No.	K25-2117	
Project Title	An integrated analysis of molecular genomic and metagenomic data in Asian colorectal cancer through international collaboration	
Principal Investigator	Tan Bee Huat Lain (National Cancer Center Singapore・Professor)	
Project Member(s)	IMSUT Host Researcher	Tatsuhiro Shibata (The Institute of Medical Science, The University of Tokyo・Professor)
	Project Member (s)	Shinichi Yachida (Department of Cancer Genome Informatics, Graduate School of Medicine, Osaka University・Professor)
	Project Member (s)	Hiromi Nakamura (Division of Cancer Genomics, National Cancer Center Research Institute・Researcher)

(Form 2)

Principal Investigator
Tan Bee Huat Iain

IMSUT International Joint Usage/Research Center Project <International>

Joint Research Report (Annual/Project Completion)

Annual Report

Report

Title
An integrated analysis of molecular genomic and metagenomic data in Asian colorectal cancer through international collaboration
Background
Colorectal cancer (CRC) is the third most common cancer worldwide, including in Japan. Recently, the number of CRC cases in Japan has increased rapidly, especially among younger patients, now reaching the highest rates globally. A similar trend is observed in Singapore, highlighting CRC as a critical health issue across Asian countries. CRC progresses through the accumulation of multiple driver mutations, such as APC, KRAS, and TP53. However, most large-scale genetic analyses have been conducted in Western countries, such as the United States (TCGA) and the United Kingdom, leaving the molecular genetic landscape of CRC in Asian populations less well understood. The gut microbiome also plays a significant role in CRC carcinogenesis, yet the diversity of gut microbiota in CRC patients across different ethnic groups remains to be fully explored
Research Aim
By integrating whole genome and transcriptome sequencing data from CRC patients in Japan and Singapore, we aim to identify unique driver genes, including non-coding mutations and structural alterations. We will also perform mutational signature analysis to investigate whether specific carcinogens are present in Asian CRC cases. Additionally, through metagenomic analysis of samples from both ethnic groups, we will uncover shared and distinct CRC-associated bacterial species and microbiome characteristics.

The project's progress
1. International collaborative CRC mutational signature analysis using whole genome sequencing dataset (published in Nature 2025)
Whole genome analysis of 981 cases of colorectal cancer was conducted through international joint research in 11 countries, including Japan. As a result of the analysis, it was revealed that 50% of Japan cases have a mutation pattern caused by colibactin toxin secreted by some intestinal bacteria. The mutation pattern caused by colibactin toxin tended to be 3.3 times more common in young patients (50 years old or younger) than in elderly cases (70 years old and older), suggesting that it may be an important cause of colorectal cancer in young people, which has been pointed out to be increasing globally including in Japan. In addition, 15% of APC mutations, which are the earliest driver abnormalities in colorectal cancer, are induced by mutations caused by colibactin toxin, so it was thought that they were involved in the early onset of colorectal cancer.
To further analyze the geographical diversity of the colibactin signature in Japan and Singapore, further collection of CRC genome data has been continued in both Japan and Singapore.
2. Metagenomic analysis (manuscript in revision)
Using AI-assisted analysis of whole metagenome sequencing data (N=120), we identified four major bacteria associated with colorectal cancer (CRC). Based on the contribution of these four, we classified colorectal cancer into four onco-enterotypes. The subtypes were associated with overall survival, epidemiological background, and somatic genetic events of cancer cells.