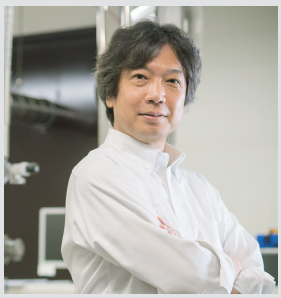
# Dynamical Ordering of Biomolecular Systems for Creation of Integrated Functions


## Department of Life and Coordination-Complex Molecular Science
## Division of Biomolecular Functions



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**Education**
1986 B.S. The University of Tokyo
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**Professional Employment**
1991 Assistant Professor, The University of Tokyo
1997 Lecturer, The University of Tokyo
2000 Professor, Nagoya City University
2008 Professor, Institute for Molecular Science
Professor, Okazaki Institute for Integrative Bioscience ( –2018)
Professor, The Graduate University for Advanced Studies
2006 Visiting Professor, Ochanomizu University
2013 Project Leader, JSPS Grant in Aid for Scientific Research on Innovative Areas "Dynamical Ordering of Biomolecular Systems for Creation of Integrated Functions"
2018 Professor, Exploratory Research Center on Life and Living Systems (ExCELLS)

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2000 The Pharmaceutical Society of Japan Award for Young Scientists
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Living systems are characterized as dynamic processes of assembly and disassembly of various biomolecules that are self-organized, interacting with the external environment. The omics-based approaches developed in recent decades have provided comprehensive information regarding biomolecules as parts of living organisms. However, fundamental questions still remain unsolved as to how these biomolecules are ordered autonomously to form flexible and robust systems (Figure 1). Biomolecules with complicated, flexible structures are self-organized through weak interactions giving rise to supramolecular complexes that adopt their own dynamic, asymmetric architectures. These processes are coupled with expression of integrated functions in the biomolecular systems.

Toward an integrative understanding of the principles behind the biomolecular ordering processes, we conduct multidisciplinary approaches based on detailed analyses of dynamic structures and interactions of biomolecules at atomic level, in conjunction with the methodologies of molecular and cellular biology along with synthetic and computational technique.

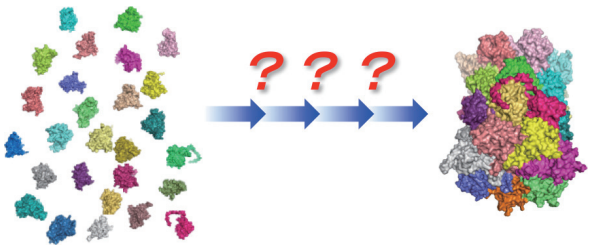


**Figure 1.** Formation of supramolecular machinery through dynamic assembly and disassembly of biomolecules.

## Selected Publications


- M. Yagi-Utsumi and K. Kato, "Conformational Variability of Amyloid-β and the Morphological Diversity of Its Aggregates," *Molecules* **27**, 4787 (2022).
- K. Kato, T. Yamaguchi and M. Yagi-Utsumi, "Experimental and Computational Characterization of Dynamic Biomolecular Interaction Systems Involving Glycolipid Glycans," *Glycoconjugate J.* **39**, 219–228 (2022).
- H. Yagi, S. Yanaka and K. Kato, "Structural and Functional Roles of the *N*-Glycans in Therapeutic Antibodies," in *Comprehensive Glycoscience, 2nd edition*, J. Barchi, Ed., Elsevier; Oxford, **vol. 5**, pp. 534–542 (2021).
- S. Yanaka, R. Yogo and K. Kato, "Biophysical Characterization of Dynamic Structures of Immunoglobulin G," *Biophys. Rev.* **12**, 637–645 (2020).
- T. Satoh and K. Kato, "Structural Aspects of ER Glycoprotein Quality-Control System Mediated by Glucose Tagging," in *Glycobiophysics*, Y. Yamaguchi and K. Kato, Eds., Springer Nature; Singapore, pp. 149–169 (2018).
- K. Kato and T. Satoh, "Structural Insights on the Dynamics of Proteasome Formation," *Biophys. Rev.* **10**, 597–604 (2018).

