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I have a financial relationship relevant to my presentation with Covidien.
THE ROLE OF NUCLEAR MEDICINE IN RENAL TRANSPLANTATION

Enhancing the identification of renoprotective treatment modalities for improved renal function following kidney transplantation

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GRAFT SURVIVAL (%)
All transplants 1985-2007

Collaborative Transplant Study 2007
Transplantation Immunology Department,
University of Heidelberg, GERMANY
(400 transplant centers in 45 countries)
CHRONIC ALLOGRAFT NEPHROPATHY
Major cause of dysfunction and loss of the transplant kidney

Pascual et al., N Engl J Med 2002
KIDNEY REGENERATION

Adapted from Haller, Internist 2007
DETERMINATION OF KIDNEY FUNCTION IN A MURINE MODEL OF RENAL ISCHEMIA-REPERFUSION INJURY

Classic
Variable
Insufficient

New
Sensitive
Specific

99mTechnetium-MAG-3
Mercapto-acetyl-tri-glycine
+ tubular excretion
+ longitudinal studies
+ long-term follow-up
+ short half life
+ unilateral kidney injury

O'Donnell et al., Transplantation 2002

Roberts et al., Am J Physiol Renal Physiol 2007
$^{99m}$Tc-MAG3 IMAGING

Whole body scintigraphy using a **triple-headed gamma camera**, each detector equipped with a LEHR collimator and a standardized dose of $\sim 3.7 \times 10^7$ Bq i.v. per mouse and simultaneous acquisition in a **dynamic planar technique**. Collection of **1 frame per 5 sec**, total scan time **10 min**.

**Image acquisition magnification** set to 4 times.

**Image analysis** using Hermes dynamic analysis software V4.1 (Hermes Medical Solution, Stockholm, Sweden).

$$f(x) = \frac{\text{(right kidney ROI – background ROI)}}{\text{(whole body ROI – injection ROI)}} \times 100 = \% \text{ID}$$
PROBLEM No. 1
Optimal ischemia time in murine model of ischemia-reperfusion injury?

35 min  40 min  45 min  Healthy

![Image of histological sections and graphs showing ischemia time effects]

- blue: pre (n=4)
- red: day 2 (n=4)
- green: day 18 (n=4)
STUDY DESIGN
Murine model of ischemia-reperfusion injury

- 99mTc-MAG3 imaging
- Renal I/R unilateral 45 min Balb/C nu/nu
- Day 0
- 10^6 hEPC/hMSC i.v.
- Day 1
- Laser doppler perfusion
- Histology
- Immunohistochemistry
- Day 2
- Day 18
STEM/ PROGENITOR CELL THERAPY IN RENAL ISCHEMIA-REPERFUSION INJURY

Histology & Scintigraphy

Healthy 45 min ischemia 45 min ischemia + ECFC 45 min ischemia + MSC
PATHOPHYSIOLOGY OF POSTISCHEMIC INFLAMMATORY EDEMA
A vicious circle

Hypoxia → Ischemia → Microcirculation↓ → Edema
ANATOMY OF THE KIDNEY

The tight fibrous kidney capsule has little ability to accommodate volume shift.
INTRACAPSULAR PRESSURE IN RENAL ISCHEMIA-REPERFUSION INJURY

The intrinsic renal compartment syndrome

Herrler et al., Transplantation 2010

* p<0.001 vs. healthy, p<0.05 vs. 35 min
** p<0.05 vs. healthy

![Graph showing intracapsular pressure over time]

Reperfusion time

- 35 min ischemia
- 45 min ischemia
- 35 min ischemia
- 45 min ischemia
- 45 min ischemia
- 45 min ischemia
- 45 min ischemia
- 45 min ischemia

45 min ischemia

6h reperfusion
12h reperfusion
24h reperfusion
48h reperfusion
SITE AND EFFECT OF SURGICAL DECOMPRESSION THERAPY IN THE ISCHEMIC KIDNEY
STUDY DESIGN

- Day -4: Renal I/R unilateral 45 min
- Day 0: 99mTc-MAG3 imaging
- Day 2: Control vs. Incision of kidney capsule
- Day 18: Laser doppler perfusion, Histology, Immunohistochemistry

99mTc-MAG3 imaging
Balb/C wt
Control vs.
Incision of kidney capsule
MICRO-CAPSULOTOMY PRESERVES KIDNEY FUNCTION IN RENAL ISCHEMIA-REPERFUSION INJURY (BALB/C WT MICE)

Herrler et al., Transplantation 2010
TUBULAR EXCRETION IN RENAL ISCHEMIA-REPERFUSION INJURY
Renoprotective effects of surgical decompression therapy

Herrler et al., Transplantation 2010
LASER DOPPLER-ASSESSED KIDNEY PERFUSION
Surgical decompression therapy preserves renal blood flow

