Actithera

Non-Confidential Overview

Building the next generation Radiotherapeutics platform

April 2023

Actithera | Executive summary

Company

Established in July 2021 in Cambridge, MA

Seed financing of $ 5.3M from **M. Ventures and Arkin BioVentures**

Looking for a **$20M + $50M tranched Series A** to progress lead program through Ph2, second program to Ph1 and expand team and pipeline

Focus

Discovering and Developing novel **Radiotherapeutics** for the treatment of cancer

Current **pipeline of several targets**

Best- and First- in class programs

Small molecule and Peptide-based

Unique Value Proposition

Unprecedented **tumor-trapping approach**[1]

Early validation of technology with first FAP-targeting lead molecules exhibiting significantly **higher tumor uptake and retention than clinical benchmark**

Exclusive In-licensing option to unique technology complimentary to Actithera's tumor-trapping approach[2]

[1, 2] Disclosed under CDA

Investors

M. VENTURES

ARKIN BIO VENTURES

Collaborations

EMORY UNIVERSITY

ICR The Institute of Cancer Research

WISCONSIN UNIVERSITY OF WISCONSIN-MADISON

UNIVERSITAS AMOIENSIS

厦門大學 XIAMEN UNIVERSITY

Team | Bringing deep molecular design expertise into radiopharmaceuticals

Andreas Goutopoulos

Co-founder & CEO

Chief Scientist, Discovery Tech at **EMD Serono**

CSO at **Metabomed**

EIR at **M. Ventures**

Affiliate Faculty at **Northeastern University**

- EMD Serono: Over 23 years of industrial drug discovery experience, both in pharma and biotech
- MetaboMed: Co-inventor behind over 15 INDs, including Pimasertib (PhII- Onc) and Evobrutinib (PhIII - MS)
- M. Ventures: VC (M. Ventures) and C suite (Metabomed, FoRx) experience
- Northeastern University: Affiliated Faculty - Northeastern University – Center for Drug Discovery

Henry Yu

Co-founder & CSO

Founder and CEO of **CanWell**

Co-founder of **TocopheRx**

Principal Scientist at **EMD-Serono**

- EMD Serono: Over 18 years of industrial drug discovery experience
- CANWELL: Raised over $45 M and brought CanWell from concept to clinic in 3 years
- TocopheRx: Inventor/co-inventor of more than 7 clinical candidates
- Expert in ADCs

Orit Jacobson

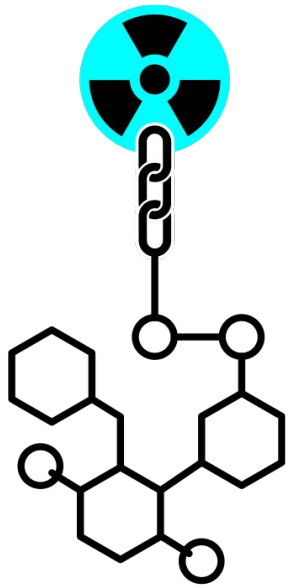
VP Head of R&D

NIH (NIBIB)

Head of Radiochemistry at **Hadassah Hebrew University Hospital**

- NIH National Institutes of Health: Radiochemist and Molecular Imaging expert with over 20 years of experience
- Deep experience with small molecule, peptide and NBE-based Theranostics
- Hadassah University Hospital: Over 100 publications in the field
- Inventor of clinically validated add-on molecular modifier for the prolongation of half life of Theranostics. Inventor of over 8 tracers that entered clinical trails (3 for therapy) in US, Germany, China

Radiotherapeutics | The new revolution in personalized cancer therapy



1. Radiopharmaceuticals are a unique class of drugs that deliver radiation by molecules directly and specifically into tumors

2. Rules of engagement are becoming clear with the first recently approved agents

   As an investment, the field is where ADCs were in 2010, or PROTACs in 2017

3. First Radiotherapeutics discovered in Academic Centers

   Actithera is industrializing radiotherapeutic discovery and development

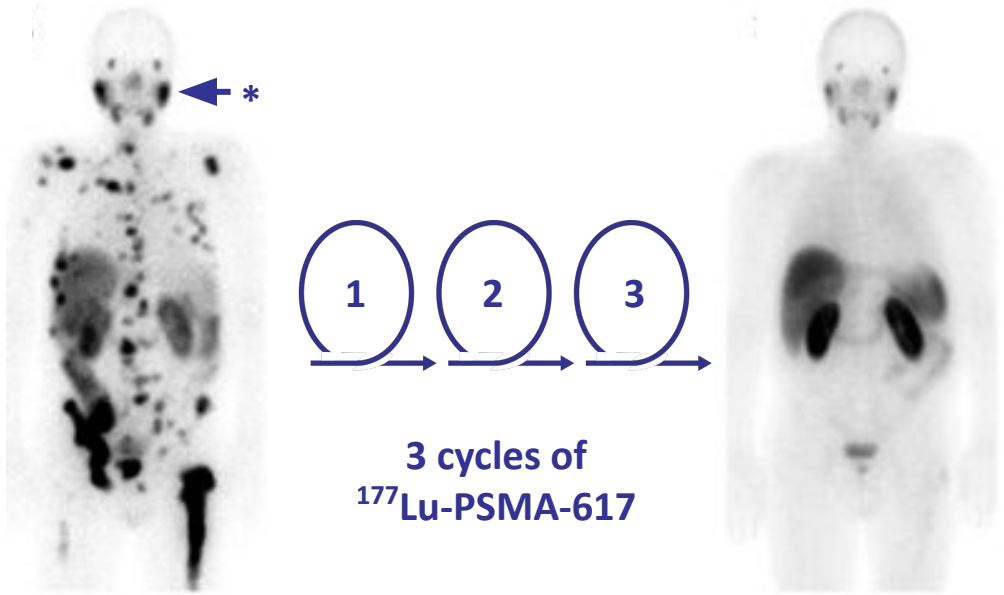
4. Actithera leverages an unprecedented approach to achieve tumor trapping and superior efficacy

