Vecteurs actuels de la thérapie par radionucléides

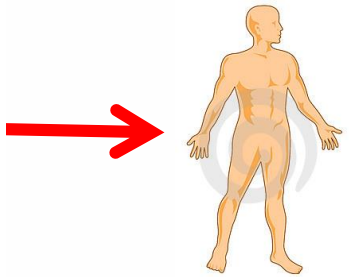
Tony Lahoutte, MD, Phd

Research Cluster Imaging and Physical Sciences (BEFY)
In vivo Cellular and Molecular Imaging Lab (ICMI)
Vrije Universiteit Brussel

ICMI Brussels

In vivo Cellular & Molecular Imaging

A multi-discplinary research team focussed on the development of drugs for biomedical imaging and therapy



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Nuclear Medicine department

- 2 Siemens PET/CT camera's
- 2 Siemens SPECT/CT systems

Brussels Imaging Pharmacy:

- 18/9 Mev Cyclotron
- 3 research Hot cells
- 6 GMP Hot cells

In vivo Cellular and Molecular Imaging - ICMI

- Radiochemistry unit
  - Alpha lab
  - Beta/Gamma lab
- Vector development unit
  - Pre-GMP and GMP
- Cell culture facilities
  - FACS
- Preclinical imaging
  - MicroSPECT/CT
  - MircoPET/CT (2022)
  - Intravital Microscopy (2022)
  - Bioluminescence
  - Fluorescence unit
  - Ultrasound unit

DISCLOSURES

Founder/Shareholder/Consultant

Precirix NV (Chief Science Officer)

ABSCINT NV (Medical Director)

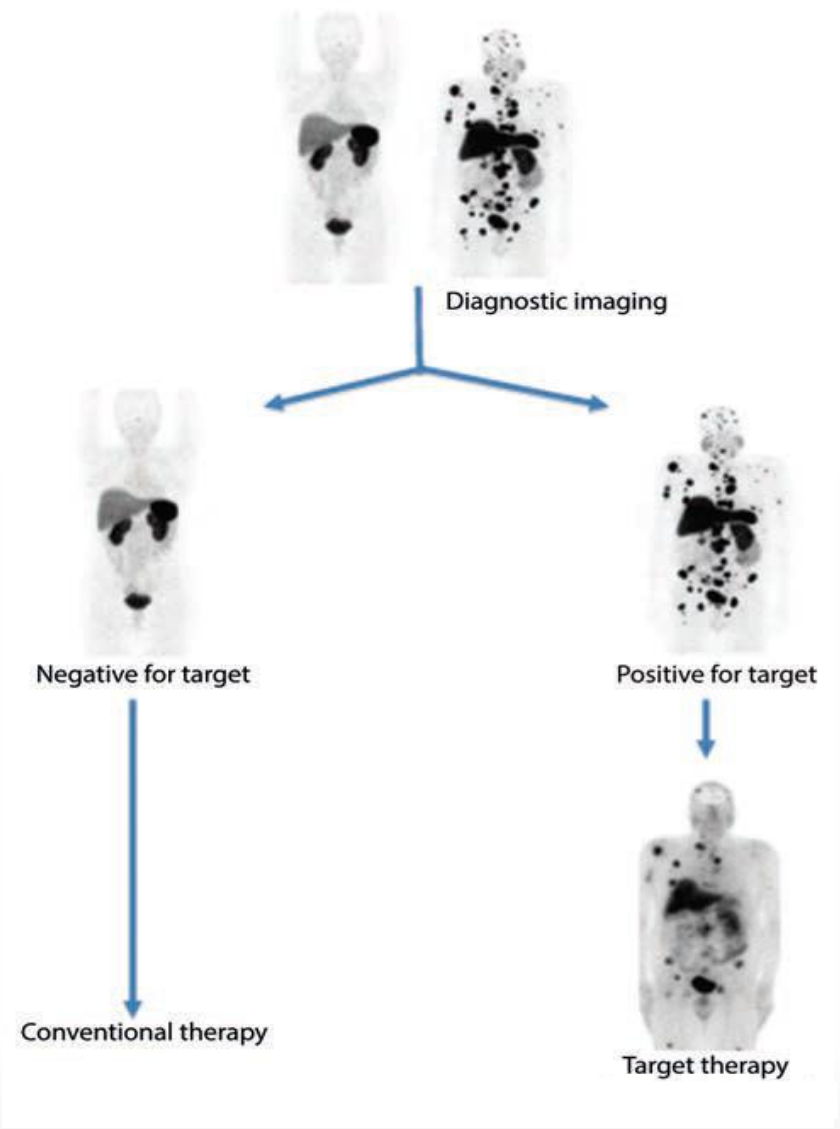
TARGETED RADIONUCLIDE THERAPY (TRNT)

- Tumor cells with a specific protein over-expressed on their surface
- Accessible for circulating agents
- Guide a therapeutic radionuclide to the expressed protein using a target-specific vehicle

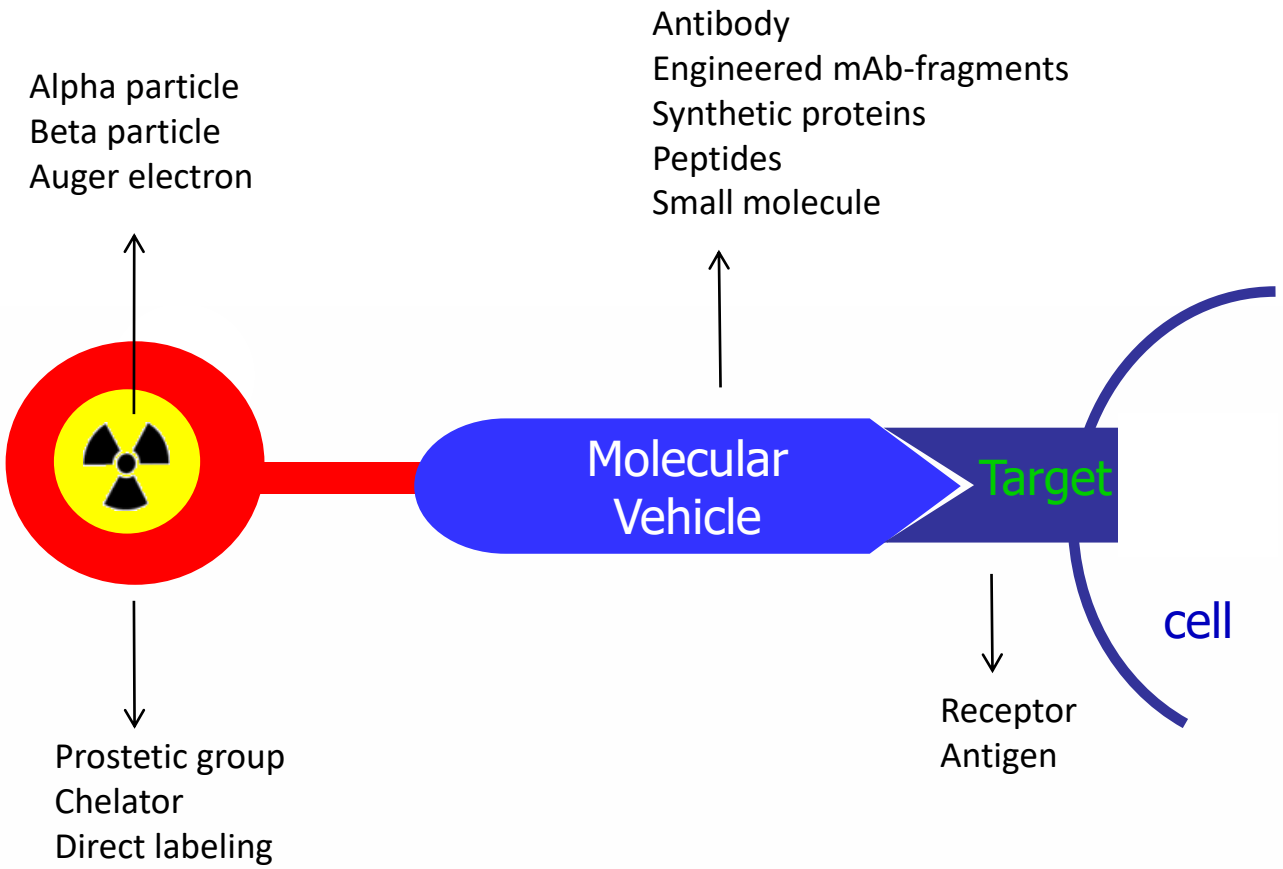
CONCEPT
THERANOSTIC APPROACH OF TRNT

- The goal of TRNT is to selectively deliver radiation to cancer cells and/or diseased tissue with minimal toxicity to surrounding normal tissues
- Integration of imaging to detect the presence of a molecular target for which a specific treatment is intended
- Imaging with a related molecular vehicle

