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C-kit mutants in GISTs and their interaction with STI 571: Insights from computer simulations and clinical trials

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Deregulation of c-kit has been implicated in the etiology of a number of cancers, including gastrointestinal stromal tumors (GISTs). Most of GISTs carry mutations in c-kit, resulting in an enhanced and constitutive ligand-independent tyrosine kinase activity that appears to play a key role in the pathogenesis of these tumors. STI 571 (Glivec®, GleevecTM), a 2-phenylaminopyrimidine derivative, has shown remarkable efficacy in the treatment of GISTs, which are notoriously unresponsive to cancer chemotherapy. In this work we report the results obtained form a combined effort of bringing together clinical evidences on known and newly discovered c-kit mutations in GISTs, the corresponding patients follow up and the structure-activity relationships between the mutated c-kit and STI 571 obtained by detailed molecular modeling.

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