Docket #: S22-163

Myc degradation by long non coding RNA for cancer therapeutics

Researchers at Stanford University have discovered that the absence of a long non coding RNA (lnc122) predisposed mice to high numbers of hepatocellular carcinomas (HCC), and its replacement decreased the risk of HCC. Mechanistic studies revealed that lnc122 acts via degradation of the oncogenic protein Myc. Consequently, methods to increase lnc122 expression can be used to treat a variety of Myc driven and/or dependent cancers.

Dysregulation of the *MYC* proto-oncogene occurs in ~70% of all human cancers and is linked to poor prognosis. Accordingly, the Myc protein is a transcription factor that is a major driver of tumorigenesis and a well-established cancer target for a variety of cancers, including liver cancer, ovarian cancer, breast cancer, and colorectal cancer, among others. However, inhibition of Myc has proven difficult due to its lack of a traditionally druggable binding pocket and primarily nuclear localization. Alternative methods for targeting Myc are being pursued, such as targeting *MYC* transcription or mRNA translation, preventing its function as a transcription factor by blocking binding of Myc to chromatin or Max, and promoting Myc degradation via the ubiquitin–proteasome system (UPS). While these strategies are promising and numerous clinical studies are being pursued, there have yet to be approved cancer drugs targeting Myc.

This technology offers a contrasting strategy to promote Myc degradation via the UPS. Current approaches to hijack the UPS include proteolysis-targeting chimaeras (PROTACs), which bring the target protein and E3 protein ligase into close proximity with a heterobifunctional molecule. This strategy is difficult in the case of Myc as high affinity ligands for the target protein are required. In contrast, here, the inventors found that a long non coding RNA present in hepatocytes, lnc122, serves as a mediator for E3 ubiquitin-protein ligase UBR5-dependent Myc degradation. Specifically, lnc122 enhances the binding of UBR5 to Myc, resulting in ubiquitination

and subsequent proteasomal degradation of Myc. While lnc122 is naturally present primarily in liver cells, UBR5-dependent ubiquitination occurs across tissues. Thus, strategies which increase the expression and/or presence of lnc122 can be applied to promote Myc degradation in a variety of tumor types.

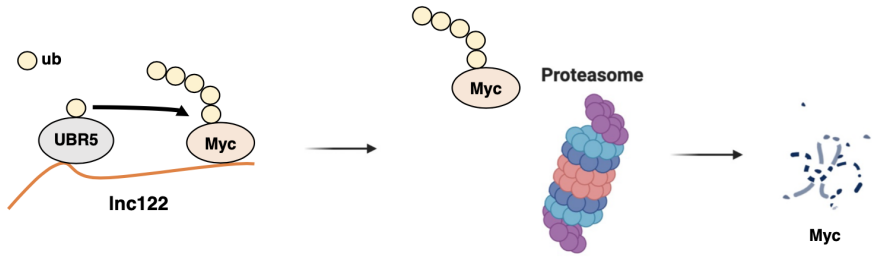

Figure 1. Schematic of lnc122-mediated targeted protein degradation of Myc. (Credit to the inventors)

Stage of Development: In vivo data

Applications

- Therapeutics for Myc driven/dependent cancers

Advantages

- By targeting a driver oncogene/protein such as Myc, therapies can be developed for cancers that currently have no targeted therapies
- Tumors are highly dependent on driver oncogenes, making targeting these drivers such as MYC highly promising for significant clinical benefit
- Myc is a promising cancer target, but is difficult to target with traditional approaches, such as small molecules and antibodies
- Lnc122 enables targeted degradation of Myc via the UPS system and can be applied to a variety of tumor types

Patents

- Published Application: WO2023212572
- Published Application: 20250277215

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