Nanobodies as a Versatile Approach for Developing Next Generation Immunotherapies

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Ablynx

Powerful platform generating potentially innovative medicines

**CORPORATE**
- Platform technology and late-stage clinical development company
- 350 staff in Ghent, Belgium

**TECHNOLOGY**
- Pioneer in next generation antibody-derived drugs – Nanobodies®
- >500 patent applications and granted patents; critical know-how
- Validation through multiple partnerships with top tier pharma companies

**PRODUCTS**
- ~40 wholly-owned and partnered programmes
- 1 Phase III and 4 Phase II studies ongoing in-house
- First potential launch in 2018

**PARTNERS**
- AbbVie, Boehringer Ingelheim, Eddingpharm, Genzyme, Merck &Co., Inc., Merck KGaA, Novartis, Novo Nordisk and Taisho Pharmaceuticals
- >€380M cash received; >€7Bn in potential milestones + royalties

**FINANCIALS**
- €262M in cash at 30th September 2015
- €277M raised in equity
- €100M of issued Convertible Bonds maturing in 2020

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What are Nanobodies?

Unique technology
Nanobodies

Derived from heavy-chain only antibodies

- *Camelid* heavy-chain only antibodies are stable and fully functional
- Nanobodies represent the next generation of antibody-derived biologics

Ablynx’s Nanobody
- small and robust
- easily linked together
- sequence homology comparable to humanised/human mAbs
- nano- to picomolar affinities
- able to bind and block challenging targets
- multiple administration routes
- manufacturing in microbial cells
Ablynx Nanobody discovery process

Rapid generation of novel biologics in 12-18 months

- **Immunize llama with antigen**
- **Draw blood 6–12 weeks later**
- **Conventional antibodies**
- **VH1**
- **CH2**
- **CH3**
- **VH2**
- **Ablynx’s Nanobody®**
- **Use proprietary synthetic Nanobody phage libraries**

- **Manufacture in micro-organisms**
- **Format and sequence optimize Nanobody to achieve desired properties**
  - plus half-life extension (HLE)
- **Selection of Nanobody lead panel via phage display, YSD, or NGS**
  - wide epitope coverage
  - low 0.1-10 nM affinity range

- **Clinical trials**

*Glycine-serine linkers from C-terminus to N-terminus*
Nanobodies
A highly versatile platform

Mix and match
Targeting different pathways at once with a single Nanobody construct, e.g. multiple checkpoint inhibitors

Multiple delivery routes
- Inhalation
- Needle-free
- Oral-to-topical
- Ocular

Customised half-life extension
- Weeks/days/hours
- Fc
- Albumin binding Nanobody

Cell killing
- Nanobody-drug conjugates
- Ag-1

Cell- / tissue-homing
- Cell specificity
- Immune cell recruitment
- Tissue-specific targeting

Manufacturing
- High-yield, high-concentration, low-viscosity, microbial production

Challenging and intractable targets
- Nanobodies against ion channels and GPCRs
- Nanobodies can reach conserved cryptic epitopes

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Unique modularity of Nanobodies

Building a custom therapeutic

Multi-specifics: Individual binding arms with tailored affinity

12-15kDa

GS-linker
(from C- to N-term): custom linker length for maximum efficacy

Bi-paratopic Nanobody:
binding multiple identical or different epitopes on same target

anti-Target A

anti-Target B

anti-HSA

payload

Half-life extension
Possibility to extend from hours to ~20 days)

Microtubulin or DNA inhibitors, toxins
Multi-valent format improves potency

Tri-valent anti-RSV Nanobody ALX-0171

- Improve activity and strain coverage by multi-valency
- Superior virus neutralisation as compared to palivizumab
- 5-fold more clinical isolates neutralised below LLOD with ALX-0171 compared with palivizumab

Improved potency over mAb

Increased strain coverage

<table>
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<th>A-strain</th>
<th>B-strain</th>
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<td>32</td>
<td>29</td>
<td>61</td>
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<td>11 (18%)</td>
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<td>23 (79%)</td>
<td>53 (87%)</td>
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<td><em>p value</em></td>
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<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
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Number of strains neutralised below lower limit of detection
Multi-specific blocks two cytokines at once

Bi-specific anti-IL-17A/IL-17F Nanobody ALX-0761

- ALX-0761 blocks both IL-17A and IL-17F for more effective blocking of the inflammatory response
- Binds human serum albumin for improved PK
- Proof of concept in primate CIA model
- ALX-0761 in development by Merck KGaA
  - completed Phase I SAD study in healthy volunteers
  - completed Phase Ib study in patients with psoriasis

