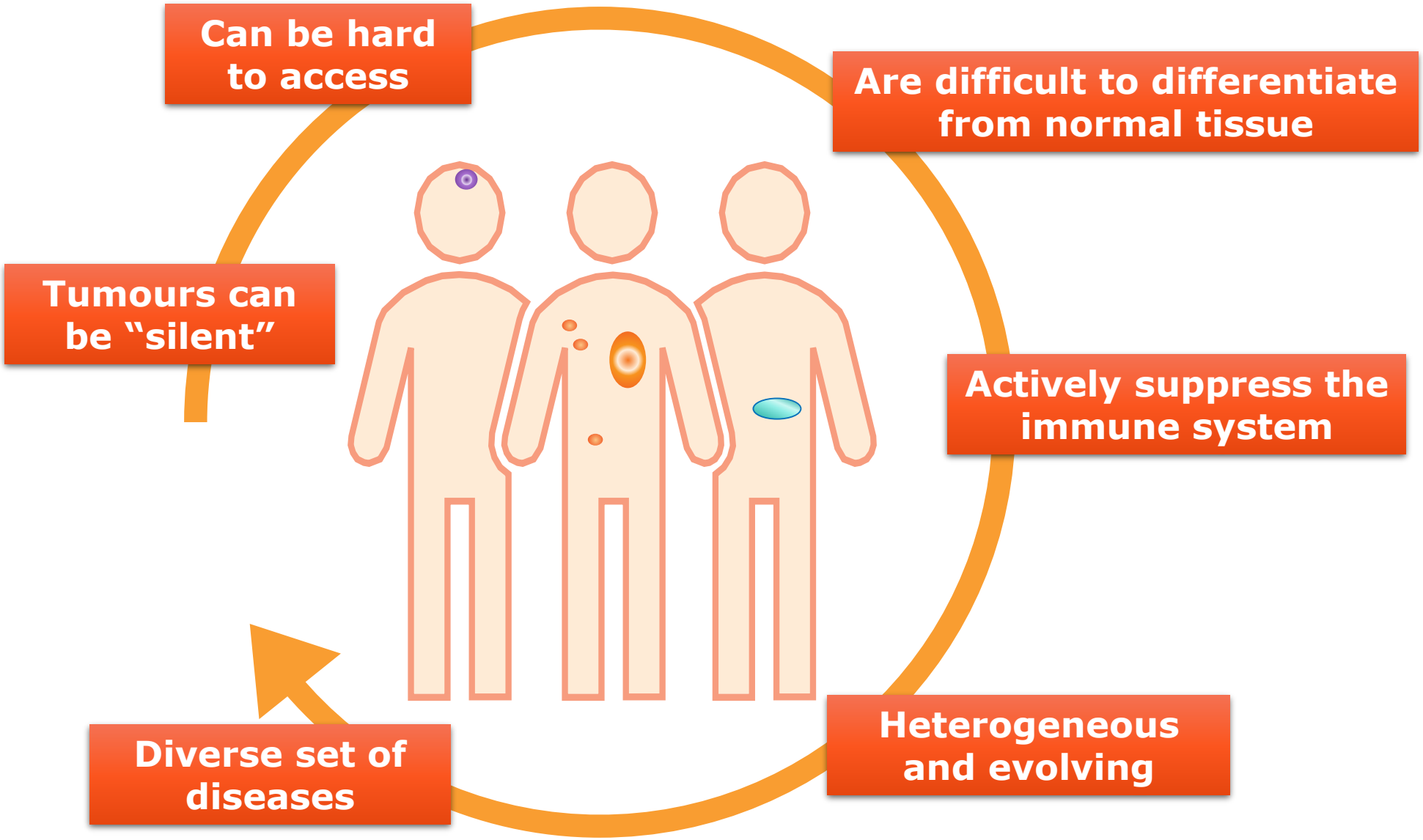
Bicycles® - An entirely new class of therapeutics

Paul Beswick
Bicycle Therapeutics

bicycle
therapeutics

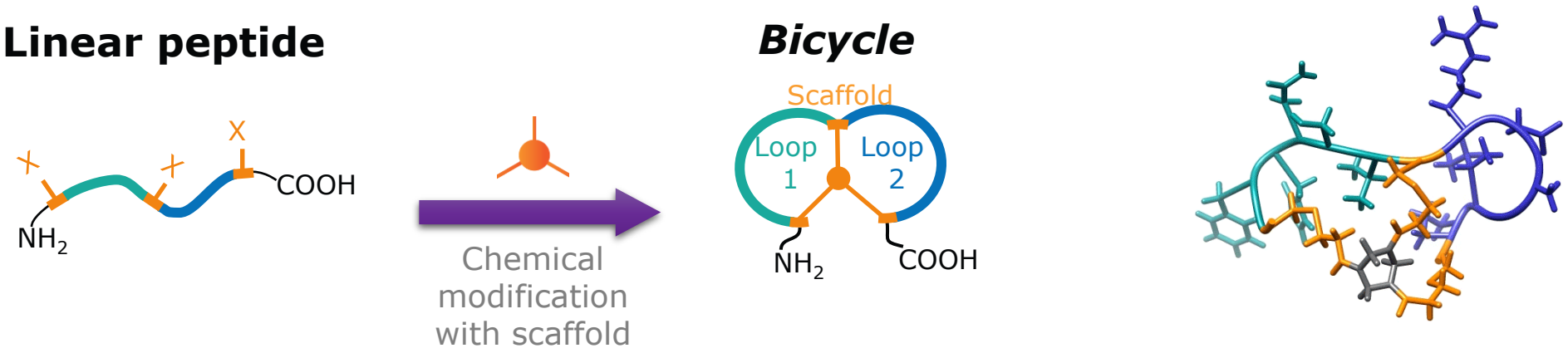
The challenges in treating cancer



Overview

- Bicyclic peptides: A completely new, disruptive therapeutic modality
- Sir Greg Winter technology, platform derisked, industrialized, reduced to practice and validated
- Internal oncology pipeline, multiple therapeutic themes, BT1718 in Ph1: funded by CRUK. Partnered outside oncology
- UK /US presence, world class team & strong clinical / scientific collaborations
- >£65M Series B funded

Bicycles®: a new therapeutic modality



Highly constrained: high affinity, exquisite selectivity, excellent stability

Large binding footprint: disrupt protein-protein interactions

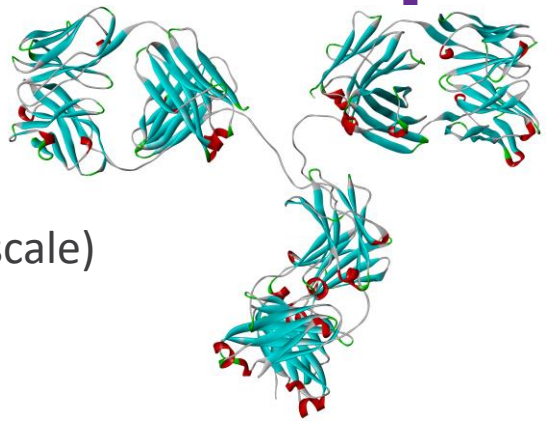
Fully synthetic: NCE classification and synthetic control

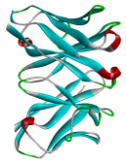
Highly flexible modality: modular building blocks retain pharmacology

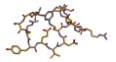
Adjustable PK: excellent tissue penetration, renal elimination, tuneable $T_{1/2}$

Comparison of therapeutic modalities

(to scale)





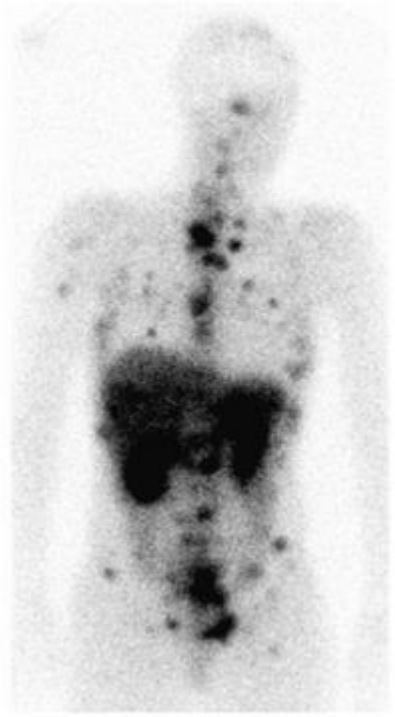


	Antibody	ScFv (fragment)	*Bicycle*	Small molecule
Mw (kDa)	150	28	1.5-2	<0.8
Volume of distribution	Low (vascular)	Intermediate	Whole body	Typically whole body
$t_{1/2}$	Days to weeks	Minutes to days	Min to hours (tunable). Days possible[2]	Hours (tunable)
Clearance	hepatic	Renal, hepatic	Renal	Renal, hepatic
Tumour penetrance	Low (outer rim only)	Low (poor exposure)	High	High
Target classes	Many, small pockets restricted	Many, small pockets restricted	All tested successful, PPI trivial	Small pockets, PPI rare
Selectivity	Highly	Highly	Highly	Poor
Modularity	Low (bi-specifics)	Possible, difficult	Trivial ("Lego like")	Low
Synthesis	Complex biologic	Complex biologic	Chemical, trivial	Chemical, trivial
Immunogenicity	Possible	Frequent	None detected	None

