

# **Current State of FAP Ligands for Diagnostic Use in Oncology**

**SOFIE Educational Webinar Series** 

6/14/23
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## **Learning Objectives**

- 1. Explain the significance of FAP as a target in oncology
- 2. Highlight the progress made to date with FAP targeting ligands for diagnostic use in oncology
- Describe the current clinical trials and regulatory landscape for FAP targeting ligands



## FAP as a target in oncology

## **FAP (Fibroblast Activation Protein)**

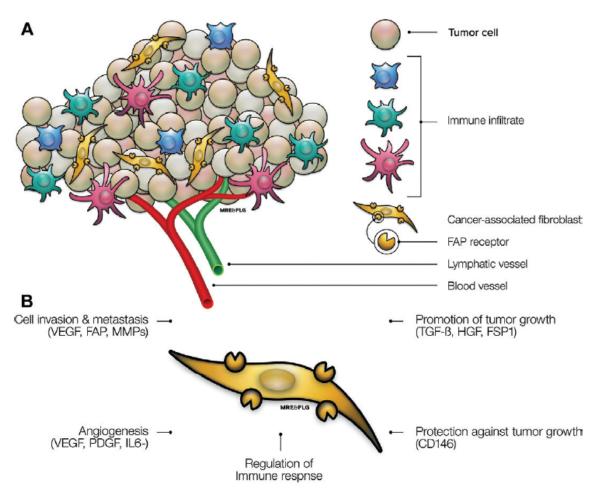
Activated Fibroblasts express high levels of FAP

Fibroblasts become activated during wound repair and regeneration. Malignant tumors are recognized as "wounds that do not heal"

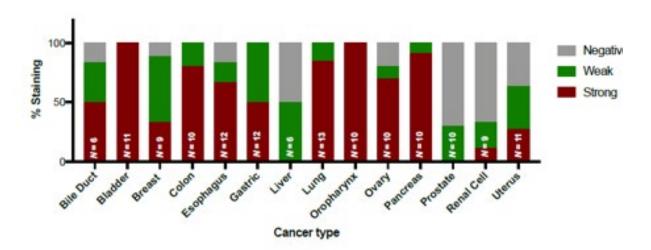
Among all the stromal cells, cancer-associated fibroblasts (CAFs) are dominant populations in the tumor microenvironment

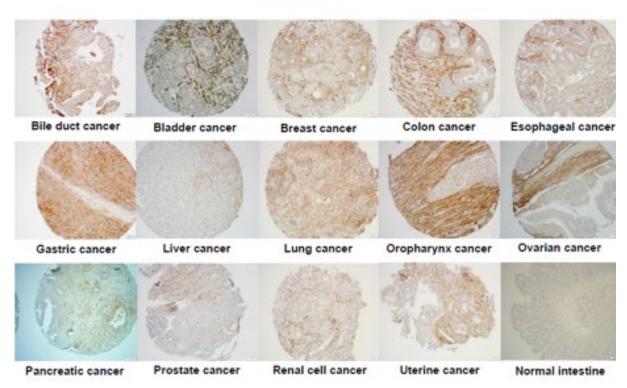
**FAP** is highly expressed on the surface of CAFs

FAP is a great target due to its overexpression in most of the cancer types (90%)



Mori Y, Dendl K, Cardinale J, Kratochwil C, Giesel FL, Haberkorn U. FAPI PET: Fibroblast Activation Protein Inhibitor Use in Oncologic and Nononcologic Disease. Radiology. 2023 Jan 3:220749. doi: 10.1148/radiol.220749. Epub ahead of print. PMID: 36594838.





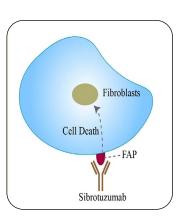
Mona et al. doi: 10.2967/jnumed.121.262426

## FAP protein expression in various cancer tissues

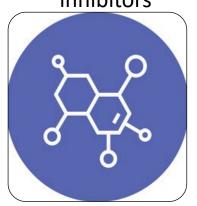
- FAP is highly expressed in an array of different cancers (stroma cells not typically tumor)
- FAP expression is detected in the tumor cells of sarcomas
- Noteworthy: Colorectal, GI/stomach, Thyroid/Oropharynx, Pancreas, Ovarian, Lung and Bladder/Urothelial show high expression of FAP in data displayed here

Note: FAP expression levels can vary based on sample size, sample location, sub-type of disease and stage of disease.

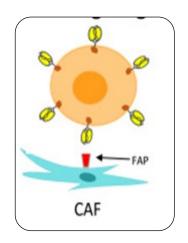
Antibody



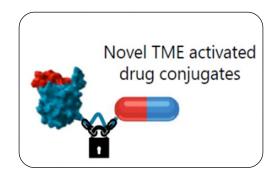
DPP-4 small molecule inhibitors



CAR T Cell Therapy



#### Pro-drug



#### **Sibrotuzumab**

Boehringer
Ingelheim product for targeting various cancers

Results did not show sufficient efficacy in 2003 Phase II study

Roche and Molecular Partners AG have active studies in clinical trials involving antibodies

## Talabostat & Linagliptin

Talabostat has shown some efficacy in Phase 2 but safety concerns paused further studies

Linagliptin is approved drug for type 2 diabetes

#### **Car T Cell Therapy**

FAP-targeting CAR-T cells genetically engineered to target CAFs in various solid cancers

Clinical trials are in early stages.

#### AVA6000

– FAPα-ActivatedDoxorubicin

Phase 1 study active

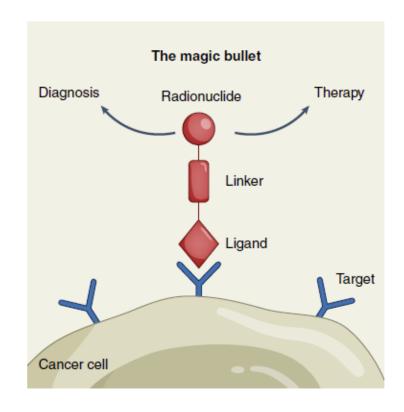
Note: these are select examples, not a comprehensive list

# Radiopharmaceuticals targeting FAP

## **Theranostics**

**Diagnostic**: PET imaging to visualize cells expressing the target of interest (FAP). Short-lived radionuclide <sup>68</sup>Ga or <sup>18</sup>F

Therapeutic: Molecular targeted radio-ablation of cancer or cancer associated cells Long-lived radionuclide <sup>177</sup>Lu ,<sup>225</sup>Ac, <sup>212</sup>Pb or other beta or alpha particle emitters



The magic bullet. Theranostics target unique properties of cancer cells using different radionuclides for diagnosis and treatment.

Credit: Marina Spence/Nature Medicine

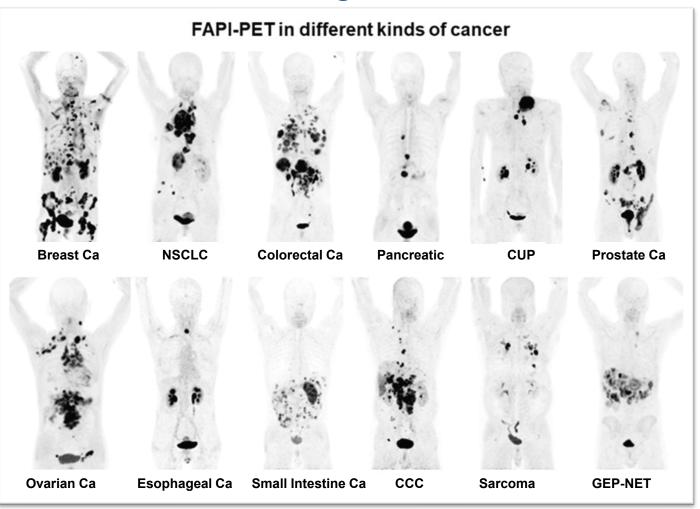
Carrie Arnold Nature News 2022



#### (Fibroblast Activation Protein Inhibitor)-FAPI family of compounds

"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."