## 1. Elucidation of Molecular Mechanisms of Regulation of Protein Glycosylation

Our research on protein glycosylation has made significant progresses over the past year. First, we identified a molecular code embedded in protein for regulating its glycosylation. Many proteins in nature exist as glycoproteins, which are molecules comprised of protein (polypeptide chain) and glycan (sugar chain). While the protein structure is determined on the basis of its genetic blueprint, the information on glycans is not directly encoded by the genome. We recently found a specific 29-amino-acid sequence in the glycoprotein LAMP-1 that promotes a specific glycan structure called Lewis X.[1] This sequence induces Lewis X modification when fused to other proteins such as erythropoietin (Figure 2). These findings on a regulatory code of protein glycosylation are expected to pave the way for controlling glycosylation of biopharmaceuticals, which is critical for their efficacy and safety.

Protein glycosylation also has implications in disease. We previously discovered the presence of a novel post-translational modification, in which glycerol phosphate (GroP) caps the core part of matriglycan, thereby blocking its elongation. We recently found that the GroP modification is mediated by PCYT2, a CDP-Gro synthase in humans, and disrupts glycan-mediated cell adhesion, thereby promoting the migration of cancer cells.[2,3] These findings can contribute to the development of cancer therapies targeting this modification.

Furthermore, we are continuously developing methodologies for structural analyses of glycoproteins, which include updating the web application GALAXY for HPLC/MS-based glycosylation profiling[4] and improving the stable isotope labeling protocol for NMR spectroscopy.[5] These methodological developments have led to the promotion of new collaborative researches as exemplified by identification of distinct N-glycosylation patterns on extracellular vesicles from small-cell and non-small-cell lung cancer cells.[6]

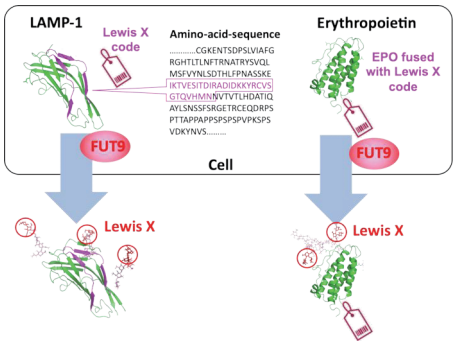


**Figure 2.** Specific 29-amino-acid sequence from the glycoprotein LAMP-1 serves as a "Lewis X code," which is deciphered by the fucosyltransferase FUT9, and it can be embedded into erythropoietin to evoke Lewis X modification.

## 2. Characterization of Biomacromolecules that Function in Extreme Environments

Our research also aims to understand the mechanisms of adaptation of life to the environments through analysis of the structure, dynamics, and function of biomacromolecules working in extreme environments. In FY2021, through collaboration with the ExCELLS groups lead by Dr. Uchihashi, Dr. Murata, and Dr. Arakawa, we published several papers on the molecular mechanisms of tardigrade unhydrobiosis. Our integrative spectroscopic and microscopic data demonstrate that CAHS1 (cytosolic-abundant heat-soluble protein 1), an abundant protein in *Ramazzottius varieornatus*, self-assembles into fibrous condensates under desiccation-mimicking conditions in a reversible manner[7] (Figure 3). This dynamic protein organization suggests multistep anhydrobiotic mechanisms, including the reversible formation of protective compartments for desiccation-sensitive biomolecules, water-holding gelation, and maintenance of the integrity of biomolecular complexes under extremely dry conditions. We also characterized structures of g12777 protein, a novel Mn-dependent peroxidase, from *R. varieornatus*,[8] and EtAHS, a novel abundant heat-soluble protein from *Echinisicus testudo*.[9] Our findings illustrate adaptation strategies of organisms to extreme environments without water.

Moreover, we applied the integrative biophysical approach to characterize the overall structure of cyanobacterial circadian clock protein complex[10] and single-molecular interactions between the complement component C1 and antibodies.[11]

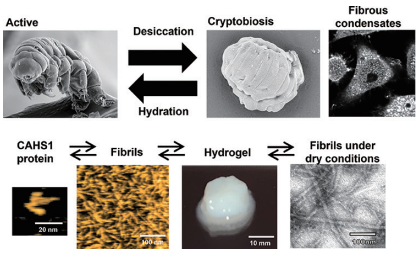


**Figure 3.** Spontaneous assembling of CAHS1 proteins into fibrous condensates under desiccation-mimicking conditions.

### References

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9) Y. Murai *et al.*, *BMC Genomics* **22**, 813 (2021).
10) Y. Yunoki *et al.*, *Commun. Biol.* **5**, 184 (2022).
11) S. Yanaka *et al.*, *Int. J. Mol. Sci.* **23**, 2090 (2022).

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