Molecular Radiotherapy

Addresses the key challenges in cancer treatment

1. **Precise patient selection** | Image first and treat only patients with high tumor tracer uptake
2. **Accurate PK, PD, efficacy and even safety* by imaging**
3. **Dosimetry** | Quantitative translation from preclinic to clinic | Dose personalization in clinic
4. Rarely seen efficacy with excellent tolerability and great improvement in quality of life
5. Unlike external beam radiation the approach is effective in disseminated metastatic disease
6. Excellent potential for combinations with immunotherapy and DDI inhibitors

Lessons from recently approved ^{177}Lu-PSMA-617 in metastatic CR Prostate Cancer



at baseline
PSA: 387.06ng/ml

after 3 cycles
PSA: 1.08ng/ml

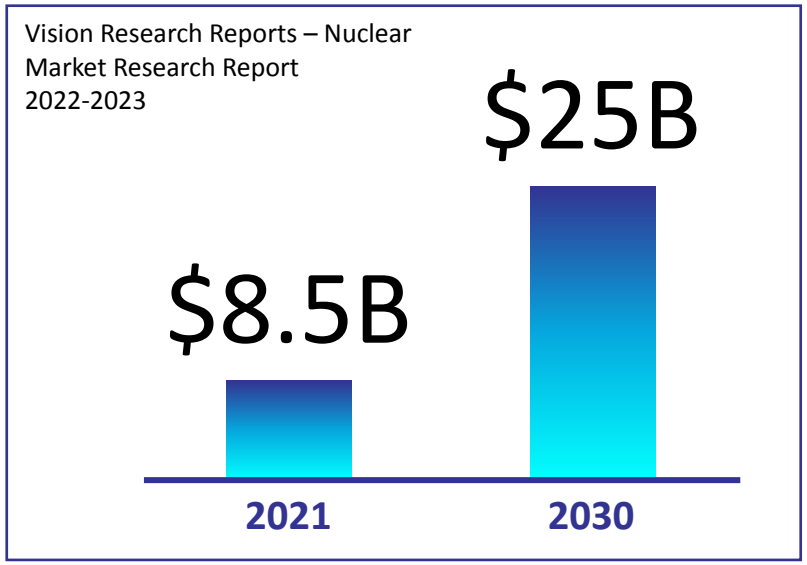
^{177}Lu-PSMA-617 (Pluvicto^{TM}) targets PSMA on the surface of prostate cancer cells

* Extratumoral uptake in parotids → explains main AE (dry mouth)