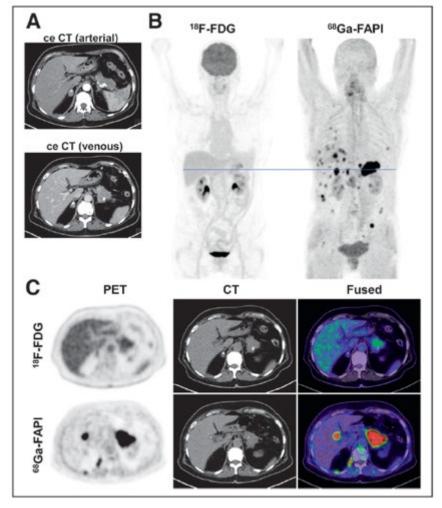
#### **SNMMI** Image of the Year 2019



#### **JNM Best Clinical Article in 2021**

Impact of 68Ga-FAPI PET/CT Imaging on the Therapeutic Management of Primary and Recurrent PDAC

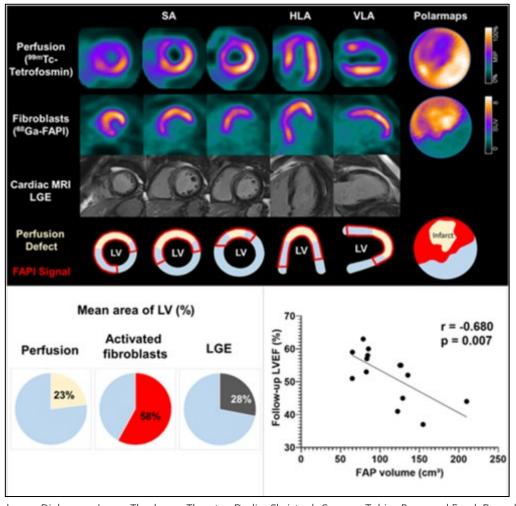
[68Ga]FAPI PET/CT results led to changes in TNM staging in 10 of 19 patients



Röhrich M, Naumann P, Giesel FL, Choyke PL, Staudinger F, Wefers A, Liew DP, Kratochwil C, Rathke H, Liermann J, Herfarth K, Jäger D, Debus J, Haberkorn U, Lang M, Koerber SA. Impact of 68Ga-FAPI PET/CT Imaging on the Therapeutic Management of Primary and Recurrent Pancreatic Ductal Adenocarcinomas. J Nucl Med. 2021 Jun 1;62(6):779-786

### **SNMMI** Image of the Year 2022

Representative case with acute anterior wall myocardial infarction: [68Ga]FAPI-46



Johanna Diekmann, James Thackeray, Thorsten Derlin, Christoph Czerner, Tobias Ross, and Frank Bengel, Department of Nuclear Medicine, Hannover Medical School, Hannover, Niedersachsen, Germany; and Tobias Koenig, Jonas Neuser, Andreas Schaefer, Jochen Tillmans, and Johann Bauersachs, Department of Cardiology and Angiology, Hannover School of Medicine, Hannover, Niedersachsen, Germany.

## FAP Radioligand as biomarker for FAP expression

#### What is a biomarker?

Live visualization and quantitation of FAP expression in humans

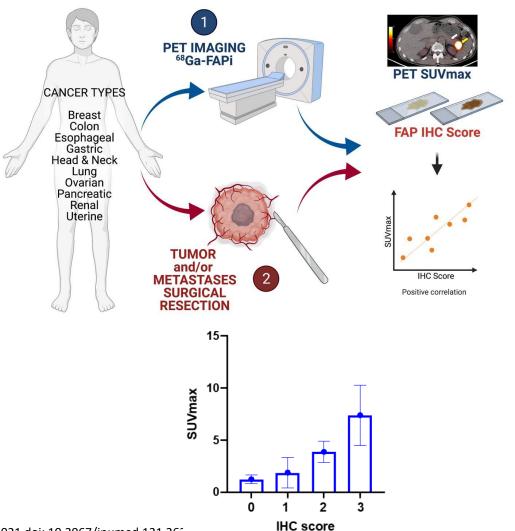
#### Why is this of value?

- Early diagnosis
- Disease staging
- Management of care
- Companion diagnostic
  - Enrich percent responders in therapy trials and in patient care
  - Patient selection assay for effective therapy
- Treatment monitoring

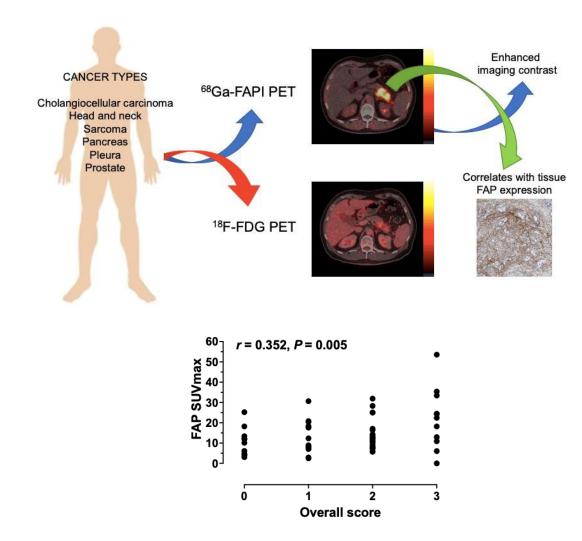


#### FAP IHC and PET signal validation- 2 independent studies for [68Ga]FAPI-46

Correlation between FAP immunohistochemistry score and <sup>68</sup>Ga-FAPI-46 PET SUVs across cancer and non-cancer tissues



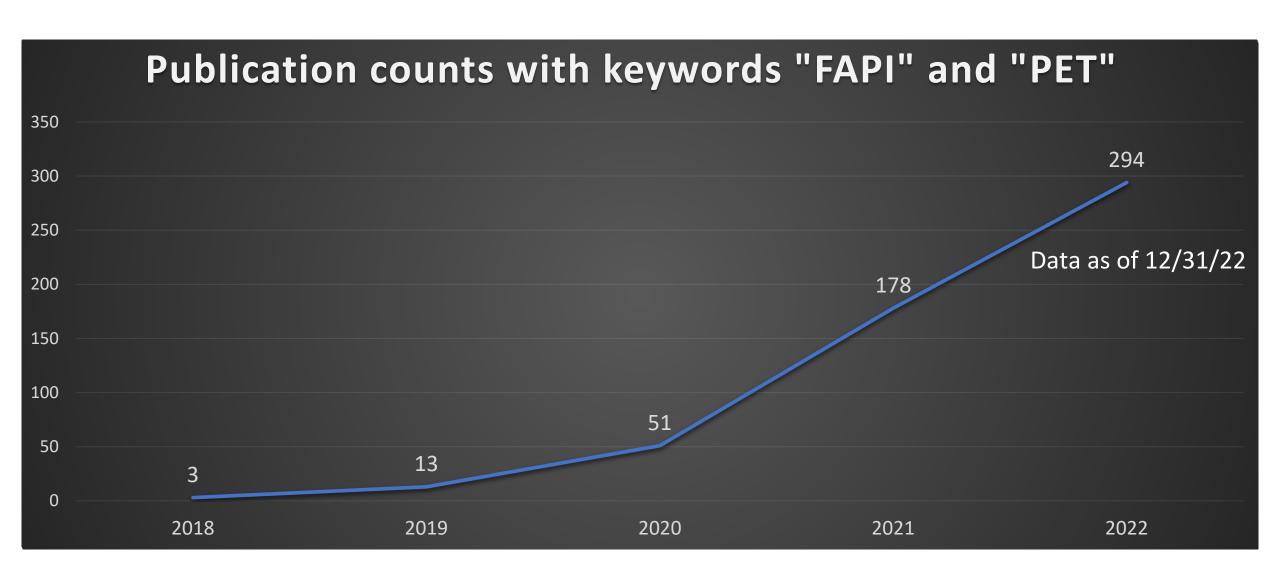
Fibroblast activation protein positron emission tomography and histopathology in a single-center database of 324 patients and 21 tumor entities



