MONASH University

MONASH INNOVATION

ANGIOTENSIN AT_2 RECEPTOR-SELECTIVE AGONISTS AS ANTI-FIBROTIC AGENTS

A novel series of highly potent peptides that selectively stimulate AT_2 receptors (AT_2R) for development as anti-fibrotic medications. Lead compounds completely reverse elevated organ fibrosis in preclinical models and are highly stable.

- **Novel anti-fibrotic peptide lead series having the ability to reverse existing fibrotic lesions**
- **Benchmarked against "gold standard" treatments with our lead series displaying greater efficacy**
- **Proof of mechanism established as well as impressive *in vivo* efficacy**

THE CHALLENGE

Chronic and progressive tissue fibrosis can affect all major organ systems and is caused by the excess accumulation of extracellular matrix components, including collagens.

Activation of the renin-angiotensin system (RAS), oxidative stress and inflammation pathways are all involved in the aetiology of fibrosis. Among the mediators of these pathways, Angiotensin II (Ang II), acting at AT_1 receptors (AT_1R), and transforming growth factor-β (TGF-β) play important roles as major drivers of tissue fibrosis in virtually all fibrotic diseases.

Inhibition of the RAS with either ACE inhibitors or angiotensin-receptor blockers are the gold standards for improvements in cardiac and renal function which can lead to a reduction in cardiovascular mortality. However, these drug classes are associated with only modest regression of total collagen fraction. Given that marked increases in extracellular matrix occurs in most hypertensive- and metabolic-related diseases, including ageing, and thus contributes to organ dysfunction, there is an unmet need to develop more effective anti-fibrotic agents.

There is a clear need to develop new drugs that can reverse organ fibrosis and prevent the development of fibrosis in those 'at-risk'.

THE TECHNOLOGY

Monash researchers Prof. Rob Widdop, Prof. Mibel Aguilar and Prof. Mark Del Borgo have developed a unique series of AT_2R agonists that prevent and (more importantly) reverse existing cardiac, kidney and liver fibroses. These small peptides are highly potent towards AT_2R (low nM) and exhibit unparalleled selectivity for AT_2R over AT_1R (>20,000-fold). The lead series has been optimised producing a number of highly stable candidates ($t_{1/2}$ >24 hrs in biological fluids).

We have conducted numerous proof-of-concept studies supporting that selective AT_2R stimulation with our lead series is beneficial in fibrosis. Key findings are:

- Pharmacological stimulation using our unique AT_2R agonists (e.g. MU23) in mice, fed a high-salt diet to induce organ fibrosis, completely reversed established cardiac fibrosis, unlike candesartan (Fig.1), and kidney fibrosis (Fig. 2) and various pro- fibrotic (TGF-β) and pro-inflammatory markers. Reduced fibrosis is also seen in liver and in other models such as spontaneously hypertensive rats.
- AT_2R stimulation has other potential clinical applications such as arthero- and vaso-protection, and improved plaque stability in diseased vessels.
- AT_2R stimulation is also neuro-protective in spontaneously hypertensive rats when given 6 hours after stroke.

A provisional application has been filed on these novel compositions and their uses.

THE OPPORTUNITY

Monash University seeks a partner with formulation and oral delivery capability to develop our lead candidates into a new class of anti-fibrotic agent for the heart, kidney and liver, as well as for other indications. The Monash research team has extensive experience in peptide drug design, cardiovascular disease and fibrosis biology (many in-house models) and all aspects of preclinical development from cellular through to *in vivo* integrative function, together with *ex vivo* analysis.

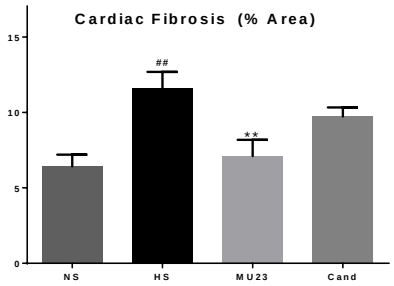

Figure 1. High salt diet (HS 5%)- induced cardiac fibrosis was reversed in FVB/N mice by a novel AT2R agonist (MU23; 100nmol/kg/day, s.c.), treated weeks 5-8 of HS (quantified using picrosirius red); NS normal salt.

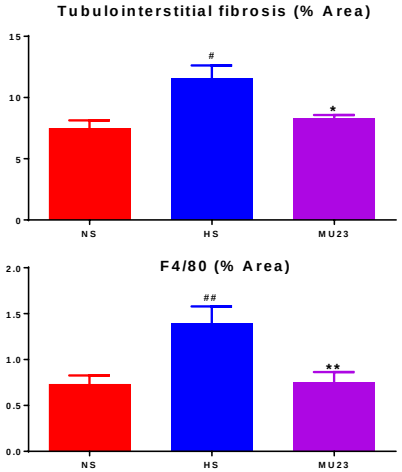

Figure 2: HS-induced kidney fibrosis (Masson's trichrome) and macrophage infiltration (F4/80) was reversed by MU23 in same protocol. #P<0.05, ##P<0.01 Vs NS; *P<0.05, **P<0.01 Vs HS

CONTACT US

Monash Innovation
T: +61 3 9905 9910
E: innovation@monash.edu

GROUP OF EIGHT AUSTRALIA

CRICOS provider: Monash University 00008C
Produced by Monash Innovation: June 2017