

Multi-Organ Antifibrotic Activity by Rencofilstat Through Inhibition of the Collagen-Regulating Enzyme, Cyclophilin B

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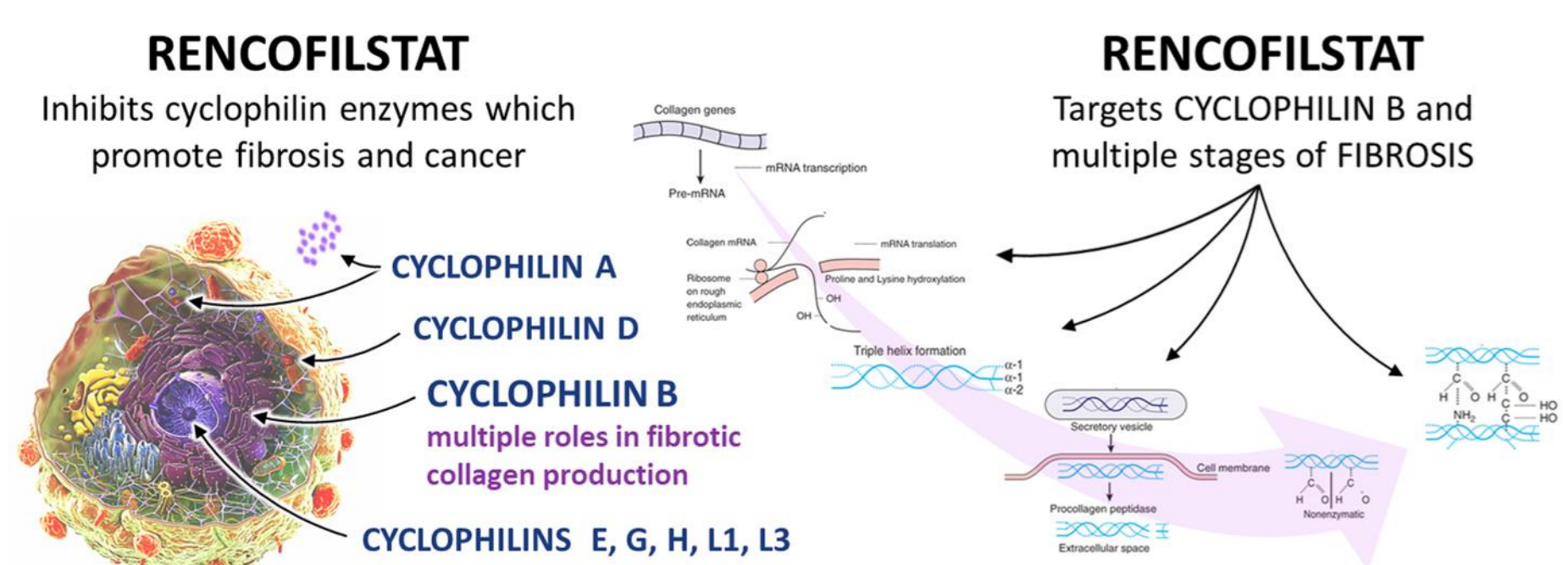
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INTRODUCTION

Cyclophilin B (Cyp B) is a proline-directed *cis-trans* isomerase that binds collagen and regulates collagen hydroxylation, folding, secretion, and crosslinking.

Rencofilstat (RCF; CRV431) is an oral, small-molecule inhibitor of cyclophilin B and other cyclophilin isoforms in clinical development for NASH and HCC.



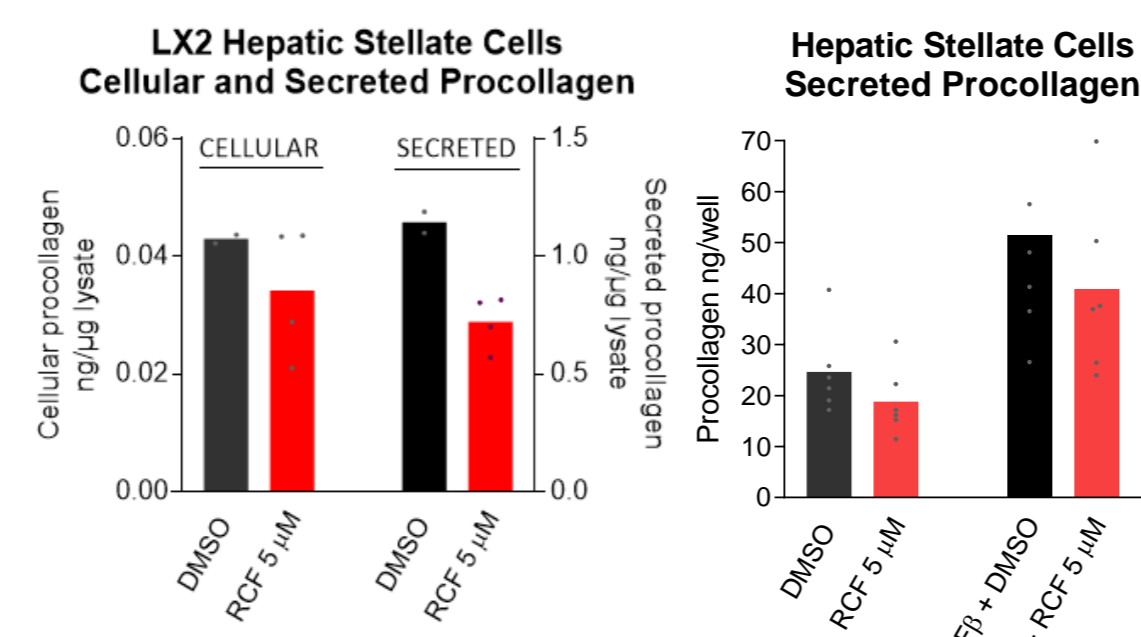
AIM

To investigate whether cyclophilin B inhibition with rencofilstat or other methods can decrease collagen production and fibrosis in multiple disease models.

