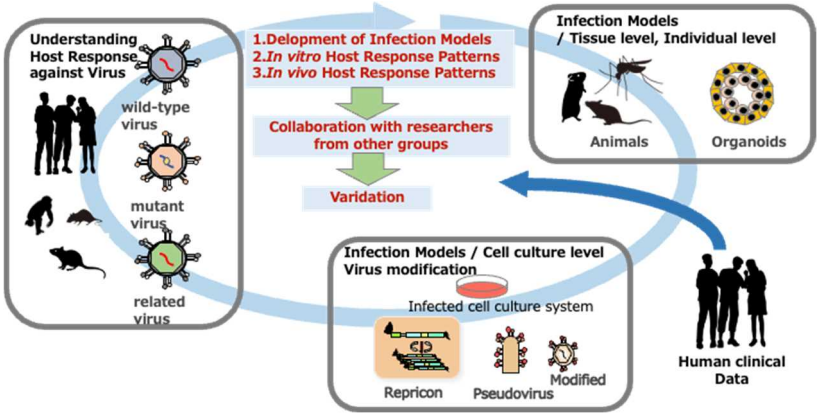
R&D item

1. Analysis of virus infection networks

Progress until FY2023

1. Outline of the Project

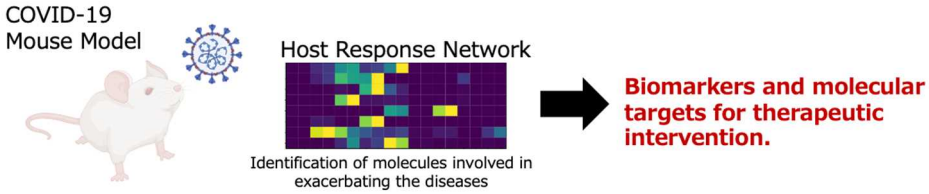
We establish in vitro and in vivo models for various viral infections, create a database of host response networks after viral infection using various omics analyses, and extract host response patterns in collaboration with researchers in immunology and mathematical sciences. Then, we aim to identify biomarkers that can predict profound pathological changes at an extremely early stage and target molecules that enable therapeutic intervention. Furthermore, through mutual feedback analysis with human clinical data, the results obtained using animal models will be scientifically verified with human clinical data, and human clinical data will be scientifically verified with animal models.



2. Research Achievements

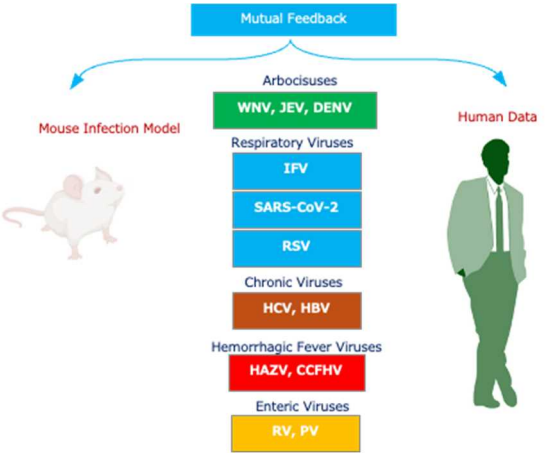
Respiratory diseases like influenza virus (IFV) and coronavirus are the most likely to cause pandemics. In this project, we focused on the SARS-CoV-2 infection model and worked with researchers from Project 3 to identify key molecules involved in severe cases. We identified several molecules involved in severe cases. We examined the therapeutic effects of the inhibitors against these molecules in mouse models and found that treatment with some inhibitors ameliorates the severity of mice infected with SARS-CoV-2.

We also established mouse infection models for respiratory syncytial virus (RSV), Japanese encephalitis virus (JEV), rotavirus, hemorrhagic fever viruses, and hepatitis C virus (HCV). Collaborating with Project3 researchers, we analyzed omics to extract host response networks.



3. Future Plans

By 2023, we have conducted comprehensive omics analyses on various virus infection models to identify molecular targets and biomarkers for early prevention and intervention of viral infectious diseases. We also performed cross-sectional analyses to define new virus classifications and develop tailored prevention and treatment methods. Data from animal models are being cross-referenced with human data to facilitate the application of our research findings to human health.