The Growth of Nuclear Medicine market

Availability of radionuclides and supply chain infrastructure are critical

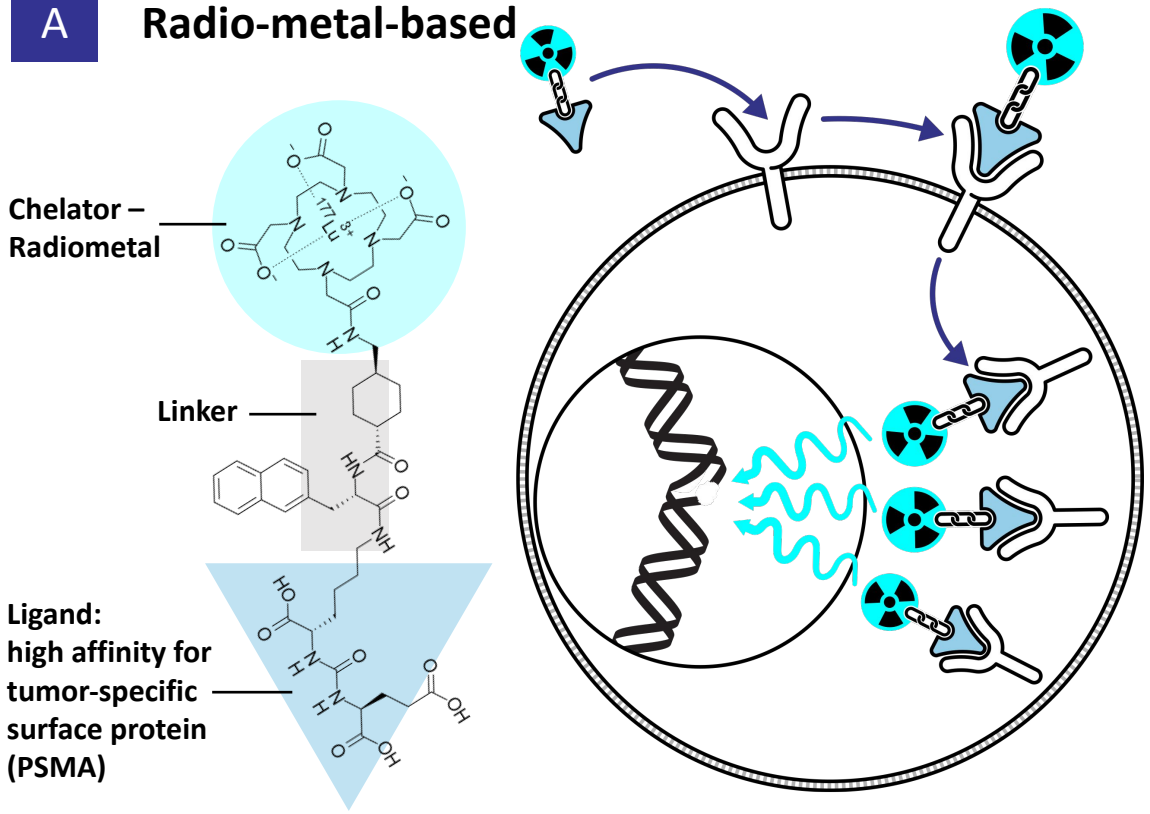
- Pluvicto ($179M in Q4 ’22) and Lutathera ($128M in Q4 ’22) are the 3rd and 4th (out of 25) highest selling Novartis solid tumor drugs in Q4 2022, although Lutathera is registered for a rare cancer and Pluvicto was approved only in March ’22. Despite occasional supply chain disruptions, both molecules had impressive launches and quick market share capture
- The Nuclear Medicine market is projected to grow with CARG 10.5% to $25B by 2030
- Availability of therapeutic radionuclides, supply chain infrastructure and number of nuclear medicine centers are bound to improve as long as differentiated therapies continue to emerge



- Actithera is currently working primarily with Isosolutions for access to radionuclides
- Planning to sign agreements with suppliers for clinical support:
  - ^{177}Lu: **ITM** (Germany), **Isotopia** (Israel) **Eczacıbaşı Monrol Nükleer Ürünler** (Türkiye), **Radiomedics** (USA)
  - ^{90}Y: **Eckert and Ziegler** (Germany)
  - ^{225}Ac: **RadioMedix** (USA), **Tri-Lab/DOE** (USA)
  - ^{131}I: **International Isotopes Inc.** (USA), **Polatum** (Poland)

