FGFR Cell Lines: A Comprehensive Approach to Drug Discovery and Evaluation, from Small Molecules to Biologics, Covering Binding to Activation

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Abstract

Fibroblast growth factors (FGFs) bind to their receptors (fibroblast growth factor receptors, FGFRs), activating downstream signaling pathways, which play crucial roles in both mitogenic processes, such as embryogenesis and growth, and non-mitogenic processes, such as neuroregulation and metabolic regulation. FGFRs primarily consist of four subtypes: FGFR1, FGFR2, FGFR3, and FGFR4. Abnormalities like high expression or mutations in these receptors can lead to the aberrant activation of their signaling pathways, resulting in tumorigenesis. Consequently, targeting FGFR is a promising strategy for cancer therapy. Current FGFR-targeting drugs, either in clinical use or under development, include small molecule inhibitors, antibodies, antibody-drug conjugates (ADCs), CAR-T therapies, and soluble FGFR receptors. Different cell models are required for efficacy evaluation of various drug types.

Kyinno has developed a comprehensive series of FGFR-related cell lines, which include Ba/F3 kinase cells, FGFR overexpression cells, knockout cells, and reporter cells. Among these, Ba/F3 cells have been meticulously engineered to depend on various FGFR point mutations and fusion mutations for survival, showcasing robust capabilities in evaluating FGFR small molecule inhibitors. The FGFR overexpression and knockout cells are crucial for assessing antibody binding, ADC drug endocytosis, and certain radioimmuno conjugates (RICs). Reporter cells, designed based on FGFR downstream signaling pathways, cover a spectrum of wild-type and point-mutated FGFR subtypes, thus effectively evaluating the impact of drugs on downstream signaling pathways. This strategic array of cell models collectively enhances the development and validation of FGFR-targeted therapies, providing invaluable insights and tools for advancing cancer treatment research. By leveraging these diverse cell models, researchers can better understand the mechanisms of FGFR-targeted interventions, ultimately contributing to more effective therapeutic strategies.

Ba/F3 Cell Lines for Small Molecule Inhibitor Evaluation

Cell ID	Cell Name	Compound IC_{50} (nm)	
		BGJ-398	TAS120
KC-2001	Ba/F3-BCR-FGFR1	30.598	5.591
KC-2002	Ba/F3-FGFR1-TACC1-M532I	3.548	1

Table 1: IC_{50} for BGJ-398 and TAS120 in FGFR1 cell lines

Cell ID	Cell Name	Compound IC_{50} (nm)	
		BGJ-398	TAS120
KC-3480	Ba/F3-FGFR2-C382R	1874	10000
KC-2654	Ba/F3-FGFR2-C491S	1324.58	10000
KC-1380	Ba/F3-FGFR2-BICC1	6.3	0.85
KC-3863	Ba/F3-FGFR2-BICC1-M537L	2710	10000
KC-1653	Ba/F3-FGFR2-BICC1-N549K	99.3	9.3
KC-1745	Ba/F3-FGFR2-BICC1-N549H	44	TBD
KC-3150	Ba/F3-FGFR2-BICC1-N549D	113	5
KC-3155	Ba/F3-FGFR2-BICC1-N549T	20	8
KC-3215	Ba/F3-FGFR2-BICC1-L550F	13	4
KC-3133	Ba/F3-FGFR2-BICC1-V562L	23	3
KC-3646	Ba/F3-FGFR2-BICC1-V564I	1211	8
KC-3781	Ba/F3-FGFR2-BICC1-V564L	1290	32

