ASX Announcement/Press Release | 2 December 2024
AdAlta Limited (ASX:1AD)

AdAlta to present at ASCEPT, APFP & APSA Joint Congress

Key highlights

- AdAlta's Senior Scientist II Jason Lynch will make an invited presentation at the 2024 ASCEPT, APFP & APSA Joint Congress, in Melbourne
- Jason will describe key experiments linking clinical results with disease models to estimate intravenous and subcutaneous doses that are likely to be effective in treating fibrosis.

AdAlta Limited (ASX:1AD) ("AdAlta" or **"the Company")**, developer of the clinical stage i-body® platform and other novel protein and cell therapeutic products is pleased to announce that Dr Jason Lynch, Senior Scientist II at AdAlta, has been invited to present results from the development of lead asset, AD-214, at the 2024 ASCEPT, APFP & APSA Joint Congress[1] being held from 1-4 December 2024.

Dr Lynch's presentation will feature in a symposium titled "Unveiling the next wave of therapies for chronic lung diseases." The symposium will combine experts in respiratory diseases and drug discovery to highlight pivotal advancements in new therapeutic strategies and medical technology breakthroughs to improve overall health in people afflicted by lung diseases, and those afflicted by the long-term consequences of respiratory infections.

During his presentation, titled "Clinical dose estimation for anti CXCR4 i-body-Fc fusion AD-214 for the treatment of fibrotic diseases," Dr Lynch will describe key experiments linking results of the Phase I clinical studies of AD-214 (including the most recent study completed earlier in 2024) with pre-clinical studies that enabled AdAlta to estimate the likely efficacious dose of AD-214. He will be highlighting the significance of this work in supporting the future development of a patient preferred subcutaneous form of AD-214.

The symposium will be held from 11:15AM to 1:15PM AEDT on 3 December 2024 at the Melbourne Convention Centre. A copy of the presentation is attached.

Commenting on the upcoming presentation, AdAlta's CEO and Managing Director, Dr Tim Oldham said:

"AdAlta is delighted that Jason has been invited to present at the 2024 ASCEPT, APFP & APSA Joint Congress. AD-214 is taking a whole new approach to fibrotic diseases where improved outcomes are desperately needed. Jason led the preclinical studies that enabled us to determine both the likely efficacious dose of intravenous AD-214, and more importantly the potential for a subcutaneous version of AD-214 that offers not only greater patient convenience but also lower cost of goods and lower healthcare system costs. Large pharmaceutical companies have been very interested in this data and it is fitting that Jason has the opportunity to present his work and the latest clinical results from AD-214's development in this symposium."

This ASX announcement has been authorised for release by the CEO of AdAlta Limited (ASX:1AD).

[1] Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT), the Asia Pacific Federation of Pharmacologists (APFP) and the Australasian Pharmaceutical Science Association (APSA)

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About AdAlta Limited

AdAlta Limited is a clinical stage drug development company headquartered in Melbourne, Australia. The Company is using its proprietary i-body technology platform to solve challenging drug targeting problems and generate a promising new class of single domain antibody enabled protein and cell therapeutics with the potential to treat some of today's most challenging medical conditions.

The i-body technology mimics the shape and stability of a unique and versatile antigen binding domain that was discovered initially in sharks and then developed as a human protein. The result is a range of unique proteins capable of interacting with high selectivity, specificity and affinity with previously difficult to access targets such as G-protein coupled receptors (GPCRs) that are implicated in many serious diseases. i-bodies are the first fully human single domain antibody scaffold and the first based on the shark motif to reach clinical trials.

AdAlta is extending Phase I clinical studies for its lead i-body candidate, AD-214, that is being developed for the treatment of Idiopathic Pulmonary Fibrosis (IPF) and other human fibrotic diseases for which current therapies are sub-optimal and there is a high unmet medical need. Preparation for Phase II clinical studies is also underway. AdAlta has a second target in discovery research, also in the field of fibrosis and inflammation.

The Company is also entering collaborative partnerships to advance the development of its i-body platform. It has a collaboration with Carina Biotech to codevelop precision engineered, i-body enabled CAR-T cell therapies (i-CAR-T) to bring new hope to patients with cancer. It has an agreement with GE Healthcare to co-develop i-bodies as diagnostic imaging agents (i-PET imaging) against Granzyme B, a biomarker of response to immuno-oncology drugs, a program now in preclinical development.

AdAlta's strategy is to maximise the products developed using its next generation i-body platform by internally discovering and developing selected i-body enabled product candidates against GPCRs implicated in fibrosis, inflammation and cancer, and partnering with other biopharmaceutical companies to develop product candidates against other classes of receptor, in other indications, and in other product formats.

To learn more, please visit: www.adalta.com.au

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AdAlta

Clinical dose estimation for anti CXCR4 i-body-Fc fusion AD-214 for the treatment of fibrotic diseases

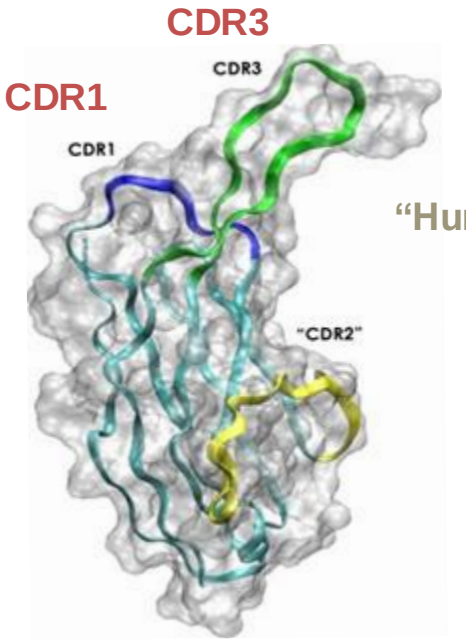
Jason P. Lynch, PhD

AdAlta Limited (ASX:1AD)
ASCEPT
December 3rd 2024

Disclosures

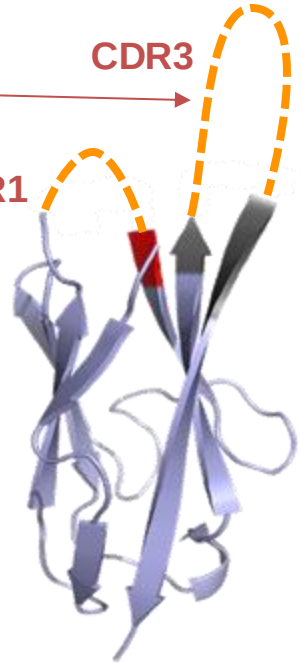
I am a paid employee for AdAlta Ltd.

i-bodies: humanized single domain Ab inspired by shark single domain VNAR Ab



"Humanizing"

Long loop



Shark VNAR Ab

- **Small size** (~15 kDa)
- **Stability**
- **High affinity** (nM-pM range)
- **Long CDR3** = active site/ligand binding site penetration in target proteins

Ribbon overlay*

… observed that shark VNARs show a high degree of structural similarity with the **i-set family** of human proteins…

Domain 1 of hNCAM (aka CD56)

… leading to the choice of human **NCAM domain 1** for the i-body scaffold …

i-body library

… introduction of randomized **synthetic VNAR-like binding loops** to develop an i-body library…

Goal: to go where mAbs generally cannot (e.g., GPCRs)

1. Streltsov et al 2004 PNAS
2. Griffiths et al 2016 JBC

CXCR4 and its role in fibrotic diseases including IPF

CXCR4:

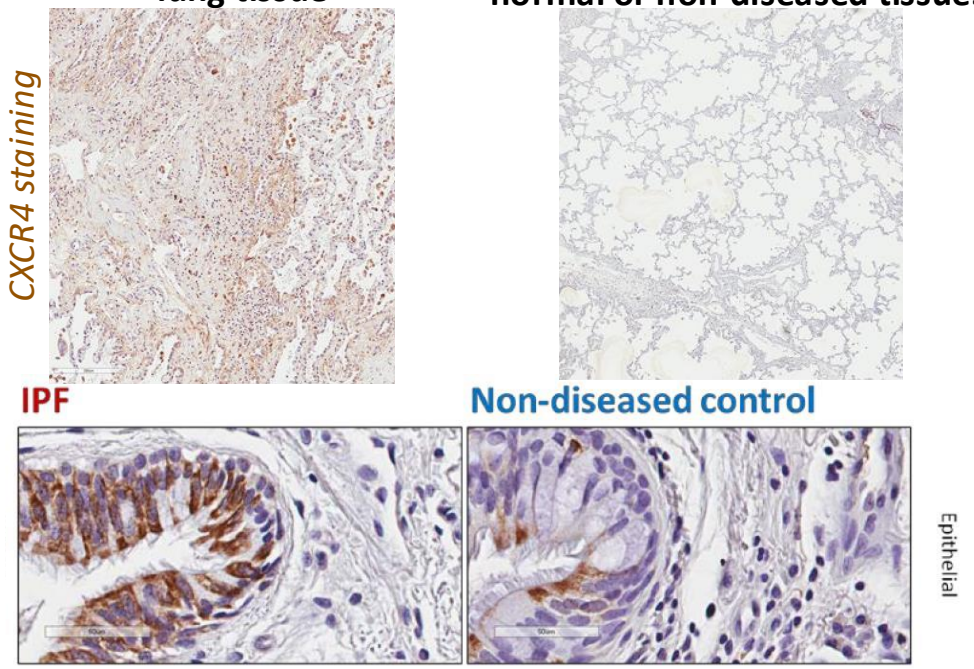
- SDF-1 receptor – **chemotaxis** of immune cells
- Important in **maintaining stem cells in bone marrow**
- Used by **HIV-1** as a co-receptor for viral entry into host cells
- Associated with more than **23 types of cancers**