LIVER FIBROSIS MODELS

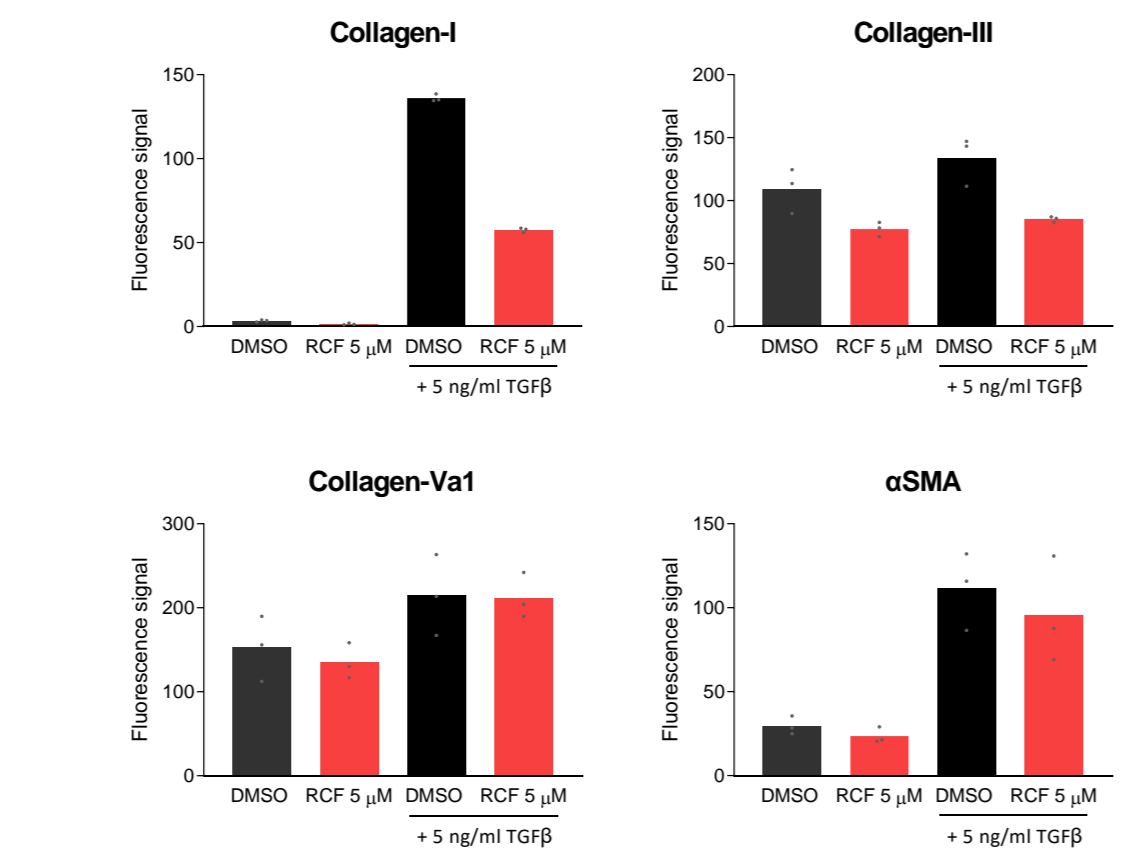
HUMAN HEPATIC STELLATE CELLS

Rencofilstat decreased cellular and secreted procollagen 1 α 1 (no intracellular "build-up")



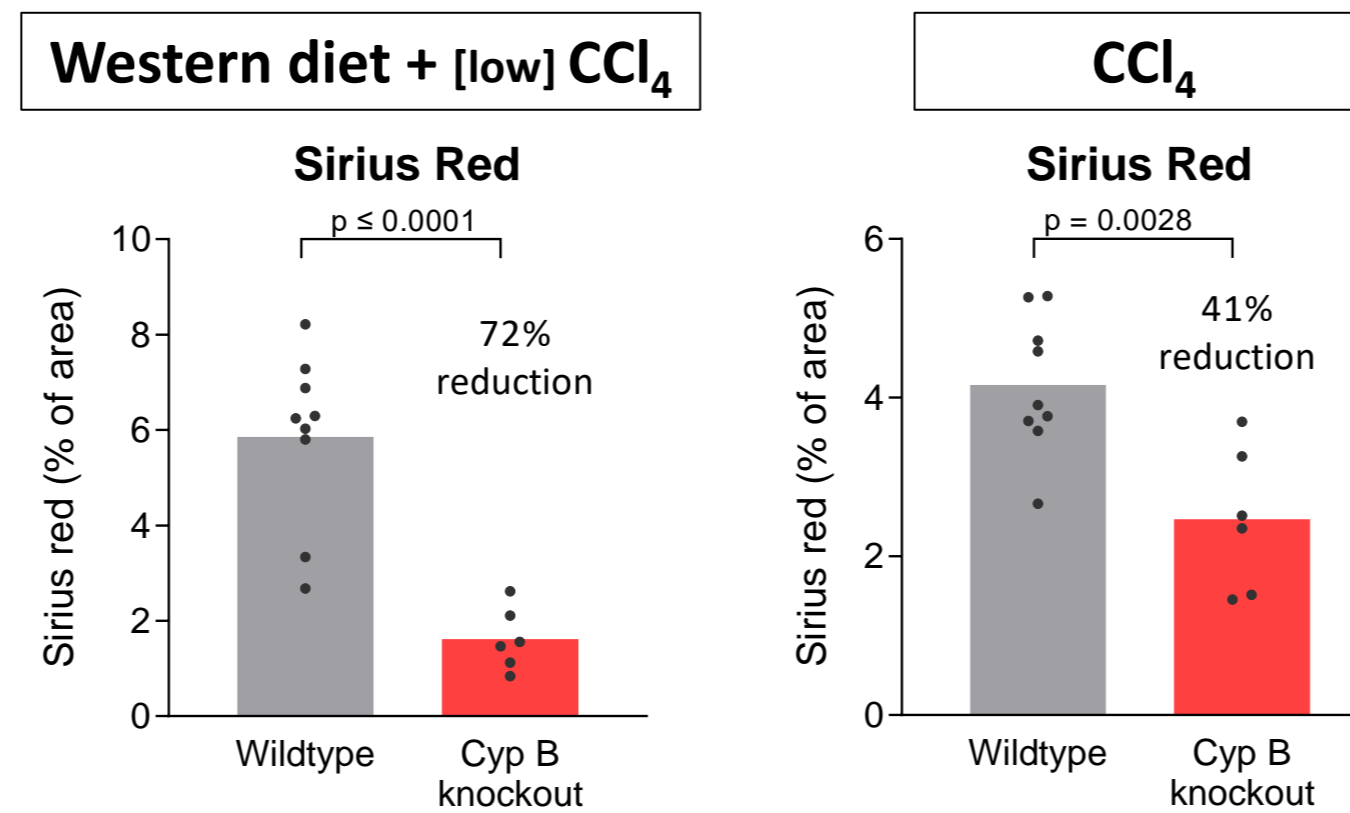
QUANTITATIVE IMMUNOHISTOCHEMISTRY

Rencofilstat decreased cellular levels of collagen-I and collagen-III. No effect on collagen-V or α SMA.



