26 September 2023

ASX Announcement

INVITED PRESENTATION AT INTERNATIONAL DISCOVERY ON TARGET CONFERENCE, BOSTON

MELBOURNE Australia, 26 September 2023: AdAlta Limited (ASX:1AD), the clinical stage drug discovery company developing novel protein and cell therapeutic products from its i-body platform, is pleased to announce that Founding Chief Scientist, Prof Mick Foley has been invited to discuss the development of AD-214 at the 20th Discovery on Target conference in Boston, 25-28 September 2023.

Organised by the Cambridge Healthtech Institute, Discovery on Target is the industry's pre-eminent event on novel drug targets and technologies.

Presentation details

Time and date:	Professor Foley's presentation will be delivered at 8:05 am US EST (10:05 pm AEST) on Thursday 28 September.
Presentation topic:	Professor Foley's presentation, titled "*Discovery and Development Story of AD-214, an Fc-Fusion Protein i-Body for Fibrosis*" is included in a stream focussed on GPCR biotherapeutics. GPCRs are a class of drug targets that have proven particularly difficult for antibodies to address and where AdAlta believes its i-body technology offers unique potential. The presentation will summarise the development of AdAlta's lead drug candidate, AD-214, from initial discovery through to the most recent clinical, *ex vivo* efficacy and dose estimation results for fibrotic diseases.
Material:	A copy of the presentation is attached and is in addition to the poster presentation released separately by AdAlta today, describing clinical dose simulations for AD-214.

Further details of the Discovery on Target conference can be found at: https://www.discoveryontarget.com/.

Authorised for lodgement by:
Tim Oldham
CEO and Managing Director
September 2023

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We encourage shareholders to update their share registry preferences to receive all communications electronically. Doing so helps us communicate with you in a time-efficient manner on important matters, while minimising our mail costs and environmental impact.

Simply click here or scan the QR code and follow the instructions.

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Notes to Editors

About AdAlta

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 ibody platform. It has a collaboration with Carina Biotech to co-develop 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 (iPET 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.

Further information can be found at: https://adalta.com.au

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AdAlta

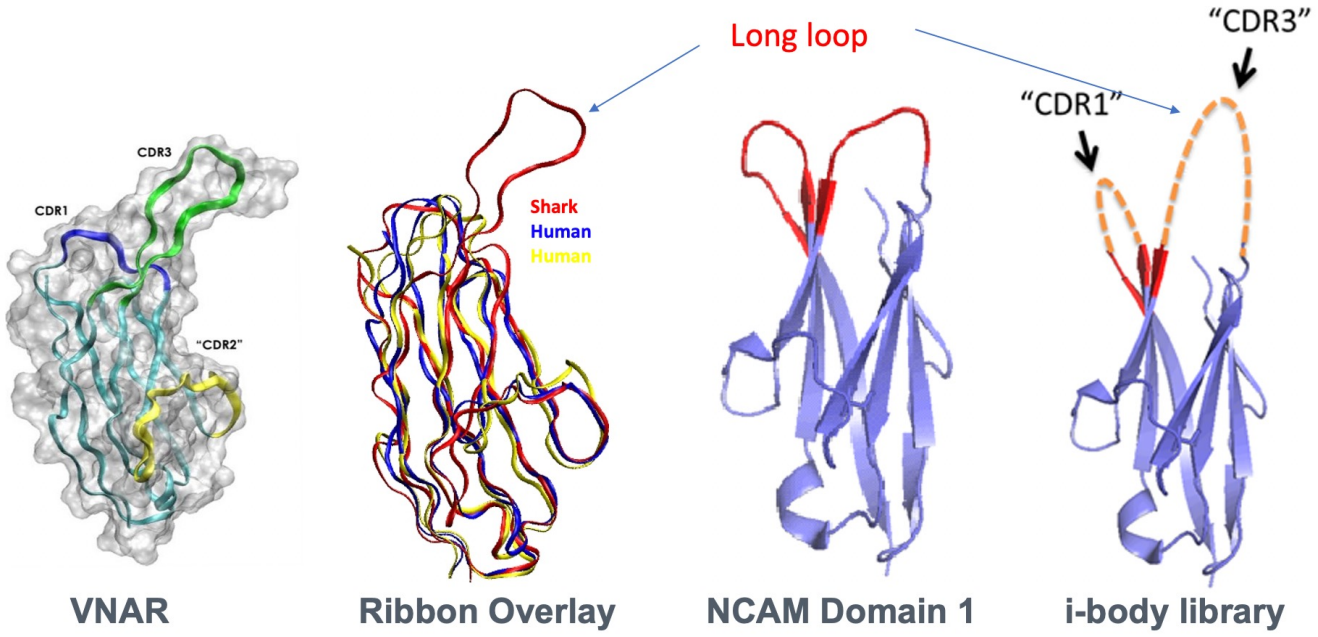
next generation protein therapeutics

Single domain i-bodies from sharks to Clinical Trials

Discovery on Target
September 26-28, 2023

i-bodies: human single domains

- i-body inspired by the shark VNAR structure
- Long CDR3 loop enables penetration of active sites/ligand binding sites and hydrophobic pockets in target proteins



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CXCR4 plays a role in Idiopathic Pulmonary Fibrosis

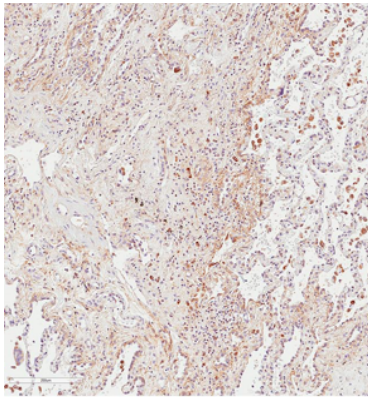
CXCR4 is a critical player in many **fibrotic indications** including:

- Lung
- Kidney
- Heart
- Eye
- Skin

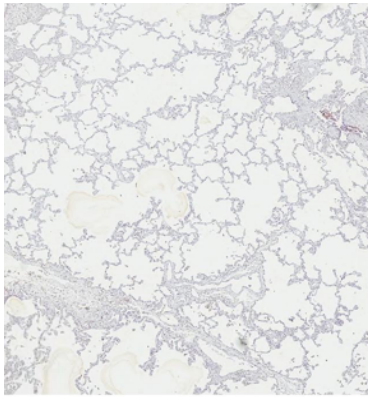
CXCR4 is also

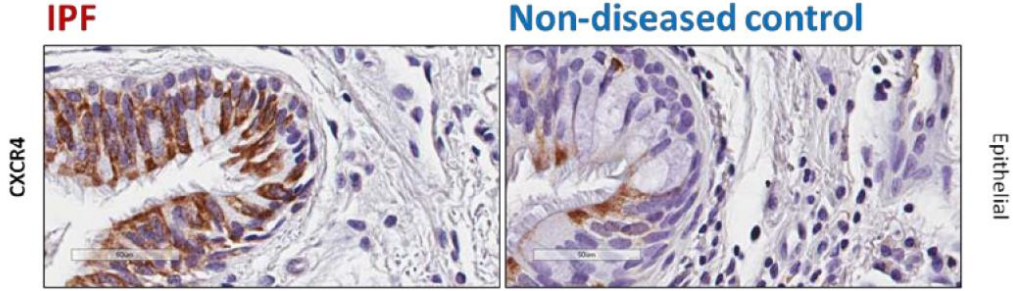
- Important in **maintaining stem cells in bone marrow**
- Used by **HIV-1** as a co-receptor for viral entry into host cells
- Associated with more than **23 types of cancers**

CXCR4 is upregulated in IPF lung tissue



Very limited expression in normal or non-diseased tissues





Brown stain shows amount of CXCR4

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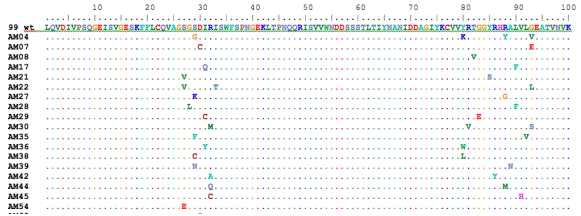
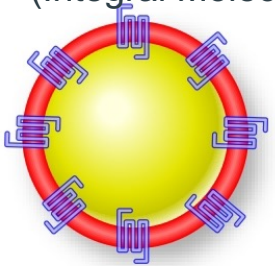
Selecting i-bodies against CXCR4

Affinity maturation

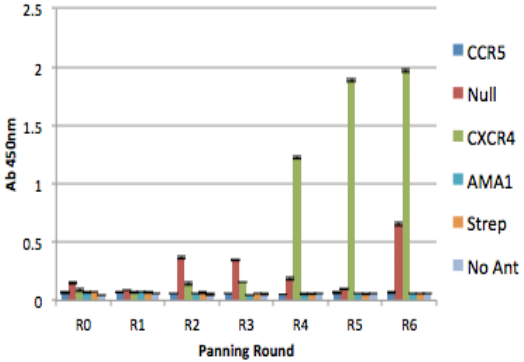


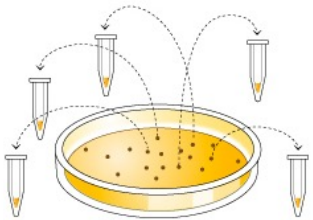
i-body library

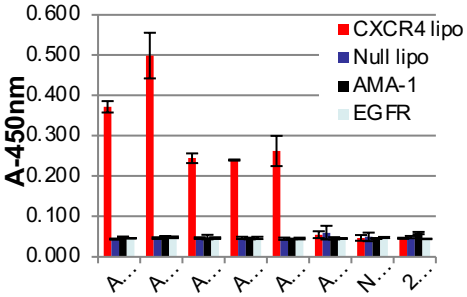
CXCR4 lipoparticles
(Integral Molecular)



