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# Efficacy of the novel thromboxane receptor antagonist *NTP42* alone, or in combination with Sildenafil, in the Sugen/hypoxia-induced model of pulmonary arterial hypertension


B. Therese Kinsella, Eamon P. Mulvaney, Helen M. Reid

ATXA Therapeutics Limited, Dublin, Ireland


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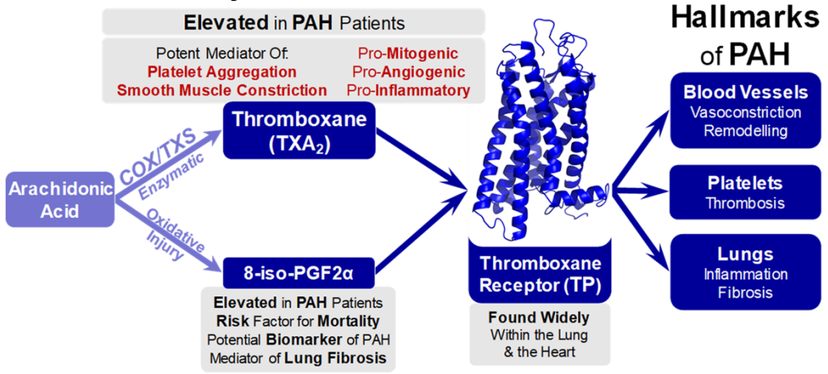
## Background & Purpose

**Pulmonary arterial hypertension (PAH)** is a devastating disease characterized by elevated pulmonary vascular resistance resulting from excessive pulmonary vasoconstriction and vessel remodeling, ultimately leading to right heart failure.

***NTP42*** is a **novel antagonist** of the thromboxane (TX)$A_2$ receptor (TP), currently in development for the treatment of PAH.

### The **TP** is a **Key Driver** of **PAH**




Mechanistically, **TP antagonists should treat most of the hallmarks of PAH**, including inhibiting the excessive vasoconstriction and pulmonary artery remodelling, *in situ* thrombosis, fibrosis and inflammation.

***NTP42*** has been confirmed to display **potent TP antagonist** activity; it also has excellent target **specificity**, **pharmacokinetic & drug safety/toxicology profiles**.

The **aim** of this study was to evaluate the **effects of *NTP42*** when used alone or as a dual-therapy, in combination with the standard-of-care (SoC) drug Sildenafil, using the **Sugen/hypoxia-induced model** of PAH in rats (Wistar Han).

## Methods

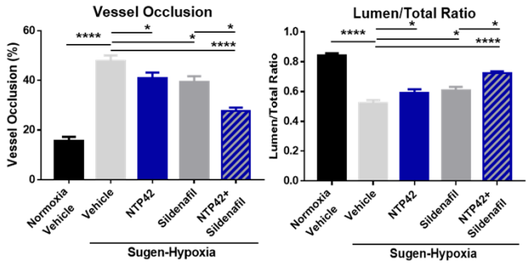

**PAH** was induced in rats by bolus injection of Sugen5416 (Su; 20 mg/kg, s.c) and exposure to hypoxia (Hx; 10% $O_2$) for 21 days. Sham control rats did not receive Su and were kept in normoxia. All rats were then returned to normoxia; treated for 28 days with either drug vehicle, ***NTP42*** (0.05 mg/kg PO, BID), Sildenafil (50 mg/kg PO, BID), or ***NTP42***+Sildenafil (0.05 + 50 mg/kg PO, BID, respectively).

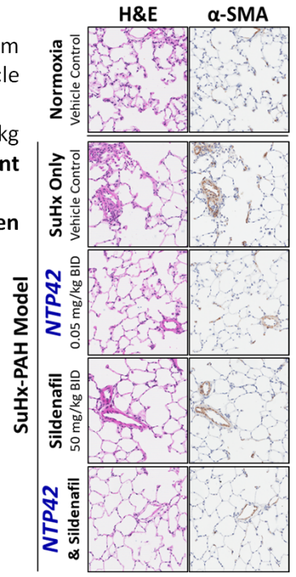
## Results

### Pulmonary Vascular Remodeling

Analysis of **pulmonary vessel remodeling** from haematoxylin and eosin (H&E) and α-smooth muscle actin (SMA) stained lung sections (see right).

