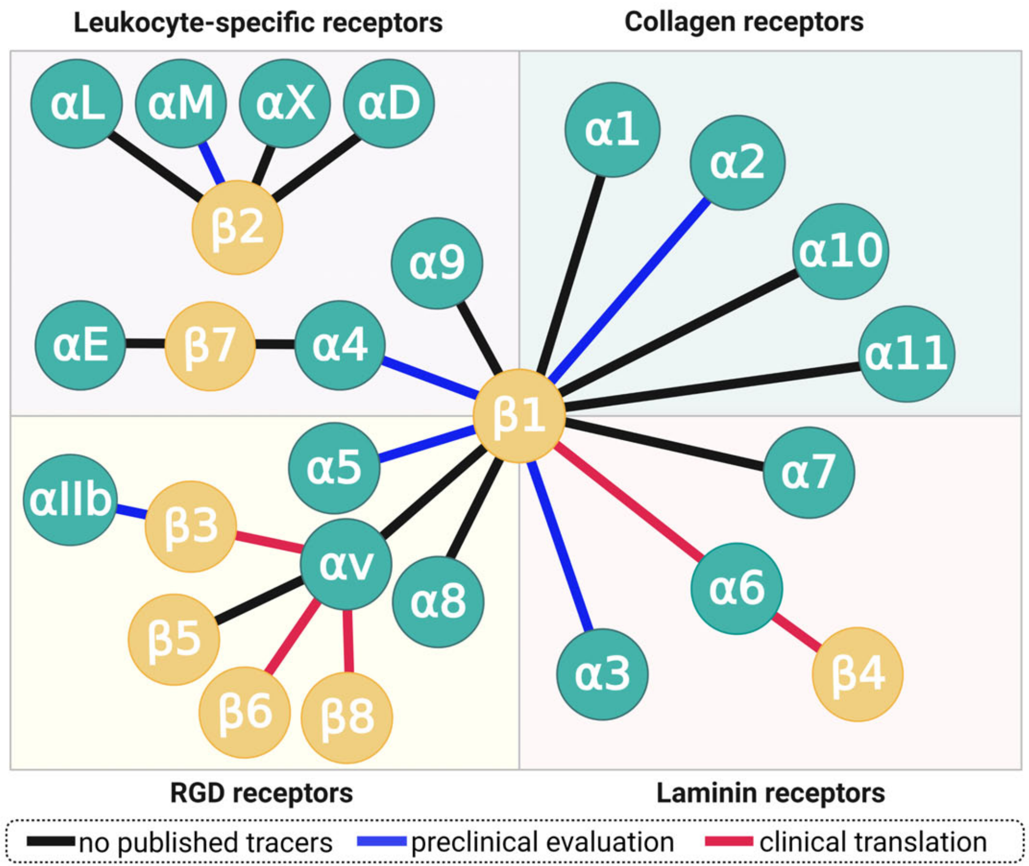
A10: The Integrin Project

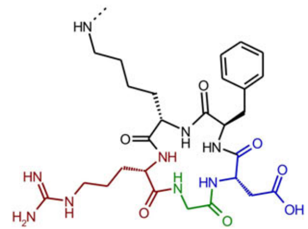
Finalizing 12 years of research on ^{68}Ga-labeled integrin-targeting PET tracers at TUM

(2009 – 2021)

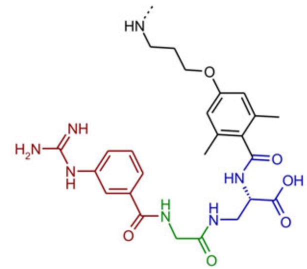
Radiotracers for Integrins – Receptors for Adhesion and Signaling



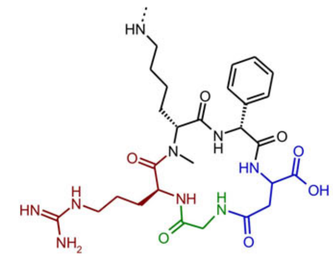
Setting The Stage: Integrin Ligands Developed (Mostly) at TUM



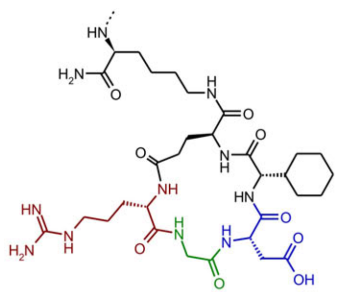
αvβ3 — c[RGDfK]



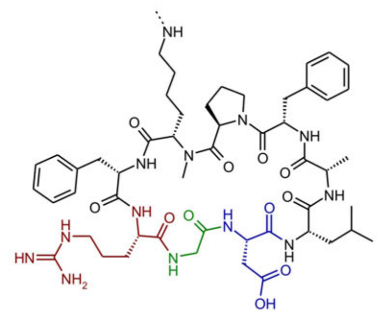
α5β1 — FR366



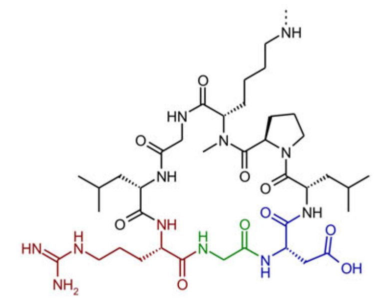
α5β1 — c[phg-*iso*D-GR(*N*Me)k]



αvβ6 — c[RGD-Chg-E]CONH$_2$



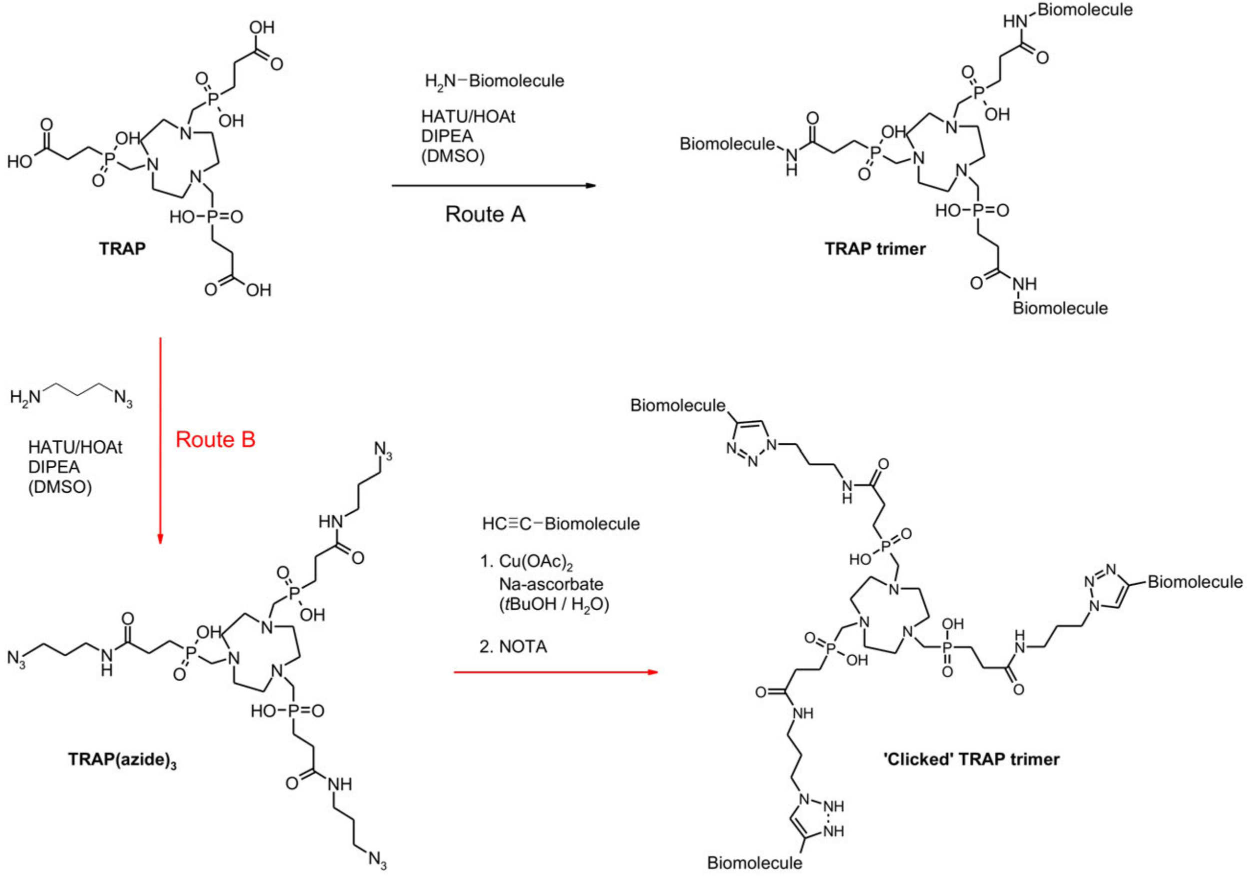
αvβ6 — c[FRGDLAFp(*N*Me)K]



