

氏 名 山内（石川） 祐  
学位の種類 博士（人間生物学）  
学位記番号 博甲第 8797 号  
学位授与年月 平成 30年 8月 31日  
学位授与の要件 学位規則 第4条第1項該当（昭和28年4月1日文部省令第9号）  
審査組織 グローバル教育院  
学位論文題目 **Functional role of the oviduct in mammalian fertilization**  
(哺乳類の受精における卵管の機能的役割)

	(職名)	(学位)	(氏名)
主 査	筑波大学教授	博士（医学）	千葉 智樹
副 査	筑波大学教授 (グローバル教育院)	博士（理学）	永田 毅
副 査	筑波大学講師	博士（医学）	田原 聡子
副 査	筑波大学教授 (グローバル教育院)	Ph. D.	George L. Gerton

### 論文の要旨

#### Abstract of thesis (Note: about 1000 words)

Fertilization takes place in the oviductal ampulla, where ejaculated sperm need to reach following migration through the female reproductive tract. However, many mechanisms during this fundamental process remain to be uncovered. In this study, the applicant focused on the role of oviductal smooth muscle (myosalpinx) contractions for the sperm migration. The applicant administered prifinium bromide (padrin) in mice, and found that the myosalpinx contractions are important for the high-speed back-and-forth/shuttling flows of oviductal fluids around the isthmus, and efficient fertilization. The applicant also found that sperm form a tight assemblage in the isthmus, while this assemblage did not occur when padrin was administered. These results suggest that myosalpinx contractions and the resulting back-and-forth/shuttling flows, contribute to the formation of the sperm assemblage in the isthmus, and the transport of the assemblage to the middle region of oviduct. It is also suggested that the motility of sperm is essential for the migration of sperm from the middle oviductal region to the ampulla.

The female reproductive tract is indispensable for the migration of ejaculated sperm and the transport of early embryos to accomplish fertilization and implantation, respectively. Oviductal peristalsis, generated by radially symmetrical contraction and relaxation of smooth muscles, is important for the transport of the embryos from the oviductal ampulla to the uterus. Shuttling flows of oviductal fluids also contribute to the transport of sperm from the isthmus to the middle region of oviduct. Although a well-known vasoactive

peptide, endothelin, has been reported to induce oviductal peristalsis during the embryo transport, the molecules involved in the oviductal contractions during the sperm transport are still unknown. Therefore, the applicant tried to identify the oviductal contraction-inducing factors by a collagen gel contraction assay system using oviductal epithelial cells (OEC). The applicant found that the oviductal extracts have high OEC contraction-inducing activity, like endothelin-3 isoform does. Moreover, the OEC contraction-inducing activity in the oviductal extracts was not inhibited by endothelin receptor antagonist tezosentan, suggesting the presence of endothelin-independent activity. When oviductal extracts were separated by reverse-phase high-performance liquid chromatography (HPLC), the applicant could separate the tezosentan-sensitive and -insensitive contraction-inducing activities. These results suggest that oviductal extracts contain OEC contraction-inducing factor(s) other than endothelin family protein. Besides, the applicant conducted microarray analyses of the oviducts and found upregulation of several genes that may be involved in contraction. It was also suggested that gene expression profiles are significantly different between the periods of sperm migration and embryo transport.

### 審査の要旨

Abstract of assessment result (Note: about 150 words)

#### 【批評 Review】

The functions of oviduct have not been well studied, because assisted reproduction technologies (ART) are now used bypass their functions. In this study, however, the applicant has analyzed the role of myosalpinx contractions by use of padrin, and found that myosalpinx contractions are important for the formation of sperm assemblage and the transport of the sperm assemblage to the middle region of oviduct. These new findings were obtained for the first time by the observation and quantitative analysis of sperm at real-time in living animals. The applicant further tried to identify the oviductal contraction-inducing factors and found an activity other than endothelin family. These results highlighted the importance and complexity of the oviductal function on the fertilization process. The applicant has opened a new research area on the oviductal function and provided important new information that may assist in the treatment of human infertility as well as triggering studies into the role of the oviduct in reproduction of agriculturally important species that are not amenable to ART.

#### 【最終試験の結果 Result】

The final examination committee conducted a meeting as a final examination on 05 June, 2018. The applicant provided an overview of dissertation, addressed questions and comments raised during Q&A session. All of the committee members reached a final decision that the applicant has passed the final examination.

#### 【結論 Conclusion】

Therefore, the final examination committee approved that the applicant is qualified to be awarded a Doctor of Philosophy in Human Biology.