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

Next-Generation Developmental Engineering

Principal Investigator	Kyoto University, CiRA, Professor TAKASHIMA Yasuhiro　Researcher Number : 70469930
Project Information	Project Number : 25A306　Project Period (FY) : 2025-2029 Keywords: stem cells, embryo model, developmental engineering, simulation, digital embryo model

Purpose and Background of the Research

●Outline of the Research

The fundamental question of how an apparently simple cluster of cells develops into a living organism remains unresolved. In recent years, it has become possible to generate reconstructed embryos—referred to as stem cell-based embryo models (in vitro embryo models)—that mimic early pre- and post-implantation development using only stem cells in vitro. This breakthrough opens new avenues for investigating early human embryogenesis, which has long been challenging due to ethical and technical limitations.

However, all in vitro embryo models reported to date arrest shortly after implantation and fail to undergo organogenesis. This suggests that current in vitro embryo models lack the developmental robustness inherent to in vivo embryos generated by normal fertilization.

This research area aims to utilize in vitro embryo models to constructively elucidate the principles of the emergence of life, wherein a collective of cells functions and develops as a living entity. To systematically understand both life emergence and embryonic integrity control systems, we will employ cutting-edge technologies—such as omics-based analyses of intercellular interactions and transcription factor networks, single-cell profiling, and advanced optical measurements—to perform multidimensional and large-scale analyses. Based on the acquired data, we will construct digital embryo models to predict key factors driving the emergence of life by in silico simulations.

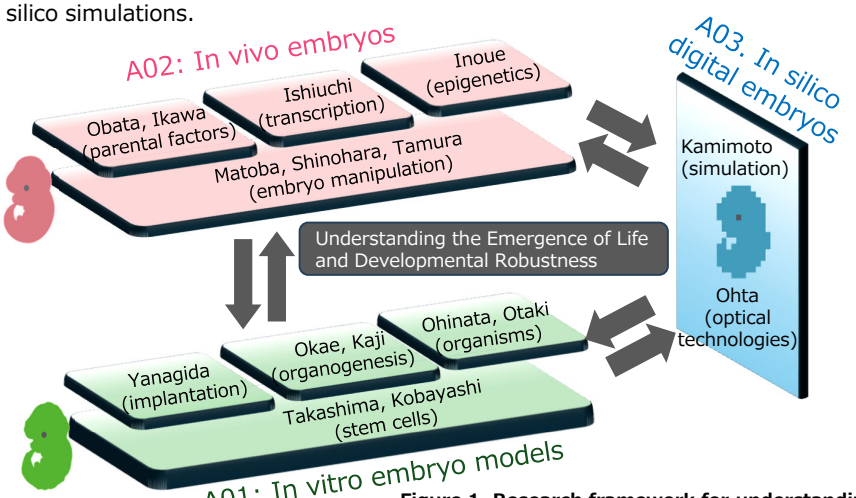

Figure 1. Research framework for understanding the emergence of life and developmental robustness

Research Strategy

We aim to understand how life emerges from small cell clusters and sustains across generations. While in vitro embryo models resemble in vivo embryos, they lack true life.

•**A01** analyzes stem cells and in vitro embryo models in terms of implantation, organogenesis, and organismal development.

•**A02** investigates in vivo embryos to uncover developmental robustness, focusing on parental factors, transcription, and epigenetics.

•**A03** supports both by applying digital science to build digital embryo models and run in silico simulations based on multimodal data.

Together, these projects form a feedback loop of data generation, analysis, and prediction to reveal the principles of the emergence of life and developmental robustness.

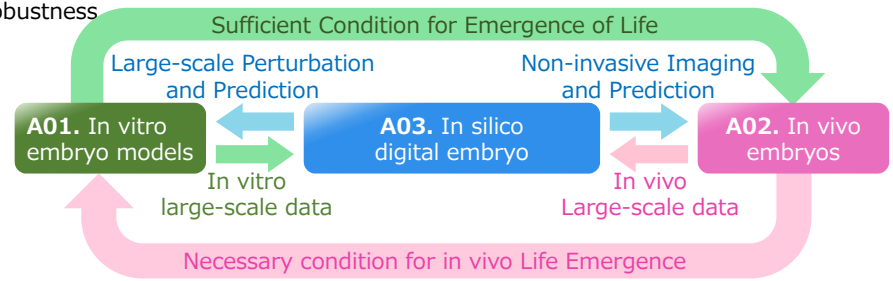

Figure 2. Promoting integrative research using In vitro embryo models, In vivo embryos, and In silico digital embryos

Expected Research Achievements

● Expected Research Achievements

A01: Develop pluripotent stem cells similar to in vivo embryos and construct advanced in vitro embryo models to elucidate key mechanisms of implantation and organogenesis, aiming to model human development and the emergence of life in vitro.

A02: Uncover the molecular systems supporting post-implantation development and transgenerational safety by analyzing parental factors, transcription, and epigenetics and compare with in vitro models to identify and overcome their limitations.

A03: Build digital embryo models based on large-scale measurements of in vivo and in vitro embryos. This model will simulate gene regulation, cell dynamics, and perturbation responses to clarify how cellular assemblies function as living systems.

●Broader Impacts of This Research Area

By integrating stem cell-based biology and digital innovation, we promote the realization of the 3Rs by minimizing the use of experimental animals. It is expected to contribute to safe infertility treatments and early diagnosis of disease risks. Moreover, the use of embryo models may advance organ-based regenerative medicine, ethical human developmental studies, drug discovery and toxicity screening, and multicellular synthetic biology. The development of digital developmental prediction models is anticipated to generate significant ripple effects across multiple fields.

Figure 3. Objectives and Impacts

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