Future of liver transplantation

Transplant Atlantic
November 4, 2016

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The problem:

- Population is becoming older, more obese and more co-morbid
- Donor population is becoming older, more obese and more co-morbid
- Quality of organs is deteriorating

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Current practice: cold static storage

- Collins & Terasaki (Lancet, 1969): kidney preservation for 30 hours

- Based on suppression of metabolism and catabolic enzymes by hypothermia (10-12% @ 4°C)

- Reduce formation of ROS, cell swelling and acidosis through manipulation of preservation solution
  - Scavengers / impermeants-colloids / buffers

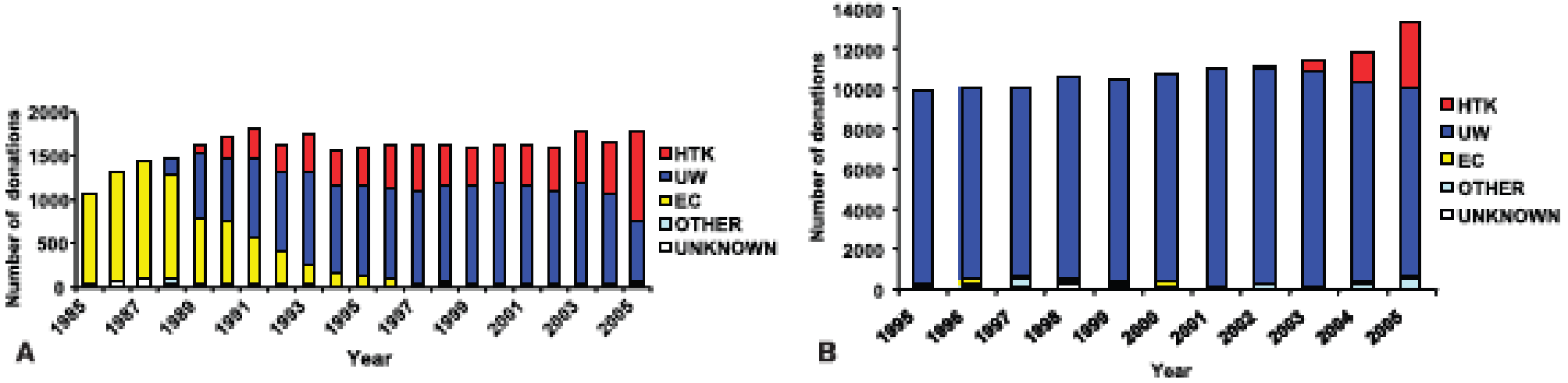

FIGURE 1. (A) Use of cold storage solutions in Eurotransplant region in deceased donors from 1985–2005 (based on Eurotransplant data of October 2006). (B) Use of cold storage solution in the United States in deceased donors from 1995–2005 (based on Organ Procurement and Transplantation Network data of October 2006).

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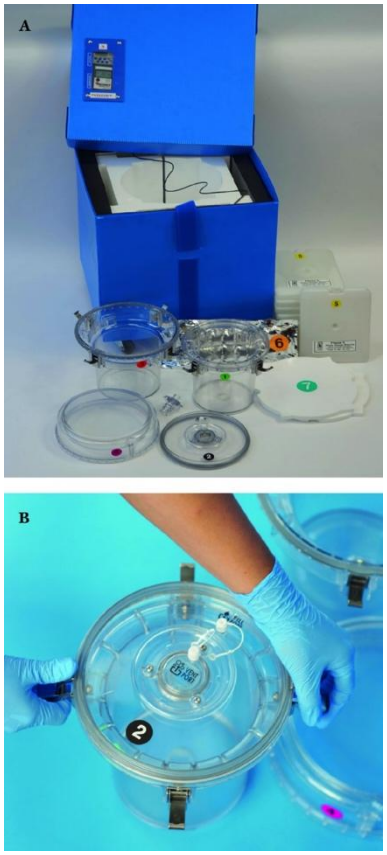
Maathuis et al, Transplantation 2007

Cold static storage: liver

10-12 hours cold ischemia time

Alternatives?

Belzer, F. O.; Ashby, B. S.; Gulyassy, P. F.; Powell, M. 1968. *Seventeen hour preservation and transplantation of cadaver kidney*. New Eng. J. Med. *278:* 608.—This is a case report of a cadaver renal transplant preserved for 17 hr (warm ischemia period 25 min, total ischemia period 55 min) through the use of an extracorporeal perfusion apparatus consisting of a membrane oxygenator, pulsatile pump, perfusion chamber, filter and heat exchanger. The recipient was



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TRANSPLANTATION

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ADVANTAGE OF COLD STORAGE OVER MACHINE PERFUSION FOR PRESERVATION OF CADAVER KIDNEYS

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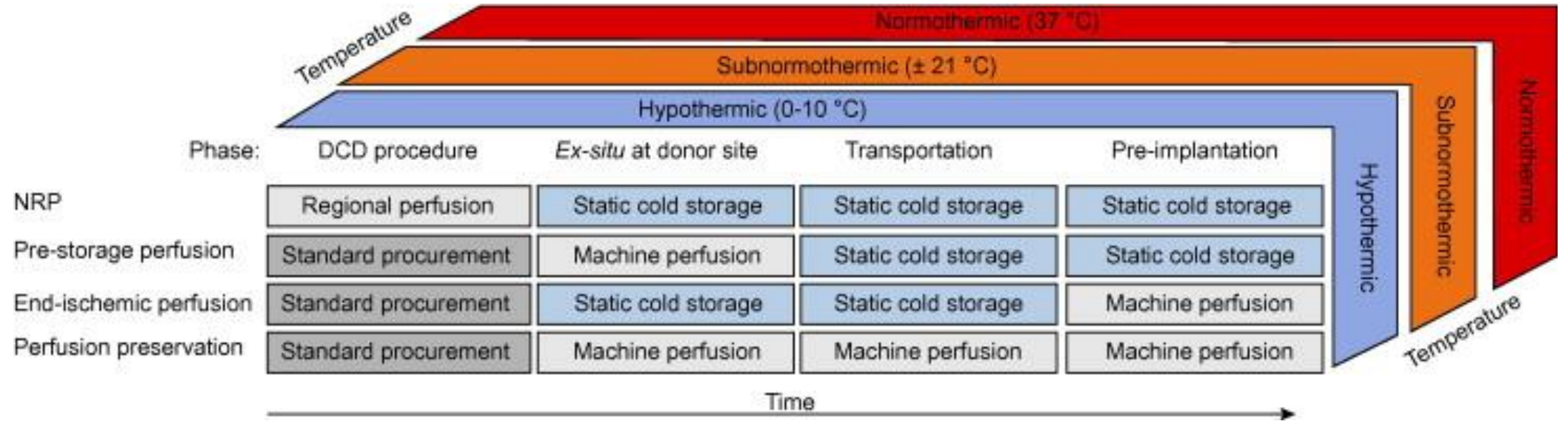
Spectrum of machine perfusion



