



# Amphilix

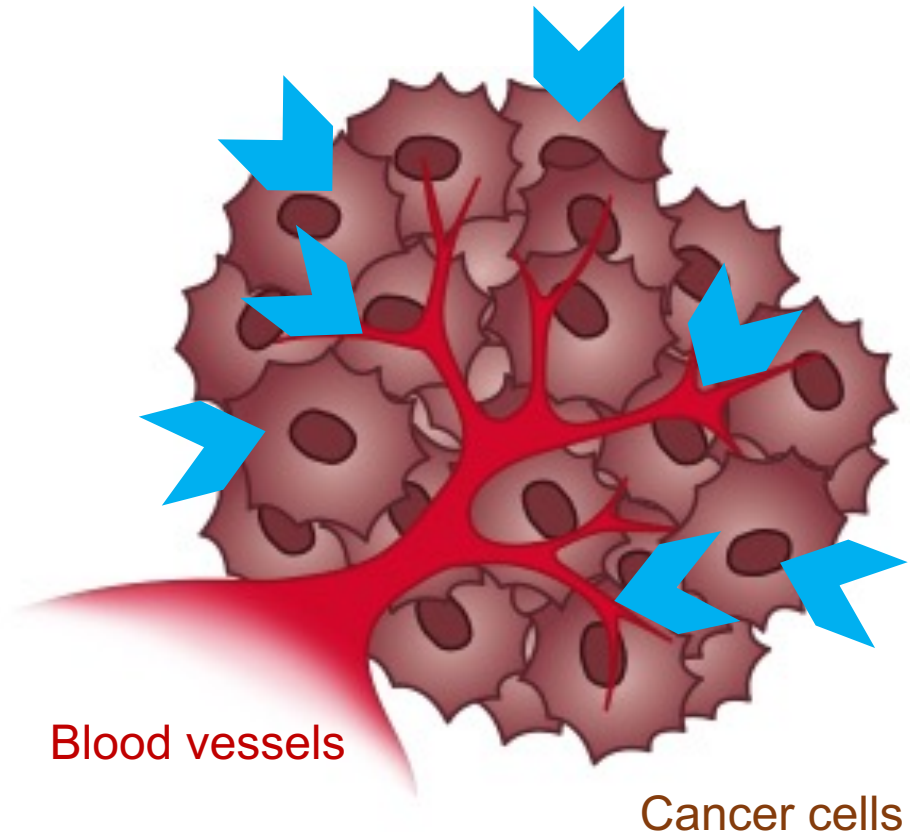
Guido Koch, PhD, CEO Amphilix AG

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Non-Confidential Information

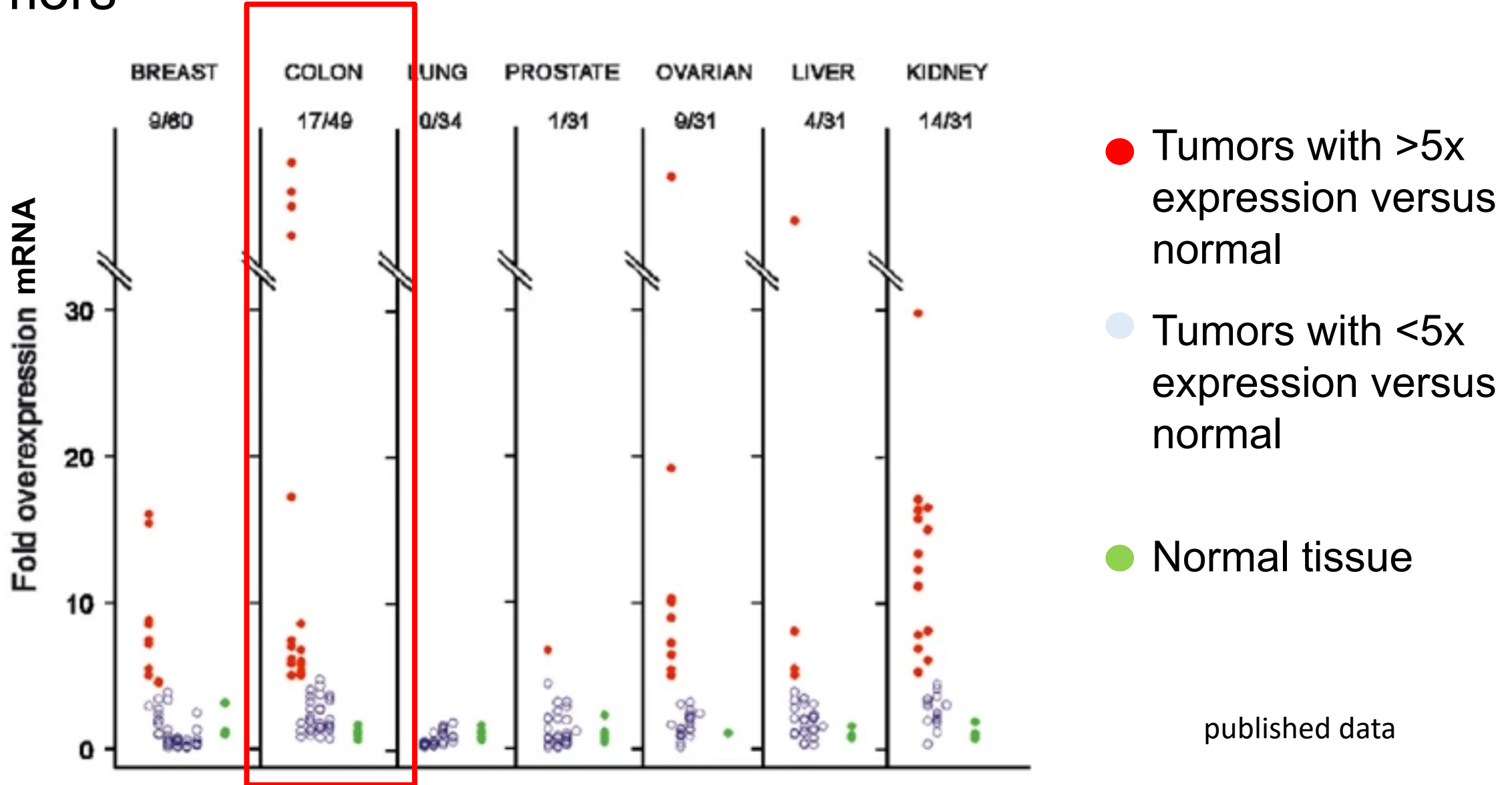
# RLT1– A new target for radioligand therapies

RLT1 on cancer cells and blood vessels



- RLT1 plays critical role in adaptation to changes in the tumour microenvironment
- Overexpressed in cancer cells and is oncogenic (preclinical & Amphilix data)
- Overexpressed in endothelium driving angiogenesis and tumour vascularisation (Clinical immunohistochemistry and preclinical angiogenesis experiments)
- Low background expression similar to SSTR2 (Lutathera) and PSMA (Pluvicto)

# RLT1 is overexpressed in CRC and many other primary tumors



# Colorectal cancer – 1<sup>st</sup> indication



- Almost **two million people** were diagnosed with colorectal cancer (CRC) globally in 2020
- Poor survival rates with **less than 20% of people living for more than five years** after diagnosis for metastatic CRC (mCRC) across Europe

*Pierre Fabre (2023)*



- Initial treatment: **chemotherapy** alone or in combination with a **biological therapy**
- Checkpoint inhibitors: treatment option for a **small subset (3-5%)** of people with advanced CRC
- For most people with advanced CRC the **options are limited**. In fact, many people at this stage receive **no treatment at all**

*Roche (2022)*

# Amphilix and PSI teamed up to make an RLT



Guido Koch, PhD  
Co-Founder, CEO



Kevin McAllister, PhD, MBA  
Co-Founder, Chairman



Martin Behe, PhD  
Group Leader  
Center for  
Radiopharmaceutical  
Sciences



Amphilix



Thomas Fessard, PhD  
Co-Founder



Peter Harboe-Schmidt, MBA  
Co-founder



CRO partner:



Financial support:

- Schweizerische Eidgenossenschaft  
Confédération suisse  
Confederazione Svizzera  
Confederaziun svizra
- Swiss Confederation
- Innosuisse – Swiss Innovation Agency

# First-in-Class small molecule radioligand binding to RLT1



## Small molecule ligand

better penetration of tumor tissue and less accumulation in kidney compared to peptides

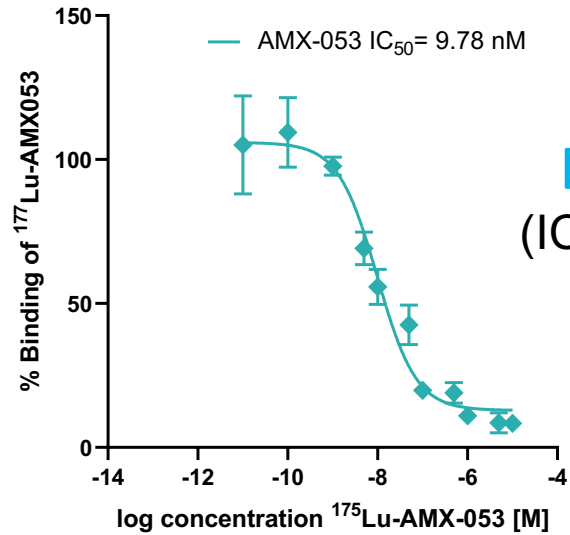
## Proprietary linker platform

3D elements are used to design optimal ligand properties

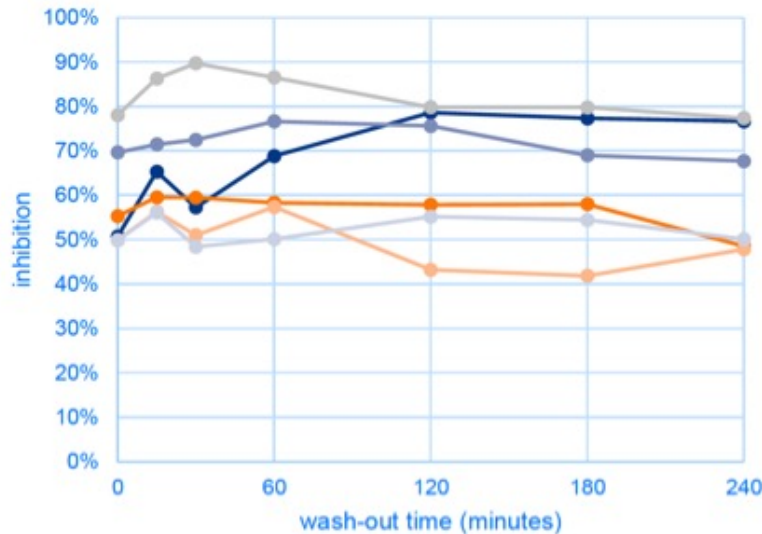
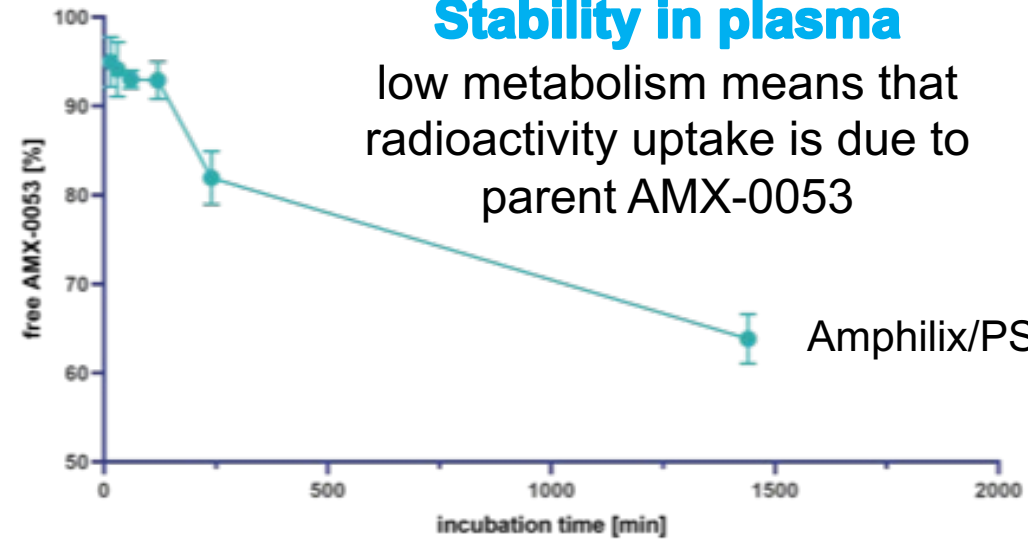
## Radioactive Payload

