Ablynx

Nanobodies®
Innovative therapeutics

Nanobodies® – A Versatile Advanced Therapeutic Platform

G Van Heeke

April 21, 2015

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Ablynx

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

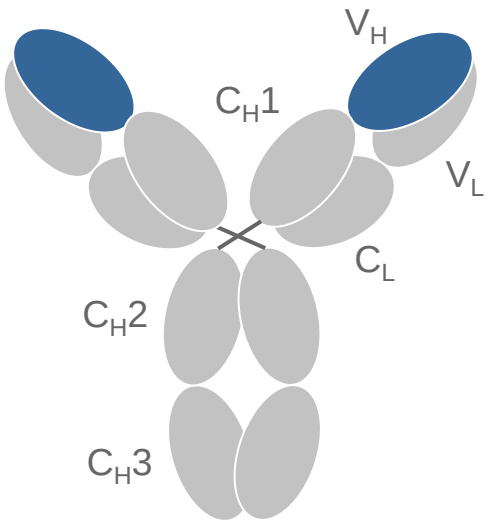
FINANCIALS

- €206M in cash at December 31st 2014

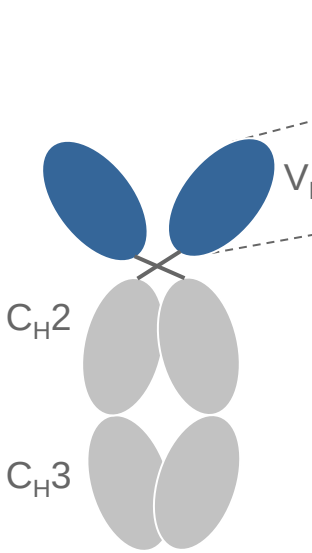
Nanobodies

Derived from heavy-chain only antibodies

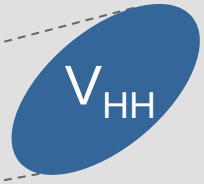
- *Camelid* heavy-chain only antibodies are stable and fully functional
- Nanobodies represent the next generation of antibody-derived biologics



Conventional antibodies



Heavy chain only antibodies



12-15kDa

Ablynx's Nanobody

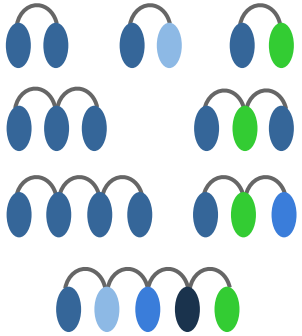
- small
- robust
- sequence homology comparable to humanised/human mAbs
- easily linked together
- nano- to picomolar affinities
- intractable targets
- multiple administration routes
- manufacturing in microbial cells

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

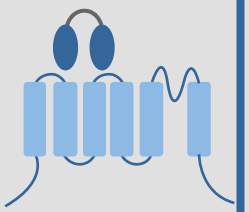
Nanobody platform

Competitive advantages

Mix and match

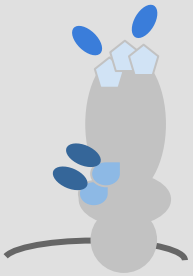
Targeting different pathways at once with a single Nanobody construct, e.g. multiple checkpoint inhibitors

Challenging and intractable targets



Nanobodies against ion channels and GPCRs

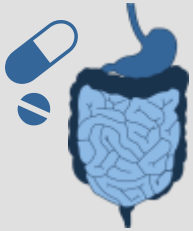
Nanobodies can reach conserved cryptic epitopes



Alternative delivery routes

Inhalation

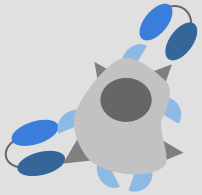
Needle-free



Oral-to-topical

Ocular

Cell- /tissue-homing



Cell specificity

Immune cell recruitment

Tissue-specific targeting

Customised half-life extension

Weeks/days/hours

Fc

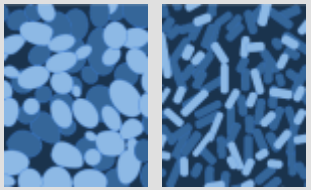
Albumin-binding Nanobody

Cell killing

Nanobody-drug conjugates

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 infection[3]
  - prolonged wheezing and increased risk for asthma development[4]

- No widely accepted drug available to treat RSV infections
  - Synagis® used as prophylaxis in high-risk pre-term infants only



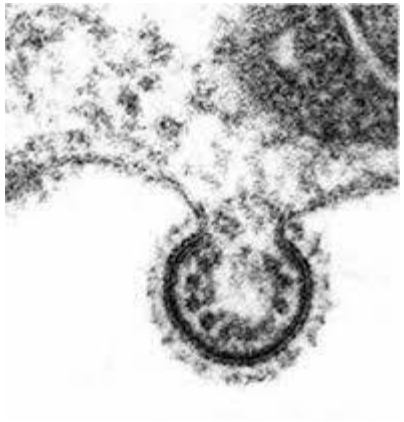

Evolves to distressing symptoms → **Symptomatic treatment including inhaled corticosteroids & bronchodilator** → **8-20% hospitalised**

* Extrapolation based on estimated US prevalence

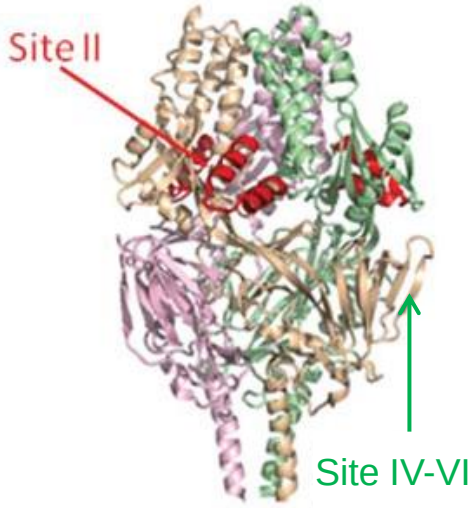
[1] Hall et al, NEJM, 2009; [2] Lee et al, Human Vaccines, 2005; [3] Shi et al, J Med Econ, 2011; [4] Sigurs et al, Thorax, 2010; Backman et al, Acta Pediatr, 2014

