SOFIE
From start to clinic

Fibroblast Activation Protein (FAP)- a promising target for radiopharmaceuticals

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Learning Objectives

1. Explain what is FAP and what role it plays in oncology
2. Identify key radiopharmaceuticals involved in FAP targeting
3. Describe the current state of clinical development for FAP Inhibitors (FAPI)

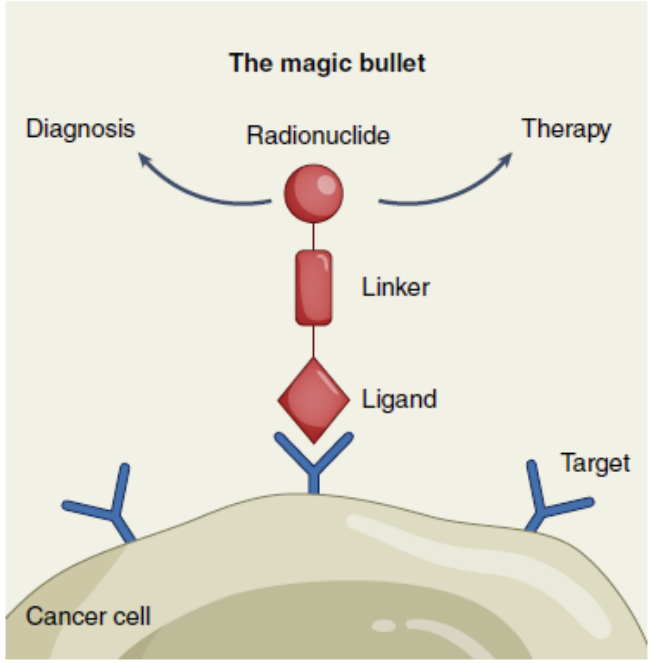
Theranostics

Diagnostic: PET imaging to Select patients whose cancer cells have the targeted protein. Short-lived radionuclide ^{68}**Ga** or ^{18}**F**

Treatment: Molecular targeted radio-ablation of cancer cells. Long-lived radionuclide ^{177}**Lu** , ^{225}**Ac** or other beta or alpha particle emitters

WHY?

- *See where the drug is going and how it is cleared from the target and the rest of the body*
- *Select patients based on having a specific target protein for therapy*
- *Monitor treatment response*



The magic bullet. Theranostics target unique properties of cancer cells using different radionuclides for diagnosis and treatment. Credit: Marina Spence/Nature Medicine

Carrie Arnold Nature News 2022

Theranostics- Neuroendocrine Tumors- First example

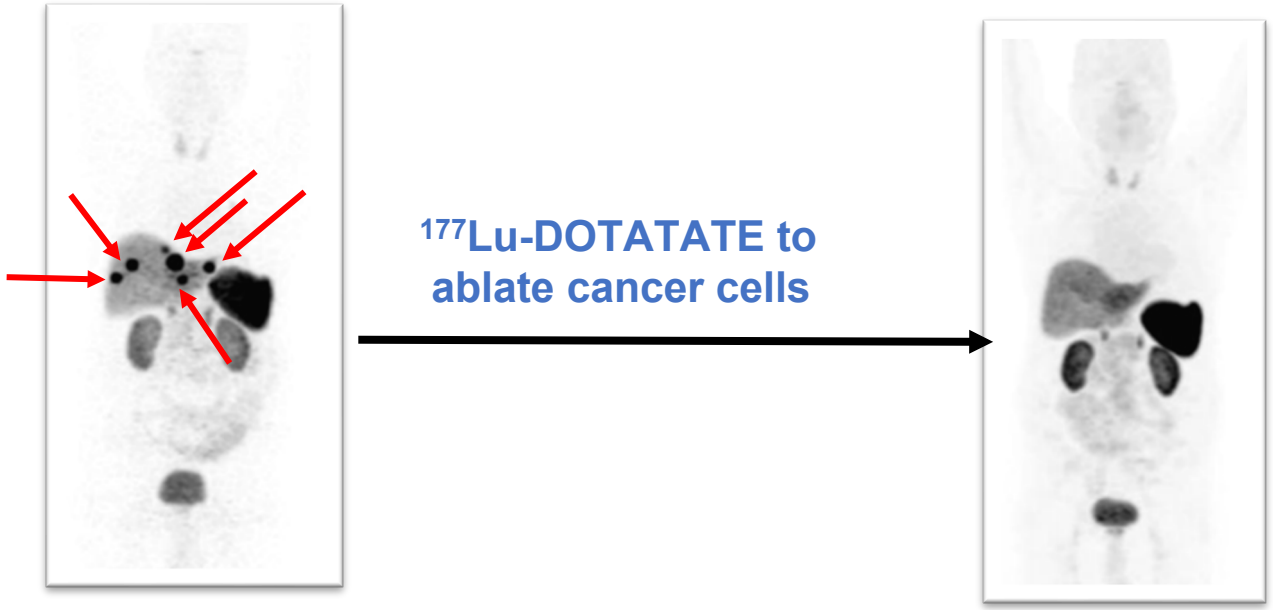
Target: Somatostatin Receptor

PET Imaging Probe is ^{68}Ga-DOTATATE
Treatment Probe is ^{177}Lu-DOTATATE
The DOTATATE probe is a small peptide

^{68}Ga-DOTATATE PET imaging

Question: Does the patient have the protein target?
Answer: Yes

Question: Have the cancer cells been ablated?
Answer: Yes



F. Giesel (U of Heidelberg), K. Herrmann (U of Essen), W. Fendler (UCLA), J. Czernin (UCLA)

Theranostics- PSMA target in prostate cancer- Second example

(Castrate resistant late-stage prostate cancer patients who have failed all accepted treatments)

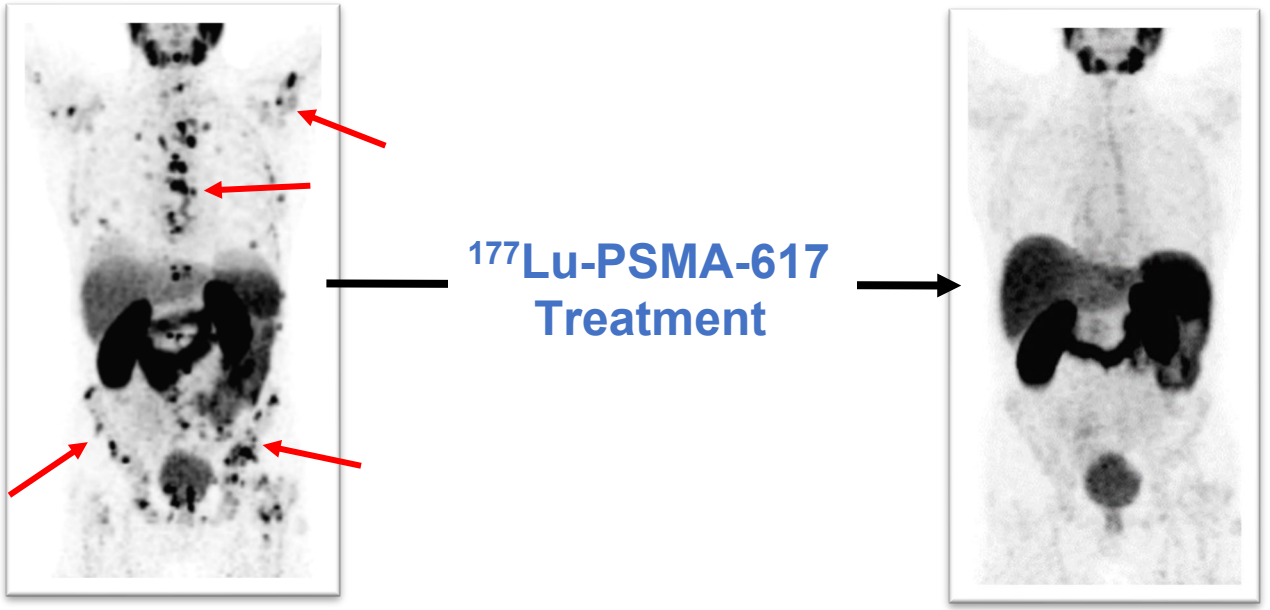
Target - Prostate-specific membrane antigen (PSMA)

