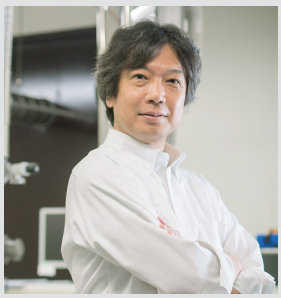
Dynamical Ordering of Biomolecular Systems for Creation of Integrated Functions

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



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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.

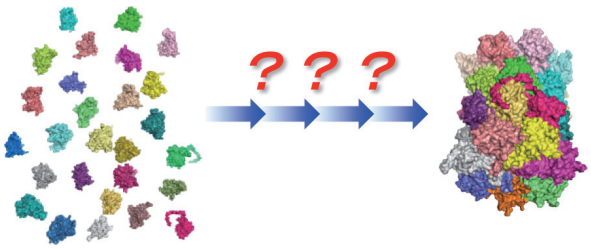

Figure 1. Formation of supramolecular machinery through dynamic assembly and disassembly of biomolecules.

Selected Publications

- K. Kato, S. Yanaka and H. Yagi, "Glycoprotein Preparation by Heterologous Expression," in *NMR of Glycoproteins*, J. Jiménez-Barbero and O.Millet, Eds., *Methods in Molecular Biology*, Humana; New York, **vol. 2961**, pp. 53–67 (2025).
- K. Kato, S. Yanaka and T. Yamaguchi, "The Synergy of Experimental and Computational Approaches for Visualizing Glycoprotein Dynamics: Exploring Order within the Apparent Disorder of Glycan Conformational Ensembles," *Curr. Opin. Struct. Biol.* **92**, 103049 (2025).
- K. Kato, S. Yanaka and H. Yagi, "Technical Basis for Nuclear Magnetic Resonance Approach for Glycoproteins," in *Experimental Approaches of NMR Spectroscopy II*, The Nuclear Magnetic Resonance Society of Japan, Ed., Springer Nature; Singapore, pp. 169–195 (2025).
- H. Yagi, K. Takagi and K. Kato, "Exploring Domain Architectures of Human Glycosyltransferases: Highlighting the Functional Diversity of Non-Catalytic Add-On Domains," *Biochim. Biophys. Acta, Gen. Subj.* **1868**, 130687 (2024).
- D. Koga, S. Kusumi, H. Yagi and K. Kato, "Three-Dimensional Analysis of the Intracellular Architecture by Scanning Electron Microscopy," *Microscopy* **73**, 215–225 (2024).
- K. Kato and H. Yagi, "Current Status and Challenges in Structural Glycobiology," *Trends Carbohydr. Res.* **15**, 38–46 (2023).

1. Structural and Kinetic Modulation of Amyloid β Fibrils: Insights from Antibody Recognition and Familial Mutation

The dynamic interaction between amyloid β (Aβ) fibrils and antibodies during fibril elongation was investigated at the single molecule level.[1] Real-time observations revealed that Aβ fibril elongation alternates between an "elongation phase," in which two protofilaments grow in a staggered manner, and a "pause phase," during which growth temporarily halts. Notably, Aβ monomers were found to alternately attach to the two protofilaments during elongation, whereas growth paused when both protofilament tips became aligned. Furthermore, a monoclonal antibody 4396C selectively bound to fibril ends in this paused state, effectively suppressing further elongation. By integrating high-speed atomic force microscopy with molecular simulations, this study provided a detailed understanding of the dynamic assembly mechanism underlying Aβ fibril formation.

In parallel, we harnessed the unique microgravity environment aboard the International Space Station to elucidate, for the first time, the detailed structure of amyloid β fibrils bearing the Tottori-type familial mutation (D7N), a rare variant linked to Alzheimer's disease.[2] Under Earth gravity, Tottori-type Aβ40 predominantly forms amorphous aggregates, hindering structural analysis. In contrast, microgravity suppressed amorphous aggregation and promoted efficient fibril formation, enabling high-resolution cryo-electron microscopy (Figure 2). The resulting structures revealed a flexible, disordered N-terminal region, suggesting that the D7N mutation disrupts the stabilizing role of the N-terminus observed in wild-type Aβ fibrils. Under microgravity, the absence of convection and sedimentation limited off-pathway aggregation and facilitated the emergence of structurally convergent, high-quality fibrils.