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



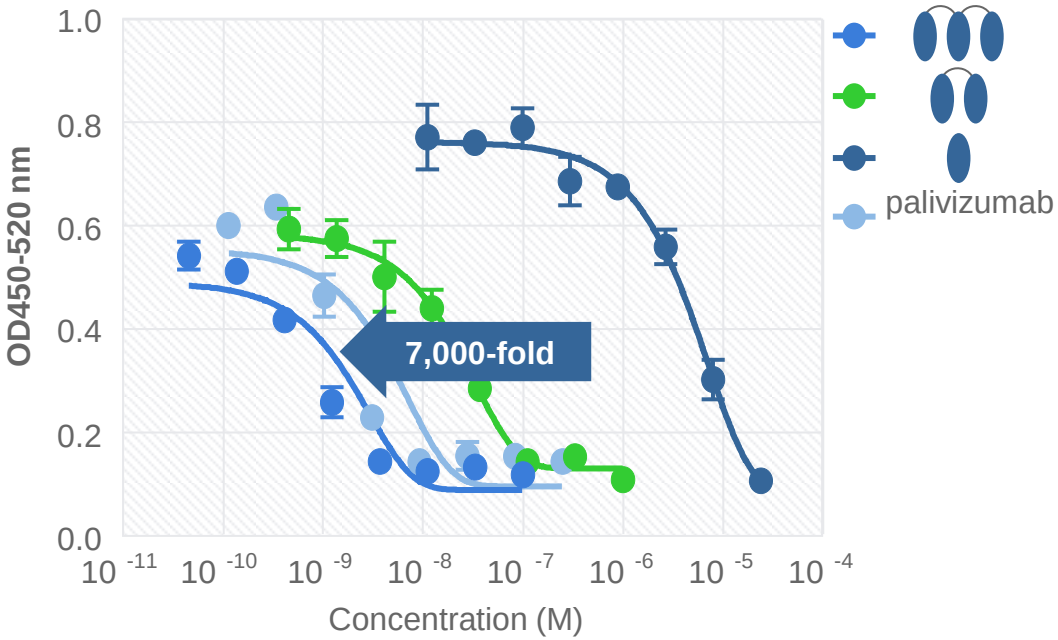
RSV F-protein
(pre-fusion)

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

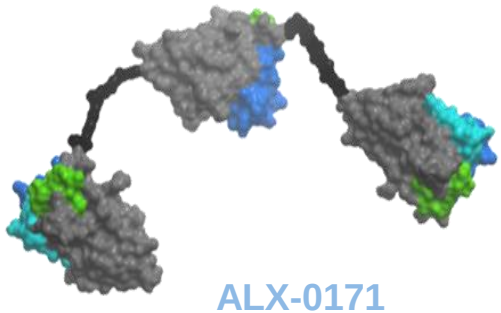
Increased strain coverage

- 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

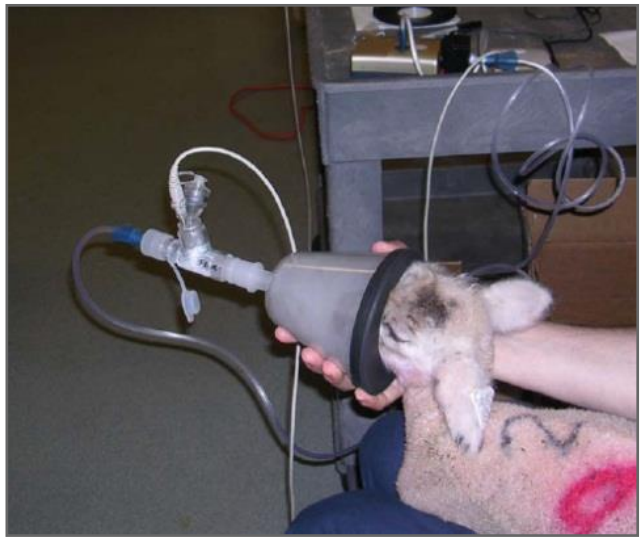


ALX-0171

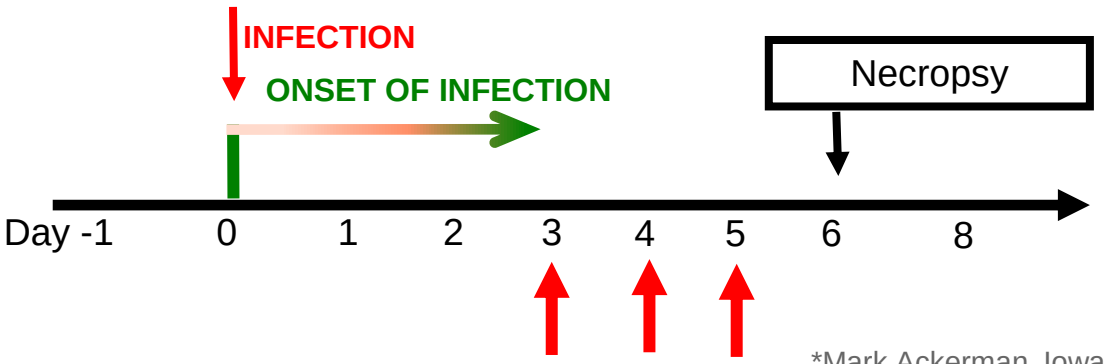
anti-RSV Nanobody

Neonatal lamb model*

Study design



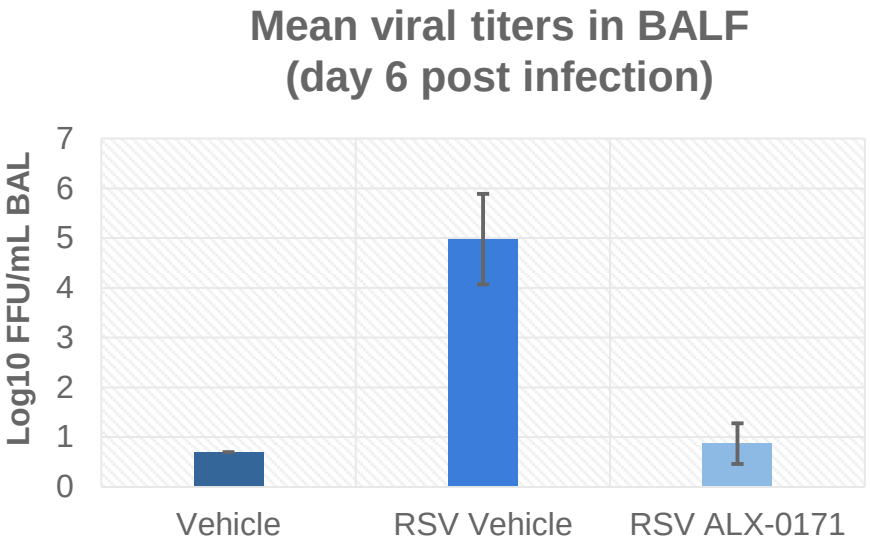
- Lambs develop lower respiratory tract infection which is associated with general malaise and specific lung pathology (comparable to infants)
- Treatment at peak of viral load on day 3 post infection (symptoms and lung pathology are already clearly present)
- Lambs develop clinical symptoms such as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