PET Imaging: ^{68}Ga-PSMA-11
Treatment: ^{177}Lu-PSMA-617

^{68}Ga-PSMA-11 PET scans

Question: Does the patient have the protein target?
Answer: Yes

Question: Have the cancer cells been ablated?
Answer: Yes



^{177}Lu-PSMA-617 Treatment

BEFORE TREATMENT

PSA = 2,923 ng/ml

AFTER TREATMENT

PSA < 0.1 ng/ml

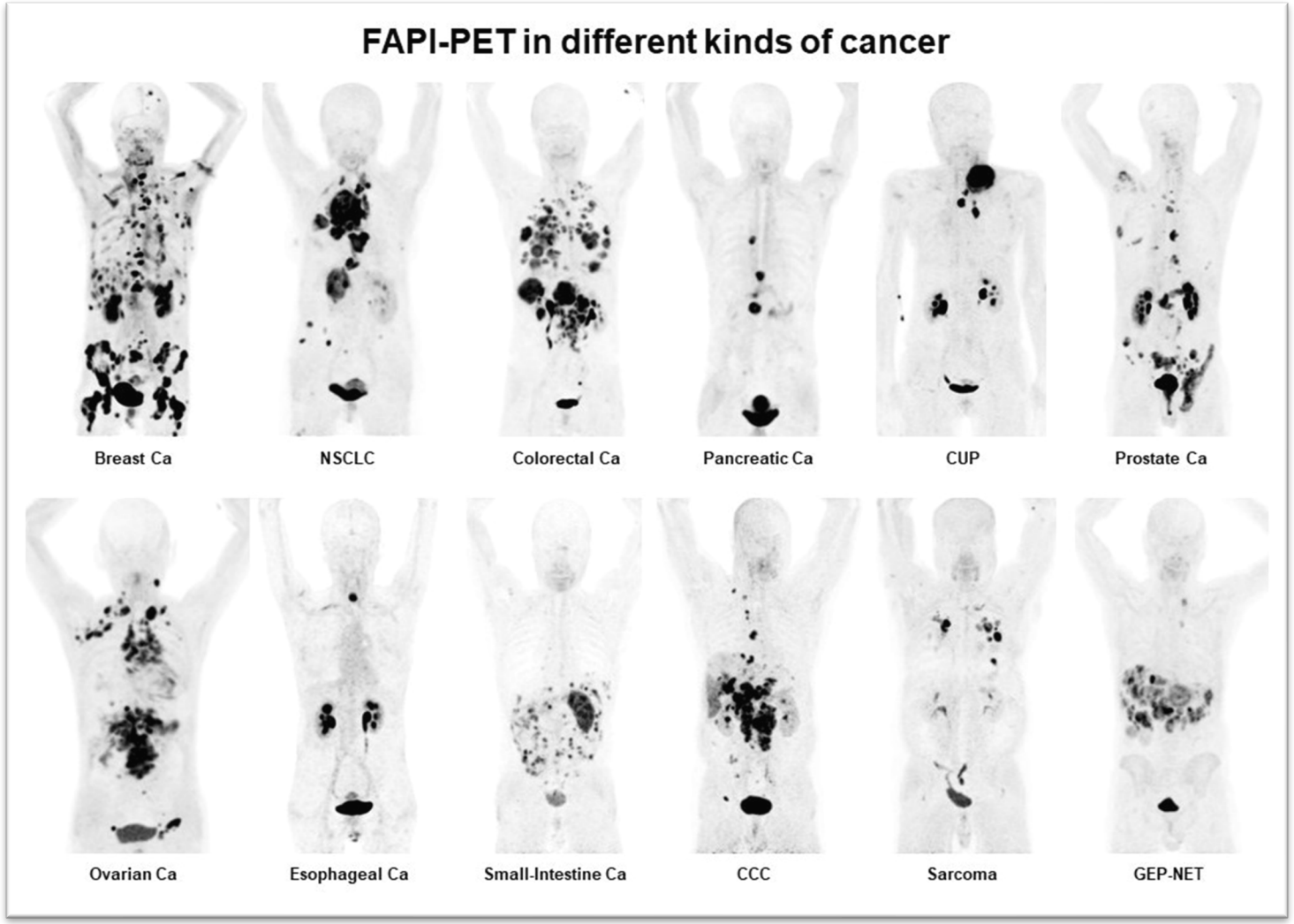
Some of the tumors →

F. Giesel (U of Heidelberg), K. Herrmann (U of Essen), W. Fendler (UCLA), J. Czernin (UCLA)

FAP target as the next theranostic breakthrough

SNMMI Image of the Year 2019

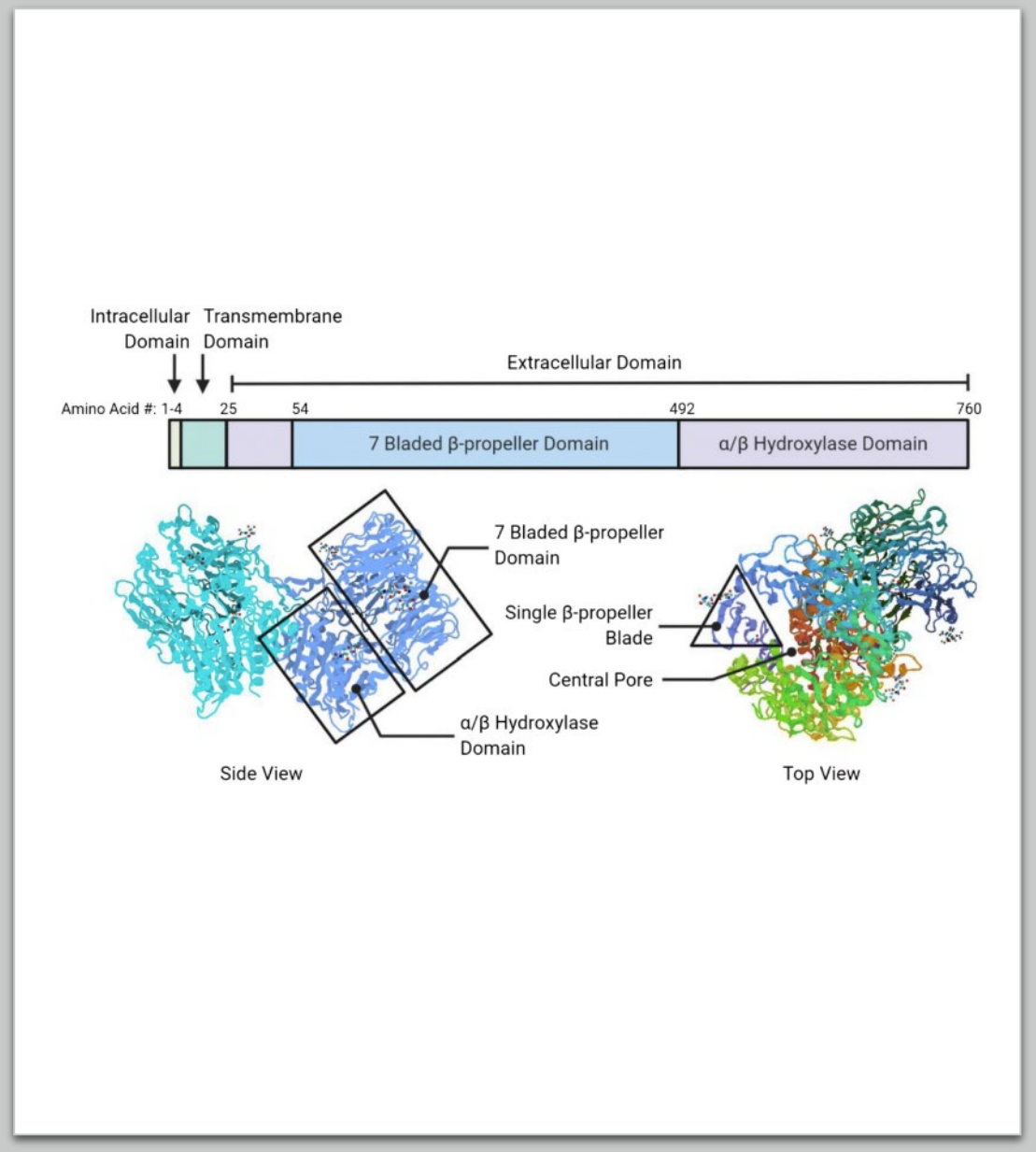
"A single radiotracer can identify nearly 30 types of cancer, allowing for new applications in noninvasive diagnosis, staging and treatment, according to research presented at the 2019 Annual Meeting of the Society of Nuclear Medicine and Molecular Imaging (SNMMI). This honor goes to a team of researchers at University Hospital Heidelberg, Germany, showcasing the efficacy of the FAPI radiotracer."



1. Explain what is FAP and what role it plays in oncology

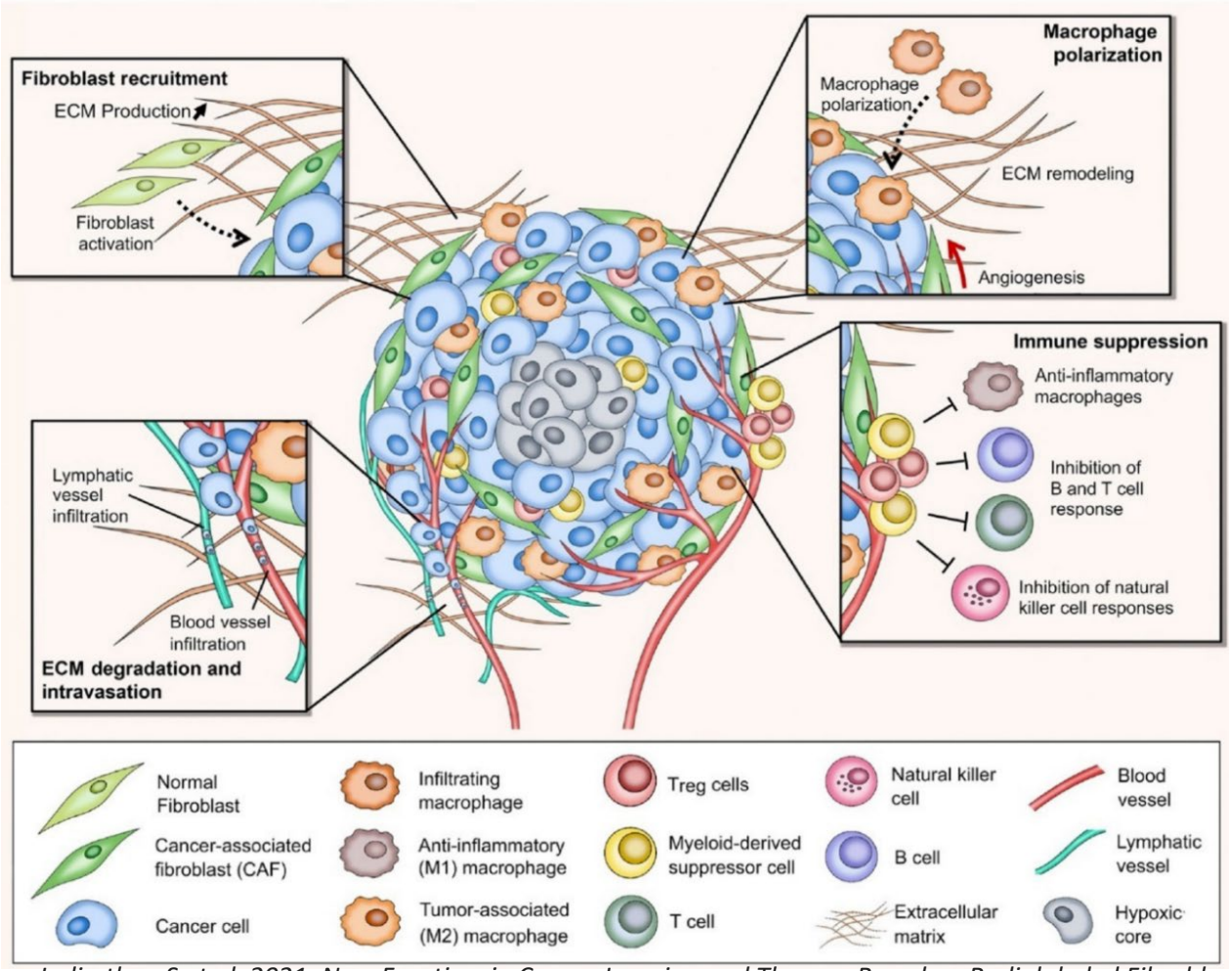
What is FAP?

- Fibroblast activation protein (FAPa or FAP)
- A Type II membrane-bound serine protease. Contains 2 enzymatic activities: dipeptidyl peptidase and endopeptidase
- Associated with fibrosis, tissue repair, inflammation, and extracellular matrix (ECM) degradation
- Through enzymatic and non-enzymatic activities, FAP demonstrates **pro-tumorigenic activity** involved in migration, invasion, and proliferation of cells in the tumor microenvironment, resulting in ECM degradation, tumor angiogenesis, invasiveness, and evasion of immune response



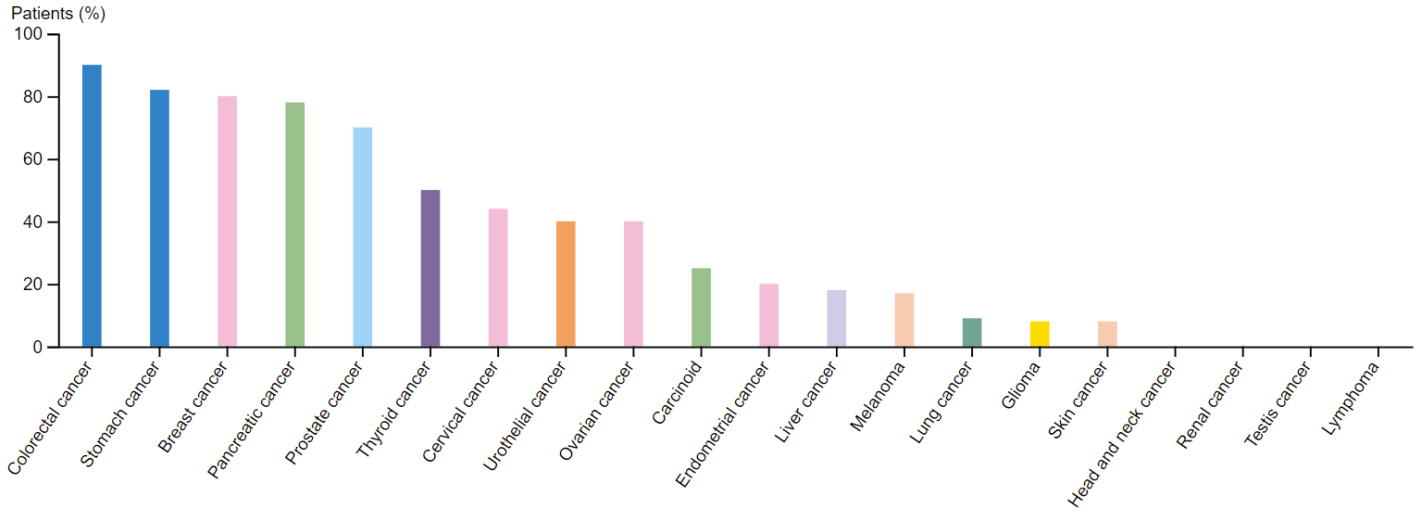
FAP and CAFs

- Among all the stromal cells, **cancer-associated fibroblasts (CAFs)** are dominant populations in the tumor microenvironment
- Fibroblasts become activated during wound repair and regeneration. Malignant tumors are recognized as **“wounds that do not heal”**
- **FAP** is highlighy expressed on the surface of CAFs
- When looking at markers of CAFs, FAP has received interest as a potential biomarker for CAF identification
- FAP is a great target due to its overexpression in most of the cancer types (90%)



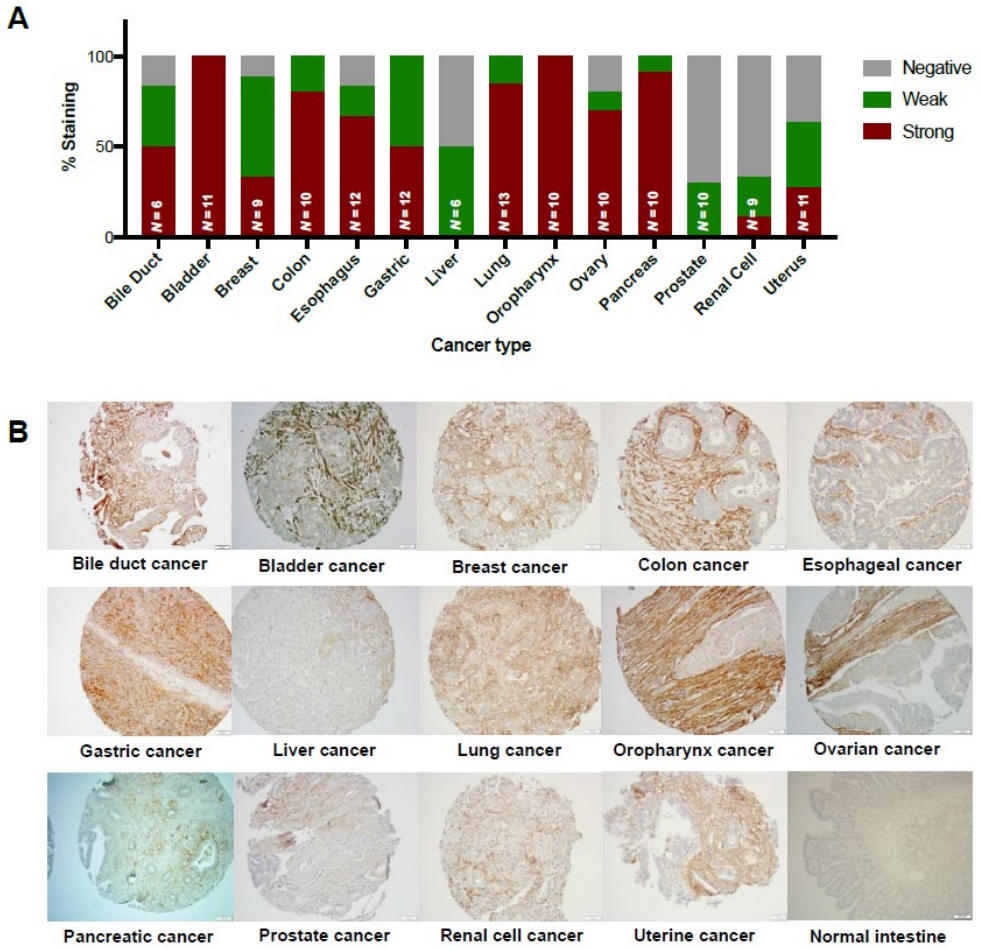
Imlimthan S et al. 2021. New Frontiers in Cancer Imaging and Therapy Based on Radiolabeled Fibroblast Activation Protein Inhibitors: A Rational Review and Current Progress. Pharmaceuticals (Basel).