Weeder et al, J Hepatol 2015

Hypothermic machine perfusion: liver

- 0-10 °C temperature
- Acellular perfusion fluid at low pressures
- Uptake of oxygen through diffusion – oxygen carrier not required
- Safe

- Not able to assess function
- Not physiologic

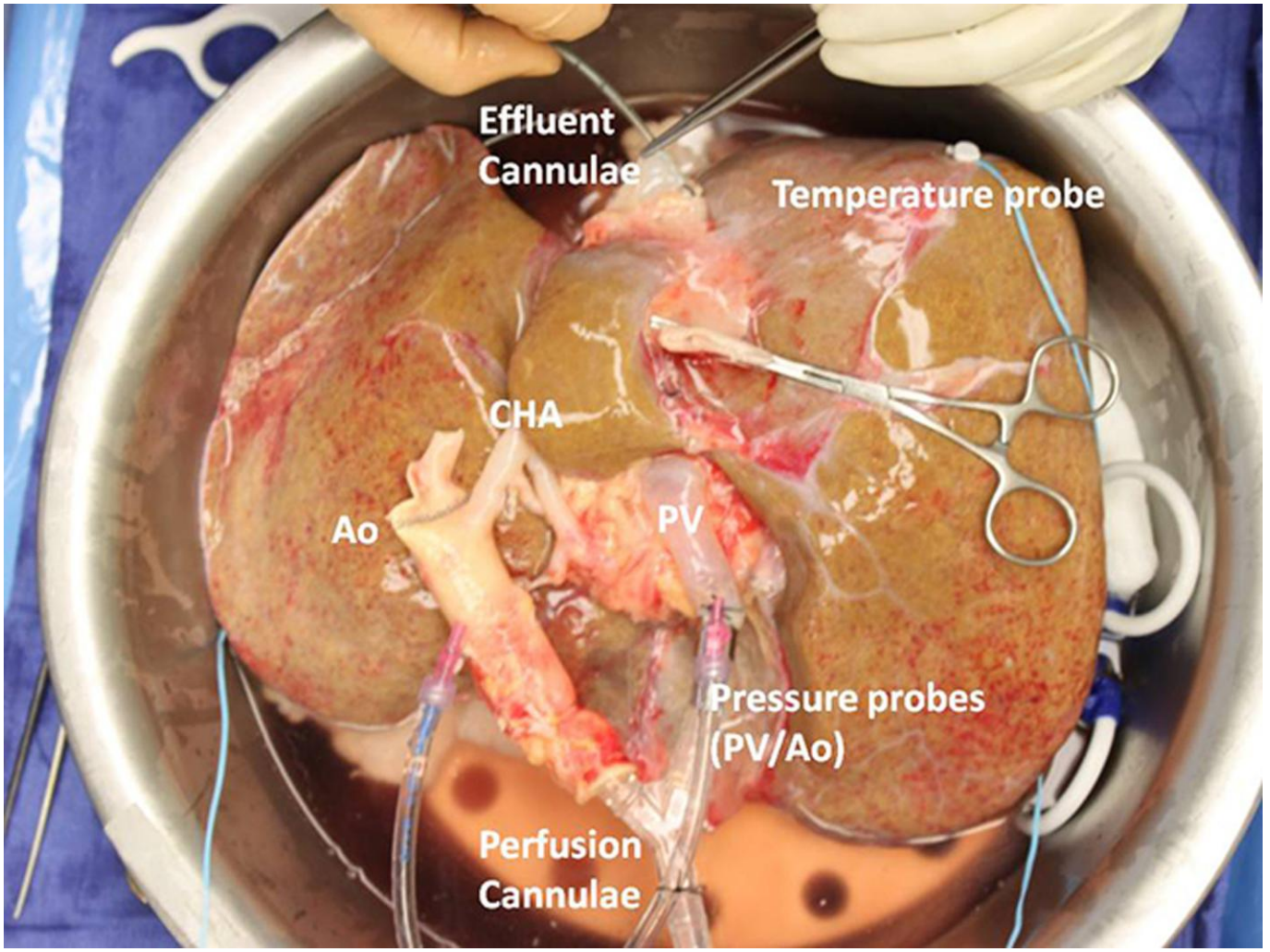
Weeder et al, J Hepatol 2015

Hypothermic machine perfusion: liver

- Case controlled study of 20 pts
  - Lower rate of early allograft dysfunction
  - Better kidney function
  - Shorter hospital LoS
- No active oxygenation
- Duration of perfusion not standardized

Graham and Guarrera, J Hepatol 2014

Hypothermic machine perfusion: liver



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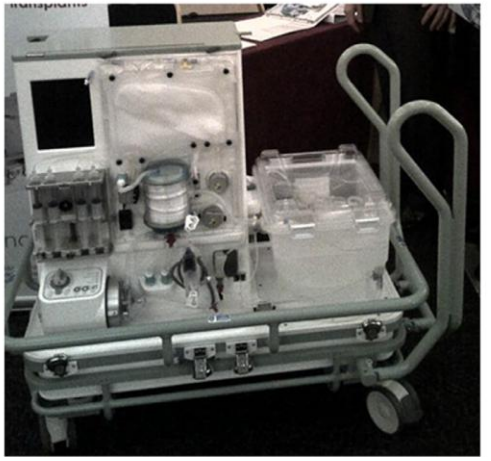
Graham and Guarrera, J Hepatol 2014

