# Relaxin, biomarkers in AKI/HRS

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Chair of Translational Liver Research


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THE UNIVERSITY of EDINBURGH

# Disclosures

**Consultancy:** Galecto Biotech, Gilde Healthcare, Caldan Therapeutics, Cypralis, Arix Bioscience, Ferring Pharmaceuticals

**Scientific Advisory Boards:** Novartis, Galecto Biotech, NIHR Leeds Medtech and In-vitro Diagnostic Cooperative (MIC)

**Research funding:** GlaxoSmithKline, Intercept Pharmaceuticals, Novartis (IIT)

# Acute kidney injury in cirrhosis

Affects up to 50% of hospitalized patients with cirrhosis

Increases mortality by 7-fold compared to patients without AKI

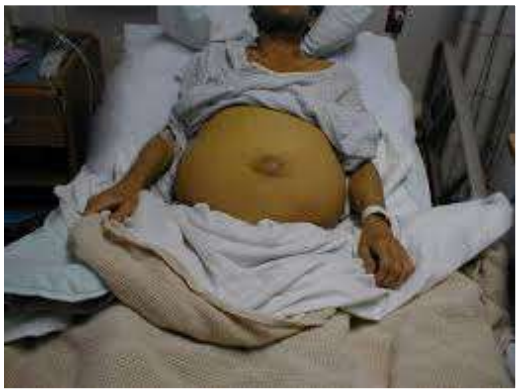
Median survival of hepatorenal syndrome (AKI-HRS) ~1 month

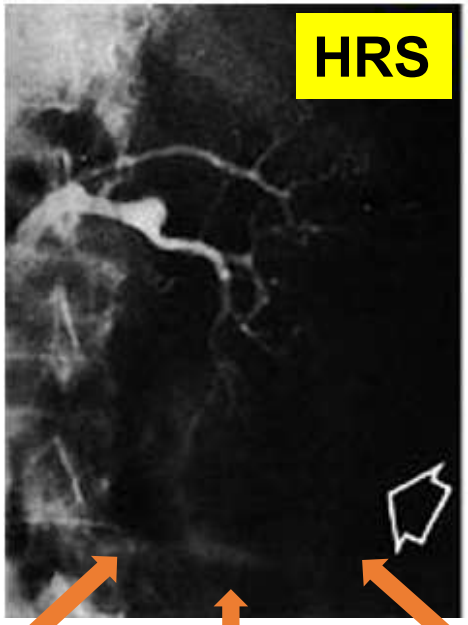
**Diagnosis is challenging** (serum creatinine is a poor proxy of renal health in cirrhosis; no specific diagnostic tests; AKI causes co-exist)

**Response to vasoconstrictor therapy** in AKI-HRS is **variable**, **sub-optimal** (~40%), **unpredictable** and **potentially hazardous**

# Pathophysiology of AKI-HRS

Central feature of HRS is intense **renal vasoconstriction** (cortex)





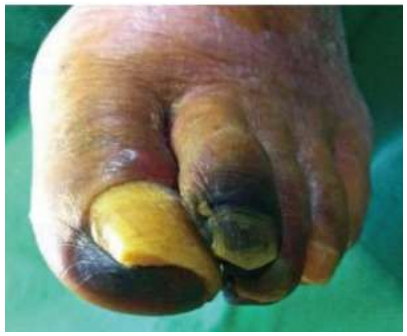

**The kidneys are potentially salvageable**


**Systemic inflammation**

**Microvascular dysfunction**

**Chronic kidney disease**

# AKI in cirrhosis - a new approach to improve outcomes



Terlipressin – off target effects in up to 20%

AP&T Alimentary Pharmacology and Therapeutics

INVITED EDITORIALS | Free Access

**Editorial: tackling hepatorenal syndrome—terlipressin for all, or time for a stratified approach?**

F. J. Gifford ✉, J. A. Fallowfield

First published: 15 June 2017 | https://doi.org/10.1111/apt.14098

**New biomarkers – blood, urine, imaging**

- Early assessment of prognosis
- Predict and monitor terlipressin response (accurate phenotyping)