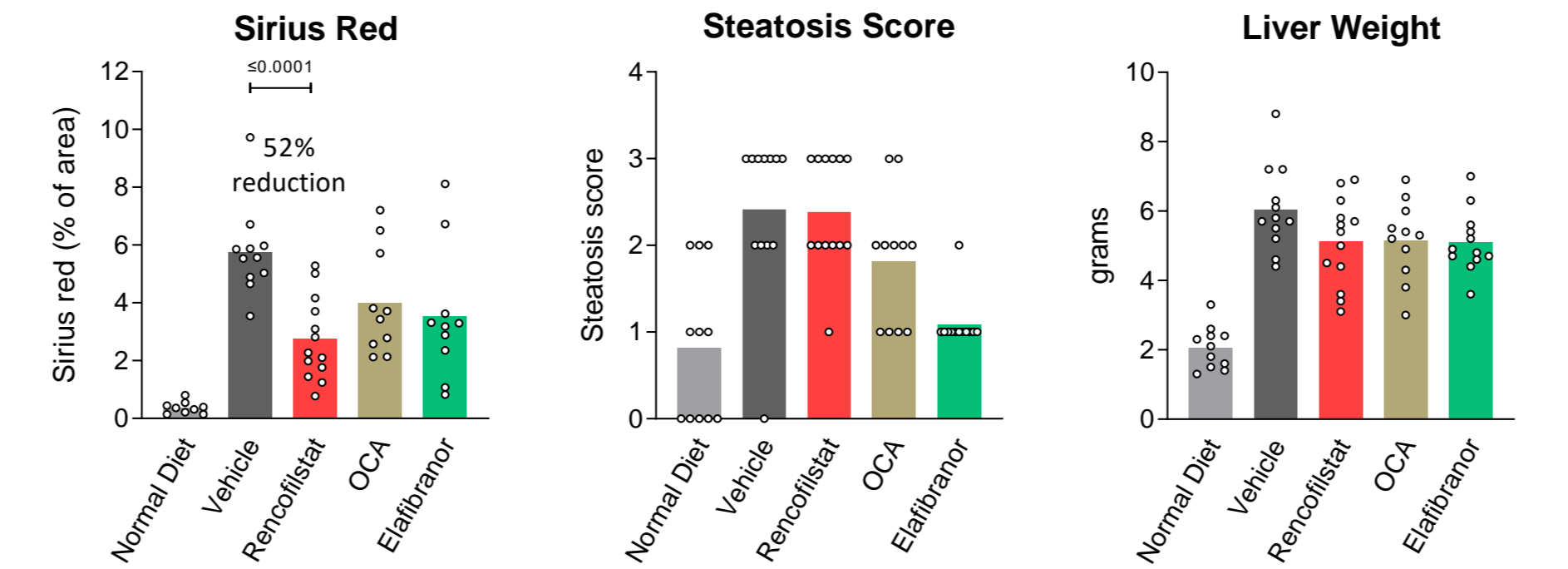
CYCLOPHILIN B KNOCKOUT MICE

Cyclophilin B knockout decreased liver Sirius red staining in two studies, confirming a role for cyclophilin B in fibrosis.



