

# **RIKEN-JSS Joint Symposium**

## **- Toward applied symbiosis biology -**

**16:00-16:10: Ken Shirasu**

**(RIKEN CSRS, Plant Immunity Research Group)**

**Opening remarks - Introduction of iSym**

**16:10-16:40: Hiroshi OHNO**

**(RIKEN IMS, Laboratory for Intestinal Ecosystem)**

**“Host-gut microbiota interaction: from humans to livestock”**

**16:40-17:10: Youxian Li/Kenya HONDA**

**(RIKEN IMS, Laboratory for Gut Homeostasis)**

**“Trypsin-degrading *Paraprevotella* maintains intestinal homeostasis”**

**17:10-17:40: Yasunori ICHIHASHI**

**(RIKEN BRC, Plant-Microbe Symbiosis Research and Development Team)**

**“Field multi-omics dissects an agroecosystem”**

**17:40-18:10: Moriya OHKUMA**

**(RIKEN BRC, Microbe Division)**

**“Cultured microbial resources and single-cell genomics of yet-uncultured for integrated symbiology”**

**18:10-18:20: Ken-ichiro Ishida**

**(Tsukuba University)**

**Closing remarks - Invitation for Japan Symbiosis Society**

**18:30-: Get-together party with beverages at Cafeteria**

# Abstracts

## **Host-gut microbiota interaction: from humans to livestock**

**Hiroshi Ohno<sup>1,2</sup>, Hirokuni Miyamoto<sup>2,3,4</sup>**

<sup>1</sup> Laboratory for Intestinal Ecosystem, RIKEN Center for Integrative Medical Sciences

<sup>2</sup> Intestinal Microbiota Project, Kanagawa Institute of Industrial Science and Technology

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The gastrointestinal mucosa is always exposed to enormous numbers of commensal bacteria, gut microbiota. This gut microbiota is the most in the colon, with more than 40 trillions in number in humans. With some 700,000 genes, the gut microbiota has a very complex metabolic system as a whole, and interacts with the host to constitute the unique gut ecosystem. With this, they deeply impact the host physiological and pathological conditions. In fact, accumulating evidence has indicated that gut microbiota affects the pathogenesis of various diseases, ranging from gastrointestinal, immunological, metabolic, to even neurological disorders.

To understand complex host-gut microbiota interaction, we employ “integrated omics approach”.

We are applying this approach to search for the gut microbiota-related pathogenic biomarkers for pediatric allergies and type 2 diabetes mellitus (T2D). For allergies, birth cohort is examined in search of biomarkers for atopic dermatitis, food allergies, and bronchial asthma, in collaboration with Dr. Naoki Shimojo (Chiba University, Chiba, Japan). T2D study is an IMS center project involving multiple IMS laboratories, in collaboration with the University of Tokyo Hospital for the recruitment of participants from those who took a complete medical checkup.

We are also studying the gut microbiota of livestock. WHO warns that antimicrobial resistance (AMR) can be a biggest threat for humans; they predict that infection with misuse and overuse of antimicrobials is accelerating AMR. Majority of antimicrobials are used for animals worldwide, including Japan. In order to reduce the use of antibiotics in livestock, we are trying to control their gut microbiota with probiotics.

## **Trypsin-degrading *Paraprevotella* maintains intestinal homeostasis**

**Youxian Li<sup>1,§</sup>, Eiichiro Watanabe<sup>1,2,3,§</sup>, Yusuke Kawashima<sup>4,§</sup>, Zhujun Wang<sup>1,2</sup>, Seiko Narushima<sup>1</sup>, Keita Nishiyama<sup>2</sup>, Sean Kearney<sup>2</sup>, Wataru Suda<sup>1</sup>, Sasajima Satoshi<sup>2</sup>, Kazuto Watanabe<sup>6</sup>, Brian A. Klein<sup>7</sup>, Atsushi Shiota<sup>2,6</sup>, Jason M. Norman<sup>7</sup>, Bernat Olle<sup>7</sup>, Bruce Roberts<sup>7</sup>, Koji Atarashi<sup>1,2,6</sup>, Masahira Hattori<sup>1,5</sup>, Osamu Ohara<sup>4</sup>, Kenya Honda<sup>1,2,6\*</sup>**

