Docket #: S21-113

CDK19-SELECTIVE INHIBITORS, AND METHODS OF USE THEREOF

Technology Reference
CZ Biohub ref. no. CZB-207S
Stanford ref. no. S21-113

Researchers at Stanford have developed compounds that act as potent anti-cancer drugs which selectively inhibit CDK19 over CD8 and promise a greater therapeutic index and reduced systemic toxicity.

Breast cancer remains the leading cause of cancer-related death among women worldwide. Patient mortality rates have been decreasing due to earlier detection methods and screening of genetic biomarkers associated with at-risk populations. However, targeted therapeutic strategies have not advanced to an equal extent, in particular against patients diagnosed with triple-negative breast cancer (TNBC). TNBC is a particularly aggressive and invasive cancer subtype and the only therapeutic intervention available to these patients is chemotherapy, which is known to be non-specific, highly toxic, and therefore limited. In addition, patients diagnosed with TNBC often experience worse survival outcomes than patients with other types of breast cancer.

Cyclin-dependent kinase 19 (CDK19) and a related isoform CDK8 are oncogenic transcription-related kinases that play a role in certain cancers, including TNBC. Compounds that non-selectively inhibit CDK19 and CDK8 have been explored for their anti-cancer properties but have shown to have undesirable side effects due to the CDK8 inhibition, which is more widely-distributed in tissues than CDK19. Therefore, there remains a need for compounds which selectively inhibit CDK19 over CDK8, as well as new methods of treating cancers such as TNBC that comprise administering such compounds.

Stage of Development
Research –

in vitro

Stage of Research
The inventors have developed compounds that are inhibitors of CDK19. Inhibition of CDK19 has been shown to be effective against breast cancer, including TNBC. The disclosed compounds bind to and inhibit the activity of CDK19, and selectively inhibit CDK19 over CDK8, thereby minimizing or avoiding side effects caused by targeting CDK8, for example gastrointestinal side effects.

Applications

- The compounds described herein can be used to inhibit CDK19 activity, and thus can be used to treat conditions mediated by CDK19, such as cancers with aberrant CDK19 activity.
- Suitable cancers which can be treated include but are not limited to breast cancer, prostate cancer, cancer of the gastrointestinal tract, bladder cancer, sarcoma, cervical cancer, esophageal adenocarcinoma, acute myeloid leukemia, melanoma, glioma and ovarian cancer.
- Combination therapy with a compound described herein with another suitable therapeutic agent including chemotherapy, radiation therapy, immunotherapy, surgery and a combination thereof.

Advantages

- The compounds described herein selectively inhibit CDK19 over CDK8. CDK8 is more widespread in the body's tissue and thereby targeting CDK8 causes more unintended side effects.

Patents

- Published Application: WO2023283488A9
- Published Application: 20240351996

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