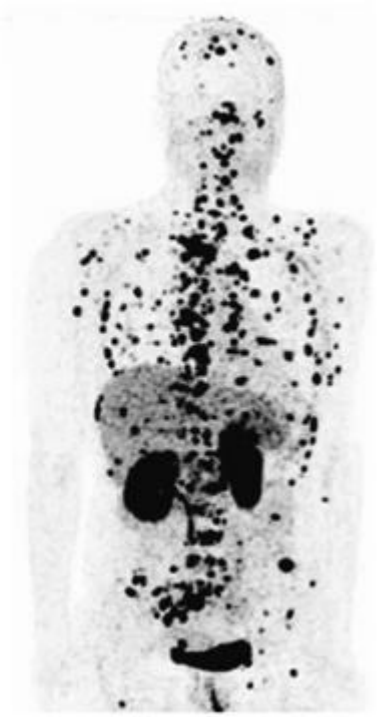
bicycle therapeutics

Current generation of peptidic imaging agents & approved drugs all inspired by nature

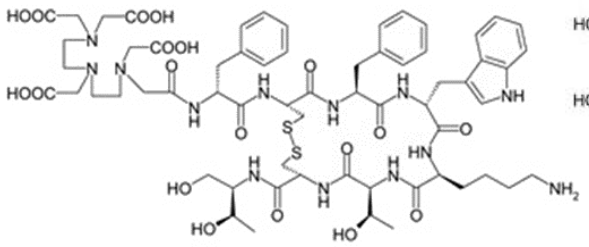
^{111}In-DTPA-Octreotide



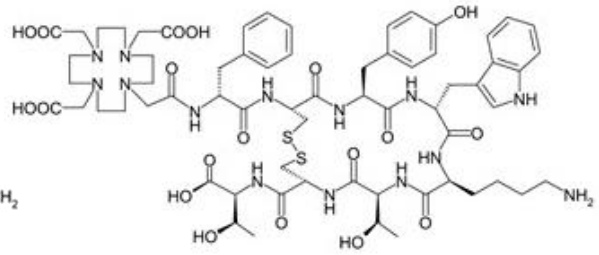
^{64}Cu-DOTA-TATE



DTPA-octreotide



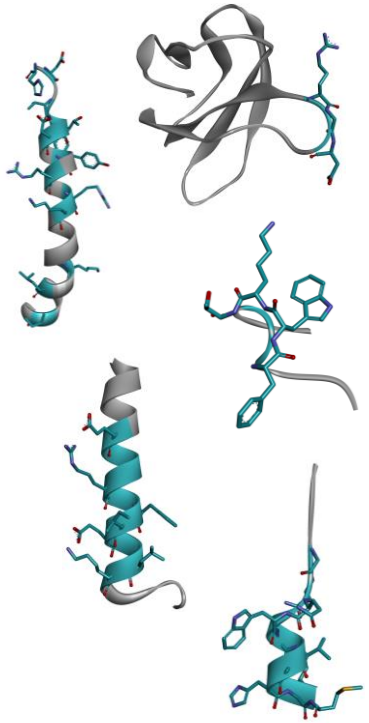
DOTA-TATE



Peptide imaging agents in the clinic based on:

Human
- RGD (fibronectin)
- Vasoactive intestinal peptide
- Somatastatin-14

Other species
- Exendin-4 (GLP-1 homologue)
- Bombesin (GRP homologue)
- Venoms & toxins

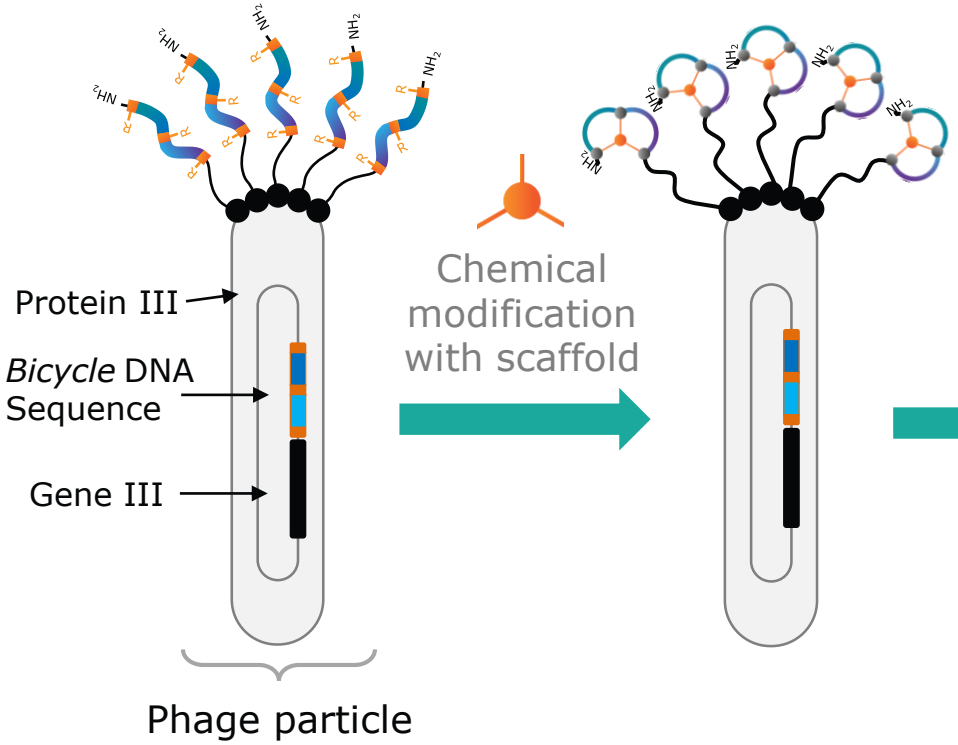


bicycle therapeutics

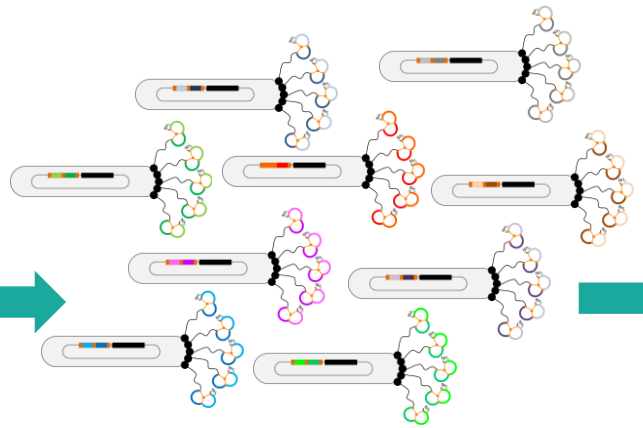
The Bicycle platform can deliver novel tumour targeting peptides

Linear peptide

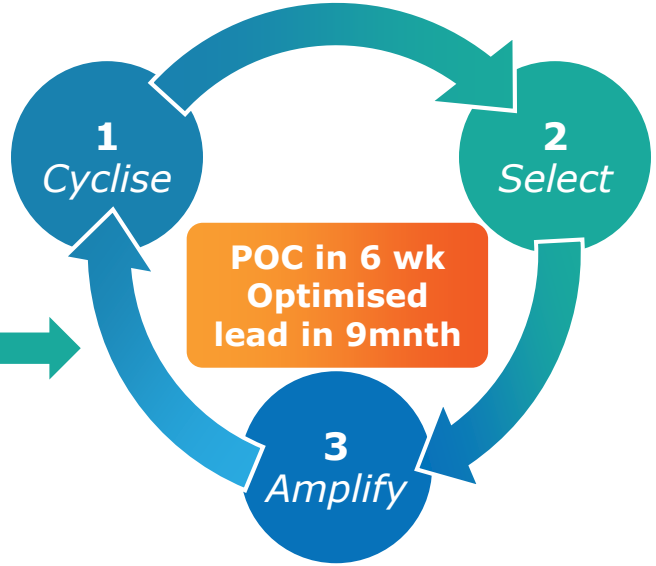
Bicycle



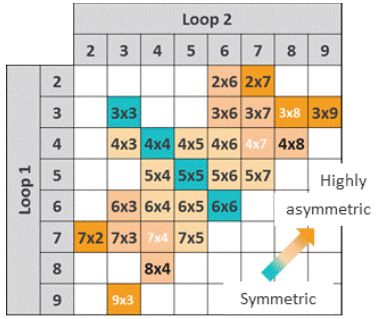
Diverse _Bicycle_ phage libraries (>10^{15})

