

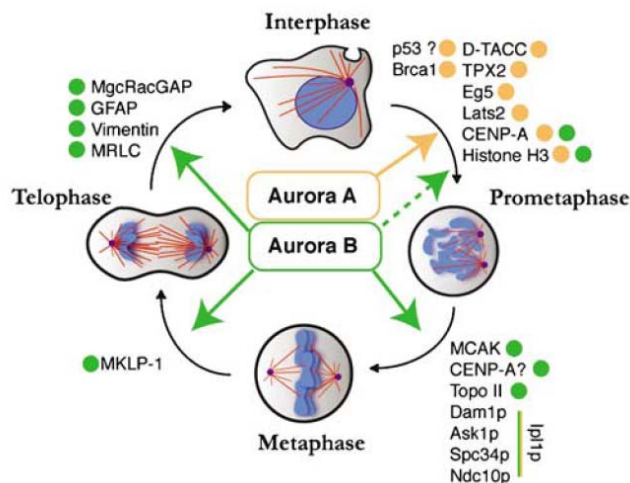
TARGET RATIONALE

A common hallmark of cancer is uncontrolled cell proliferation, and a number of cancer drugs currently used in the clinic target this characteristic by interfering with various phases of the cell division cycle, including DNA synthesis and mitosis. The chemotherapeutics that interfere with mitosis have been exceptionally efficacious, as exemplified by spindle poisons such as taxanes and vinca alkaloids. Thus, disrupting mitosis is a clinically validated approach for developing cancer therapeutics. However, current anti-mitotic drugs are often associated with serious side effects such as myelosuppression and peripheral neuropathy, illuminating a significant medical need for novel anti-mitotic agents.

Aurora kinases are implicated in tumor formation and are important regulators of cell cycle events such as entry into mitosis, centrosome function, spindle formation, chromosome segregation and cytokinesis. A strong case can be made for targeting these kinases as targets for cancer therapy, especially in light of recent identification of novel binding partners, key downstream effectors, and small-molecule inhibitors that display efficacy against tumors.

The vascular endothelial growth factor receptor 2 (VEGFR2) plays a pivotal role in angiogenesis and metastasis. The formation of new blood vessels is necessary for support of primary tumor growth and coincident with the development of metastasis. As a result, inhibition of this receptor's interaction with vascular endothelial growth factor is an attractive strategy for fighting cancer.

Dual inhibitors of these targets can provide a significant advantage in combating cancer by simultaneously attacking both cell replication and the formation of new blood vessels that are necessary for primary tumor growth.



PD Andrews, *Oncogene* (2005) 24, 5005–5015

Aurora Kinase/VEGFR2 Inhibitors Discovered by TRAP®

- Dual kinase inhibitors were discovered using Telik's proprietary drug discovery technology TRAP®.
- We identified novel small-molecule antagonists of human Aurora A, Aurora B and VEGFR2, from which we selected potent leads with IC₅₀ between 1 and 10 nM against Aurora A, Aurora B and VEGFR2 enzymes.
- We confirmed the crystal structure of a compound bound to Aurora A by 2.5 Å x-ray.
- Selected compounds demonstrated inhibition of human cancer cell growth *in vitro*, with IC₅₀ between 15 and 500 nM.
- Experiments showed inhibition of VEGFR2-dependent endothelial cell proliferation *in vitro*, with IC₅₀ below 100 nM.
- We confirmed Aurora-based mechanism of action in cancer cells, including endo-reduplication leading to polyploid cells, apoptosis and inhibition of histone H3 phosphorylation.
- More than 300 compounds based on novel chemotypes were prepared and tested.
- We found two additional chemotypes with nanomolar activity.
- Compounds were optimized for solubility and stability in blood, and we found they inhibited tumor growth *in vivo*.
- We confirmed the mechanism of tumor-growth inhibition in murine models of human cancer.

ACTIVITY PROFILE

In Vitro Activity

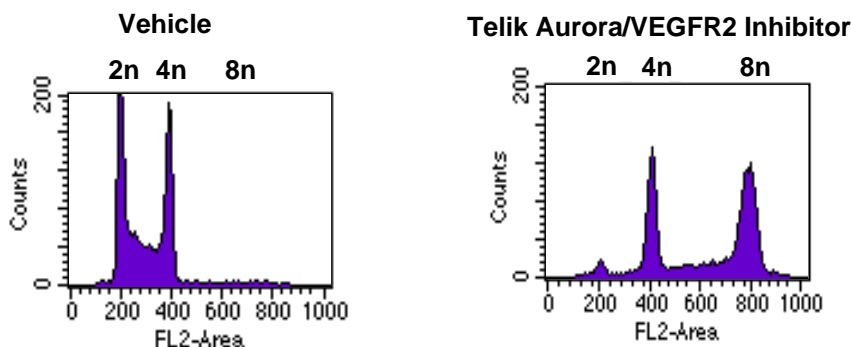
A TRAP[®] screening campaign identified novel classes of inhibitors of human Aurora A, Aurora B and VEGFR2 using fluorescence polarization-based kinase assays with purified recombinant enzymes.

Cellular Activity

Compounds inhibited HCT116 (human colon) and HL60 (human leukemia) cancer-cell growth with IC₅₀ between 15 and 500 nM. Compounds also inhibited growth of other cancer cells, including lung, pancreatic, ovarian and prostate cell lines.

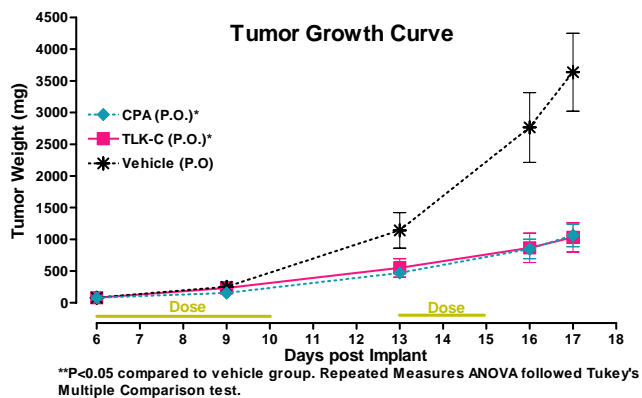
Anti-angiogenic compound activities were observed with IC₅₀ below 100 nM, using VEGF-dependent endothelial cell (HUVEC) proliferation assays.

Aurora-based mechanism of action was confirmed in cancer cells using quantitative immunoblot assays to demonstrate that compounds were potent inhibitors of histone H3 phosphorylation. Cell-cycle analysis, illustrated below, indicated that compounds caused endo-reduplication leading to polyploidy at concentrations of 200-500 nM.



In Vivo Activity

Compounds inhibited the growth of human HCT116 colon and HL60 promyelocytic leukemia cancer xenografts in mice when administered IV, IP or PO. Illustrated below is the result from a representative Telik Aurora/VEGFR2 inhibitor that produced 72% tumor-growth inhibition.



A Telik Aurora/VEGFR2 inhibitor was administered orally once daily for eight days to ten athymic mice bearing HL60 human promyelocytic leukemia cells. No overt toxicity was observed as determined by behavioral changes or significant weight loss.

CONTACT INFORMATION

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