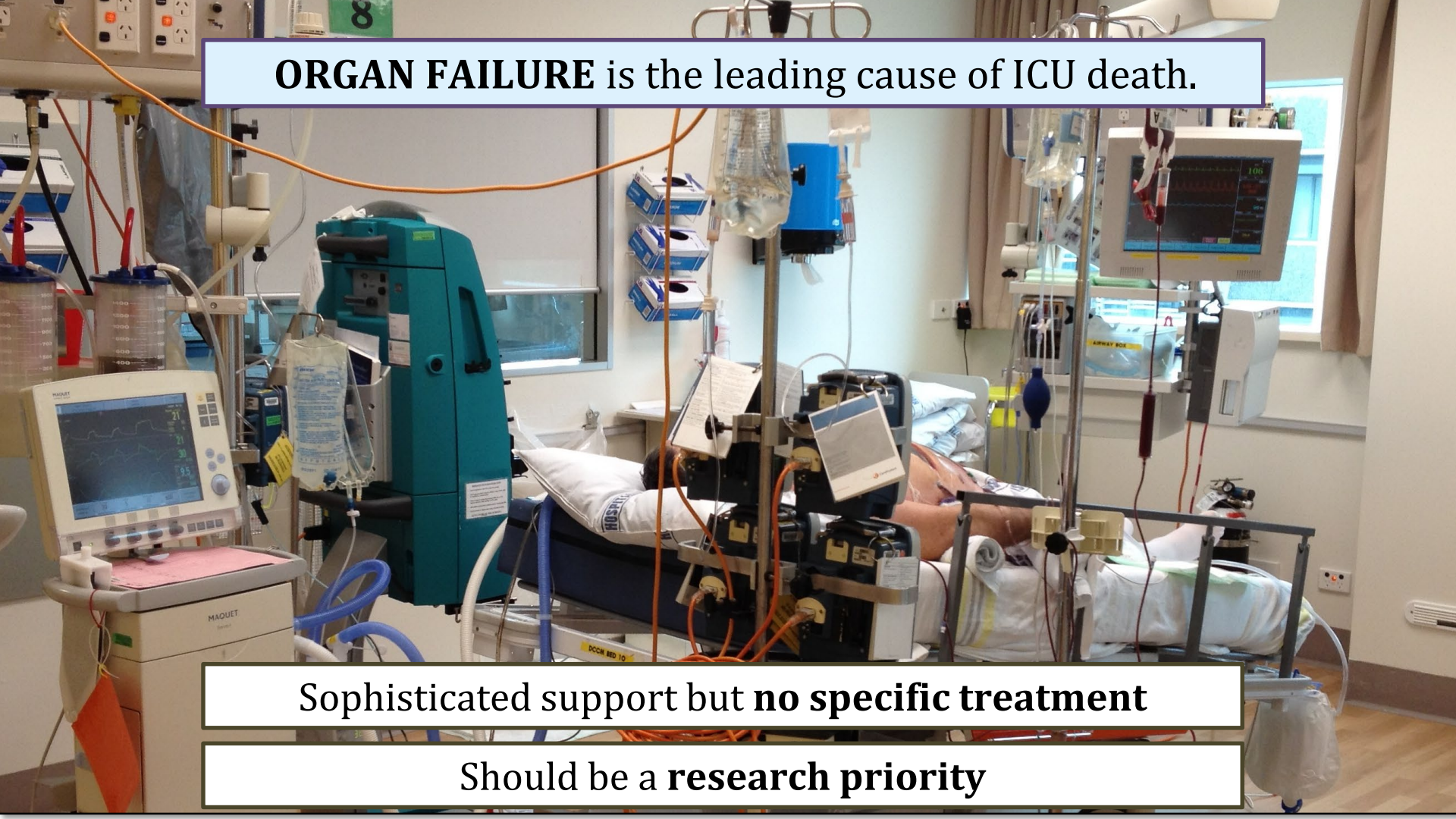
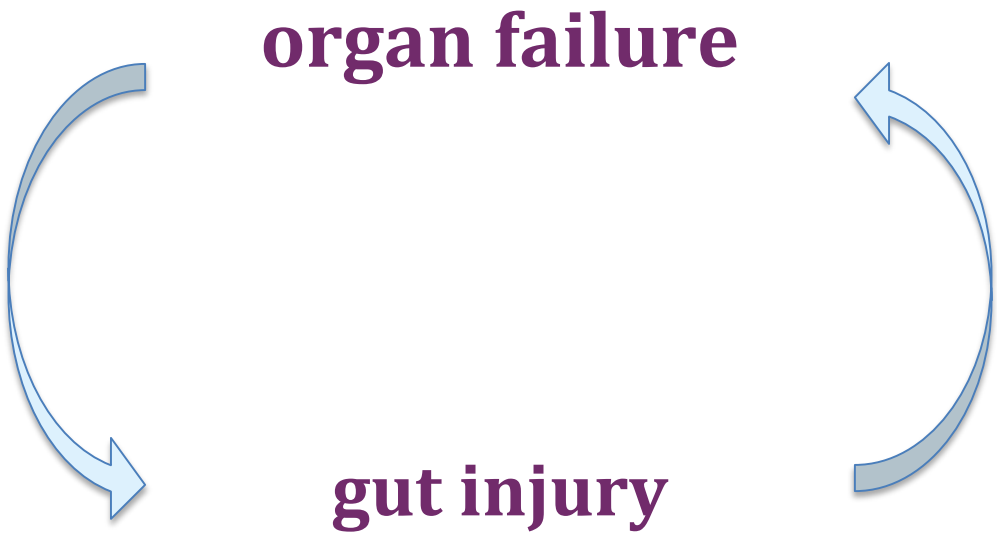
New treatment strategies for organ failure: the gut lymph model

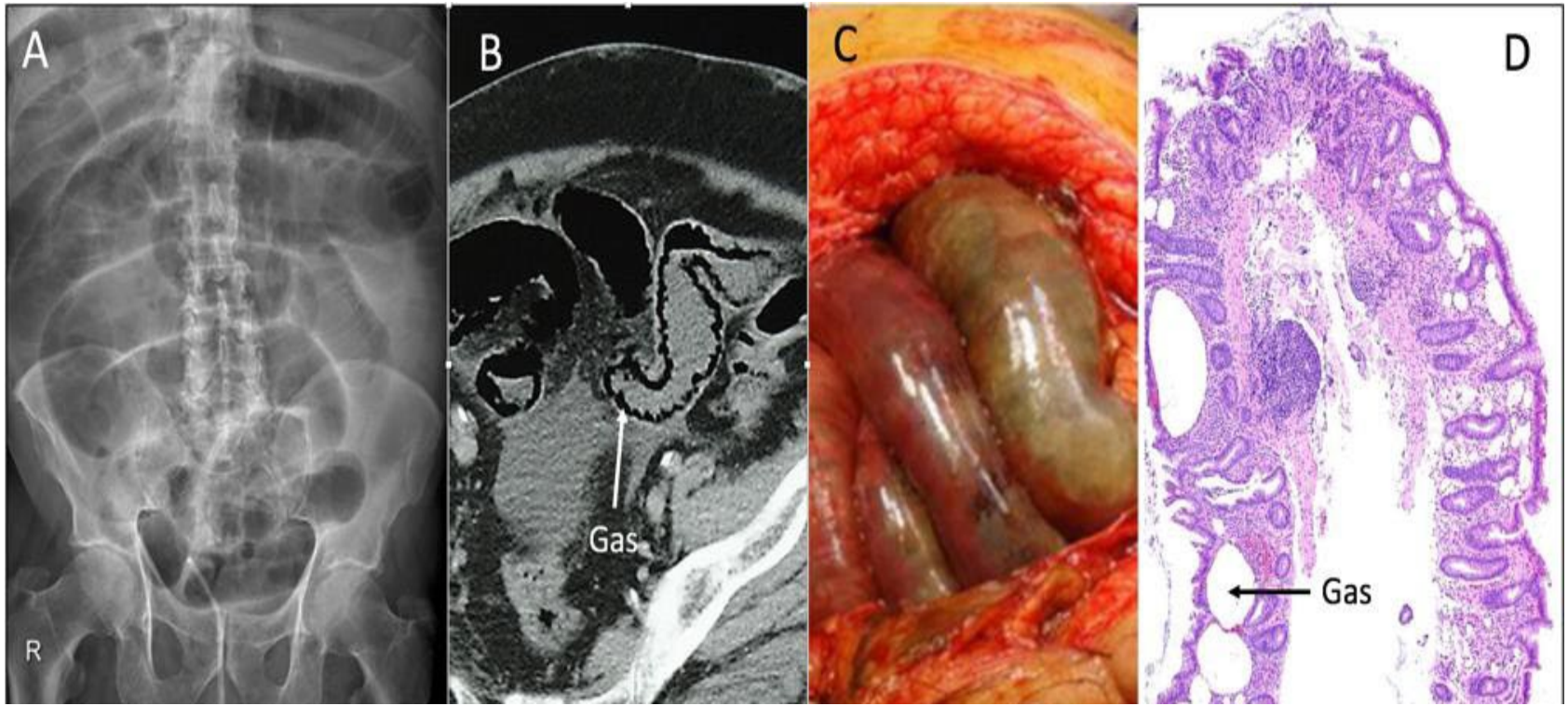
Professor John A Windsor
Surgical and Translational Research Centre
University of Auckland


‘ORGAN FAILURE is the plague of modern medicine’


ORGAN FAILURE is the leading cause of ICU death.
Sophisticated support but **no specific treatment**
Should be a **research priority**


organ failure
gut injury

Gut injury is a common feature of severe acute pancreatitis



Role of the gut in organ failure ?