$^{68}\text{Ga}$  (imaging) and  $^{177}\text{Lu}$  (therapeutic) are first choice because clinically validated

# AMX-0053 lead has an excellent in vitro profile



**Potency**  
( $IC_{50}$ : 9.8nM)



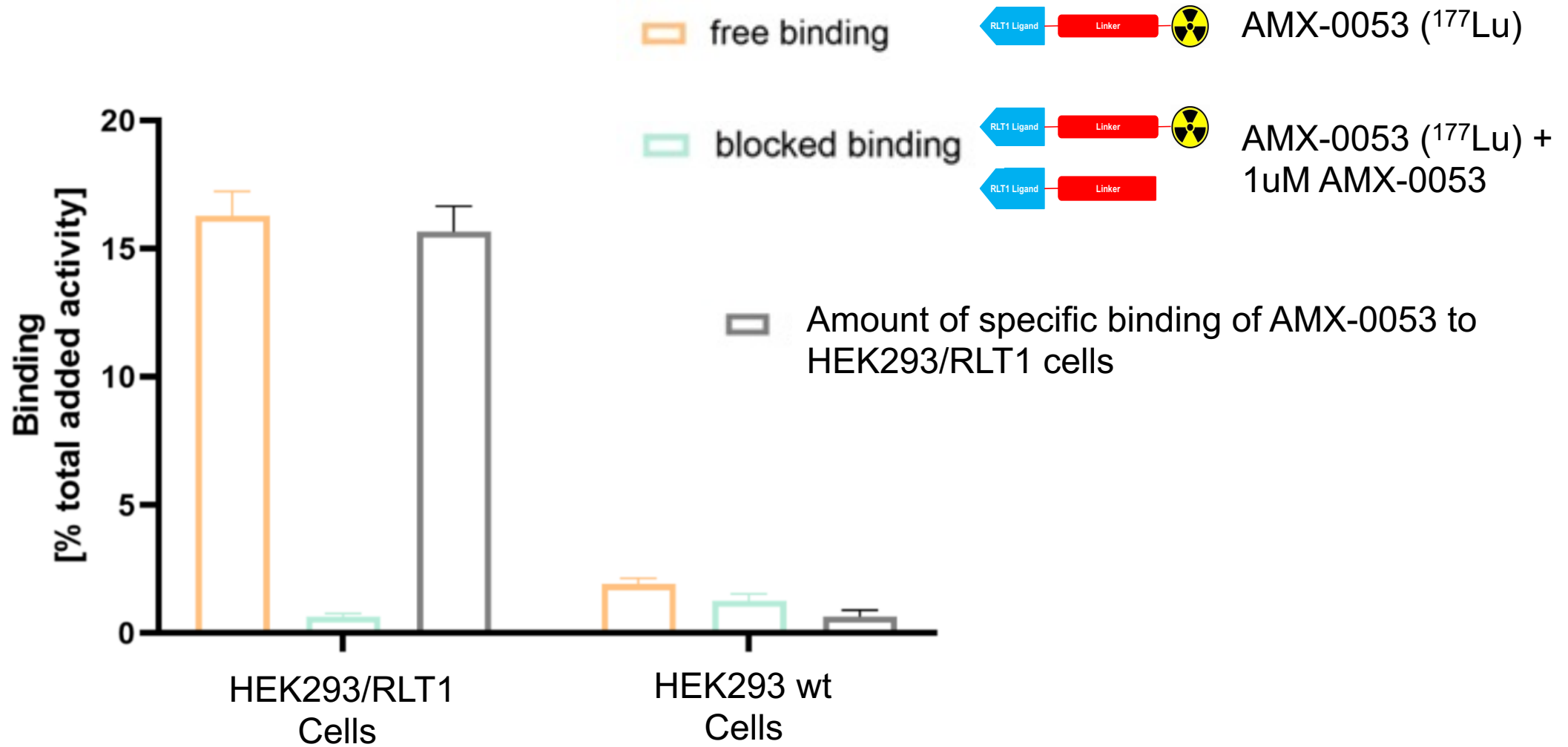
**Long residence time on target**

means that drug adheres to tumors ensuring good uptake

Amphilix/Eurofins

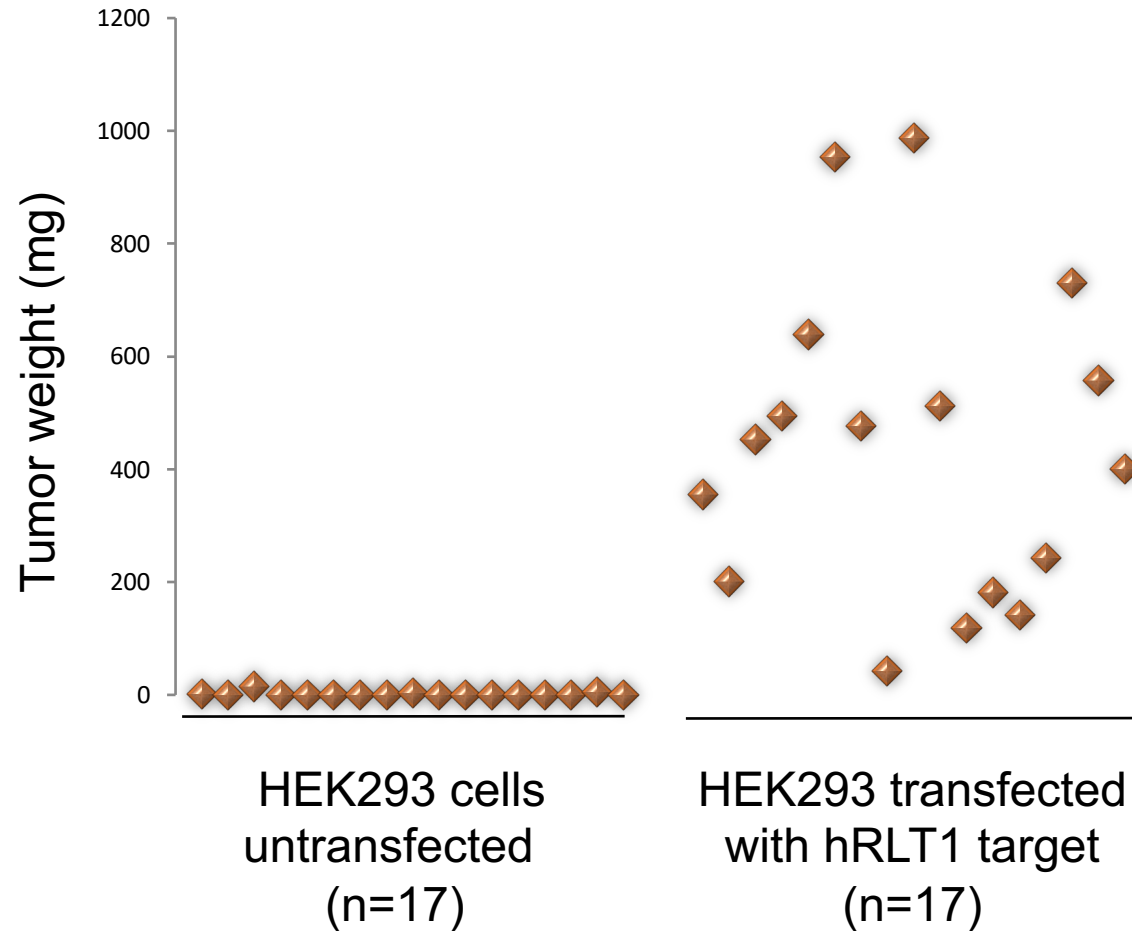


# *In vitro* binding of AMX-0053 to HEK293/RLT1 cells is specific to RLT1





# RLT1 transfected into HEK293 cells promotes tumor growth in nude mice – clear link of target overexpression to cancer



Amphilix/PSI

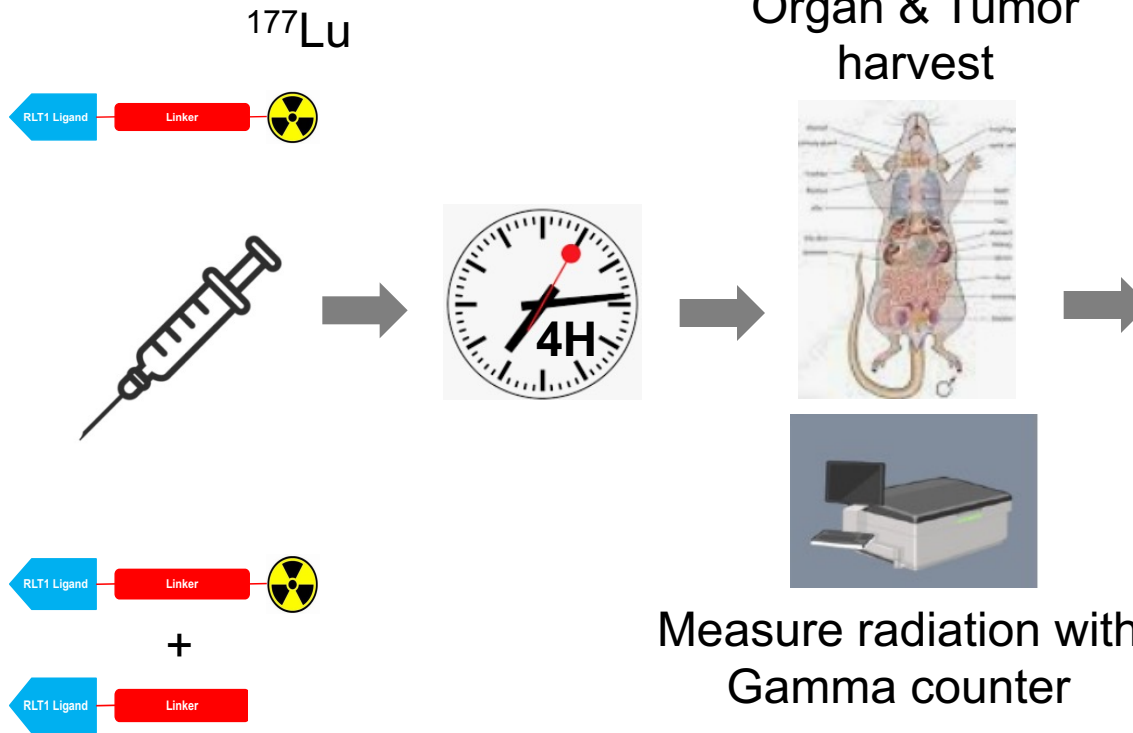
# *In vivo* biodistribution study - similar concept to showing binding specificity *in vitro*



HEK293/RLT1 tumor

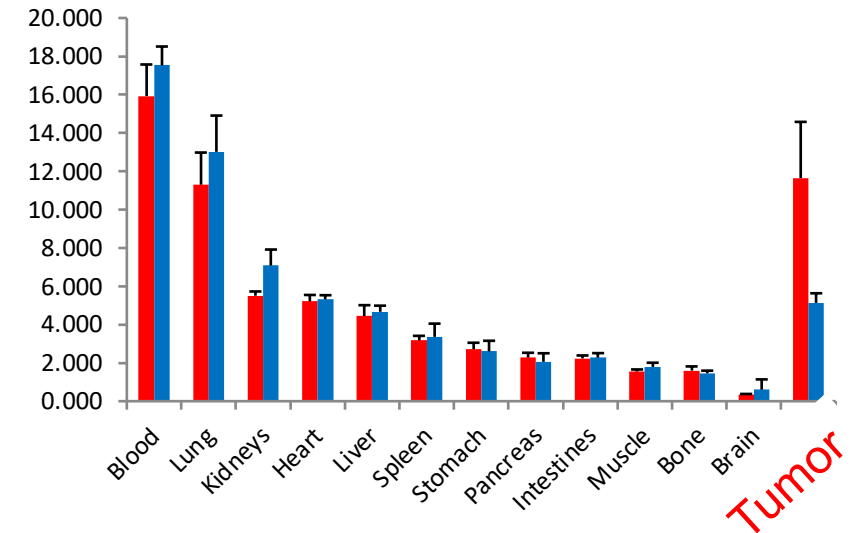


HEK293/RLT1 tumor



177Lu radiolabelled AMX-0053 + 3000-fold unlabelled AMX-0053 to block binding of radiolabelled AMX-0053