Hypothermic machine perfusion: liver



Graham and Guarrera, J Hepatol 2014

Hypothermic machine perfusion: liver

- Comparison of 8 DCD livers with machine perfusion to NDD cold static storage

- ‘Extended’ DCD
- Oxygenated
- PV only

	DBD n = 8	DCD n = 8
Primary non-function	0/8	0/8
Delayed graft function	0/8	0/8
Acute kidney failure requiring intermediate dialysis/hemofiltration	3/8	2/8
Arterial thrombosis	0/8	0/8
Extrahepatic biliary complications (strictures, leaks)	2/8	2/8
Intrahepatic biliary cholangiopathy	0/8	0/8
Rejection (biopsy proven within 6 mo after transplantation)	5/8	1/8
Infection Sepsis (+ SIRS)	1/8 0/8	1/8 1/8
Secondary tumor	0/8	2/8‡
Tumor (HCC) recurrence	0/1*	0/6*
Re-listing	0/8	0/8
Re-transplantation	0/8	0/8
6 month graft survival	100% (8/8)	100% (8/8)

*No. of HCC in cohort.
‡1× intrahepatic lymphoma, 1× lung cancer.

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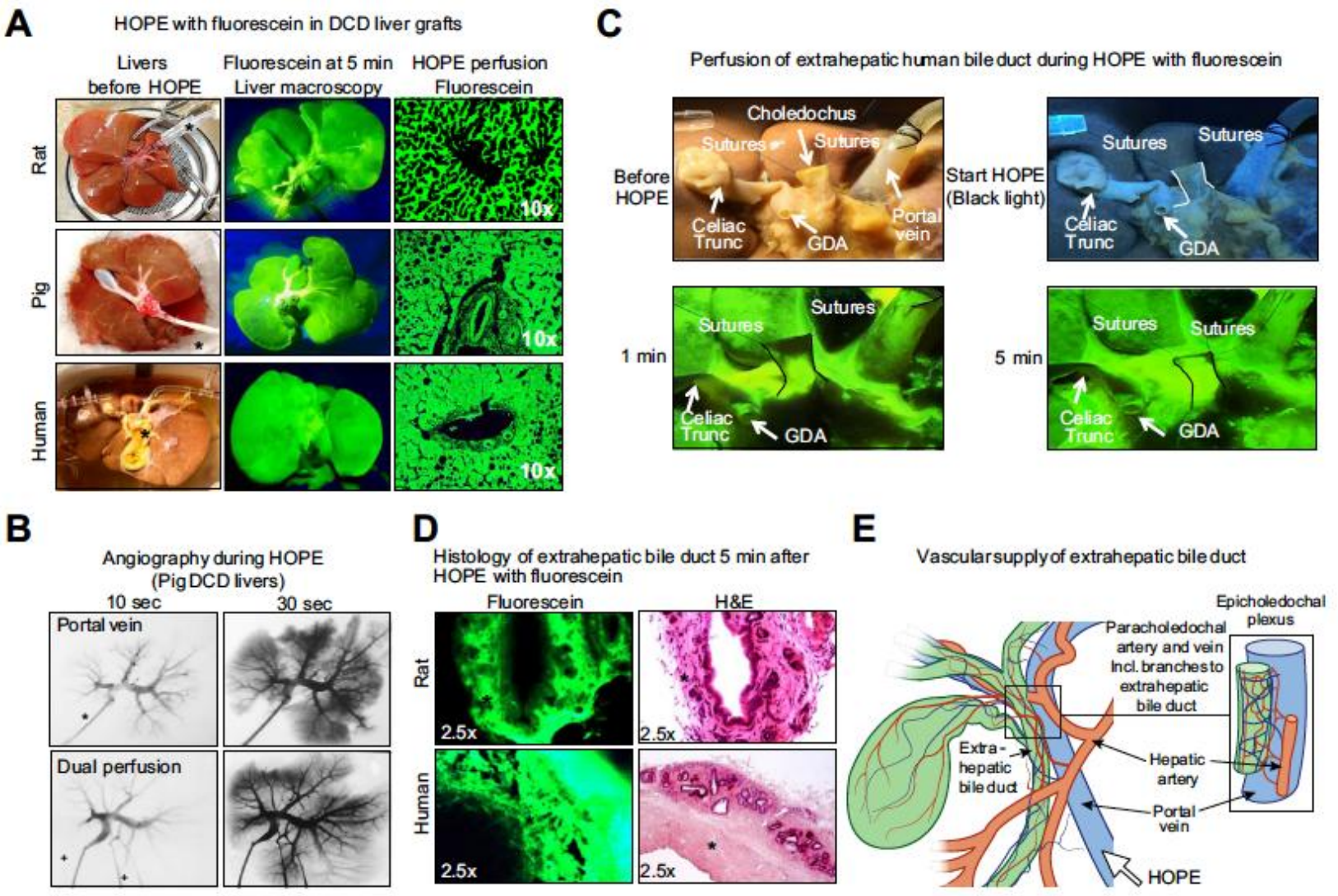
Dutkowski et al, J Hepatol 2014

Hypothermic machine perfusion: liver

Dutkowski et al, J Hepatol 2014

Hypothermic machine perfusion: liver



Dutkowski et al, J Hepatol 2015

Hypothermic machine perfusion: liver

Not inferior to CSS

Perhaps some benefits related to bile duct preservation

Normothermic machine perfusion: liver

- Physiological temperatures & metabolism
- Requires an oxygen carrier

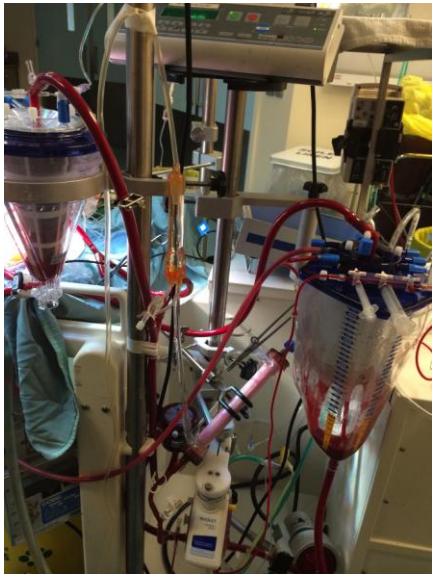
- Functional assessment
- Vulnerable to failure

