AdAlta
next generation protein therapeutics

ASX Announcement

AdAlta to present at Anti-Fibrotic Drug Development Summit in Boston

MELBOURNE Australia, 13 November, 2017: AdAlta Limited (ASX:1AD), the biotechnology Company advancing its lead i-body candidate towards clinical development, announces Chief Scientific Officer, Associate Professor Michael Foley has been invited to speak at the Anti-Fibrotic Drug Development Summit in Boston, Massachusetts between 13-14 November, 2017.

The conference provides an opportunity for cross-disciplinary discussions between drug developers of innovative, new therapies for fibrotic diseases such as NASH, Idiopathic Pulmonary Fibrosis (IPF) and Scleroderma for which is there is significant unmet medical need.

Presentation details

Presentation date / time:	13 November 2017 from 1:30 pm local time
Location:	Hyatt Regency, Boston
Presentation title:	i-bodies: a novel therapeutic approach for IPF

Through the presentation, A/Prof Foley will:

- Highlight the critical role of the chemokine receptor, CXCR4, in the development of Idiopathic Pulmonary Fibrosis
- Provide an overview of AdAlta's proprietary technology platform used to identify AD-114, a unique, selective inhibitor of CXCR4 Discuss the broad anti-fibrotic properties of AD-114 in multiple animal and *in vitro* models of fibrosis, including the eye, liver and kidney.

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

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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 fibrosis

Anti-Fibrotic Drug Development, Boston

November 2017

Mick Foley, CSO

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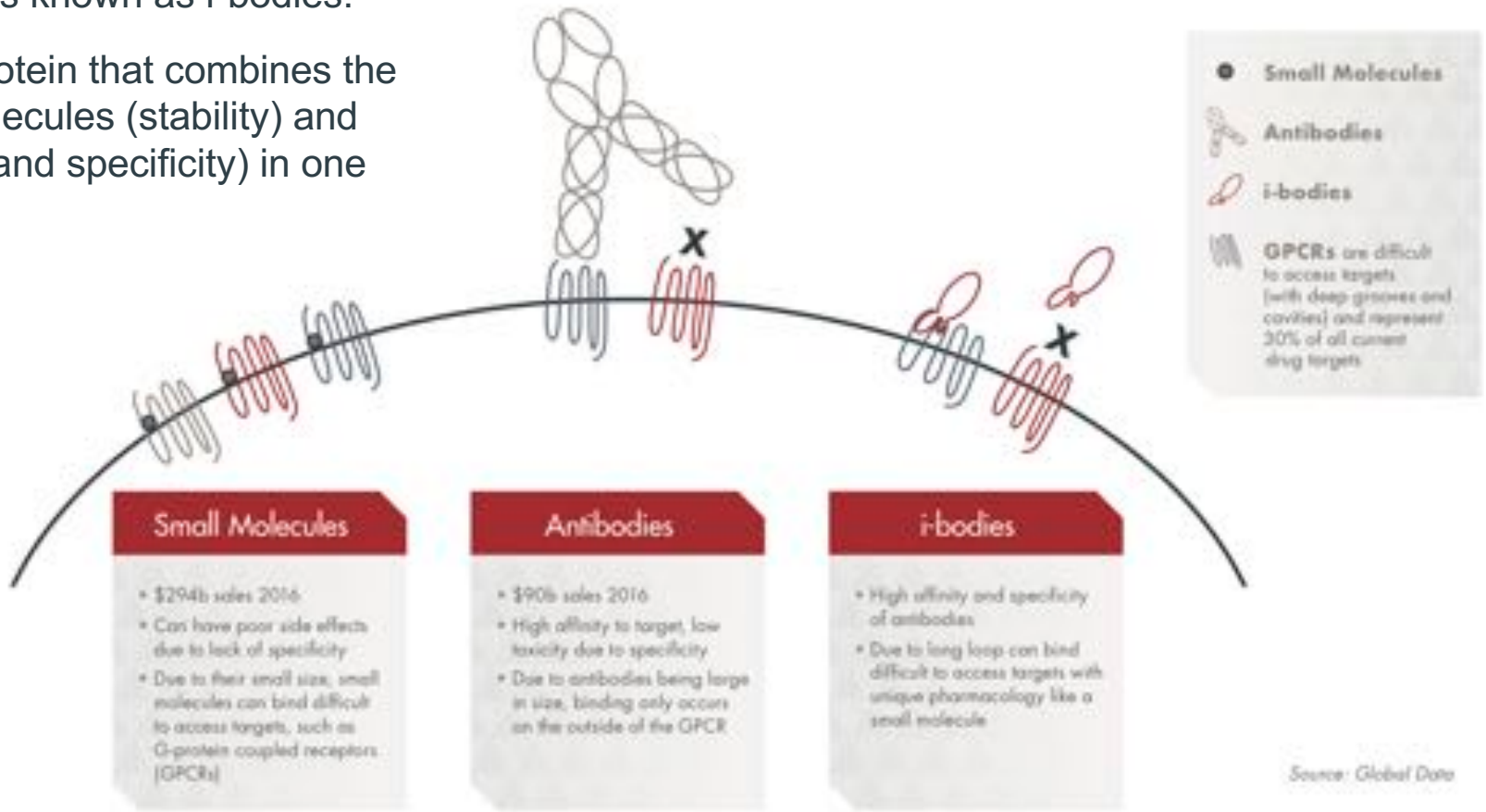
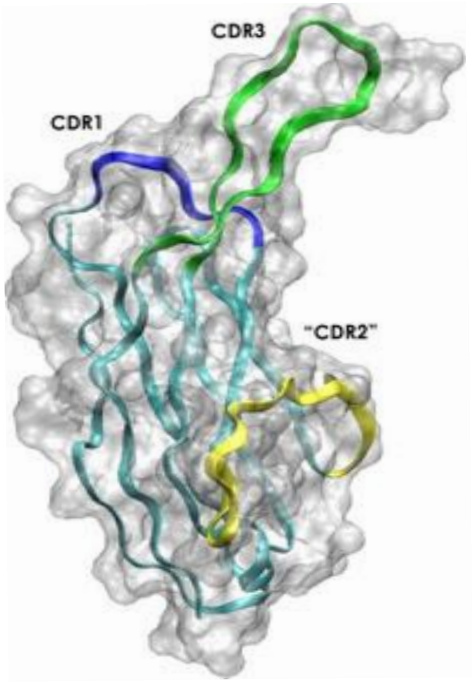
i-body technology

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

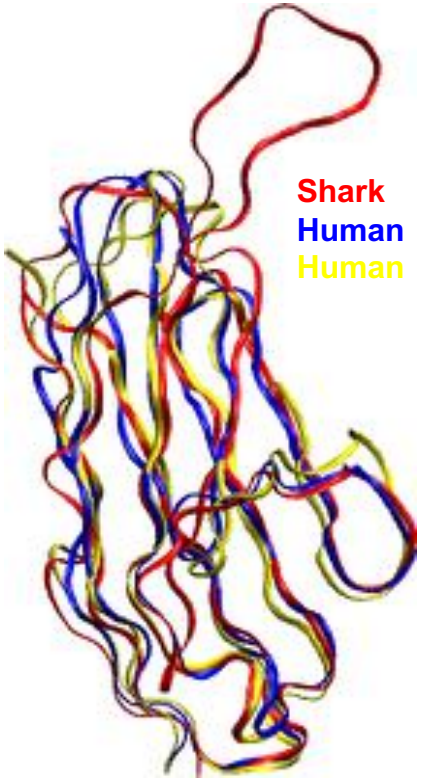
An i-body is a human protein that combines the advantages of small molecules (stability) and antibodies (high affinity and specificity) in one powerful treatment.



i-bodies: human single domains



VNAR



Ribbon Overlay

NCAM Domain 1

i-body library

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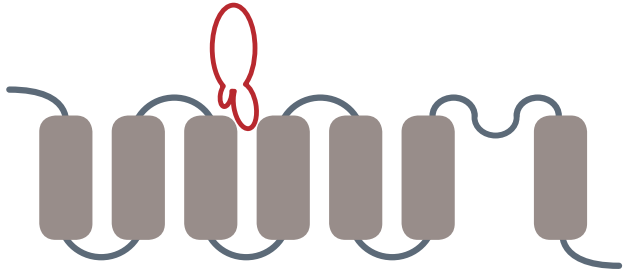
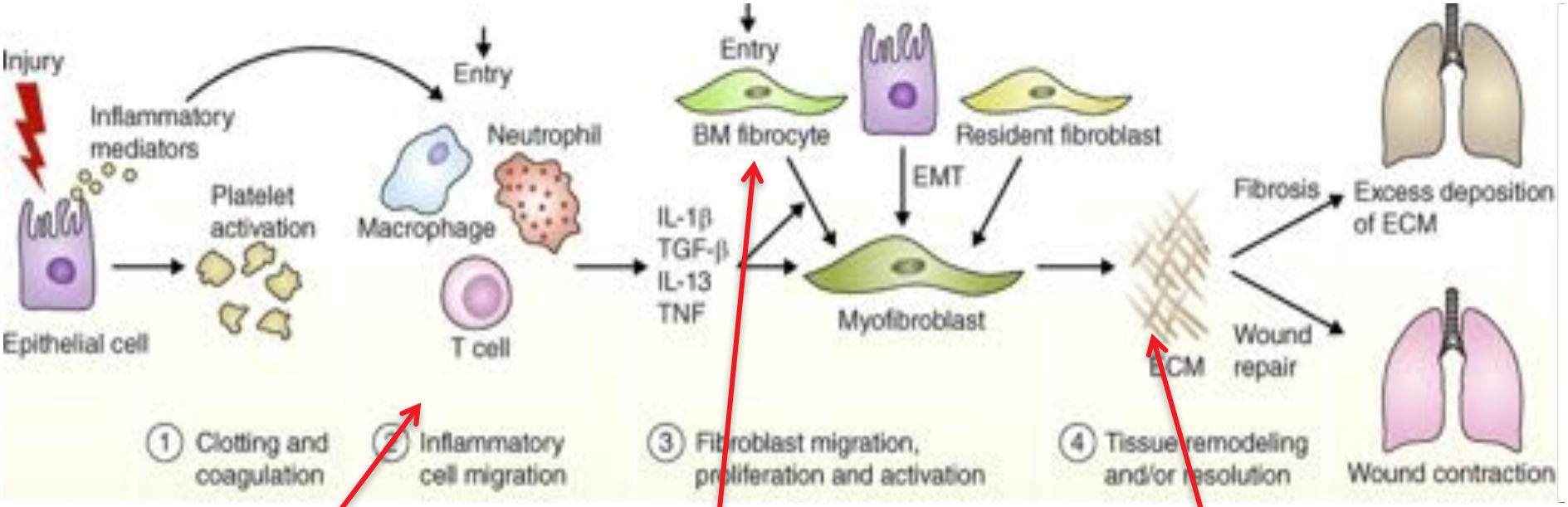
i-body technology advantages

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.