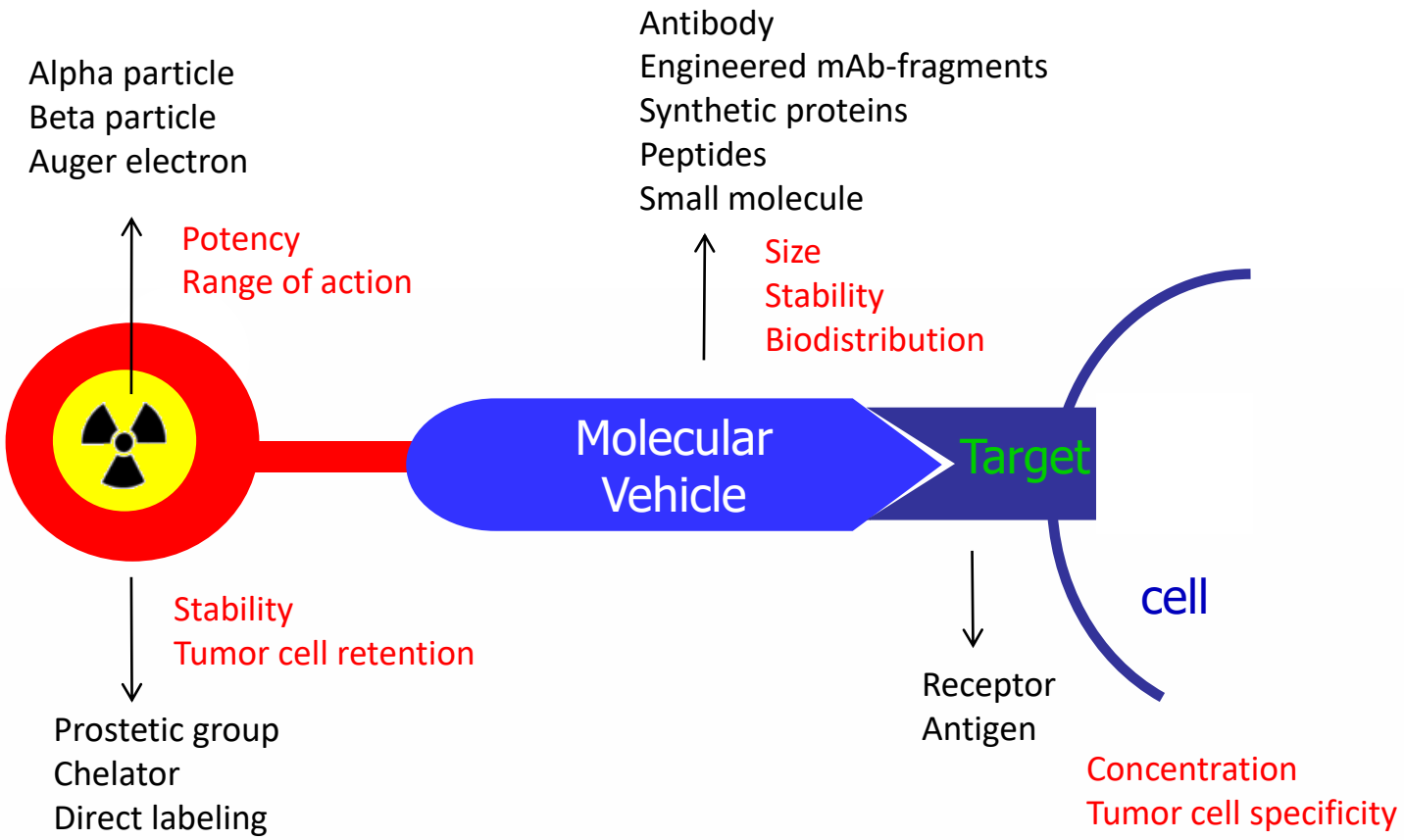
⇒ support for dose estimation
⇒ treatments based on dose-effect relationships
⇒ monitor response to treatment



