

ASX Announcement

AdAlta to present kidney fibrosis data at Australian and New Zealand Society of Nephrology Annual Scientific Meeting

MELBOURNE Australia, 4 September, 2017: AdAlta Limited (ASX:1AD), the biotechnology company advancing its lead i-body candidate towards clinical development, announces that AdAlta, the Kolling Institute and the University of Sydney will present data on AdAlta's lead compound, AD-114, for the treatment of kidney fibrosis at the Australian and New Zealand Society of Nephrology's Annual Scientific Meeting 2017 (ANZSN ASM 2017).

The ANZSN ASM 2017 will be held from September 4-6 2017, in Darwin, in Australia's Northern Territory. The meeting provides a platform for individuals from academia to industry to discuss novel targets and disease pathways along with the latest advances in nephrological science and clinical care.

Following a collaborative research project with AdAlta and the Kolling Institute, the University of Sydney, will present data on AdAlta's lead candidate, AD-114, which examines its potential use in the treatment of kidney fibrosis. The presentation (attached) which summarises the research project, concludes that AD-114 may provide a novel treatment for Chronic Kidney Disease using a different mechanism of action to currently-approved therapies. Chronic Kidney Disease currently affects an estimated 1.7million Australians.

AdAlta's CEO, Sam Cobb said, "An increase in diabetes and obesity across the world is leading to a massive surge in the number of people diagnosed with Chronic Kidney Disease. The medical community is looking for alternate treatment options, so this early work with AD-114 is encouraging.

"This research collaboration with the Kolling Institute and University of Sydney further informs our pre-clinical package and shows that AD-114 works across a range of fibrotic disease areas. We know this data helps speak to the value of AD-114 and will be important to potential pharmaceutical partners."

Details of the oral presentation

Presentation Type: Mini Orals

Mini Orals | Waterfront 3, Cardiovascular / Hypertension / CKD-Mineral Bone Disease / Anaemia / Adequacy

Session Date/Times: September 5, 2017 from 12:05 PM to 1:05PM

The session presentation entitled "*A novel and unique protein i-body AD-114 inhibited TGF- β 1-induced expression of fibronectin and collagen 4 in renal proximal tubular cells*" follows this cover page and is also available on the Company's 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. In addition to fibrosis of the lung, AdAlta has also shown broad fibrotic application of AD-114 for the treatment of fibrosis of the eye, liver and skin.

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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A NOVEL AND UNIQUE PROTEIN I-BODY AD-114 INHIBITED TGF β 1-INDUCED EXPRESSION OF FIBRONECTIN AND COLLAGEN 4 IN RENAL PROXIMAL TUBULAR CELLS

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Background

- **Renal fibrosis** is the final common manifestation of CKD¹.
- **TGF- β** is the master regulator of renal fibrosis¹.
- **CXCR4** (Chemokine receptor type 4) is a member of the G protein-coupled chemokine receptor (GPCRs) family.
- **CXCR4** plays an important role in inflammatory and fibrotic responses in various tissues.
- **CXCR4** has been demonstrated to be significantly upregulated in the fibrotic kidney in a mouse model of unilateral ureteral obstruction(UUO). Importantly, sustained activation of CXCR4 enhanced the development of renal fibrosis.

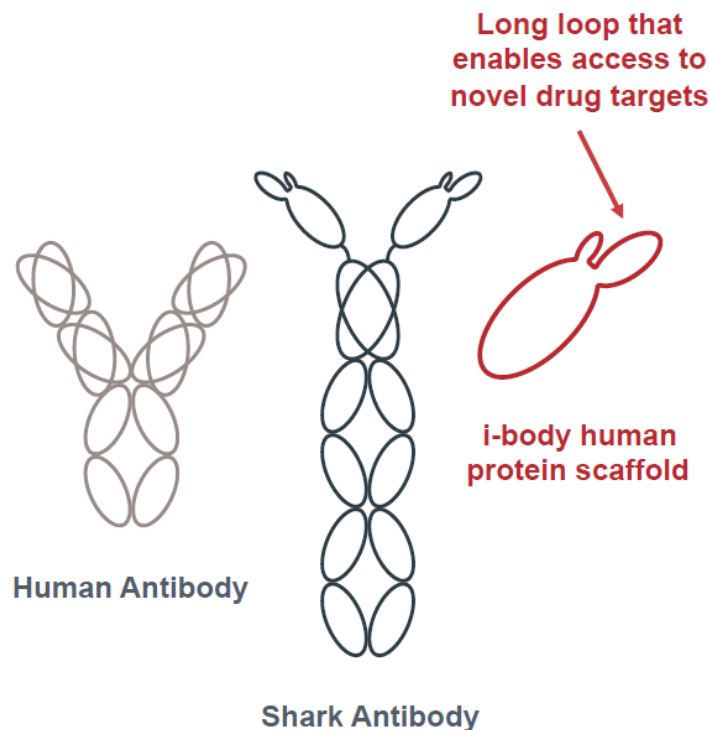
1. Meng XM, Nikolic-Paterson DJ and Lan HY. *Nat Rev Nephrol.* 2016.