% injected total dose/gram tissue

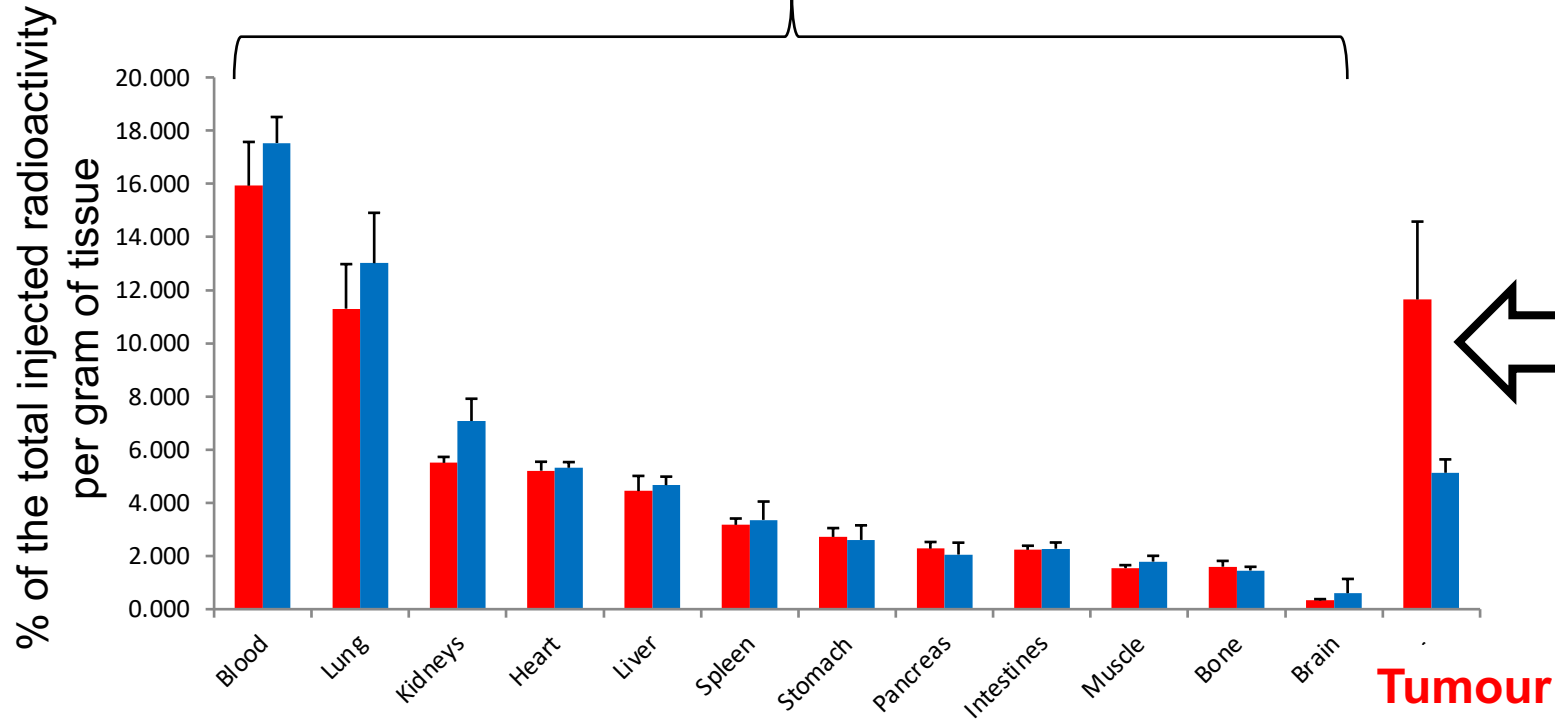


177Lu AMX-0053

177Lu AMX-0053 + 3000x AMX-0053 (cold)

# The radioligand AMX-0053 shows specific and high tumor uptake in implanted HEK293 cells bearing RLT1

No specific uptake of AMX-0053 in any other tissue or organ (no effect from receptor blocking)



**Specific uptake in tumour**

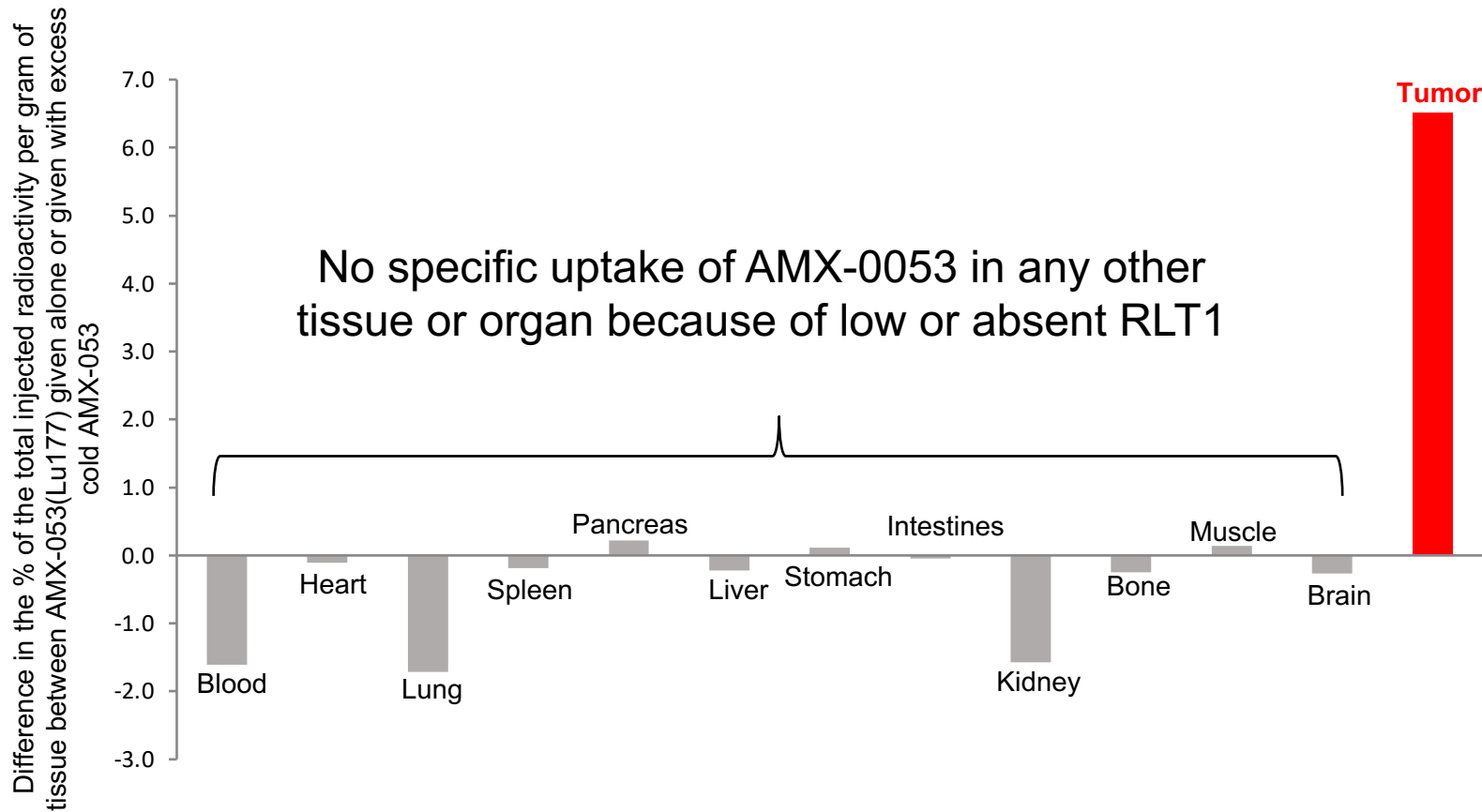
- Uptake of radioactive AMX-0053 is only blocked in the tumour indicating tumour specificity of binding
- 12% of injected dose taken up in tumour

<sup>177</sup>Lu AMX-0053

<sup>177</sup>Lu AMX-0053  
+ 3000x  
AMX-0053  
(cold)

Amphilix/PSI 2022

# Absolute specific uptake in Tumour compared to other tissues and organs

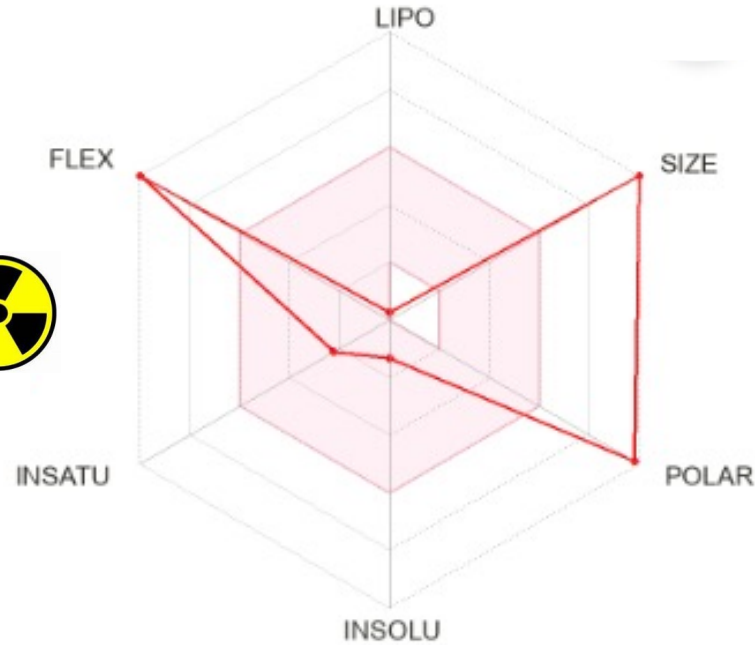


## Specific uptake in HEK293 tumors overexpressing RLT1

- Radiolabelled (Lu177) AMX-0053 binds to RLT1 on the HEK293 tumor producing a high gamma count
- Co-injection with excess 'cold' AMX-053 competes with 'hot' AMX-053 for the RLT1
- Reduces gamma count because it displaces the radiolabelled ligand from the target

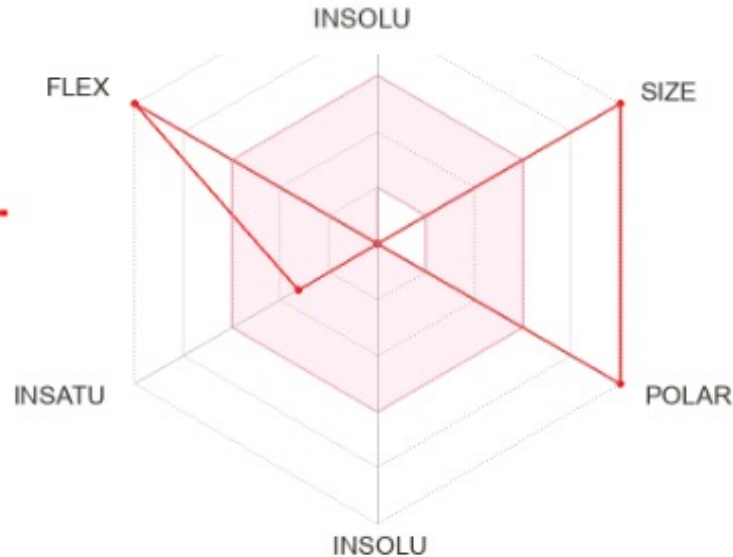
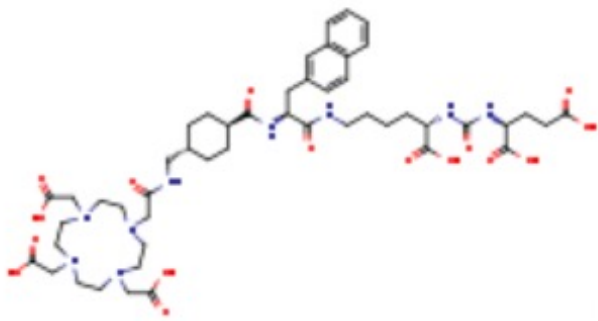
Amphilix/PSI

# AMX-0053 has a long half life in circulation due to high lipophilicity



AMX-0053  
 MW: 1050.34 g/mol  
 PSA: 235.30 Å<sup>2</sup> ↑  
 cLogP\*: 0.03 ↓

Enhance PSA,  
 lower cLogP



Pluvicto  
 MW: 1042.14 g/mol  
 PSA: 365.19 Å<sup>2</sup>  
 cLogP\*: -1.81

\*SwissADME consensus logP  
[SwissADME](#)

# Innosuisse innovation project for optimisation of radioligand leads and clinical candidate generation

## Goal:

Reduce  $t_{1/2}$  in systemic circulation while maintaining potency on target and avoiding high kidney uptake. 2 strategies are applied:

