

## Human Genome Center

# Division of Health Medical Intelligence

## 健康医療インテリジェンス分野

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# Laboratory of Sequence Analysis

## シーケンスデータ情報処理分野

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*Our mission is to realize genomic medicine based on the integrated data analysis of whole genomes of human and commensal microbiota by supercomputing. Development of computational data analysis methods including artificial intelligence for genomic, health, and medical big data is one of our main focuses. We promote integrative analysis of human whole genome, RNA and other omics data, commensal microbiota including bacteriome and virome, and health and medical-related big data. Furthermore, health medical intelligence aims at using the analysis results of such big data to create personalized health-medical action plan of individuals.*

### 1. Whole Genome Sequencing and Genomic Medicine

#### a. Creating New Genomic Medicine by Integrating Human Whole Genome and Commensal Microbiota

Katayama K, Sato N, Shimizu E, Kasajima R, Yamaguchi K, Yokoyama K, Yadome M, Hyugaji T, Komura M, Yamamoto M, Saito A, Zhang Y-Z, Fujimoto K, Kobayashi M, Ogawa M, Takei T, Yasui H, Yuji K, Takane K, Ikenoue T, Robert B, Shibuya T,

Hiroshima Y, Hasegawa T, Miyagi Y, Muto K, Goyama S, Shida D, Boku N, Kawabata K, Miyano S, Yamaguchi R, Uematsu S, Kumasaka N, Takahashi S, Nanya Y, Furukawa Y, Imoto S

Using state-of-the-art genome analysis and artificial intelligence, our mission is to implement “new genomic medicine” by integrating human genome information and human symbiotic microbial metagenome information.

In Japan, gene panel testing was covered by national health insurance from Jun 2019, however, it

analyzed several hundreds of genes, which were known cancer-related genes. Since the gene panel has trivial limitation due to its focused genes, Japanese government considered to extend the gene panel to whole genome. However, it remains a question that whether the whole genome sequence information is enough to realize precision medicine.

Although human genome has 20 thousand genes, intestinal microbiota has 20 million genes, and they work together with human genes for keeping homeostasis of our lives. In recent years, with the advancement of sequencing technology, we could have a whole figure of intestinal microbiota and found its dysbiosis leads to various diseases. We are proceeding a research for utilizing the information of intestinal microbiota (meta-genome) and human genome to create new genomic medicine in Society5.0. For this purpose, we need to establish an artificial intelligence to translate the information of human genome and meta-genome to clinical actions of physicians.

#### **b. Establishment of Data Analysis Center in Action Plan for Whole Genome Analysis of Ministry of Health, Labour and Welfare**

**Katayama K, Shibuya T, Yamaguchi R, Kumasaka N, Matsuda K, Miyo K<sup>1</sup>, Okamura H<sup>2</sup>, Ota K<sup>2</sup>, Shintani A<sup>2</sup>, Shiraishi Y<sup>3</sup>, Kohno T<sup>3</sup>, Kato M<sup>3</sup>, Okada Y<sup>4</sup>, Fujimoto A<sup>4</sup>, Kasai S<sup>5</sup>, Imoto S:** <sup>1</sup>National Center for Global Health and Medicine, <sup>2</sup>Osaka Metropolitan University, <sup>3</sup>National Cancer Center, Japan, <sup>4</sup>University of Tokyo School of Medicine, Japan, <sup>5</sup>Information-Technology Promotion Agency, Japan

Based on the Whole Genome Analysis Action Plan (Version 1) formulated on December 20, 2019 by the Ministry of Health, Labour and Welfare, the AMED project was launched in 2021 aiming at returning the result of WGS analysis to the patients as medical actions. This national project covers a wide range of intractable cancers, including gastrointestinal, hematological, pediatric, rare, gynecological, and respiratory cancers. A total of 9,900 patients will be subjected to whole genome sequencing analysis with depth of 30x for normal and 120x for tumor samples, and RNA sequencing will also be conducted.