Examples of Radiotherapeutics | Key learning from approved agents

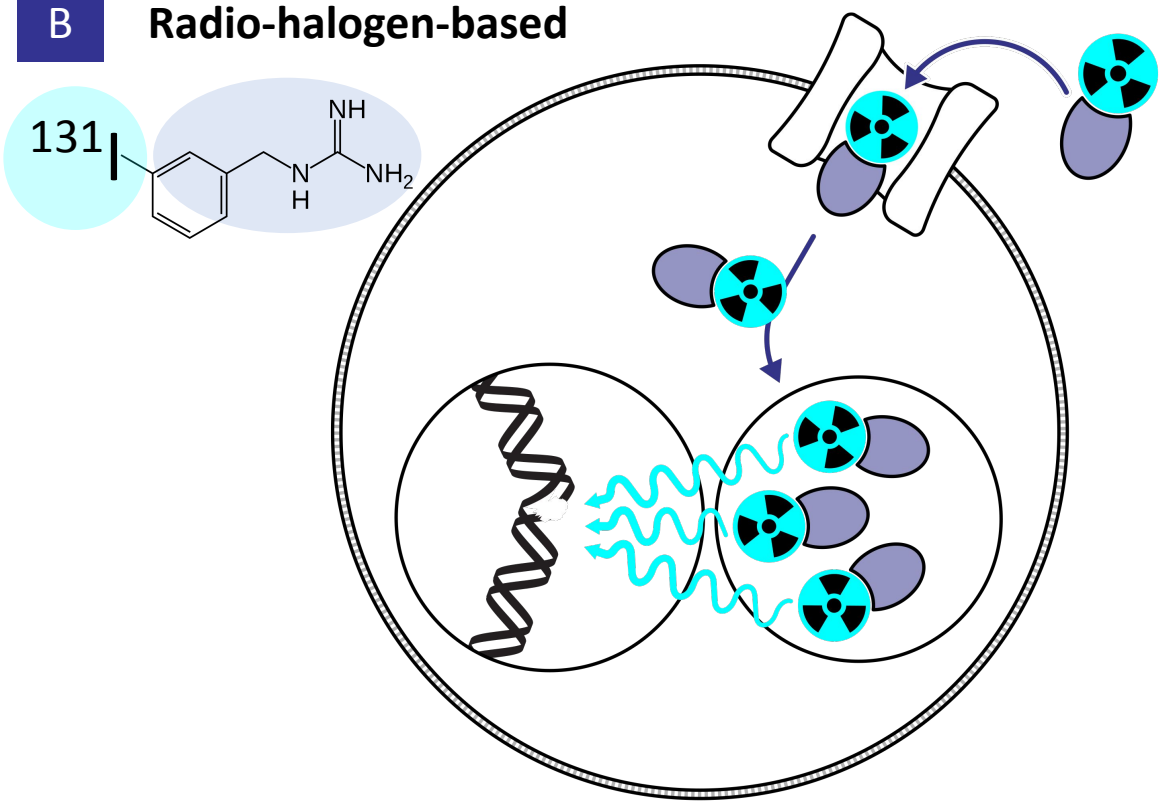
A Radio-metal-based



^{177}Lu PSMA-617 (Pluvicto™) approved in 2022 for mCRPR

^{177}Lu PSMA-617 is not cell-permeable. It is actively internalized inside prostate cells that express PSMA on their surface, resulting in selective **trapping and accumulation** of radioactivity inside cancer cells only

