Inhibition of Aminoacylase 3 (Aa3) in the Treatment of Cancer

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OTHER INFORMATION

KEYWORDS

Cancer, hepatocellular carcinoma, HCC, therapeutics, enzyme inhibitors, Ras

CATEGORIZED AS

- **Biotechnology**
  - Health
- **Medical**
  - Disease: Cancer
  - Therapeutics

RELATED CASES

2015-397-0

SUMMARY

UCLA researchers have developed aminoacylase 3 (AA3) inhibitors to treat hepatocellular carcinoma (HCC) and other Ras driven cancers.

BACKGROUND

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death world-wide and accounts for 75% of all liver cancer cases. Unregulated activation of Ras signaling pathways controlling cell proliferation and survival is a molecular hallmark of HCC. While Ras proteins play a major role in cancer pathogenesis, no effective treatment has been developed to address Ras driven cancers. Sorafenib, a multi-kinase inhibitor with anti-angiogenic and anti-proliferative properties, is the only approved treatment for HCC that offers only limited survival benefits for advanced, unresectable HCC. UCLA researchers have identified new targets in the Ras pathway that will potentially provide novel approaches to treat Ras driven cancers.

INNOVATION

UCLA researchers have developed Ras pathway inhibitors with anti-proliferative effects in HCC cell models. Ras proteins require translocation and insertion into the plasma membrane to function, a process that is mediated by post-translational prenylation of Ras proteins. The rate of prenylation is regulated by the biosynthesis and regeneration of prenyl moiety precursors. Normal regeneration of the prenyl moiety is controlled by N-acetylation of precursors. It has also been uncovered that elevated levels of aminoacylase 3 (AA3) in HCC cells compared to healthy cells may be responsible for increased deacetylation of prenyl group precursors leading to increased Ras prenylation and subsequent activation HCC cell proliferation. Inhibition of AA3 with novel compounds was shown to significantly decrease membrane bound Ras and reduce cell viability in multiple HCC cell lines with little to no effect on normal hepatocytes. Initial results are promising for the adaption of AA3 inhibition to address the unmet therapeutic needs of HCC and Ras driven cancers.

APPLICATIONS

- AA3 inhibitors can be developed into a therapeutic against HCC or other Ras driven cancers.

ADVANTAGES

- AA3 inhibitors stop cell proliferation and are toxic specifically to HCC cells and not normal hepatocytes.

STATE OF DEVELOPMENT

- Anti-proliferative properties of the authors' AA3 inhibitors have been demonstrated in multiple cell culture models.
- Pre-clinical studies in animal models planned to further confirm the efficiency of these AA3 inhibitors.

PATENT STATUS

Country	Type	Number	Dated	Case
United States Of America	Issued Patent	11,464,784	10/11/2022	2015-397
Germany	Published Application	WO2019/055825	03/21/2019	2015-397

RELATED MATERIALS

- Structures of aminoacylase 3 in complex with acetylated substrates. PNAS (2010).

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