2. Yuan A, Lee Y and Choi U et al. *Am J Physiol Renal Physiol*, 2015.



I-body: Human Protein Scaffold

- › Proteins that mimic the shape of shark antibody binding domain and engineer their key stability features into human proteins.



Griffiths K, Dolezal O and Cao B et al. *J Biol Chem.* 2016.

Advantages of i-body

- **High target specificity** and **high affinity**.
- **Small proteins**; 10% the size of a typical human antibody.
- **Highly stable** to proteases, high temperatures and low pH.
- **Long loop** that can bind to a diverse range of therapeutically relevant targets including those that are difficult for current antibody therapies such as CXCR4.
- **Human protein** – reduced risk of immune response.

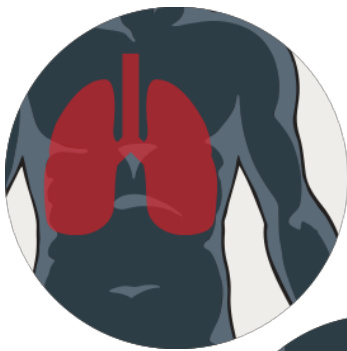


Griffiths K, Dolezal O and Cao B et al. J Biol Chem. 2016.



Lead i-body candidate AD-114

- Binds CXCR4 with high specificity and affinity.
- Has anti-fibrotic effects in lung, liver and eye fibrosis.
- Has been taken to clinical trial for idiopathic pulmonary fibrosis (IPF).
- However, the role of AD-114 in renal fibrosis has not been studied.



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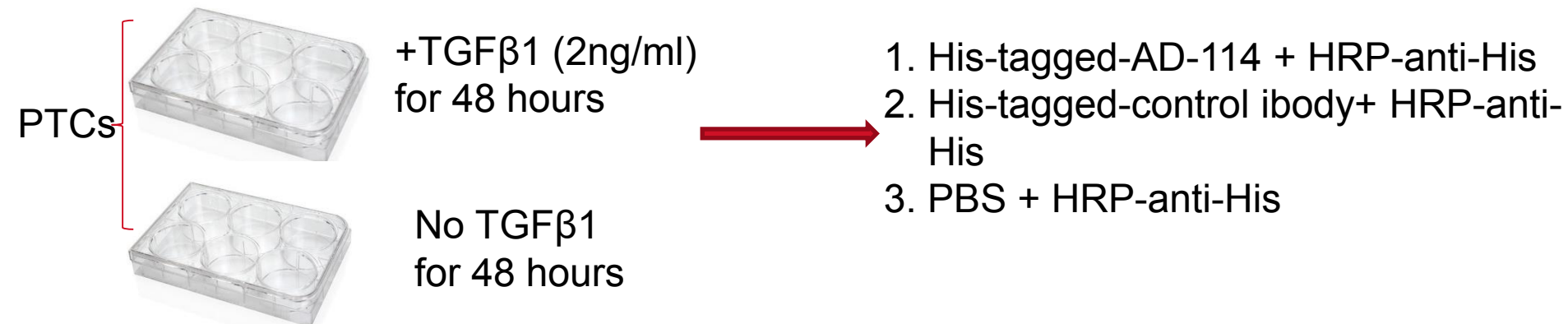


Aim

To define the role of i-body AD-114 in renal fibrosis.

