NTP42 alleviates experimental pulmonary arterial hypertension and promotes beneficial right ventricular adaptation, preserving right heart function

E. Mulvaney[1], F. Renzo[1], R. Adão[2], G. Conceição[2], E. Dupre[3], C. Laurent[4], P. Mendes-Ferreira[2], C. Brás-Silva[2], B. T. Kinsella[1]

[1]ATXA Therapeutics Limited, Dublin, Ireland, [2]Faculty of Medicine, University of Porto, Portugal, [3]IPS Therapeutique Inc., Sherbrooke, Canada, [4]ToxiPharm Laboratories Inc., Sherbrooke, Canada

ATXA Therapeutics Limited
www.atxatherapeutics.com

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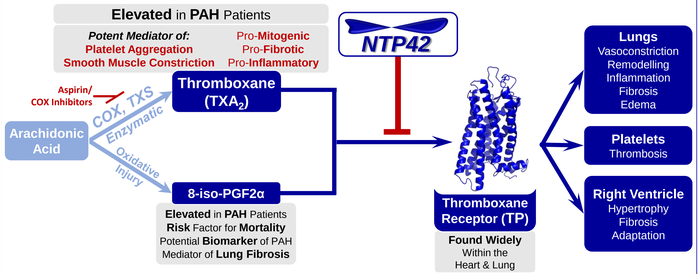
Aims

Pulmonary arterial hypertension (PAH) is a rare yet devastating disease. While characterised by pulmonary vascular remodelling and increased pulmonary vascular resistance, PAH mortality is determined by the response of the right ventricle (RV). Recent studies by us reported that the novel thromboxane A_2 receptor (TP) antagonist ***NTP42*** attenuated multiple disease hallmarks of PAH in two preclinical models of the disease (1,2).



Thromboxane (TXA_2) and 8-iso-$PGF_{2\alpha}$ (F_2-IsoP) Bind to and Activate the TP. TXA_2 Levels are Elevated in Multiple Diseases, including PAH. F_2-IsoP is elevated under various pathological settings of Oxidative Injury, including PAH, exacerbating the clinical pathology.

NTP42 has been confirmed to display **potent TP antagonist** activity; it also has excellent target **specificity**, **pharmacokinetic & drug safety/toxicology profiles**. ***NTP42*** is in development for the treatment of PAH and was recently tested in a Phase I First-in-Human clinical trial (**ClinicalTrials.gov: NCT04919863**).

The **aim** of this study was to assess the efficacy of a novel oral formulation of ***NTP42*** developed for pharmaceutical use (***NTP42:KVA4***) in the **monocrotaline (MCT)-induced and pulmonary artery banded (PAB) models** of PAH and RV dysfunction in rats, and when compared with PAH standard-of-care (SOC) drugs. The expression of the TP, the target for ***NTP42***, was also investigated in cardiac tissue from experimental models and human PAH and other RV pathologies.

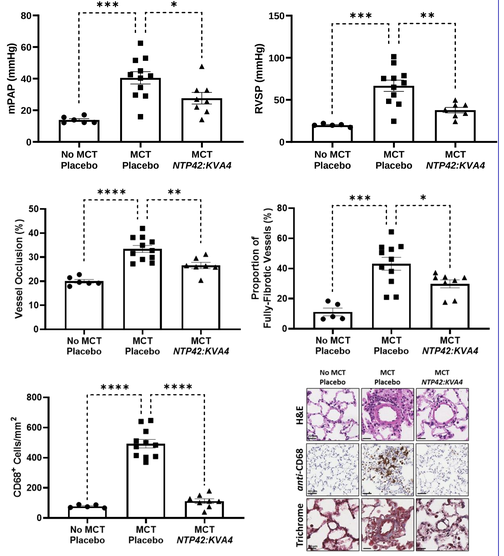
Methods

MCT-PAH was induced using a single injection of 60 mg/kg MCT, where twice-daily oral treatment with placebo or ***NTP42:KVA4*** (1 mg/kg; equivalent to 0.2 mg ***NTP42***/kg) or PAH SOC (Sildenafil, Macitentan, Selexipag or Riociguat) was started on Day 7 post-MCT and continued to Day 28. The PAB model used surgical banding of the pulmonary artery, where twice-daily oral treatment with placebo or ***NTP42:KVA4*** (1 mg/kg) or the PAH SOC Riociguat was started on Day 2 post-PAB and continued to Day 27.

Results

Cardiopulmonary Haemodynamics:

- ***NTP42:KVA4*** significantly reduced the MCT-induced rises in mean pulmonary arterial pressure (**mPAP**) and in right ventricular systolic pressure (**RVSP**).
- ***NTP42:KVA4*** led to comparable or **improved efficacy** relative to other PAH SOC therapies.



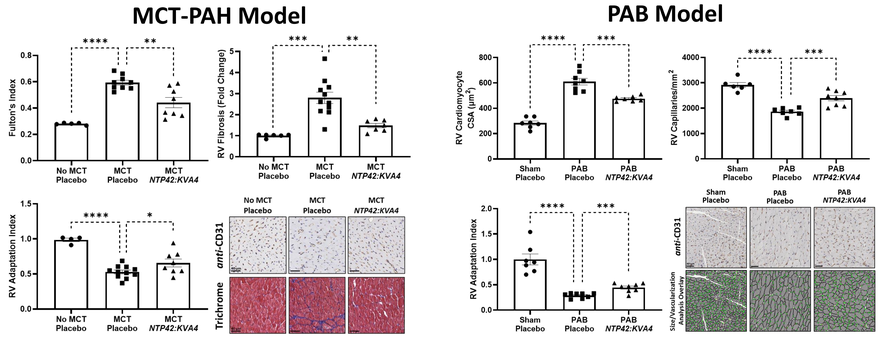
Pulmonary Pathologies:

Analysis of **pulmonary vessel remodeling**, **perivascular pulmonary fibrosis** and **$CD68^+$ macrophages** from haematoxylin and eosin (H&E), Masson's Trichrome and CD68 stained lung sections (images, see right).

