27 September 2021

ASX Announcement

NEW PRECLINICAL DATA PRESENTED AT "DISCOVERY ON TARGET" MEETING

Key points

- **Prof Mick Foley, CSO, presenting at Discovery on Target meeting, Boston**
- **New pre-clinical data on AD-214 in kidney fibrosis**
- **AD-214 pre-clinical and clinical development summarised**

MELBOURNE Australia, 27 September 2021: AdAlta Limited (ASX:1AD), the clinical stage biotechnology company developing novel therapeutic products from its i-body platform advises that Chief Scientific Officer, Professor Mick Foley, is presenting virtually at the 19th Annual Discovery on Target conference being hosted in Boston from 27-30 September 2021.

Professor Foley's presentation, "CXCR4 antagonist AD-214 as a therapy for Interstitial Lung Disease" includes new preclinical data showing potential efficacy of AD-214 in a mouse model of kidney fibrosis. It also provides a summary of the development of AD-214, including the previously reported safety, pharmacokinetic and biomarker data from the recently completed Phase I studies of AD-214, and the Company's plans to progress an inhaled version into Phase II studies for Idiopathic Pulmonary Fibrosis (IPF).

The new pre-clinical data shows potential efficacy of AD-214 in a mouse model of kidney fibrosis known as the Unilateral Ureteral Obstruction (UUO) model. In this model, one ureter is blocked in each mouse (the other serves as a control), inducing inflammation and fibrosis and increasing levels of collagen in the obstructed kidney.

Studies conducted in collaboration with Professor Carol Pollock at the University of New South Wales showed that treatment with AD-214 by intraperitoneal administration resulted in a statistically significant reduction in the level of collagen and fibrosis in the UUO obstructed kidney compared with both no treatment and treatment with a non-CXCR4 specific control i-body. Illustrative results are shown in the figure below.

This finding is consistent with previously reported studies of AD-114 (the anti-CXCR4 i-body incorporated in AD-214) in a different model of kidney fibrosis (the Folic Acid model). Full results have been submitted for publication.

Discovery on Target is the pharmaceutical industry's preeminent event on novel drug targets and technologies for drug discovery professionals, highlighting advances in current and emerging "hot" targets and technologies as well as target validation strategies for the discovery and development of novel therapeutic agents.

Professor Foley's presentation forms part of a session focussed on targeting G-protein coupled receptors (GPCRs), a critically important target class for the pharmaceutical industry and is attached to this announcement.

Authorised for lodgement by:

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September 2021

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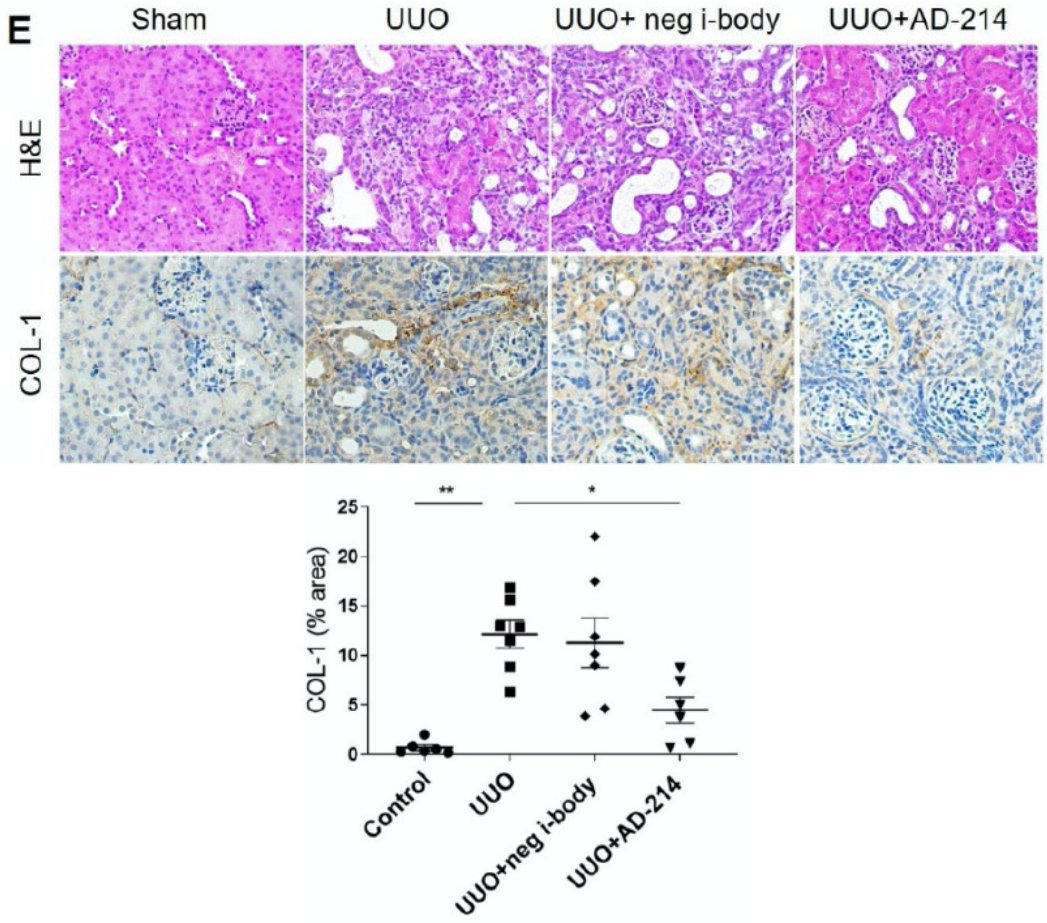
Figure 1: AD-214 protects kidneys and reduces collagen expression in a mouse UUO model of kidney fibrosis



Collagen levels, a marker of fibrosis, were measured in normal (sham/control) mouse kidneys and in kidneys that were obstructed but untreated (UUO), obstructed and treated with a non-specific control i-body (UUO+neg i-body) or obstructed and treated with 5 mg/kg AD-214 administered by intraperitoneal injection (UUO+AD-214). Treatments were administered every second day for 14 days commencing the day after obstruction.

The top panel shows illustrative kidney slices stained with hematoxylin and eosin stain (H&E) to visualise tissue structural details. This panel shows that obstruction of the ureter (UUO image) results in severe disruption of the normal tissue structure (Sham). Treatment with AD-214 (UUO+AD-214) but not with the negative control i-body (UUO+neg i-body) reduces the amount of tissue damage.

The lower panel shows illustrative kidney slices stained to detect COL-1, a marker of collagen and fibrosis. The level of COL-1, (brown staining) correlates with the level of tissue damage and shows that AD-214 treatment reduces COL-1 (fibrosis) in this model.

The chart shows that the severity of fibrosis as measured by percentage of the kidney slice area stained for COL-1 (COL-1(%area)) was significantly lower following treatment with AD-214. Data points are individual mice and horizontal lines represent the average.

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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 protein 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 has completed 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.

