

## 【Grant-in-Aid for Transformative Research Areas (B)】

### Section III



**Title of Project : A new foundation for primate developmental biology**

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#### 【Purpose of the Research Project】

Developmental biology is the study of mechanisms whereby a fertilized egg (embryo) grows into a full-fledged organism. The implantation of a human embryo initiates dynamic biological processes, such as gastrulation and organogenesis, that are essential to the embryo's growth and survival. The mechanisms of human embryonic development, particularly in the early post-implantation stages, are poorly understood because legal, ethical, technical, and other issues restrict scientific experimentation concerning this biological process.

Research using model animals, especially mice, has also achieved remarkable results, but due to recent technological development and accumulation of knowledge, the species difference between mice and humans has reached a level that cannot be overlooked. Also, even in the more closely related non-human primate (NHP), it is difficult to collect embryo samples due to various primate-specific factors such as cost, long generation time, and low number of offspring. Furthermore, the production of genetically modified animals, which is essential for investigating the molecular mechanism, is still difficult even with the remarkable advances of recent gene editing technology, and the hurdle to comprehensive research is still extremely high. (Fig. 1)




	Mouse	NHP	Human
<b>Sampling</b>	cylindrical  easy	Disk-shape  Possible but difficult	Disk-shape  impossible
<b>available information</b>	morphology Gene expression Molecular mechanisms	morphology Gene expression	Morphology only
<b>Genome editing</b>	Various technologies are available	Possible but Difficult & Limited	Not ethically Allowed
<b>Knowledge At molecular level</b>		Limited	none

Fig. 1. Current situation of primate post-implantation embryology

Thus, study on the primate post-implantation development has not progressed much enough for a long time due to the difficulty of sampling and research experiments at the molecular level. To overcome these hurdles, we will lay the new foundation for the primate developmental biology using non-human primate (NHP) models.

#### 【Content of the Research Project】

In this area, using cynomolgus macaques and marmosets, we focus on (A) the establishment of the "pseudo-implantation" culture model of primate embryos implanting on in vitro produced endometrial environment (ex vivo culture system) that accurately reproduces physiological development, and (B) the development of innovative genetic engineering techniques optimized for primates.

In (A), we will acquire the necessary knowledge of embryogenesis in vivo for the reconstruction of physiological development conditions. And reproduce the functional endometrial environment corresponding to the maturity stage in the sexual cycle, then construct a primate embryo implantation model in vitro. In (B), we will develop methods by two strategies; improving a method of the conventional gene modification technology for fertilized eggs and developing stem cell-based method of inducing functional germ cells starting from the genetically modified ESC / iPSC.

#### 【Expected Research Achievements and Scientific Significance】

With the novel pseudo-implantation model and genome engineering technology for primates, we expect that the traditional experiments, such as time lapse imaging and loss/gain of function assays which have been carried out in other species will be practical. In addition, further expansion of the pseudo-implantation model is expected to enable comprehensive research on the organogenesis in primates, as a system with all related cell types including the mother. Furthermore, in vivo research is acceptable with NHP. Therefore, it is possible to conduct research across in vivo – ex vivo – in vitro, and it will strongly promote the study of post-implantation embryogenesis in primates. We hope that when these goals are achieved, we will be able to understand primate development at molecular level and bring a paradigm shift in primate developmental biology.

#### 【Key Words】

Non-human primate; Among the species of Mammalia Primates excluding humans. Cynomolgus macaques and marmosets are members of old and new world monkey and they are permitted for use in biological research.

【Term of Project】 FY2020-2022

【Budget Allocation】 122,000 Thousand Yen

【Homepage Address and Other Contact Information】

<https://www.primate-dev-biol.ashbi.kyoto-u.ac.jp/>