Methods

- › 1: Immunohistochemistry(IHC) on kidney biopsies from: Three mouse models:
 - UUO-
 - folic acid (FA)-
 - Streptozotocin(STZ)-induced DNDN patients
- › 2: Immunocytochemistry (ICC) and Western-blot (WB) to examine the binding of AD-114 with CXCR4 in PTCs.



- › 3: Using WB to examine secretory fibronectin (FN) and collagen 4 (Col 4) in cell culture supernatant.



Results

Upregulation of CXCR4 in diabetic renal fibrosis

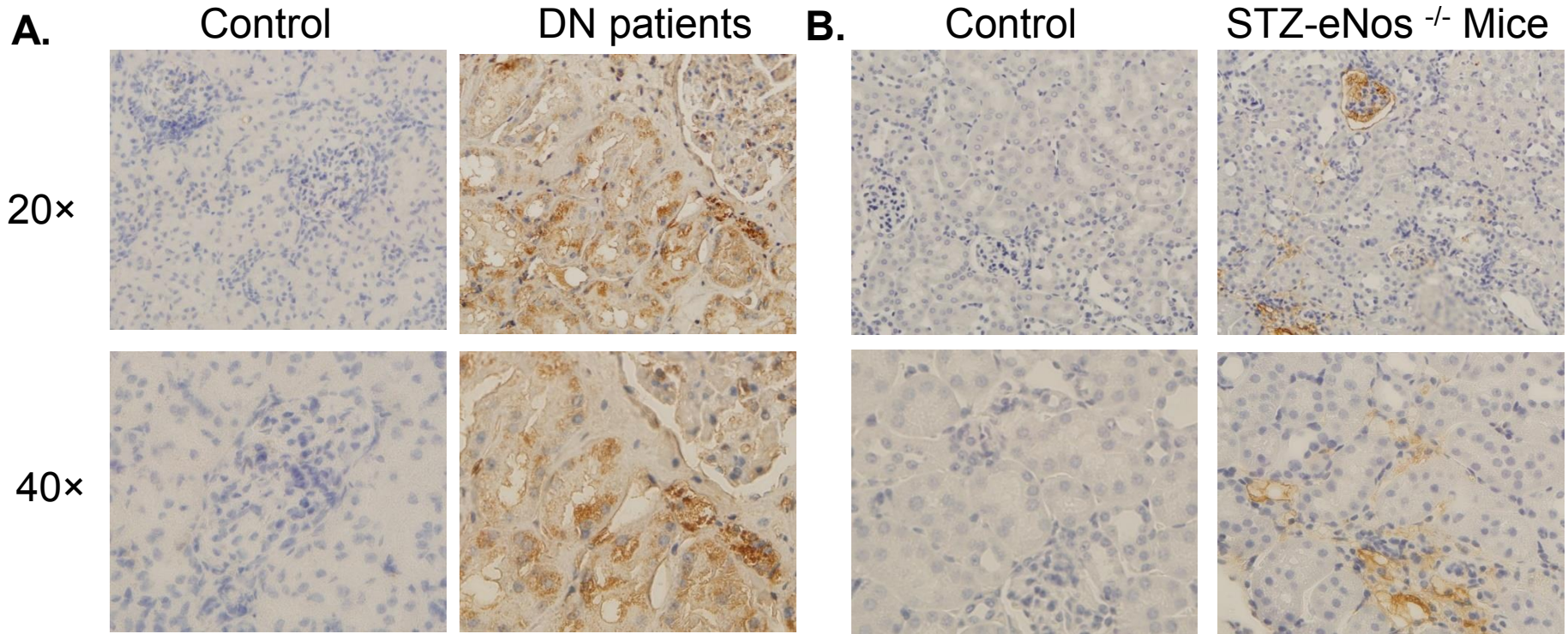


Fig 1: CXCR4 expression is examined in kidney biopsies from (A) DN patients or (B) STZ-eNos^{-/-} mice by IHC.



