



Nanobodies® – A Versatile Advanced Therapeutic Platform

G Van Heeke
April 21, 2015

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Corporate snapshot

CORPORATE

- Drug discovery and development company in Ghent, Belgium
- >300 employees

TECHNOLOGY

- Pioneer in next generation biological drugs – Nanobodies®
- >500 granted and pending patents

PRODUCTS

- >30 programmes – six at the clinical development stage
- Three clinical proof-of-concepts (POC)
- 2 wholly-owned products in later stage clinical development (Phase III & Phase II)
- >10 new clinical programmes anticipated over the next 3 years

PARTNERS

- AbbVie, Boehringer Ingelheim, Eddingpharm, Merck & Co, Merck Serono and Novartis

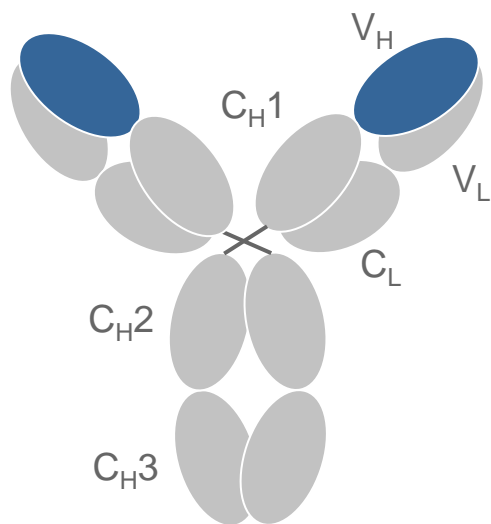
FINANCIALS

- €206M in cash at December 31st 2014

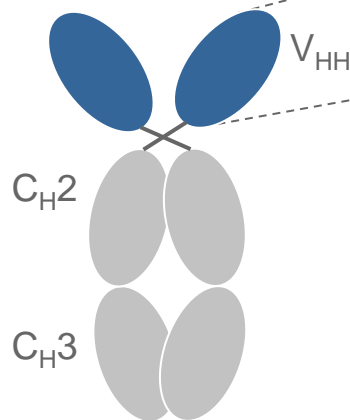
Nanobodies

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



Conventional antibodies



Heavy chain only antibodies



Ablynx's Nanobody

- small
- robust
- sequence homology comparable to humanised/human mAbs
- easily linked together
- nano- to picomolar affinities
- intractable targets
- multiple administration routes
- manufacturing in microbial cells

Ablynx's platform

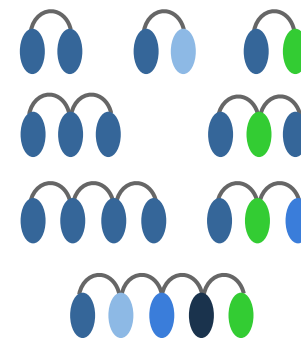
Rapid generation of high quality biologics



Immunise llamas
with antigen or
use synthetic library



Wide range of highly
diverse Nanobodies
with 0.1-10nM affinities



Formatted*
Nanobodies ready
for *in vivo* testing

Cloning and production in microbial systems



~12-18 months

*Glycine-serine linkers from C-terminus to N-terminus

Nanobody platform

Competitive advantages

Mix and match

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



Alternative delivery routes



Inhalation



Needle-free



Oral-to-topical



Ocular

Customised half-life extension



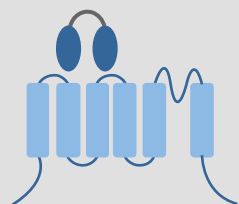
Fc

Weeks/days/hours



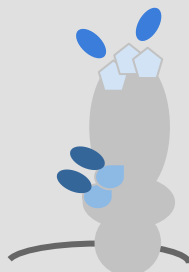
Albumin-binding Nanobody

Challenging and intractable targets



Nanobodies against ion channels and GPCRs

Nanobodies can reach conserved cryptic epitopes

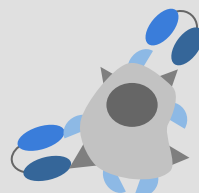


Cell killing

Nanobody-drug conjugates



Cell- /tissue-homing



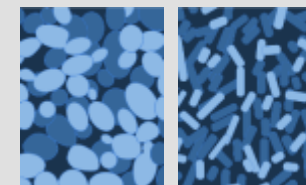
Cell specificity

Immune cell recruitment

Tissue-specific targeting

Manufacturing

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



RSV infection in infants

High unmet medical need

- Leading cause of infant hospitalisation and primary viral cause of infant death
 - ~300,000 children* (< 5 years) hospitalised per year in 7 major markets^{1,2}
 - 1.9 million outpatient visits per year for infants under 1 year of age
 - increased medical cost in the first year following RSV infection³
 - prolonged wheezing and increased risk for asthma development⁴
- No widely accepted drug available to treat RSV infections
 - Synagis[®] used as prophylaxis in high-risk pre-term infants only



**Evolves to
distressing
symptoms**

**Symptomatic treatment
including inhaled
corticosteroids & bronchodilator**

**8-20%
hospitalised**

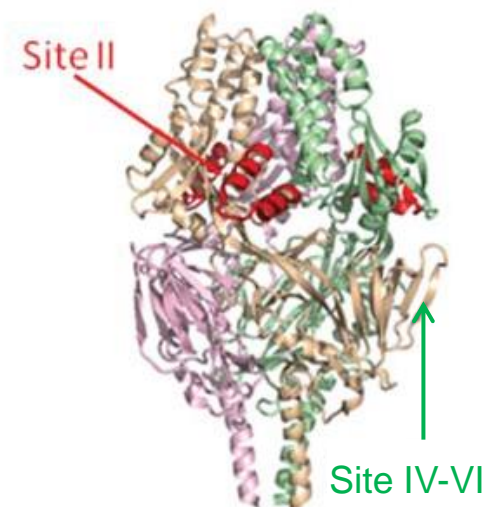
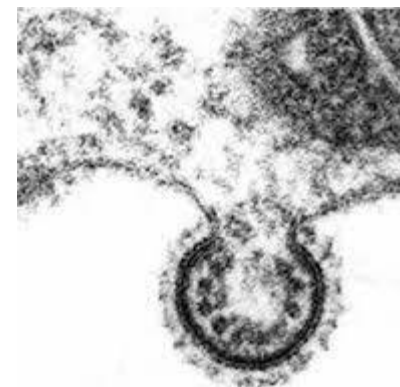
* Extrapolation based on estimated US prevalence

¹ Hall et al, NEJM, 2009; ² Lee et al, Human Vaccines, 2005; ³ Shi et al, J Med Econ, 2011; ⁴ Sigurs et al, Thorax, 2010; Backman et al, Acta Paediatr, 2014

Respiratory syncytial virus (RSV)

Generation of Nanobodies to the F-protein

- Glycoprotein F trimer
 - essential for viral entry/fusion of viral and host membranes
 - highly conserved
 - several neutralisable regions / epitopes



