Universität Basel

Research Project

inhibiTOR / Novel selective mTORC1 inhibitors

Third-party funded project

Project title inhibiTOR / Novel selective mTORC1 inhibitors
Principal Investigator(s) Hall, Michael N. ;
Co-Investigator(s) Gonzalez Sevine, Asier ; Imseng, Stefan ;
Organisation / Research unit
Departement Biozentrum / Biochemistry (Hall)
Department
Project start 01.08.2019
Probable end 31.03.2021
Status Completed

Hepatocellular carcinoma (HCC) is the predominant form of liver cancer and the fourth leading cause of cancer-relatedădeaths worldwide. The multikinase inhibitor sorafenib is the only approved drug to treat HCC and on average enhancesăsurvival by three months. Thus, the efficacy of current HCC treatment options is very limited. Studies in the context of ourăERC-Synergy grant revealed that sorafenib resistance correlates with upregulation of mammalian target of rapamycinăcomplex 1 (mTORC1) signaling. The central role of mTORC1 in conferring therapy resistance suggests that effective therapyăagainst HCC may require combination of a primary inhibitor (e.g., sorafenib) and an mTORC1 inhibitor. The mTORC1ăinhibitor rapamycin and its derivatives (rapalogs) are approved for a few advanced cancers, but not for HCC. Their clinicalăapplicability is limited by their effectiveness and safety. Rapalogs fail to completely inhibit mTORC1 as they have little effectăon inhibiting phosphorylation of 4E-BP, one of the two main targets of mTORC1. Moreover, rapamycin and rapalogs alsoăinhibit mTORC2 when chronically administered, leading to undesirable effects such as hyperglycemia, hyperlipidemia, andăinsulin resistance. We have established a biophysical assay to identify selective mTORC1 inhibitors with a novel, rapalogunrelated,ămechanism of action. We predict these inhibitors to be more selective, more effective, and potentially safer thanămTORC1 inhibitors currently used in the clinic. In this Proof of Concept project, we aim to study the pharmacologicalăpotential of selective and efficient mTORC1 inhibition alone or in combination therapy with sorafenib to treat HCC.

Keywords mTOR signaling, hepatocellular carcinoma, mTORC1 inhibition, drug development, biophysical screening
Financed by
Commission of the European Union

Add publication

Add documents

Specify cooperation partners