MICHIGAN MEDICINE
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Precision Medicine approach identifies patients with IgA nephropathy at risk for progression using endothelin activation signatures

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MICHIGAN KIDNEY TRANSLATIONAL MEDICINE CORE

CHINOOK THERAPEUTICS

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Disclosures

- Funding from Chinook Therapeutics

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Background and Aims

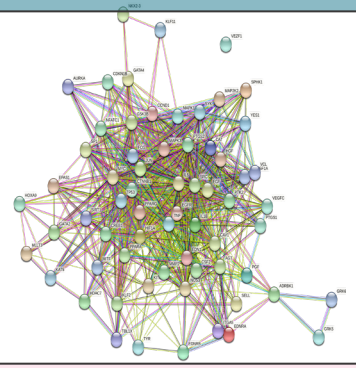
- IgA nephropathy (IgAN) is the most common glomerulonephritis globally, with up to 40% of patients at risk of progressing to ESKD
- The aim of this study is to
  - Identify intra-renal transcriptional signatures of endothelin-1 (ET1)-activation network
  - Generate an ET1 activation score
  - Characterize the cellular location in the kidney of the signature genes
  - Relationship of ET1 activation and phenotype
  - Stratify patients at high risk of IgAN progression
  - Experimental evaluation of ETA receptor antagonist atrasentan treatment on the ET1 activation score in mesangial cells and animal models

Methods overview

Pathway Databases

EDN1/EDNRA network

Endothelin-1 Signature (60 genes identified)



Human Mesangial Cell Culture

Treatment

(ET1 +/- atrasentan)