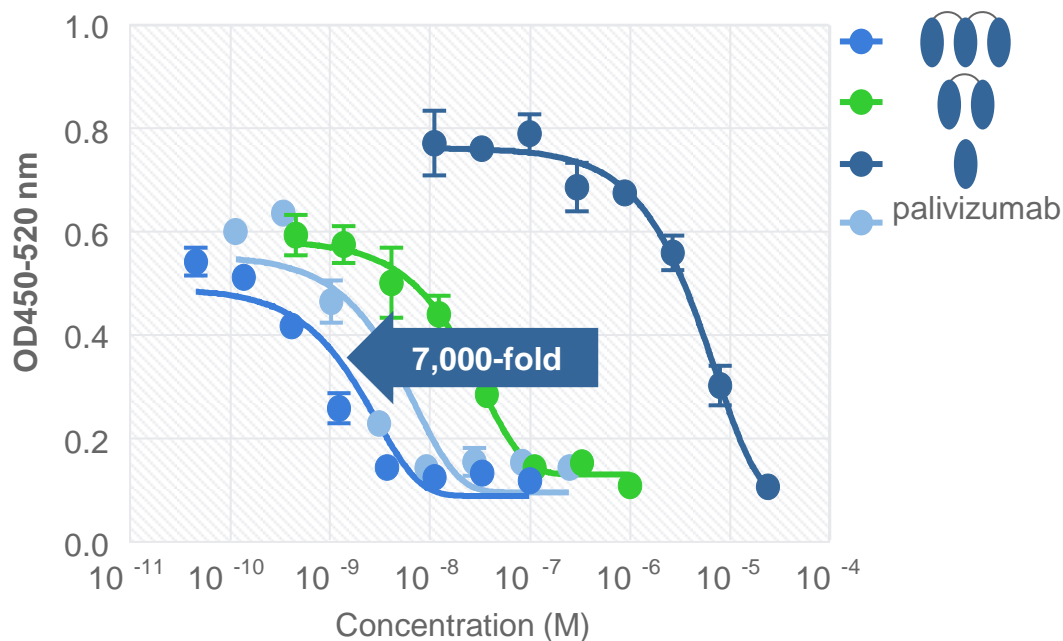
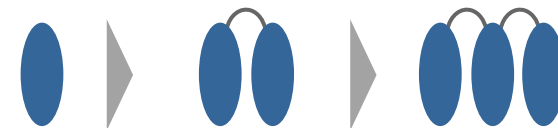
RSV F-protein
(pre-fusion)

McLellan *et al.* 2013 Science

Anti-RSV Nanobody ALX-0171

Multi-valent formatting to improve potency

- Tri-valent anti-RSV (ALX-0171)
 - improve activity and strain coverage by multi-valency
 - superior virus neutralisation as compared to palivizumab



Improved potency over mAb

Anti-RSV Nanobody ALX-0171

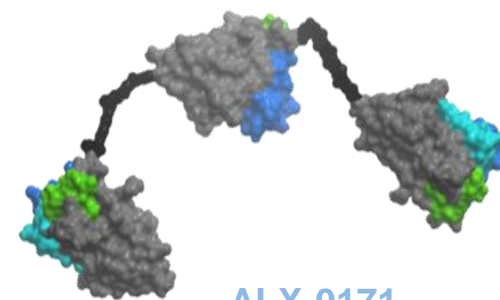
Increased strain coverage

- Tri-valent anti-RSV (ALX-0171)
 - 5-fold more clinical isolates neutralised below LLOD with ALX-0171 compared with palivizumab

	A-strain	B-strain	Total
n	32	29	61
palivizumab	0 (0%)	11 (38%)	11 (18%)
ALX-0171	30 (94%)	23 (79%)	53 (87%)
p value	<0.0001	<0.0001	<0.0001

Number of strains neutralised below LLOD

Increased strain coverage

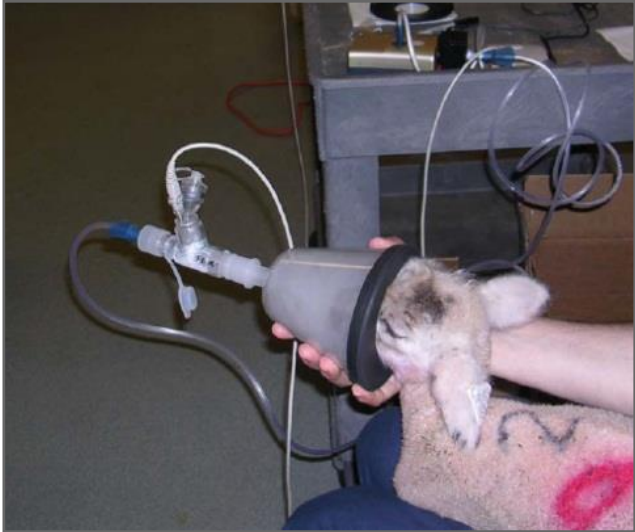


ALX-0171

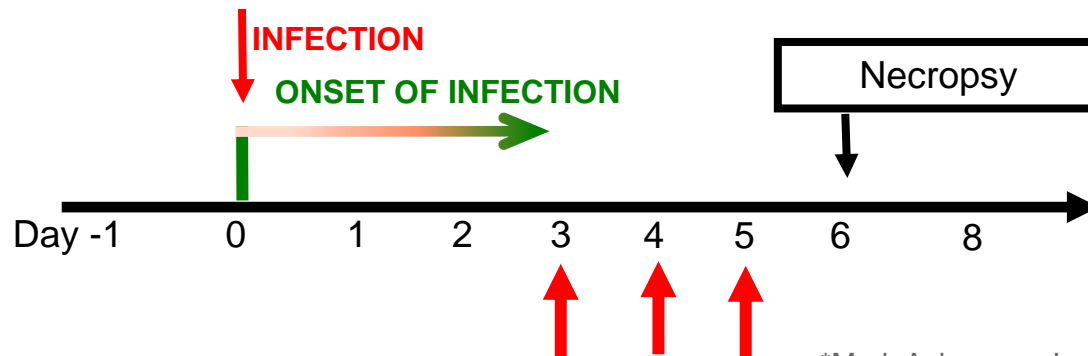
*anti-RSV
Nanobody*

Neonatal lamb model*

Study design



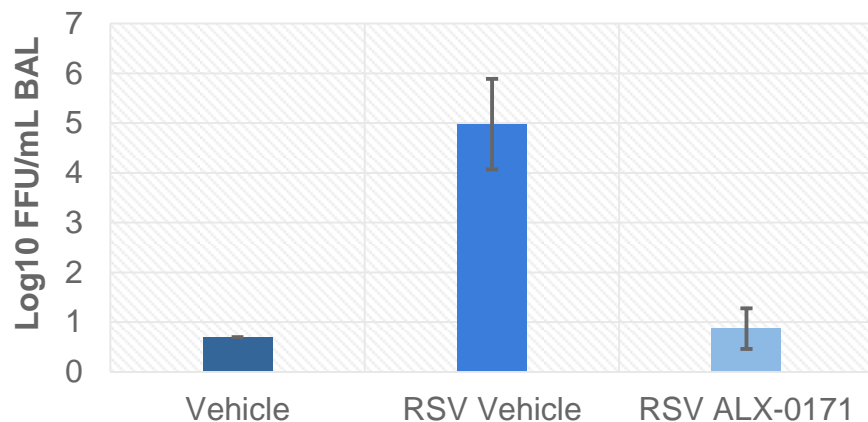
- Lambs develop lower respiratory tract infection which is associated with general malaise and specific lung pathology (comparable to infants)
- Treatment at peak of viral load on day 3 post infection (symptoms and lung pathology are already clearly present)
- Lambs develop clinical symptoms such as wheezing (comparable to infants)



