Factor Quinolinone Inhibitors of TFCP2, an Oncogene in Cancer

Boston University

1 May 2023

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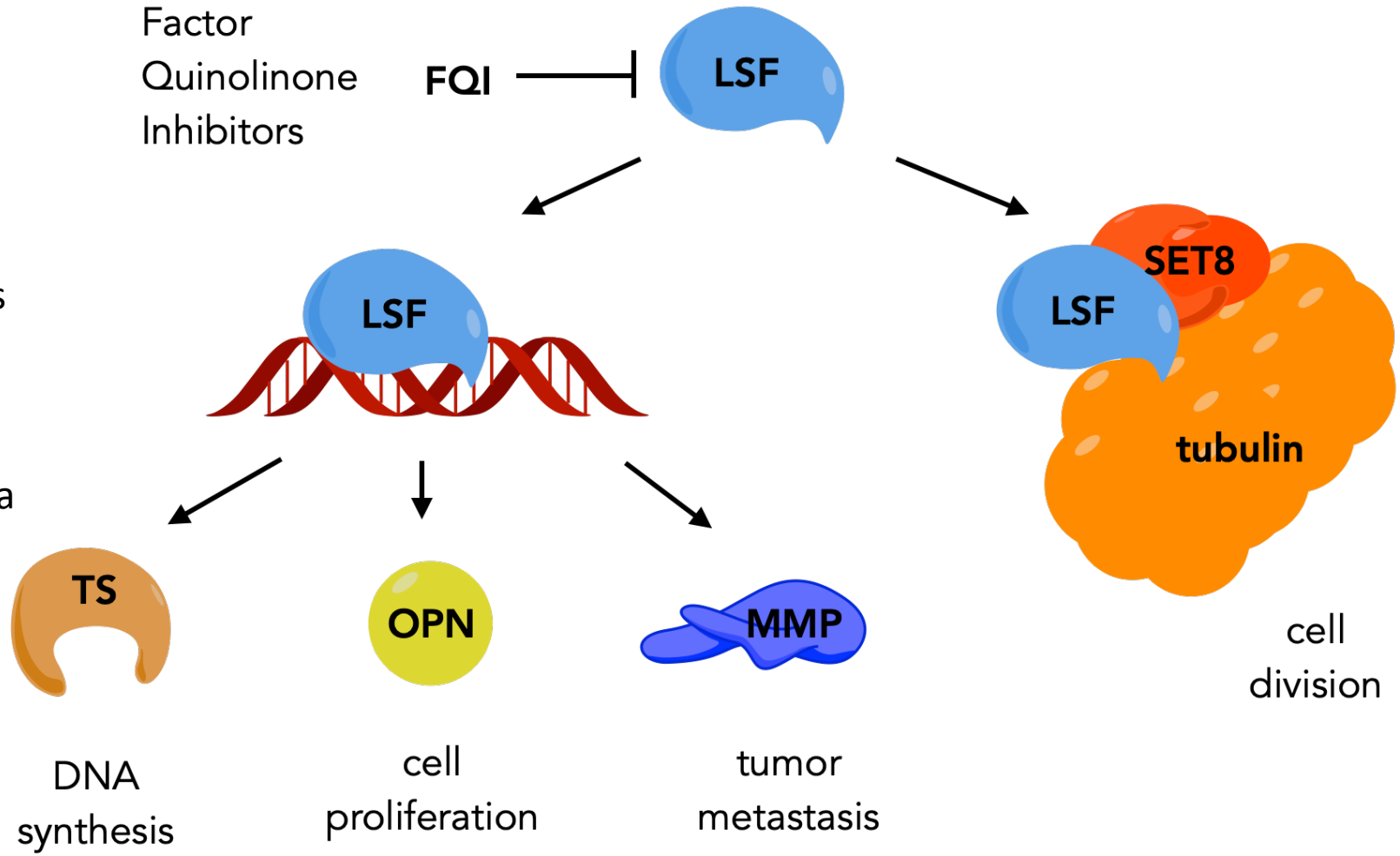
Factor Quinolinone Inhibitors (FQI) of TFCP2

- TFCP2 (LSF) is a transcription factor that functions as an oncogene in aggressive liver cancers
- TFCP2 also has important roles in colorectal cancer and pancreatic cancer cell biology
- Compounds that target TFCP2 significantly inhibit cancer cell proliferation and in vivo tumor cell growth
- The FQI compound class currently has 6 lead compounds covered by 5 granted patents
- Oral formulation of lead FQI compound results in significant in vivo inhibition of liver cancer and colorectal cancer tumor growth
- Compounds are well tolerated with minimal to no toxic side effects

TFCP2 (LSF) and Liver Cancer Cell Growth

TFCP2 (Late SV40 Factor, LSF) is a transcription factor that functions as an oncogene in aggressive liver cancers. As as transcription factor it controls the expression of genes necessary for cell growth, replication, and metastasis. LSF also has an important role in cell division by interaction with SET8, a methyltranferase involved in tubulin polymerization.