… and a critical player in many **fibrotic indications** including:

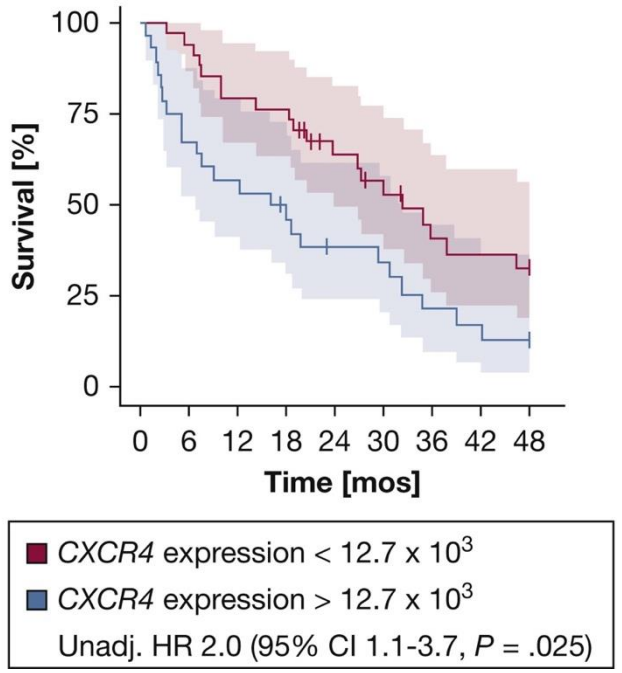
- Lung (e.g., IPF)
- Kidney
- Heart
- Eye
- Skin

CXCR4 is upregulated in IPF lung tissue

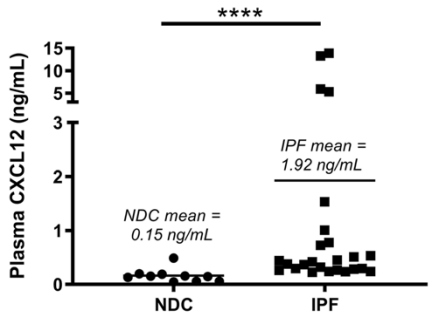
Very limited expression in normal or non-diseased tissues

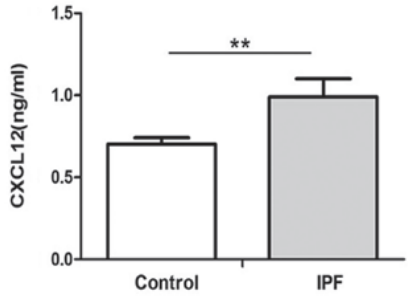


High BAL cell CXCR4 expression correlates with worse outcomes in IPF patients



Circulating SDF1 levels increased in IPF





Liu et al 2020

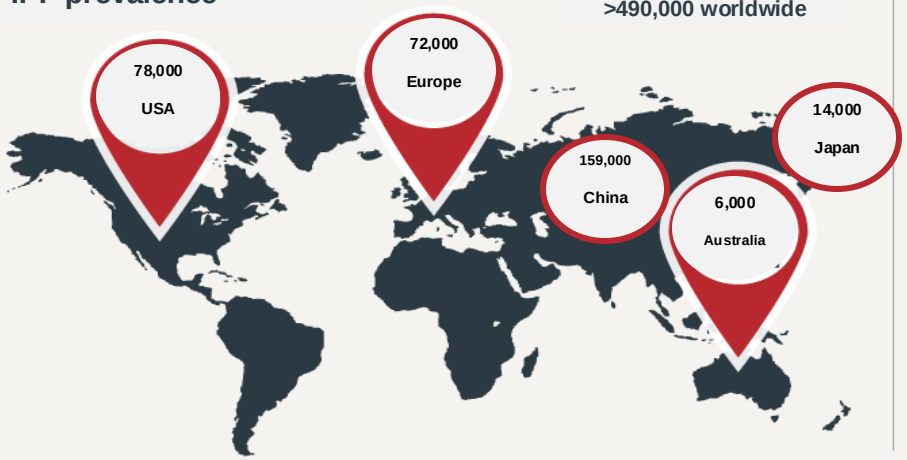
In collaboration with Prof Glen Westall (Alfred Hospital)

1. Griffiths et al 2018; Jaffar et al 2020
2. Derlin et al 2017
3. Chen et al 2014

The need: Better outcomes for IPF and other fibrotic diseases

IPF prevalence

>490,000 worldwide



of sufferers die within 3-5 years following diagnosis

>100,000 pa

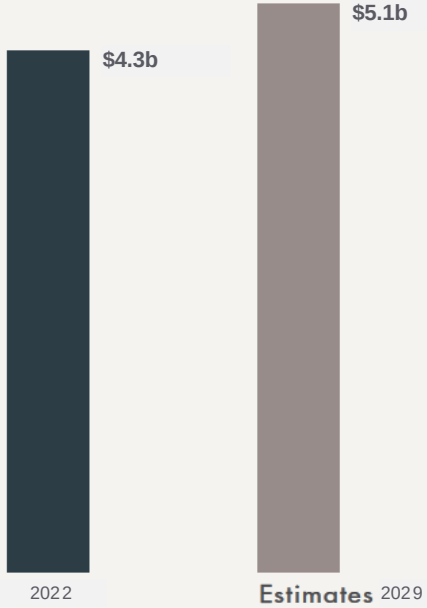
Current IPF treatments

Pirfenidone **Nintedanib**

Roche Boehringer Ingelheim

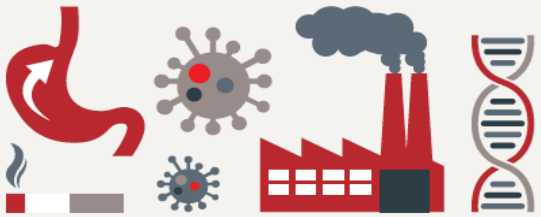
Slow, but do not halt progression. Serious side effects limit compliance, tolerability

IPF Therapy Sales (US$)



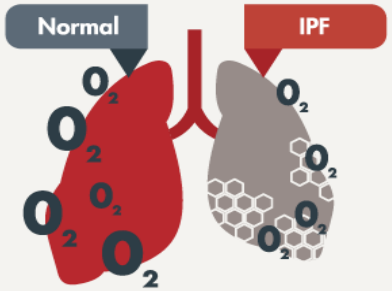
Source: GlobalData,[2] company financial reports, AdAlta analysis

Causes



The cause is unknown but risk factors may include: smoking, environmental exposures, chronic viral infections, abnormal acid reflux and family history of the disease.

Pathology



Resultant scarring/honeycombing in the lung restricts breathing and oxygen exchange.

[1] PM George, et al, "Pulmonary fibrosis and COVID-19: the potential role for antifibrotic therapy", Lancet published online May 15, 2020.
[2] GlobalData, Idiopathic Pulmonary Fibrosis: Competitive Landscape, April 2023
[3] GlobaData, disease analysis reports

i-bodies, Human Single Domain Antibodies That Antagonize Chemokine Receptor CXCR4*[S]

Received for publication, February 10, 2016, and in revised form, March 30, 2016 Published, JBC Papers in Press, April 1, 2016, DOI 10.1074/jbc.M116.721050

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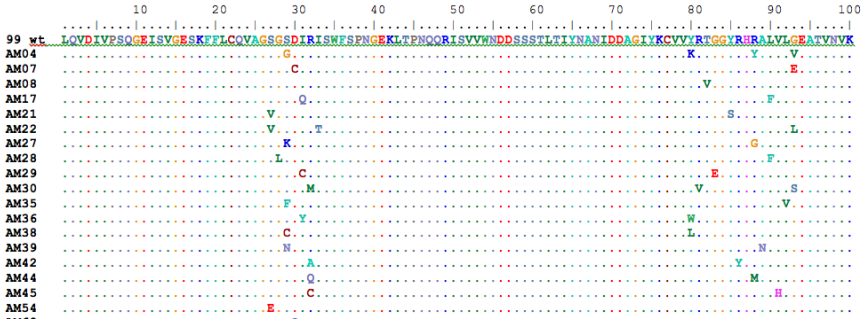
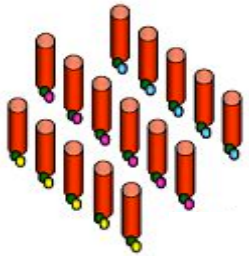
Affinity maturation