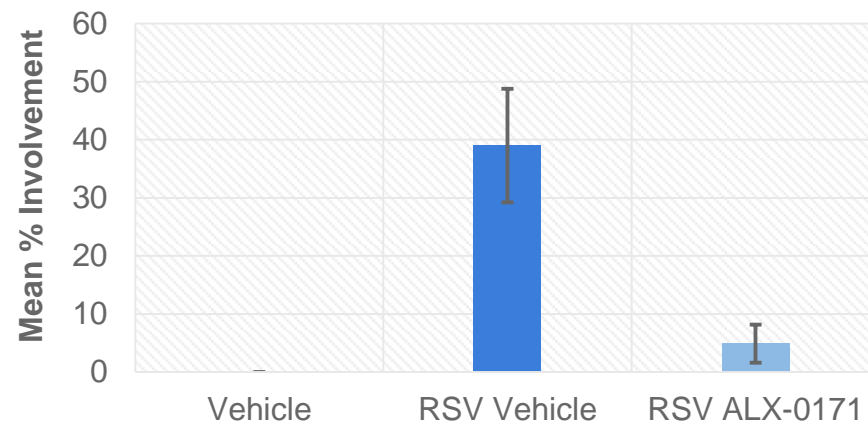
*Mark Ackerman, Iowa State University

In vivo proof-of-concept achieved

Mean viral titers in BALF
(day 6 post infection)



Lung viral lesions
(day 6 post infection)



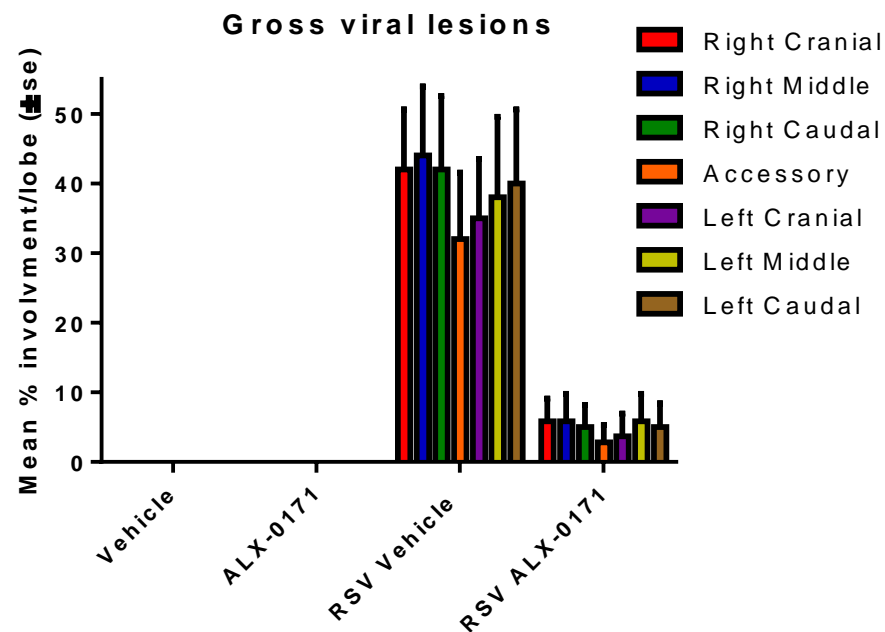
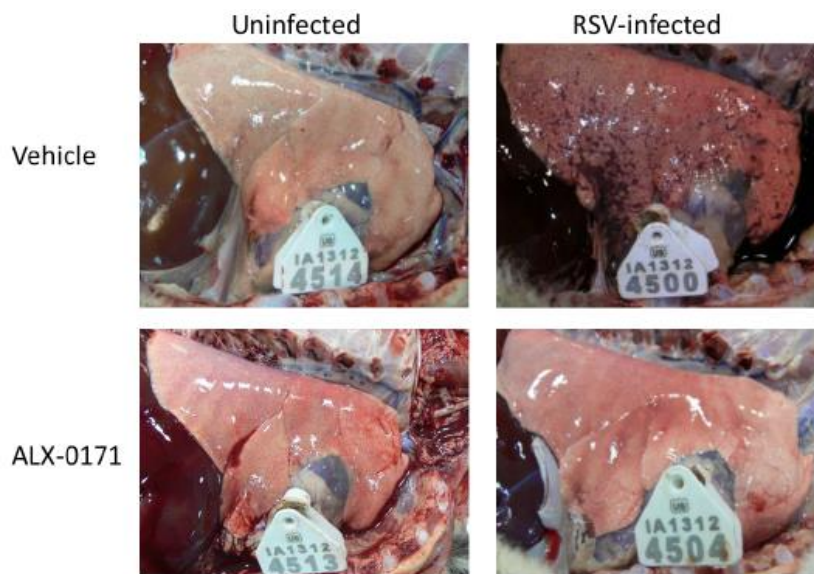
ALX-0171 treatment results in

- strong reduction of viral titres in bronchoalveolar lavage fluid (BAL)
- strong reduction of gross viral lung lesions (% involved lung tissue)
 - coincides with strong reduction F-protein expression
- a clear effect on general health status
 - weakness, depression, lethargy, drooping of ears, not eating