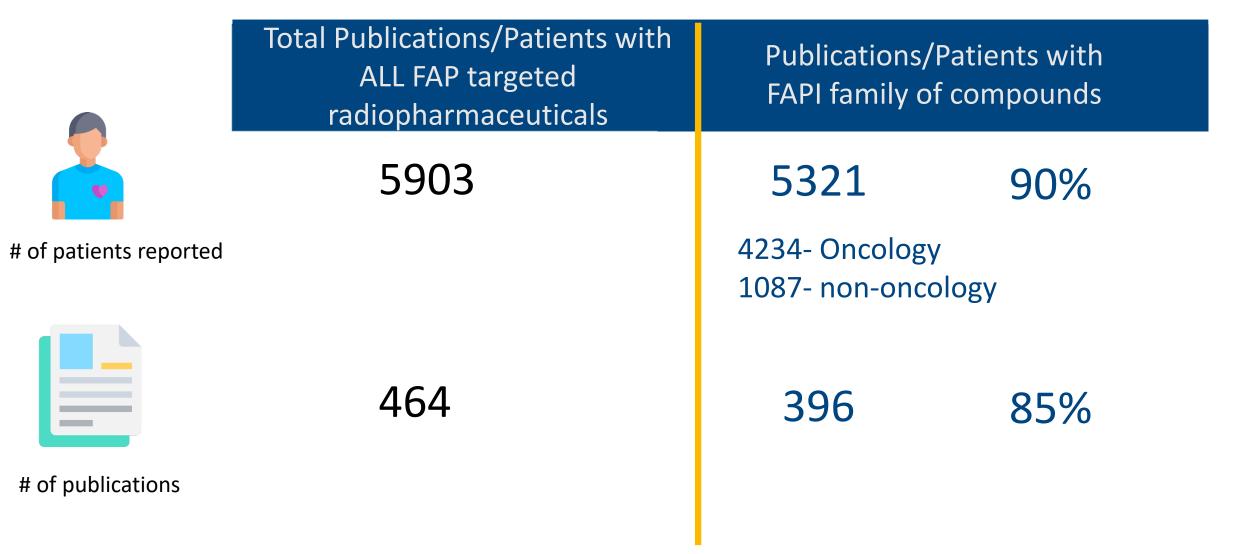


Progress made to date with FAP targeting ligands for diagnostic use in oncology

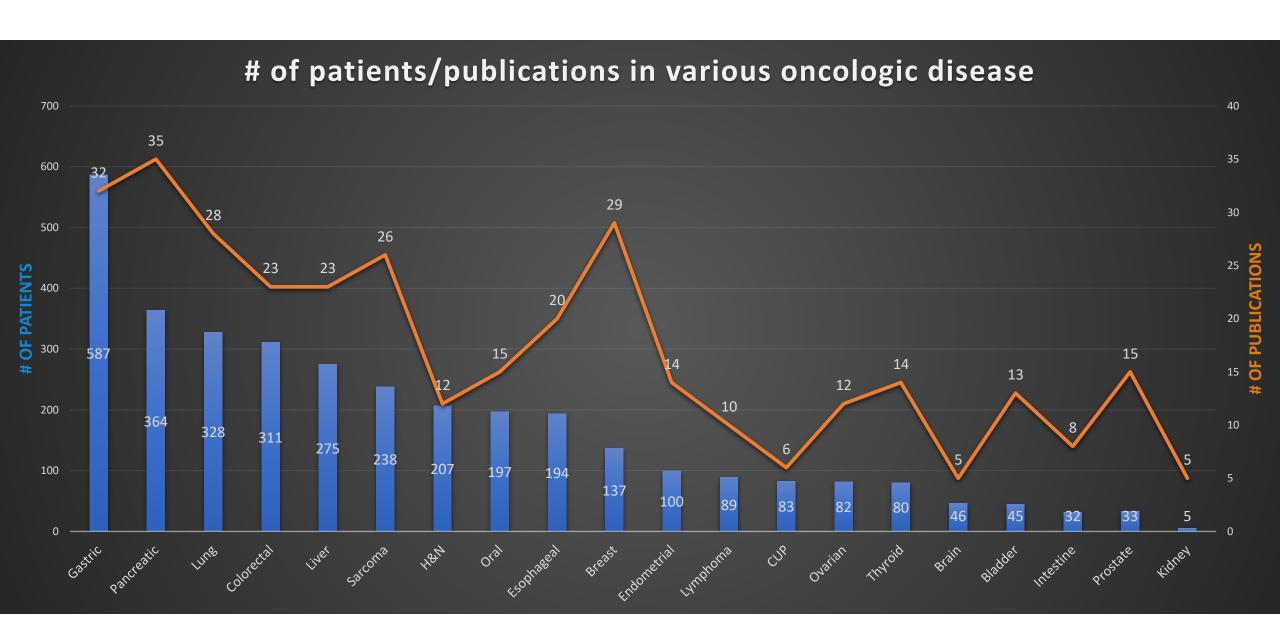
## Mounting interest and growth in published evidence with FAPI



## **Publication analysis**



Takeaway: FAPI family of compounds comprise the majority of publications and patient reported data to date (May 2023). (Review articles are excluded)

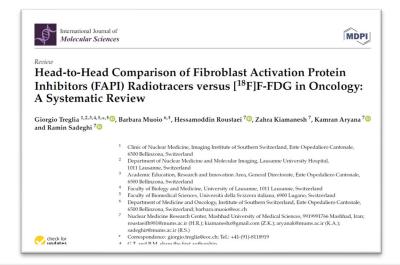


GI cancers encompass majority of the patient numbers reported with FAPI

## Meta Data Analysis of FAP radioligands in imaging

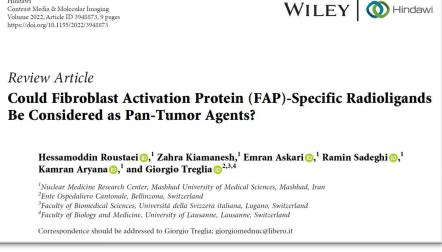
Takeaway: strong prelim data of performance in various cancers, especially GI/biliary/liver











> Front Oncol. 2023 Feb 17;13:1093861. doi: 10.3389/fonc.2023.1093861. eCollection 2023.

