SELECTIVELY TARGETING POLO-LIKE KINASE 1 (PLK1) USING NOVEL INHIBITORS OF THE POLO-BOX DOMAIN

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ABSTRACT

Polo-like Kinase 1 (PLK1) is a serine/threonine protein kinase that is expressed in dividing cells. It is a widely studied protein that plays an important role in regulating mitotic progression. PLK1 is over-expressed in several tumor types, and studies have shown that down-regulating PLK1 expression inhibits cancer cell proliferation, validating PLK1 as an oncogenic target. Efforts to target this protein therapeutically has led to the development of several ATP-based inhibitors, although these are not exclusively specific. Because other PLK family members are tumor suppressors, it is important that PLK1 inhibitors selectively bind to PLK1 and not the other PLKs, particularly PLK3. Moreover, resistance is always a problem with single agent therapies. PLK1 is comprised of two structural domains, the N-terminus catalytic kinase domain, and the C-terminus polo-box domain (PBD). The PBD is a phospho-peptide binding motif that determines substrate recognition and sub-cellular localization. By targeting the PBD, we can develop selective PLK1 inhibitors to inhibit cancer cell proliferation. REPLACE (Replacement with Partial Ligand Alternatives for Computational Enrichment) uses the structure activity relationships of peptide binding fragments to generate pharmaceutically acceptable lead molecules. We began by replacing the N-terminus tripeptide sequence of known PLK1 substrates like Cdc25C (LLCSpTPNGL) with molecular fragment mimics. This generates partially peptidic compounds termed FLIPs (Fragment Ligated InhibitoryPeptides). FLIPs were analyzed by fluorescence polarization (FP) to determine PLK1 and PLK3 PBD binding. Our most promising FLIPs were analyzed in cellular assays. N-terminal FLIP SAR was also used to develop non-peptidic small
molecules by carrying out a compound library search. This led to the development and characterization of more than 40 small molecules from a lead structure that was tested as part of a structure activity relationship program. In summary, the work described advances our understanding of the binding determinants for the PBD of PLK1 and produced lead molecules worthy of further exploration in their ability to target PLK1 in cancer.