ALX-0171

Effect on viral lung lesions

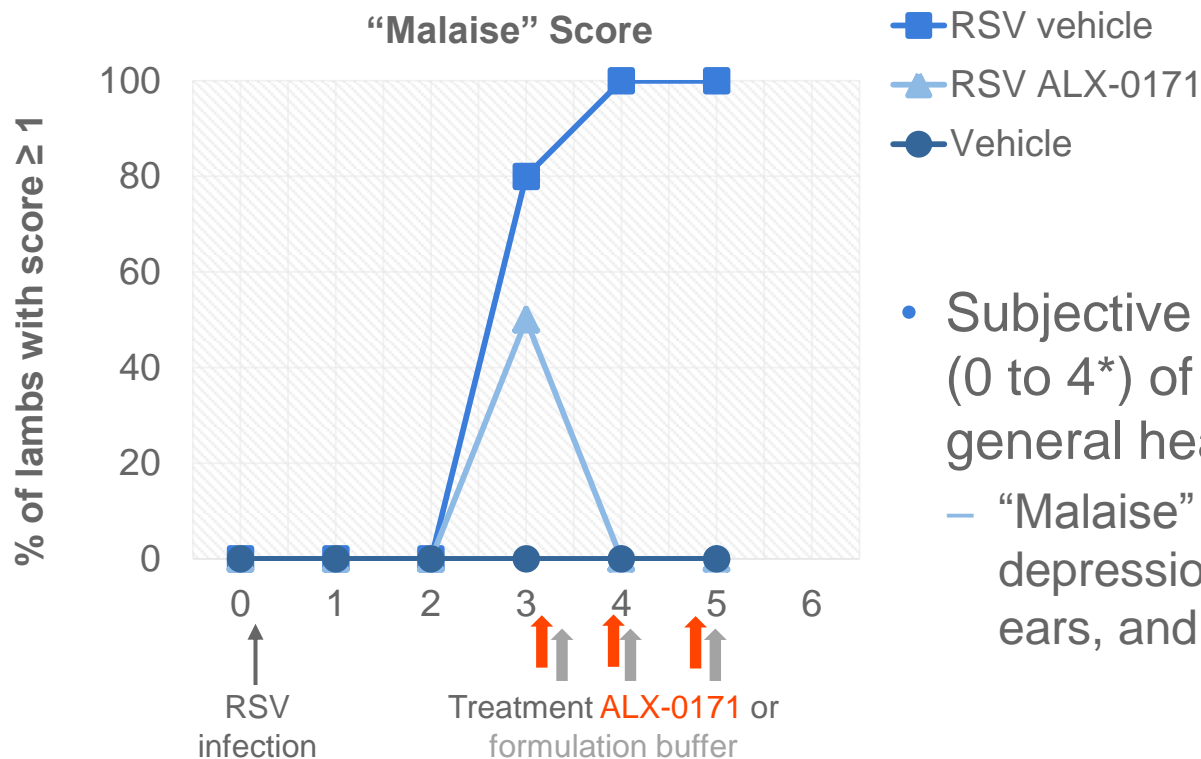
- Plum red RSV lesions seen in lungs of RSV-infected lambs on day 6 post-infection
 - present on all lung lobes assessed



Daily inhalation of ALX-0171 markedly reduced gross lung viral lesions

ALX-0171

Highly effective in RSV-infected lambs



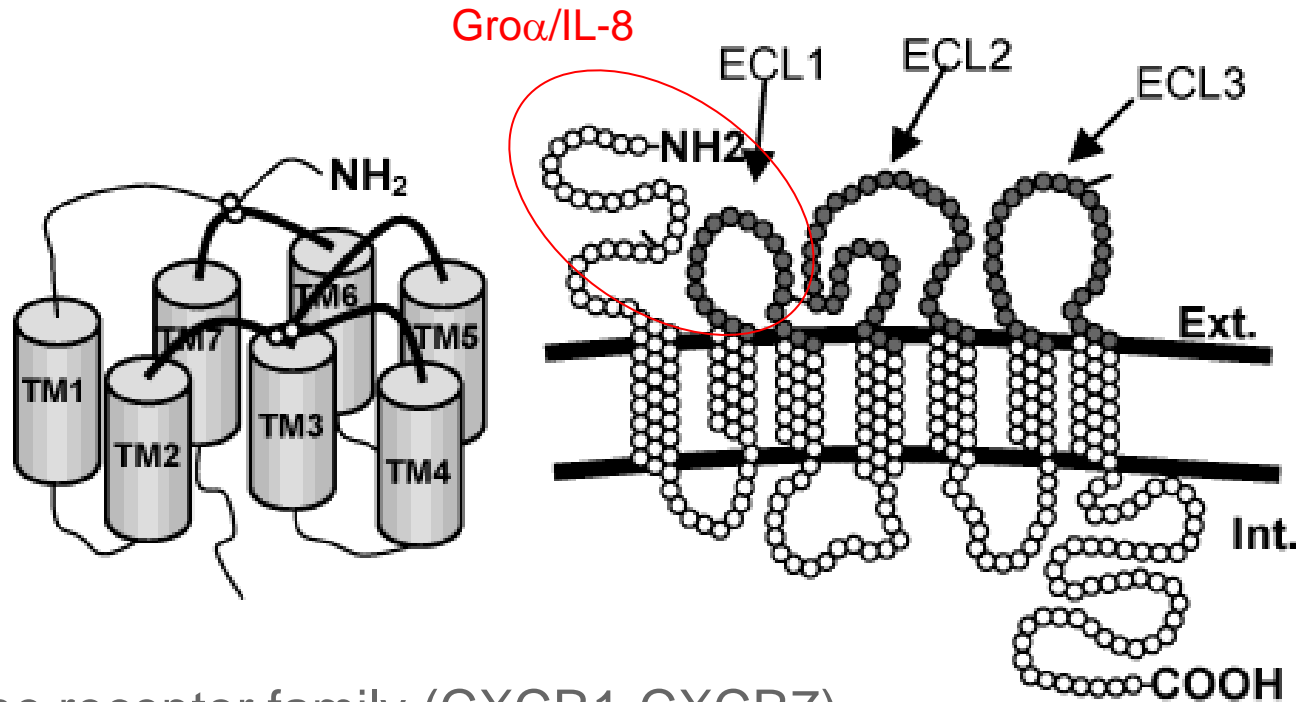
- Subjective scoring (0 to 4*) of parameters that measure general health
 - “Malaise” score: weakness, depression, lethargy, drooping of ears, and not eating

Daily inhalation of ALX-0171 markedly reduced symptoms of illness in RSV infected neonatal lambs