- **Gut ‘motor’ concept** 1993

  Bacterial translocation

- **Gut ‘starter’ concept** 1994

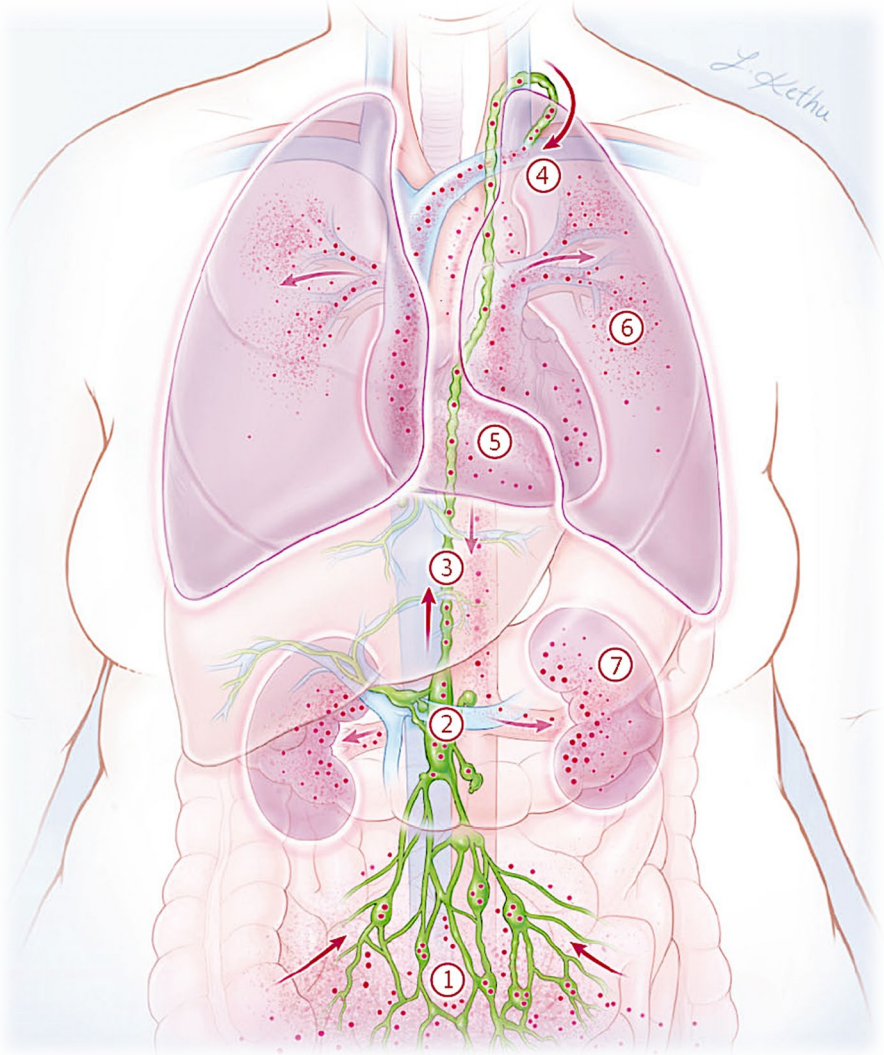
  Neutrophil activation

- **Gut ‘lymph’ concept** 2006

  Gut-lymph toxicity

Gut-lymph model of organ failure

Windsor et al.
JAMA Surgery 2022

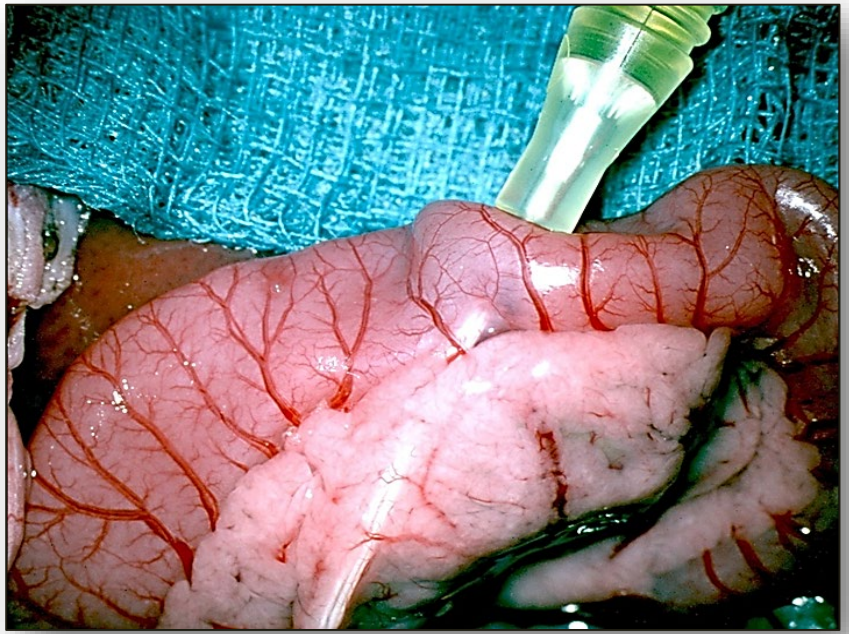


Evidence for gut-lymph model

- Gut lymph undergoes profound **compositional changes** that correlates with disease severity.
- Gut lymph collected during acute and critical illness is **toxic to cells and organs**.
- Gut lymph diverted by external drainage of thoracic duct lymph **attenuates organ failure**: acute respiratory distress syndrome (in trauma/hemorrhagic shock) and prevented cardiac dysfunction (in severe acute pancreatitis).

Windsor, Phillips, Trevaskis. JAMA Surgery. 2022

Gut lymph impairs organ function in AP

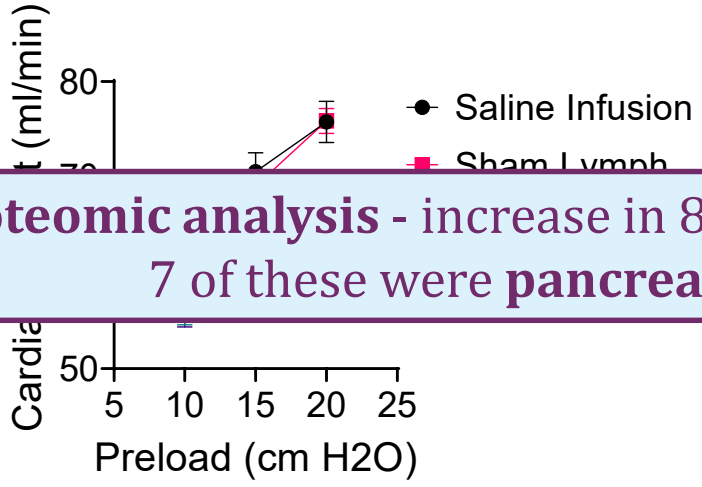


4% TC AP model and gut-lymph collection

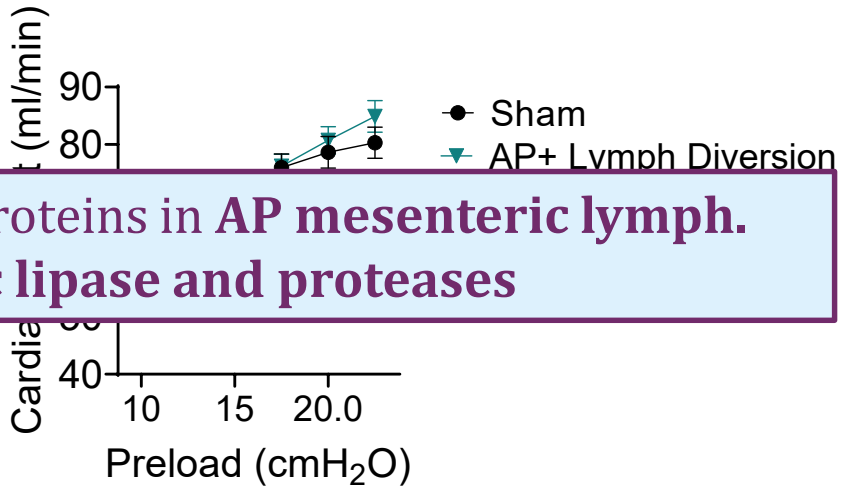
Ex vivo perfused and paced heart model

Gut lymph impairs organ function in experimental AP

Ex vivo working heart



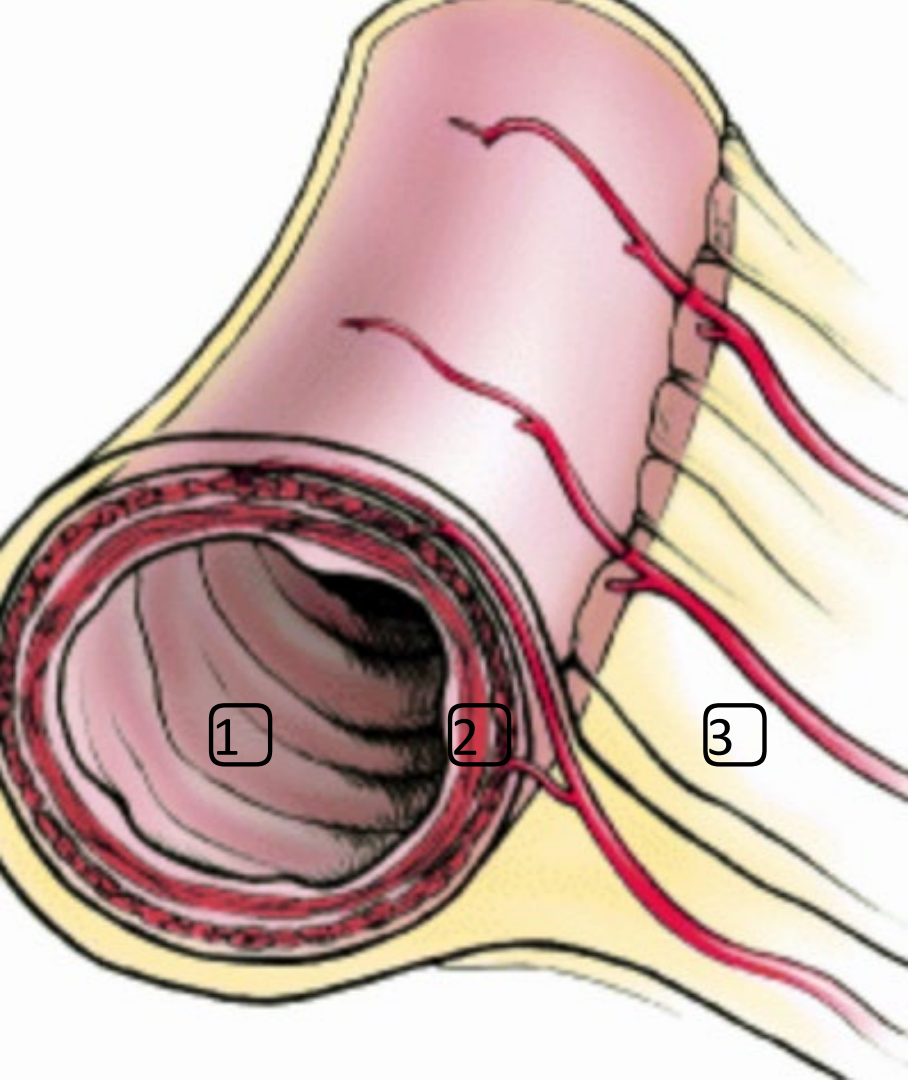
In vivo cardiac output



Proteomic analysis - increase in 8 proteins in **AP mesenteric lymph.**
7 of these were **pancreatic lipase and proteases**

- AP conditioned gut-lymph but not sham lymph reduces organ function (cardiac output)
- Cardiac output reduced in rats with AP but restored on gut-lymph diversion out of body

Shanhbag et al. ***Surgery*** *163 (2018) 1097–1105*
Mittal et al. ***Journal of Pancreas*** *2009 Mar 9; 10(2):130-142*