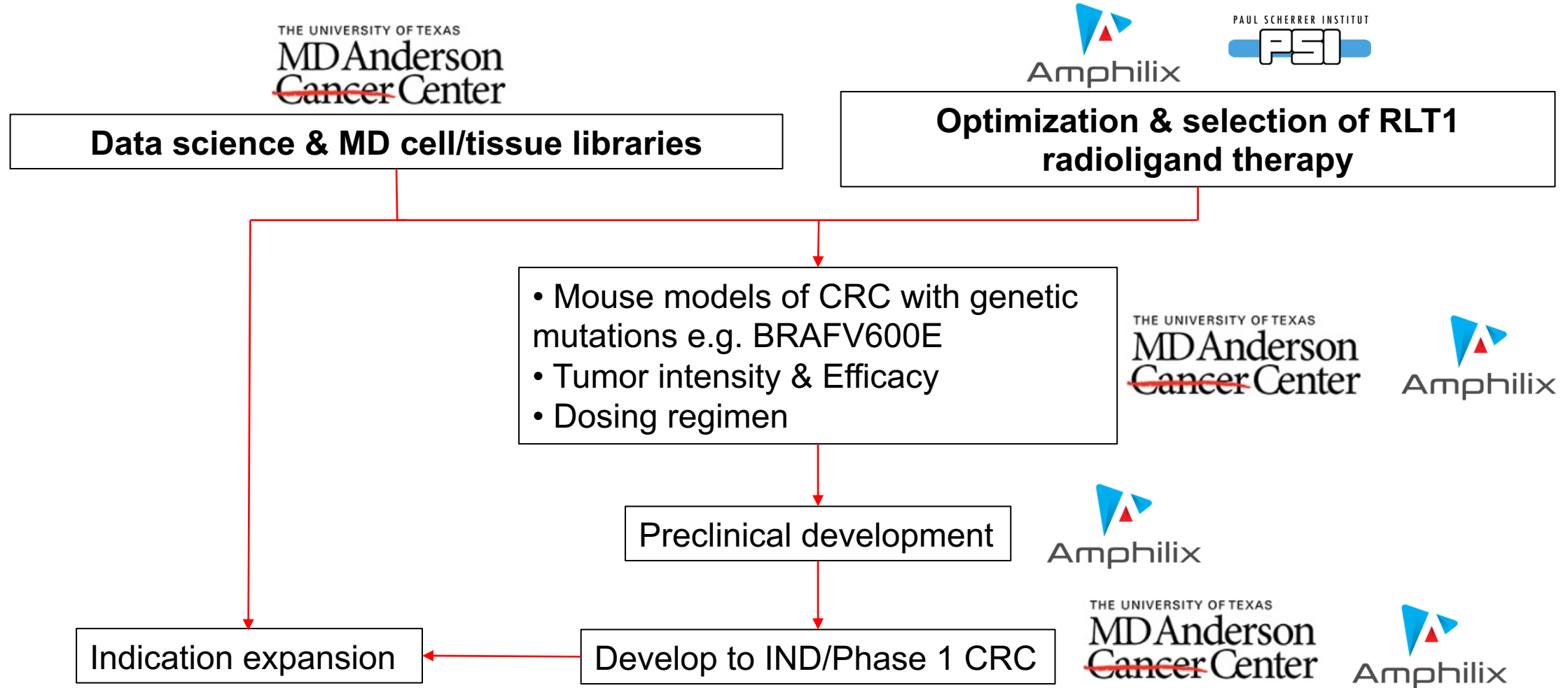
## Strategy A: reduce lipophilicity and enhance PSA

- Apply computational chemistry and in silico prediction to select candidates with similar  $clogP$  / PSA values as Pluvicto for synthesis and direct testing in biodistribution studies in mice

## Strategy B: enhance in-vivo clearance with specific linker elements

- Apply SAR knowledge to selectively incorporate linker elements that will result in higher in vivo clearance

# Collaboration with MD Anderson Cancer Center for CRC and indication expansion opportunities



- ✓ Composition-of-Matter IP protects linked molecules for RLT1 (radioligands and homodimers, homotrimers)
- ✓ Patent applications filed on Dec 7, 2023
  - 2 patents covering innovative products for radioligand therapy and homodimeric modulators
  - Exclusive ownership by Amphilix for IP of radioligand therapy in negotiation with PSI
- ✓ IP strategy and FTO
  - FTO for linking a class of known pharmacophores confirmed with Rentsch Partners Zürich
  - IP strategy worked out in collaboration with Vossius Partners Basel, Switzerland



# Commercial assessment for radioligand CRC treatment

- In 2020 there were approx **632,000 new cases of CRC** (USA 142,462, Center Disease Control, Europe 341,000, ECIS and Japan 148505, WHO)
- Assuming 10% market penetration: **63,200 patients** can be treated per year
- Commercial benchmark: Lutathera<sup>®</sup>, a radioligand therapy for neuroendocrine tumors (not a competitor) costs **\$20k per dose** (4-6 doses)

## **Amphilix CRC radiotherapy will generate total sales of \$6.3bn/year**

- assuming 5 doses of AMX drug and same price across geographical regions, the per patient costs are \$100k
- this calculation excludes other cancer indications (e.g. ovarian, kidney....)

# The commercial value of targeted radiotherapy drives in-licensing and acquisitions



Acquisition of **Advanced Accelerator Applications (AAA)** for \$3.9bn 2017

**Lutathera®** (pancreatic/stomach tumours) sales \$445mn in 2020  
**Pluvicto®** (prostate cancer) approved by FDA 2022

Acquired **Noria and PSMA Therapeutics** in 2021. Deal terms undisclosed

**Xofigo®** (prostate cancer and bone metastasis) generated sales of €261mn in 2021

October 2023. acquisition announced of **Point Pharma** for \$1.4bn

Investment in \$175m Series B for **Mariana Oncology** (2023)

Collaboration on discovery and development of peptide-radioisotope drug conjugates with **Peptidream**  
Upfront payment of \$40m, milestones up to \$1bn

Acquisition of **RayzeBio** for \$4.1bn (2023)  
Phase 3 lead asset for SSTR-positive gastroenteropancreatic neuroendocrine tumours

# No competition on RLT1 & clear differentiation with small molecules based on linker platform



Most companies focus on common targets:

- SST2
- PSMA
- GPRP
- FAP

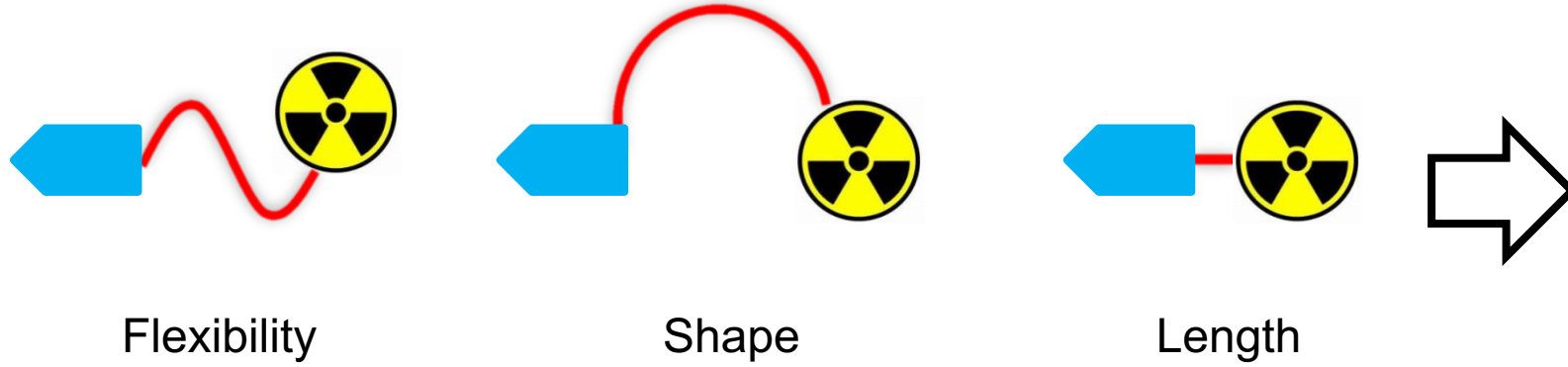
and common ligand modalities:

- Cyclic peptides
- Antibodies

[PharmaShots 2023](#)

# The Amphilix linker platform

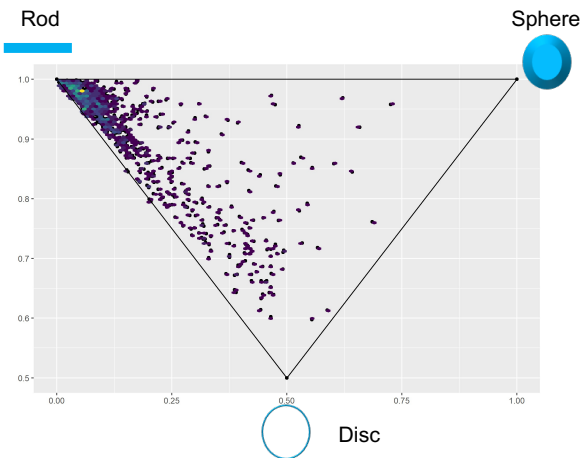
## Linkers define properties of radioligands



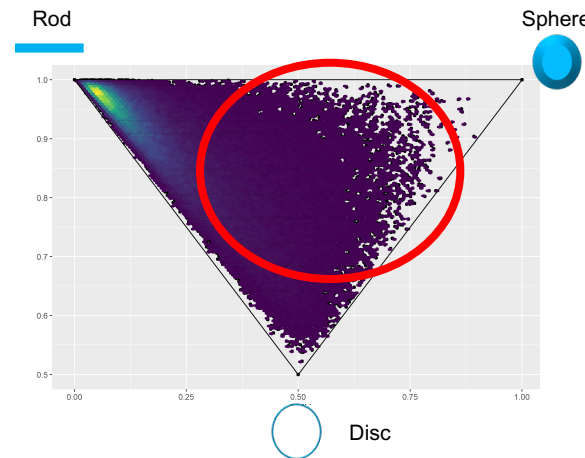
- Solubility
- Permeability
- Affinity to the target
- **PK profile**

## 3D elements in linkers exponentially increase the diversity of new radioligands and enables property guided synthesis

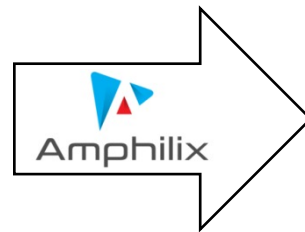
Standard linear linkers



Linkers with 3D elements



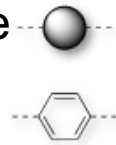
Select candidates for synthesis with optimal calculated properties



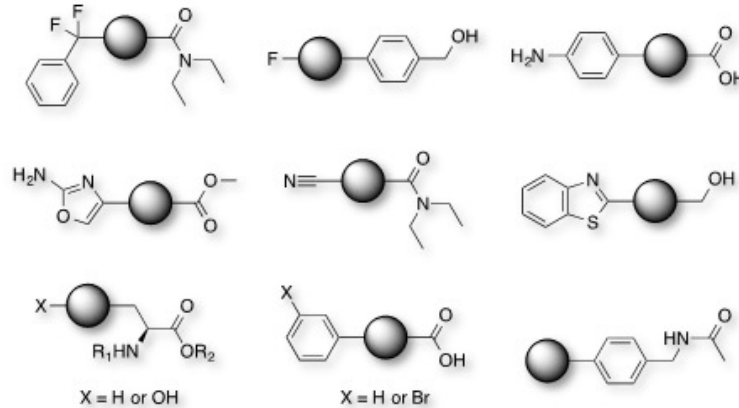
# 3D-linker modules enable the design of drug-drug conjugates with optimal profiles

## Switching from 2D to 3D structural motifs...

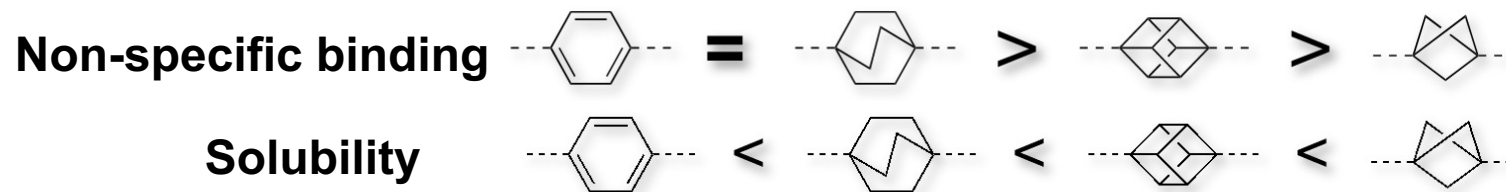
2D (flat disc-like structures)



