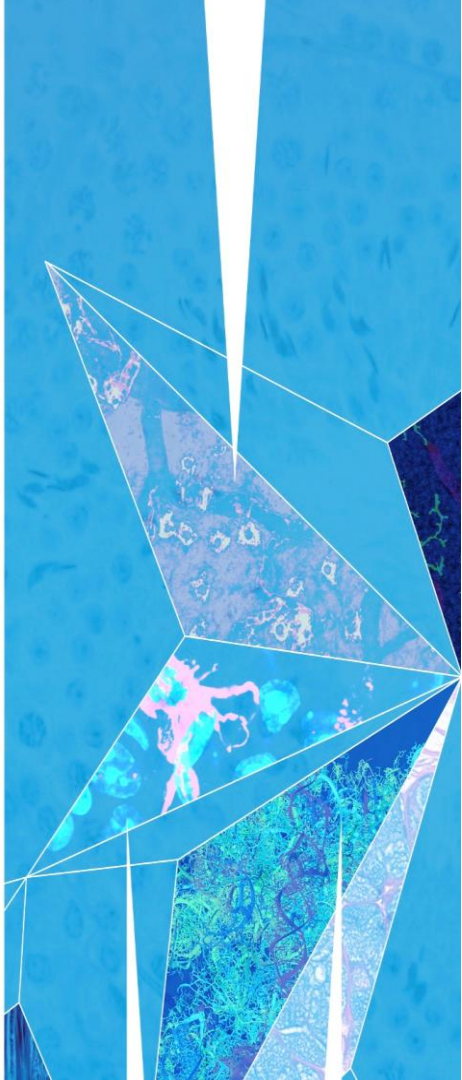
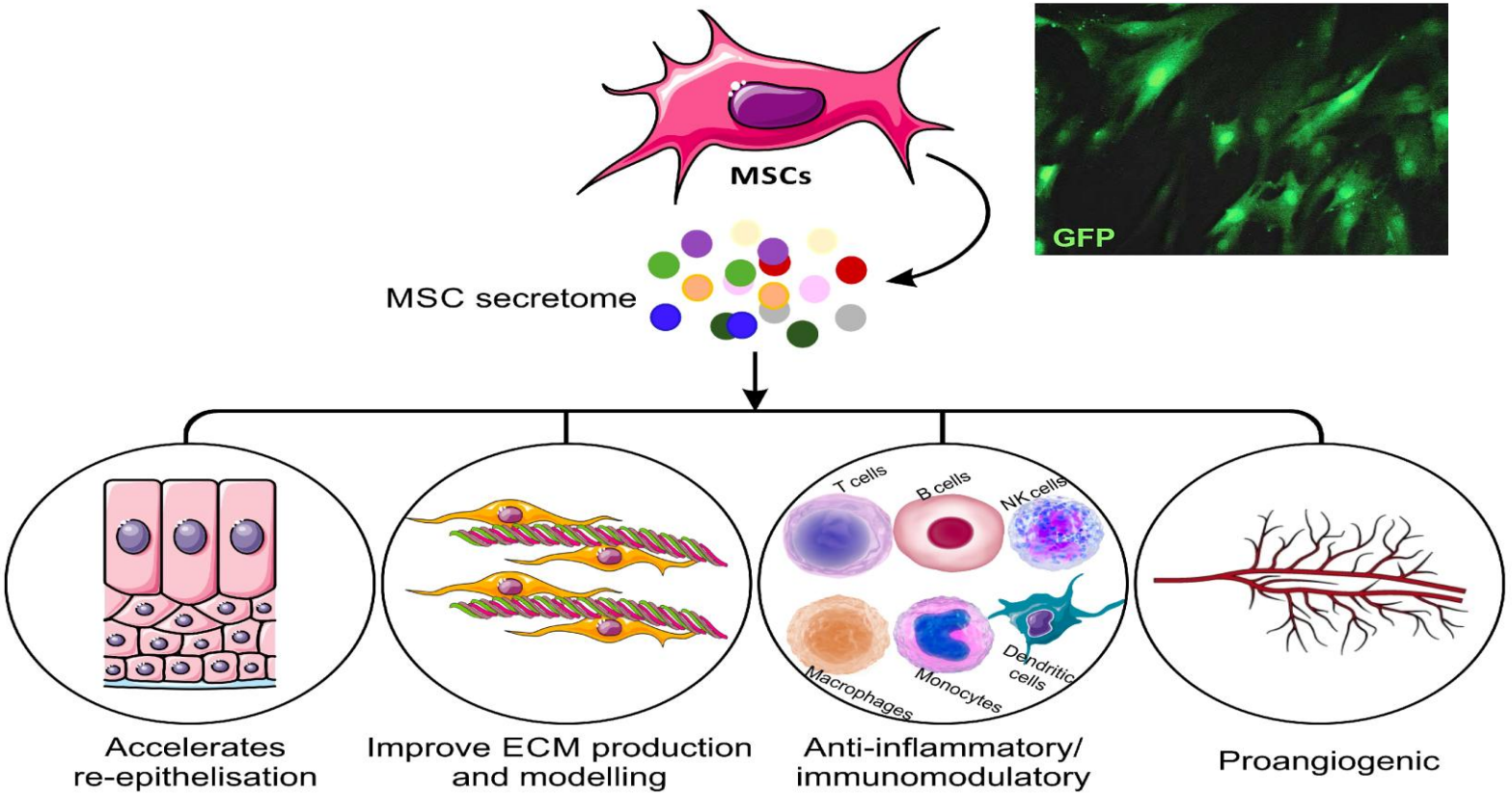
A combined anti-fibrotic cell therapy for treating chronic kidney disease

