"*Joint Research with Fuji Micra Inc.*"

Infrastructural set-up for iPS cells' clinical applications:
"From Mini Pig to Micro Pig"

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The team of Prof. Keichi Fukuda, Department of Cardiology, Keio University School of Medicine has been intensively elaborating basic researches for regenerative medicine to create myocardial cells from iPS cells. In order to upgrade the research for clinical application, they have been focusing on the development of diseased pig model through the integrated research method of non-clinical and clinical sciences. In 2012 the team of Prof. Sjinya Yamanaka received the Nobel Prize in Physiology or Medicine for his research on the initialization of cells through the creation of iPS cells. It has led to the nationwide enormous expectations to the regenerative medicine through the application of stem cells.

At Jichi Medical University I started a research on the creation of myocardial infarction by using experimental pig with around 40kg in weight. Simultaneously Prof. Yutaka Hanazono of Jichi Medical University started a joint research on the characteristics of iPS cells generated from Mini Pigs (*Mizukami Y, et al. PLOSOne 2014*).

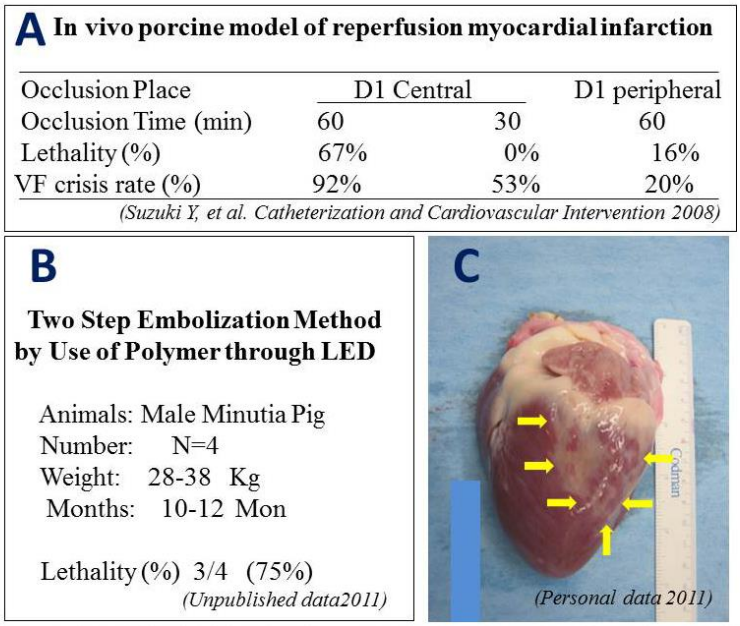

Figure A: Data from published reference B: Data from commercially avertable method
C: Ischemic area induced by polymer obtained from the one month surviving minutia pig

The myocardial infarction model of pig has been created by the insertion of catheter in coronary arteries from which the data was provided by using the very young livestock pig. However, the our data shows the survival rate for matured mini pig has been extremely low (See the attachment 1).

On the other hand, there exists another method to bind with Ameroid ring to create chronic ischemic model, however, as the regular ameroid ring is made from metal, it is not applicable for the human MRI clinical evaluation. Then, we have developed a resin ameroid ring to establish a stable chronic ischemic evaluation model by using mini pigs (See the attachment 2).