Fibrosis is a complex interplay of inflammation and wound healing



Inflammation

Fibrocyte migration

Deposition of collagen/ECM

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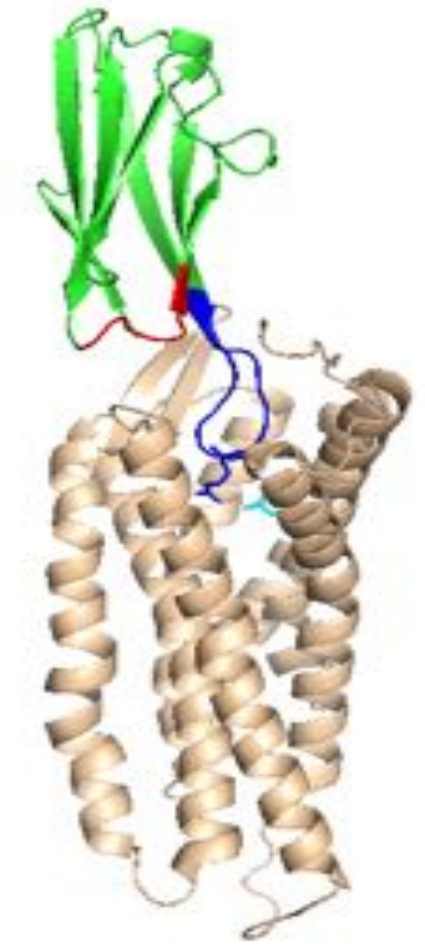
CXCR4 is involved in fibrosis and other disease states

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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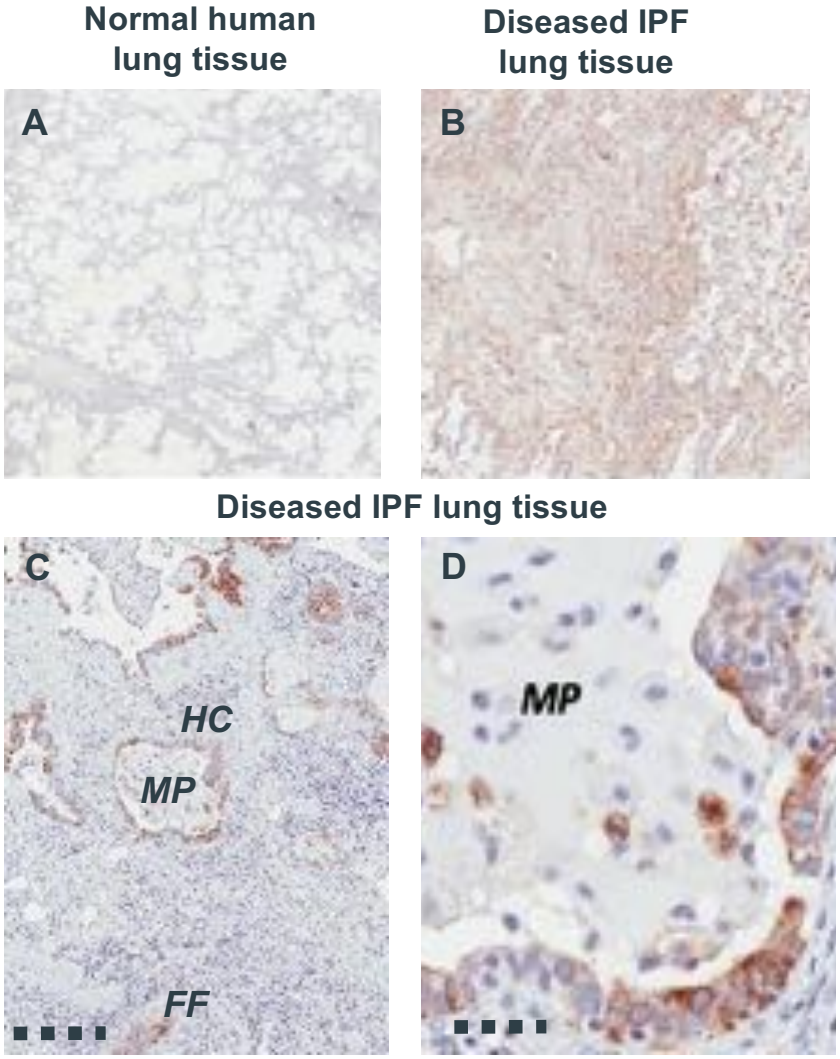
CXCR4 increased in disease

- IPF diseased lung tissue (B) has increased CXCR4 expression as compared with normal lung tissue (A)
- CXCR4 present in
  - hyperplastic epithelium (EP) of honeycomb cysts (HC) and also within a mucus plug (MP),(C), and higher magnification (D)
  - immediately adjacent to fibroblastic foci (FF) of IPF diseased lung tissue
  - Also found in cells of epithelial appearance in the fibrotic airway

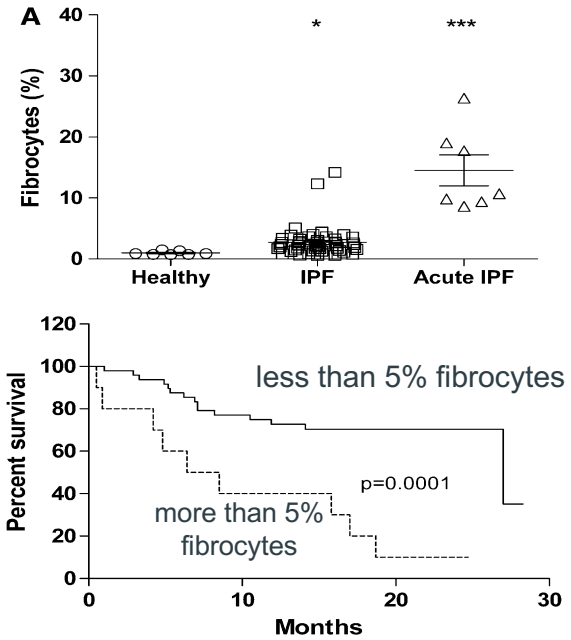


CXCR4 as a biomarker in IPF

- 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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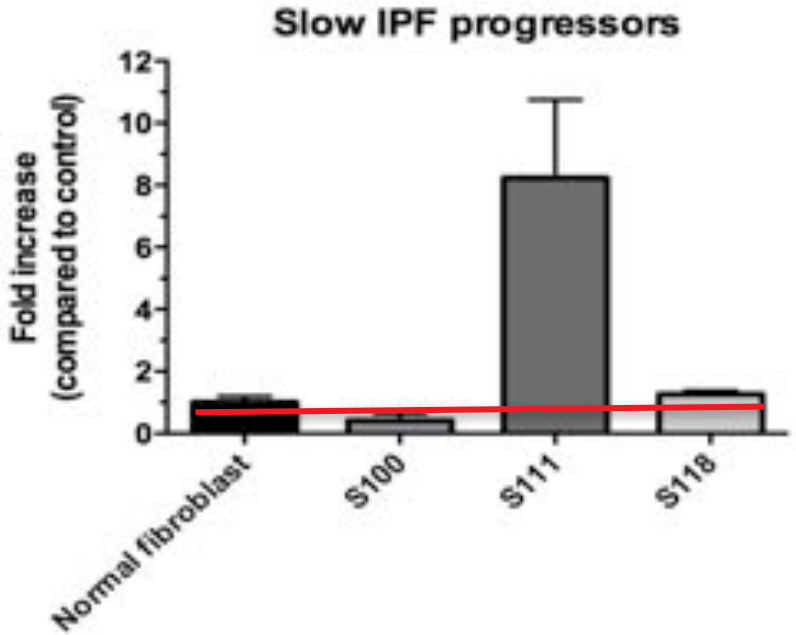
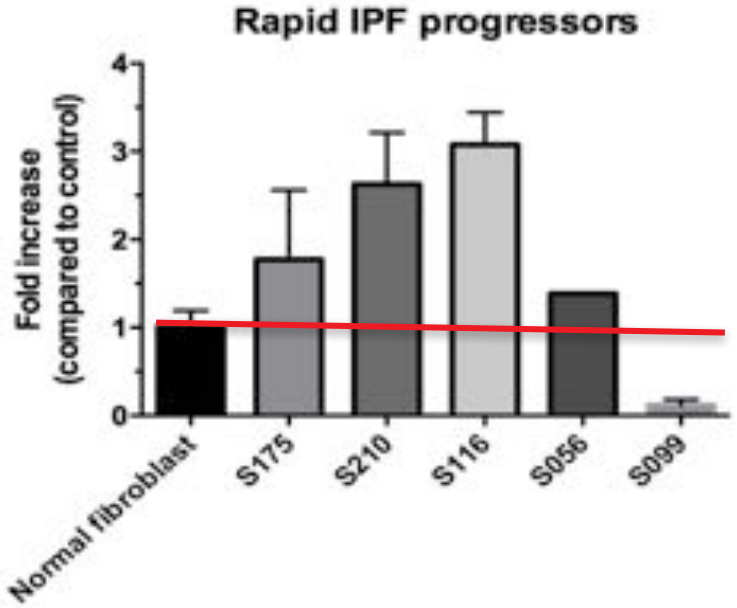
CXCR4 increased in fast progressing IPF patients

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





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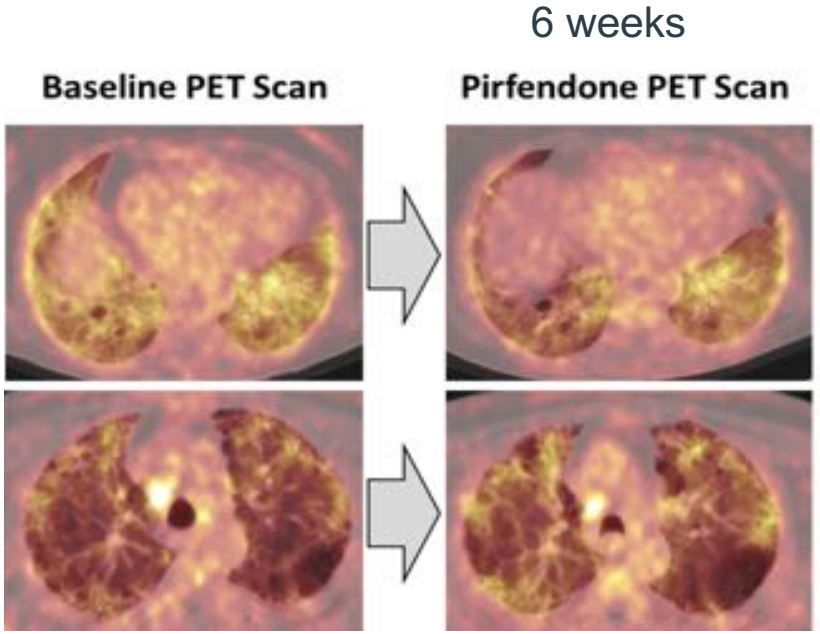
CXCR4 as a biomarker in IPF