Professor Chrishan S. Samuel, PhD

Deputy Head, Cardiovascular Disease Program,
Monash Biomedicine Discovery Institute and
Head, Fibrosis Laboratory, Department of Pharmacology, Monash University,
Melbourne, Victoria, Australia

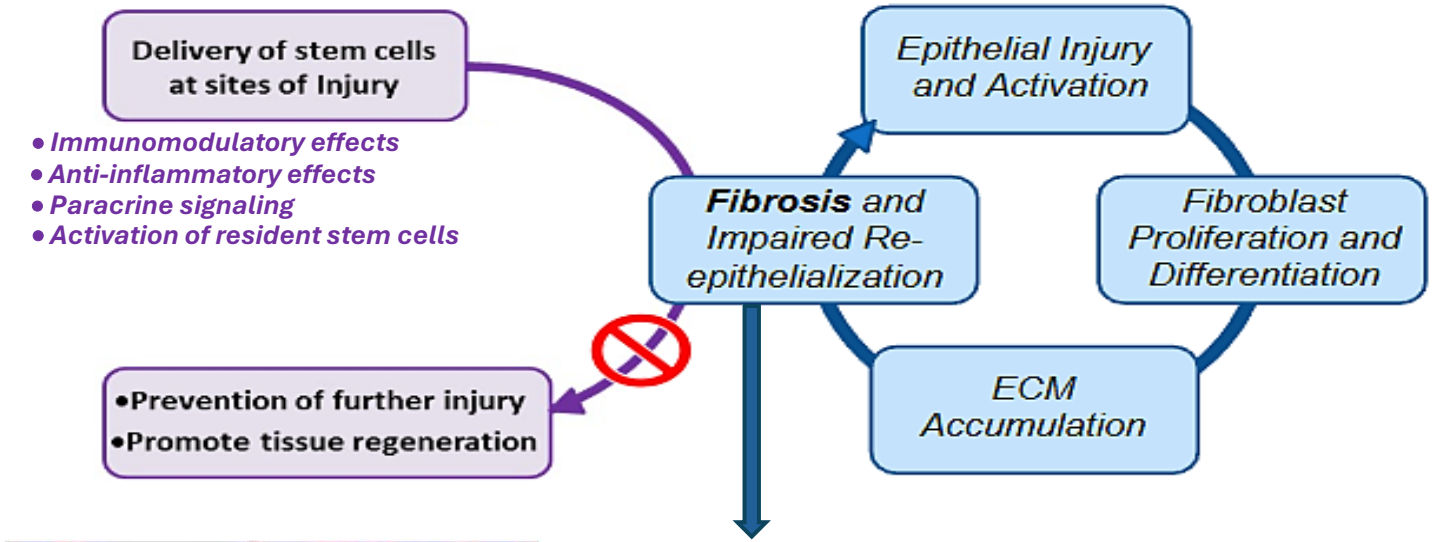


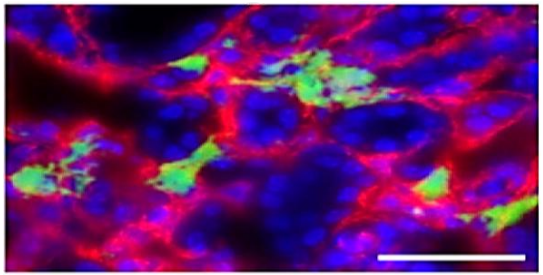
MESENCHYMAL STEM/STROMAL CELLS (BM-MSCs)



Uccelli A et al., Nat Rev Immunol 2008; 8:726-736

ESTABLISHED FIBROSIS ACTS AS A PHYSICAL BARRIER TO BM-MSC VIABILITY





Established fibrosis affects BM-MSC:

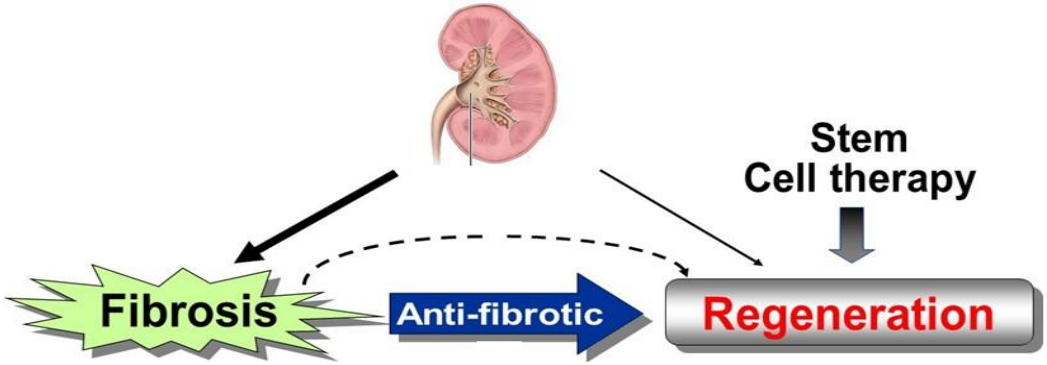
- ↓survival and homing
- ↓proliferation and migration
- ↓integration with resident cells
- ↓differentiation