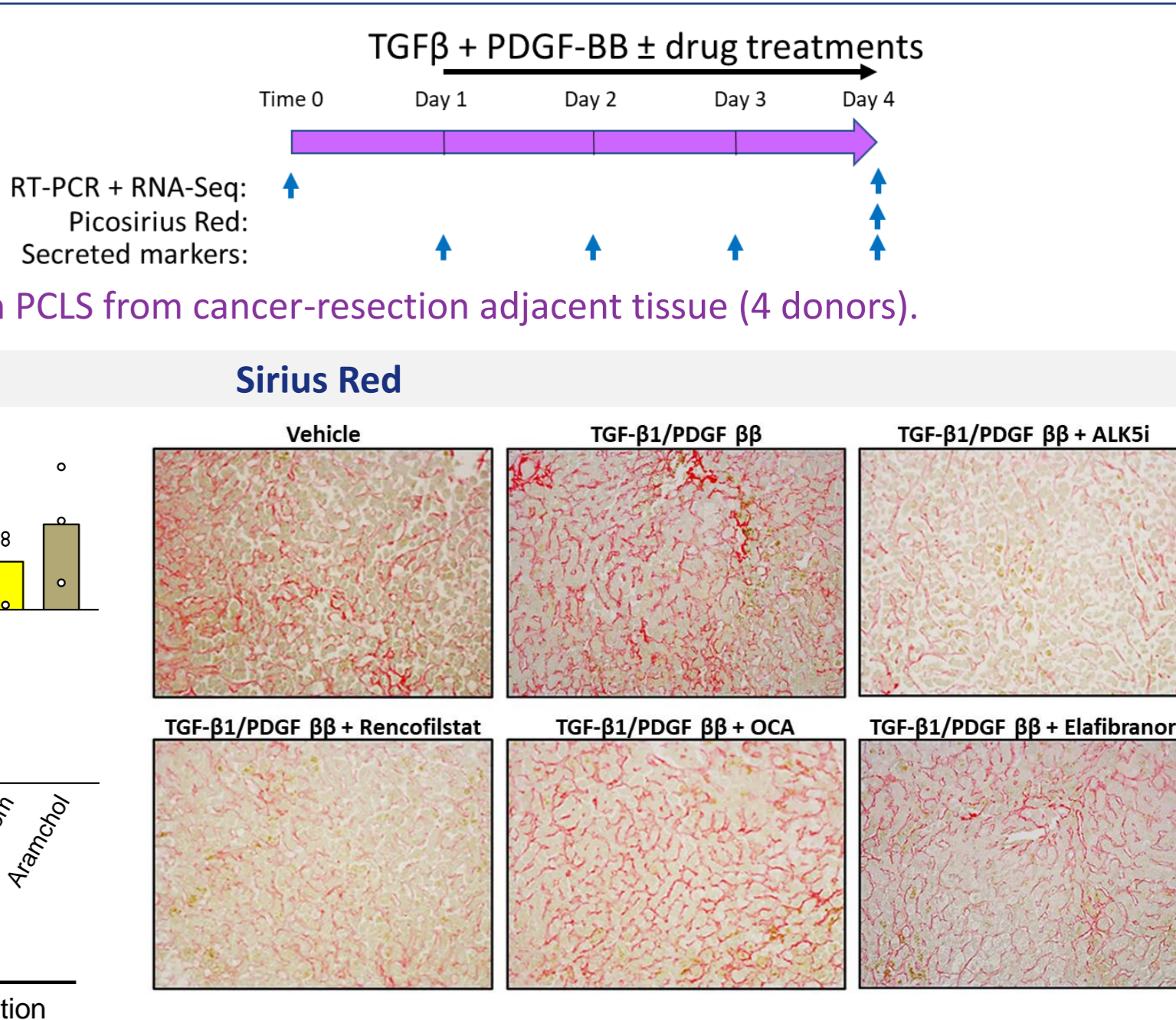
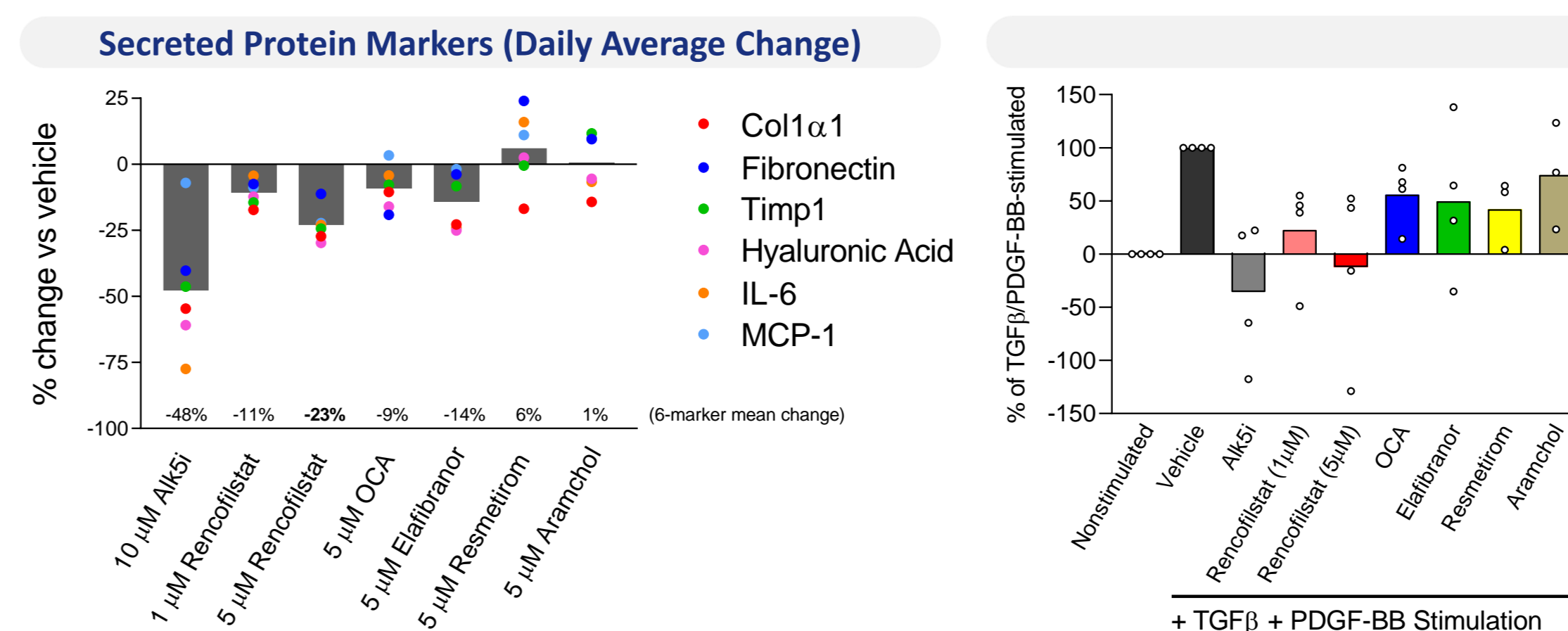
NASH: DIAMOND MICE

Rencofilstat decreased Sirius red but not steatosis score in a NASH treatment protocol



HUMAN PRECISION CUT LIVER SLICES (FibroFind)

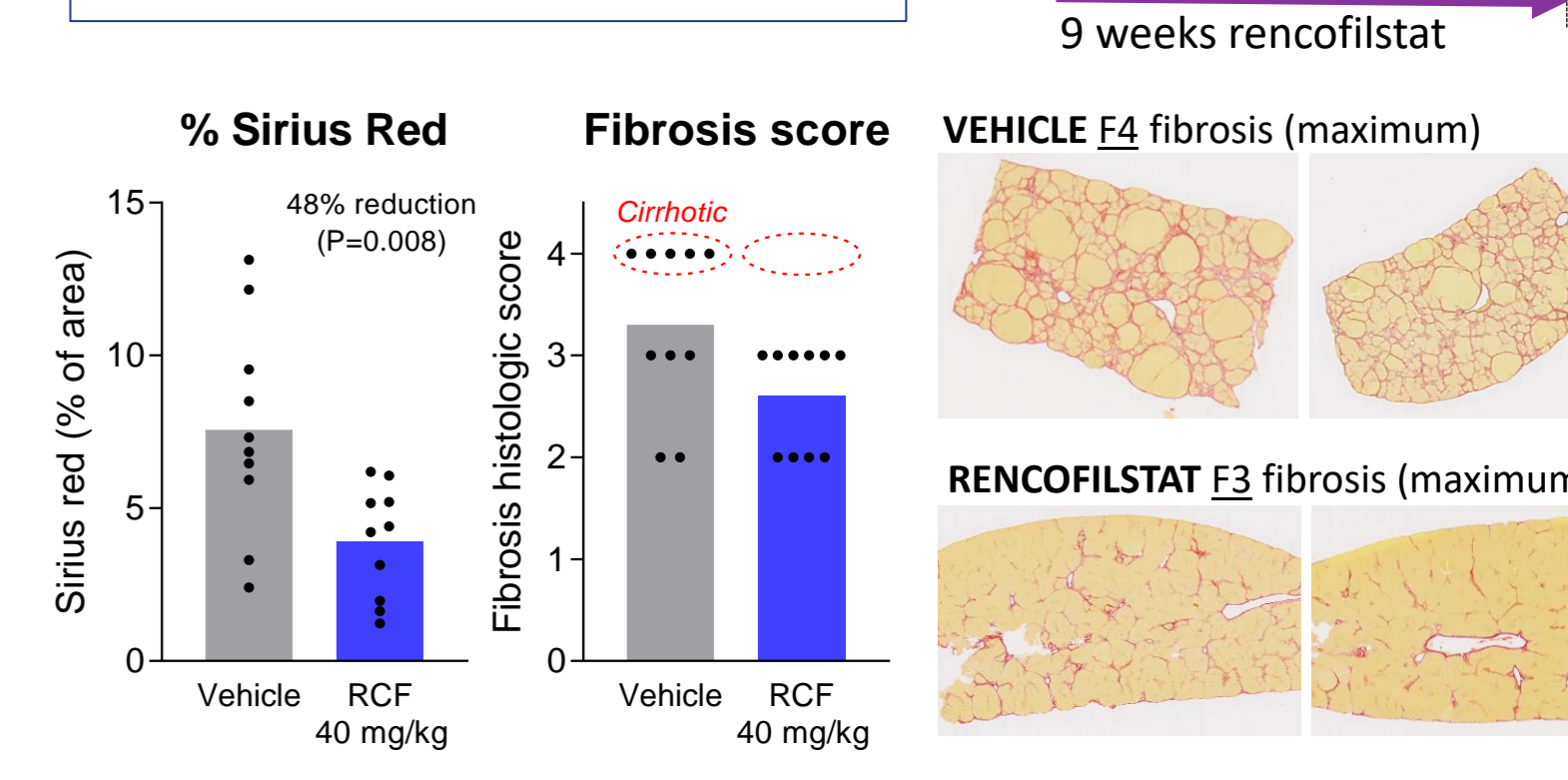
Rencofilstat decreased secretion of fibrosis and inflammation markers and decreased Sirius red in PCLS from cancer-resection adjacent tissue (4 donors).