Examples of new treatment strategies based on gut-lymph model

1. Lumen
2. Mural
3. Lymph

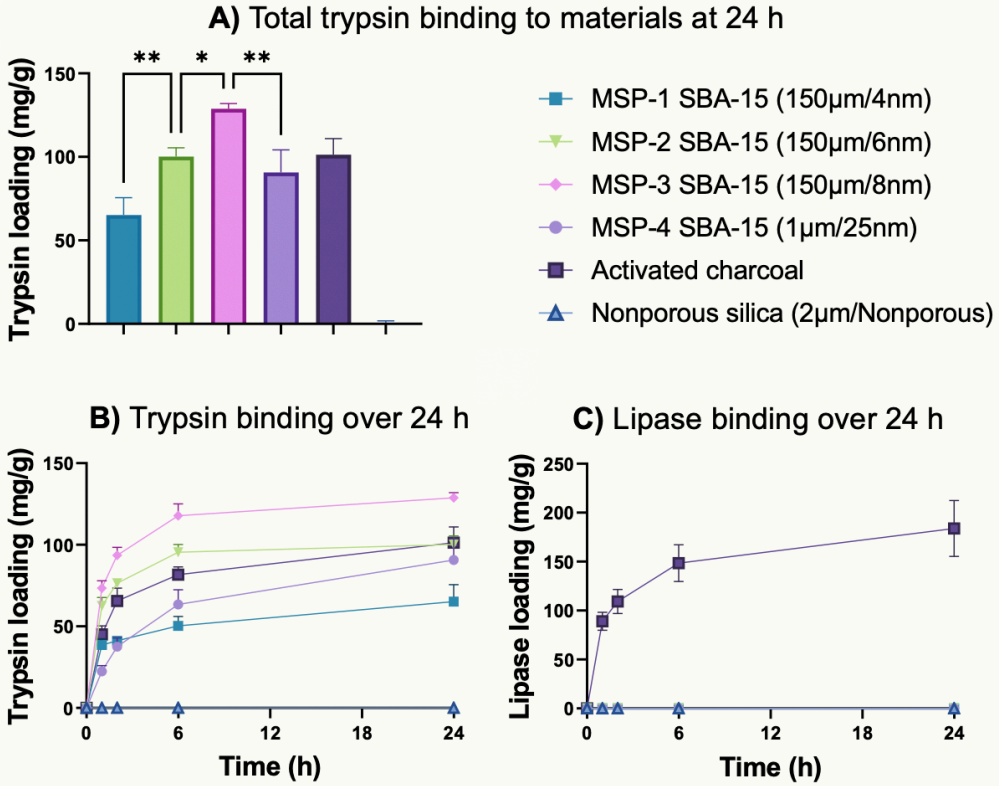
Luminal treatment strategies

Adsorption of pancreatic enzymes

- **Rationale:** Activated pancreatic enzymes in gut lumen exacerbate gut injury and enter mesenteric lymphatics
- **AIM:** To evaluate the ability of different adsorbent materials to bind and inhibit toxic pancreatic enzymes in gut lumen *in vitro* and *in vivo*.
- **Mesoporous silica particles** (MSP) with different particle sizes (1 - 150 µm) and pore sizes (4 - 25 nm) **and activated charcoal** were tested

hrc Health Research Council of New Zealand
THE UNIVERSITY OF AUCKLAND Te Whare Wānanga o Tāmaki Makaurau NEW ZEALAND
MEDICAL AND HEALTH SCIENCES
SURGICAL AND TRANSLATIONAL RESEARCH CENTRE
MONASH University
Pharmacy and Pharmaceutical Sciences

Ability of adsorbent materials to load pancreatic enzymes *in vitro*

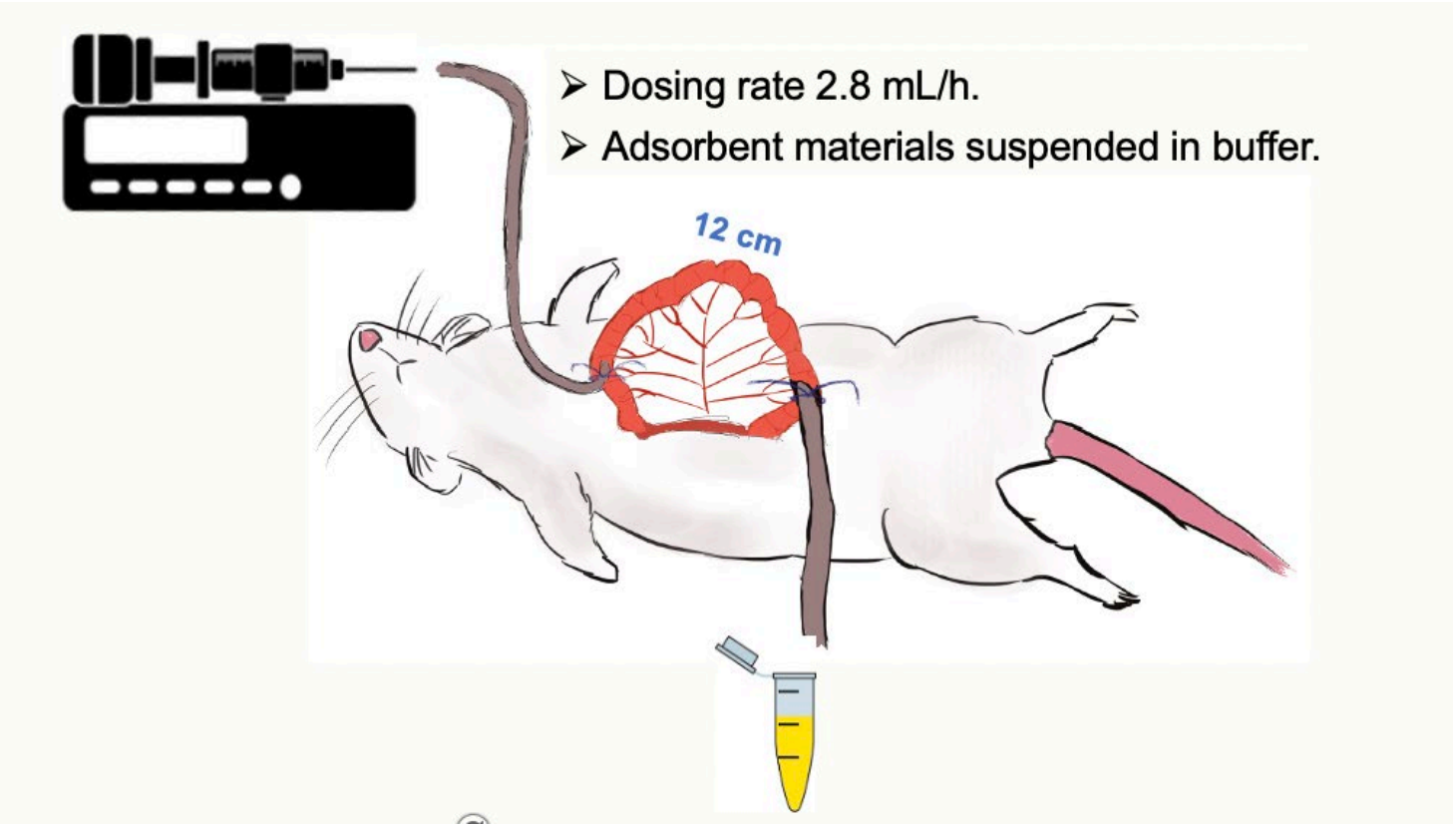


- Incubation with enzymes in Tris buffer

- **Pancreatic derived trypsin** was adsorbed by both MSPs and activated charcoal
- **Pancreatic derived lipase** only adsorbed by activated charcoal

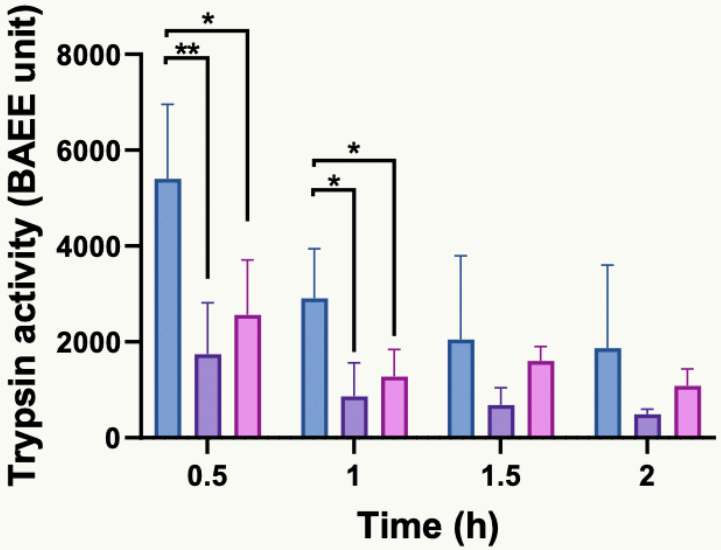
Ability of adsorbent materials to inhibit pancreatic enzymes in vivo