Proof-of-concept achieved in primate collagen induced arthritis model\(^1\)

1 Poster available on Ablynx website: [R&D>pipeline](#)
Bi-specific synergistically improves potency

**Anti-CXCR4/CD4 enhances HIV neutralisation**

- Synergistic improvement in HIV blockade of CXCR4/CD4 bi-specific Nanobody over mono-valent Nanobodies
  - up to 320-fold enhancement with bi-specific versus mono-specifics
  - only 2-fold enhancement with mixture of mono-specifics in solution (1:1) over mono-specifics alone

**Blockade of HIV infection *in vitro***

*Infection of MT-4 T cells with NL4.3 (X4) HIV strain*

Bi-specific Nanobody is ~160 fold more potent than mixture of mono-specifics
Bi-specifics improve cell targeting

Increased activity on specific cell populations

- Increase selectivity to specific cells by combining
  - functional arm: antagonist of a functional receptor with low affinity
  - anchor arm: cell-specific binder with moderate-high affinity

Bi-specific yield improvements in cell targeting typically of 10-1000-fold depending on target combinations
Multi-valent and multi-specific Nanobodies

Proven capability and performance

- Ease of formatting and manufacture of multi-valent, bi-paratopic, and multi-specifics allows rapid development of differentiating biologics
  - achieve “order of magnitude” increases in potency and specificity
  - obtain “best-in-class” molecules
  - ability to develop drugs against multiple targets simultaneously

- Multiple commercial collaborations with focus on multi-specific Nanobodies
  - Merck & Co., Inc.: immuno-oncology
  - Boehringer Ingelheim: oncology; ocular
  - Merck KGaA: oncology; inflammation and osteo-arthritis
  - Novo Nordisk: undisclosed
Use in Immuno-Oncology
Immuno-oncology

Changing the cancer treatment paradigm

Huge market potential
- Proven substantial survival impact
- Market expected to grow to >$43bn by 2020*
- I/O drugs expected to treat 60% of cancers*

Multiple targets
- Increasing number of targets
- Combination therapies are the next generation

Multi-specific Nanobodies
- Bind multiple targets (2, 3, 4 or 5) with one Nanobody molecule
- Potential to increase efficacy and avoid escape mechanisms
- Technology allows rapid exploration of combinations
- Manufacturing simplicity and cost-effectiveness

*BofA Merrill Lynch July 2015
Multi-specific Nanobodies

Nanobody-based T cell recruitment

- Nanobody recruiters potentially offer several key advantages
  - formatting to allow high affinity on low density tumour antigens
  - multi-specific formats to increase efficacy and/or avoid escape
  - use of either TCR- or CD3-based recruitment
  - clinically validated half-life extension to reduce dosing frequency
  - excellent CMC properties
  - robust manufacturing
Multi-specific Nanobodies

Immunology collaboration with Merck & Co., Inc.

- Heavily investing in I/O R&D pipeline (~80% of total R&D budget*)
- Keytruda® approved in advanced melanoma (first line) and metastatic NSCLC
- Sales of Keytruda® estimated to reach $6Bn by 2020**
- >160 clinical studies for Keytruda® in >30 tumor types

Merck & Co., Inc. leader in the field

- Targeting multiple immune-checkpoint modulators
- Up to 17 fully-funded Nanobody programmes
- Focus on multi-specific combinations
- €33M upfront; up to €5.7Bn in potential future milestones plus royalties

Merck & Co., Inc. and Ablynx in collaboration

First *in vivo* pre-clinical milestone (€3.5M) achieved in October 2015 with a bi-specific Nanobody

*Bryan Garnier Oct 2015  **Leerink August 2015
Ablynx’s anti-GITR Nanobody programme

**Target background**

- GITR is a member of the TNF receptor super family
  - expressed on multiple important immune cell types

- Unique mechanism of action and strong pre-clinical tumour model data
  - promote tumor regression through differential effects on $T_{\text{Eff}}$ and $T_{\text{Reg}}$
  - enhances anti-tumor immunity through effects on other immune cells
  - synergizes with chemotherapy, radiation, cancer vaccines, checkpoint inhibitors, etc.