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

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

CXCR4 antagonist AD-214 as therapy for Interstitial Lung Disease

DOT September 2021

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CXCR4 plays a role in IPF

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

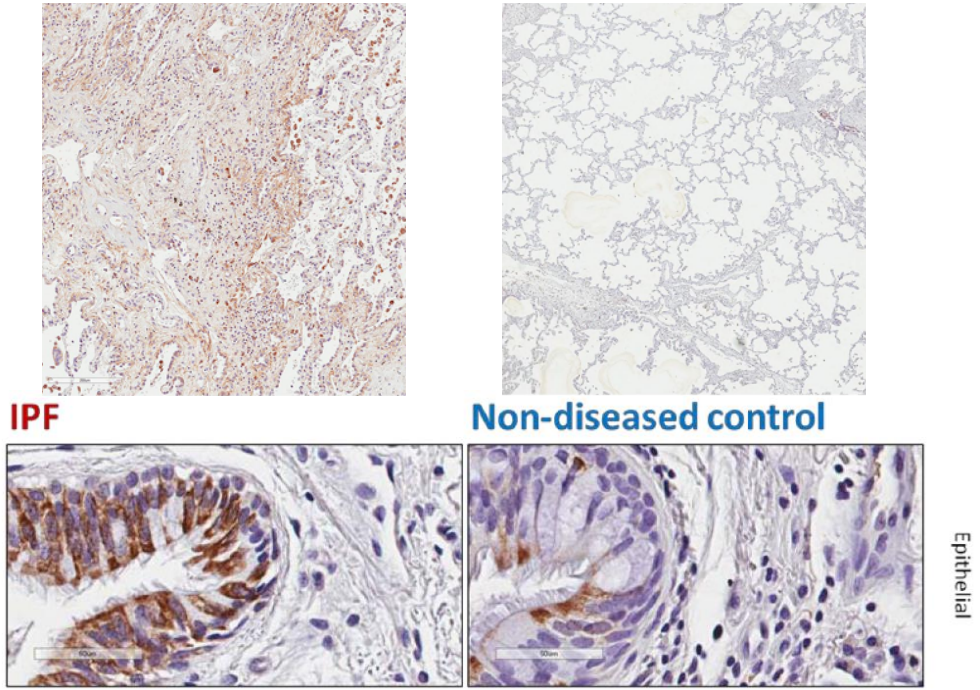
- Lung
- Kidney
- Heart
- Eye
- Skin

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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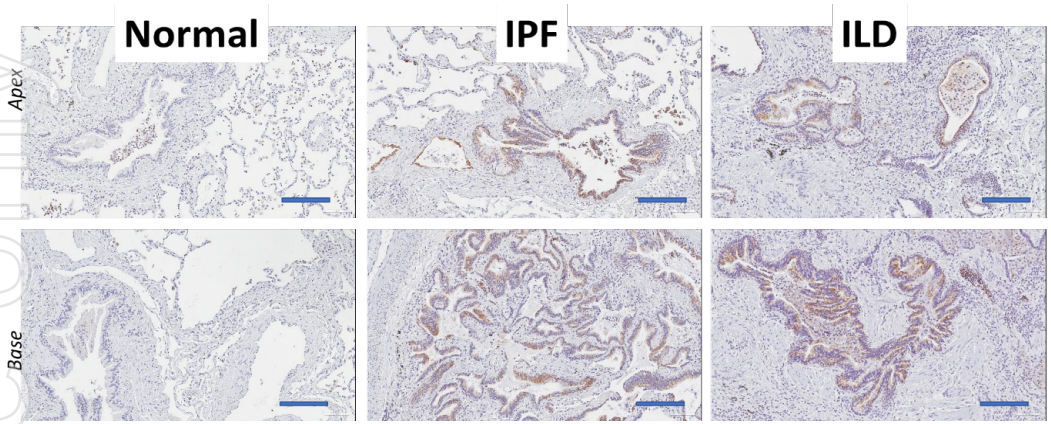
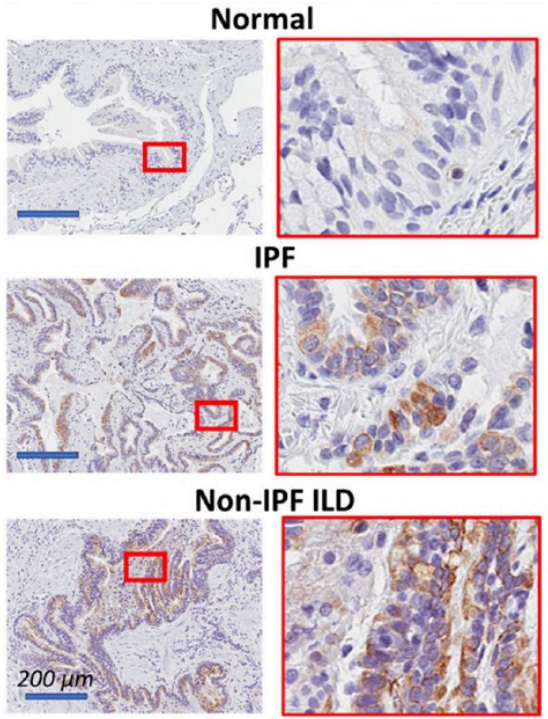
CXCR4 is expressed in both IPF and ILD patient lung tissue and in multiple cell types



- CXCR4 was abundantly expressed in **both IPF and ILF donors** compared with non-diseased controls
- CXCR4 is expressed on **circulating immune cells** and in patients with IPF and other fibrotic ILDs we have demonstrated that CXCR4 is significantly upregulated in the **fibrotic airway epithelial** and **fibrotic loci myeloid cells**



CXCR4 stained brown

Source: Jaffar et al, Respiratory Research (2020) 21: 221

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Why targeting CXCR4 could improve IPF/ILD outcomes

Observation

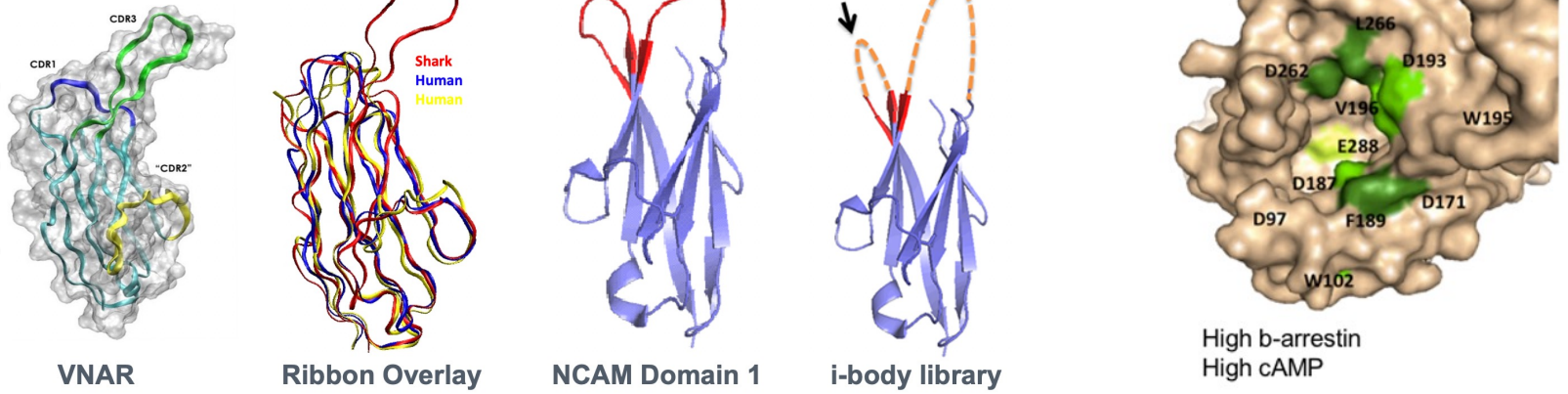
- CXCR4 is up-regulated in ILD patients as well as IPF patients
- CXCR4 is upregulated in epithelial and myeloid cells in fibrotic tissue
- CXCR4 is also involved in the migration of fibroblasts and inflammatory cells such as macrophages in a disease specific way

