

From nanobodies to megabodies for applications in cryo-EM

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Abstract

Nanobodies (Nbs) are highly popular and versatile tools for structural biology. Here we report the development of megabodies, whereby Nbs are rigidly grafted into selected protein scaffolds to increase their molecular weight while retaining the full antigen binding specificity. The megabody design principles are applicable to other scaffolds without size limitations and expand cryo-EM analysis to proteins that are small and/or display preferential orientation in ice, two major factors that limit the resolution of reconstructed density maps. Such megabodies have been instrumental to solve the first structures of the human heteropentameric GABAA receptor in complex with well known drugs.

References:

1) Uchański, T., et al. (2021). "Megabodies expand the nanobody toolkit for protein structure determination by single-particle cryo-EM." *Nat Methods* 18: 60-68.