Tilvestamab, a function-blocking monoclonal antibody inhibitor of AXL RTK signalling, limits the onset of renal fibrotic changes in human kidneys ex vivo

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Background

- Kidney fibrosis is characterized by accumulation of myofibroblasts with subsequently substantial extracellular matrix (ECM) deposition which directly correlates to progressive CKD, secondary to inflammatory, immunologic, obstructive or metabolic causes.

- The receptor tyrosine kinase AXL is found upregulated in fibrotic human renal tissue and regulates and modulates key fibrogenic pathways.

- Pharmacological modulation of Axl by a small molecule inhibitor inhibits fibrosis development and inflammation in multiple pre-clinical models of fibrosis of kidney (UUO), liver (CCl4/HighFatDiet), and lung (Asthma, Bleo, IPF, smoke induced PF) supporting AXL as a promising target for the pharmacologic intervention of fibrosis.

- Tilvestamab is a novel function blocking fully humanized anti-Axl antibody currently in Phase Ib first-in-patient trial.

Hypothesis: Axl inhibition by the anti-AXL antibody tilvestamab blocks development of kidney fibrosis.
Experimental model: Human *ex vivo* kidney tissue

**Study outline:**
n= 6 PCKS from one individual human donor kidney for each experimental test condition

**Test agents:**
- **Tilvestamab** - Anti-AXL antibody (1 – 125 μg/mL)
- **Enalapril** - Angiotensin-converting enzyme (ACE) inhibitor commonly used in clinical treatment of chronic kidney disease (0.15 μM; equivalent to average clinical exposure)

Tilvestamab inhibits markers of myofibroblast activation and synergizes with the ACE inhibitor enalapril

Tilvestamab dose-dependently reduce tissue αSMA, the marker of myofibroblast activation

Low dose tilvestamab synergize with the ACEi enalapril and reduce collagen 1a1 secretion and tissue αSMA

Alpha-Smooth Muscle Actin (αSMA) was stained by IHC in FFPE slides 72 hrs after drug administration. Data presented as mean % area positive of tissue (± SEM) for α-SMA. Significance by one-way ANOVA, ****p<0.0001

Secreted Collagen 1a1 was measured in supernatants 72 hrs after drug administration. n=3 technical replicates, mean ± SEM is shown.
Conclusions

- Tilvestamab inhibits activation of myofibroblasts, a key cell population in the pathogenesis of fibrosis.

- In combination, lower doses of tilvestamab and enalapril appeared to have more potent in vitro anti-fibrotic effects than either agent alone.

- These findings warrant further investigations by
  1. Confirmation of combination effect in additional models of CKD.
  2. Evaluation of the mechanism of action and the interaction between inhibition of Axl signalling and modulation of the renin-angiotensin axis.

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