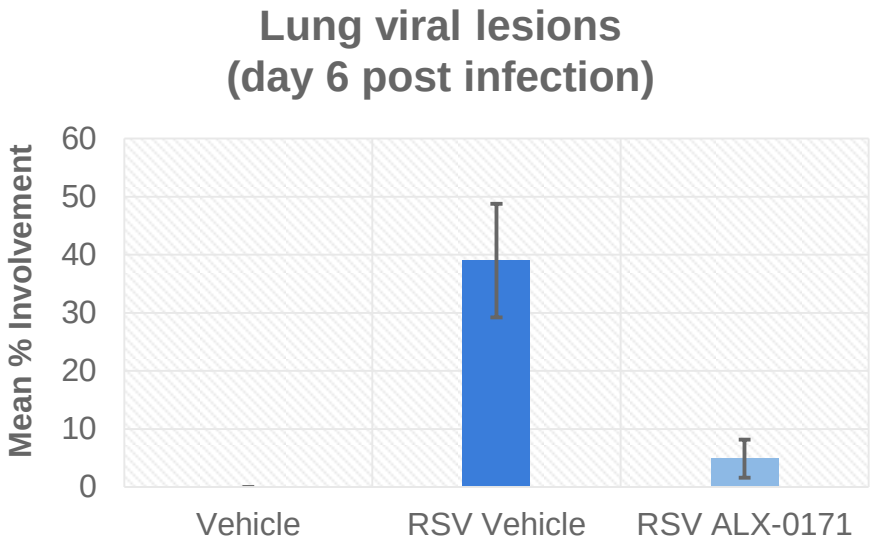


*Mark Ackerman, Iowa State University

ALX-0171

In vivo proof-of-concept achieved





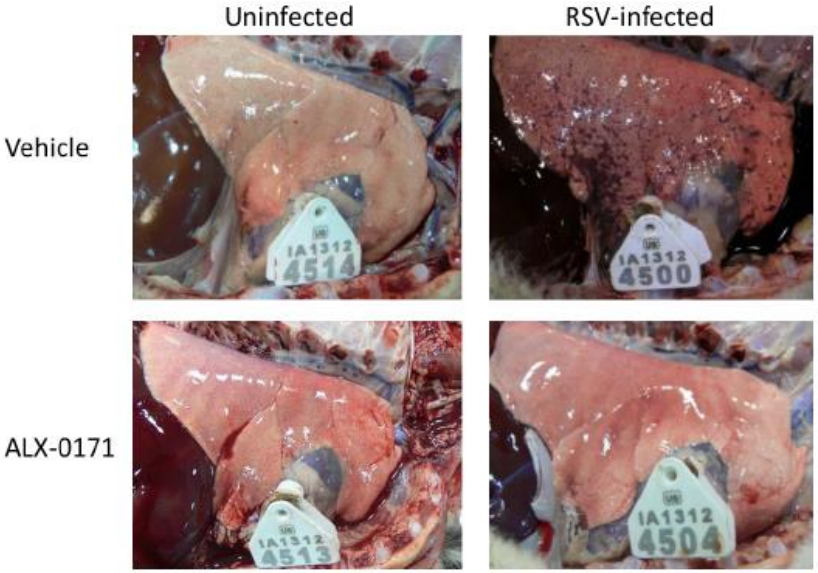
ALX-0171 treatment results in

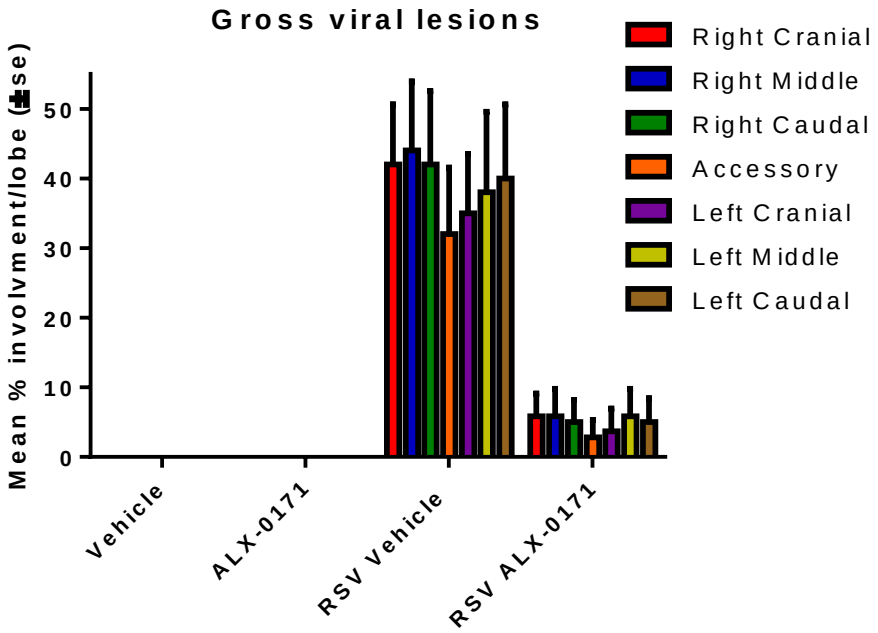
- strong reduction of viral titres in bronchoalveolar lavage fluid (BAL)
- strong reduction of gross viral lung lesions (% involved lung tissue)
  - coincides with strong reduction F-protein expression
- a clear effect on general health status
  - weakness, depression, lethargy, drooping of ears, not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

