Development of a Pan Ras Inhibitor

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Oncogenic Ras isoforms are the subject of intense study due to the difficulty in targeting these biomedically important yet "undruggable" proteins. Recent success in covalent targeting of a Ras mutant illustrates avenues for ligand design; however, many mutant Ras forms do not feature appropriately-placed nucleophiles, suggesting that strategies for noncovalent engagement of Ras are required. This presentation will describe the design of a conformationally-defined proteomimetic that reproduces a key binding surface of Sos, a well-characterized effector of Ras.[1] The proteomimetic binds wild-type and various mutant forms of Ras and modulates downstream signaling. Significantly, the compound shows enhanced internalization and selective toxicity toward cancer cells that up-regulate macropinocytosis. We anticipate these studies will foster new therapeutic modalities to engage mutant Ras.

[1] Hong, S. H.; Yoo, D. Y.; Conway, L.; Richards-Corke, K. C.; Parker, C. G.; Arora, P. S.: A Sos proteomimetic as a pan-Ras inhibitor. *Proc. Natl. Acad. Sci. USA* **2021**, *118*, e2101027118.