AdAlta
next generation protein therapeutics

ASX Announcement

AdAlta CEO to present at the inaugural IPF Summit in Boston

MELBOURNE Australia, 21 August, 2017: AdAlta Limited (ASX:1AD), the biotechnology Company advancing its lead i-body candidate towards clinical development, announces CEO Sam Cobb has been invited to speak at the inaugural IPF Summit in Boston, Massachusetts between 21-23 August, 2017.

The IPF Summit will bring together academic, international biotech and pharma speakers from the likes of Genentech, Bristol-Myers Squibb, Celgene and Medimmune to discuss the treatment of Idiopathic Pulmonary Fibrosis (IPF). AdAlta will be the only Australian company in the presentation line-up.

AdAlta CEO Sam Cobb stated, "Being invited to speak alongside world experts at the IPF Summit immensely validates the significance of our lead program. Idiopathic pulmonary fibrosis is a disease with high unmet clinical need and we believe AD-114 has the potential to provide a much needed new treatment option."

Details of the presentation

Session date / time:	Wednesday 23 August 2017 from 2:00 pm
Session title and details:	Novel Therapeutic Approaches to the Treatment of IPF

In her presentation, entitled i-Bodies: a novel therapeutic approach for the treatment of IPF, CEO Sam Cobb will cover:

- The critical role of chemokine receptor, CXCR4, in the development of IPF;
- An overview of AdAlta's unique i-body, AD-114, which antagonizes CXCR4 and displays both anti-inflammatory and anti-fibrotic effects in a number of models, including the bleomycin mouse model of IPF; and
- The specificity of AD-114 for diseased human IPF tissue; demonstrating minimal binding to normal lung tissue and no evidence of off-target effects.

AdAlta's Chief Scientific Officer Associate Professor Mick Foley will also present data on AD-114, in a poster session.

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Details of the poster presentation

Session date / time:	Tuesday 22 August 2017 from 5:30 pm
Session title and details:	i-body AD-114 targeting CXCR4 has anti-fibrotic activity

A copy of the presentation and poster are attached with this cover note and will also be made available on the corporate website at www.adalta.com.au.

Notes to Editors: About AdAlta

AdAlta Limited is an Australian-based drug development company headquartered in Melbourne. The Company is focused on using its proprietary technology platform to generate i-bodies, a new class of protein therapeutics, with applications as therapeutic drugs to treat disease.

I-bodies are a promising, novel class of drugs that offer a new and more effective approach to treating a wide range of human diseases. They are identified and developed using our proprietary technology platform.

We have pioneered a technology that mimics the shape and stability of a crucial antigen-binding domain, that was discovered initially in sharks and then developed as a human protein. The result is a range of unique compounds, now known as i-bodies, for use in treating serious diseases.

AdAlta is developing its lead i-body candidate, AD-114, 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.

IPF is a fibrotic lung condition that causes persistent and progressive scarring of the tiny air sacs (alveoli) in the lungs, with a median survival rate of only three to five years from diagnosis.

Granted orphan status by the FDA for the treatment of IPF, AdAlta's lead program, AD-114, has demonstrated both anti-inflammatory and anti-fibrotic activity, representing a vital, potential new therapy for IPF.

The Company also plans to continue further drug discovery and development directed towards other drug targets and diseases with its i-body technology platform.

Further information can be found at: www.adalta.com.au.

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AdAlta

next generation protein therapeutics

i-bodies: a novel therapeutic approach for the treatment of IPF

August 2017

Sam Cobb, CEO and Managing Director

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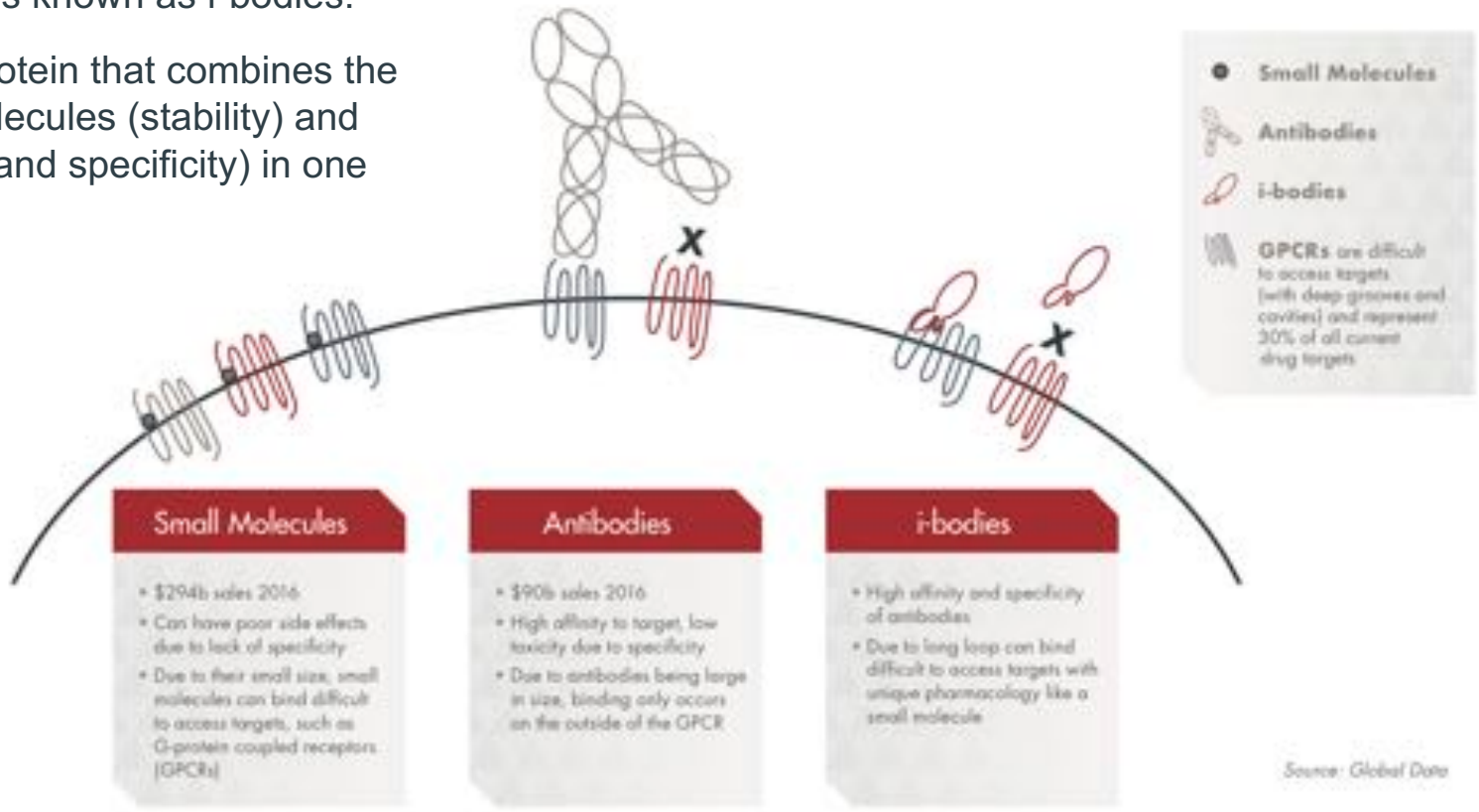
This presentation is not an offer or invitation for subscription or purchase of or a recommendation of securities. It does not take into account the investment objectives, financial situation and particular needs of the investor. Before making any investment in AdAlta, the investor or prospective investor should consider whether such an investment is appropriate to their particular investment needs, objectives and financial circumstances and consult an investment advisor if necessary.