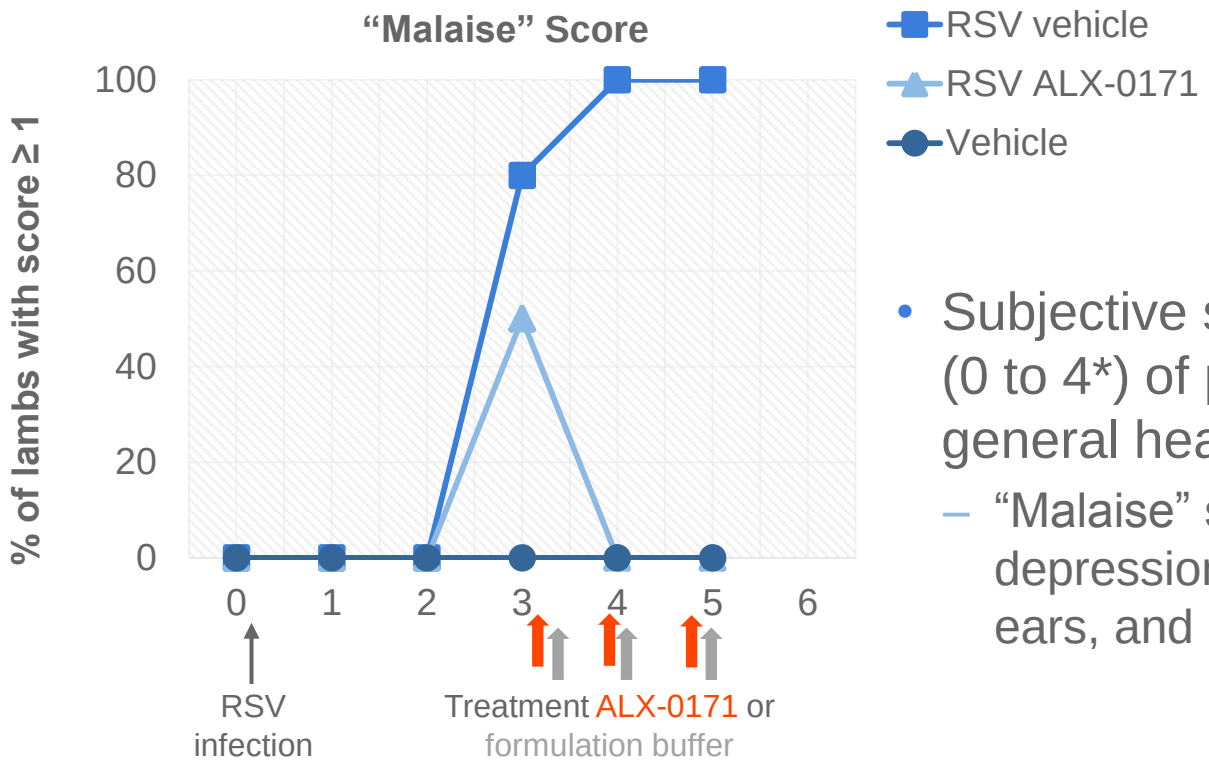




Daily inhalation of ALX-0171 markedly reduced gross lung viral lesions

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

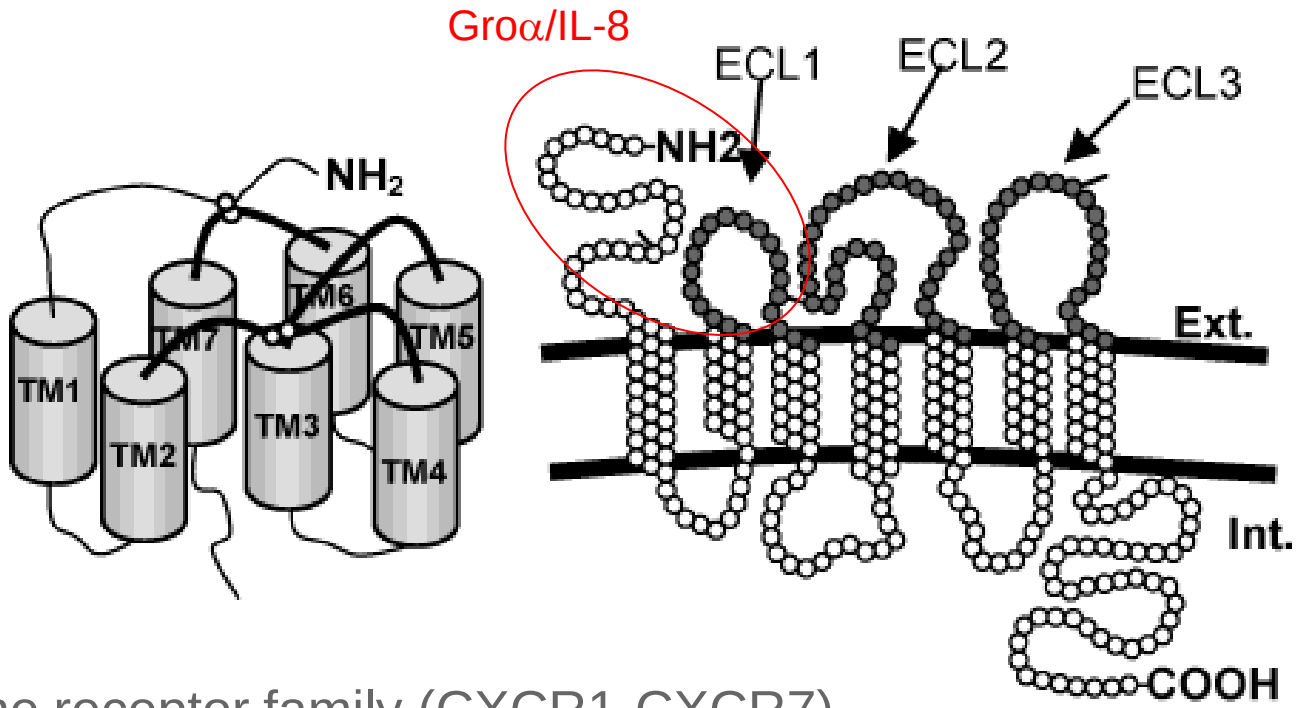
- * 0 = no clinical signs; 4 = animals down

