Preclinical evaluation of a novel, selective pan-FGFR kinase inhibitor CPL-304-110 as a potential anticancer targeted therapy

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INTRODUCTION
Fibroblast growth factor receptors (FGFRs) signalling plays an essential role in cancer cell proliferation, progression and angiogenesis. Dysregulated FGFRs function as driving oncogenes in certain tumor types including bladder, gastric, endometrial and lung cancer. Since aberrantly activated FGFRs serve as an oncogenic “driver”, a great number of FGFR inhibitors are currently in clinical development. However, most of them are multikinase inhibitors, which show numerous adverse effects, mostly related with KDR inhibition. Up to date, no selective small-molecule FGFR inhibitor has been approved for clinical use. There is still a niche for the potent compounds with properly balanced selectivity profile.

The aim of this study was to identify an innovative, highly potent pan-FGFR kinase inhibitor with excellent selectivity and high biological activity.

RESULTS

KINASE ACTIVITY AND SELECTIVITY IN VITRO

ACTIVITY WITHIN FGFR KINASE FAMILY

The determination of IC50 for the FGFR family kinases revealed high activity of CPL-304-110.

SELECTIVITY PROFILES

Activity within additional kinases

Among 13 protein kinase representing families of the human kinase, 5 kinases were significantly inhibited by CPL-304-110 at 30 μM by more than 50%, KDR (PDGFR), JAK2, JAK2, JAK2, however, when compared estimated IC50 for KDR, PDGFR, FLT, JAK2 with IC50 for PDGFR, this represents a selectivity of approximately 129, 680, 244, and 2000-fold, respectively.

Panel of 96 kinases

Selectivity of the compound was tested on the panel of 96 selected kinases by DiscoveRx. The activity of kinases was measured in 200 nM concentration of CPL-304-110. Dots represent individual kinase with > 50% inhibition. FGFRs family inhibition is shown in blue.

CPL-304-110 inhibits ERK 1/2 phosphorylation at low nanomolar concentrations in a dose-dependent manner. These results confirm specific inhibition of FGFR pathway.

CONCLUSIONS

A potent and selective compound CPL-304-110 with a novel chemical scaffold has been identified.

CPL-304-110 potently inhibits human FGFR1-3 tyrosine kinase with IC50 values in the low nanomolar range.

Compound shows selectivity over a panel of kinases, including the most structurally related.

CPL-304-110 exhibits inhibitory activity towards the FGFR-mediated pathway in vitro potently reduces cell viability of FGFR-dependent cancer cell lines with selectivity against cell lines with no abnormalities as well as completely abolishes downstream signaling at low nanomolar concentrations.

Oral administration of CPL-304-110 resulted in strong anti-tumor efficacy in FGFR3-dependent xenograft models.

The activity and selectivity of CPL-304-110 in preclinical analysis qualifies it for the consideration as a drug with a wide therapeutic window and limited side effects in clinical use for patients with FGFR aberrations.

IN VIVO EFFICACY

CPL-304-110 suppresses tumor growth of FGFR3-dependent xenograft models

Oral twice-a-day administration of CPL-304-110 inhibits tumor growth of FGFR driven xenograft models. Separation of tumor growth in groups treated with both doses of CPL-304-110, has been observed. The dose-response relationship was notable. The difference in tumor volume between control versus CPL-304-110-treated groups reached statistical significance in third day of treatment. No body weight loss was observed at tested doses data not presented.