This presentation may contain forward-looking statements regarding the potential of the Company's projects and interests and the development and therapeutic potential of the company's research and development. Any statement describing a goal, expectation, intention or belief of the company is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercialising drugs that are safe and effective for use as human therapeutics and the financing of such activities. There is no guarantee that the Company's research and development projects and interests (where applicable) will receive regulatory approvals or prove to be commercially successful in the future. Actual results of further research could differ from those projected or detailed in this presentation. As a result, you are cautioned not to rely on forward-looking statements. Consideration should be given to these and other risks concerning research and development programs referred to in this presentation.

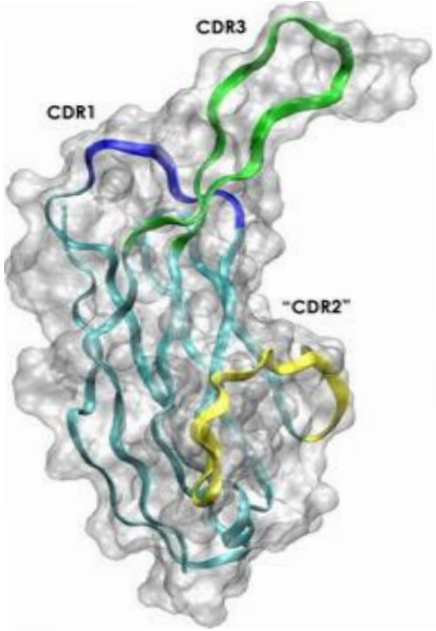
i-body technology

AdAlta is developing a new technology platform that produces unique proteins known as i-bodies.

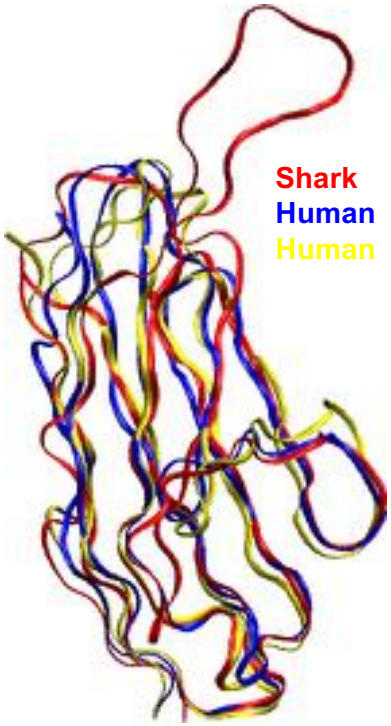
An i-body is a human protein that combines the advantages of small molecules (stability) and antibodies (high affinity and specificity) in one powerful treatment.



i-bodies: human single domains



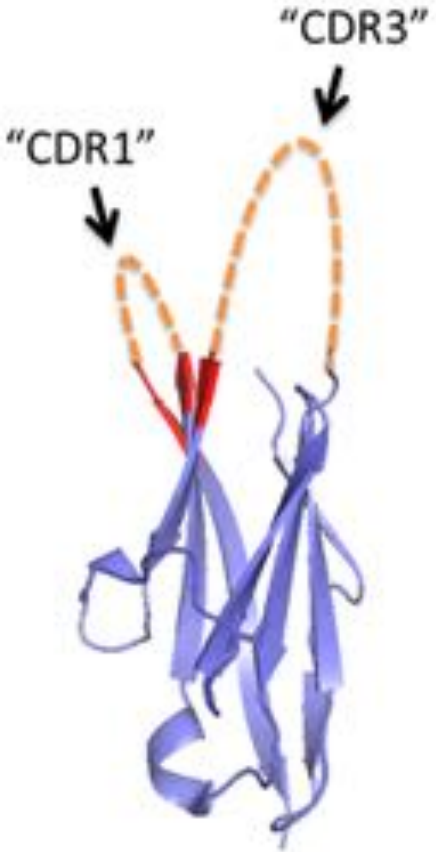
VNAR



Ribbon Overlay



NCAM Domain 1

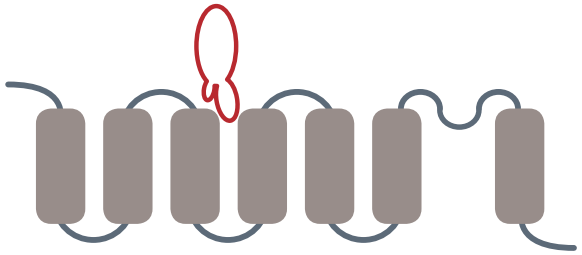


i-body library

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i-body technology advantages

Challenging targets



Because of the long binding loop of the i-body, that is lacking in traditional antibodies, i-bodies recognise and bind to a diverse range of therapeutically-relevant targets including those that are difficult/intractable to access by current antibody therapies such as G-protein coupled receptors (GPCRs) and ion channels.

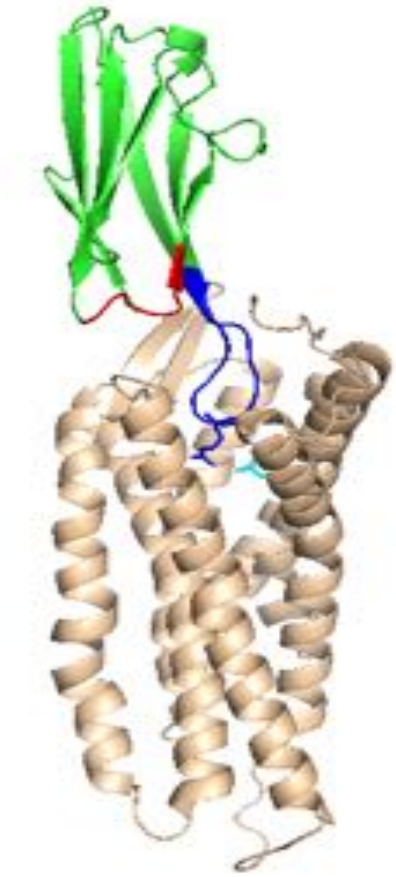
CXCR4 is involved in fibrosis and other disease states

CXCR4 is important in maintaining stem cells in bone marrow with Mozobil (AMD3100) approved for single use.

HIV-1 uses CXCR4 as a co-receptor for viral entry into host cells and CXCR4 has been associated with more than 23 types of cancers

CXCR4 has more recently been recognised as a critical player in development of a number of areas of fibrosis including:

- Lung
- Kidney
- Heart
- Eye
- Skin



Evidence supporting CXCR4 as a fibrosis target

Significant literature to support hypothesis of the involvement of CXCR4 in fibrosis

The SDF-1/CXCR4 ligand/receptor pair is an important contributor to several types of ocular neovascularization

Raquel Lima e Silva,* Jikui Shen,* Sean F. Hackett,* Shu Kachi,* Hideo Akiyama,* Katsuji Kiuchi,* Katsutoshi Yokoi,* Maria C. Hatara,* Thomas Lauer,* Sadia Aslam,* Yuan Yuan Gong,* Wei-Hong Xiao,* Naw Htee Khu,* Catherine Thut,† and Peter A. Campochiaro*,1

A potential role of SDF-1/CXCR4 chemotactic pathway in wound healing and hypertrophic scar formation

Leah Campeau[1], Jie Ding[1], Edward E Tredget[1,2]

CXCR4 dysfunction in non-alcoholic steatohepatitis in mice and patients

Hédia Boujedidi*†1, Olivier Robert*†1, Alexandre Bignon*††, Anne-Marie Cassard-Doulcier*†, Marie-Laure Renoud†, Hélène Gary-Gouy†, Patrice Hemon†, Hugo Tharinger†, Sophie Prévot*§, Françoise Bachelerie*††, Sylvie Naveau*†‖, Dominique Emilie*††¶2, Karl Balabanian*†† and Gabriel Perlemuter*†‖