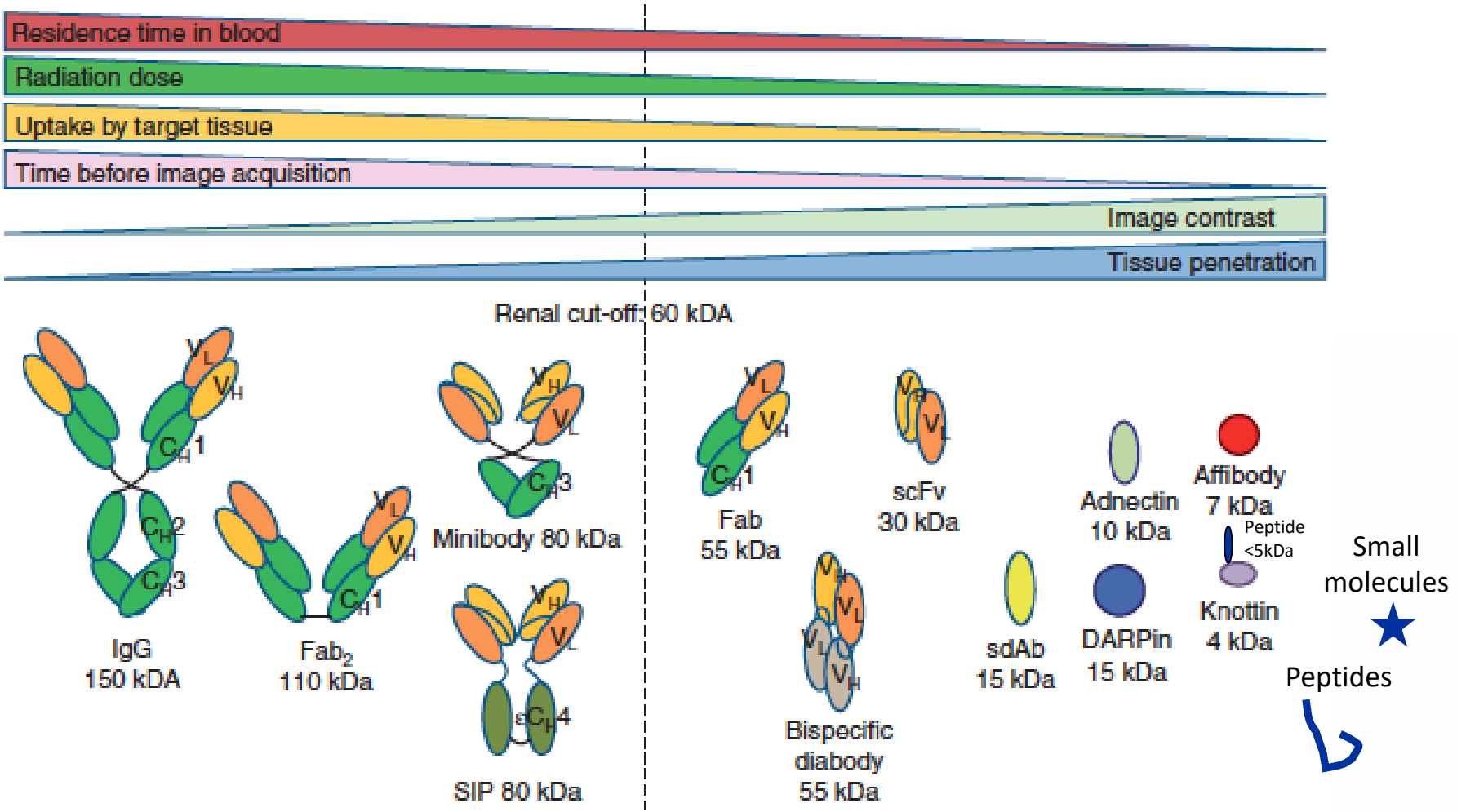
CONCEPT
TARGETING



CONCEPT
TARGETING

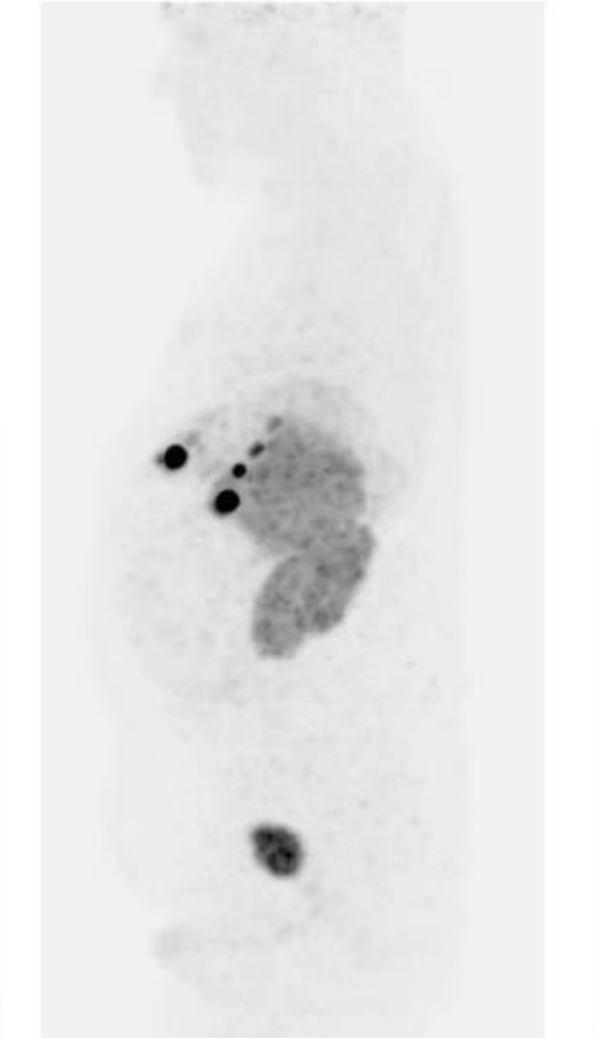


VECTORS

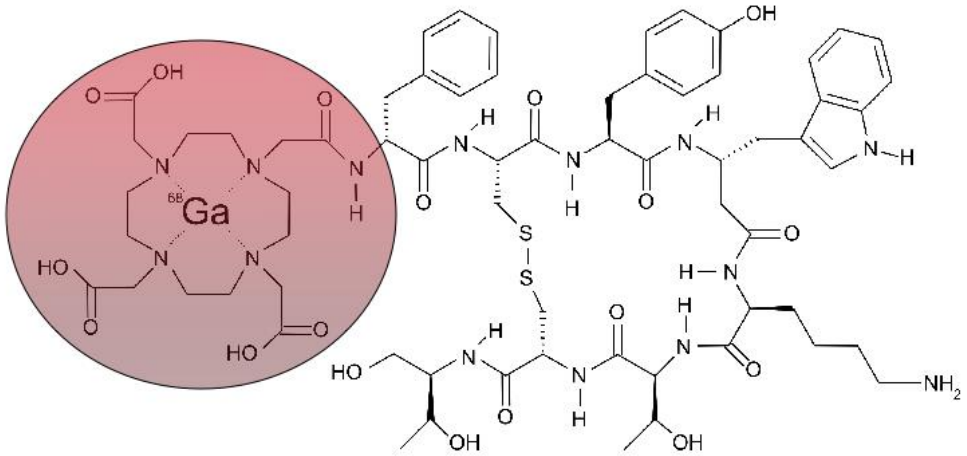


De Vos et al., Expert Opin Biol Ther, 2013

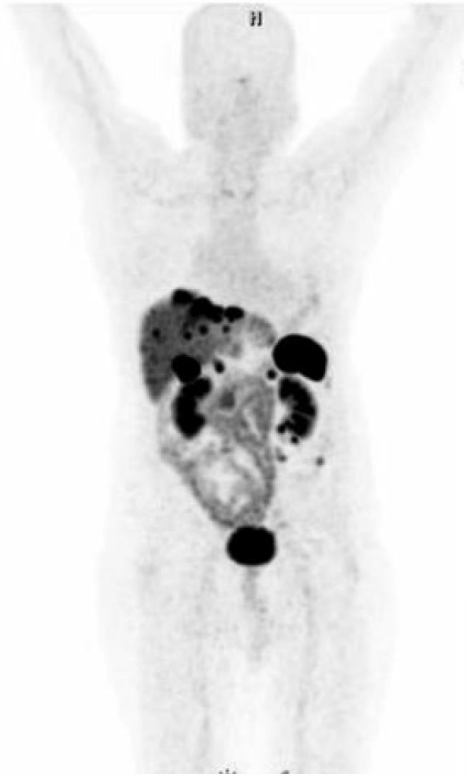
^{68}Ga-Octreo-PET

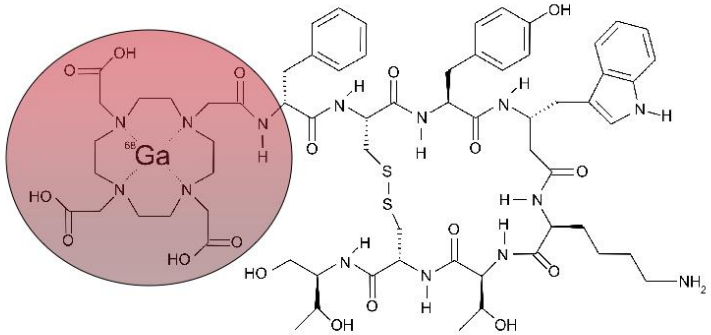


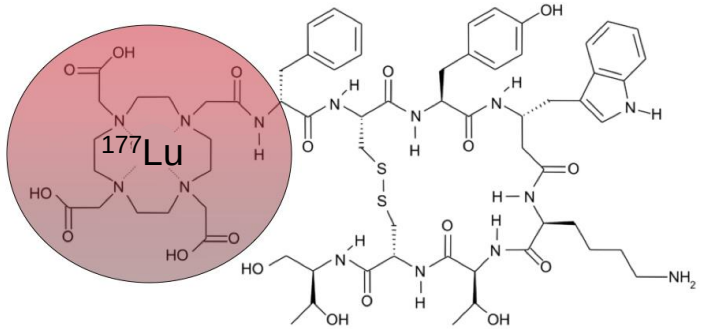
- **Target**: somatostatine receptor
- **Vector**: peptide
- Overexpressed on cell membrane in neuro endocrine cancers

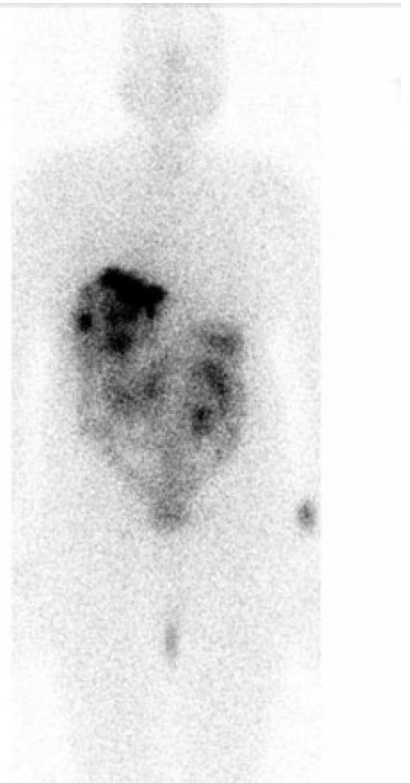


Diagnosis and Therapy







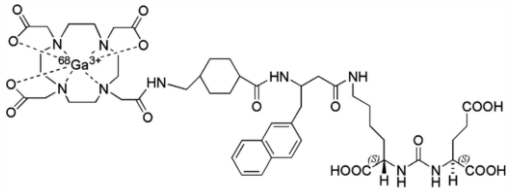


FDA approved drug: **Lutathera (Novartis)**

^{68}Ga-PSMA-PET

PSMA

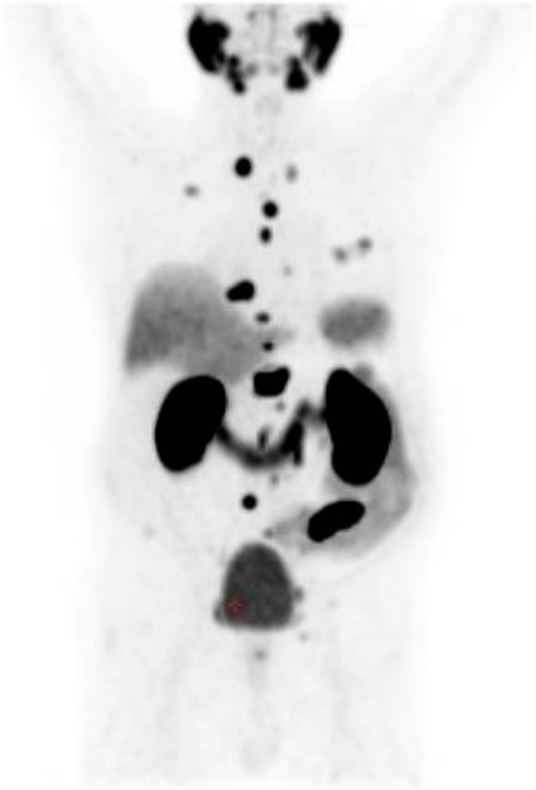
- High expression on prostate cancer cells
- Detection of metastatic prostate lesions
- **Vector**: small molecule



Normal biodistribution

- Intense salivary and lacrimal glands
- Intense kidney
- Moderate liver-biliary elimination

^{68}Ga-PSMA-PET



PSMA

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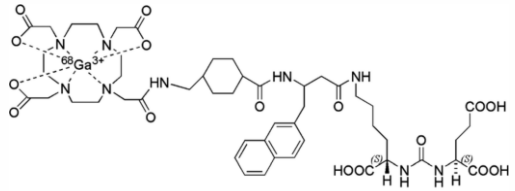
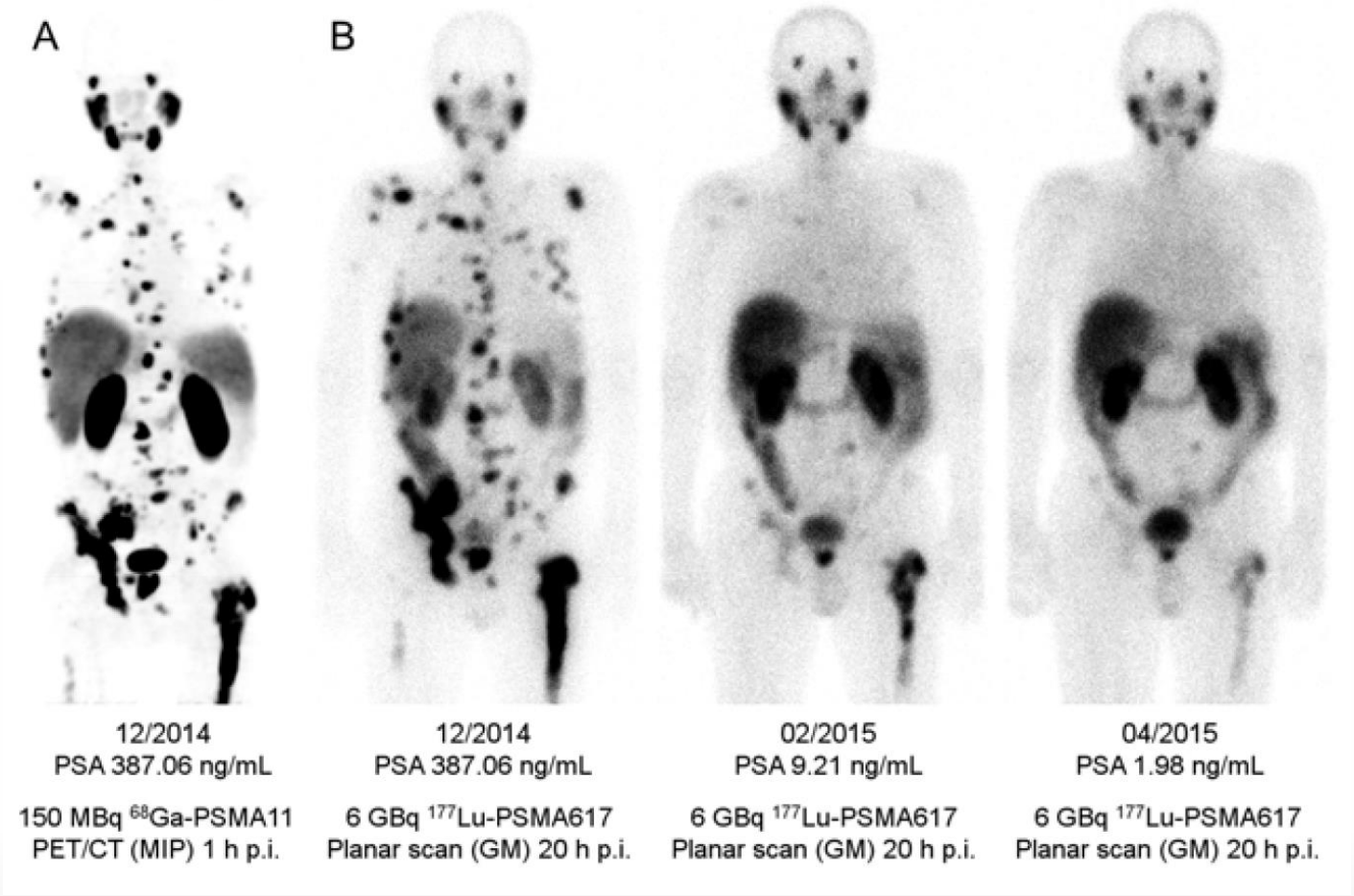


Treatment

- Beta and alpha irradiation

^{177}Lu-PSMA treatment



68Ga-PSMA11 / 177Lu-PSMA 617 is commercialized by **Novartis**

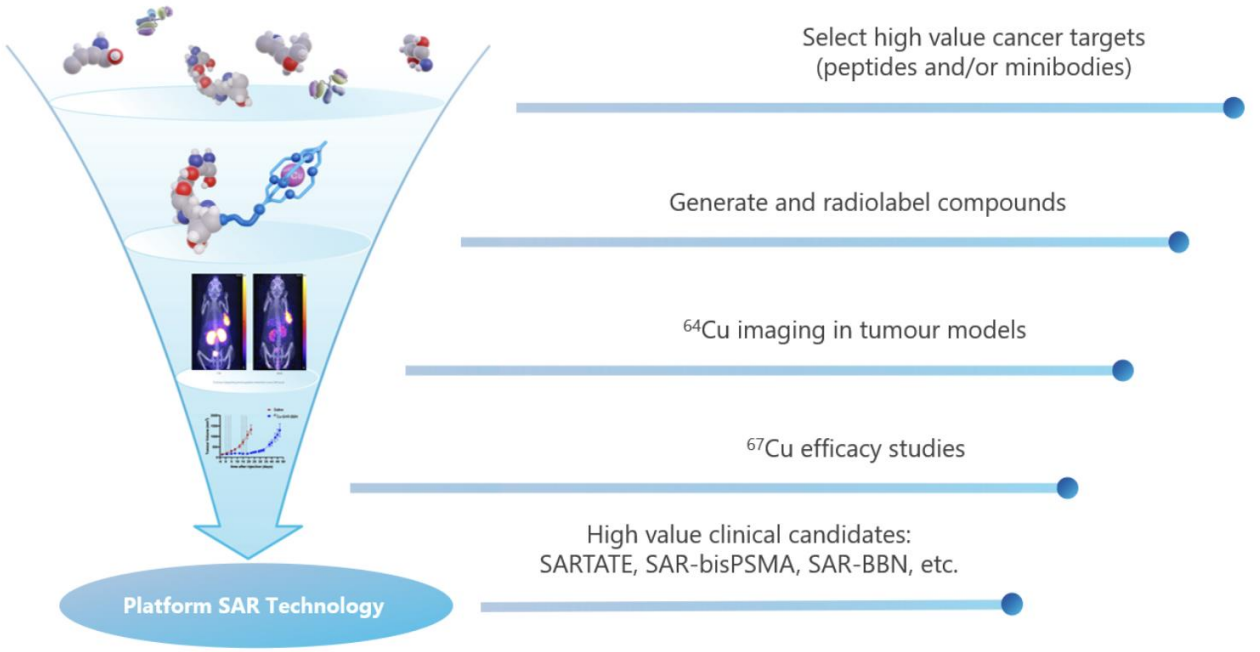
CURRENT VECTORS IN RADIONUCLIDE THERAPY?