Schaus, Hansen & Sarkar, *J Am Cancer Res* **2012**, 269.
Chin, Schaus & Hansen, *J Biol Chem* **2020**, *295*, 4748.

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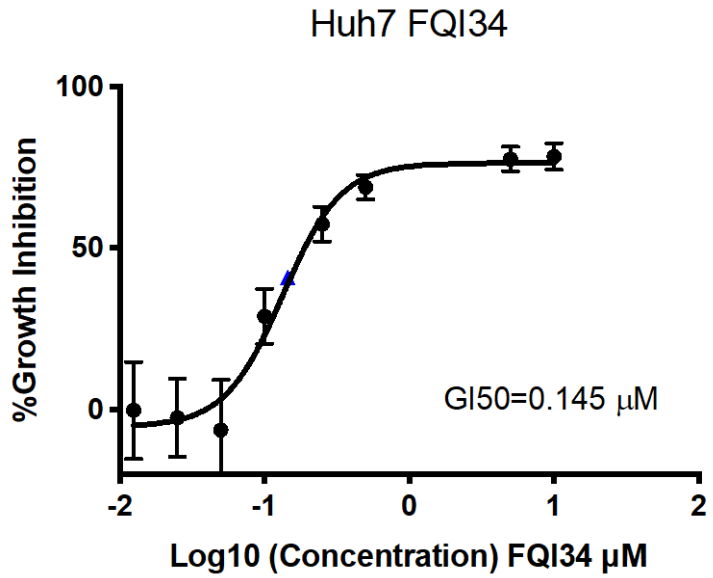
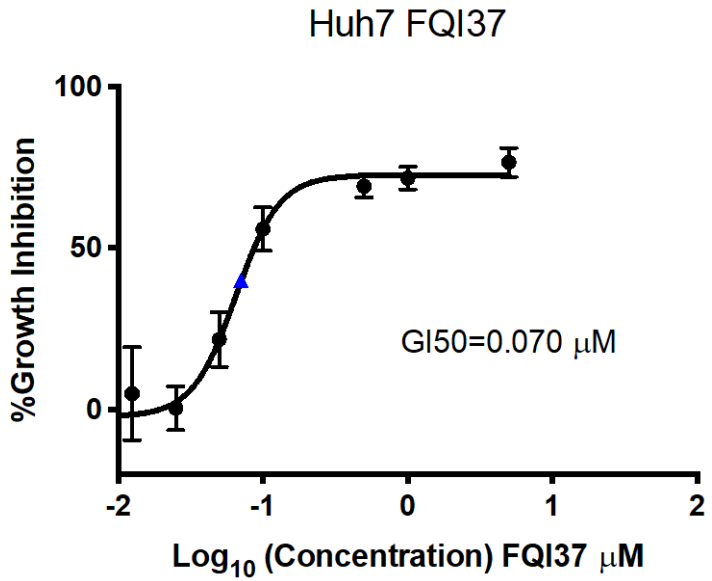
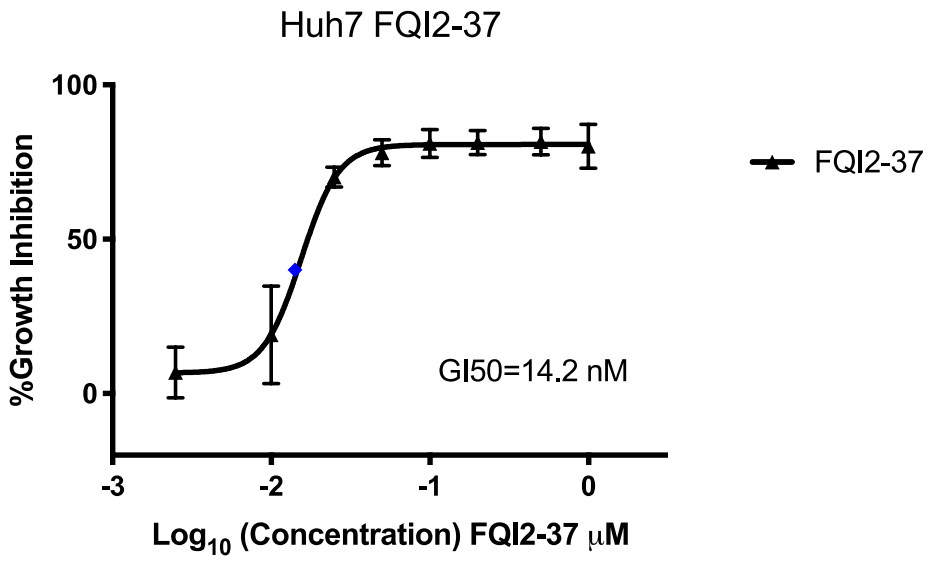
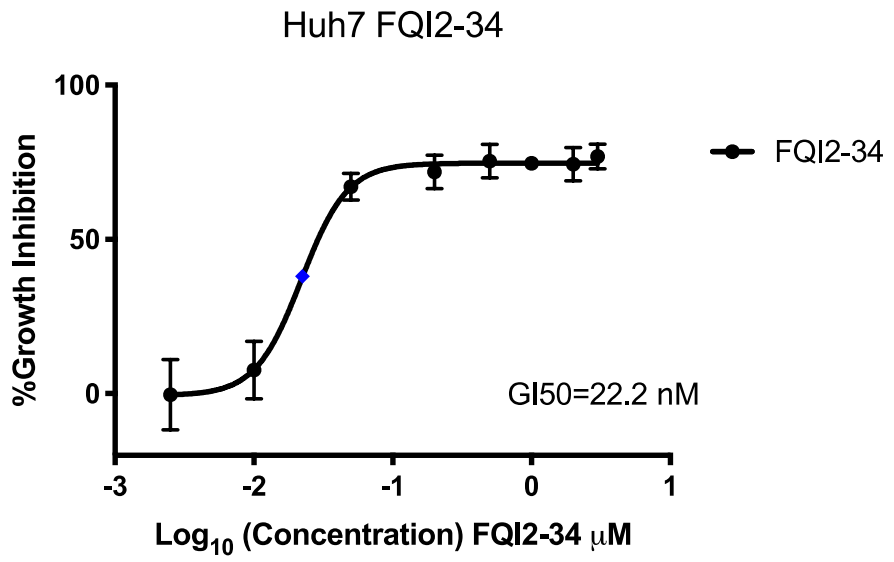
FQIs Inhibit Liver Cancer Cell Growth at nM Concentrations