Enrichment for CXCR4







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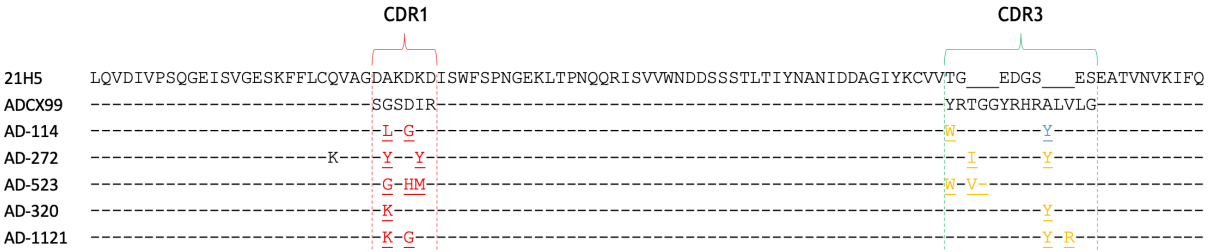
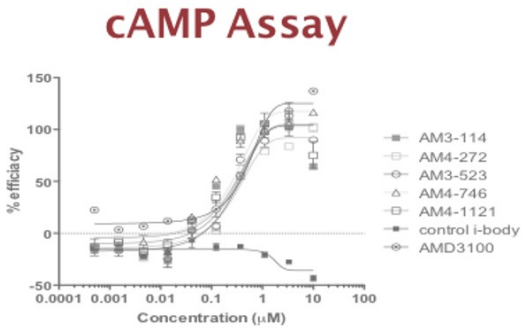
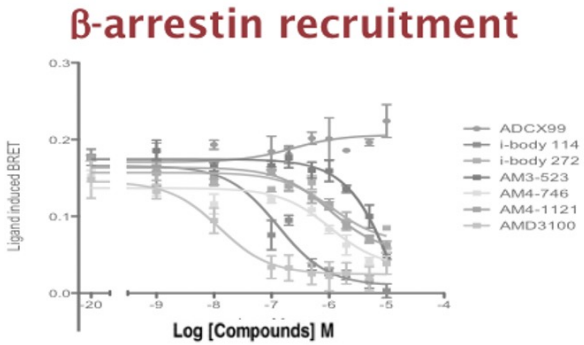
CXCR4 i-bodies: novel pharmacology







Protein	Affinity to CXCR4 (nM)	IC50 (nM) in b-Arrestin BRET assay
ADCX-99	700	No activity
AD-320	21.8	1419
AD-245	14.88	~uM
AD-126	14.75	610
AD-466	13.83	6322
AD-661	9.53	1544
AD-523	8.55	12713
AD-613	7.83	1826
AD-1121	7.21	796
AD-920	7.18	~uM
AD-746	5	741
AD-114	4.85	164
AD-272	1.6	861

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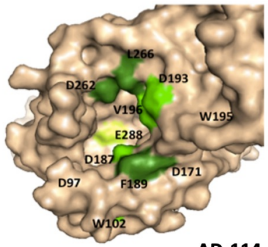
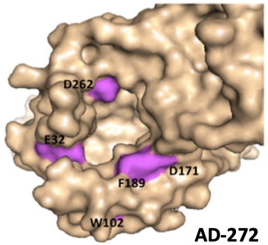
CXCR4 i-bodies: novel physiological outcomes



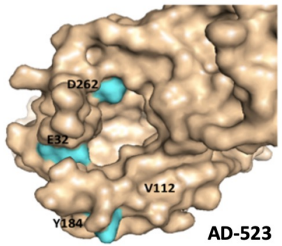
AD-114

High b-arrestin
High cAMP



AD-272

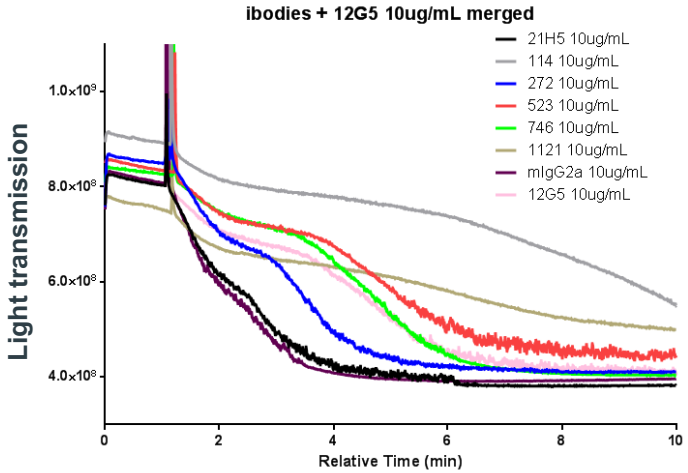
Low b-arrestin
High cAMP

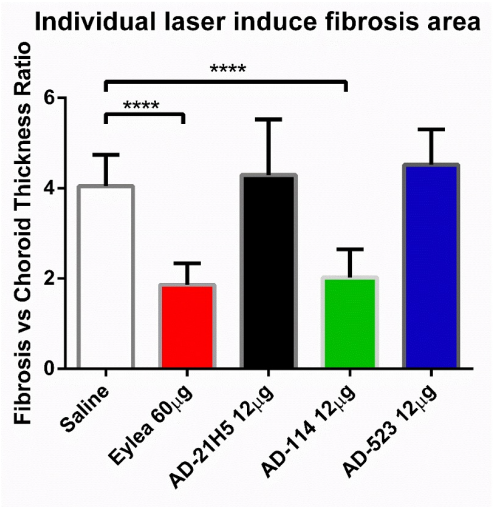


AD-523

Medium b-arrestin
Medium cAMP

- AD-114 inhibits SDF-1 induced platelet aggregation (AD-272 & AD-523 Inhibit to a Lesser Degree)
- AD-114 Reduces fibrosis in a mouse model of macular degeneration AD-523 does not





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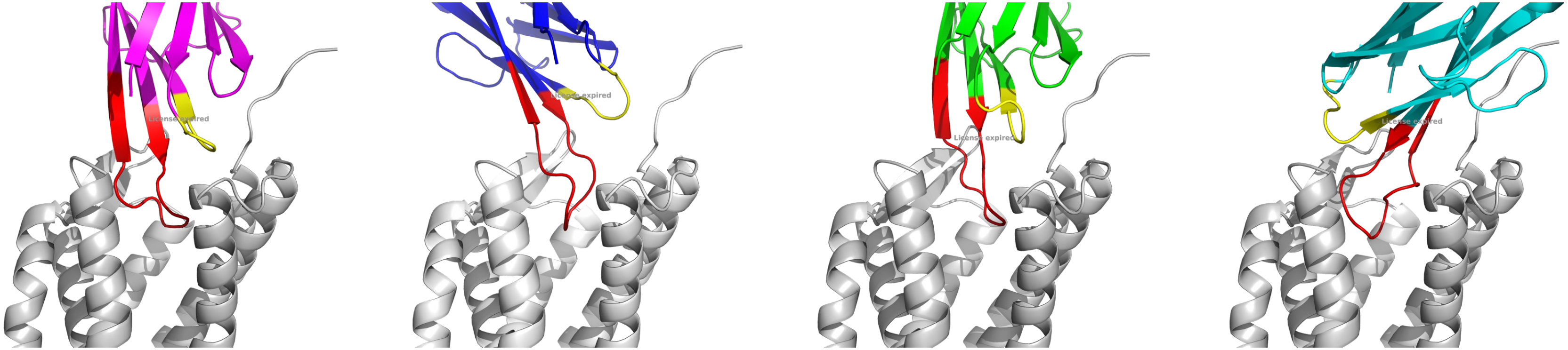
Biased signaling?

