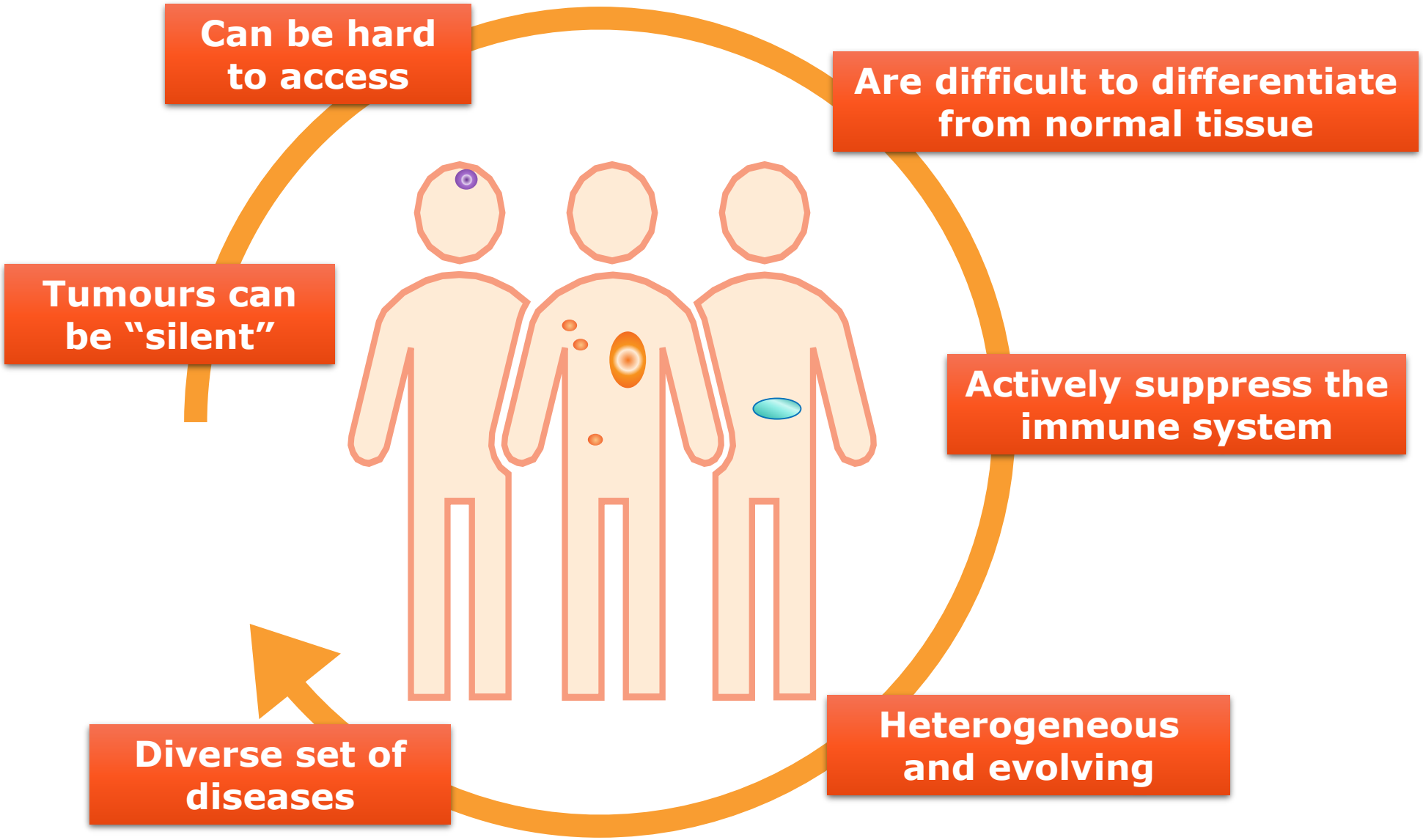
Bicycles® - An entirely new class of therapeutics

Paul Beswick
Bicycle Therapeutics

bicycle
therapeutics

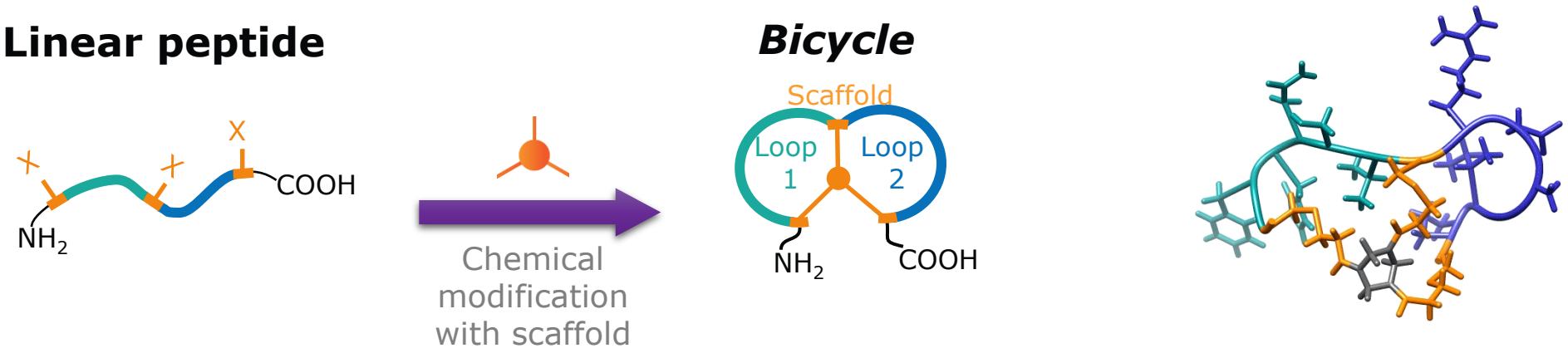
The challenges in treating cancer



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

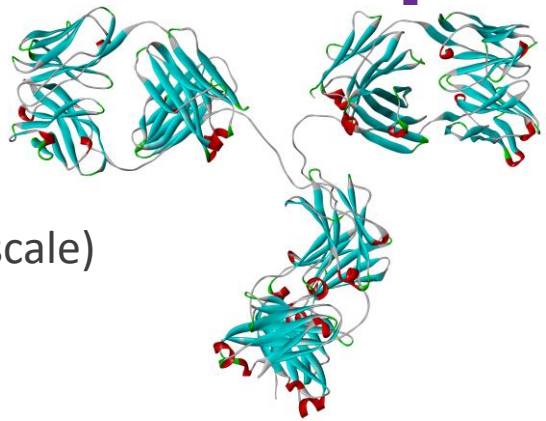
Fully synthetic: NCE classification and synthetic control