Weeder et al, J Hepatol 2015

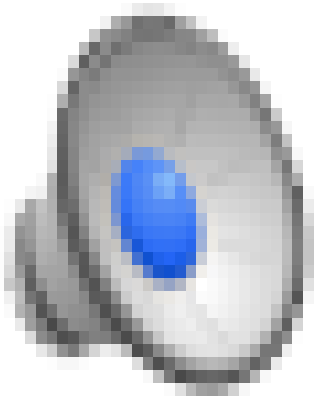
Normothermic machine perfusion: liver

- Clinical trials
  - Phase I safety and feasibility using OrganOx system (20 transplanted livers UK)
  - Multi-centre randomised controlled trials in Europe, USA and Canada comparing OrganOx to CSS

Normothermic machine perfusion: liver



Normothermic machine perfusion: liver



Normothermic machine perfusion: liver

Liver can be kept ‘alive’ for 24 hours…

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Normothermic machine perfusion: liver

Appears superior to CSS

Allows for longer ‘preservation’ of liver

Safety still not guaranteed..

What's next..?

- Assess
- Repair
- Improve

CNTRP
PNRTC

Project 1
Ex vivo organ transplant protection and repair

Project 2
Increasing solid organ and hematopoietic cell donation

Core 1
Ethical, economic, legal and social (EELS) platform

Project 3
Understanding, predicting and preventing early graft rejection and GVHD

Project 4
Strategies for immunomodulation and transplant tolerance

Core 2
Research infrastructure and registries support platform

Project 5
Predicting and controlling viral complications of transplantation

Project 6
Improving pediatric outcomes in transplantation

Core 3
Training and career development platform

Assess: biomarkers

PLOS ONE

RESEARCH ARTICLE

Mitochondrial Damage-Associated Molecular Patterns (MTDs) Are Released during Hepatic Ischemia Reperfusion and Induce Inflammatory Responses

Qianni Hu[1], Caroline Ruth Wood[2], Sanem Cimen[2], Ananda Baskaran Venkatachalam[2], Ian Patrick Joseph Alwayn[3]*

In vitro and *in vivo* models of ischemia / reperfusion injury

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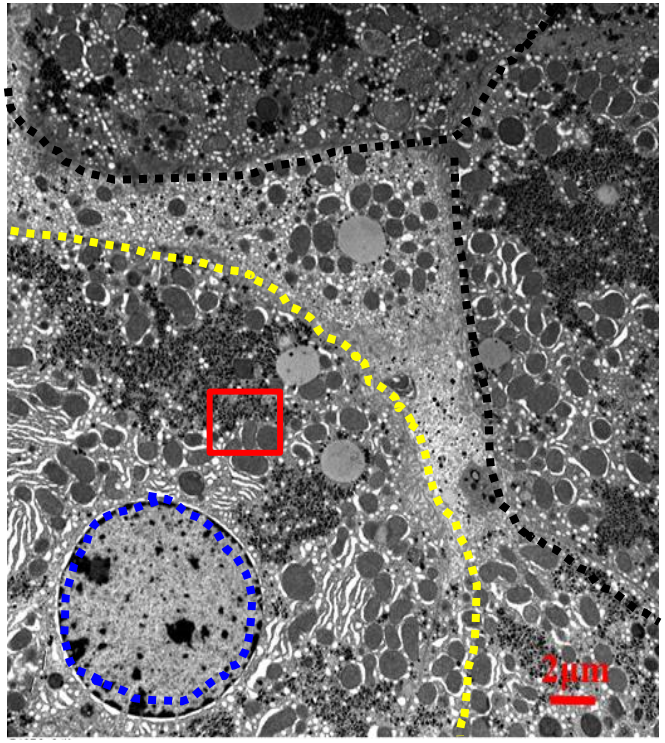
IR injury causes mtDAMPs release