- Modelling suggests the panel of affinity matured have different fine specificities which may drive diverse signaling events resulting in distinct pharmacologies

```
                                   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------------
```



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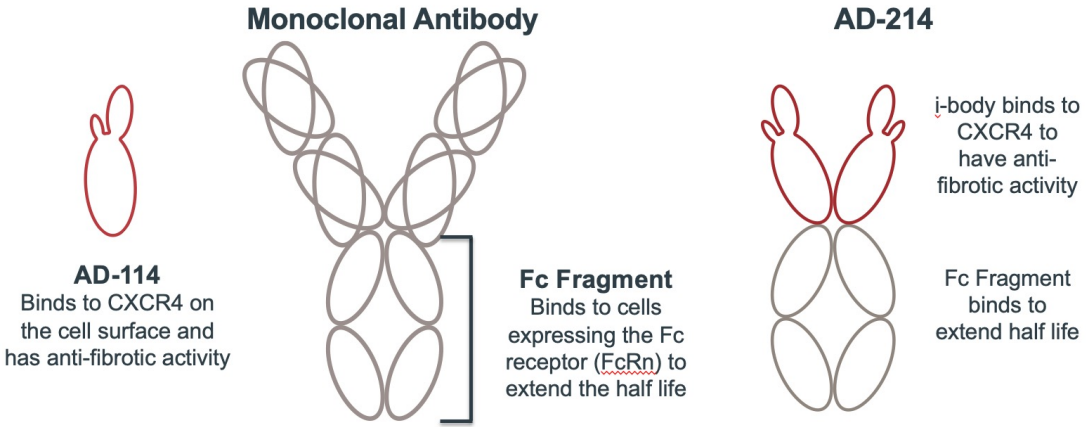
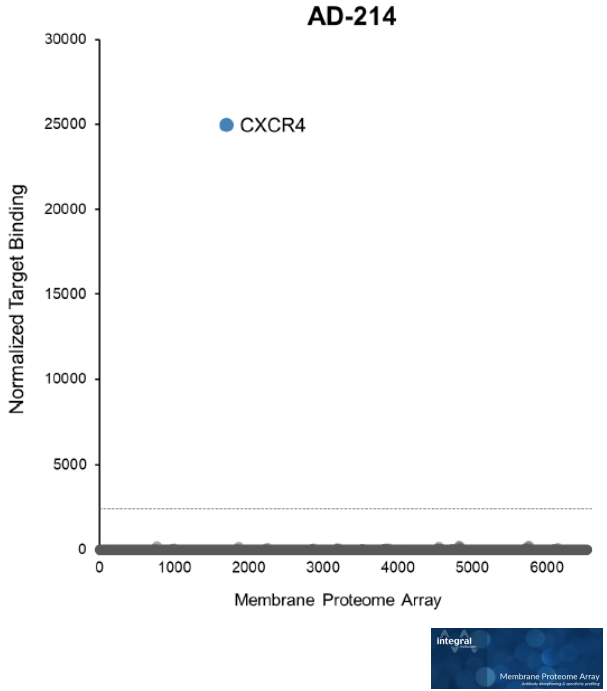
AD-214 retains specificity for CXCR4

- AD-214 consists of the CXCR4 binding i-body (AD-114) fused to human Fc
- AD-214 binds specifically to CXCR4

When combined, the i-body and Fc fragment create a superior drug, which will be better for patients and for potential commercial partners





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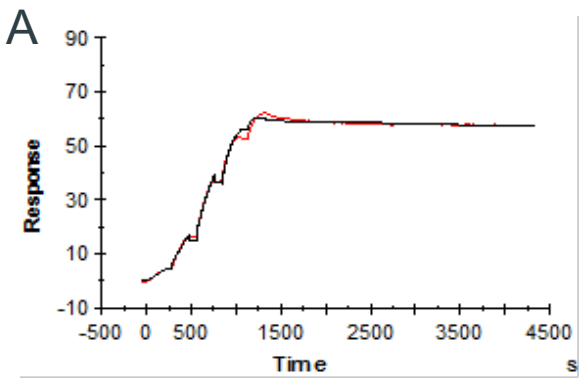
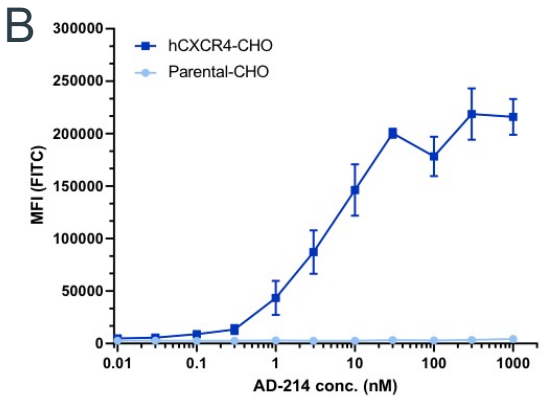
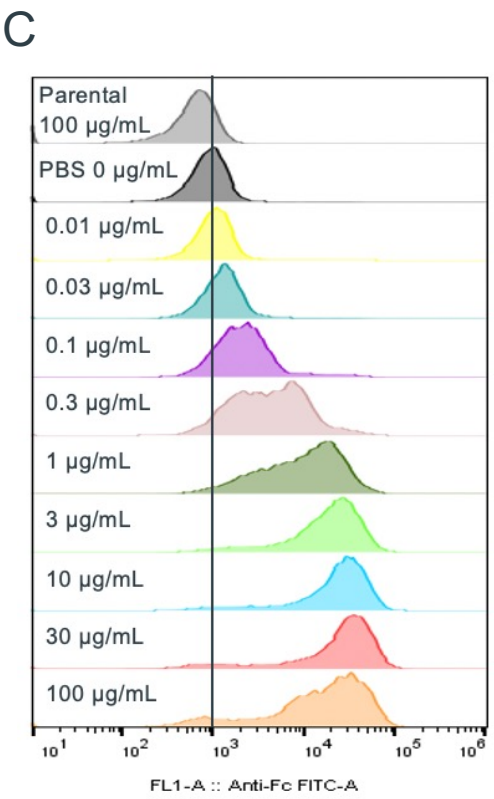
AD-214 binds with high affinity to CXCR4

- AD-214 binds to human CXCR4 lipoparticles with affinity of ~4pM (**A**)
- AD-214 binding to CXCR4 expressing CHO cells but not to parental cells (**B**)
- Flow cytometry shows that AD-214 can bind to CXCR4 expressed on human CD3^{+} T cells (**C**).







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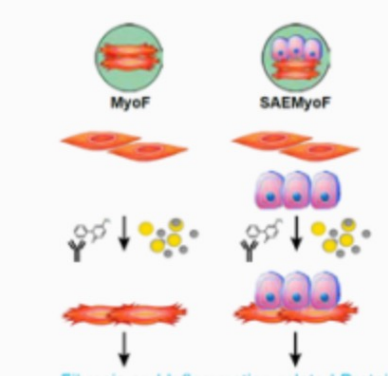
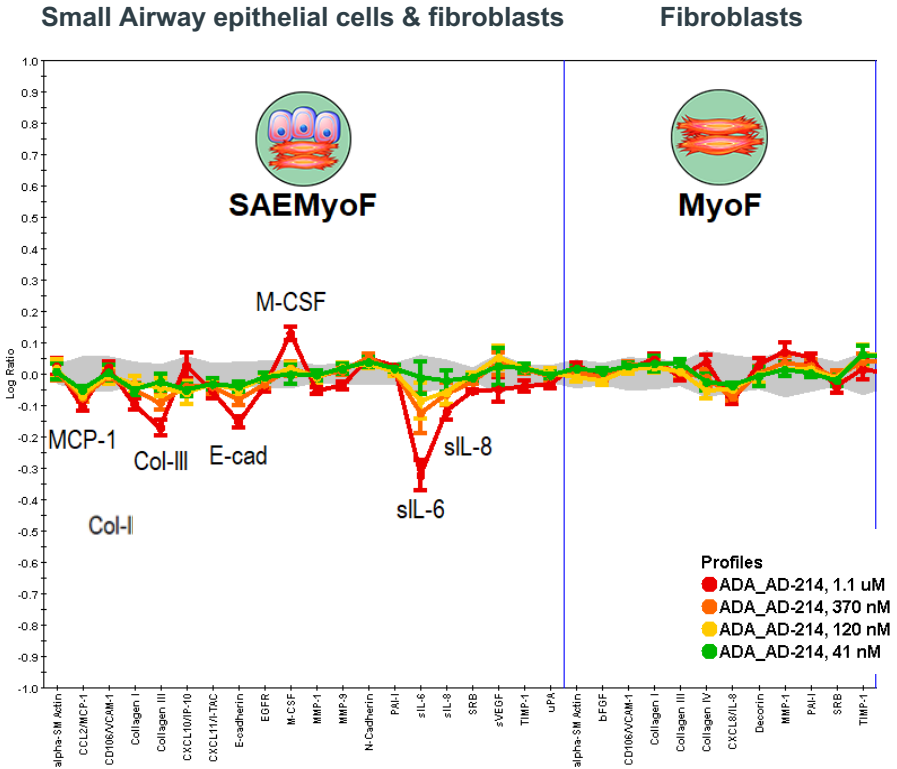
AD-214 Phenotypic profile lung fibrosis panel

SAEMyoF and MyoF consisting of a co-culture of lung fibroblasts and small airway epithelial cells.