Herrler et al., Transplantation 2010
ANALYSIS OF KIDNEY SIZE AND WEIGHT
Surgical decompression therapy prevents atrophy

Herrler et al., Transplantation 2010
HISTOLOGICAL ANALYSIS (H&E)
Surgical decompression preserves integrity of renal structures

45 min renal ischemia - 18 days reperfusion
control  therapy  healthy

Herrler et al., Transplantation 2010
TUBULAR FUNCTION FOLLOWING RENAL ISCHEMIA-REPERFUSION INJURY

Renoprotective effects of combination therapy

* p<0.01 vs. control

* p<0.01 vs. control
LASER DOPPLER-ASSESSED KIDNEY PERFUSION
Surgical decompression therapy preserves renal blood flow

<table>
<thead>
<tr>
<th></th>
<th>Renal blood flow (% of contralateral healthy kidney)</th>
</tr>
</thead>
<tbody>
<tr>
<td>control (n=4)</td>
<td>*</td>
</tr>
<tr>
<td>ECFC alone (n=4)</td>
<td>**</td>
</tr>
<tr>
<td>decompression alone (n=5)</td>
<td>*</td>
</tr>
<tr>
<td>ECFC + decompression (n=4)</td>
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</tr>
</tbody>
</table>

45 min ischemia

* p<0.001 vs. control
** p< 0.05 vs. control
HISTOLOGICAL ANALYSIS (H&E)
Preservation of the integrity of renal structures using combination therapy

Tubular injury score
- cellular necrosis
- loss of brush border
- cast formation
- vacuolization,
- tubule dilation

0: none
1: 10%
2: 11 to 25%
3: 26 to 45%
4: 46 to 75%
5: >76%.

* p<0.01 vs. control  ** n.s. vs. control

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IMMUNOSUPPRESSIVE AGENTS IN KIDNEY TRANSPLANTATION

Therapy evaluation using $^{99m}$Tc-MAG3 imaging

<table>
<thead>
<tr>
<th></th>
<th>Renal function peak (% baseline)</th>
<th>Tubular excretion rate (% baseline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td><img src="image1" alt="Renal function peak graph" /></td>
<td><img src="image2" alt="Tubular excretion rate graph" /></td>
</tr>
<tr>
<td>CsA</td>
<td><img src="image3" alt="Renal function peak graph" /></td>
<td><img src="image4" alt="Tubular excretion rate graph" /></td>
</tr>
<tr>
<td>DEX</td>
<td><img src="image5" alt="Renal function peak graph" /></td>
<td><img src="image6" alt="Tubular excretion rate graph" /></td>
</tr>
<tr>
<td>SRL</td>
<td><img src="image7" alt="Renal function peak graph" /></td>
<td><img src="image8" alt="Tubular excretion rate graph" /></td>
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</table>

45 min ischemia – 48 h reperfusion

<table>
<thead>
<tr>
<th></th>
<th>Renal function peak (% baseline)</th>
<th>Tubular excretion rate (% baseline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td><img src="image9" alt="Renal function peak graph" /></td>
<td><img src="image10" alt="Tubular excretion rate graph" /></td>
</tr>
<tr>
<td>CsA</td>
<td><img src="image11" alt="Renal function peak graph" /></td>
<td><img src="image12" alt="Tubular excretion rate graph" /></td>
</tr>
<tr>
<td>DEX</td>
<td><img src="image13" alt="Renal function peak graph" /></td>
<td><img src="image14" alt="Tubular excretion rate graph" /></td>
</tr>
<tr>
<td>SRL</td>
<td><img src="image15" alt="Renal function peak graph" /></td>
<td><img src="image16" alt="Tubular excretion rate graph" /></td>
</tr>
</tbody>
</table>

Contralateral healthy kidney – 48h reperfusion

CsA  cyclosporine A
DEX  dexamethasone
SRL  sirolimus/ rapamycin
99mTc-MAG3 IMAGING IN PRECLINICAL RESEARCH…

Conclusion and perspectives

- represents reliable endpoint for the determination of early and long-term renal function following renal ischemia-reperfusion injury
- enabled us to establish micro-capsulotomy for enhanced functional recovery
- demonstrated that decompressive treatment is required to exploit additional benefits of a cell-based therapy for kidney recovery after ischemia-reperfusion injury
- provides more insights into functional effects of immunosuppressive agents following renal ischemia-reperfusion injury for optimized clinical application.
- contributes to the identification of effective treatment modalities in renal ischemia-reperfusion injury for improved function and survival of the renal allograft.
- facilitates pre-clinical therapy evaluation

Next steps:

- Verification in preclinical model of kidney transplantation
- Translation into clinical application
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KIDNEY ANATOMY

- Interlobar vessels
- Arcuate vessels
- Glomerulus
- Bowman’s capsule
- Efferent arteriole
- Proximal tubule
- Cortical capillary network
- Collecting tubule
- Henle’s loop
- Interlobar vessels
- Arcuate vessels