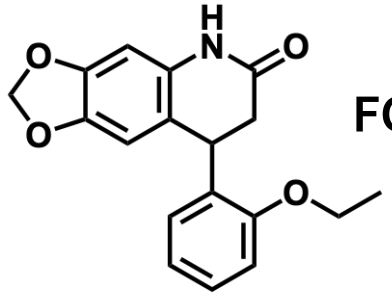






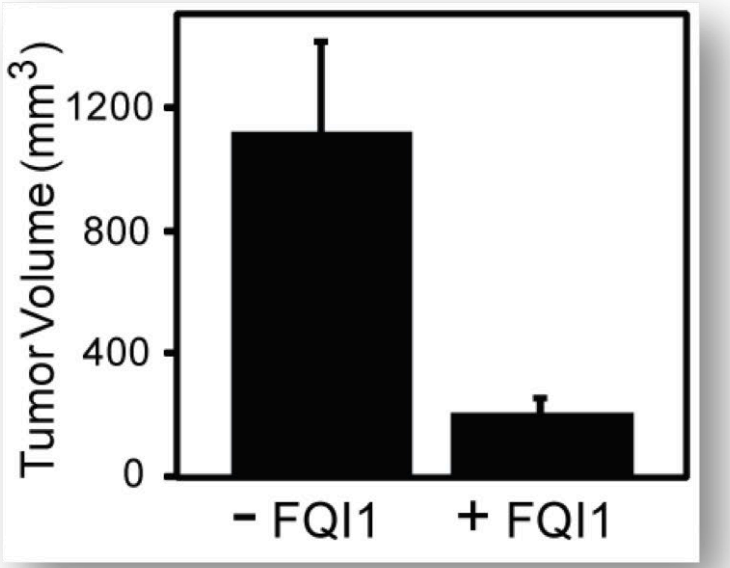


In vivo Tumor Reduction



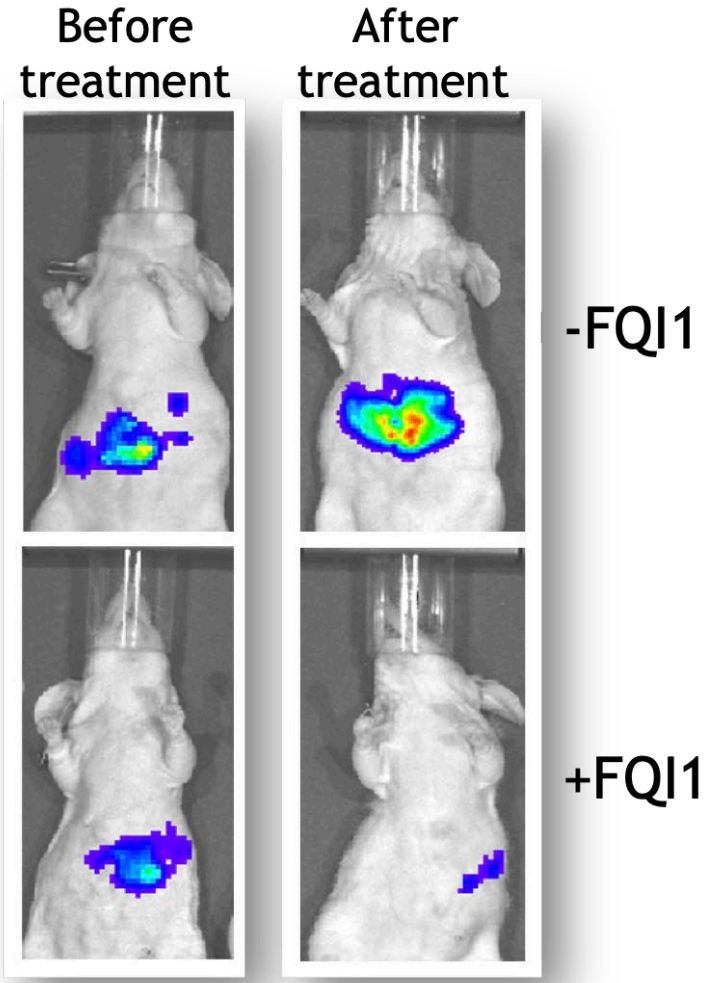
FQI1

xenograft model



2 mg/kg I.P.
2 weeks, treat on 3rd day
