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Comparative Biodistribution and Radiotherapeutic Efficacy of the Fibroblast Activation Protein (FAP)–Targeting Agents FAP-2286 and FAPI-46

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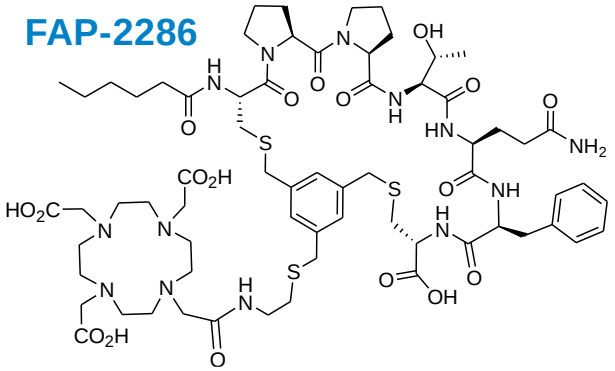
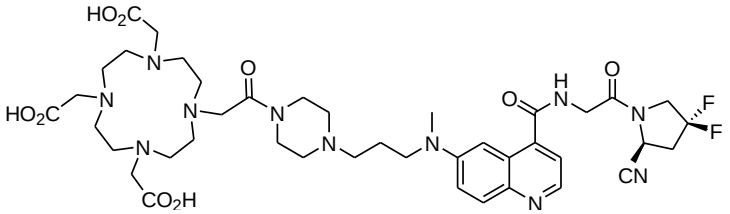
Introduction

- Fibroblast activation protein (FAP) is a membrane-bound protease under investigation as a pan-cancer target given its limited expression in normal adult tissues but high expression on cancer-associated fibroblasts[1]
- FAP-targeting agents, FAP-2286 and FAPI-46, have shown great promise as positron emission tomography (PET) imaging agents when chelated to Gallium-68
- The goals of these studies were to evaluate the biodistribution of FAP-2286 and FAPI-46, when chelated to the beta emitter Lutetium-177, and to correlate these results with the efficacy observed in the HEK-FAP mouse tumor model

FAP-2286



FAPI-46



[1]Pure et al. *Oncogene*. 2018;37:4343-57

SPECT/CT Imaging in HEK-FAP Mice

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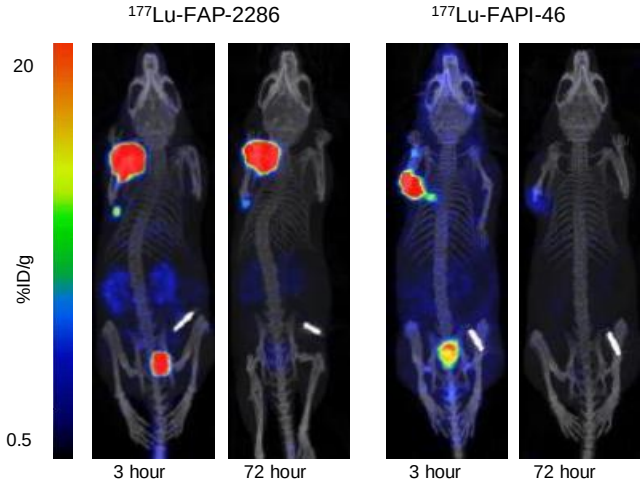

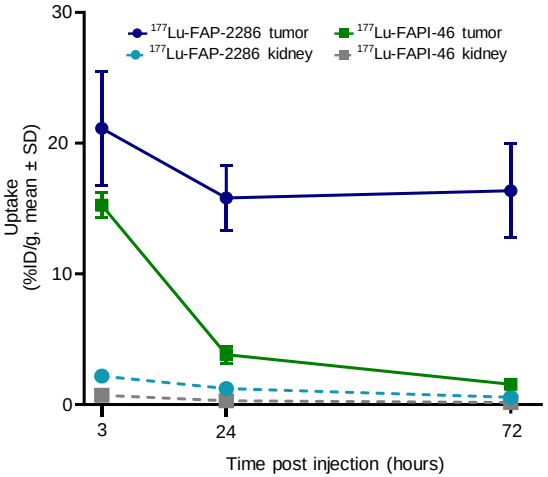

Tumor Uptake in HEK-FAP Xenograft Model

Compound	Tumor uptake (%ID/g, mean ± SD)			TIAC (MBq*h/MBq)	Absorbed dose (Gy/MBq)
	3 hour	24 hour	72 hour		
^{177}Lu-FAP-2286	21.1 ± 4.4	15.8 ± 2.5	16.4 ± 3.6	6.6	1.6
^{177}Lu-FAPI-46	15.3 ± 1.0	3.8 ± 0.7	1.6 ± 0.4	0.7	0.2

SPECT/CT imaging showed longer HEK-FAP tumor retention of ^{177}Lu-FAP-2286 compared with ^{177}Lu-FAPI-46, resulting in more than 8-fold higher absorbed dose delivered to the tumors

%ID/g, percent injected dose of test article per gram of tissue; CT, computerized tomography; SD, standard deviation; SPECT, single-photon emission computerized tomography; TIAC, time-integrated activity coefficient

Tumor Efficacy in HEK-FAP Mice

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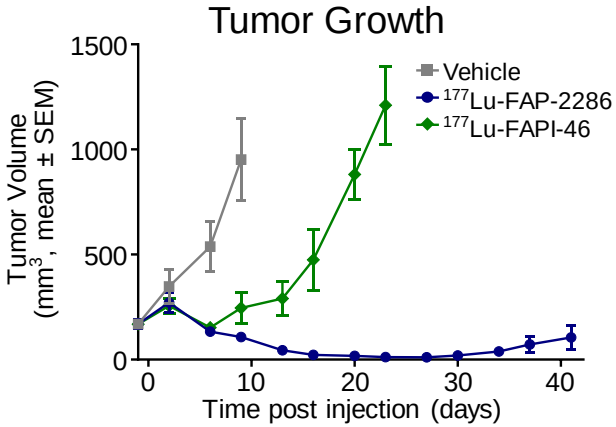