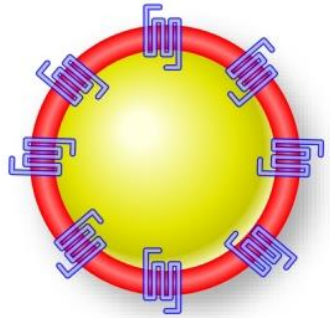




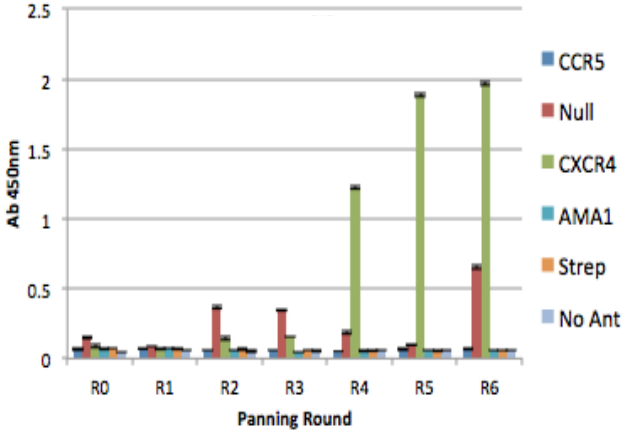
i-body library
(phage display)

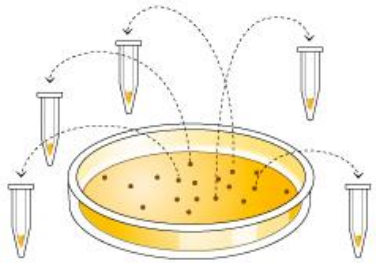
Biopanning

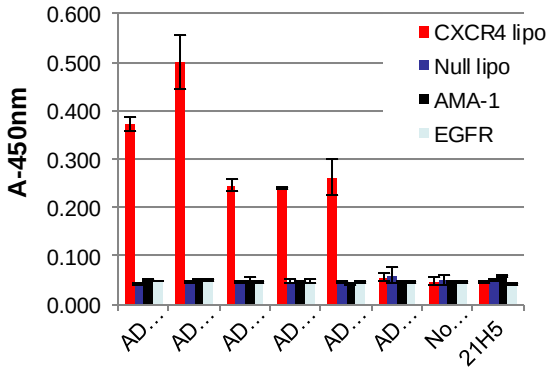
CXCR4 lipoparticles
(Integral Molecular)



Enrichment for CXCR4 binders





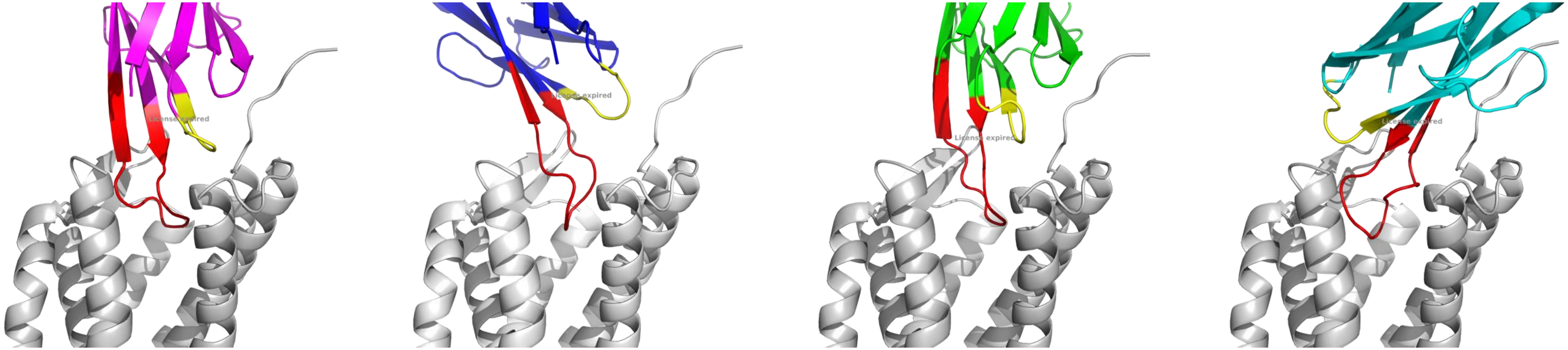


Griffiths et al 2016

Characterised library of CXCR4 binding i-bodies

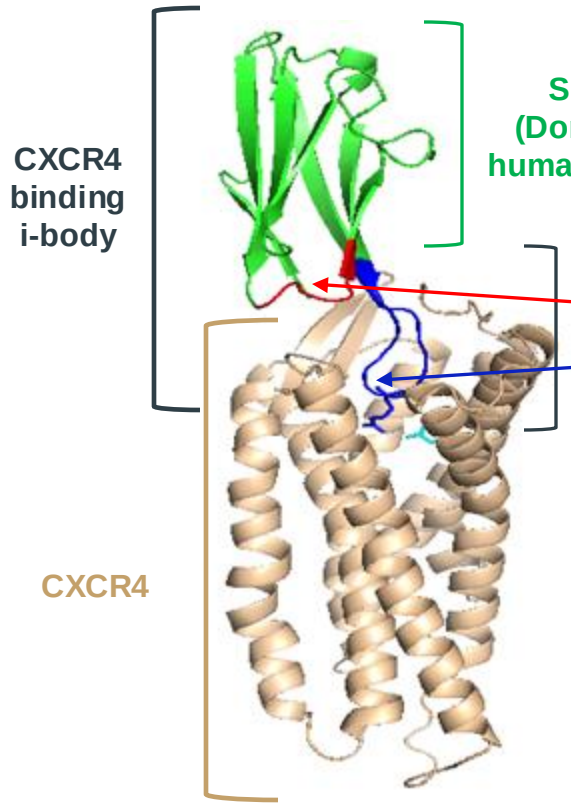
- Affinity matured anti-CXCR4 i-bodies differ in only a few residues and modeling suggests they engage different epitopes.

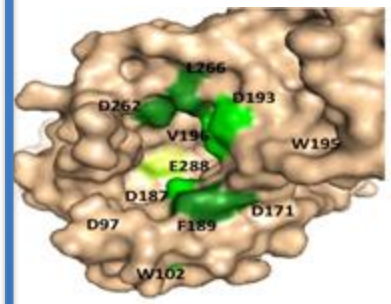
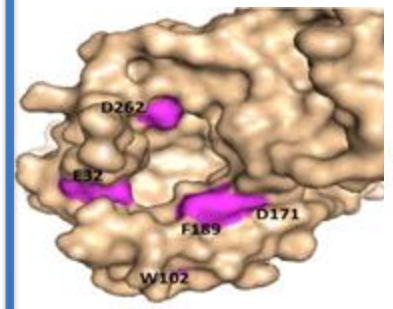
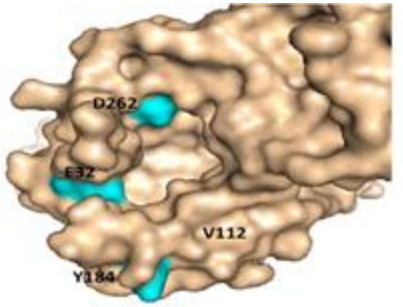
```
                                      CDR1                                                     CDR3
21H5     LQVDIVPSQGEISVGESKFFLCQVAGDAKDKDISWFSPNGEKLTPNQQRISVVWNDDSSSTLTIYNANIDDAGIYKCVVTG___EDGS___ESEATVNVKIFQ
ADCX99   --------------------------SGSDIR-----------------------------------------------YRTGGYRHRALVLG----------
AD-114   ---------------------------L-G-------------------------------------------------W--------Y--------------
AD-272   ----------------------K-----Y--Y-------------------------------------------------I------Y--------------
AD-523   ---------------------------G-HM------------------------------------------------W-V---------------------
AD-320   ---------------------------K---------------------------------------------------------------Y--------------
AD-1121  ---------------------------K-G--------------------------------------------------------Y-R------------
```



Griffiths et al 2016

Distinct pharmacological outcomes of anti-CXCR4 i-bodies: biased signaling?