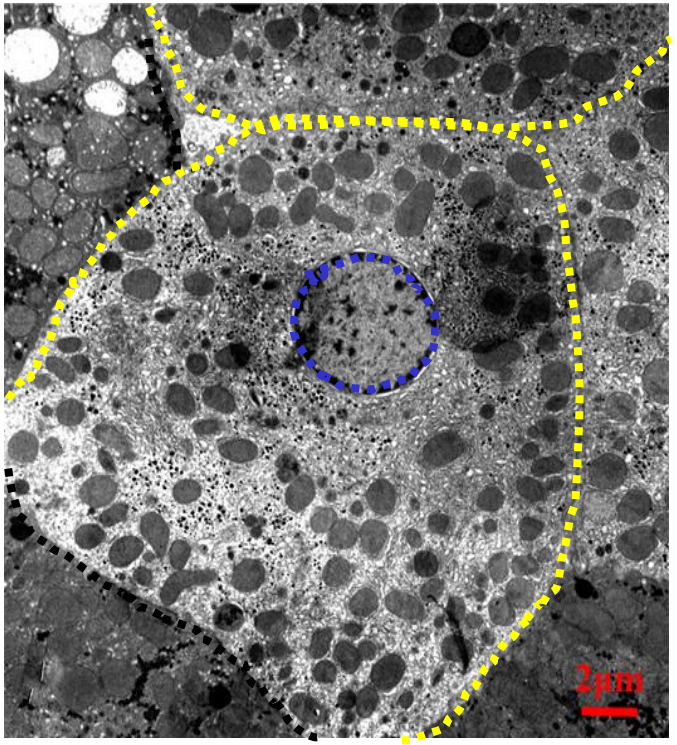
Mitochondrial DNA

Mitochondrial peptides

IR

Sham





Cell membrane

Cell nucleus

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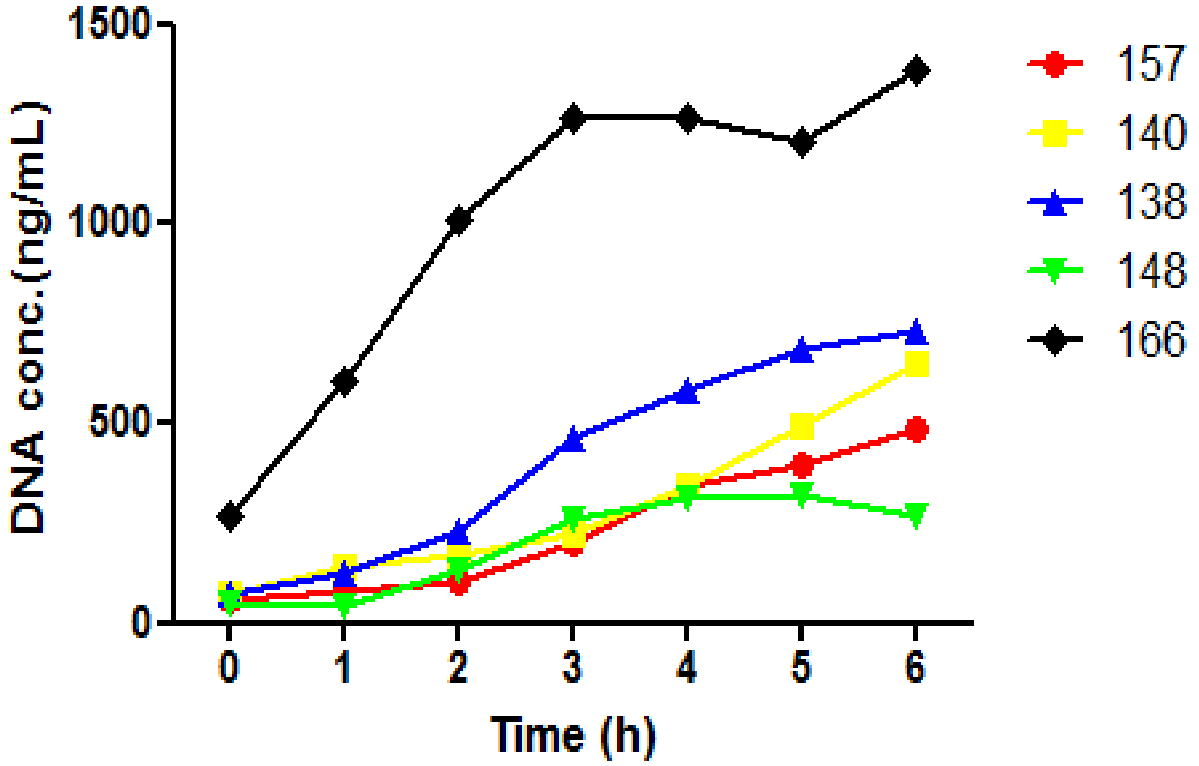
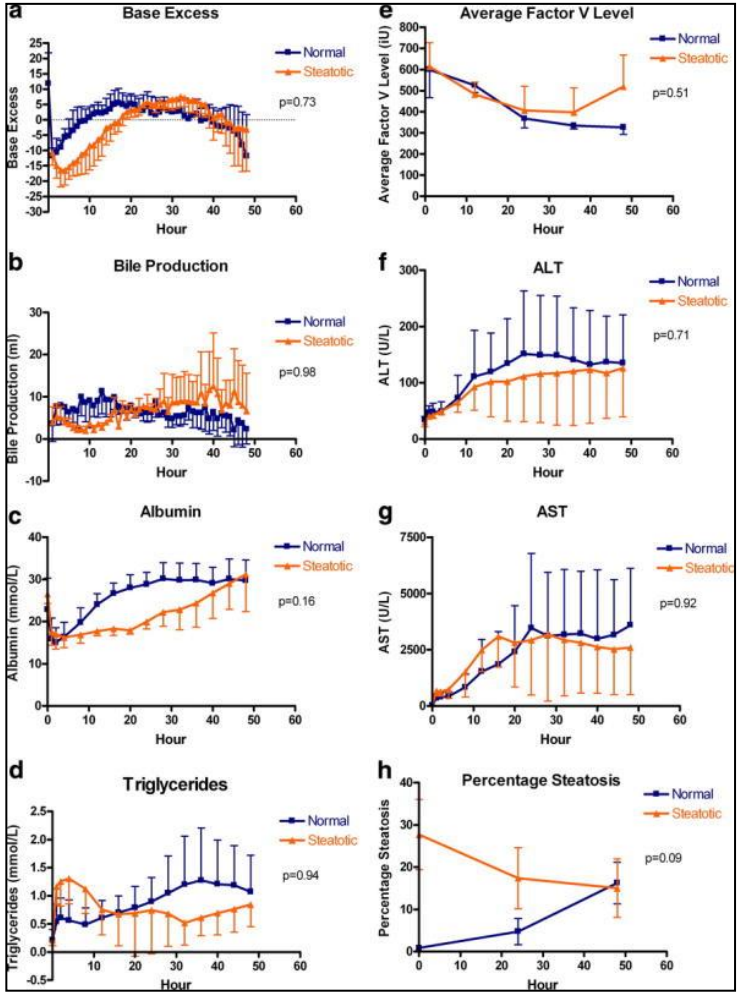
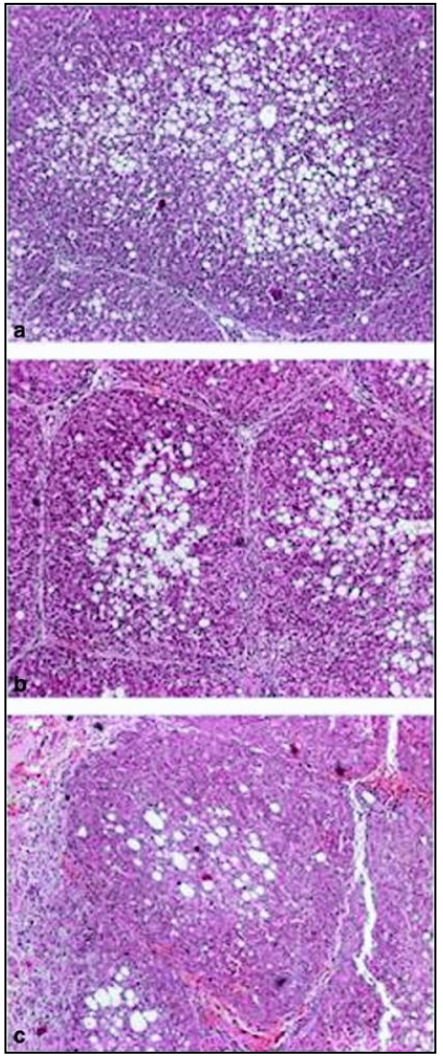
Porcine SNEVLP perfusate