Comparison of <sup>68</sup>Ga-FAPI and <sup>18</sup>F-FDG PET/CT for the diagnosis of primary and metastatic lesions in abdominal and pelvic malignancies: A systematic review and meta-analysis

Xue Liu <sup>11</sup>, Huiting Liu <sup>13</sup>, Cailiang Gao <sup>11</sup>, Wenbing Zeng <sup>2</sup>

PMID: 36874127 PMCID: PMC9982086 DOI: 10.3389/fonc.2023.1093861

Affiliations + expand

## Evaluation of the Diagnostic Accuracy of FAPI PET/CT in Oncological Studies: Systematic Review and Meta-Analysis

FAPI is a promising radiotracer for oncological molecular imaging due to FAP overexpression in most cancerous tissues



Determine the pooled diagnostic accuracy of FAPI PET/CT vs [18F]FDG PET/CT reported in oncological studies

Search Updated April 2022





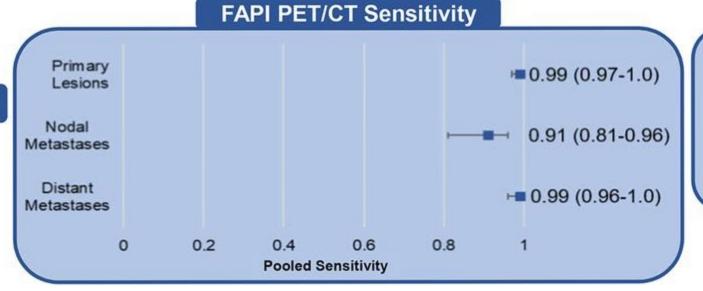
34 compared FAPI and [18F]FDG
5 looked at FAPI alone



1259 Patients

Various Cancer Types



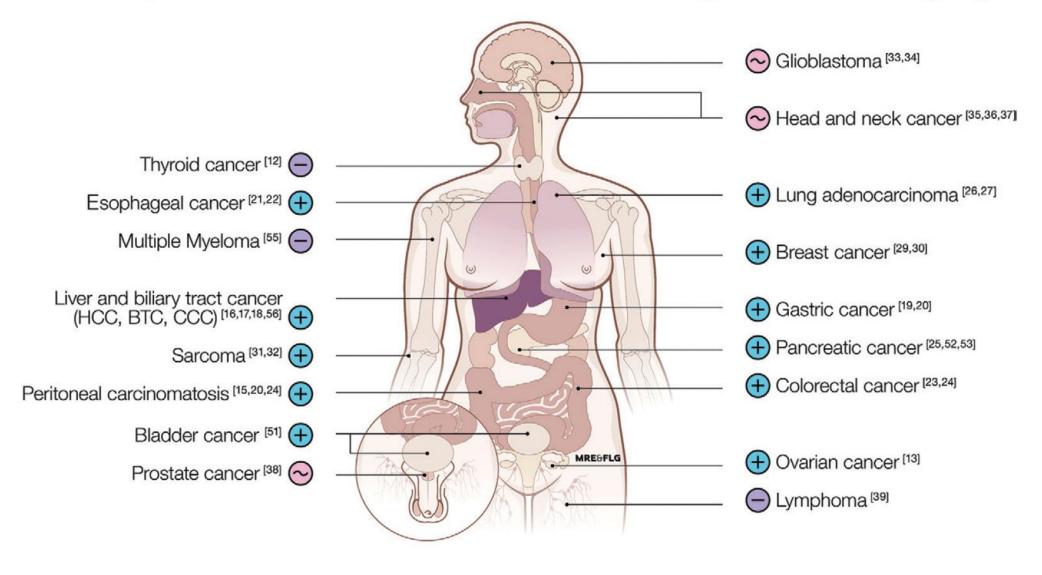


FAPI is highly sensitive in the detection of primary, nodal, and metastatic lesions.

In comparison to [18F]FDG PET/CT, FAPI PET/CT had a higher sensitivity in the detection of all three lesion types

Wass G, Clifford K, Subramaniam RM. Evaluation of the Diagnostic Accuracy of FAPI PET/CT in Oncologic Studies: Systematic Review and Metaanalysis. J Nucl Med. 2023 Jun

### Comparison of FAPI vs. FDG in oncological PET-imaging



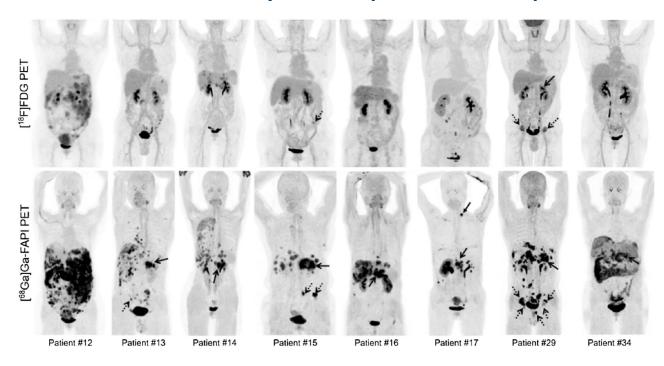






## **Pancreatic Cancer**

#### FDG and FAPI side by side comparison in same patients



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

#### Changes in care management/staging due to FAPI

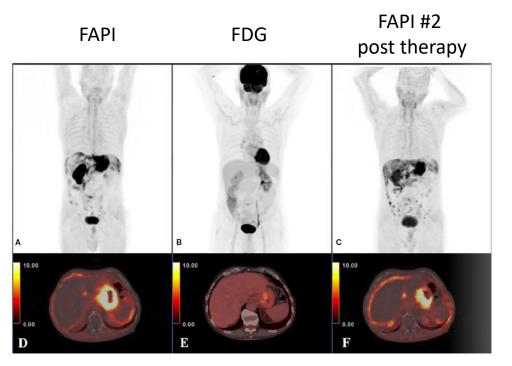
TABLE 2

Comparison of ceCT-Based and <sup>68</sup>Ga-FAPI PET/CT-Based TNM Staging of 19 Patients with Primary and Recurrent/Progressive PDAC

Patient	Clinical indication	TNM stage (CT-based)	TNM stage (FAPI PET-based)	Additional finding in FAPI PET	Staging change
1	Relapse/progression	T1 N2 M1 (LYM, PUL)	T1 N0 M1 (LYM)	(Recurrent) mediastinal lymph node metastases	Up
2	Relapse/progression	T4 N0 M1 (PER)	T4 N0 M1 (PER)	None	None
3	Relapse/progression	T3 N0 M0	T3 N0 M1 (OSS)	Bone metastasis	Up
4	Relapse/progression	T4 N0 Mx	T4 N0 M1 (PER)	Peritoneal carcinosis	Up
5	Primary staging	T1 N0 M0	T1 N0 M0	None	None
6	Relapse/progression	T3 N0 M0	T3 N0 M0	None	None
7	Relapse/progression	T4 N0 Mx	T4 N0 M0	None	None
8	Primary staging	T4 N0 Mx	T4 N0 M0	None	None
9	Primary staging	T4 N0 M0	T4 N0 M0	None	None
10	Relapse/progression	T2 N0 M0	T0 N0 M0	No local recurrence (T0)	Down
11	Relapse/progression	T4 N0 M1 (LYM, HEP)	T4 N2 M1 (LYM, HEP, OSS)	Abdominal lymph node metastases, 2 more liver metastases, bone metastasis	Up
12	Primary staging	T4 N0 Mx	T4 N0 M0	None	None
13	Primary staging	T3 N0 M0	T3 N0 M0	None	None
14	Relapse/progression	T4 N2 M1 (HEP)	T4 N2 M1 (HEP, PER)	Peritoneal carcinosis	Up
15	Primary staging	T4 N2 Mx	T4 N2 M1 (PER, PLE)	Pleural carcinosis, peritoneal carcinosis, liver metastases	Up
16	Relapse/progression	T0 N2 M1 (LYM, HEP)	T0 N2 M1 (LYM, HEP, OSS)	Bone metastasis	Up
17	Relapse/progression	T2 N0 Mx	T2 N0 M1 (HEP, PUL)	Liver metastases without CT correlate, pulmonary metastasis	Up
18	Primary staging	T1 N0 Mx	T1 N0 M0	None	None
19	Relapse/progression	T4 Nx M1 (PER)	T4 N1 M1 (PER, OSS, HEP)	Lymph nodes definable from tumor conglomerate, bone metastases, liver metastases	Up

