NATIONAL CANCER INSTITUTE
Technology Transfer Center

Peptide Mimetic Ligands of Polo-like Kinase 1 Polo Box Domain ("Plk1 PBD Portfolio")

Summary

Researchers at the National Cancer Institute (NCI) have developed peptidomimetic inhibitors that disrupt Polo-like kinase 1 (Plk1)-mediated protein interactions by targeting polo-box domain (PBD). These compounds are designed to selectively cause mitotic arrest in cancer cells with abnormal Plk1 expression. Researchers seek licensing and/or co-development research collaborations to further develop the inhibitors.

NIH Reference Number

E-181-2009

Product Type

- Therapeutics

Keywords

- Polo-like kinase 1 (Plk1), polo-box domain (PBD), mitosis, peptide inhibitor, Therapeutic, Cancer, Burke

Collaboration Opportunity

This invention is available for licensing and co-development.

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Description of Technology

Polo-like kinase 1 (Plk1) is a critical protein involved in regulation of mitosis, and aberrant expression of this kinase is found in various cancer types. Inhibition of Plk1 is currently being pursued in pre-clinical drug development for novel anti-cancer therapeutics. Plk1 contains an allosteric domain, known as the polo-box domain (PBD), that is responsible for localizing the kinase domain to mitotic structures through protein-protein interactions.

The invention is directed to improved peptidomimetic inhibitors that disrupt Plk1-mediated protein interactions by targeting PBD. These compounds are designed to selectively cause mitotic arrest in cancer cells with abnormal Plk1 expression by inhibiting proper localization of Plk1. In doing so, such ligands could avoid issues of off-target

activity and dose-limiting toxicities that are characteristic of some ATP-competitive kinase inhibitors.

This invention is an improvement and continuation of Dr. Terry Burke's research program centered around PBD inhibition. Related technologies within the "Plk1 PBD" portfolio currently consist of:

(1) E-181-2009;
(2) E-094-2013 "Peptidomimetic antagonists of Plk-1 PBD";
(3) E-186-2015 "Efficient synthesis of 2-amino-3-methyl-4-phosphonobutanoic acid, a phosphatase stable phosphor-amino acid analog";
(4) E-254-2016 (closed) "Fragment-based Optimization of Ligand interactions within a key cryptic binding pocket of Plk1 PBD;
(5) E-178-2017 "Bivalent Ligands of Plk-1 that exhibit Exceptional Affinity"; and
(6) E-179-2017 "Macrocyclic Peptidomimetic of Plk-1 PBD".

Potential Commercial Applications

• Disruption of Plk1-driven cellular proliferation.
• Potential new approach to anticancer therapies.
• May afford complementarity to anticancer treatment when used with Plk1 kinase inhibitors.

Competitive Advantages

• Mechanism of Plk1 down-regulation is different from agents that bind at the Plk1 kinase domain ("classical kinase inhibitors").
• Due to the uniqueness of polo-box domains to the Plk family of kinases, selectivity, PBD-directed inhibitors may afford selectivity advantages over classical kinase inhibitors.
• Among the highest affinity Plk1 PBD-binding ligands known.

Inventor(s)

Terrence Burke Ph.D. (NCI)

Development Stage

• Discovery (Lead Identification)

Publications

Hymel D, et al. Phosphatase-stable phosphoamino acid mimetics that enhance binding affinities with the polo-box domain of polo-like kinase 1. [PMID 27992122]

Zhao XZ, et al. Application of oxime-diversification to optimize ligand interactions within a crytpic pocket of the polo-like kinase 1 polo-box domain. [PMID 27624074]

Zhao XZ, et al. Enhancing polo-like kinase 1 selectivity of polo-box domain-binding peptides, (Symposium in Print on "Bioactive Molecules"). [PMID 28285924]

Patent Status

- **U.S. Patent Filed:** U.S. Patent Application Number , Filed 15 Nov 2011
- **U.S. Patent Filed:** U.S. Patent Application Number US Non-Provisional App. No. 14/111,540, Filed 11 Oct 2013
- **U.S. Patent Filed:** U.S. Patent Application Number US Non-Provisional App. No. 14/776,512, Filed 14 Sep 2015
- **Foreign Filed:** - Patent Application International App. No. PCT/US2015/060629, Filed 13 Nov 2015
- **U.S. Provisional:** U.S. Provisional Patent Application Number US Provisional App. No. 62/520,907, Filed 16 Jun 2017
- **U.S. Provisional:** U.S. Provisional Patent Application Number US Provisional App. No. 62/525,160, Filed 26 Jun 2017

Related Technologies

- 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

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