followed by 2 weeks no treatment

orthotopic



PNAS **2012** *109*, 4503.

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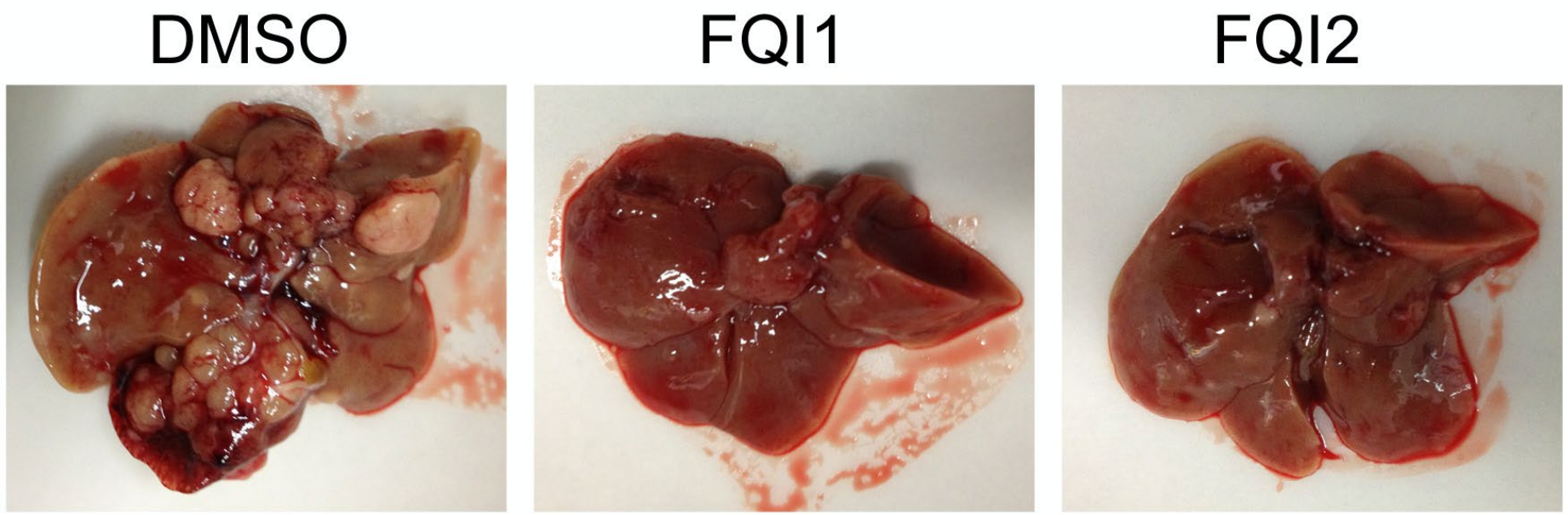
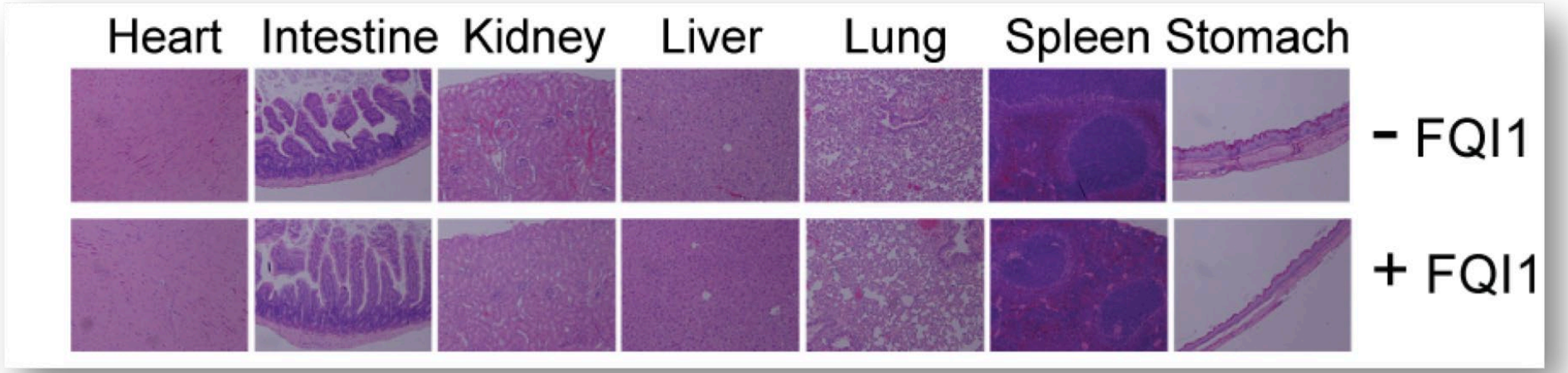
FQI2 Endogenous Liver Cancer Mouse Model

