TYRA-430: First reversible FGFR4/3 inhibitor designed to overcome current challenges in FGF19-driven hepatocellular carcinoma treatment

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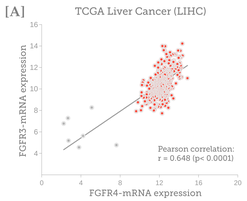
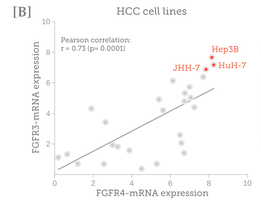
Unmet need, unfulfilled promise

Liver cancer is the third leading cause of cancer related mortality worldwide (Bray et al). Abnormal activation of fibroblast growth factor 19 (FGF19) has been implicated as an oncogenic driver in a subset (~30%) of hepatocellular carcinoma (HCC). In this subtype, excessive FGF19 is thought to over-activate the receptor tyrosine kinase FGFR4 thus driving cancer cell proliferation, survival, and resistance to apoptosis. This hypothesis led to the development of highly specific covalent inhibitors of FGFR4 which target a unique cysteine (C552) not present in the FGFR1-3 isoforms. Based on this idea, two covalent inhibitors entered the clinic and while they performed better in FGF19+ patients than FGF19– patients, overall response rates (ORR) in FGF19+ patients were modest, ~17% ORR, 3.3 mos. PFS for fisogatinib (BLU-554) (Kim et al) and ~21% ORR for roblitinib (FGF401) (Chan et al). These results suggest that signaling through the FGF19/FGFR4 axis is not the complete story.

The role of FGFR3 was unrecognized

Expression data from HCC patients and liver cancer cell lines indicate a strong correlation between FGFR3 and FGFR4. This suggested the possibility that FGFR3 plays a role in driving disease progression in addition to FGFR4 that was previously unrecognized. Indeed, Tao et al (2022) showed through biochemical and genetic approaches that inactivation of FGFR3 and FGFR4 together or that inactivation of the co-receptor Klotho beta which is used by FGFR3 and FGFR4 were both more effective in prohibiting FGF19+ cancer cell growth than FGFR4 inactivation alone.

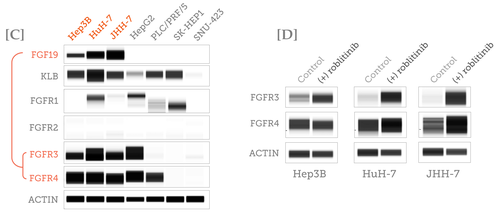




FGFR3 and FGFR4 are highly expressed and correlated in HCC.

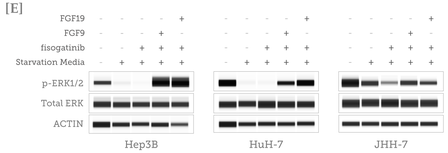
Significant correlation was observed between FGFR3 and FGFR4 in liver cancer patients [A] and HCC cell lines [B].

Sources: TCGA and DepMap Portal



FGFR3 serves as a possible bypass route for FGFR4

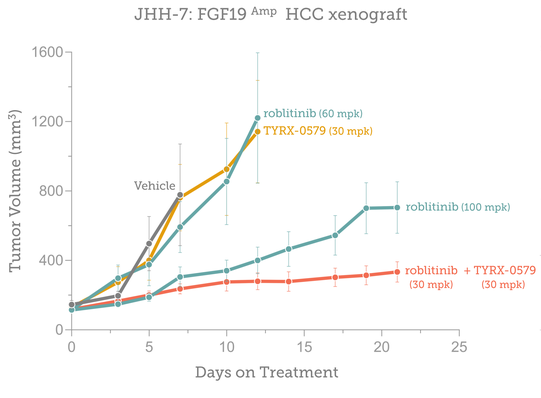
In FGF19^{Amp} HCC cell lines, western blot confirmed that both FGFR3 and FGFR4 are highly expressed [C]. In addition, FGFR3 is upregulated in response to FGFR4 inhibition in FGF19^{Amp} HCC cell lines [D]



FGF19 can signal via FGFR3

In FGFR4-silenced Hep3B, HuH-7, and JHH-7 cells, stimulation with FGF9 (an FGFR3-specific ligand) or FGF19 followed by ERK activation analysis confirmed that FGF19 can activate FGFR3 [E].