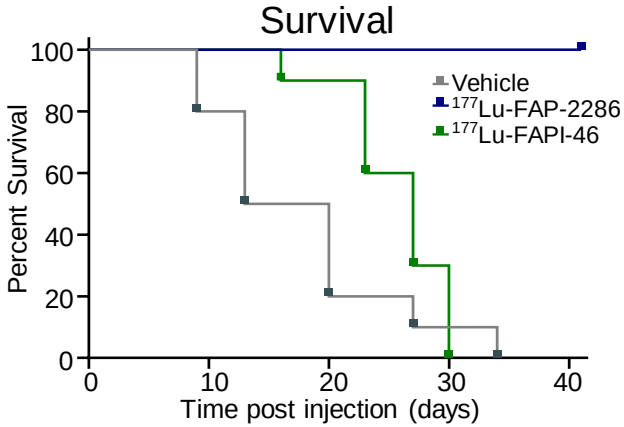

Tumor Efficacy in HEK-FAP Xenograft Model

Compound	MTV ± SEM (mm³, day 0)	MTV ± SEM (mm³, *P* value, day 9)	MTV ± SEM (mm³, day 23)	TGI (%, day 9)	MST (day)
Vehicle	169 ± 21	952 ± 195	NA	NA	16.5
^{177}Lu-FAP-2286	169 ± 23	107 ± 15 (*P*<0.0001)*	12 ± 4	108	undefined
^{177}Lu-FAPI-46	168 ± 22	245 ± 76 (*P*=0.0006)*	1210 ± 185 (*P*<0.0001)*	90	27.5

MST, median survival time; MTV, mean tumor volume; TGI, tumor growth inhibition

**P* value was determined for day 9 comparisons to the vehicle group (n=10 for all groups), while day 23 comparison was between ^{177}Lu-FAP-2286 (n=10) and ^{177}Lu-FAPI-46 (n=9).

^{177}Lu-FAP-2286 demonstrated greater HEK-FAP tumor growth inhibition compared with ^{177}Lu-FAPI-46

Live Cell Fluorescence Microscopy

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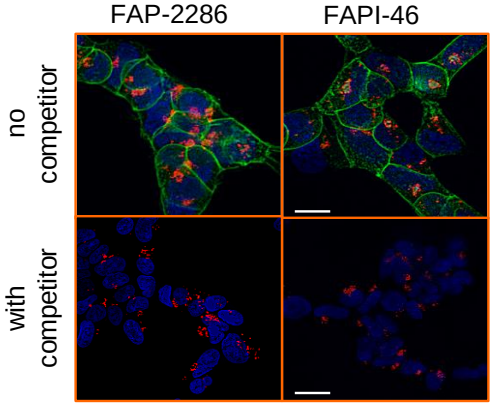
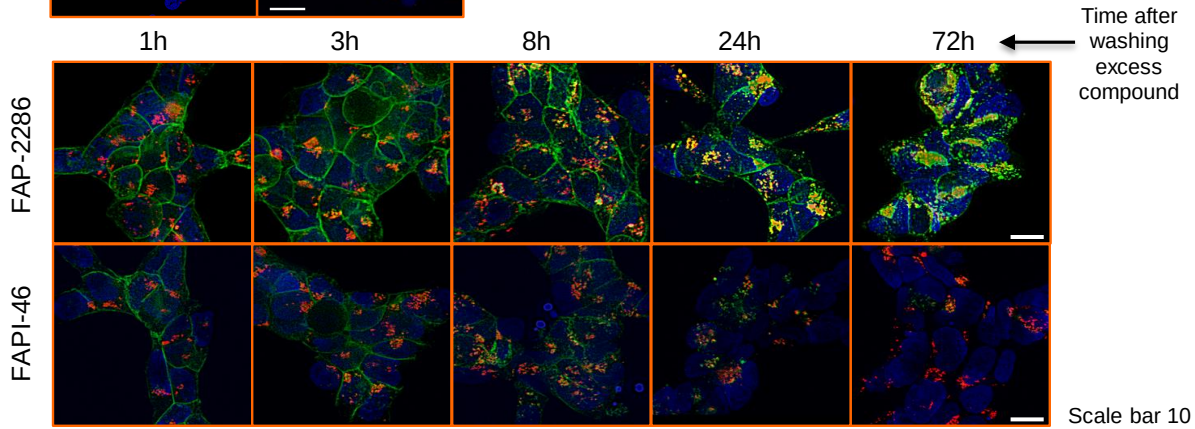


- Similar extracellular binding to HEK-FAP cells
- Blocking with unlabeled competitor showed specific binding



Live cell fluorescence microscopy with AlexaFluor488-labeled compounds showed longer intracellular retention for FAP-2286 compared to FAPI-46

Summary

- ^{177}Lu-FAP-2286 showed longer tumor retention, resulting in greater tumor growth inhibition as compared to ^{177}Lu-FAPI-46
- The prolonged tumor retention of FAP-2286 correlated with a higher intracellular accumulation
- The phase 1/2 LuMIERE clinical trial (NCT04939610) is evaluating FAP-2286 as a therapeutic (^{177}Lu-FAP-2286) and imaging (^{68}Ga-FAP-2286) agent in multiple FAP-expressing tumor types

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