Docket #: S20-084

CDK19- Selective Inhibitors, and Methods of Use thereof

Researchers at Stanford University have identified new CDK19-selective inhibitors for the treatment of triple negative breast cancer.

Breast cancer remains the leading cause of cancer-related mortality among women worldwide. While early cancer detection methods such as genetic biomarker screening and regular mammograms have significantly reduced breast cancer mortality in resource-rich settings, treatment options have lagged. Triple-negative breast cancer (TNBC) refers to breast cancer that is estrogen receptor (ER), progesterone receptor (PR), and HER2 negative and is known to have significantly worse treatment outcomes than other breast cancer subtypes, reducing median survival time by 13 months. This decreased survival time is in part due to available treatment strategies as TNBC is unable to be treated with target-specific therapies. Subsequently, the only treatment available to TNBC patients are non-specific treatments such as chemotherapy, which is often less effective, highly cytotoxic, and results in long-term sequelae. Cyclin-dependent kinases, specifically CDK19 and its related isoform CDK8, form complexes with other proteins to regulate RNA polymerase association and transcriptional activity. Compounds that inhibit both CDK19 and CDK8 have been of interest in recent years as anti-cancer therapies, including in TNBC. However, these targets have been abandoned due to off-target effects of CDK8 inhibition, likely caused by its wider tissue distribution as compared to CDK19. A compound that selectively inhibits CDK19 while limiting off-target inhibition of CDK8 has not yet been described in the literature. Given the current lack of treatment options, there is an urgent unmet need to investigate potential therapeutic targets for TNBC.

Stage of Development
Research-

in vitro

Stage of Research
The inventors isolated and characterized a number of compounds that selectively inhibit CDK19 over CDK8. These compounds were assayed using FRET displacement to determine CDK19 selectivity indexes (CDK19 IC50 / CD8K IC50). It was determined that many of the isolated compounds had high CDK19 selectivity, with compound A4 performing exceptionally well with a selectivity index of greater than 50. Furthermore, treatment with CDK19-selective inhibitors in an in vitro TNBC cell line resulted in significant cell death, indicating its efficacy in killing TNBC cancer cells. When CDK19-selective inhibitors were incubated with a human fibroblast cell line in vitro, they did not exhibit significant cell death as compared to controls, suggesting that CDK19-selective inhibitors are not broadly cytotoxic. Indeed, when patient-derived TNBC organoids were treated with compound A4 and subsequently allowed to regrow without pharmacological intervention, TNBC cancer cells failed to regrow when compared to organoids treated with a non-selective CDK19/CDK8 inhibitor and DMSO negative controls. Taken together, these studies suggest that CDK19 selective inhibitors described by the inventors are promising therapeutic candidates for TNBC, with compound A4 being especially promising.

Technology Reference
Stanford ref. no. S20-084
CZ Biohub ref. no. CZB-162S

Applications

- Targeted, non-cytotoxic therapeutic for triple negative breast cancer (TNBC)

Advantages

- In vitro studies suggest that these compounds are not broadly cytotoxic
- These compounds are a targeted therapy, which lends to them being a more effective treatment option than non-specific TNBC therapies such as chemotherapy
- The compounds described by the inventors selectively inhibit CDK19 over CDK8, leading to fewer off-target effects

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