The ALCADIA (AutoLogous Human Cardiac-Derived Stem Cell To Treat Ischemic cardiomyopathy) Trial

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Clinical trials of current cell therapy

To exceed current cell therapies of cardiac regeneration..

1. New cell source; Cardiac derived stem cell
   : high potential of cardiac differentiation
   : rapid expansion as stem cell

2. New application; Tissue engineering
   : promotion of the efficacy of cell therapy
   cell survival, blood supply, cytokine effect..
To generate autologous cardiac-derived stem cell (CSC) from minimum cardiac biopsy specimens
To achieve graft survival of transplanted cell in host ischemic myocardium
~ Hybrid cell therapy using Biodegradable scaffold ~

**ALCADIA Study Design**

- **Primary Purpose: Safety**
- **Eligibility criteria: Ischemic cardiomyopathy**
  - with past history of congestive heart failure (NYHA III, IV)
  - with LV dysfunction (15% < LVEF < 35%)
- **Study Phase: Phase 1, Open Label, Non-Randomized**
- **Intervention Model : hybrid cell therapy concomitant with CABG**
  - intramyocardial injection (20 sites) of autologous CSC (total $5 \times 10^5$ cell/kg)
  - sustained release of human recombinant bFGF (200µg)
- **Masking: Endpoint Classification**
  - Safety: MACE (Major cardiac event), serious adverse event
  - Preliminary efficacy study
    - NYHA classification, LV function (echocardiography)
    - infarct volume (MRI), wall motion score (MRI)
- **Enrollment: 6 [Anticipated]**
ALCADIA Study Scheme

A. 

Endomyocardial biopsy

B. 

2.5±0.3 mg/piece

C. 

Total 21.7±2.3 mg

D. 

33.8 ±2.7 days

E. 

Total 3.7±0.8×10^7 cell
20 cites

F. 

bFGF 200μg
**ALCADIA: Flow Diagram**

<table>
<thead>
<tr>
<th>Enrollment</th>
<th>7</th>
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<tbody>
<tr>
<td>Safety analysis set (6 month)</td>
<td>6</td>
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<tr>
<td>Age</td>
<td>55.5±10.8</td>
</tr>
<tr>
<td>Sex (male;%)</td>
<td>83.3</td>
</tr>
<tr>
<td>BMI</td>
<td>25.5±4.1</td>
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<tr>
<td>DM (%)</td>
<td>83.3</td>
</tr>
<tr>
<td>HT (%)</td>
<td>66.7</td>
</tr>
<tr>
<td>Infarct artery</td>
<td>2.5±1.0</td>
</tr>
<tr>
<td>LAD</td>
<td>100</td>
</tr>
<tr>
<td>LCX</td>
<td>16.7</td>
</tr>
<tr>
<td>RCA</td>
<td>100</td>
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</table>
# ALCADIA: baseline characteristics

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>treatment</td>
<td>6</td>
</tr>
<tr>
<td>NYHA classification</td>
<td>3.6 ± 0.5</td>
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<tr>
<td>LVEF (%)</td>
<td>26.7 ± 5.7</td>
</tr>
<tr>
<td>LVESV index (ml/m²)</td>
<td>74.1 ± 28.2</td>
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<tr>
<td>infarct volume (mass: g)</td>
<td>30.4 ± 13.0 g</td>
</tr>
<tr>
<td>infarct volume / LV mass (%)</td>
<td>22.5 ± 6.0 %</td>
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<tr>
<td>Wall motion score (0 ~ 54)</td>
<td>17.2 ± 3.1</td>
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</table>

18 segment model: 6 segments at basal, mid, apex normokinesis=0, hypokinesis=1, akinesis=2, dyskinesis=3
Cardiac-derived stem cell from ischemic cardiomyopathy patients

A

Day 1

Day 31

B

population doubling

0 11 17 24 32
day

- Case01
- Case02
- Case03
- Case04
- Case05
- Case06

C

Cell surface marker

CD105 CD90 Stro1 CD29 CD45 MHC II

98.9 50.7 9.4 90.9 0.2 0.6

D

case 1 case 2 case 3 case 4 case 5 case 6 Human iPS

Nanog

Oct 3/4

Rex1

NKx2.5

GATA4

GAPDH
# Results: Safety of ALCADIA

<table>
<thead>
<tr>
<th>Serious Adverse event(SAE)</th>
<th>ALCADIA</th>
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<tbody>
<tr>
<td>• Adverse event</td>
<td>0</td>
</tr>
<tr>
<td>• MACE (6Mo)</td>
<td>1</td>
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<tr>
<td>VT/Vf</td>
<td>0</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>1</td>
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<tr>
<td>Tumor</td>
<td>0</td>
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<tr>
<td>Death</td>
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</table>

- No complication of right ventricular biopsy
- 1 graft occlusion within 3 weeks after cardiac bypass surgery (case 6)
Results: Efficacy of ALCADIA

~ Restore the loss of LV function ~

LVEF (TTE: %)

baseline  4 weeks  24 weeks

Case 1  Case 2  Case 3
Case 4  Case 5

LVEF (MRI: %)

baseline  24 weeks

diastole  systole

p=0.0117

p=0.0133

5cm
**Results: Efficacy of ALCADIA**

~ improve symptom of heart failure and exercise capacity ~

<table>
<thead>
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<th>NYHA Classification</th>
<th>24 months</th>
<th>baseline</th>
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<tr>
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</tr>
<tr>
<td>II</td>
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</tr>
<tr>
<td>III</td>
<td>III</td>
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<tr>
<td>IV</td>
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<td>0</td>
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</table>

<table>
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<tr>
<th>NYHA Classification</th>
<th>III</th>
<th>IV</th>
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<tr>
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<td>1</td>
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<td>III</td>
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<td>0</td>
</tr>
<tr>
<td>IV</td>
<td>0</td>
<td>0</td>
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**maximal oxygen consumption (ml/kg/min)**

- Baseline: p=0.0308
- 24 weeks

Bar graph showing a significant increase from baseline to 24 weeks.
Results: Efficacy of ALCADIA

~ partial reverse remodeling in cell transplantation area ~

![Graph showing wall motion score over time]

Wall motion score (MRI)

- Baseline
- 24 weeks

- p=0.0013

![Graph showing infarct volume/LV mass over time]

Infarct volume/LV mass (%)

- Baseline
- 24 weeks

- p=0.1742

Images showing MRIs at baseline and 24 weeks.
Conclusion

1. The transplantation of human cardiac-derived stem cell with controlled release of bFGF is safe and feasible to ischemic cardiomyopathy patients.

2. This novel biotherapy may have a potential to restore the injured heart to functional repair with reconstruction of post-ischemic environment.

Acknowledgements

Grant in aid of Ministry of Education, Culture, Sports, Science and Technology - Japan.