Unique classes of small molecules that inhibit the site specific acetylation of SMAD3 to prevent its fibrosis promoting activity in response to TGF-β 1 signalling, without inhibiting its other transcriptional functions. These molecules form the basis of a development program for creating novel, safe and effective anti-fibrotic drug compositions.

- Potential ‘Best in Disease’ anti-fibrotic drugs
- Differentiated mechanism of action
- Proof of mechanism in vivo efficacy for hit molecules
- Potential single agent and combination therapies

THE CHALLENGE
Chronic and progressive tissue fibrosis is a major mechanism in many non-infectious diseases, including chronic kidney disease, chronic obstructive pulmonary disease, liver cirrhosis, cardiovascular disease and sclerosis.

Currently, there are no specific anti-fibrotic therapies available for these indications. There is strong evidence that transforming growth factor-β (TGF-β) is a major driver of tissue fibrosis in many, or indeed, all of these diseases. Therefore, there is great interest in blocking the actions of TGF-β.

However, TGF-β is also an important negative regulatory of the immune response, so the downstream signalling events from the TGF-β receptor on the cell surface have become potential therapeutic targets. It is well known that part of TGF-β signalling (in particular, the pro-fibrotic aspects of TGF-β signalling) operate via the SMAD transcription factors.

Importantly, SMAD3, but not SMAD2 KO mice are protected from fibrosis of kidney, lung, heart, liver. These mice have only minor abnormalities in immune function compared to TGF-β1 KO mice, identifying SMAD3 as a potential therapeutic target. In addition, SMAD3 is regulated by posttranslational modifications with acetylation at four lysine (K) residues in the C-terminal MH2 domain known to play a key role in TGF-β1 induced SMAD3 transcriptional activity in an in vitro assay of collagen production.

There may be an opportunity to inhibit TGF-β induced tissue fibrosis by blocking a specific mechanism involved in TGF-β/SMAD3 signalling.

THE TECHNOLOGY
Monash Researchers have extended the previously known in vitro role of SMAD3 acetylation to an in vivo approach by creating novel transgenic mice expressing SMAD3 featuring lysine to arginine mutation (SMAD3K/R). The team then demonstrated that these mice are protected from fibrosis in models of kidney and lung fibrosis.

These data support the proposed role for SMAD3 acetylation in promoting fibrosis in vivo. Acetylation of SMAD3 has also been identified in human biopsies of fibrotic kidney diseases, supporting this hypothesis.

Lead series identification
The team screened a large library of known compounds in silico to a ‘druggable’ site of interest in SMAD3 and identified multiple classes of lead compounds that could inhibit SMAD3 acetylation and SMAD3 transcriptional activity. These molecules were screened in vitro and in vivo using the UUO model of renal fibrosis as preliminary proof of mechanism, where three separate classes of molecules were identified.

There is clear potential to perform detailed chemical modification of these structures to develop novel series of compounds that block acetylation of SMAD3 lysine and provide significant intellectual property.

THE OPPORTUNITY
Monash University seeks a partner to optimise lead series candidates and develop new lead drug candidates.

The Monash team has extensive experience in TGF-β/SMAD3 signalling and fibrosis biology, with several relevant fibrosis models, and preclinical profiling expertise.

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Figure 1: Groups of 6 wild type, SMAD3WT, SMAD3−/−, and SMAD3K/R mice were sacrificed on day 7 after unilateral ureteric obstruction (UUO), with a sham surgery control. Area of collagen IV staining. Both SMAD3−/− and SMAD3K/R mice are substantially protected from renal fibrosis. Mice were treated with our lead SMAD3 acetylation inhibitor (JL-0365) or vehicle.