

Next-generation ART: Building a global network to create innovative technologies in mammalian reproductive engineering

	Principal Investigator	Osaka University, Graduate School of Medicine, Professor HAYASHI Katsuhiko Researcher Number : 20287486
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Purpose and Significance of the Research

● Development of Next-Generation ART

Our society now faces serious problems stemming from infertility or low fecundity in animals and humans (**Fig. 1**). For example, reduced gametogenesis caused by aging or cancer therapy results in declining birth rates. Continuous decline in the reproductive rate of large livestock animals in recent years has caused severe economic damage to society. Reservation of genetic resources of endangered species is another great challenge: there are 1,200 mammalian species critically endangered. However, there are still limited success of breeding wild animals by assisted reproductive technologies (ART) such as artificial insemination. In order to solve these problems, it is necessary to develop "Next-Generation ART" for germ cell manipulation and preservation in various mammalian species.

In this international joint research, with collaboration of world-leading scientists that possess various animal and human resources, we aim to achieve (1) Reconstitution of reproductive organs including germ cells from pluripotent stem cells and (2) Establishment of GS cell culture, transplantation and cryopreservation techniques in various mammalian species including humans (**Fig. 2**). Furthermore, using these resources and techniques, we also aim to achieve (3) Identification of small molecules that enhance gametogenesis and fertilization in vitro and in vivo. These achievements will provide unique and valuable platforms for research, manipulation and preservation of germ cells in various mammalian species, which will make significant contribution to solving the current problems caused by decline in gamete function and fertility.

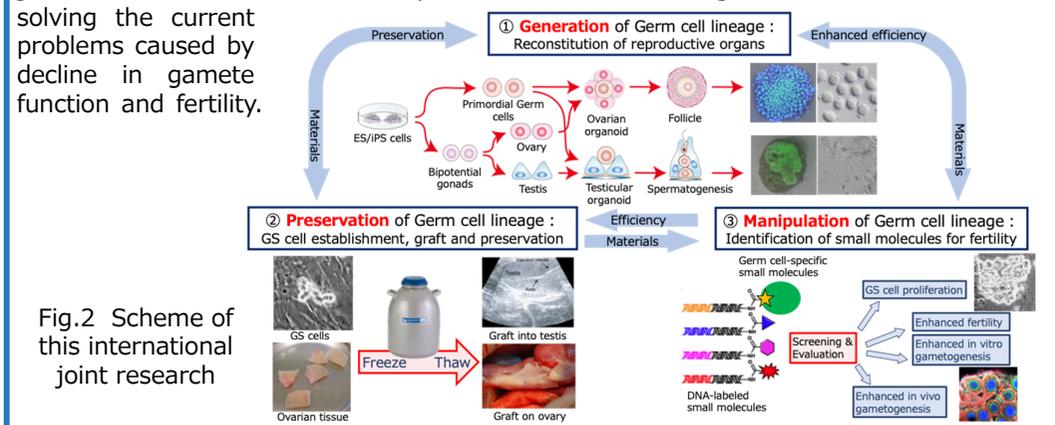


Fig.2 Scheme of this international joint research

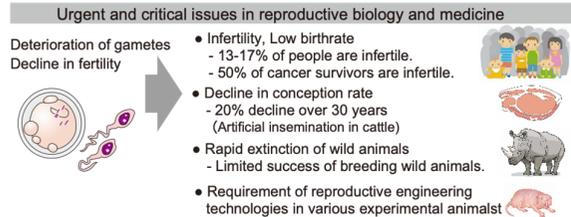
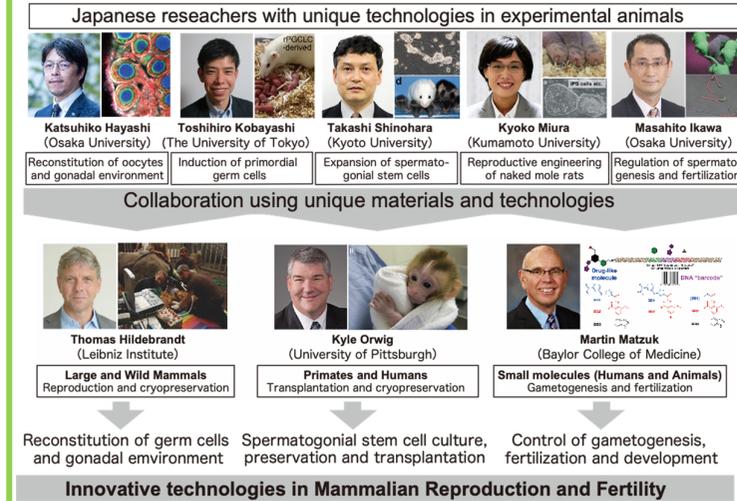


Fig.1 Current issues in reproductive biology and medicine

Organization of the Project Team

Five Japanese researchers (Professors Hayashi, Shinohara, Ikawa, Miura and Kobayashi), who have unique expertise in reproductive engineering in experimental animals, will collaborate with three foreign researchers (Professors Hildebrandt, Orwig and Matzuk) who are world-leading scientists in reproductive biology and possess various animal resources and technologies (**Fig. 3**). These international teams will achieve reconstitution of reproductive organs, establishment of GS cells and identification of small molecules effective for gameto-



genesis and fertilization in various mammalian species other than mice; specifically in rats, naked mole-rats, rabbits, cattle, northern white rhinoceroses, rhesus macaques, and humans.

Fig.3 Framework of this International Joint Research.

Plan for Fostering Early-career Researchers

In this joint research program, a total of 19 young researchers will participate in the project in year one and two years and we will continue to accept young researchers according to the progress of the projects.

For fostering early career researchers, we will focus on three points: (1) Networking of researchers and materials, (2) Career development, (3) Feedback to Japanese society.

(1) Networking of researchers and materials: Human networking is achieved by sending young researchers to overseas research institutions, and where appropriate, inviting young researchers from the three international groups to enhance mutual research interactions. We will hold annual virtual retreats, where all members participate and update the current status of their research, to further enhance collaborative research as well as exchange information of career development. (2) Career development: we will help young researchers to get independent research positions throughout the project to continue their research as smoothly as possible. We will set up an in-house grant (2 million JPY/grant) to stimulate young researchers to start projects of their own. (3) Feedback to Japanese society: we aim to contribute to practical feedback of our research to Japanese society. For example, we will have our young medical doctors learn not only the technical procedure of sample collection and storage but also the systematic framework of the program that supports fertility protection protocols. This will contribute to construction of the framework of fertility protection therapies in Japan. For the academic field, we will provide research fields where young researchers acquire skills and knowledges of the model and wild animals. With these experiences, young investigators will be leaders in the academic field and thereby stimulate Japanese academic societies.