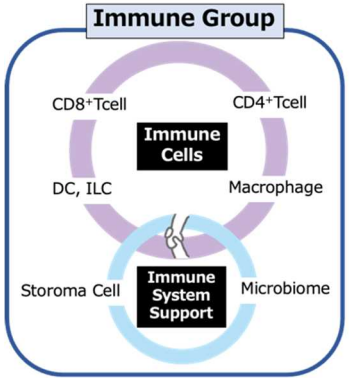
R&D item

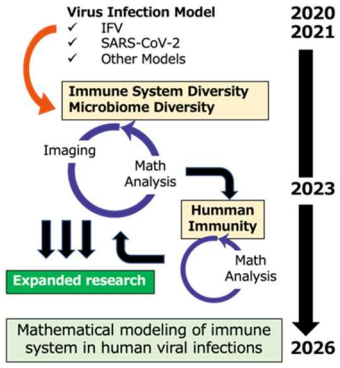
2. Analysis of Host Response Network

Progress until FY2023

1. Outline of the Project

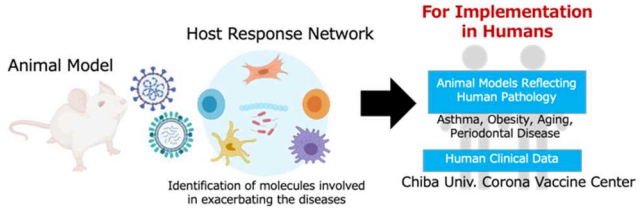
Using mice infection models, gene expression of innate immune cells such as effector and memory T cells, macrophages, dendritic cells, and innate lymphocytes in the acute and chronic stages are analyzed at the single cell level and visualize gene expression patterns in collaboration with researchers in molecular imaging. We will acquire information essential for classifying the response patterns of immune cells to viral infection, create a mathematical model of immune response patterns in collaboration with mathematical researchers, and construct a database. Furthermore, we will identify the key molecules and networks of immune cells against each viral infection, investigate the gene expression patterns of immune-supporting cells in lymph nodes and bone marrow and those of cells in the respiratory tract and blood vessels, and clarify their roles in viral infection responses. In addition, we will examine the microbiome to clarify their roles in the host response to viral infection. In collaboration with mathematical and imaging researchers, we will explore the networks of immune cells, immune-supporting cells, and the microbiome and elucidate the molecular mechanisms that control the networks between groups. Regarding the microbiome, we aim to identify critical bacterial groups in the response of immune cells and immune-supporting cells to viral infections.





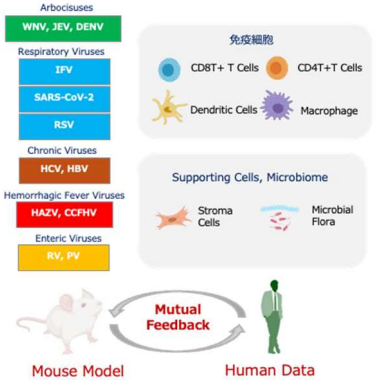
2. Research Achievements

We conducted comprehensive gene expression analysis focusing on immune cells using infection models of influenza virus and SARS-CoV-2. In collaboration with researchers from Project 3, we identified molecules involved in exacerbating the diseases. Furthermore, we examined the effects of the inhibitors against identified molecules in mouse models, assessing their validity as biomarkers and molecular targets for therapeutic intervention. To facilitate the application of our research findings to humans, we analyzed the correlation between viral infections and human conditions, such as obesity, aging, and allergies. Additionally, we obtained clinical data from various cohorts, including the Chiba University Corona Vaccine Center staff cohort. We analyzed the immunological characteristics related to the maintenance of a pre-symptomatic state.



3. Future Plans

From the host response patterns extracted from infection models, we aim to identify markers and molecular targets that enable ultra-early treatment and prevention before severe pathological changes such as exacerbation occur. We will advance scientific validation and analysis towards their implementation in humans. Additionally, we will define a new classification of viruses based on the obtained host response patterns and develop prevention and treatment methods according to these patterns. We aim to create a society capable of preventing infectious disease outbreaks before a pandemic occurs.



R&D item

3. Development of analysis frameworks for imaging and math analysis to comprehend Virus-Human Interaction Networks.

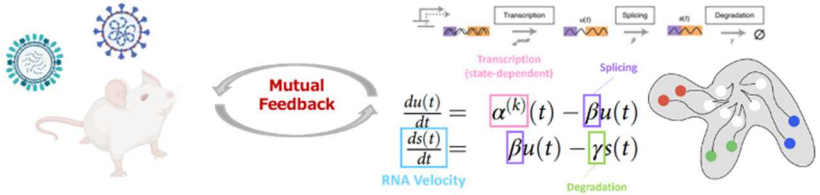
Progress until FY2023

1. Outline of the Project

By advancing imaging technology and combining it with omics technology, we will promote the development of comprehensive and chronological next-generation measurement technology. We also aim to achieve high scalability through advanced multiplexing of measurements, focusing on the parallelism of imaging technology. As a method for analyzing the large-scale, high-dimensional data obtained, we use tensor analysis to estimate dynamic time-varying intercellular interaction networks from comprehensive time-series data. Furthermore, we apply network motif analysis and network topology analysis to the cell-cell interaction network and decompose it into modules that reflect the dynamics of the entire network. We construct a multi-layered mathematical model based on modularized cell-cell interaction networks and perform simulations and sensitivity analyses. Combining multi-layered mathematical models with generative models such as generative adversarial networks (GANs), we generate fictitious time-series data based on experimental data and use it to stratify immune response patterns.

2. Research Achievement

The Imaging Group, in collaboration with researchers from Project 1 and 2, developed measurement techniques and conducted imaging analysis using influenza virus and SARS-CoV-2 infection models. We performed spatial transcriptome analysis, three-dimensional lung observations, virus particle detection in tissue section by EM, and imaging technology development. These efforts visualized host responses to viral infection from various perspectives. Additionally, we began planning for the commercialization of our microscopy technology. The Mathematical Group developed a technique to integrate bulk RNA-seq and scRNA-seq data, enabling the extraction of host network models and identifying factors linked to severe disease. These findings were shared with Project 1 and 2 for experimental validation.
We also used a multi-layered mathematical model to replicate time-series data from SARS-CoV-2 and influenza virus infections, considering the impact of various immune cells. We especially performed Single-cell colocalization analysis using a deep generative model named “DeepCOLOR” and published it in Cell Systems.



3. Future Plan

Imaging Group: Establish measurement techniques to visualize host response networks after virus infection. Collaborating with Project 1 and 2, we will improve these techniques to understand host responses to viral infections comprehensively.
Mathematical Group: The Mathematical Group will enhance the elucidation of host response networks using developed analytical techniques, identifying molecular targets and biomarkers for early disease prediction. We will also analyze human clinical data and integrate it with animal model data, advancing the implementation of our research findings in humans.