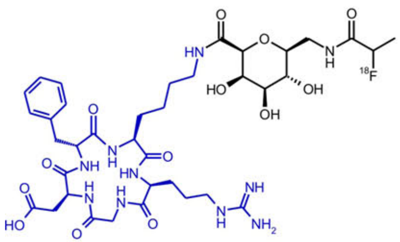
αvβ8 — c[LRGDLp(*N*Me)K]

H. Kessler et al.: *FEBS Lett.* **1991**, *291*, 50–54. | *Angew. Chem. Int. Ed.* **2013**, *52*, 1572–1575. | *J. Med. Chem.* **2018**, *61*, 2490–2499. | *Angew. Chem. Int. Ed.* **2016**, *55*, 1535–1539. | *J. Med. Chem.* **2019**, *62*, 2024–2037. L. Marinelli et al.: *Angewandte Chem. Int. Ed.* **2018**, *57*, 14645–14649.

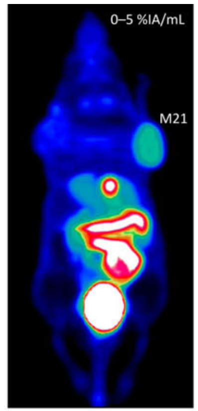
The Making Of (since 2008): ^{68}Ga-TRAP Trimers

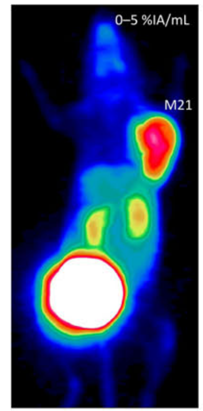


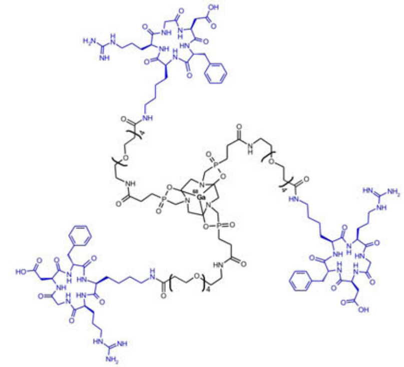
The Prequel: αvβ3-Integrin (2011) and α5β1-Integrin (2015)



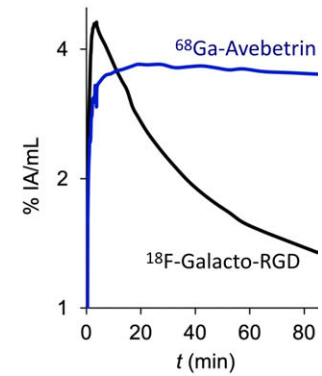
^{18}F-Galacto-RGD 5 nM

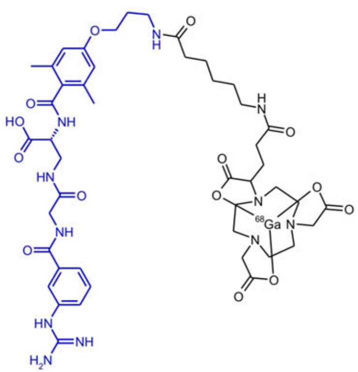




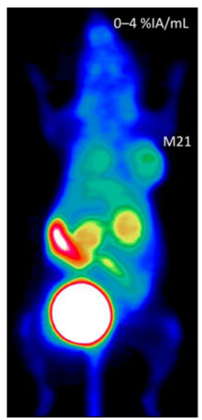


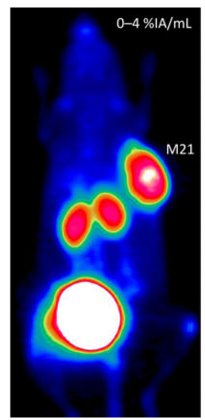
^{68}Ga-Avebetrin 0.22 nM

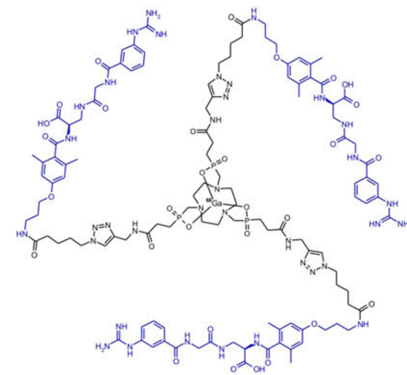




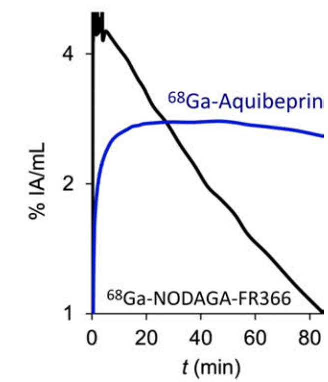
^{68}Ga-NODAGA-FR366 2.3 nM







^{68}Ga-Aquibeprin 0.08 nM

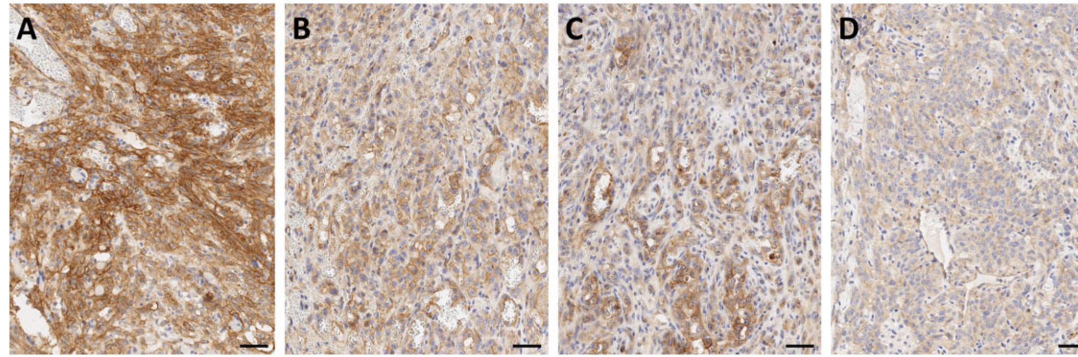


Haubner et al., *J. Nucl. Med.* **2001**, *42*, 326. | Rechenmacher et al., *Angew. Chem. Int. Ed.* **2013**, *52*, 1572. | Notni et al., *J. Nucl. Med.* **2016**, *57*, 460.