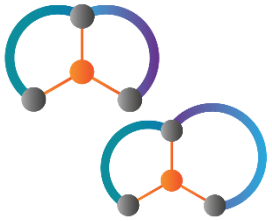


Evolution driven, informed selection



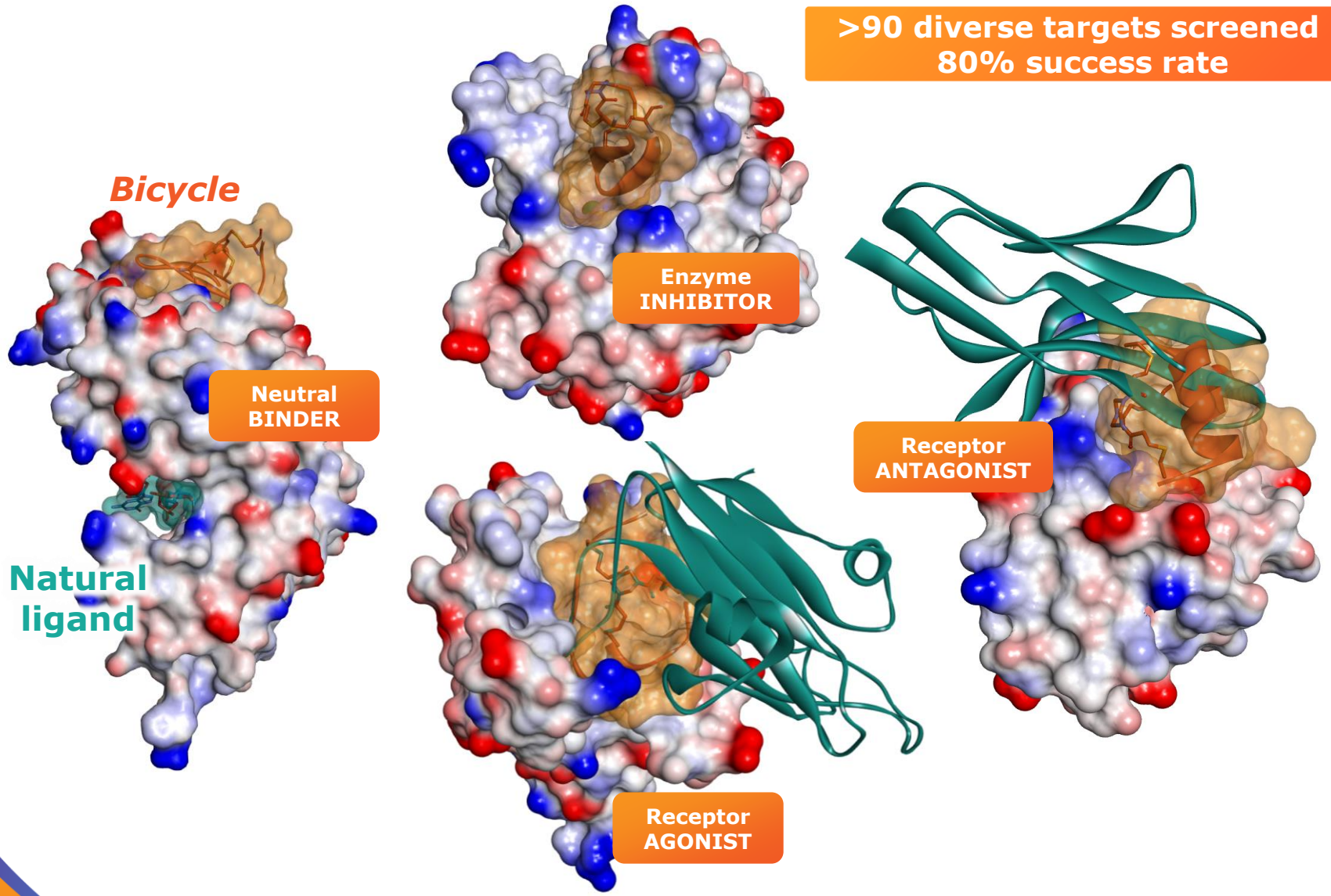
Extremely large and diverse chemical library
Low synthetic burden





bicycle therapeutics

Bicycles®: many shapes to drug many targets

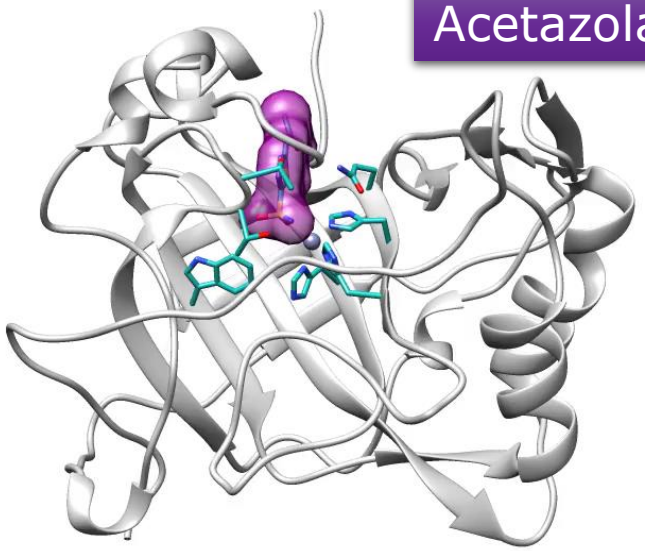


>90 diverse targets screened
80% success rate

Tractable target classes	
Enzymes	Serine proteases
	Other proteases
	Metalloenzymes
	Matrix metalloproteinases
	Coagulation factors
	Other enzymes
Immune checkpoint	**TNFR superfamily members**
	IG domain receptors
Signalling	**Receptor Tyrosine kinases**
	Interleukin receptors
	Interleukins
	Growth Factors
	Cytokines
Adhesion	**Integrins**
	Other cell adhesion proteins
GPCRs	Chemokine receptors
	Adrenergic receptors
Other	Heat shock proteins
	Serum proteins

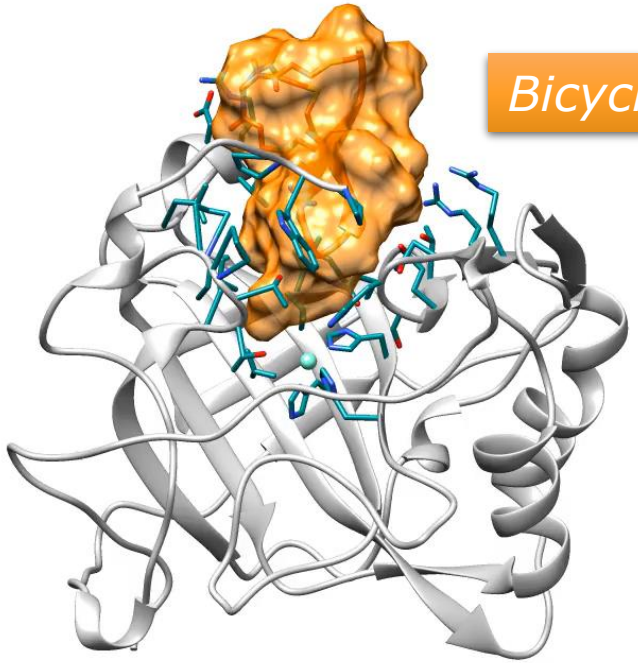
bicycle therapeutics

Bicycle® – large molecular footprint drives affinity and selectivity between close homologues



Acetazolamide

CA IX K_i = 25 nM
CA XII K_i = 6 nM



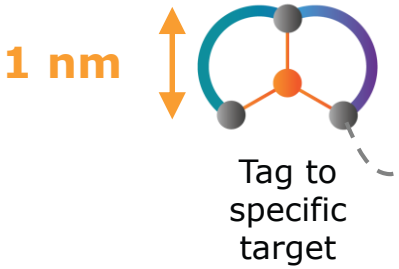
Bicycle

CA IX K_i = 7.5 nM
CA XII K_i > 2000 nM

Bicycle inhibitors	Human Kallikrein K_i (nM)	Rat Kallikrein K_i (nM)	Thrombin K_i (nM)	Plasmin K_i (nM)	FactorXIa K_i (nM)	FactorXIIa K_i (nM)
Exemplar 1	0.8	17.6	>10,000	>15,000	>50,000	>10,000
Exemplar 2	0.2	3.7	>10,000	>35,000	15,000	>10,000
Homologue active site sequence identity			85%	92%	100%	85%