Lu L et al., Biochem Biophys Res Commun 2004; 320:907-913

Eun LY et al., Tissue Cell 2011; 43:238-245

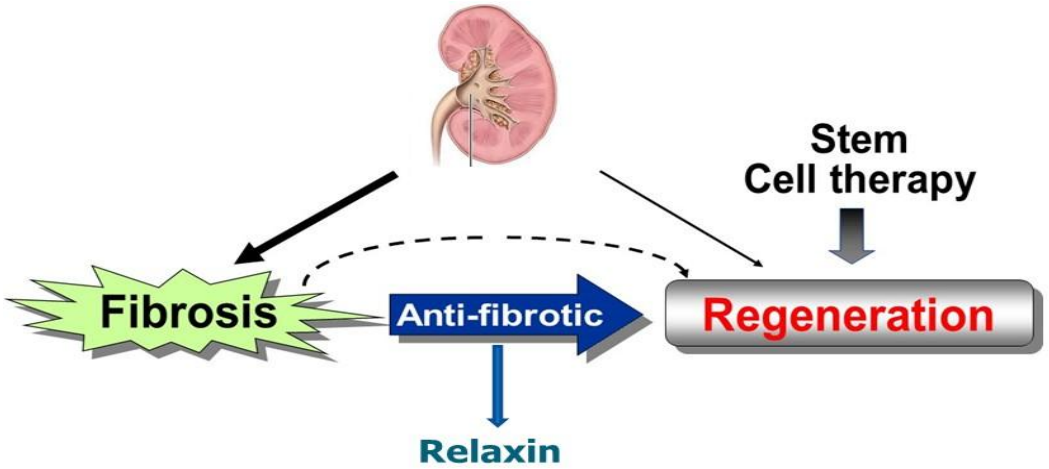
COMBINING STEM CELLS WITH AN ANTI-FIBROTIC THERAPY:

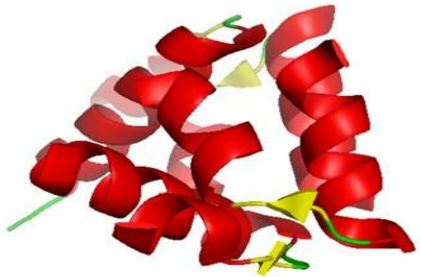
RELAXIN



COMBINING STEM CELLS WITH AN ANTI-FIBROTIC THERAPY:

RELAXIN





- Anti-inflammatory
- Anti-apoptotic
- Anti-hypertrophic
- Vasodilatory
- Tissue reparative

Anti-fibrotic peptide-drug

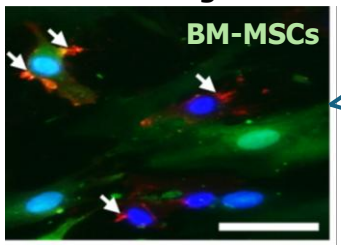
Samuel CS et al., Trends Pharmacol Sci 2016; 37:485-497 Samuel CS et al., Biochem Pharmacol 2022; 197:114884

COMBINING STEM CELLS WITH AN ANTI-FIBROTIC THERAPY:

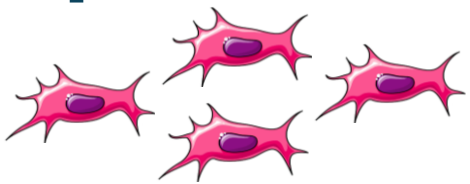
RELAXIN

RELAXIN (RLX)

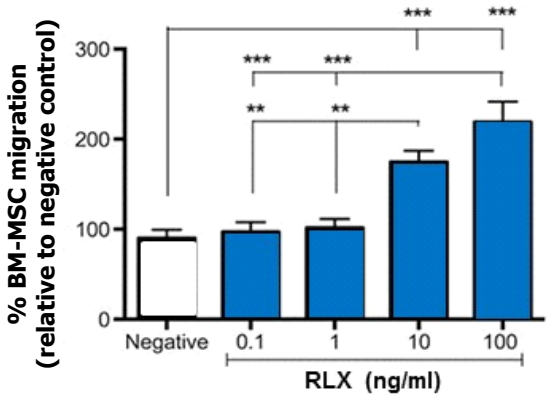
RXFP1 (relaxin receptor) staining



BM-MSC proliferation



BM-MSC migration



Huuskes BM et al., FASEB Journal 2015; 29:540-553

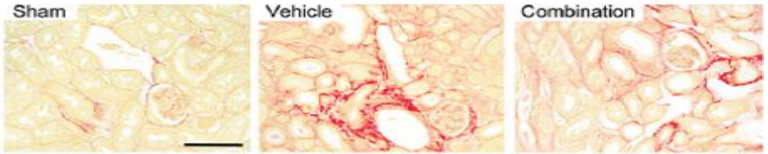
COMBINING STEM CELLS WITH AN ANTI-FIBROTIC THERAPY:

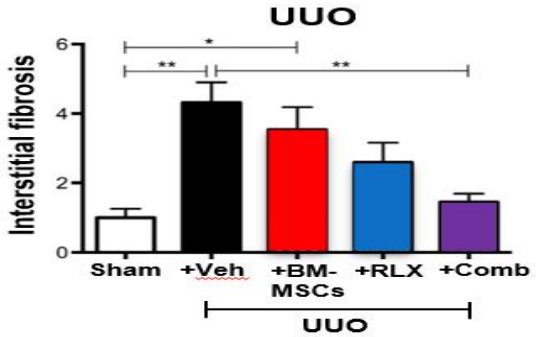
RELAXIN

The FASEB Journal • Research Communication **[2015; 29:540]**

Combination therapy of mesenchymal stem cells and serelaxin effectively attenuates renal fibrosis in obstructive nephropathy

