COMPOUNDS AND METHODS FOR THE TREATMENT OF CHOLANGIOCARCINOMA

A novel pharmacological approach for the treatment of cholangiocarcinoma has emerged from the collaborative efforts of research groups from CIBER, IIS Biogipuzkoa, EHU and DIPC.

The Need

Cholangiocarcinoma (CCA), is an aggressive form of cancer originating from biliary epithelial cells. CCA is highly lethal due to its asymptomatic growth, aggressiveness, late diagnosis, and high chemoresistance. Surgery combined with adjuvant capecitabine, remains as the only potentially curative option. However, this therapeutic approach is indicated in less than 30% of patients due to late-stage diagnosis, and even after surgical resection the chances of tumor recurrence are high. In unresectable cases, first-line pharmacological treatment for advanced CCA consisting in the triple combination of gemcitabine, cisplatin and immunotherapy (*i.e.*, durvalumab or pembrolizumab) provides modest benefits in terms of overall survival, being therefore considered palliative. Therefore, there is an urgent need for the development of safe and effective therapeutic alternatives for CCA.

The Solution

The present invention relates to a new family of selective histone deacetylases inhibitors (HDCAis) that derive from ursodeoxycholic acid (UDCA) and to their use for the treatment of cancer, in particular of CCA.

Bioinformatic analysis of the expression levels of the different HDACs in tumor tissue samples from 9 international cohorts of patients with CCA identified several HDAC isoforms as promising pharmacological targets for the treatment of CCA. On the other hand, UDCA is an endogenous bile acid with hepatotropic and hepatoprotective features. Therefore, we have integrated the beneficial capacities of UDCA into a novel family of highly selective UDCA-derived HDAC inhibitors as an epigenetic-based therapeutic strategy for CCA and other types of cancer.

The experimental results highlight the promising therapeutic potential of these novel chemical entities for the treatment of different types of naïve and cisplatin-resistant cancers, including CCA.

Innovative Aspects

1.- Novel target for CCA treatment. Selective inhibition of upregulated HDAC isoforms in CCA cells.

2.- The designed molecules exert the following effects on tumor cells:

A.- inhibit the growth of different human cancer cell lines, including leukemia, NCS lung, colon, central nervous system (CNS), melanoma, ovarian, renal cancer, prostate, CCA and breast cancer,

B.- decrease cell viability and proliferative capacity of human CCA cells,

C.- induce apoptosis of CCA cells,

D.- inhibit growth of 3D human CCA spheroids and murine tumor organoids promoting tumor cell death,

E.- enhance efficacy of chemotherapy in experimental models of naïve and cisplatin-resistant CCA,

F.- decrease the invasiveness of human CCA cells.

Intellectual Property:

- Priority European patent application filed (February 2025)
- International PCT application (February, 2026)

Aims

Looking for a partner interested in a license and/or a collaboration agreement to develop and exploit this asset.

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