Upregulation of CXCR4 in UUO- and FA-induced renal fibrosis

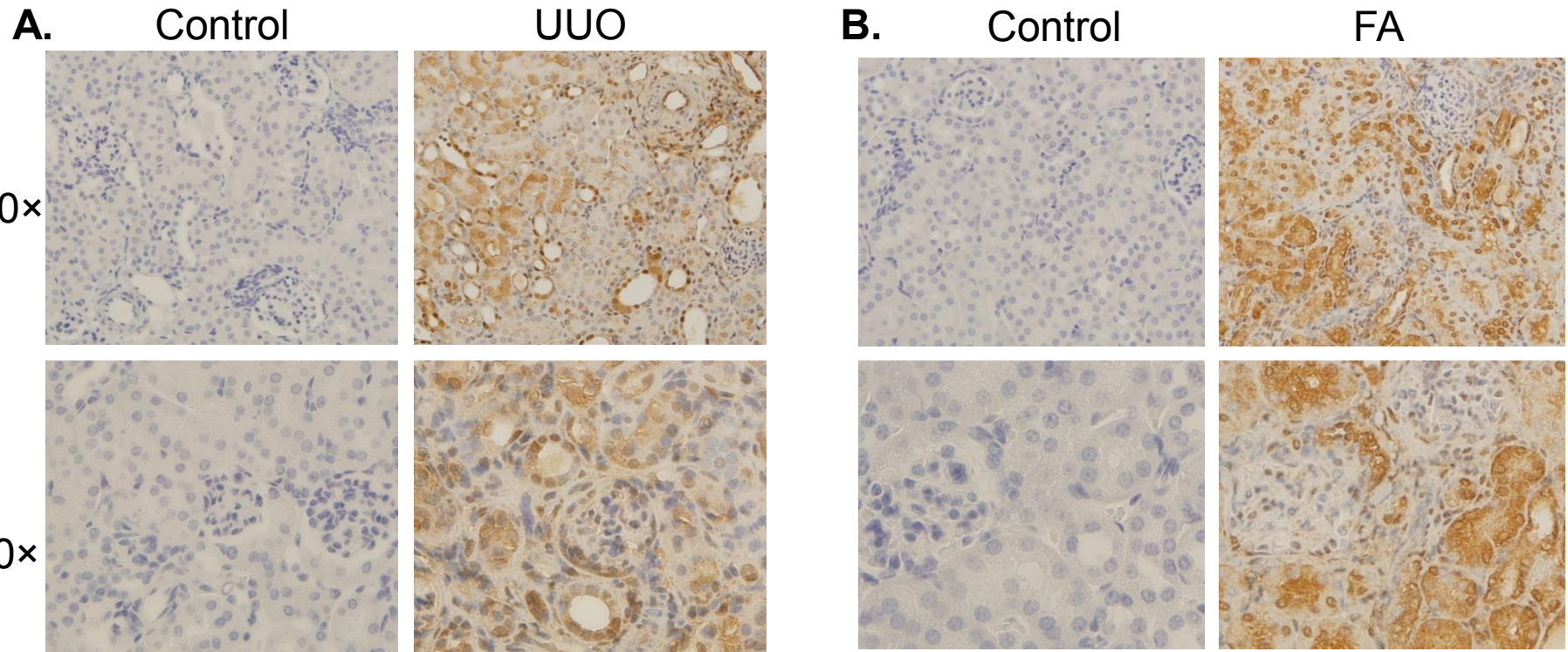


Fig 2: CXCR4 expression was examined in kidney biopsies from (A) UUO- or (B) FA-mice by IHC.