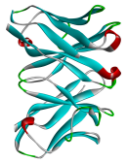
Highly flexible modality: modular building blocks retain pharmacology

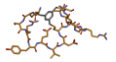
Adjustable PK: excellent tissue penetration, renal elimination, tuneable $T_{1/2}$

Comparison of therapeutic modalities

(to scale)



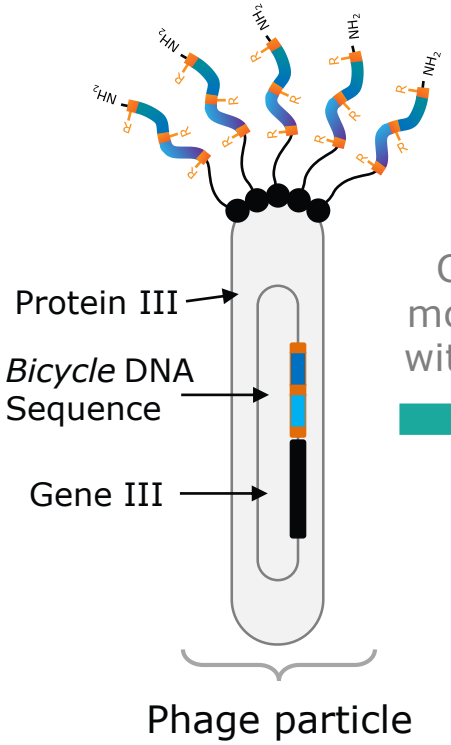




	Antibody	ScFv (fragment)	*Bicycle*	Small molecule
Mw (kDa)	150	28	1.5-2	<0.8
Volume of distribution	Low (vascular)	Intermediate	Whole body	Typically whole body
$t_{1/2}$	Days to weeks	Minutes to days	Min to hours (tunable). Days possible[2]	Hours (tunable)
Clearance	hepatic	Renal, hepatic	Renal	Renal, 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

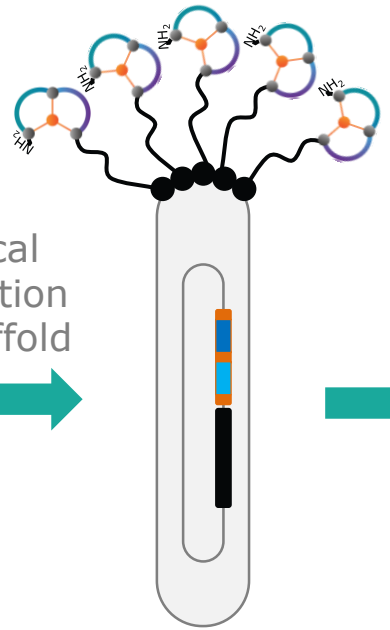
The Bicycle platform can deliver novel tumour targeting peptides

Linear peptide

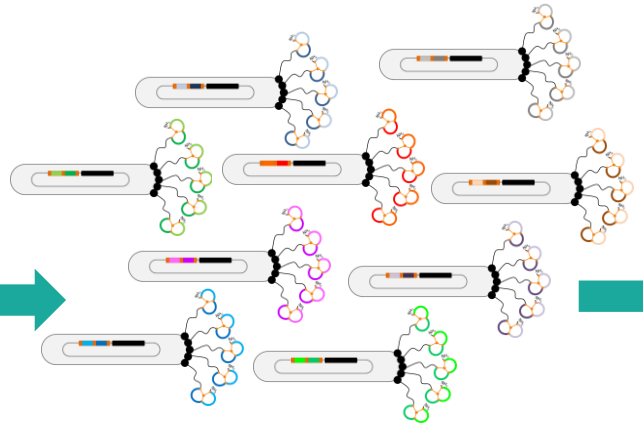


Chemical modification with scaffold

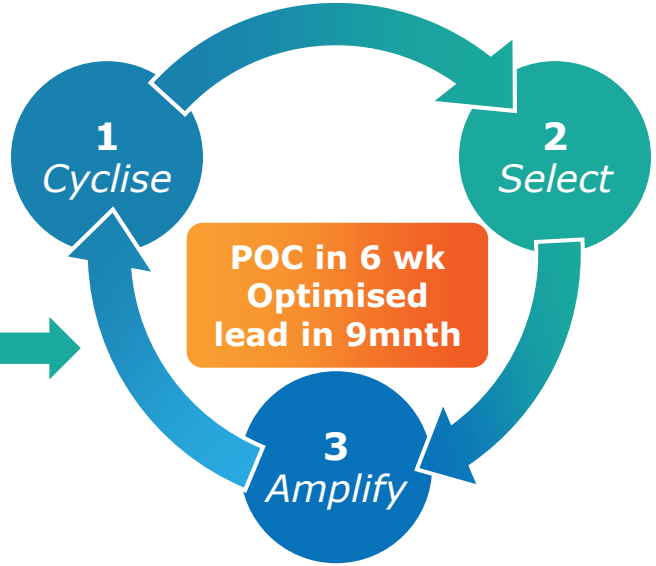
Bicycle



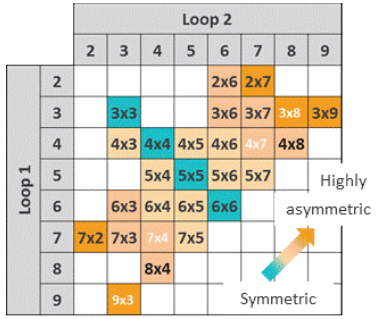
Diverse *Bicycle* phage libraries (>10^{15})