ADDITIONAL MOUSE NASH MODELS

Model	Rencofilstat Effect on Sirius Red
Western diet + [low] CCl ₄ / 6 weeks treatment	82% reduction
STAM / 3 weeks treatment	57% reduction
STAM / 6 weeks treatment	46% reduction
STAM / 11 weeks treatment	37% reduction

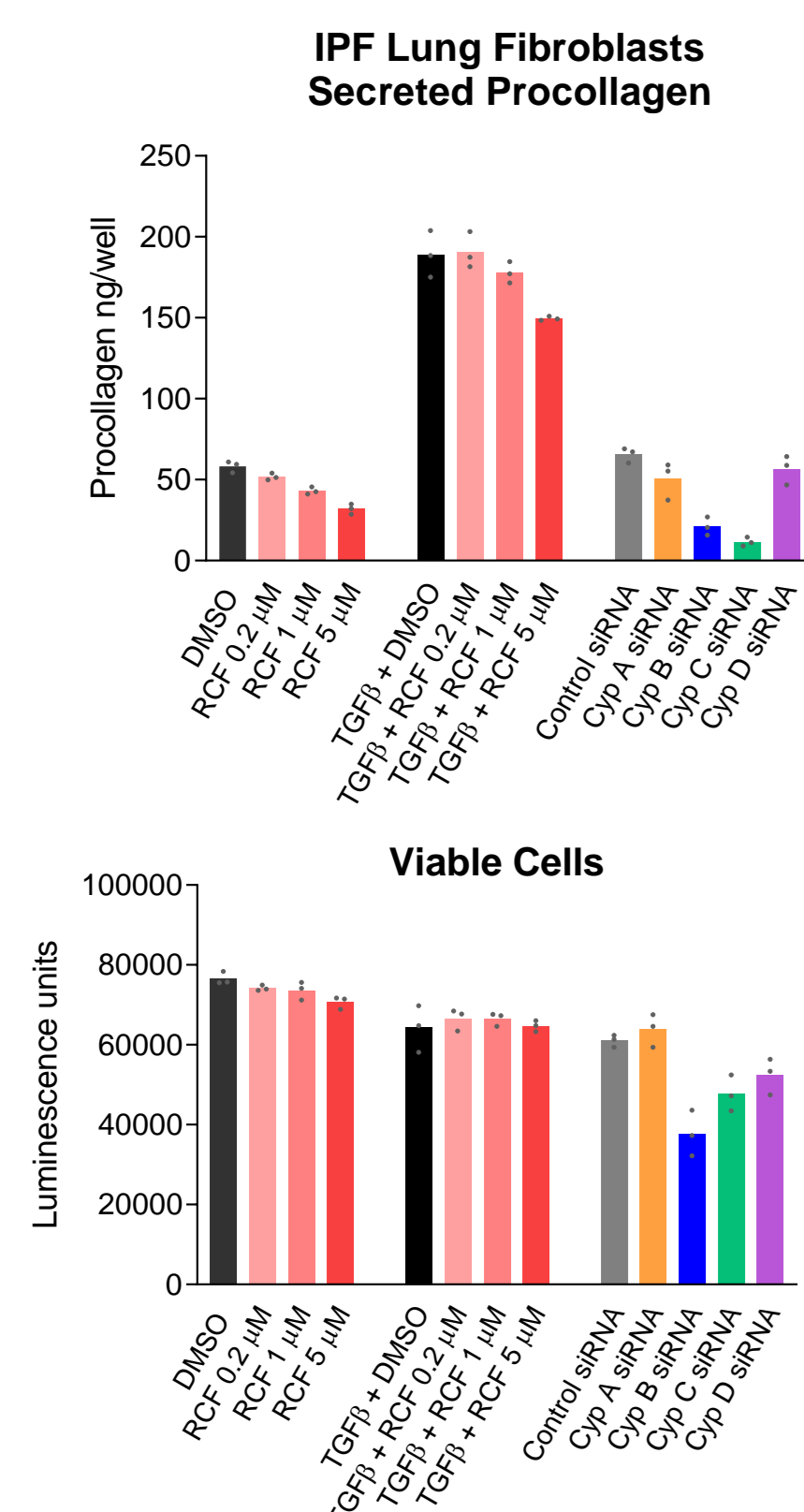
THIOACETAMIDE RATS



LUNG FIBROSIS MODELS

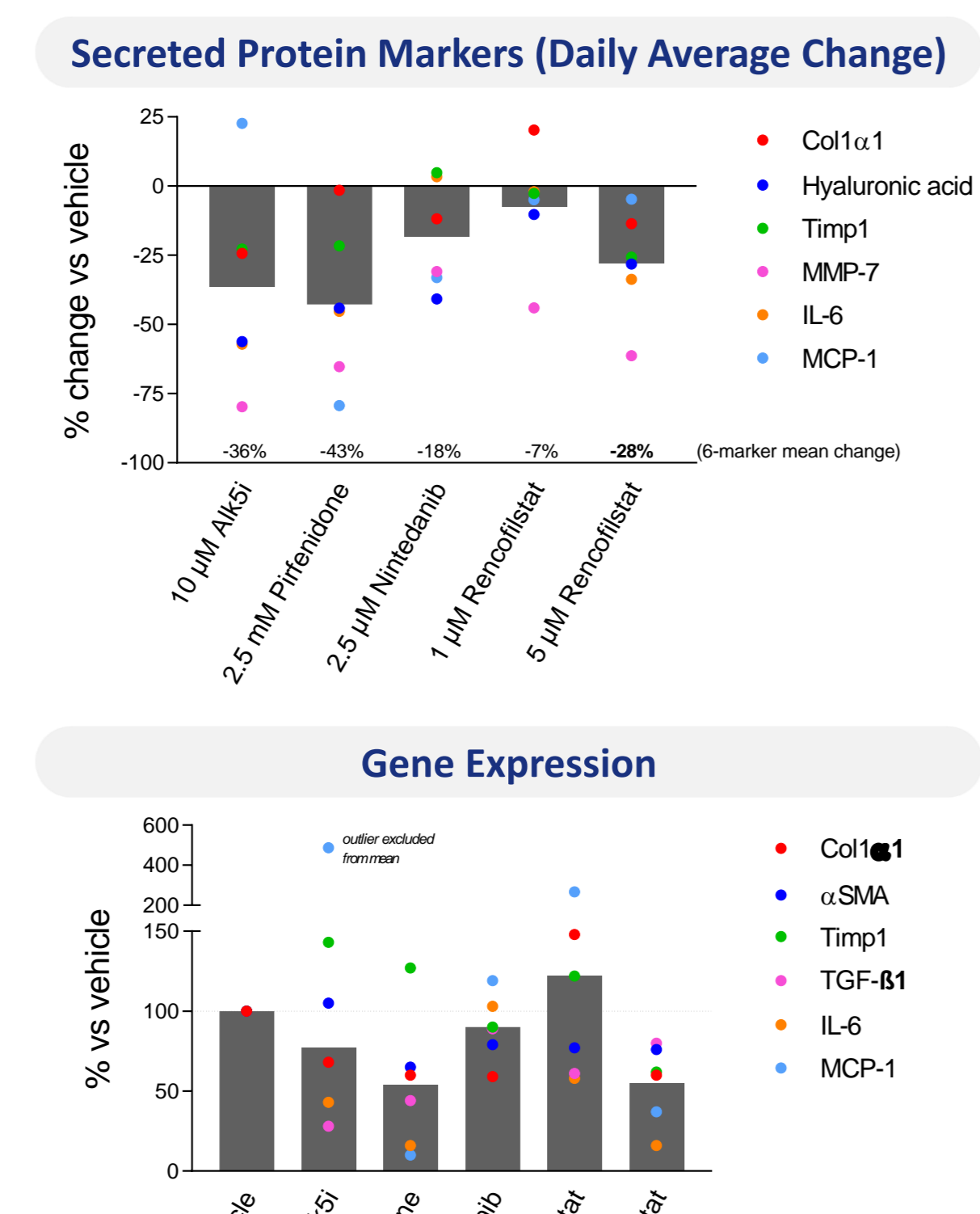
HUMAN IPF FIBROBLASTS