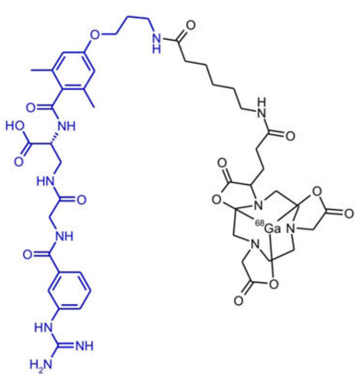
The Prequel: α5β1-Integrin (2015)

Possible Application:

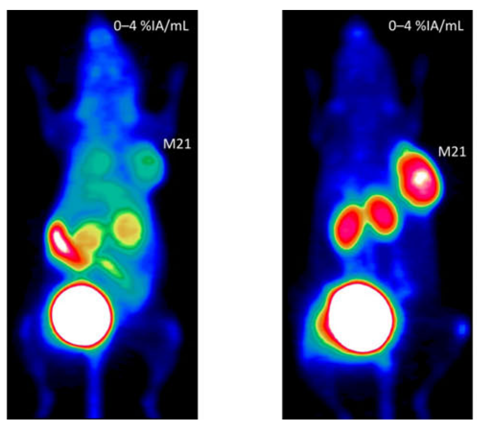
Imaging of Angiosarcoma. ⟶

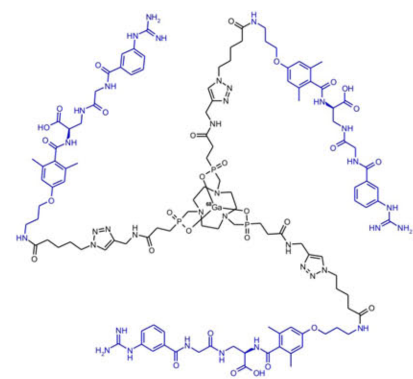


α5-IHC of human angiosarcoma specimen *(courtesy of PD Katja Steiger)*.
11 out of 12 showed strong to moderate expression (examples in A–C), one weak expression (D).