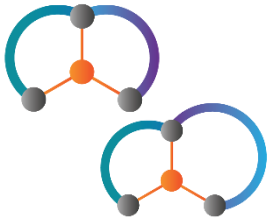


Evolution driven, informed selection



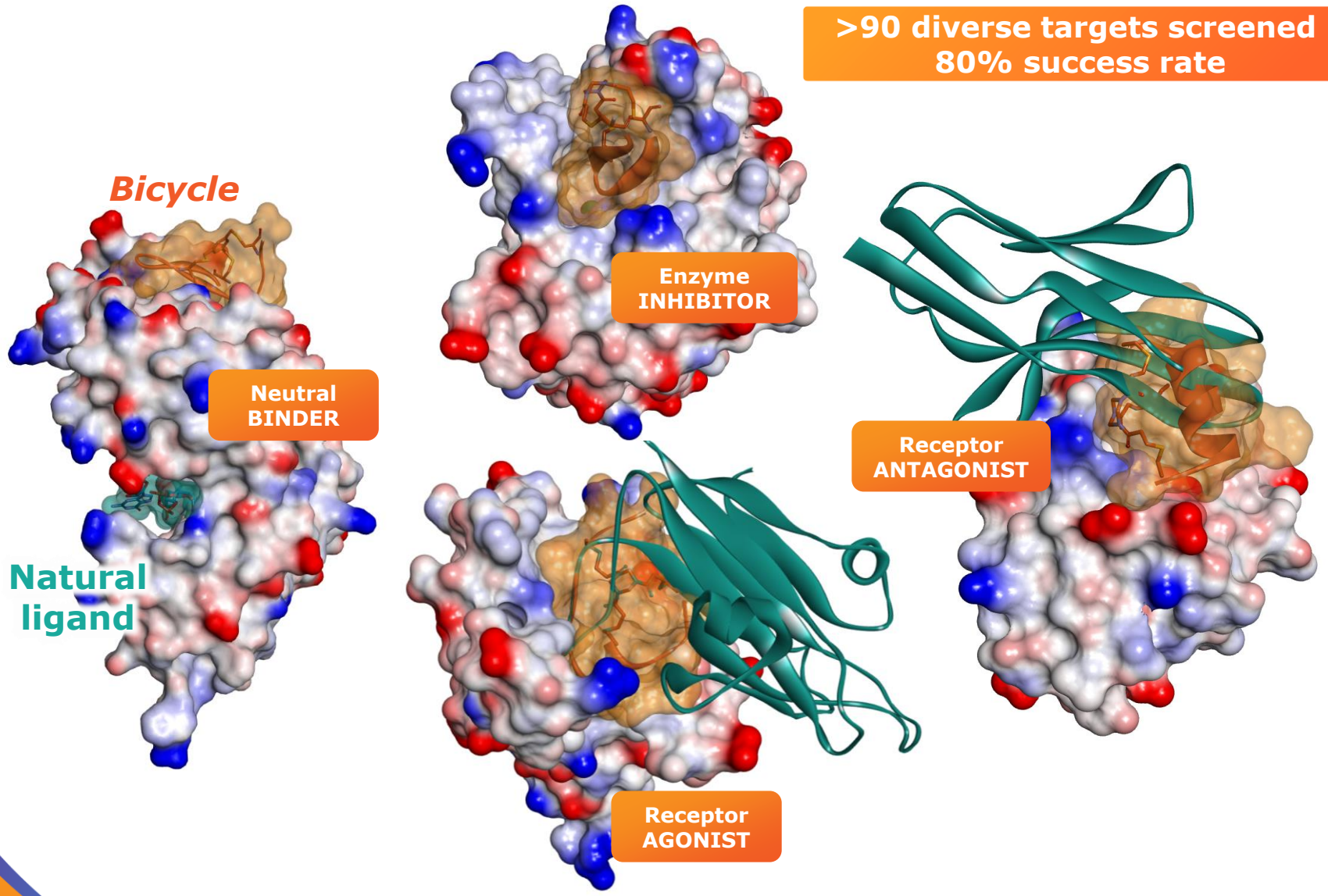
Extremely large and diverse chemical library
Low synthetic burden





bicycle therapeutics

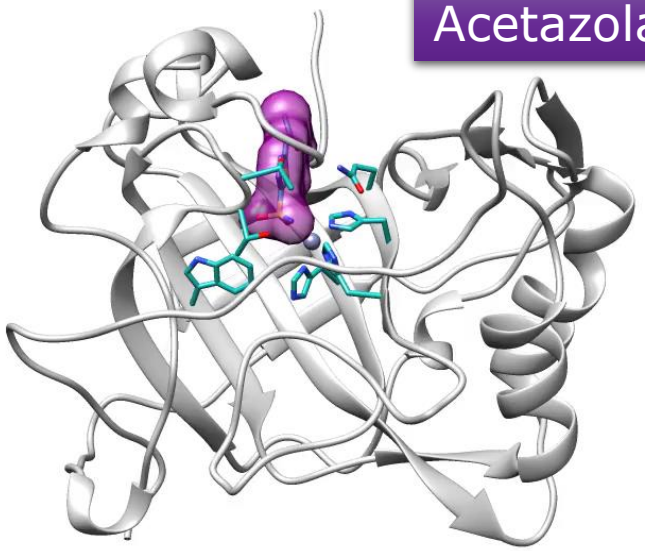
Bicycles®: many shapes to drug many targets



>90 diverse targets screened
80% success rate

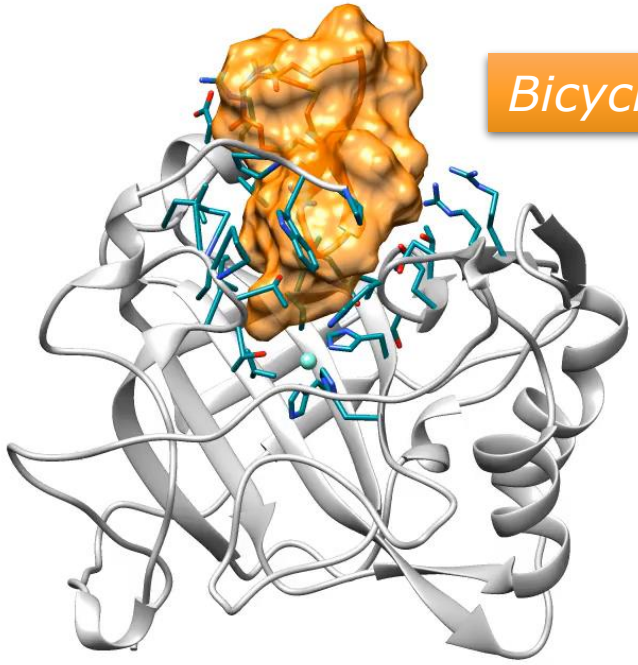
Tractable target classes	
Enzymes	Serine proteases
	Other proteases
	Metalloenzymes
	Matrix metalloproteinases
	Coagulation factors
	Other enzymes
Immune checkpoint	**TNFR superfamily members**
	IG domain receptors
Signalling	**Receptor Tyrosine kinases**
	Interleukin receptors
	Interleukins
	Growth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