Rat intestinal perfusion model

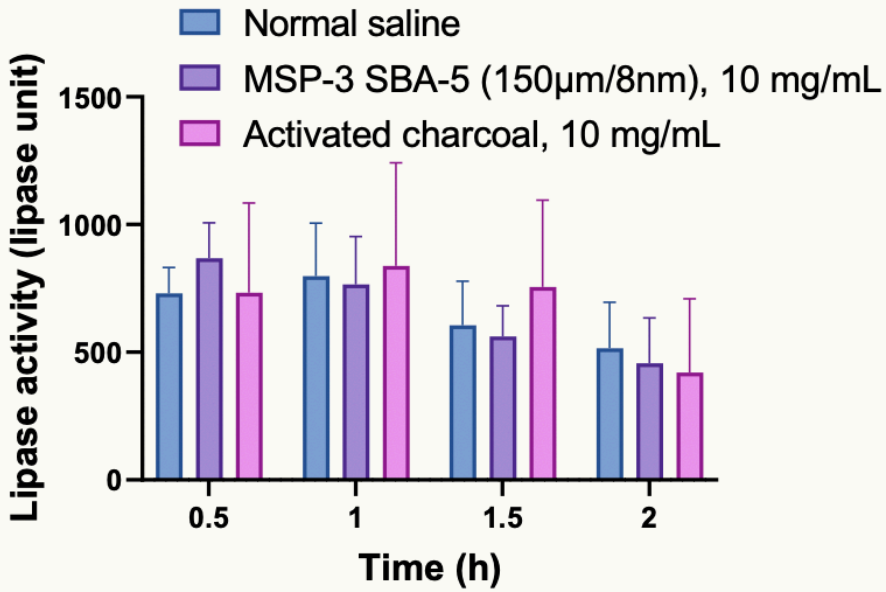


Ability of adsorbent materials to inhibit pancreatic enzymes *in vivo*

D) Pancreatic trypsin inhibition by adsorbent materials in rat intestine fluid



E) Pancreatic lipase inhibition by adsorbent materials in rat intestine fluid



Ability of adsorbent materials to inhibit pancreatic enzymes *in vivo*

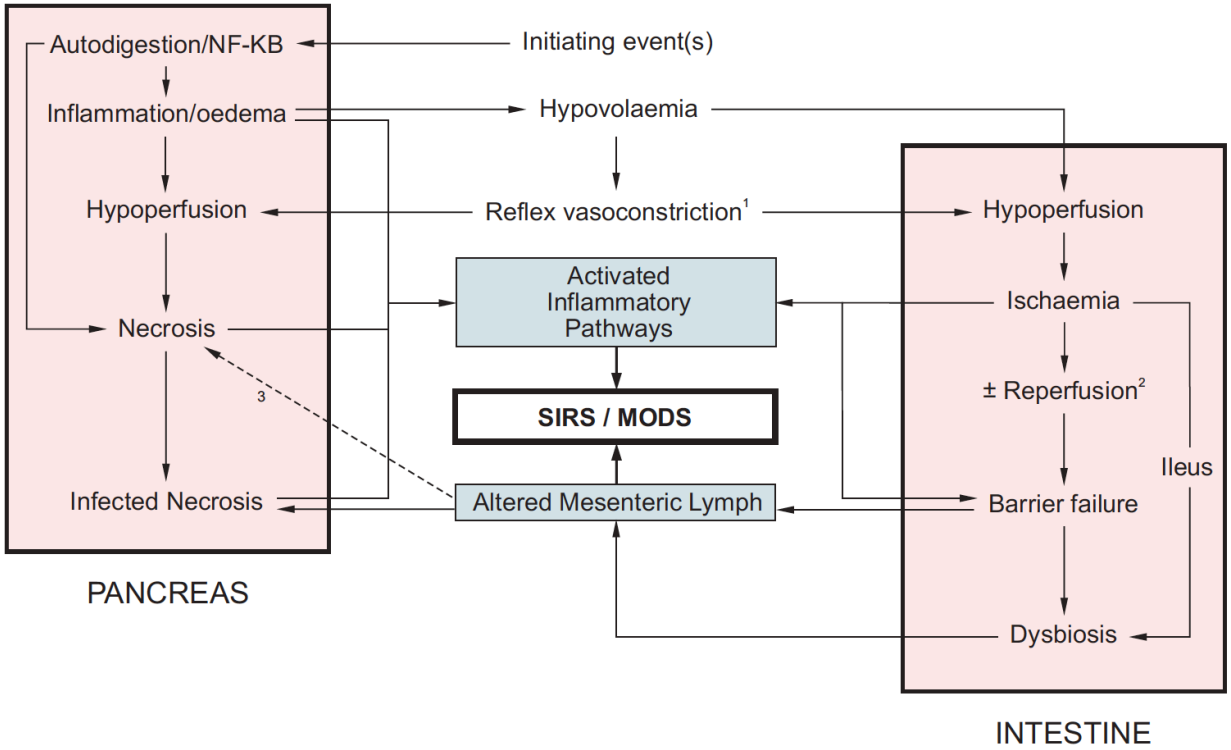
CONCLUSIONS

- Pancreatic trypsin activity in rat intestine significantly reduced in the first hour of MSP or activated charcoal infusions
- Pancreatic lipase activity in rat intestine did not change after either MSP or activated charcoal
- MSPs do not bind lipase because of slight negative charge, adding amine group (slight positive charge), changing pore size ± higher dose will be enough to bind lipase

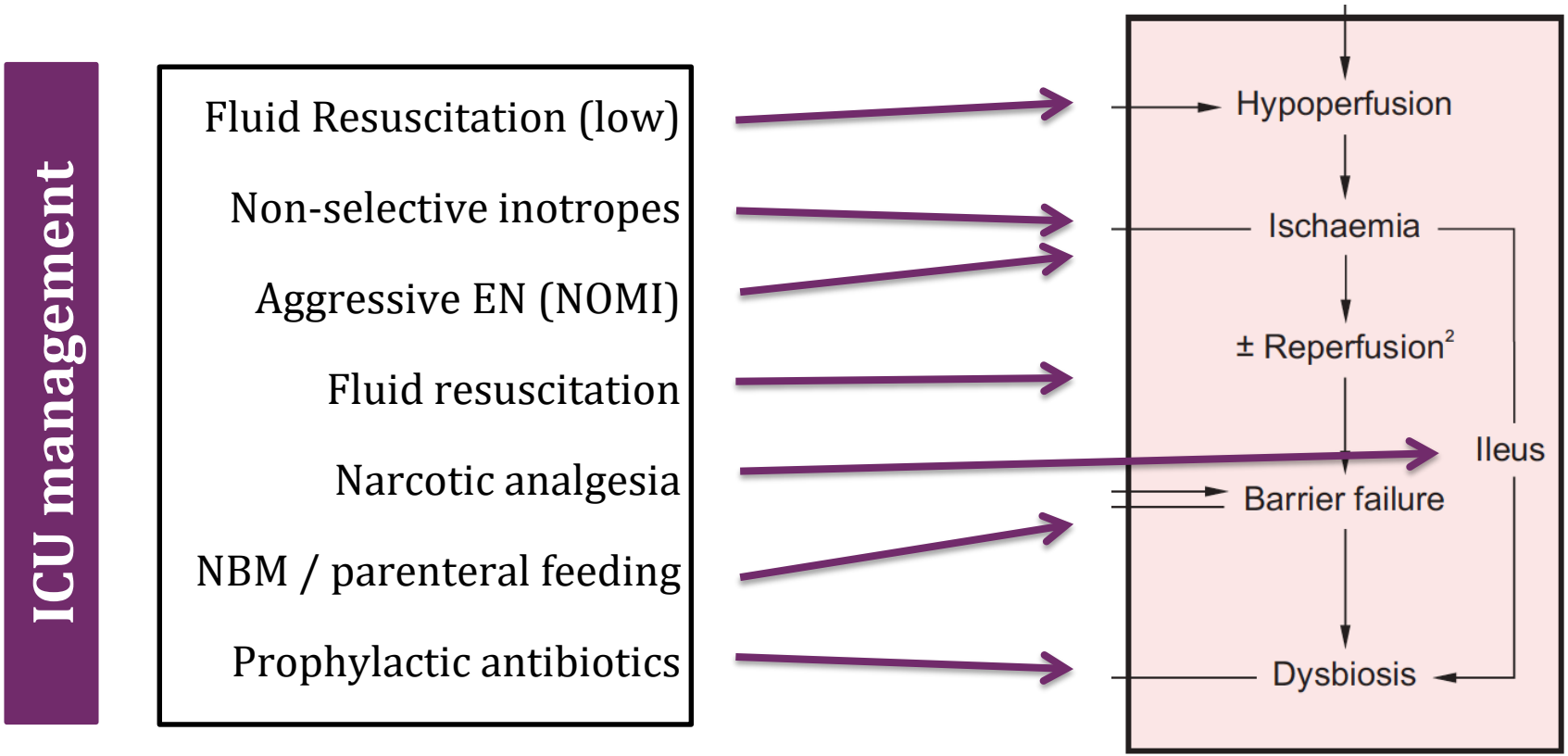
Mural treatment strategies

- Gut protection strategies
- Oxygen microbubbles
- Sodium butyrate

Management of severe acute pancreatitis can increase gut injury



Some of the gut injury is iatrogenic



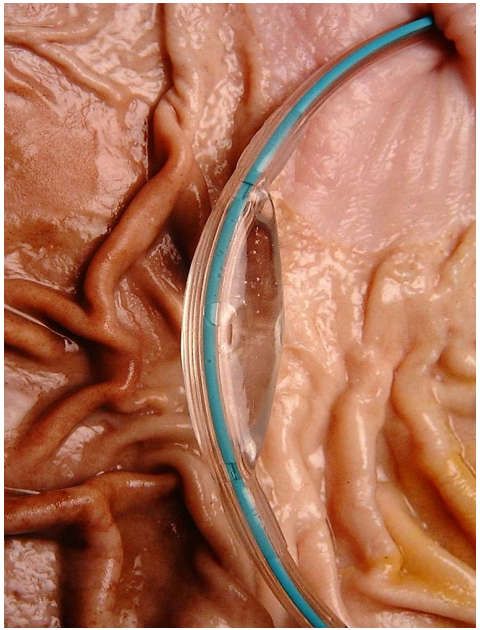
‘Gut protection’ strategies

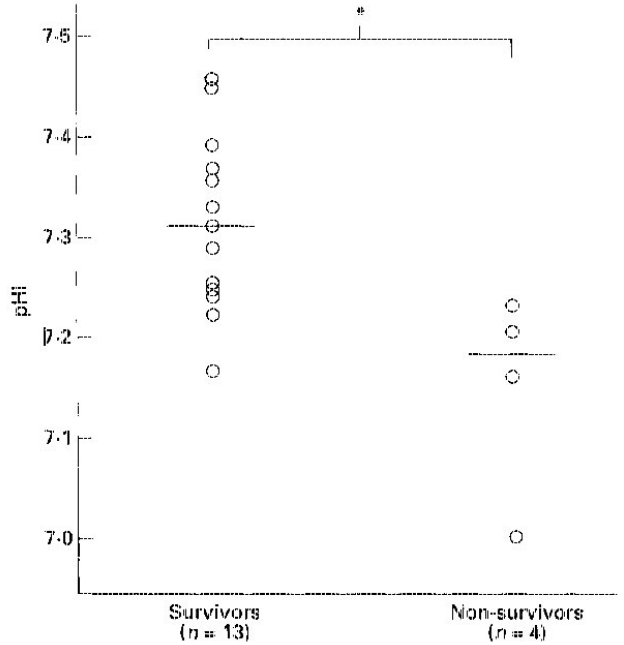
- **Improved current ICU management, by avoiding**
  - Nil by mouth
  - Too much or too little resuscitation fluid
  - EN until volume replete
  - Opioid analgesia when possible
  - Non-selective inotropes
  - Unnecessary and prolonged use of antibiotics
- **Investigate new management strategies**