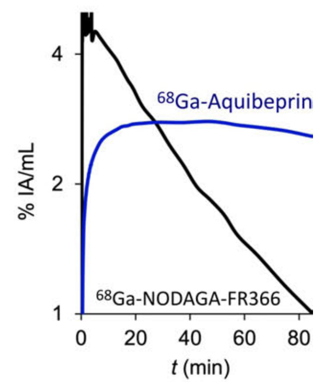


^{68}Ga-NODAGA-FR366 2.3 nM

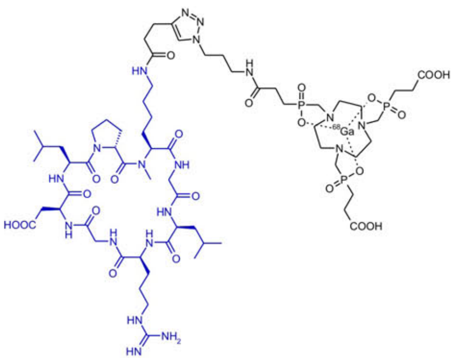




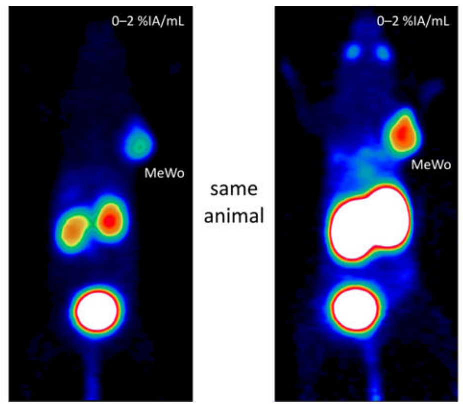
^{68}Ga-Aquibeprin 0.08 nM

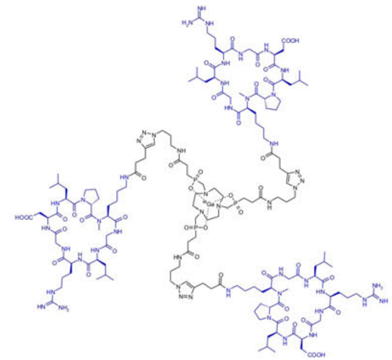


Episode VIII (2019): αvβ8-Integrin

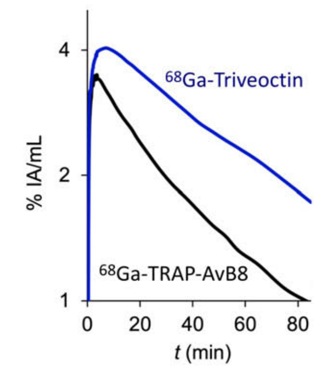


^{68}Ga-TRAP-AvB8 38 nM

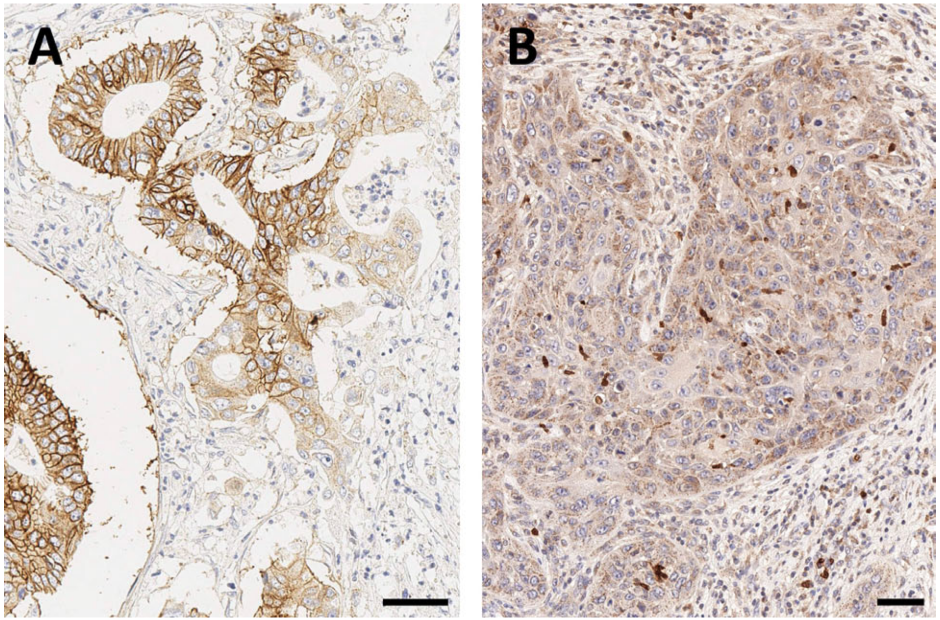




^{68}Ga-Triveoctin 5.7 nM

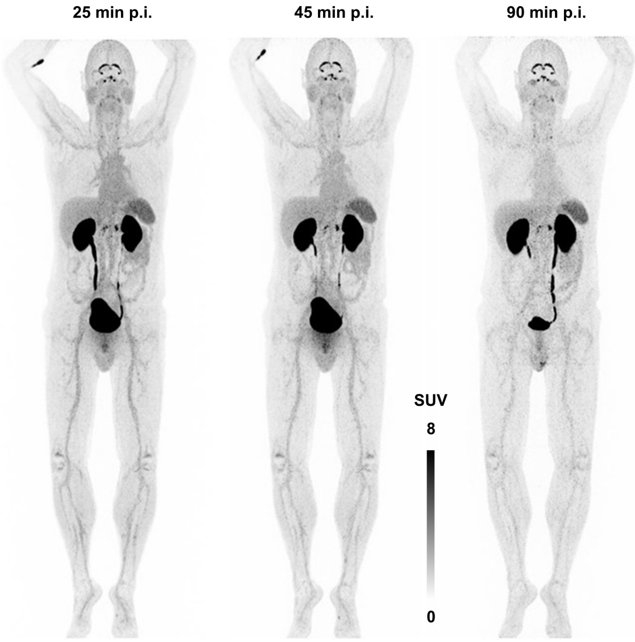


Episode VIII (2019): αvβ8-Integrin



β8-IHC of human PDAC β8-IHC of human HNSCC

(IHC courtesy of PD Katja Steiger).



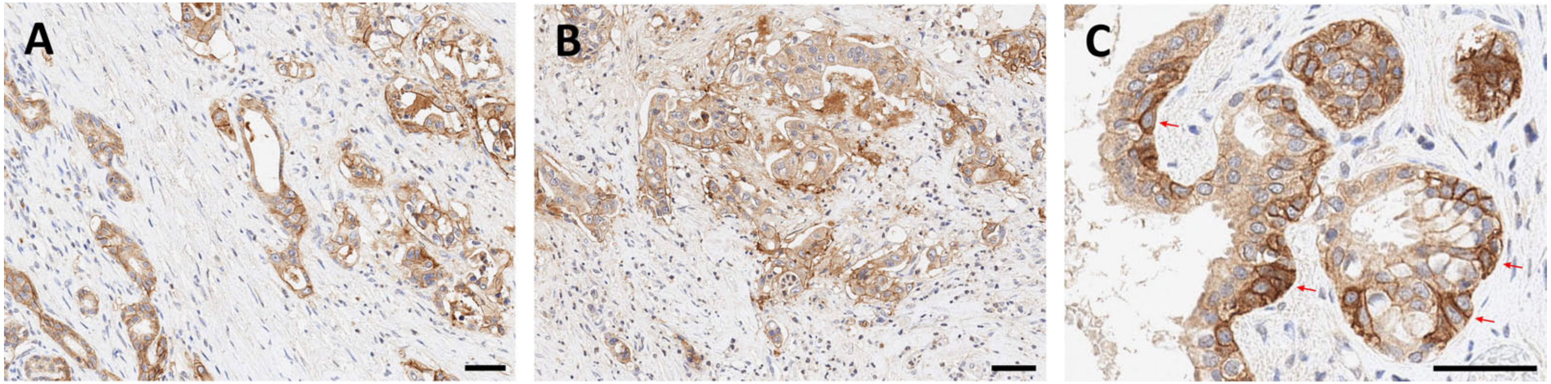
[68]**Ga-Triveoctin** (αvβ8-integrin) PET

N.G. Quigley et al., *EJNMMI Res.* **2020**, *10*, 133.

The Sequel: αvβ6-Integrin

Expression on **epithelial** cells. — **Absent** in adult tissues.

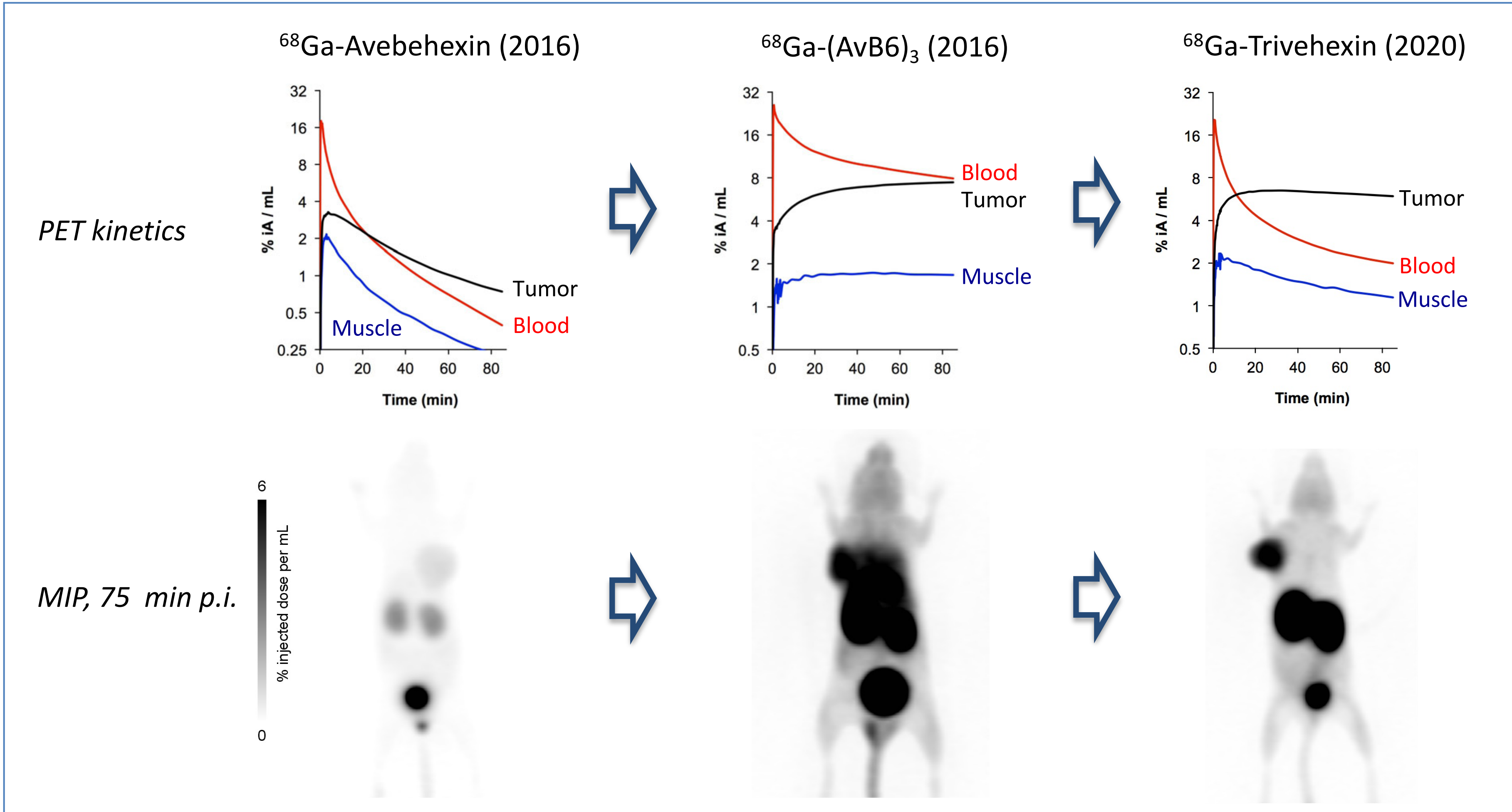
Overexpressed by carcinomas: Pancreatic (**PDAC, 88%**), Squamous (**HNSCC**), and others.



