Xenograft models for development of new drugs targeting Fibroblast Growth Factor Receptor (FGFR)

Lan Zhang1, Juan Zhang2, Ying Jin3, Guizhong Lu4, Meng Qiao5, Qian Shi1 Cancer Pharmacology, CrownBio Inc., China

Abstract

The fibroblast growth factor receptors (FGFR) are tyrosine kinases that are present in many types of endothelial and tumor cells. There are 4 different fibroblast growth factor receptors (FGFR) in the cell: FGFR1, FGFR2, FGFR3, and FGFR4. The activation of FGFR pathway plays an important role in tumor angiogenesis, tumor growth, survival, as well as migration. Mutation or amplification/overexpression of FGFR has been found in several types of tumors, including breast cancer, bladder cancer, gastric cancer, prostate cancer, colon cancer, multiple myeloma, and non-small cell lung carcinoma. Therefore, targeting FGFRs represents an attractive strategy for development of new cancer therapeutics. However, the lack of suitable models hinders the progress of research on FGFR inhibitors. Here we successfully validate subcutaneous models in several cancer types, in which FGFR is mutant or amplified/overexpressed, such as breast cancer MDA-MB-134 (FGFR1 amplification), gastric cancer SNU-16 (FGFR2 amplification), endometrial cancer AN3CA (FGFR2 N549K310R mutation), bladder cancer RT-4 (FGFR3 overexpression) and RT-112 (FGFR3 overexpression), lung cancer NCI-H1581 (FGFR1 amplification), as well as human derived gastric cancer GA114 (FGFR2 amplification). In conclusion, the validated cell line derived (CDX) and patient derived xenograft models (PDX) in several cancer types provide valuable platforms for the development of new compounds targeting FGFRs.

Materials and Methods

Animals: NOD/SCID and BALB/c nude mice purchased from Beijing HFK Bio-Technology Co. Ltd. (HFK, Beijing, China) and Shanghai Laboratory Animal Center (SLAC, Shanghai, China).

Tumor Inoculation: For subcutaneous human xenograft models, each mouse was inoculated at the right flank with tumor cells for tumor development.

Group and Treatment: The treatments for the therapeutic study were started when mean tumor size reached 150-200 mm³ in subcutaneous model.

Endpoints: Tumor volume was calculated as the formula: V (mm³) = (a x b²) / 2, where a and b were the long and short diameters of the tumor, respectively.

Statistical Analysis: For comparison between two groups, an independent sample t-test were used. For comparison among three or more groups, a one-way ANOVA was performed followed by multiple comparison procedures. All data were analyzed using SPSS 18.0. p < 0.05 was considered to be statistically significant.

References


Contact information:
Dr. Juan Zhang, zhangjuan@crownbio.com; Dr. Qian Shi, shiqian@crownbio.com

Conclusion

In conclusion, we have established several FGFR targeted CDX and PrimeXeno models, including FGFR1 and FGFR2 amplification and FGFR2 mutation.