British Journal of Surgery 1997, 84, 1670–1674

Gastric intramucosal pH predicts death in severe acute pancreatitis

M. J. D. BONHAM, F. M. ABU-ZIDAN, M. O. SIMOVIC and J. A. WINDSOR

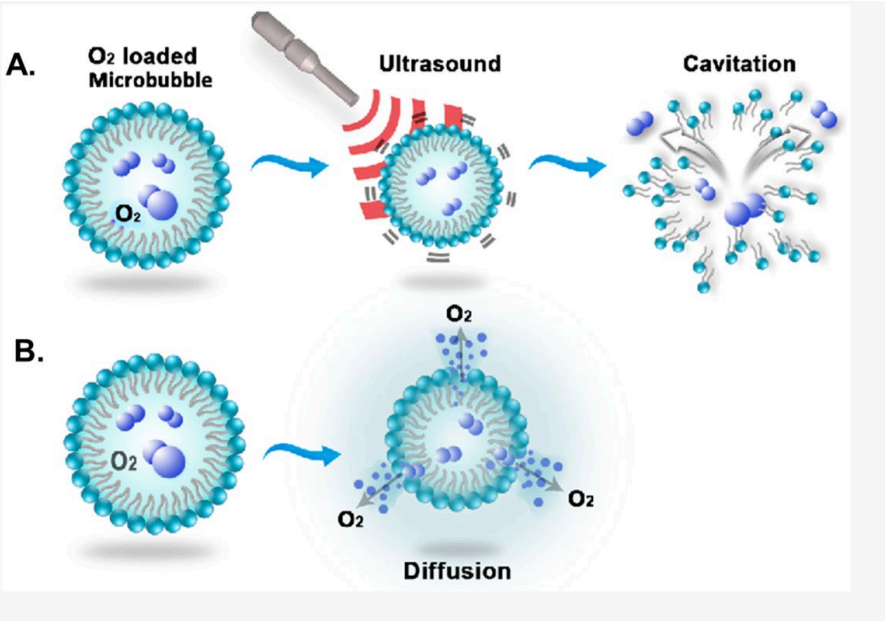




Fishers Exact
P = 0.009

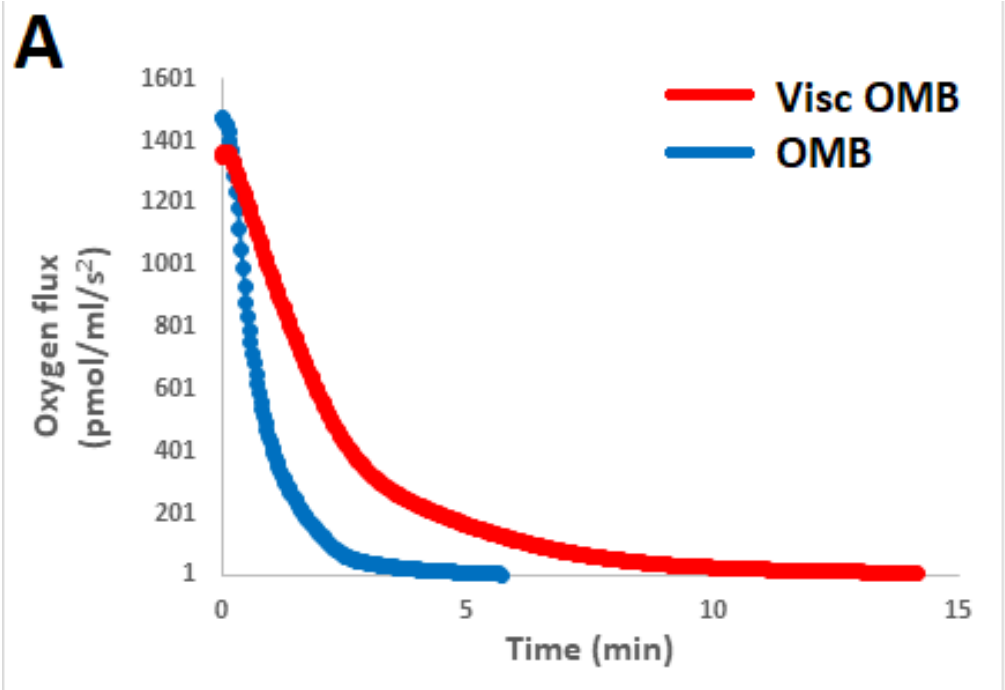
82% accuracy in predicting mortality (cut-off pH 7.25)

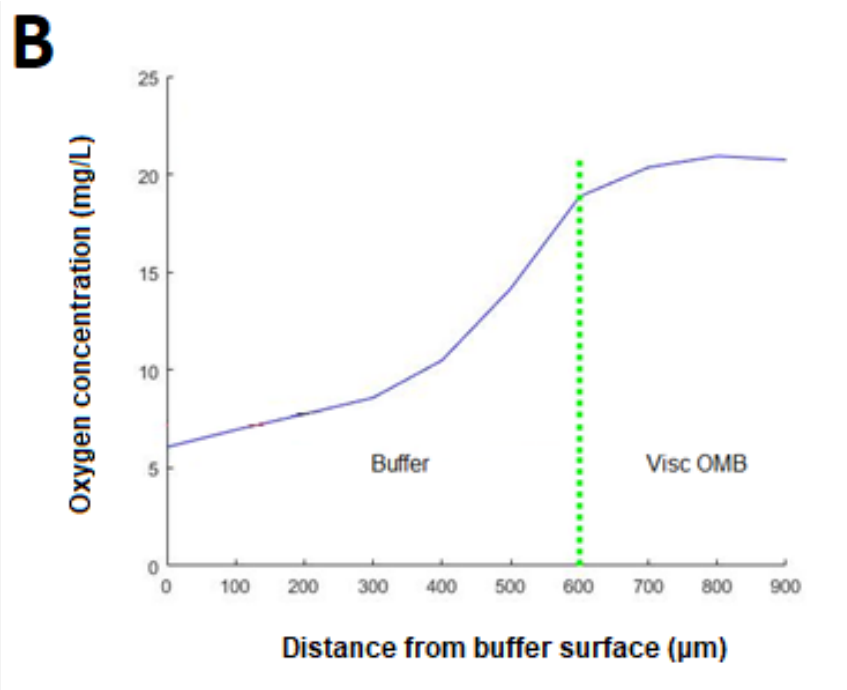
Intraluminal oxygen delivery by ‘microbubbles’ to reduce intestinal mucosal ischaemia



- **Hypothesis**: oxygen-loaded microbubbles (OMB) delivered to the lumen of ischaemic gut will reduce the histologic severity of gut injury.
- Develop **formulation** to optimise **viscosity** which governs oxygen **diffusion**
- Avoid NJ tube occlusion or intestinal obstruction due to viscosity

Comparing O_2 release profiles



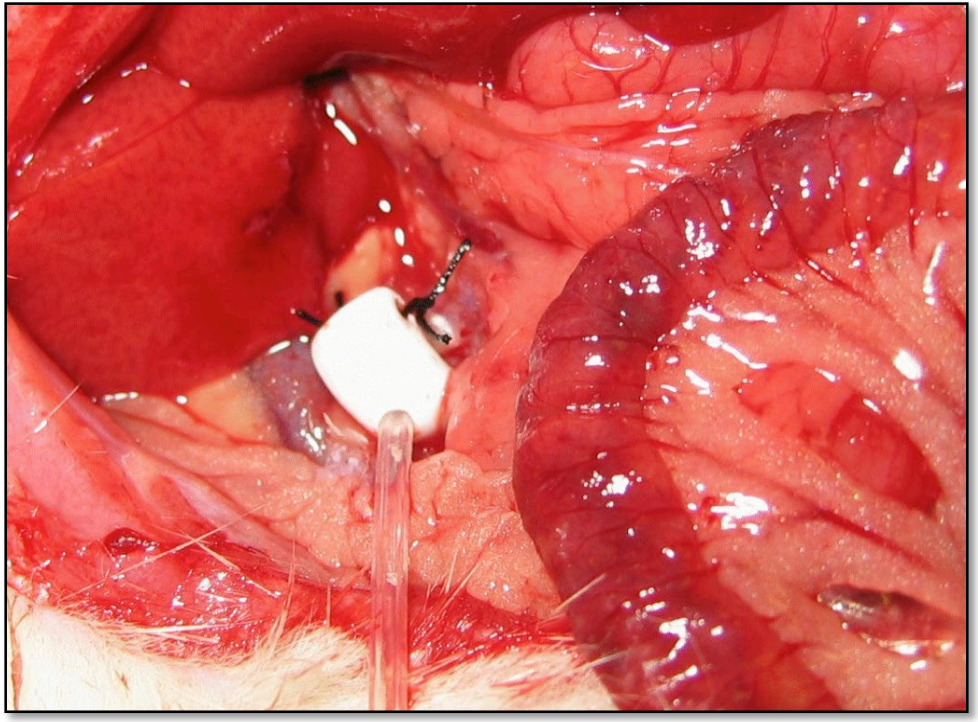


Oxygen release from hydrogel 2.5x longer

Concent^{n} gradient retained > 45 min

Animal experiment

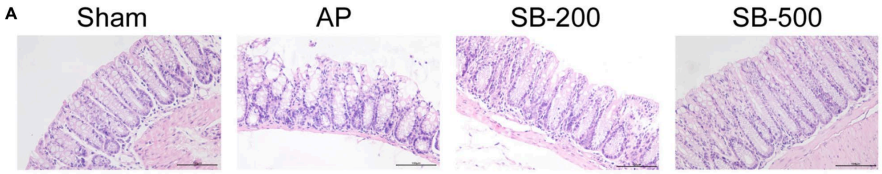
- Model of intestinal ischaemia-reperfusion
- Reproducible injury with inflatable SMA cuff)
- Cellulose hydrogel
- Histology for grade of injury

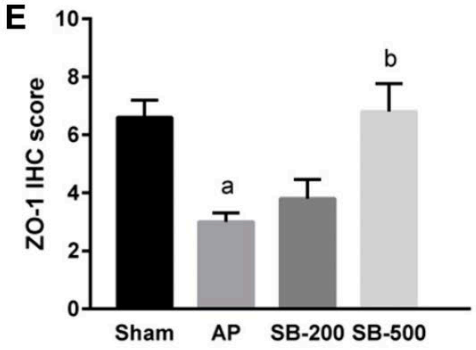


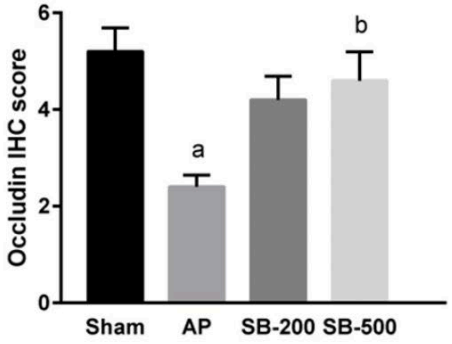
Sodium Butyrate Attenuates Taurocholate-Induced Acute Pancreatitis by Maintaining Colonic Barrier and Regulating Gut Microorganisms in Mice

