Selective NRAS-Binding Monobodies for the Treatment of Cancer

A selective and efficacious inhibitor of NRAS applicable to all NRAS-driven cancers.

Technology

The Koide Lab at NYU Langone Health is a pioneer and world expert in engineering monobodies, which are synthetic binding proteins constructed on the fibronectin type III domain scaffold, for therapeutic and diagnostic applications. This group has developed new monobodies that selectively bind NRAS, but not related RAS isoforms KRAS and HRAS, to universally target and treat all NRAS-driven cancers. As described in the published PCT patent application, biolayer interferometry analysis identified three monobody clones with low- to sub-nanomolar affinity for NRAS in both the GDP- or GTP-bound nucleotide states, with the best clone displaying 1.8 nM and

0.83 nM affinities, respectively. Importantly, none of the clones showed any detectable binding affinity toward KRAS or HRAS. The binding epitope for these anti-NRAS monobodies was determined to be the alpha4-alpha5 region; an area integral to NRAS function but distinct from the Switch region which harbors the vast majority of oncogenic NRAS mutations. Moreover, this region is also the epitope of the extensively characterized KRAS- and HRAS-specific monobody NS1, which as described in *Spencer-Smith et al. Nat Chem Biol 2017*, potently inhibits the tumorigenesis of these respective RAS isoforms. Consequently, the identified anti-NRAS monobodies are agnostic to NRAS oncogenic mutations, and by extension of NS1's demonstrated functionality, are expected to inhibit NRAS-mediated signaling in cells and tumorigenesis in mouse xenografts. In all, these monobody clones are promising therapeutic candidates for selective inhibition of NRAS-mediated oncogenic activity that are agonist to tumor-specific NRAS mutations, while unencumbering to the essential cellular functions of KRAS and HRAS.

Background

NRAS is one of three major isoforms of the GTPase RAS, which collectively regulate cellular signaling events that are critical to normal cellular processes. The dysregulation of these RAS isoforms is highly associated with oncogenesis, with more than 25% of all human cancers containing missense RAS mutations. Oncogenic RAS mutant proteins have long been considered undruggable, due to an apparent lack of binding pockets suitable for small molecule inhibitors and the minute structural differences between either RAS isoforms or between the wildtype and mutant variants. Despite extensive research, selective NRAS inhibitors have yet to be approved and sold, rendering NRAS-mediated cancers difficult to treat without off-target effects. Current treatments predominantly focus on downstream effectors of the MAPK pathway, which often carry adverse side effects. Therefore, innovative strategies for selectively targeting NRAS, that are non-discriminate against the variety of oncogenic NRAS mutants, are urgently needed.

Applications

Technology ID

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Category

Life Sciences/Biologics

Doug Brawley

Life Sciences/Research tools/Oncology

Authors

Shohei Koide, PhD

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Monobodies are expected to treat NRAS-mediated cancers, such as colon cancer, rectal cancer, follicular thyroid cancer, melanoma, leukemia, and myeloma, when administered via:

- Peptide format
- Polynucleotide format using lipid nanoparticle delivery
- bioPROTAC format (as either a peptide or polynucleotide)

Advantages

- **High Selectivity:** Monobodies bind specifically to NRAS, but not KRAS or HRAS
- **High Affinity:** Monobodies bind NRAS with sub-nanomolar affinity
- **Pan-NRAS Applicability:** Monobodies are agonistic to tumor-specific NRAS mutations
- **Flexible and Adaptable:** Monobodies, in peptide or polynucleotide format, can be conjugated with various agents for a variety of applications

Development Stage

Researchers have shown anti-tumor specificity and efficacy in NRAS-mutant tumor cell lines and are confirming these findings in *in vivo* xenograft models.

Intellectual Property

NYU has filed a U.S. non-provisional patent application covering the compositions of the NRAS-binding monobodies, their polynucleotide embodiments, and their method of use.