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



Acetazolamide

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



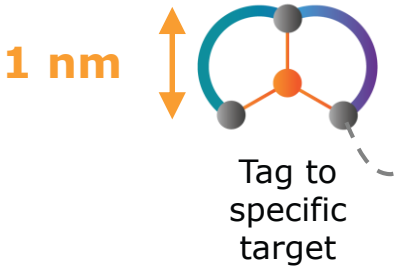
Bicycle

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

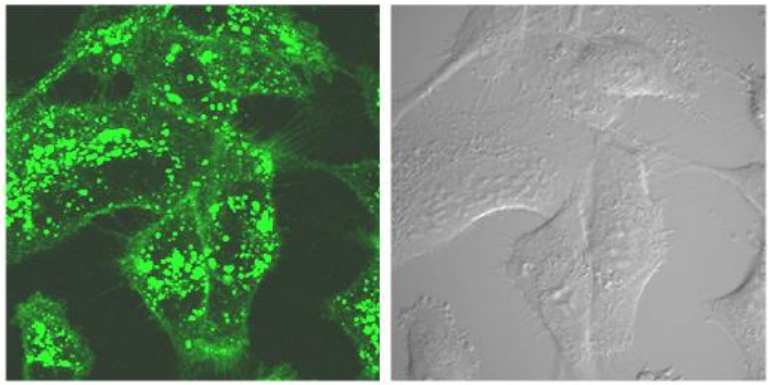
900 nm x 7 nm

Phage bulk readily replaced without compromising binding

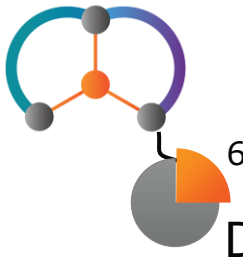
- Small molecule drugs
- Other *Bicycles* (tandems)
- Chelated radionuclides
- Fluorescent dyes
- Affinity tags
- PK extenders

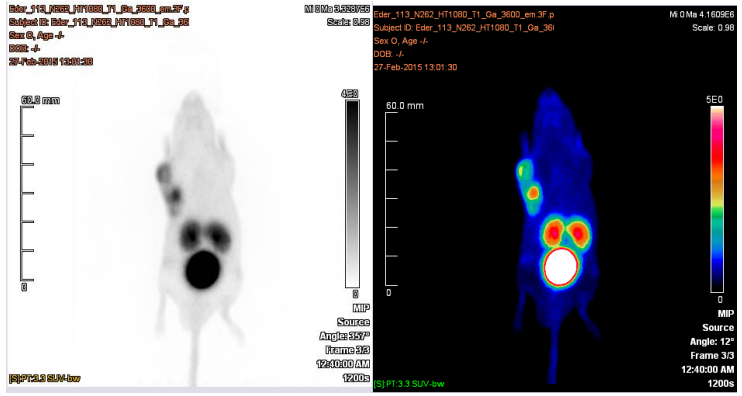
In vitro tools

Fluorescent probe



In vivo tools/ diagnostics

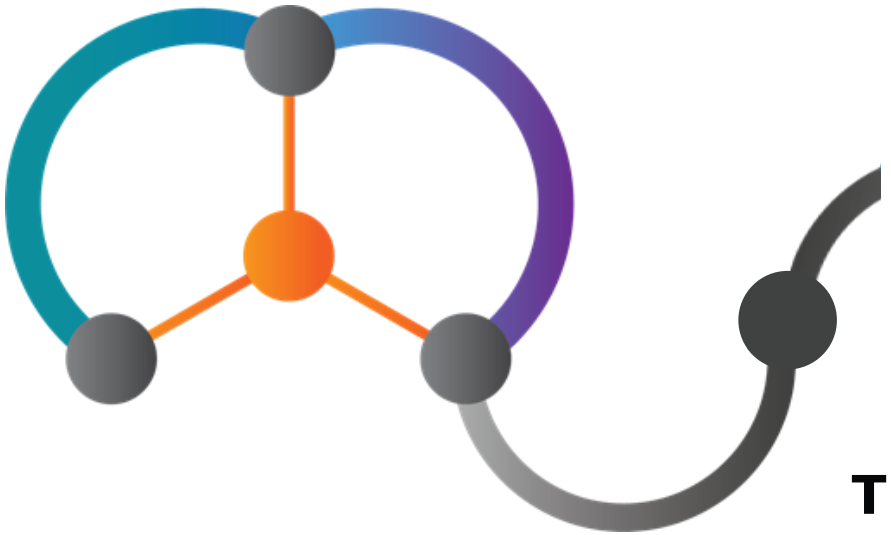




bicycle therapeutics

Bicycle® Toxin Conjugates (BTCs)

Bicycle **selectively binds tumour**



Cell permeable
Cytotoxin

- Too potent to be dosed alone
- Not toxic once conjugated

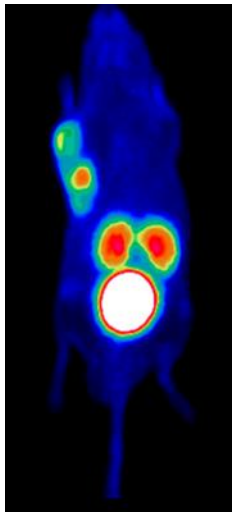
Tumour-selective
Cleavable Linker

- Negligible drug release outside tumour microenvironment
- Payload released extracellularly