β6-IHC of human PDAC. Central area (A), infiltrative margin (B). Elevated β6-ITG expression on basal cell layer (C). *(courtesy of PD Katja Steiger)*

Associated with **invasive growth** of tumors. — Involved in development of **fibrosis**.

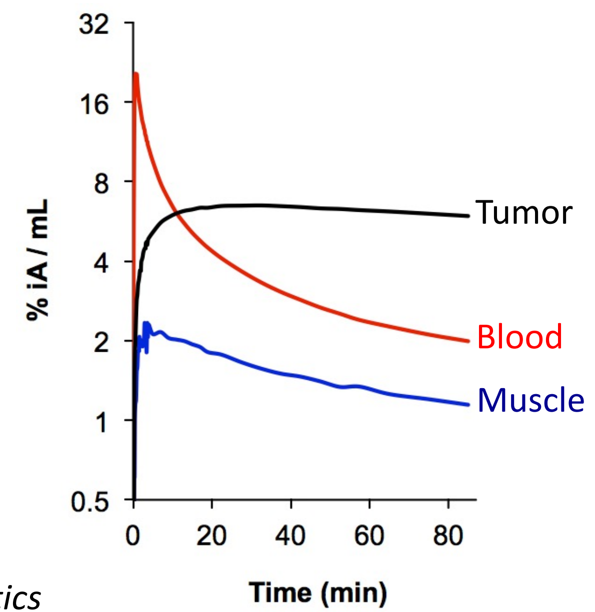
Summary – Preclinical Optimization of αvβ6-Integrin Ligands



Notni et al., *J Nucl. Med.* **2017**, *58*, 671.

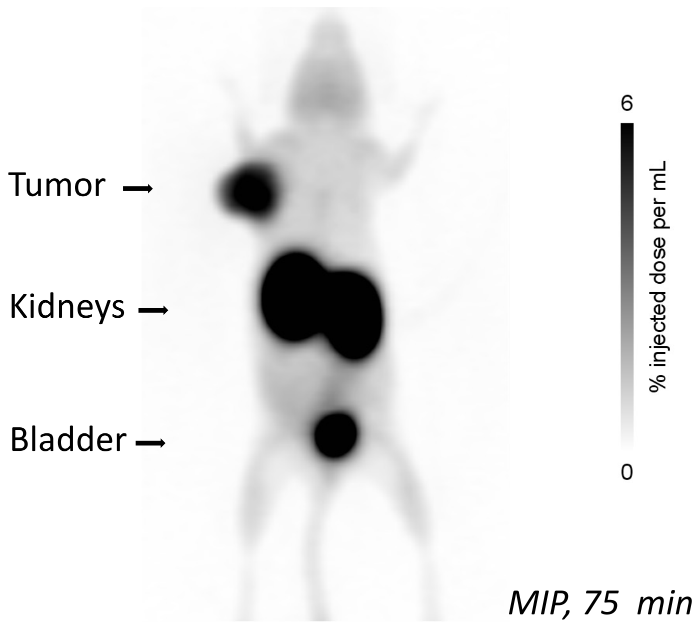
^{68}Ga-Trivehexin – Preclinical µPET Imaging

Rapid target-specific uptake &
fast clearance from non-target tissue



PET kinetics

Excellent PET contrast



MIP, 75 min p.i.

Highest tumor uptake & best PET contrast of all known αvβ6-integrin PET Tracers!

Current Status of Clinical Tracers for αvβ6-Integrin

Citation	Tracer	PET Application
Altmann, Haberkorn et al., *Clin. Cancer Res.* **2017**;*23*:4170. Haberkorn, Altmann et al., *Mol. Imaging Biol.* **2019**;*21*:973.	^{68}Ga-SFITGv6	NSCLC, recurrent hypopharynx tumor
Haberkorn, Altmann et al., *J. Nucl. Med.* **2018**;*59*:1679.	^{68}Ga-SFLAP3	HNSCC
Hausner, Sutcliffe et al., *Clin. Cancer Res.* **2019**;*25*:1206.	[^{18}F]αvβ6-BP	Mammary-, lung-, pancreatic- & colon adeno ca.
Müller, Haberkorn et al., *Nuklearmedizin* **2019**;*58*:309.	^{68}Ga-SFLAP3	PDAC
Kimura, Gambhir et al., *Nat. Commun*. **2019**;*10*:4673.	[^{18}F]FP-R01-MG-F2 [^{68}Ga]-R01-MG-F2	Pancreatic-, cervical- & lung cancer, **Fibrosis**

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-019-11863-w OPEN

Evaluation of integrin $\alpha v\beta_6$ cystine knot PET tracers to detect cancer and idiopathic pulmonary fibrosis

Richard H. Kimura[1], Ling Wang[2,13], Bin Shen[1,13], Li Huo[2,13], Willemieke Tummers[1,13], Fabian V. Filipp[3,4,13], Haiwei Henry Guo[1,13], Thomas Haywood[1], Lotfi Abou-Elkacem[1], Lucia Baratto[1], Frezghi Habte[1], Rammohan Devulapally[1], Timothy H. Witney[1], Yan Cheng[1], Suhas Tikole[3,4,5], Subhendu Chakraborti[1], Jay Nix[6], Christopher A. Bonagura[7], Negin Hatami[1], Joshua J. Mooney[8], Tushar Desai[9], Scott Turner[10], Richard S. Gaster[1], Andrea Otte[1], Brendan C. Visser[11], George A. Poultsides[11], Jeffrey Norton[11], Walter Park[8], Mark Stolowitz[1], Kenneth Lau[1], Eric Yang[12], Arutselvan Natarajan[1], Ohad Ilovich[1], Shyam Srinivas[1], Ananth Srinivasan[1], Ramasamy Paulmurugan[1], Juergen Willmann[1], Frederick T. Chin[1], Zhen Cheng[1], Andrei Iagaru[1], Fang Li[2] & Sanjiv S. Gambhir[1]

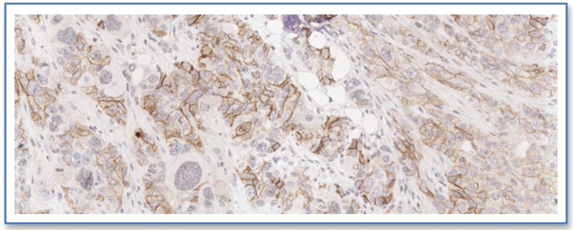
⟶ Comparison on next slide

Comparison of Preclinical Data (Mouse Xenografts)

	^{68}Ga-Trivehexin	^{68}Ga-NODAGA-R01-MG (*Nat. Commun.* 2019)
Affinity	**0.03 nM** *(IC_{50})*	1.24 nM *(K_D)*
Tumor *(%IA/g)*	**7.5**	2.8
Liver *(%IA/g)*	**0.7**	1.2
Muscle *(%IA/g)*	**0.68**	0.59
Pancreas *(%IA/g)*	**0.27**	*n/d*
Tumor/Liver	**10.5**	2.3
Tumor/Muscle	**11.4**	4.7
Tumor/Pancreas	**28.5**	*n/d*