Key activities of AD-214:

- AD-214 is not cytotoxic at the concentrations tested in this study.
- Fibrosis-related matrix activities: decreased Collagen I, Collagen III
- Inflammation-related activities: decreased MCP-1, sIL-8, sIL-6; increased M-CSF



BioMAP
HUMAN PHENOTYPIC PROFILING SERVICES

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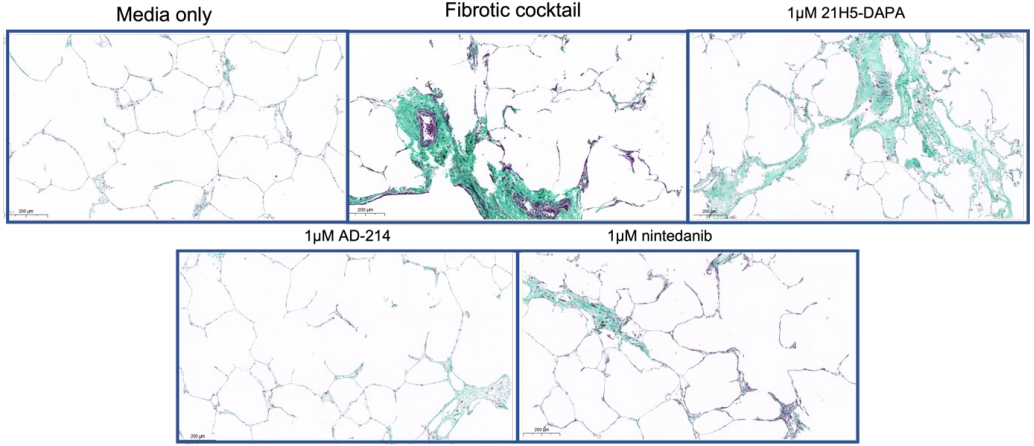
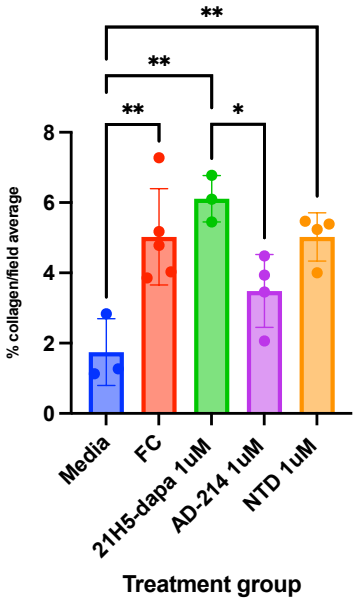
AD-214 attenuates collagen deposition in human PCLS

- **AD-214 *in vitro* at 1 µM attenuated collagen deposition in Precision Cut Lung Slices treated with a fibrotic cocktail**



Representative images of Masson trichrome stained PCLS (collagen in blue)



Experimental design: PCLS (n=3 donors with 1 or 2 slices per donor) were cultured *in vitro* in control media or media with a fibrotic cocktail (FC) (TGF-β, PDGF-AB, TNF-α and LPA) and treated with either: 1 µM AD-214, 1 µM 21H5-DAPA (AD-214 control) or 1 µM nintedanib. Sections of fixed PCLS were stained with H&E and Masson's trichrome for collagen staining and scanned into digital images with a slide-scanner for analysis of degree of fibrosis of 10 non-overlapping fields, with no tissue artifacts or large blood vessels to give a percent of collagen/ total area of interstitial lung tissue. The average of all 10 fields is then calculated to provide a mean percent of collagen/ total area per section. Data is mean ± S.D. Statistics: one-way ANOVA, ** $p<0.01$, * $p<0.05$, n=3

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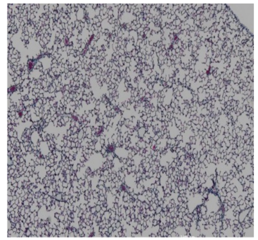
AD-214 efficacy validated in IPF murine model

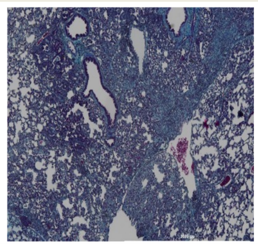
AD-214 inhibited the development of fibrosis in a bleomycin mouse model of lung fibrosis at concentrations as low as 1 mg/kg every two days and 10 mg/kg every four days

Normal mouse lung tissue



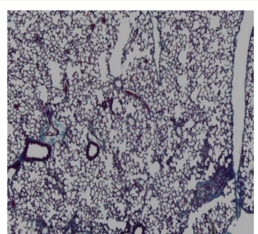
IPF mouse lung tissue

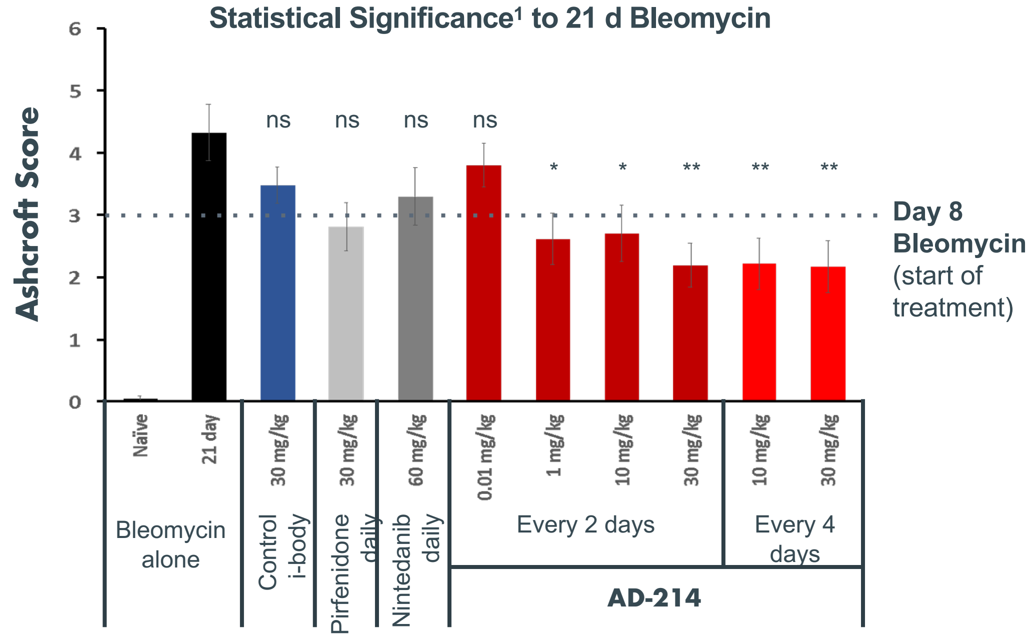
21 days after bleomycin



IPF mouse lung tissue + AD-214

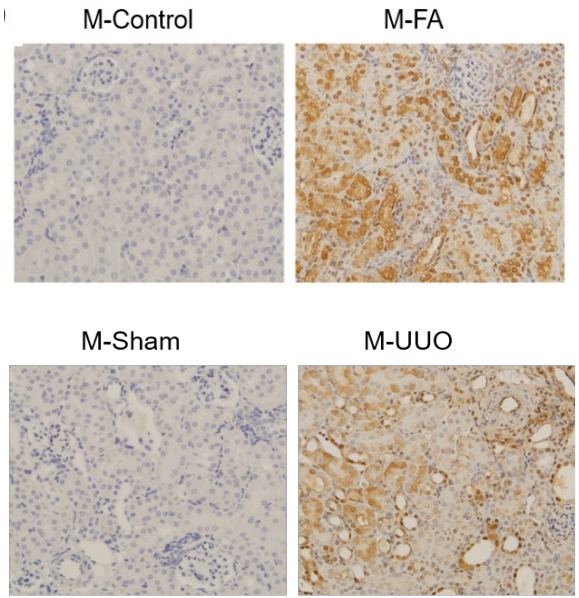
21 days after bleomycin and AD-214 at 10 mg/kg every 4 days from day 8

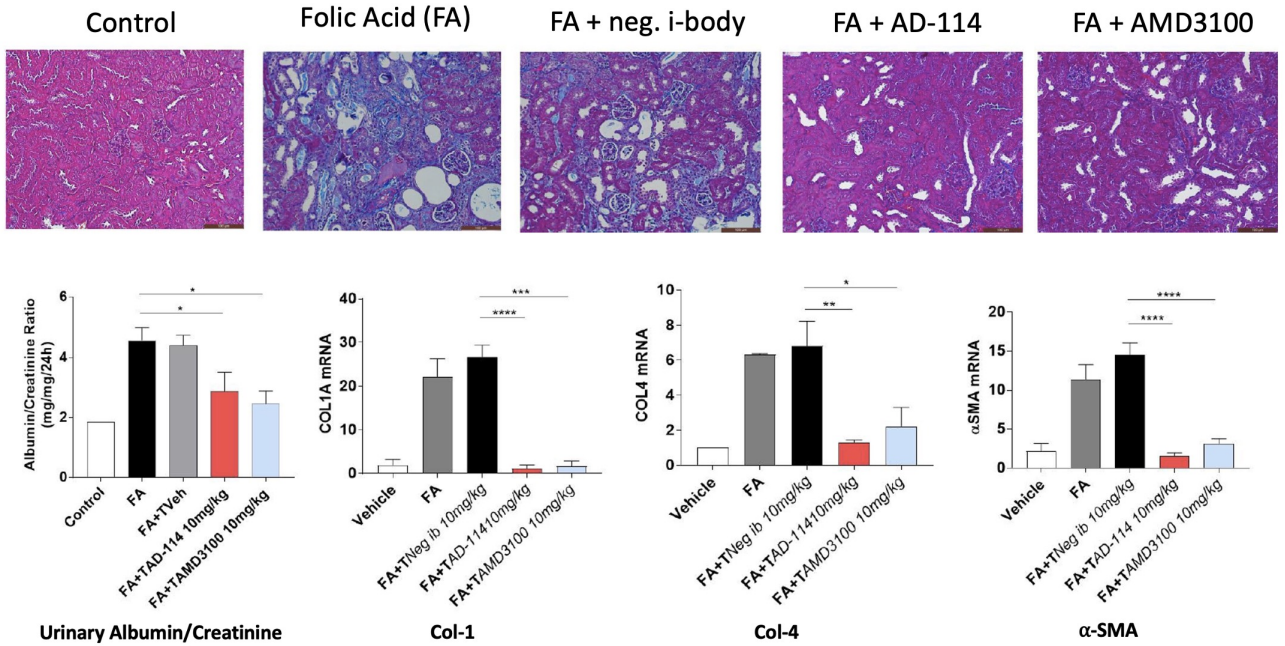




AD-114 is antifibrotic in a mouse model of kidney fibrosis

- CXCR4 is upregulated in several models of kidney fibrosis
- AD-114 administration attenuated tissue damage when given at the time of injury or after fibrosis was established
- AD-114 blocked TGF-β–induced production of extracellular matrix and activation of AKT signaling