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<sup>7</sup> Vedanta Biosciences, Cambridge

<sup>§</sup>These authors equally contributed to this work

The gastrointestinal tract is constitutively exposed to proteases, including a serine protease trypsin originated from the pancreas. Elevated trypsin levels in the lower intestine have been implicated in pathological conditions including inflammatory bowel disease (IBD). Here we show that trypsin is degraded in the lower intestine by members of the gut microbiota, *Paraprevotella*. After passing through the small intestine, trypsin activity is markedly reduced in the cecum and colon of SPF mice, and germ-free (GF) mice have considerably higher fecal

trypsin levels than SPF mice. We have successfully isolated *Paraprevotella clara* and *Paraprevotella xylaniphila* from the microbiome of healthy human donors as potent trypsin-degrading species. Mechanistically, trypsin specifically binds to the surface of *Paraprevotella*, and binding of trypsin to *Paraprevotella* promotes its autolysis. Intestinal colonization with *Paraprevotella* and consequent reduction of trypsin contribute to the maintenance of mucosal integrity and protect colon tissue from invasion by a colitogenic pathogen, *Citrobacter rodentium*. Such a microbiome-based approach targeting excessive proteases may represent a therapeutic strategy for colonic diseases through restoring intestinal homeostasis.

## **Field multi-omics dissects an agroecosystem**

**Yasunori Ichihashi**

RIKEN BRC, Plant-Microbe Symbiosis Research and Development Team

Both inorganic fertilizer inputs and crop yields have increased globally, with the concurrent increase in the pollution of water bodies due to nitrogen leaching from soils. Designing agroecosystems that are environmentally friendly is urgently required. Since agroecosystems are highly complex and consist of entangled webs of interactions between plants, microbes and soils, identifying critical components in crop production remain elusive. To understand the network structure in agroecosystems engineered by several farming methods including environmentally-friendly soil solarization, we utilized a multi-omics approach on a field planted with *Brassica rapa*. We found that the soil solarization showed an increase in plant shoot biomass irrespective of the type of fertilizer applied. Our multi-omics and integrated informatics revealed complex interactions in the agroecosystem showing multiple network modules represented by plant traits heterogeneously associated with soil metabolites, minerals and microbes. Unexpectedly, we identified soil organic nitrogen induced by soil solarization as one of the key components to increase crop yield. A germ-free plant *in vitro* assay confirmed that specific organic nitrogen, namely alanine and acetylcholine, directly increased plant biomass; alanine was utilized as a nitrogen source, while acetylcholine behaved as a biologically active compound. Thus, our study provides evidence at the agroecosystem level that organic nitrogen shows a significant contribution to plant growth, leading a potential solution to make crop production more sustainable by utilizing the natural nutrient cycle.

## **Cultured microbial resources and single-cell genomics of yet-uncultured for integrated symbiology**

**Moriya Ohkuma**

RIKEN BRC, Japan Collection of Microorganisms

A major obstacle of the studies on symbiosis is the formidable difficulty culturing relevant microbial symbionts. Development of next generation technologies and availability of representative cultured strains of symbionts are keys for understanding the nature of symbiosis and its future application.

Flagellated protists (single-cell eukaryotes) and their associated bacteria are predominant components of the complex microbial community in the gut of termites. The associations are crucial for decomposition of recalcitrant lignocellulose and thriving of the host on its nutrient poor diet. We have been investigating the associated bacteria with single-cell genomics and the gut protists with single-cell transcriptomics, respectively. These culture-independent approaches, by revealing the functional potentials of each partner, gradually advance our understanding how the symbiotic relationships work efficiently.

In addition, as a world-leading microbial resource center, we have been collecting cultured, taxonomically identified representatives of symbionts from a variety of isolation sources. Enrichment of such a collection of microbial symbionts, characterizations of them, and opening to public are surely beneficial to enhance research in symbiology.