FAP expression levels in different cancers



Several breast, colorectal, prostate, stomach and pancreatic cancers along with a few squamous cell carcinomas, ovarian and urothelial cancers displayed moderate to strong cytoplasmic and membranous positivity for FAP. Remaining cancer tissues were weakly stained or negative. Human Protein Atlas: https://www.proteinatlas.org/ENSG00000078098-FAP/pathology

- FAP is highly expressed in an array of different solid tumors (ECM/stroma)
- Noteworthy: Colorectal, GI/stomach, Thyroid/Oropharynx, Pancreas, Ovarian, Lung and Bladder/Urothelial show high expression of FAP in data displayed here
- FAP expression is detected in the tumor cells of sarcomas



Mona et al. doi: 10.2967/jnumed.121.262426

Note: inconsistency in FAP expression levels between these studies displayed could be due to sample size, sub-type of disease and stage of disease.

Select examples of FAP targeted therapies- non RLT

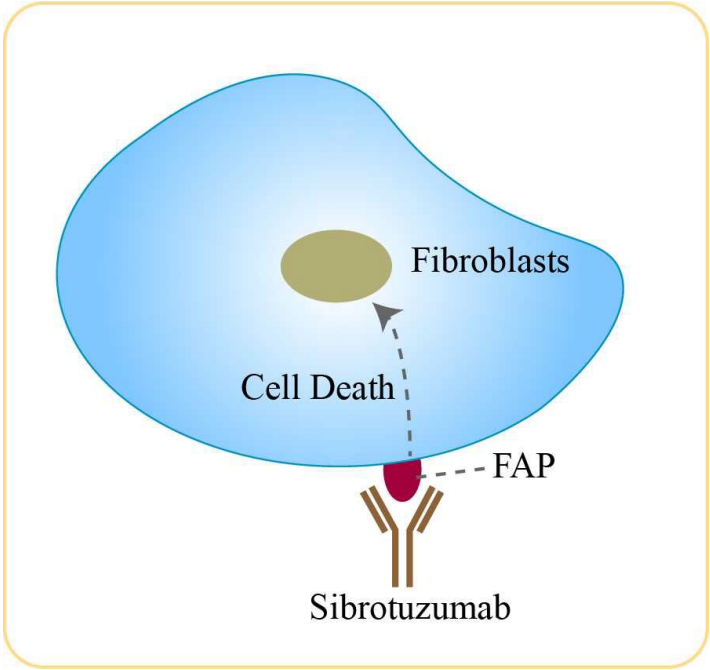
Note: this is not meant to be a comprehensive list of all FAP targeted non RLT

Targeting FAP

Antibody

Example: Sibrotuzumab (also known as BIBH 1) is a humanized monoclonal antibody (mAb) with high affinity to bind to fibroblast activation protein (FAP)

- Developed by Boehringer Ingelheim Pharma KG for the treatment of cancer
- Studied as a drug therapeutic for colorectal, non-small cell lung, breast, as well as head and neck cancers
- Results did not show sufficient efficacy in 2003 Phase II study



Targeting FAP

Small molecule inhibitors

- Examples include Talabostat and Linagliptin
- Dipeptidyl peptidase-4 (DPP-4) inhibitors
- Talabostat blocks dipeptidyl peptidases, such as fibroblast activation protein (FAP), resulting in induction of cytokine and chemokine. **Promoting immune response**. Studies have been conducted in Phase 2, which demonstrated some clinical response, but safety concerns have halted further investigation
- Linagliptin is an approved drug, which has been shown, along with diet and exercise, to lower blood sugar levels in patients with type 2 diabetes

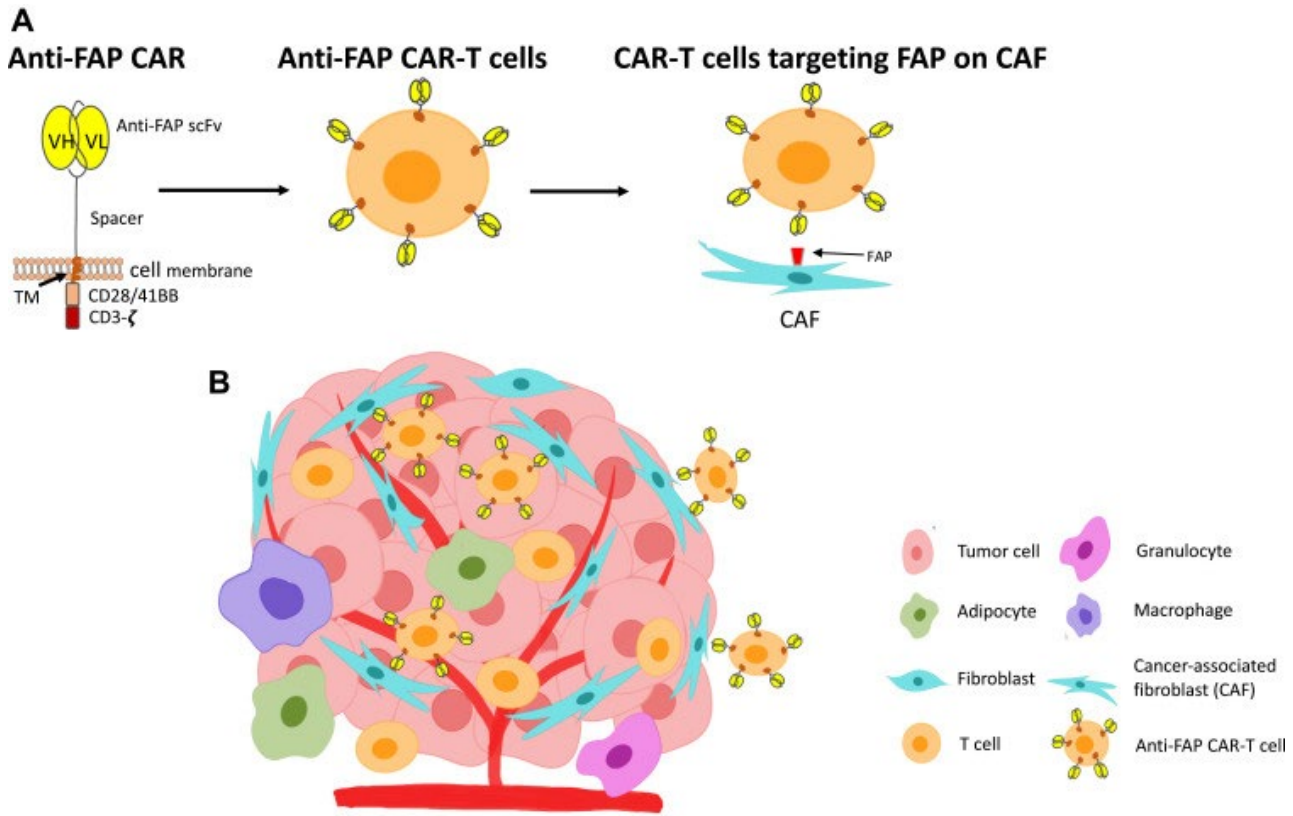
Targeting FAP

CAR T cell therapy

FAP-targeting CAR-T cells have been genetically engineered to target CAFs in various solid cancers, such as mesothelioma, lung and pancreatic cancers

Clinical trials are in early stages. Examples:

- The Sixth Affiliated Hospital of Wenzhou Medical University
- University of Zurich



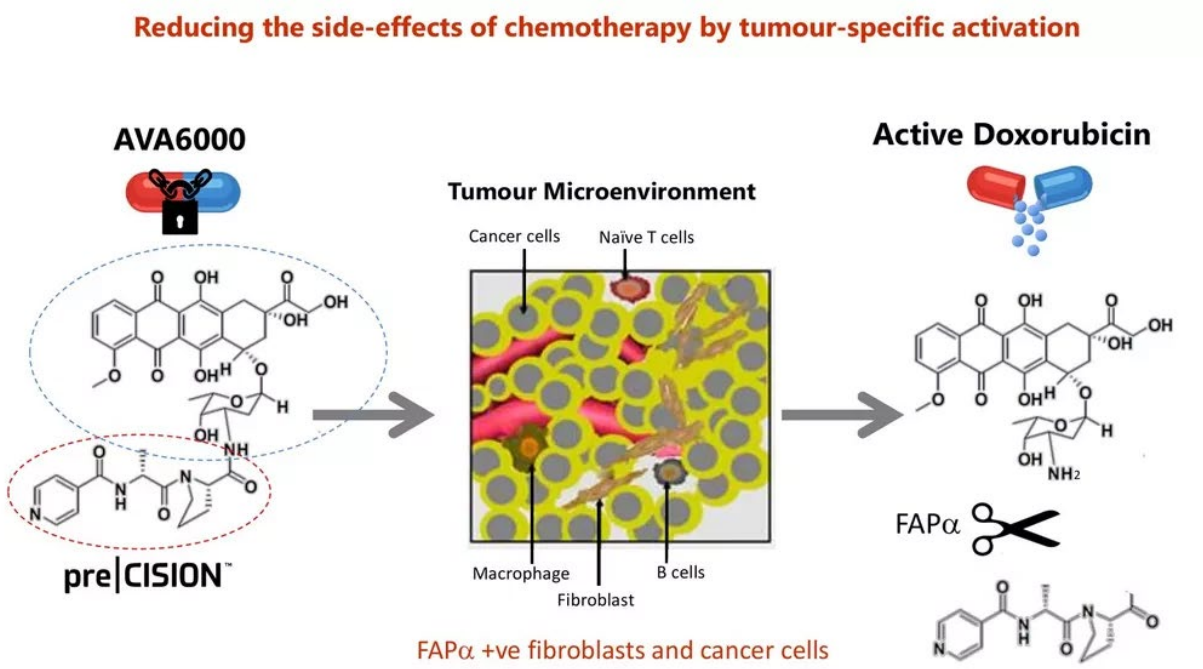
10.2147/ITT.S291767

Targeting FAP

Prodrugs

Prodrugs are inactive medications that chemicals or enzymes provide targeting by their activation after the medication enters the body.