Brooke M. Huuskes,* Andrea F. Wise,* Alison J. Cox,† Ee X. Lim,* Natalie L. Payne,‡ Darren J. Kelly,† Chrishan S. Samuel,§,1 and Sharon D. Ricardo*,1



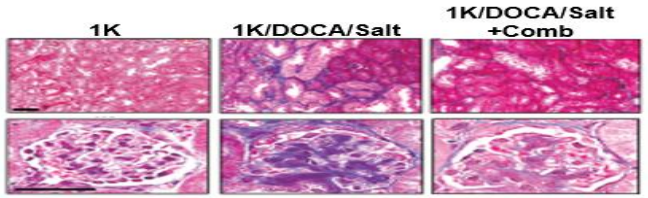


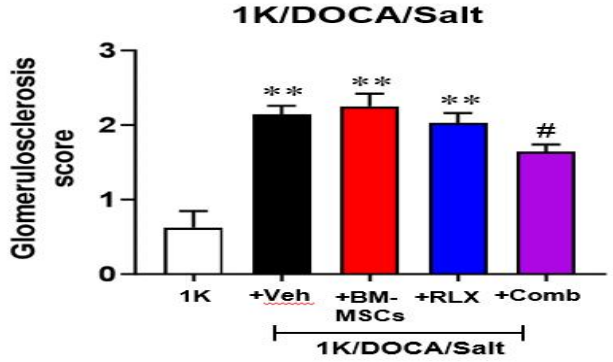
Huuskes BM et al., FASEB Journal 2015; 29:540-553

RESEARCH PAPER **[2021; 178:1164]**

Combining mesenchymal stem cells with serelaxin provides enhanced renoprotection against 1K/DOCA/salt-induced hypertension

Yifang Li[1,2] | Matthew Shen[1,2] | Dorota Ferens[1,2] | Brad R.S. Broughton[1,2] | Padma Murthi[1,2] | Sheetal Saini[1,2] | Robert E. Widdop[1,2] | Sharon D. Ricardo[1,2] | Anita A. Pinar[1,2] | Chrishan S. Samuel[1,2,3]





Li Y et al., Br J Pharmacol 2021; 178:1164-1181

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COMBINING STEM CELLS WITH AN ANTI-FIBROTIC THERAPY:

RELAXIN

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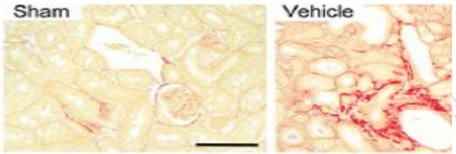
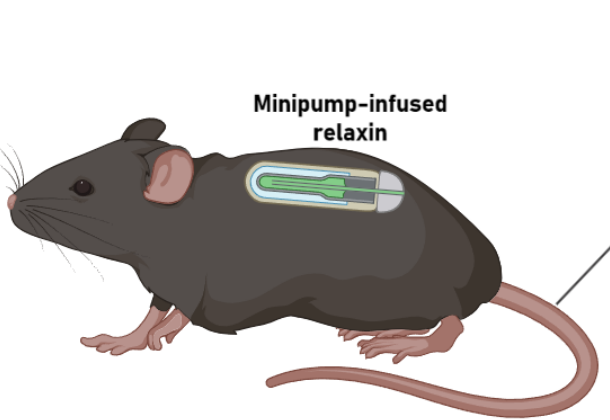
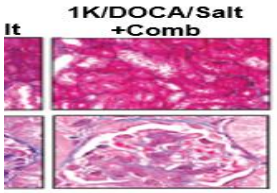
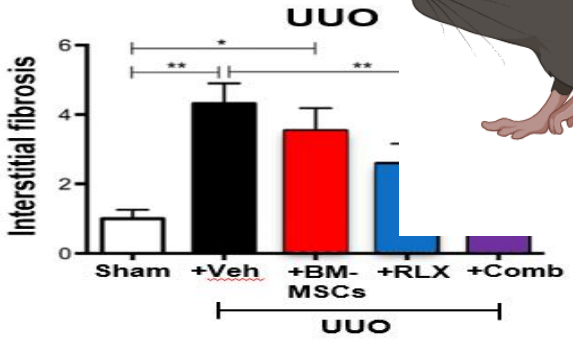
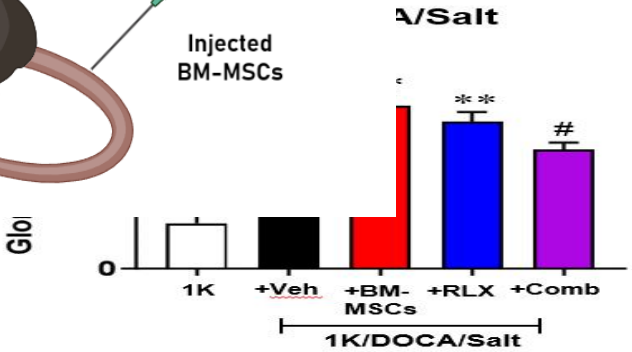