Impact of 68Ga-FAPI PET/CT Imaging on the Therapeutic Management of Primary and Recurrent Pancreatic Ductal Adenocarcinomas Manuel Rohrich et al, 2021

## **Gastric Cancer**



Kuten et al. 2022

Lesion location	<sup>18</sup> FDG PET-CT		<sup>68</sup> Ga-FAPI PET-CT		
	Mean	Median (min-max)	Mean	Median (min-max)	p value
Primary cancer	8.4	7.5 (0.0–19.0)	14.6	13.2 (4.7–33.0)	< 0.001
Peritoneal metastasis	3.1	2.6 (0.0-17.8)	10.7	8.1 (3.5-27.4)	< 0.001
Lymph node metastasis	4.9	3.9 (0.0-17.6)	9.9	8.3 (0.0-21.5)	0.006
Lung metastasis	1.23	4.0 (0.0-3.7)	0.0	4.5 (2.5-5.0)	0.109
Liver metastasis	5.0	4.7 (0.0-14.8)	12.2	8.5 (0.0-55.0)	0.002
Bone metastasis	4.87	0.0 (0.0-14.5)	20.3	13.4 (3.4-62.0)	0.018

Comparison of 68Ga-FAPI PET/CT and 18FDGPET/CT Modalities in Gastrointestinal System Malignancies with Peritoneal Involvement. Elboga et al

#### FDG and FAPI side by side comparison in same patients

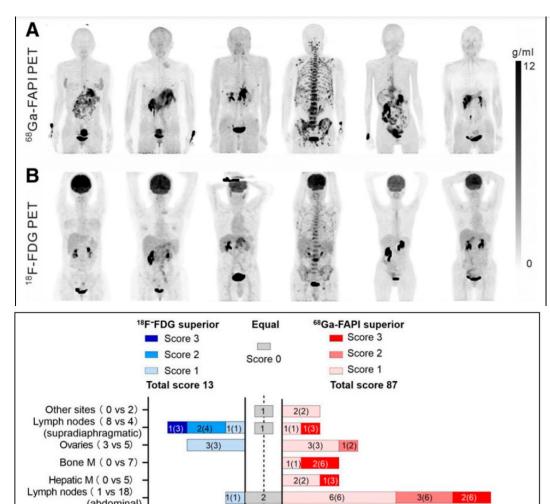


FIGURE 2. Comparison of visual assessment between <sup>68</sup>Ga-FAPI PET and <sup>18</sup>F-FDG PET. n(n) in each bar refers to patient number (scores); M = metastases.

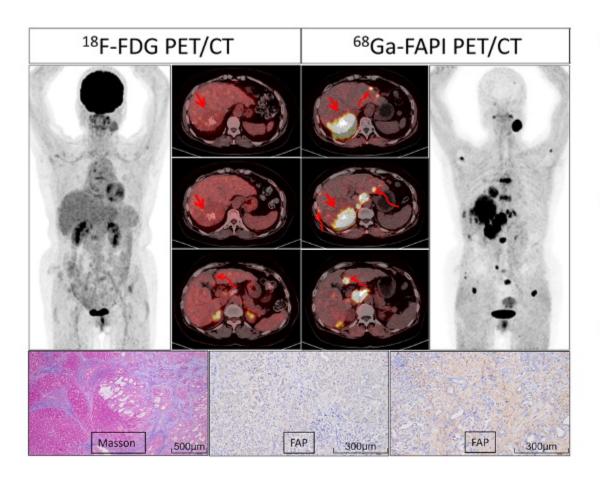
10 Patients

Comparison of 68Ga-FAPI and 18F-FDG Uptake in Gastric, Duodenal, and Colorectal Cancers. Pang et al.

(abdominal)

Peritoneal M (0 vs 23) Primary tumor (1 vs 23)

#### Influence of Cirrhosis on <sup>68</sup>Ga-FAPI PET/CT in Intrahepatic Tumors



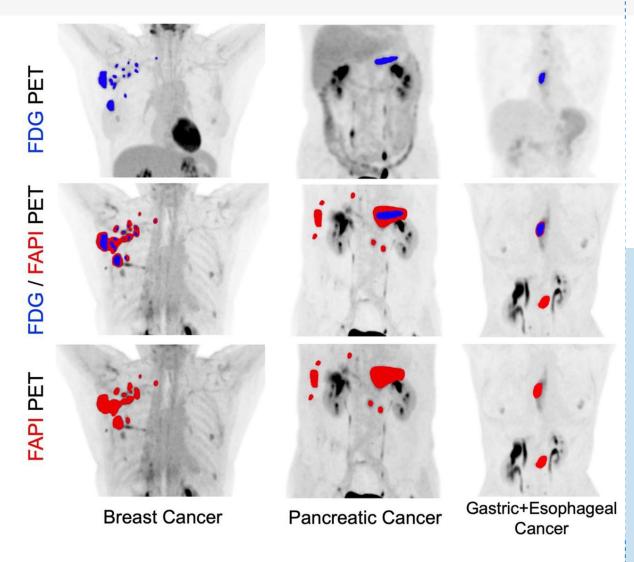
- In a secondary analysis of a prospective trial, 48
  patients without cirrhosis underwent <sup>68</sup>Ga-FAPI PET/CT
  and 39 patients with cirrhosis underwent <sup>68</sup>Ga-FAPI
  and <sup>18</sup>F-FDG PET/CT.
- Patients with cirrhosis had higher uptake of <sup>68</sup>Ga-FAPI in the liver than patients without cirrhosis (average SUV, 1.4 [IQR, 0.6–2.9] vs 0.5 [IQR 0.4–2.7]).
- 68Ga-FAPI PET/CT identified 104 of 106 (98%) and 66 of 71 (93%) intrahepatic tumors in patients with and those without cirrhosis, which was higher than the 41% of tumors identified with <sup>18</sup>F-FDG PET/CT in patients with cirrhosis.