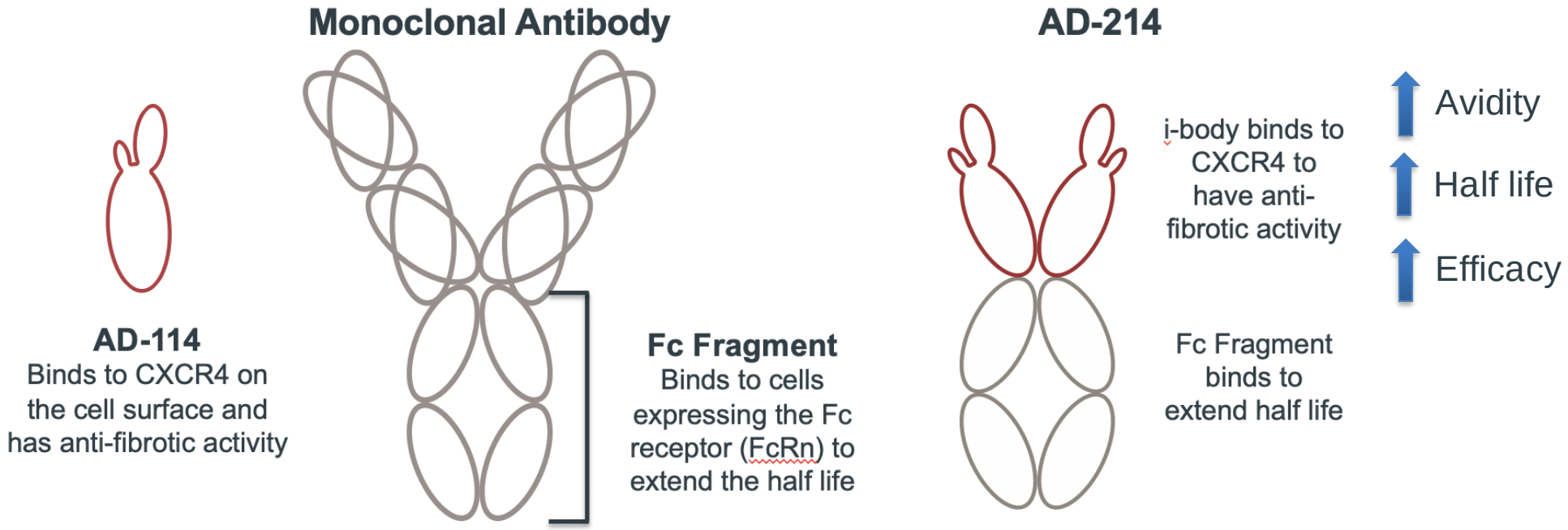
	AD-114	AD-272	AD-523
			
Affinity to CXCR4 (K_D/nM)[1]	4.2		
Inhibition of β-arrestin (IC_{50}/μM)[1]	1.18		
Inhibition of cAMP (IC_{50}/nM)[1]	99		
Inhibition of HIV entry (IC_{50}/nM)[1]	131		
Attenuation of laser induced eye leakage and fibrosis[2]	YES		
Efficacy in bleomycin model of IPF[3]	YES	-	-

- ✓ Affinity to CXCR4, low nM
- ✓ Competes with SDF1
- ✓ Antagonist:
  - ✓ Potent
  - ✓ Efficacious (*in vitro* + *in vivo*)

1. Griffiths et al 2016
2. Fletcher et al unpublished
3. Griffiths et al 2018

AD-114 has been developed into therapeutic candidate AD-214

AD-214, an Fc (human)-fusion
Fc = “silent” (point mutated to remove effector function)

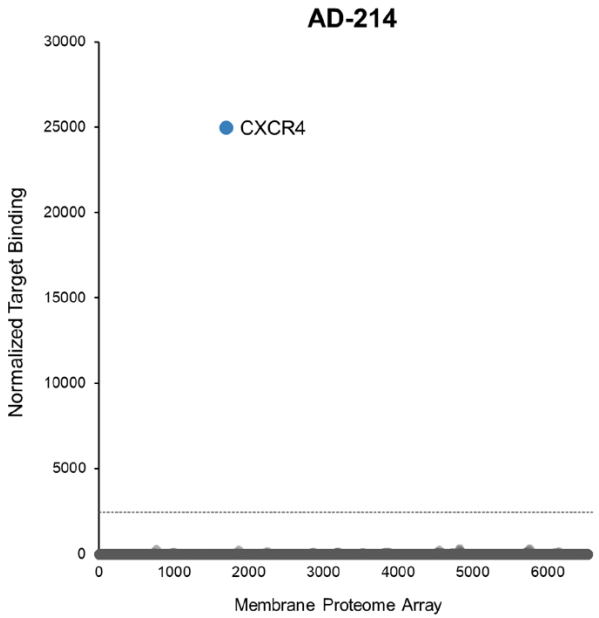


Lynch *et al* [under review]. Preprint on Research Square.

AD-214: Fc-fusion increases affinity and potency; specificity retained

Specificity[1]

5,300 human membrane protein array, including 94% of all single-pass, multi-pass and glycosylphosphatidylinositol (GPI)-anchored proteins.



1. Integral Molecular 20190709

Affinity and Potency[2]

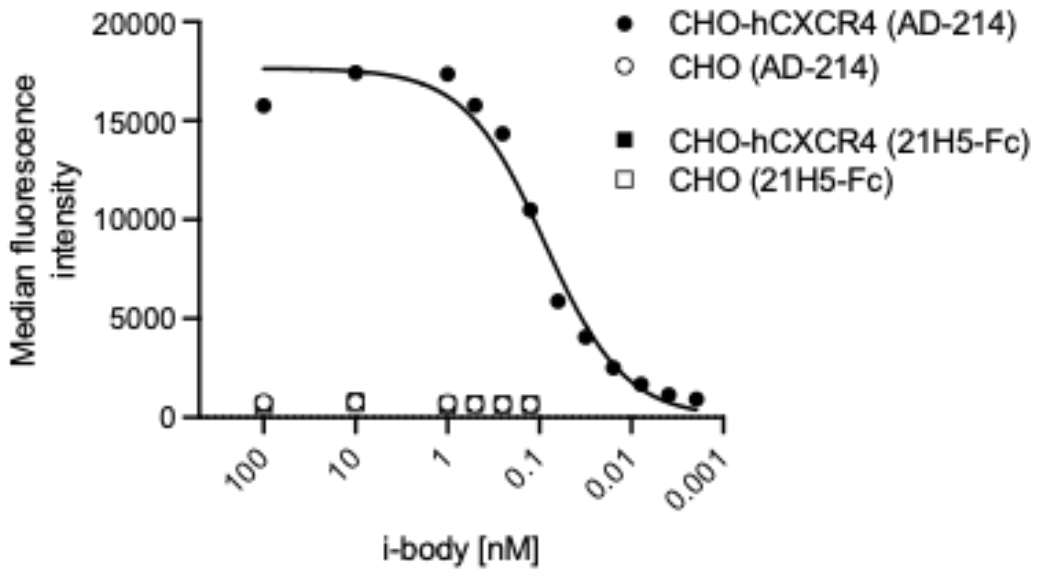
	SPR CXCR4 K_D Human [2]	SPR FcRN K_D Human[2]	β-Arrestin IC50 Human[2]	cAMP IC50 Human[2]	Internalisation IC50 Human[2]	Calcium Flux IC50[2]
AD-214	4 pM	48 nM	7.0 nM	8.9 nM	7.4 nM	73.5 nM
AD-114	3.5 nM	N/A	2.2 uM	610 nM	440 nM	1600 nM

2. Aldevron, AdAlta in-house data, Excellerate Biosciences 20190325

Lynch *et al* [under review]. Preprint on Research Square.

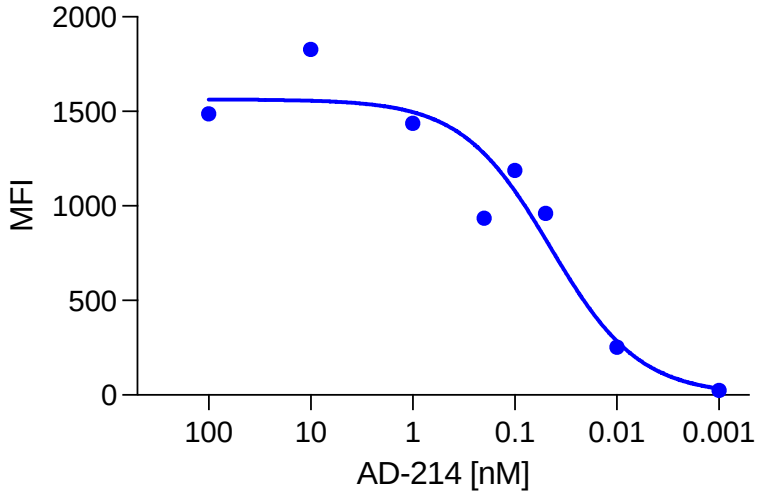
AD-214 binds to CXCR4 on cells with high affinity

High hCXCR4 expressing cell line[1]



K_D = 100-300 pM

Primary CXCR4+ CD3+ T cells[1]



K_D = 45 pM (donor 1, above)
495 pM (donor 2)
556 pM (donor 3)

1. Lynch *et al* [under review]. Preprint on Research Square.

AD-214 and AD-114: preclinical efficacy, MOA in IPF and GLP-toxicology

Preclinical efficacy:

AD-214 and AD-114 ≥ standard of care treatments

in vitro / ex vivo

- **Potently inhibits** SDF-1-induced **CXCR4+ cell migration** (AD-214[1] and AD-114[2])
- Dose dependent **reduction in pro-fibrotic, pro-inflammatory and pro-remodeling processes** in co-cultures of lung fibroblasts and epithelial cells (BioMAP, AD-214[1] and AD114[2])
- **Blocking upregulation of collagen and a-SMA** in alveolar epithelial cells treated with SDF-1 or TGF-b (AD-114) [2]
- **Reduces IPF airway basal cell proliferation and organoid formation** in a dose dependent manner (AD-114) [2]
- **Inhibition of migration of fibroblasts and collagen secretion from IPF patients**, but not from healthy individuals (AD-114)[2]
- **Attenuation of collagen deposition in precision cut (human) lung slices** treated with a fibrotic cocktail (Dr Louise Organ, AD-214)[1]

in vivo

- **Inhibited the development of fibrosis in a bleomycin mouse model of lung fibrosis** at concentrations as low as 1 mg/kg every two days and 10 mg/kg every four days (AD-214[1])
- **Antifibrotic in a mouse model of kidney fibrosis** (AD-214 and AD-114 Cao *et al* 2022 JCI Insight)

GLP toxicology (AD-214)

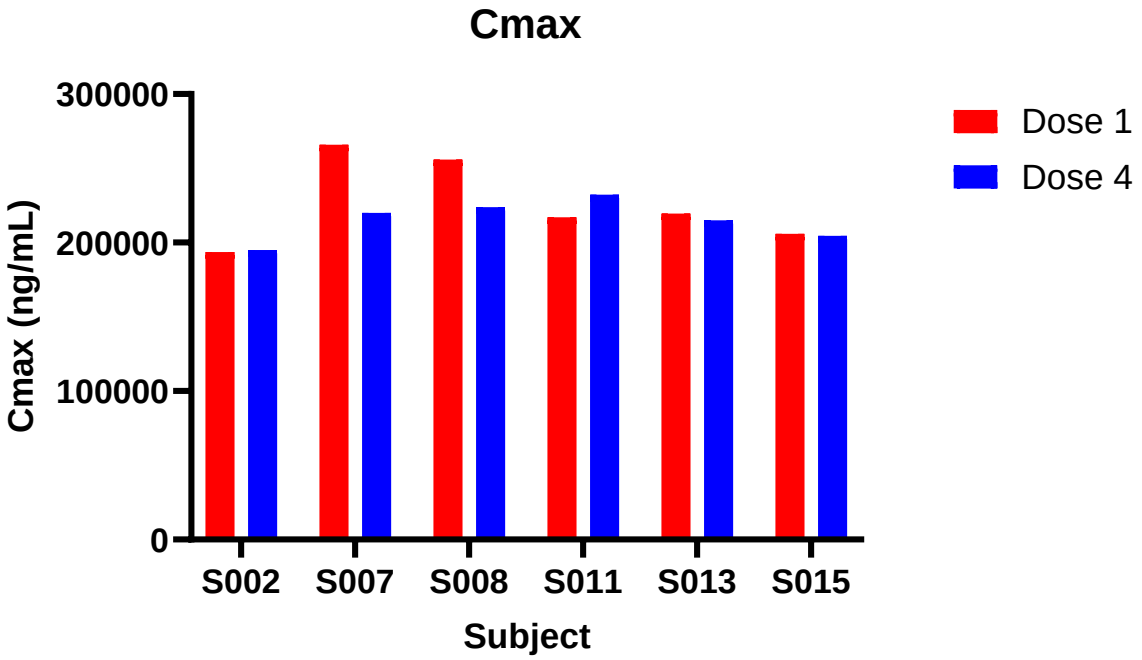
- 3 non-human primate studies completed.
- **AD-214 well tolerated** with no deaths, no AD-214-related clinical signs, no changes in a panel of clinical observations
- **AD-214** demonstrated receptor engagement: **sustained receptor occupancy** well beyond serum half-life supports extended dosing; transient and low level CD34+ mobilisation

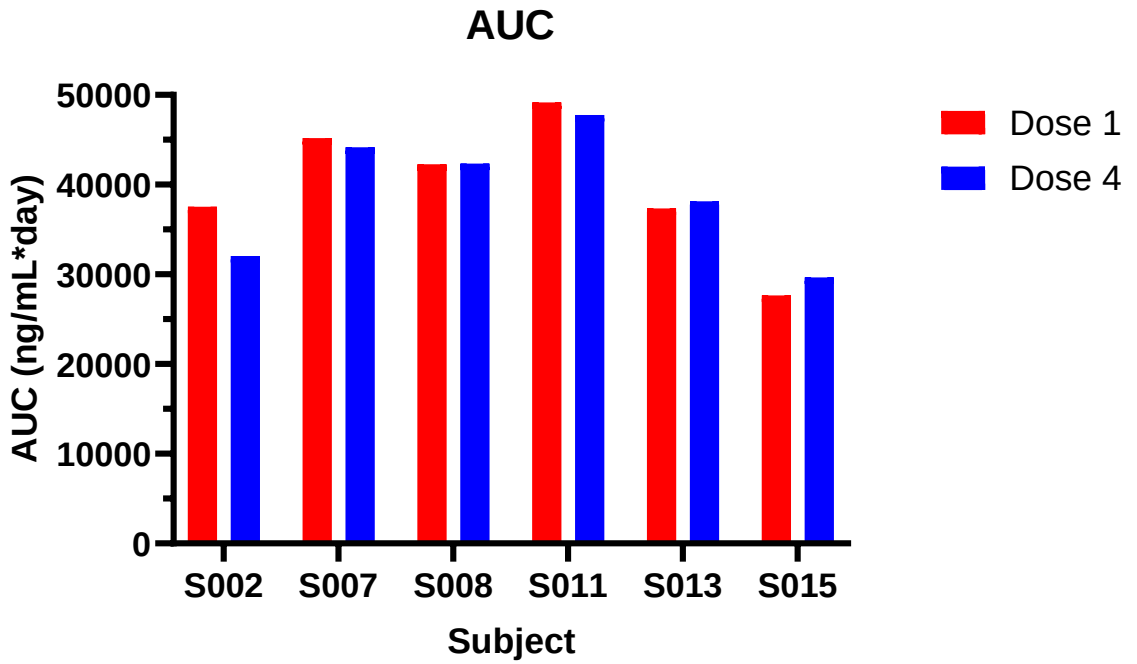
Summary of Phase 1 clinical trials in healthy subjects administered AD-214 via IV infusion

AD-214 was evaluated in single IV doses to 20 mg/kg (42 participants) and multiple doses at 5-10 mg/kg (16 participants) in two placebo-controlled Phase I clinical study in healthy volunteers

- **AD-214 was well tolerated**
  - No dose limiting toxicities in single doses; IRRs were moderate and rapidly resolving in 3 multidose participants including placebo
  - No concerning clinical or laboratory results; no adverse liver or other organ function tests
  - No serious adverse events
- **Immune responses not concerning**
  - No clinically consistent changes in cytokines
  - ADAs observed at low titres, particularly after multiple doses
  - No correlation of cytokines or ADAs with adverse events or infusion reactions
  - No observable effect of ADAs on PK or PD (see next slide)

PK profile was consistent between dose 1 and dose 4 and independent of ADA response for all extension study participants

