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Targeting Protein Translation with Novel Small Molecules for Treating Pancreatic and Prostate Cancer

Investigators

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Description

Mnk-eIF4E antagonists to treat prostate and pancreatic cancer

Field

Medicinal chemistry
Oncology

Status

Available for licensing & sponsored research

Patent Status

Composition: U.S. Patent 9,694,005, JP Patent 6417392; & AU Patent 2014247941 (others pndg)
Methods of treatment: WO 2016/054472;
Synthetic method: WO 2017/223320

UMB Docket#

VN-2013-094; VN-2015-009; VN-2016-127

References

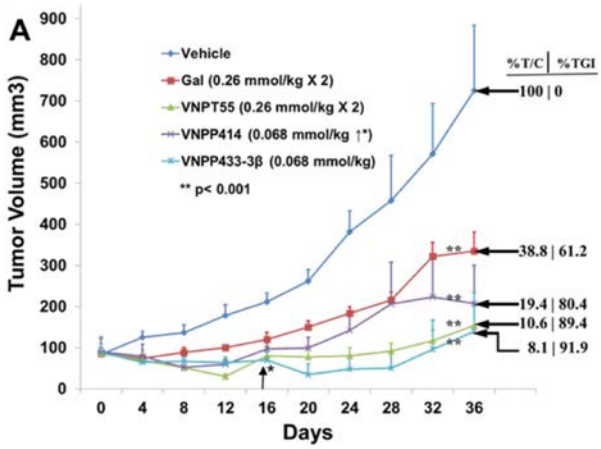
Ramamurthy (2017). *Curr Opin Oncol*. 29(3):210-220. DOI:10.1097/CCO.0000000000000367

Kwegyir-Afful (2016) *FEBS*. 283(21):3898-3918. DOI: 10.1111/febs.13895

Kwegyir-Afful (2017) *Oncotarget*. DOI:10.18632/oncotarget.14154

Overview

Medicinal chemists at UMB designed a family of **novel small molecules** which block key drivers of the protein translational complex by **degrading MNK1/2** (i.e., mitogen-activated protein kinase (MAPK)-interacting kinase 1/2), thus inhibiting the activation of the eIF4E axis and inhibiting tumor growth. Lead compounds designated "**VNPP414"** and **"VNPP433-3β"** are promising candidates for the treatment of prostate (PC) and pancreatic cancer (PANC). Originating from Prof. Njar's group at University of Maryland, Baltimore was an earlier drug candidate ("galeterone"), which was well tolerated in clinical studies and advanced to a Phase III trial for the treatment of patients with castration-resistant prostrate cancer. The new leads VNPP414 and VNPP433 described here are chemically related to galeterone.



In a study with leads VNPP414 and VNPP433 (*Kwegyir-Afful et al.*, Oncotarget 2017), both compounds inhibited cell viability of gemcitabine-naïve and gemcitabine-resistant PANC cells, and potentiated the effects of gemcitabine treatment in both cell types. *In vivo* treatment with each compound inhibited tumor growth in PANC tumor xenografted mice, with tumor growth inhibition ranging from 80% to 92%, compared to controls. When measuring the efficacy of the compounds as %T/C, the growth inhibition ranged from 8.1 to 19.4%T/C, classifying these agents as highly efficacious according to criteria set by the National Cancer Institute. In xenograft mouse models of castration-resistant prostate cancer, lead compounds VNPP414 and VNPP433 as well as VNPT55 suppressed tumor growth, including in treatment-resistant tumors expressing AR-V7 (*preliminary data*).

Market and Applications

PANC is typically fatal, representing the 7th most common cause of death from cancer. Currently there are 4 FDA-approved therapies for its treatment, all chemotherapies. PC is the second most common cancer in men worldwide. There are currently 5 FDA-approved drugs for the treatment of PC but the development of drug resistance is the norm, highlighting an unmet clinical need. Enzalutamide and abiraterone target the androgen receptor and have global sales of over $2 billion each.

Technology Advantages/Status

- Lead compounds targeting protein translation as important new treatment paradigm
- Excellent oral bioavailability and saftety is predicted for lead compounds
- Prostate cancer Rx: Lead compounds show potential as a new class of drugs for CRPC
- Pancreatic cancer Rx: Lead compounds show potential either as monotherapies or in combination with current elective PDAC drugs for the treatment of various forms of pancreatic cancer

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