CXCR4 Antagonism Attenuates the Development of Diabetic Cardiac Fibrosis

Po-Yin Chu[1], Ken Walder[2], Duncan Horlock[1], David Williams[1], Erin Nelson[1], Melissa Byrne[1], Karin Jandeleit-Dahm[3], Paul Zimmet[4], David M. Kaye[1]*

Chemokine receptor Cxcr4 contributes to kidney fibrosis via multiple effectors

Amy Yuan,[3] Yashang Lee,[3] Uimook Choi,[1] Gilbert Moeckel,[2] and Anil Karihaloo[3]

[1]Laboratory of Host Defense, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland; [2]Department of Pathology, Yale School of Medicine, New Haven, Connecticut; and [3]Department of Medicine, Section of Nephrology, Yale School of Medicine, New Haven, Connecticut

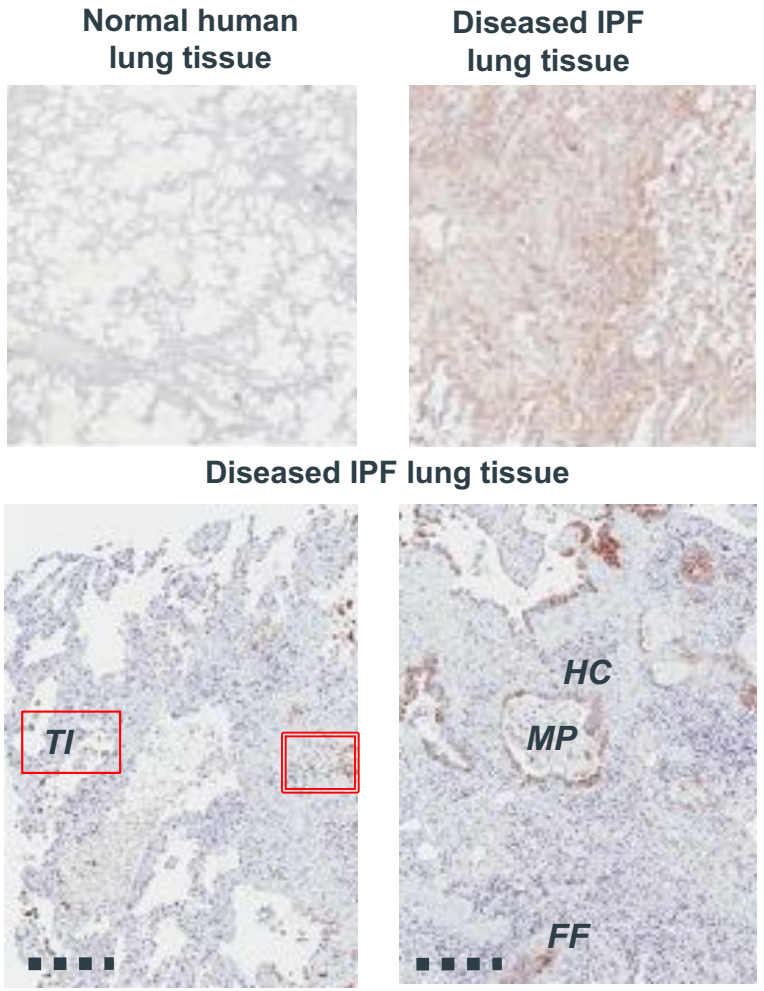
Submitted 12 March 2014; accepted in final form 19 December 2014

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CXCR4 increased in disease

- IPF diseased lung tissue in upper right panel compared with normal lung tissue has increased CXCR4 expression
- CXCR4 present in hyperplastic epithelium (EP) of honeycomb cysts (HC), within a mucus plug (MP), and immediately adjacent to fibroblastic foci (FF) of IPF diseased lung tissue (bottom right). CXCR4 can also be seen lining thickened interstitium (TI) and within fibrotic interstitial tissue (bottom left).

CXCR4 is shown to be increased in diseased IPF tissue and not present in normal lung tissue



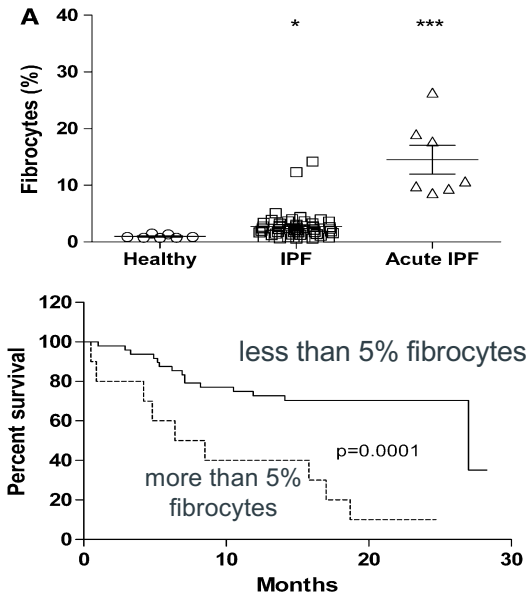
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CXCR4 as a biomarker in IPF

- Fibrocyte cells (CXCR4 positive cells) were elevated in stable IPF patients, and further increased during acute exacerbations
- Fibrocytes (CXCR4 positive cells) not only correlated with lung function but were an ***independent predictor of early IPF patient mortality***
  - 7.5 months with more than 5% fibrocytes
  - 27 months with less than 5% fibrocytes

CXCR4 may have a role in predicting disease progression

Fibrocyte numbers predict mortality

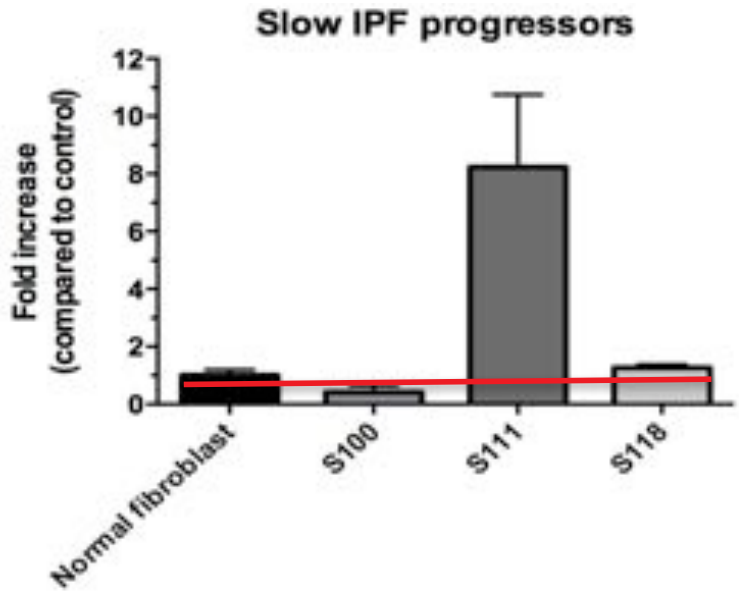


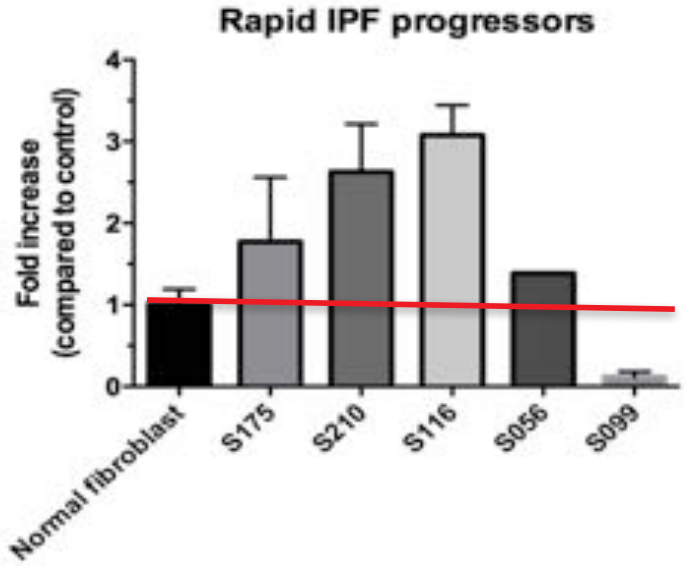
REF: Moeller, et al. Am J Respir Crit Care Med Vol 179. pp 588–594, 2009