**Alternative treatments (e.g. serelaxin)**

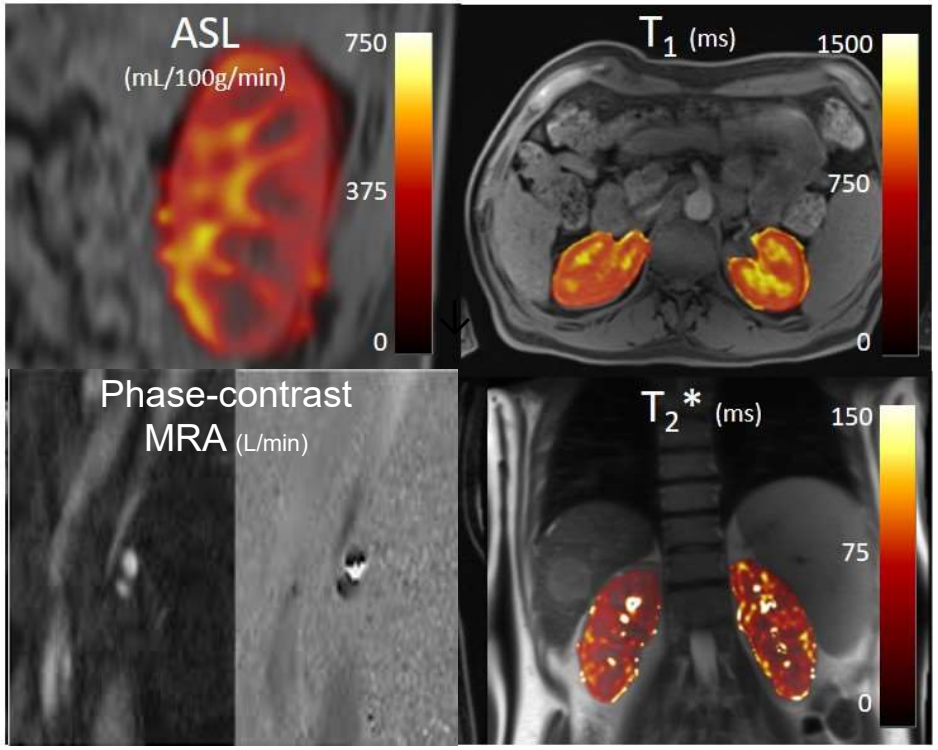
# AKI biomarker studies

- Chief Scientist Office (CSO) Catalytic Grant (Ref: CGA/16/45): 'Prognostic Biomarkers for Acute Kidney Injury in Liver Cirrhosis'
  - n=53; pKIM-1, FeNa, uL-FABP, uPCR, uKIM-1 on admission
- Edinburgh and Lothians Health Foundation Research Grant (Ref: SO7074): 'Superior markers of renal dysfunction in patients admitted for liver transplant assessment could improve both short and long term outcomes'
  - n=?; pre-transplant biofluid biomarkers, renal MRI, impedance cardiography, aortic pulse wave velocity, retinal optical coherence tomography
- Sir Jules Thorn application (unsuccessful) – MRI to phenotype AKI, stratify/monitor terlipressin response – resubmission ?NIHR EME

# Multiparametric renal MRI

## A composite biomarker of kidney microstructure and haemodynamics

↓ **cortical perfusion** is a landmark feature of HRS




↓ **cortical $T_1$** linked to disease severity, adverse outcomes
↑ **$T_1$ in CKD**

Progressive ↓ in cirrhosis; can **monitor response** to vasoactive drugs

Reflects degree of intra-renal hypoxia and **progression of AKI**

Edinburgh Imaging
www.ed.ac.uk/edinburgh-imaging

SIEMENS Healthineers

THE RENAL ASSOCIATION founded 1950

BRS British Renal Society Multi-professional working

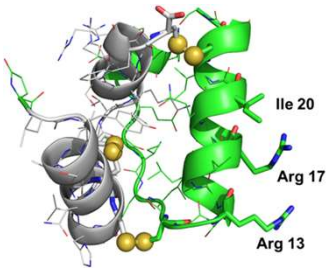
Kidney Research UK Funding research to save lives

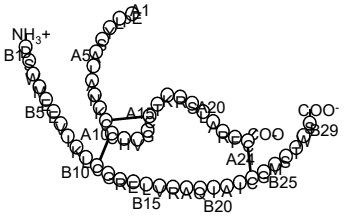
**A single, <30 minute, non-contrast, free-breathing MRI scan**

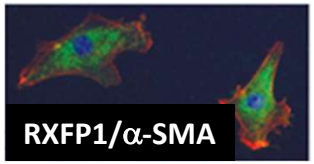
Cox E *et al*., Front Physiol 2017; Bradley C *et al*., J Hepatol 2018; Snowdon V *et al*., PLoS Med 2017