AD-114 binds TGF β -induced CXCR4 in PTCs

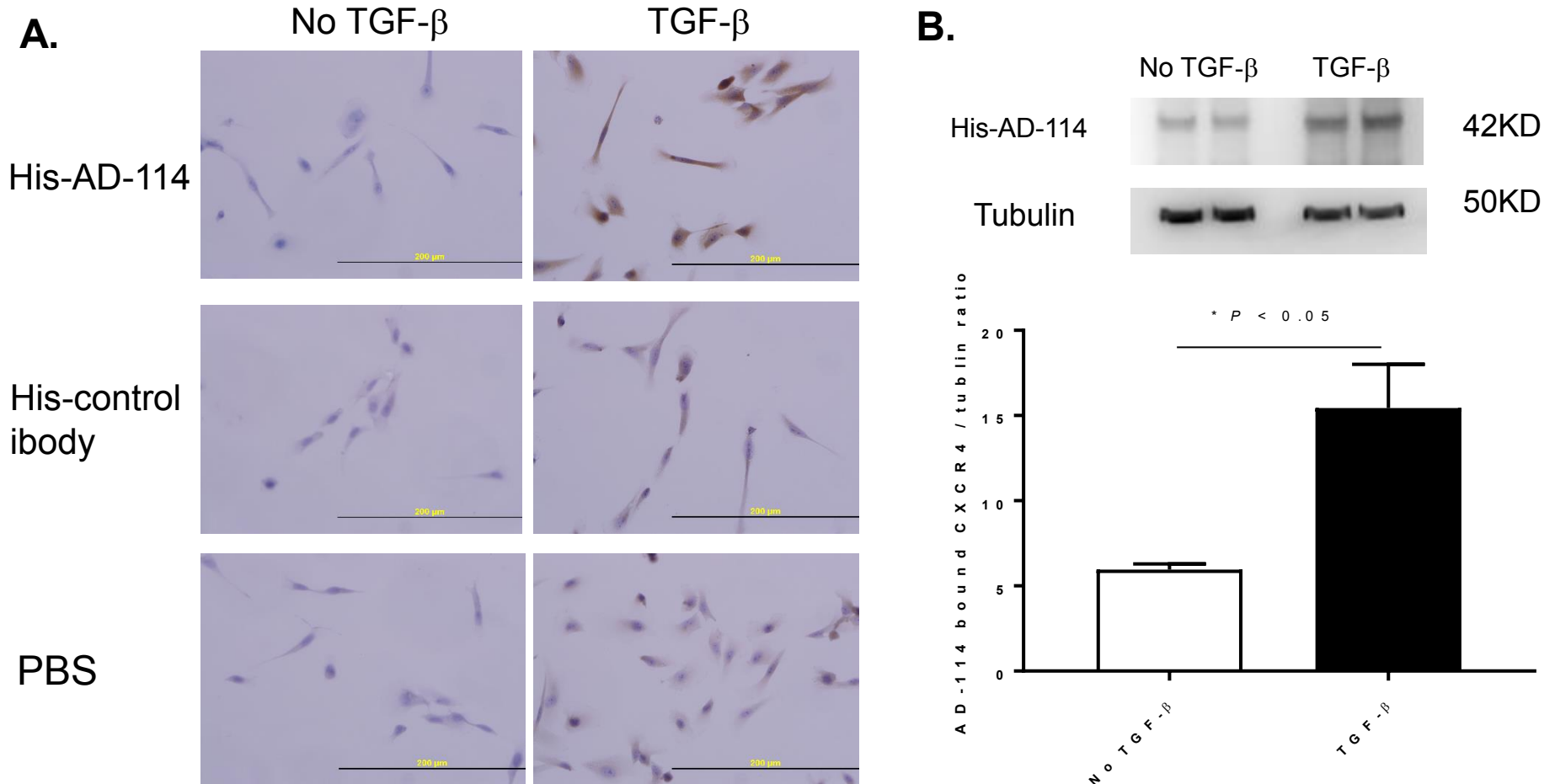


Fig 3: i-body bound CXCR4 in PTCs exposed to TGF- β . Human PTCs were incubated with/without TGF β (2ng/ml) for 48 hours. A. Cells were grown on glass slides. Cells were then washed, fixed and analysed by ICC. (40x) B. Cell lysates were collected and analyzed by Western blot. (n=4)