Preclinical Model:

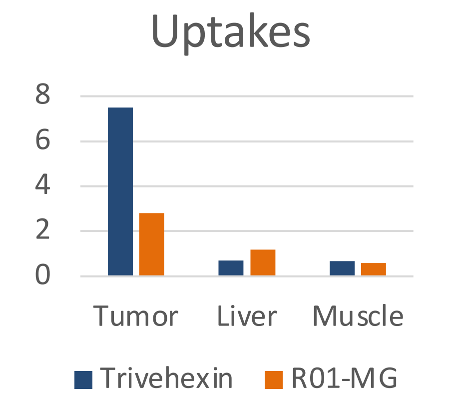
H2009 human lung adenocarcinoma

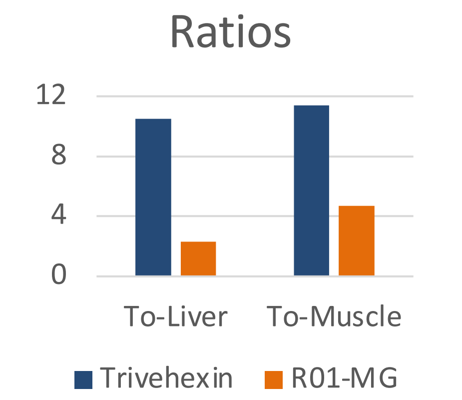


not transfected, medium β6 expression density

BxPC-3 human pancreatic carcinoma

(no IHC available)



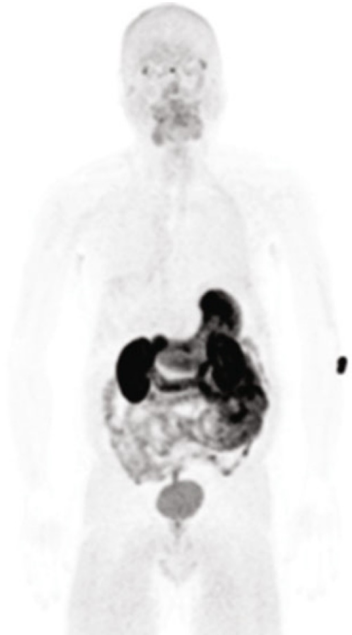


Current Status of Clinical Tracers for αvβ6-Integrin

^{68}Ga-DOTA-SFITGv6

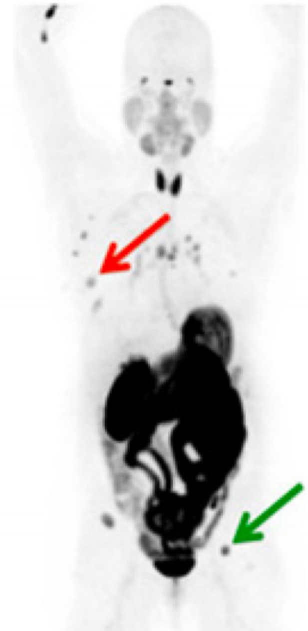
Altmann, Haberkorn et al.,
Clin. Cancer Res. **2017**;*23*:4170.

[^{18}F]FP-R01-MG-F2



Kimura, Gambhir et al.,
Nat. Commun. **2019**;*10*:4673.

[^{18}F]αvβ6-BP



Hausner, Sutcliffe et al.,
Clin. Cancer Res. **2019**;*25*:1206.

^{68}Ga-Trivehexin

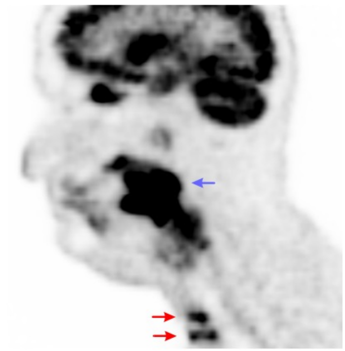
Quigley et al., **2021**.

Head-and-Neck Squamous Cell Carcinoma (142 MBq ^{68}Ga-Trivehexin, 62 min p.i.)