A look into the current industrial developments …

CURRENT VECTORS IN RADIONUCLIDE THERAPY?

CLARITY PHARMACEUTICALS

Peptides
Minibodies



CURRENT VECTORS IN RADIONUCLIDE THERAPY?

CLARITY PHARMACEUTICALS

Peptides
Minibodies

Indication	Product		Discovery	Preclinical	Phase I	Phase 2	Phase 3
Prostate Cancer	SAR-bisPSMA	Theranostic					
	SAR-bisPSMA	Diagnostic					
	SAR-BBN	Diagnostic					
	SAR-BBN	Theranostic					
Neuroblastoma	SARTATE	Theranostic					
	SARTATE	Diagnostic					
NETs	SARTATE	Diagnostic					
Pan cancer (GRPr positive tumours)	SAR-BBN	Diagnostic					
SAR Discovery Platform	Undisclosed	Undisclosed					
	Undisclosed	Undisclosed					

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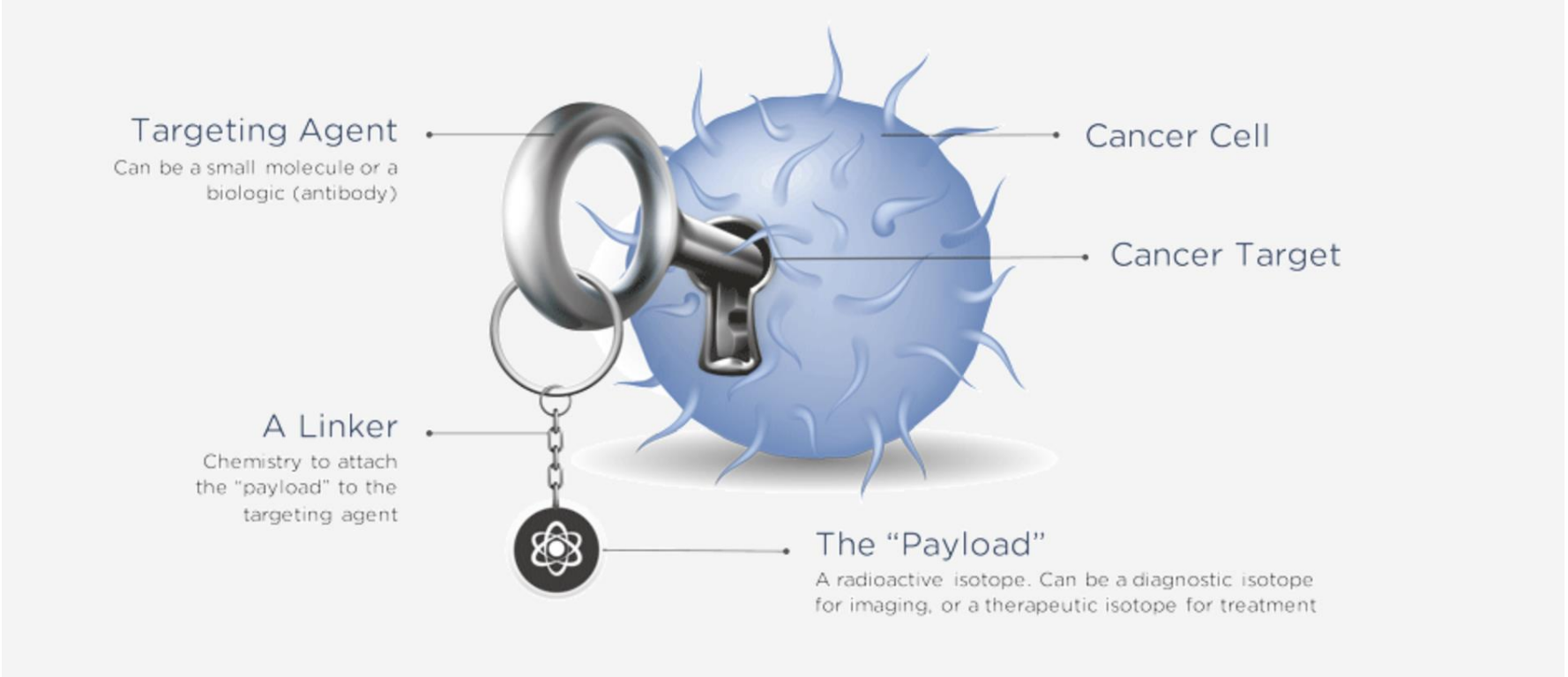
CURRENT VECTORS IN RADIONUCLIDE THERAPY?

TELIX PHARMACEUTICALS

Small molecule
Antibodies



CURRENT VECTORS IN RADIONUCLIDE THERAPY?

TELIX PHARMACEUTICALS

Small molecule
Antibodies

	Targeting Molecule	Target	Radioactive Isotope	Phase I	Phase II	Phase III	Commercial
Prostate	Small molecule	PSMA[1]	^{68}Ga	TLX591-CDx (^{68}Ga-PSMA-11, Illuccix®)			Imaging
	Antibody	PSMA	^{177}Lu	TLX591 (^{177}Lu–rosopatamab)			Therapy
	Antibody	PSMA	^{225}Ac	TLX592 (^{225}Ac–RADmAb®)			Therapy (2nd Gen)
	Small molecule	PSMA	^{99m}Tc	TLX599-CDx (^{99m}Tc-iPSMA)*			Imaging/Surgery
	Small molecule	PSMA	^{68}Ga	TLX591-Sx (^{68}Ga-PSMA-IRDye)			Imaging/ Surgery
Kidney	Antibody	CA9[2]	^{89}Zr	TLX250-CDx (^{89}Zr–girentuximab)			Imaging
	Antibody	CA9	^{177}Lu	TLX250 (^{177}Lu–girentuximab)			Therapy
Brain	Small molecule	LAT-1[3]	^{18}F	TLX101-CDx (^{18}F-FET)			Imaging
	Small molecule	LAT-1	^{131}I	TLX101(^{131}I-IPA)			Therapy
BMC/RD[4]	Antibody	CD66[5]	^{99m}Tc	TLX66-CDx (^{99m}Tc-besilesomab, Scintimun®)			Imaging
	Antibody	CD66	^{90}Y	TLX66 (^{90}Y-besilesomab)			Therapy

Shaded arrows indicate expected development stage in the next 12 months

1. Prostate-specific membrane antigen.
2. Carbonic anhydrase IX.
3. Large amino acid transporter 1.
4. Bone Marrow Conditioning / Rare Diseases.
5. Cluster of differentiation 66.

* Registry Study

With the exception of Telix's ^{68}Ga PSMA-11 imaging agent in Australia and the United States, none of Telix's products have received a marketing authorisation in any jurisdiction. Any use of Telix products is on an investigational basis only.

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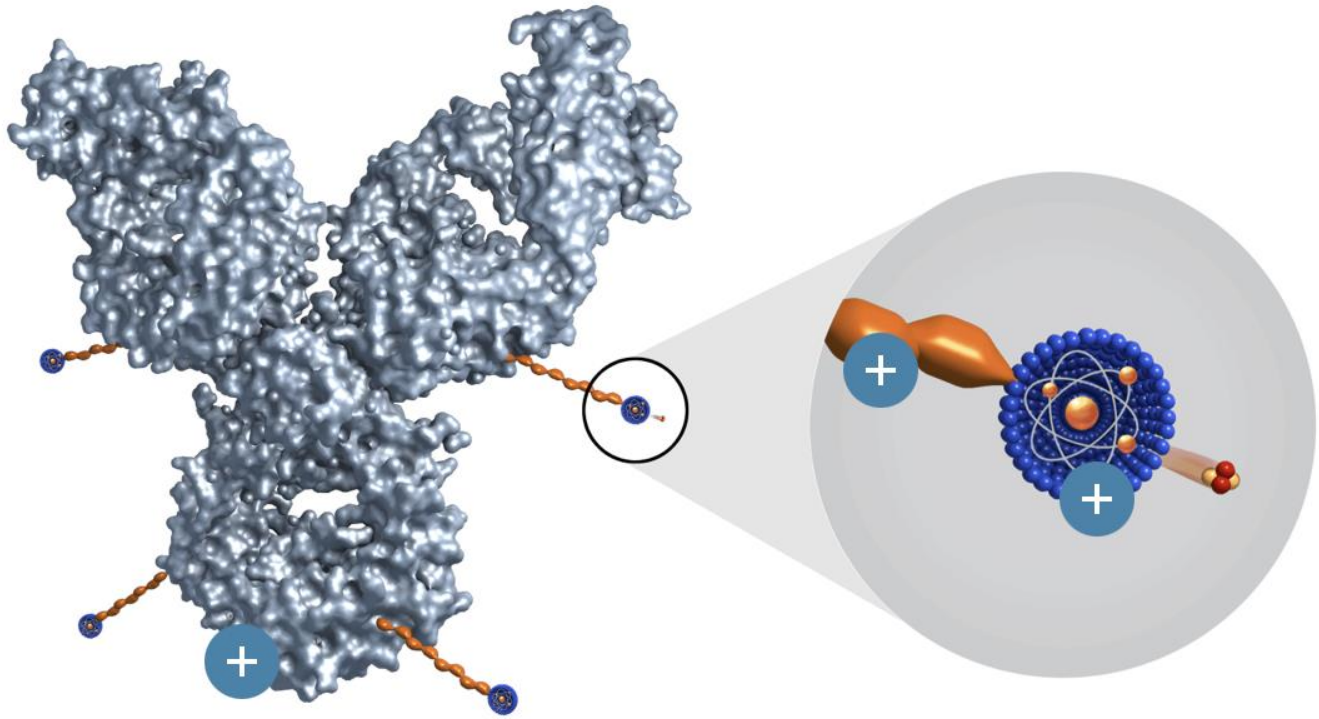
CURRENT VECTORS IN RADIONUCLIDE THERAPY?

