

Targeting hard-to-attack protein-protein interaction surfaces using UV-reactive surface fragments

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KRas G12D is one of the most challenging intracellular protein targets in medicinal chemistry. The absence of targetable binding pockets on the surface generated a still unsolved problem. The small surface area of small molecular drug candidates led to numerous unsuccessful attempts in cases of hard-to-attack proteins. Thus compounds with a larger surface area are worth trying, which might cover extended protein-protein interaction surfaces.

We hypothesised that a hard-to-drug protein like KRas G12D could be a relevant and illustrative example of testing our novel fragment-based approach based on UV-reactive peptidomimetic fragments. Our goal was to map the surface of Kras G12D with a 100-membered fragment library and then increase the affinity by linking the foldamer fragments, thus extending fragment-based drug development to targets without a binding pocket.

We tested the 100-membered UV-reactive foldamer library with HPLC-MS. Photolabeling made a direct and sensitive screening method possible. The binding site of the most effective fragments was determined by proteomic MS-MS analysis and ¹⁵N HSQC NMR titration. In dynamic covalent library experiments, foldamer dimers with higher affinity were created with a systems chemistry approach.

The surface fragments were able to recognize the protein surface and bind to the target. We found numerous foldamers with a side chain-dependent binding pattern with KRas G12D. The UV-reactive marker made the screening efficient, and we were able to localize the binding site of the fragments. The foldamers found the known protein-protein interaction surfaces of the target but also discovered new, potentially attackable regions. In protein-templated dynamic covalent library experiments, dimers with higher affinity were created.

Using the protein surface mimetic foldamer fragment library and connecting the building blocks can be a viable general hit generation strategy for challenging protein targets.