B Radio-halogen-based

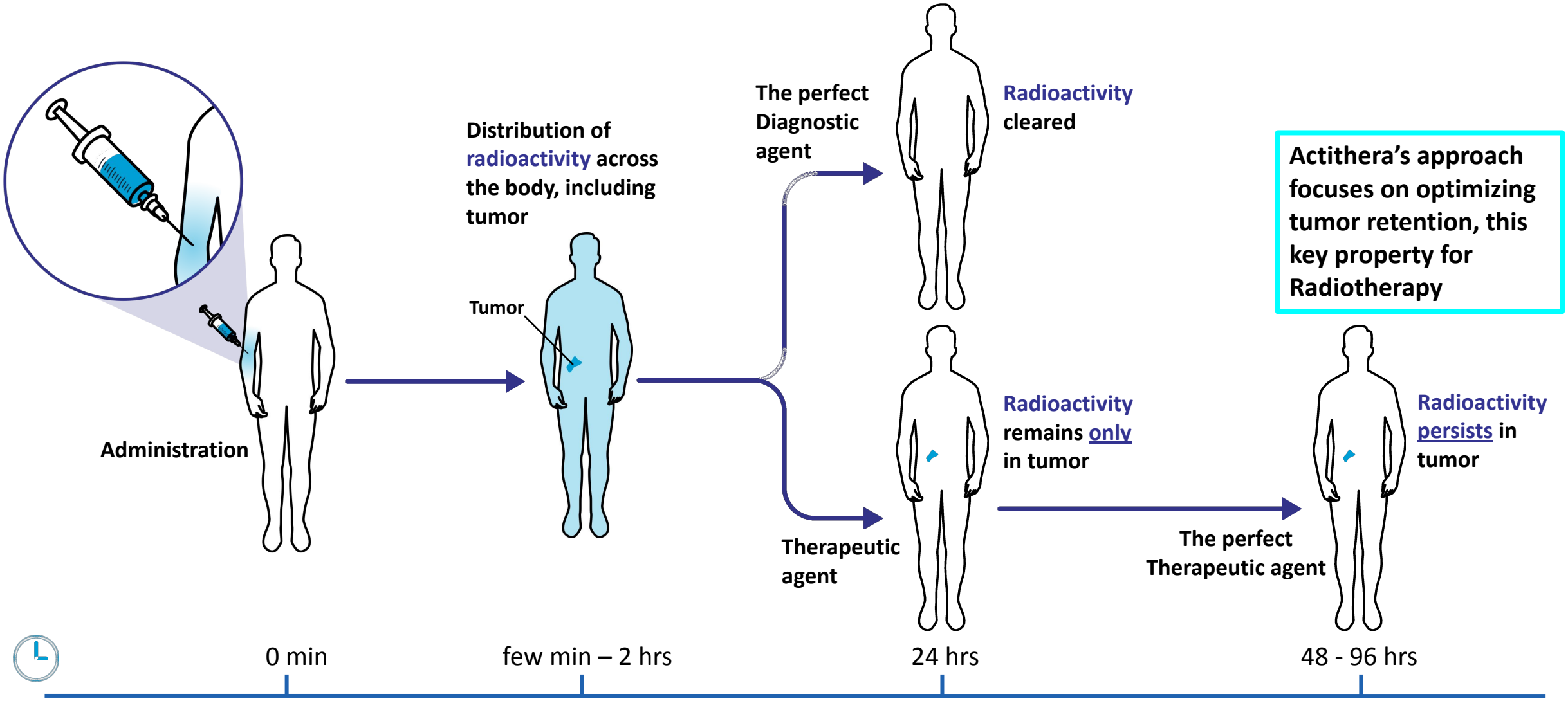


^{131}I MIBG (Azedra®) approved for PPC-PPNG in 2018

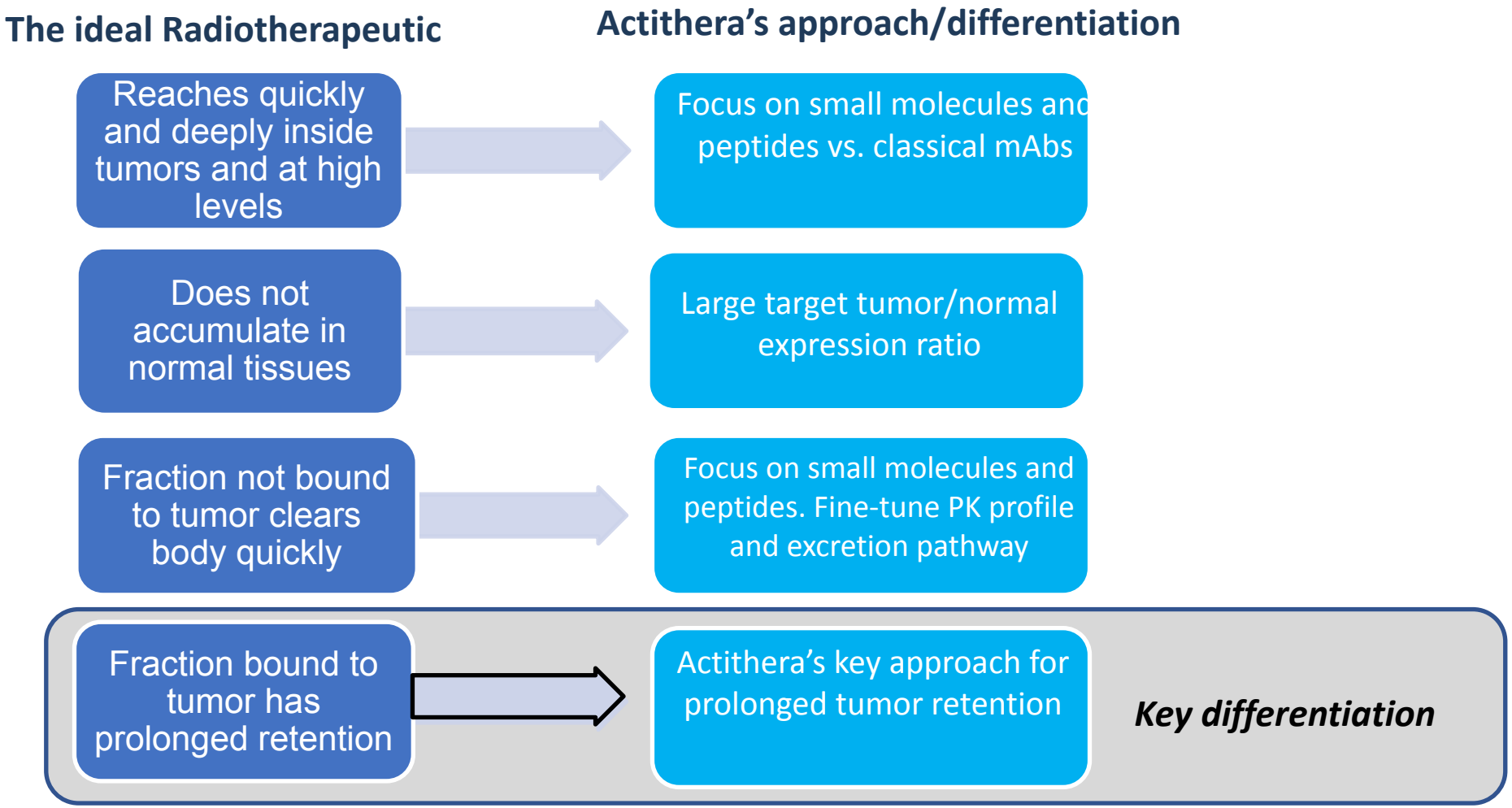
^{131}I MIBG is taken up by NET (Nor-Epinephrine Transporter) into adrenergic system tumors and **accumulates/gets trapped** within adrenergic granules inside tumor cells