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CXCR4 increased in fast progressing IPF patients

Patients that rapidly progress express more CXCR4 compared to slow IPF progressors



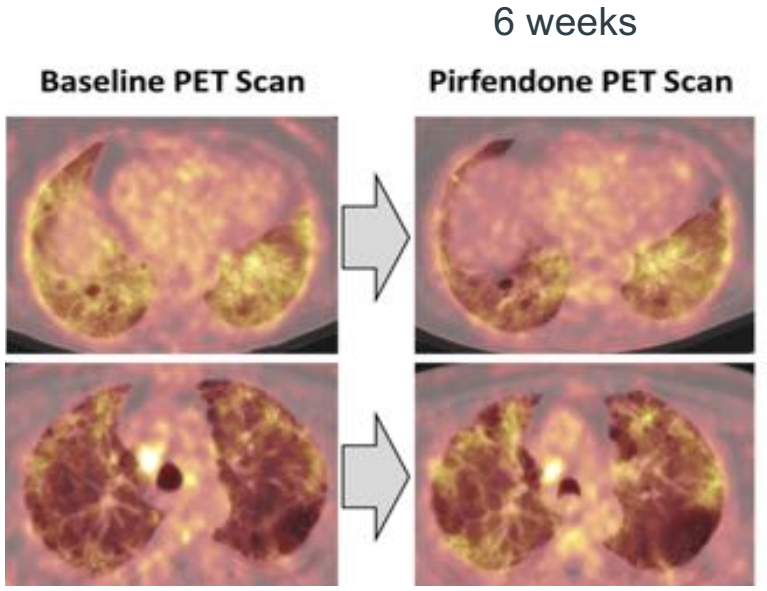


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CXCR4 as a biomarker in IPF

- Strong CXCR4 expression from PET imaging agent, correlated with areas of honeycombing (associated with IPF) and with clinical parameters known to be predictive of outcome in IPF
  - Patient A (top panels) had lower expression of CXCR4 at 6 weeks and responded to Pirfenidone treatment with lung function improvement
  - Patient B (bottom panels) had a high expression of CXCR4 at 6 weeks and did not respond to Pirfenidone treatment, with no lung function improvement



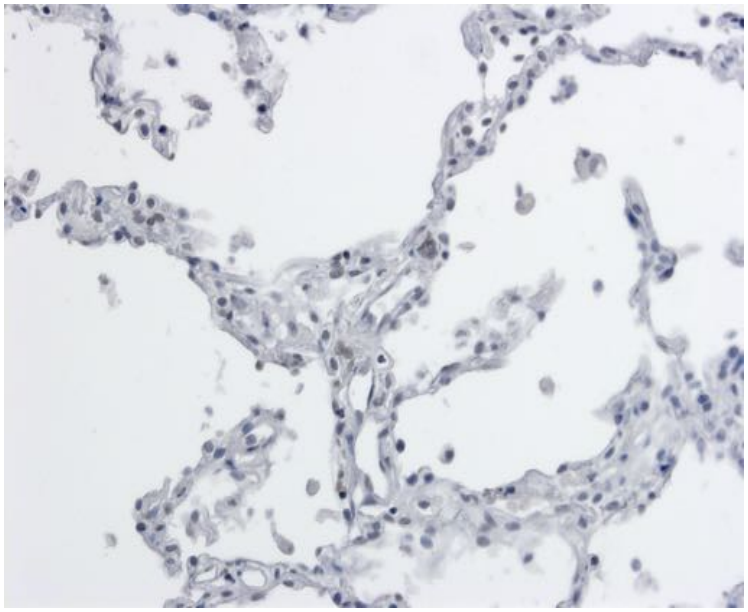
REF: Prasse A, et al. American Journal of Respiratory and Critical Care Medicine 2017;195:A7678

CXCR4 imaging may have a role in monitoring disease progression and may predict response to treatment with Pirfenidone

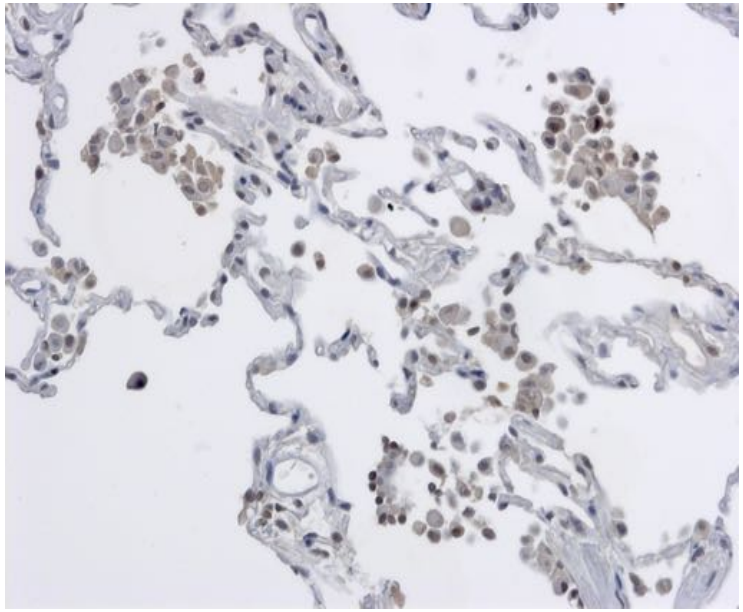
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AD-114 binds to lung tissue from patients with fibrosis

AD-114 was used for Immunohistochemical (IHC) staining of normal and diseased lung tissues to verify expression of CXCR4 *in situ*



AD-114 does not bind lung tissue from normal lungs



AD-114 binds to lung tissue from lungs with fibrosis

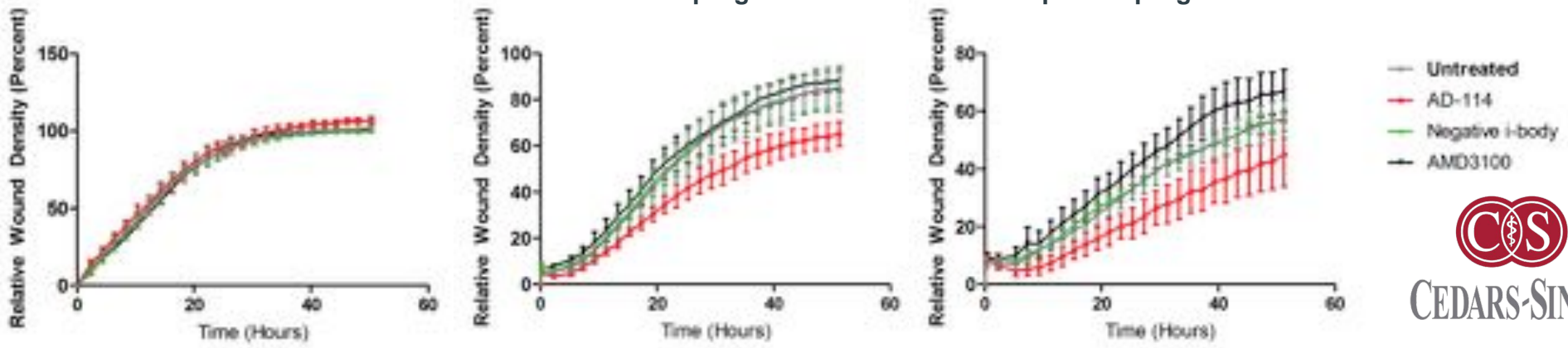
AD-114 specifically reduced migration/invasion with IPF lung fibroblasts

AD-114 specifically inhibited migration of slow and rapid IPF fibroblast migration but did not have any effect on normal fibroblasts.