Peng D and Cao J et al. Published Online: May 23, 2023

https://doi.org/10.1148/radiol.222448



Initial Evaluation of
[18F]FAPI-74 PET for
Various Histopathologically
Confirmed Cancers and
Benign Lesions



Tadashi Watabe et al. J Nucl Med 2023;jnumed.123.265486



## Challenges to overcome

#### **PUBLICATIONS**

- Many case studies. Shortage of larger cohort studies
- Many retrospective/compassionate use studies
- Use of various FAP targeting compounds (FAPI-04 for example is an older generation instead of FAPI-46 or FAPI-74)

#### **ANALYSIS**

- Comparison to FDG as the accepted standard instead of standard of care imaging
- Much emphasis on lesion number detection and less on management of care

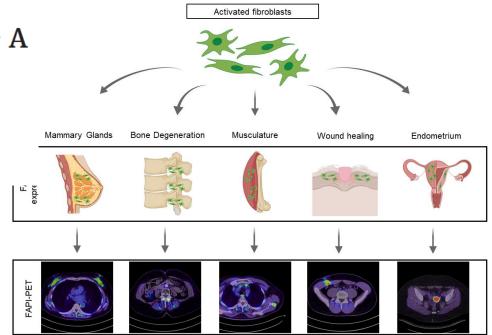


Pitfalls and common findings in <sup>68</sup> Ga-FAPI-PET - A pictorial analysis

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

#### **University Hospital Essen**

Common pitfall findings were **degenerative lesions** mostly associated to joints and vertebral bones



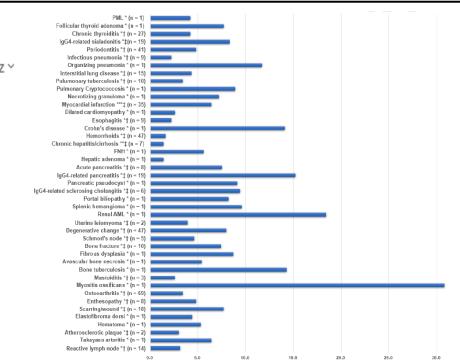
#### Non-oncologic incidental uptake on FAPI PET/CT imaging

Masatoshi Hotta Y, Angela C Rieger Y, Mahbod G Jafarvand Y, Nandakumar Menon Y, Andrea Farolfi Y, Matthias R Benz Y Jeremie Calais Y

Published Online: 13 Jul 2022 · Doi: https://doi.org/10.1259/bjr.20220463

#### **UCLA**

In this review article, they describe for each organ system the patterns of physiological FAPI uptake and the main causes of nononcological uptake reported from the literature



#### **Considerations**

- Identifying and pursuing indications that address an area of unmet need
- Focusing on FAP ligand's impact on management of care
- For each disease area identifying value in:
  - Detection of primary lesion
  - Detection of lymph node mets
  - Detection of distant metastasis
  - 4. Treatment monitoring
- Confirming identity of lesions seen by FAP PET not simply # of lesions
- Pursuing value of FAP ligands for imaging as companion diagnostics for RLT and non-RLT in oncology and non oncology



Current State of Clinical Development & Regulatory for FAP targeting ligands

## FAP targeting radioligands with clinical data

Affiliation	Product	Diagnostic	Therapy
SOFIE	FAPI family of compounds	[ <sup>68</sup> Ga]FAPI-46 [ <sup>18</sup> F]FAPI-74	
Heidelberg University	FAPI family of compounds		FAPI-46 (alpha/beta)
Novartis	FAP-2286	[ <sup>68</sup> Ga]FAP-2286	[ <sup>177</sup> Lu]FAP-2286
Point Biopharma	PNT6555	[ <sup>68</sup> Ga]PNT6555	[ <sup>177</sup> Lu]PNT6555
Yantai LNC Biotech	EB-FAPI/LNC1004		[ <sup>177</sup> Lu]LNC1004
Philogen	OncoFAP	[ <sup>68</sup> Ga]OncoFAP	[ <sup>177</sup> Lu]OncoFAP
3BP			3BP-3940
	SA.FAPI	[ <sup>68</sup> Ga]DOTAGA(SA.FAPI) (variations)	[ <sup>177</sup> Lu]DOTAGA(SA.FAPI) (variations)

Note: 3BP, Ratio Therapeutics and other industry groups have additional FAP assets not demonstrated here. This list contains products under clinical studies

Clinics Review Articles

#### PET Clinics



## FIBROBLAST ACTIVATION PROTEIN IMAGING

ABASS ALAVI

EDITORS

RODNEY J. HICKS FREDERIK L. GIESEL KEN HERRMANN

July 2023

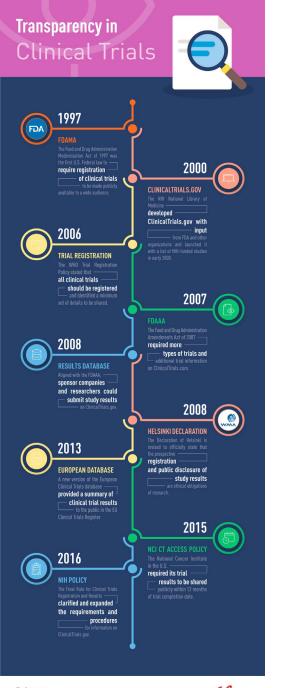


Review

> PET Clin. 2023 Jul;18(3):429-439. doi: 10.1016/j.cpet.2023.02.010. Epub 2023 Mar 27.

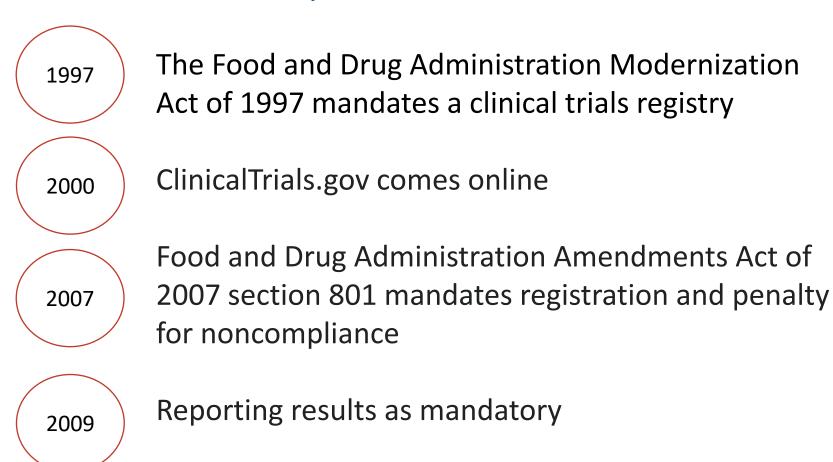
#### Current State of Clinical Trials and Regulatory Approvals with Fibroblast Activation Protein Targeting Interventions

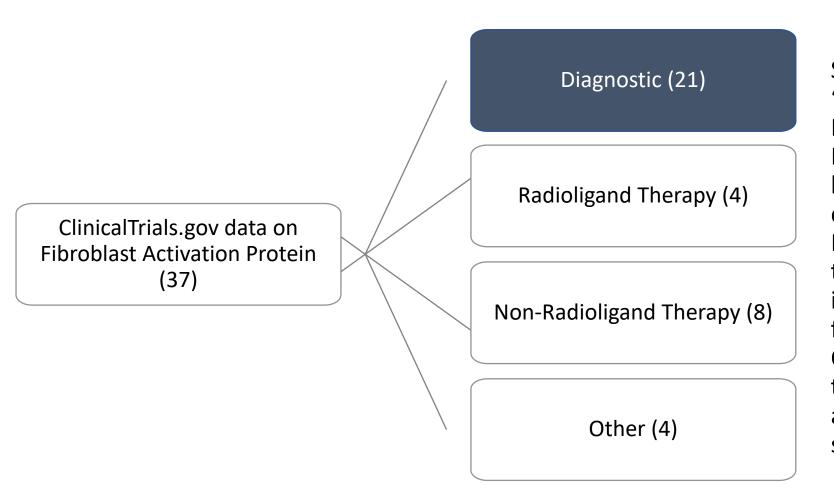
Sherly Mosessian <sup>1</sup>, Jessica D Jensen <sup>2</sup>, Aaron S Enke <sup>3</sup>





ClinicalTrials.Gov is the Largest clinical trials database, holding registrations from over **329,000** trials from **209 countries** 