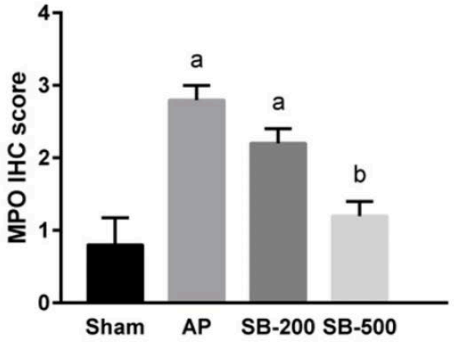
Frontiers in Physiology. 2022

Yangyang Xiong, Li Ji, Yi Zhao, Ailing Liu, Dong Wu and Jiaming Qian**







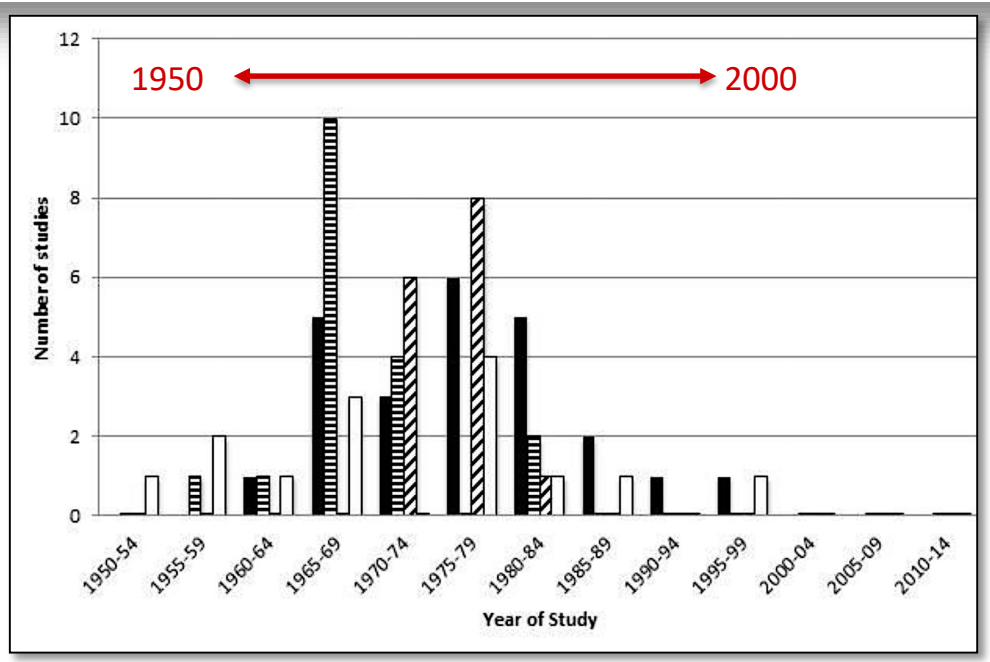


Lymphatic treatment strategies

- External thoracic duct drainage
- Lymph targeted drugs

Indications, techniques, and clinical outcomes of thoracic duct interventions in patients: a forgotten literature?

Hsiang-Wei Wang, MBChB,[a,b] Alistair Brian James Escott, MBChB (Otago),[a] Kian Luke Phang, MBChB,[a,b] Maxim S. Petrov, MD, MPH,[a] Anthony Ronald John Phillips, MBChB, PhD,[b] and John Albert Windsor, BSc, MBChB, MD, FRACS, FRSNZ[a,]*



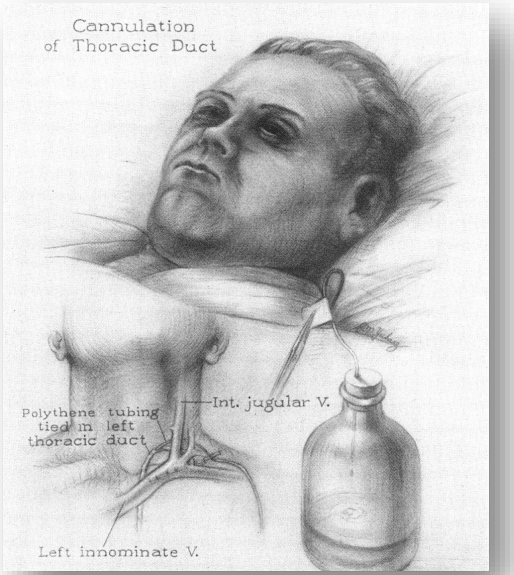
J Surg Research 2016

Prospective evaluation of thoracic-duct drainage in the treatment of respiratory failure complicating severe acute pancreatitis

T. Dugernier[1], M.S. Reynaert[1], G. Deby-Dupont[4], J.J. Roeseler[1], M. Carlier[2], J.P. Squifflet[3], C. Deby[5], J. Pincemail[5], M. Lamy[4], S. De Maeght[1] and P.J. Kestens[3]

In patients with early SAP

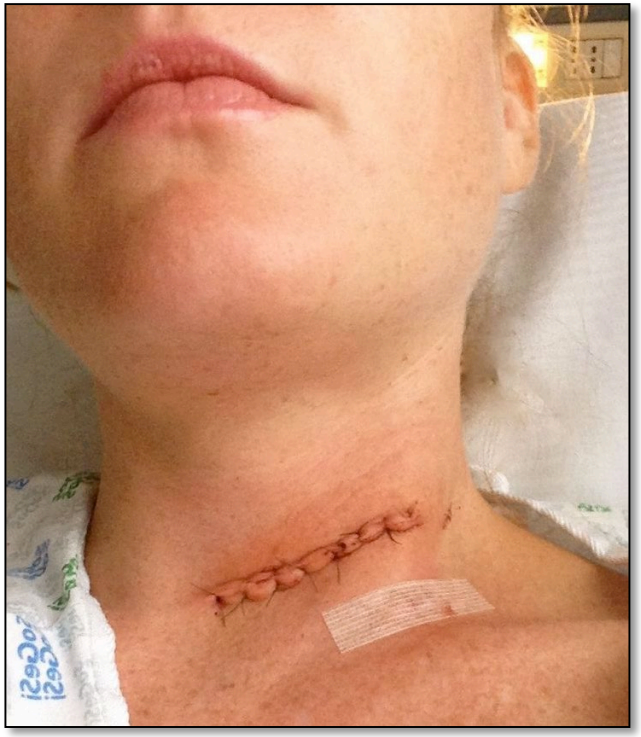
- External drainage was **safe**
- Improved **pulmonary gas exchange, circulatory status** and **survival**
- TDD should be regarded as 'a **useful adjunct** to the treatment of life-threatening complications of the early phase of SAP'



Intensive Care Medicine 1989

Reasons for discontinuation

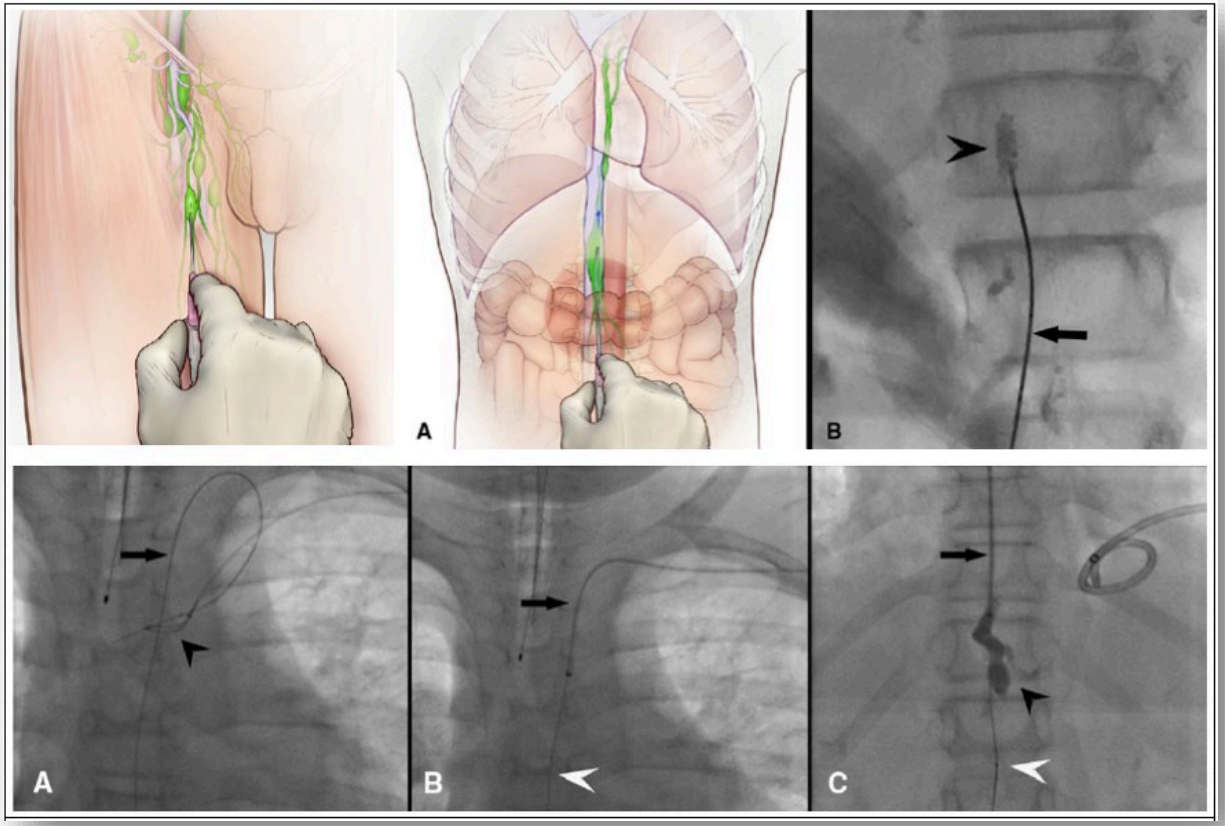
- Invasive procedure, requiring GA
- Complications, including lymph leak
- Equivocal evidence due to poor clinical trial design



UPENN Trial

Professor Maxim Itkin

Accessing thoracic duct lymph for study



- U/S groin node injection with lipiodol
- Transabdominal needle opacification of cisterna chyli
- Antegrade TD guidewire
- Snare from left PICC access
- Retrograde cannulation of TD

UPENN trial underway

- Septic patients (≥ 7 SOFA score)
- Recruited within 24 hours of admission
- External drainage of TD lymph for 7 days
- Primary endpoint - inflammatory markers
- No results available yet