Fusion Pharmaceuticals Inc.

Antibodies

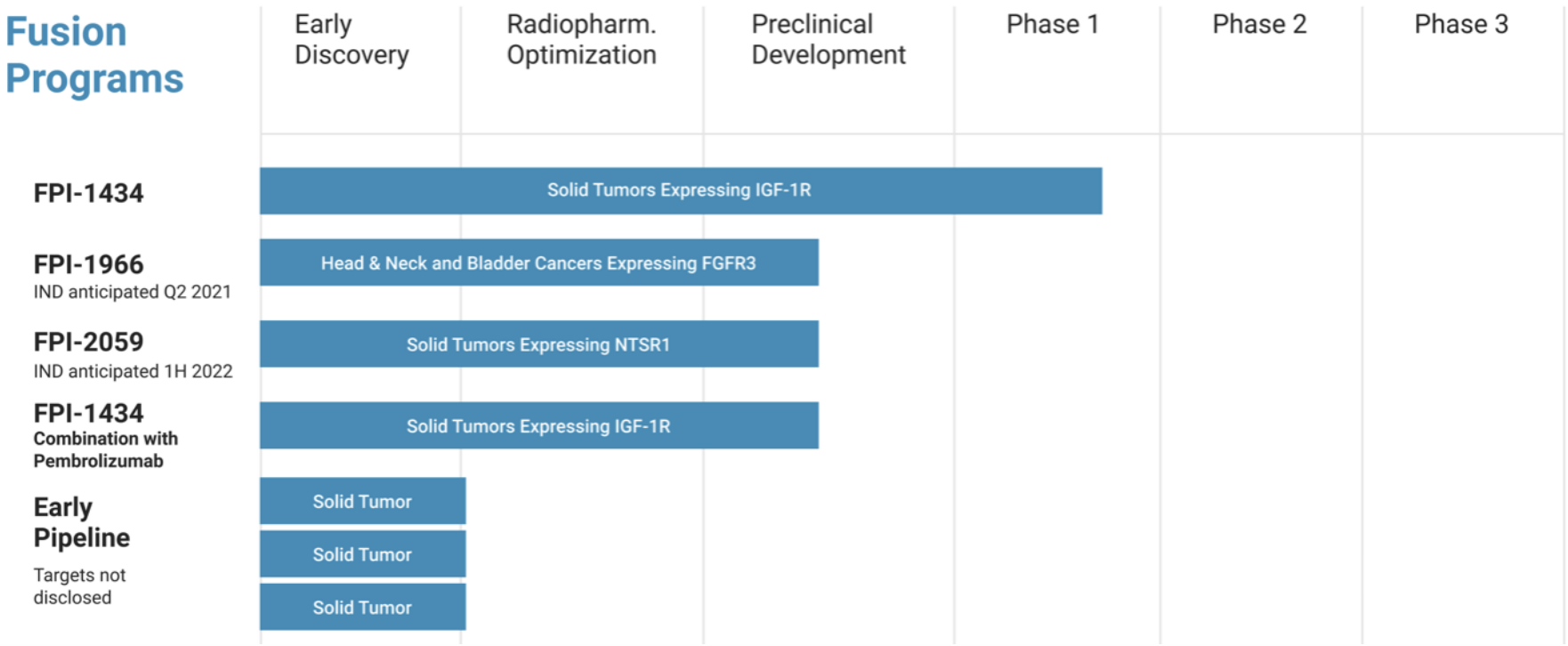
'Fast clear linker technology'



CURRENT VECTORS IN RADIONUCLIDE THERAPY?

Fusion Pharmaceuticals Inc.

Antibodies
Small molecule



CURRENT VECTORS IN RADIONUCLIDE THERAPY?

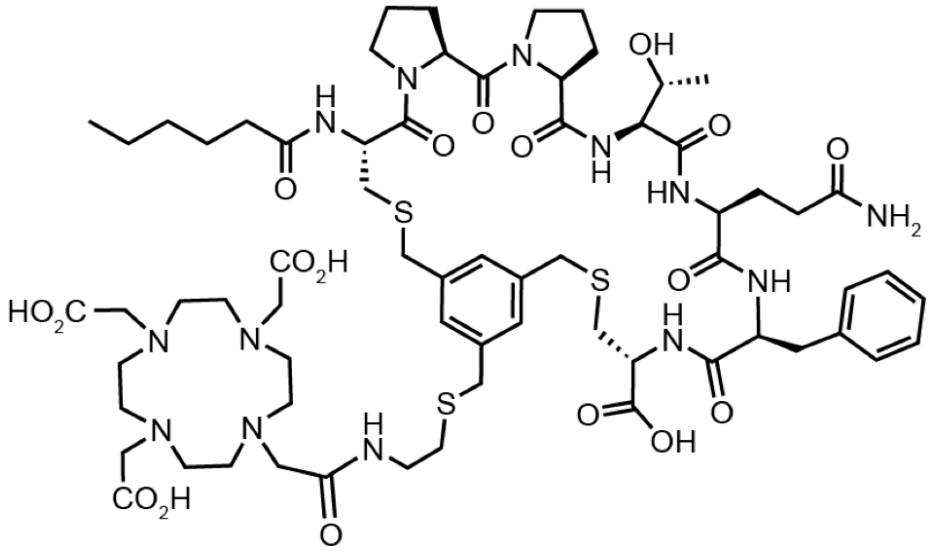
CLOVIS ONCOLOGY

Peptide

Fibroblast Activation Protein

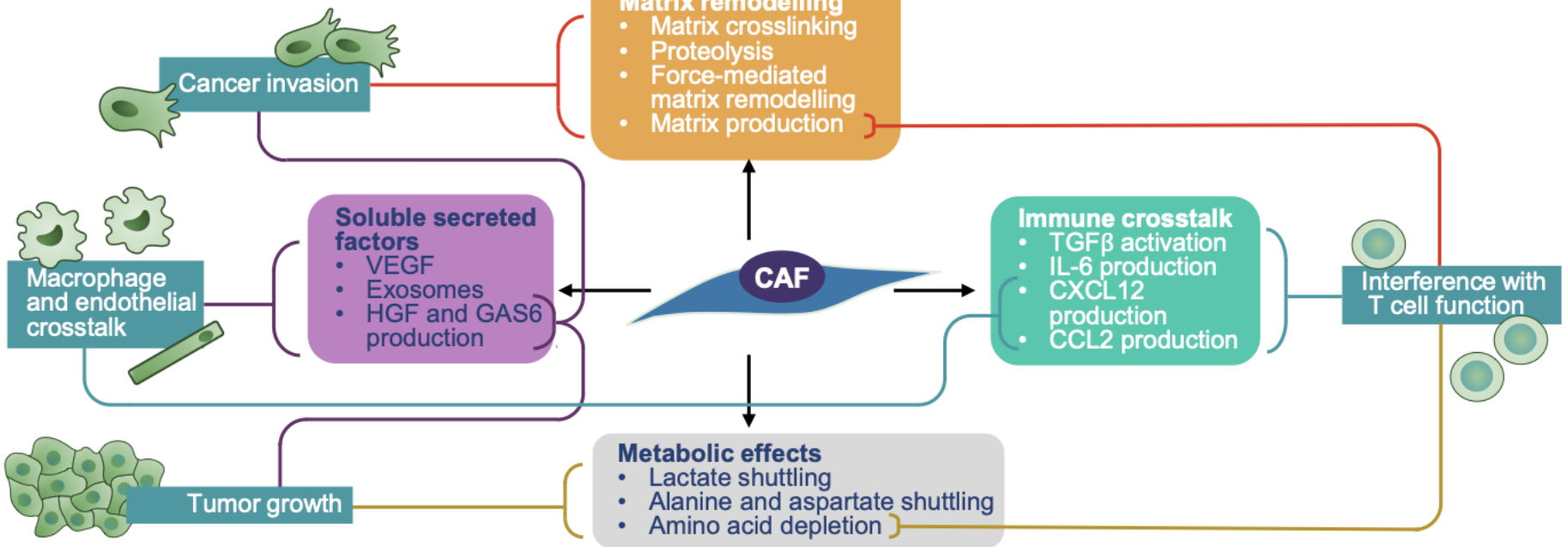
Phase I trial with 177 Lu-FAP-2286

FAP-2286



CURRENT VECTORS IN RADIONUCLIDE THERAPY?

CLOVIS ONCOLOGY



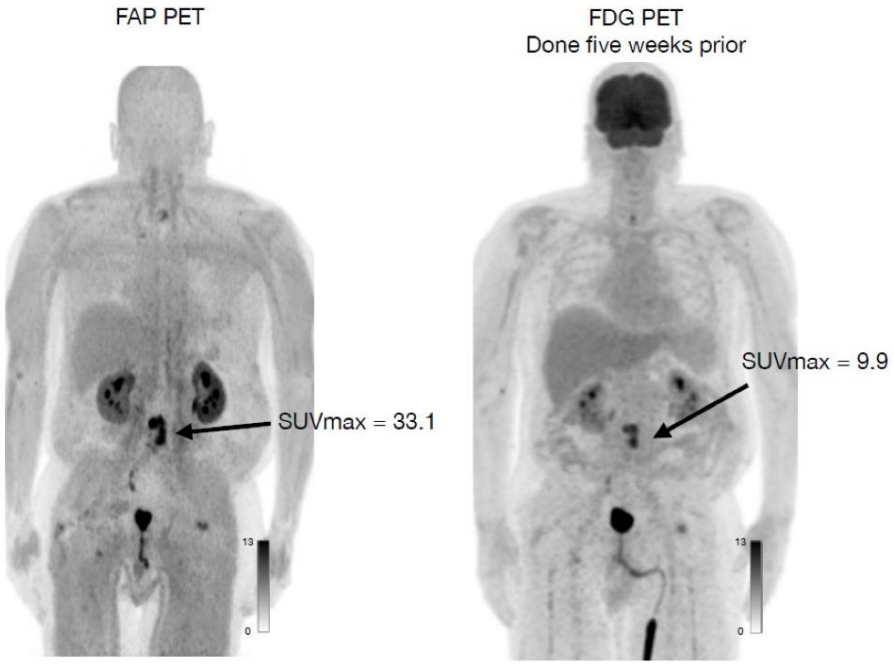
TRP TARGETED RADIOPHARMACEUTICALS SUMMIT

Figure was adapted from Sahai E et al. Nat Rev Cancer. 2020;20:174–186

1. Sahai E et al. Nat Rev Cancer. 2020;20:174–186; 2. Joshi RS et al. Cancers. 2021;13:1399; 3. Baker AT et al. J Immunol. 2021; 206:310–320

CURRENT VECTORS IN RADIONUCLIDE THERAPY?