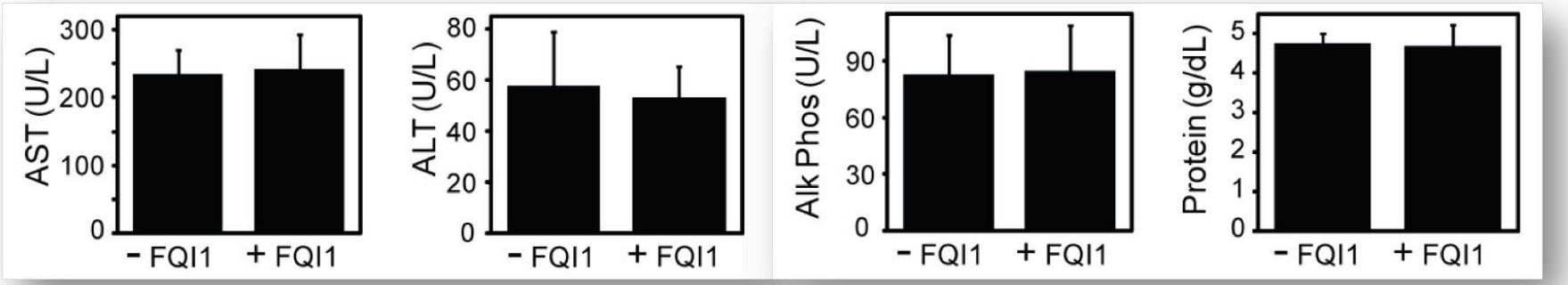


- Transgenic Alb/c-myc mice treated with liver carcinogen DEN
- Treated with DMSO, FQI1 or FQI2 (4 mg/kg) i.p. injection
- Three cycles of treatment (5 injections per week per cycle) over 6 weeks
- Sacrificed 2 weeks after the last injection

Schaus, Hansen, & Sarkar *Oncotarget* **2015** *6*, 26266.

No observed toxicity in mouse models





FQIs are tolerated up to 50 mg/kg in rats administered by IV

PNAS **2012** *109*, 4503.