3D  
(structures occupy 3-dimensions)



...results in better solubility and lower non-specific binding



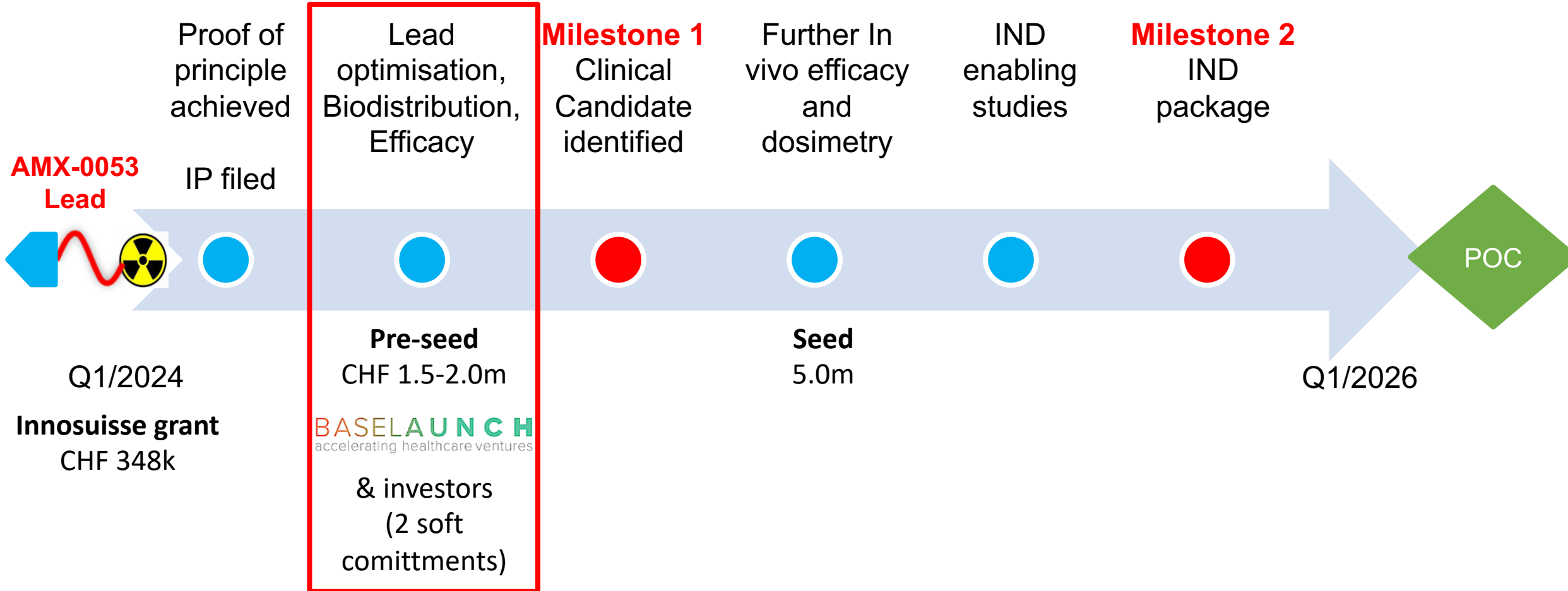
T. Fessard, G. Koch *et al.*  
*ChemMedChem* **2017**

# Illustration of changing solubility & bioavailability of dimeric molecule using 3-D chemistry in linkers

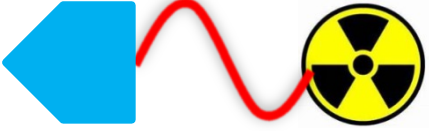
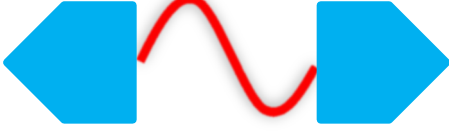
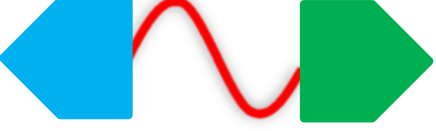
|          | MW   | 3-D elements in linker | IC50 (nM) on Target | Solubility (uM) | Plasma Exposure (ng.h/ml) after 5mg/kg PO in mice |
|----------|------|------------------------|---------------------|-----------------|---|
| AMX-0025 | 1014 | 1                      | 13                  | 44.7            | 6   |
| AMX-0030 | 1014 | 1                      | 41                  | 177.2           | 6   |
| AMX-0009 | 1404 | 2                      | 20                  | 198.4           | 56.5  |

|          |                 |                   |                     |                        |
|----------|-----------------|-------------------|---------------------|------------------------|
| AMX-0009 | Bigger molecule | Potency preserved | Solubility improved | Exposure increased 10x |
|----------|-----------------|-------------------|---------------------|------------------------|

# Financing plan and use of BaseLaunch pre-seed



# Portfolio opportunities for drug-drug conjugates with proprietary linker platform

| Targeted Radiotherapeutics   | Single Target Pharmacology  | Dual Target Pharmacology   |
|--|---|--|
|  <ul style="list-style-type: none"> <li>• Radioligands from small molecule binders</li> <li>• AMX-0053 First-in-Class RLT1 targeting RLT for CRC</li> </ul> |  <ul style="list-style-type: none"> <li>• Linker used to restrict drug to target tissue</li> <li>• Enhancing the safety profile for selected for new IBD drug</li> </ul> |  <ul style="list-style-type: none"> <li>• Ligand dimers affecting <b>two</b> targets with synergistic or complementary effects</li> <li>• Addressing the underlying complexity many diseases</li> </ul> |

## Outside Amphilix portfolio

- Collaboration with companies interested in linker technology



# Amphilix drug-drug conjugates portfolio



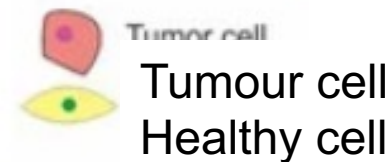
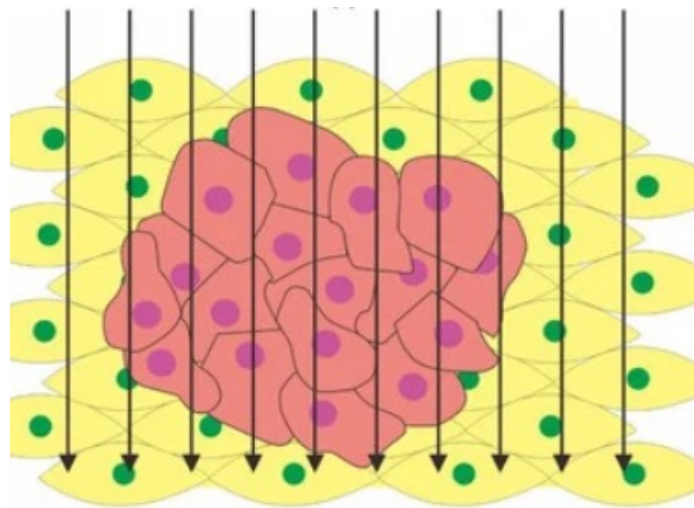
| Project | In silico                   | In vitro                                      | In vivo | PoC in human | Collaborator |
|---------|-----------------------------|---|---------|--------------|--------------|
|         | Colorectal Cancer           |   |         |              | <br>         |
|         | Ind. expansion              | <i>(Data science, human tissues)</i>          |         |              |              |
|         | GI Diseases (IBD, fibrosis) |   |         |              |              |
|         | Cancers                     | <i>(Synergistic targets identified by AI)</i> |         |              |              |

**Backup slides**

The new Radioligand therapy approach provides effective tumor selective irradiation and is safer and less burdensome than radiation therapy

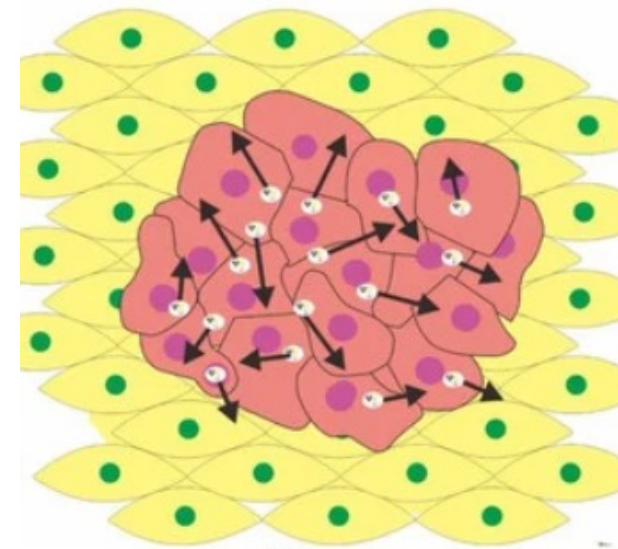
## Radiation therapy

- External beam irradiates many more healthy cells than tumour cells
- 5 times per week for up to 9 weeks



## Targeted radioligand therapy

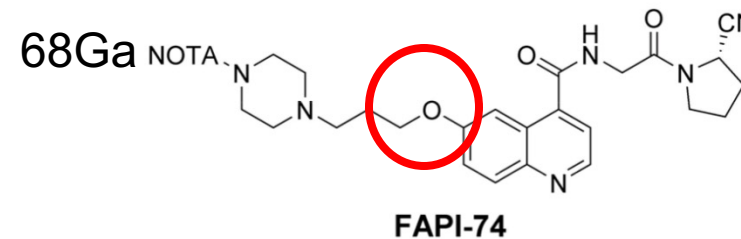
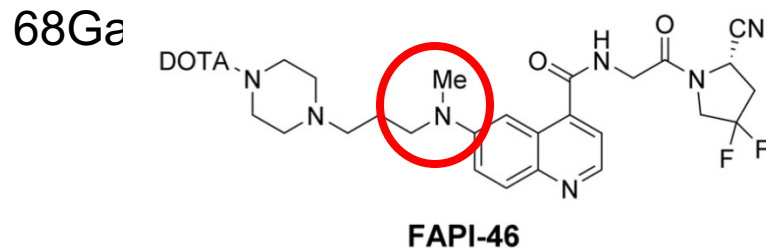
- Local irradiation of tumour cells
- 1 time per week, 4-6 cycles



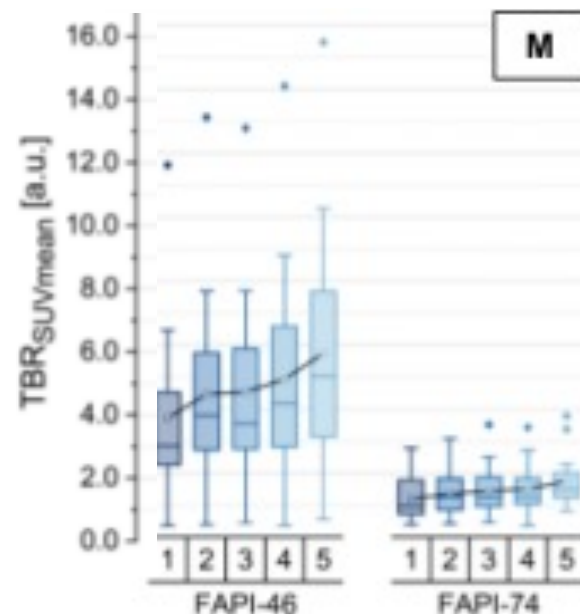
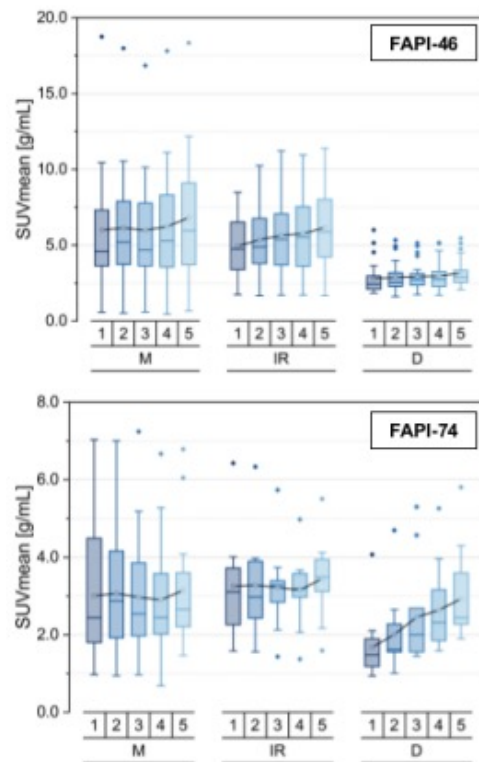
Adapted from Salih 2022