AD-114 has greater *in vitro* efficacy in this assay compared to the only approved therapies Nintedanib and Pirfenidone for IPF treatment.

MIGRATION	No effect on normal fibroblasts	Inhibits slow IPF progressors	Inhibits fast IPF progressors
i-body AD-114	✔	✔	✔
Nintedanib (Boehringer)	✗	✔	✔
Pirfenidone (Roche)	✔	✗	✗
Other CXCR4 drug (Sanofi)	✔	✗	✗

Normal fibroblasts | **Slow/stable IPF progessor fibroblasts** | **Rapid IPF progressor fibroblasts**

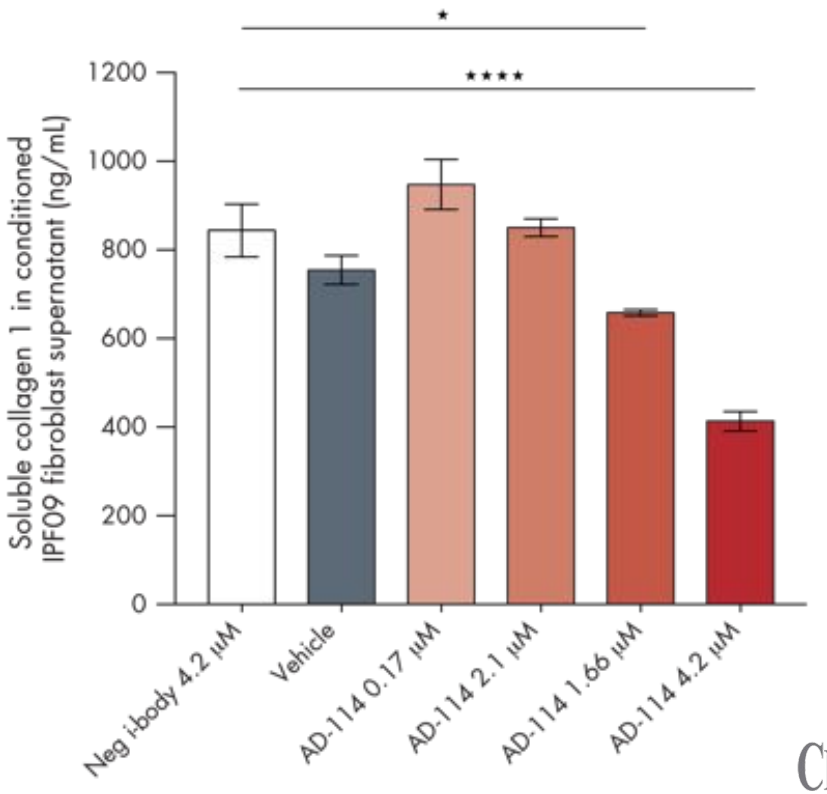


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AD-114 reduced collagen secretion in IPF fibroblasts

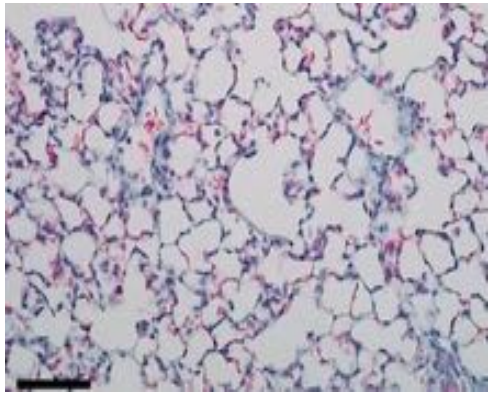
- AD-114 reduced soluble collagen 1 expression in IPF patient fibroblasts
- The negative i-body had no effect on soluble collagen 1 production



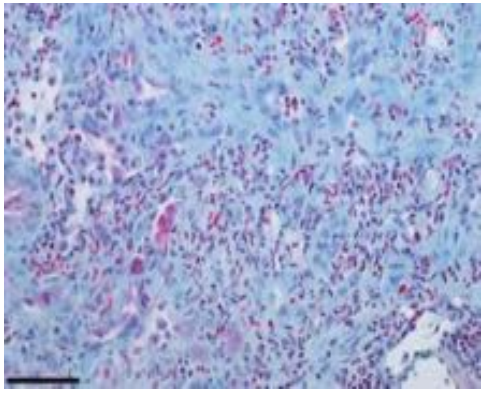
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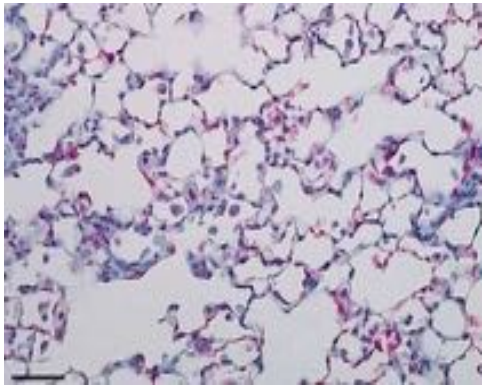
AD-114 prevents fibrosis in Bleomycin mouse model



Normal
lung tissue



IPF lung tissue
(lung disease mouse model)

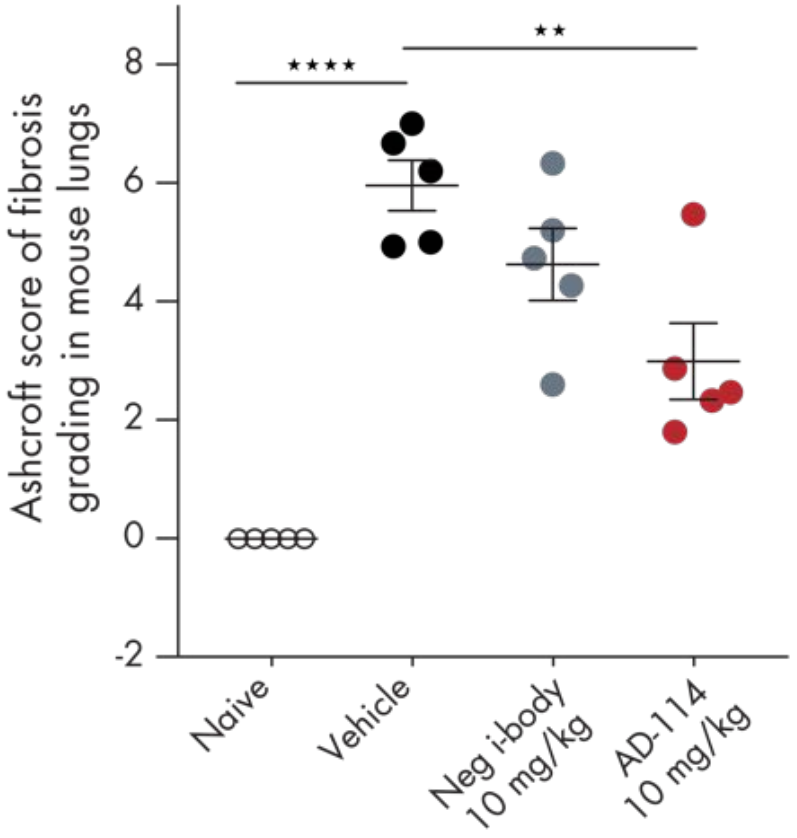


IPF lung tissue + AD-114
dosed for 21 days
(lung disease mouse model)