^{68}Ga-FAP-2286 Shows High Uptake in Patient with Osteosarcoma



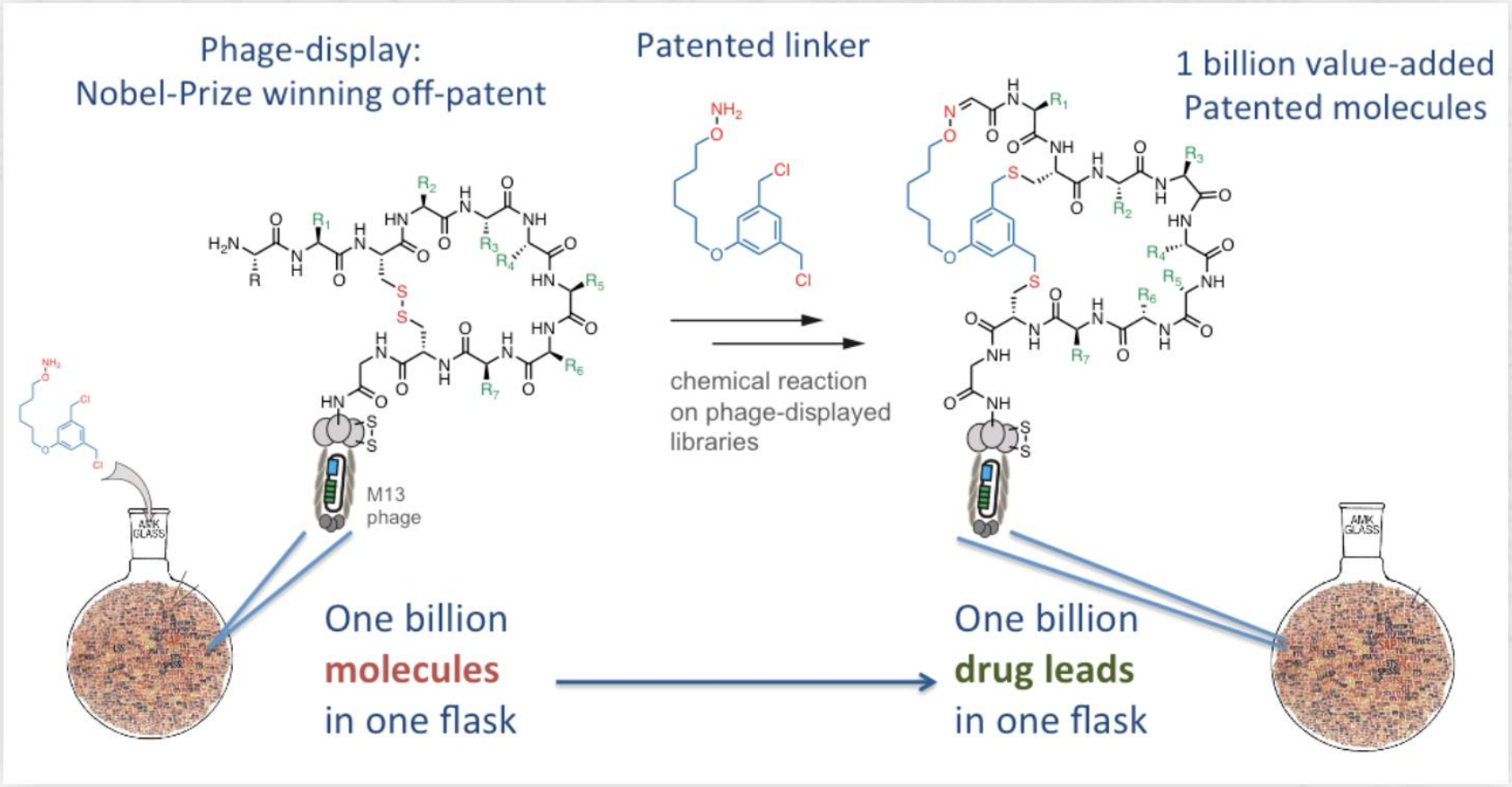
TRP TARGETED RADIOPHARMACEUTICALS SUMMIT

Source: Thomas Hope (UCSF). Data on File. 2021.

CURRENT VECTORS IN RADIONUCLIDE THERAPY?

RayzeBio

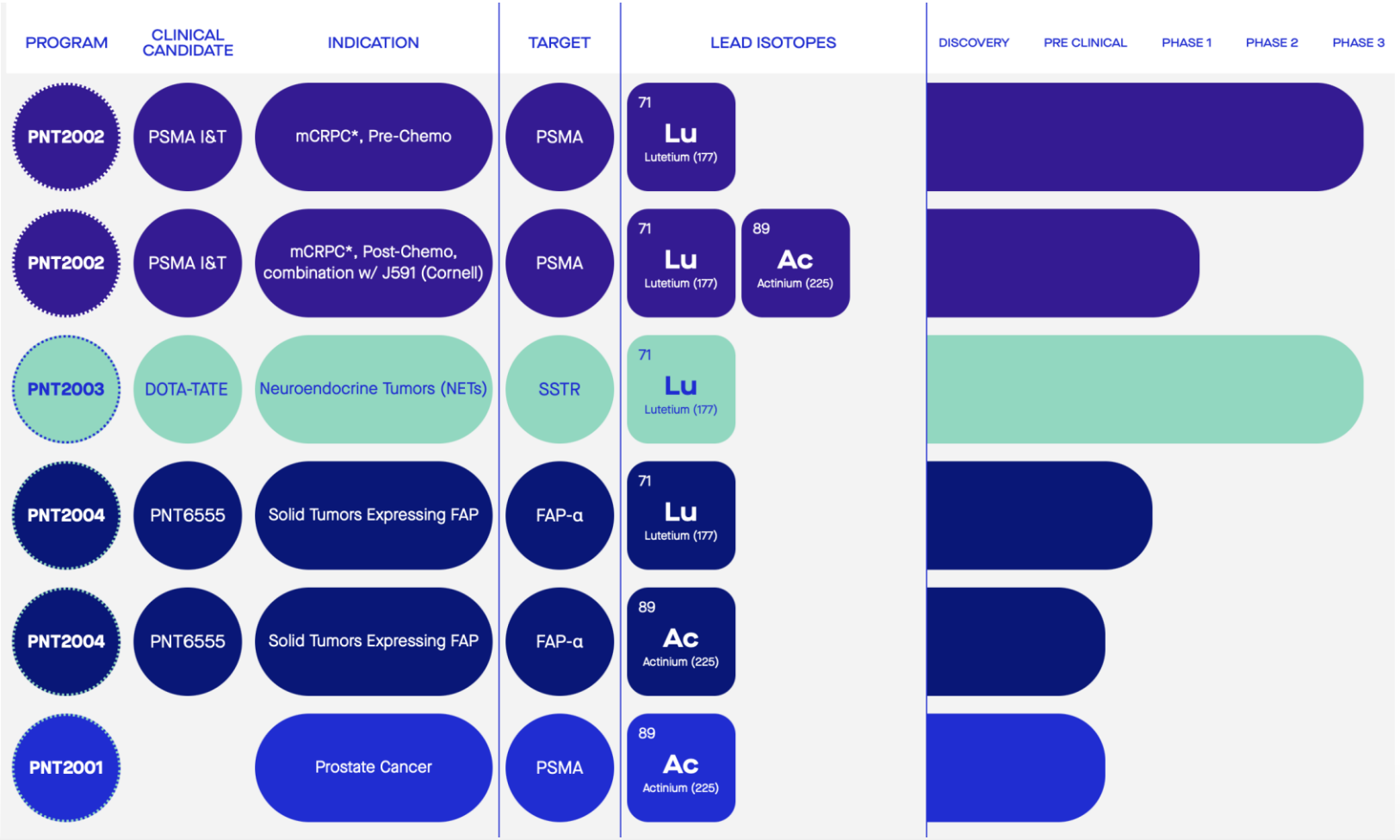
Peptides



CURRENT VECTORS IN RADIONUCLIDE THERAPY?

POINT BIOPHARMA

Peptides
Small molecules



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CURRENT VECTORS IN RADIONUCLIDE THERAPY?