- 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 for 6 months with lung function improvement
  - Patient B (bottom panels) had a high expression of CXCR4 at 6 weeks and did not respond to Pirfenidone treatment for 6 months, 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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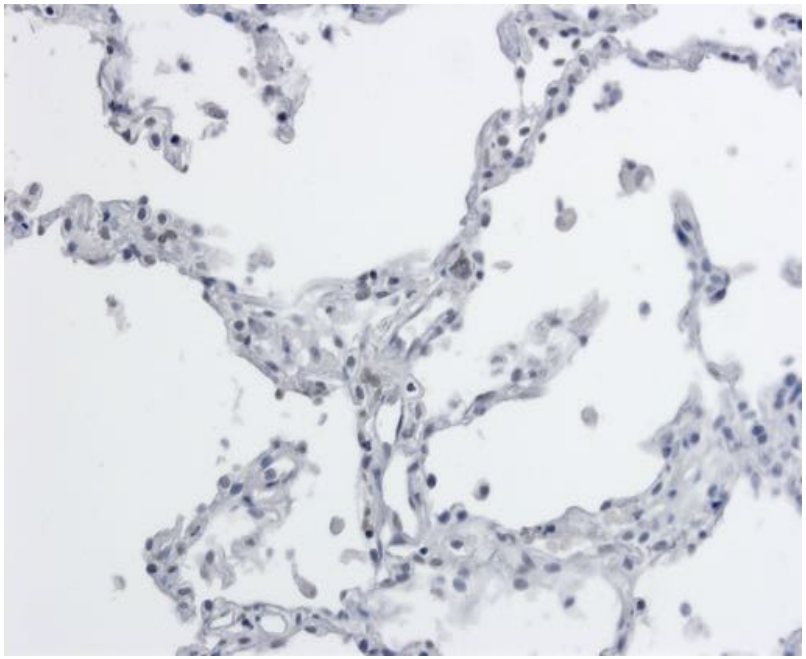
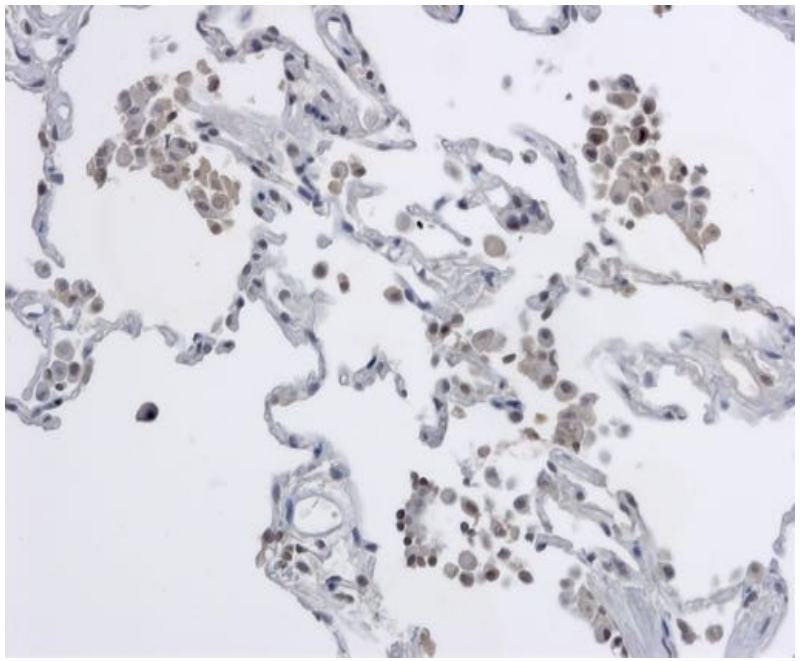
AD-114 binds to lung tissue from patients with fibrosis

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

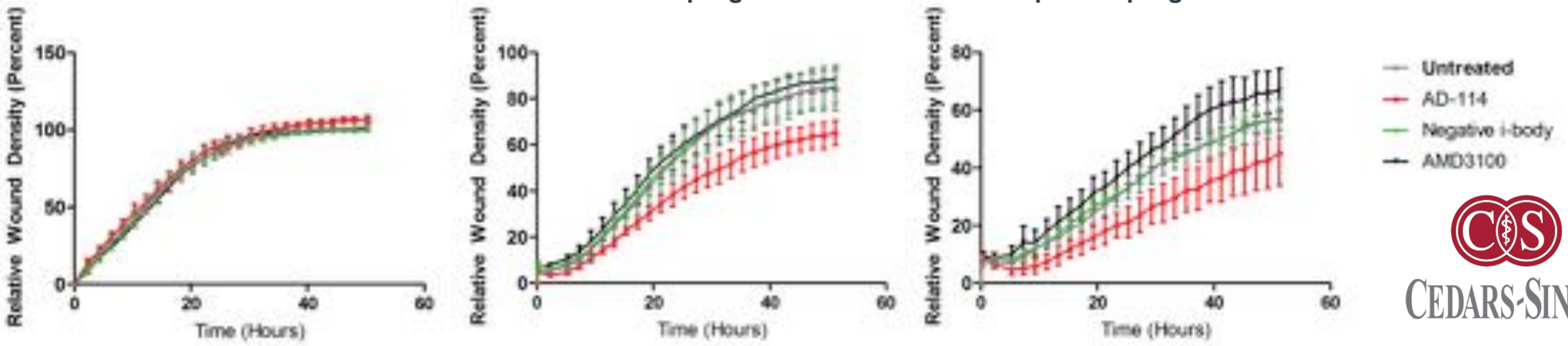
AD-114 specifically reduced migration/invasion with IPF lung fibroblasts

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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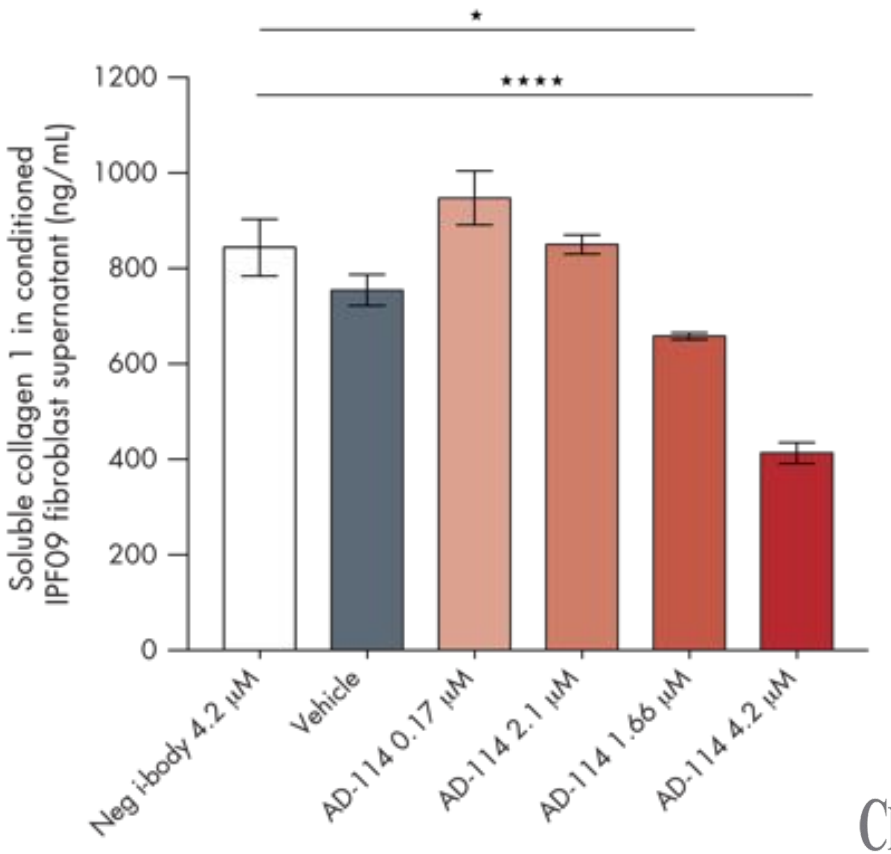
AD-114 reduced collagen secretion in IPF fibroblasts

- 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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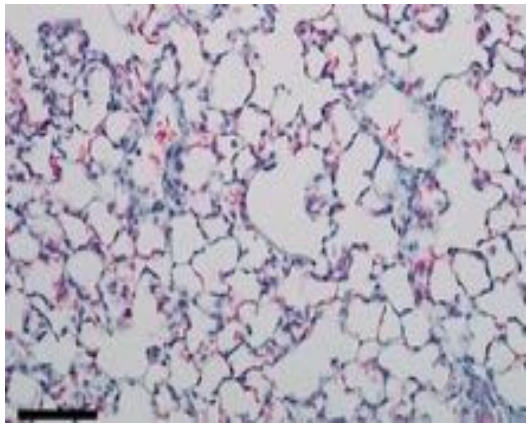
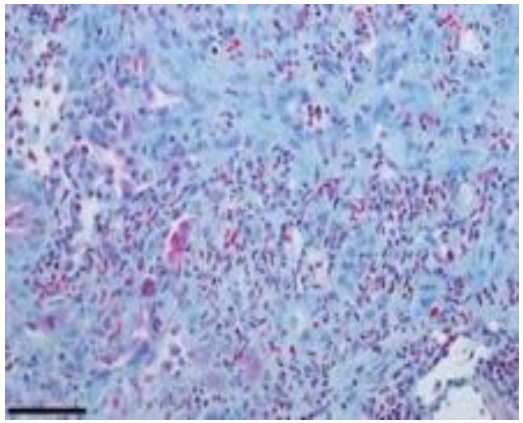
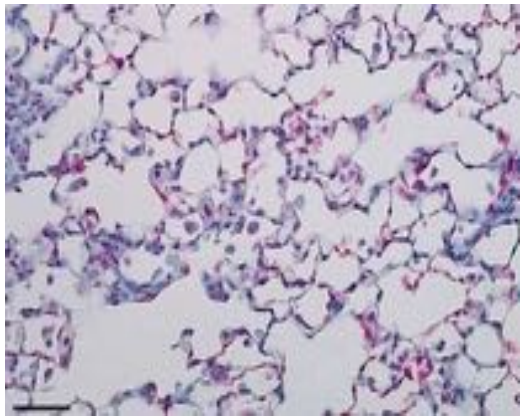
AD-114 prevents fibrosis in Bleomycin mouse model



Normal
lung tissue



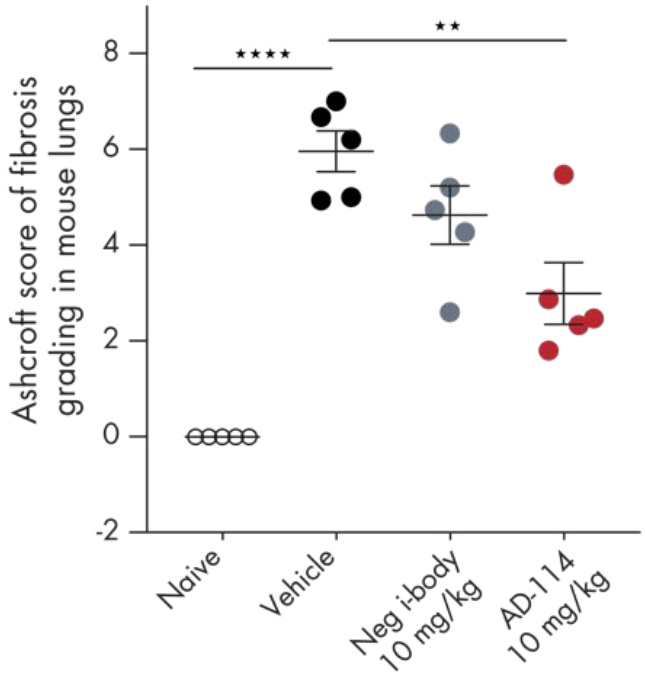
IPF lung tissue
(lung disease mouse model)