Repair: defatting the fatty liver





Jamieson et al, Transplantation 2011

Defatting the fatty liver

4 hours of subnormothermic oxygenated perfusion

Normal rat livers versus fatty rat livers

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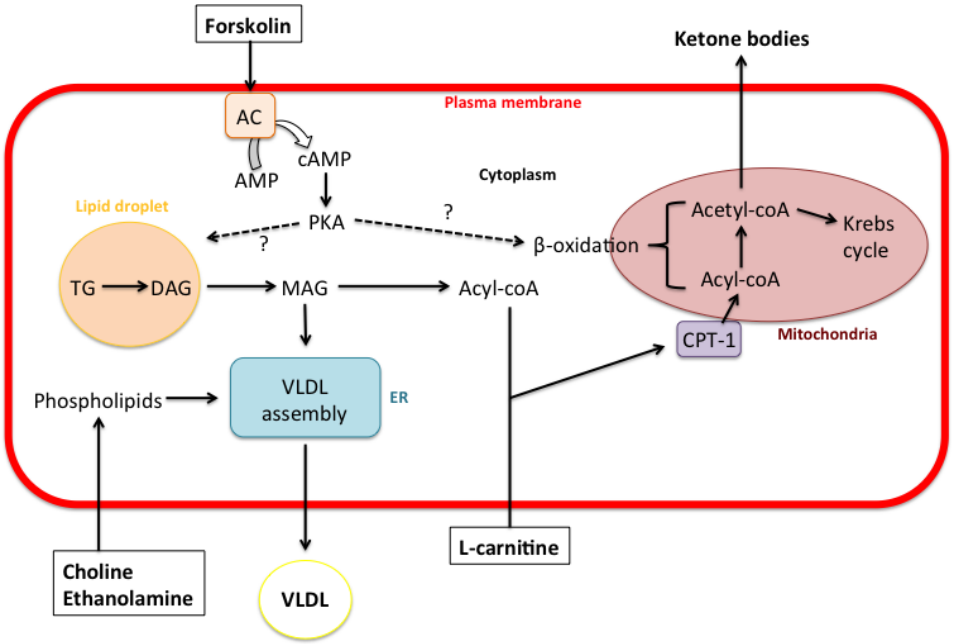
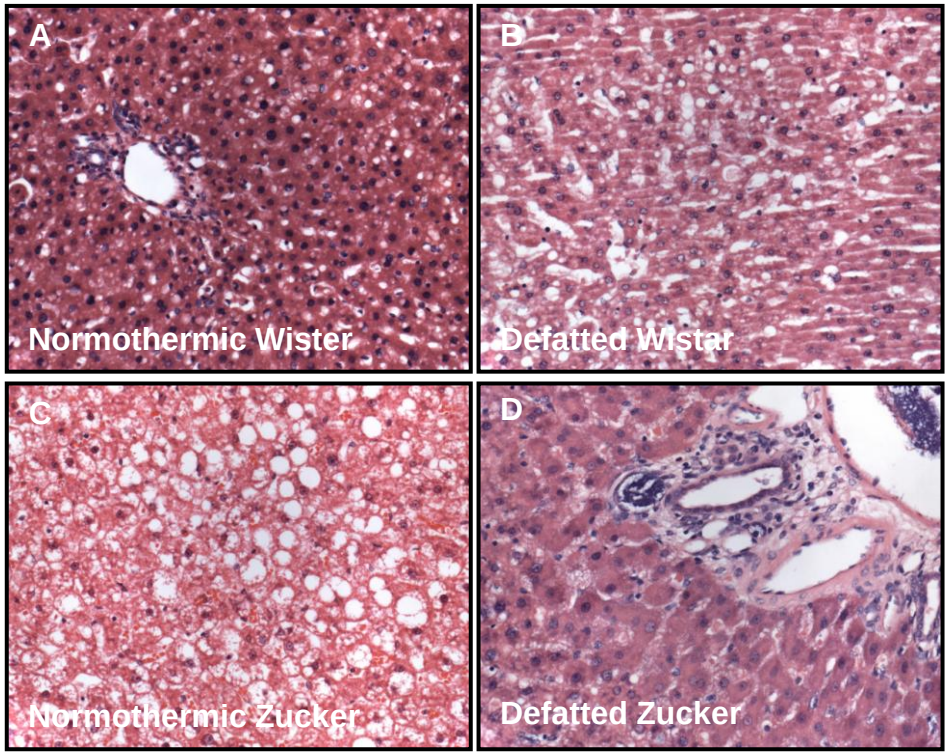
Defatting the fatty liver





