MONASH University

MONASH INNOVATION

NEW TARGET FOR ANTI-FIBROTIC DRUGS

We have identified and validated a novel anti-fibrosis target. Inhibition of this target with the proprietary small molecule lead series completely reversed cardiac and renal fibrosis in clinically relevant disease models. We now seek a partner to develop novel lead candidate inhibitors as safe and effective anti-fibrotic drugs.

- **Potential to develop 'Best in Disease' anti-fibrotic drugs that reverse existing fibrotic lesions**
- **'Proof of Mechanism' with *in vivo* efficacy for small molecule inhibitors**
- **Differentiated and vasoprotective mechanism of action**

THE CHALLENGE

Fibrosis is caused by excess accumulation of extracellular matrices such as collagen. Chronic and progressive tissue fibrosis causes pathology and dysfunction in many organ systems. Activation of the renin-angiotensin system as well as oxidative stress and inflammation pathways are all implicated in the pathogenesis of cardiovascular and renal fibrosis.

Currently, there are no specific anti-fibrotic therapies available for cardiac or renal fibroses. Angiotensin converting enzyme inhibitors and angiotensin AT1 receptor blockers have only a modest effect on regressing total collagen fraction.

There is a clear need for new drugs that can reverse fibrosis in affected individuals and prevent the development of fibrosis in at-risk individuals. Ideally the drugs will be tissue-protective, acting without adversely disrupting collagen metabolism in other organs.

THE TECHNOLOGY

Researchers from the Monash BioMedicine Discovery Institute (A/Prof. Siew Chai, Prof. Rob Widdop & Dr. Tracey Gaspari) and Monash Institute of Pharmaceutical Sciences (A/Prof. Phil Thompson) have identified IRAP as a new target for the treatment of cardiac, kidney, liver and potentially other organ fibroses. IRAP is an extracellular protein that is 'druggable' with small molecule inhibitors. A compelling body of evidence supporting proof-of-mechanism and validation with a lead series has shown that IRAP inhibition can prevent and reverse fibrosis.

THE TARGET

- IRAP deficiency/inhibition protects against the development of cardiac and renal fibrosis in aged mice and cardiac fibrosis in Ang II-treated mice (Fig.1).
- IRAP inhibition completely reverses cardiac fibrosis in aged mice (Fig.2), with corresponding decreases in inflammatory and oxidative stress markers and increases in NO bioavailability.
- IRAP deficiency/inhibition protects against ischemia-reperfusion damage (Fig.3) and improves function of aged ischemic hearts.
- IRAP inhibition protects and reverses age-mediated renal fibrosis and high salt-induced cardiac/renal fibrosis

Lead series: Two structurally distinct small molecule lead series having sub-μM potency and high selectivity for the target have been developed. These have significant anti-fibrotic efficacy in a range of animal models.

Intellectual property: Two patent applications covering lead series composition (PCT/AU2016/050332) and use of target inhibitors in fibrosis treatment and prevention (PCT/AU2016/050681).

Model of fibrosis	IRAP gene deletion	IRAP inhibition	
	prevention	prevention	reversal
Aging	√	√	√
AngII-induced	√	√	√
High salt	√	√	√

THE OPPORTUNITY

We seek a partner to optimise the lead series and develop new lead drug candidate(s) against this exciting target. The Monash team has extensive experience in IRAP and fibrosis biology, having an array of in house models including *in vitro* target screen, functional assay, specific knockout models, fibrosis and other pathological models, plus target SAR and preclinical profiling expertise.

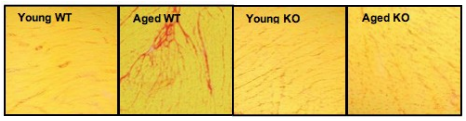

Figure 1: IRAP gene deletion protects against development of age-induced cardiac fibrosis

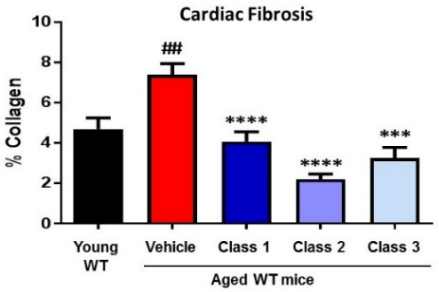

Figure 2: Complete reversal of age-induced cardiac fibrosis after chronic 4 wk. s.c. infusion in 22 mth aged C57Bl/6J mice with 3 distinct classes of IRAP inhibitor.

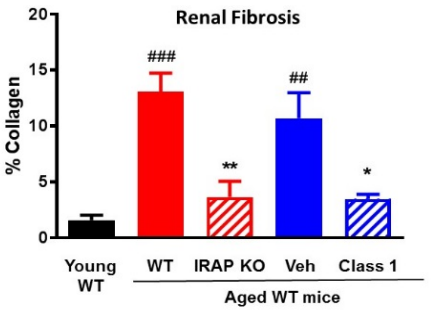

Figure 3: Complete reversal of age-induced tubule-interstitial fibrosis in kidneys from IRAP deficient or IRAP inhibitor treated mice.

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