Cell ID	Cell Name	Compound IC_{50} (nm)	
		BGJ-398	TAS120
KC-1654	Ba/F3-FGFR2-BICC1-V564F	1000	56.7
KC-1655	Ba/F3-FGFR2-BICC1-E565A	33.4	6.6
KC-1656	Ba/F3-FGFR2-BICC1-E565G	20.5	2.7
KC-1657	Ba/F3-FGFR2-BICC1-L617M	45.4	2.9
KC-1671	Ba/F3-FGFR2-BICC1-L617V	51.5	1.4
KC-3160	Ba/F3-FGFR2-BICC1-D650Y	8	2
KC-3131	Ba/F3-FGFR2-BICC1-N652S	5	1
KC-1658	Ba/F3-FGFR2-BICC1-K659N	10.7	1.1
KC-3132	Ba/F3-FGFR2-BICC1-K659Q	13	1
KC-2914	Ba/F3-FGFR2-BICC1-H682L	21	0.3
KC-2913	Ba/F3-FGFR2-BICC1-K714R	11	3
KC-3644	Ba/F3-FGFR2-BICC1-Q746L	6683	8982
KC-2420	Ba/F3-FGFR2-BICC1-C491F-V679I	5.5	TBD
KC-3485	Ba/F3-FGFR2-BICC1-M535I-Q746L	7	1
KC-3129	Ba/F3-FGFR2-BICC1-N549K-V564L	985	91
KC-3130	Ba/F3-FGFR2-BICC1-N549H-V564L	1253	168
KC-3399	Ba/F3-FGFR2-BICC1-N549H-V564F	2593	1474
KC-1703	Ba/F3-FGFR2-BICC1-K659N-K714R	5.8	TBD

Table 2: IC_{50} for BGJ-398 and TAS120 in FGFR2 cell lines

Cell ID	Cell Name	Compound IC_{50} (nm)	
		BGJ-398	TAS120
KC-2928	Ba/F3-FGFR3-S249C	1201	10000
KC-3556	Ba/F3-FGFR3-G375C	1180	1988
KC-3128	Ba/F3-FGFR3-V555M	786	10000
KC-3373	Ba/F3-FGFR3-S249C-V555M	494	299
KC-2517	Ba/F3-FGFR3-BAIAP2L1	4	0.34
KC-2562	Ba/F3-ETV6-FGFR3	10	0.25
KC-3550	Ba/F3-FGFR3-TACC3-G370C	27	7
KC-2480	Ba/F3-FGFR3-TACC3-G380R	8	4
KC-2563	Ba/F3-FGFR3-TACC3-N540K	239.2	26.7
KC-1297	Ba/F3-FGFR3-TACC3-V555L	592	TBD
KC-2462	Ba/F3-FGFR3-TACC3-V555M	1215	3400
KC-2735	Ba/F3-FGFR3-TACC3-D576Y	49	10
KC-2564	Ba/F3-FGFR3-TACC3-L608V	41.64	10.53
KC-2458	Ba/F3-FGFR3-TACC3-K650E	11	4
KC-2871	Ba/F3-FGFR3-TACC3-K650N	9	3
KC-2846	Ba/F3-FGFR3-TACC3-R669G	7	5
KC-2918	Ba/F3-FGFR3-TACC3-G697C	998	5752
KC-3534	Ba/F3-FGFR3-TACC3-G375C-V555L	1589	61

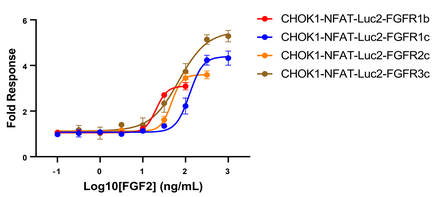
Table 3: IC_{50} for BGJ-398 and TAS120 in FGFR3 cell lines

Cell ID	Cell Name	Compound IC_{50} (nm)	
		BGJ-398	TAS120
KC-1280	Ba/F3-FGFR4-N535K	1399	219
KC-1244	Ba/F3-ETV6-FGFR4	89.84	TBD
KC-1777	Ba/F3-ETV6-FGFR4-C477A	207	TBD
KC-1961	Ba/F3-ETV6-FGFR4-C477S	91	3396
KC-1245	Ba/F3-ETV6-FGFR4-N535D	2430.36	TBD
KC-1333	Ba/F3 ETV6-FGFR4-N535K	10000	288
KC-1246	Ba/F3-ETV6-FGFR4-V550L	3171.13	TBD
KC-1776	Ba/F3-ETV6-FGFR4-C552S	681	TBD