Procollagen 1 α 1 secretion was decreased by rencofilstat and siRNA-mediated knockdown of cyclophilins B and C. Cyp B and C siRNA also moderately decreased cell numbers.



IPF PRECISION CUT LUNG SLICES (FibroFind)

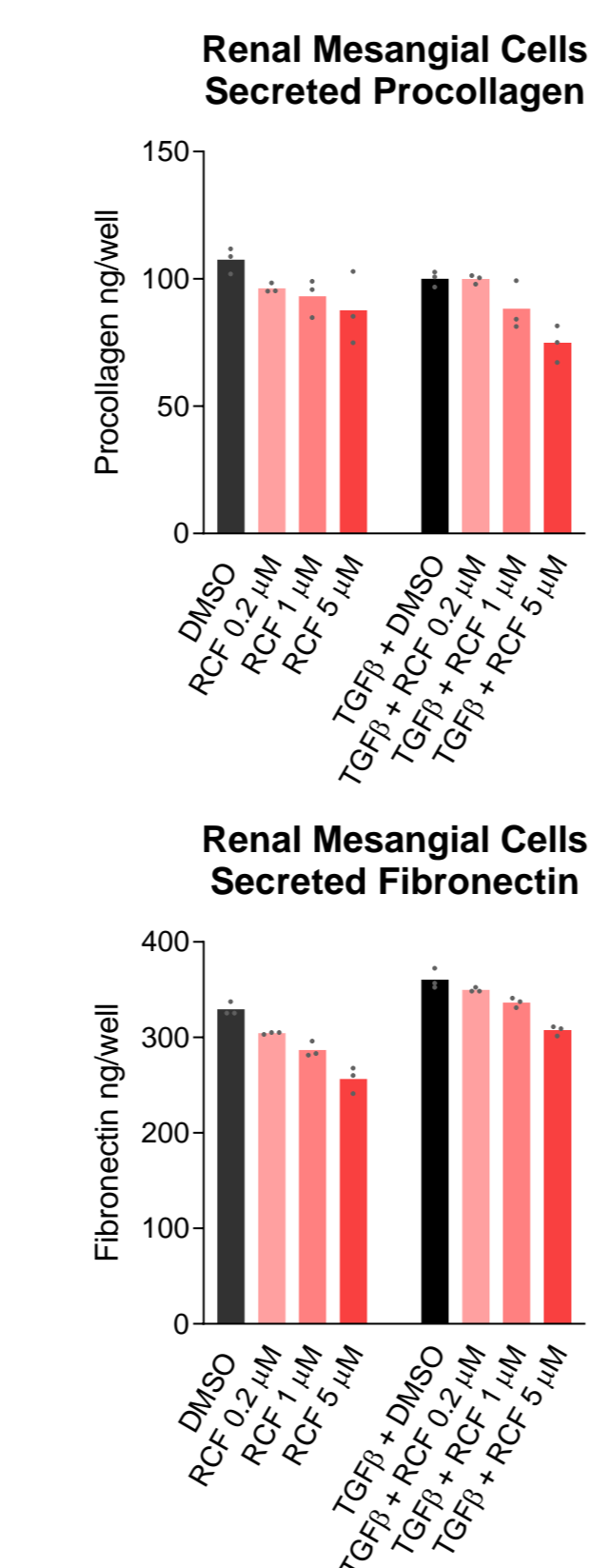
Rencofilstat decreased gene expression and secretion of fibrosis and inflammation markers in similarity to pirfenidone and nintedanib.