# Clinical evidence that linker structure plays major role in biodistribution

Fibroblast activation protein (FAPI) –based imaging agents In Phase 2



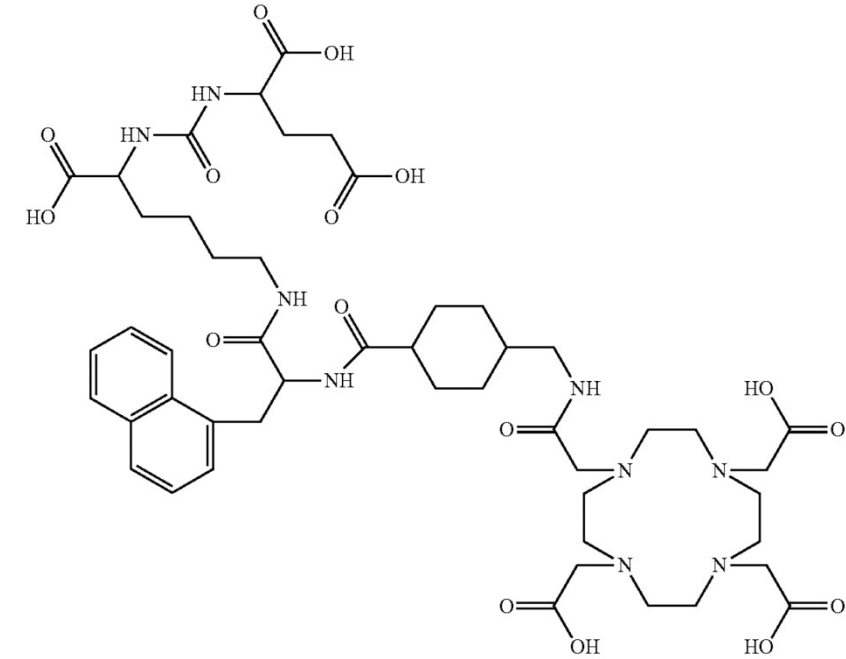
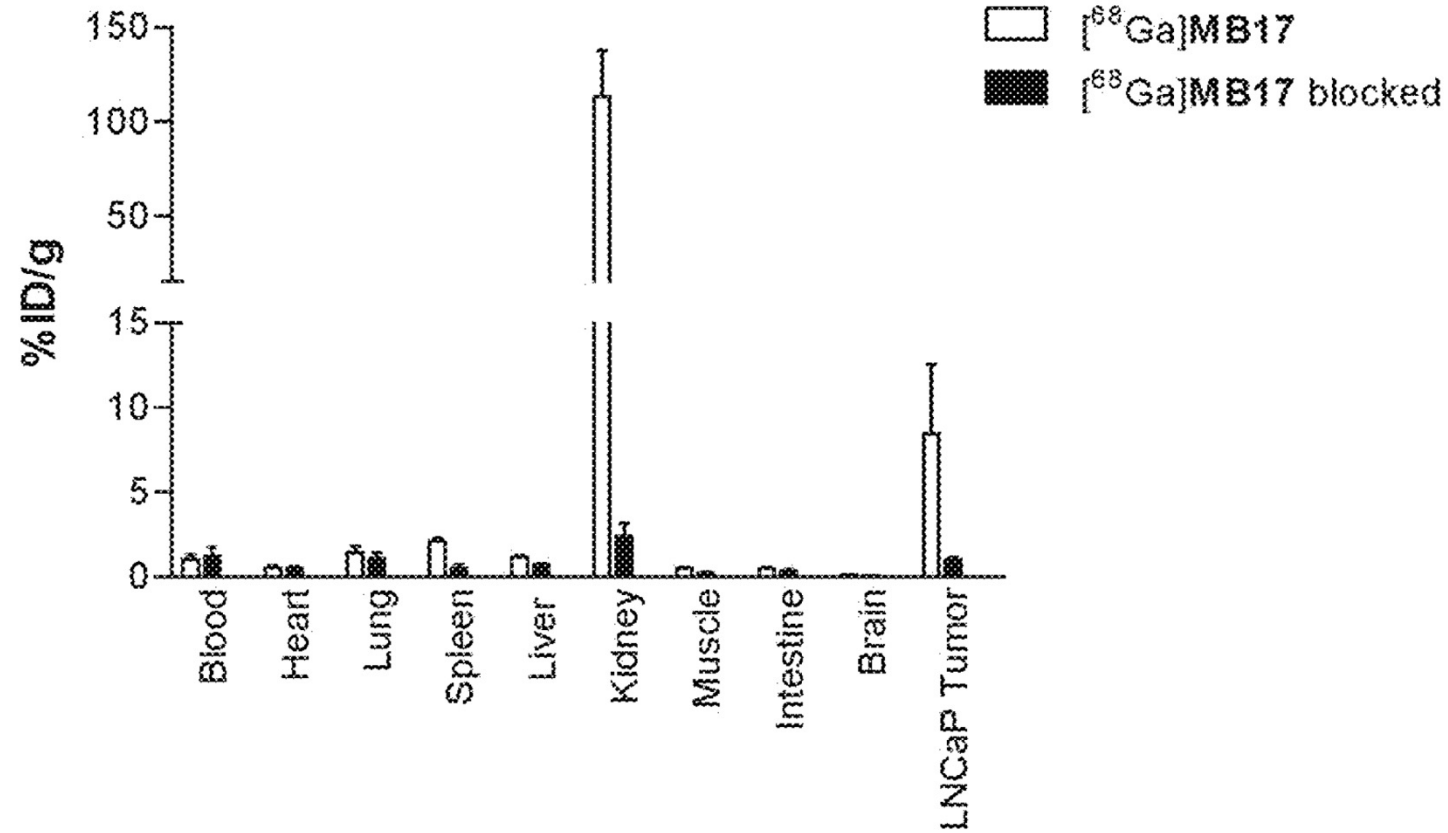
FAPI-46 shows higher uptake in Malignant, Inflammatory and Degenerative pathologies



FAPI-46 has higher Target-to-Background distribution

***'FAPI tracer variants show significant differences in their time-dependent biodistributional behaviour and should be selected carefully depending on the clinical setting' Glatting 2022***

# Biodistribution profile of Pluvicto

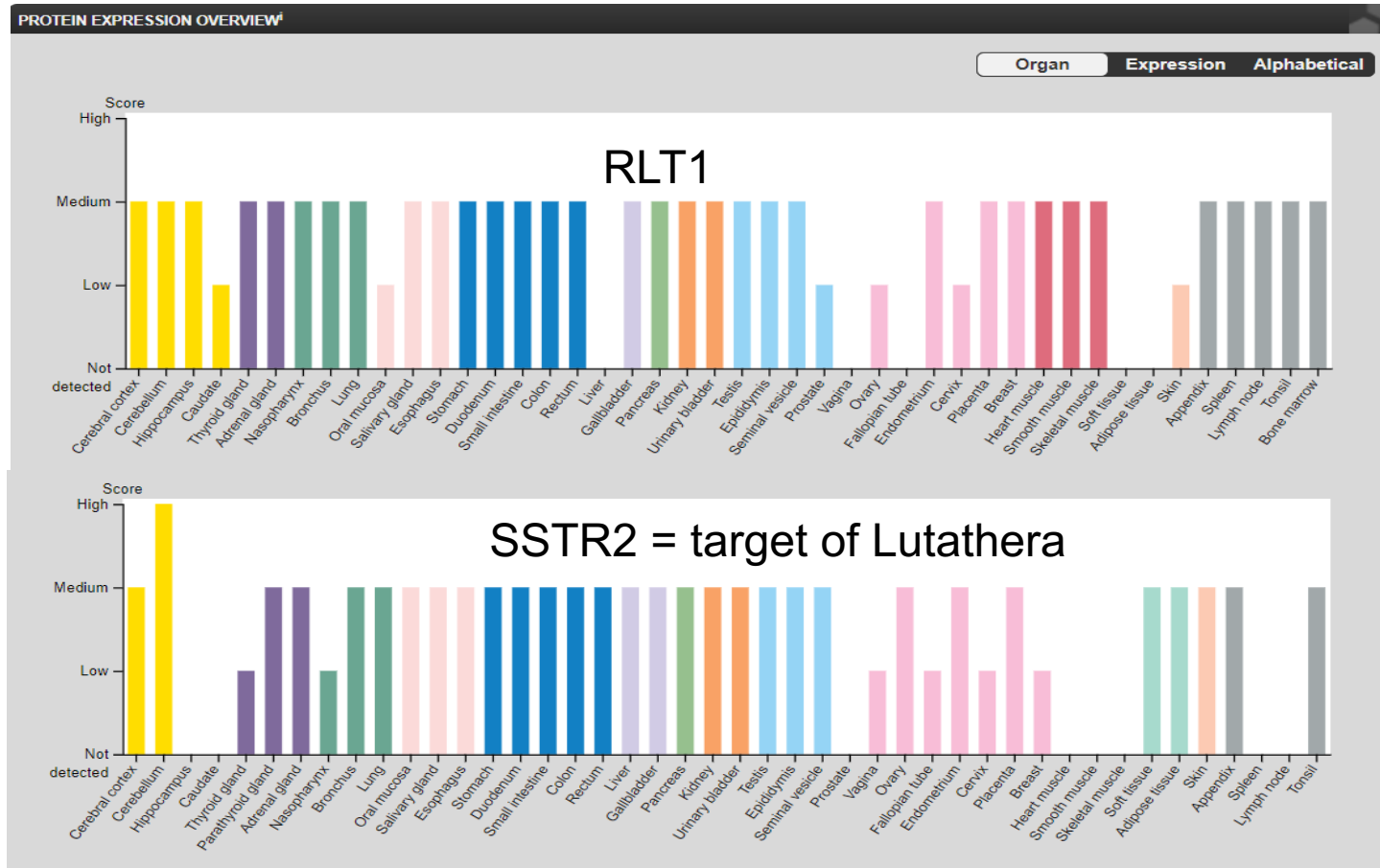


MB17 = Pluvicto

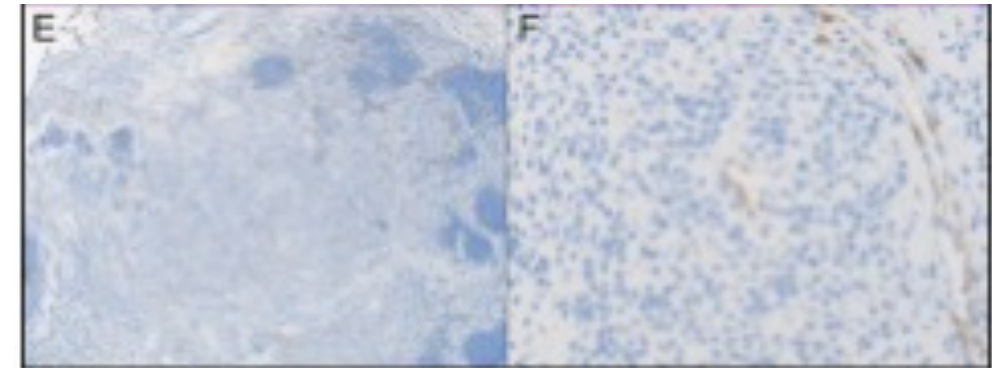
Patent: US10398791B2 (2019)

# Tumor specificity? SSTR2 shows wide expression...

## Human protein atlas expression profiles



....indeed, expression in endothelial cells has been used as a positive control for lack of SSTR2 in tumor !