AD-114 reduces collagen content and inflammatory cell infiltration in the Bleomycin mouse model and demonstrates a similar architecture to that of the normal lung

AD-114 prevents fibrosis in Bleomycin mouse model

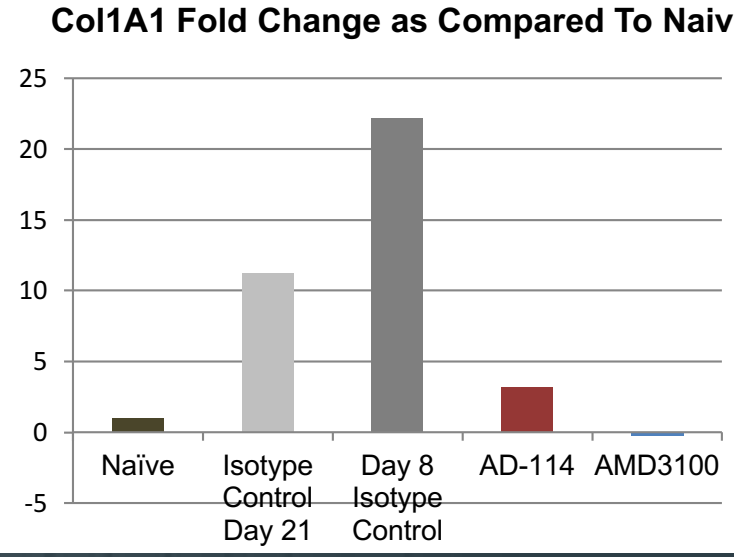
- AD-114 significantly reduced the Ashcroft score compared to the Bleomycin treated mice
- The negative i-body at the same dose as AD-114 had no signficiant effect on preventing fibrosis

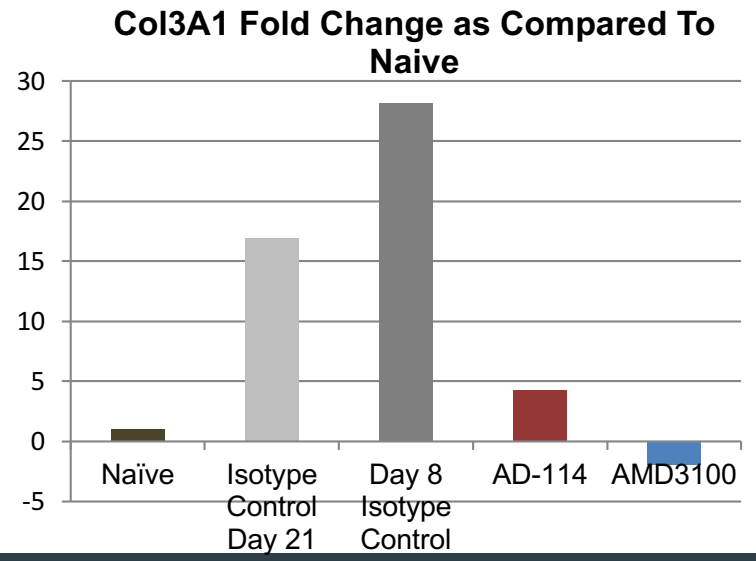


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AD-114 reduces fibrotic gene expression in Bleomycin mouse model

- RNA extracted and analyzed for collagen gene expression
- Both *COL1A1* and *COL3A1* reduced in mice treated with i-body AD-114 in the Bloemycin mouse model
- The negative control i-body had no effect on either *COL1A1* or *COL3A1*

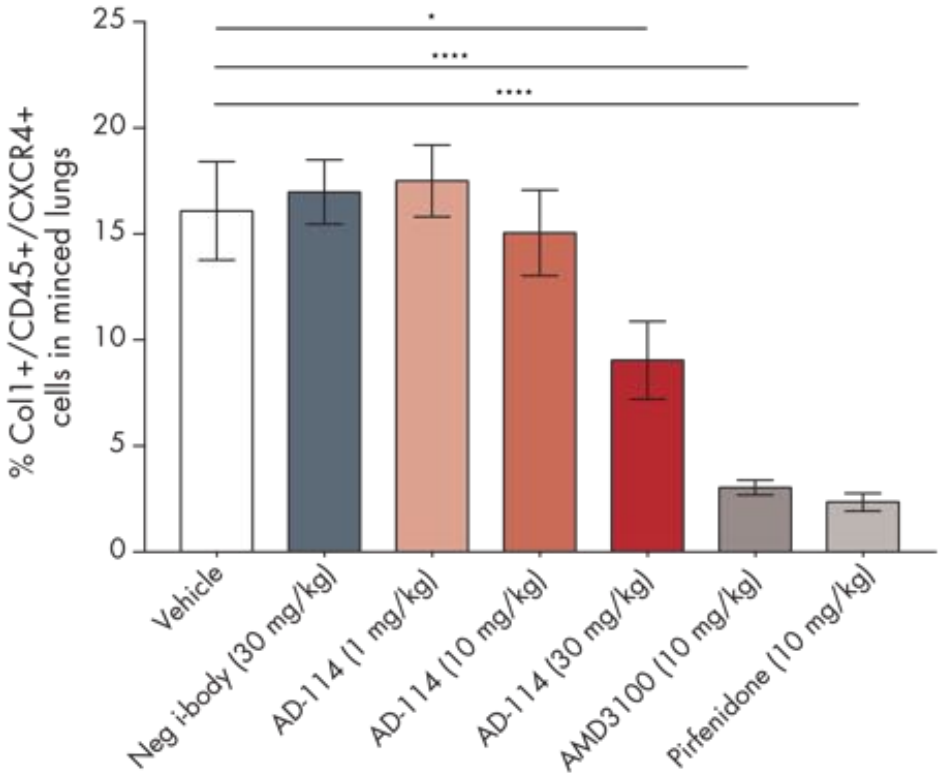




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AD-114 reduces pulmonary infiltration of fibrocytes in the Bleomycin mouse model

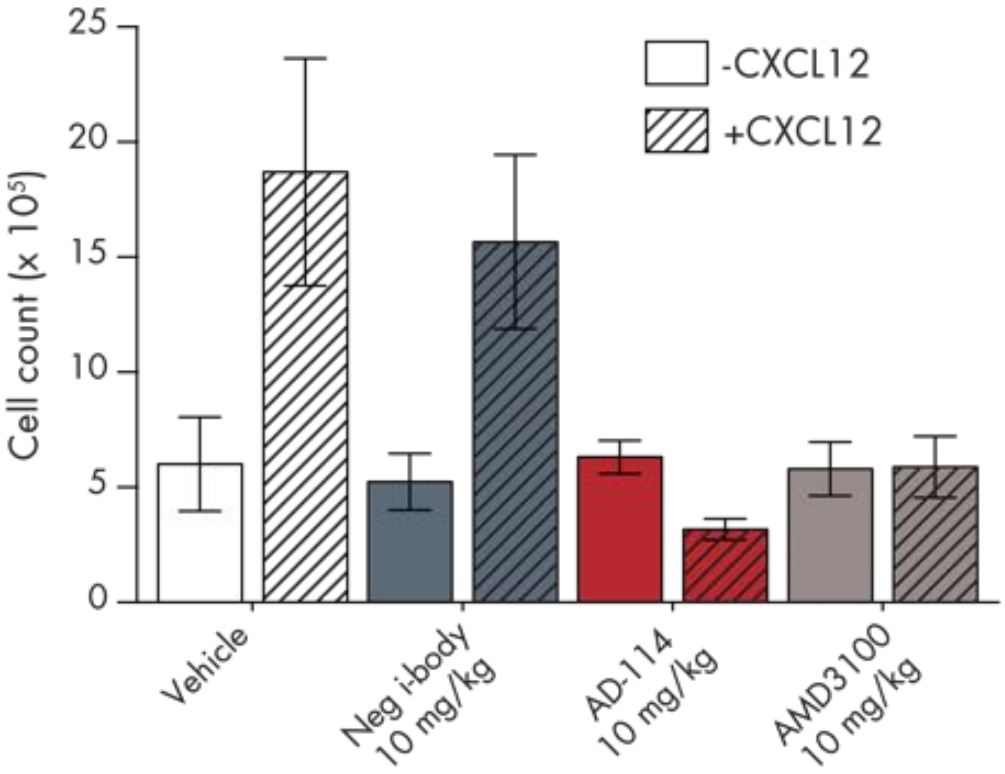
- Pulmonary infiltration of Cola1+, CD45+ and CXCR4+ cells were also evaluated in the bleomycin mouse model
- Mice treated with AD-114 had reduced levels of CXCR4+ cells in their lungs when compared to the mice treated with the negative control i-body