KIDNEY FIBROSIS MODELS

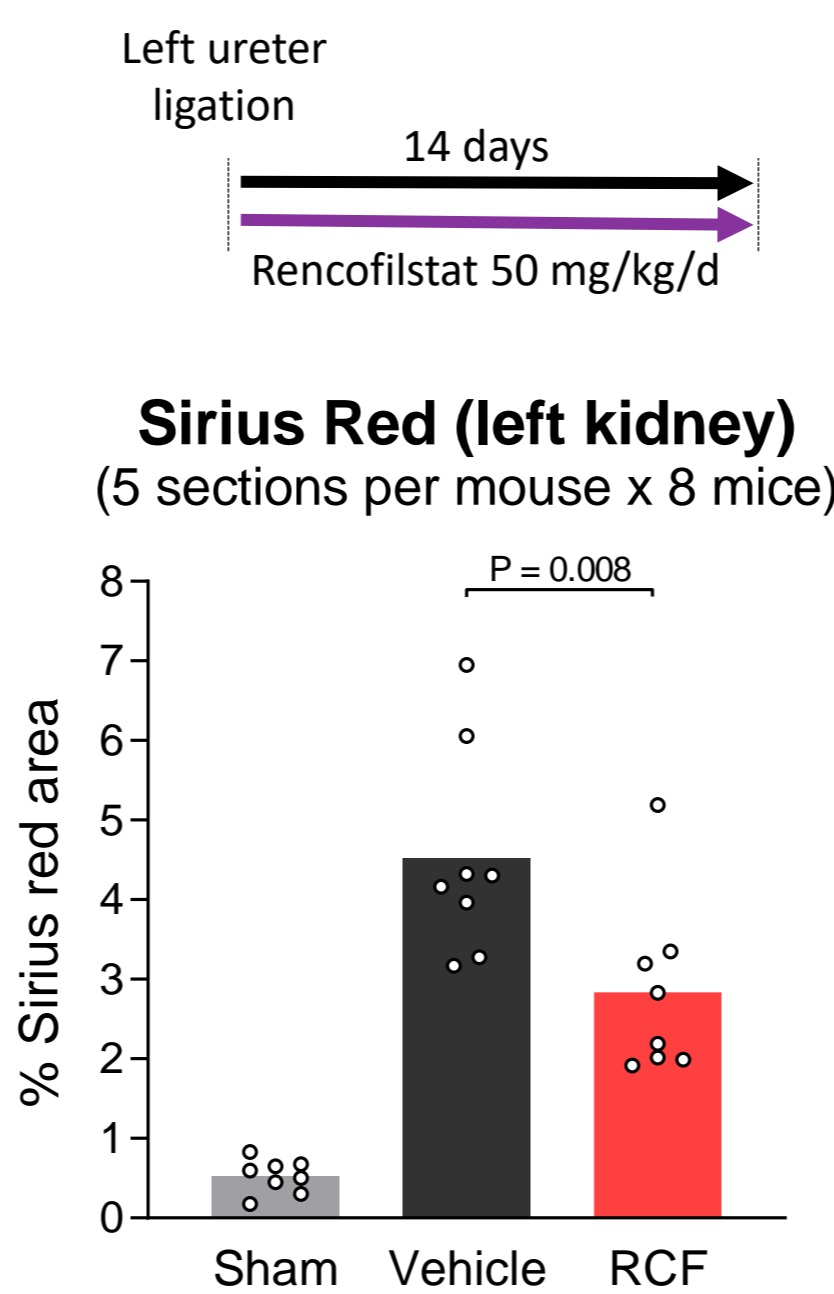
HUMAN RENAL MESANGIAL CELLS

Rencofilstat decreased secretion of procollagen 1 α 1 and fibronectin.



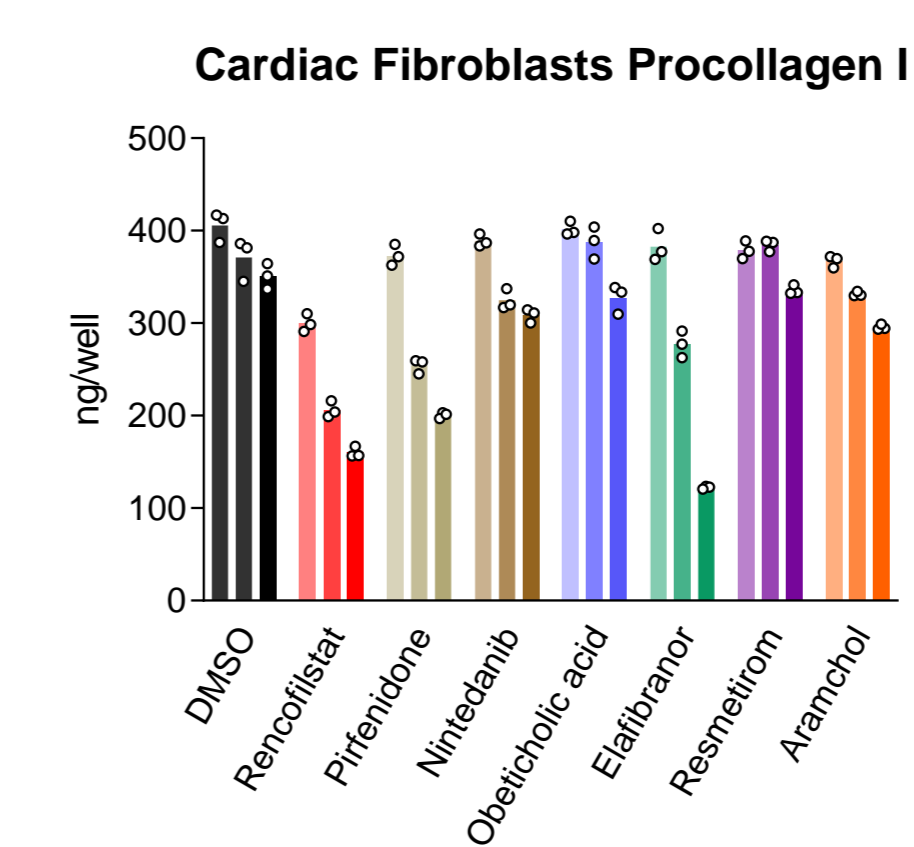
MURINE UNILATERAL URETERAL OBSTRUCTION

Rencofilstat decreased Sirius red (% of area) in the murine UUO model (SMC Labs).