Experimentally derived Endothelin-1 activation signature

ET1 activation score with clinical measures and outcomes

Cellular localization of signature in Single cell

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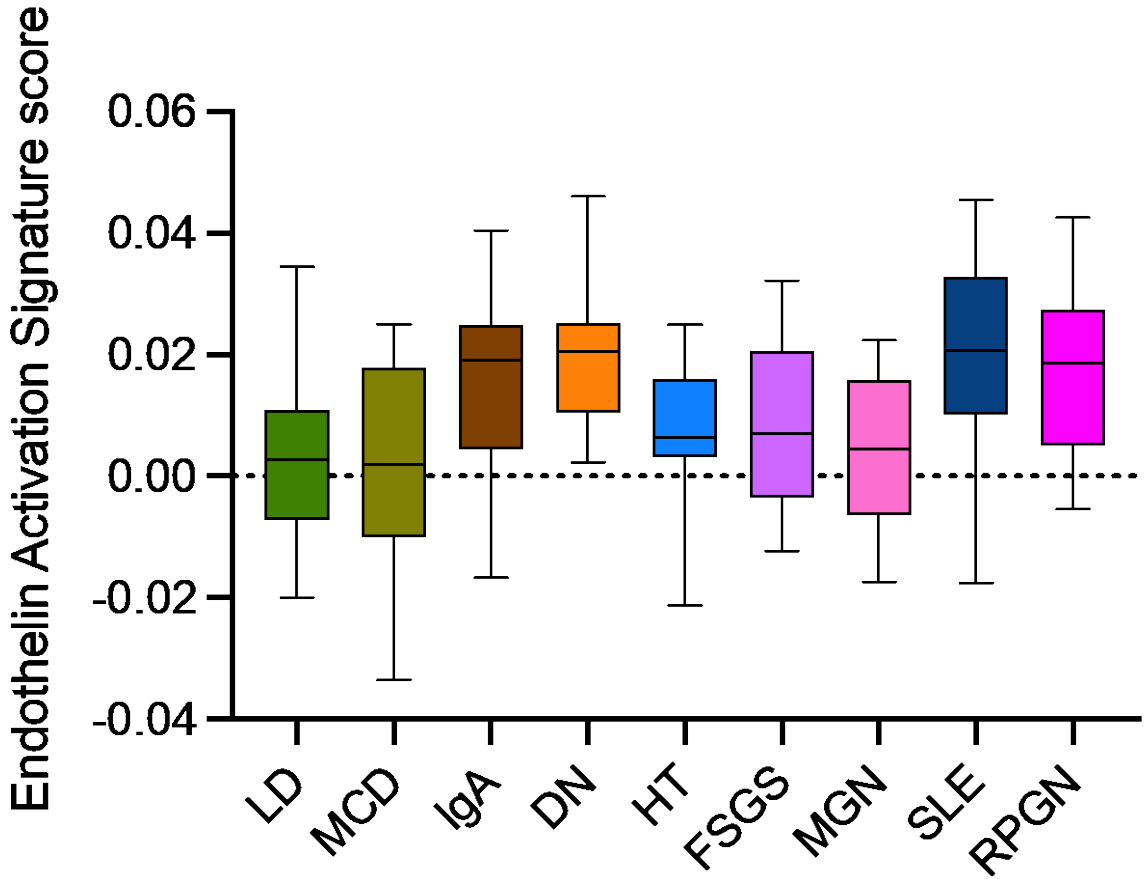
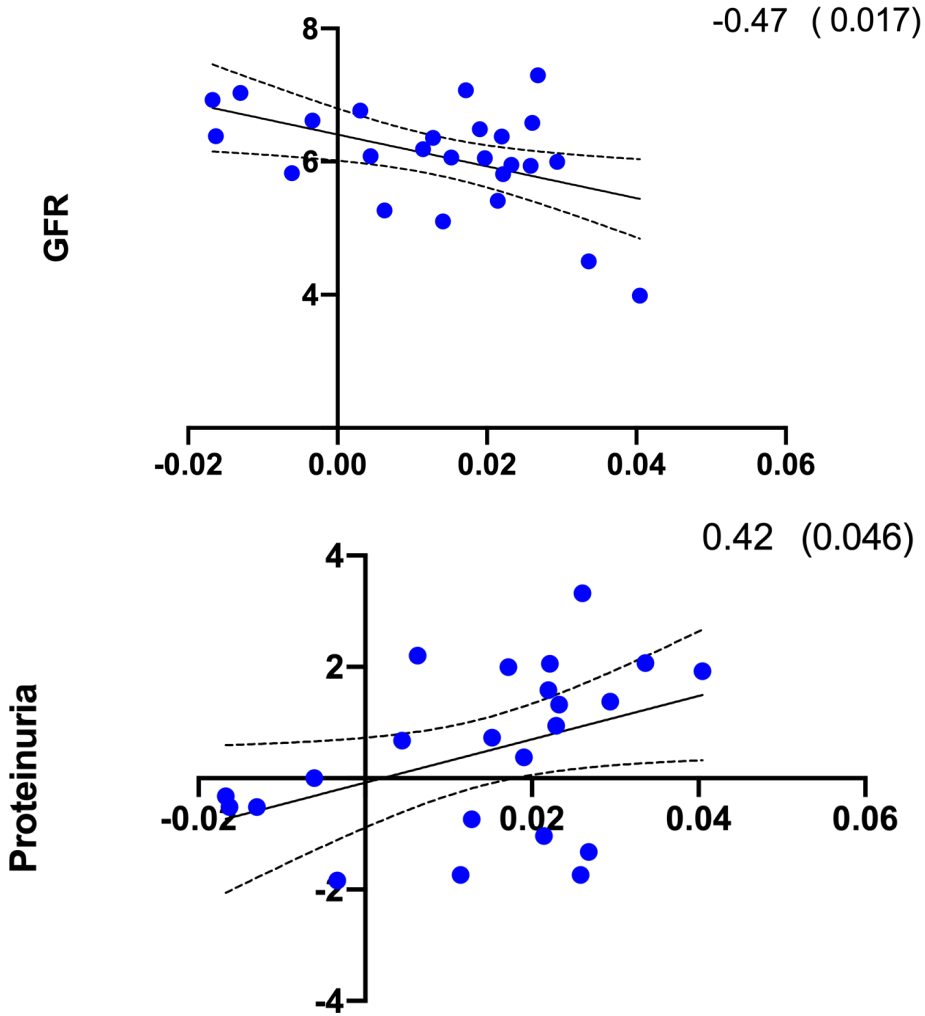
ET1 activation in glomerular diseases (ERCB cohort)