Huuskes BM et al., FASEB Journal 2015; 29:540-553

Li Y et al., Br J Pharmacol 2021; 178:1164-1181

MONASH University

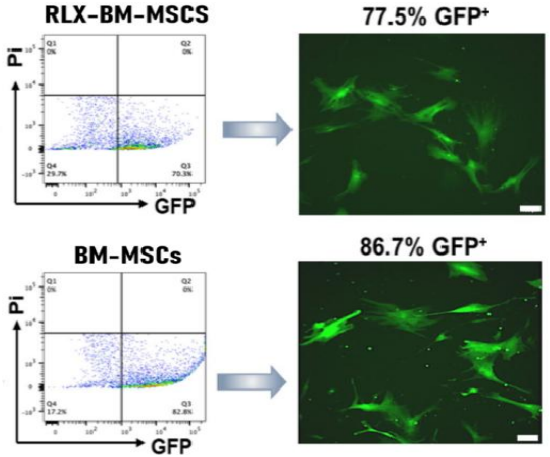
COMBINING STEM CELLS WITH AN ANTI-FIBROTIC THERAPY:

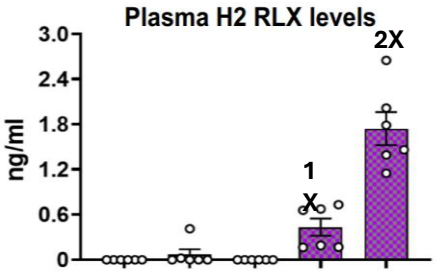
RELAXIN

The renoprotective efficacy and safety of genetically-engineered human bone marrow-derived mesenchymal stromal cells expressing anti-fibrotic cargo

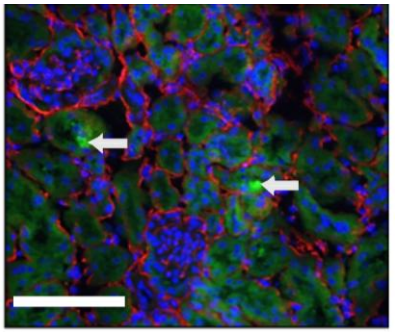
Yifang Li[1,3], Alex Hunter[1,3], Miqdad M. Wakeel[1,3], Guizhi Sun[2,4], Ricky W. K. Lau[2,3], Brad R. S. Broughton[1,3], Ivan E. Oyarce Pino[1,3], Zihao Deng[5], Tingfang Zhang[2,3], Padma Murthi[1,3], Mark P. Del Borgo[1,3], Robert E. Widdop[1,3], Jose M. Polo[2,4,6,7], Sharon D. Ricardo[2,3*] and Chrishan S. Samuel[1,2,3,8*]

Stem Cell Res Therapy 2024; 15:375

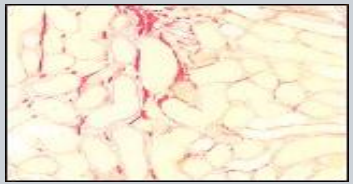
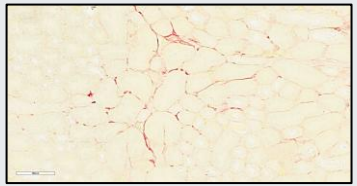




RLX-BM-MSC (7 days)



KEY FINDINGS FROM MURINE MODELS OF KIDNEY DISEASE

Model	Results
Ischemia reperfusion injury (IRI)  *7 days*	↓ epithelial damage ↓ inflammation ↓ interstitial fibrosis ↓ glomerulosclerosis
High-salt induced hypertensive injury  *8 weeks*	↓ hypertension ↓ inflammation ↓ interstitial fibrosis ↓ vascular rarefaction ↓ proteinuria *Maintained in the presence of an ACE inhibitor (perindopril)
Safety study – 9 months after cell treatment cessation	No adverse effects on animal mortality No major organ abnormalities

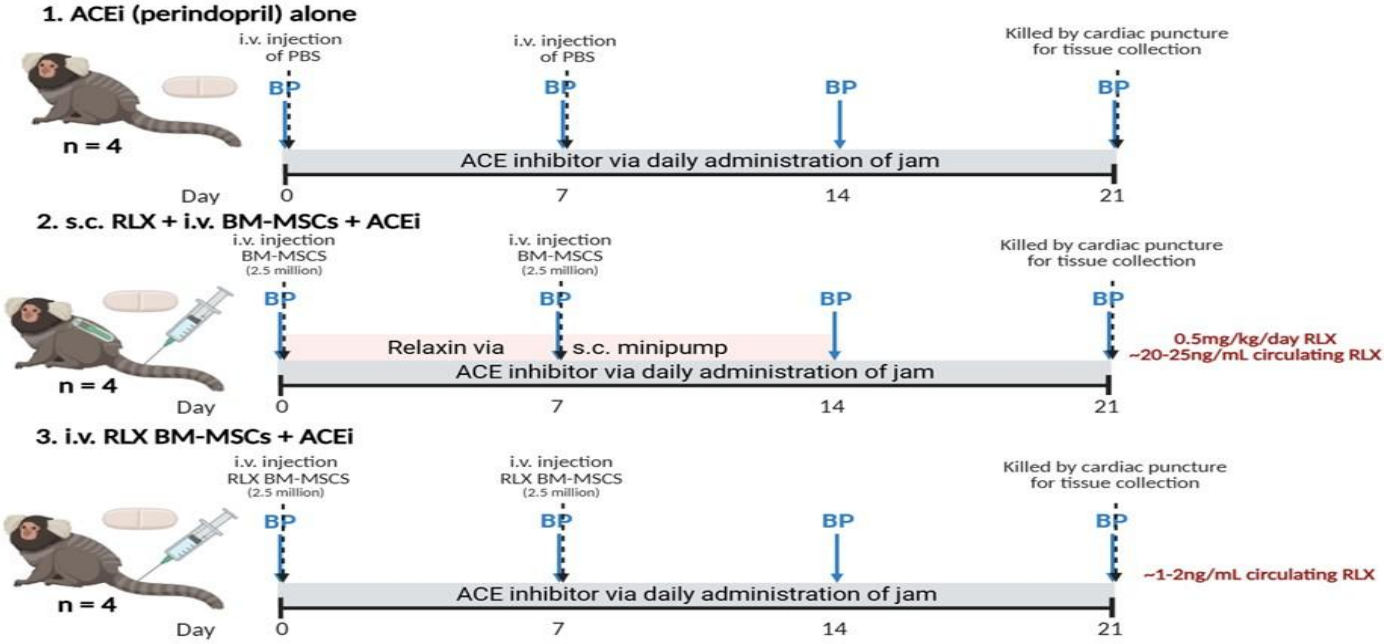
Li Y et al., Stem Cell Res Therapy 2024; 15:375