ALX-0171

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

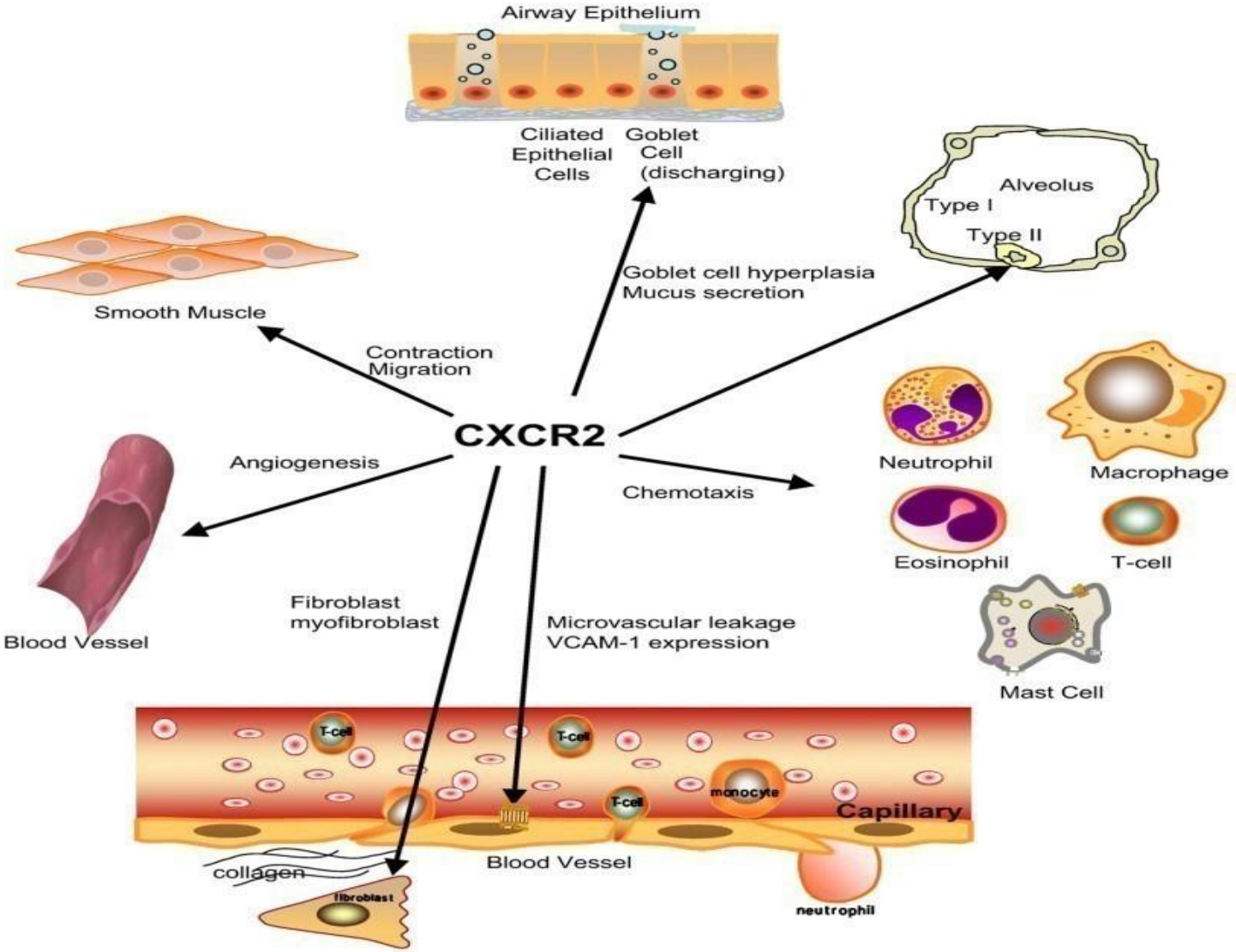
CXCR2



- CXC chemokine receptor family (CXCR1-CXCR7)
- Binds multiple ligands incl GROα, IL-8, ENA-78, GROβ, GROγ, 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

Immunise llamas

Construction of Nb libraries on phage + panning

Binding assays (Phage ELISA, FACS)

In vitro functional assays:
CHO-huCXCR2 GTPγS/FLIPR
Isolated and whole blood nphil shape-change
Nphil chemotaxis

Selectivity vs CXCR1, 4, CCRs

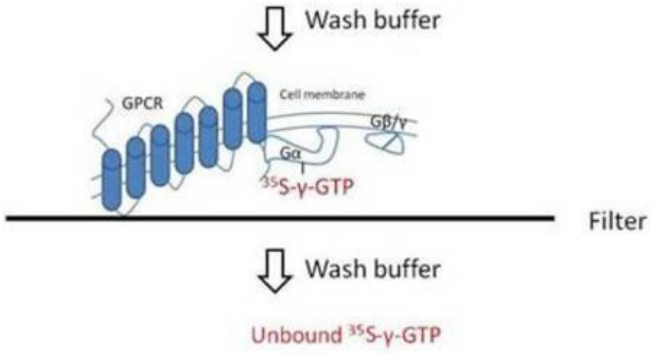
X-reactivity with NHP and rabbit CXCR2

Formatting and humanise

Half-life extension, DAS, epitope mapping
MoA, *in vivo* PK/PD

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

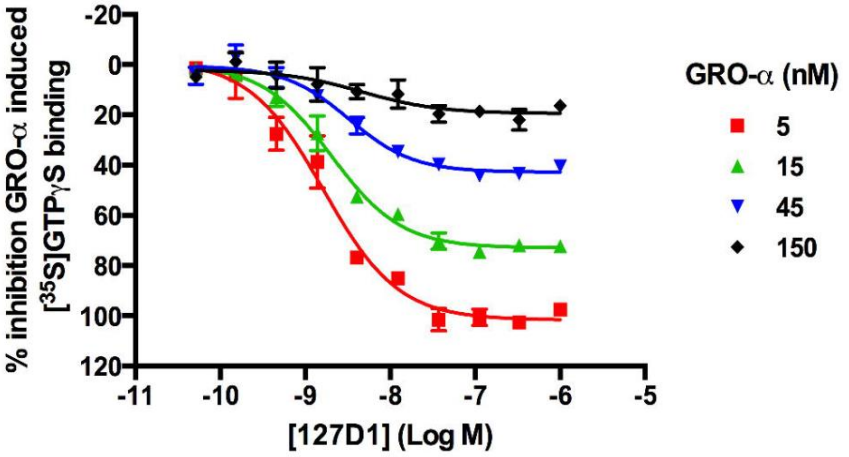
92 % homology with cyCXCR2
73 % homology with rabbitCXCR2