Our team (PI: Prof. Seiya Imoto of IMSUT) is building the Analysis Data Center to collect and compile a database of genomic data and clinical information of these cancer patients. The mission of the Analysis Data Center is to construct a unified analysis pipeline for primary analysis of genomic data, to collect clinical information, to build a reporting system that can be used in expert panels, to build a secure data sharing system, and to build an analysis environment that can perform advanced secondary analysis in a hybrid computational environment of on-premises and cloud.

## **2. Metagenome Analysis of Intestinal Microbiota**

### **a. Unveiling viral dark matter by whole metagenome analysis of bacteriome and virome**

**Fujimoto K, Kimura Y, Shimohigoshi M, Sato N, Zhang Y-Z, Katayama K, Satoh M, Sato S, Tremmel G, Uematsu M, Kawaguchi Y, Usui Y, Nakano Y, Hayashi T, Kashima K, Yuki Y, Yamaguchi K, Furukawa Y, Kakuta M, Akiyama Y<sup>4</sup>, Yamaguchi R, Crowe SE<sup>5</sup>, Ernst PB<sup>6</sup>, Miyano S, Kiyono H, Imoto S, Uematsu S:** <sup>4</sup>Department of Computer Science, Tokyo Institute of Technology, Japan, <sup>5</sup>Department of Medicine, University of California, San Diego, USA, <sup>6</sup>CU-UCSD Center for Mucosal Immunology, Allergy and Vaccines, University of California San Diego, USA.

The application of bacteriophages (phages) is proposed as a highly specific therapy for intestinal pathobiont elimination. However, the infectious associations between phages and bacteria in the human intestine, which is essential information for the development of phage therapies, have yet to be fully elucidated. Here, we report the intestinal viral microbiomes (viromes), together with bacterial microbiomes (bacteriomes), in 101 healthy Japanese individuals. Based on the genomic sequences of bacteriomes and viromes from the same fecal samples, the host bacteria-phage associations are illustrated for both temperate and virulent phages. To verify the usefulness of the comprehensive host bacteria-phage information, we screened *Clostridioides difficile*-specific phages and identified antibacterial enzymes whose activity is confirmed both in vitro and in vivo. These comprehensive metagenome analyses reveal not only host bacteria-phage associations in the human intestine but also provide vital information for the development of phage therapies against intestinal pathobionts.

### **b. An enterococcal phage-derived enzyme suppresses graft-versus-host disease**

**Fujimoto K, Hayashi T<sup>7</sup>, Yamamoto M, Sato N, Shimohigoshi M<sup>7</sup>, Miyaoka D<sup>7</sup>, Yokota C<sup>7</sup>, Watanabe M<sup>7</sup>, Hisaki Y<sup>7</sup>, Kamei Y<sup>7</sup>, Yokoyama Y<sup>7</sup>, Yabuno T<sup>7</sup>, Hirose A<sup>7</sup>, Nakamae M<sup>7</sup>, Nakamae H<sup>7</sup>, Uematsu M, Sato S<sup>7</sup>, Yamaguchi K, Furukawa Y, Akeda Y<sup>8</sup>, Hino M<sup>7</sup>, Imoto S, Uematsu S:** <sup>7</sup>Osaka Metropolitan University, <sup>8</sup>National Institute of Infectious Diseases.

Changes in the gut microbiome have pivotal roles in the pathogenesis of acute graft-versus-host disease (aGVHD) after allogeneic haematopoietic cell transplantation (allo-HCT). However, effective methods for safely resolving gut dysbiosis have not yet been established. An expansion of the pathogen *Enterococcus faecalis* in the intestine, associated with dysbiosis,