AD-114 inhibits FN expression in supernatant

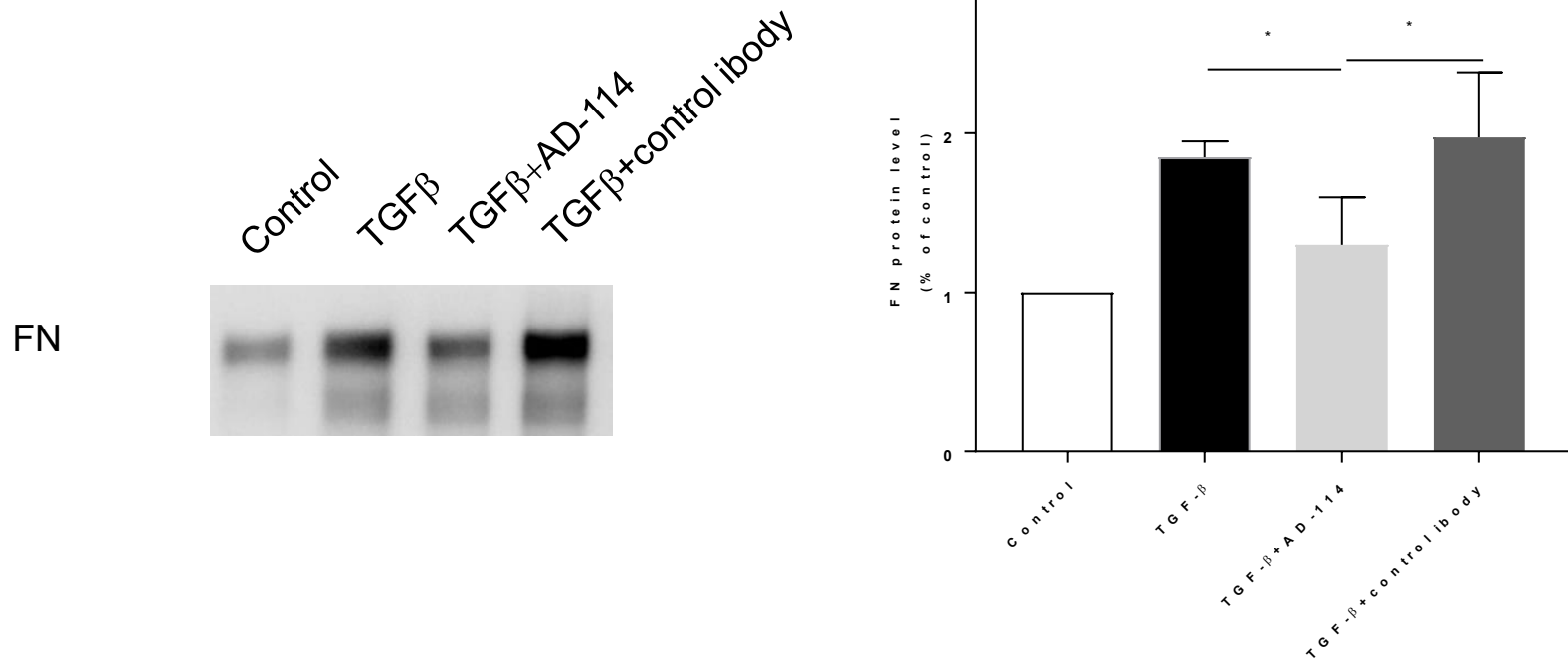


Fig 4: Ibody AD-114 (3μM) suppressed TGFβ-induced overexpression of FN compared to a negative control i-body. Supernatants were collected and FN level was analysed by western-blot. * $P < 0.05$, $n = 3$. (Dosage response and cytotoxicity of AD-114 were determined initially using MTS assay).