COMBINING STEM CELLS WITH AN ANTI-FIBROTIC THERAPY:

RELAXIN

Hypertensive marmosets
[7-10 years]

- Hypertensive from 5 years (>140mmHg)
- Age-related organ damage and dysfunction from 6-8 years



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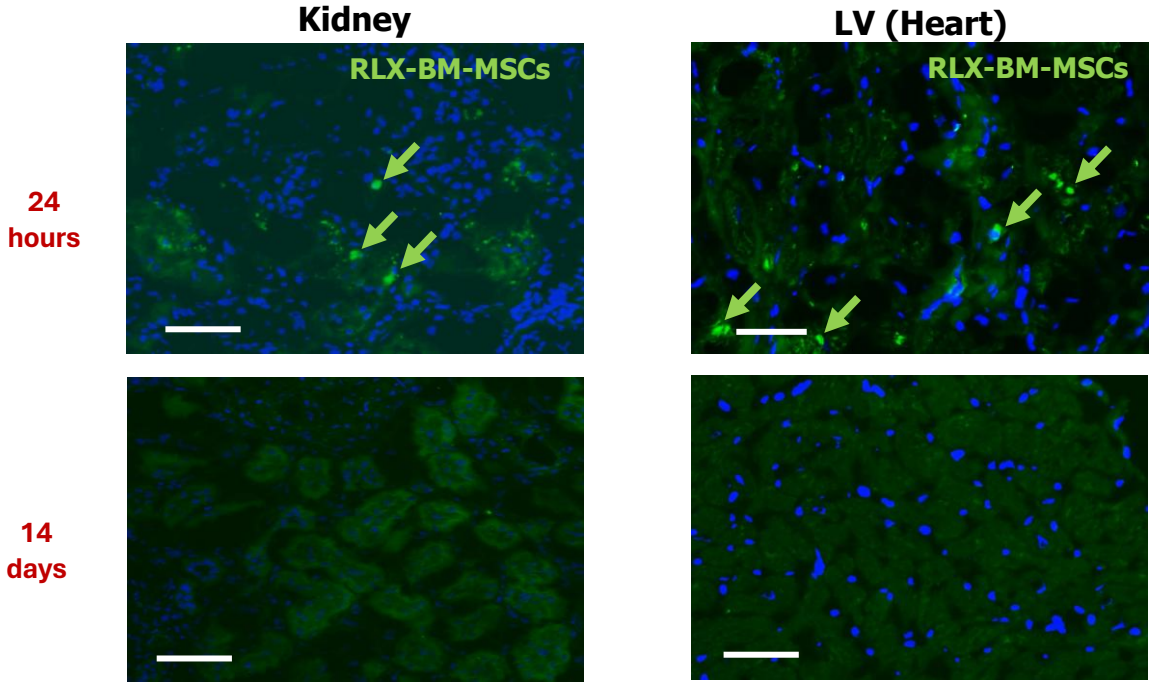
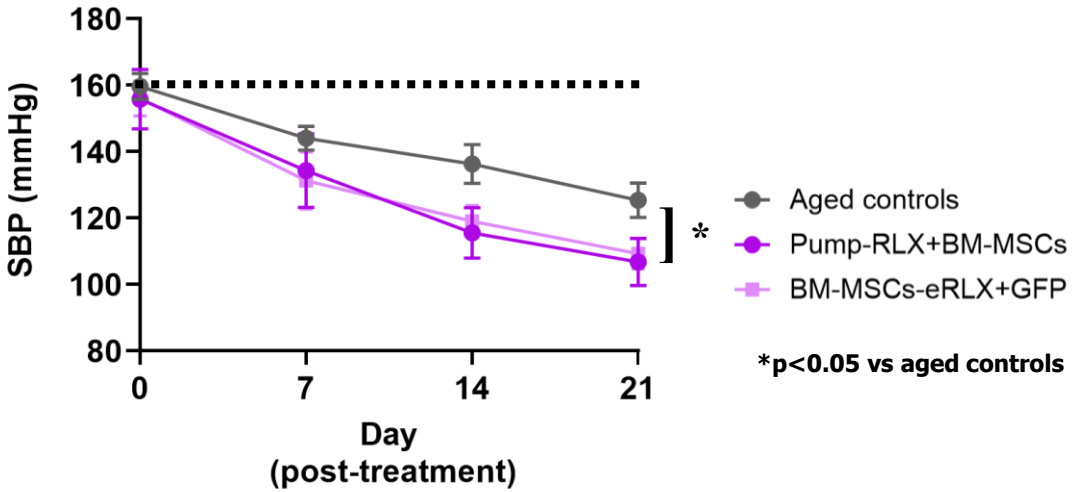
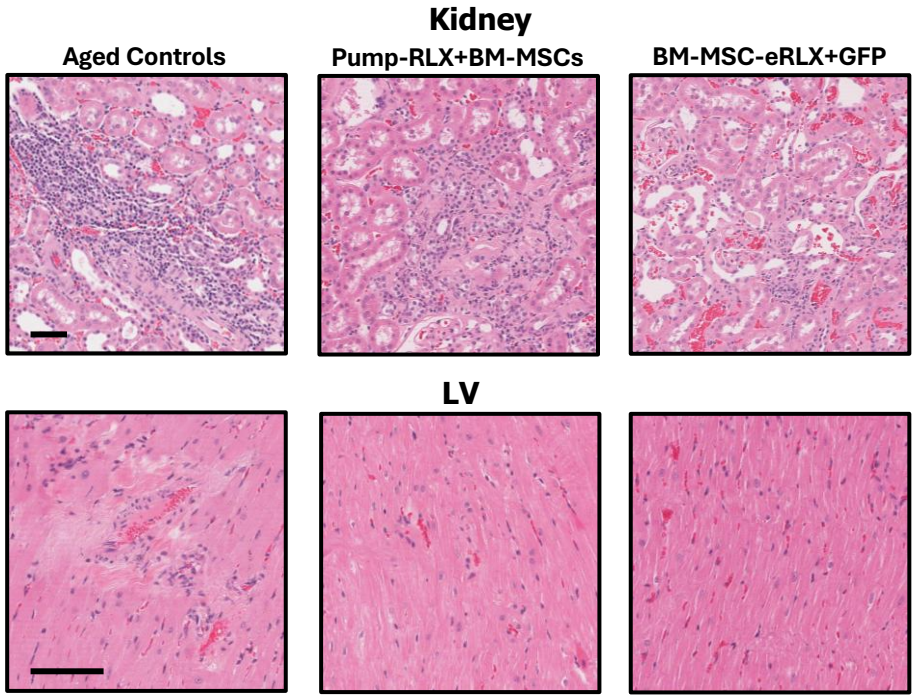
RLX-BM-MSCs MIGRATED TO SITES OF INJURY