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

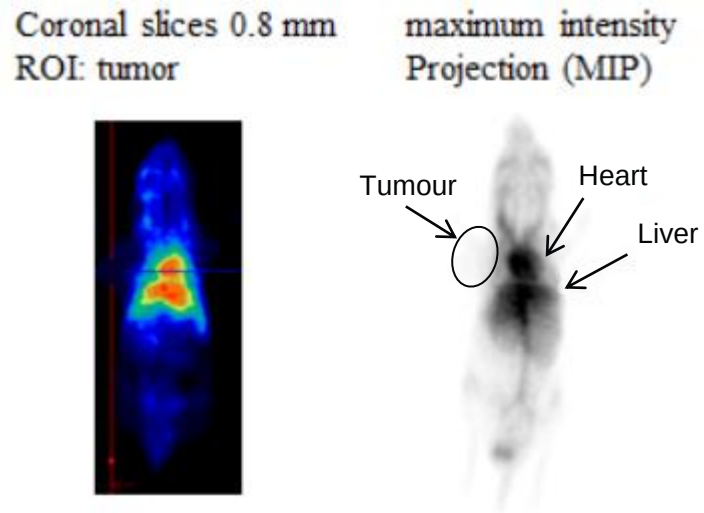
Ideal distribution for imaging

^{68}Ga MT1-MMP *Bicycle*



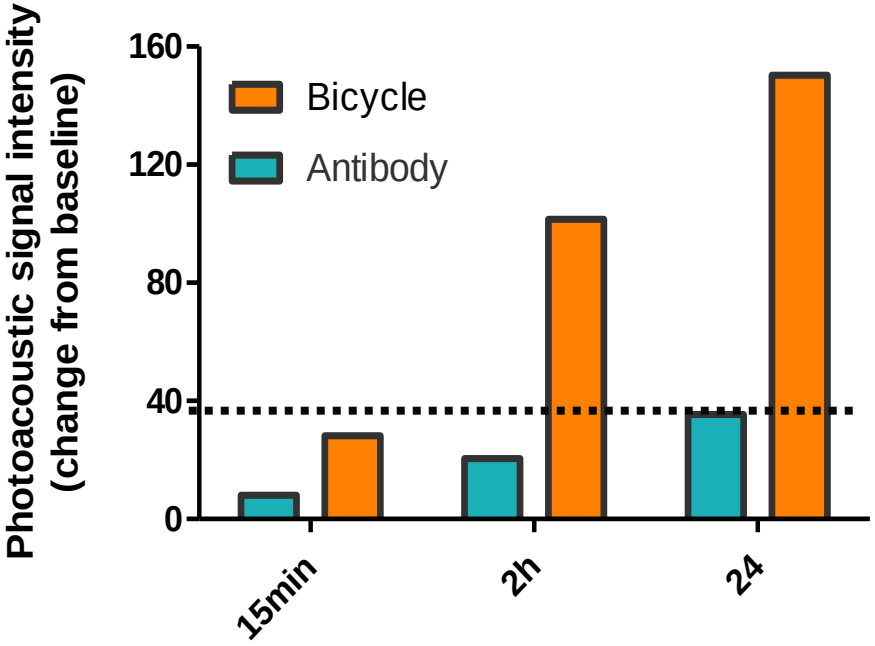
40-60 min

^{68}Ga MT1-MMP Antibody



40-60 min

High tumour retention



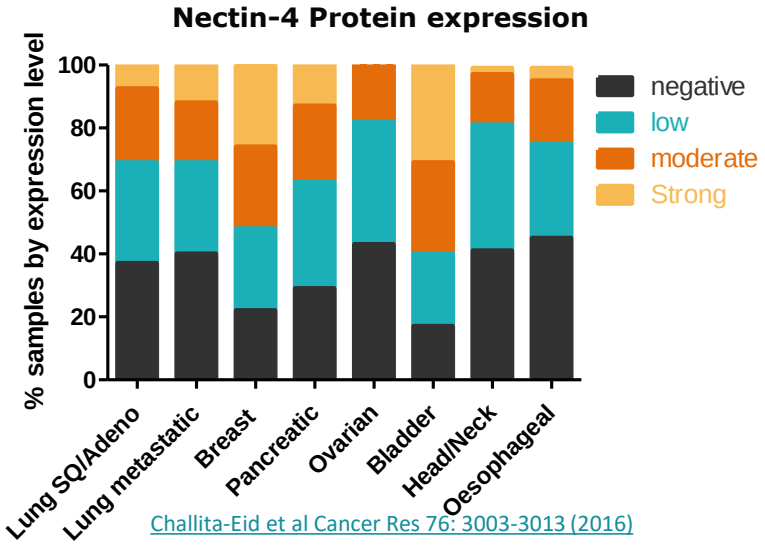
***Bicycle* show superior retention in tumours and lower background vs antibodies**

Case study: Nectin 4 targeting BTC – BT8009

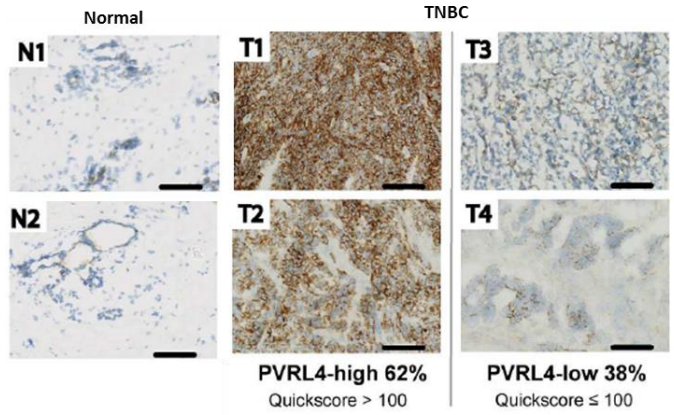
bicycle therapeutics

Biological rationale for Nectin-4 as tumour target

- Nectin-4 cell adhesion molecule
- Wide expression during development,
  - restricted expression in maturity – epithelial cells e.g. skin, airways, eosophagus/stomach and bladder.
- Member of Nectin family and close relative to Nectin-like family
- Other family members more widespread through body
- Over expression in tumours, highest frequency in bladder, breast, and pancreatic, but also in lung, gastric ovary
- Immunoreactivity predominantly on cell membrane and/or cytoplasm of tumour cells
- Nectin-4 targeting ADC, enfortumab vedotin, in Phase 1 - 3 trials, for metastatic urothelial carcinoma, with "Breakthrough Therapy Designation"



Challita-Eid et al Cancer Res 76: 3003-3013 (2016)



Rabet et al Annals of Oncology 28:769-776 (2017)

