Development of Peptide-Based Cancer Drugs Targeting the Polo-Box Domain of Polo-like Kinase 1

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Polo-like kinase 1 (Plk1) is a master regulator of mitosis through its activation of key proteins that are involved in processes such as spindle fiber assembly and anaphase regulation. Certain types of cancers, including breast and stomach cancers, rely heavily on Plk1 overexpression for their proliferation. Efforts to inhibit the Plk1 active site have focused on the development of small-molecule drugs. However, these drugs are not highly selective and are ineffective in blocking the active site of Plk1, causing unexpected side effects. I synthesized and evaluated novel, highly-selective, and potent peptidomimetics derived from proteins that interact with Plk1, in which the sequence of the peptide drug is derived from known protein-protein interactions. These drugs target the polo-box domain, which is the binding region of Plk1 that regulates kinase activity. My results showed that analogs of three Plk1-binding proteins, Map205, PBIP1, and BUB1, were able to exhibit modest binding activity with Plk1. In addition, I further optimized two highly potent peptides derived from Map205 and PBIP1 that are able to bind to Plk1 with nanomolar affinity. These compounds bound to Plk1 3 to 8 times more effectively than the parent sequence. This optimization is critical for the development of an anti-cancer peptidomimetic drug that can selectively induce mitotic arrest in cancer cells.

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