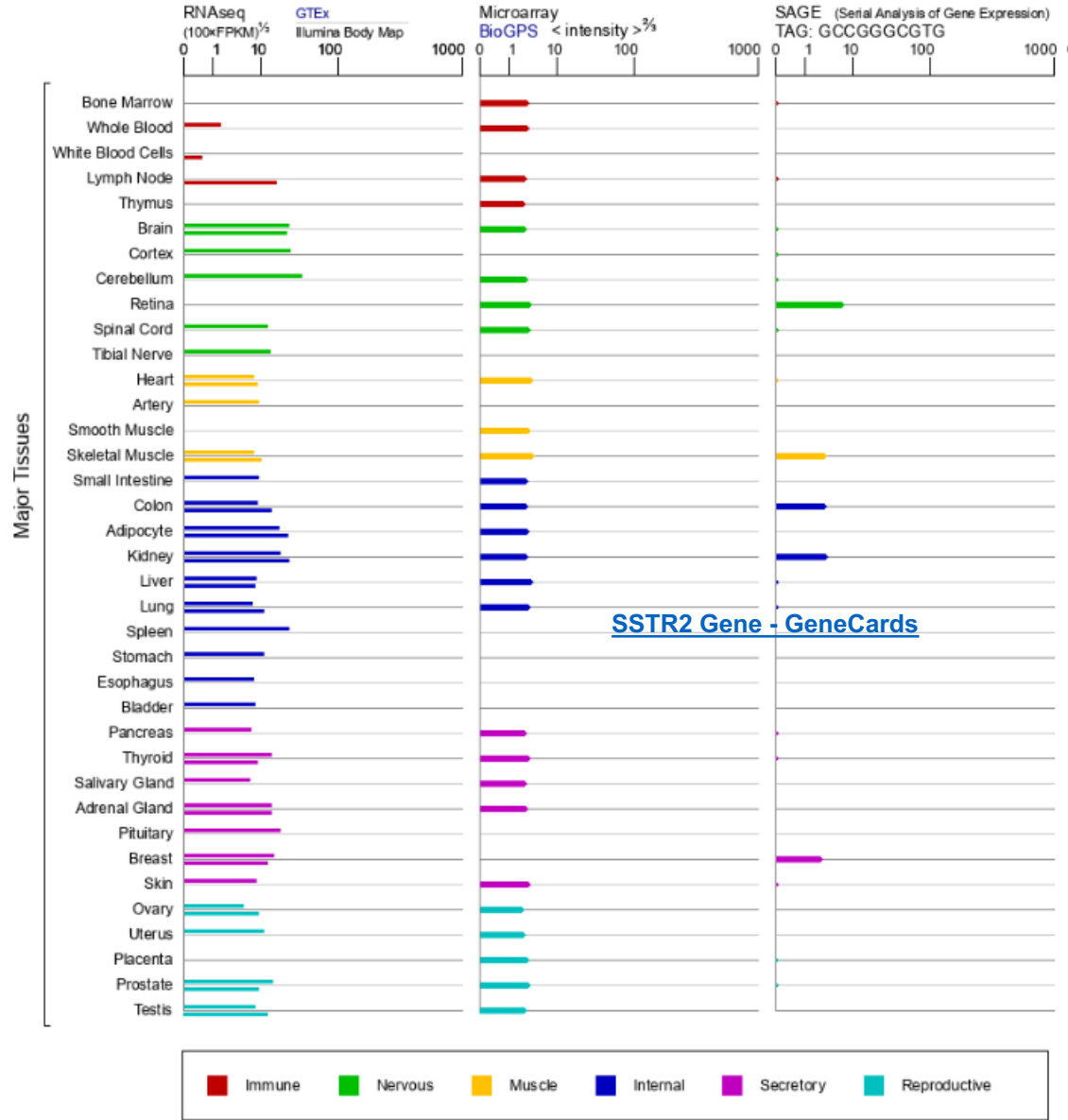


(E) There is no expression of SSTR2 in tumor cells.  
(F) Note SSTR2 expression in endothelial cells serving as internal control. Magnification, H&E x

Roden 2022



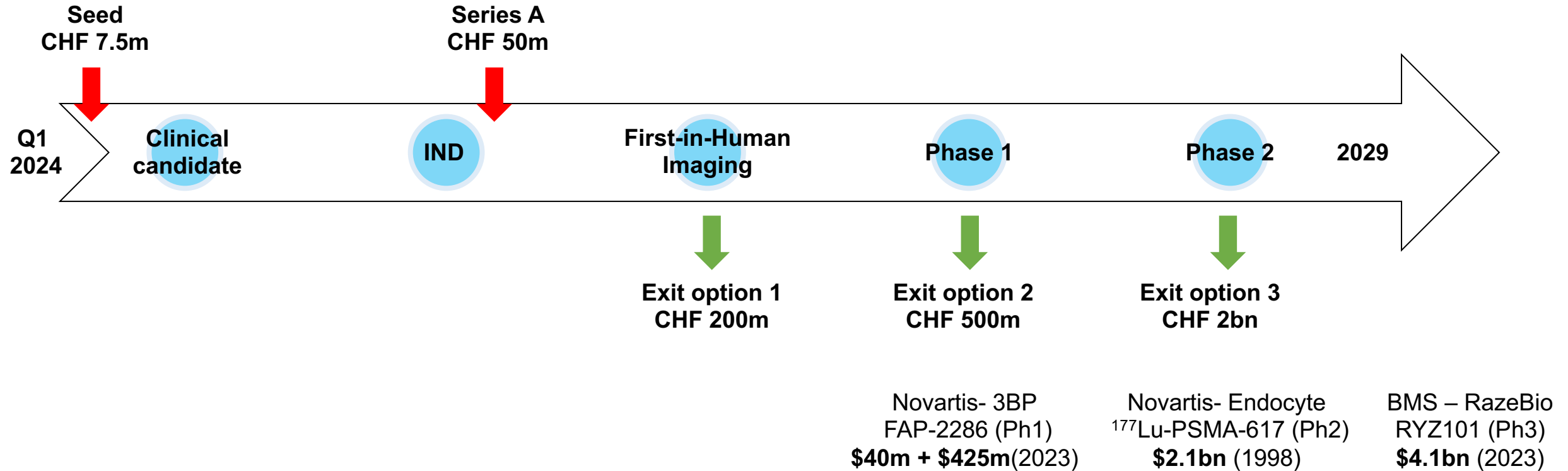
mRNA expression in normal human tissues from [GTEX](#), [Illumina](#), [BioGPS](#), and [SAGE](#) for [SSTR2 Gene](#)



mRNA expression in normal human tissues from [GTEX](#), [Illumina](#), [BioGPS](#), and [SAGE](#) for [RLT1 Gene](#)



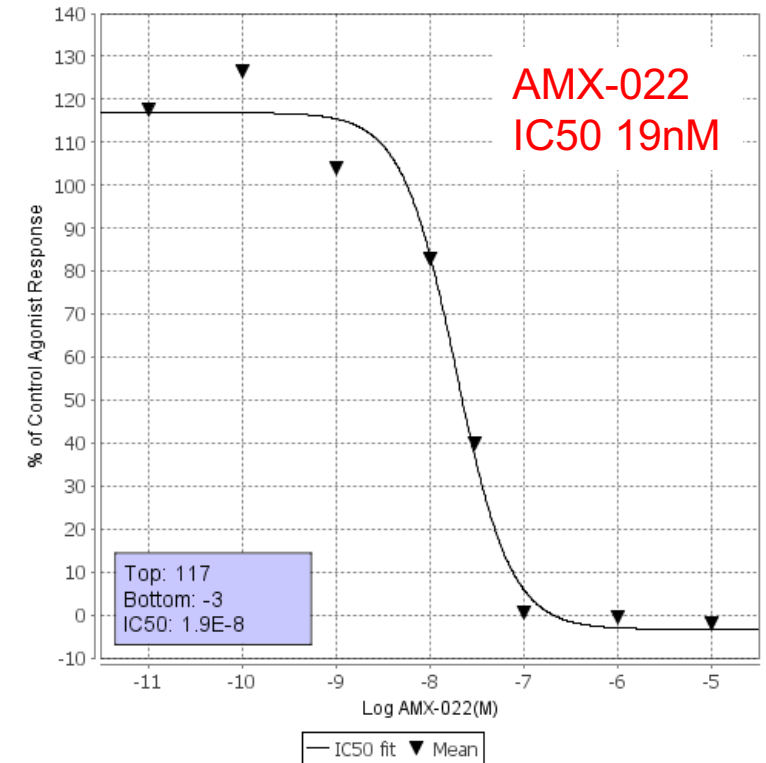
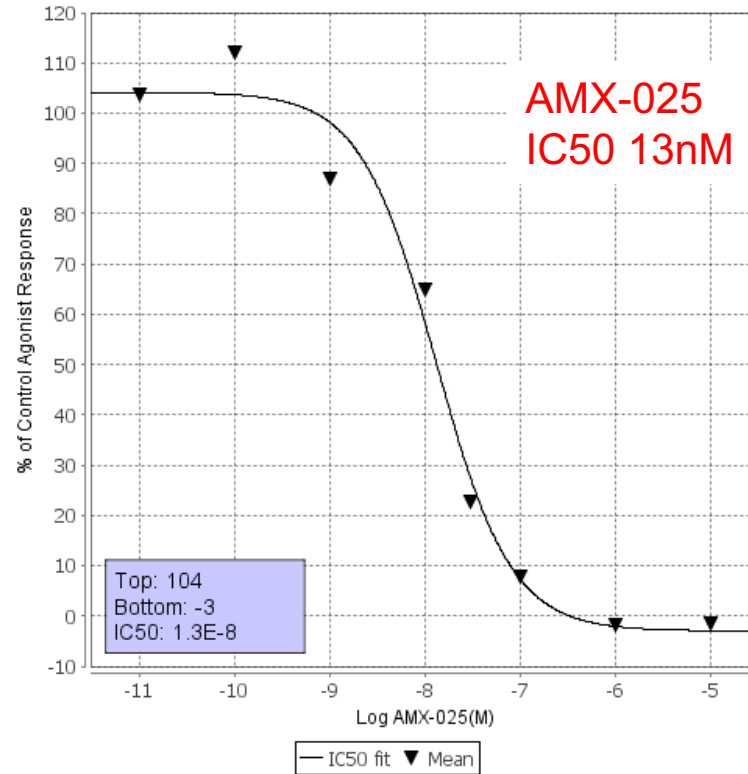
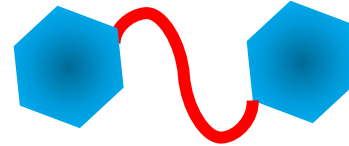
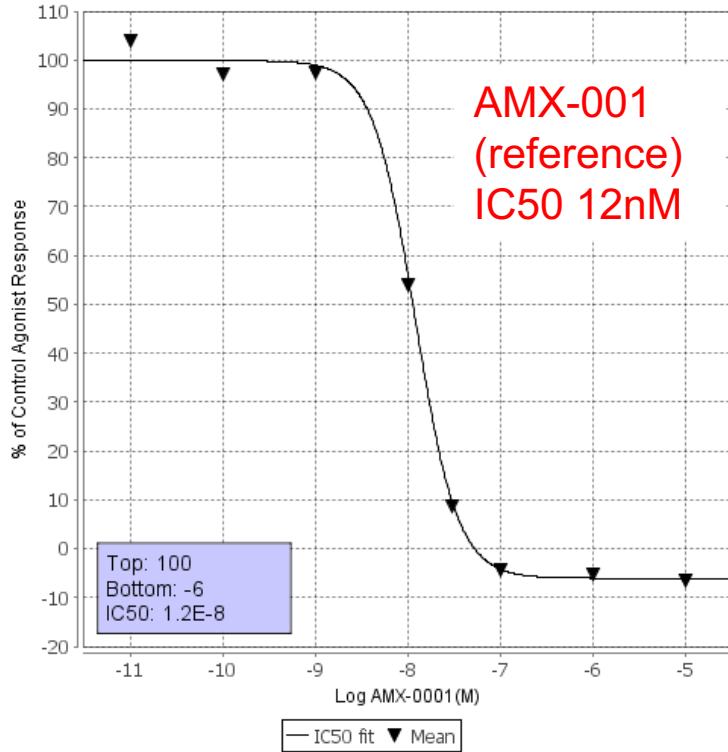
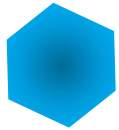
# Investments in Amphilix' RLT has the potential for high returns



- Investment of CHF 57.5m over a period of 5 years generates CHF 2bn in return (35x)
- Exit opportunities at earlier development stage by licensing or trade sale

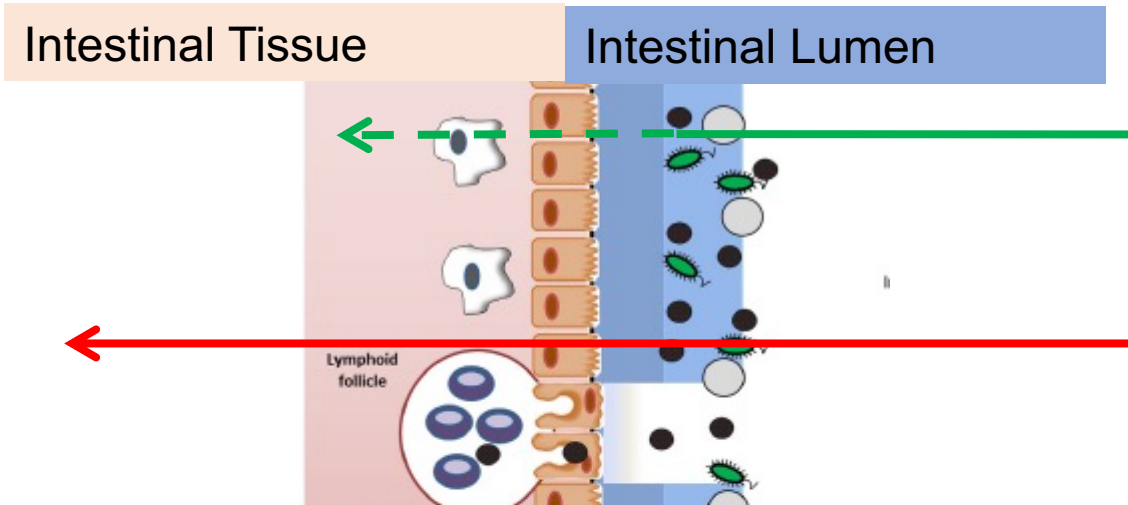


# The linker does not affect potency on the target

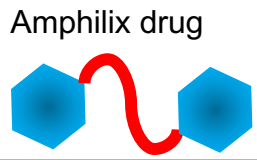


Functional assay on HEK293 cells stably transfected with the human target

# The linker modifies tissue permeation of homodimers




Penetration to intestinal tissue but low systemic exposure



Amphilix drug

Full penetration leading to high systemic exposure and higher chance of side effects