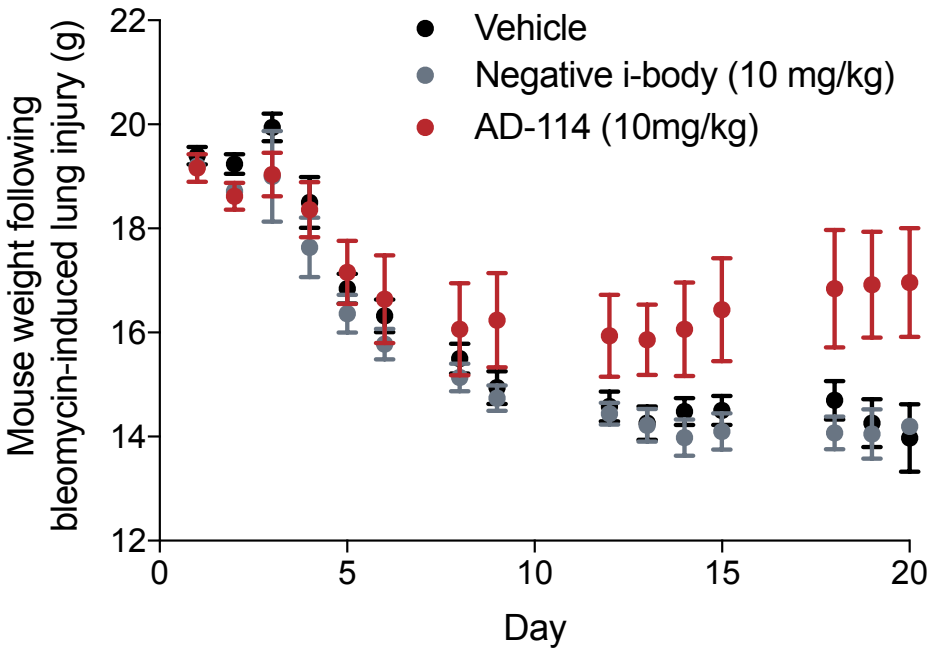


IPF lung tissue + AD-114
dosed for 21 days
(lung disease mouse model)

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 Bleomycin treated mice
- AD-114 significantly prevented the Bleomycin induced loss in body weight in mice

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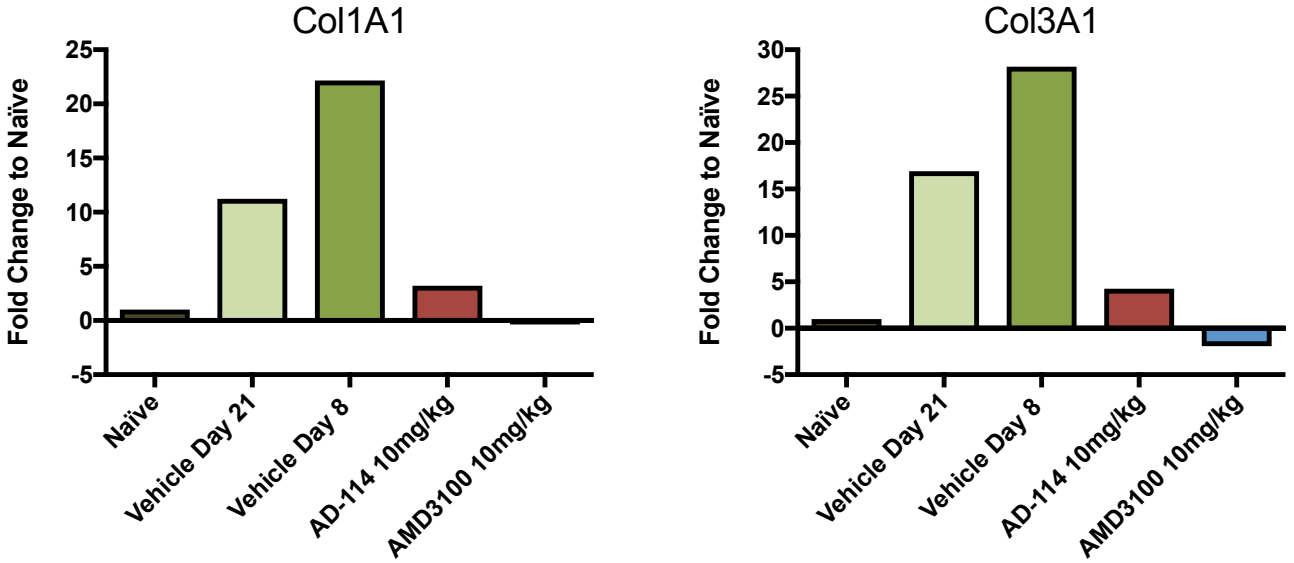
AD-114 reduces fibrotic gene expression in Bleomycin mouse model

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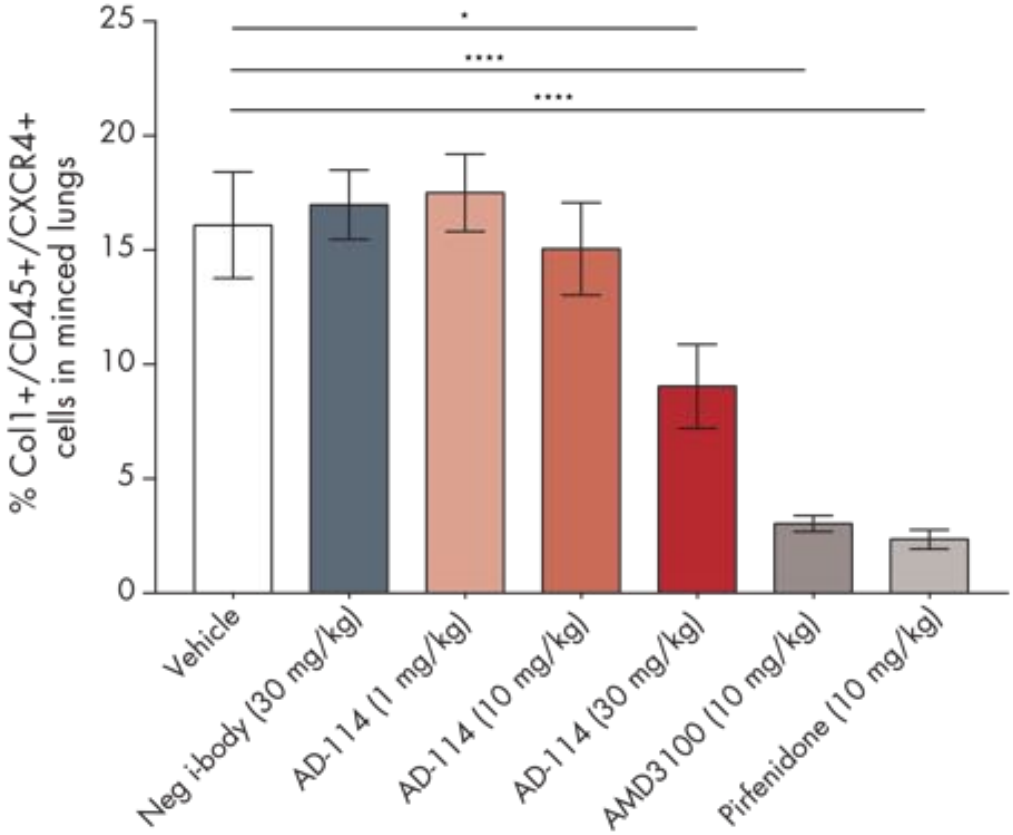
AD-114 reduces pulmonary infiltration of fibrocytes in the Bleomycin mouse model

- 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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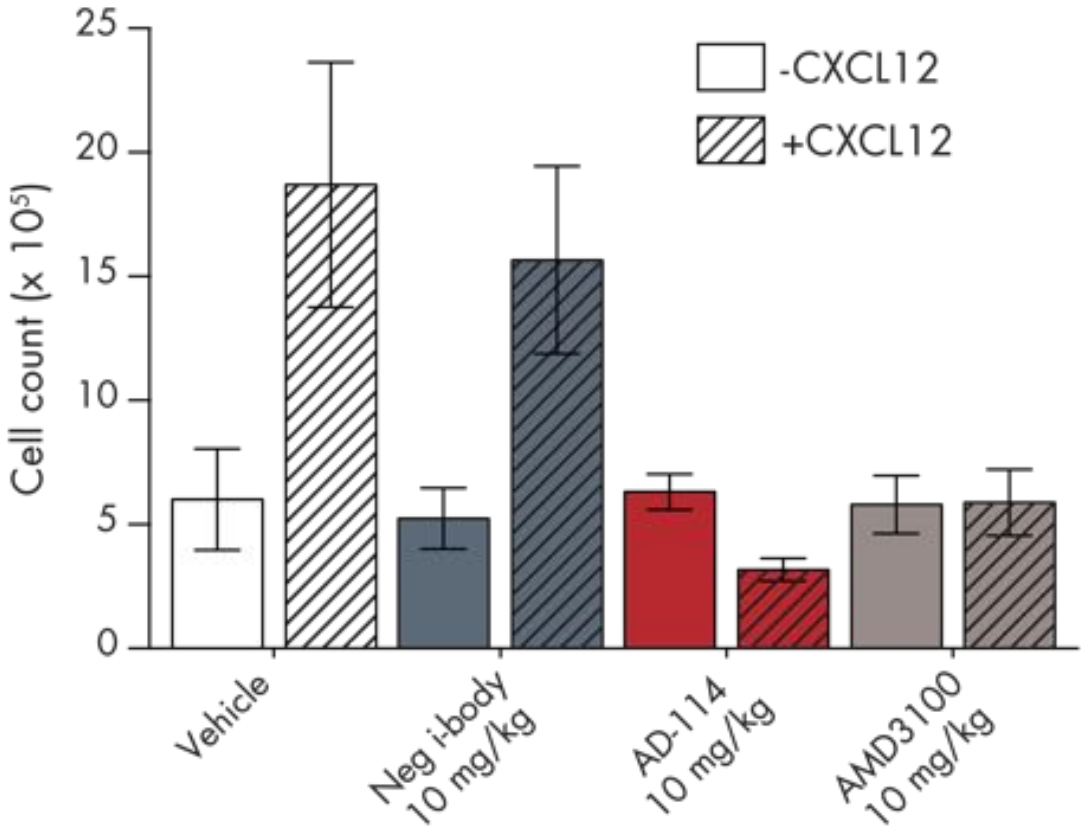
AD-114 blocks infiltration of leukocytes

