FGFRs in Cancer

The fibroblast growth factor receptor (FGFR1-4) family of tyrosine kinases plays an important role in normal physiological processes, including angiogenesis, wound healing, and regulation of calcium and phosphate metabolism. In addition, dysregulation of FGFR signaling through genetic alterations or altered expression of individual receptors and their ligands has been frequently observed in human tumors. While tyrosine kinase inhibitors (TKIs) with anti-FGFR activity have produced clinical responses in patients whose tumors harbor FGFR alterations, currently available FGFR TKIs inhibit multiple other kinases, including multiple FGFRs. As a result, dose-limiting toxicities have been observed frequently in patients, including hyperphosphatemia, which may arise from the inhibition of FGFR1 in the kidney. These toxicities may be reduced by the availability of pan-FGFR inhibitors. However, the ability to develop inhibitors that spare individual FGFRs has been hampered by the high degree of structural similarity between FGFR1, FGFR2, and FGFR3.

Introduction

Methods

FGFR inhibitors that target select members of the FGFR family will allow for more targeted treatment of cancers harboring distinct FGFR alterations, while improving our understanding of the biology of selective FGFR inhibition. The availability of FGFR inhibitors that target select members of the FGFR family will allow for more targeted treatment of cancers harboring distinct FGFR alterations, while improving our understanding of the biology of selective FGFR inhibition.

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X-ray crystal structures of FGFR

FGFR structures (in order from top): wild-type FGFR1, wild-type FGFR3, R248C FGFR3, G372C FGFR3, and R248C/G372C FGFR3. Residues identical between FGFR1 and 3 are colored purple, residue differences are colored yellow.

The ICS50s for inhibition of the purified FGFR1 and FGFR3 kinase domains were determined at 1mM ATP concentration. Compounds (colored circles) shifted down and to the right are more potent against FGFR3 than FGFR1.

Results

Greater selectivity for FGFR 3 over 1 in enzyme and cell-based assays than pan-FGFR inhibitors

Comparison of in vitro parameters for compound F001 and a pan-FGFR inhibitor (15-A-659) in clinical trials. Selectivity is shown in parentheses as the ratio of IC50s for FGFR1 compared to each indicated kinase.

Each cell line was treated with 10 concentrations of each inhibitor in triplicate for 72 hours, following by DAPI staining and cell counting. The median IC50 for all FGFR2 or 3 mutant cell lines is shown as a green diamond, for FGFR1 mutant cell lines as a blue rectangle, and values for individual FGFR1/2/3 wild-type cell lines as gray circles.

Dose-dependent inhibition of phospho-FGFR and tumor growth in RT112/84 FGFR3-TACC3 xenografts


Blood phosphate levels were determined after 28 days of treatment from the same tumor-bearing mice used for the efficacy analysis.

Summary

We have discovered a novel, potent and selective series of FGFR inhibitors. The activity of a representative compound and that of related analogs in relevant in vitro and in vivo models is presented.