Tolerance to conjugation is built-in

Bicycle



Bacteriophage

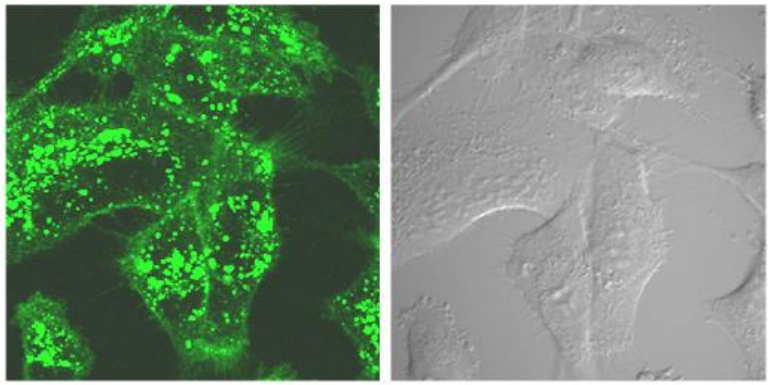
900 nm x 7 nm

Phage bulk readily replaced without compromising binding

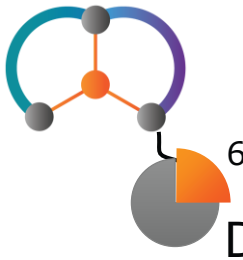
- Small molecule drugs
- Other *Bicycles* (tandems)
- Chelated radionuclides
- Fluorescent dyes
- Affinity tags
- PK extenders

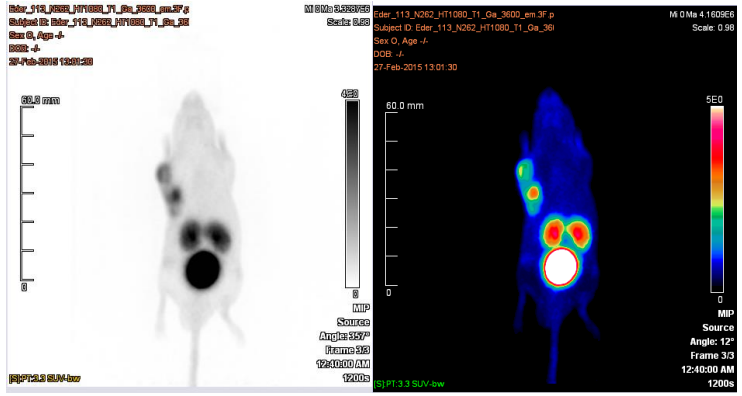
In vitro tools

Fluorescent probe



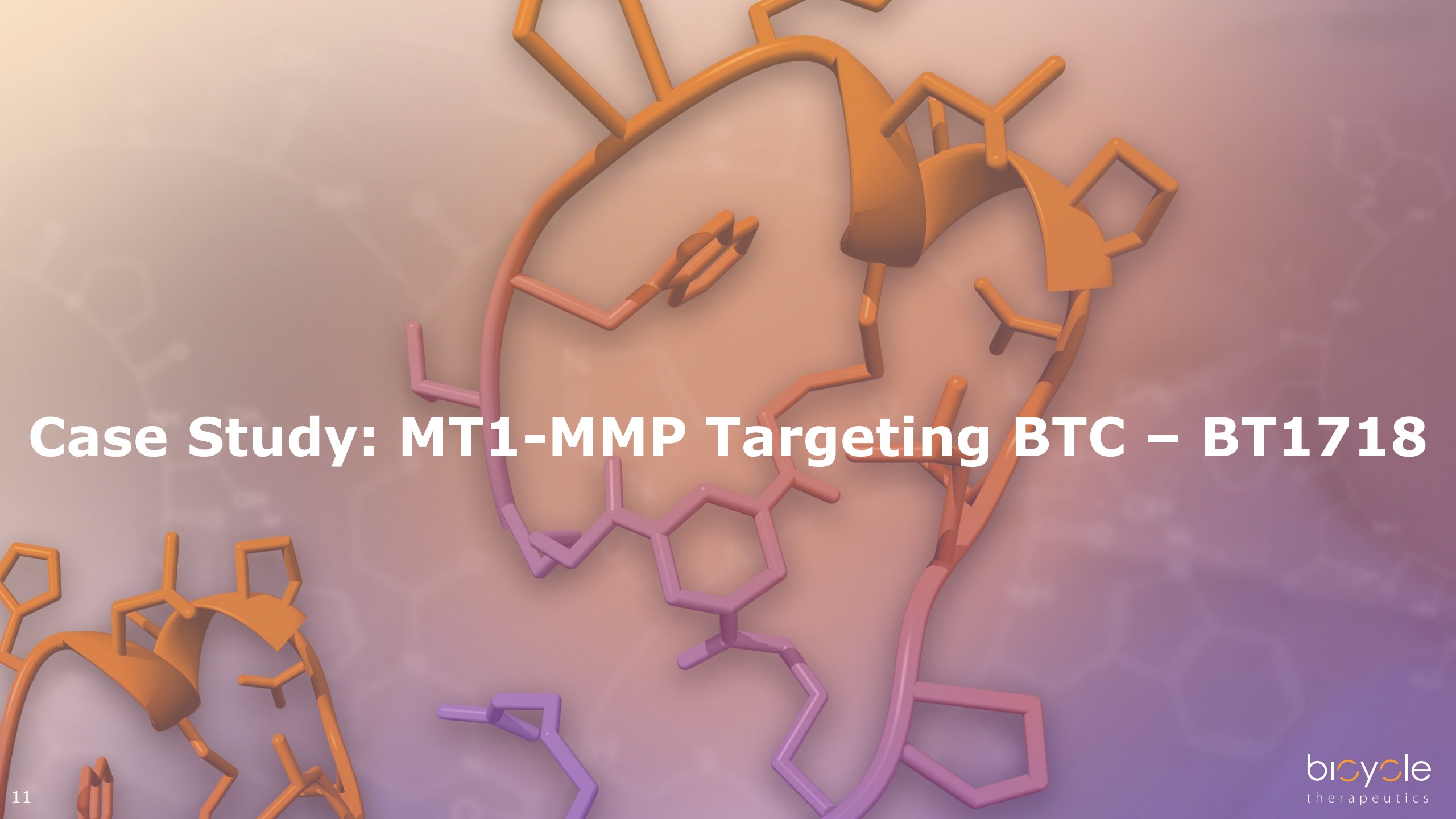
In vivo tools/ diagnostics





bicycle therapeutics

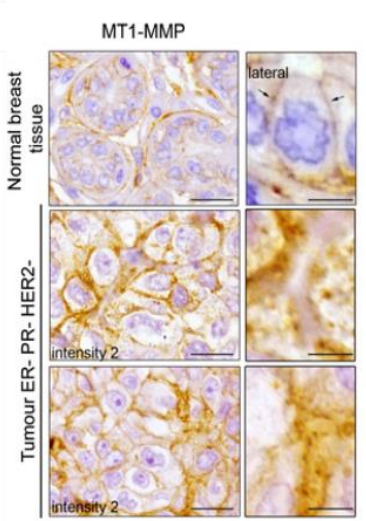
Case Study: MT1-MMP Targeting BTC – BT1718



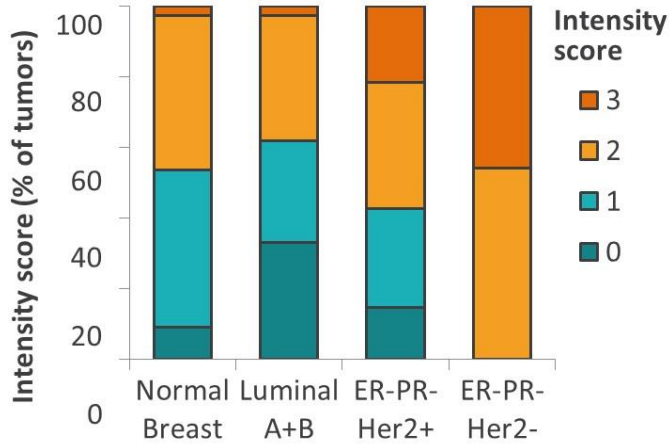
bicycle therapeutics

Proven tumour delivery with *Bicycle* Toxin Conjugates: targeting MT1-MMP

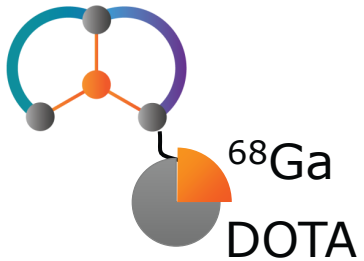
- Membrane type 1 matrix metalloproteinase
- Low expression in normal adult
- Strong correlation with invasiveness in cancer cells



Rosse *et al.*, 2014, PNAS 111, pp1872–1879



Bicycle binder to MT1-MMP:



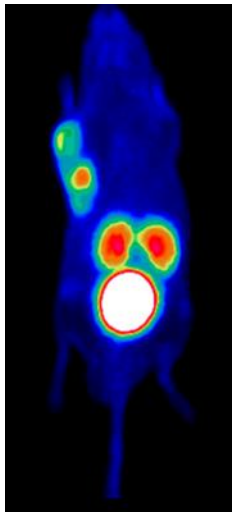
Human MT1-MMP K_d (nM)	Mouse MT1-MMP K_d (nM)	MT2-MMP K_d (nM)	MT3-MMP K_d (nM)	MT5-MMP K_d (nM)	MMP1 K_d (nM)	MMP2 K_d (nM)
2.6	1.8	>10000	>10000	>2000	>1000	>1000

bicycle therapeutics

Bicycles® are retained in tumours and rapidly cleared from systemic circulation

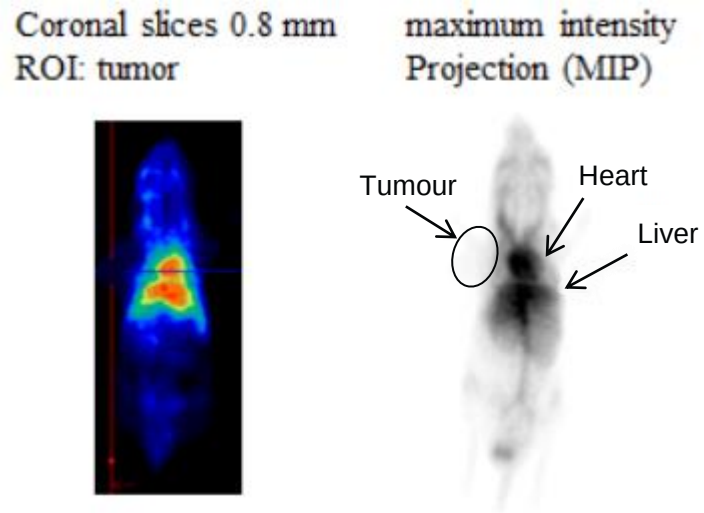
Ideal distribution for imaging

^{68}Ga MT1-MMP *Bicycle*



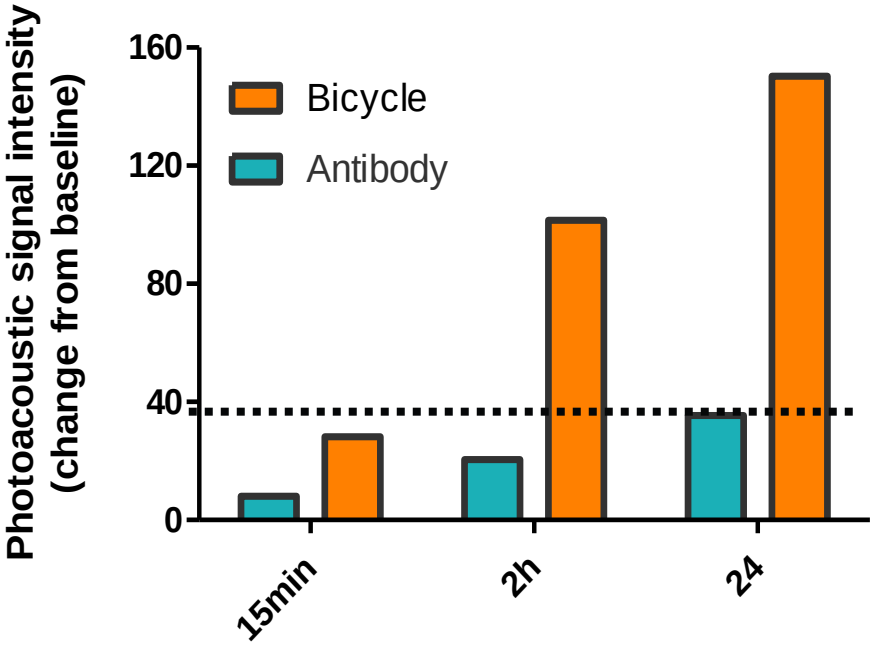
40-60 min

^{68}Ga MT1-MMP Antibody



40-60 min

High tumour retention



***Bicycle* show superior retention in tumours and lower background vs antibodies**

Bicycle® radio conjugate - kinetics of distribution and clearance

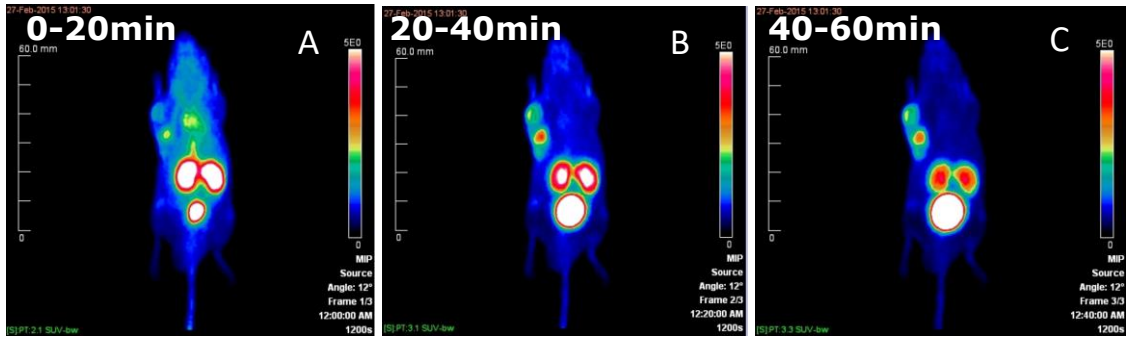
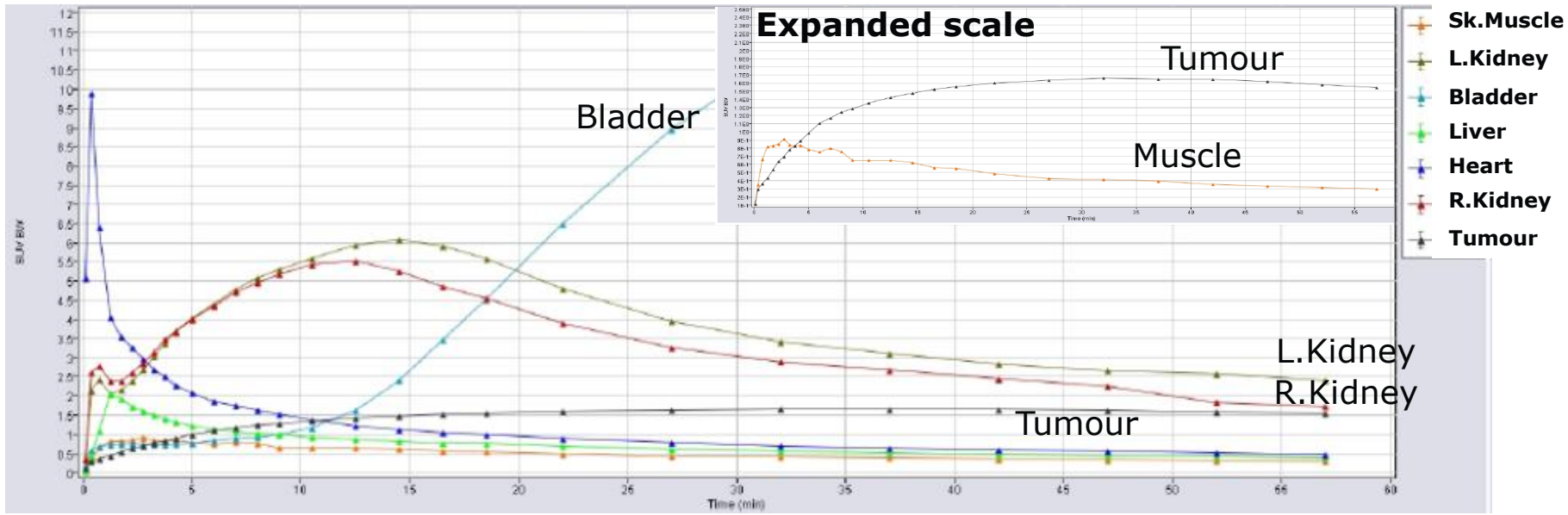


Figure 22. Whole-body coronal slices (0.8 mm) from μPET imaging 0-20 min p.i. (A), 20-40 min p.i. (B), and 40-60 min p.i. (C).