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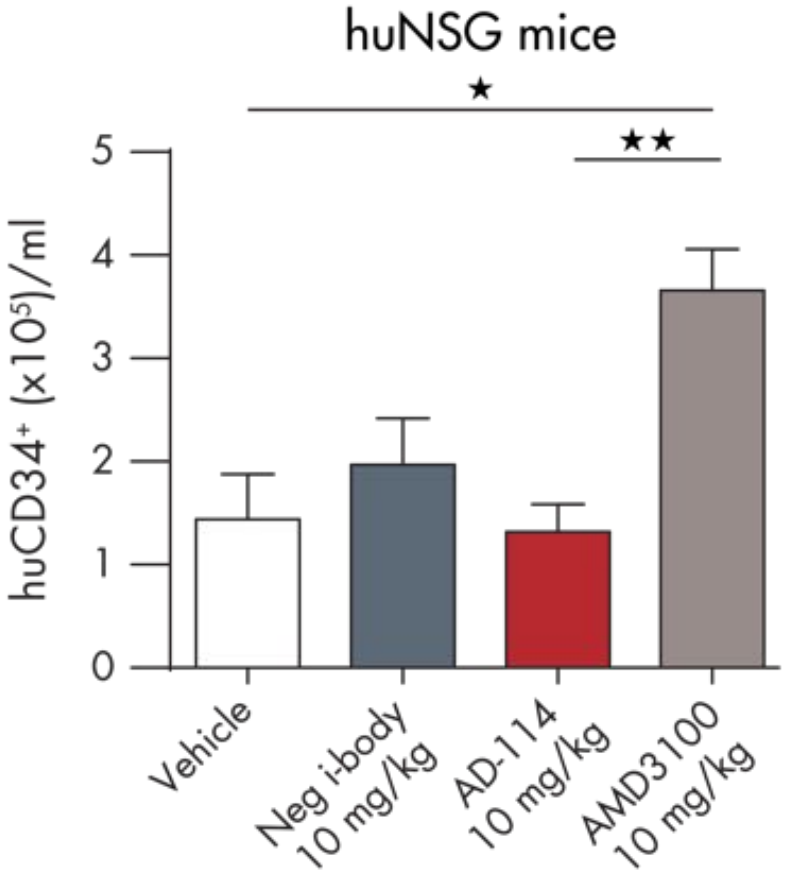
AD-114 does not mobilize stem cells *in vivo*

- 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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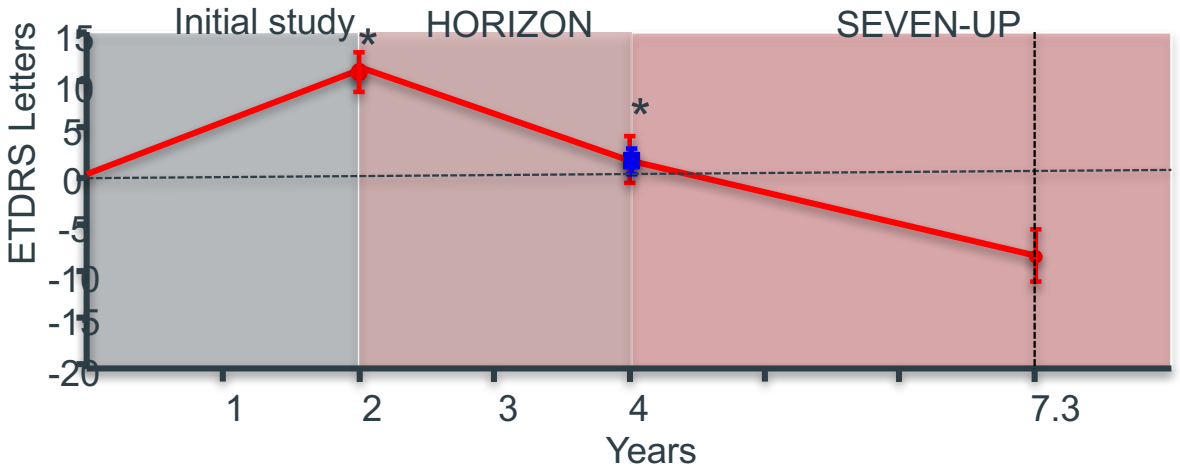
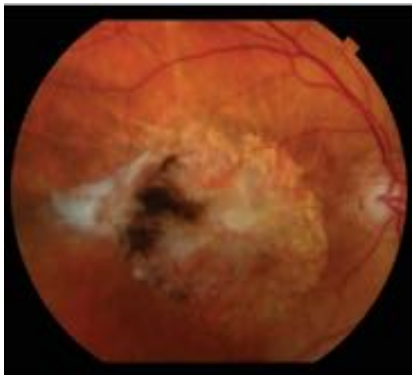
Fibrosis in the eye

Subretinal fibrosis is the end stage of wet AMD

Eylea
Lucentis



Rosenfeld et al, N Engl J Med 2006; 355(14): 1419.
Brown et al, N Engl J Med 2006; 355(14); 1432



Subretinal scarring

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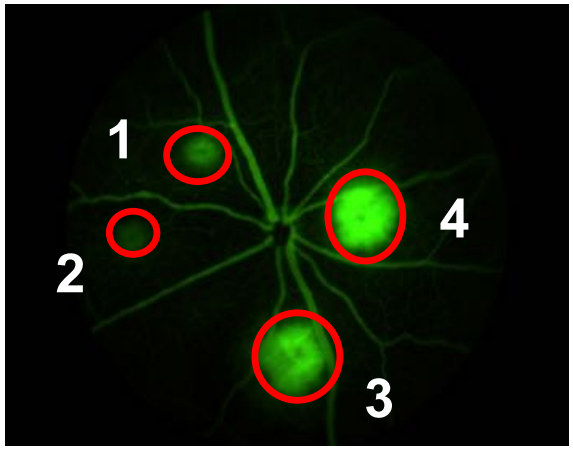
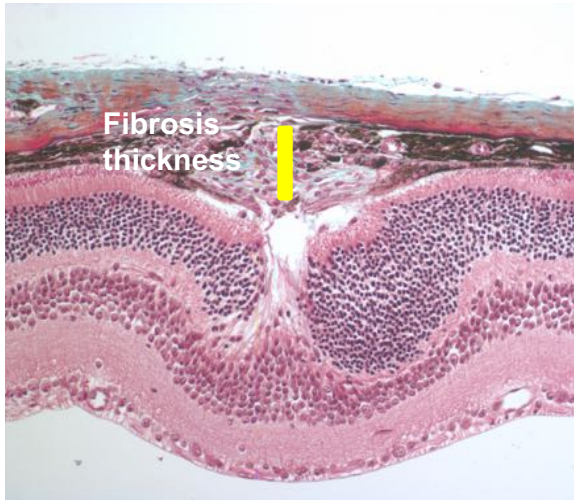
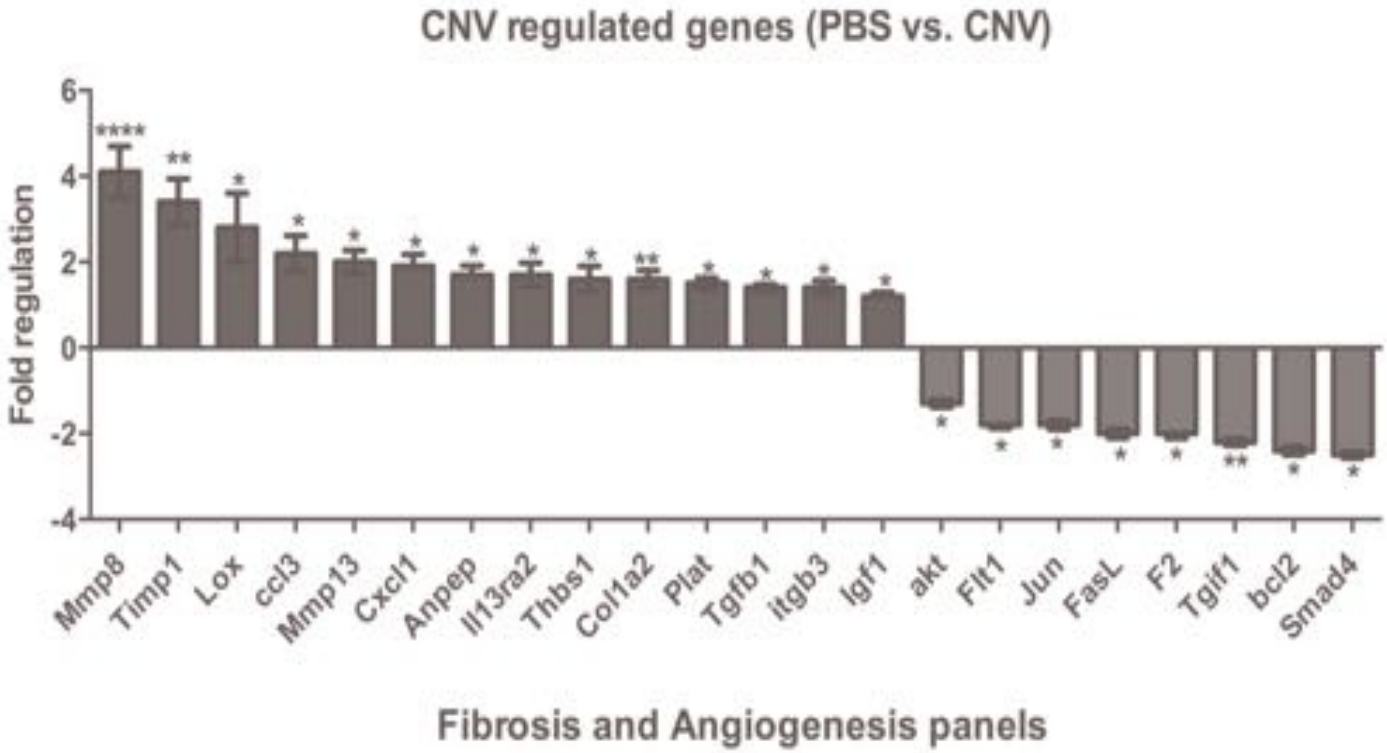
What genes are altered in laser induced CNV?