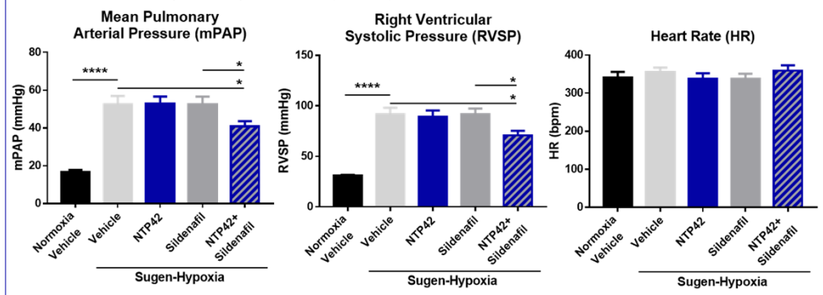
- ***NTP42*** (0.05 mg/kg BID) and Sildenafil (50 mg/kg BID) mono-therapy resulted in **significant reductions in vessel remodeling** (see charts).
- **Combined** use of ***NTP42***+Sildenafil showed **even greater benefits**.



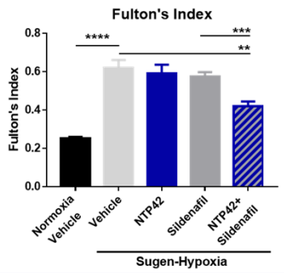

### Pulmonary & Cardiac Haemodynamics

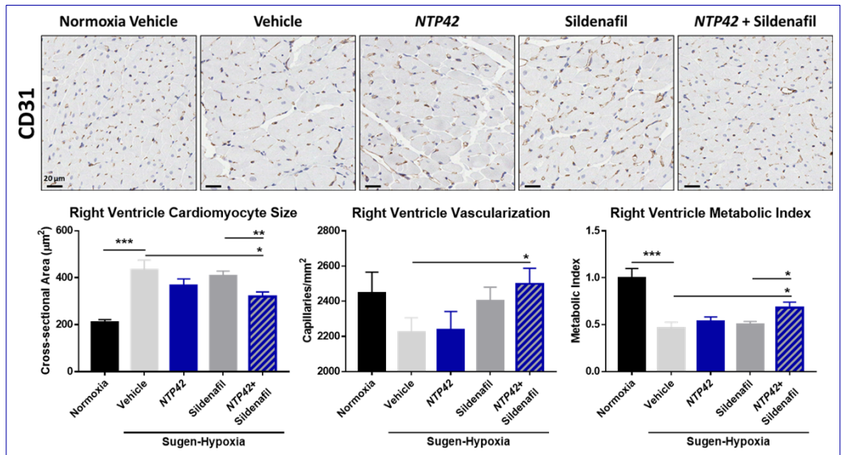
- **Combined** use of ***NTP42***+Sildenafil in **dual-therapy** significantly reduced the SuHx-induced rises in mean pulmonary arterial pressure (mPAP) and in right ventricular systolic pressure (RSVP).




### Right Ventricular Hypertrophy

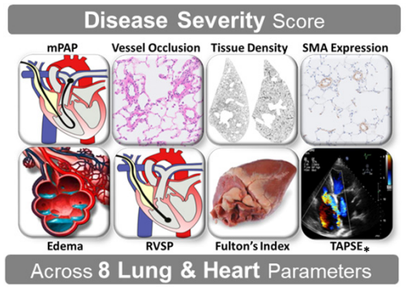
- ***NTP42***+Sildenafil also **significantly reduced** the increase in **cardiac hypertrophy (Fulton's Index)**.
- ***NTP42***+Sildenafil treatment also **reduced cardiomyocyte size** and increased levels of **right-ventricular vascularization** (CD31⁺ capillaries).
- **Metabolic Index**, a measure of metabolic supply (vascularization) and demand (cardiomyocyte size), showed that ***NTP42***+Sildenafil promotes a **beneficial adaptive ventricular hypertrophy**.



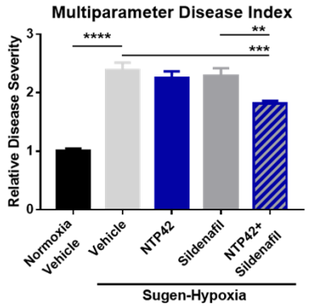




### Multiparameter Disease Efficacy

A **multiparameter score** of key cardiac & pulmonary PAH disease indices showed that ***NTP42***+Sildenafil when used in combination resulted in a **highly significant treatment benefit**, confirming a **synergistic effect** of ***NTP42*** with Sildenafil.




* TAPSE, Tricuspid Annular Plane Systolic Excursion




## Conclusions

- Assessment of key PAH disease parameters shows **equivalent or greater efficacy** of the TP antagonist ***NTP42*** compared with the SoC therapy Sildenafil when used as monotherapies in the SuHx-induced preclinical model of PAH.
- Combined use of both drugs **in dual therapy form** confirms an even greater benefit in treating or offsetting the key etiologies underlying PAH.
- These findings suggest that ***NTP42***, through its antagonism of TP signaling, may alleviate PAH pathophysiology, representing a **novel therapeutic for use** in mono-, dual-, or even triple-therapy regimens.

## Declaration of Interest

*All authors declare that they have no competing interests.*


**Contact**

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

Email: info@atxatherapeutics.com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