CXCR2 lead Nanobodies

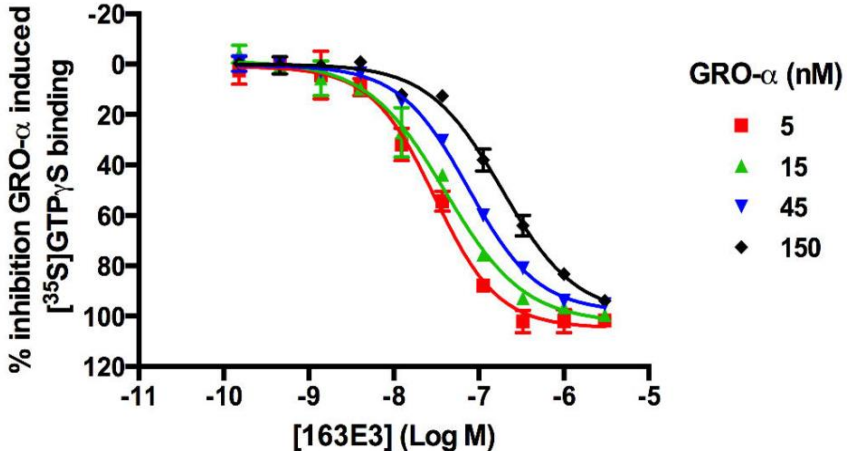
Two classes with distinct properties

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

Class 1



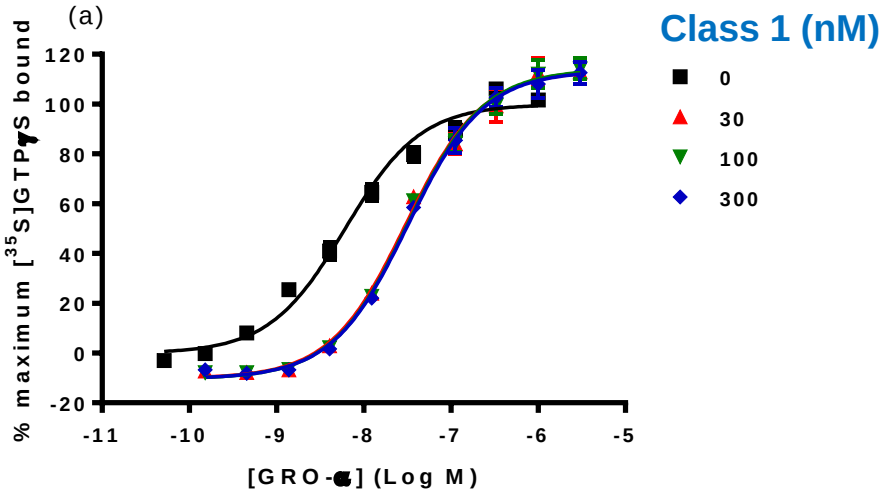
Class 2

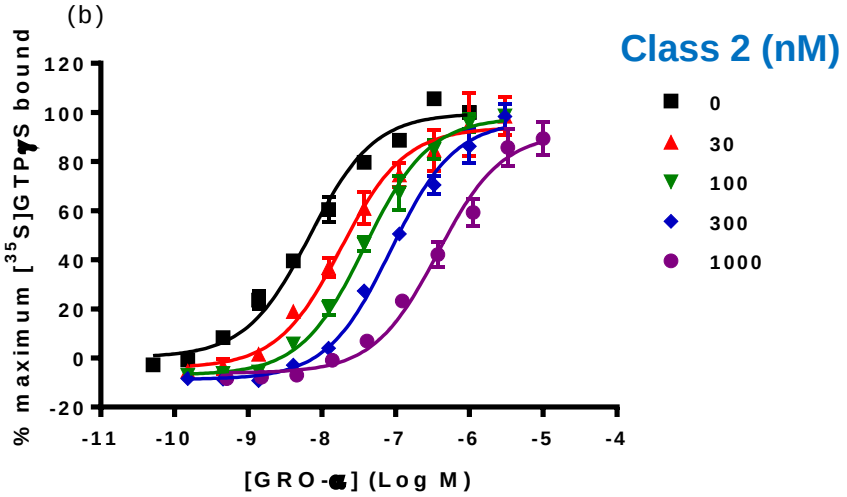


M. Bradley, B. Dombrecht *et al.*, (2015) Mol Pharmacol. 87(2):251-62

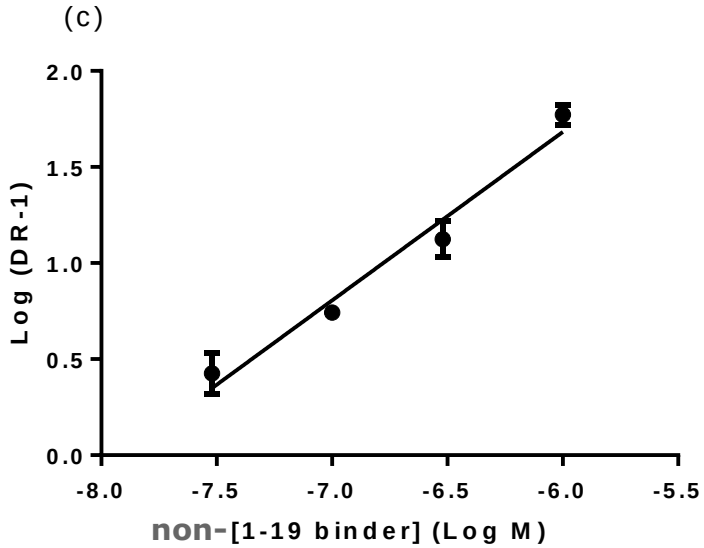
CXCR2 Nanobodies