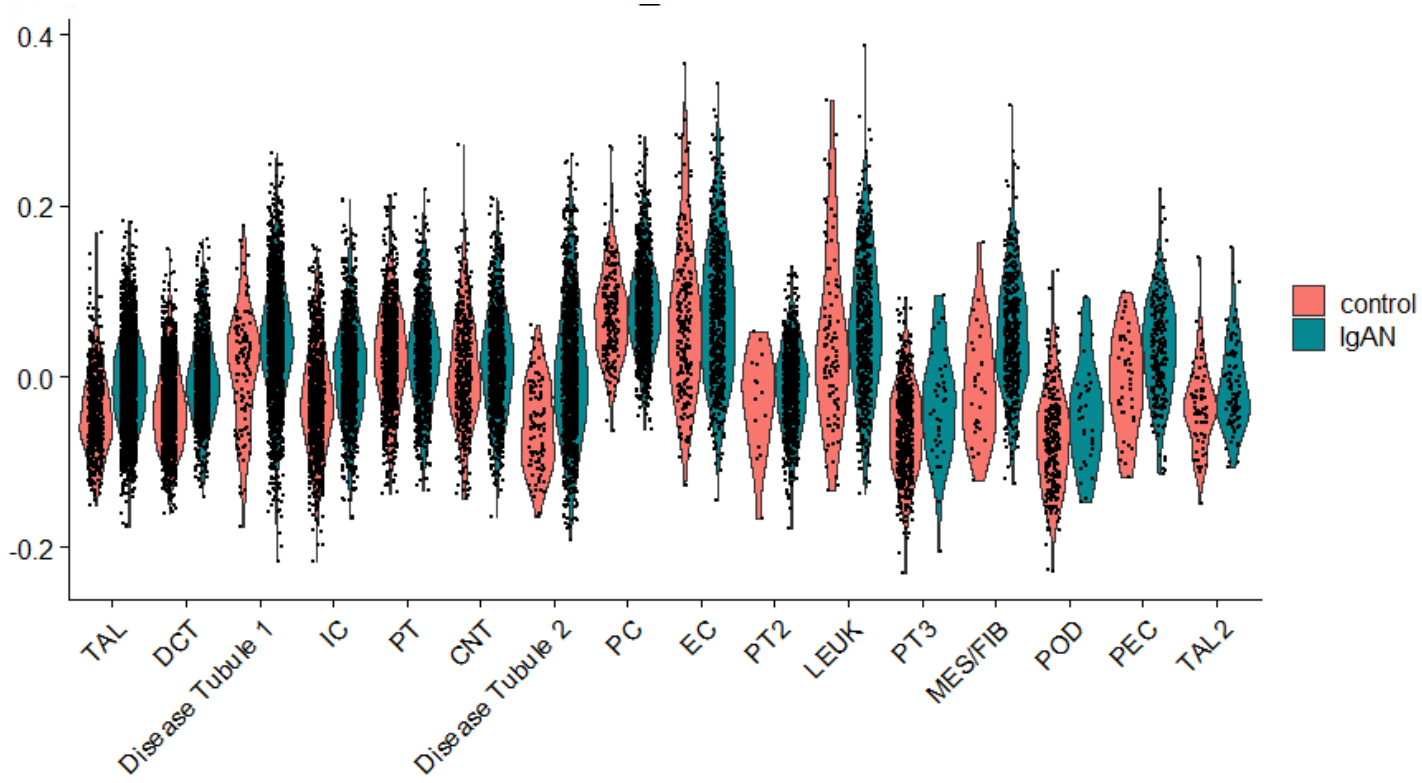


ET1 activation scores strongly correlated with GFR/Proteinuria in IgAN patients



ET-1 activation signatures in Single cell profiles derived from IgAN patients

- ET1 activation scores in cell cluster profiles from IgAN patients*
- The scores show higher enrichment in the mesangial cells, endothelial cells and Myeloid cells