* 0 = no clinical signs; 4 = animals down

Current status and next steps

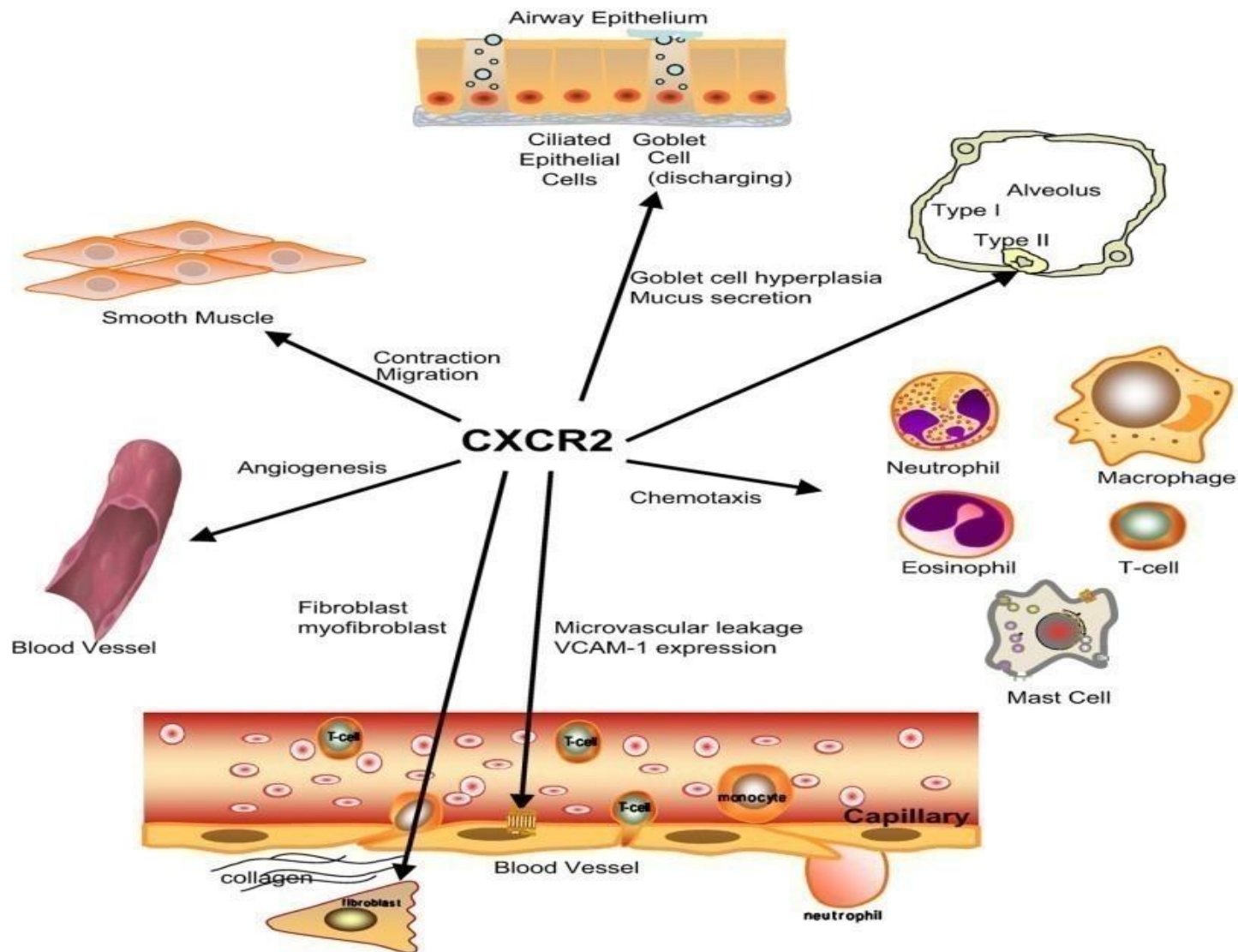
- Strong therapeutic effect demonstrated in a neonatal animal model for infant RSV infection
- Well tolerated in multiple Phase I studies in adults
- First-in-infant Phase IIa study initiated in Northern Hemisphere; lead-in phase successfully completed and confirmation to proceed with placebo-controlled phase of the study
- Recruitment of Phase IIa study to continue in parts of the southern hemisphere and Asia to complete recruitment in 2015 with results anticipated in H1 2016



- CXC chemokine receptor family (CXCR1-CXCR7)
- Binds multiple ligands incl $GRO\alpha$, IL-8, ENA-78, $GRO\beta$, $GRO\gamma$, GCP-2, NAP-2
- Human vs NHP
 - high sequence diversity at N-terminus, ECL2 and ECL3
- CXCR2 vs CXCR1
 - conserved EL1

