Apelin Agonist

EXECUTIVE SUMMARY

- Two candidate quality biased APJ agonist peptides have been generated, possessing excellent DMPK properties with the potential for subcutaneous dosing
- Both leads demonstrate reduced APJ receptor internalisation compared to endogenous APJ agonists
- Ongoing work is focussed on building the biology package to support their use for PAH focussing on haemodynamic responses and anti-inflammatory actions in both rodent and primary human tissue
- In addition to PAH, opportunities exist for an APJ agonist in other therapeutic areas such as sepsis, heart failure, diabetes and pre-eclampsia
- Differentiation: Our APJ peptides present a FIC opportunity, incorporating actions on inflammatory PAH pathophysiology in addition to precedented hemodynamic properties, with biased agonism increasing the probability of a sustained clinical response

TARGET AND DISEASE INDICATION(S)

- Lead Indication – Pulmonary Arterial Hypertension
- Estimated peak sales – $500–800m across US/5EU for IV/infusion formulation; $600-900m across US/5EU for oral formulation[1]

RATIONALE

- APJ agonists will address PAH symptomology via vasodilatory and positive inotropic effects, decreasing vascular pulmonary resistance and pulmonary arterial pressure, while increasing cardiac output.
- In addition, APJ agonists will reduce the inflammatory drivers of PAH.

TARGET PRODUCT / MOLECULE PROFILE

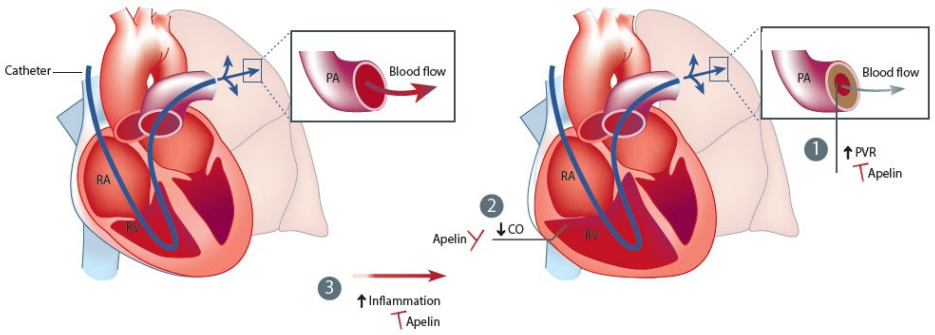
- Once daily subcutaneous peptide APJ biased agonist in combination with current SoC for the treatment of PAH

CURRENT STATUS

- Candidate Profiling

PROPOSED MECHANISTIC HYPOTHESES IN PAH

Normal physiological conditions | PAH



Pulmonary Hypertension patients display reduced plasma levels of Apelin-12 in plasma [a]

1. **Vascular resistance** – APJ agonists reduce pulmonary vascular resistance via endothelial dependent vasodilation in PAH patients.[b]
2. **Cardiac output-** APJ agonists increase cardiac output in PAH patients.[b]
3. **Inflammation** – PAH pathogenesis linked to an inflammatory response in lung. Apelin reduces pulmonary inflammation, fibrin deposition, and right ventricular hypertrophy.[c]

Sources: [1] Globe Life Sciences; [a] Arteriosclerosis, Thrombosis, Vasc Biol, 2011, 31, 814-820. [b] JACC Basic to Translational Research 2018 , 3(2) 176-186. [c] Am J Respir Crit Care Med 2010, 182(10), 1239-1250
Figure adapted from Cir Res 2014, 115(1); 115-130.

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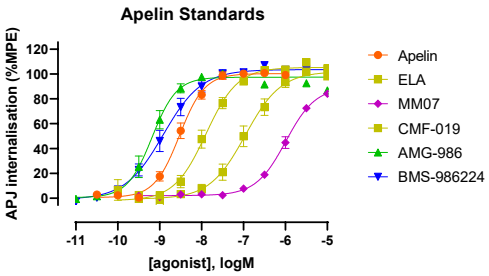
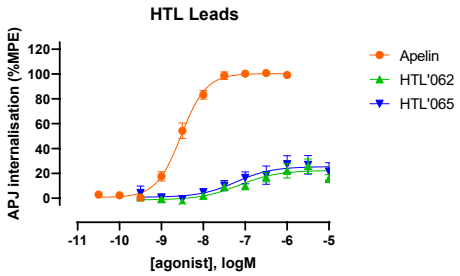
DATA SUMMARY

- Progressed 2 advanced leads, HTL'062 and HTL'065 into late lead optimisation with up to @10g material available
- Leads show G-protein biased agonism vs β-arrestin, reduced APJr internalisation and improved blood stability

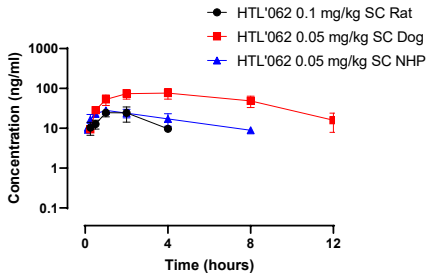
	HTL'062	HTL'065	Apelin-13	ELA
APJ cAMP pEC50 (Emax)	8.6 (55)	8.9 (61)	8.8 (117)	7.7 (100)
APJ β-arrestin pEC50 (Emax)	<5	<5	8.6 (175)	7.4 (142)
Human pKi	7.3	7.0	10.4	7.8
Rat pKi	7.0	6.7	-	-
Rat Blood Stability $t_{1/2}$ (min)	>180	>180	<5	<5
Rat in-vivo CL (mL/min/kg)	6.6	1.8	(too rapid to measure)	(too rapid to measure)
APJ internalisation pEC50 (emax)	6.8 (10)	6.9 (9)	8.6 (35)	7.8 (41)

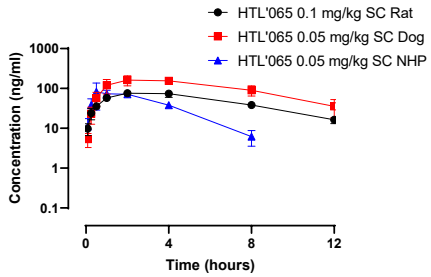
- HTL leads demonstrate significantly reduced receptor internalisation compared to all currently standards
- Consistent with medicinal chemistry design strategy to generate optimised biased apelin receptor agonists with reduced potential for desensitisation / tachyphylaxis





- Leads demonstrate good in vivo pharmacokinetic profiles consistent with support SC (or if preferred) IV dosing strategies





Opportunity to collaborate either with academia to further explore the Apelin system or with Biotech to complete characterisation of the peptide leads in hand with a view to licencing and collaboration