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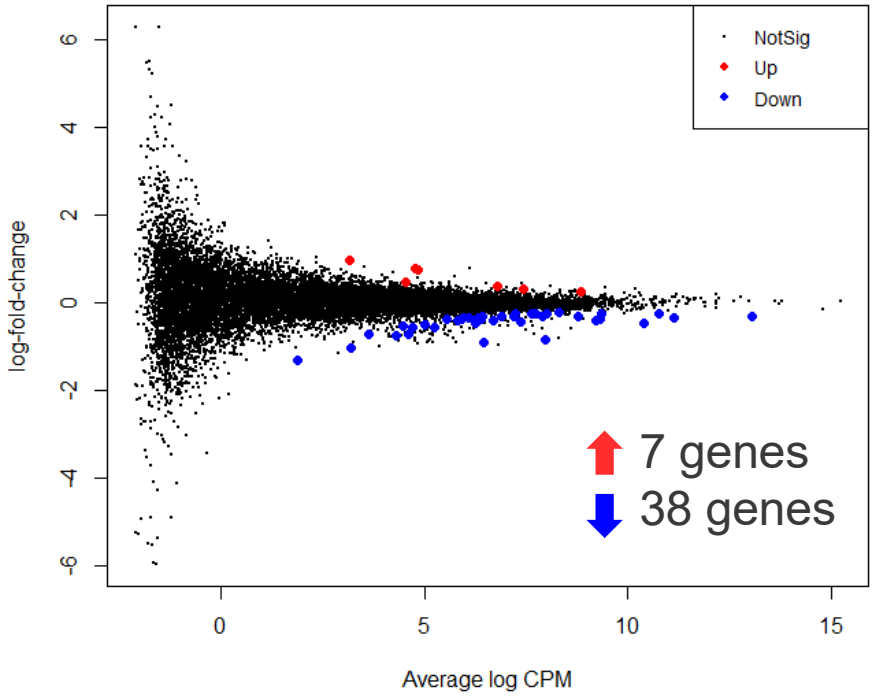
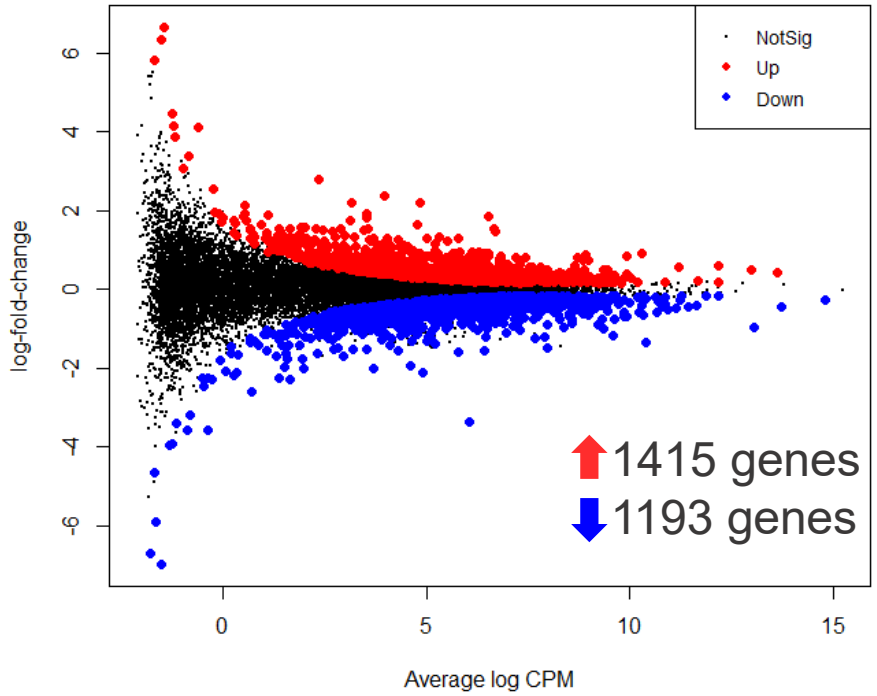
*Tang R, Meng T, Lin W, Shen C, Ooi JD, Eggenhuizen PJ, Jin P, Ding X, Chen J, Tang Y, Xiao Z, Ao X, Peng W, Zhou Q, Xiao P, Zhong Y, Xiao X. A Partial Picture of the Single-Cell Transcriptomics of Human IgA Nephropathy. Front Immunol. 2021 Apr 16;12:645988.

Atrasentan treatment shows dose-dependent blockade of ET-1 response in mesangial cells

Atra 1 nM (+ ET1) vs. ET1 (+DMSO)



Atra 25 nM (+ ET1) vs. ET1 (+DMSO)



Study design:

- In triplicates, cultured primary human renal mesangial cells from ScienCell were treated with ET-1 (4 nM) in the presence or absence of atrasentan (1 nM and 25 nM).
- 0.1% DMSO acted the vehicle control group.
- RNA-seq was performed 24 hours post-treatment.