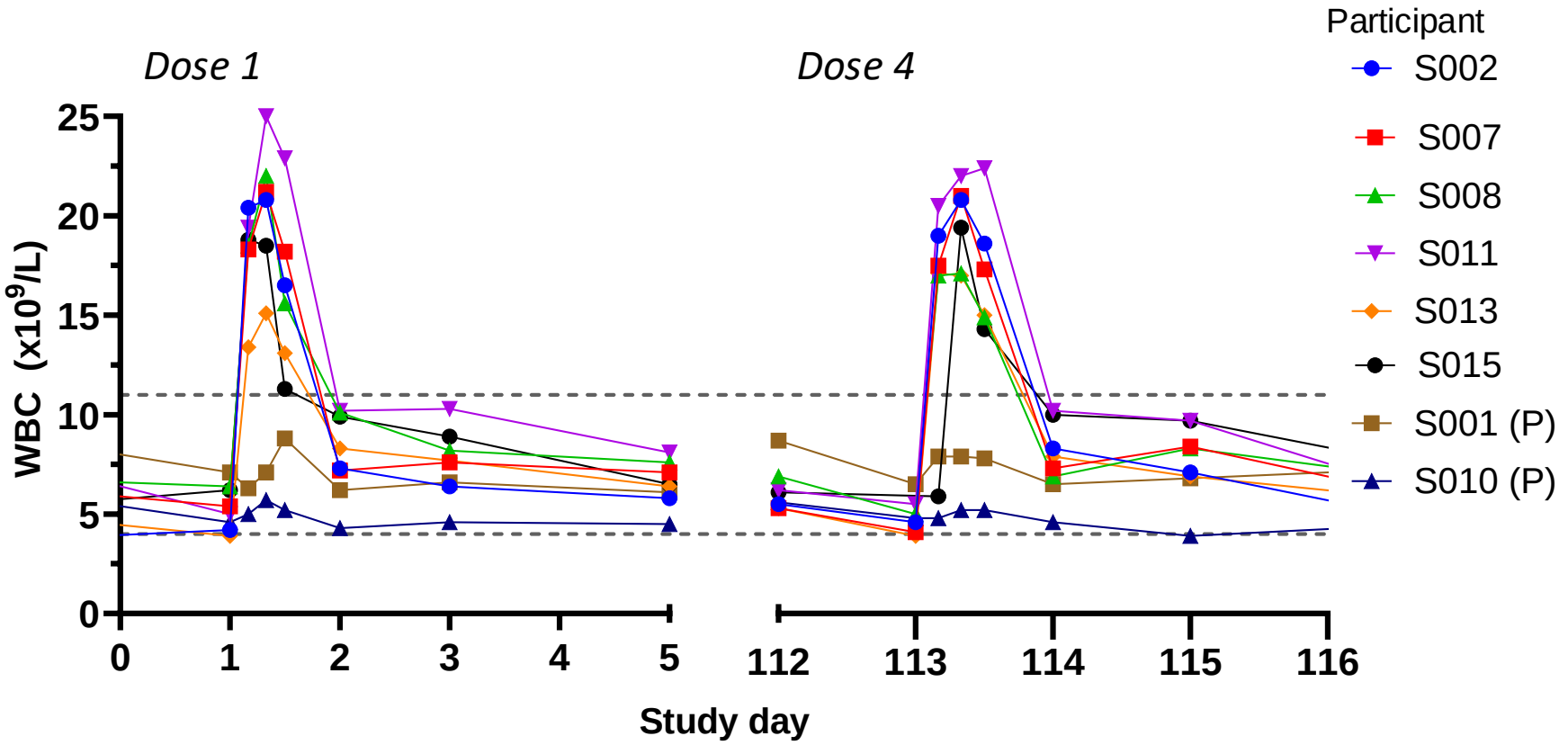




10 mg/kg IV

PK was assessed by measuring the concentration of AD-214 in the blood over time. At dose four, every participant receiving AD-214 achieved the same maximum concentration of AD-214 (Cmax, left hand chart) and total exposure (concentration multiplied by time at that concentration or AUC, right hand chart) as at dose one, despite different levels of ADAs. Slight variations between doses for individual participants reflect experimental variability and were not correlated with ADA levels or any other measured parameter. Variations between participants are normal and expected. Placebo results not shown.

White blood cell counts (a PD marker) were consistent across all participants and all doses in extension study



10 mg/kg IV

PD was assessed by measuring the increase in white blood cells (WBC) circulating over time (chart above) and the level and duration of RO (data not shown). Every participant receiving AD-214 achieved the same maximum WBC count at dose four as at dose one, despite different levels of ADAs. No increase in WBC counts was observed in placebo recipients (marked P). Dotted lines show lower and upper limits of normal WBC levels in the absence of CXCR4 blocking.

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  - No correlation of cytokines or ADAs with adverse events or infusion reactions
  - No observable effect of ADAs on PK or PD (see next slide)
- **PK/PD findings:**
  - C_{max} and AUC increase essentially linearly with dose
  - Rapid distribution from serum followed by slower elimination with 39h half life
  - CXCR4 receptor saturation on circulating T cells achieved at low doses (see next slide)

AD-214 is well tolerated and demonstrates expected target engagement in healthy volunteers

Sustained high levels of CXCR4 receptor occupancy on T- cells: a key PD readout

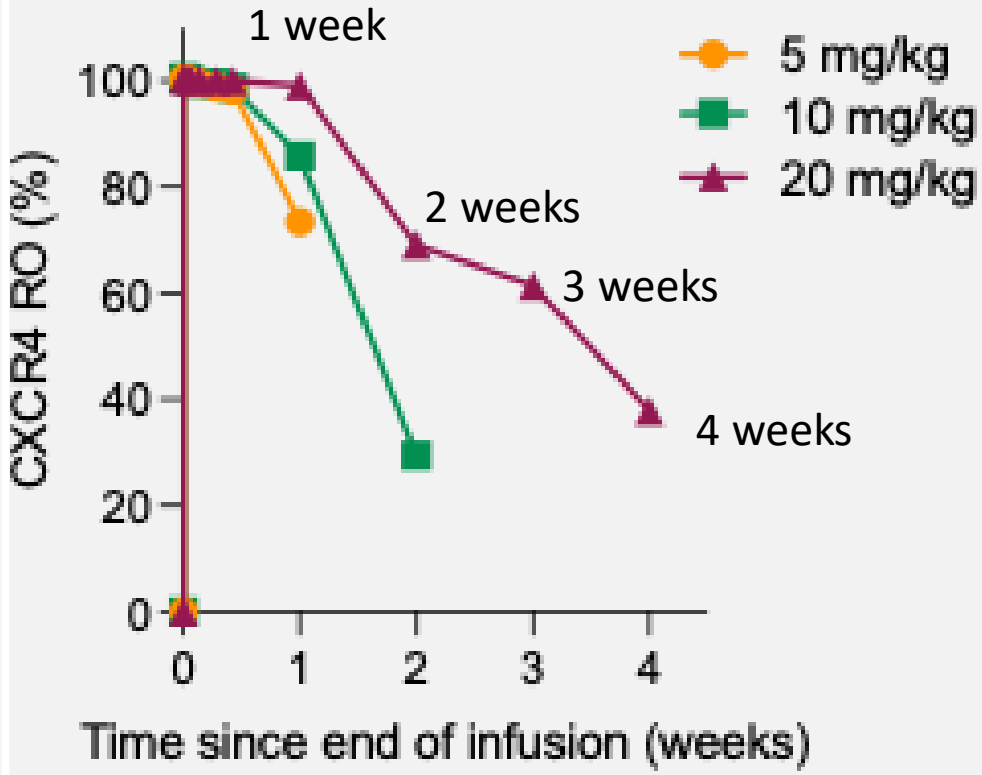
Understanding duration of receptor occupancy (RO) is critical to inform dosing

Blood T cells express CXCR4 in healthy individuals, providing an accessible surrogate for AD-214 target engagement or RO

Results:

- >70% CXCR4 RO at 7 days after 5-10 mg/kg infusion
- >60% CXCR4 RO at 21 days after 20 mg/kg infusion*
- ***Duration of RO is considerably longer than PK profile***

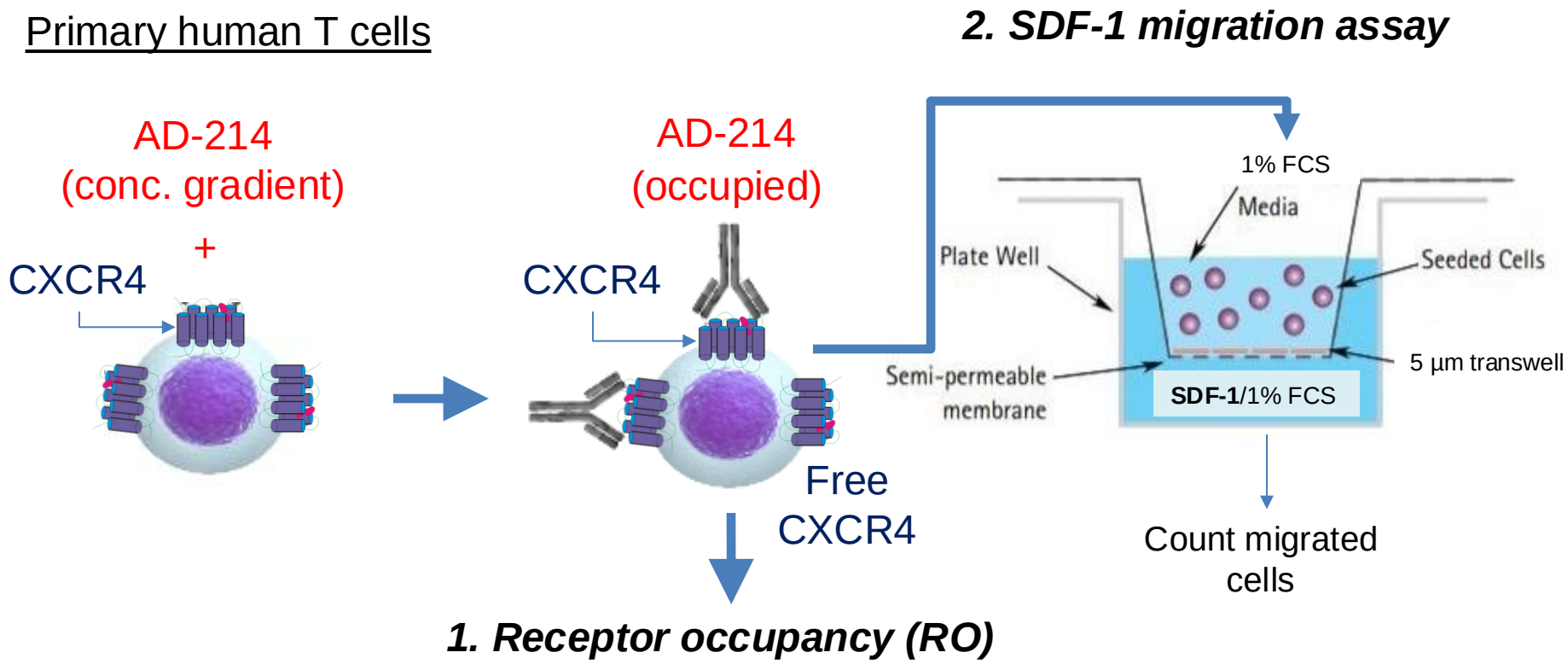
Result supports extended dosing intervals despite relatively rapid AD-214 clearance



