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Targeting polo-like kinase 1 in cancer therapy

Development of mono-specific anti-cancer therapeutics against important protein kinase targets has long been sought by pharmaceutical and academic laboratories. Until now, the current prevailing strategy of inhibiting the catalytic activity of the kinases has suffered from a high level of cross-reactivity with other unrelated kinases. Protein-protein interaction inhibitors are thought to be highly specific and, therefore, more amenable for combinatorial therapy with less toxicological problems. However, largely due to the difficulty of finding a right target with a small, well-defined, and unique binding cleft has hampered the development of this class of therapeutic agents. Recently, polo-like kinase 1 (Plk1) has been singled out as the only kinase essentially required for the viability of activated Ras or inactivated p53 mutation-bearing cancer cells, but not the respective normal cells. Consistently, Plk1 overexpression has shown to be tightly associated with poor prognosis for various types of cancers in humans. Thus, Plk1 is undoubtedly one of the most attractive anti-cancer drug targets. We have identified a minimal peptide, PLHSpT, which specifically binds to the non-catalytic polo-box domain (PBD) of Plk1 with an unusually high affinity. Inhibition of the PBD function was sufficient to kill cancer cells of diverse origins, but not the respective normal cells. In line with this observation, provision of a novel, non-hydrolysable, phospho-Thr mimetic peptide, PLHS-Pmab, induced mitotic arrest and apoptosis in cancer cells by disrupting the function of Plk1. Currently, we employ both structure-based drug design and novel chemical synthesis methods to generate mono-specific anti-Plk1 therapeutic agent. We use the PLHS-Pmab mimetic peptide as a template and covalently conjugate it with rationally designed chemical moieties to further enhance its binding affinity to the PBD. This work involves both innovative design and synthesis of a wide spectrum of chemical moieties to achieve site-specific chemical properties with distinct biological activities. We believe that this study may likely lead to the generation of a new class of mono-specific anti-Plk1 therapeutic agent that could facilitate a broad range of anti-cancer therapy.

Biography

Dr. Kyung Lee received his Ph.D. in 1994 from the Department of Biochemistry at the Johns Hopkins University in Baltimore. He then worked with Raymond Erikson at Harvard University as a postdoctoral fellow and studied in the fields of cellular proliferation and mitotic controls. In 1998, he joined National Institutes of Health as a tenure-track investigator in the Laboratory of Metabolism at National Cancer Institute. In 2005, Dr. Lee became a senior investigator and head of the Chemistry Section, Laboratory of Metabolism.