Significance

- If AD-214 works in IPF it is more likely to work in ILD as well … and there are at least as many non-IPF ILD patients as IPF patients
- Epithelial cells involved in the fibrosis cascade: blocking CXCR4 could have a broader effect than simply shutting down collagen deposition
- Blocking CXCR4 may also have an immune modulation effect and inhibit immune/ inflammatory cell infiltration to the lungs

i-bodies: human single domains

- i-body inspired by the shark VNAR structure
- AD-114 is a CXCR4 binding i-body that binds in the ligand binding site and antagonizes the receptor



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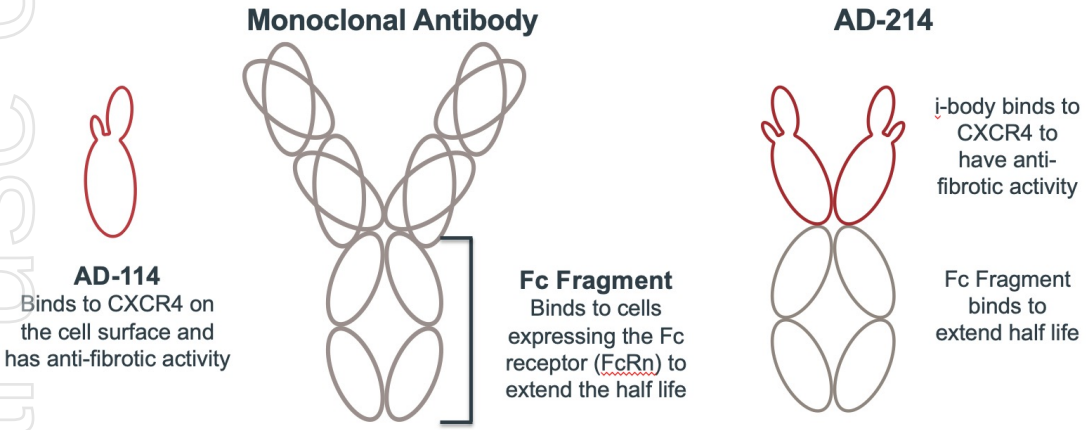
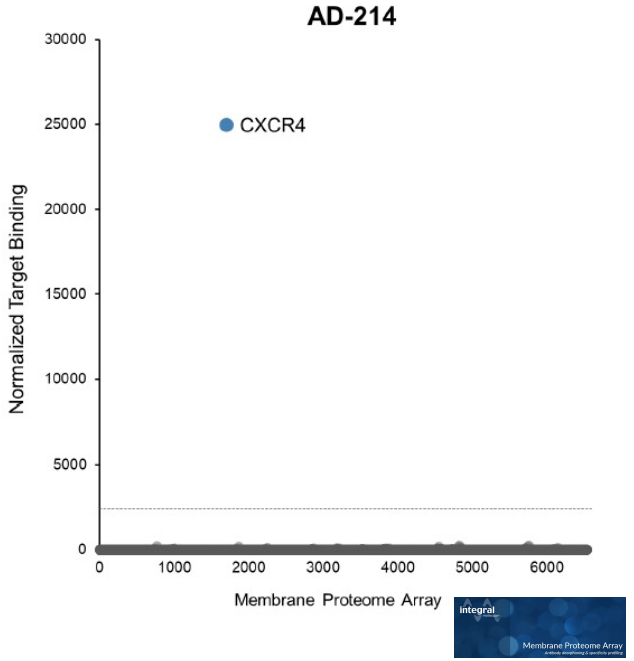
AD-214 retains specificity for CXCR4

- AD-214 consists of the CXCR4 binding i-body (AD-114) fused to human Fc
- AD-214 had no binding to proteins other than 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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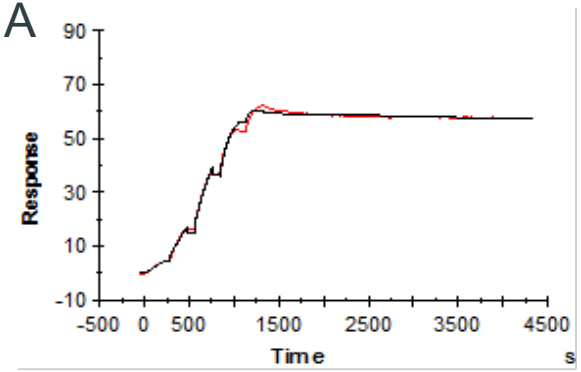
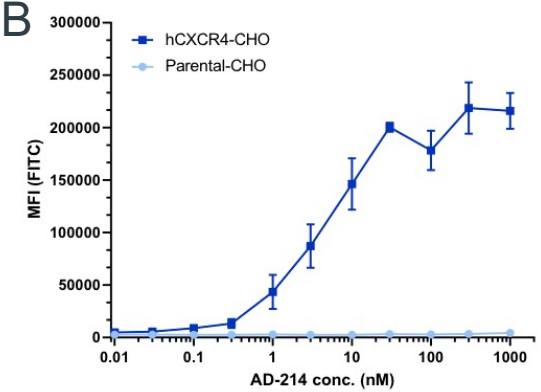
AD-214 binds with high affinity to CXCR4

- 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**).