* Receptor occupancy was monitored for one week at all dose levels except 20 mg/kg (4 weeks) and 10 mg/kg (2 weeks)

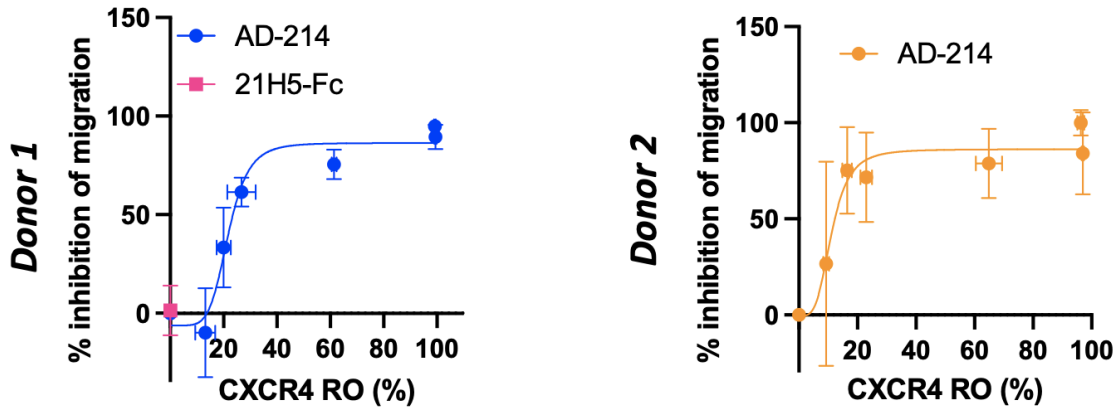
Are these RO levels sufficient for efficacy?

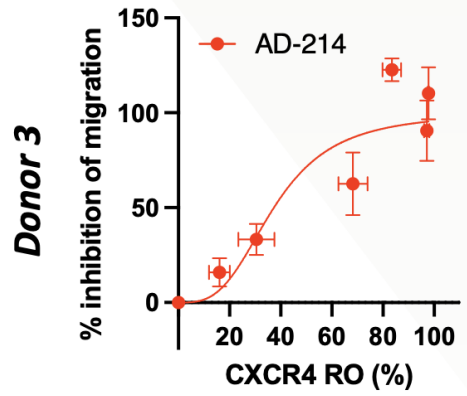
Model system to link RO with inhibition of a model fibrotic process (T cell migration)



Linking inhibition of T cell migration, a model fibrotic process, and CXCR4 receptor occupancy

- Maximal inhibition of primary human T cell migration can be achieved with just 60-85% CXCR4 receptor occupancy and low serum concentrations of AD-214
- Potentially meaningful inhibition occurred with far lower 11-37% receptor occupancy



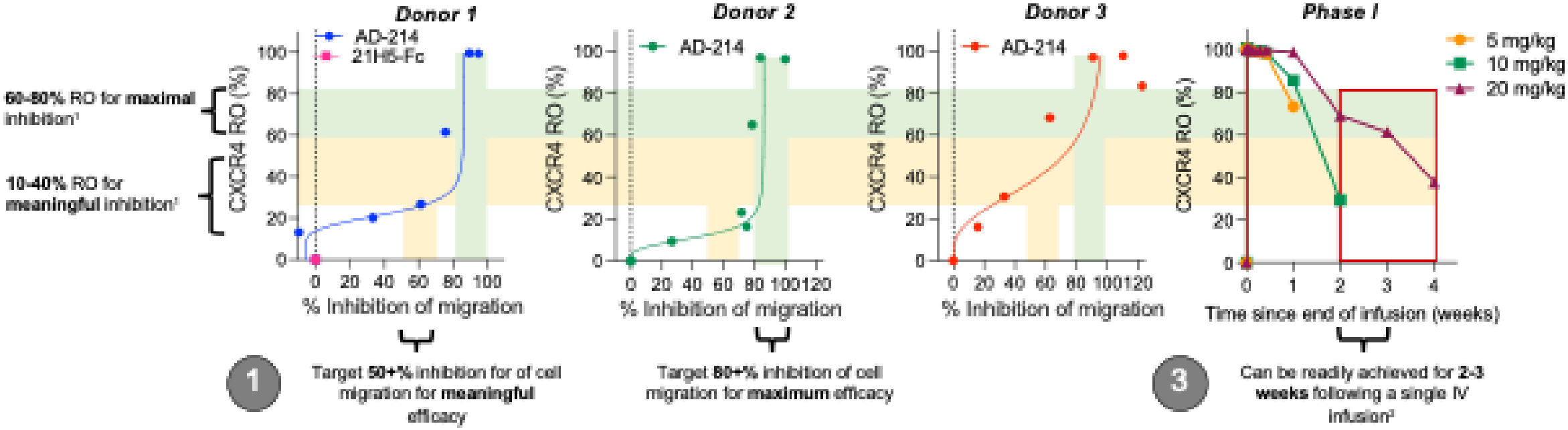


Inhibition of CD3+ T cell migration		Donor 1	Donor 2	Donor 3
Maximal inhibition	%RO	57%	57%	85%
	[AD-214]	0.7 nM	0.8 nM	1 nM
IC_{50}	%RO	22%	11%	37%
	[AD-214]	0.15 nM	0.07 nM	0.1 nM

1 nM of AD-214, the serum concentration detectable in clinical trial participants 72h after IV administration of 10 mg/kg AD-214, is sufficient to achieve high (57-85%) CXCR4 occupancy and maximally inhibit SDF-1α induced migration of primary human CD3+ T cells. Meaningful inhibition can be achieved at 0.1-0.2 nM AD-214

Phase 1 trial data informs dosing schedule

Potentially efficacious receptor occupancy can be maintained for at least two weeks after an IV infusion in humans, a clinically viable dosing regimen



Enabled us to set **target** RO needed to inhibit fibrotic process (i.e. migration):

- 30% = potential to *materially* inhibit
- 60% = potential to *maximally* inhibit

Further exploring clinically viable AD-214 dosing using PK/PD modeling

- A model of IV AD-214 administration was developed and validated using SPR derived binding data and Phase I human PK, RO and total CXCR4 receptor data.
- Preclinical PK results and reasonable assumptions allowed this to be extrapolated to subcutaneous (SC) AD-214 administration, a more convenient route of administration.
- Example output (RHS graph) showing predicted CXCR4 RO at trough after IV and SC doses; *target RO highlighted*.

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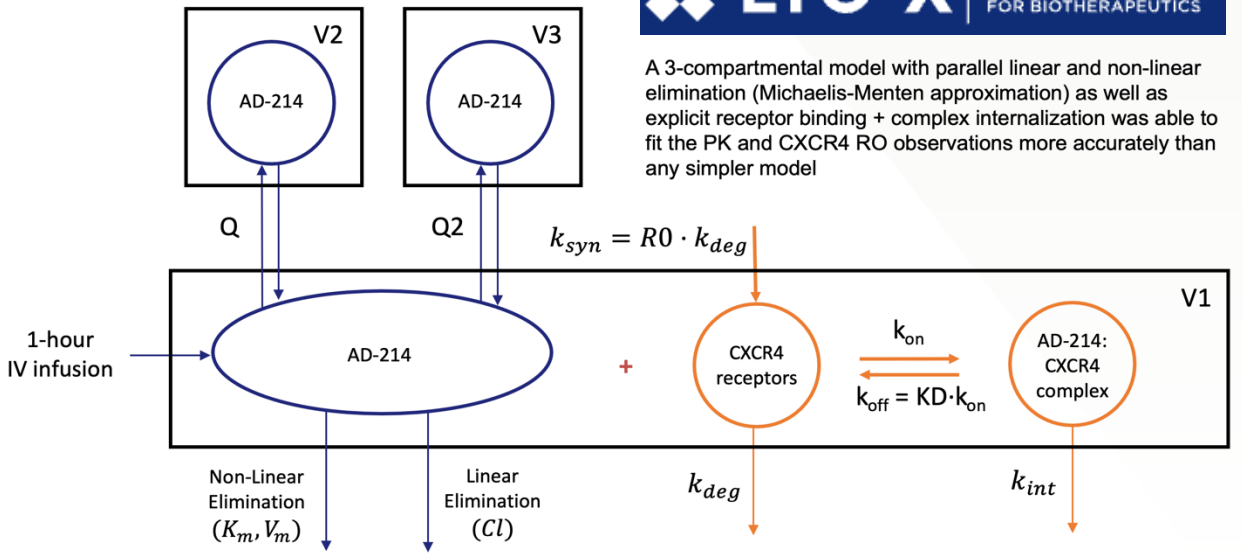
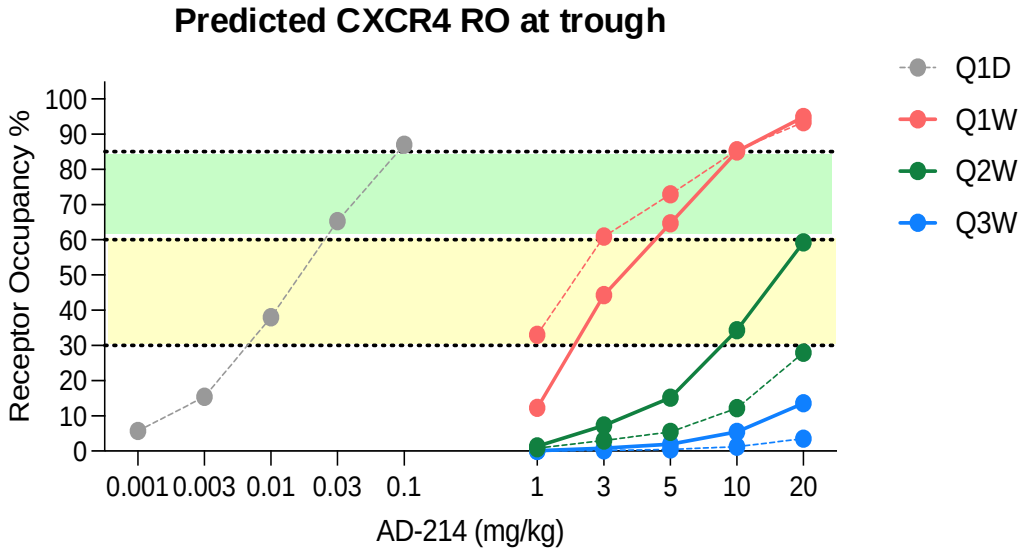
A 3-compartmental model with parallel linear and non-linear elimination (Michaelis-Menten approximation) as well as explicit receptor binding + complex internalization was able to fit the PK and CXCR4 RO observations more accurately than any simpler model