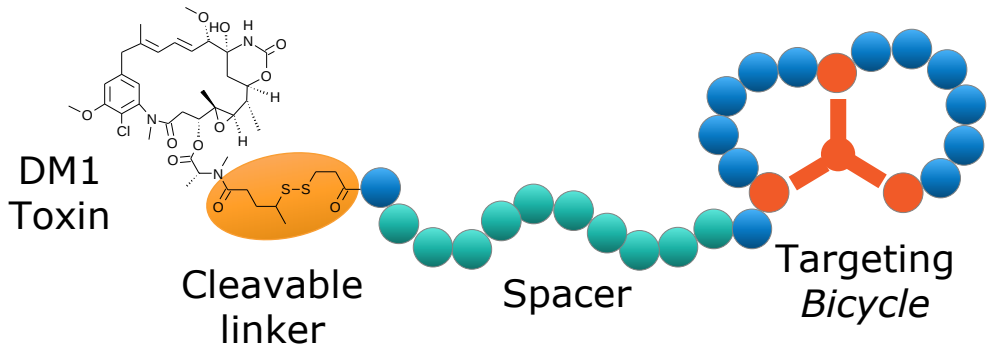
^{68}Ga conjugated MT1-MMP targeting *Bicycle*



bicycle therapeutics

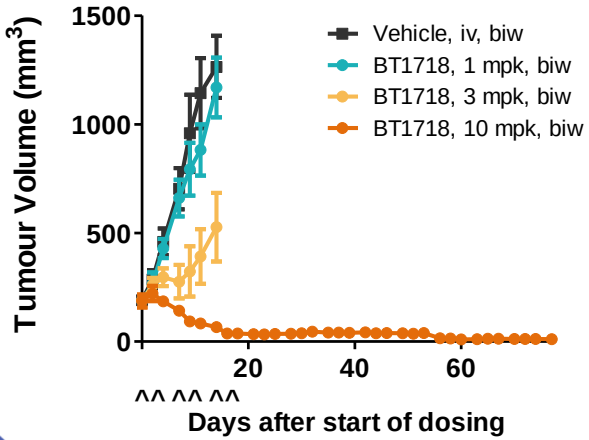
Bicycle® toxin conjugates show profound efficacy

BT1718: MT1-MMP targeting Bicycle Drug Conjugate



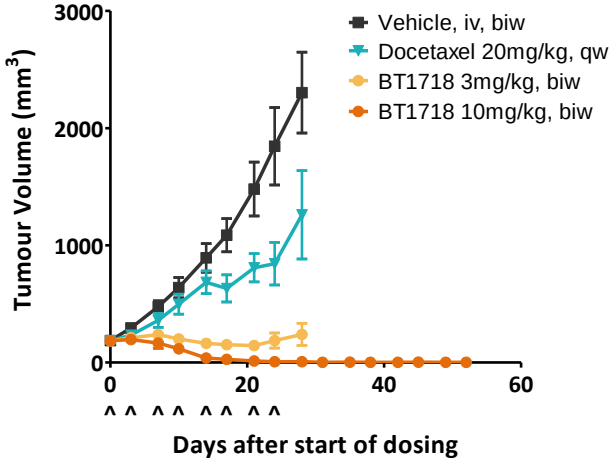
Antigen mediated cell killing

Cell-derived xenografts



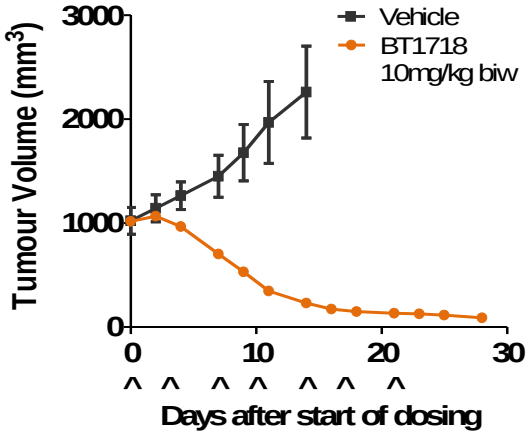
Clears heterogenous PDXs

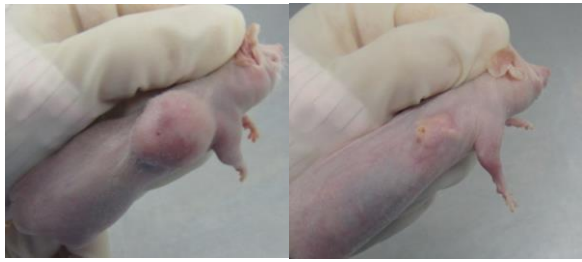
Patient-derived xenografts



Clears large tumours as quickly as small

Large 1000mm^3 CDX (EBC1)

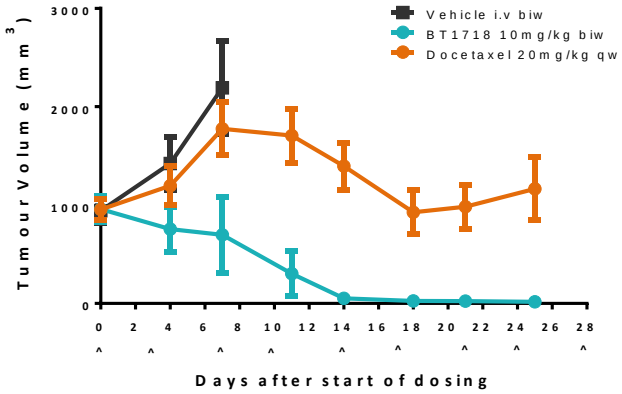


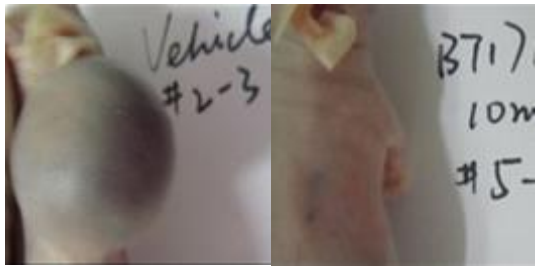


Vehicle
day 14

BT1718
day 28

Large 1000mm^3 PDX (Lu-01-0046)