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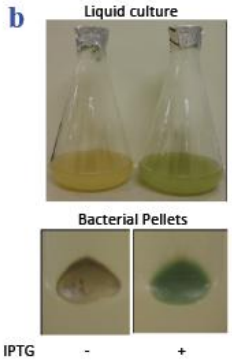
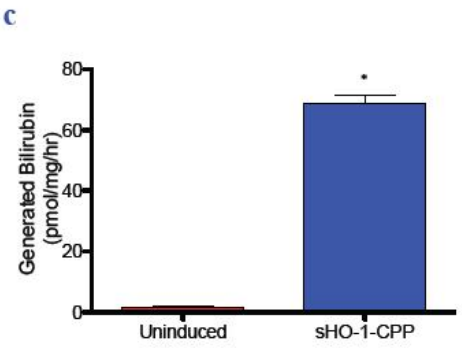
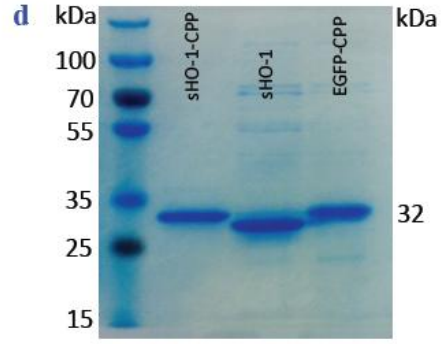
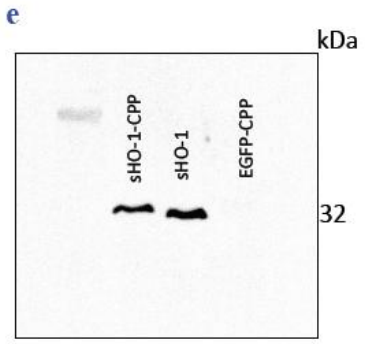
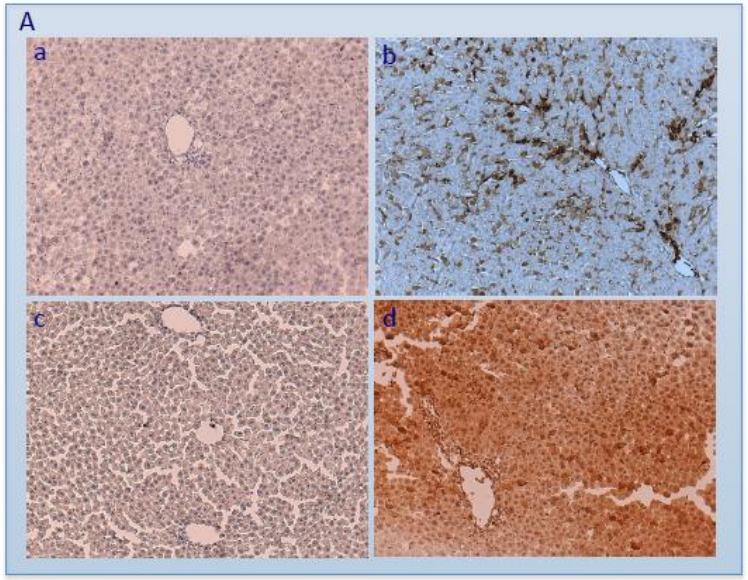
Protect: from ischemia/reperfusion injury

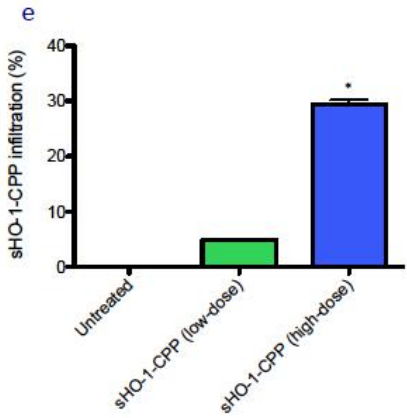












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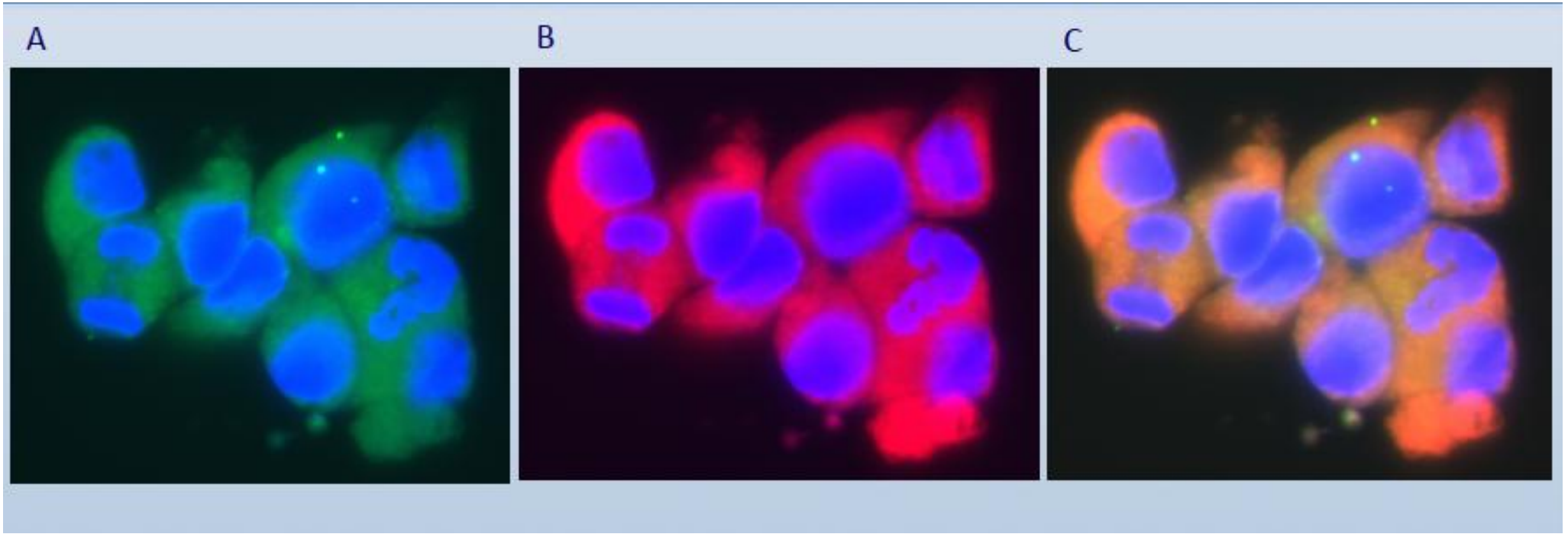
Protection from ischemia/reperfusion injury