Cao etal JCI Insight 2022

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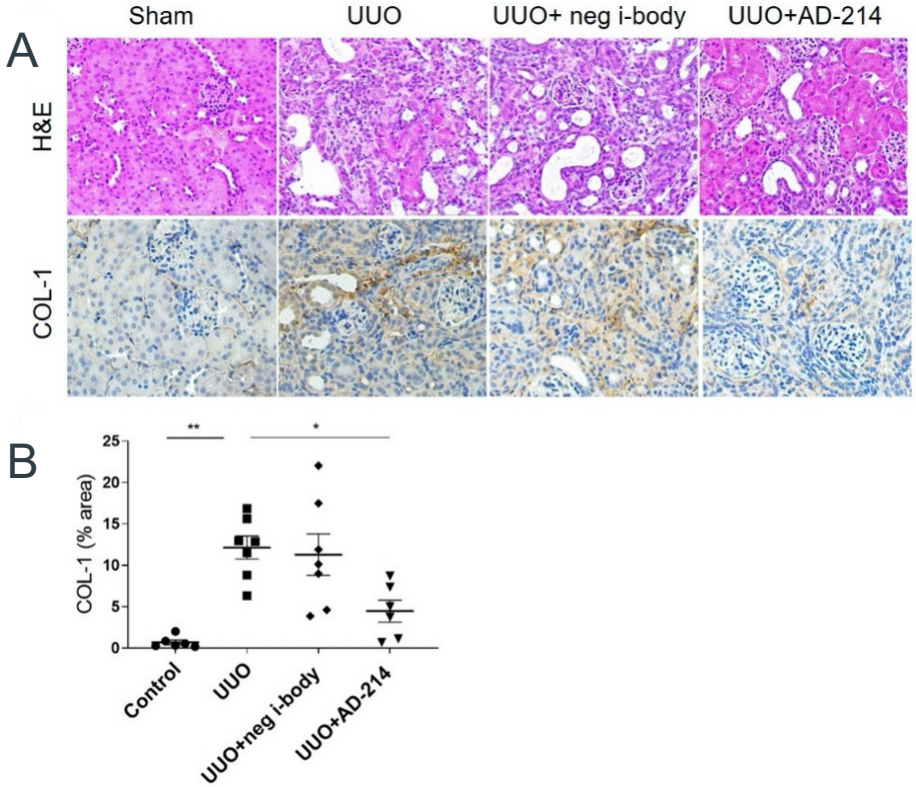
AD-214 is antifibrotic in a mouse model of kidney fibrosis

- The effect of AD-214 on fibrosis induced by Unilateral Ureteral Obstruction (UUO) was examined
- Mice were dosed with negative i-body or AD-214 i.p. the day following UUO and were then administered every second day until day 14.
- Representative images of H&E staining and IHC staining for COL-1 (A)
- Quantification of stained area as percentage of total area (B)



Statistical analysis was performed using one-way ANOVA followed by Tukey's multiple comparisons test. Results presented as mean±SEM. *P<0.05, **P<0.01. n=6-8. Original magnification: ×200.

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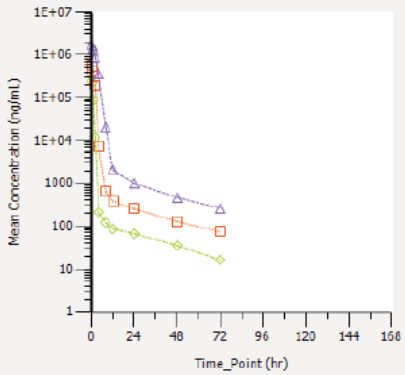
Non-human primate GLP toxicology: Phase I dose justification

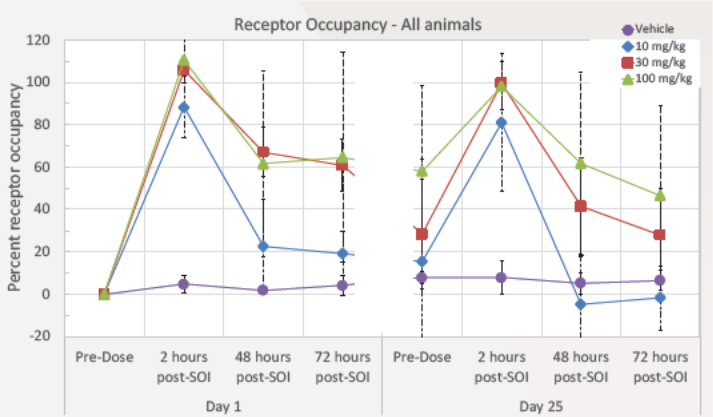
Pharmacokinetics

- Elimination half-life 22-29h
- Human equivalent: ~71h (estimate)
- AD-214vailable for >3 days



Pharmacodynamics

- >60% receptor occupancy* for 72h at >30mg/kg
- Human equivalent: ~10mg/kg (estimate)
- High receptor binding for >3 days



Safety

- 3 non-human primate studies completed.
- Good Laboratory Practice (GLP) study to evaluate safety and toxicology
- **AD-214 well tolerated with no deaths, no AD-214-related clinical signs, no changes in a panel of clinical observations**
- Pre-clinical PET imaging revealed rapid distribution of intravenous AD-214 to liver in mice and NHP. No major organ toxicity has been observed on repeat dosing at high doses . No suggestion of off-target toxicities

Supportive of human therapeutic dose window including 10mg/kg intravenously, weekly or every second week

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AD-214 IV administration Phase I healthy volunteer results

AD-214 molecule has an excellent safety profile in single doses to 20 mg/kg and multiple doses to 5 mg/kg

- No dose limiting toxicities or adverse events of clinical concern in single doses to 20 mg/kg
- Moderate infusion related reactions (IRRs) in 3 participants (2 drug, 1 placebo) receiving multiple 5mg/kg doses
  - Rapidly resolved at end of infusion
  - *Appear formulation related*
- No concerning clinical laboratory results, no adverse liver or other organ function detected
- *HREC approved progressing to 10 mg/kg*

AD-214 clearly engages the target CXCR4 receptor *in vivo*

- Dose dependent changes in biomarkers of CXCR4 engagement observed
- High and extended duration of receptor occupancy on circulating T cells
- *Biomarker response consistent across multiple doses at 5 mg/kg – no evidence of tolerance*

AD-214 intravenous pharmacokinetics are dose proportionate

- Peak and total AD-214 exposure increases in a dose proportionate or more manner to 20 mg/kg, consistent across multiple doses at 5 mg/kg
- Elimination half-life 44±15 hours at 20 mg/kg
- *No evidence of tolerance or drug induced clearance*
- *Rapid distribution from plasma observed at all doses, consistent with rapid increase/saturation of receptor occupancy and rapid liver localization (observed in preclinical imaging)*

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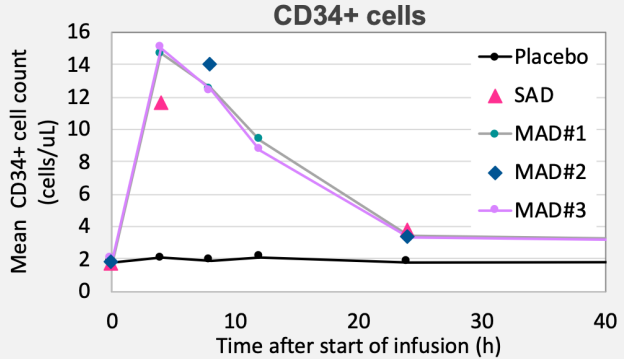
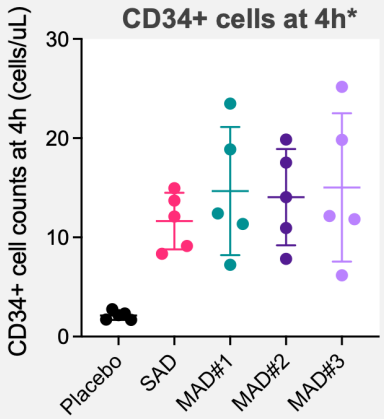
Biomarkers of CXCR4 receptor engagement (5mg/kg)

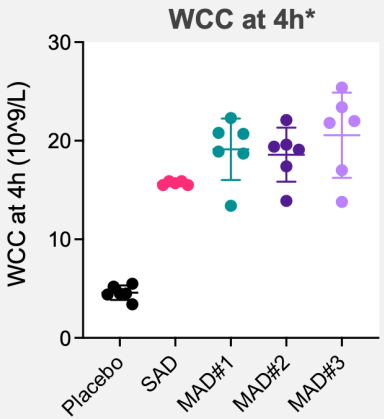
- **Transient increases in blood biomarkers demonstrate consistent engagement of the target receptor, CXCR4 across multiple AD-214 doses**

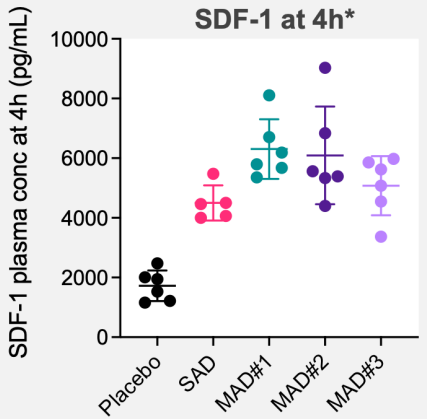
Biomarker data confirm single dose findings, consistent across multiple doses: no drug induced tolerance or accumulation