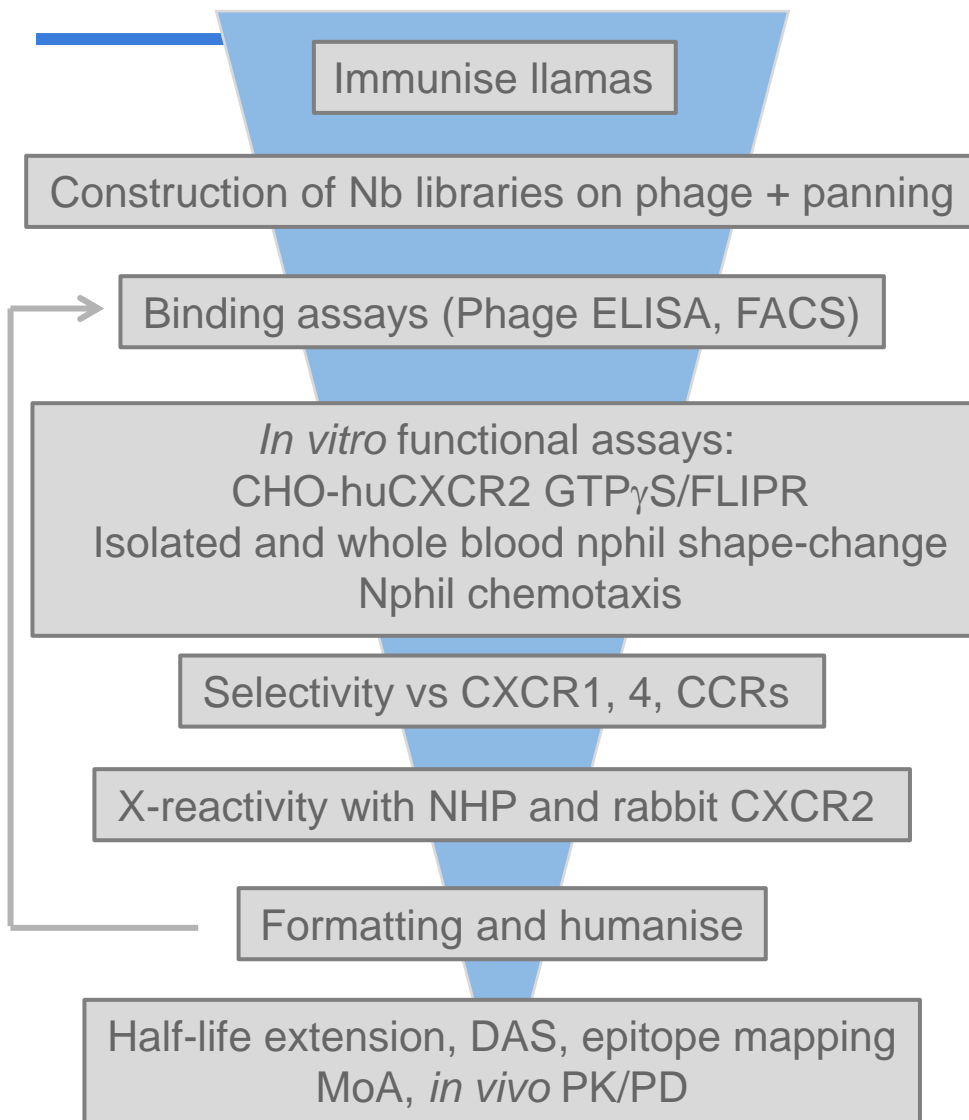
CXCR2

Scientific/Therapeutic Rationale



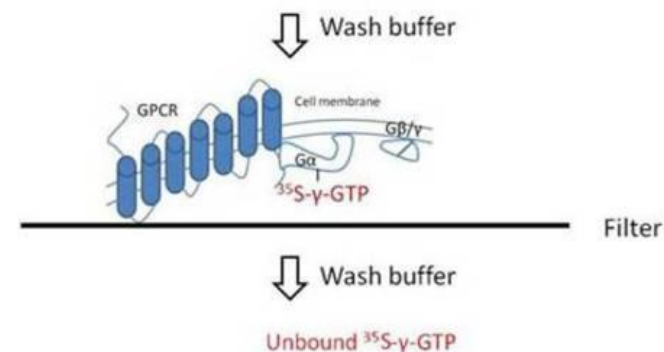
CXCR2

Generation of Nanobodies



3x RBL/huCXCR2 and 1x RBL/cyCXCR2

3 rounds of panning against whole cells,
cell membranes, peptides



77 % homology with CXCR1
33 % homology with CXCR4

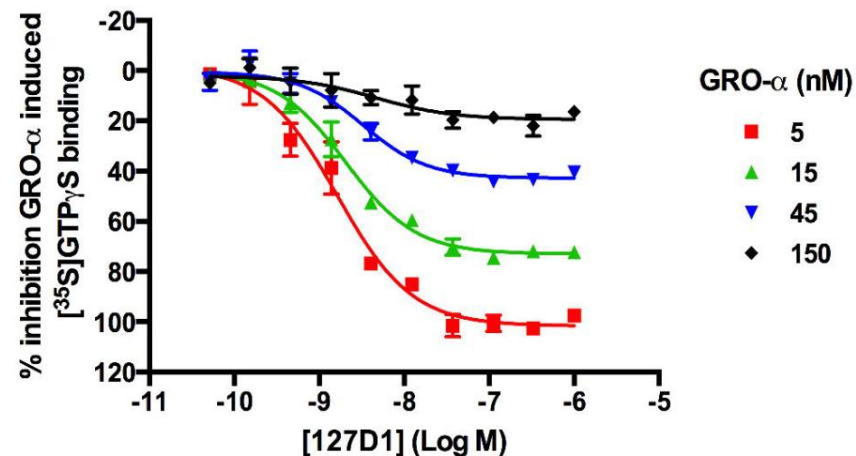
92 % homology with cyCXCR2
73 % homology with rabbitCXCR2

CXCR2 lead Nanobodies

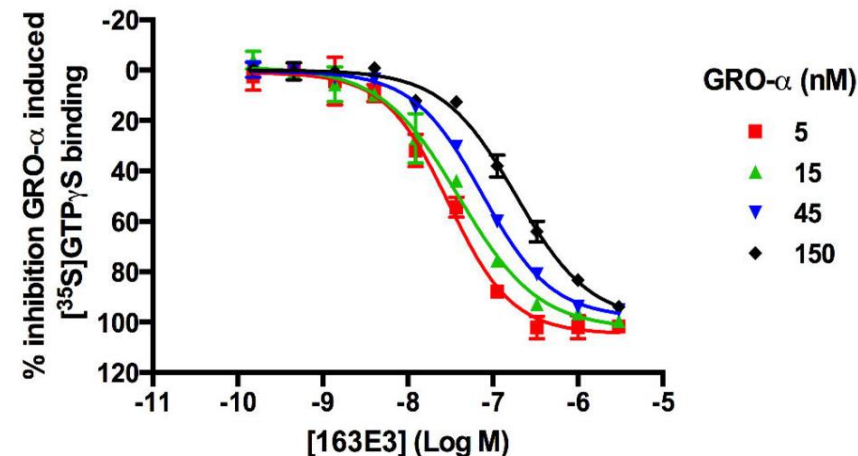
Two classes with distinct properties

- Large panel of Nanobodies identified
- Class 1 (Nb 127D1)
 - bind to 1-19 N-terminal peptide
 - partial but very potent inhibition of $\text{GRO}\alpha$ -activation
- Class 2 (Nb 163E3)
 - do not bind to 1-19 N-terminal peptide
 - full but less potent inhibition of $\text{GRO}\alpha$ -binding
- Bind to human and cynomolgus CXCR2
- Nanobodies do not bind CXCR1

Class 1

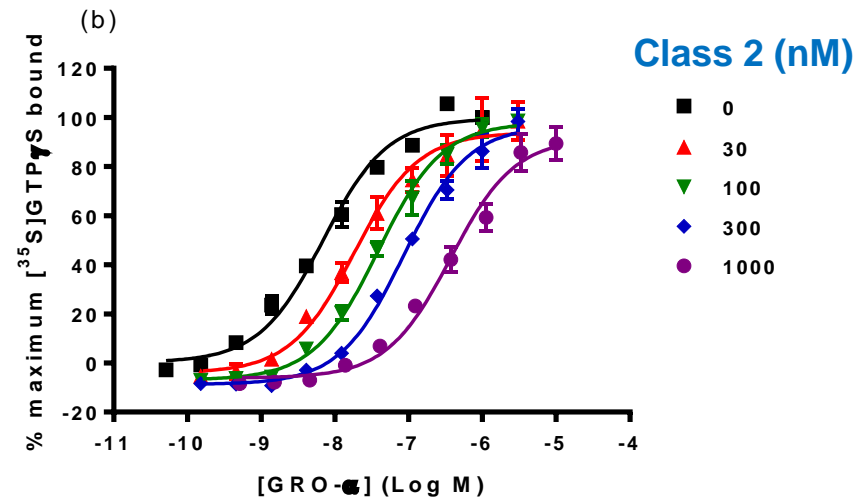
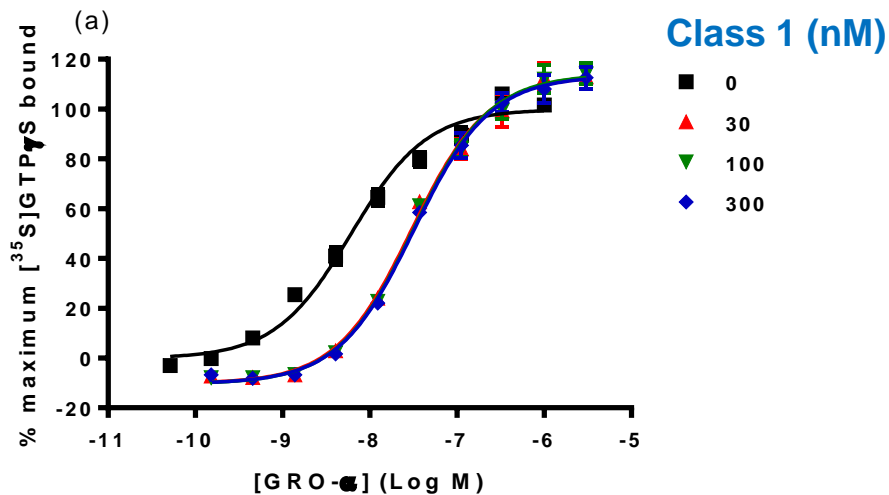