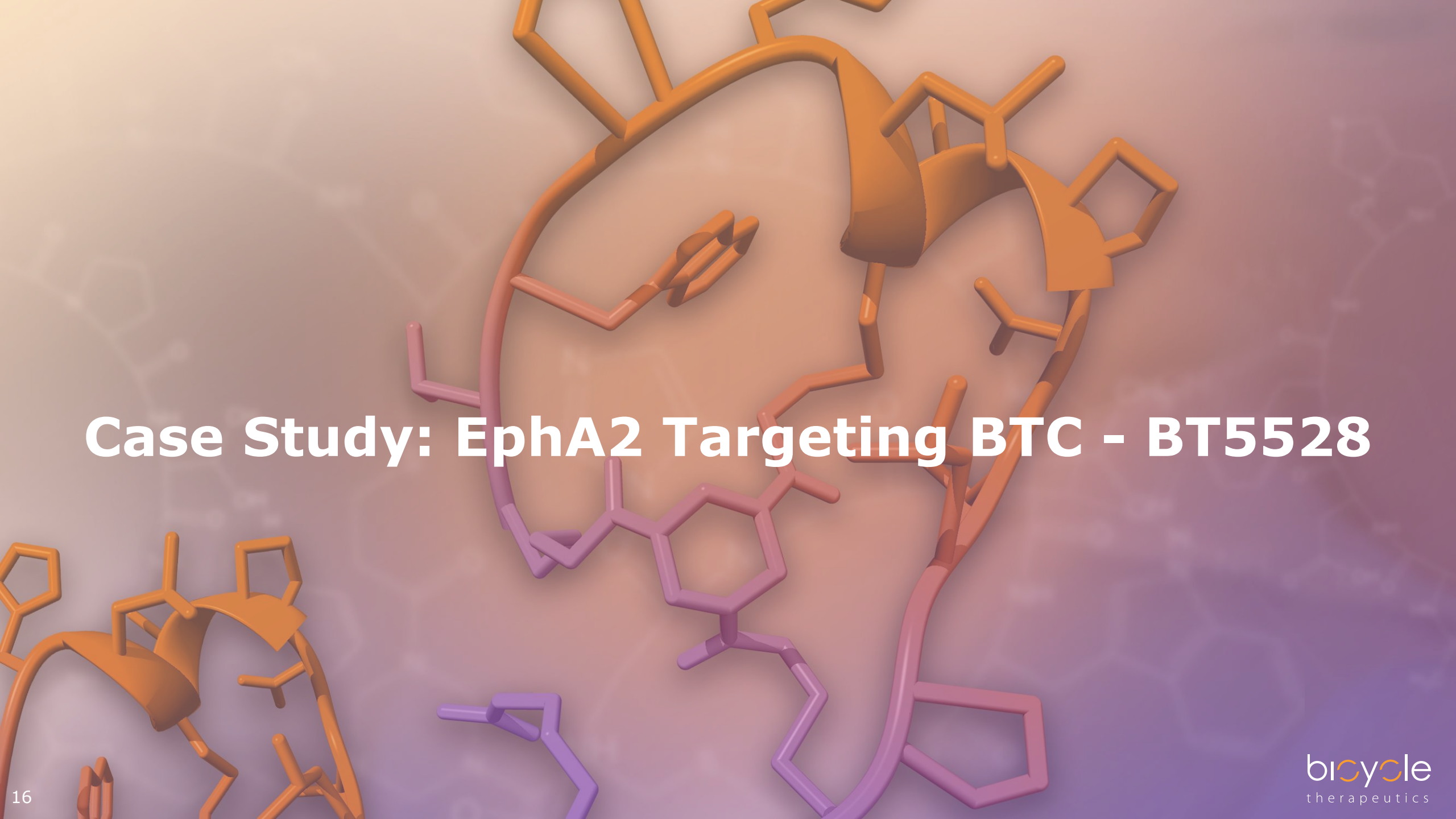


Vehicle
day 7

BT1718
day 28

bicycle therapeutics

Case Study: EphA2 Targeting BTC - BT5528

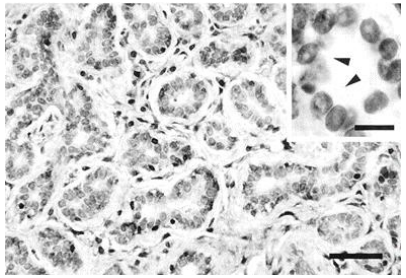


bicycle therapeutics

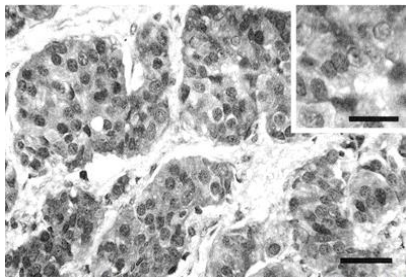
EphA2: Biological rationale

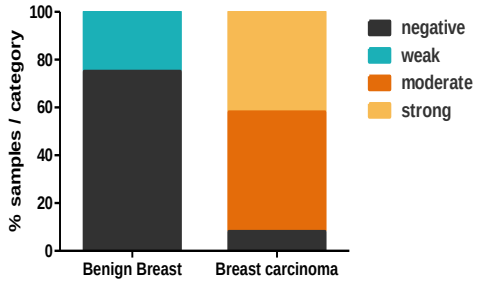
- Erythropoietin-producing hepatocellular A2 receptor
- Member of Eph subfamily of receptor tyrosine kinases
- Regulates cell migration, adhesion proliferation and differentiation
- Overexpression in human cancers, correlates with tumour progression
- Key area for pharma companies, multiple programs in discovery, and clinical stages

Benign Breast



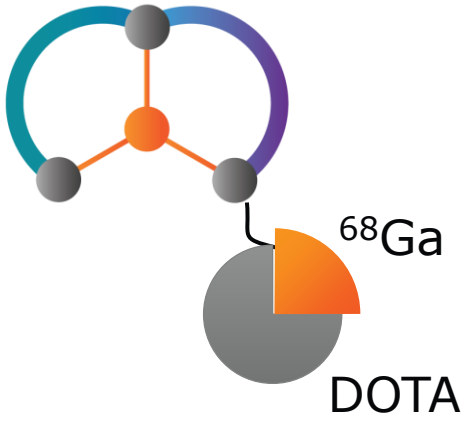
Invasive ductal carcinoma



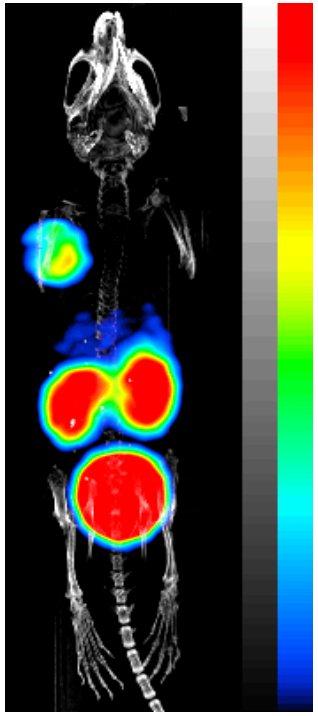


Zelinski et al
Cancer Res 61: 2301-2306 (2001)

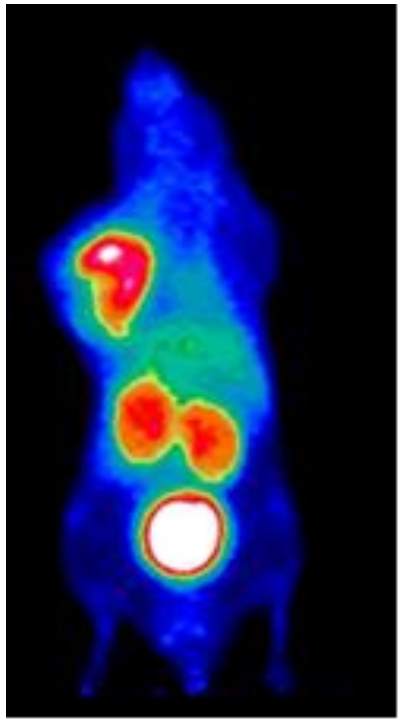
Biodistribution of ^{68}Ga labelled *Bicycle*® shows excellent tumour targeting



PET imaging of HT-1080 xenograft at 60 minutes



BCY6099



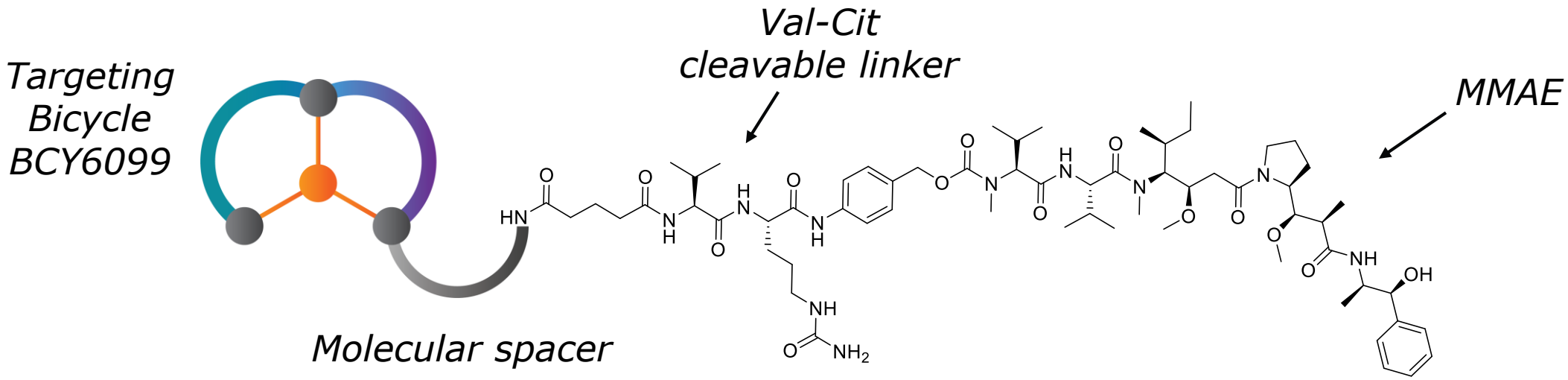
Prototype *Bicycle* (hydrophobic)

Physicochemical properties of *Bicycles* have profound effect on distribution

BT5528: Rapid discovery of EphA2 targeted *Bicycle*® Toxin Conjugate

- Matrix of ~70 conjugates synthesized and screened
- Identify optimal toxin, cleavable linker, molecular spacer
- BT5528 identified as candidate BTC