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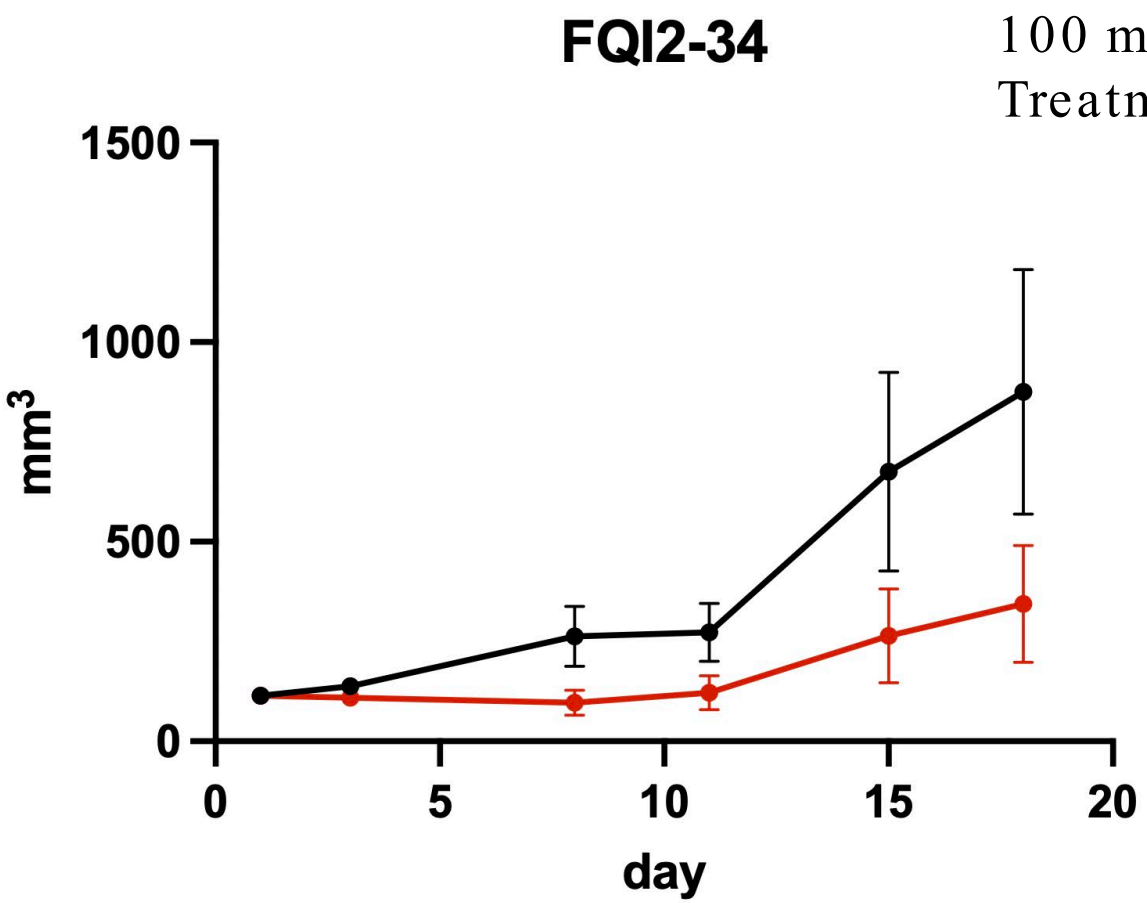
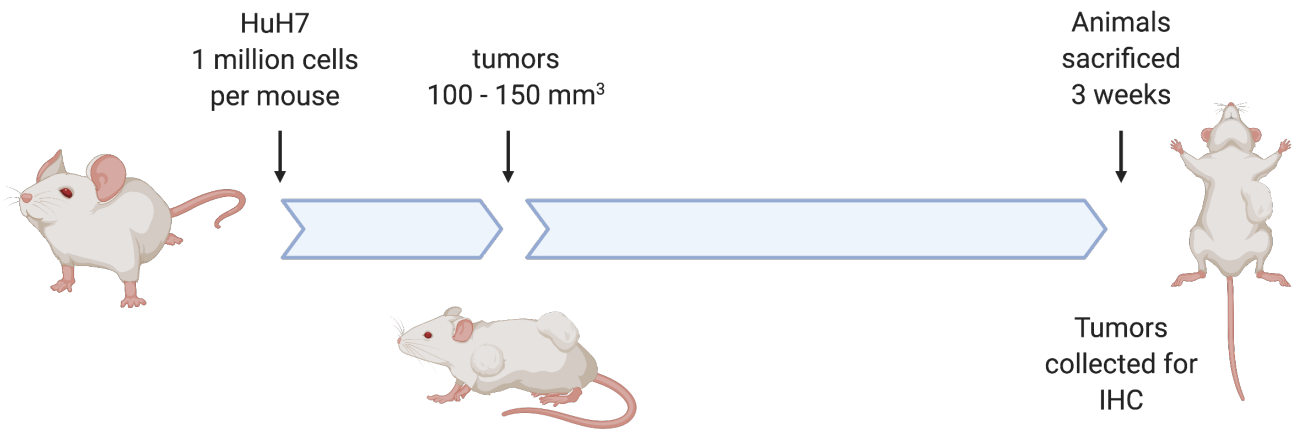
Oral Efficacy of FQIs in Liver Cancer Tumor Model