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AD-114 blocks infiltration of leukocytes

- AD-114 has also been evaluated for its anti-inflammatory activity
- In a mouse air-pouch model, the inflammatory stimulant CXCL12 is added to an air-pouch created on the back of a mouse, which results in a dramatic increase in the amount of infiltrating inflammatory cells
- When a single dose of AD-114 is injected into the mouse (IP), the migration of the inflammatory cells to the air-pouch is blocked
- The negative i-body had no effect

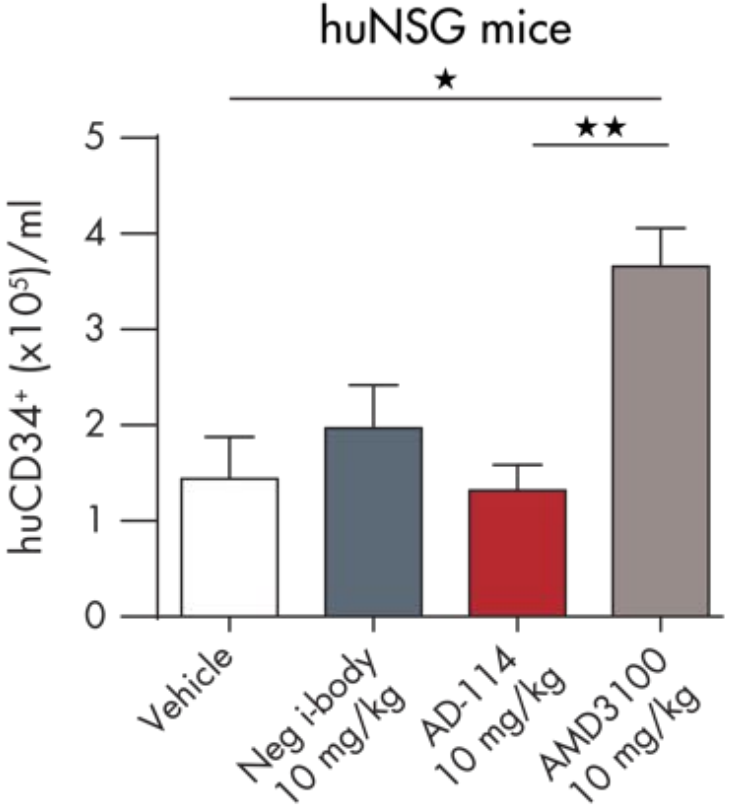


REF: Griffiths et al JBC June 2016

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AD-114 does not mobilize stem cells *in vivo*

- AD-114 does not mobilize stem cells in humanised mouse model unlike the small molecule AMD3100 (Mozobil)
- AD-114 does not mobilise stem cells in non-human primates with single dose IV and SC, nor via increasing doses
- This data demonstrates that the long loop of the i-body has a unique activity and AD-114 is differentiated from competing CXCR4 antagonist products



REF: Griffiths et al JBC June 2016

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AD-114 efficacy and safety

- **Efficacy**
  - Lung: IPF
    - Animal models
    - Human IPF tissue
    - Biomarker assessments (Alfred Health & others)
  - Broad fibrotic application with demonstration in other animal models and human tissues
    - Eye: wet-AMD
    - Liver: NASH
    - Kidney: CKD
    - Skin: HT Scarring



- **Safety**
  - NHP studies demonstrate AD-114 well tolerated and no adverse effect:
    - PK: IV and SC
    - Dose range finder
    - Multi dosing studies
  - PK-PD assays developed demonstrating target engagement
  - Cytokine analysis (20 human blood donors)

AD-114 development: key milestones



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AdAlta summary

- **Powerful proprietary technology platform to develop a pipeline of i-bodies for the treatment of a wide range of human diseases**
  - Extreme stability of i-body similar to single domain shark antibody
  - Long loop of i-body binds deep in GPCR pocket and has functional activity
- **Advanced lead candidate AD-114 with significant pre-clinical validation**
  - has specificity for diseased human tissue with effects only shown on IPF tissue and no effects displayed on normal lung tissue nor any evidence of off target effects;
  - is more effective than existing IPF approved drugs showing greater *in vitro* efficacy compared to the only approved therapies Nintedanib and Pirfenidone;
  - demonstrates both anti-fibrotic and anti-inflammatory effects in multiple animal models in multiple areas of fibrosis; and
  - is a novel mechanism of action for fibrosis making AD-114 a potential “first in class” therapy.



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next generation protein therapeutics

Sam Cobb, CEO

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I-BODY AD-114 TARGETING CXCR4 HAS ANTI-FIBROTIC ACTIVITY

K. Griffiths[1], D. M. Habiel[2], W. Darby[1], C. Hosking[1], C. M. Hogaboam[2] and M. Foley[1]

[1] *AdAlta Limited, 15/2 Park Drive Bundoora, Australia 3083 and Department of Biochemistry and Genetics, La Trobe Institute for Molecular Science, La Trobe University, Bundoora, Melbourne, Australia, 3086*

[2] *Cedars-Sinai Medical Center, Women's Guild Lung Institute, Los Angeles, CA 90048 USA*

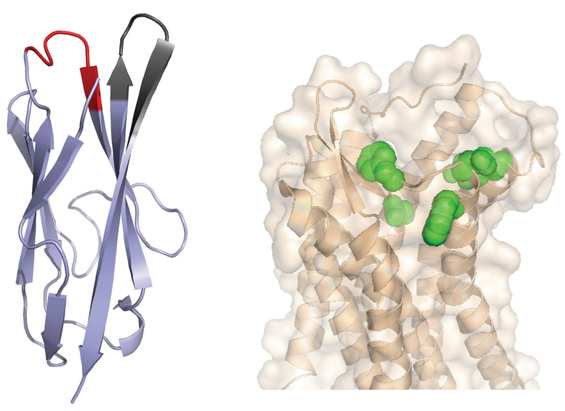
Contact: enquiries@adalta.com.au www.adalta.com.au

Introduction

- AdAlta Ltd has generated a promising new class of protein therapeutics known as i-bodies
- i-bodies have the potential to treat a range of challenging diseases, such as Idiopathic Pulmonary Fibrosis (IPF)
- IPF is characterized by excessive collagen deposition and remodeling of the lung parenchyma
- G-protein coupled receptor protein CXCR4 is a candidate therapeutic target for IPF due to:
  - increased expression in fibrotic lung tissue
  - recruitment of CXCR4$^+$ cells from the bone marrow to fibrotic lung tissue

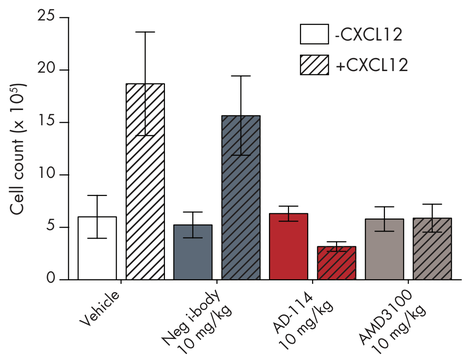
i-body AD-114 binds with high affinity to human CXCR4

