インシリコ解析ユニット

補助事業代表者（所属・職名）

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分子設計、超分子モデリング、シミュレーションを用いた バイオマーカーの探索および創薬技術支援

補助事業分担者（所属・職名）

Soyoung Park（東京科学大学 地球生命研究所・准教授）

概要

SUPPORT

Our group is one of several research groups within the In Silico Analysis Unit. We provide structure- and sequence-based computational support to experimental and clinical researchers across Japan. Our activities include structural modeling and simulation of proteins, protein complexes, and protein-nucleic acid assemblies; adaptive immune receptor repertoire analysis for biomarker discovery and patient stratification; and large-scale sequence, genomic, and omics analysis using machine learning. During the current project period, our group directly handled 22 support projects, supervised two additional projects, and received support from three other BINDS groups for problems requiring complementary expertise. These projects span basic immunology, infectious disease, autoimmune disease, and cancer, and range from individual structural predictions to long-term collaborations that develop alongside experimental and clinical research. Six directly supported projects and one supervised project were completed during this period, while several ongoing projects have already produced peer-reviewed publications. Representative outcomes include structural analysis of DHX29 interactions with the translating ribosome, which helped reveal how this conserved protein detects nonoptimal codon usage and regulates mRNA stability. This work was published in *Science*. AlphaFold-based modeling and mutational analysis of the *Toxoplasma* protein MIC11 identified a motif required for its trafficking and its role in parasite egress from host cells, resulting in a publication in *Nature Communications*. Other supported studies have contributed to publications in *Immunity*, *PNAS*, *Nature Cell Biology*, and *Science Translational Medicine*. Ongoing cryo-EM work is examining how Regnase-1 and its binding partners recognize specific cytokine RNAs, with the aim of understanding the molecular basis of selective cytokine mRNA degradation.

SOPHISTICATION

Our sophistication activities aim to advance methods for large-scale biological data analysis, machine learning, database construction, genome annotation, molecular prediction, and visualization. These methods are developed using sequence, genomic, structural, and omics data and are evaluated through applications to biological and biomedical research. A major focus has been the development and evaluation of computational methods for adaptive immune receptor repertoire analysis. We reviewed current approaches for using immune-receptor repertoires to stratify responses to cancer immunotherapy, including conventional repertoire metrics and sequence-based machine-learning methods. We also discussed the requirements for standardization, data sharing, and clinical translation in *Trends in Molecular Medicine*. We developed FACTS, a scalable classification framework that combines paratope sequence representation, rapid clustering, and machine learning. Applied to approximately 81 million TCR sequences from 1,421 donors representing 15 diseases and a healthy control cohort, FACTS achieved a mean multiclass ROC-AUC of approximately 0.99 and a mean accuracy of 81.77%. We also systematically benchmarked protein language models against conventional sequence-alignment methods for immune-receptor retrieval. This analysis showed that much of the apparent advantage of protein language models for full-length receptor sequences can arise from conserved germline and framework information. The results emphasize the importance of appropriate sequence representation, dataset construction, and train-test splitting when evaluating machine-learning methods for immune receptors. A further advance was the development of AbSapien, a method for identifying functionally related antibodies across individuals and even across species. In an initial experimental evaluation, 40% of 20 antibodies selected from healthy human BCR repertoires bound their predicted targets by ELISA. Antibodies predicted to resemble many known therapeutic antibodies could also be identified in healthy human repertoires, supporting the possibility of using natural human B-cell diversity as a source of therapeutic antibody candidates. Beyond immune-repertoire analysis, we developed and applied a comparative genome-alignment strategy to improve immune-receptor gene annotation. Application to the bovine TRG locus identified previously unannotated genes and produced an updated annotation integrating evidence from multiple genome assemblies, as reported in *BMC Genomics*. Through collaboration, we also established an Adjuvant Database containing standardized transcriptomic profiles for 25 adjuvants. Integration with toxicity data and machine-learning methods enabled prediction and experimental evaluation of both adjuvant activity and toxicity, with the results published in *Cell Chemical Biology*. Our molecular analysis and visualization activities produced chemically tunable, microenvironment-sensitive fluorescent nucleosides for studying G-quadruplex and nucleolin interactions and for live-cell imaging, published in *Sensors and Actuators B: Chemical*. A related project developed NiTA, an environment-sensitive fluorescent probe for visualizing lipid droplets and monitoring changes in their local environment in immune cells and living medaka, published in *Analytica Chimica Acta*.