A



B



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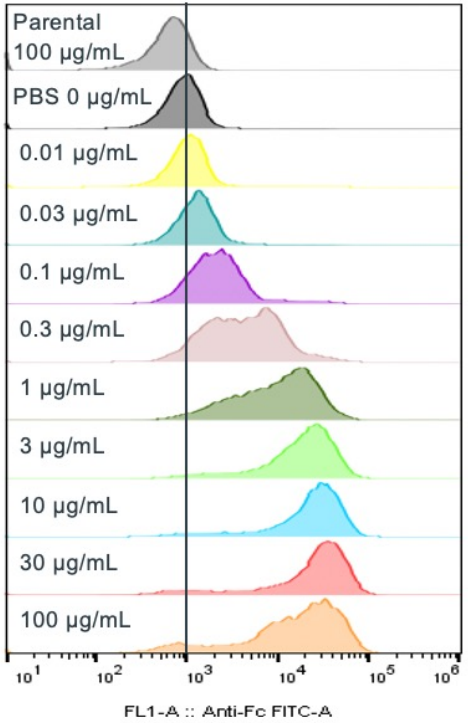

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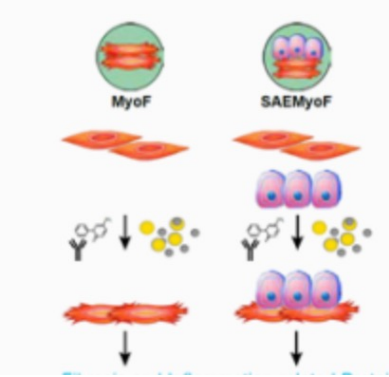
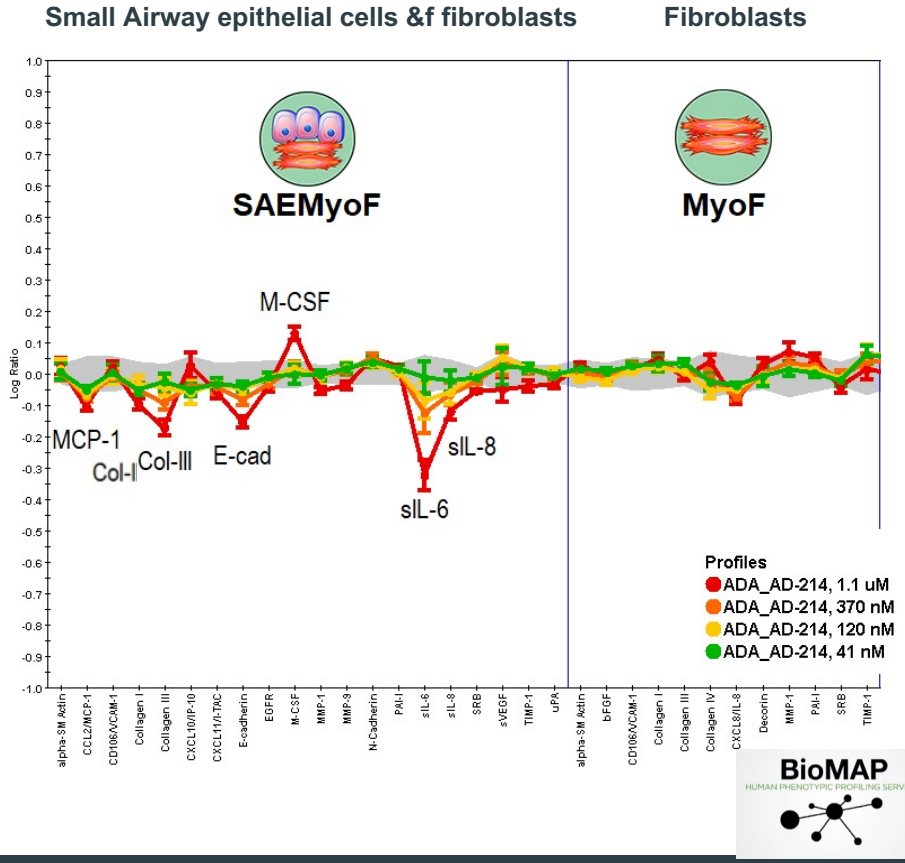
AD-214 Phenotypic profile lung fibrosis panel

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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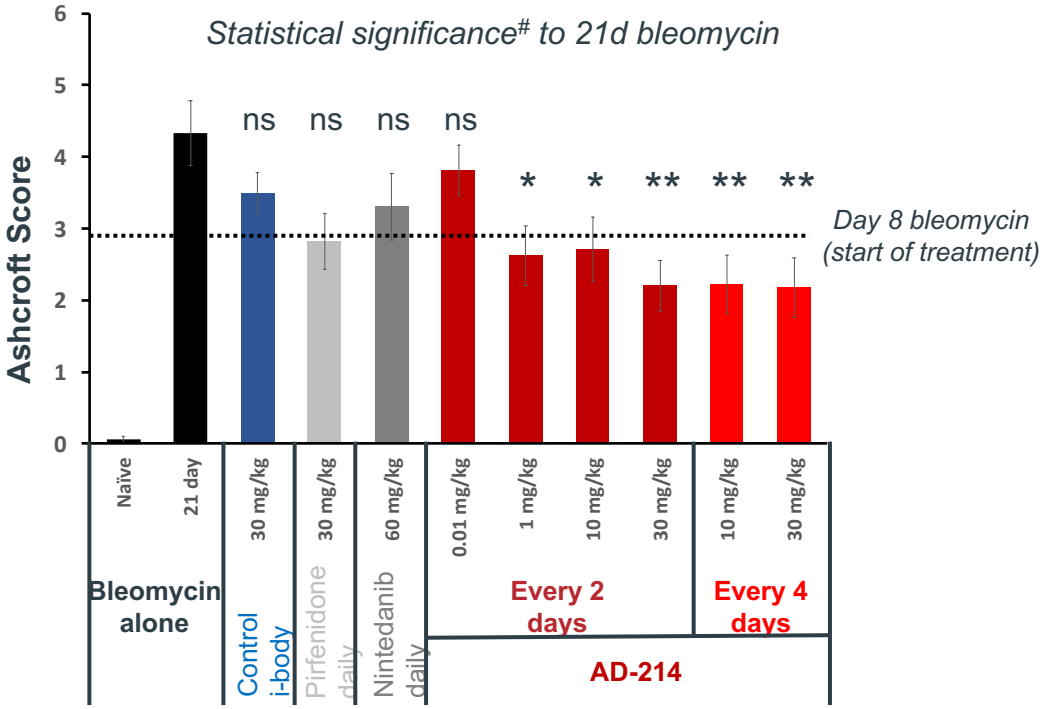
AD-214 attenuates fibrosis of the mouse lung

- Bleomycin induced lung fibrosis
  - gold standard *in vivo* animal model of pulmonary fibrosis
- AD-214 significantly improved lung fibrosis pathology (Ashcroft score) when compared to the 21-day bleomycin vehicle-treated controls
  - 1, 10 and 30 mg/kg every second day
  - 10 and 30 mg/kg every fourth day

AD-214 efficacy demonstrated in gold standard IPF disease model

Supportive of potential human therapeutic window beginning as low as 1mg/kg



Statistical significance assessed using ANOVA and post-hoc Dunnett's test; ns (not significant) = p >0.05, * = p<0.05, ** = p < 0.01 relative to 21-day bleomycin vehicle; negative control is an i-body that does not bind specifically to CXCR4; error bars are standard error of the mean