- Example: AVA6000 – FAPα-Activated Doxorubicin by Avacta Life Sciences
- In its FAPα activated form, the doxorubicin drug moiety is not cell permeable
- In the tumor microenvironment, where the level of the enzyme FAP is substantially higher than elsewhere in the body, the FAP substrate is cleaved and the active doxorubicin drug is released causing a significant differential targeting of tumor compared with healthy tissue
- Phase 1 study- currently active



https://www.voxmarkets.co.uk/articles/avacta-announces-dose-escalation-in-the-phase-i-clinical-study-of-ava6000-pro-doxorubicin-0c53383/

2. Identify key radiopharmaceuticals involved in FAP targeting

A Tumor-Imaging Method Targeting Cancer-Associated Fibroblasts

Anastasia Loktev*[1–3], Thomas Lindner*[1], Walter Mier[1], Jürgen Debus[4,5], Annette Altmann[1,2], Dirk Jäger[6], Frederik Giesel[1], Clemens Kratochwil[1], Philippe Barthe[7], Christian Roumestand[7], and Uwe Haberkorn[1,2,8]

[1]Department of Nuclear Medicine, University Hospital Heidelberg, Heidelberg, Germany; [2]Clinical Cooperation Unit Nuclear Medicine, German Cancer Research Center (DKFZ), Heidelberg, Germany; [3]Faculty of Biosciences, Heidelberg University, Heidelberg, Germany; [4]Department of Radiation Oncology, University Hospital Heidelberg, Heidelberg, Germany; [5]Clinical Cooperation Unit Radiation Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany; [6]Department of Medical Oncology, National Center for Tumor Diseases (NCT), Heidelberg, Germany; [7]Centre de Biochimie Structurale, Université de Montpellier, CNRS, INSERM, Montpellier, France; and [8]Translational Lung Research Center Heidelberg (TLRC), German Center for Lung Research (DZL), Heidelberg, Germany

2018- Identification of **FAPI-02** with enhanced binding and uptake in human FAP expressing cells in vitro and mouse models

Development of Fibroblast Activation Protein–Targeted Radiotracers with Improved Tumor Retention

Anastasia Loktev[1,2], Thomas Lindner[1], Eva-Maria Burger[1], Annette Altmann[1,2], Frederik Giesel[1], Clemens Kratochwil[1], Jürgen Debus[3,4], Frederik Marmé[5], Dirk Jäger[6], Walter Mier[1], and Uwe Haberkorn[1,2,7]

[1]Department of Nuclear Medicine, University Hospital Heidelberg, Heidelberg, Germany; [2]Clinical Cooperation Unit Nuclear Medicine, German Cancer Research Center, Heidelberg, Germany; [3]Department of Radiation Oncology, University Hospital Heidelberg, Heidelberg, Germany; [4]Clinical Cooperation Unit Radiation Oncology, German Cancer Research Center, Heidelberg, Germany; [5]Department of Gynecologic Oncology, National Center for Tumor Diseases and Department of Obstetrics and Gynecology, University Women's Clinic, University Hospital Heidelberg, Heidelberg, Germany; [6]Department of Medical Oncology, National Center for Tumor Diseases, Heidelberg, Germany; and [7]Translational Lung Research Center Heidelberg, German Center for Lung Research, Heidelberg, Germany

2019- Identification and characterization of **FAPI-46** as the lead FAPI theranostic compound with improved tumor to background ratio and tumor retention

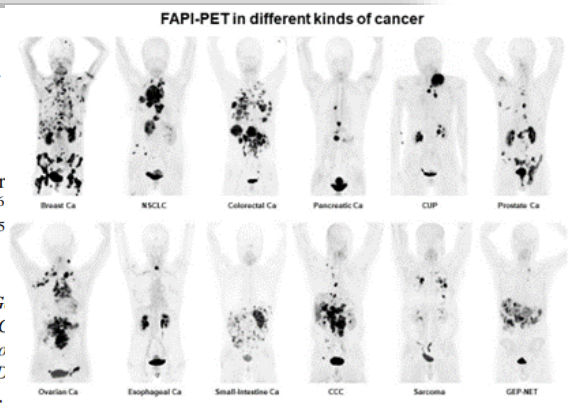
Development of Quinoline-Based Theranostic Ligands for the Targeting of Fibroblast Activation Protein

Thomas Lindner*[1], Anastasia Loktev*[1–3], Annette Altmann[1,2], Frederik Giesel[1], Clemens Kratochwil[1], Jürgen Debus[4,5], Dirk Jäger[6], Walter Mier[1], and Uwe Haberkorn[1,2]

[1]Department of Nuclear Medicine, University Hospital Heidelberg, Heidelberg, Germany; [2]Clinical Cooperation Unit Nuclear Medicine, German Cancer Research Center (DKFZ), Heidelberg, Germany; [3]Faculty of Biosciences, Heidelberg University, Heidelberg, Germany; [4]Department of Radiation Oncology, University Hospital Heidelberg, Heidelberg, Germany; [5]Clinical Cooperation Unit Radiation Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany; and [6]Department of Medical Oncology, National Center for Tumor Diseases (NCT), Heidelberg, Germany

2018- Identification and proof of concept of **FAPI-04** with enhanced tumor retention and tumor to blood ratio

^{68}Ga-FAPI PET/CT: Tracer Uptake in of Cancer



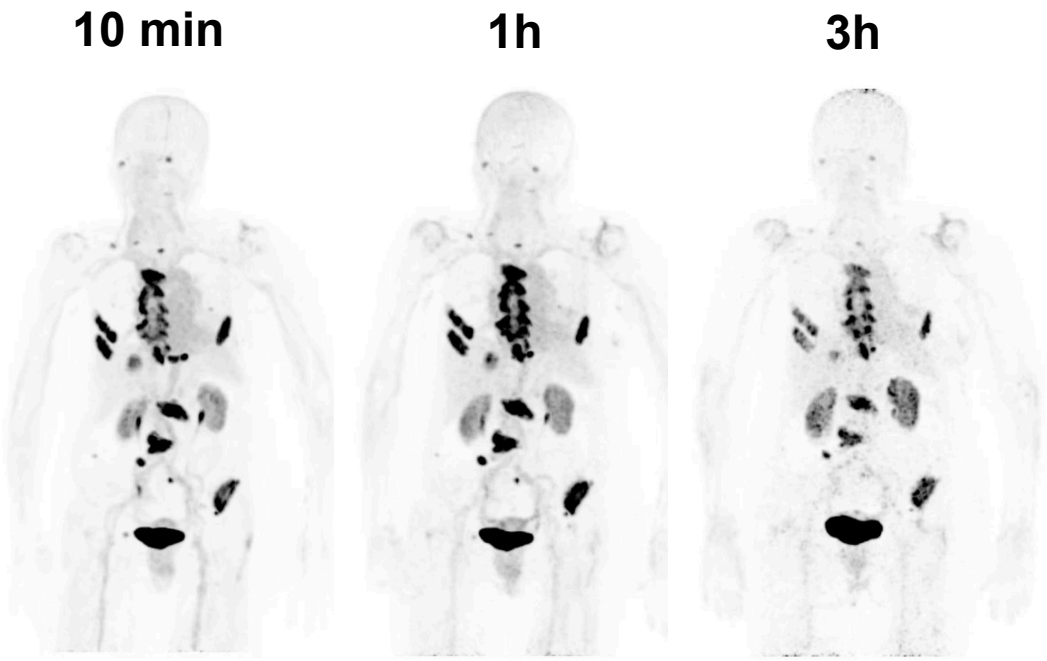
Clemens Kratochwil*[1], Paul Flechsig*[1,2], Thomas Lindner[1], Labidi Abderr
Sebastian Adeberg[4,5], Hendrik Rathke[1], Manuel Röhrich[1], Hauke Winter[2,6]
Matthias Lang[10], Hans-Ulrich Kauczor[2,11], Dirk Jäger[12,13], Jürgen Debus[4,5]
Frederik L. Giesel[1]

*[1]Department of Nuclear Medicine, University Hospital Heidelberg, Heidelberg, G
Heidelberg, German Center for Lung Research, Heidelberg, Germany; [3]Clinical C
Cancer Research Center, Heidelberg, Germany; [4]Department of Radiation Oncolo
Germany; [5]Heidelberg Institute for Radiation Oncology, Heidelberg, Germany; [6]L
Hospital Heidelberg, Heidelberg, Germany; [7]Department of Otorhinolaryngology,*

2019- First study of FAPI biodistribution in **eighty patients** with 28 different tumor entities

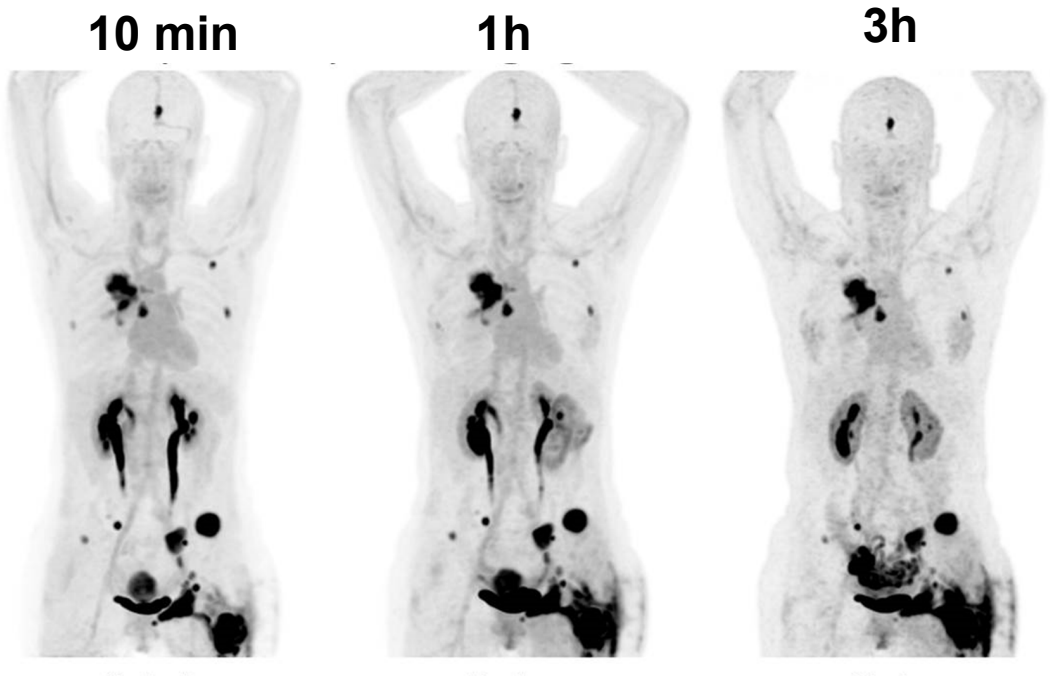
Kinetics of FAP targeting ligands

Kinetic study with ^{68}Ga-FAPI-02 in a breast cancer patient



Loktev et., al., JNM 2018, 59: 1423-14209 (Uwe Haberkorn lab, Univ. of Heidelberg)

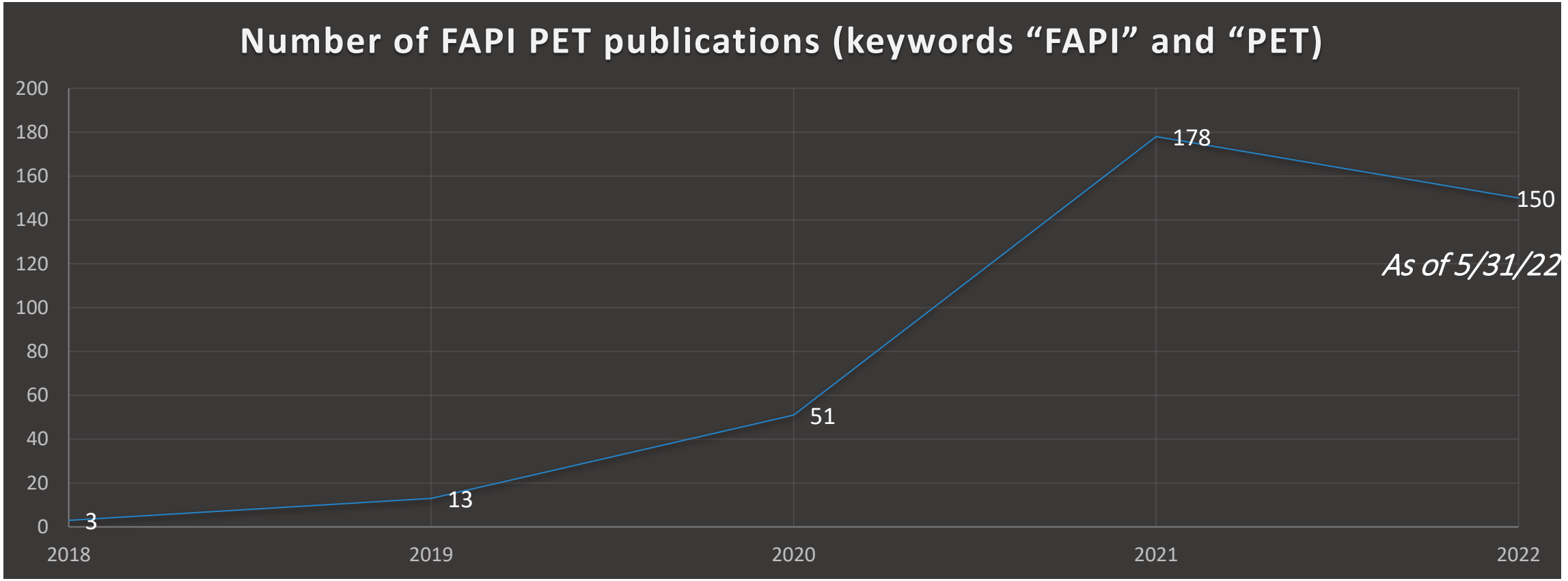
Kinetic study with ^{18}F-FAPI-74 in a lung cancer patient