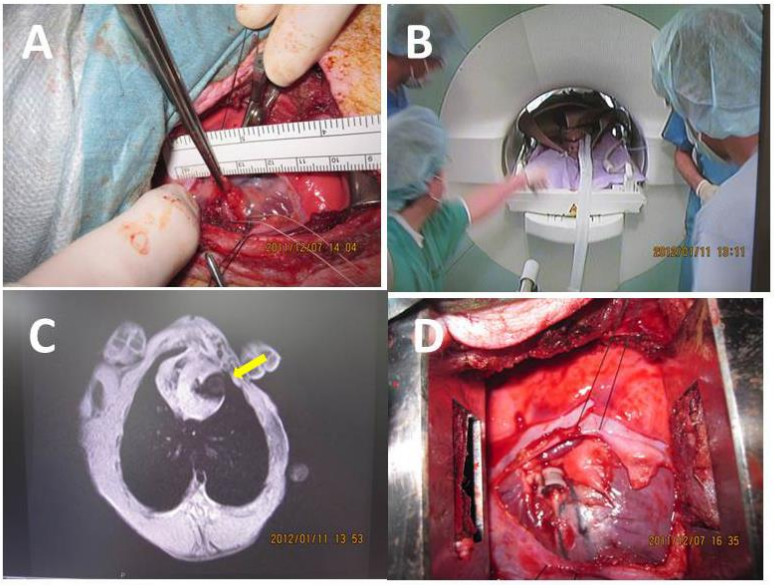

Figure A: Exposure of LDA in Minutia Pig B: Breath-controlled pig in MRI Evaluation
C: Defect Shadow (Yellow arrow) by use of Metal Ameroid D: Application of Resinous Ameroid

Also the evidence shows that the myocardial induction from iPS cells from pigs does not react sufficiently against the protocol of inductive differentiating factors used for human iPS cells. Therefore, our next research target is set to ensure the method to inject directly into mini immunosuppressed pigs the cardiac muscle induced from human iPS cells. Then the smallest experimental pig, micro-mini pig "MMP" has been chosen to accelerate the research in order to minimize the human-iPS-derived cardiac muscle and the amount of immunosuppressive agent (See the attachment 3).

Nevertheless, as the fundamentals for MMP has not been well established yet to convey the effectiveness of the pig among researchers, I have decided to start joint research with Fuji Micra Inc. Currently myocardia-damaged MMP sample has been completed. In the consequence, the development of complete thymectomy technology has been ongoing in time for creating SPF newborn MMP pigs(See the attachment 4).

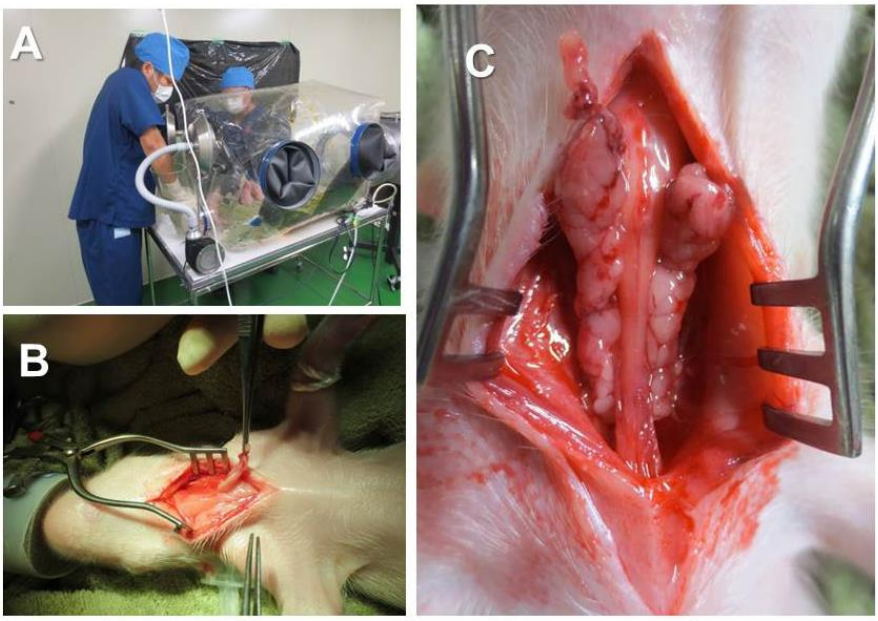

Figure A: Newborn piglets B: Sufficient general anesthesia
C: Macro-View of Cervical Thymus
Complete thymectomy with thoracic part was done by throracotomy