Therapeutic vs. Diagnostic

Prolonged tumor retention is critical for successful Therapeutic agents



The Ideal Radiotherapeutic | Actithera's differentiation



Strategic considerations

Target Selection

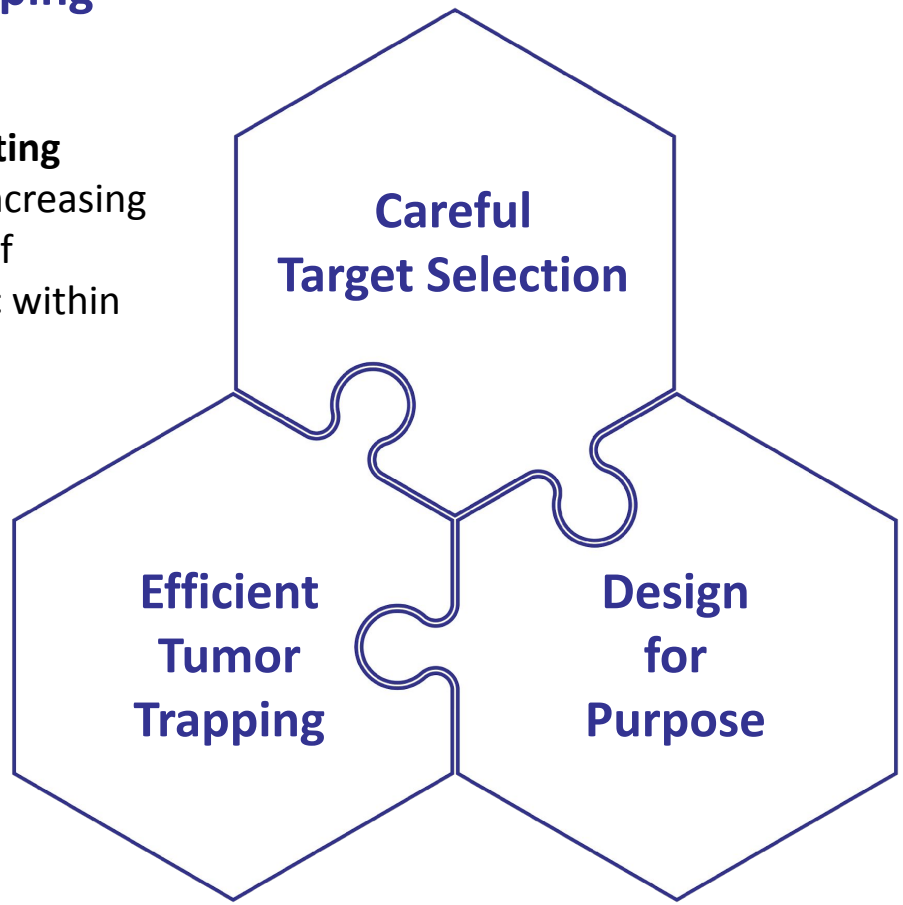
- High tumor to normal expression ratio
- High absolute tumor expression
- Other means of attaining selectivity
- Target biological role is not of major importance (main reason for failures in PhII in biopharma industry)

Design for Purpose

- Modular design (similar in a way to PROTACs)
- Bespoke DMPK optimization (focus on $t_{1/2}$ and excretion route) primarily by optimizing linker properties
- Dial-in appropriate for each case level of energy, range and type of radiation by radionuclide choice (**radionuclide agnostic**)

Tumor Trapping

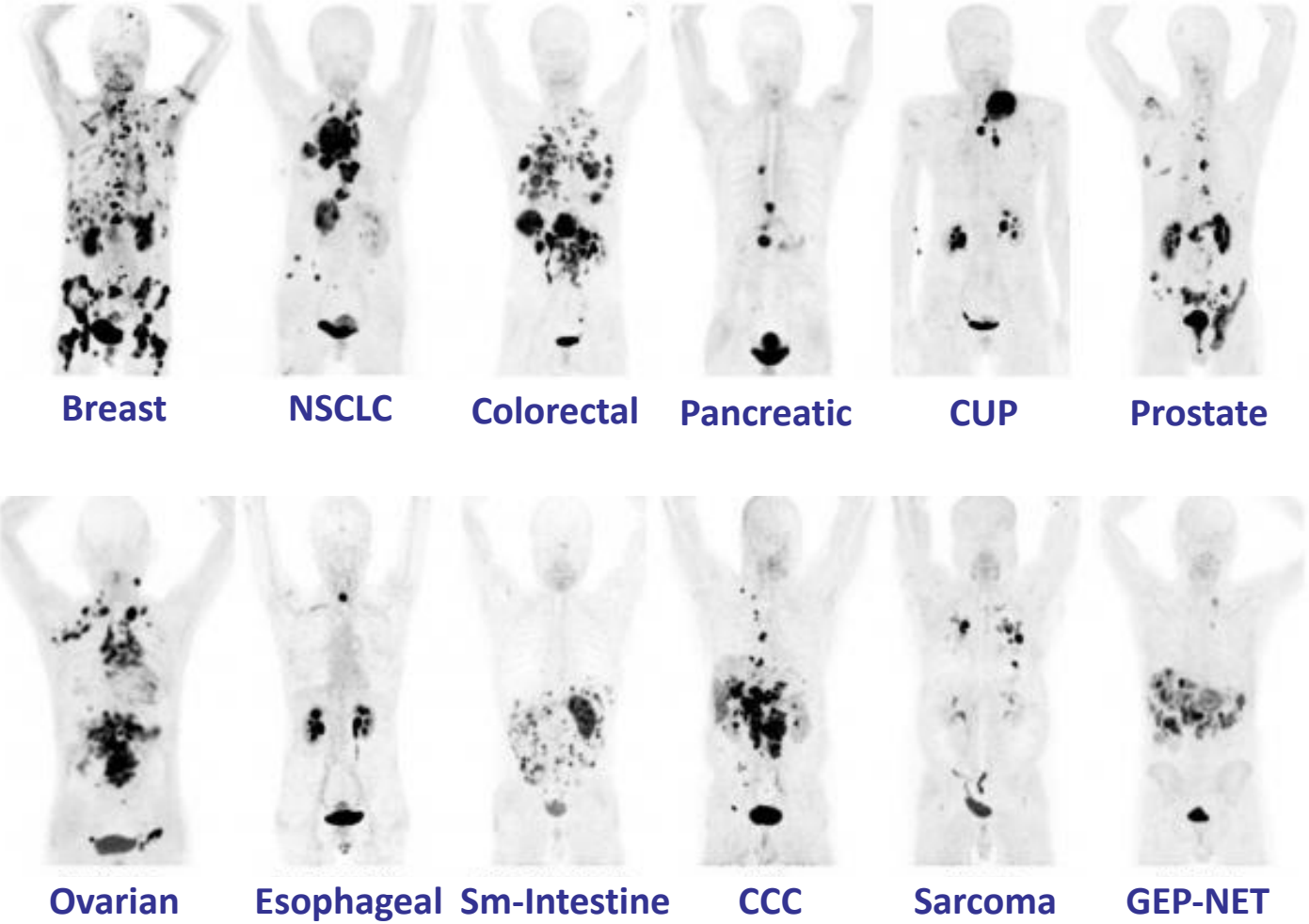
- Actithera's **differentiating angle** for increasing retention of theranostic within tumor