AD-114 inhibits COL 4 expression in supernatant

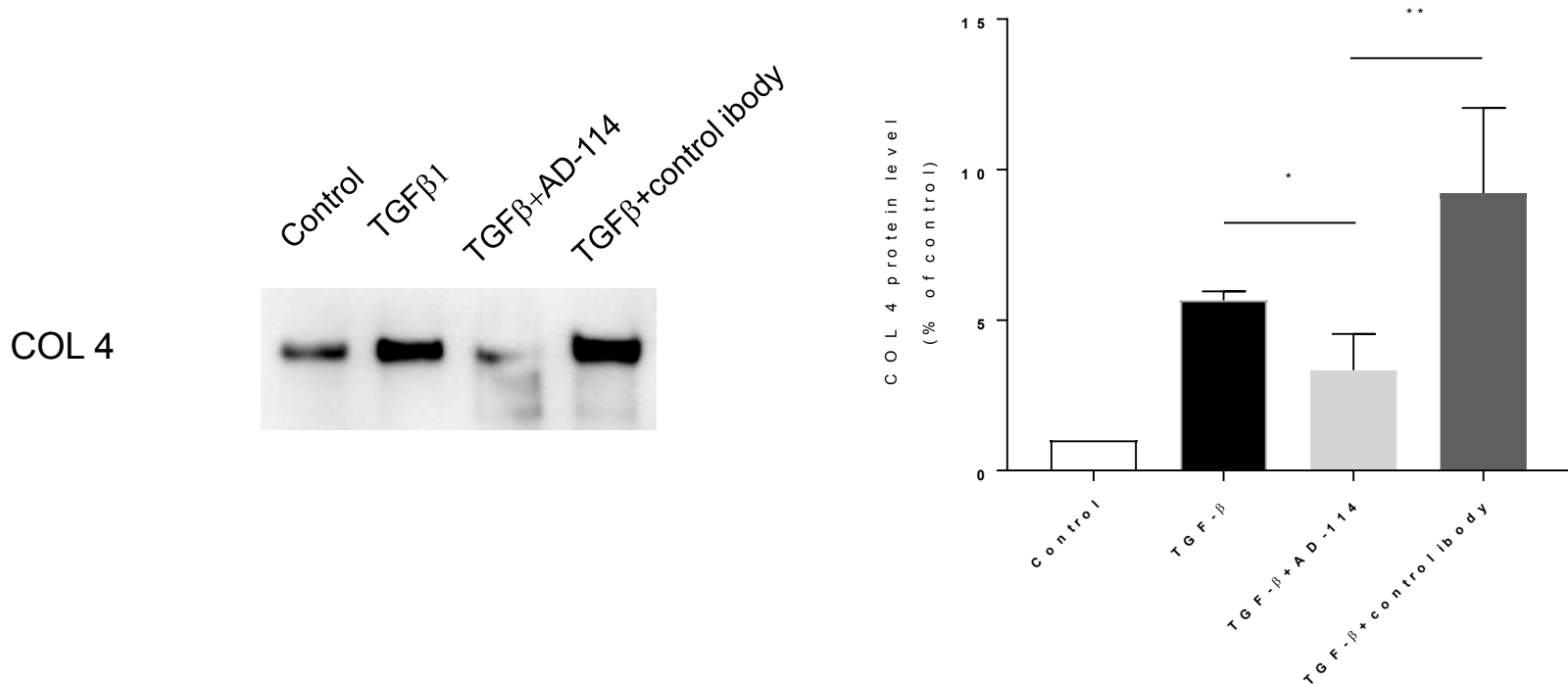
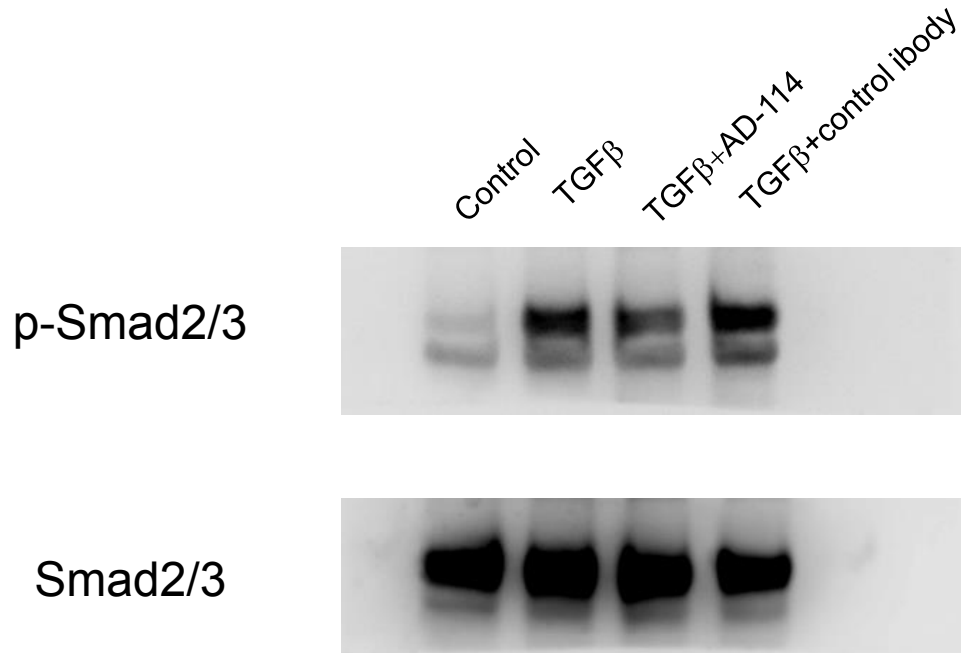


Fig 5: Ibody AD-114 (3 μ M) suppressed TGF β 1-induced overexpression of COL 4 compared to a negative control i-body. Supernatants were collected and COL 4 level was analysed by western-blot. * P <0.05, n =3. * P <0.05, ** P <0.01, n =3.