has been shown to be a risk factor for aGVHD. Here we analyse the intestinal microbiome of patients with allo-HCT, and find that *E. faecalis* escapes elimination and proliferates in the intestine by forming biofilms, rather than by acquiring drug-resistance genes. We isolated cytolysin-positive highly pathogenic *E. faecalis* from faecal samples and identified an anti-*E. faecalis* enzyme derived from *E. faecalis*-specific bacteriophages by analysing bacterial whole-genome sequencing data. The antibacterial enzyme had lytic activity against the biofilm of *E. faecalis* in vitro and in vivo. Furthermore, in aGVHD-induced gnotobiotic mice that were colonized with *E. faecalis* or with patient faecal samples characterized by the domination of *Enterococcus*, levels of intestinal cytolysin-positive *E. faecalis* were decreased and survival was significantly increased in the group that was treated with the *E. faecalis*-specific enzyme, compared with controls. Thus, administration of a phage-derived antibacterial enzyme that is specific to biofilm-forming pathogenic *E. faecalis*—which is difficult to eliminate with existing antibiotics—might provide an approach to protect against aGVHD.

### 3. Health Medical Data Science

#### a. *stana*: an R package for metagenotyping analysis and interactive application based on clinical data

Sato N, Katayama K, Miyaoka D, Uematsu M, Saito A, Fujimoto K, Uematsu S, Imoto S

Metagenotyping of metagenomic data has recently attracted increasing attention as it resolves intraspecies diversity by identifying single nucleotide variants. Furthermore, gene copy number analysis within species provides a deeper understanding of metabolic functions in microbial communities. However, a platform for examining metagenotyping results based on relevant grouping data is lacking. Here, we have developed the R package, *stana*, for the processing and analysis of metagenotyping results. The package consists of modules for preprocessing, statistical analysis, functional analysis and visualization. An interactive analysis environment for exploring the metagenotyping results was also developed and publicly released with over 1000 publicly available metagenome samples related to human diseases. Three examples exploring the relationship between the metagenotypes of the gut microbiome and human diseases are presented—end-stage renal disease, Crohn's disease and Parkinson's disease. The results suggest that *stana* facilitated the confirmation of the original study's findings and the generation of a new hypothesis.

#### b. Predicting cell types with supervised contrastive learning on cells and their types

Heryanto YD, Zhang YZ, Imoto S.

Single-cell RNA-sequencing (scRNA-seq) is a powerful technique that provides high-resolution expression profiling of individual cells. It significantly advances our understanding of cellular diversity and function. Despite its potential, the analysis of scRNA-seq data poses considerable challenges related to multicollinearity, data imbalance, and batch effect. One of the pivotal tasks in single-cell data analysis is cell type annotation, which classifies cells into discrete types based on their gene expression profiles. In this work, we propose a novel modeling formalism for cell type annotation with a supervised contrastive learning method, named SCLSC (Supervised Contrastive Learning for Single Cell). Different from the previous usage of contrastive learning in single cell data analysis, we employed the contrastive learning for instance-type pairs instead of instance-instance pairs. More specifically, in the cell type annotation task, the contrastive learning is applied to learn cell and cell type representation that render cells of the same type to be clustered in the new embedding space. Through this approach, the knowledge derived from annotated cells is transferred to the feature representation for scRNA-seq data. The whole training process becomes more efficient when conducting contrastive learning for cell and their types. Our experiment results demonstrate that the proposed SCLSC method consistently achieves superior accuracy in predicting cell types compared to five state-of-the-art methods. SCLSC also performs well in identifying cell types in different batch groups. The simplicity of our method allows for scalability, making it suitable for analyzing datasets with a large number of cells. In a real-world application of SCLSC to monitor the dynamics of immune cell subpopulations over time, SCLSC demonstrates a capability to discriminate cell subtypes of CD19<sup>+</sup> B cells that were not present in the training dataset.

#### c. Biotextgraph: graphical summarization of functional similarities from textual information

Sato N, Zhang YZ, Gu Z<sup>9</sup>, Imoto S: <sup>9</sup>National Center for Tumor Diseases, Heidelberg, Germany

Functional interpretation of biological entities such as differentially expressed genes is one of the fundamental analyses in bioinformatics. The task can be addressed by using biological pathway databases with enrichment analysis. However, textual description of biological entities in public databases is less explored and integrated in existing tools and it has a potential to reveal new mechanisms. Here, we present a new R package *biotextgraph* for graphical sum-

marization of omics' textual description data which enables assessment of functional similarities of the lists of biological entities. We illustrate application examples of annotating gene identifiers in addition to enrichment analysis. The results suggest that the visualization based on words and inspection of biological entities with text can reveal a set of biologically meaningful terms that could not be obtained by using biological pathway databases alone. The results suggest the usefulness of the package in the routine analysis of omics-related data. The package also offers a web-based application for convenient querying.