Other benefits of accessing TD lymph

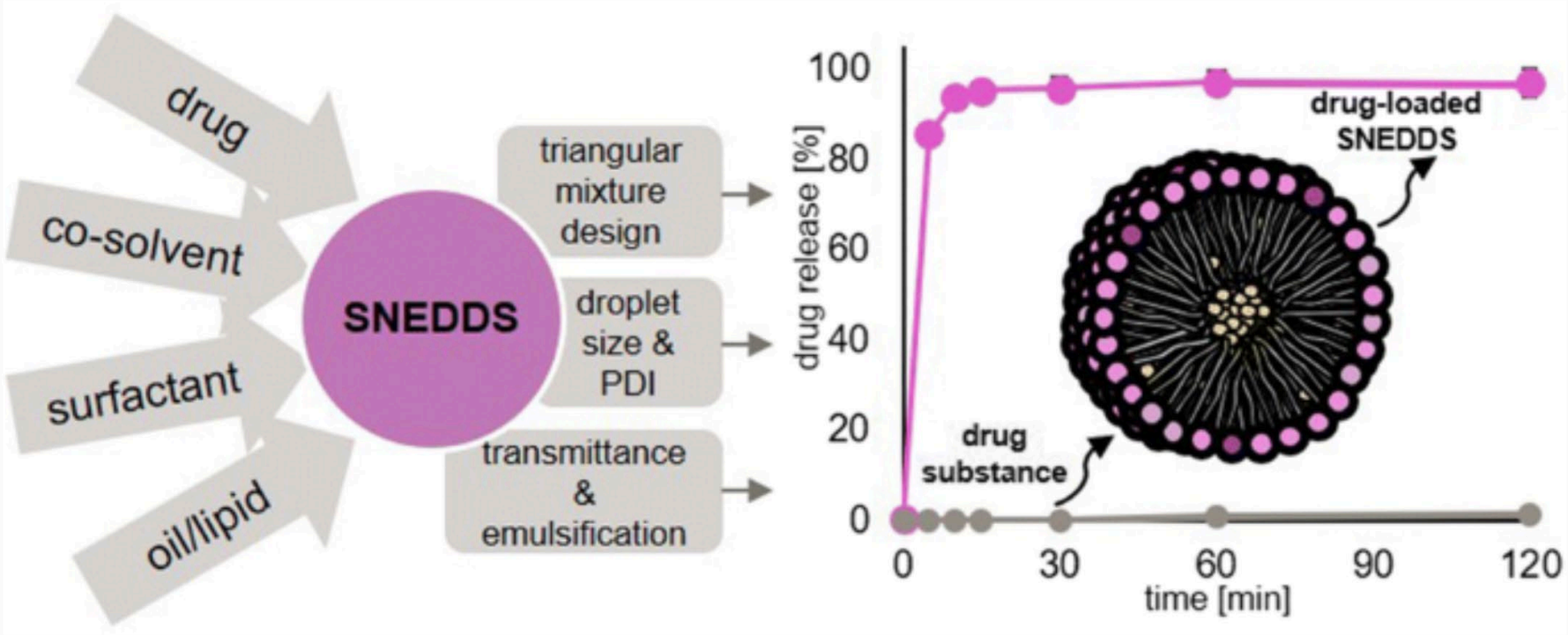
- Therapeutic **external drainage**
- Study **composition changes** during disease course
  - Correlate with severity and outcomes
- Study **toxicity** on cells and *in vivo*
  - identify potential drug target
- Design **gut-lymph targeted treatments**
- Measure **bioactivity** of drugs that target lymph

From sewer to saviour — targeting the lymphatic system to promote drug exposure and activity

Natalie L. Trevaskis[1], Lisa M. Kaminskas[1] and Christopher J. H. Porter[1,2]

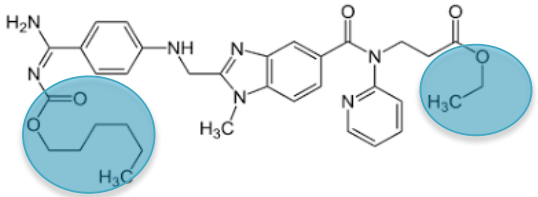
Nature Reviews/Drug Discovery 2015

Self-nanoemulsifying drug delivery systems (SNEDDS)

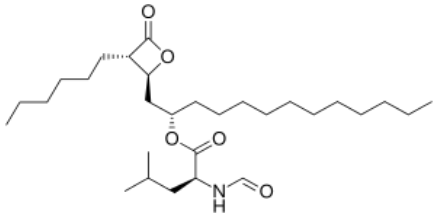


SNEDDS to deliver enzyme inhibiting drugs to gut-lymph

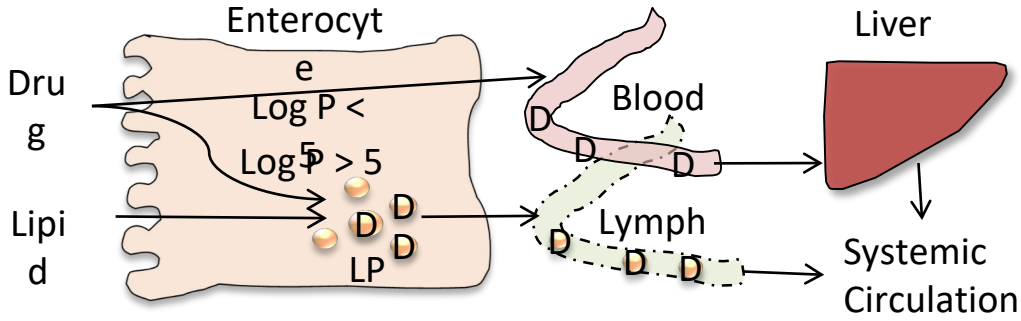
Dabigatran etexilate
- Serine protease inhibitor
- Log P ~5.8



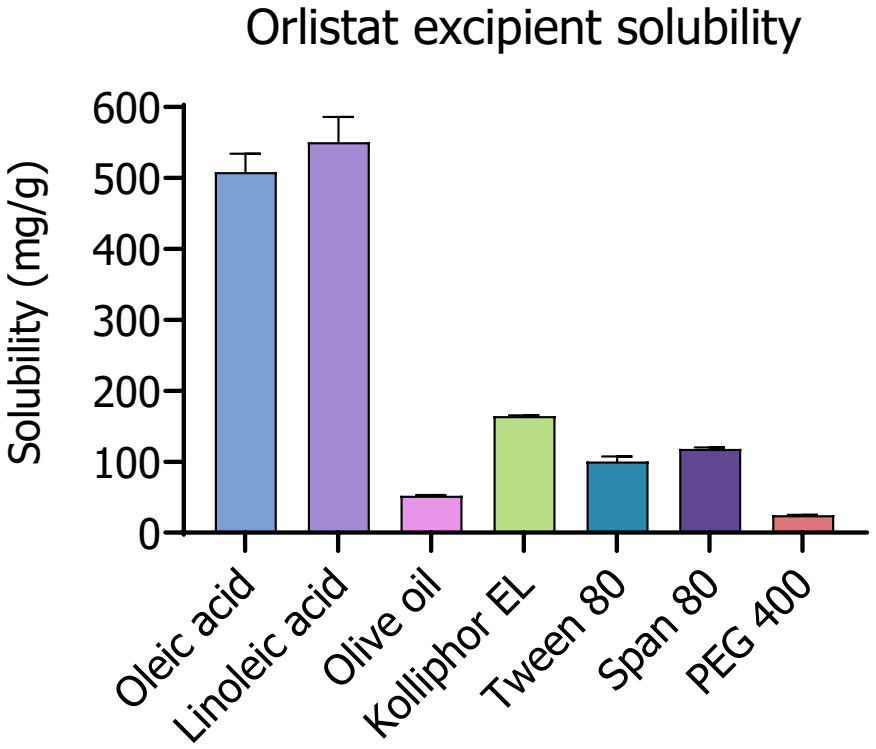
Orlistat
- Lipase inhibitor
- Log P ~8



- Most drugs transported from intestine via blood
- Lymphatic drug transport occurs via association with lipid transport pathways - requires a highly lipophilic pro/drug (log P>5, TG solubility >50 mg/g) and co-dosed lipid

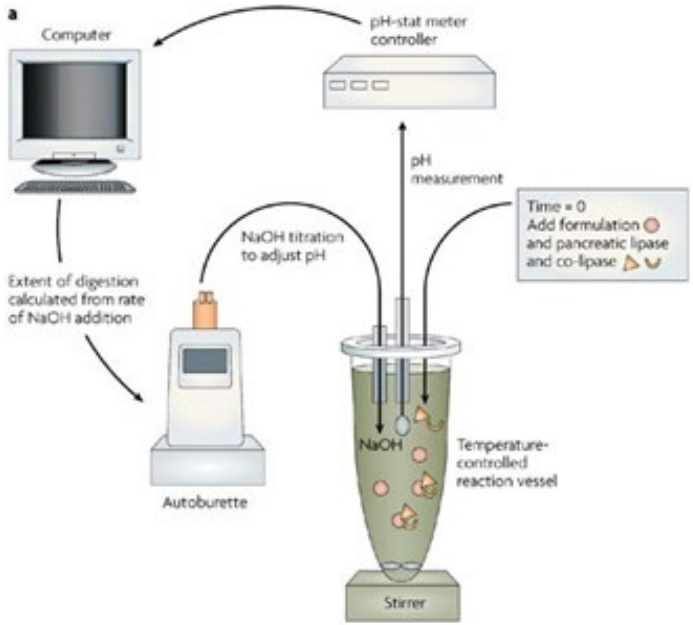


SNEDDs development for lipase inhibitor orlistat

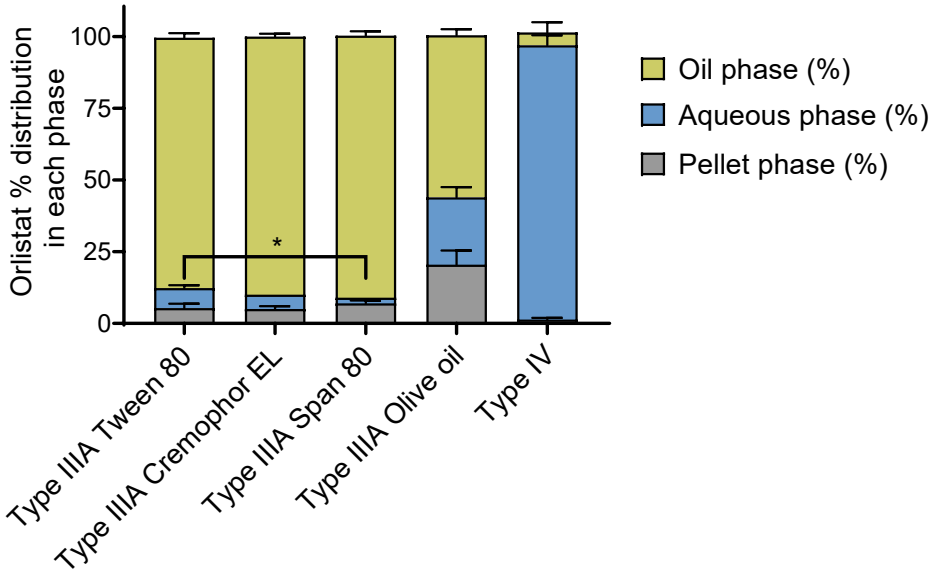


- Orlistat shows good solubility in excipients
- Long-chain lipids chosen to stimulate lipoprotein formation and intestinal lymphatic transport

All SNEDDs supported orlistat solubilisation during simulated intestinal digestion