Unpublished. Courtesy of Prof. Giesel. University Hospital Dusseldorf, Germany

Images and publications illustrate the rapid binding of the probe to FAP and rapid clearance from off target tissues

Mounting interest in FAP targeted radiopharmaceuticals



Current state of publications

STATISTICS*

- Publications: 326
- Oncology
  - Publications: 217
  - Patients reported: 4,915
- Non-oncology
  - Publications: 109
  - Patients reported: 856

COMPOUNDS

- FAPI family of compounds
- FAPI derivatives
- OncoFAP
- **SA.FAPI compounds
- FAP-2286
- RPS-209

* Publications as of 5/20/22. Excluding reviews. Using “FAP”, “FAPI” and “PET” as combination of keywords

** SA: squaramide (SA) linker

List of DIAGNOSTIC radiopharmaceuticals under investigation & published

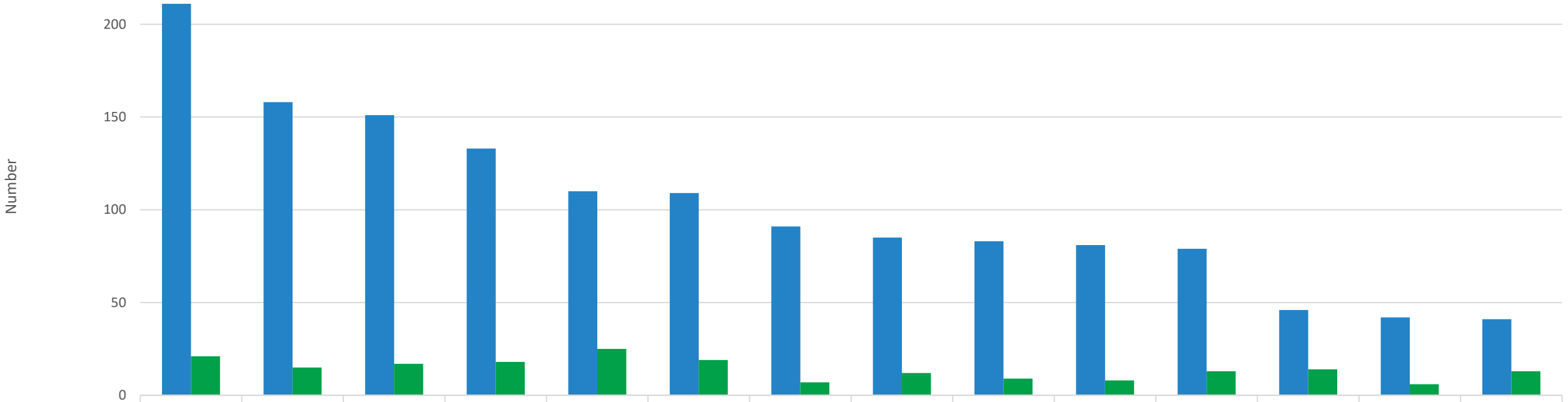
Compounds used for Imaging with published clinical data

- FAPI family
  - ^{68}Ga: FAPI-04, FAPI-46 and FAPI-74
  - ^{18}F: FAPI-74
  - ^{99m}Tc: FAPI-34
- DOTA.(SA.FAPI)2
- OncoFAP
- FAP-2286
  - listed under therapy but also has 68Ga version for imaging

Radionuclide	Inhibitor	Quality of Radiation		Evaluation Phase
		Imaging	Radiotherapy	
^{18}F	FAPI-74	PET	-	Clinical: patients with lung cancer
	Glc-FAPI-04			Preclinical: fibrosarcoma and glioblastoma xenografts
^{68}Ga	FAPI-02	PET	-	Clinical: various cancers
	FAPI-04			Clinical: various cancers
	FAPI-20			Preclinical: fibrosarcoma xenograft
	FAPI-21			Clinical: various cancers
	FAPI-22			Preclinical: fibrosarcoma xenograft
	FAPI-31			
	FAPI-35			
	FAPI-36			
	FAPI-37			
	FAPI-46			Clinical: various cancers
	FAPI-74			Clinical: patients with lung cancer
	DOTA.SA.FAPi			Preclinical: colorectal adenocarcinoma xenograftClinical: various cancer patients
	DATA^{5m}.SA.FAPi			Preclinical: in vitro modelsClinical: restaging of tumor manifestation, liver tumor and metastases imaging
	DOTA.(SA.FAPi)$_2$			Clinical: patient with thyroid and pancreatic neuroendocrine tumors
	DOTAGA.(SA.FAPi)$_2$			
	RPS-309			Preclinical: liposarcoma xenograft
^{68}Ga	Onco-FAP	PET		Clinical: patients with various cancers primarily breast cancer
^{111}In	QCP02	SPECT	-	Preclinical: glioblastoma xenograft
^{99m}Tc	FAPI-34	SPECT	-	Clinical: patients with ovarian metastasis and pancreatic cancer

Imlimthan S et al. 2021. New Frontiers in Cancer Imaging and Therapy Based on Radiolabeled Fibroblast Activation Protein Inhibitors: A Rational Review and Current Progress. Pharmaceuticals (Basel).

Cancer indications with more than 40 patients published with FAP radiopharmaceuticals



	Lung Cancer	Sarcoma	Gastric	Liver	Breast	Pancreatic	H&N	Oral	Lymphoma	Endometrial	Colorectal	Esophageal	CUP	Tyroid Carcinoma
Patient #	211	158	151	133	110	109	91	85	83	81	79	46	42	41
Publication #	21	15	17	18	25	19	7	12	9	8	13	14	6	13

Publications as of 3/18/22. Excluding reviews. Using “FAP”, “FAPI” and “PET” as combination of keywords

Reviews of findings with FAP targeted tracers

biomedicines

MDPI

Review

Imaging Cancer-Associated Fibroblasts (CAFs) with FAPi PET

Laura Gilardi [1], Lighea Simona Airò Farulla [1,2], Emre Demirci [3], Ilaria Clerici [4], Emanuela Omodeo Salè [4] and Francesco Ceci [1,2,*]

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* Correspondence: francesco.ceci@ieo.it

International Journal of Molecular Sciences

MDPI

Review

Head-to-Head Comparison of Fibroblast Activation Protein Inhibitors (FAPI) Radiotracers versus [^{18}F]F-FDG in Oncology: A Systematic Review

Giorgio Treglia [1,2,3,4,5,*,†], Barbara Muoio [6,†], Hessamoddin Roustaei [7], Zahra Kiamanesh [7], Kamran Aryana [7] and Ramin Sadeghi [7]

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3 Academic Education, Research and Innovation Area, General Directorate, Ente Ospedaliero Cantonale, 6500 Bellinzona, Switzerland
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7 Nuclear Medicine Research Center, Mashhad University of Medical Sciences, 9919991766 Mashhad, Iran; roustaeifh981@mums.ac.ir (H.R.); kiamaneshz@gmail.com (Z.K.); aryanak@mums.ac.ir (K.A.); sadeghir@mums.ac.ir (R.S.)
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† G.T. and B.M. share the first authorship

check for updates

Hindawi
Contrast Media & Molecular Imaging
Volume 2022, Article ID 3948873, 9 pages
https://doi.org/10.1155/2022/3948873

WILEY | Hindawi

Review Article

Could Fibroblast Activation Protein (FAP)-Specific Radioligands Be Considered as Pan-Tumor Agents?

Hessamoddin Roustaei [1], Zahra Kiamanesh, [1] Emran Askari [1], Ramin Sadeghi [1], Kamran Aryana [1] and Giorgio Treglia [2,3,4]

[1]*Nuclear Medicine Research Center, Mashhad University of Medical Sciences, Mashhad, Iran*
[2]*Ente Ospedaliero Cantonale, Bellinzona, Switzerland*
[3]*Faculty of Biomedical Sciences, Università della Svizzera italiana, Lugano, Switzerland*
[4]*Faculty of Biology and Medicine, University of Lausanne, Lausanne, Switzerland*

Correspondence should be addressed to Giorgio Treglia; giorgiomednuc@libero.it

State-of-the-art of FAPI-PET Imaging: A Systematic Review and Meta-Analysis

Martina Sollini
HUNIMED: Humanitas University
Margarita Kirienko
Fondazione IRCCS Istituto Nazionale dei Tumori
Fabrizia Gelardi (fabrizia.gelardi@humanitas.it)
HUNIMED: Humanitas University https://orcid.org/0000-0001-7120-333X
Francesco Fiz
IRCCS Humanitas Research Hospital
Noemi Gozzi
Istituto Clinico Humanitas: Humanitas Research Hospital
Arturo Chiti
HUNIMED: Humanitas University

Publication review highlights FAPI's performance compared to FDG in a number of indications (including: GI, nasopharyngeal) in primary and metastatic lesion detection

Table 2. Oncological setting: Gliomas, primary liver cancer and gastro-entero-pancreatic cancers.

Authors	*n* of Patients	Tumor Type	Clinical Setting	Injected Activity	Acquisition Timing	Image Analyses	Reference Standard	^{68}Ga-FAPI Performance	^{18}F-FDG Performance	MRI Performance
Röhrich M et al. [23]	18	Gliomas	Staging, Restaging	150–250 MBq	30 min (FA-Pi04); 10, 60 and 180 min (FAPi-02)	S	MRI	SE 83.3%	-	SE 100%
Windisch P et al. [24]	13	GBM	RT planning	150–250 MBq	30 min	S	MRI	SE 100%	-	SE 100%
Guo W et al. [26]	34	Hepatic nodules	Staging	148–259 MBq	60 min	V, S	HP, imaging follow-up	SE 87.4%	SE 64.9%	-
Şahin E et al. [27]	31	GEP	Staging and follow-up after treatment	2–3 MBq/Kg	45 min	V, S	Imaging follow-up, tumor biomarker findings, HP	SE 93.5% (patient based)	SE 71% (patient based)	-
								SE 95.9% (lesion based)	SE 79.6% (lesion based)	-
Pang Y et al. [28]	35	GI tract	Staging, Restaging	1.8–2.2 MBq/Kg	60 min	V, S	HP	SE 100%	SE 43.8%	-
								T: SE 100%	T: SE 52.6%	-
								N: SE 78.6%, SP 82.1%	N: SE 53.6%, SP 89.3%	-
								M: SE 88.6%, SP 28.6%	M: SE 57.1%, SP 85.7%	-
Jiang D et al. [29]	38	Gastric cancer	Staging	111–185 MBq	60 min	S	HP	T: SE 100%	T: SE 75%	-
								N: SE 60%, SP 92.9%	N: SE 50%, SP 92.9%	-

V, visual analyses; S, semi-quantitative analyses; HP, histopathology; T, primary tumor; N, lymph node(s); M, distant metastases; SE, sensitivity; SP, specificity; GBM, glioblastoma; GEP, gastro-entero-pancreatic; GI tract, gastro-intestinal tract.

Gilardi et al DOI: 10.3390/biomedicines10030523

Publication review highlights FAPI's performance compared to FDG in a number of indications (including: GI, nasopharyngeal) in primary and metastatic lesion detection

Table 3. Oncological setting: Head and neck cancers.

Authors	*n* of Patients	Tumor Type	Clinical Setting	Injected Activity	Acquisition Timing	Image Analyses	Reference Standard	^{68}Ga-FAPI Performance	^{18}F-FDG Performance	MRI Performance
Zhao L et al. [30]	45	Nasopharyngeal carcinoma	Staging, Restaging	1.8–2.2 MBq/Kg	40 min	V, S	HP, imaging follow-up	T: SE 86.7%	T: SE 84.4%	-
								N: SE 95%	N: SE 75.2%	N: SE 97.5%
Qin C et al. [31]	15	Nasopharyngeal carcinoma	Staging, Restaging	1.85–3.7 MBq/Kg	30–60 min	V, S	MRI	T: SE 100%	T: SE 100%	-
								N: SE 48%	N: SE 100%	-
								M: SE 100%	M: SE 0%	-
Chen H et al. [32]	68	Various cancer (13 types)	Staging, Restaging	1.8–2.2 MBq/Kg	60 min	V, S	HP, imaging and clinical follow-up	T: SE 86.4%	-	-
Chen H et al. [33]	75	Various cancer (12 types)	Staging, Restaging	1.8–2.2 MBq/Kg	60 min	V, S	HP	T: SE 98.2%	T: SE 82.1%	-
								N: SE 86.4%, SP 58.8%	N: SE 45.5%, SP 76.5%	-
								M: SE 83.8%, SP 41.7%	M: SE 59.5%, SP 58.3%	-

V, visual analyses; S, semi-quantitative analyses; HP, histopathology; T, primary tumor; N, lymph node(s); M, distant metastases; SE, sensitivity; SP, specificity.

