

Biparatopic sherpabody inhibitors for potent neutralization of H5 influenza viruses

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Highly pathogenic avian influenza H5 viruses remain a major pandemic threat, highlighting the need for antivirals active across antigenically diverse strains. We are developing compact, modular sherpabody (Sb)-based inhibitors that can be engineered into multispecific formats targeting influenza hemagglutinin (HA).

Cross-reactive H5-binding Sbs were isolated from a synthetic phage display library by alternating selection against divergent HA variants. To enhance potency and cross-reactivity, we developed biparatopic inhibitors through two complementary strategies: rational pairing of Sbs recognizing non-overlapping HA epitopes and selection from biparatopic libraries comprising a fixed lead Sb linked to a diversified Sb module.

Both strategies have yielded functional biparatopic inhibitors. Preliminary pseudovirus neutralization studies demonstrate potent inhibition of H5 virus entry, with lead constructs reaching low-nanomolar IC50 values. Ongoing work focuses on multimerization of the most promising biparatopic inhibitors to further enhance avidity, neutralization potency, and cross-reactivity. Together, these results establish a versatile strategy for generating high-avidity, multispecific influenza inhibitors and support further development toward intranasal prophylaxis against emerging H5 viruses.

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No, I am not a junior scientist.

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