

PROTEIN KINASE INHIBITORS AS ANTILEUKEMIC AGENTS

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The development of selective protein kinase inhibitors that can block or modulate diseases with abnormalities in their signalling pathways is considered a promising approach for drug development. These drug-discovery efforts have generated inhibitors and small molecular weight therapeutics directed against the ATP binding site of various protein kinases which are in various stages of development (up to Phase II/III clinical trials).

Three examples of this type of drug discovery will be discussed, including PKC412, low molecular weight compounds targeting Flt-3, and STI571 (GleevecTM), a promising targeted drug therapy directed towards the Bcr-Abl, Kit and PDGF-R.

Gain of function mutations in the Flt-3 receptor, resulting in the constitutive activation of Flt-3 tyrosine kinase activity, have been found in 35% of patients with acute myeloblastic leukemia (AML). PKC412 has been shown to inhibit the autophosphorylation of constitutively active Flt-3 in Ba/F3 cells which correlated with the inhibition of proliferation and induction of apoptosis without affecting the growth of untransformed Ba/F3 cells, or leukemic cells not expressing mutant Flt-3.

In addition PKC412 was efficacious *in vivo* in Balb/c mice receiving marrow transduced with retrovirus-expressing mutant Flt-3 and which develop myeloproliferative disease that is fatal in 60-90 days. Overall, these results indicate that PKC412 is a potent inhibitor of mutant FLT3 tyrosine kinase activity and is a candidate for testing as an anti-leukemia agent in AML patients with mutant FLT3 receptors.

Based on its clear disease association, the c-Kit and Bcr-Abl tyrosine kinase represents an ideal target for validating the clinical utility of protein kinase inhibitors as a therapeutic agent in GIST and CML, respectively. In fact, STI571 (GleevecTM, a 2-phenyl-aminopyrimidine) has shown impressive clinical haematological/cytogenetic responses in CML and GIST that are driven by cKit. These outstanding clinical efficacy data of STI571 clearly demonstrate the utility and the potential of a targeted therapy by protein kinase inhibition.