Table 3. Main results of the included studies about the comparison among [^{18}F]F-FDG and FAPI radiotracers.

Authors	Cancer Evaluated	Significant Higher Uptake of Radiolabeled FAPI Compared to [^{18}F]F-FDG	Significant Higher TBR of Radiolabeled FAPI Compared to [^{18}F]F-FDG	Comparison in the Detection of Primary Tumors	Comparison in the Detection of Metastases
Ballal et al. [10]	Various cancers	only for brain metastases	only for brain metastases	NR	NR
Chen et al. [11]	Various cancers	yes	yes	FAPI > FDG	FAPI > FDG
Chen et al. [12]	Various cancers	yes	yes	FAPI > FDG	FAPI > FDG
Dendl et al. [13]	Gynecological cancers	no	only for distant metastases	NR	NR
Elboga et al. [14]	Breast cancer	yes	NR	FAPI > FDG	FAPI > FDG
Giesel et al. [15]	Various cancers	no	only for liver and bone metastases	NR	NR
Guo et al. [16]	Liver cancer	yes	yes	FAPI > FDG	FAPI > FDG
Jiang et al. [17]	Gastric cancer	no	yes	FAPI > FDG	FAPI = FDG
Kessler et al. [18]	Sarcoma	no	yes	FAPI = FDG	FAPI = FDG
Kömek et al. [19]	Breast cancer	yes	yes	FAPI > FDG	FAPI > FDG
Kreppel et al. [20]	Liver metastases of NETs	yes	NR	NR	FAPI > FDG
Kuten et al. [21]	Gastric cancer	no	yes	FAPI > FDG	FAPI > FDG
Lan et al. [22]	Various cancers	yes	no	FAPI > FDG	FAPI > FDG
Linz et al. [23]	Oral cancer	no	NR	FAPI = FDG	FAPI = FDG
Pang et al. [24]	Gastrointestinal cancers	yes	NR	FAPI > FDG	FAPI > FDG
Qin et al. [25]	Gastric cancer	yes	yes	FAPI > FDG	FAPI > FDG
Qin et al. [26]	Nasopharyngeal cancer	no	NR	FAPI = FDG	FAPI > FDG
Qin et al. [27]	Bone metastases or bone and joint lesions	no	NR	NR	FAPI > FDG
Sahin et al. [28]	Liver metastases of gastrointestinal cancers	no	yes	NR	FAPI > FDG

Treglia G et al. 2021- Head-to-Head Comparison of Fibroblast Activation Protein Inhibitors (FAPI) Radiotracers versus [^{18}F]F-FDG in Oncology: A Systematic Review. Int J Mol Sci

Treglia G et al. 2021- Head-to-Head Comparison of Fibroblast Activation Protein Inhibitors (FAPI) Radiotracers versus [^{18}F]F-FDG in Oncology: A Systematic Review. Int J Mol Sci

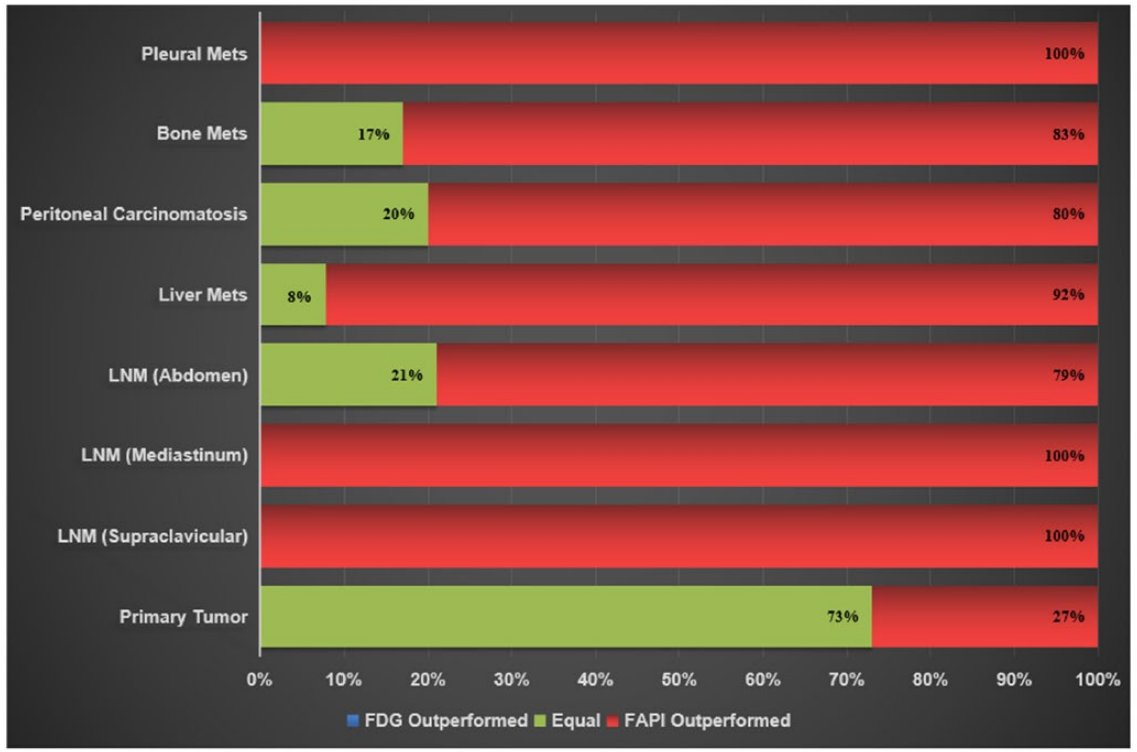
Authors	Cancer Evaluated	Significant Higher Uptake of Radiolabeled FAPI Compared to [^{18}F]F-FDG	Significant Higher TBR of Radiolabeled FAPI Compared to [^{18}F]F-FDG	Comparison in the Detection of Primary Tumors	Comparison in the Detection of Metastases
Serfling et al. [29]	Suspicious tonsillary tumor or CUP	no	yes	FAPI = FDG	FAPI < FDG
Shi et al. [30]	Liver cancer	yes	yes	FAPI > FDG	FAPI > FDG
Wang et al. [31]	Various cancers	no	yes	FAPI = FDG	FAPI > FDG
Wang et al. [32]	Liver cancer	no	yes	FAPI > FDG	FAPI > FDG
Zhao et al. [33]	Esophageal cancer	yes	NR	NR	NR
Zhao et al. [34]	Peritoneal carcinomatosis	yes	NR	NR	FAPI > FDG
Zhao et al. [35]	Nasopharyngeal cancer	yes	NR	FAPI = FDG	FAPI > FDG

Legend: [^{18}F]F = fluorine-18; CT = computed tomography; FAPI = fibroblast activation protein inhibitor; FDG = fluorodeoxyglucose; NR = not reported; PET = positron emission tomography; TBR = tumor-to-background ratio.

- Equal or superior detection performance of FAP targeted radioligands compared to FDG in various cancers
- Preliminary results in the following cancers look promising for detection FAP targeted radioligands:
  - Gastrointestinal (liver, pancreatic, colorectal, gastric etc)
  - Esophageal
  - Head and Neck/CUP
  - Breast
  - Lung
- Seeing superior performance compared to FDG in metastatic lesion detection