# Recombinant human relaxin-2 (serelaxin)

## Anti-fibrotic and vasoactive effects in preclinical models



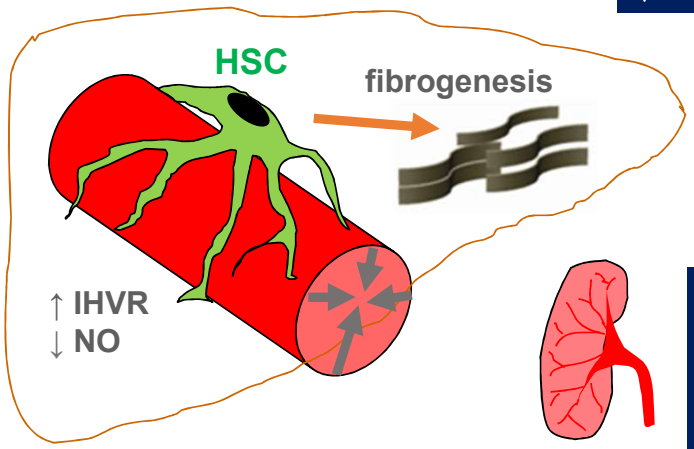






liver

↓ HSC-myofibroblast activation, contractility

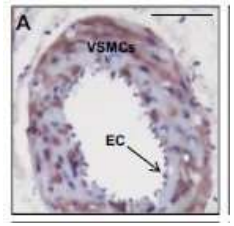
↑ matrix metalloproteinases
↓ fibrosis




kidney

↓ portal pressure
↑ intrahepatic NO
↑ / ↔ hepatic perfusion
↔ mean arterial BP

↓ endothelial dysfunction ↓ renal vascular resistance
↑ renal blood flow
↑ GFR
↔ mean arterial BP





Fallowfield JA *et al.*, Hepatology 2014
Snowdon VK *et al.*, PLoS Medicine 2017
McBride A *et al.*, Sci Rep 2017

# Serelaxin: renal and hepatic haemodynamic data

## Novartis sponsored Phase II Trial (NCT01640964)

**Percent changes in blood flow from baseline (95% CI)**

| VESSEL | Total (left + right) renal artery | Superior abdominal aorta | Superior mesenteric artery | Portal vein | Hepatic artery | Total liver blood flow (portal vein + hepatic artery) |
|---|---|---|---|---|---|---|
| Serelaxin | **+ 65.4** (40.0, 95.5) | **+ 7.8** (1.8, 14.2) | **– 1.5** (–8.0, 18.1) | **– 11.9** (–22.1, –0.3) | **+ 18.0** (3.4, 44.2) | **- 0.54** (-7.3, 7.8) |
| Terlipressin | **+ 13.5** (3.3, 33.3) | **– 18.8** (–23.6, –13.7) | **– 36.9** (–45.0, –27.6) | **– 40.0** (–57.2, –16.1) | **– 7.1** (–32.7, 28.1) | **- 34.7** (-13.3, -50.8) |

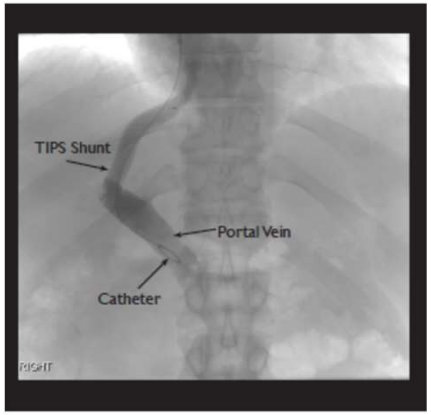
- Link between improved renal haemodynamics and renal *function* has not yet been established

**Snowdon V *et al*., PLoS Medicine 2017**

# Serelaxin: portal pressure effect in TIPSS patients

## Novartis sponsored Phase II Trial (NCT01640964)

- Small exploratory sub-study (*n*=6)
  - TIPSS portogram ✓
  - PPG (PVP-IVCP) >5mm Hg ✓
  - Serelaxin i.v. infusion with PVP monitoring for 120 min
- Serelaxin was well tolerated in advanced cirrhosis
- Rapid and potentially clinically significant ↓ in PP



