

# INTESTINAL PRESERVATION FOR TRANSPLANTATION: TRANSLATIONAL APPROACHES

## AKADEMISK AVHANDLING

Som för avläggande av medicine doktorexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentlig försvaras i Ragnar Sandbergs hörsal, Medicinargatan 7A, fredagen den 6 december, klockan 13:00

av

**John Mackay Søfteland**

Leg. Läkare

Fakultetsopponent:

**Prof. Kishore Iyer M.D., Ph.D.**

Recanati/Miller Transplantation Institute

Icahn School of Medicine at Mount Sinai Medical Center

New York, USA

### Avhandlingen baseras på följande delarbeten:

- I. Casselbrant A\*, **Søfteland JM\***, Hellström M, Malinauskas M, and Oltean M. *Luminal Polyethylene Glycol Alleviates Intestinal Preservation Injury Irrespective of Molecular Size*. J Pharmacol Exp Ther. 2018 Jul; 366(1):29-36. \* Shared first authorship
- II. **Søfteland JM**, Casselbrant A, Biglarnia A-R, Linders J, Hellström M, Pesce A, Padma AM, Jiga LP, Hoinoiu B, Ionac M, and Oltean M. *Intestinal Preservation Injury: A Comparison Between Rat, Porcine and Human Intestines*. Int. J. Mol. Sci. 2019, 20, 3135.
- III. **Søfteland JM**, Casselbrant A, Akyurek L, Hellström M, and Oltean M. *The Impact of Age and Luminal Preservation on the Development of Intestinal Preservation Injury in Rats*. (Transplantation, in press, 2019)
- IV. **Søfteland JM**, Padma AM, Casselbrant A, Zhu C, Wang Y, Pesce A, Hellström M, Olausson M, and Oltean M. *Luminal Preservation of the Human Small Bowel Using a Polyethylene-Glycol Based Solution*. (in manuscript)

**SAHLGRENKA AKADEMIN**  
**INSTITUTIONEN FÖR KLINISKA VETENSKAPER**



**GÖTEBORGS  
UNIVERSITET**

# INTESTINAL PRESERVATION FOR TRANSPLANTATION: TRANSLATIONAL APPROACHES

John Mackay Søfteland

Department of Transplantation Surgery, Institute of Clinical Sciences  
Sahlgrenska Academy at the University of Gothenburg  
Gothenburg, Sweden, 2019

## ABSTRACT

**Background:** Intestinal preservation injury (IPI) may result in various degrees of mucosal damage, which may later favor bacterial translocation, post-reperfusion syndrome, and upregulation of alloreactivity. Experimental evidence suggests that combining vascular perfusion and cold storage with luminal interventions using polyethylene glycol (PEG) solutions may mitigate the mucosal damage and extend the safe storage time. During the last years, there has been an increasing trend towards using livers and kidneys from older donors for transplantation, yet the field of intestinal transplantation is far more conservative as the impact of age on the preservation injury is unknown. Clinical translation of various experimental models is hampered by interspecies differences, as little is known about how IPI development differs between rodents, pigs, and humans. The current thesis aimed to explore if the size of the PEG molecule or the donor age has an impact on the development of IPI and whether the development of IPI differs between rats, pigs, and humans. It also examines if luminal preservation (LP) with PEG is safe and efficient in delaying the development of IPI in the human intestine.

**Methods:** In Paper I, we used small intestines from rats to study the effect of PEG size on the development of IPI. Paper II compared the development of IPI in rat, porcine, and human intestinal specimens. Paper III assessed the effect of donor age on IPI in a rat model. Paper IV studied the effect of LP with a low-sodium PEG solution on human small intestinal specimens. In all studies, we analyzed injury development using histological and molecular biological approaches. We also used Ussing chamber experiments for intestinal functional assessment in Paper I.

**Results:** The luminal presence of PEG rather than its molecular size appears to reduce and delay the development of IPI when compared with controls undergoing standard cold preservation. Increasing donor age does not appear to accelerate the development of the IPI in rats. LP is effective in all age groups. Pig intestines are more ischemia resistant than human and rat intestines. LP with a low-sodium PEG solution is effective in delaying tissue injury in human specimens and does not cause excess edema.

**Conclusions:** The development of IPI differs significantly between species, with the rat being a sensitive model when studying IPI. LP is effective in protecting against IPI regardless of the size of the PEG molecule or donor age. LP appears to delay the development of IPI in humans without causing tissue edema and could be introduced in clinical practice.

Keywords: intestinal preservation, luminal preservation, tight junction, apoptosis.