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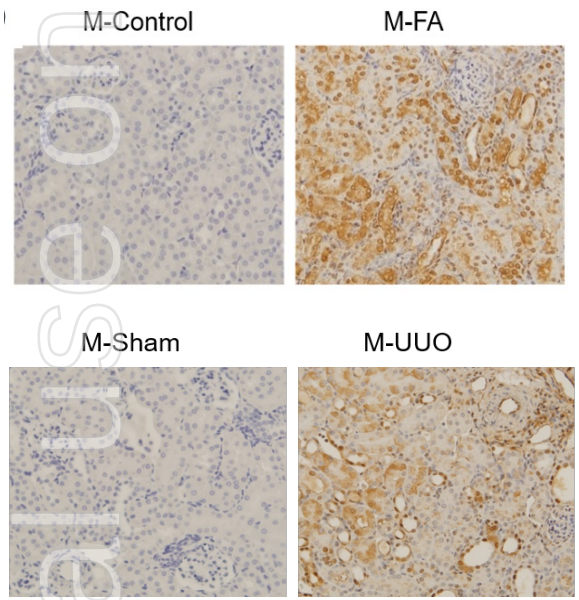
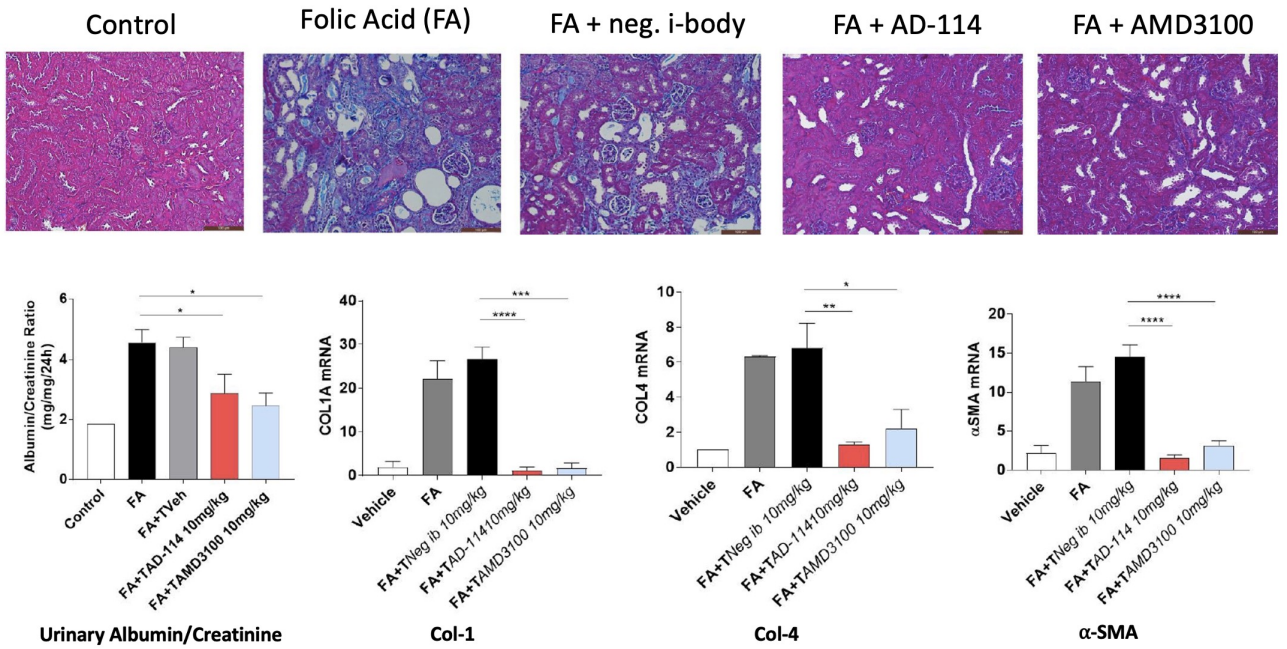
AD-114 is antifibrotic in a mouse model of kidney fibrosis

- CXCR4 is upregulated in several models of kidney fibrosis
- AD-114 protects from liver damage in therapeutic mode of folic acid kidney injury





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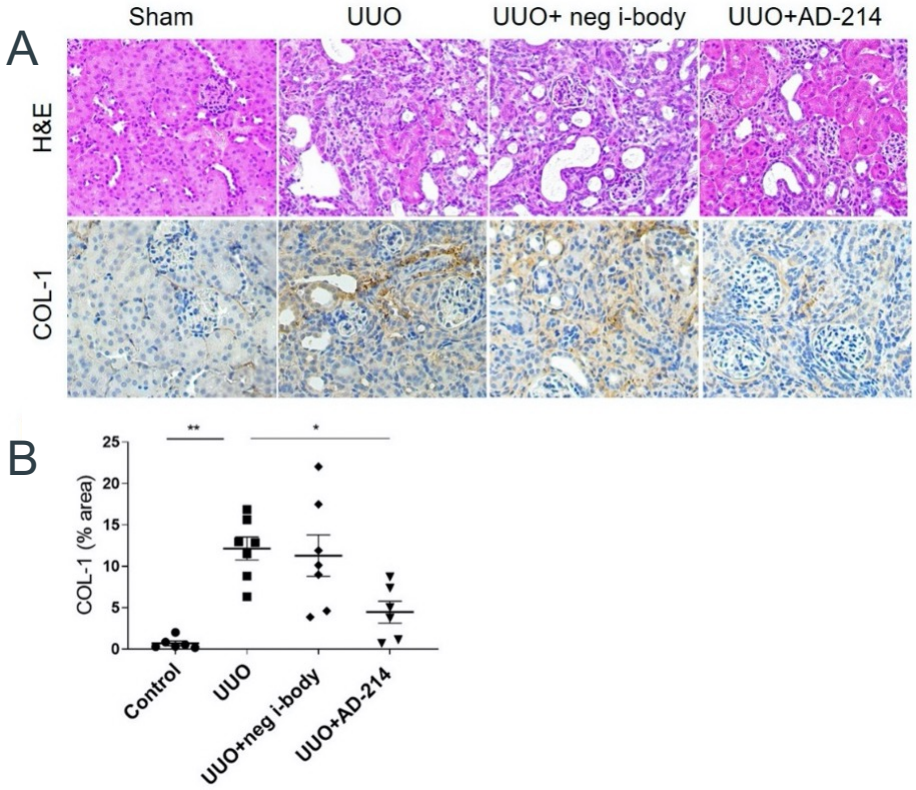
AD-214 is antifibrotic in a mouse model of kidney fibrosis

- 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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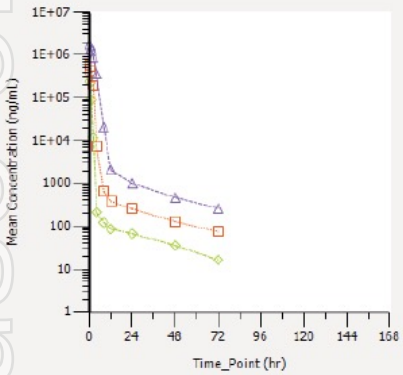
Non-human primate GLP toxicology: Phase I dose justification