支援の内容

A. 担当課題一覧 — support provided (22)

ID	支援番号	Applicant	Project	Status	%	Outcome
7591	S03481001	藤本 学	Dermatomyositis subtype classification by immune repertoire analysis	ongoing	20	—
6921	S03135001	齋藤 義修	Immune repertoire and biliary / pancreatic disease	ongoing	10	—
6920	S03135002	齋藤 義修	Immune repertoire and liver disease	ongoing	20	—
6910	S03133001	河野 まひる	Lymphocyte repertoire for early detection of ovarian cancer	ongoing	40	—
6867	S03118001	白石 貴一	Repertoire analysis of receptors from macromolecular hapten sensitization	ongoing	90	—
6763	S03240001	塚本 健太郎	Simulation of novel compounds for pertussis prevention	ongoing	60	Ota, Microbiol Immunol 2025
6127	S02753001	田部 陽子	B cell response after COVID-19 vaccination in people living with HIV	ongoing	60	Paran, Front Immunol 2025
5246	S02080001	今里 聡	Single-cell gene expression profiles of human dental pulp	completed 2023/08	100	Jiravejchakul, BMV Genomics 2024
5244	S02289001	木下 允	Structural modeling of self-peptide presentation in NMOSD and MG	ongoing	60	—
5241	S02017001	佐藤 荘	In silico structural analysis of a receptor	completed 2023/06	100	Mitsui et al Immunity 2023
5233	S02284001	竹内 理	Structural modeling of immune regulatory proteins	ongoing	90	Hia, Science 2026; Yasuda, PLoS Pathog 2025
5088	S02196001	田中 淳	In silico modeling of autoimmune induction from TCR repertoire + transcriptome	ongoing	80	—
5086	S01523002	仁田 亮	Inactivation of IFN-inducible GTPase IRGB6 by Switch I phosphorylation	completed 2023/09	100	Tachibana, Nat Commun 2025
4884	S02067001	上田 泰己	Post-transcriptional regulation of the clock gene Per2	completed 2024/04	100	Millius et al PNAS 2023
4863	S01563002	鈴木 一博	Structural modeling of protein complex X	ongoing	10	—
4802	S02020001	星野 温	Structure / function prediction of spike protein mutations	completed 2023/12	100	Ikemuara Sci Transl Med 2022
4801	S02018001	原 英二	Age-related changes in the IgA repertoire	completed 2023/06	100	Kawamoto Nat Cell Biol 2023
4377	S01736001	森 健	Anti-PEG antibody / PEG interaction analysis	ongoing (終)	20	—
4368	S00476007	溝端 栄一	In silico GroEL–ATP interaction analysis	paused	100	—
4312	S01685001	審良 静男	Cryo-EM analysis of Regnase-1 protein ※1	ongoing	90	—
4241	S01493001	田部 陽子	BCR clone neutralization in fatal vs. recovered COVID-19 cases	ongoing (終)	90	—
4240	S01643001	吉田 光毅	Phylogenetic analysis of plant genes	ongoing	20	—

B. 部下の課題一覧 — supervised support (2)

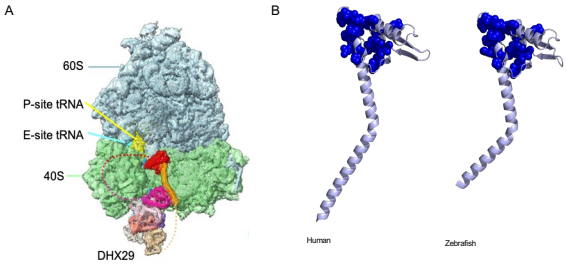
ID	支援番号	Applicant	Project	Status	%	Outcome
5955	S02652001	河本 佑介	Structure of chemically modified TLR9-ligand DNA （支援責任者: 朴 昭映）	completed	100	*Kumagai, Sens Actuators B 2025; Wee, Anal Chim Acta 2025*
4240	S01643001	吉田 光毅	Phylogenetic analysis of plant genes （支援担当: Standley / 加藤 和貴）	ongoing	20	—

C. 被支援課題一覧 — support received (3)

ID	支援番号	支援責任者	Project	Status	%	Outcome
6398	—	本間 光貴	Identification of ligands targeting TCR	ongoing (終)	60	—
6110	—	加藤 貴之	Structure of antibodies targeting pertussis	支援責任者確認中	—	—
4364	—	関嶋 政和	Protein structure prediction and MD simulation (Tsubame)	ongoing	60	—

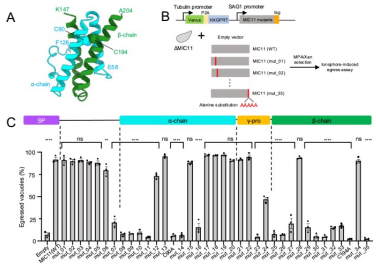
支援の成果

Hia F et al. Human DHX29 detects nonoptimal codon usage to regulate mRNA stability. *Science*. 2026.



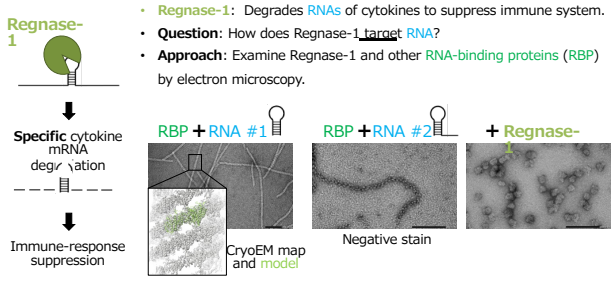
A. DHX29 directly interacts with the translating 80S ribosome. B. The structure and interacting residues are well-conserved across species, including human, Mouse and zebrafish.

Tachibana Y et al An in vivo fitness gene of *Toxoplasma*, MIC11, is essential for PLP1-mediated egress from host cells *Nat Commun* 2025



Scanning mutagenesis reveals a motif within the γ-propeptide essential for MIC11 trafficking to micronemes. A. Structural model of mature MIC11 composed of the α-chain (cyan) and β-chain (green) predicted by AlphaFold3. B. Schematic of the MIC11 alanine-scanning strategy. C. Top: schematic of MIC11 domain. SP, signal peptide. Bottom: quantification of ionophore-induced egress for empty vector, wild-type, and alanine-substituted MIC11 mutants.

Structural Basis of Specific Cytokine RNA Recognition by Regnase-1 and Its Binding Partners



- Regnase-1: Degrades RNAs of cytokines to suppress immune system.
- **Question**: How does Regnase-1 target RNA?
- **Approach**: Examine Regnase-1 and other RNA-binding proteins (RBP) by electron microscopy.

COI開示：本補助事業代表者 Daron M. Standley は、MyImmune 株式会社の共同創業者であり、同社の株式を保有し、Chief Scientific Advisor を務めています。本課題の成果に関連する特許2件が同社にライセンスされています。上記以外に開示すべき利益相反はありません。