Maximal inhibition of fibrotic process
Meaningful inhibition of fibrotic process

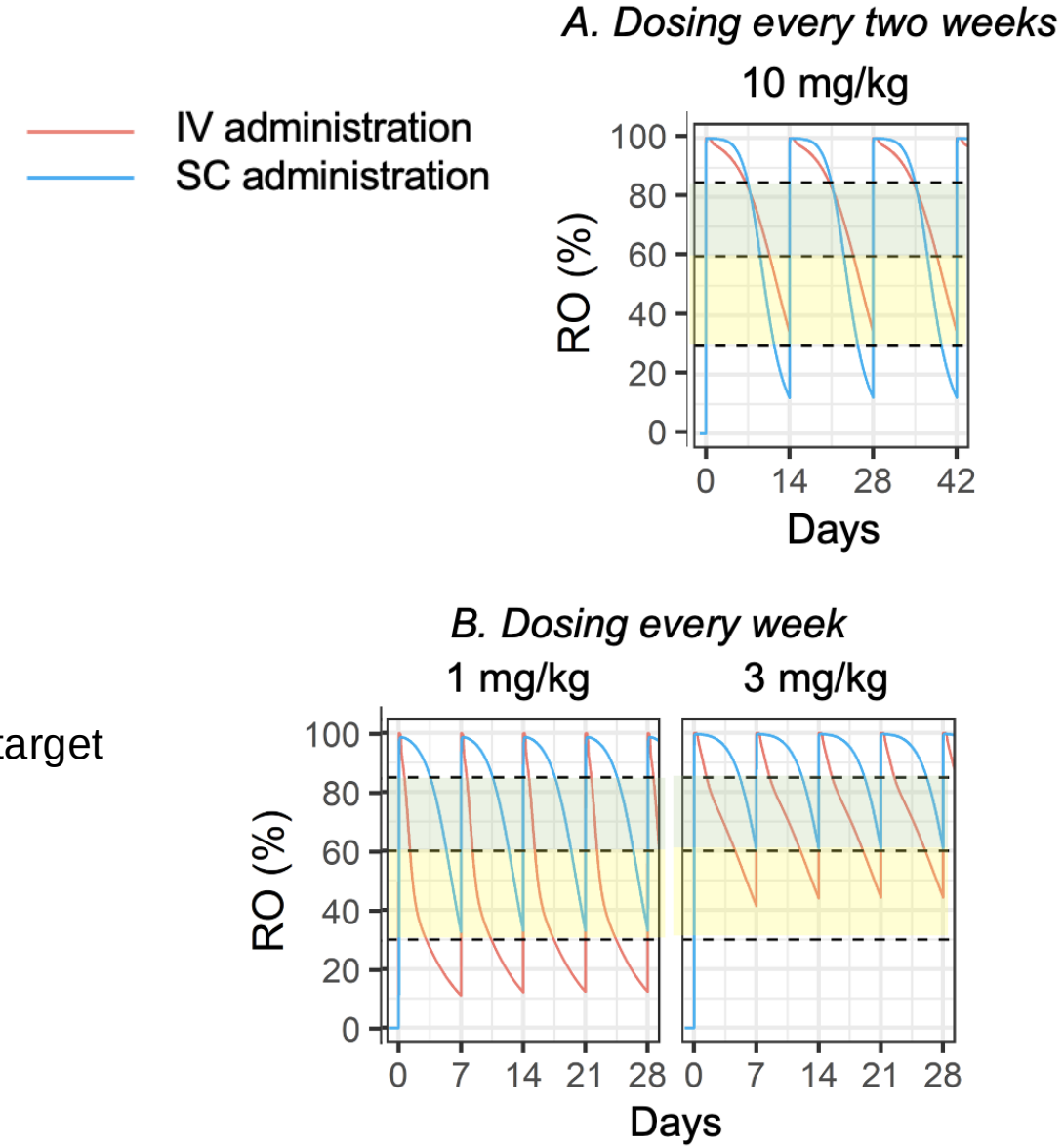
q2w ≥10 mg/kg and q1w ≥1 mg/kg IV or SC predicted to achieve target RO

Intravenous (IV)

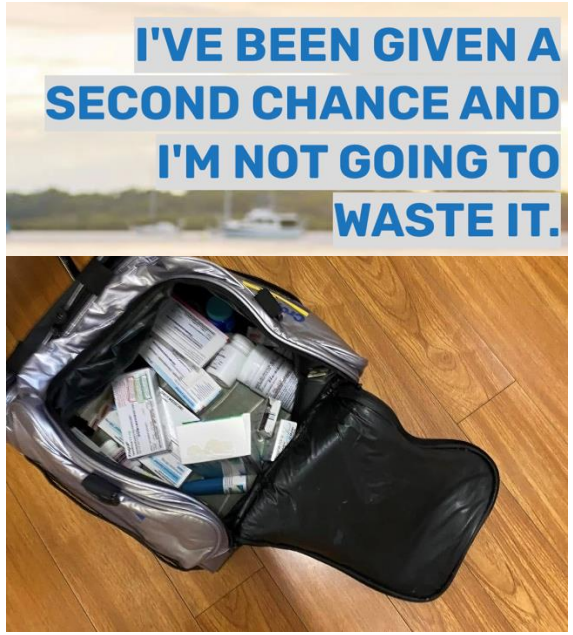
- q2w 10 mg/kg IV maintains >30% RO (potential to materially inhibit fibrosis) throughout the two-week interval between doses and greater than 60% receptor occupancy (potential to maximally inhibit fibrosis) for at least 75% of that time

Subcutaneous (SC) – patient convenient, lower COGs

- q1w 1-3 mg/kg SC weekly could achieve or exceed the target RO – potential to maximally inhibit fibrosis



Bill van Nierop: IPF survivor speaks to challenge of living with IPF



*"…**[diagnosis: 2015] 6 yrs with IPF before a double lung transplant**…"*

"… sadly I am one of a few who can actually relate to the lived experience with and without IPF …" "***You see our symptoms are basically an ongoing internal struggle to breathe freely*** … and it's invisible to all, including family, friends and the general community."

"I talked with a 60 something grandmother, who really enjoyed days looking after grandkids, but as disease progressed she found sometimes she needed to reduce the time a bit. You won't believe that her daughter in law suggested she would just bring them around less, 'you're always tired but you look really well', so I won't bother you as much. Shattering to the poor woman obviously, but again demonstrates the absolute lack of understanding of this debilitating disease. ***Looks well, so can't be too ill, except she's struggling to breathe and is on a journey with an inevitable end***."

- **City to Surf, 2016: 14 km run CBD-Bondi, ~$16,000**
- **Long Walk For Lungs, 2017: 700 kms walk through rural NSW, ~$100,000**
- **Long Kayak For Lungs, 2018: 2,200 kms down the Murray river, ~$100,000**
- **Long Kayak For Lungs 2, 2023, 800+kms down the Murrumbidgee, $56,000+**

Funds for IPF research

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