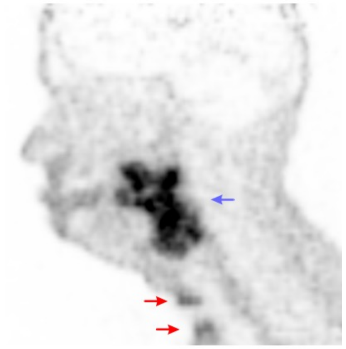
[^{18}F]FDG

^{68}Ga-Trivehexin

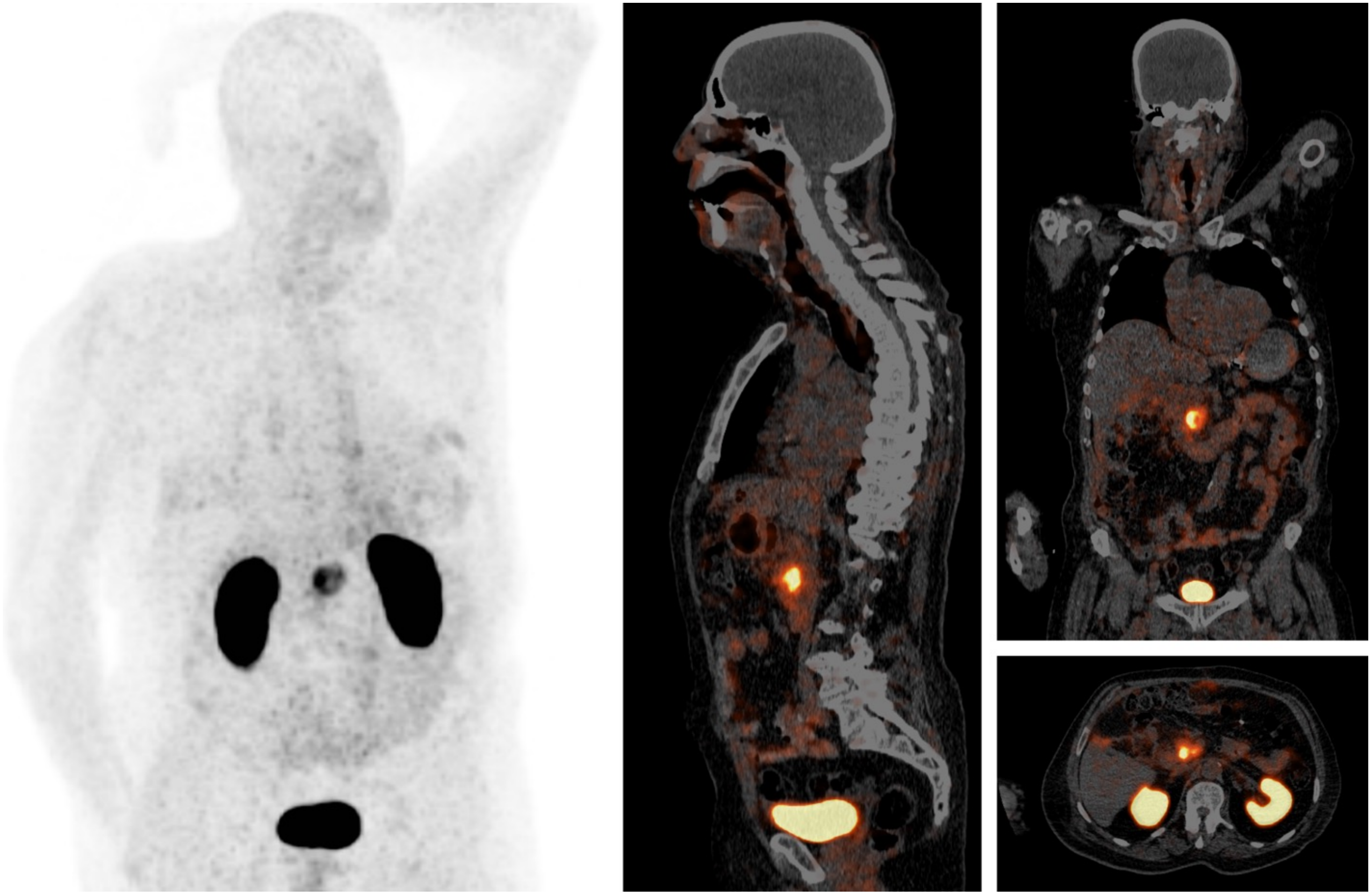
[^{18}F]FDG



^{68}Ga-Trivehexin

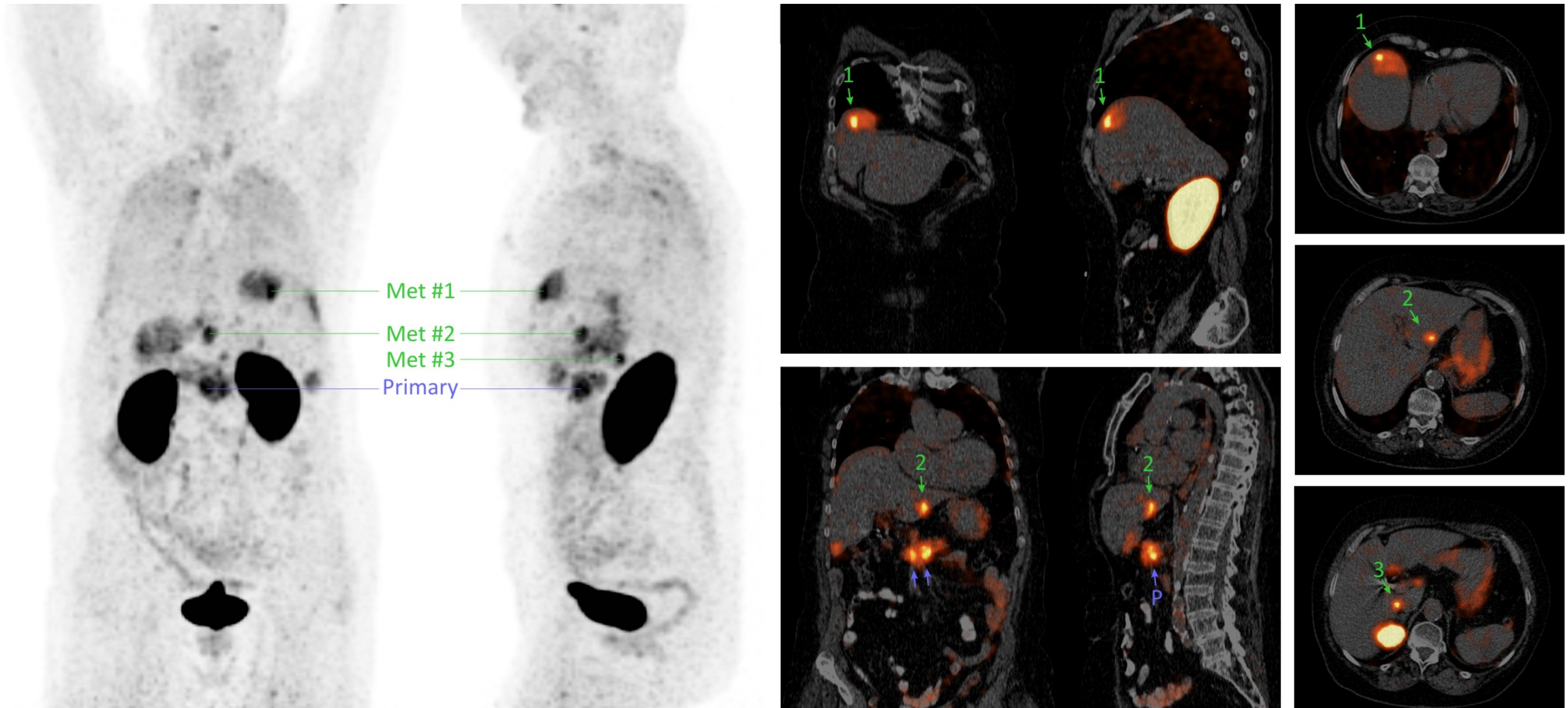


PDAC (87 MBq ^{68}Ga-Trivehexin, 70 min p.i.)



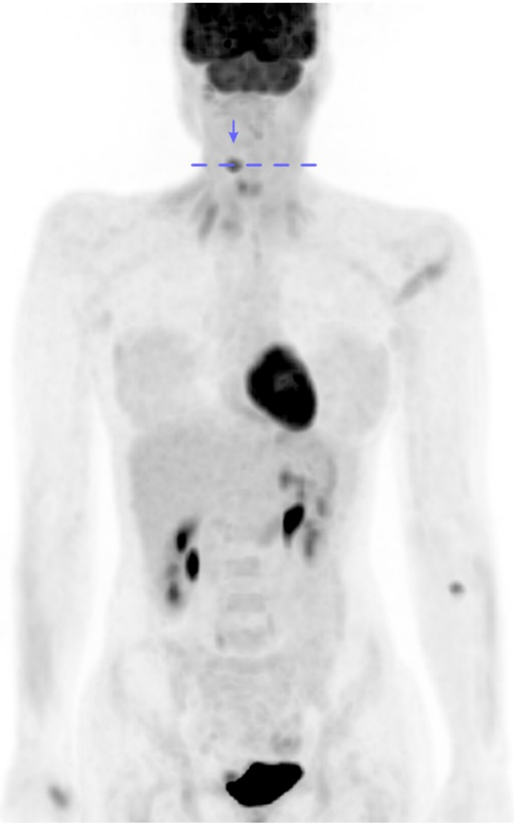
N.G. Quigley et al., *Eur. J. Nucl. Med. Mol. Imaging* **2021**, *48*, doi:10.1007/s00259-021-05443-8.

Metastatic PDAC (103 MBq ^{68}Ga-Trivehexin, 120 min p.i.)

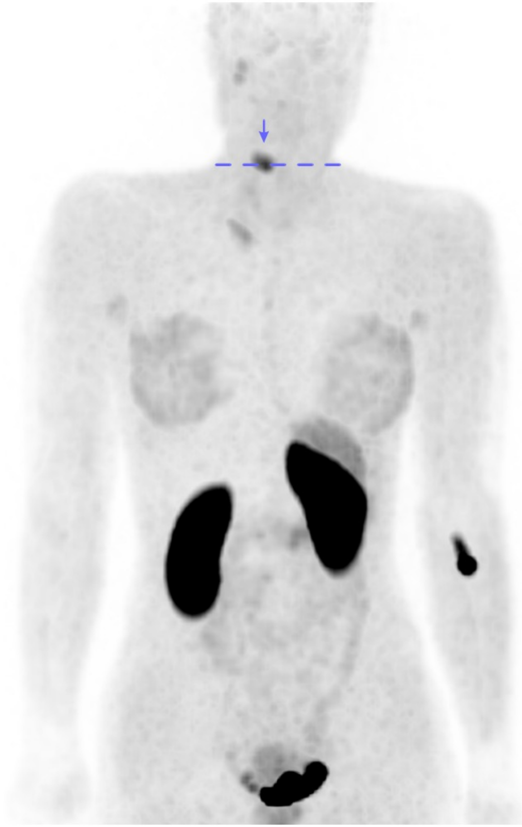


Parotid duct CA metastasis (135 MBq ^{68}Ga-Trivehexin, 67 min p.i.)

