CDK12-Specific Modulators and Methods for the Treatment of Cancer

INVENTION:
Investigators at Salk have identified a novel protein that binds to the cyclin-dependent kinase CDK12 in a specific manner. This binding partner provides an effective and selective inhibition of CDK12 kinase activity. Identification of the interaction domain between CDK12 and its binding partner allows for the development of CDK12-specific peptomimetics and small molecule inhibitors for use in combating drug resistance and to render cells more sensitive to many types of cancer chemotherapy and immunotherapy.

APPLICATIONS:
Discovery and development of new and improved cancer therapeutics

ADVANTAGES:
Potential to circumvent drug resistance and improve sensitivity to existing cancer therapies

STAGE OF DEVELOPMENT:
Discovery, preclinical in-vitro. Our scientists are interested in collaborations to screen for potential therapeutic agents that target the interaction between CDK12 and its binding partner.

BACKGROUND:
CDK12 is a member of the cyclin-dependent kinase (CDK) protein family. CDK proteins regulate the cell cycle and CDK inhibitors are therefore considered a potential target for anti-cancer agents. A number of CDK inhibitors are currently under investigation by various groups around the world.

CDK12 has an important role in DNA repair and homologous recombination, and thus is directly implicated in enabling cancers to survive exposure to PARP inhibitors, such as camptothecin. Therefore, loss of Cdk12 protein or inactivation of Cdk12 kinase activity leads to genome instability and renders cells more sensitive to genotoxic insults. Several CDK12 targets, including ATR and histones, are involved in multiple DNA repair pathways, including mismatch repair. Importantly, defects in mismatch repair have been found to confer sensitivity of cells to cancer immunotherapy. It is therefore possible that a modulator of CDK12 could help overcome drug resistance to current cancer therapeutic agents.

Salk investigators have also found that Cdk12 cooperates with mTORC1 to phosphorylate 4EBP1 and control translation of target mRNAs, including Chk1, suggesting that that Cdk12 inhibitors could augment the activity of existing mTORC1 and Chk1 inhibitors for a variety of different cancers.

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PATENT STATUS: U.S. patent pending

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