- White blood cell counts (WCC), haematopoietic stem cell (CD34+) counts and concentration of SDF-1 are biomarkers of CXCR4 engagement by AD-214
- Profile of biomarkers is consistent across multiple doses at 5 mg/kg*
- 100% T cell CXCR4 receptor occupancy achieved for at least 24h (data not shown, maximum duration analysis pending)

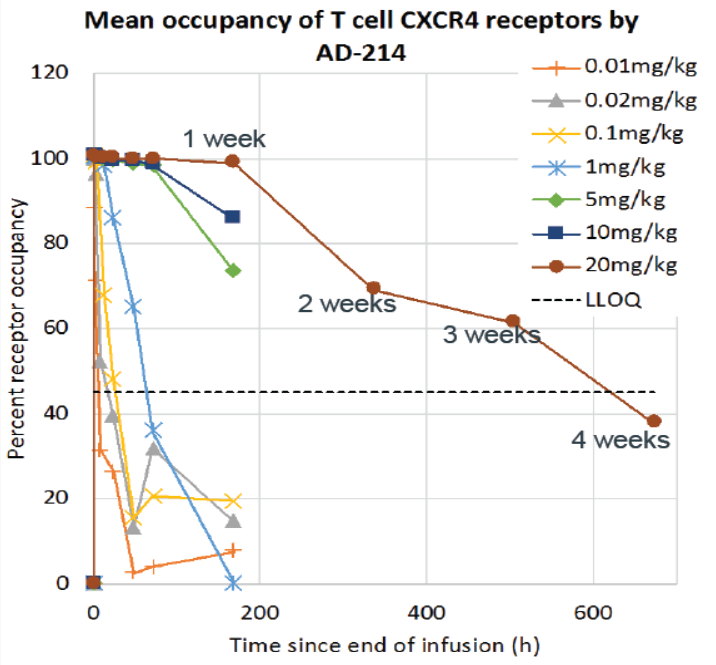








Sustained high levels of CXCR4 receptor occupancy on T-cells



White blood cells naturally express CXCR4 in healthy individuals, providing an accessible surrogate for AD-214 target engagement or receptor occupancy (RO)

Understanding duration of RO is critical to inform dosing

Primary

- >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***

If replicated on CXCR4 receptors in fibrotic tissues, result supports extended dosing intervals despite relatively rapid clearance from circulation

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

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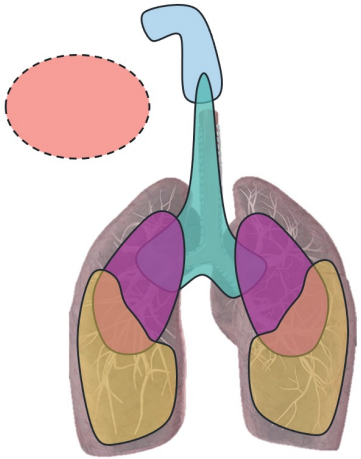
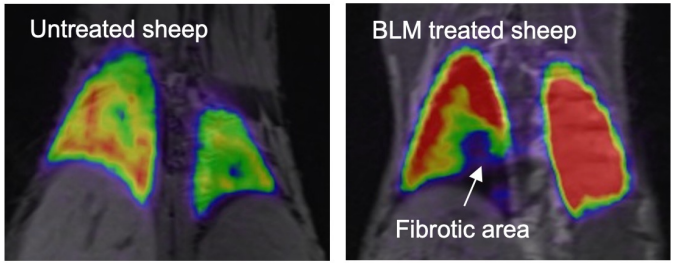
Feasibility of direct lung delivery via inhalation demonstrated; SC under evaluation

- The ICRP66[1] model predicts that 17 - 46% of AD-214 delivered from commercial nebulisers will be delivered to the smallest (alveolar/interstitial) airways of the lungs where most IPF is found. PET imaging confirms AD-214 delivery via inhalation to all regions of the lungs. SC AD-214 PK simulations pending



	Device A
Aerosol particle size (volume mean diameter)	4.8 μm
Fine particle fraction (% particles ≤ 5 μm)	55%
Deposition fraction	
Extra thoracic	17%
Tracheobronchial	8%
Bronchiolar	15%
Alveolar / interstitial	***46%***
Total lung (BB, bb, AI)	**69%**
Exhaled	14%

PET imaging of inhaled ^{89}Zr-AD-214 in sheep



SC administration potential

- Pilot study and high CXCR4 affinity encouraged review of SC feasibility
- PK simulations under way as part of Phase II dose schedule simulations
- To be followed by pilot toxicology studies in mice

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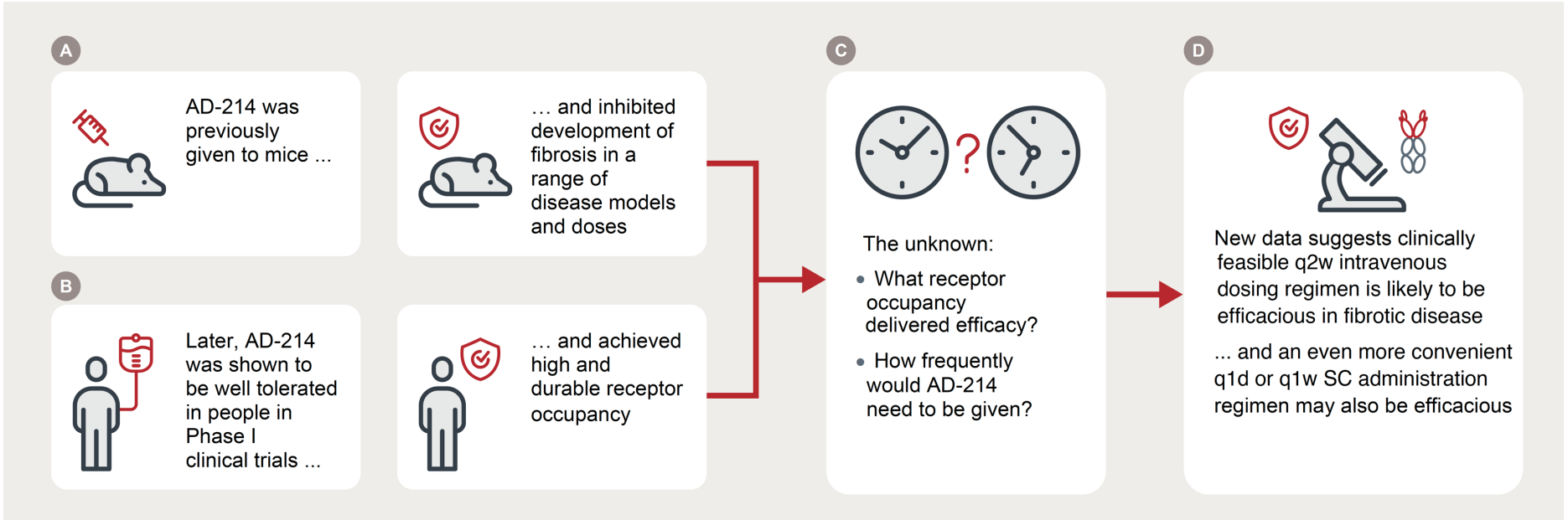
AD-214 is safe but is there a viable clinical product?



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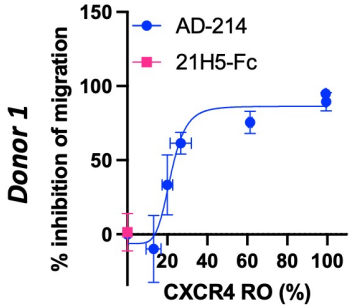
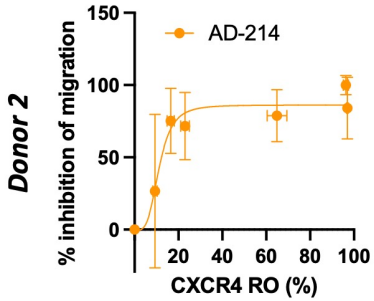
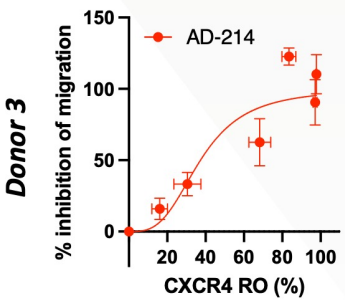
Linking inhibition of T cell migration and CXCR4 receptor occupancy

- Maximal inhibition of T cell migration can be achieved with just 60-85% CXCR4 receptor occupancy and low serum concentrations of AD-214







