A novel series of highly potent peptides that selectively stimulate AT\textsubscript{2} receptors (AT\textsubscript{2}R) 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\textsubscript{1} receptors (AT\textsubscript{1}R), and transforming growth factor-\(\beta\) (TGF-\(\beta\)) 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\textsubscript{2}R agonists that prevent and (more importantly) reverse existing cardiac, kidney and liver fibres. These small peptides are highly potent towards AT\textsubscript{2}R (low nM) and exhibit unparalleled selectivity for AT\textsubscript{2}R over AT\textsubscript{1}R (>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\textsubscript{2}R stimulation with our lead series is beneficial in fibrosis. Key findings are:

- Pharmacological stimulation using our unique AT\textsubscript{2}R 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-\(\beta\)) and pro-inflammatory markers. Reduced fibrosis is also seen in liver and in other models such as spontaneously hypertensive rats.

- AT\textsubscript{2}R stimulation has other potential clinical applications such as arthero- and vaso-protection, and improved plaque stability in diseased vessels.

- AT\textsubscript{2}R stimulation is also neuro-protective in spontaneously hypertensive rats when given 6 hours after stroke.

**Intelectual Property:** Provisional application AU 2017902801 filed on these novel compositions and their uses.

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