- ***NTP42:KVA4*** treatment led to **highly significant reductions in vessel remodeling**.
- ***NTP42:KVA4*** **significantly reduced pulmonary fibrosis and pulmonary inflammation** (CD68+ macrophages).
- ***NTP42:KVA4*** led to comparable or **improved efficacy** relative to other PAH SOC therapies.

Right Ventricular (RV) Pathologies:

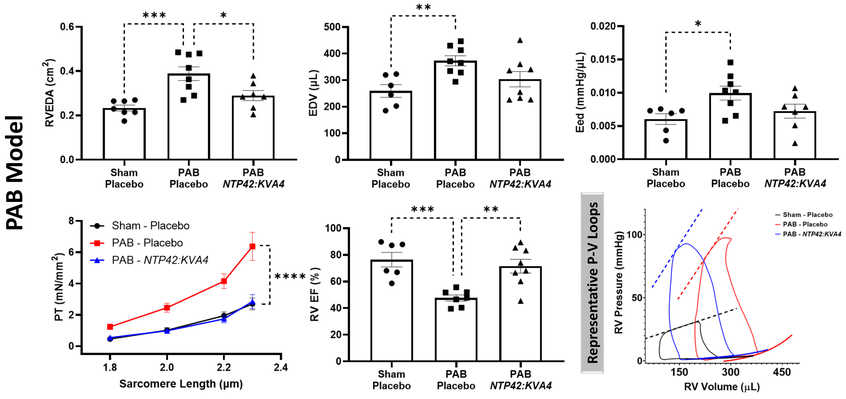
- In the **MCT-PAH** model, ***NTP42:KVA4*** **significantly reduced cardiac hypertrophy (Fulton's Index)** and **RV Fibrosis**. ***NTP42:KVA4*** also **significantly reduced** the **Index of RV Adaptation** (Level of $CD31^+$ RV Vascularization divided by RV Cardiomyocyte Size).
- In the **PAB** model, ***NTP42:KVA4*** also **significantly reduced RV Cardiomyocyte Size** and **increased RV** Vascularization leading to improved **RV Adaptation**.
- ***NTP42:KVA4*** led to comparable or **improved efficacy** relative to other PAH SOC therapies in both models.



*/**/***/**** - P<0.05, P<0.01, P<0.001, P<0.0001 vs MCT Only Control or PAB-Placebo

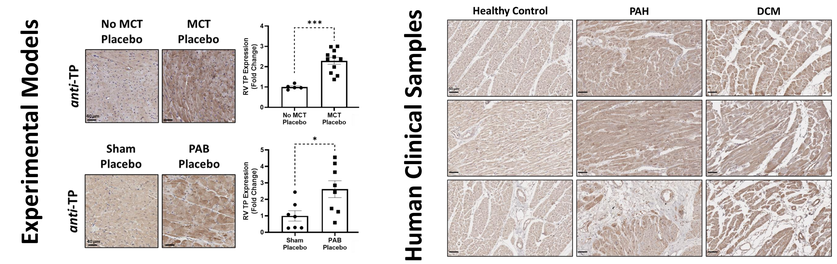
RV Echocardiogram, Pressure-Volume Loop & Isolated Cardiomyocyte Analysis:

- ***NTP42:KVA4*** improved **RV geometries** (RV end-diastolic area, RVEDA, and end-diastolic volume, EDV) and **contractility** (end-diastolic elastance, Eed), normalized **RV passive tension (PT) development**, and significantly increased **RV ejection fraction (RV EF)**.
- ***NTP42:KVA4*** led to **improved efficacy** relative to Riociguat (a PAH SOC) in this PAB model.



Target Receptor (TP) Expression:

- Upregulation of **TP expression** in RV tissue from both the MCT-PAH and PAB **experimental models** and in **clinical PAH** and other **RV pathologies** (*e.g.,* dilated cardiomyopathy, DCM) was observed.



Conclusions

- ***NTP42:KVA4*** alleviates **pulmonary pathologies**, promotes **beneficial RV hypertrophy**, **and improves cardiac function** in experimental PAH and RV dysfunction models.
- Expression of the TP (target receptor for ***NTP42***) is **significantly upregulated** within the RV in experimental models and in clinical samples, highlighting the importance of this largely-ignored PAH target **ripe for pharmaceutical intervention**.
- The findings suggest a **cardioprotective effect** for ***NTP42:KVA4***, and its potential to be a disease-modifying therapy **in PAH and other cardiac conditions**.

Contact
ATXA Therapeutics Limited
UCD Conway Institute,
University College Dublin,
Belfield, Dublin 4, IRELAND

Email: info@atxatherapeutics.com

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References:
(1) Mulvaney, *et al.*, BMC Pulm Med, 2020. **20**(1): p. 85.
(2) Mulvaney, *et al.*, Eur J Pharmacol, 2020. **889**: p. 173658.