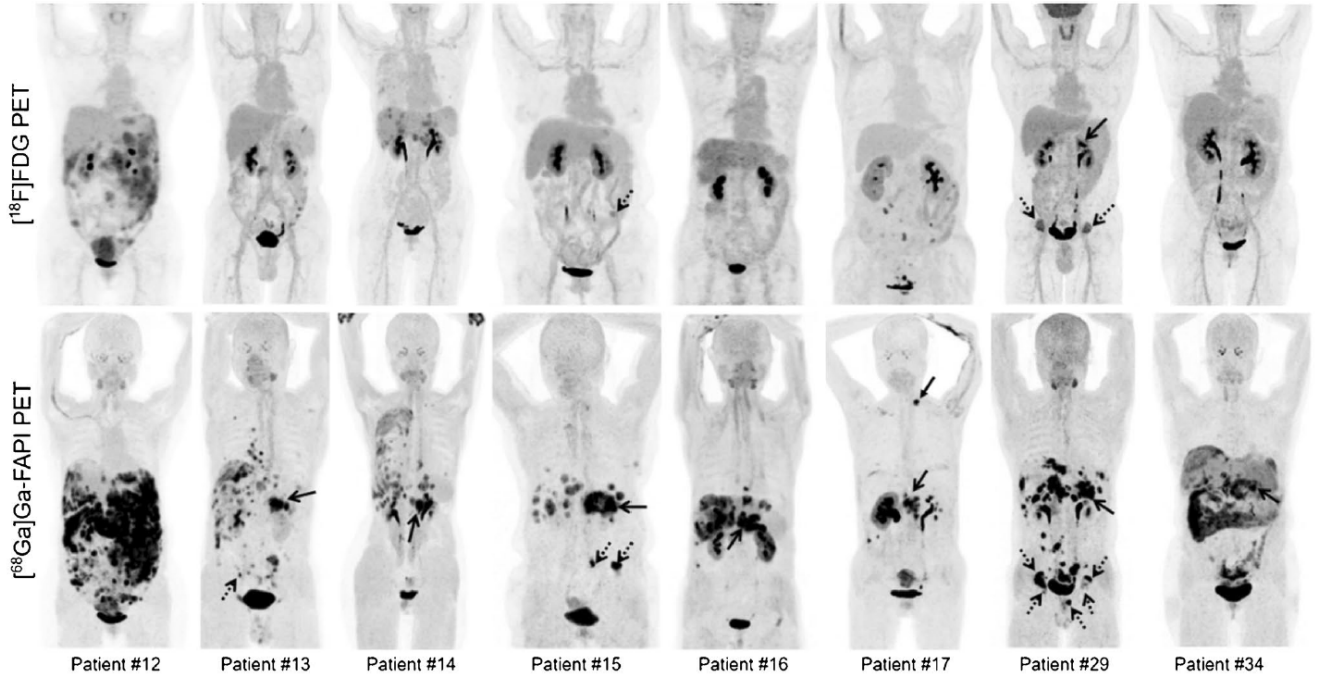
Examples

Pancreatic Cancer

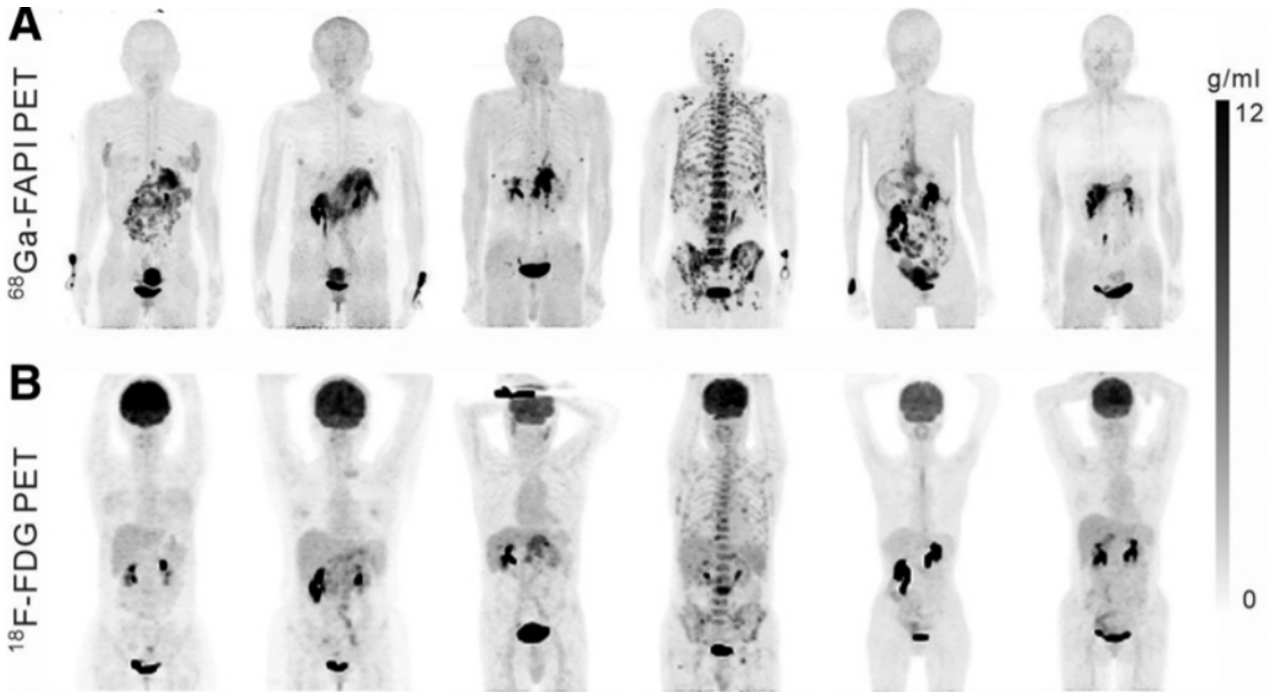


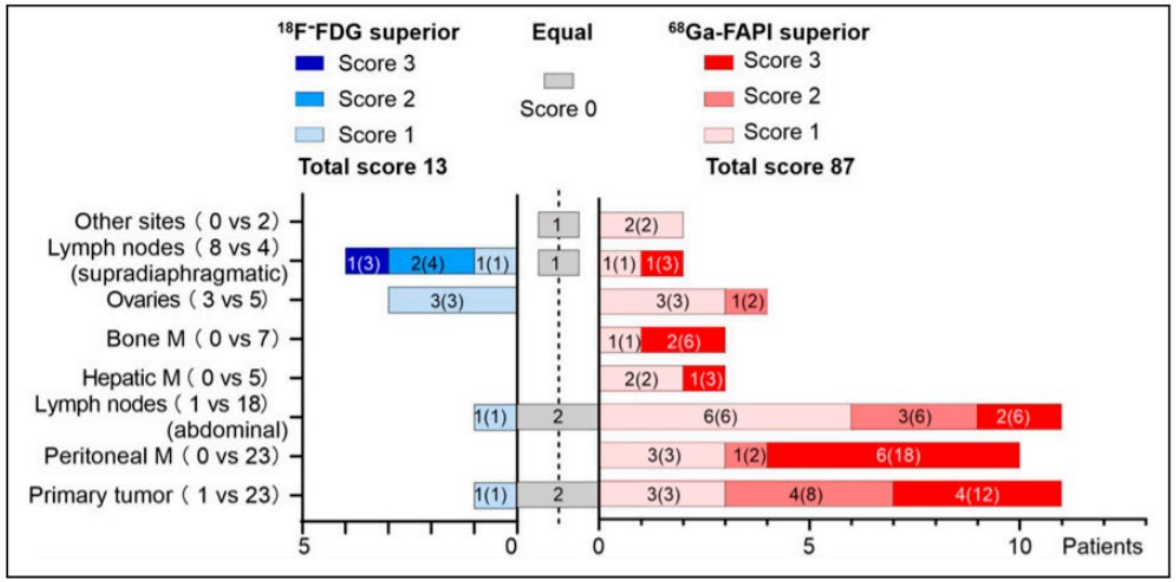
Parameters	Primary Tumor	LNM (Supraclavicular)	LNM (Mediastinum)	LNM (Abdomen)	Liver Mets	Peritoneal Carcinomatosis	Bone Mets	Pleural Mets
FAPI Outperformed	7	1	1	11	11	8	5	2
Equal	19	0	0	3	1	2	1	0
FDG Outperformed	0	0	0	0	0	0	0	0

Pang et. al, 2021- Positron emission tomography and computed tomography with [68Ga]fibroblast activation protein inhibitors improves tumor detection and staging in patients with pancreatic cancer



Gastric Cancer

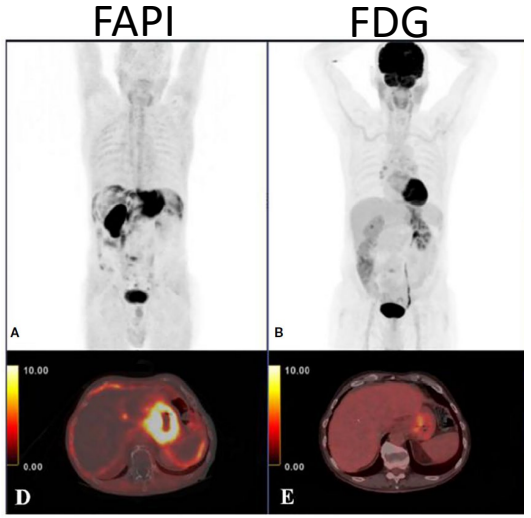




Qin et al. ^{68}Ga-DOTA-FAPI-04 PET/MR in the Evaluation of Gastric Carcinomas: Comparison with 18F-FDG PET/CT

FAPI PET was superior to FDG PET in both patient-based and lesion-based evaluation in primary and metastatic (1 exception highlighted below)

Kuten et al. Head-to-head comparison of [68Ga]Ga-FAPI-04 and [18F]-FDG PET/CT in evaluating the extent of disease in gastric adenocarcinoma



Poorly differentiated gastric adenocarcinoma and peritoneal carcinomatosis.

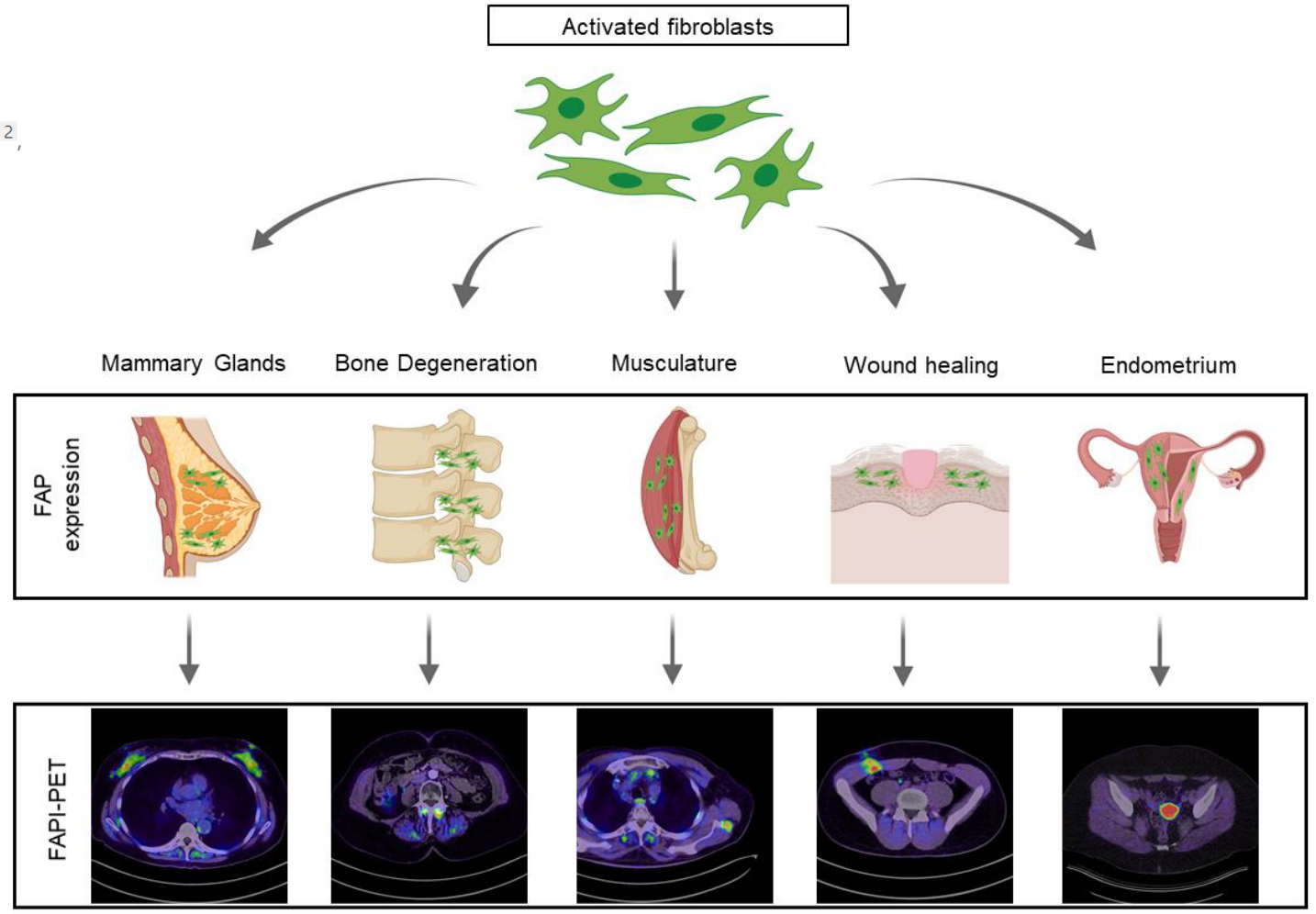
Pitfalls- Considerations to be made in FAP targeting image interpretations

Pitfalls and common findings in ^{68}Ga-FAPI-PET – A pictorial analysis

Lukas Kessler [1], Justin Ferdinandus [1], Nader Hirmas [1], Fadi Zarrad [1], Michael Nader [1], David Kersting [1], Manuel Weber [1], Sandra Kazek [1], Miriam Sraieb [1], Rainer Hamacher [2], Katharina Lueckerath [1], Lale Umutlu [3], Wolfgang P Fendler [1], Christoph Rischpler [1]

University Hospital Essen

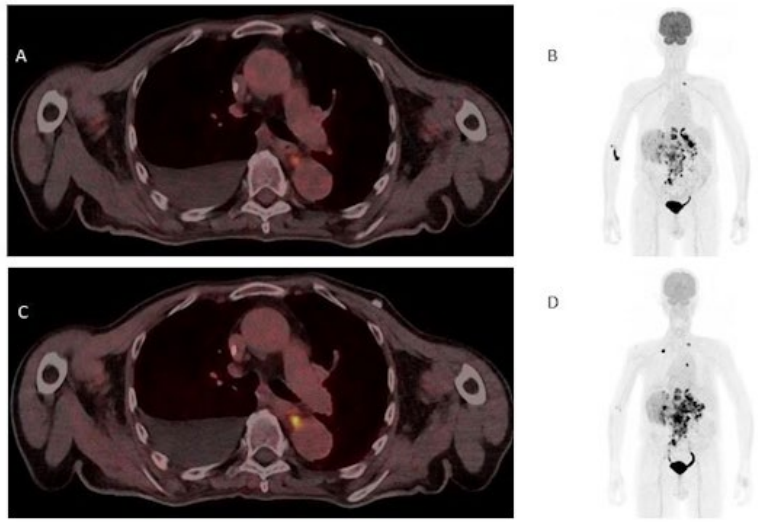
- 91 patients underwent whole-body PET/CT. Findings were rated in a consensus session of two experienced readers
- Non-tumor specific [^{68}Ga]-FAPI uptake in degenerative lesions, muscle, head-and-neck, scarring, mammary glands or uterus
- Common pitfall findings were **degenerative lesions** mostly associated to joints and vertebral bones



What is to come for FAP targeting in Diagnostics?

- Utility of FAP radiotracers will need to be evaluated in specific indications and tumor state (primary, nodal and distant metastasis) under prospective trials
- Identifying unmet clinical need
- FDG and FAP targeted radiopharmaceuticals image different critical biological processes in tumorigenesis. Each add respective value informing us of biology of disease. Important to focus on biology of disease information provided by each probe

"We hereby introduce a practicable single session/dual-tracer protocol combining the strengths of two tracers without losing any diagnostic information relevant to cancer staging," wrote first author Dr. Katrin Roth of University Hospital Cologne and colleagues."



