In Silico - Guided Design of Therapeutic Antibodies Based on Molecular Dynamics Simulation and Machine Learning

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1. Project Purpose

This project aims to utilize molecular dynamics simulations in combination with machine learning techniques to design and optimize switchable antibodies that address the on-target, off-tumor challenge. The research will analyze structural dynamics, identify key molecular interactions, and develop predictive models to assess the feasibility of incorporating switchable features into antibody frameworks.

2. Results

Our current results focus on the pH-dependent behavior of the antibody Ipilimumab. Building on experimental work that generated Ipilimumab variants (Ipi95, Ipi105, Ipi106) through charged amino acid substitutions in complementarity-determining regions, we employed molecular dynamics simulations to examine their interactions with CTLA-4 in physiological and acidic conditions. All variants exhibited enhanced binding affinity at acidic pH, with a reasonable agreement between computational and experimental binding free energies (R^2 = 0.7736; Pearson's r = 0.8795, p = 0.0039; Spearman's ρ = 0.8333, p = 0.0102). Statistical analysis revealed notable differences across conditions, most notably for Ipi95, which demonstrated the highest degree of pH sensitivity, supported by both computational and experimental data.

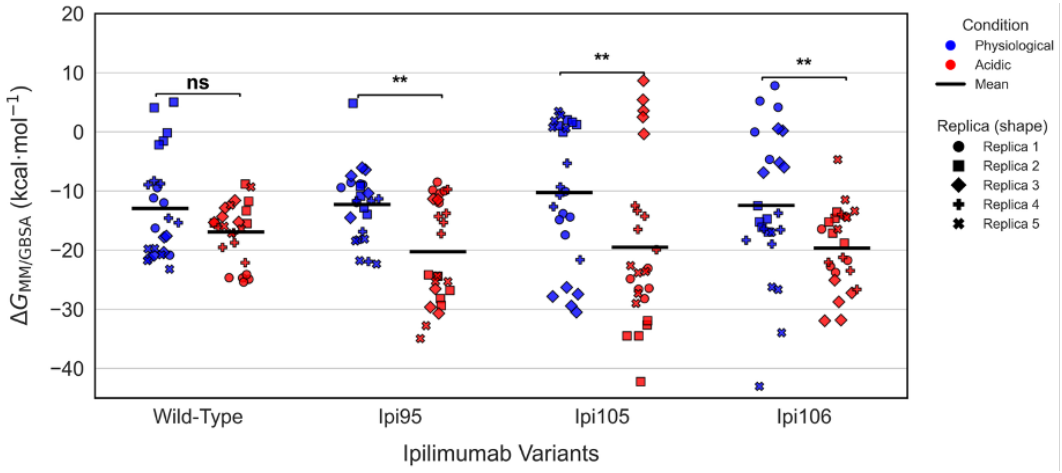

Fig 3. Destiarani, W.; Hengphasatporn, K.; Shigeta, Y., Harada, R. 2026. PCCP (accepted).

Despite these binding differences, our MD simulations revealed no major global structural changes between acidic and physiological conditions, indicating that pH-dependent behavior arose primarily from local energetic and interfacial rearrangements rather than large conformational transitions. The binding-free-energy decomposition analysis further showed that the overall antigen-binding mode and epitope recognition were largely preserved across the WT and mutant complexes, while the mutations mainly redistributed local interaction strengths at the interface. Together, these findings indicate that pH-dependent affinity in engineered antibodies is governed not simply by the introduction of charged residues, but by their precise placement, local interaction network, and coupling to surrounding interfacial residues. This mechanistic understanding is highly valuable for guiding the rational design of next-generation therapeutic antibodies, where careful consideration of the TME, especially the balance and placement of charged amino acids, can enhance selectivity and reduce adverse effects.

３．Roles of the MCRP and its significance

Our research on molecular dynamics simulations of antibody-antigen systems requires extensive computational power beyond standard computing capabilities. These simulations involve complex biomolecular structures with thousands of atoms and require long microsecond-scale molecular dynamics simulations to capture key interactions and conformational changes. Therefore, MCRP is critical for providing access to supercomputing resources to perform these advanced calculations. Access to high-performance computing has significantly enhanced the speed, accuracy, and scope of our research, enabling the rational design of therapeutic antibodies and contributing to advancements in computational immunology.

４．Future plan

Continuing from our current findings, we will propose a pipeline for the automatic design and assessment of pH-dependent antibodies using machine learning for CDR sequence prediction and constant-pH molecular dynamics with OpenMM to evaluate mutant antibodies under both physiological and acidic pH conditions. Compiling a database of both wild-type and mutant antibody data at different pH levels will present challenges, but it is essential for training the model.Our focus will be on designing antibodies with reduced toxicity by incorporating pH-responsive residues such as Histidine, Aspartate, and Glutamate into the CDR sequences. By integrating computational and machine learning-based approaches, we aim to accelerate the development of novel antibody therapeutics with enhanced precision and therapeutic potential.

5. Publications and conference presentations

(1) Journal papers

Destiarani, W.; Hengphasatporn, K.; Shigeta, Y.; Harada, R. Computational Insights into the pH-Dependent Behavior of Ipilimumab-CTLA-4. 2026. *Physical Chemistry Chemical Physics.* (accepted). DOI:10.1039/d5cp04018c

(2) Presentations

- Best Poster presentation: Destiarani, W.; Hengphasatporn, K.; Shigeta, Y.; Harada, R. Computational Insights into the pH- dependent Antibody Behavior of Ipilimumab – CTLA-4: A Switchable Antibody. The 5th International Symposium on Frontiers in Molecular Science (ISFMS). Kyoto, August, 2025.
- Poster presentation: Destiarani, W.; Hengphasatporn, K.; Shigeta, Y.; Harada, R. Atomic-level Analysis of pH-dependent Switchable Binding in Ipilimumab-CTLA-4 Complex for Designing Therapeutic Antibodies. The 63rd Annual Meeting of the Biophysical Society of Japan. Nara, September, 2025.

(3) Others

Supercomputer	Use	Allocated resources*		
		Initial resources	Transferred resources**	Purchased resources
Pegasus	Yes	16000		7419
Miyabi-G	Yes	45000	-	1000
Miyabi-C	No	-	-	-
	*in units of node-hour product ** If the budget transfer was performed, fill in here, such as “+2000” and “−1000”.			