#### 4. COVID-19

##### a. Statistically and functionally fine-mapped blood eQTLs and pQTLs from 1,405 humans reveal distinct regulation patterns and disease relevance

Wang QS, Hasegawa T, Namkoong H, Saiki R, Eda-hiro R, Sonehara K, Tanaka H, Azekawa S, Chubachi S, Takahashi Y, Sakaue S, Namba S, Yamamoto K, Shiraishi Y, Chiba K, Tanaka H, Makishima H, Nannya Y, Zhang Z, Tsujikawa R, Koike R, Takano T, Ishii M, Kimura A, Inoue F, Kanai T, Fukunaga K, Ogawa S, Imoto S, Miyano S, Okada Y, Japan COVID-19 Task Force

Studying the genetic regulation of protein expression (through protein quantitative trait loci (pQTLs)) offers a deeper understanding of regulatory variants uncharacterized by mRNA expression regulation (expression QTLs (eQTLs)) studies. Here we report *cis*-eQTL and *cis*-pQTL statistical fine-mapping from 1,405 genotyped samples with blood mRNA and 2,932 plasma samples of protein expression, as part of the Japan COVID-19 Task Force (JCTF). Fine-mapped eQTLs ( $n = 3,464$ ) were enriched for 932 variants validated with a massively parallel reporter assay. Fine-mapped pQTLs ( $n = 582$ ) were enriched for missense variations on structured and extracellular domains, although the possibility of epitope-binding artifacts remains. *Trans*-eQTL and *trans*-pQTL analysis highlighted associations of class I HLA allele variation with KIR genes. We contrast the multi-tissue origin of plasma protein with blood mRNA, contributing to the limited colocalization level, distinct regulatory mechanisms and trait relevance of eQTLs and pQTLs. We report a negative correlation between *ABO* mRNA and protein expression because of linkage disequilib-

rium between distinct nearby eQTLs and pQTLs.

##### b. Quantitative association of SARS-CoV-2 in wastewater and clinically confirmed cases in different areas of the Tokyo 2020 Olympic and Paralympic Village

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International mass gathering events, such as the Olympic and Paralympic Games, face the risk of cross-border transmission of infectious diseases. We previously reported that wastewater-based epidemiology (WBE), which has attracted attention as a COVID-19 surveillance tool, was implemented in the Tokyo 2020 Olympic and Paralympic Village to gain a comprehensive understanding of COVID-19 incidence in the village. In the present study, we explored the quantitative association of wastewater viral load and clinically confirmed cases in various areas of the village. From July 14 through September 8, 2021, 360 passive samples and 329 grab samples were collected from seven distinct areas within the village through manholes and examined for SARS-CoV-2 RNA by the Efficient and Practical virus Identification System with Enhanced Sensitivity (EPISENS) methods. The detection rates of SARS-CoV-2 RNA in passive and grab samples showed a significant association ( $P < 0.001$ ,  $\phi = 0.32$ , chi-square test), with passive sampling showing higher positive rate. Based on the Receiver Operating Characteristic (ROC) curve analysis on the wastewater viral load and clinically confirmed cases, the most sensitive cutoff point was judged to be the limit of quantification (LOQ) for the passive three-day samples. Under this optimal condition, the sensitivity and specificity were 0.78 and 0.40, respectively. The present study demonstrated the effectiveness of passive sampling for building-level wastewater surveillance based on the quantitative analysis of wastewater viral load and reported cases. Wastewater surveillance can be a powerful tool to monitor the incidence of infectious diseases among temporary residents, such as tourists and participants in international mass gathering events, provided that proper analytical methods and quantitative cutoff point are employed.

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