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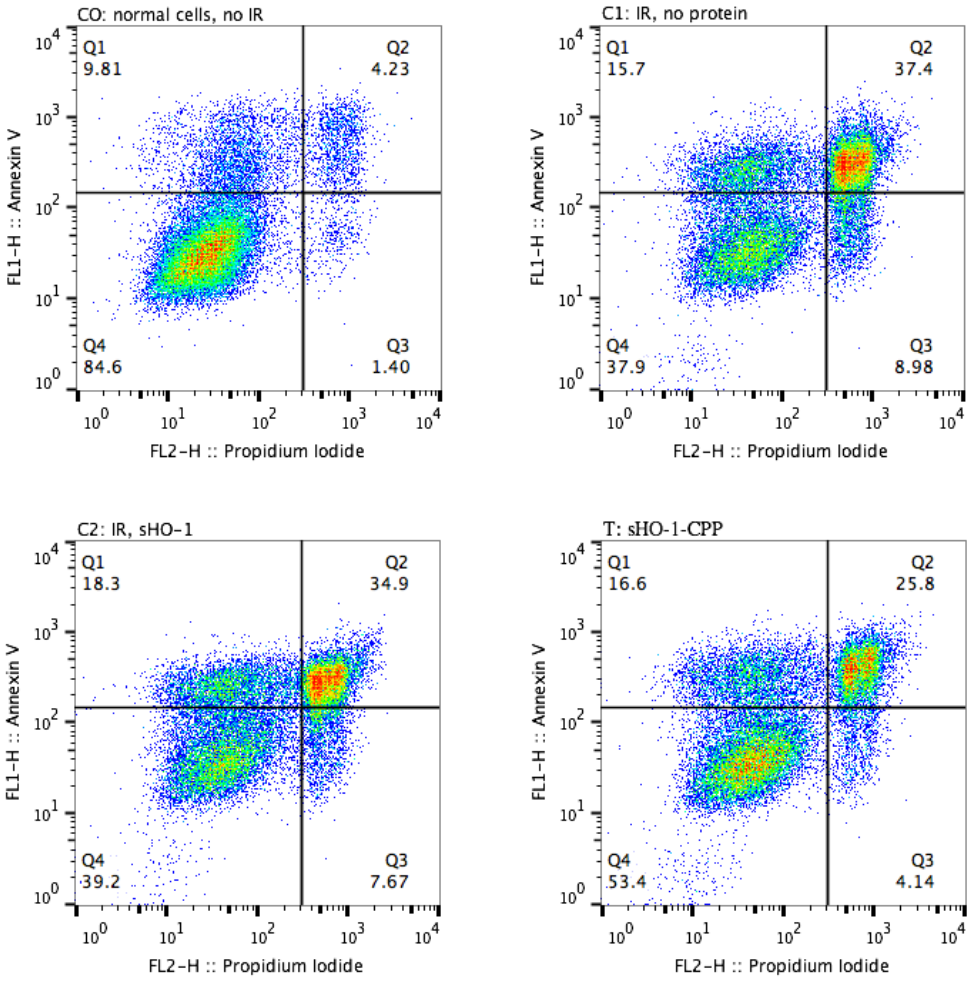
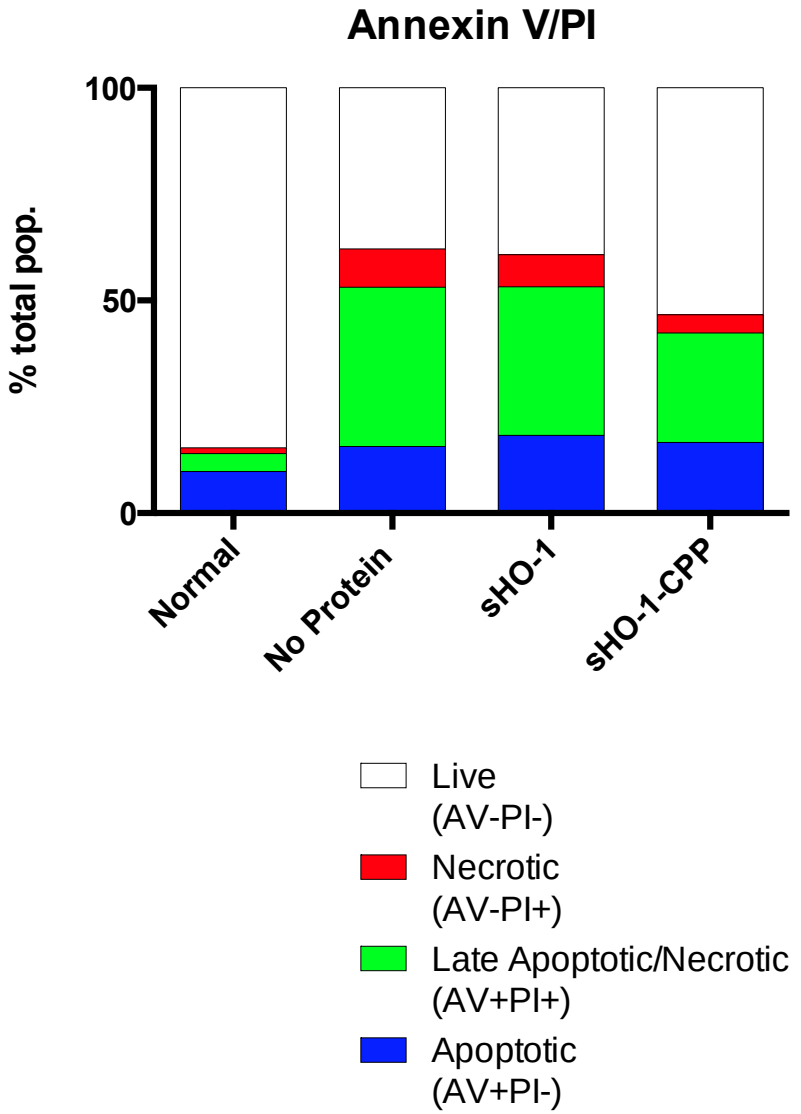
Protection from ischemia/reperfusion injury





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Summary

- Dogmas are being challenged
- New technologies have been developed and are in testing phases
- Not clear what technology has most potential
- Shifting from ‘preservation’ to ‘assessment, repair and improvement’

Other innovations..

- Pre-donation
- Stem cell technologies/tissue engineering
- Expanding indications
- New drugs?

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