ANGIOTENSIN AT₂ RECEPTOR-SELECTIVE AGONISTS AS ANTI-FIBROTIC AGENTS

A range of highly potent and selective ligands that stimulate AT₂ receptors for the development of anti-fibrotic medications. Lead compounds completely reverse elevated cardiac fibrosis in preclinical models. Further optimisation is needed to develop novel, safe and effective anti-fibrotic drugs.

Key findings are:

- AT₂ receptor stimulation is athero- and vaso-protective in ApoE-/- mice on a high fat diet, and provides improved plaque stability in vessels where it is difficult to reverse actual plaque burden.
- AT₂ receptor stimulation is neuro-protective in spontaneously hypertensive rats when given 6 hours after stroke.
- Pharmacological stimulation of the AT₂ receptor using our unique AT₂ receptor agonists in mice fed a high-salt diet to induce cardiac fibrosis, completely reverses the established cardiac fibrosis and TGF-β (Fig.1) with a corresponding decrease in various inflammatory markers. A reduction in fibrosis is seen in a number of other organs.

Figure 1. High salt (5%) induced marked cardiac fibrosis in FVB/N mice indicated by collagen deposition within 4 weeks. A novel AT₂ receptor agonist (~100nmol/kg/day, s.c.), treated from 4-8 weeks of high salt diet, reversed established cardiac fibrosis (quantified using polarised light microscopy with picrosirius red) and TGF-β (Western).

** THE TECHNOLOGY **

Our researchers have developed a series of unique AT₂ receptor agonists that can prevent and (more importantly) reverse existing cardiac and kidney fibrosis. These short peptides are highly potent towards the AT₂ receptor (nM) and exhibit unparalleled selectivity for AT₂R over AT₁R (>20,000-fold). We have created analogues that are highly stable in biological fluids and are working on developing modifications and formulations for improved bio-availability.

A number of proof-of-concept studies support AT₂ receptor stimulation as beneficial in fibrosis.

** THE OPPORTUNITY **

Monash University seeks a partner to optimise our exquisitely selective and potent lead series to improve oral bioavailability and develop a lead candidate as an anti-fibrotic agent for the heart, kidney and liver. The Monash research team has extensive experience in cardiovascular disease and fibrosis biology (having an array of in-house models) and all aspects of preclinical development from cellular through to in vivo integrative function, together with ex vivo analysis.

** 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 AT₁ receptors, and transforming growth factor-β (TGF-β) play important roles as major drivers of tissue fibrosis in virtually all fibrotic diseases.

Using the heart and kidney as examples, evidence suggests that Ang II and TGF-β₁ do not act independently from one another but act as part of a signalling network to promote cardiac and kidney remodelling, a key determinant of clinical outcomes.

Inhibition of the RAS with either ACE inhibitors or angiotensin-receptor blockers improves cardiac functional parameters with an overall ~7% reduction in cardiovascular mortality compared with non-RAS treatments. These improvements are associated with only modest regression of total collagen fraction.

There is a clear need for new drugs that can reverse fibrosis and prevent the development of fibrosis in those ‘at-risk’.

** KEY CONTACT **

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