Single-tracer PET/CT with F-18 FDG

Transverse section of fused dual-tracer F-18 FDG and Ga-68 FAPI-46 PET/CT of the same patient

List of THERAPEUTIC radiopharmaceuticals under investigation & published

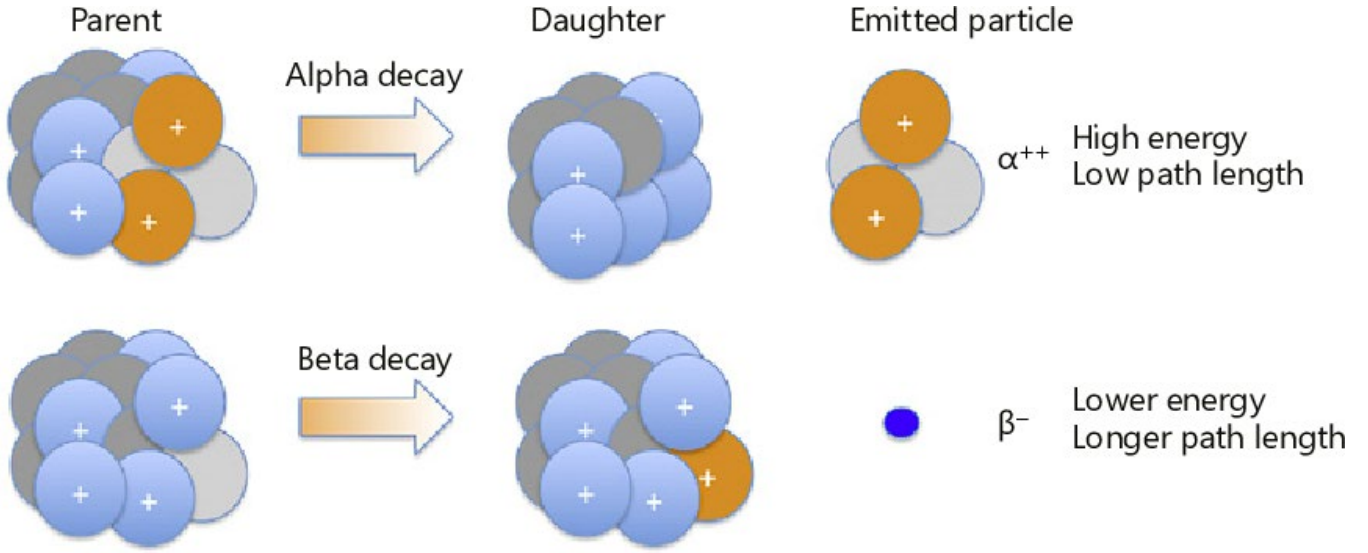
Compounds used for Radiotherapy with published clinical data

- FAPI family
  - FAPI-46
- FAP-2286
- [177Lu]-DOTAGA.(SA.FAPi) (Nov 2021 publication)

Radionuclide	Inhibitor	Quality of Radiation		Evaluation Phase
		Imaging	Radiotherapy	
^{177}Lu	FAPI-02	SPECT	Yes	Preclinical: glioblastoma xenograft
	FAPI-04			
	FAPI-46			Fully automated radiosynthesis unit
	RPS-309			Preclinical: liposarcoma xenograft
	OncoFAP			Preclinical: renal carcinoma and fibrosarcoma xenografts
	FAP-2286			Preclinical: HEK-FAP tumor bearing animalsClinical: Patients with diverse adenocarcinomas
^{153}Sm	FAPI-46	Scintigraphy	Yes	Clinical: Patient with lung metastatic, fibrous spindle cell soft tissue sarcoma
^{90}Y	FAPI-04	-	Yes	Clinical: metastatic breast cancer patient
	FAPI-46			Clinical: patient with metastasized breast and colorectal cancers
				Clinical: patients with metastatic soft tissue or bone sarcoma, and pancreatic cancer
^{225}Ac	FAPI-04	-	Yes	Preclinical: pancreatic cancer xenograft
^{64}Cu	FAPI-04	PET	Yes	

Imlimthan S et al. 2021. New Frontiers in Cancer Imaging and Therapy Based on Radiolabeled Fibroblast Activation Protein Inhibitors: A Rational Review and Current Progress. Pharmaceuticals (Basel)

Radioligand therapy: Considerations to be made



DOI:10.1159/000494760

Type of damage	Radionuclide	Half life
dsDNA damage	^{225}Ac	T1/2 = 10 days
	^{212}Pb/^{212}Bis*	T1/2 = 1 h
ssDNA damage	^{177}Lu	T1/2 = 6.7 d
	^{90}Y	T1/2 = 64 h
	^{212}Pb	T1/2 = 10.6 h

*^{212}Pb, by itself is a β-emitter, but acts as an in vivo generator for its short-lived α-emitting daughters.

- Assessment of RLT utility of FAP targeted radioligands is in early clinical investigation
- Alpha vs beta emission vs both
- Monotherapy vs Combination therapy (RLT followed by non RLT)
- Patient disease state and best course of treatment for the patient

3. Describe the current state of clinical development for FAP Inhibitors (FAPI) in diagnostic and companion diagnostic use

Evolution of FAPI Family of compounds

To Date
145 studies
88 unique institutions
34 countries
^{18}F-FAPI-74 and ^{68}Ga-FAPI-46

Apr 2018 — Development of **FAPI-02** and **FAPI-04** compounds by University Clinic Heidelberg (UKHD)

Mar 2019 — Development of **FAPI-46** with improved tumor retention as a theranostic agent

Apr 2019 — Investigation of FAPI compounds in **20+ cancers**

June 2019 — **SOFIE licensed FAPI** compounds from UKHD

July 2019 — Launch of the SOFIE **Global Outreach Program** for FAPI precursor

Mar 2021 — **Novartis** acquired **therapeutic** global rights for FAPI compound. **SOFIE** retained **diagnostic** global rights

Nov 2021 — SOFIE obtained an **IND for ^{68}Ga-FAPI-46** in PDAC

May 2022 — **NYU** as first clinical trial site activated for ^{68}Ga-FAPI-46 in US under IND

June 2022 — SOFIE schedules **Pre-IND meeting** with FDA for **^{18}F-FAPI-74** in GI cancers

SOFIE's Product Pipeline

Product	Indication	Pre-Clinical	Phase 1	Phase 2	Phase 3
SOFIE Sponsored Clinical Research program					
[^{18}F]-FAPI-74	Gastrointestinal Cancers	Pre-IND in support of Phase 2 scheduled			
[^{68}Ga]-FAPI-46	Pancreatic Cancer	Phase 2 initiated			
SOFIE FAPI Global Outreach Program: 140+ Investigator Initiated Studies being conducted by 80+ sites globally					
[^{18}F]-FAPI-74 [^{68}Ga]-FAPI-46	Oncology	✓	✓	✓	
[^{18}F]-FAPI-74 [^{68}Ga]-FAPI-46	Non-Oncology: Fibrosis Inflammation Cardiovascular	✓	✓	✓	

Family of compounds

[^{68}Ga]-FAPI-46

Gallium isotope

Number 46
Specific compound

- Lead **gallium** labeled compound.
- DOTA chelator in the molecular structure allows coupling of the FAPI molecules for theranostic use
- SOFIE has obtained an **IND** for [^{68}Ga]-FAPI-46 for a Phase 2 study
- A **Phase 2**, Multicenter, Single Arm, Open Label, Non-Randomized Study of [^{68}Ga]FAPI-46 PET in Patients with Resectable or Borderline Resectable **Pancreatic Ductal Carcinoma**
- Total number of patients: **60**
- Study launch: **May 2022**
- First site activated: **NYU**

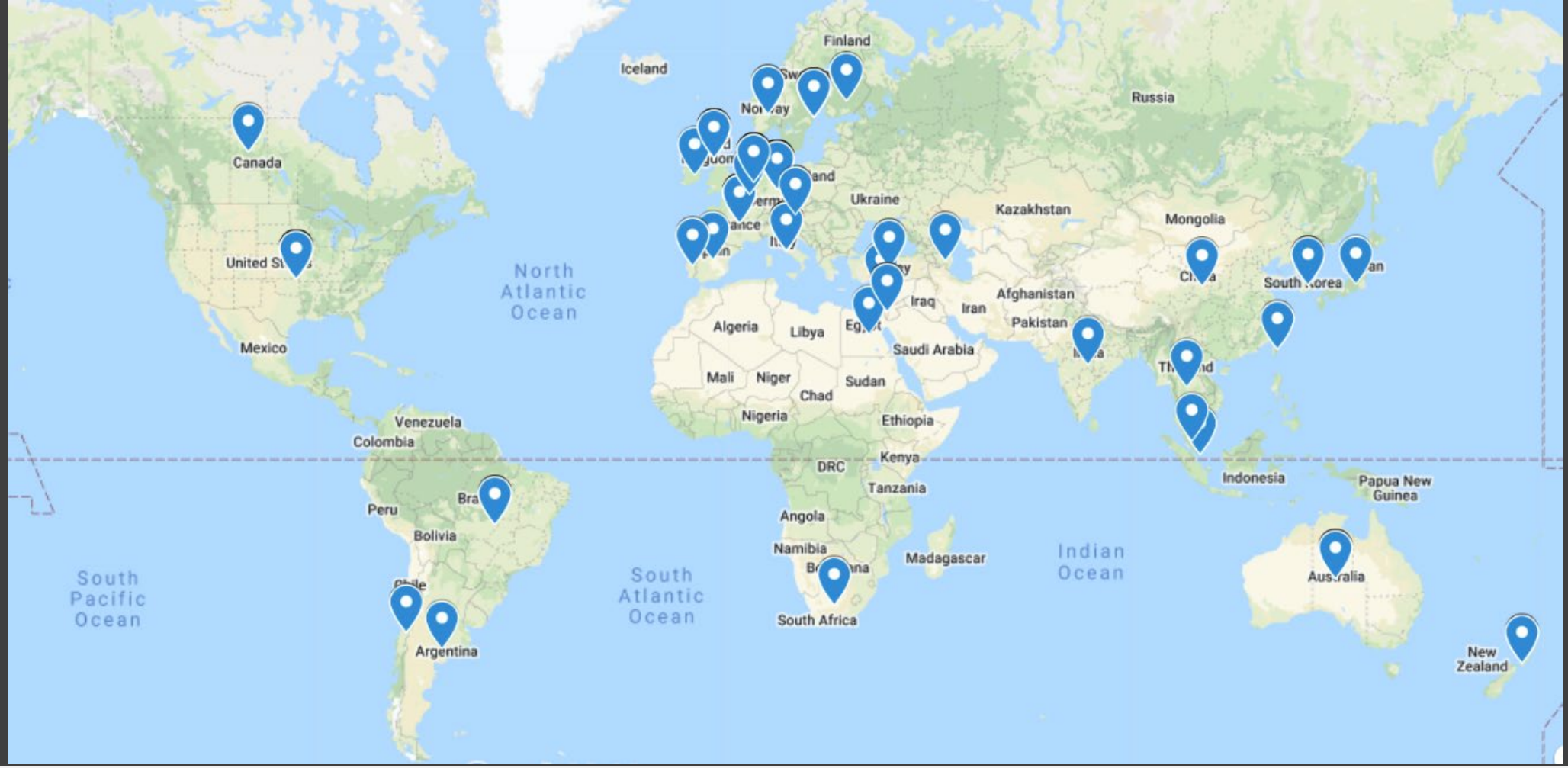
Family of compounds

[^{18}F]-FAPI-74

Fluorine isotope

Number 74
Specific compound

- Lead **Fluorine 18** compound
- Allows for broader applicability of FAPI PET through 18-F radiolabeling
  - Established supply chain with higher level of supply capacity with convenience to imaging practices
  - Provides advantage of a longer half life (2 hours)
  - Meeting the capacity to support larger studies with high patient throughput
- **Automated synthesis** consumables available through Trasis for MiniAIO and AIO
- Pre-IND meeting scheduled with FDA for **July 2022**
- IND enabling data completed



SOFIE's FAPI Global Outreach Program

- 34 Countries
- 140+ research studies
- Studies include: Chemistry, pre-clinical, clinical, oncology and non-oncology
- 80+ unique institutions
- Compounds: [^{18}F]-FAPI-74 and [^{68}Ga]-FAPI-46

SOFIE's FAPI Global Outreach Program

- **Gain access to GMP grade precursor and reference standard in support of investigator-initiated trial**
- **Technical manufacturing assistance to get the sites started**
- **Cross Reference to SOFIE's IND(s) or IND content to pursue investigator-initiated trial**
- **Allows sites to expand their research program and grant opportunities**

Process for access to FAPI precursor

Introductory Call → Application Completion → Application Approval → MTA Signature → Material Shipment

SOFIE's vision is to improve patient outcomes by developing and delivering molecular diagnostics and therapeutics (theranostics).

With our robust radiopharmaceutical production and distribution network, mature contract manufacturing services in a new, 20,000 ft^2 facility in New Jersey and FAPI intellectual property, we are poised to deliver on the promise of theranostics.

6:30–8:30 pm PDT

CLOVIS ONCOLOGY POINT BIOPHARMA SOFIE From start to clinic

FAP Ligands for Imaging and Therapy

FAP (fibroblast activation protein) as a diagnostic and therapeutic target for radiopharmaceuticals has seen many advances in recent years. This special session will bring together researchers and industry sponsors to discuss the latest progress in this space.

Click here for SOFIE FAPI Flyer.

Moderators:

Professor Ken Herrmann, MD, MBA, University Hospital Essen
Professor Johannes Czernin, MD, University of California, Los Angeles

Speakers:

Professor Frederik L. Giesel, MD, MBA, University Hospital Düsseldorf, Germany
Associate Professor Jeremie Calais, MD, MSc, University of California, Los Angeles
Professor Thomas Hope, MD, University of California, San Francisco
Robin Hallett, PhD, VP Discovery and Translational Sciences, POINT Biopharma
Sherly Mosessian, PhD, Chief Scientific Officer, SOFIE Biosciences
Elcin Zan, MD, Director, Nuclear Theranostics, New York University
Curt Wolfgang, PhD, VP, Clinical Development, Clovis Oncology

Visit SOFIE at the upcoming meeting from June 11 – 14, 2022 in Vancouver, Canada at Booth #319.

FAP Satellite Symposium at SNMMI – Sunday, June 12, 2022 from 6:30–8:30 pm PDT

Questions? Reach out to me at Sherly.Mosessian@sofie.com