AD-114 is a novel, fully humanized single domain 'i-body' that binds to CXCR4 with high affinity



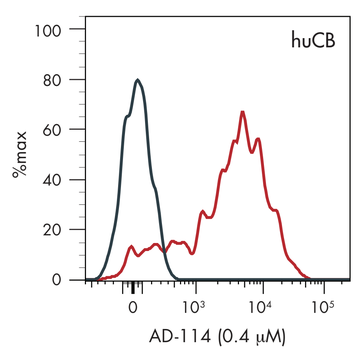
AD-114 blocks CXCL12-mediated cell migration

Murine air-pouch model

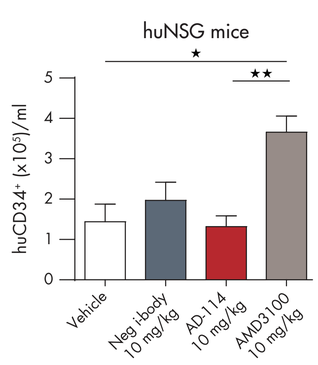


AD-114 binds cord blood cells but does not mobilize human stem and progenitor cells

CD34$^+$ CD38$^+$ Cells



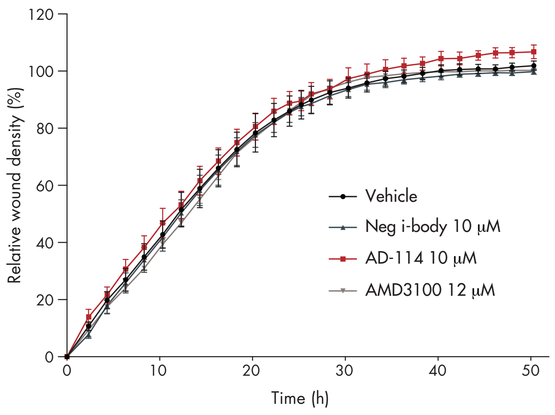
muCD45$^-$ HuCD45$^+$, CD34$^+$ cells in NSG mice



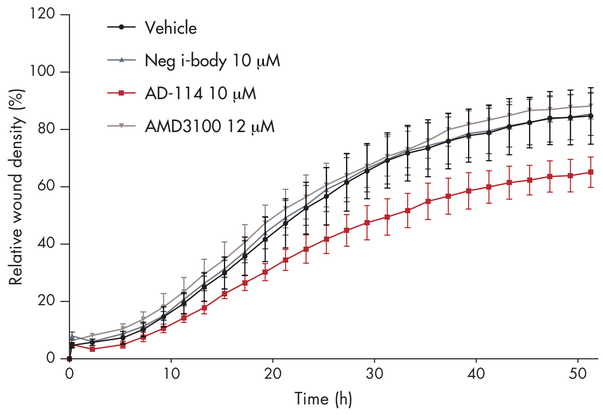
AD-114 reduces invasion and collagen production in human IPF fibroblasts

AD-114 reduces invasion of IPF but not normal lung fibroblasts

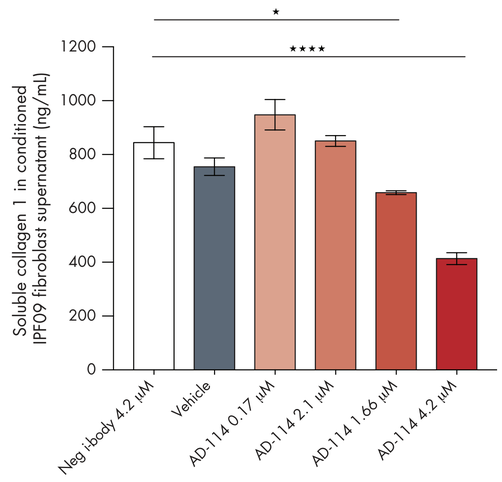
Non-diseased Control



IPF



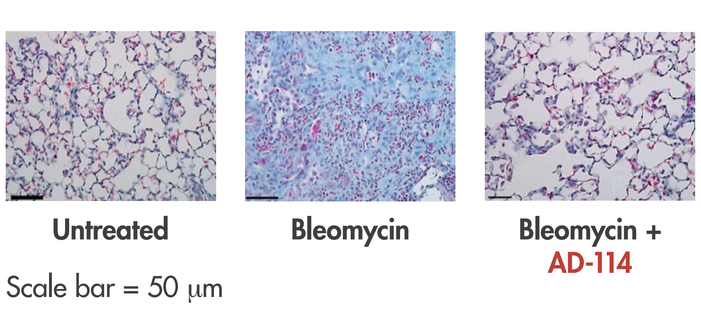
AD-114 reduces collagen secretion in IPF fibroblasts



AD-114 reduces fibrosis in the bleomycin mouse model of lung fibrosis

AD-114 ameliorates bleomycin-mediated fibrotic lung remodeling, collagen deposition and body weight loss

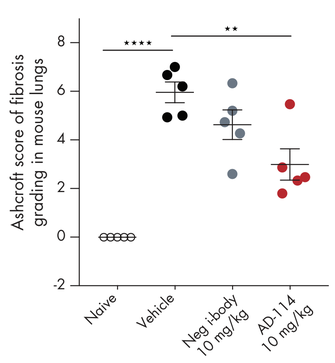
Masson's trichrome staining



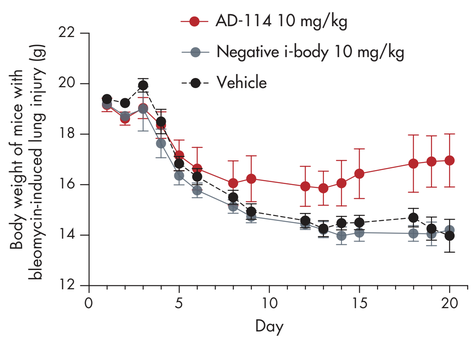
Untreated **Bleomycin** **Bleomycin + AD-114**

Scale bar = 50 μm

Ashcroft Score

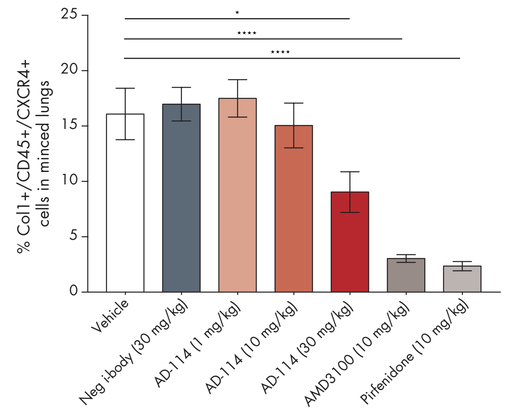


Body Weight



AD-114 reduces pulmonary infiltration of profibrotic cells

Col1a$^+$ CD45$^+$ CXCR4$^+$ cells



Pre-clinical studies have shown AD-114:

- has specificity for diseased human tissue with effects only shown on IPF tissue and no effects displayed on normal lung tissue nor any evidence of off target effects
- demonstrates both anti-fibrotic and anti-inflammatory effects in multiple animal models
- has unique pharmacology compared to other CXCR4 antagonist AMD3100 having activity with human fibroblasts without mobilising stem cells
- has a novel mechanism of action for fibrosis making AD-114 a potential "first in class" therapy

Griffiths *et al.* "i-bodies, Human Single Domain Antibodies That Antagonize Chemokine Receptor CXCR4", JBC, 2016

AdAlta next generation protein therapeutics

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