# Innovative Clasping Antibody Platform for Producing High-Performance Antibodies to Challenging Targets

**An innovative platform for generating antibodies with high affinity, high specificity, and low lot-to-lot variability against challenging target antigens.**

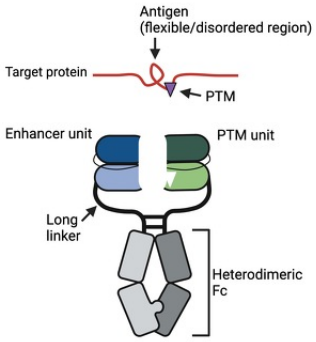


Figure 1. Schematic illustrating one configuration, the long-neck scFvFc format, of the clasping antibody platform to Post-Translationally Modified (PTM) targets.

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Life Sciences/Biologics
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## Technology

The NYU innovators have developed a synthetic platform for generating heterodimeric “clasping” antibodies to target challenging antigens, such as site-specific post-translational modifications (PTMs), utilizing a binding mode-guided approach. The platform is built based on the mechanistic understanding of the unique antigen-binding mode that the innovators previously discovered, dubbed antigen-clasping, where two antigen-binding sites cooperatively clasp a single antigen. The antigen clasping creates extensive interactions between the antibody and the antigen, leading to selective and tight binding with a low nanomolar to sub-nanomolar affinity range. The binding mode of the clasping antibodies differs from bispecific antibodies in that the clasping antibodies cooperatively recognize the same antigen with overlapping epitopes. The innovators rationally generated clasping antibodies by utilizing a synthetic yeast-display system where the single-chain variable fragment (scFv) enhancer arm is tethered to the other PTM-specific scFv arm via a long linker to facilitate intra-molecular dimerization. The innovators also developed a novel IgG-like antibody format suitable for antigen clasping (Figure 1).

In contrast to traditional polyclonal and monoclonal antibodies produced through animal immunization, clasping antibodies are recombinant, and thus they have minimal lot-to-lot variation. As described in the published work (see below under “POC STUDIES”), an anti-trimethylated histone H3 at Lys 27 (H3K27me3) clasping antibody exhibited superior specificity

to a widely used conventional antibody in a head-to-head, chromatin immunoprecipitation (ChIP)-based performance comparison, where it notably captured symmetric and asymmetric nucleosomes in a less biased manner. The innovators have also generated clasping antibodies to other PTMs, including H3K9me3, H3K56me3, H4K20me30, and to phosphotyrosine antigens, including PDGFRb pY716, and BCR pY177. Altogether, these results suggest the broad generalizability of the platform for creating high-performance clasping antibodies against diverse PTMs, such as histone modifications, phosphorylation, methylation, glycosylation, and ubiquitination, without the need for extensive efforts to improve affinity and specificity.

### Development Stage

A suite of anti-PTM clasping antibodies has been functionally validated by immunoprecipitation (IP), biolayer interferometry (BLI), western blot, and ChIP, for which NYU now seeks an industry partner to support their commercialization. The antigen-clasping platform may also be utilized to generate bespoke high-performance antibodies.

### Background

PTMs are critical to the structure and function of proteins, and the dysregulation of PTMs has been linked to the etiologies of many diseases, including cancer and autoimmune diseases. Thus, detecting site-specific PTMs is critical for understanding the molecular mechanisms of diseases and diagnosis. Antibodies targeting site-specific PTMs are an essential tool for this purpose. However, targeting PTMs with antibodies has presented many fundamental difficulties; the chemical moieties of PTMs are usually minute, and the differences among PTMs (such as mono-, di-, and trimethylation) are subtle. In addition to specifically recognizing the target PTM, antibodies need to discriminate closely related sequences surrounding the modification. Furthermore, the PTM sites are usually located in the flexible or disordered regions on proteins, and thus, unfavorable entropic loss of a flexible peptide segment upon antibody engagement hinders high affinity binding. The clasping antibody platform described here has overcome these fundamental challenges, achieving higher levels of specificity and affinity relative to conventional antibodies while maintaining minimal lot-to-lot variability.

### Applications

- Diagnostic tool for detecting etiological PTMs
- Research tool for selectively detecting and analyzing site-specific PTMs.
- Platform for generation of antibodies against challenging antigens, including diverse PTMs, such as phosphorylation, SUMOylation, glycosylation, ubiquitination, etc., for diagnostic or research uses.

### Advantages

- **Target antigen applicability:** Clasping antibodies can engage antigen targets (e.g., PTMs) that are less tractable to conventional antibodies.
- **Improved specificity and affinity:** The cooperative clasping mechanism more efficiently engages the target antigen.
- **Lower lot-to-lot variation:** Given that these antibodies are recombinant, they are consistent across lots and offer a long-term, stable supply.

### Intellectual Property

NYU has filed a U.S. provisional patent application covering the design of the clasping antibody platform, the compositions of current anti-PTM clones, and the method of use thereof.

## References

1. Takamitsu Hattori, et al. , https://www.pnas.org/doi/10.1073/pnas.2411720121