Table 4: IC_{50} for BGJ-398 and TAS120 in FGFR4 cell lines

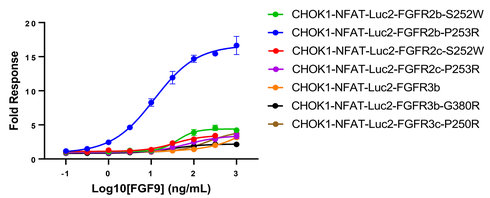
1 10000 (nM)

Reporter Cell Lines for Signaling Pathway Evaluation



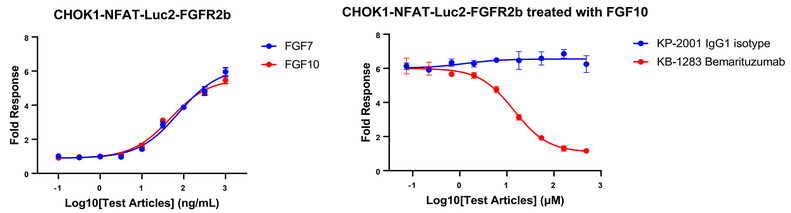
Cell Line	FGF2 EC_{50} (ng/mL)
CHOK1-NFAT-Luc2-FGFR1b	21
CHOK1-NFAT-Luc2-FGFR1c	124
CHOK1-NFAT-Luc2-FGFR2c	47
CHOK1-NFAT-Luc2-FGFR3c	69

Figure 1: FGFRs' reporter cell lines respond to FGF2



Cell Line	FGF9 EC_{50} (ng/mL)
CHOK1-NFAT-Luc2-FGFR2b-S252W	41
CHOK1-NFAT-Luc2-FGFR2b-P253R	12
CHOK1-NFAT-Luc2-FGFR2c-S252W	35
CHOK1-NFAT-Luc2-FGFR2c-P253R	71
CHOK1-NFAT-Luc2-FGFR3b	NA
CHOK1-NFAT-Luc2-FGFR3b-G380R	30
CHOK1-NFAT-Luc2-FGFR3c-P250R	211

Figure 2: FGFRs' reporter cell lines respond to FGF9



Cell Line	EC_{50} (ng/mL)	
	FGF7	FGF10
CHOK1-NFAT-Luc2-FGFR2b	75	48

Figure 3: FGFR2b reporter cell line activated by FGF7 and FGF10, and blocked by Bemarituzumab

In vivo model for FGFR cell lines

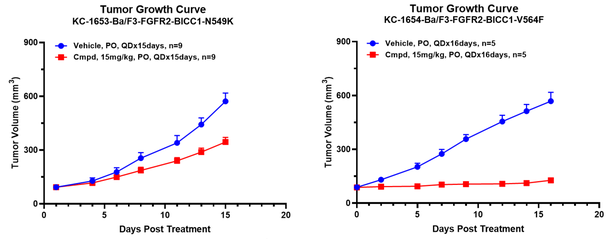


Figure 4: In vivo models for Ba/F3 cell lines to evaluate small molecule efficacy

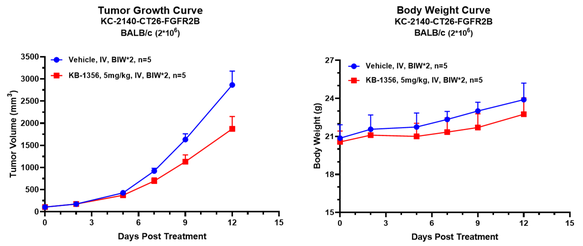


Figure 4: In vivo models for overexpression cell lines to evaluate antibody efficacy

Conclusion

- Kyinno has constructed comprehensive FGFR-related cell lines, including Ba/F3 cell panel, overexpression cell lines and reporter cell lines.
- These cell models can be utilized to accurately evaluate the activation of FGFR signaling pathway, in *in vitro* efficacy of small molecules and biologics, and the establishment of *in vivo* models.

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