- Several anti-GITR mAbs in phase I
  - GITR Inc., Merck, Medimmune
Anti-GITR agonist for immuno-oncology

Advantages of a Nanobody approach

• Agonistic anti-GITR Nanobodies may have several advantages over Fc-enabled antibodies
  - smaller size – more access to tumor environment
  - multi-valency and flexible linkers – better GITR cross-linking and agonist activity
  - lack of Fc – potentially better safety profile; no T-effector cell depletion; no impact of Fc receptor polymorphisms

• Nanobody platform also offers additional flexibility
  - the ability to tailor circulating half-life from days to weeks by incorporating an anti-human serum albumin Nanobody
  - option to include Fc functionality into a multi-valent construct

Anti-GITR Nanobody

Anti-HSA Nanobody

Trivalent anti-GITR Nb (+ anti-HSA Nb)

Tetravalent anti-GITR Nb (+ anti-HSA Nb)

Tetravalent anti-GITR Nb-IgG
Nanobody formatting flexibility

Valency and linker length can improve functionality

• Increased valency

Bivalent anti-GITR Nb

Trivalent anti-GITR Nb

• Variable linker lengths

35GS

9GS

Human GITR NF-κB luciferase reporter assay

0 10000 20000 30000 40000

0 10^-14 10^-13 10^-12 10^-11 10^-10 10^-9 10^-8 10^-7 10^-6

Concentration (M)

Luminescence (r lu)

Anti-GITR Nb, bivalent, 35GS
Anti-GITR Nb, trivalent, 35GS

0 20000 40000 60000 80000

0 10^-13 10^-12 10^-11 10^-10 10^-9 10^-8 10^-7 10^-6

Concentration (M)

Luminescence (r lu)

Anti-GITR Nb, trivalent, 9GS
Anti-GITR Nb, trivalent, 35GS
In vitro activity of lead anti-GITR Nanobodies

Benchmarking versus clinical stage mAbs

- Human GITR NF-κB luciferase reporter assay

Trivalent anti-GITR Nb

Tetravalent anti-GITR Nb-IgG1

Merck & Co anti-GITR mAb (36E5)
Trivalent anti-GITR Nb1
Trivalent anti-GITR Nb2

Gitr Inc anti-GITR mAb (TRX518)
Merck & Co anti-GITR mAb (36E5)
Tetravalent anti-GITR Nb1-hlgG1
IgG1: isotype control
**In vitro** activity of lead anti-GITR Nanobodies

**Benchmarking versus clinical stage mAbs**

- Human CD4+ T cell activation assay

![Trivalent anti-GITR Nb](image1)

![Tetravalent anti-GITR Nb-IgG1](image2)

**Trivalent anti-GITR Nb**

**Tetravalent anti-GITR Nb-IgG1**
Proprietary tetravalent anti-GITR Nanobody

Efficacy as monotherapy or in combination with anti-PD1 mAb

Tumor efficacy in a syngeneic mouse model

Vehicle
Irrelevant Nb + PD-1 mAb
GITR Nb
GITR Nb + PD-1 mAb

p < 0.0001
p < 0.0001
Proprietary tetravalent anti-GITR Nanobody

Efficacy as monotherapy or in combination with anti-PD1 mAb

Individual tumor efficacy plots

- **Vehicle**: 0/10 reg
  - Tumor Volume (mm³)
  - Days post treatment
  - p = 0.0215

- **GITR Nb**: 1/10 Reg
  - Tumor Volume (mm³)
  - Days post treatment
  - p < 0.0001

- **Irr Nb + PD-1 mAb**: 0/10 Reg
  - Tumor Volume (mm³)
  - Days post treatment

- **Irr Nb + PD-1 mAb**: 5/10 Reg
  - Tumor Volume (mm³)
  - Days post treatment
  - p = 0.0215

Reg = regressed below baseline volume
Nanobodies in immuno-oncology

Using a clinically validated platform

- Key elements of the Nanobody platform are clinically validated
  - 3 different phase 2 clinical POC achieved
  - excellent safety profile
  - >1,000 patients dosed
  - iv., s.c, and inhaled delivery
  - mono-specific and multi-specific drugs
  - half-life extension possible via albumin binding

- Oncology and immuno-oncology space is vast
  - combination therapies expected to provide optimum patient benefit
  - hundreds of combinations possible, but difficult to predict best one

- “Mix and match” approach
  - rapidly make multi-specific Nanobody-based T cell recruiters and antagonists
  - get *in vivo* POC for different multi-specific combinations in 12-18 months

- “Multi-valency” to dramatically improve agonist activity
  - proven for different TNFR family members

- Further formatting flexibility
  - choose half-life
  - combine with $F_C$ receptor

- Nanobodies can also be used as companion diagnostic
Questions

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