

Collapsed star copolymers exhibiting near perfect mimicry of the therapeutic protein 'TRAIL'

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Here we introduce amphiphilic star polymers as versatile protein mimics capable of approximating the activity of certain native proteins. Our study focusses on designing a synthetic polymer capable of replicating the biological activity of TRAIL, a promising anticancer protein that shows very poor circulation half-life.^{1,2} Successful protein mimicry requires precise control over the presentation of receptor-binding peptides from the periphery of the polymer scaffold, while maintaining enough flexibility for protein-peptide binding. We show that this can be achieved by building hydrophobic blocks into the core of a star-shaped polymer, which drives unimolecular collapse in water (**Figure 1**). By screening a library of diblock copolymer stars we were able to design structures with IC₅₀'s of ~4 nM against a colon cancer cell line (COLO205), closely approximating the activity of the native TRAIL protein. The effect of polymer architecture, size, and glass transition temperature (T_g) on the presentation of the peptide ligands and the biological activity of these materials will be discussed. This finding highlights the broad potential for simple synthetic polymers to mimic the biological activity of complex proteins.

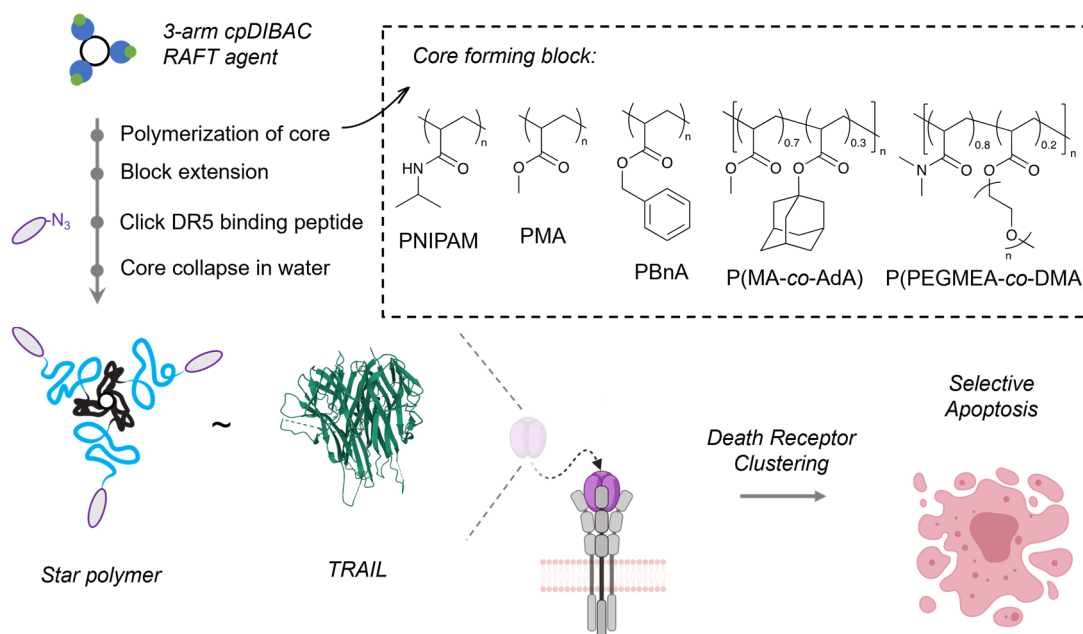


Figure 1: Schematic showing the structure of our star-shaped TRAIL mimics and the TRAIL driven receptor clustering mechanism which leads to selective apoptosis in a wide variety of cancer cell lines.

References:

¹ Ashkenazi, V. M. Dixit; *Science* **1998**, *281*, 1305–1308.

² Thapa, R. Kc, H. Uludağ; *J. Controlled Release* **2020**, *326*, 335–34.