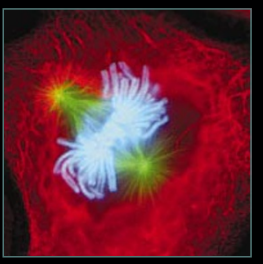
CYTOKINETICS / GlaxoSmithKline

COLLABORATION

Leading the way to the next generation of anti-mitotics

Historical experience has demonstrated that important progress is often made in clinical medicine with the introduction of pharmaceuticals that act by novel mechanisms of action. Such is the case in the area of anti-cancer therapy. Existing anti-mitotics (taxanes and vinca alkaloids) are all directed at tubulin, the intracellular protein that comprises the mitotic spindle, and are perhaps the most clinically and commercially successful anti-cancer agents. Since their introduction 20 years ago, these agents have dramatically advanced cancer patient care and have served as a cornerstone of modern chemotherapy. However, use of these agents can be constrained by dose-limiting toxicities related to the broad role tubulin plays in important cellular processes unrelated to mitosis. In contrast, mitotic kinesins represent a family of newly identified enzymes, each of which appears to perform discrete and non-redundant roles in mitotic spindle formation and function during cell division. Unlike tubulin, mitotic kinesins are expressed only in proliferating cells and appear to play no role outside of mitosis. Inhibition of mitotic kinesins disrupts the cell cycle, thereby inducing apoptosis or cell death. Inhibitors of mitotic kinesins may therefore represent the next generation of anti-mitotics; they target a new set of molecular enzymes specifically involved in the mitotic process, yet within a well-validated area of pharmaceutical development. Because mitotic kinesin inhibitors differ from existing anti-mitotic drugs in their molecular targets and mechanism of action, they are being investigated for their potential therapeutic profile. In April 2002, at the annual meeting of the American Association for Cancer Research, Cytokinetics and GlaxoSmithKline jointly unveiled the results of intensive research efforts in the field of mitotic kinesins, which covered the breadth of anti-tumor activity observed for kinesin spindle protein (KSP) inhibitors in multiple preclinical studies of cancer and demonstrated the absence of neuropathy in animal models. Based on these preclinical findings, Cytokinetics and GlaxoSmithKline initiated a broad-based clinical development program with the first of several anticipated pharmaceutical candidates that are direct inhibitors of mitotic kinesin targets.



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