Understanding the MoA





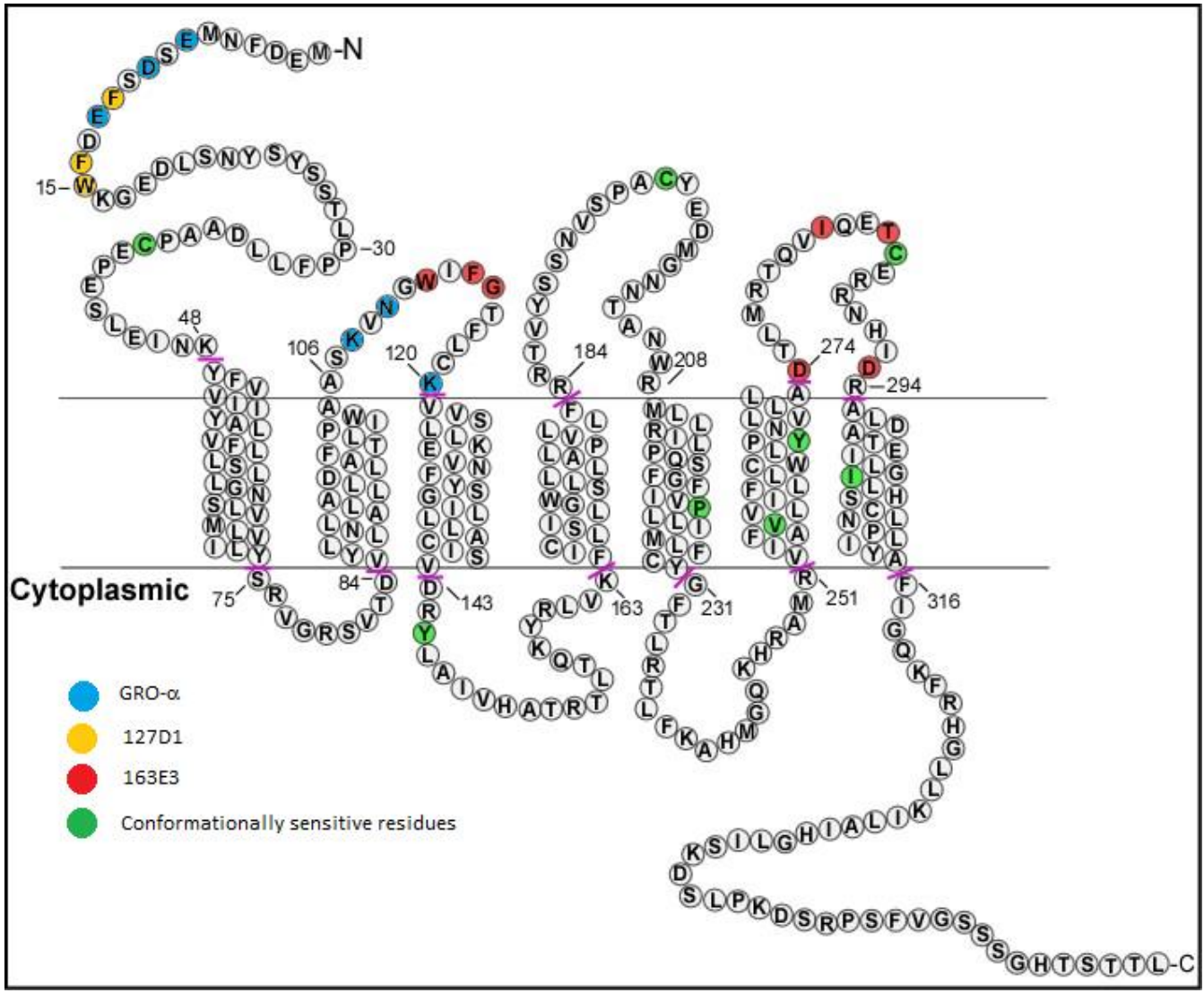
- Schild experiments performed using GRO-α-stimulated [^{35}S]GTPγS binding in the presence of a range of concentrations of
  - (a) Class 1 Nb (1-19 binder)
  - (b) Class 2 Nb (non-1-19 binder
  - (c) Schild plot for Class 2 binder derived from data shown in (b)



CXCR2 Nanobodies

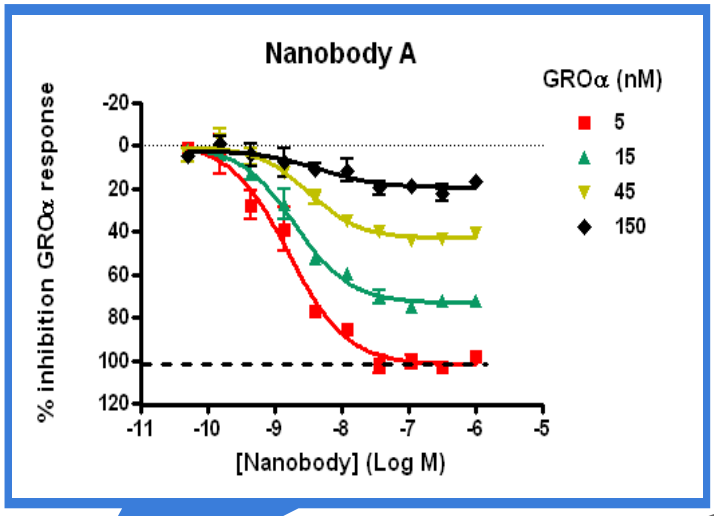
Where do they bind?

