KRP203 AS A DESIRABLE IMMUNO-MODULATOR FOR ISLET TRANSPLANTATION

Ibrahim Fathi¹, Ryuichi Nishimura², Takehiro Imura¹, Akiko Inagaki¹, Akira Ushiyama³, Hiroaki Yamaguchi⁴, Masafumi Goto¹,²

¹ Division of Transplantation and Regenerative Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan
² Department of Surgery, Tohoku University Graduate School of Medicine, Sendai, Japan
³ Department of Environmental Health, National Institute of Public Health, Wako, Japan
⁴ Department of Pharmaceutical Science, Tohoku Uni. Hospital, Sendai, Japan
Drawbacks of current immunosuppressives


Aim

1. Examine the effect of KRP203 on blood glucose levels, glucose tolerance, and islet function.

2. Examine the effect of KRP203 on in-vivo islet vascularity.

3. Explore the possibility of omitting calcineurin-inhibitors in KRP203 based regimen for islet allo-transplantation.
IPGTT

![Graph showing blood glucose levels over time for different treatments. The graph has two main lines, one for CTRL and another for KRP 3mg/kg, and a third line for KRP 1mg/kg. The x-axis represents time in minutes (0 to 120), and the y-axis represents blood glucose levels in mg/dl (0 to 450). The graph includes error bars indicating variability.]
Functional assays

- KRP 3mg/kg
- Methyl cellulose

**Results:**

- Functional assays
  - p = 0.813
  - p = 0.398
  - p = 0.481

**Graph:**

- SGS index
- Breathing index
- Insulin/DNA (ug/ug)
Control

Tacrolimus

Day1  Day4  Day7  Day11  Day14

Islet Vascularity

Image acquisition: *FluoView FV1000MPE; OLYMPUS, Tokyo, Japan.*
Vascular volume analysis: *Volocity 3D system, PerkinElmer, Waltham, MA, USA*
Islet Vascularity

KRP 3mg/kg
Control

p=0.351
p=0.951
p=0.970
p=0.092

Day 4
Day 7
Day 11
Day 14

Vascular volume (compared to day 1)
Islet allotransplantation (Balb/c to B/6)

Graft survival

Normoglycaemia

Days

Nephrectomy

5 10 15 20 25 30 35 40 45 50 55 60

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

1 mg/kg 3 mg/kg
Immunohistochemistry (Anti-insulin)

<table>
<thead>
<tr>
<th>NO REJECTION</th>
<th>REJECTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRP 1 mg/kg</td>
<td>KRP 3 mg/kg</td>
</tr>
</tbody>
</table>
Co-stimulatory blockade + KRP203

Daily KRP203 (1mg/kg) + Anti-LFA1α (100 μg from day 0 to day 6)

No rejection beyond 50 days of follow-up (2/2 mice)
Conclusions

KRP203 is a desirable immunomodulator for islet transplantation

- Preserving endocrine function
- Preserving revascularization of transplanted islet grafts.

Therefore, KRP203 in combination with co-stimulatory blockade could be an attractive alternative to current standard immunosuppressive regimen.