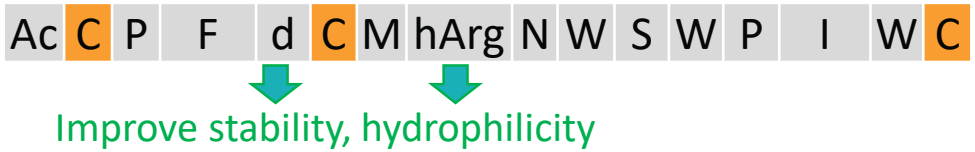
Bicycle® optimization

Parent *Bicycle*

Poor solubility, short half-life. AAs required for binding identified

Ki (nM)	cLogP	$T_{1/2}$ (plasma)
18.4	-6.98	1.3h

Stabilised *Bicycle*

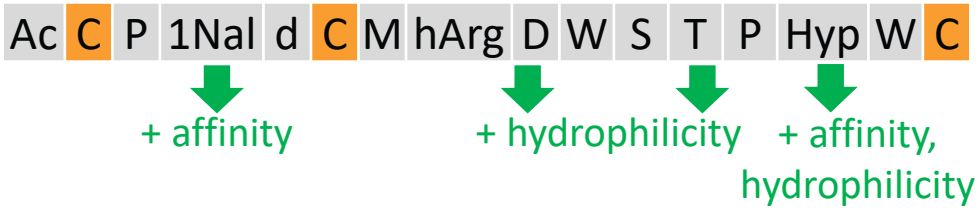


Improvements made to half-life and hydrophilicity, whilst retaining binding AAs

Ki (nM)	cLogP	$T_{1/2}$ (plasma)
13	-6.74	>24h

Solubility = 4.9 ug/ml, LogD = -0.7

Optimised *Bicycle*

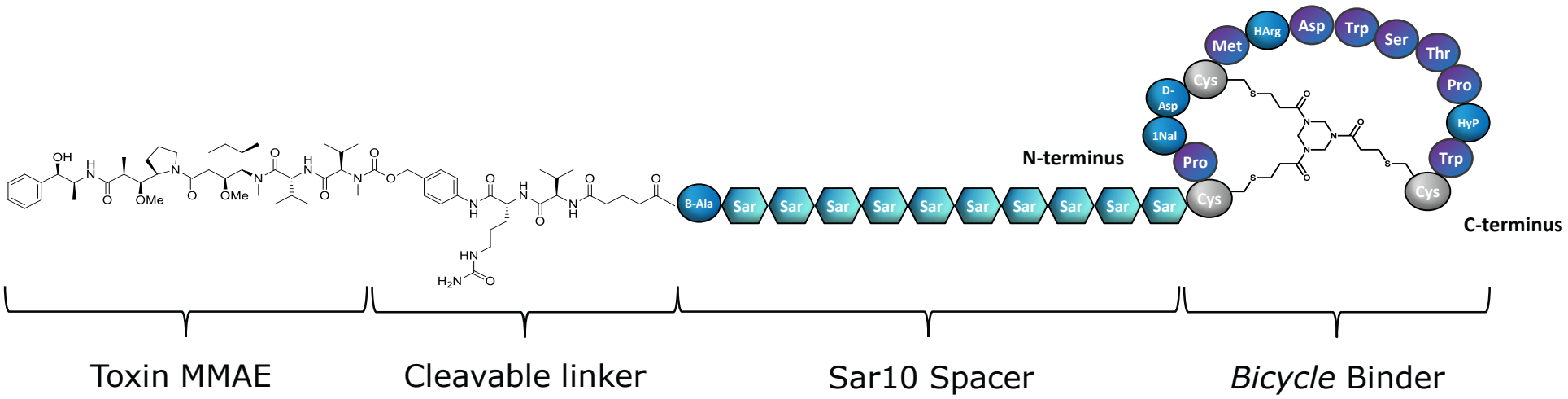


Optimised to increase affinity and improve hydrophilicity. Selected as candidate peptide binder for *Bicycle* Toxin conjugate, BT8009

Ki (nM)	cLogP	$T_{1/2}$ (plasma)
3.21	-13.32	>24h

Solubility = 420 ug/ml, LogD < -2.2

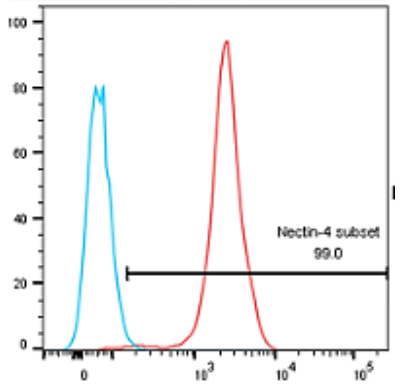
Bicycle® Toxin Conjugate, BT8009

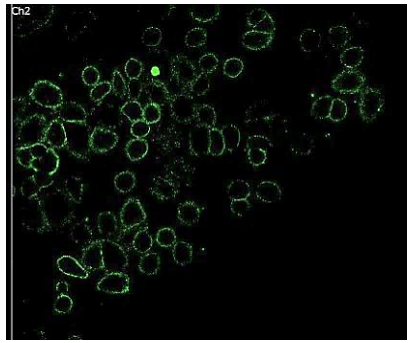


bicycle therapeutics

BT8009 shows binding to MDA-MB-468 cells, and efficacy in xenograft model

FACS shows Nectin-4 surface expression



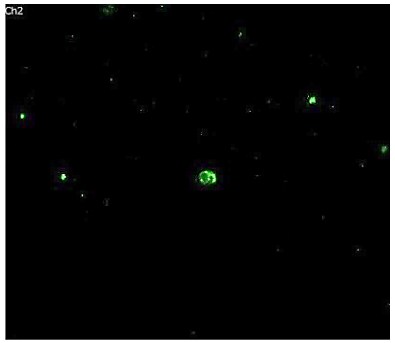


Preincubated with 1μM BT8009

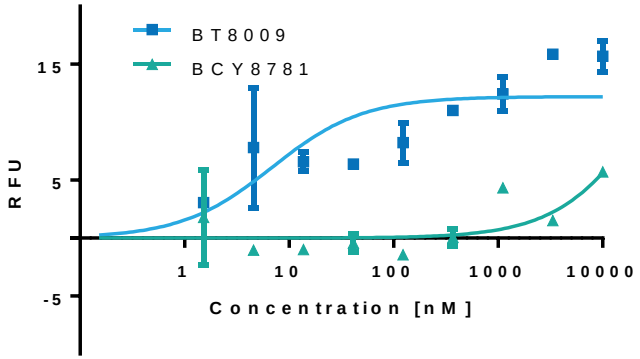
ICC of cells using anti-MMAE antibody. After preincubation with BT8009, a non-binding *Bicycle* Toxin Conjugate (BTC) or MMAE demonstrates only BT8009 is retained on cell surface.