HuH7 tumor xenografts
100 mg/kg PO
Treatment once a day, daily administration





60% tumor reduction at 100 mg/kg PO

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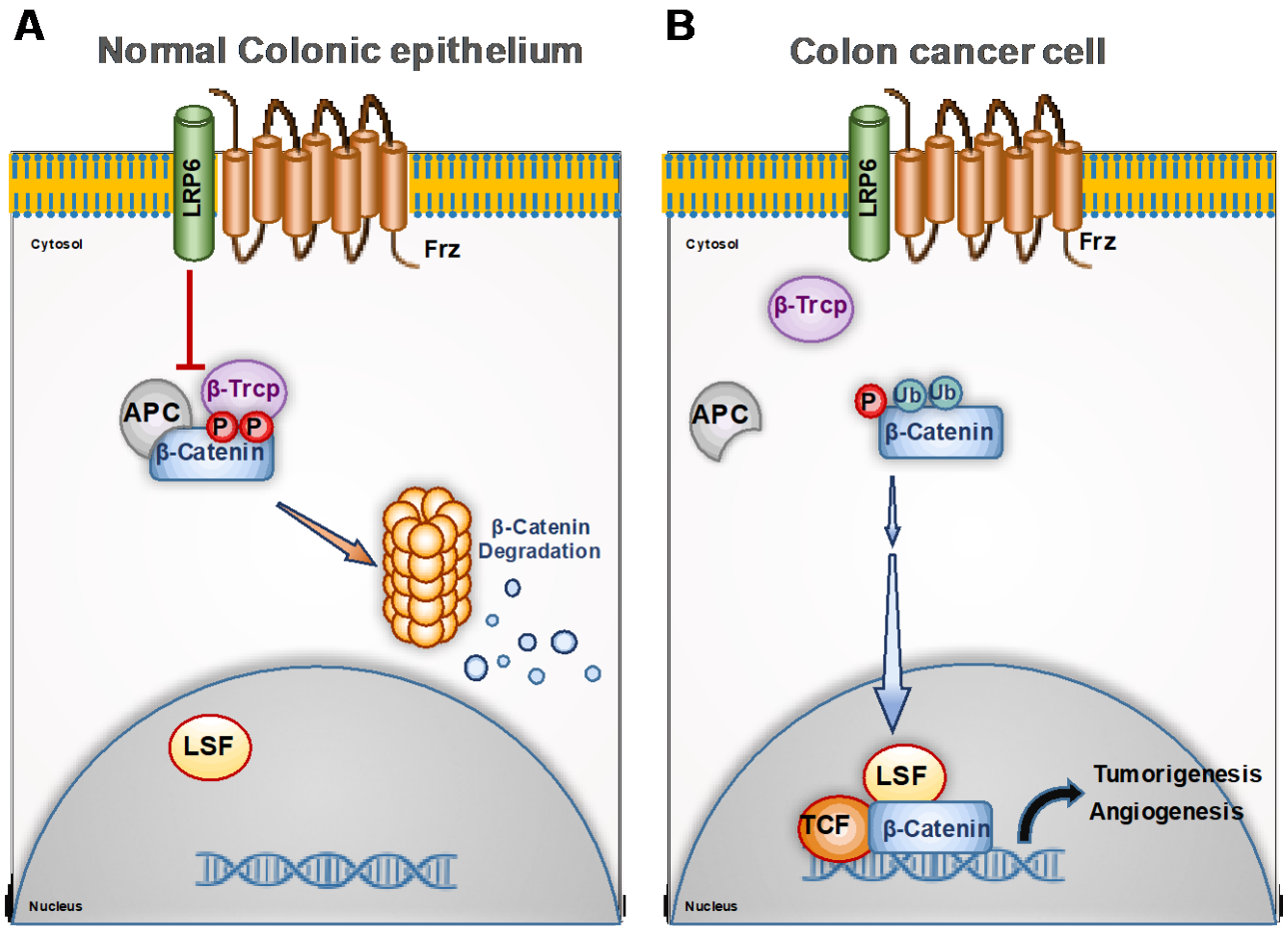
TFCP2 (LSF) Role in Wnt/β-catenin Pathway in Colorectal Cancer

