Research Update

Rat Model
Rat

- **The size**
  - large enough for complex surgical model

- **Sample amount**
  - larger tissues and blood samples for sensitive assays

- **Resemblance to the human condition**
  - a standardized physiological and toxicological model in the pharmaceutical industry

- **The rat genome database**
  - more translational to represent human physiology

Emerging Innovations in Liver Preservation and Resuscitation

J. Kim, M.A. Zimmerman, and J.C. Hong*

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Table 3. Clinical Organ Resuscitation Trials in Human Liver Transplantation

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>Methods</th>
<th>Vessel</th>
<th>Duration (hours)</th>
<th>Temperature*</th>
<th>Oxygenation</th>
<th>Blood</th>
<th>Main Perfusate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guerrera [67]</td>
<td>2010</td>
<td>Ex situ</td>
<td>Dual</td>
<td>3–7</td>
<td>Hypothermic</td>
<td>No</td>
<td>No</td>
<td>Vasosol solution</td>
</tr>
<tr>
<td>Dutkowski [68]</td>
<td>2014</td>
<td>Ex situ</td>
<td>Portal vein</td>
<td>1–2</td>
<td>Hypothermic</td>
<td>Yes</td>
<td>No</td>
<td>KPS</td>
</tr>
<tr>
<td>Guerrera [69]</td>
<td>2015</td>
<td>Ex situ</td>
<td>Dual</td>
<td>3–7</td>
<td>Hypothermic</td>
<td>No</td>
<td>No</td>
<td>Vasosol solution</td>
</tr>
<tr>
<td>van Rijn [70]</td>
<td>2017</td>
<td>Ex situ</td>
<td>Dual</td>
<td>2</td>
<td>Hypothermic</td>
<td>Yes</td>
<td>No</td>
<td>UW-MP solution</td>
</tr>
<tr>
<td>Mergental [71]</td>
<td>2016</td>
<td>Ex situ</td>
<td>Dual</td>
<td>5–9</td>
<td>Normothermic</td>
<td>Yes</td>
<td>Yes</td>
<td>Blood and albumin solution</td>
</tr>
<tr>
<td>Ravikumar [72]</td>
<td>2016</td>
<td>Ex situ</td>
<td>Dual</td>
<td>3–18</td>
<td>Normothermic</td>
<td>Yes</td>
<td>Yes</td>
<td>Blood and colloid solution</td>
</tr>
<tr>
<td>Selzner [73]</td>
<td>2016</td>
<td>Ex situ</td>
<td>Dual</td>
<td>6–10</td>
<td>Normothermic</td>
<td>Yes</td>
<td>Yes</td>
<td>Blood and Steen solution</td>
</tr>
<tr>
<td>Bral [74]</td>
<td>2017</td>
<td>Ex situ</td>
<td>Dual</td>
<td>3–23</td>
<td>Normothermic</td>
<td>Yes</td>
<td>Yes</td>
<td>Blood and gelofusine</td>
</tr>
<tr>
<td>Watson [75]</td>
<td>2017</td>
<td>Ex situ</td>
<td>Dual</td>
<td>2–9</td>
<td>Normothermic</td>
<td>Yes</td>
<td>Yes</td>
<td>Blood and succinylated gelatin solution</td>
</tr>
</tbody>
</table>

Abbreviations: MP, machine perfusion; KPS, kidney preservation solution; UW, University of Wisconsin.
*Hypothermic refers to the temperature setting between 0°C and 12°C; midthermic, 13°C and 24°C; subnormothermic, 25°C and 34°C; and normothermic, 35°C and 39°C.

Alteration of MRP2 expression and the graft outcome after liver transplantation

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Pre-Hepatectomy Assessment of Bile Transporter Expression by Gadoxetic Acid-Enhanced MRI in a Rat Model of Liver Cirrhosis

Joohyun Kim,1,2 Tae Kim,3 Kwan Soo Hong,4 Hyeyoung Moon,4 In-Kyung Oh,5 Sang Mok Lee,5 Mark D. Hohenwalter,6 Michael A. Zimmerman,1,2 David C. Cronin, II,1,2 Johnny C. Hong1,2

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Optical imaging for the assessment of hepatocyte metabolic state in ischemia and reperfusion injuries

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Effects of Hepatic Ischemia–Reperfusion Injuries and NRF2 on Transcriptional Activities of Bile Transporters in Rats

Joohyun Kim, MD, PhD, Alicia Martin, MS, MBA, Jennifer Yee, BS, Lynn Fojut, AS, CVT, Aron M. Geurts, PhD, Kiyoko Oshima, MD, PhD, Michael A. Zimmerman, MD, FACS, and Johnny C. Hong, MD, FACS

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Department of Physiology, Medical College of Wisconsin, Milwaukee, Wisconsin
Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, Maryland

A transverse abdominal incision was made, and the abdomen was temporarily closed during ischemia to minimize reperfusion injuries. At each stage of IRI, the serum levels of amino transferase, total bilirubin, and bile acids were measured. In addition, hepatic tissue was sampled to determine the histologic score of IRI (Suzuki score), measure adenosine triphosphate, and identify the quantitative real-time polymerase chain reactions of Nrf2.

Statistical analysis

The relationships between BT expression and other variables were evaluated using Spearman’s rho correlation analysis. The normality of residuals was validated by the Kolmogorov–Smirnov test, and the presence of multiple comparisons was evaluated using the Bonferroni’s correction after the Kruskal–Wallis test. Differences in the mean among the groups of Sprague Dawley rats were considered significant. Differences in the mean among the groups of Sprague Dawley genetic background were considered significant.

The data were expressed as median with IQR.

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b Department of Physiology, Medical College of Wisconsin, Milwaukee, Wisconsin
C Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, Maryland

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Current Project: Methods

NRF2 Activation: Bardoxolone methyl

Control Group
(Vehicle only)
0.9 mL of [0.2% Tween 80 in normal saline]
+ 100ul of DMSO

BARD Group
(Bardoxolone methyl 2 mg/kg)
0.9 mL of [0.2% Tween 80 in normal saline]
+ 100ul of [5mg/ml BARD in DMSO]

1 mL intravenous injection (IVC, 1 mL/min infusion)
5 min before ischemia
Current Project: Results

Bile Transporter mRNA expression: Control vs. Bardoxolone methyl injection

60 min ischemia + 24 hr reperfusion

90 min ischemia + 24 hr reperfusion
Current Project: Results

**Blood tests:** Control vs. Bardoxolone methyl injection

**60 min ischemia + 24 hr reperfusion**

- **AST**
- **ALT**
- **T-Bil**
- **Bile Acids**

**90 min ischemia + 24 hr reperfusion**

- **AST**
- **ALT**
- **T-Bil**
- **Bile Acids**
Future Plan

RNA-sequencing

**Hypothesis:** Brief ischemia in liver tissue induces defensive genes against IRI, whereas prolonged ischemia induces injurious genes.

**Specific Aim:** To profile whole-genome transcriptomes affected by brief vs. prolonged ischemia in the rat liver.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Gene expression levels compared to the control at 60 min of ischemia</th>
<th>Gene expression levels compared to the control at 90 min of ischemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early-responding</td>
<td>Increased</td>
<td>Not increased</td>
</tr>
<tr>
<td>Late-responding</td>
<td>Not increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Indiscriminate</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Quiescent</td>
<td>Not increased</td>
<td>Not increased</td>
</tr>
</tbody>
</table>