Class 2

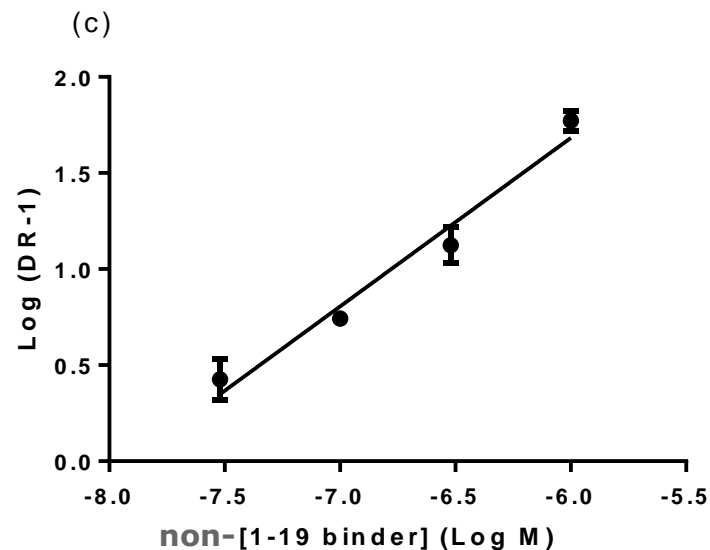


CXCR2 Nanobodies

Understanding the MoA



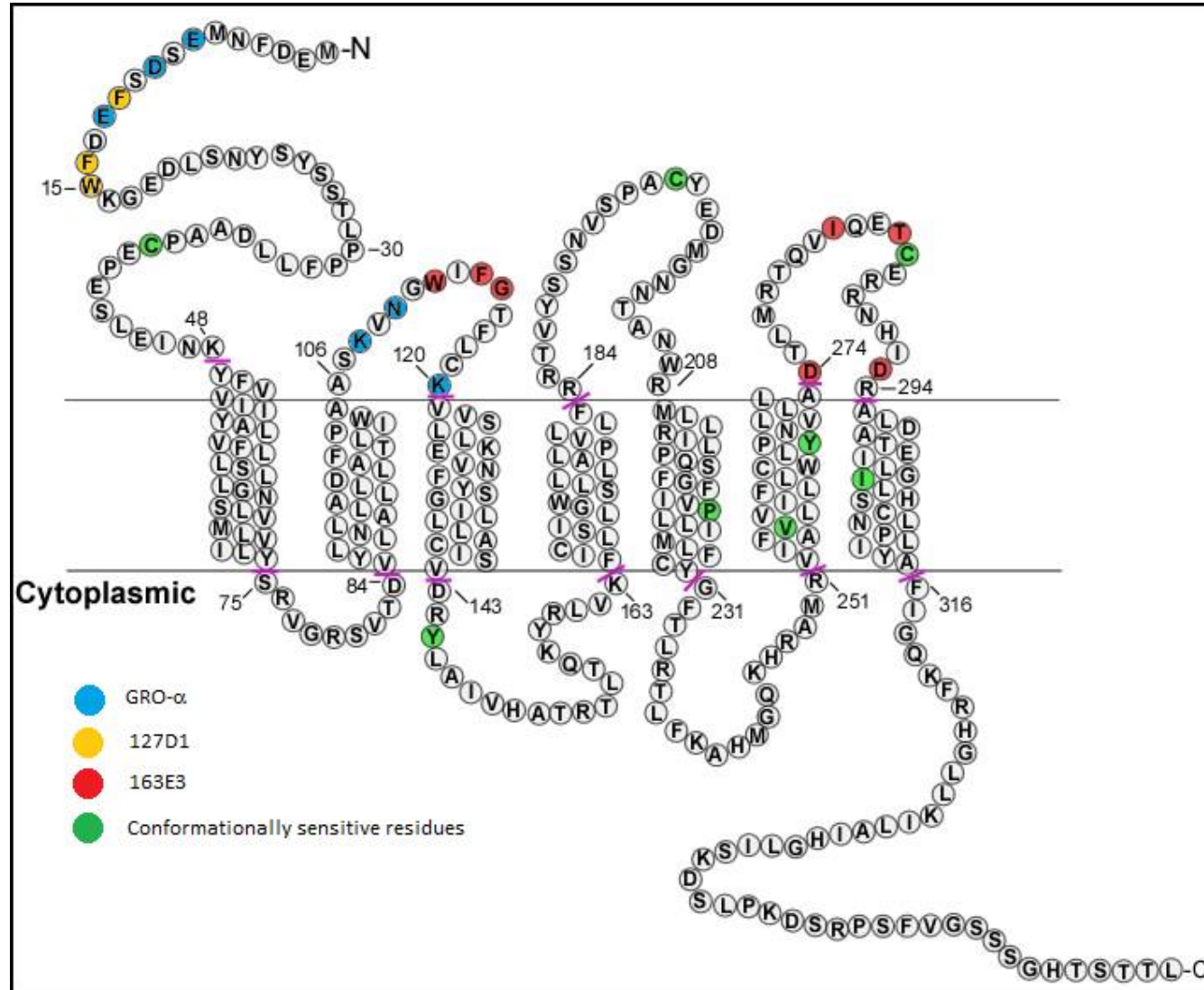
- Schild experiments performed using GRO- α -stimulated $[^{35}\text{S}]\text{GTP}\gamma\text{S}$ binding in the presence of a range of concentrations of
 - (a) Class 1 Nb (1-19 binder)
 - (b) Class 2 Nb (non-1-19 binder)
 - (c) Schild plot for Class 2 binder derived from data shown in (b)



CXCR2 Nanobodies

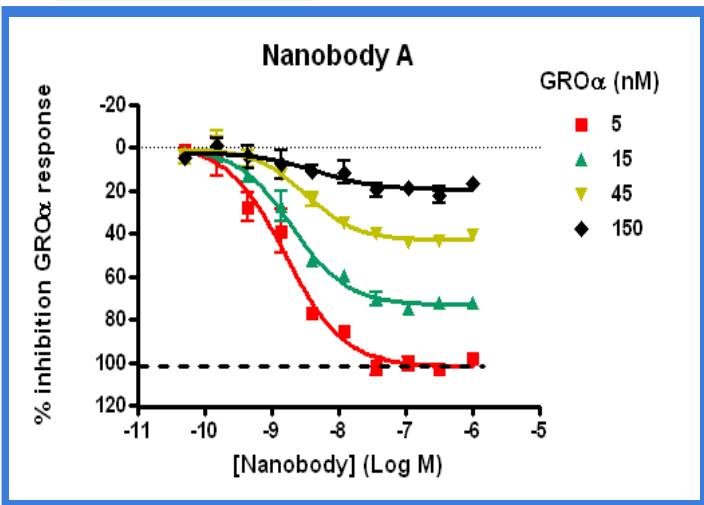
Where do they bind?

- Class 1
 - N-terminal peptide
 - linear epitope
- Class 2
 - ECL1 and ECL3
 - complex epitope
 - conformationally sensitive
- Class 1 and 2 recognize non-overlapping epitopes

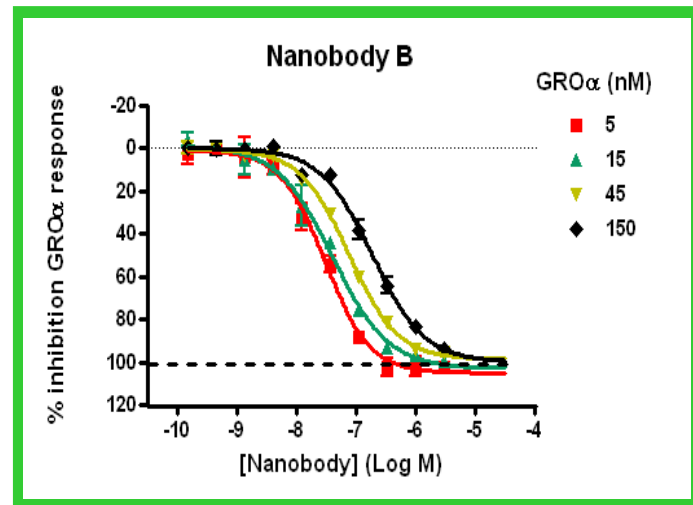
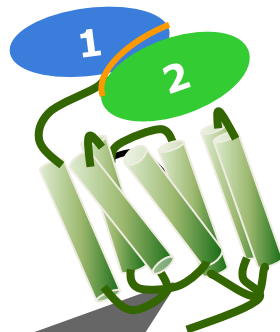
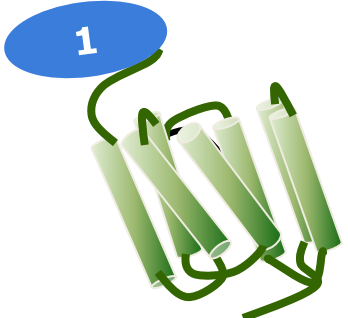