FAP Program | The most promising theranostic target currently

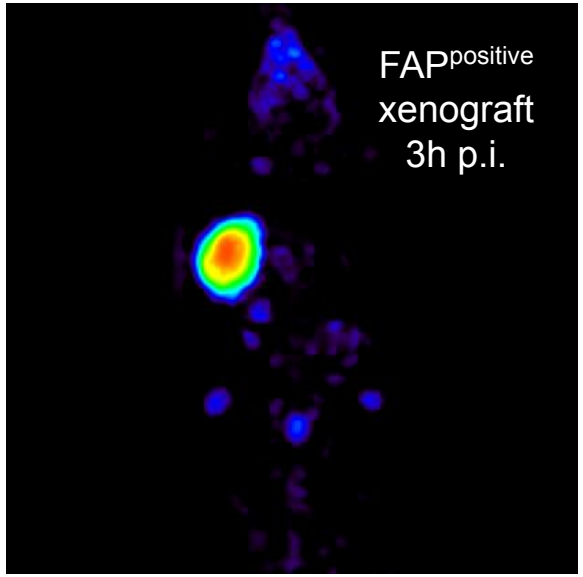
- **Fibroblast activation protein (FAP)** is an endopeptidase highly expressed in Cancer Associated Fibroblasts of most epithelial and mesencymal carcinomas but almost not at all in healthy tissues. **FAP is also highly expressed in certain tumor cells, such as sarcomas**
- FAP-targeting agents are very promising as pan-cancer diagnostics, differentiated from currently widely used FDG-PET
- Generating ligands with high and prolonged tumor residence time is key for the development of successful FAP-targeting cancer therapeutics

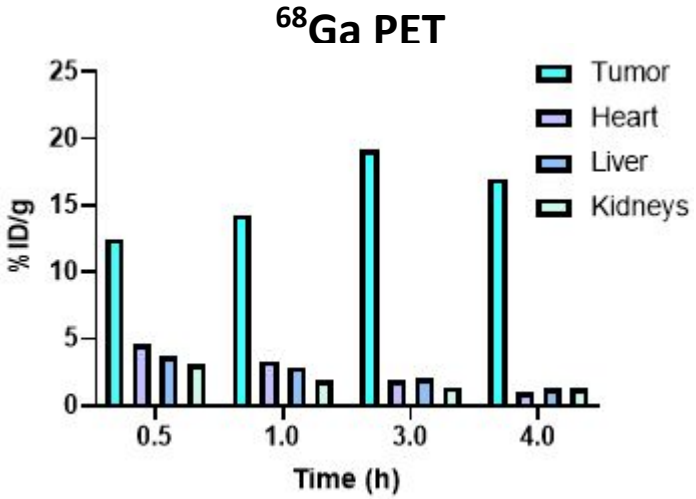
FAPI-PET in different kinds of cancer

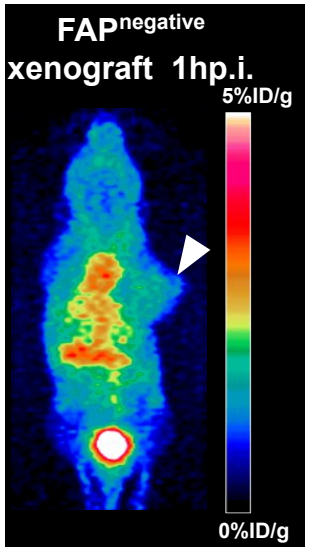


Actithera's FAP lead molecule

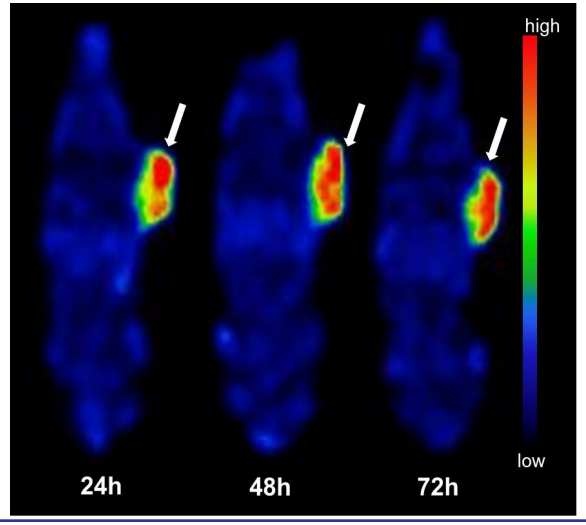
ACT-3-12 is an early validation of Actithera's approach

