1. Immunize llama with antigen
2. Draw blood 6–12 weeks later
3. Conventional antibodies
4. Select Nanobodies of interest
5. Manufacture in micro-organisms
6. Format Nanobody to achieve desired properties, plus half-life extension (HLE)
7. Ablynx’s Nanobody®
8. Clinical trials
9. Select Nanobodies of interest

Ablynx
The unique potential of Nanobodies ... combines the best of both worlds

- Small molecules (chemical substances)
- Conventional antibodies (biological)

- Easy manufacturing
- Stable and small
- Selective and efficient
- Low toxicity
- Broad applicability
- Flexible formatting
- Alternative delivery
- Broad applicability
- Flexible formatting
- Alternative delivery

www.ablynx.com
Outline

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## Pipeline – internal and funded programmes

<table>
<thead>
<tr>
<th>Therapeutic area</th>
<th>Product name</th>
<th>Target</th>
<th>Discovery</th>
<th>Pre-clinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
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<td>caplacizumab</td>
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<td>ALX-0061</td>
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**Validated targets (clinic)**

**1st in class**

Blank boxes: non-disclosed targets
ALX-0061 – designed to be potentially best-in-class

<table>
<thead>
<tr>
<th>Features</th>
<th>Potential Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small (26kD)</td>
<td>• penetrates faster and more effectively into tissues</td>
</tr>
<tr>
<td>Targets human serum albumin (HSA)</td>
<td>• prolongs half-life</td>
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<td></td>
<td>• improved trafficking to inflamed tissue</td>
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<tr>
<td>Monovalent binding</td>
<td>• avoids target cross-linking</td>
</tr>
<tr>
<td>Preferential binding of soluble vs. membrane bound IL-6R</td>
<td>• superior benefit/risk profile</td>
</tr>
<tr>
<td>Strong affinity to soluble IL-6R</td>
<td>• fast target engagement resulting in fast onset of action</td>
</tr>
<tr>
<td>Low immunogenic potential</td>
<td>• improved safety profile</td>
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<tr>
<td>Tailored PK</td>
<td>• extended therapeutic window</td>
</tr>
<tr>
<td></td>
<td>• convenient dosing and scheduling</td>
</tr>
</tbody>
</table>
ALX-0061 – Phase II study design (MAD)

Dose modification based on EULAR response at week 10

24/28 patients completed the study at their ALX-0061 starting dose
ALX-0061 – ACR scores further improved from week 12 to 24
ALX-0061 – strong induction of DAS28 remission

- All DAS28 components contributed substantially to the score
- 20/24 patients achieved low disease activity or remission
Caplacizumab (anti-vWF) – designed to address an unmet medical need in TTP

<table>
<thead>
<tr>
<th>Unique Nanobody Format</th>
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<tbody>
<tr>
<td><strong>Small</strong></td>
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<tr>
<td>not an antibody</td>
</tr>
<tr>
<td>no Fc</td>
</tr>
<tr>
<td>rapid distribution and</td>
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<tr>
<td>onset of action</td>
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<tr>
<td>rapid clearance</td>
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<tr>
<td>limits toxicity risk</td>
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<tr>
<td><strong>Specific</strong></td>
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<tr>
<td>high potency towards</td>
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<tr>
<td>target</td>
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<tr>
<td>avoid “off-target”</td>
</tr>
<tr>
<td>effects</td>
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<tr>
<td><strong>Robust</strong></td>
</tr>
<tr>
<td>high stability</td>
</tr>
<tr>
<td>good manufacturability</td>
</tr>
<tr>
<td><em>iv</em> and <em>sc</em> formulation</td>
</tr>
<tr>
<td>liquid, lyophilised</td>
</tr>
<tr>
<td><strong>Modular</strong></td>
</tr>
<tr>
<td>bivalent interaction</td>
</tr>
<tr>
<td>with target</td>
</tr>
<tr>
<td>increased avidity</td>
</tr>
<tr>
<td>leads to higher</td>
</tr>
<tr>
<td>potency</td>
</tr>
</tbody>
</table>

- Orphan Drug designation in US and EU
- Patent term (excluding extensions) will run until 2026
- Potential pivotal Phase II study on-going with the aim to complete recruitment in 2013
Caplacizumab – blocks the platelet and ULvWF interaction

Microthrombi form which block the small blood vessels in thrombotic thrombocytopenic purpura (TTP)

Anti-vWF Nanobody inhibits platelet string formation caused by UL-vWF in plasma of TTP patients

Ex vivo platelet string formation

Target for the Nanobody is in the bloodstream, i.v. and s.c. formulations ensure desired exposure
Acquired TTP – an unmet medical need

Healthy active adult

Sudden onset:
severe fatigue,
headache, bizarre
behaviour, vertigo,
seizures, coma,
various other symptoms

Potentially:
fewer days of PEX
reduction in relapse/exacerbations
improved longer term outcome

+ caplacizumab

Diagnosis of TTP

Daily plasma exchanges in hospital until recovery of platelets count
Respiratory syncytial viral (RSV) infections – unmet need

Duration: 1-2 weeks

*medical cost year after infection
**risk asthma

Evolves to distressing symptoms
Symptomatic treatment including inhaled corticosteroid & bronchodilator
8-20% hospitalised

“RSV infection is the most common cause of lower respiratory tract disease and hospital admission in infants. No effective therapy is available at present. Current prophylaxis with a mAb is expensive and only partially protective. Any new treatment strategy for RSV bronchiolitis is very welcome”

Prof De Boeck, Pediatric Pulmonology

* Shi et al., J Med Econ, 2011; **Sigurs et al., Thorax, 2010; Krishnamoorthy et al., Nature Medicine 2012
ALX-0171 – anti-RSV Nanobody designed for delivery to site of infection

Unique Nanobody Format

2,000 fold increase in potency compared with monovalent structure

<table>
<thead>
<tr>
<th>Specific</th>
<th>Robust</th>
<th>Convenient</th>
</tr>
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<tbody>
<tr>
<td>high potency towards the virus</td>
<td>high stability</td>
<td>inhalation</td>
</tr>
<tr>
<td>avoid “off-target” effects</td>
<td>efficient nebulisation</td>
<td>opportunity for once or twice daily dosing</td>
</tr>
<tr>
<td>well tolerated in Phase I study</td>
<td>without loss in potency</td>
<td>dosing time &lt; 3 minutes</td>
</tr>
<tr>
<td></td>
<td>potentially reduces viral replication in the lungs</td>
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</tbody>
</table>

Patent term (including extensions) will run until 2035
ALX-0171 – potential for transformational treatment of RSV

**Safe**
- Biologic targeting the virus
- Well tolerated in Phase I
- In contrast to some vaccines, not associated with enhanced RSV disease

**Potent**
- Potentially most potent drug in clinical development
- Broad coverage of viral clinical strains

**Fast**
- Virus in the respiratory tract targeted immediately through nebulisation

**Inhaled**
- Opportunity for once daily dosing (< 3 minutes)
- Airway model shows efficient delivery to infant lung

ALN-RSV01: Alnylam (PhII b completed to treat progressive bronchiolitis obliterans syndrome; primary endpoint not met); MDT637: Microdose (PhI completed to treat RSV)
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