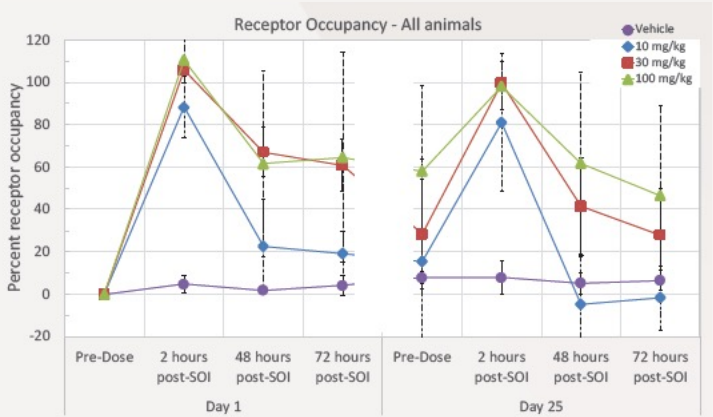
Pharmacokinetics

- 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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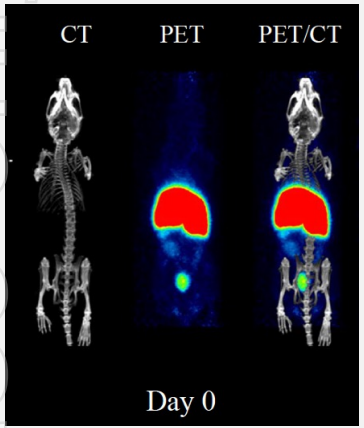
AD-214 distribution by PET imaging

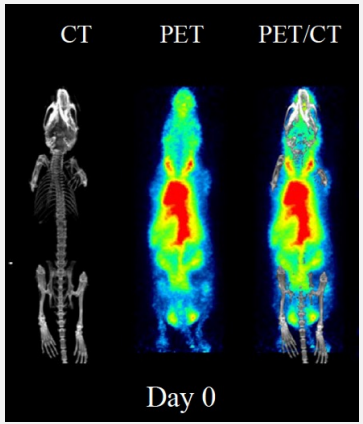
- Pre-clinical PET imaging shows that while AD-214 distributes to tissues containing CXCR4 expressing cells, more than half the administered dose rapidly distributes to, or is cleared via, the liver. This is not seen with other i-bodies

PET/CT images in healthy mice

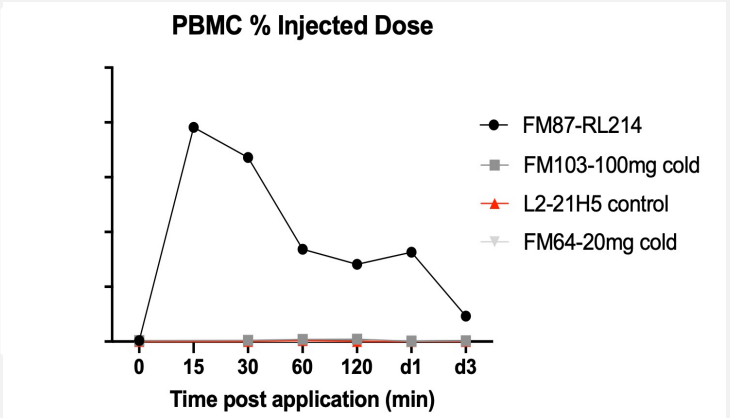
^{89}Zr-AD-214



^{89}Zr-ADLP-16-Fc



Radiation count from i-bodies bound to NHP PBMC



Radiolabelled AD-214 successfully developed

- Conjugated with DFOSq (Telix Pharma) and labelled with ^{89}Zr
- Imaging in healthy mice, NHPs

AD-214 substantially and rapidly distributes to liver (left)

Other i-bodies studied distribute more generally (right)

^{89}Zr-AD-214 still able to be detected on white blood cells and in tissues with resident immune cells eg spleen, bone marrow

- High doses of unlabelled AD-214 block the signal in these tissues, confirming specific binding via CXCR4

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PET imaging studies with radiolabelled AD-214 supports early transition to inhaled route of administration

Rapid liver distribution and clearance reduces bioavailability

- Consistent with pharmacokinetic profile and a first pass clearance mechanism
- More than half administered dose not available to target site of action

CXCR4 binding capability retained, supportive of potential efficacy

- Consistent with observed biomarker, receptor occupancy and bleomycin mouse efficacy data

Liver distribution does not appear to affect safety profile

- No localization in hepatocytes (responsible for metabolic activity in liver)
- Consistent with lack of observed changes in liver function or toxicity in toxicology and clinical studies

Direct lung delivery of AD-214 could achieve a therapeutic dose at lower levels than intravenous delivery

Radiolabelled AD-214 will continue to be a useful development tool

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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*

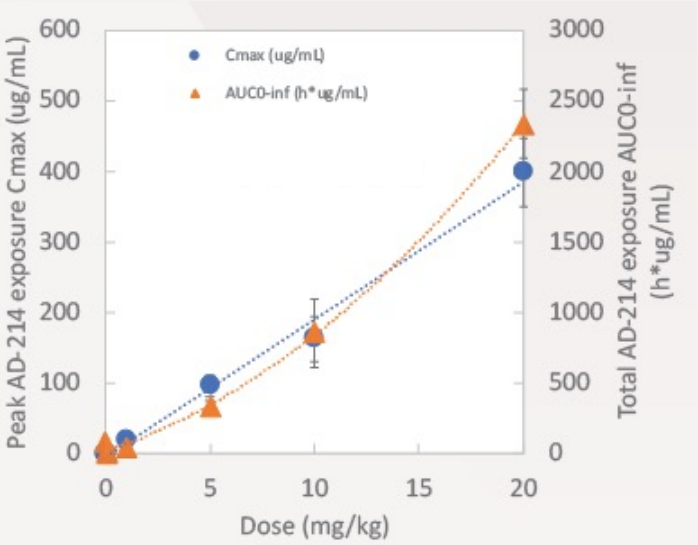
AD-214 intravenous pharmacokinetics are dose proportionate

- 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)*

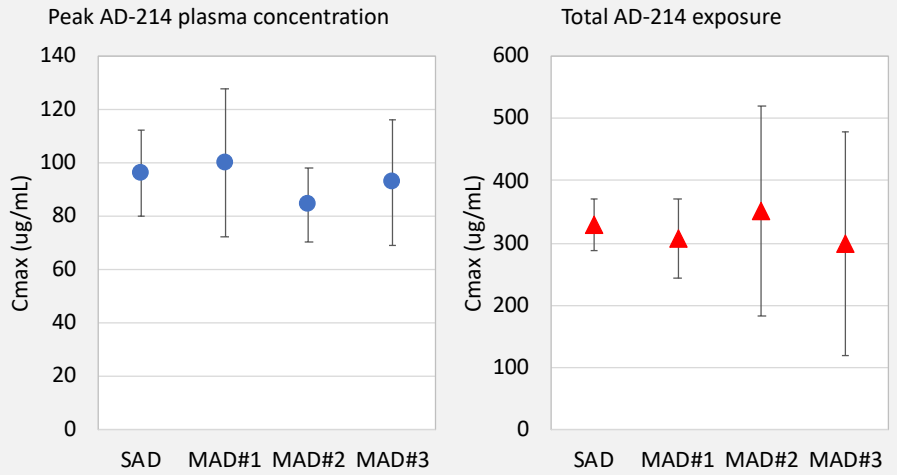
AD-214 pharmacokinetics

Maximum exposure, Cmax, and total exposure, AUC0-inf, increase in a dose proportionate manner and are consistent across multiple doses of AD-214 at 5 mg/kg, supporting absence of drug induced tolerance or clearance