	BT8009	Non-binding BTC
Bmax	12.21	22.84
Kd	6.861	30624

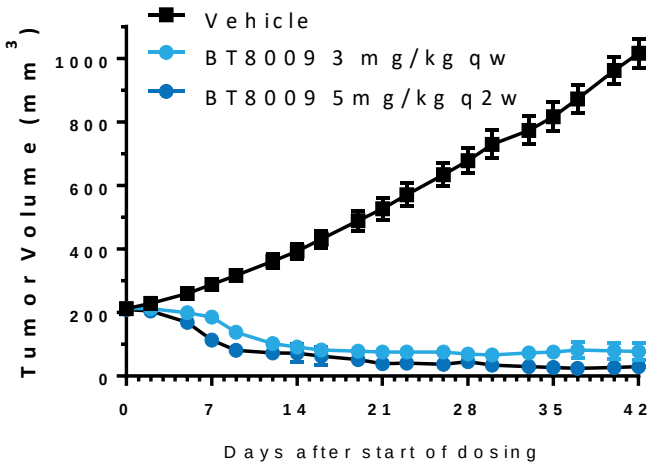
Preincubated with 1μM non-binding BTC



Preincubated with 1μM MMAE



BT8009 shows excellent efficacy in MDA-MB-468 xenografts

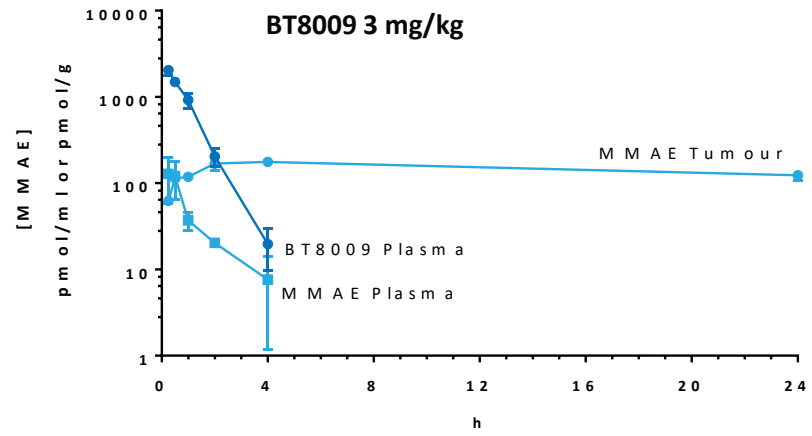


BT8009: *In vivo* PK

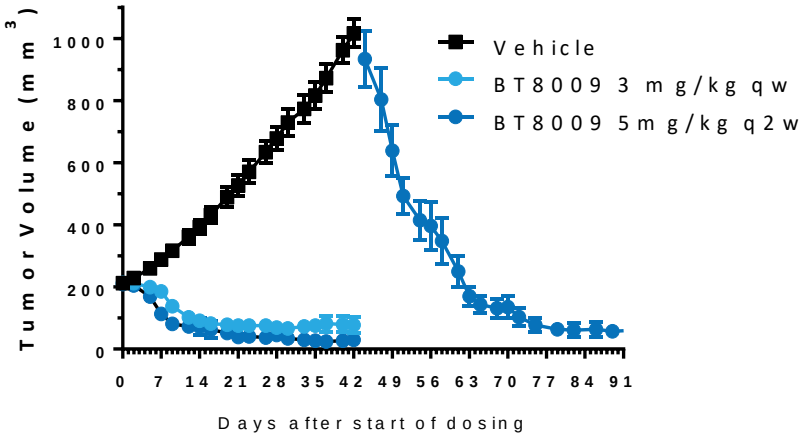
BT8009 shows high Cmax with a short plasma half-life, reflective of rapid clearance from systemic circulation

BT8009 1 mg/kg	CLp (ml/min/kg)	Vss (L/Kg)	t 1/2 (h)	BT8009		MMAE	
				Cmax (uM)	AUC (uM. h)	Cmax (uM)	AUC (uM. h)
Mouse	3.5	0.25	0.98	1.401	1.131	0.065	0.103
Rat	9.4	0.44	0.86	1.114	0.432	0.013	0.022

BT8009 affords long lasting MDA-MB-468 tumour retention of MMAE, with rapid plasma clearance of toxin and parent