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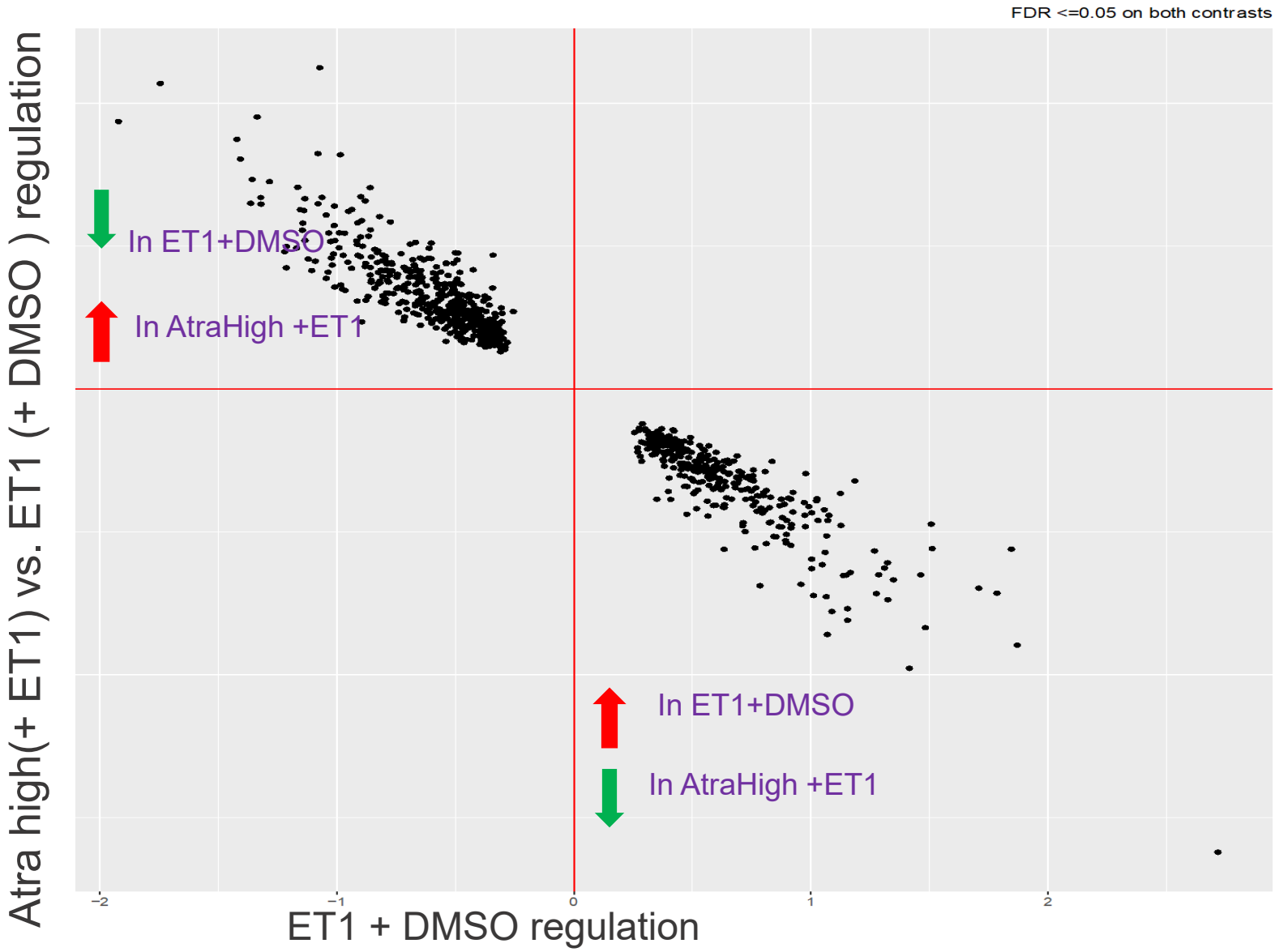
Reversal of ET-1 Gene Regulation by Atrasentan



- Gene set enrichment analysis in MCs revealed up-regulation of cell proliferation, inflammatory and fibrotic networks, with ET1 treatment, which were blocked by atrasentan