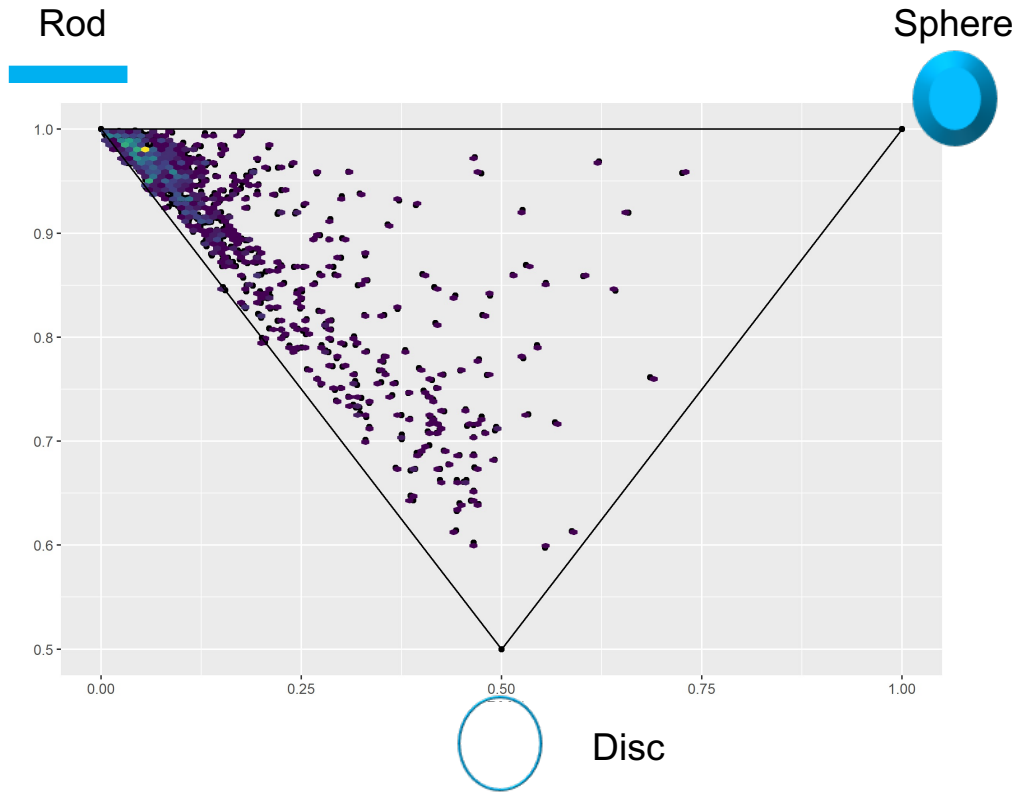
AMX-001

| Cpd ID               | 3D elements in linker | IC50 (nM) | Solubility (uM) (pH 7.4 / FaSSiF) | Permeability (10 <sup>-6</sup> cm/s) (Caco2 cells) | Plasma levels (ng/ml) after 5mg/kg PO in mice 1h, 3h, 6h |
|----------------------|-----------------------|-----------|-----------------------------------|--|--|
| AMX-0025             | 1                     | 13        | 44.7 / 104.3                      | <b>13.5</b>  | <b>4, 2, 0</b>   |
| AMX-0001 (reference) | no linker             | 12        | 184.7 / 186.5                     | <b>11.8</b>  | <b>1890, 1112, 282</b>                                   |
| AMX-0030             | 1                     | 41        | 177.2 / 183.9                     | <b>1.6</b>   | <b>4, 2, 0</b>   |
| AMX-0009             | 2                     | 20        | 198.4 / 191.3                     | <b>1.2</b>   | <b>16, 20, 1</b>   |
| AMX-0011             | 2                     | 29        | 180.7 / 188.7                     | <b>1.0</b>   | n.d  |
| AMX-0022             | 1                     | 19        | 28.9 / 65.5                       | <b>0.2</b>   | n.d  |
| AMX-0004             | 1                     | 35        | 164.5 / 176.6                     | <b>0</b>   | n.d  |

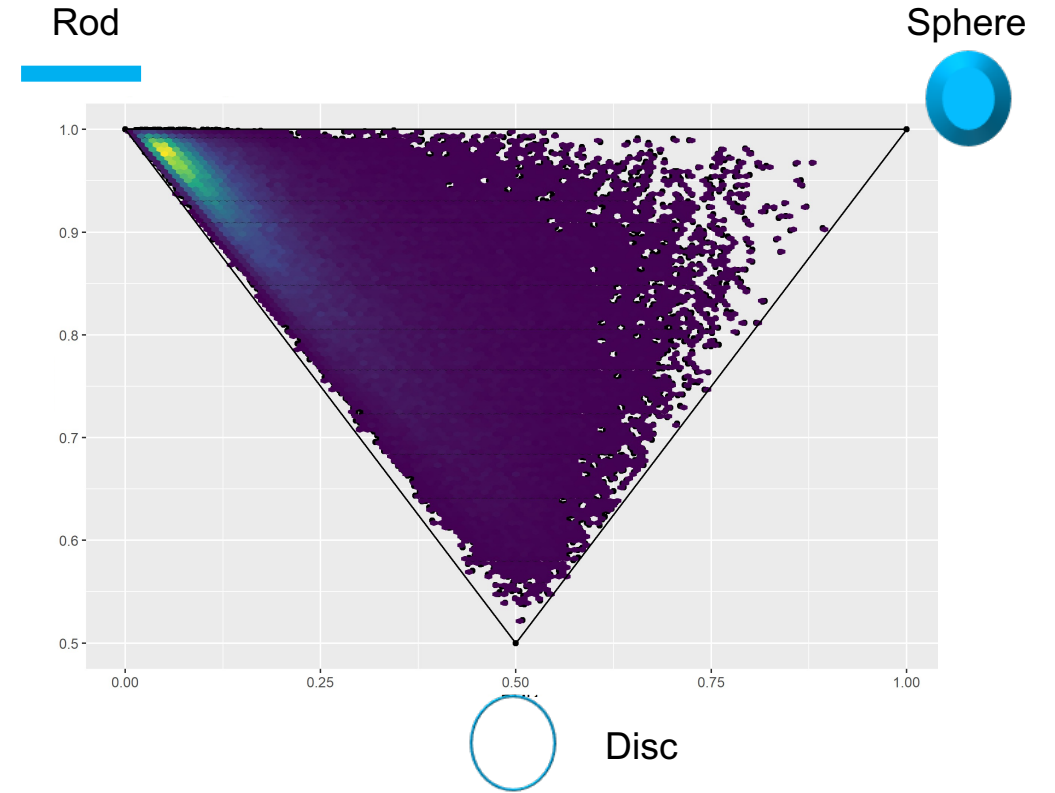
3D-linker design modulates permeability without affecting the potency (IC50) of the drugs

# 3D elements in linkers exponentially increase the diversity of multimeric molecules

## Linear linkers

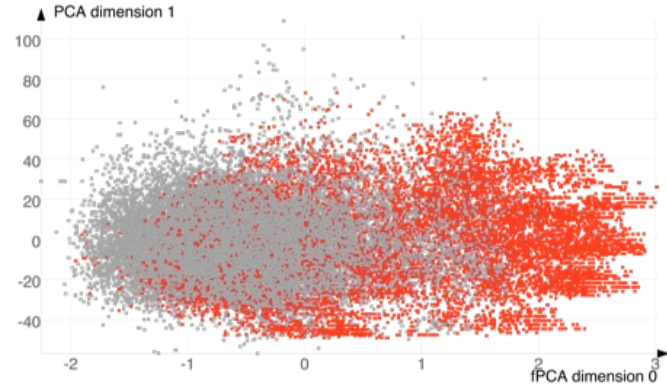


## Linkers with 3D-elements

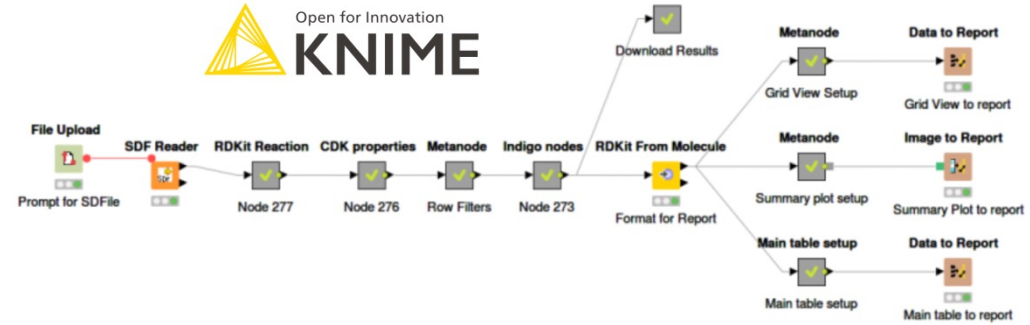


**Proprietary virtual library of candidates with extended property profiles**

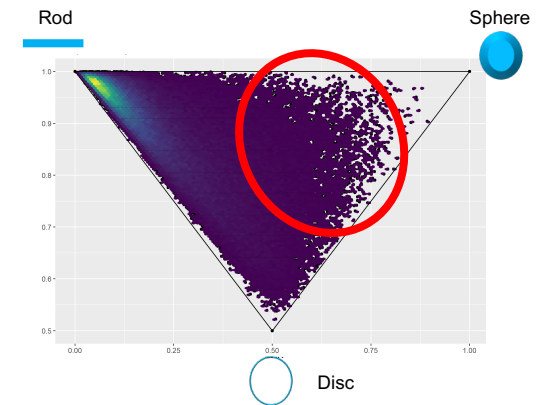
# Platform workflow – computational design, synthesis and testing of new radioligands



Proprietary 3D-linker elements synthesized at Spirochem



Virtual library generation and property filtering (PSA, cLogP, etc)



Shape analysis

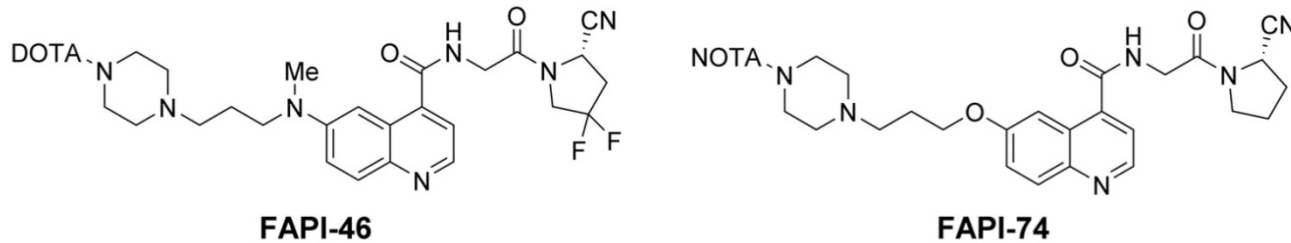


Synthesis of selected candidates

# Most advanced small molecule RLTs - Optimising biodistribution is a major goal

## 1. Fibroblast activation protein (Sofie Biosciences/Novartis)

- Diagnostics. Therapeutic value is impaired by the short tumor residence time; Ph2



**➔ Amphilix' ligands bind to a different target with long occupancy**

## 2. Neurotensin receptor 1 (Fusion Pharmaceuticals/AZ)

- FPI-2059, Alpha-emitter, Ph1 in March 2023

## 3. Carbonic anhydrase IX

- RayzeBio: Preclinical, undisclosed structure
- Philochem: PHC-102, Diagnostic purposes only