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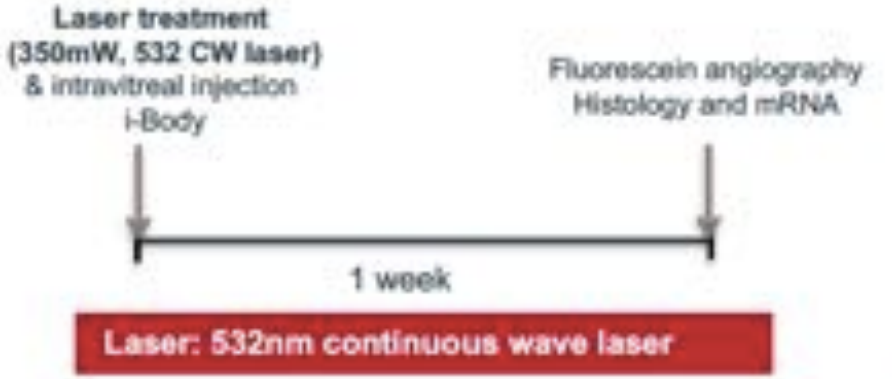
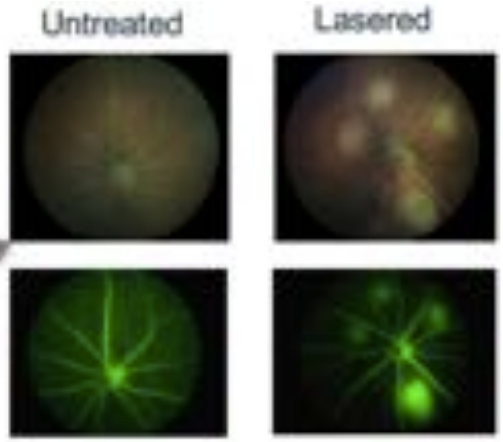
Effect of AD-114 in Laser induced CNV and fibrosis in preventative mode





Analysis

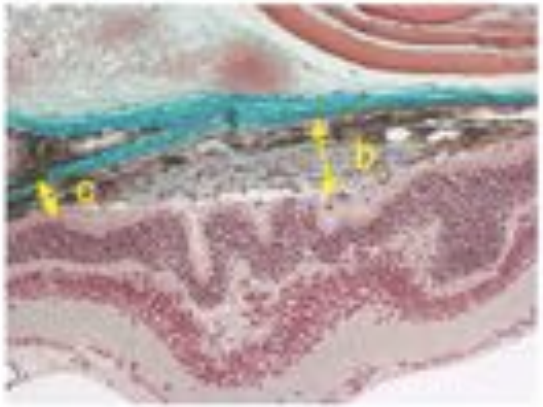
Lesions: % lesions that leak at 7 days
Size of FA lesion

Histology: Height of lesion relative to choroid.
Trichrome stain

IMCC: Iba1, Col1 and GFAP

Gene: Angiogenesis and fibrosis PCR array

Lesion height was quantified by measuring the height of the lesion (b), and normalising to the choroid (c) or b/c ratio.



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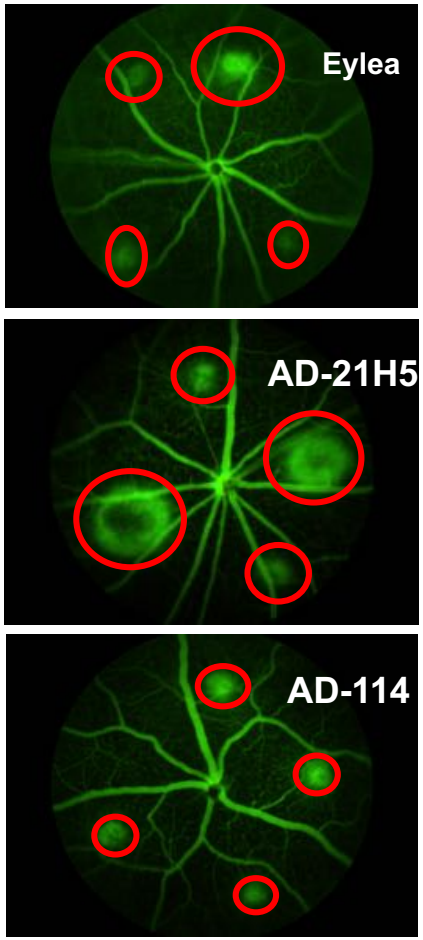
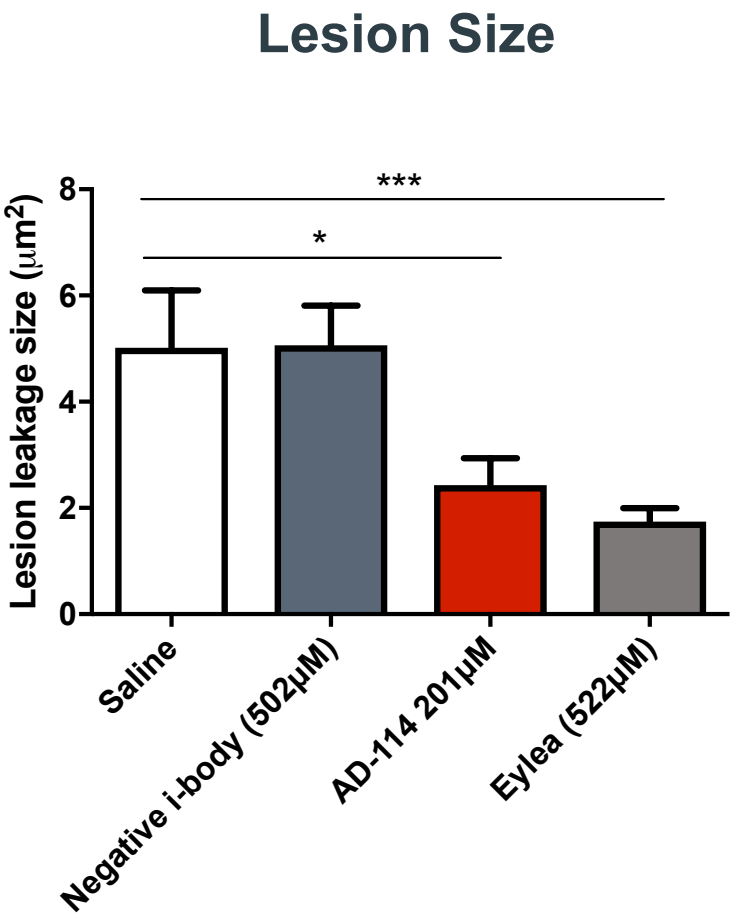
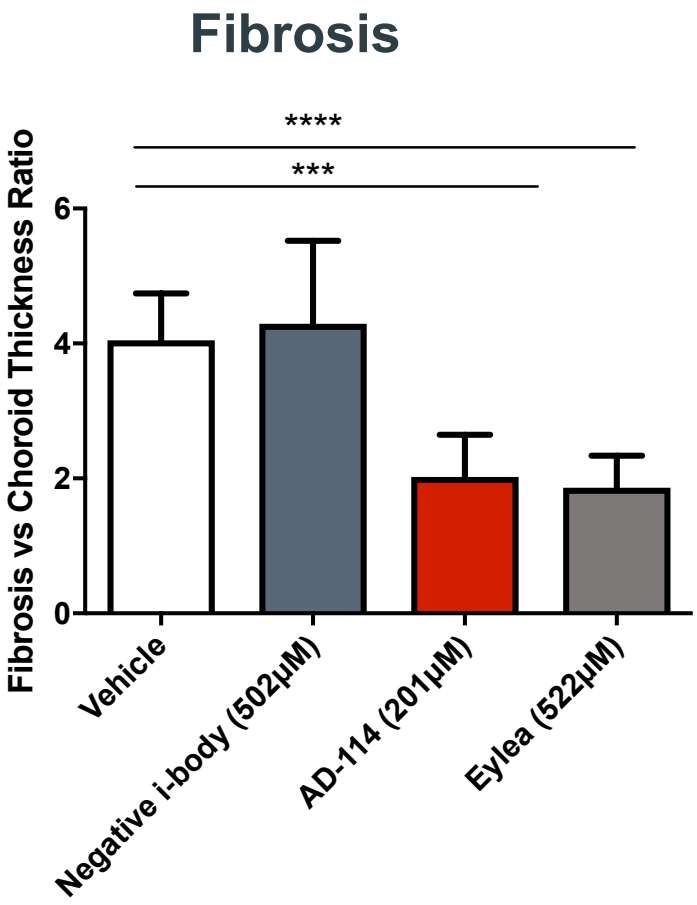
AD-114 reduces fibrosis in Laser induced CNV







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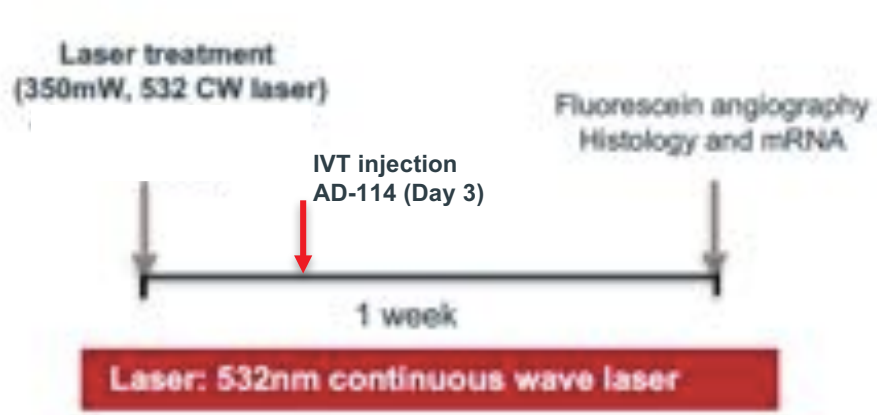
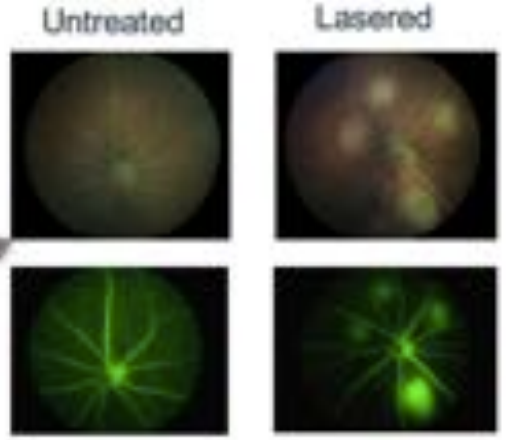
Affect of AD-114 in Laser induced CNV and fibrosis in therapeutic mode





Analysis

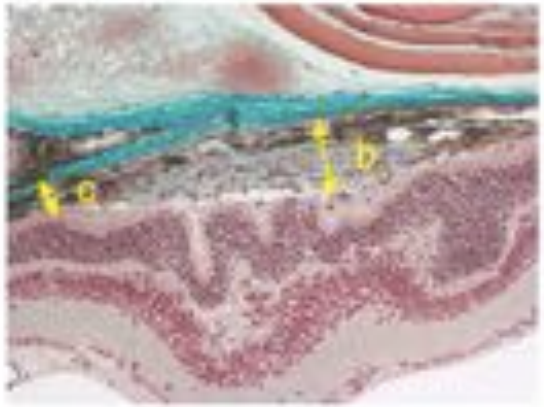
Lesions: % lesions that leak at 7 days
Size of FA lesion

Histology: Height of lesion relative to choroid.
Trichrome stain

IMCC: Iba1, Col1 and GFAP

Gene: Angiogenesis and fibrosis PCR array

Lesion height was quantified by measuring the height of the lesion (b), and normalising to the choroid (c) or b/c ratio.



