ascenion Technology transfer for academic research
A company of the LifeScience Foundation

REFERENCE NUMBER
TO 02-00386

INHIBITORS OF ACONITATE DECARBOXYLASE 1 – A NOVEL IMMUNO-THERAPEUTIC TARGET

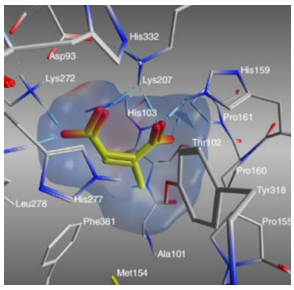
Keywords: ACOD1, IRG1, itaconic acid production, cancer, interferon response, oxidative stress, inflammation, cell metabolism

INVENTION NOVELTY

Provided are analogs of citraconic acid as first-on-target first-in-class inhibitors of aconitate decarboxylase 1 (ACOD1 or IRG1) for treatment of medical conditions benefitting from inhibiting the activity of the immuno-therapeutic target ACOD1 such as boosting tumor immunogenicity and efficacy of existing immune checkpoint inhibitors in cancer therapy.

VALUE PROPOSITION

Immunometabolism is fundamental in health and diseases. Aconitate decarboxylase 1 (ACOD1; also known as IRG1), a mitochondrial enzyme catalyzing the production of itaconate, has been proven to act as a regulator of immunometabolism in inflammation and infection. Hence, ACOD1 expression is upregulated in activated immune cells (e.g., macrophages and monocytes). ACOD1 plays dual roles in immunity and diseases. Thus, activation of the ACOD1 pathway may limit pathogen infection, however, abnormal ACOD1 expression can lead to tumor progression. Recent work has shown that ACOD1 is overexpressed in various tumors and that itaconate released from tumor cells and from infiltrating myeloid cells inhibits anti-tumor immunity by CD8+ T cells. Overexpression of ACOD1 in tumor tissue is an independent risk factor for a poor response to treatment with immune checkpoint inhibitors. Therefore, inhibition of ACOD1 resulting in decreased synthesis of endogenous itaconate thereby subsequently preventing accumulation of itaconate in the tumor microenvironment constitutes a promising new approach to boosting tumor immunogenicity and efficacy of existing immune checkpoint inhibitors. Up to date there are no specific ACOD1 inhibitors available.



Ligand-target model showing the active site of ACOD1 binding its competitive inhibitor citraconic acid (Chen F, Nat Metab 2022)

TECHNOLOGY DESCRIPTION

The invention relates to novel pharmacologically improved citraconic acid analogs as first-on-target first-in-class specific competitive inhibitors of ACOD1 for use as immuno-modulators in the treatment of inflammation-associated and/or non-inflammation associated medical conditions. The spectrum of potential applications of the novel ACOD1 inhibitors comprises e.g. treatment of acute or chronic inflammation as well as application in cancer therapy as a monotherapy or as an adjuvant therapy combined with current checkpoint inhibitors.

COMMERCIAL OPPORTUNITY

Application as monotherapy or adjuvant therapy with checkpoint inhibitors in cancer therapy as well as immune-modulator for treatment of inflammation-associated diseases. The technology is offered for co-development and/or licensing.

DEVELOPMENT STATUS

Three analogs based on the citraconate backbone with significantly increased activity against ACOD1 in cell-free and cellular assays and a wide therapeutic window have been generated. Tests in *in vivo* models, such as a LPS model of sepsis and in the field of tumor immunity, are in preparation.

PATENT SITUATION

Priority application was filed in April 2021, the international (PCT-)application was published in 2022 (WO2022223778).

FURTHER READING

Chen F, Elgaher WAM, Winterhoff M, Bussow K, Waqas FH, Graner E, et al. Citraconate inhibits ACOD1 (IRG1) catalysis, reduces interferon responses and oxidative stress, and modulates inflammation and cell metabolism. Nat Metab. 2022;4(5):534-46

HZI HELMHOLTZ Zentrum für Infektionsforschung

Ascenion GmbH
Herzogstraße 64
D-80803 München
info@ascenion.de
www.ascenion.de

Licensing Contact
Dr. Sabina Heim
Senior Technology Manager
T: +49 531 618120-90
heim@ascenion.de