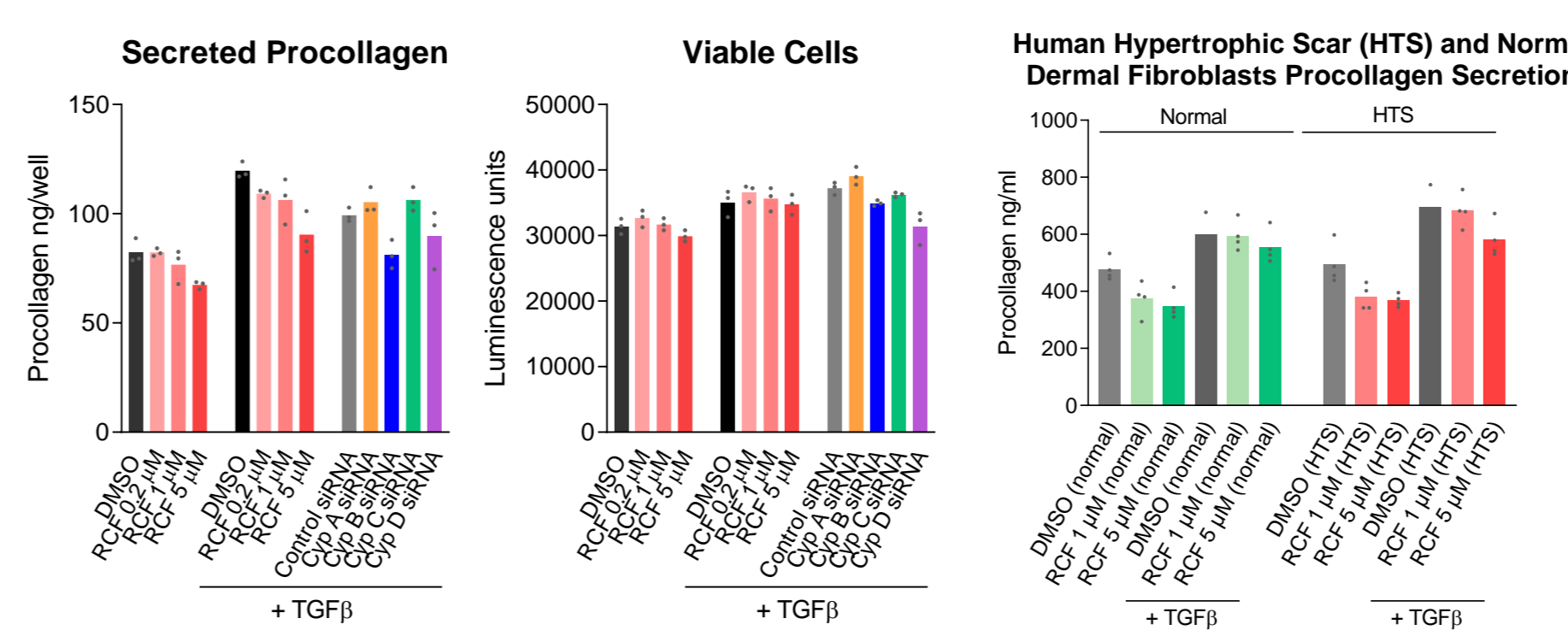
CARDIAC FIBROBLASTS

Rencofilstat decreased secretion of procollagen 1 α 1 from human cardiac fibroblasts in similarity to or better than other compounds.



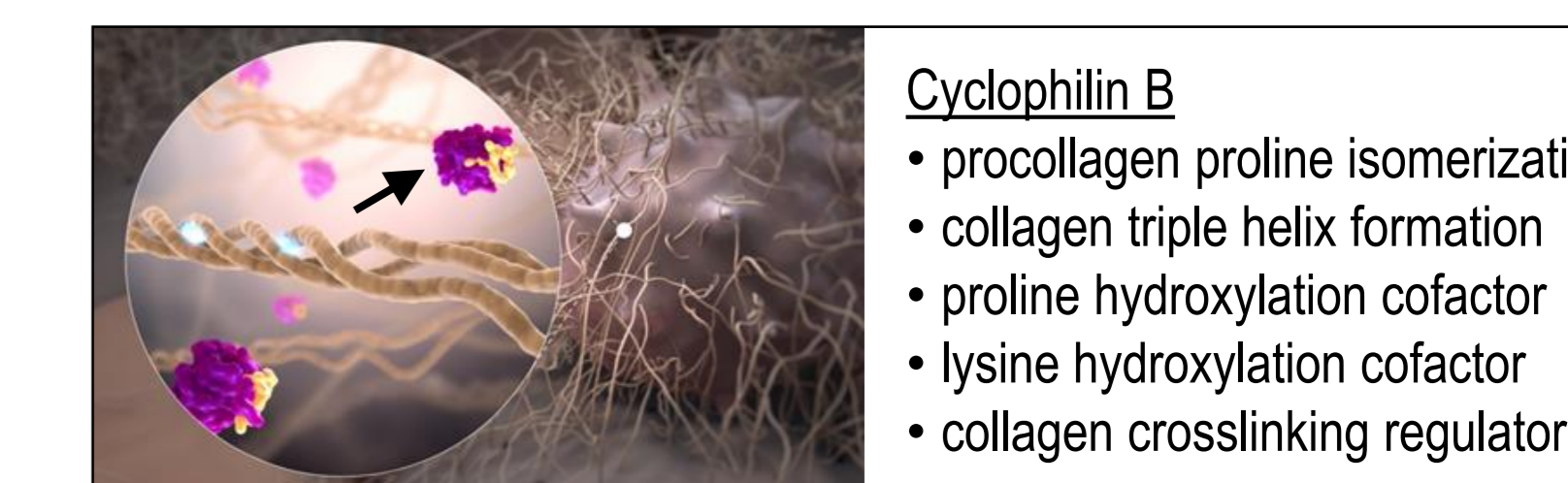
DERMAL FIBROBLASTS

Procollagen 1 α 1 secretion was decreased by rencofilstat and siRNA knockdown of Cyp B (viability unchanged), including from hypertrophic scar fibroblasts.



CONCLUSIONS

Cyclophilin B inhibition with rencofilstat or genetic knockdown/knockout decreased collagen production and fibrosis in multiple experimental models.



Rencofilstat has shown a strong safety profile to date in preclinical and clinical studies and therefore shows potential as a versatile antifibrotic agent for diverse fibrotic diseases.

ACKNOWLEDGEMENTS

- Jelena Mann and Lee Borthwick (FibroFind, Newcastle, UK) for human liver and lung slice studies
- François Briand (Physiogenix, France) for rat thioacetamide study
- SMC Labs for murine STAM and UUO model studies

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