- CRC patients often carry a loss-of-function mutation in APC as well as aberrant activation of the Wnt/β-catenin pathway in colonic epithelium
- LSF was recently described to be an interactor of β-catenin and enhancer of Wnt activity
- LSF can complex with β-catenin to enhance its interaction with TCF4 and enhance Wnt signaling and in our findings, FQIs inhibited Wnt activity in CRC cell lines



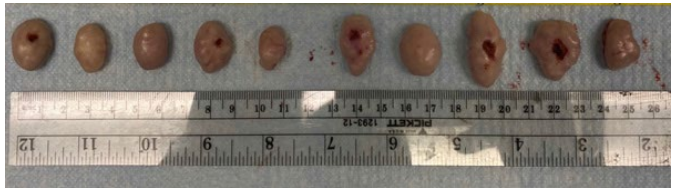
Model of Wnt activation in CRC cell and LSF augmenting Wnt activation by interacting with β-catenin in the nucleus

Am J Pathol **2022**, *192*, 1167.

FQIs inhibit LSF Interaction with β-catenin

Am J Pathol **2022**, *192*, 1167.

FQIs Inhibit CRC Tumor Growth



FQIs inhibit growth of allogenic colorectal cancer xenograft
5 mg/kg IP

Am J Pathol **2022**, *192*, 1167. CMD

FQIs Inhibit Cancer Cell Proliferation

The FQI compounds have been profiled against >100 cancer cell lines at the Netherlands Translational Research Center B.V. (NTRC)

Sensitivity to FQI compounds include Wnt driven cancers such as colorectal, liver, pancreatic, breast, and certain types of oral cancers

Current efforts include establishing the role of TFCP2 in Wnt driven oral squamous cell carcinomas

Summary table

Show 10 entries Search:

Cell line name	ATCC ref	Tissue	Disease	IC_{50} (nM)	Max effect (%)	GI_{50} (nM)		LD_{50} (nM)
RL	CRL-2261	Lymphoid	Diffuse large B-cell lymphoma	91	93	94	>	10000
SU-DHL-6	CRL-2959	Lymphoid	Diffuse large B-cell lymphoma	98	100	96		383
COLO 829	CRL-1974	Skin	Cutaneous melanoma	69	76	69	>	10000
HCT 116	CCL-247	Bowel	Colon carcinoma	94	97	93	>	10000
RKO	CRL-2577	Bowel	Colon carcinoma	102	99	100		195
COLO 205	CCL-222	Bowel	Colon adenocarcinoma	121	94	119	>	10000
DLD-1	CCL-221	Bowel	Colon adenocarcinoma	175	93	173	>	10000
HCT-15	CCL-225	Bowel	Colon adenocarcinoma	80	97	78		537
LoVo	CCL-229	Bowel	Colon adenocarcinoma	84	93	82	>	10000
LS 174T	CL-188	Bowel	Colon adenocarcinoma	129	93	125	>	10000

Showing 61 to 70 of 103 entries Previous 1 … 6 7 8 … 11 Next

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Patents

1. Inhibitors of Late SV40 factor (LSF) as cancer chemotherapeutics. Hansen, U.; Schaus, S.; Grant, T.; Bishop, J.; Kavouris, J.; Christadore, L. M. U.S. Patent 9,802,948 B2, Oct. 31, 2017.

2. [1,3]Dioxolo[4,5-g]quinoline-6(5H)thione and [1,3]dioxolo[4,5-g][1,2,4]triazolo[1,5-a]quinoline derivatives as inhibitors of Late SV40 Factor useful for treating hepatocellular carcinoma or other cancer types. Schaus, S. E.; Hansen, U.; Bishop, J. U.S. Patent 9,175,001 B2, Apr. 16, 2019.

3. Quinolin-2(1H)-one inhibitors of Late SV40 Factor. Schaus, S. E.; Hansen, U.; York, E. A.; Pokharel, N. U.S. Patent 11,458,132 B2, Oct. 04, 2022.

4. Heterocyclic LSF inhibitors and their uses. Schaus, S. E.; Hansen, U.; Kavouris, J. A.; York, E. A.; Pokharel, N. U.S. Patent 11,242,353 B2, Feb. 8, 2022.

5. Late SV40 (LSF) inhibitors. Schaus, S. E.; Hansen, U.; Chin, H. G. U.S. Patent 11,420,977 B2, Aug. 23, 2022.

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