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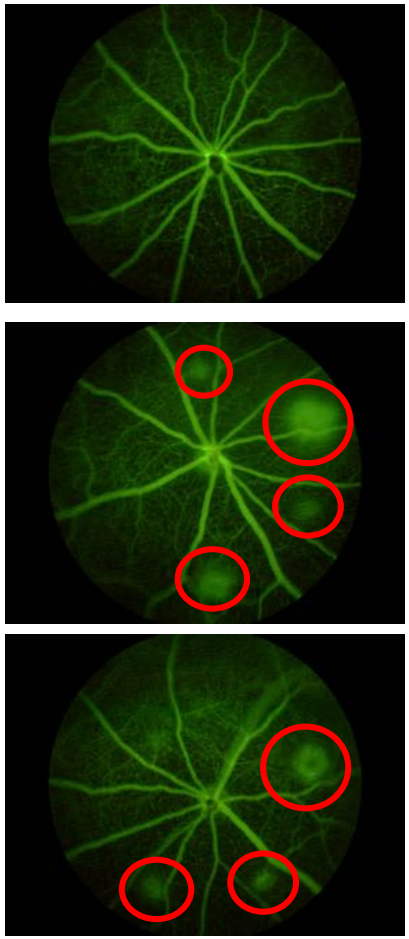
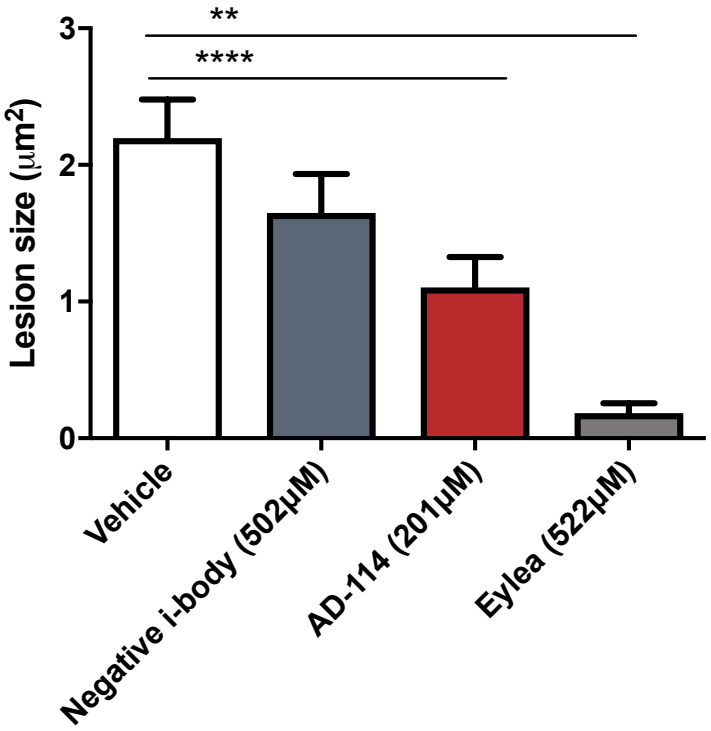
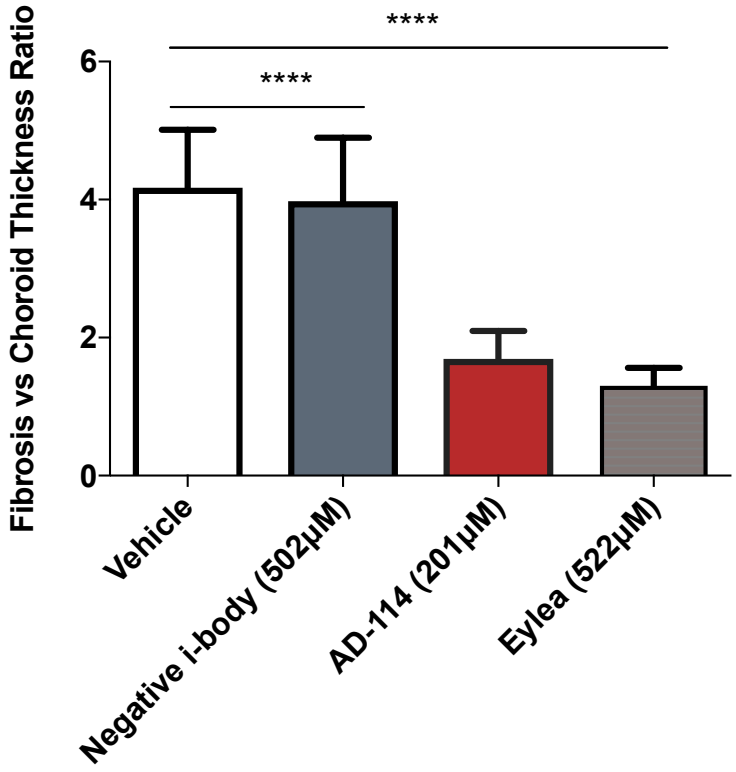
AD-114 reduces fibrosis in Laser induced CNV



Lesion Size



Fibrosis



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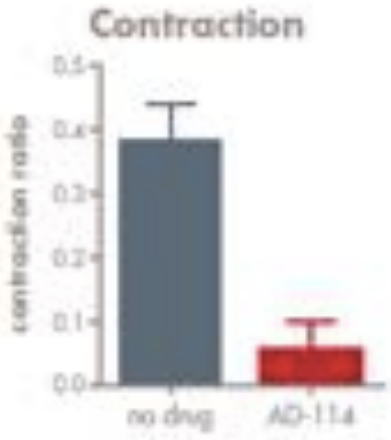
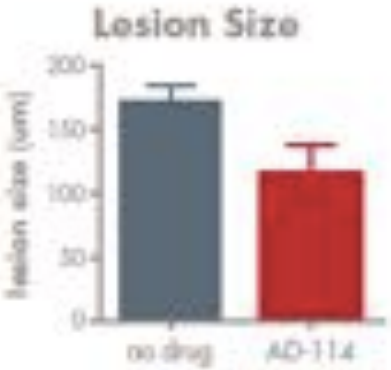
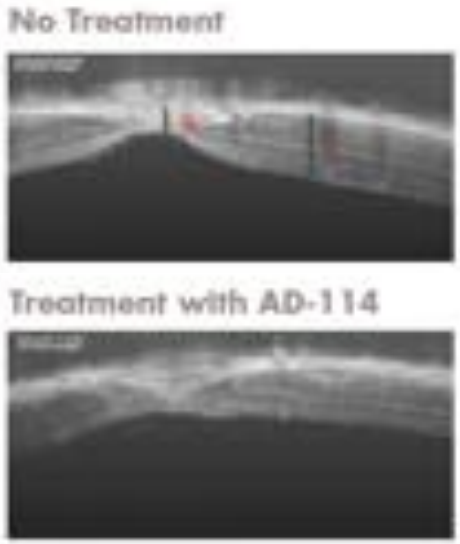
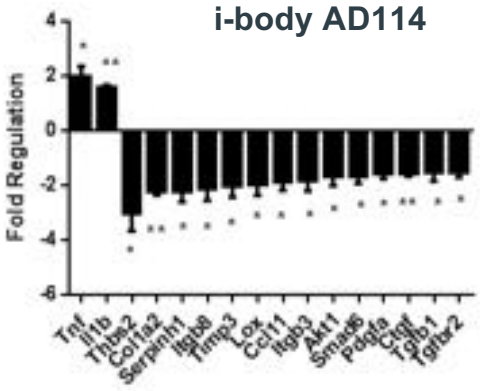
Model: Laser induced sub retinal haemorrhage

- Mouse CNV model; laser burn to retina:
  - Induces subretinal haemorrhage
  - Contraction of retinal tissue
  - Upregulation of fibrotic genes
- IVT injection of single dose of AD-114
  - Reduces lesion size
  - Dramatically reduces retinal contraction
  - Reduces pro-fibrotic gene expression









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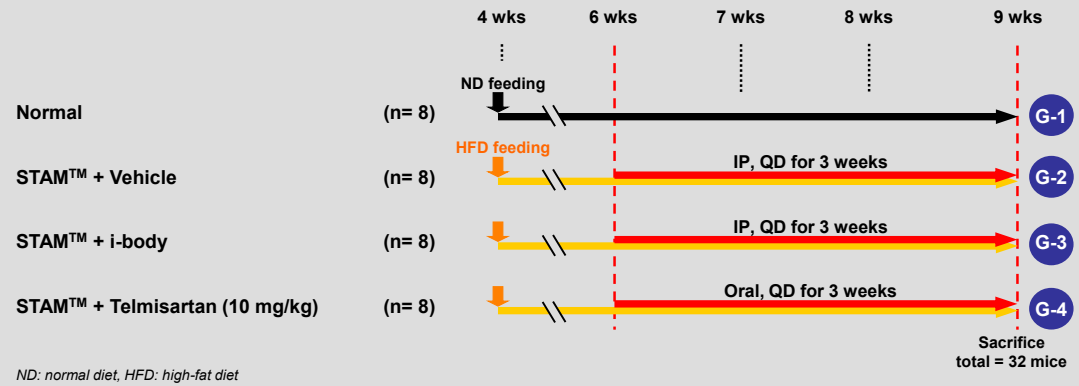
Liver Fibrosis

Stellic Institute- STAM NASH mouse model:

Study plan for assessing the anti-NASH/fibrosis effects of i-body in STAM™ model of NASH



ND: normal diet, HFD: high-fat diet

Analyses

1. General
- Body weight
- Liver weight
- Liver-to-body weight ratio

2. Biochemistry
- Liver TG
- Serum ALT

3. Histopathological analyses
- HE staining (NAFLD Activity score)
- Sirius red staining (Fibrosis area)

4. Gene expression assay
- TNF-α, MCP-1, α-SMA, TIMP-1, TGF-β, Col1a

5. Sample collection
- Frozen liver samples
- Frozen serum samples

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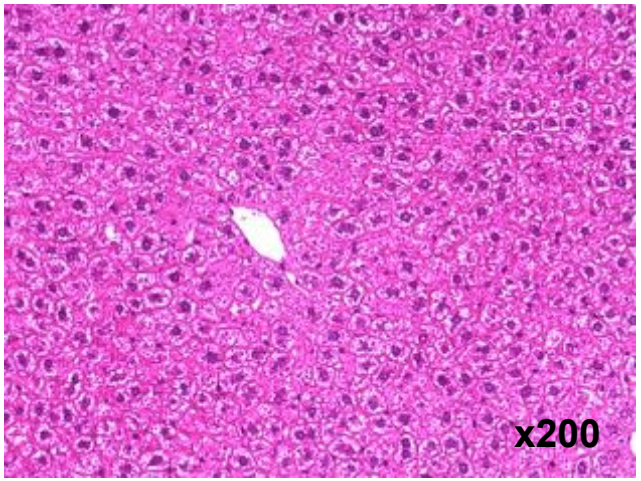
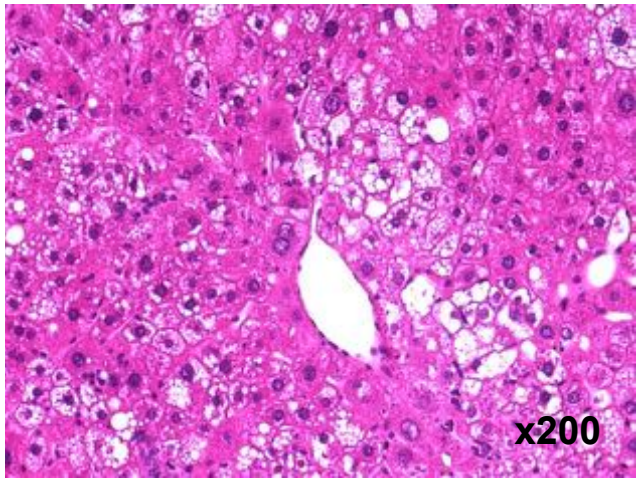
AD-114 prevents fibrosis in a mouse model of liver fibrosis