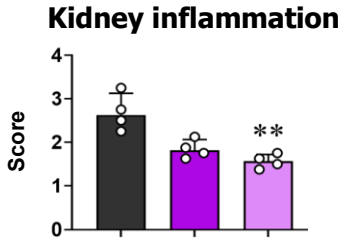


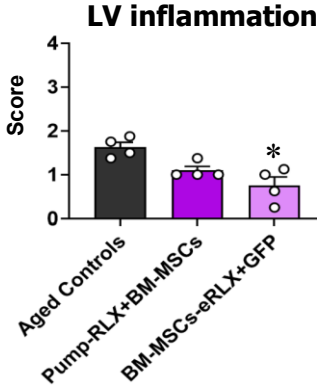
COMBINATION CELL TREATMENTS FURTHER REDUCED SYSTOLIC BLOOD PRESSURE



RLX-BM-MSCs REDUCED ORGAN INFLAMMATION





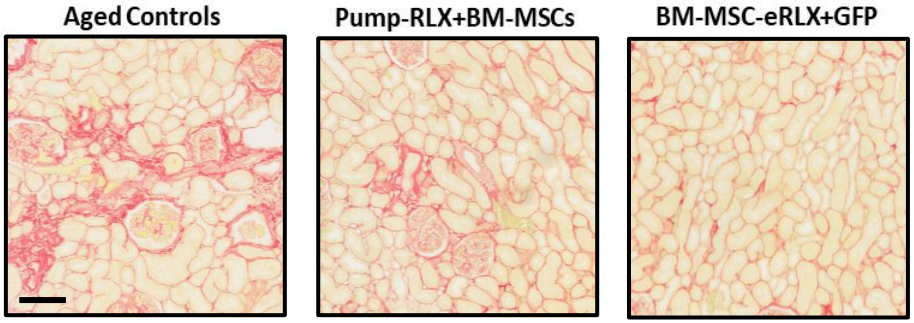


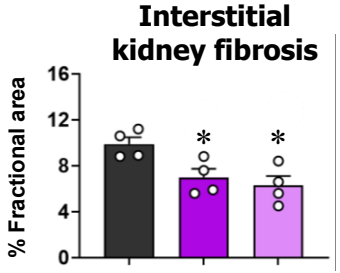
*p<0.05, **p<0.01 vs aged controls

0-4 grading system: Hsieh C et al., Arthritic Care Res 2011; 63:865-874

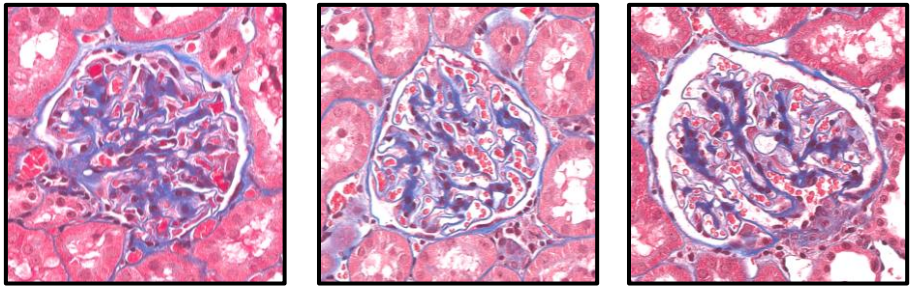
RLX-BM-MSCs REDUCED KIDNEY FIBROSIS

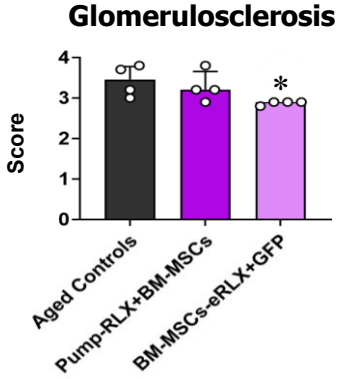
Interstitial kidney fibrosis





Glomerulosclerosis





*p<0.05 vs aged controls

0-4 grading system: Kelly DJ et al., Kidney Int 1998; 54:343-352

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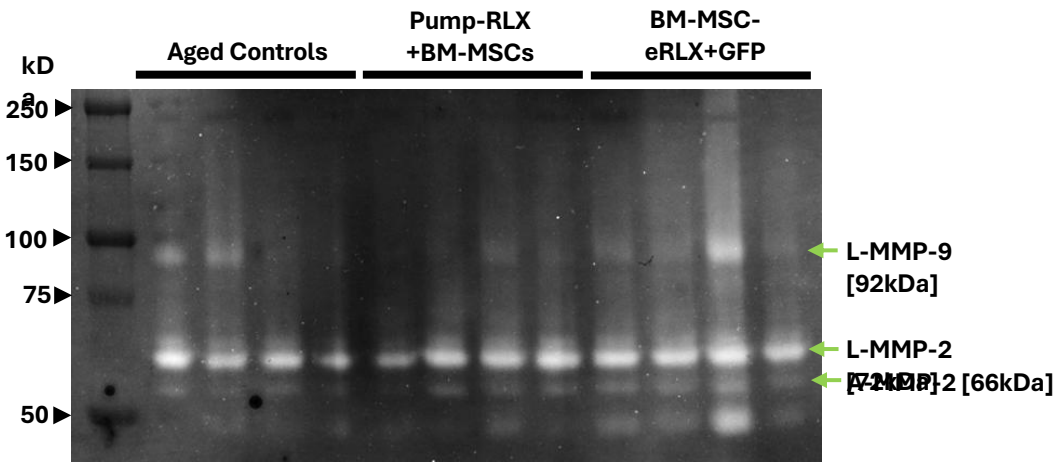
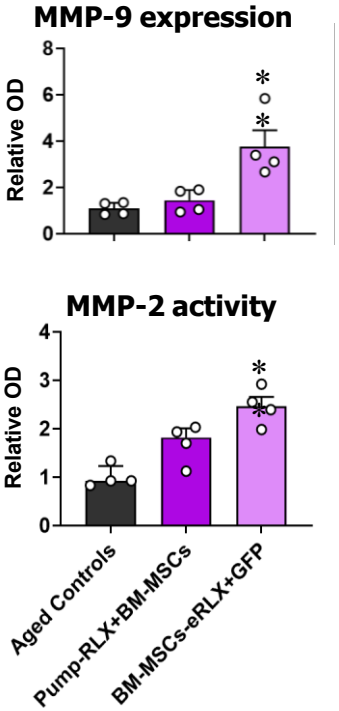
RLX-BM-MSCs INCREASED RENAL GELATINASE LEVELS AND ACTIVITY





**p<0.01 vs aged controls

SUMMARY & CONCLUSIONS

Treatment	Results
Pump-RLX+BM-MSCs	↓ hypertension ↓ interstitial fibrosis (kidney, LV) ↓ cardiomyocyte hypertrophy (LV) ↓ vascular rarefaction (kidney)