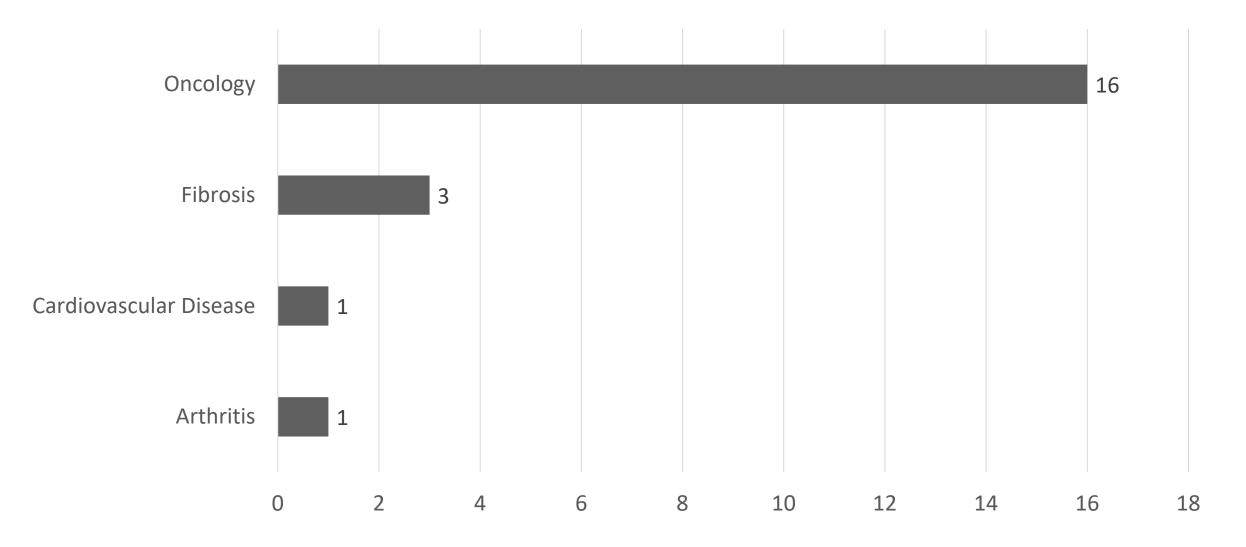


Search results with keywords "FAP" and "Fibroblast Activation Protein" resulted in 37 studies. Further classification of the results broke down the data into 21 diagnostic studies with PET, PET/CT, four studies in radioligand therapy, eight therapeutic studies in non-radioligand therapy, followed by four studies under Other. The Other studies include three completed genetic studies and one biologic intervention study currently active.

## Industry sponsored trials with FAP radioligands for imaging & therapy

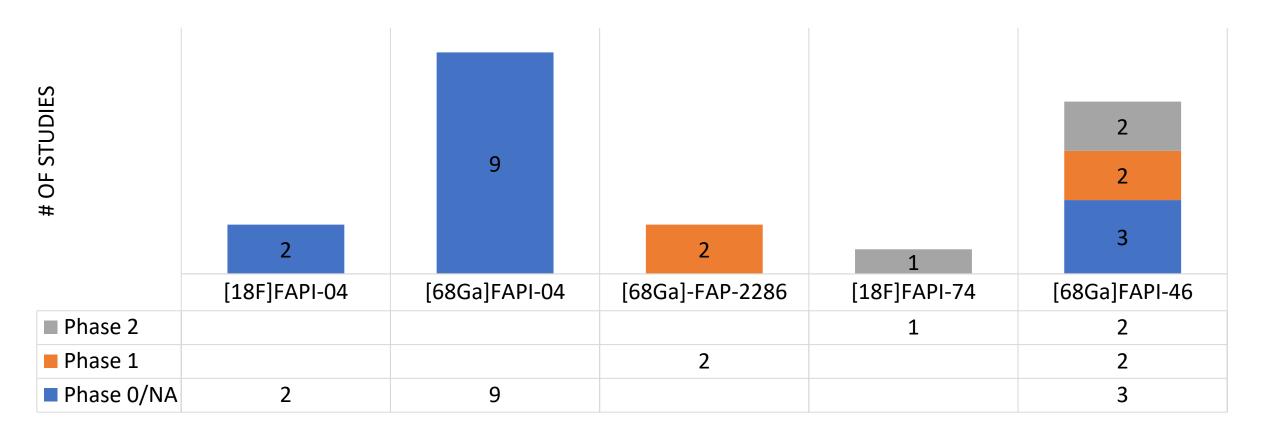
Sponsor	Study Title	Study type	Intervention(s)	Trial Phase
SOFIE	Study of [18F]FAPI-74 PET in Patients With Gastrointestinal Cancers	Diagnostic	[18F]FAPI-74	Phase 2
SOFIE	Study of [68Ga]FAPI-46 PET in Patients With Pancreatic Ductal Carcinoma	Diagnostic	[68Ga]FAPI-46	Phase 2
Novartis	A Study of 177Lu-FAP-2286 in Advanced Solid Tumors (LuMIERE)	Theranostic	[68Ga]-FAP-2286 [177Lu]-FAP-2286	Phase 1/Phase 2
POINT Biopharma	FAPi Radioligand Open-Label, Phase 1 Study to Evaluate Safety, Tolerability and Dosimetry of [Lu- 177]-PNT6555; A Dose Escalation Study for Treatment of Patients With Select Solid Tumors (FRONTIER)	Theranostic	[68Ga]-PNT6555 [177Lu]-PNT6555	Phase 1

## Diagnostic studies by disease type



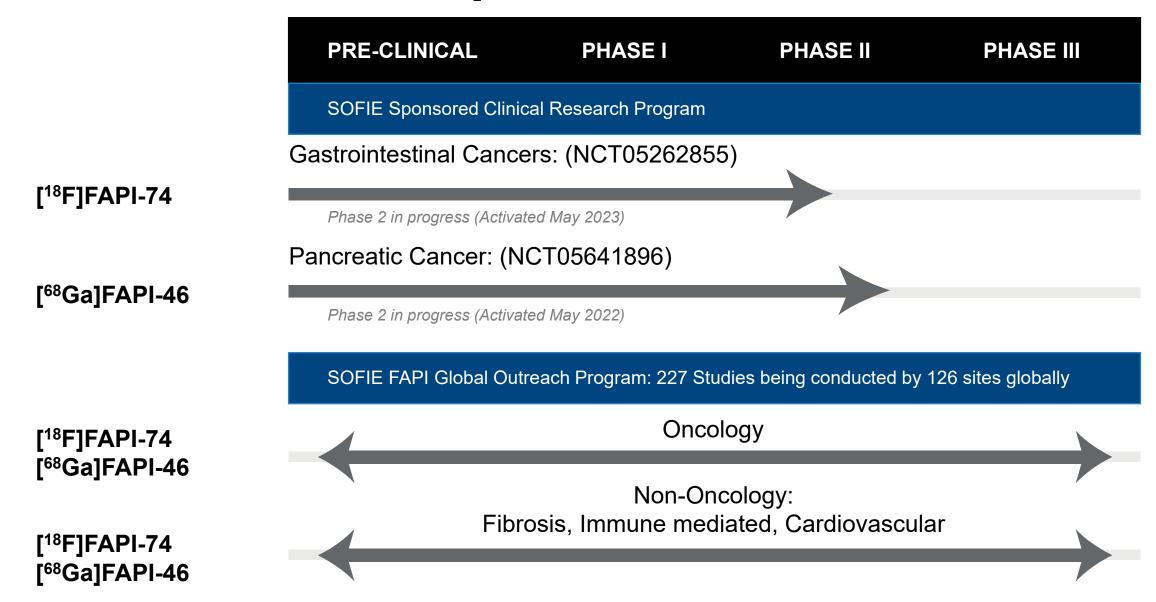
Oncology encompasses the largest number of diagnostic studies