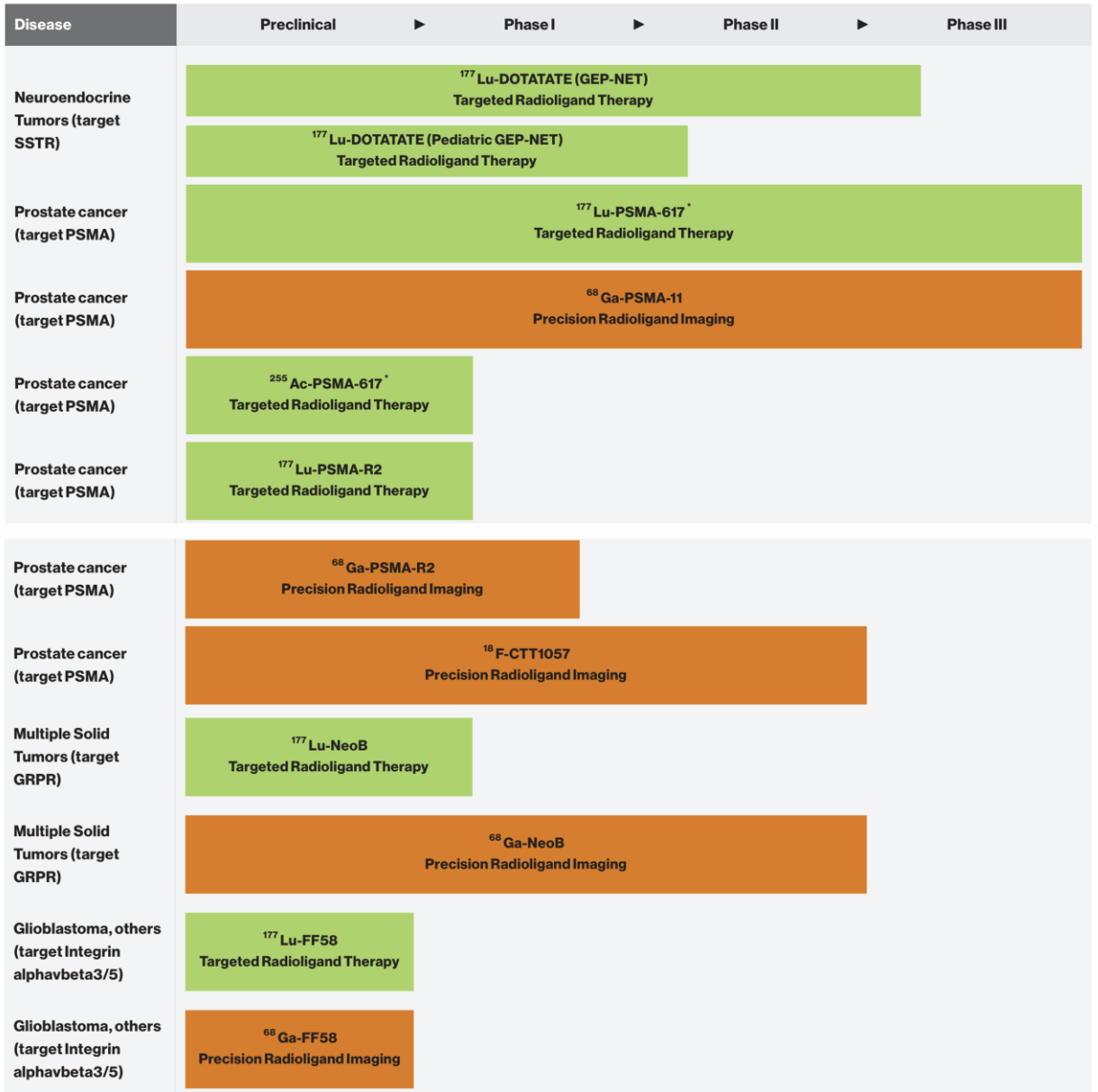
Monoclonal Ab

	Phase	
Oncology	I	^{227}Th-Pelgifatamab Corixetan (PSMA-Targeted Thorium Conjugate)
Oncology	I	HER2-TTC (HER2-Targeted Thorium Conjugate)

CURRENT VECTORS IN RADIONUCLIDE THERAPY?

Advanced Accelerator Applications
A Novartis Company

Peptides
Small Molecules



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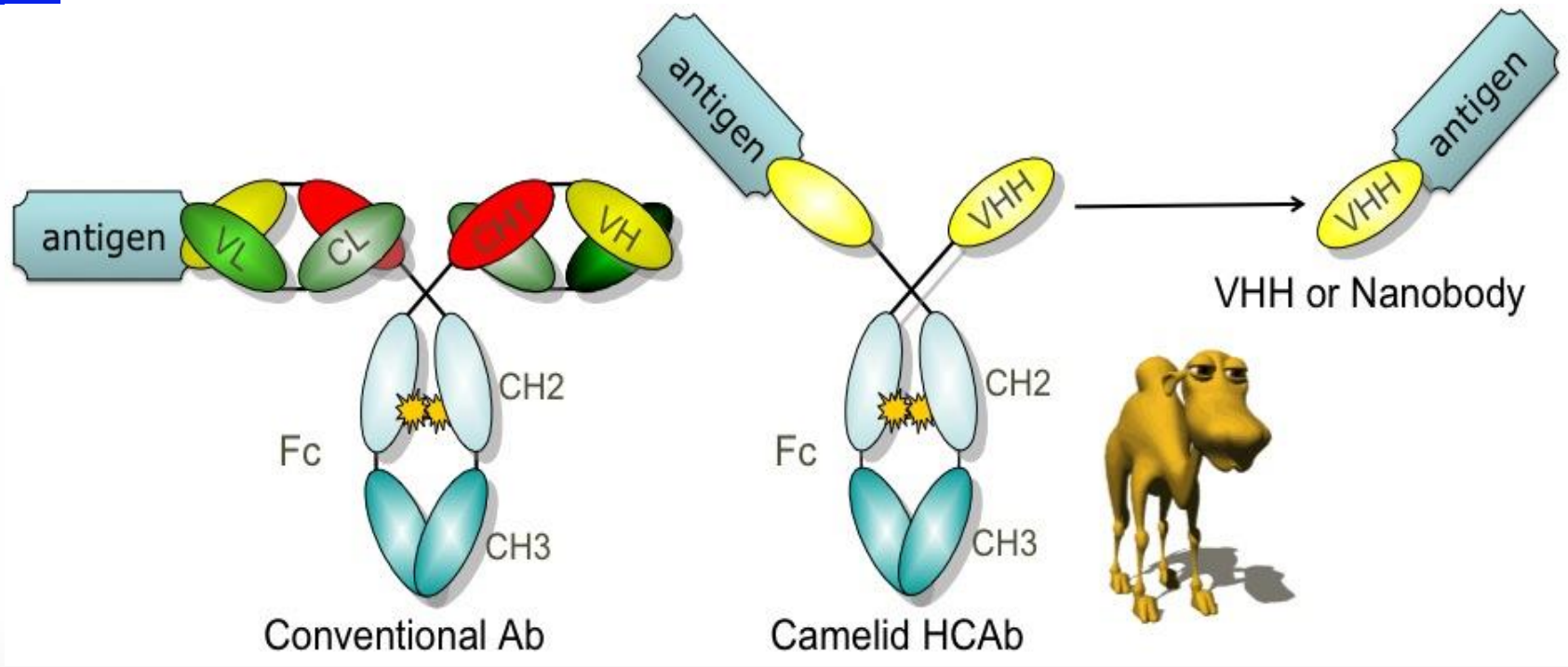
CURRENT VECTORS IN RADIONUCLIDE THERAPY?

PRECIRIX®

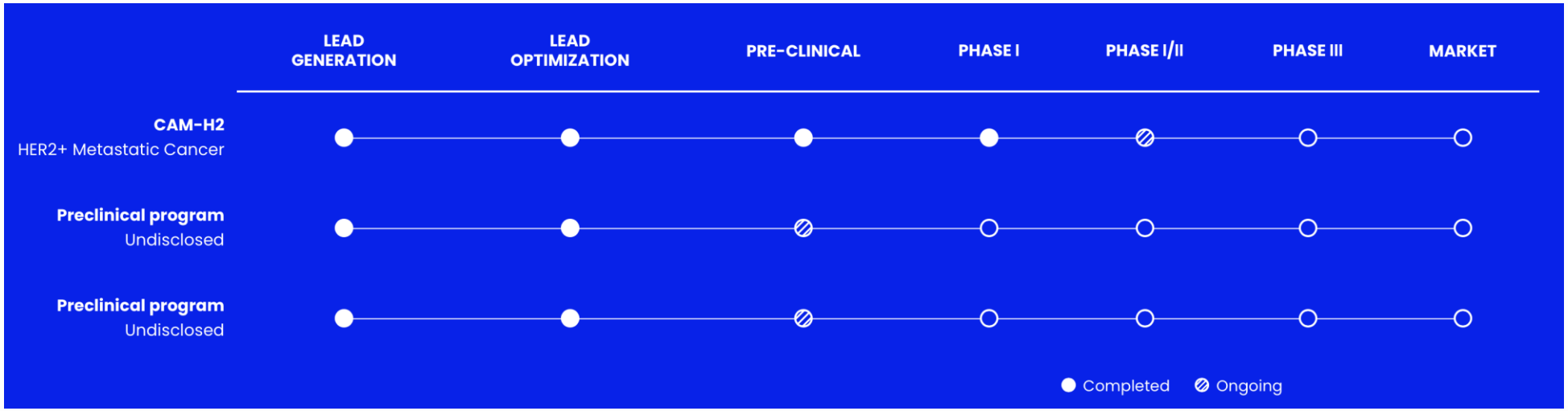
Single domain antibodies



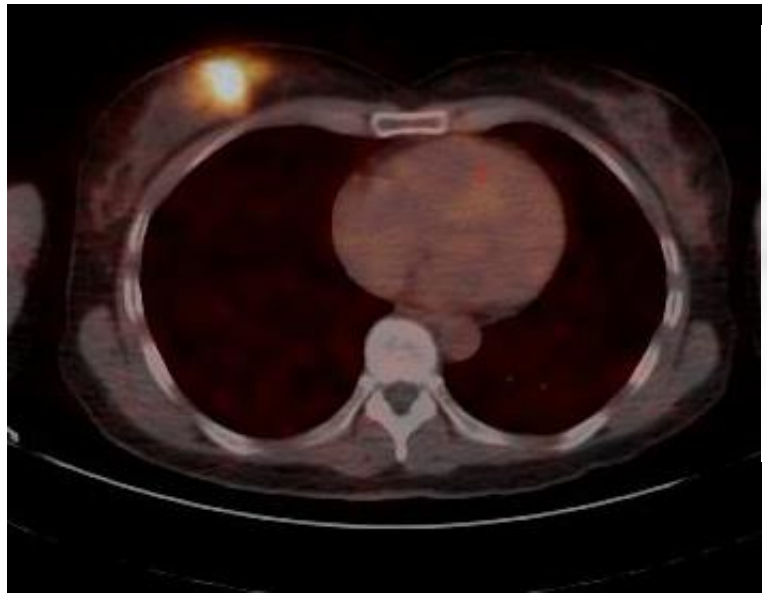
CURRENT VECTORS IN RADIONUCLIDE THERAPY?