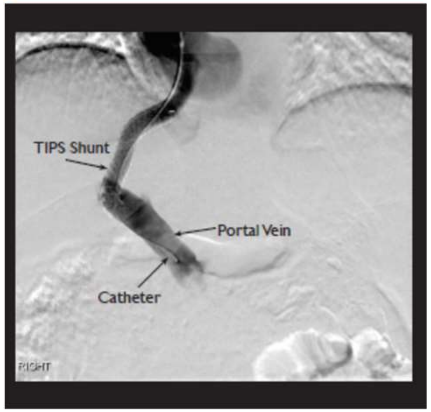




**Table 1. Percent reductions in PPG and PVP from baseline during serelaxin infusion**

| | PPG | PVP | | | |
|---|---|---|---|---|---|
| Time point (min) after initiation of serelaxin | ≥120 (n=6) | 30 (n=6) | 60 (n=6) | 120 (n=6) | 135 (n=5) |
| % reduction geometric mean (95% CI) | 31.3 (–66.5, 71.6) | 7.2 (–16.4, 26.1) | 15.5 (–13.8, 37.2) | 25.2 (–12.7, 50.3) | 33.9 (–15.4, 62.1) |

**Lachlan NJ *et al*., AASLD 2016**

# Serelaxin To Lower Portal Pressure (STOPP)

## Novartis funded Investigator Initiated Trial (NCT02669875)

- Randomised, double-blind, placebo-controlled, Phase II, single centre study
- Male and female adult patients with cirrhosis and CSPH (HVPG >10mmHg) at baseline
- n=9 serelaxin, n=2 placebo before drug supply expired (target n=20)
- Studied the effects of serelaxin on portal and systemic haemodynamics (ICG clearance, impedance cardiography, APWV)
- Data in submission
- Novartis have closed all global serelaxin programmes

Experimental Physiology
A Publication of The Physiological Society

RESEARCH PAPER | Full Access

## Serelaxin attenuates renal inflammation and fibrosis in a mouse model of dilated cardiomyopathy

Beverly Giam, Po-Yin Chu, Sanjaya Kuruppu, A. Ian Smith, Duncan Horlock, Aishwarya Murali, Helen Kiriazis, Xiao-Jun Du, David M. Kaye, Niwanthi W. Rajapakse

First published: 12 October 2018 | https://doi.org/10.1113/EP087189

American Journal of Transplantation
AST AMERICAN SOCIETY OF TRANSPLANTATION ASTS

BRIEF COMMUNICATION | Full Access

## Serelaxin induces Notch1 signaling and alleviates hepatocellular damage in orthotopic liver transplantation

Shoichi Kageyama, Kojiro Nakamura, Bibo Ke, Ronald W. Busuttil, Jerzy W. Kupiec-Weglinski

First published: 21 February 2018 | https://doi.org/10.1111/ajt.14706 | Cited by: 6

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ORIGINAL RESEARCH

## Effects of human relaxin-2 (serelaxin) on hypoxic pulmonary vasoconstriction during acute hypoxia in a sheep model

SCIENTIFIC REPORTS

OPEN

## Serelaxin improves cardiac and renal function in DOCA-salt hypertensive rats

Dong Wang[1], Yuhuan Luo[1], Komuraiah Myakala[1], David J. Orlicky[2], Evgenia Dobrinskikh[1], Xiaoxin Wang[1] & Moshe Levi[1]

Received: 5 June 2017
Accepted: 26 July 2017

*Am J Physiol Renal Physiol* 314: F70–F80, 2018.
First published October 4, 2017; doi:10.1152/ajprenal.00201.2017.

RESEARCH ARTICLE | *Renal Hemodynamics*

## Effects of serelaxin on renal microcirculation in rats under control and high-angiotensin environments

**Weijian Shao, Carla B. Rosales, Camila Gonzalez, Minolfa C. Prieto, and L. Gabriel Navar**
*Department of Physiology, Tulane Hypertension and Renal Center of Excellence, Tulane University School of Medicine, New Orleans, Louisiana*

ELSEVIER

European Journal of Pharmacology

Volume 807, 15 July 2017, Pages 190-197

Cardiovascular pharmacology

# B7-33 replicates the vasoprotective functions of human relaxin-2 (serelaxin)

Sarah A. Marshall [a], Kelly O'Sullivan [a], Hooi Hooi Ng [a], Ross A.D. Bathgate [b, c], Laura J. Parry [a], Mohammed Akhter Hossain [b, d, 1], Chen Huei Leo [a] [1]

Bioconjugate Chemistry

Article

Cite This: Bioconjugate Chem. 2019, 30, 83−89

pubs.acs.org/bc

# Design and Synthesis of Potent, Long-Acting Lipidated Relaxin-2 Analogs

Avinash Muppidi, Sang Jun Lee, Che-Hsiung Hsu, Huafei Zou, Candy Lee, Elsa Pflimlin, Madhupriya Mahankali, Pengyu Yang, Elizabeth Chao, Insha Ahmad, Andreas Crameri, Danling Wang, Ashley Woods, and Weijun Shen*

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Supporting Information