New Heterocyclic Scaffold-Based Inhibitors of the Polo-Box Domain of Polo-like Kinase 1 for the Treatment of Cancer

Summary
Researchers at the National Cancer Institute (NCI) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) have developed novel heterocyclic scaffold-based inhibitors of the polo-box domain (PBD) of Polo-like kinase 1 (Plk1). These compounds effectively arrest mitotic progression and cell proliferation in cell-based assays. The National Institutes of Health (NIH) seeks licensing and/or co-development research collaborations to further develop these inhibitors for the treatment of cancer.

NIH Reference Number
E-211-2020

Product Type
- Therapeutics

Keywords
- Polo-Box Domain, PBD, Polo-Like Kinase 1, Plk1, Heterocyclic Scaffold, Triazoloquinazolinone, Mitosis, Cell Cycle, Cancer, Oncology, Prodrugs, Lee

Collaboration Opportunity
This invention is available for licensing and co-development.

Contact
- Michael Pollack
  NCI TTC
  Michael.Pollack@nih.gov (link sends e-mail)

Description of Technology
Polo-like kinase 1 (Plk1), a member of the Polo-like kinase family, plays a critical role in regulating mitosis and cell cycle progression. Aberrant expression of Plk1 has been observed in a variety of human cancers, and it is known to be associated with tumorigenesis as well as poor prognosis in cancer patients. Unlike normal cells, some cancer cells are dependent on augmented Plk1 levels to remain viable and are killed when Plk1 function is attenuated. Although Plk1 has proven to be an attractive target in cancer treatment, currently available Plk1 inhibitors have shown limited efficacy with significant dose-limiting toxicity and non-specificity in various preclinical or clinical trials.
Thus, there remains an unmet need to develop anti-cancer drugs that are highly specific against Plk1 and have better clinical outcomes.

Scientists at the National Institutes of Health have identified a new heterocyclic scaffold with unique structural and chemical features that can be leveraged for anti-Plk1 drug discovery. This triazoloquinazolinone scaffold can be used to synthesize various S-methyl prodrugs that effectively inhibit the functionally essential, polo-box domain (PBD) of Plk1 without affecting its related Plk2 and Plk3 PBDs. These prodrugs effectively arrest mitotic progression and cell proliferation in cell-based assays. Low molecular weight and moderate hydrophobicity of these prodrugs increase their availability in intracellular compartments. Promising chemical features of these compounds could offer a new avenue for developing therapeutics against Plk1-dependent cancers.

The National Institutes of Health is seeking commercial partners to co-develop and/or license this technology.

**Potential Commercial Applications**
- Anticancer therapeutics

**Competitive Advantages**
- Potentially superior toxicity profile while maintaining specificity
- Inhibition of Plk1-driven cellular proliferation
- PBD-directed inhibitors show selectivity advantages over classical inhibitors of Plk1
- Exhibit specific anti-Plk1 PBD activity in both in vitro biochemical and cell-based assays without affecting Plk2 and Plk3 PBDs
- Anticipated not to be chemically reactive unlike many of the current inhibitors of Plk1 PBD that contain electrophilic groups
- Exhibit ≥10-fold higher inhibitory activity than the previously characterized Plk1 PBD-specific phosphopeptide, PLHSpT
- Low molecular weight and moderate hydrophobicity of these molecules increases their anti-cancer activity in intracellular compartments

**Inventor(s)**
Kyung S Lee Ph.D. (NCI), Kenneth A Jacobson Ph.D (NIDDK), Celeste N Alvarez Ph.D (NCI), Jung-Eun Park Ph.D (NCI)

**Development Stage**
- Discovery (Lead Identification)

**Publications**

**Patent Status**
- **U.S. Provisional:** U.S. Provisional Patent Application Number 63/082,813,Filed 24 Sep
2020

**Related Technologies**
- E-181-2009 - Peptide Mimetic Ligands of Polo-like Kinase 1 Polo Box Domain (“Plk1 PBD Portfolio”)
- E-094-2013 - Peptide Mimetic Ligands of Polo-like Kinase 1 Polo Box Domain
- E-186-2015
- E-254-2016
- E-178-2017
- E-179-2017

**Therapeutic Area**
- Cancer/Neoplasm

**Updated**
Sunday, September 11, 2022

**Source URL:** https://techtransfer.cancer.gov/availabletechnologies/e-211-2020