## Diagnostic studies by Product and Trial Phase

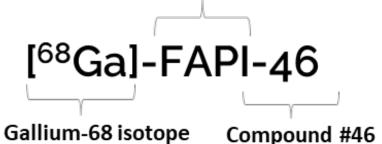


- Majority of the studies are in Phase 0/1 Investigator Initiated Studies
- 2 diagnostic agents are the most advanced in Phase 2: [18F]FAPI-74 and [68Ga]FAPI-46

## **SOFIE's Product Pipeline**



#### Family of compounds



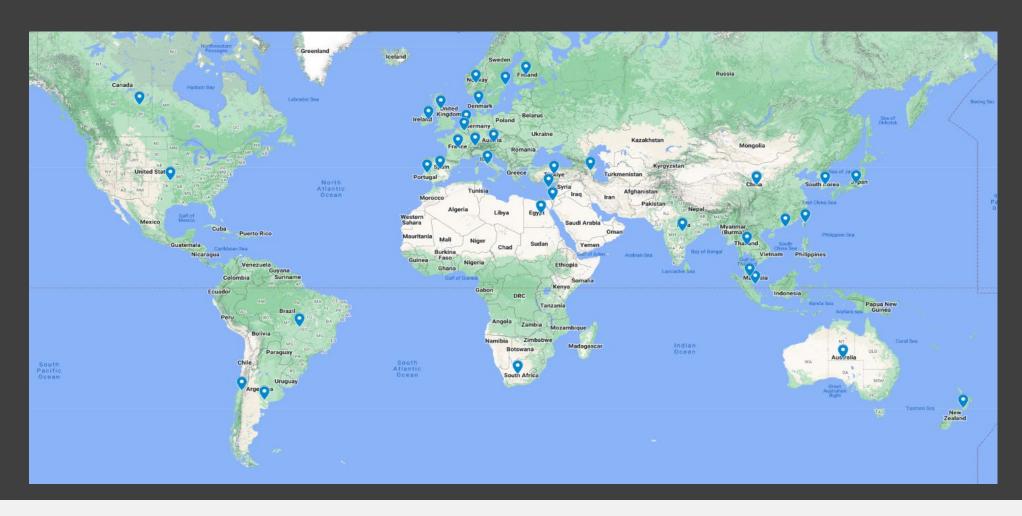
- Lead Gallium-68 labeled compound
- 68 minutes half life
- 60 patients planned; 21 patients imaged
- Phase 2 study in patients with Pancreatic Ductal Adenocarcinoma (PDAC), initiated May 2022
- Four clinical sites selected and activated
  - NYU Langone
  - Mayo Clinic
  - UCLA
  - BAMF Health

#### Family of compounds



Fluorine-18 isotope Compound #74

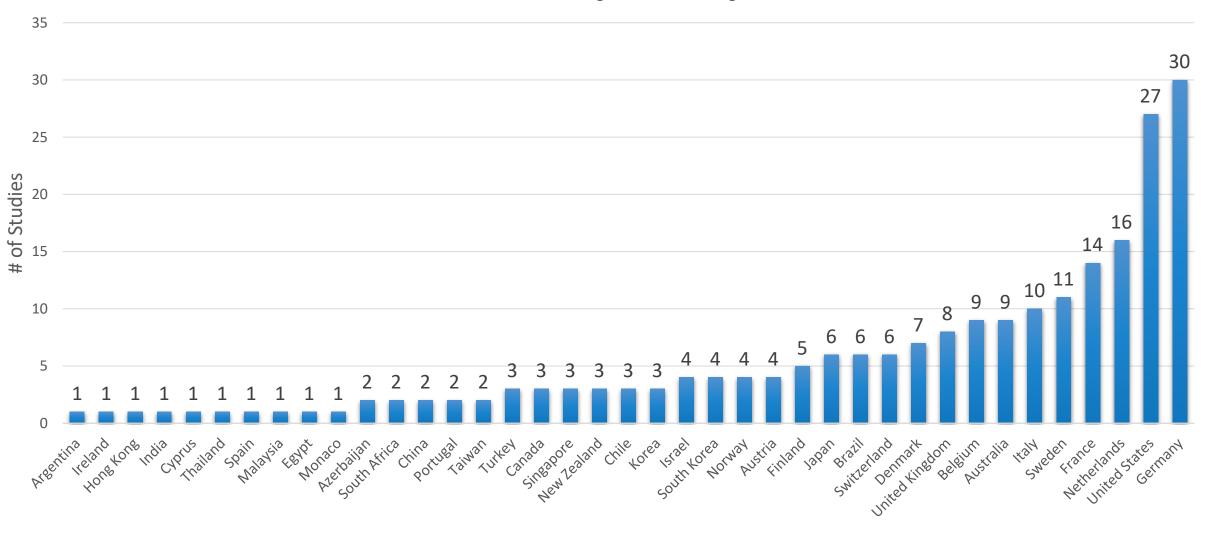
- Lead Fluorine-18 labeled compound
- 110 minutes half life
- 120 patients planned; 1 patient imaged
- Phase 2 study in patients with hepatocellular carcinoma, gastric cancer cholangiocarcinoma, colorectal cancer and pancreatic cancer, initiated May 2023
- MGH launched as the first site. Four additional sites in activation process
- Automated synthesis and consumables available with Trasis Mini-AIO and AIO



#### SOFIE's FAPI Global Outreach Program

- 39 Countries
- 227 research studies
- 126 unique institutions
- Compounds: [18F]-FAPI-74 and [68Ga]-FAPI-46

#### **Studies by Country**



FAPI studies by country. 39 countries are part of our FAPI Global Outreach Program, conducting studies with FAPI. The countries conducting the highest number of studies in descending order are: Germany (30), United States (27), Netherlands (16), France (14), Sweden (11) and Italy (10).



## 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





Application Completion



Application Approval



MTA Signature



Material Shipment



# SOFIE and the FAPI team will be at SNMMI 2023 in Chicago

Visit us at the exhibit hall. Booth #6055

We have 3 posters that can be accessed on the app or at science pavilion

- P230 Clinical development updates with [68Ga]FAPI-46 and [18F]FAPI-74
- P231 FAPI Global Outreach Program
- P261 Automated Production of [18F]FAPI-74 on the miniAllinOne Module

For FAPI-related inquiries, e-mail FAPIprogram@sofie.com

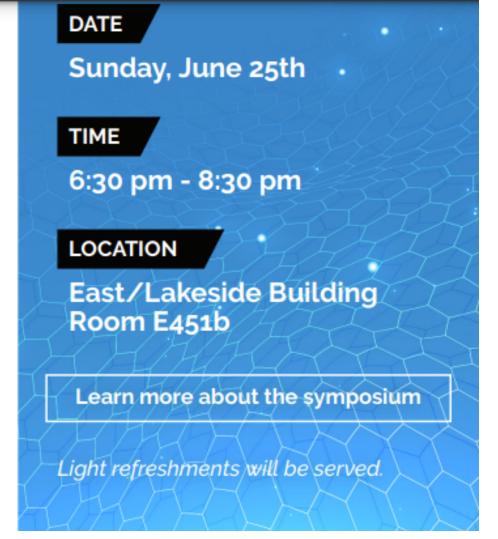




## FAP Ligands for Imaging and Therapy

Sponsored by: SOFIE

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.



Additional Industry Participants







## Thank you



For FAPI-related inquiries, e-mail us: FAPIprogram@sofie.com