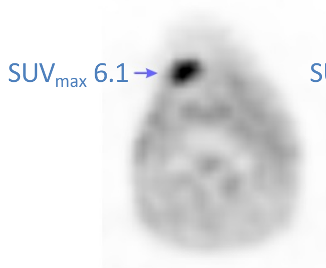
$[^{18}F]$FDG



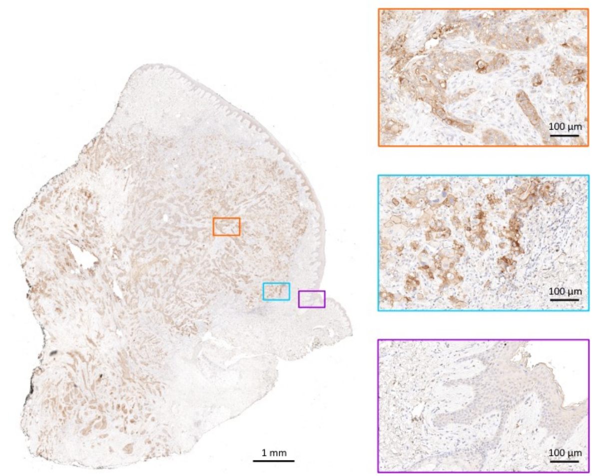
^{68}Ga-Trivehexin



$[^{18}F]$FDG

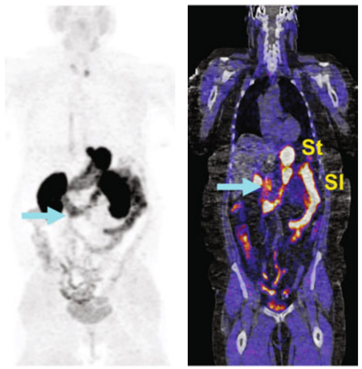


^{68}Ga-Trivehexin



~~Conclusion~~ Comparison: αvβ6-Integrin Targeted PET/CT Imaging of PDAC

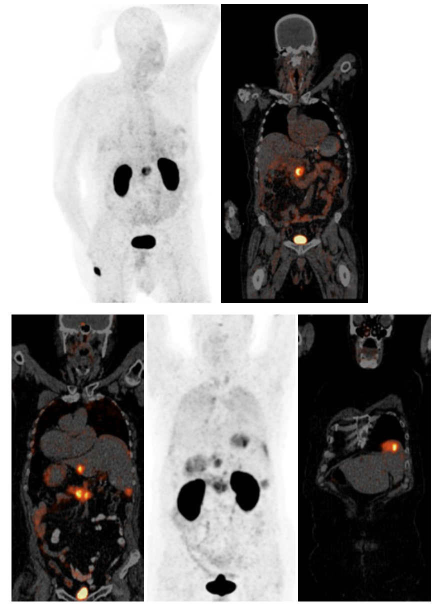
[^{18}F]FP-R01-MG-F2



Kimura, Gambhir et al.,
Nat. Commun. **2019**;*10*:4673.

PDAC primary hard to discover, PET/CT readout complicated by uptake in abdominal organs

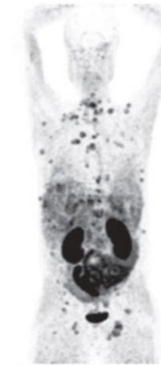
^{68}Ga-Trivehexin



Quigley, Notni et al., *EJNMMI* ***2021***.

Clear presentation of PDAC primaries and metastases.

^{68}Ga-DOTA-SFLAP3

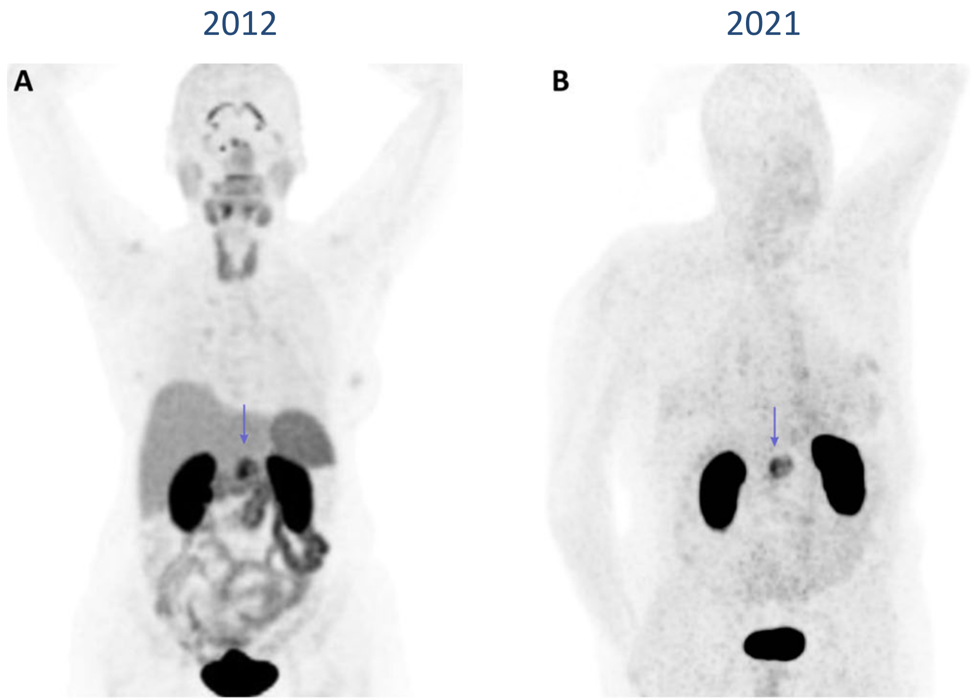


Müller, Haberkorn et al.,
Nuklearmedizin **2019**;*58*:309.

Multiple PDAC metastases in a heavily metastasized terminal case can be discerned, but abdominal background uptake is too high to clearly delineate e.g. liver metastases or a primary.

Previous difficulties to clinically establish αvβ6-integrin PET were not caused by an intrinsic unsuitability of the target, but rather a result of not fully optimized tracers.

In A Nutshell: Progress of Integrin Targeted PET/CT Imaging of PDAC



^{68}Ga-Avebetrin — αvβ3-integrin

^{68}Ga-Trivehexin — αvβ6-integrin

Contrary to a still widely-held view, integrins in general, and αvβ6 in particular, are valuable theranostic targets (αvβ3 representing the only proven exception).

Acknowledgement

The „Project A10“ people

Neil Quigley, MSc. — Dr. Frauke Richter — Max Zierke, MSc. — Prof. Johannes Notni

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Clinic for Nuclear Medicine, TUM

Chair of Pharmaceutical Radiochemistry, TUM

The Kessler group, Dept. of Chemistry, TUM