Efficacy increases synergistically when both FGFR3 and FGFR4 are inhibited



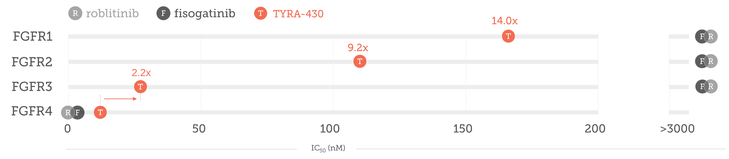
FGFR3 inhibition can synergistically potentiate the activity of FGFR4-selective TKI against FGF19^{+} HCC

FGF19^{Amp} JHH-7 xenograft harboring mice that received the combination of roblitinib and TYRX-0579 (FGFR3-biased inhibitor) showed significant tumor regression compared to those treated with either drug alone. Mice were treated with roblitinib alone (60 mpk BID or 100 mpk BID), TYRX-0579 (30 mpk QD), or a combination of roblitinib (30 mpk BID) and TYRX-0579 (30 mpk QD).

	roblitinib	TYRX-0579
FGFR1 Kd	3000	44
FGFR2 Kd	3000	11
FGFR3 Kd	3000	2.6
FGFR4 Kd	2.3	17

TYRX-0579 is an FGFR3 biased TKI

FGFR3 and FGFR4 inhibition can be combined into one molecule: TYRA-430



TYRA-430 shows biased selectivity for FGFR4 and FGFR3 over other FGFR isoforms in *in vitro* Ba/F3 Cellular IC50 (nM).

References

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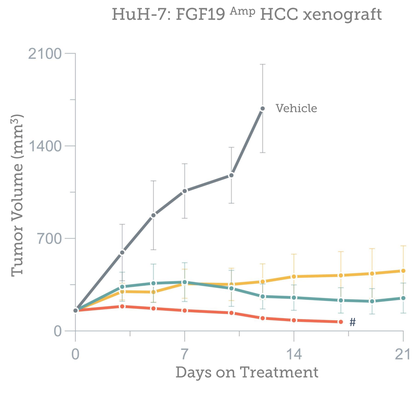
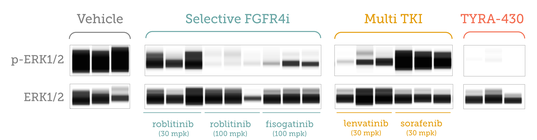
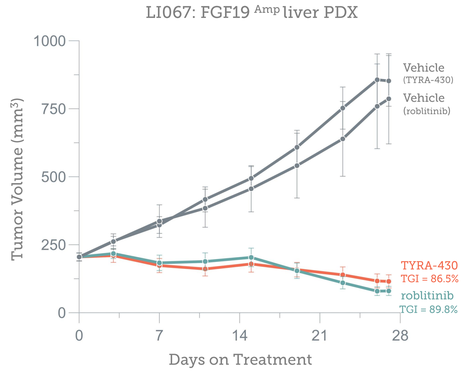
TYRA-430 demonstrates efficacy in multiple xenograft models



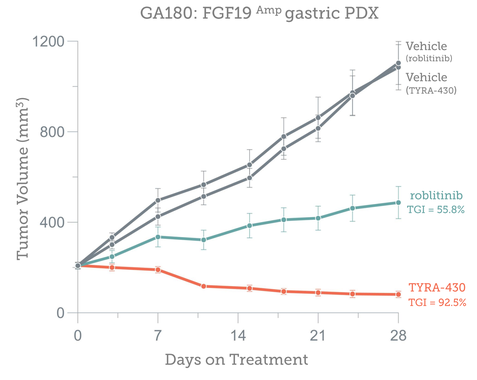


Nude mice harboring HuH-7 xenografts were treated for 3 days with either vehicle (0.5% methylcellulose/0.5% tween80), roblitinib (30 mpk BID or 100 mpk BID), fisogatinib (100 mpk BID), lenvatinib (30 mpk QD), sorafenib (30 mpk QD), or TYRA-430 (25 mpk BID). Tumors were collected, homogenized in lysis buffer, and protein lysates were used to detect p-ERK1/2 as a readout for FGFR signaling using automated western blotting (Jess), shown above.

The regression of HuH-7 xenograft in response to treatment with lenvatinib (30 mpk QD), roblitinib (100 mpk BID), and TYRA-430 (25 mpk BID) and the resulting tumor growth inhibition is shown to the left. TGI was calculated on Day 12 due to the vehicle group tumor volume cutoff attrition.
TYRA-430 group was stopped early due to compound availability.



LI067 (FGF19+ liver cancer) PDX study performed at GenenDesign (Shanghai). TYRA-430 25 mpk BID; roblitinib 100 mpk BID.



GA180 (FGF19+ gastric cancer) PDX study performed at GenenDesign (Shanghai). TYRA-430 25 mpk BID; roblitinib 100 mpk BID.

Into the clinic

TYRA-430 was designed as an oral, reversible small molecule inhibitor to target both FGFR4 and FGFR3, which may overcome limitations of the earlier covalent FGFR4 inhibitors. It is highly potent against FGFR4, but its additional potency against FGFR3 aims to address the previously unrecognized role of FGFR3 in hepatocyte biology, which may limit the effectiveness of first-generation FGFR4 inhibitors.

The Phase 1 clinical study (SURF431) will evaluate TYRA-430 in patients with advanced hepatocellular carcinoma (HCC) and other solid tumors with FGF/FGFR pathway abnormalities.