AD-114 inhibits phosphorylation of Smad2/3

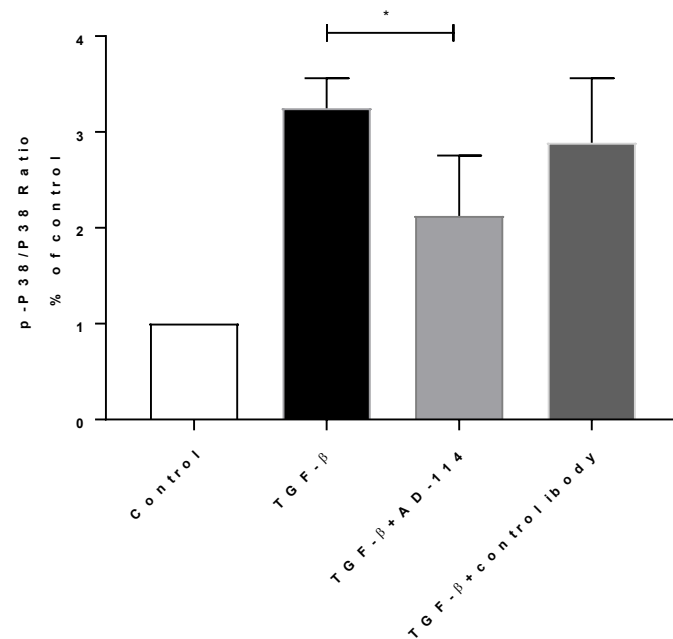
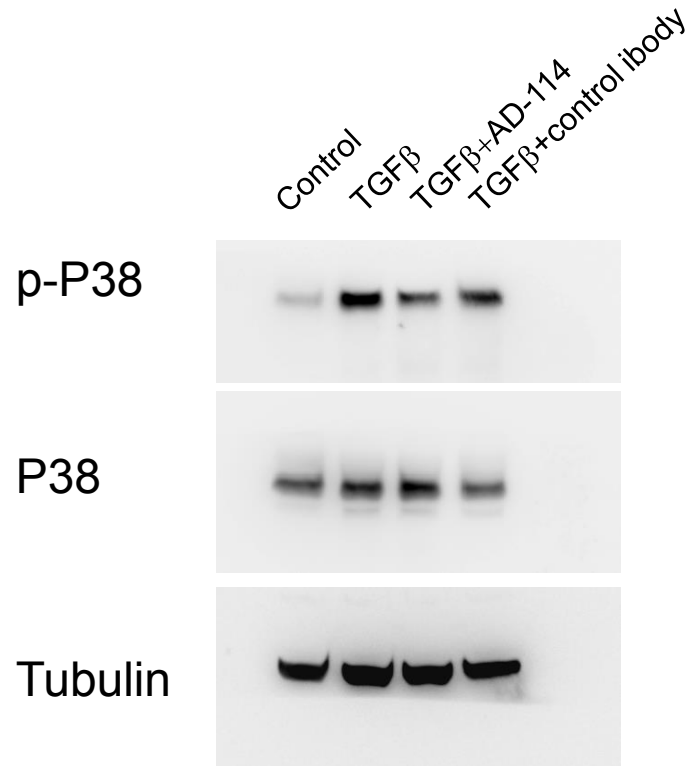
p-Smad2/3 and Smad2/3





AD-114 inhibits phosphorylation of P38

P38



Conclusions

- › (1) CXCR4 is significantly upregulated in fibrotic kidneys of animal models and human.
- › (2) AD-114 can bind TGF- β induced CXCR4 in human renal PTCs.
- › (3) AD-114 inhibits TGF β -induced overexpression of FN and Col 4 and compared to negative control i-body.
- › (4) AD-114 reduces the downstream p-Smad2/3 and P38 signaling.

Acknowledgment

To Supervisor team: A. Pro Xin-Ming Chen,

Pro. Carol A. Pollock

Dr Chunling Huang

Adalta: Sam Cobb (AdAlta Managing director & CEO)

Michael Foley(AdAlta CSO)

All Colleagues in Renal group