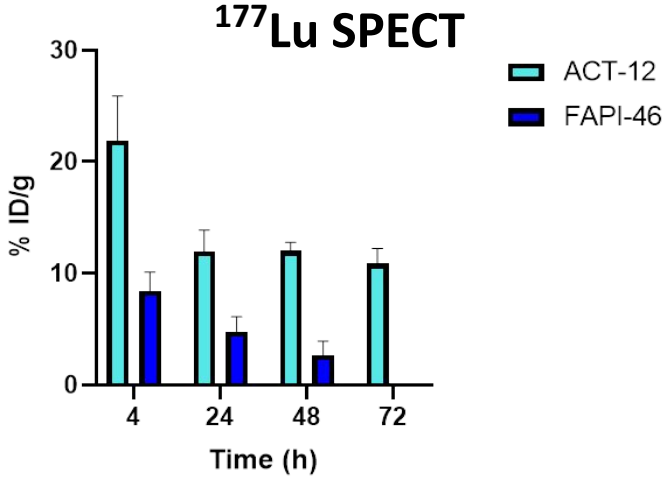






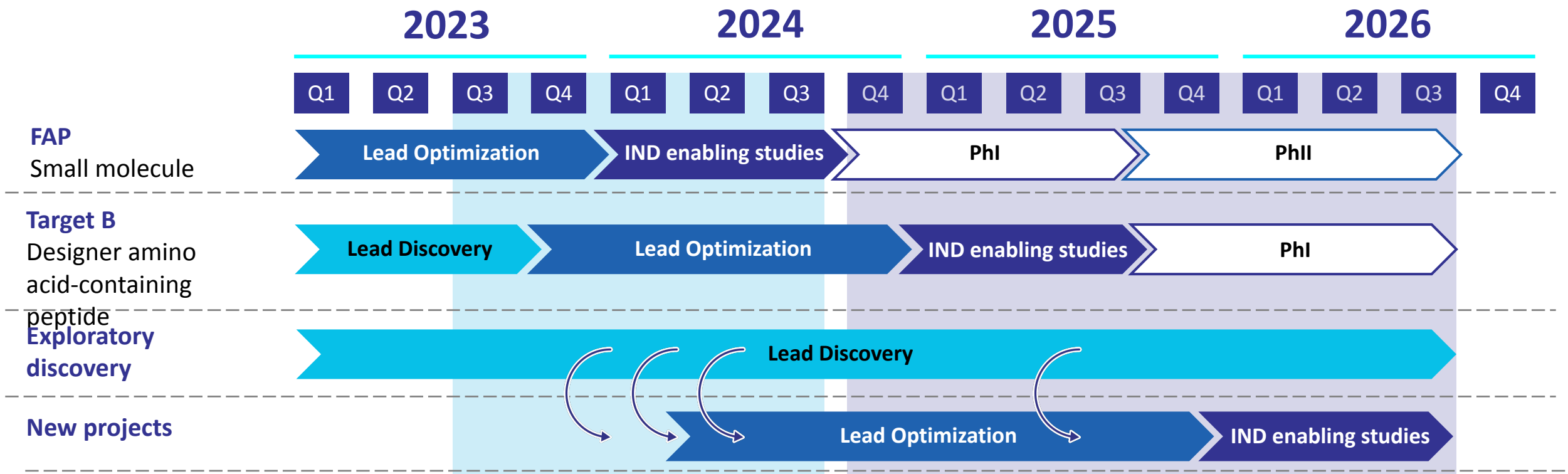
Actithera lead show high and specific tumor uptake, low background and renal clearance





Tumor retention remains high over at least 72hr, a lot longer than clinical benchmark FAPI-46

Pipeline and financing



Seed stage achievements so far:

- Established core team
- Signed four academic collaborations
- Built early project pipeline
- Achieved promising lead in key Theranostic target (FAP)
- Signed exclusive option agreement to in-license complimentary technology

$20M: 14 mo

- 1 IND
- 2nd Lead
- Pipeline growth
- Team expansion
- Establish labs

Another $50M: 22 mo further

- Clinical POC
- 2nd PhI
- 2nd, 3rd IND
- Pipeline growth
- Team expansion

Summary

Actithera has a **unique medicinal chemistry approach** for the design of Radiotherapeutics with prolonged tumor retention

It is seeking **$20 + 50M tranched series A** to bring first program through clinical POC, a second program through PhI and expand pipeline and team

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