Nanobody formatting

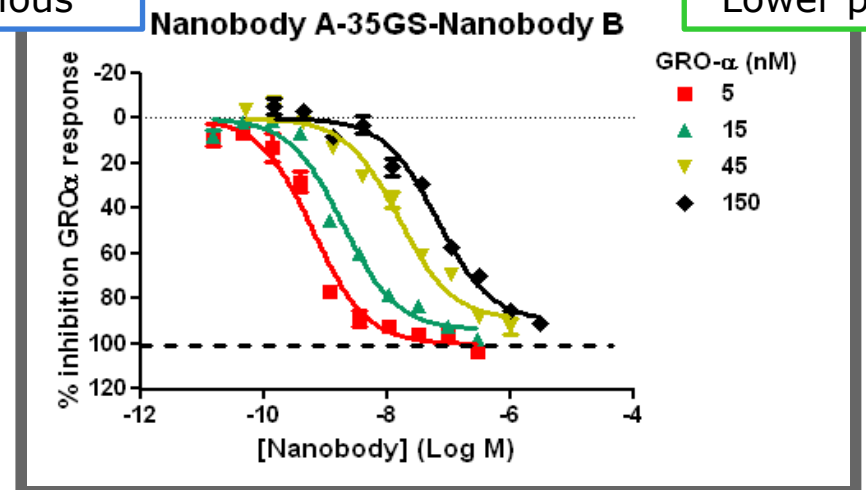
Biparatomic format yields the required potency and efficacy



Potent but not efficacious



Lower potency but efficacious



Biparatomic is both potent and efficacious

RSV

Ablynx, Gent, Belgium

Koen Allosery, Patricia Crabbe, Joke D'Artois, Veronique De Brabandere, Steven De Bruyn, Erik Depla, Bram De Rammelaere, Tim De Smedt, Katrien Derveaux, Laurent Detalle, Holger Neecke, Thomas Stohr, Catelijne Stortelers, Katrien Vlassak, and the subteams from the Discovery, Pharma, CMC and ClinDev departments

Iowa State University

Mark Ackermann, Jack Gallup, Albert Van Geelen, Alejandro Larios

Baylor College of Medicine, Houston, TX

Brian Gilbert, Pedro A Piedra
(Dept Mol. Virol. & Microbiol. Dept Paediatrics)

Instituto de Salud Carlos III, Madrid, Spain

José Melero, Olga Cano, Concepción Palomo
(Centro Nacional de Microbiología)

Aragen Bioscience, Inc

Malavika Ghosh, Rashmi Munshi

IWT, Belgium

Grant 100333 and 130562

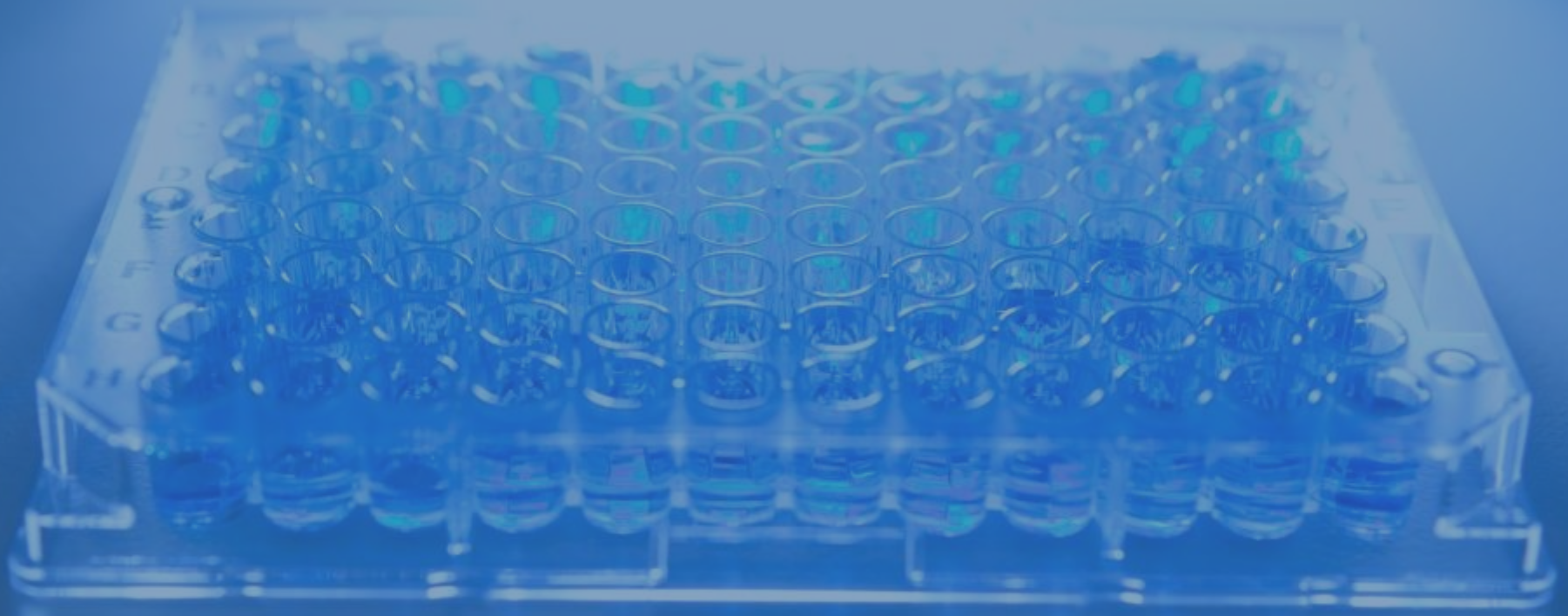
CXCR2

Ablynx, Gent, Belgium

Bruno Dombrecht, David Vlerick, Toon Laeremans, Soren Steffensen, A Roobrouck, S De Taeye, K Van den Heede, Karen Cromie

Novartis, NIBR, Horsham, UK

Zarin Brown, James Hunt, Michelle Bradley, SJ Charlton, Jodie Manini, Jenny Willis, Andrew Green, Emma Grot, Jack Heath, Suchete Hunjan



Questions

CONTACT DETAILS

Investor
Relations



+32 9 262 00 00



investors@
ablynx.com



www.ablynx.com