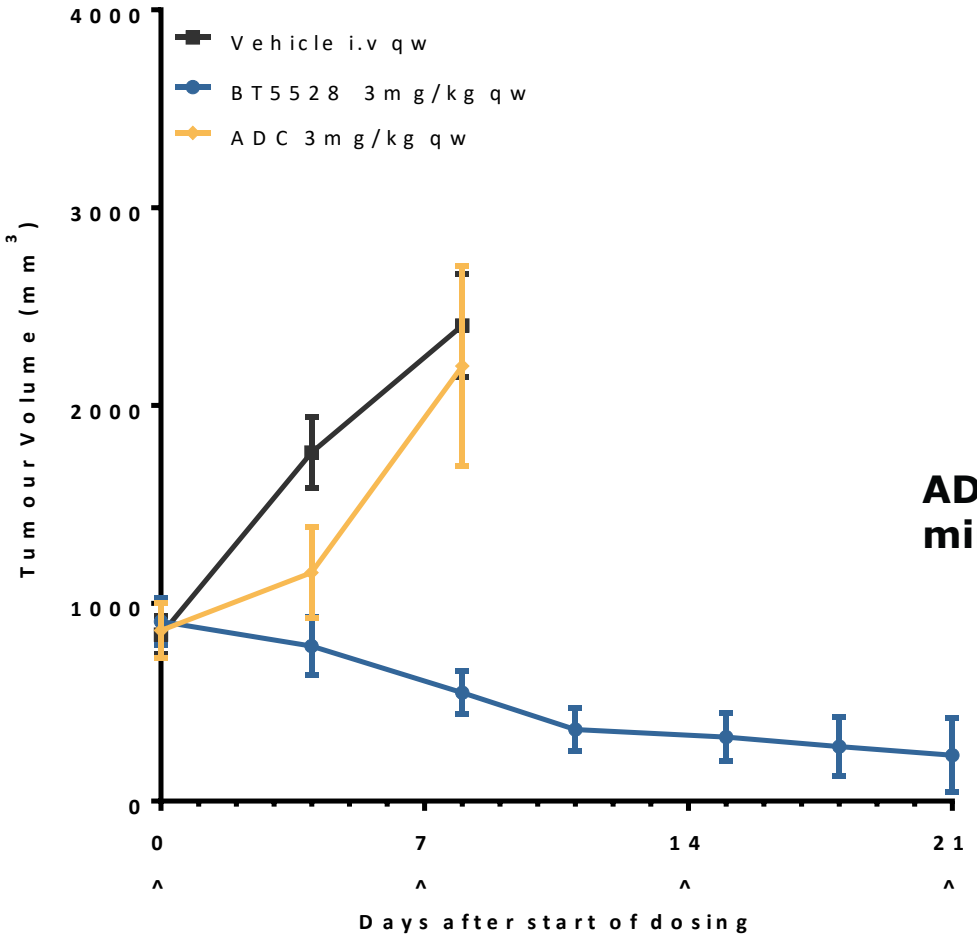
Phage hit → Candidate selection: 1 year



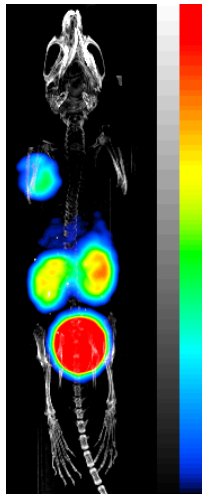
huEphA2 K_d (nM)	moEphA2 K_d (nM)	ratEphA2 K_d (nM)	huEphA1 K_d (nM)	huEphA3 K_d (nM)	huEphA4 K_d (nM)	huEphA5 K_d (nM)
1.2	2.5	3	>5000	>5000	>5000	>25000

Extensive tumour penetration maintains efficacy even in very large PDX model

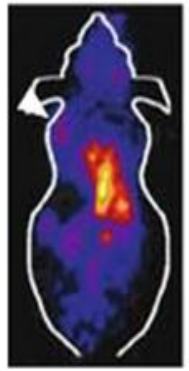
- BT5528 maintains efficacy seen in CDX models even in large PDX
  - Patient-derived xenograft
    - Lung adenocarcinoma
  - Heterogeneous tumour
  - 1000mm^3 at dosing start
- Significant regression of tumour after 21d dosing 3mg/kg qw
- ADC shows no efficacy
  - Dosed 3mg/kg qw
- PET imaging shows rapid penetration of *Bicycle* conjugate into tumour
  - ADC data shows largely vascular distribution
- BT5528 in pre-clinical development



Bicycle distribution at 60 min



ADC distribution at 60 min



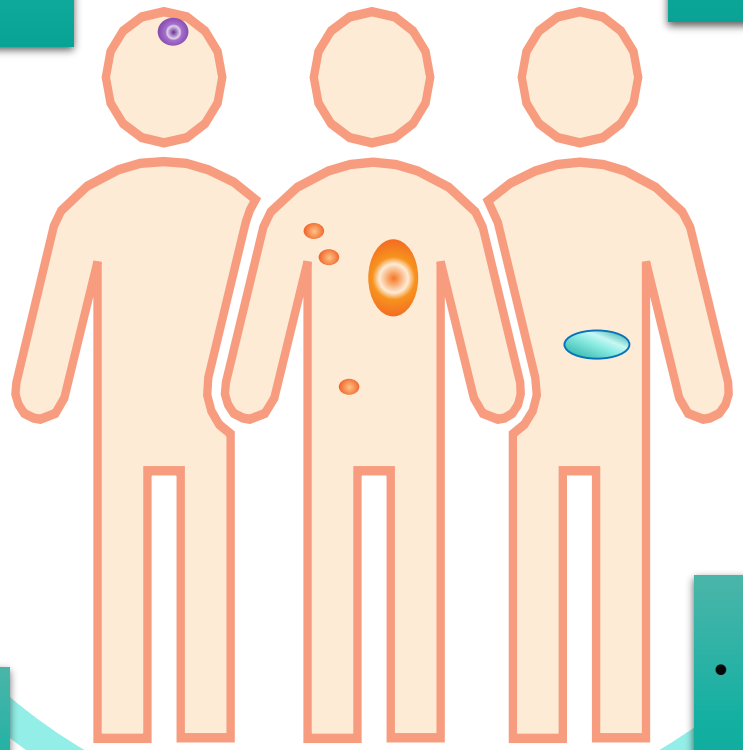
Cai W *et al*, Quantitative radioimmunoPET imaging of EphA2 in tumor-bearing mice. Eur J Nucl Med Mol Imaging. 2007

Bicycles® can meet many of the challenges in oncology

Can be hard to access
- Size and PK accesses tumours efficiently

Are difficult to differentiate from normal tissue
- Highly selective to tumour target
- Combine in bispecifics tandem etc.

Tumours can be "silent"
- Large toolkit of novel probes



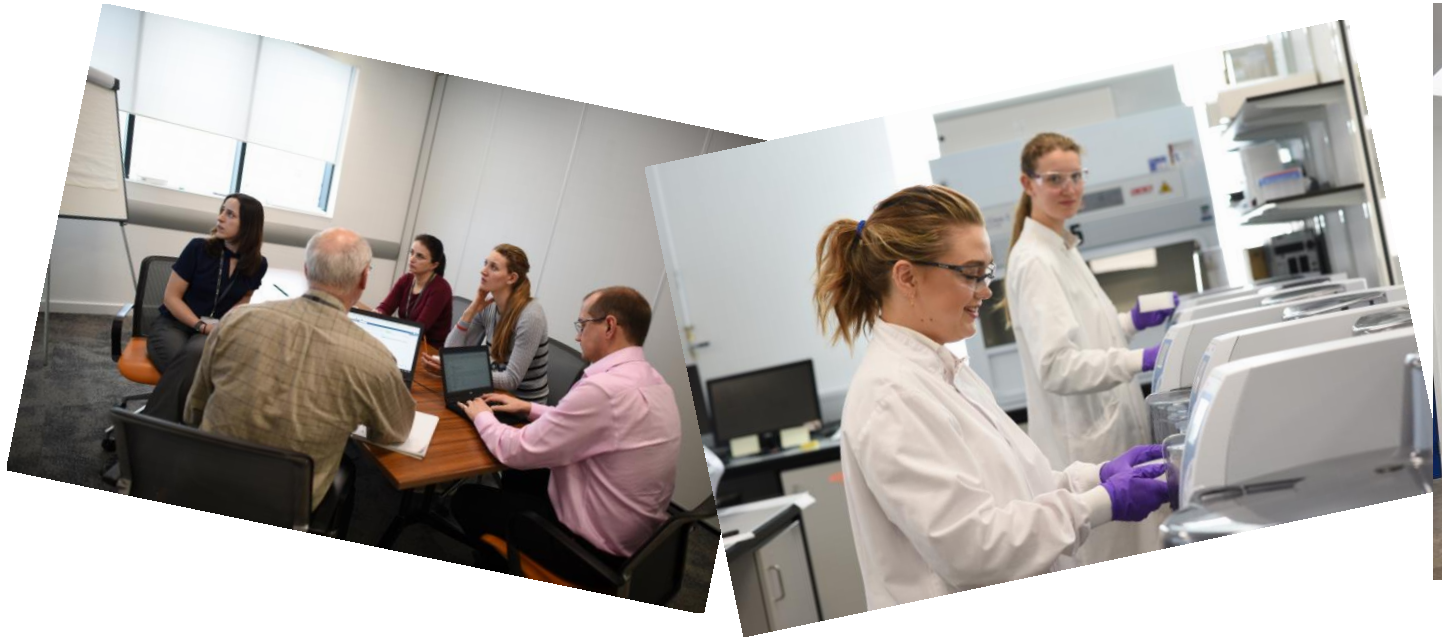
Actively suppress the immune system
- Multimeric immune receptor agonists
- Targeted systemic delivery of innate immune activators

Diverse set of diseases
- Companion diagnostics to stratify patients

Heterogeneous and evolving
- Superior penetration & bystander effect kills whole tumour
- Extensive arson of different anti-cancer targeting agents

Acknowledgements

- Prof. Matthias Eder and group at DKFZ, Heidelberg
  Deutschen Krebsforschungszentrum/German Cancer Research Centre
- Bioprobe Ltd
- Team at Bicycle UK & US



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