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

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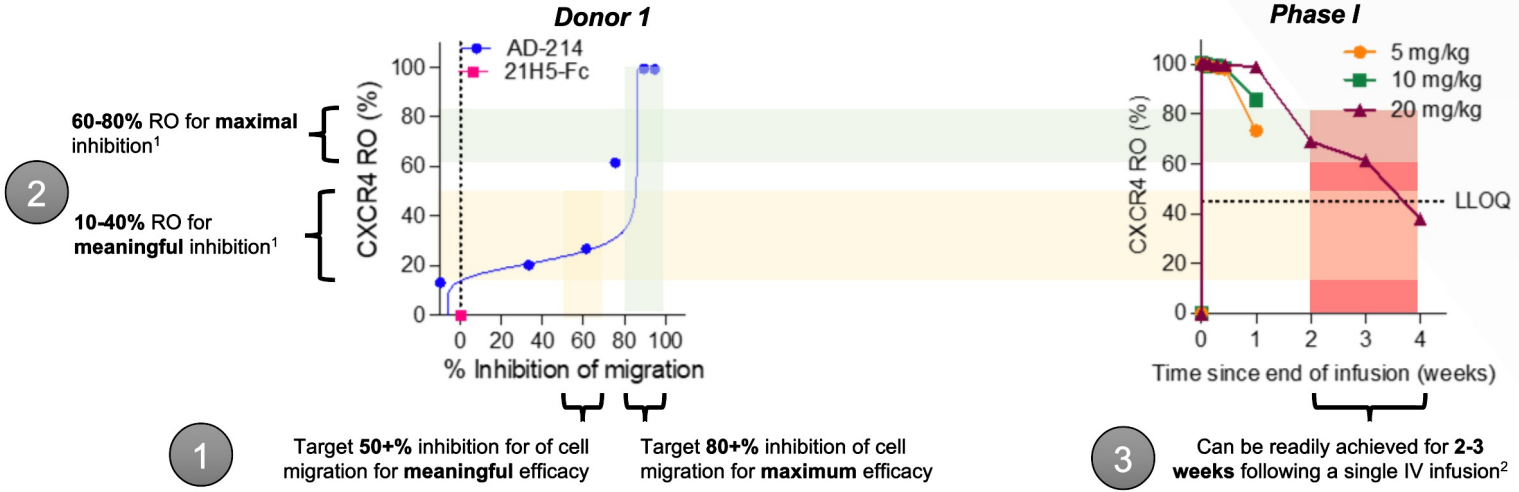
Phase 1 information to inform dosing schedule

1. ***Ex vivo* cell migration is a model fibrotic process and inhibition of migration is a model of efficacy**
   - Maximum efficacy at >80% inhibition of migration (green). Meaningful efficacy at >50% inhibition (yellow)

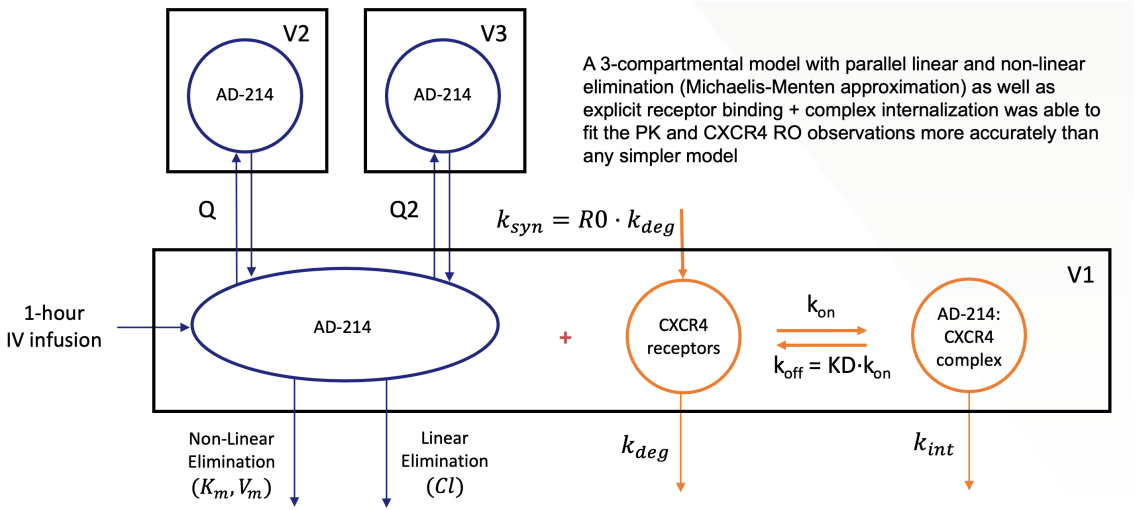
2. **Less than full receptor occupancy (CXCR4 RO) is required for efficacy (meaningful inhibition of cell migration)**
   - 60-85% receptor occupancy is sufficient for maximum inhibition of cell migration
   - Meaningful inhibition at receptor occupancy as low as 10-40%

3. **Maintaining efficacious receptor occupancy levels is the objective of dose selection**
   - **Efficacious receptor occupancy can be maintained for at least two weeks after an IV infusion in humans, a clinically viable dosing regimen[2]**

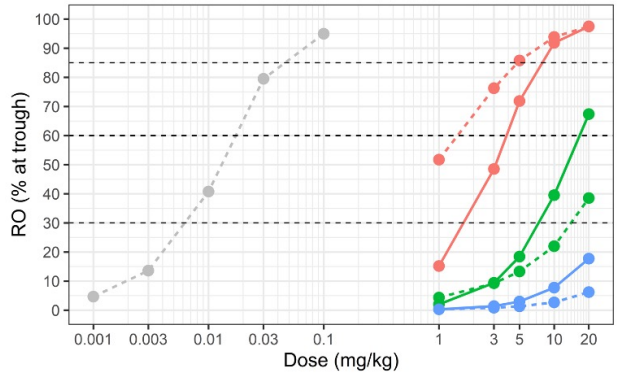


[1] AdAlta studies correlated AD-214 concentration with level of CXCR4 receptor occupancy and level of inhibition of SDF-1α induced migration *ex vivo* on human T cells. Ranges are average of results from three healthy donors, only one donor shown
[2] Clinical Study Report: Protocol ID: ADA-AD-214-1A : Version 1 Dated 07 October 2022

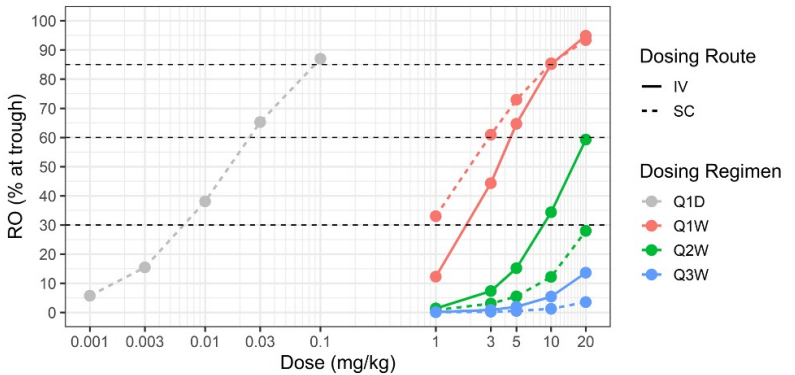
Does modelling support the dosing schedule?



Version A: Fitting PK + RO data[1]



Version B: Fitting PK + RO + total receptor data[1]



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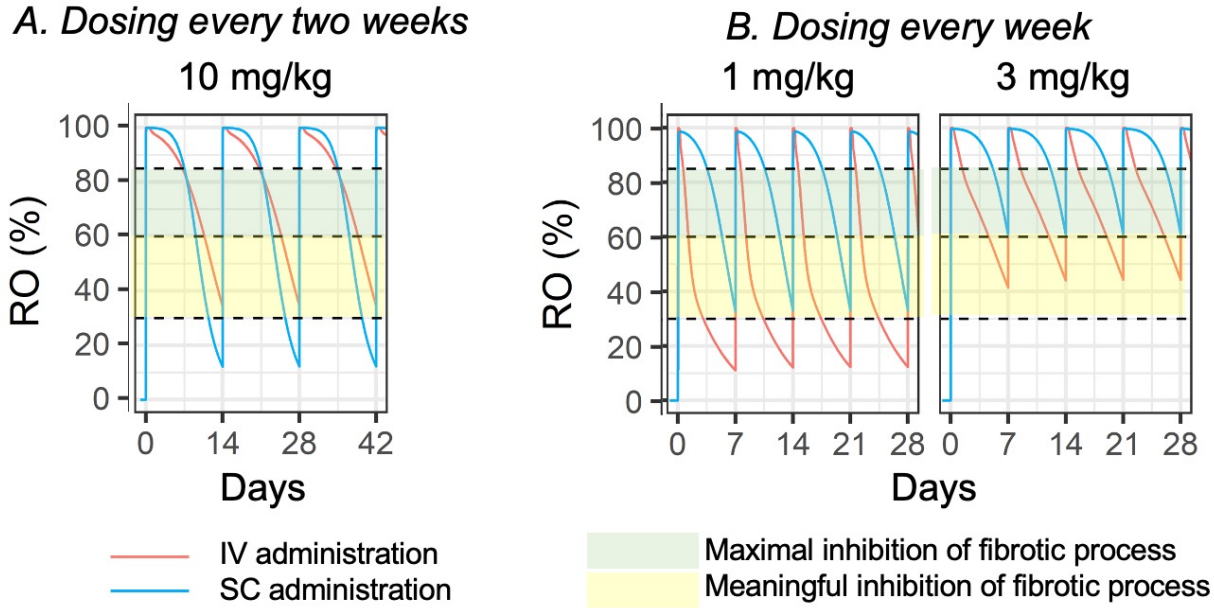
IV and SC doses: predicted AD-214 plasma concentrations and CXCR4 RO



Simulated CXCR4 receptor occupancy following IV (red) and SC (blue) administration of AD-214 doses. Panel A simulates 10 mg/kg AD-214 administered every two weeks. Panel B simulates 1 mg/kg (left) and 3 mg/kg (right) AD-214 administered every week. Shading represents receptor occupancy required for maximal (green) and meaningful (more than 50%, yellow) inhibition of a model fibrotic process in ex vivo experiments. *RO = receptor occupancy*.