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

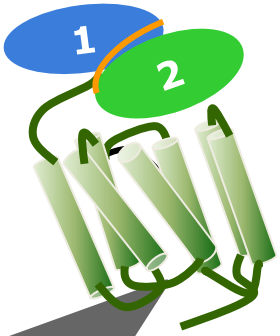


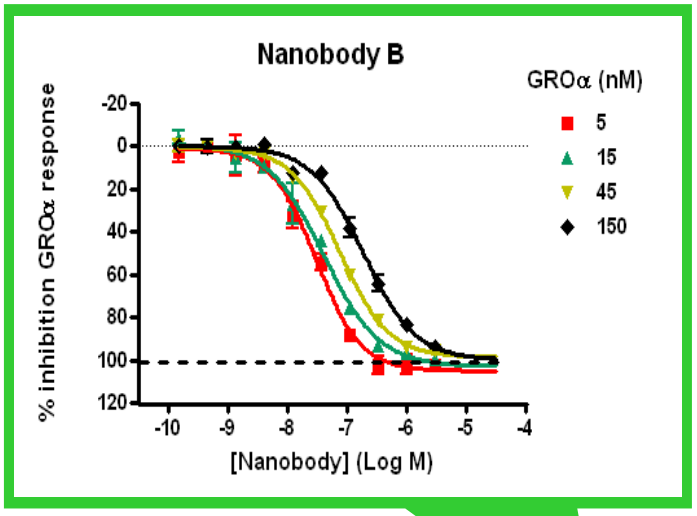
Nanobody formatting

Biparatopic format yields the required potency and efficacy

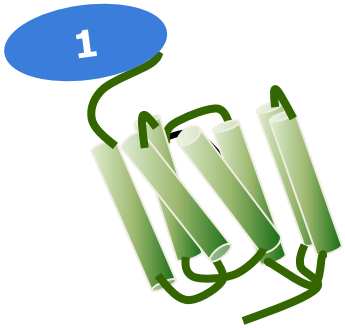


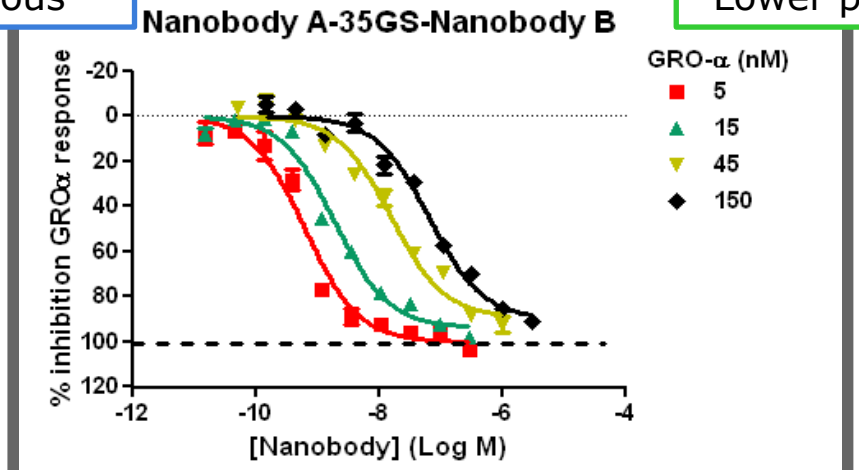
Potent but not efficacious



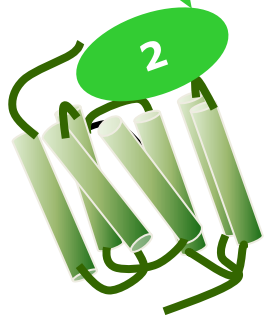


Lower potency but efficacious





Biparatopic is both potent and efficacious



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CXCR2

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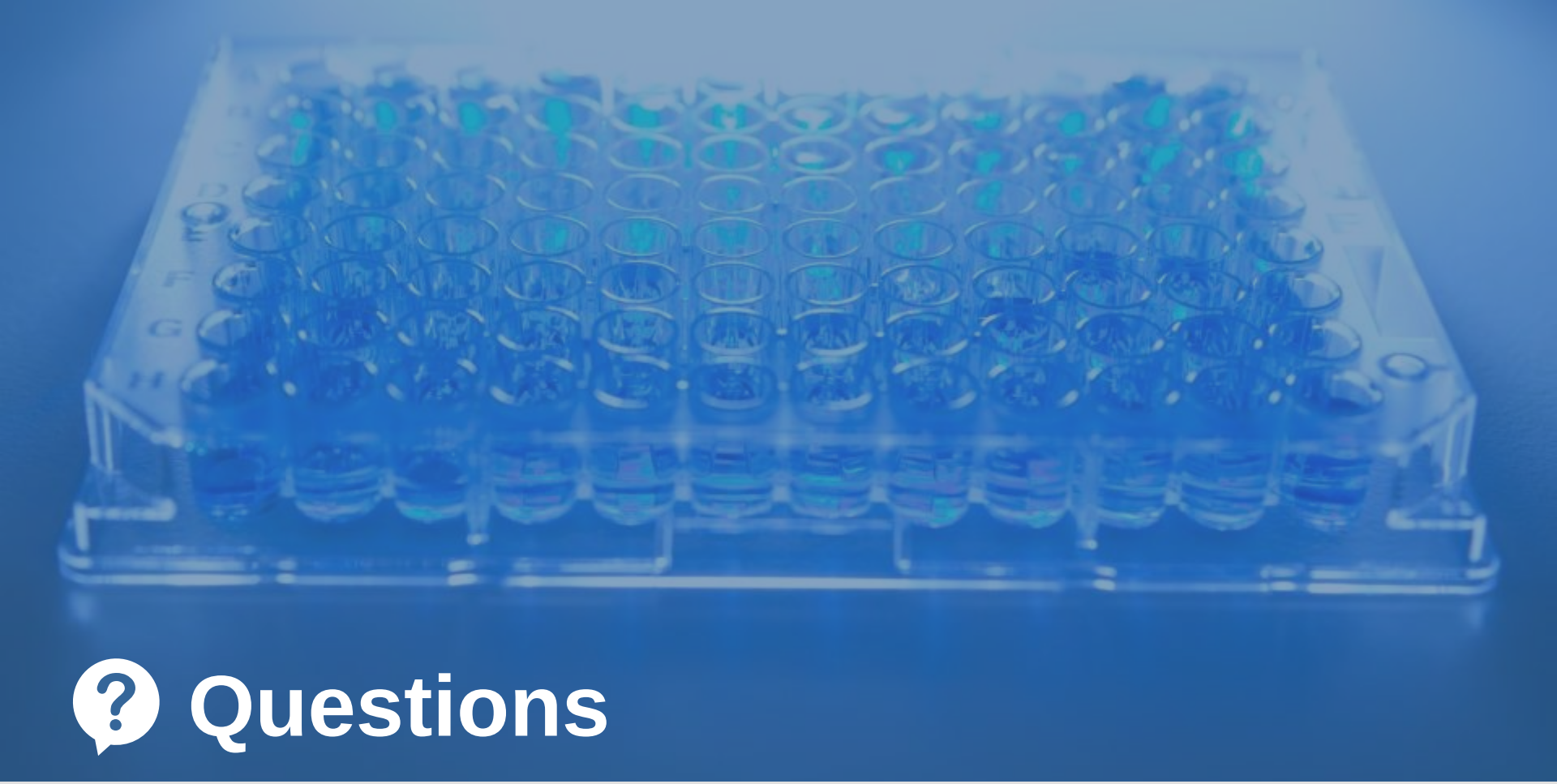

Questions

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