【Grant-in-Aid for Specially Promoted Research】

**Biological Sciences**

# Title of Project： Unraveling the principles of microbiota function for rationally-designed biotherapeutics

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Research Project Number: 20H05627 Researcher Number：60334231
Keyword：microbiota, vaccine, colorectal cancer, multidrug-resistant organisms, metabolic disease

## 【Purpose and Background of the Research】

Culture-independent metagenomic profiling of the microbiota by next-generation sequencing is powerful to associate certain microbiota with human health and disease, but unable to address the causality and directionality of the host-microbial relationship. In this context, we have established a top-down approach using anaerobic culture and gnotobiotic techniques, which enables us to narrow down the complex microbiota to individual bacteria or minimal consortia that causally induce a specific phenotype in the host. In this study, by applying our expertise, we aim to define the effector microbes and their metabolites with significant impact on health and disease in the context of; **vaccine responses** (**Aim 1**), **multidrug-resistant bacterial infections** (**Aim 2**), **colorectal cancer** (**Aim 3**), **metabolic disease** (**Aim 4**), and **aging** (**Aim 5**). In addition, we will explore **novel strategies for microbial manipulation** (**Aim 6**) by advancing the culture techniques and genetic tools to manipulate commensal genes and community. Ultimately, our goal is to decipher the basic principles that govern interactions between the microbiota and the host and to develop "rationally designed biotherapeutics" that can modify host physiology.

## 【Research Methods】

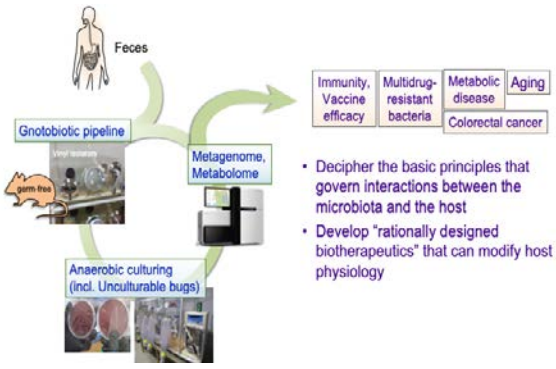


Figure 1 Identification of minimal effector bacterial consortia that causally induce a specific phenotype in the host

**Aim 1. Vaccine responses:** Fecal samples from individuals who have recovered from COVID-19 and showed effective antibody (Ab) responses will be orally administered to germ-free mice. We will immunize the mice with inactivated SARS-CoV2 and follow up on the group of mice which show effective Ab response. We will serially transplant their feces into another germ-free mice and isolate bacterial strains to obtain minimal effector strains.

**Aim 2. Multidrug-resistant bacterial infection:** From healthy volunteers, we previously isolated 37 strains that potently decolonize antimicrobial resistant *K. pneumoniae* strains. We will narrow down them to get minimum effectors and interrogate the mechanism of action.

**Aim 3. Colorectal cancer (CRC):** We have previously isolated 40 bacterial strains from the surface of surgical specimens of CRC patients. We will evaluate the influence of these isolates on the development of CRC using germ-free APC;K-ras mice and identify a minimal effector (oncogenic) consortium.

**Aim 4. Metabolic disease:** We found that fat browning (Beige cell induction) is induced by dietary intervention, which occurs in a microbiota-dependent manner. We will investigate the effector bacteria and the responsible molecules for the fat browning.

**Aim 5. Aging:** We found that centenarians have distinct gut microbiome enriched in microbes capable of generating unique secondary bile acids. We will identify and isolate responsible bile acid-metabolizing bacterial strains.

**Aim 6. Novel strategies for microbial manipulation:** We aim to develop effective methods to genetically manipulate commensals using artificial plasmid and CRISPR-Cas system. We will also develop methods to culture "Unculturable bacteria".

## 【Expected Research Achievements and Scientific Significance】

Our objective is to decode the convoluted cross-talk between the microbiota and host cells to understand the "causation" in various clinical contexts with a significant amount of unmet medical needs. The gnotobiotic pipeline is powerful for testing the community of microbes directly in vivo. Completion of this research proposal will not only address the principles of microbial functions but also lead to a series of transformative medicine.

## 【Publications Relevant to the Project】

・ Tanoue T, Nature. 565(7741): 600-605. (2019)
・ Atarashi K, Science. 358:359-365 (2017)
・ Honda K, Nature. 535:75-84 (2016)
・ Atarashi K, Cell. 163(2):367-80 (2015).

【Term of Project】 FY2020-2025

【Budget Allocation】 492,900 Thousand Yen

## 【Homepage Address and Other Contact Information】

http://www.microbiolimmunol.med.keio.ac.jp/home.html