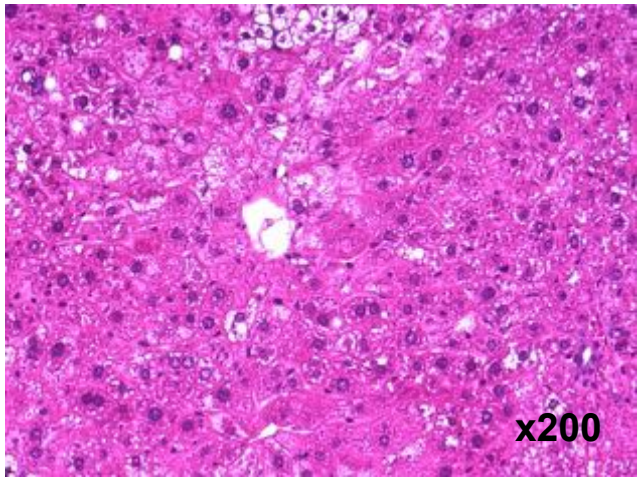
Therapeutic setting



Normal liver tissue



NASH liver tissue
(liver disease mouse model)



NASH liver tissue + AD-114 dosed for 21 days
(liver disease mouse model)

AD-114 significantly reduces hepatocellular ballooning, a key feature required for the diagnosis of NASH

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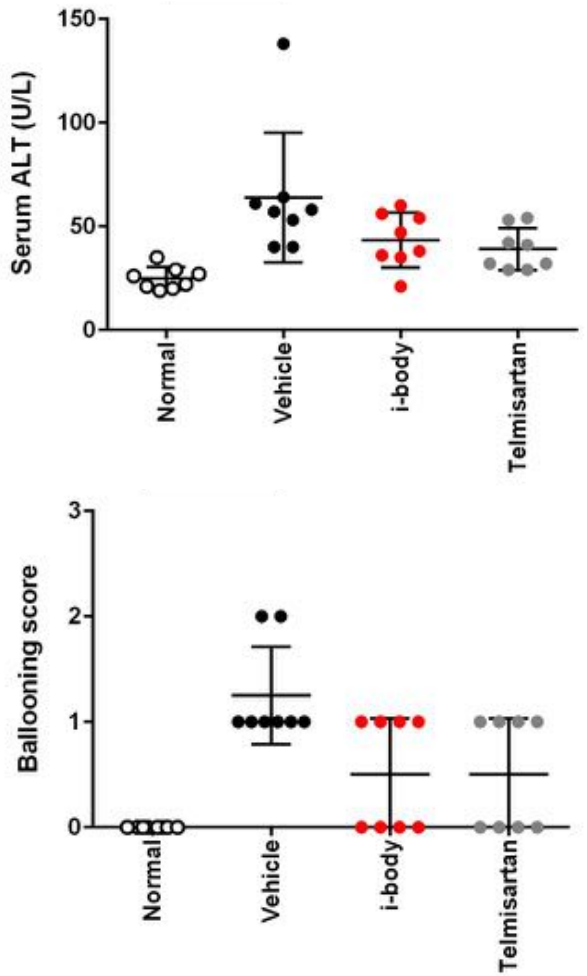
AD-114 prevents fibrosis in a mouse model of liver fibrosis

- AD-114 decreased serum ALT levels compared with the vehicle or disease model group suggesting that i-body ameliorated hepatocellular injury and inflammation preventing progression of disease
- Hepatocyte ballooning was significantly decreased compared with the vehicle or diseased group
- AD-114 possess hepatoprotective and anti-NASH effects



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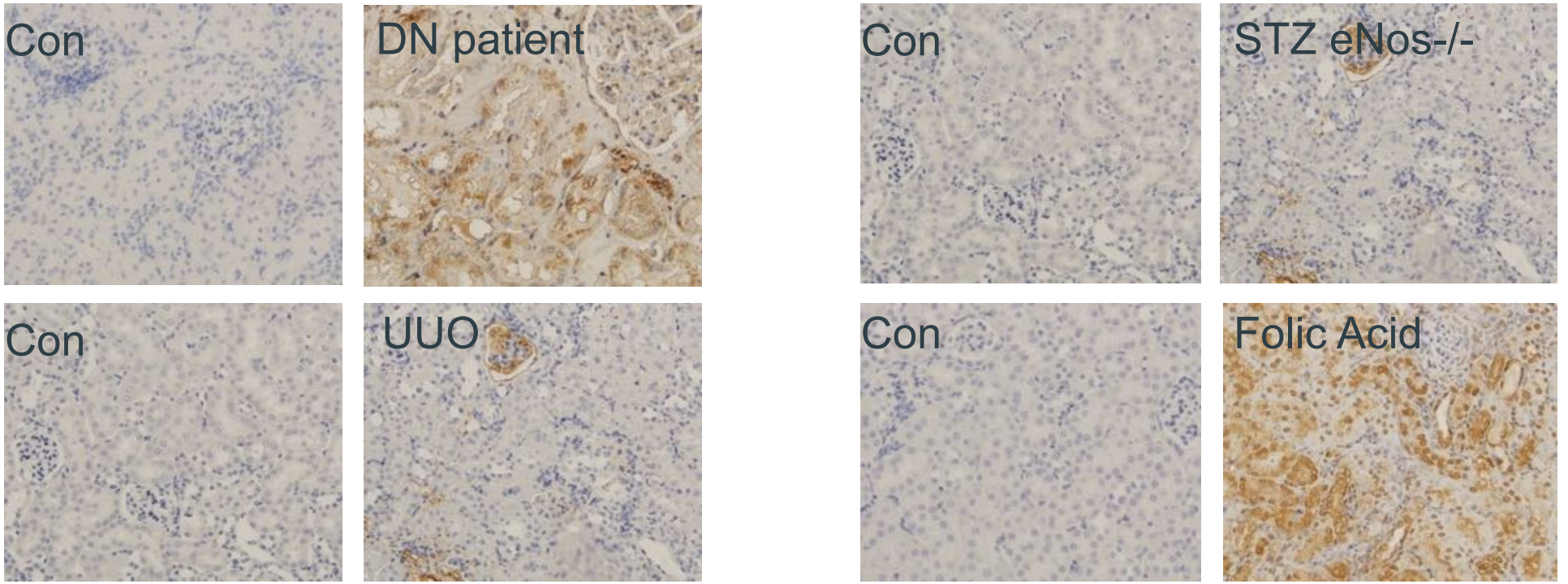
AD-114 is anti-fibrotic in the liver

- AD-114 also reduced the expression of inflammatory genes TNF-a, MCP1 and fibrosis gene TIMP-1 in a mouse model of liver fibrosis in therapeutic model
- AD-114 also decreased non-alcoholic fatty liver disease (NAFLD) score compared with the vehicle or disease model group
- **These data together with the reduction in hepatocyte ballooning and the reduction in collagen deposition suggest that AD-114 possess hepatoprotective and anti-NASH effects**

Kidney Fibrosis

CXCR4 is upregulated in fibrotic kidneys of animal and human patients



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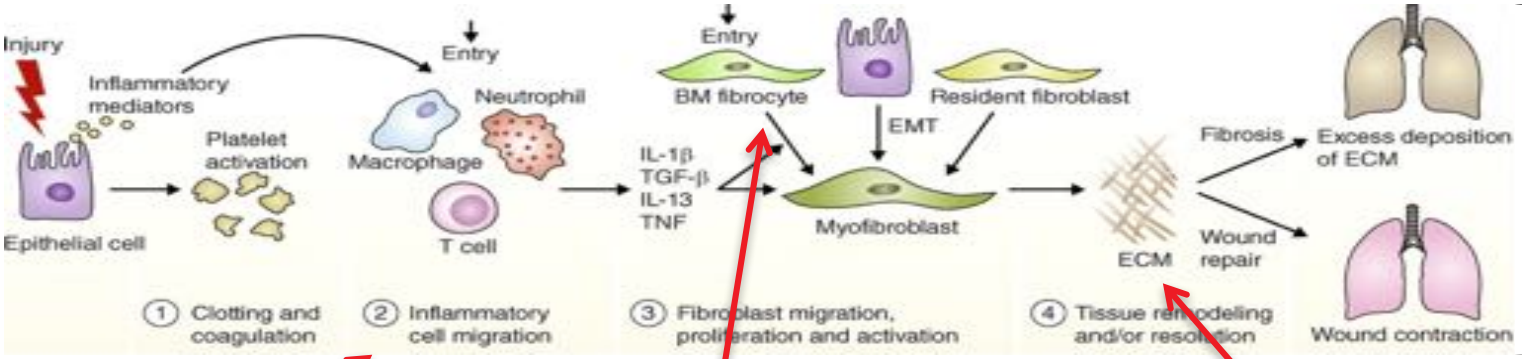
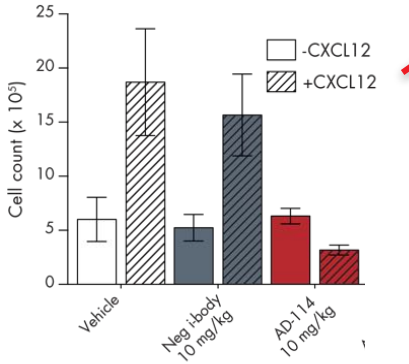
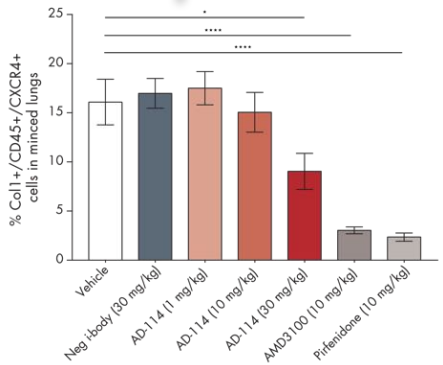
AD-114 inhibits key features of the fibrogenic pathway with novel MOA

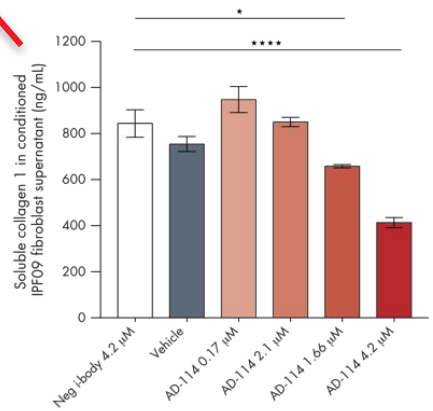




Modulate aspects of inflammation



Block fibrocyte recruitment into the damaged tissue



Reduce ECM deposition during tissue remodeling

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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.

AdAlta

next generation protein therapeutics

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