Maximum and total plasma exposure - SAD



Maximum and total plasma exposure – 5 mg/kg



Pharmacokinetic profile

- Rapid distribution from plasma (consistent with rapid and high CXCR4 receptor occupancy and PET imaging studies)
- Elimination half-life 44±15 h at 20 mg/kg

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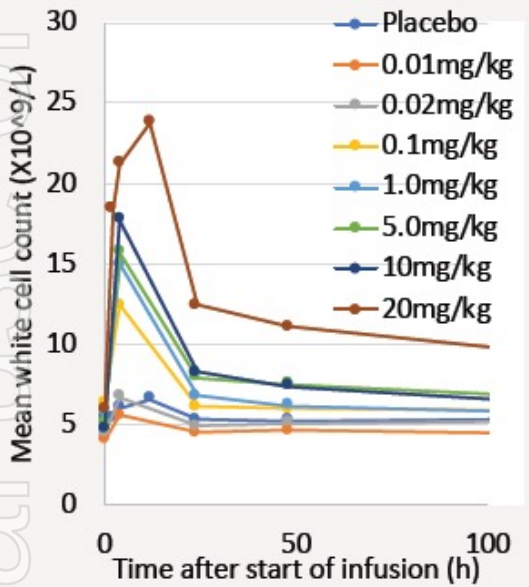
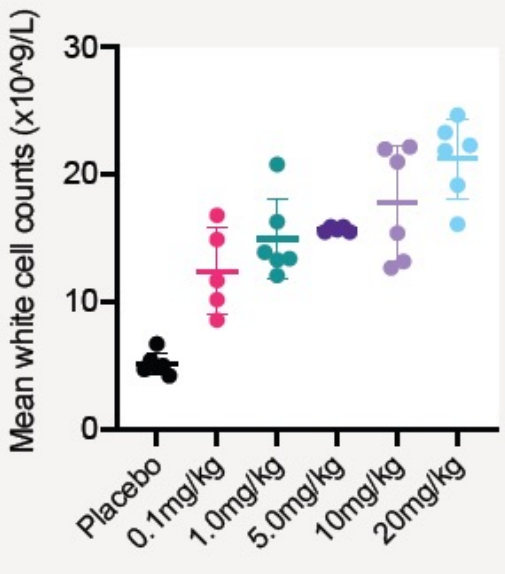
CXCR4 engagement

Transient, dose dependent, increase in WCC and CD34+ counts at 4-12 hours consistent with CXCR4 blockade in Phase 1 SAD

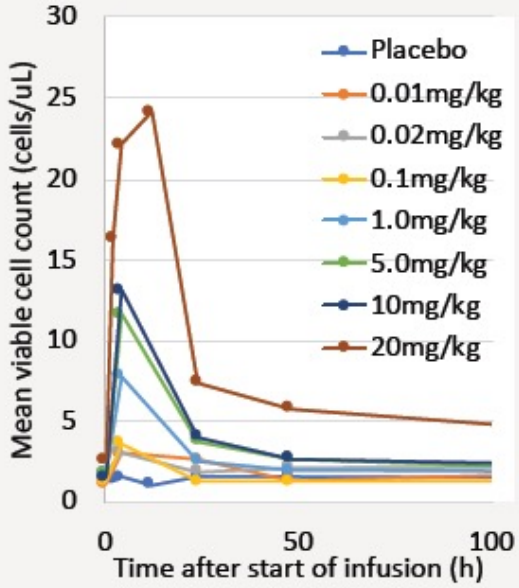
WCC counts



WCC counts at 4h



CD34+ cell counts



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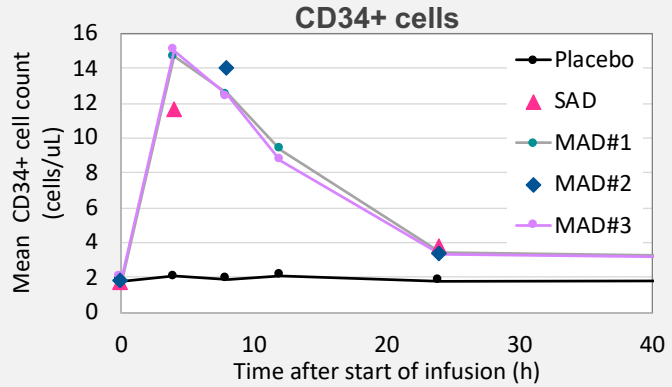
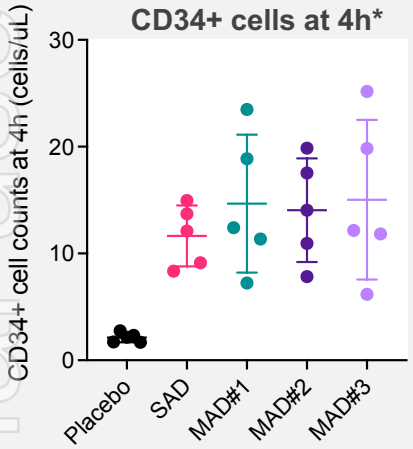
Biomarkers of CXCR4 receptor engagement (5mg/kg)

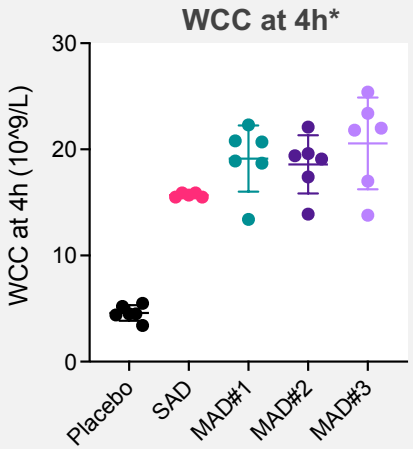
Transient increases in blood biomarkers demonstrate consistent engagement of the target receptor, CXCR4 across multiple AD-214 doses

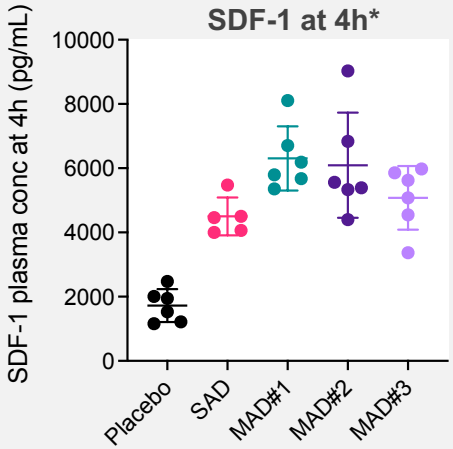
Biomarker data confirm single dose findings, consistent across multiple doses: no drug induced tolerance or accumulation

- 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)









