Development of the small molecule HTR-81 compound: a cancer targeting, anti proliferative compound

Sydney Beese

Abstract

Proper mitochondrial functioning is essential for regulation of cell metabolism and therefore cellular function. It has been suggested that the inhibition of mitochondrial function may stimulate cell senescence due to the down regulation of metastasis and metabolism. The mitochondrial protein caseinolytic protease P (ClpP) is a1 mitochondrial protease that inhibits mitochondrial transcription impeding cell growth and proliferation. The lab has identified ClpP as being protein specific for binding by using immobilized TR compounds and mass spectrometry. TR compounds are a more 2 potent analog of a group of ClpP agonists known as ONC201 that have been developed by Madera Therapeutics. Due to this higher potency, TR compounds have been found to inhibit cell proliferation as well as establish a continual ClpP presence causing the degradation of mitochondrial proteins and inhibiting mitochondrial transcription and translation. By testing for the protein presence in cell lysates, via immunoblotting, the3 TR compounds can be characterized to determine how ClpP-induced mitochondrial stress communicates with the nucleus to remodel the cancer cell. Additionally, by investigating the characteristics of TR-81, the pharmacological properties of this bifunctional molecule will be classified and its effects on cancer cell lines determined.

References:

1. Daglish SCD, Fennell EMJ, Graves LM. Targeting mitochondrial DNA transcription by POLRMT inhibition or depletion as a potential strategy for cancer treatment. MDPI. May 31,

2023. https://www.mdpi.com/2227-9059/11/6/1598. Graves PR;Aponte-Collazo LJ;Fennell EMJ;Graves AC;Hale AE;Dicheva N;Herring LE;Gilbert TSK;East

2 MP;McDonald IM;Lockett MR;Ashamalla H;Moorman NJ;Karanewsky DS;Iwanowicz EJ;Holmuhamedov
E;Graves LM; Mitochondrial protease CLPP is a target for the anticancer compounds ONC201 and related analogues. ACS chemical biology. https://pubmed.ncbi.nlm.nih.gov/31021596/. Fennell, E. M. J.; Aponte-Collazo, L. J.; Wynn, J. D.; Drizyte-Miller, K.; Leung, E.; Greer, Y. E.; Graves, P.

3 R.; Iwanowicz, A. A.; Ashamalla, H.; Holmuhamedov, E.; Lang, H.; Karanewsky, D. S.; Der, C. J.; Houry, W. A.; Lipkowitz, S.; Iwanowicz, E. J.; Graves, L. M. Characteriza+on of TR-107, a Novel Chemical Ac+vator of the Human Mitochondrial Protease ClpP. *Pharmacology Research & Perspec:ves* 2022, *10* (4), e00993. hcps://doi.org/10.1002/prp2.993.