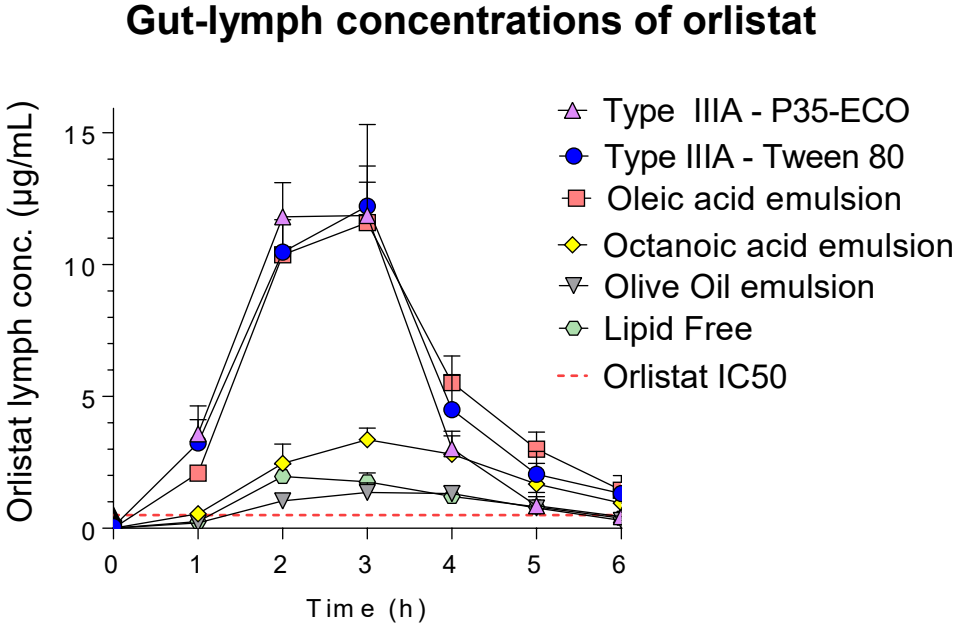


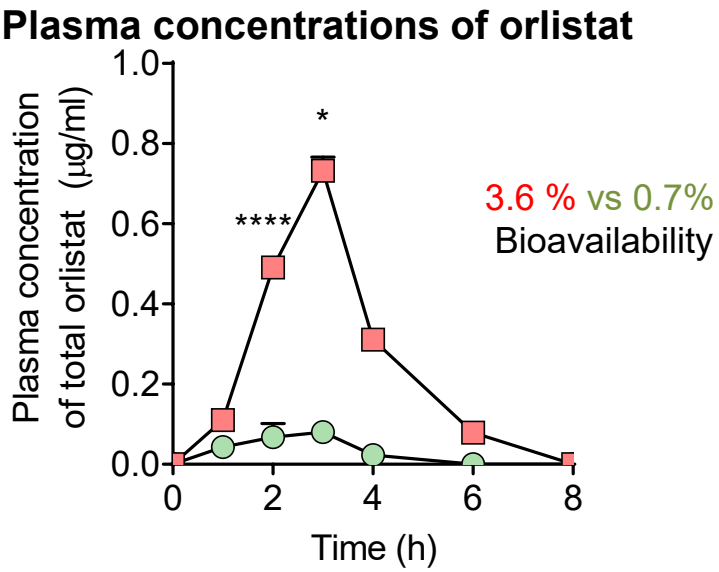
Digestion experiment



Porter, Trevaskis, Charman ***Nature Rev Drug Discov*** *(2007) 6(3):231-48*

Long-chain fatty acid SNEDDs support orlistat uptake into lymph and blood

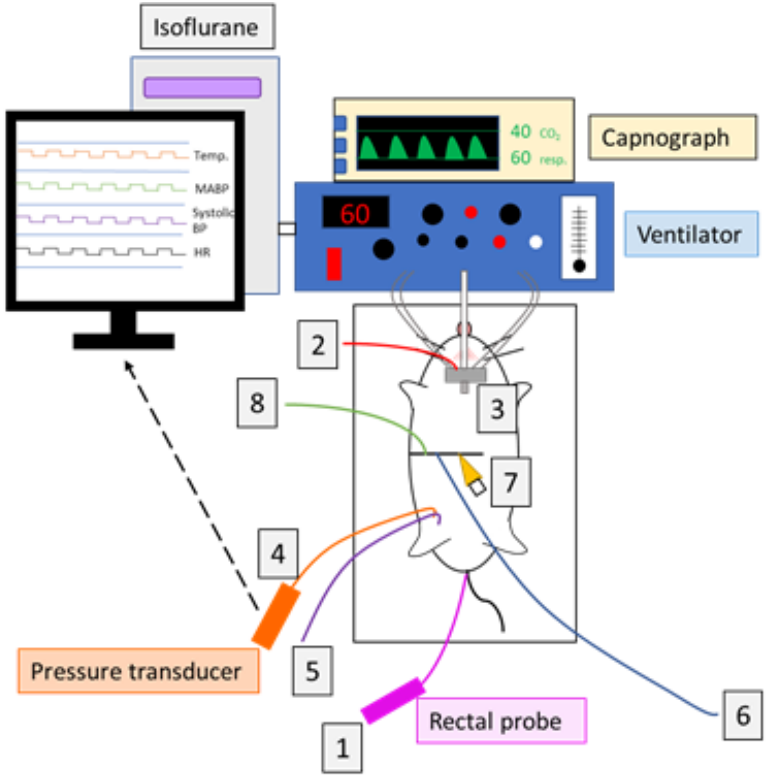




- Long-chain fatty acid (oleic acid) formulations deliver orlistat to gut-lymph and plasma
- Medium-chain fatty acid and long-chain triglyceride formulations did not

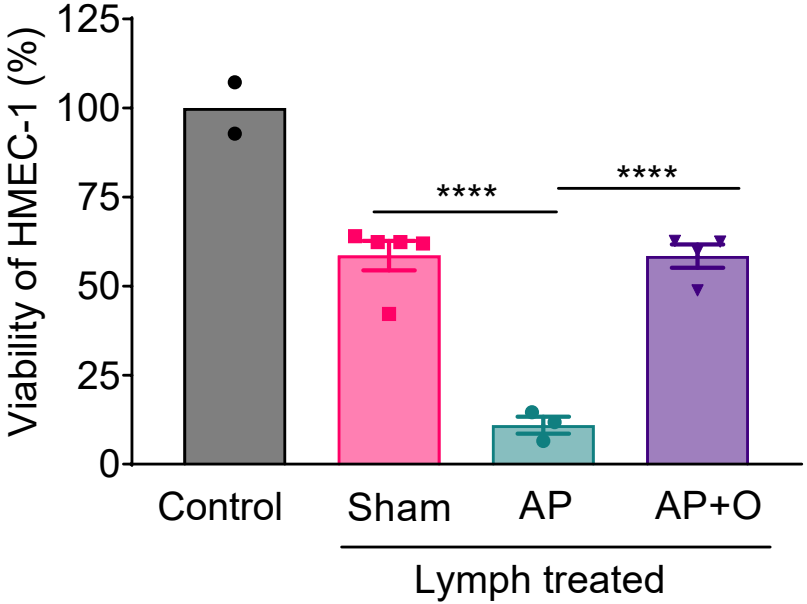
Efficacy of orlistat formulation in AP

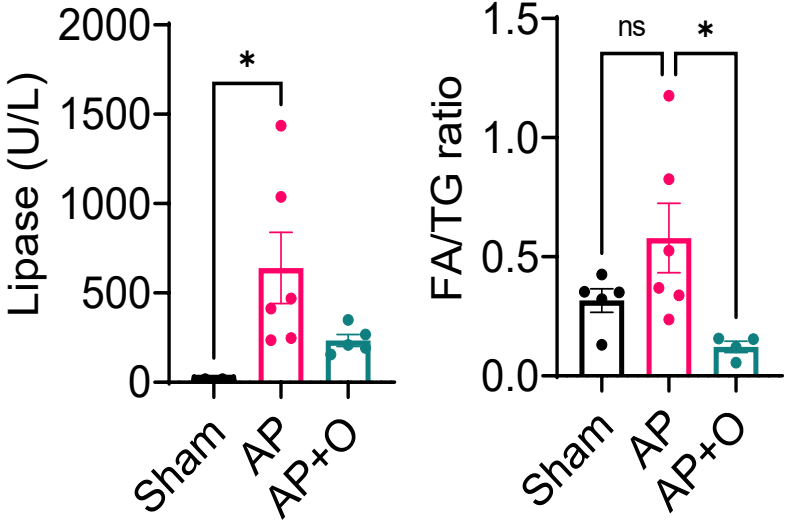
- Efficacy tested in rat sodium taurocholate infusion model of acute pancreatitis (AP)
- Monitor lymph cytotoxicity, organ biomarkers and function



Trevaskis et al. Lymph-targeting oral formulation of orlistat; Patent, DCC ref: 35548449/MJC/GDB, Filing Date 26/10/20

Efficacy of orlistat formulation in AP

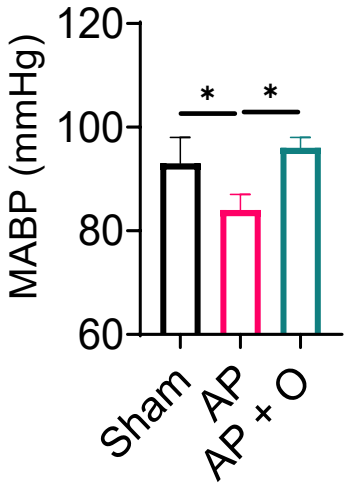


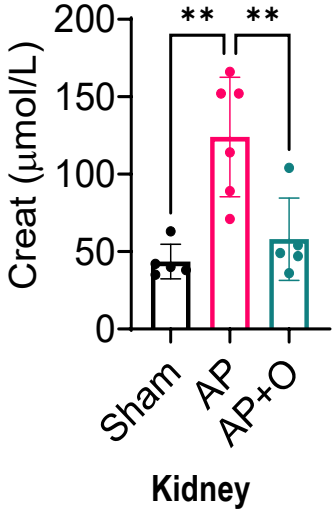


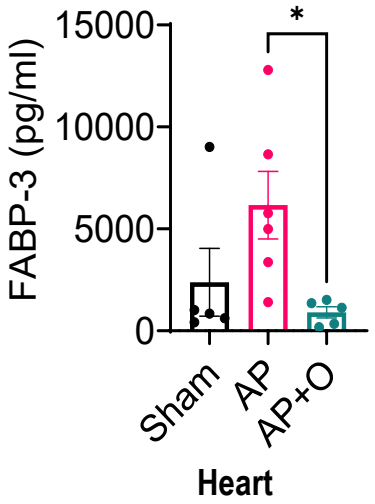
Lymph cytotoxicity to cells
reduced by orlistat (O)

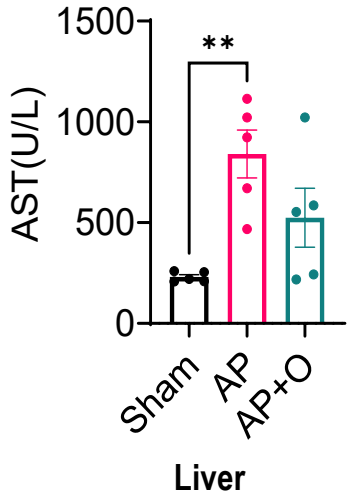
Plasma lipase activity and FFA
reduced by orlistat (O)

Efficacy of orlistat formulation in AP









Blood pressure
restored by orlistat (O)

Biomarkers of organ function
improved by orlistat (O)

Conclusions

- Organ failure defines AP severity and #1 cause of death
- Gut-lymph model offers new treatment paradigm develop specific treatments
- Examples of luminal, mural and lymph based treatment strategies to mitigate organ dysfunction in patients with AP
- Other strategies include reducing end-organ oedema, promoting pulmonary lymphatic clearance, stimulating lymphatic contraction.

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Thank you

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