BM-MSC-eRLX+GFP	↓ hypertension ↓ inflammation (kidney) ↓ interstitial fibrosis (kidney, LV) ↓ glomerulosclerosis (kidney) ↓ cardiomyocyte hypertrophy (LV) ↓ vascular rarefaction (kidney, LV) ↑ MMP-9 expression/MMP-2 activity (kidney)
Safety study – 6 months after cell treatment cessation	No adverse effects on animal mortality No major organ abnormalities

- **The cell-based treatments induced greater organ protection compared to ACEi treatment alone**
- **The cell-based treatments were able to maintain therapeutic efficacy in the presence of ACEi**

RLX-BM-MSCs represent a novel treatment option for CKD

MONASH University

ACKNOWLEDGEMENTS

Samuel Lab

Former members

Dr. Brooke Huuskes
Dr. Amril Badawi
Dr. Yifang Li
Mr. Miqdad Wakeel
Dr. Padma Murthi
Dr. Chao Wang
Ms. Zoe Brown

Current members

Dr. Adriana Knezic
Dr. Amlan Chakraborty
Chen Wei
Jennie Charoenphannathon
Deidree Somanader
Mahesh Dharmakumara
Thi (Khloe) Pham
Yandi Ding
Adem Goktepe

MONASH University

Prof. Sharon Ricardo

Prof. Robert Widdop

Prof. Jose Polo

Prof. Peter Kerr

Australian Government
National Health and Medical Research Council
NHMRC

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