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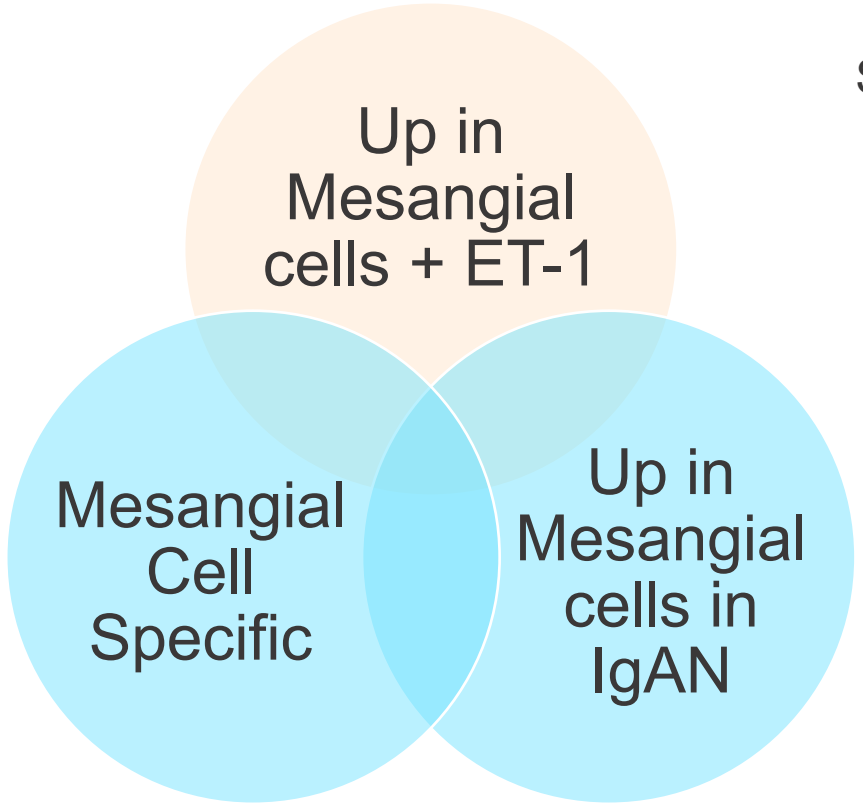
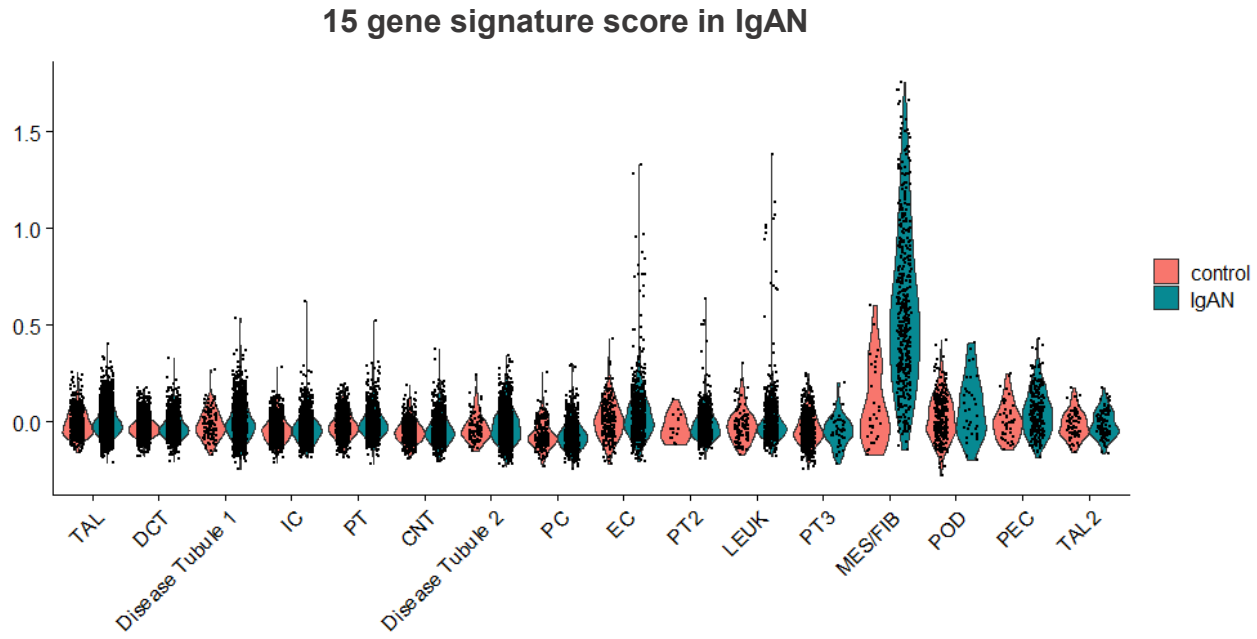
An approach to refine ET-1 activation signature for mesangial cell specificity



Strong activation of the ET1 signature in IgAN patient mesangial cells



Other datasets –
Bulk and snRNA-seq
In vivo models +/- Atrasentan
In vitro models +/- ET-1/Atrasentan

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Conclusions

- Endothelin (ET) A receptor activation results in mesangial cell activation, proteinuria, inflammation, and fibrosis, all considered hallmarks of IgAN progression, suggesting the potential for therapeutic benefit of ETA antagonists

- ET1 transcriptional signatures show activation in IgAN patients, including in mesangial cells, and were significantly associated with clinical progression

- ET1 mediated transcript changes in mesangial cells, including hallmarks of mesangial cell activation (proliferation, inflammation and fibrosis) were dose-dependently inhibited by atrasentan