These two perspectives jointly deepen our mechanistic understanding of Aβ fibril formation and offer new avenues for identifying therapeutic targets associated with Alzheimer's disease pathogenesis.

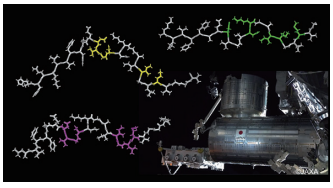

Figure 2. Fibril formation of the Aβ Tottori variant (D7N) was investigated under microgravity on the International Space Station.[2]

2. Decoding Glycan Dynamics and Engineering Precision in Glycoprotein Function

Glycans play vital roles in cellular recognition, immune signaling, and protein stability, yet their dynamic and heterogeneous structures remain difficult to characterize. We reported a series of studies that deepen our understanding of glycan conformational behavior, its influence on protein function, and its potential in glycoengineering and biopharmaceutical design.

To explore glycan dynamics, we developed an analytical framework integrating molecular dynamics (MD) simulations with NMR-guided constraints. Using nonlinear correlation metrics such as the Hilbert-Schmidt Independence Criterion and Maximal Information Coefficient, we uncovered hidden structural relationships beyond conventional intuition.[4] This data-driven approach reveals how glycan flexibility modulates protein interactions.

We next examined how glycosylation affects the structure and immune functions of human IgG antibodies.[5] Through isotope-assisted NMR and MD simulations, we analyzed four IgG1-Fc glycoforms differing in galactose and fucose content. Galactose residues acted as molecular "anchors" and "wedges," stabilizing the Fc domain and enhancing binding to Fcγ receptors and complement C1q (Figure 3). In contrast, the absence of core fucose altered dynamics of residues critical for ADCC, offering atomic-level insights for antibody optimization.

In parallel, we identified a 10-amino-acid "passport sequence" that enhances N-glycan maturation as well as secretion. When appended to therapeutic glycoproteins such as erythropoietin, the passport sequence is recognized by NUCB1, which resides near B4GALT1 in the Golgi and promotes its enzymatic activity. This facilitates N-glycan maturation and, in turn, enhances pharmacokinetics and therapeutic efficacy.[6]

Additional studies revealed temporal and sex-dependent N-glycosylation changes in rat serum[7] and unusual glycan structures in tardigrades,[8] underscoring the evolutionary diversity of glycosylation.

Together, these findings offer new strategies for precision glycoengineering and deepen our understanding of glycan-mediated regulation.

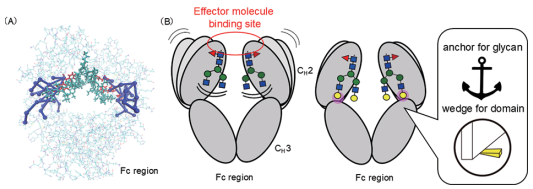

Figure 3. (A) Structural propagation pathways originating from galactose residues within the Fc-linked glycan. (B) Galactose residues (indicated by yellow circles) suppress glycan mobility by acting as molecular anchors, and constrain Fc domain dynamics by serving as molecular wedges—together enhancing the stability of the functional site and promoting effector molecule binding.[5]

References

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4) K. Kato *et al.*, *Chem. Pharm. Bull.* **73**, 639–644 (2025).
5) S. Yanaka *et al.*, *Proc. Natl. Acad. Sci. U. S. A.* **122**, e2505473122 (2025).
6) H. Yagi *et al.*, *iScience* **27**, 111457 (2024).
7) H. Yagi *et al.*, *Int. J. Mol. Sci.* **26**, 7266 (2025).
8) H. Yagi *et al.*, *Mol. Cell Proteomics* **24**, 100974 (2025).

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