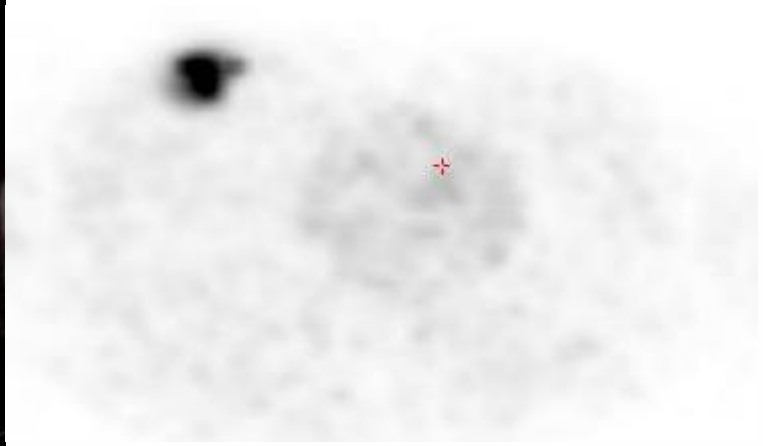
PRECIRIX®

Single domain antibodies

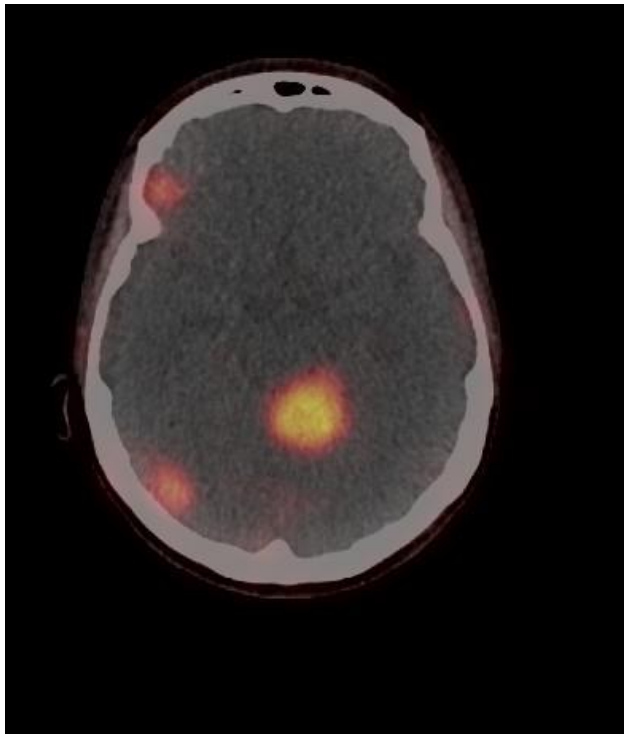


BREAST CANCER TARGETING: PRIMARY CANCER



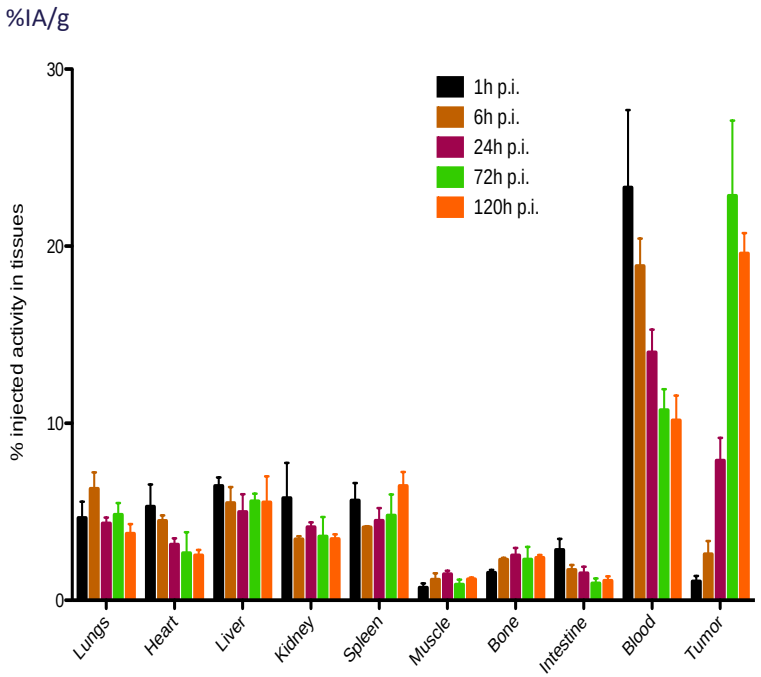


PHASE II BRAIN METASTASIS TRIAL

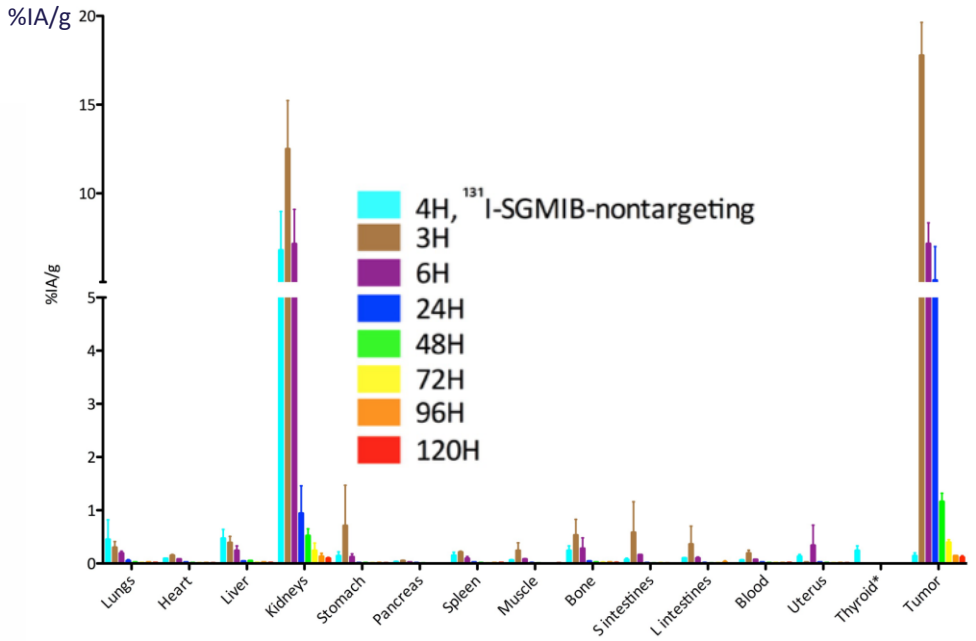


TUMOR AND HEALTHY TISSUE RADIATION NANOBODY VS. TRASTUZUMAB

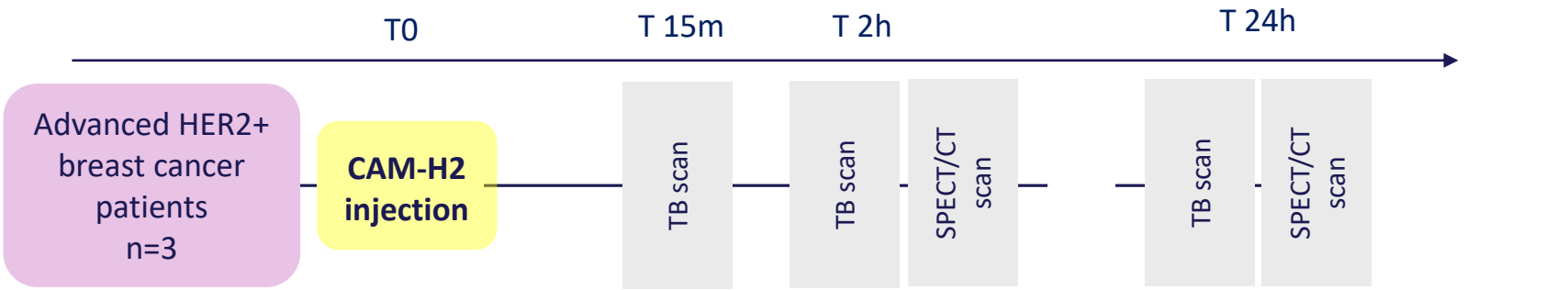
Trastuzumab



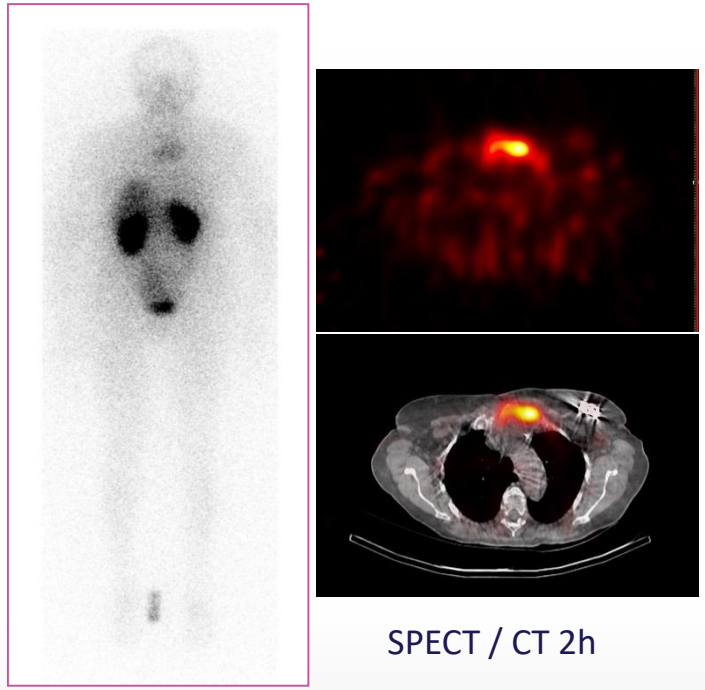
131I-SGMIB nanobody



FIRST IN HUMAN STUDY: CAM-H2 131I-SGMIB-ANTI HER2

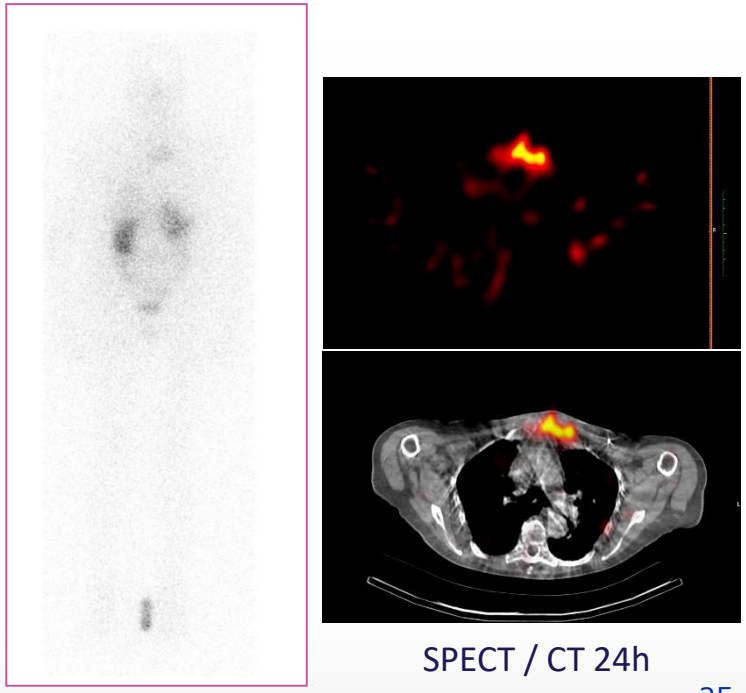


2h



SPECT / CT 2h

24h



SPECT / CT 24h

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Camel-IDS
STRIKE THE CANCER, NOT THE PATIENT

CURRENT VECTORS CONCLUSION

- Current success stories are based on peptides & small molecules
- New peptides and small molecules are developed for a range of cancer targets, however finding strong binders is complicated
- Existing monoclonal antibodies against cancer targets are ‘refurbished’ towards radiopharmaceuticals, however long residence time in the circulation requires innovative linker methods to limit toxicity
- Antibody fragments can be generated against any target and approach the PK properties of peptides
- All developments are matched by radionuclide diagnostic for patient selection