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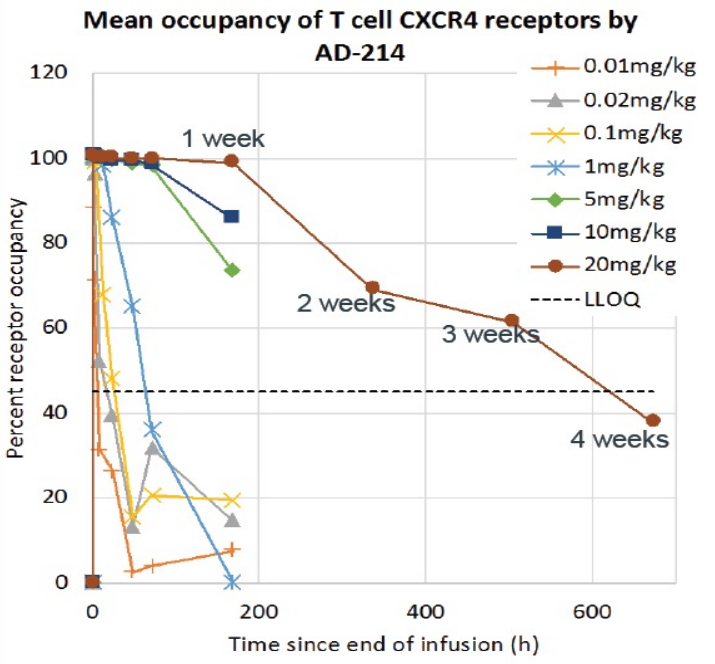
Sustained high levels of CXCR4 receptor occupancy on T-cells



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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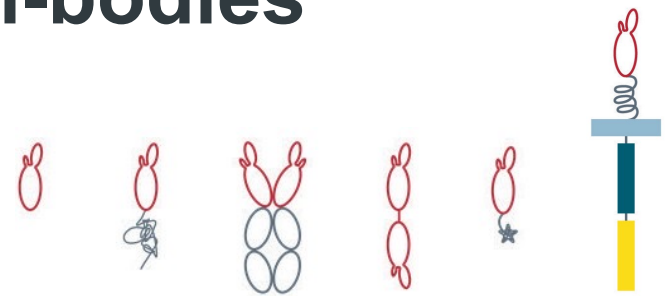
Phase II planned with inhaled formulation

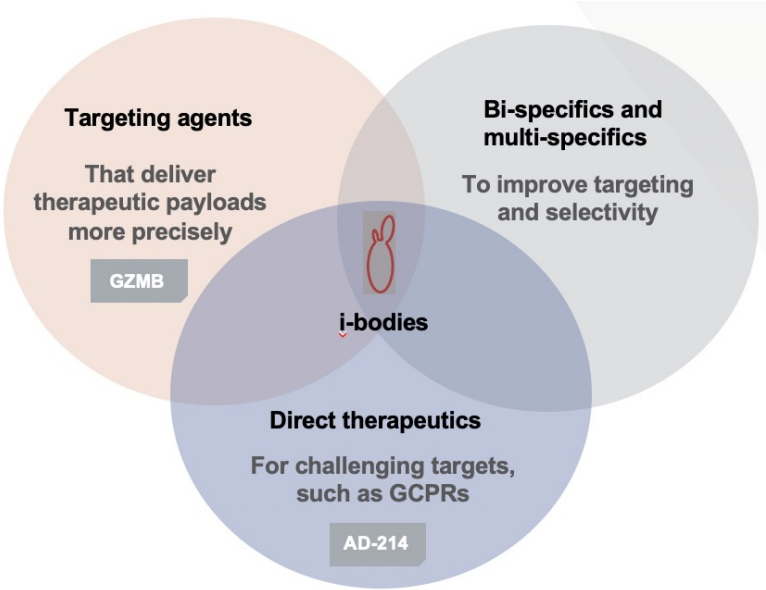
Delivery of AD-214 by inhalation has potential to improve bioavailability, be more convenient for patients, be more cost effective, and improve partnering flexibility

Improved bioavailability	• AD-214 delivered direct to fibrotic areas • First pass liver clearance avoided • Dosing schedule flexibility to optimise receptor coverage
Greater patient convenience	• Self administration (no scheduled clinic visits; freedom of movement) • Less invasive
Enhanced cost effectiveness	• Lower drug dose means lower cost of goods • Lower healthcare costs for administration
Diversified partnering options	• Potential to partner AD-214 by indication using different routes of administration - broadens potential long term options

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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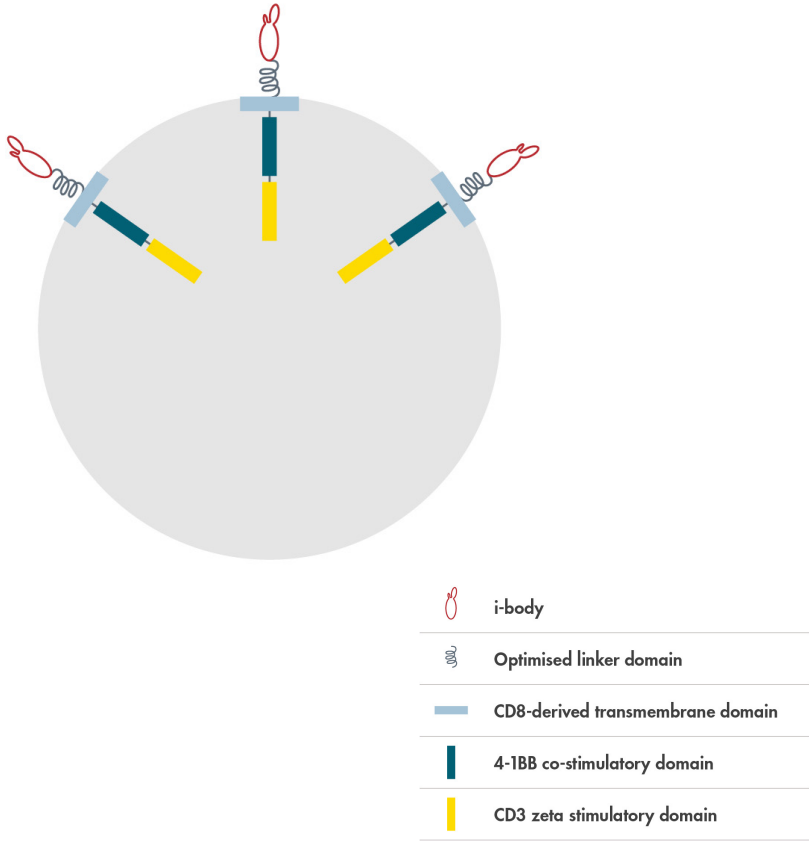
i-bodies in CAR-T format

- Approximately half the size of the traditional CAR binding domain, enabling greater flexibility in CAR design – ideally suited to bispecific CARs
- Specifically designed to target antigens considered difficult or intractable for traditional antibodies and CAR constructs
- In vitro proof of principle established for i-bodies in a CAR-T platform (in collaboration with Carina Biotech)



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