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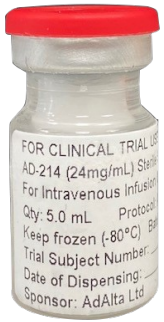
Phase I extension study delivers new data in 2023 to support partnering and Phase II

AD-214 multidose Phase I extension clinical study

- Evaluating safety, PK and PD of multiple 10 mg/kg doses
- Similar design to prior Phase I study
- Utilises existing AD-214 inventory
- Top line data end-2023

COMMENCED



Establishes safety of AD-214 at likely maximum dose to be used in Phase II studies

- ✓ ***Shorter dose escalation stage, reduced cost in Phase II study***

Further explores PK, PD and safety trends observed in Phase I

- ✓ ***Strengthens safety profile***
  - ✓ *Infusion related reaction management, ADAs*
- ✓ ***Better informs dosing levels and schedule for Phase II***
  - ✓ *Receptor occupancy at 10 mg/kg over 2-4 weeks*
  - ✓ *Dose regimen optimised to test IV efficacy and find therapeutic RO, set up for SC route in Phase II*
  - ✓ *Potential for fixed rather than weight based dosing*

Enhances partnering process

- ✓ ***Additional data to address known and potential questions***
- ✓ ***Maintains product development momentum***
  - ✓ *8 HV's have received at least one dose, 4 received 3 doses with no reported issues*
  - ✓ *Interim results Nov 2023*
  - ✓ *Final results Q1 2024*

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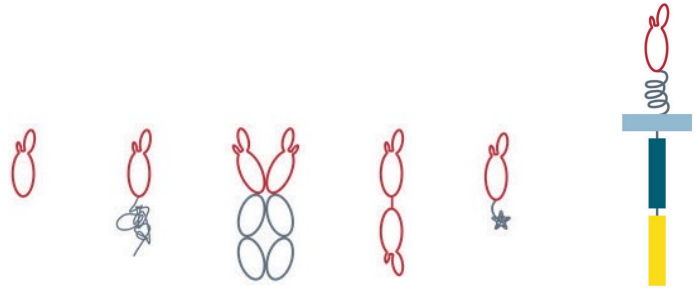
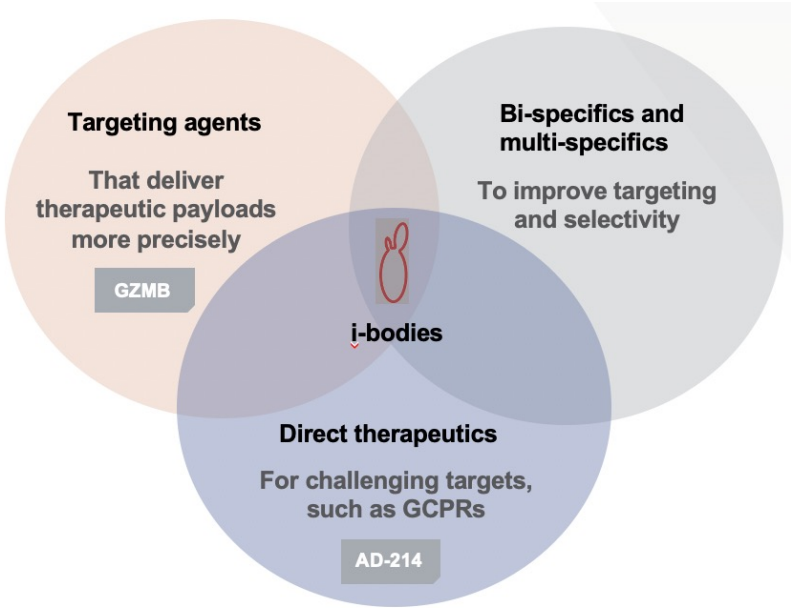
Diverse applications of i-bodies

- **Therapeutic:** Flexible modular format i-bodies with variable C-termini allow direct therapeutics (AD-214)
- **PET Imaging**: untagged i-body against important diagnostic targets eg i-body to GZMB (GE Healthcare)
- **CAR-T**: therapy is a fast-emerging form of cancer therapy. i-bodies can be utilised as the binding domain of a CAR receptor that engages the tumour antigen





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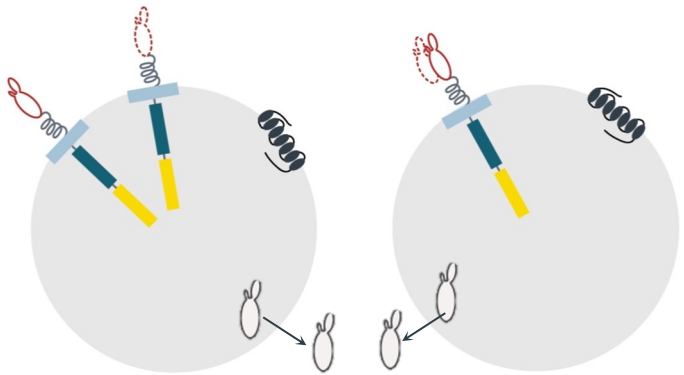
i-bodies enable optimized CAR constructs (i-CARs)

SUPERIOR i-CAR PRODUCTS

- **CARs against novel tumor antigens**
- **Dual and bi-specific CARs for enhanced specificity, reduced tumor escape and logic gated CARs**
- **Secreted antibodies to modulate TME**



FEATURE	BENEFIT
Small Size	Increased CAR gene cassette/vector capacity, efficient multi-functional CAR cell creation
Long CDR3 binding domain	Access to unique tumor antigens/epitopes and TME modulating proteins in cancer tissue
Tunable binding	Control of immune synapse (length + strength)
Robust conformation	Natural stability delivers robust CAR binding domain and stable secreted molecules

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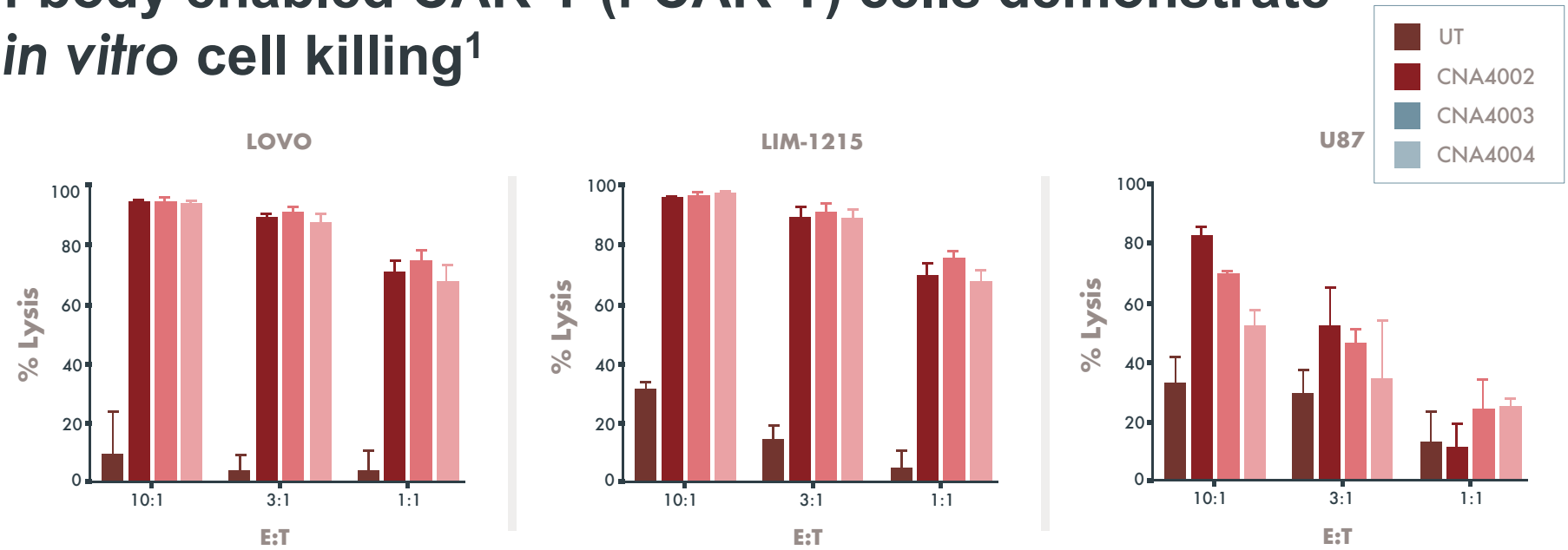
i-body enabled CAR-T (i-CAR-T) cells demonstrate *in vitro* cell killing[1]



- Cell lines: colorectal cancer (LOVO and LIM1215); glioblastoma (U87)
- CAR-T constructs: CNA4002/CNA4003/CNA4004 incorporate an i-body against target "X" and variable linker lengths
- Control: unmodified T cell (UT) that does not result in significant killing of these cell lines
- i-CAR-T cells manufactured with 97% transduction (i-body CAR insertion) efficiency
- i-CAR-T cells included 60-70% CD4+ (helper) and 20-30% CD8+ (cytotoxic – killer) T cells

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next generation protein therapeutics

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