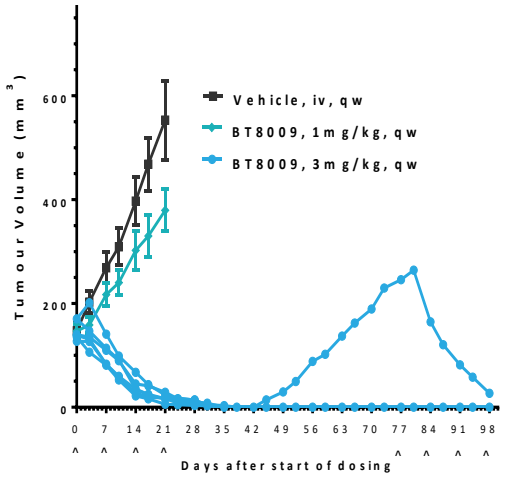


BT8009 efficacy in both "normal and large" MDA-MB-468 xenografts

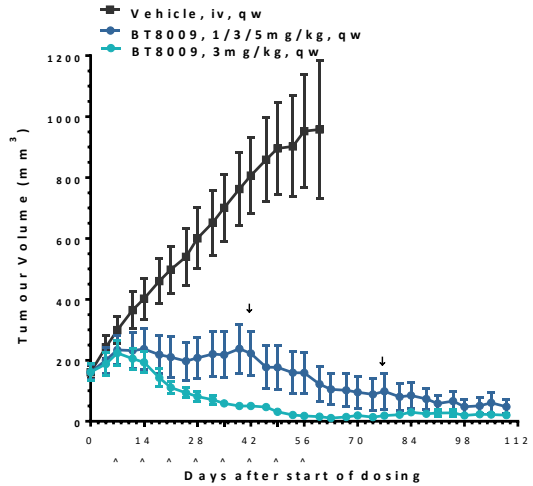


BT8009 efficacy correlates with expression CDX/PDX xenografts

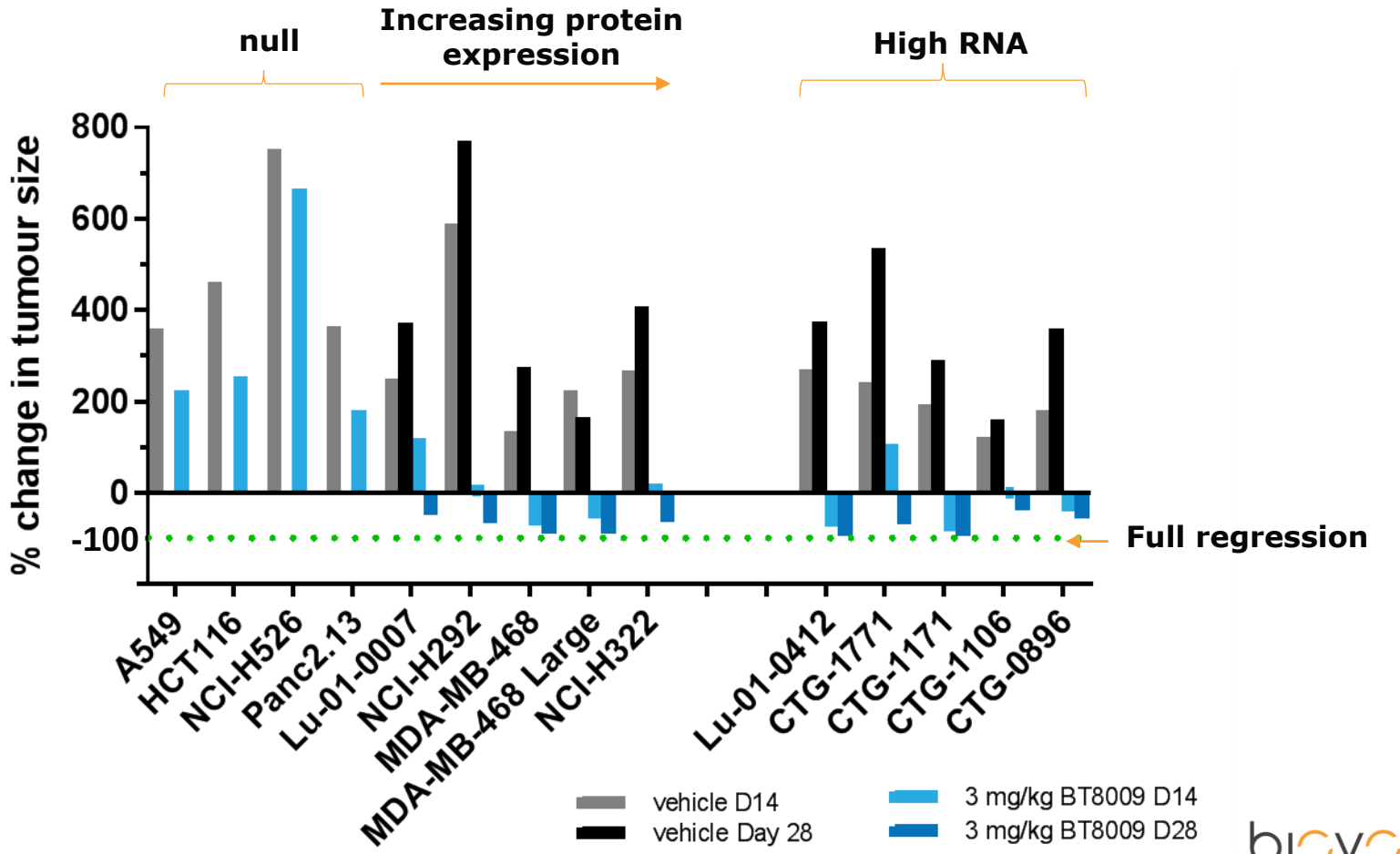
Lung adenocarcinoma PDX



Lung squamous carcinoma PDX



Xenografts with little/no Nectin-4 expression show reduced tumour growth rate.
Xenografts expressing Nectin-4 show regressions of tumour



bicycle therapeutics

BT8009: A Nectin-4 targeting *Bicycle*® Toxin Conjugate, for the treatment of solid tumours

- Nectin-4 is highly expressed on tumour cell surface in a wide range of solid tumours

- BT8009 was developed as a *Bicycle* Toxin Conjugate to target Nectin-4
  - High affinity binding, selective for Nectin-4
  - Short half–life with renal elimination
  - Hit and run delivery of toxin

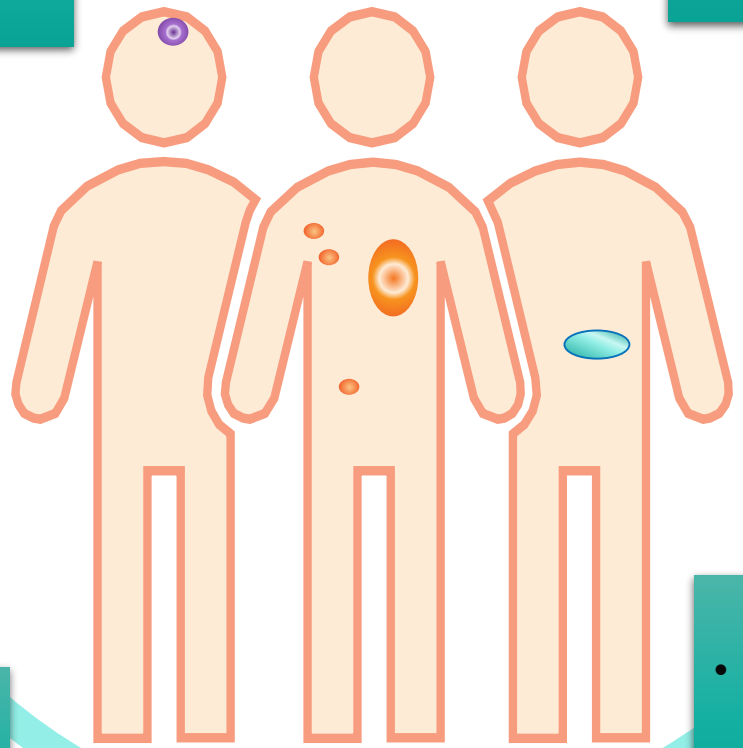
- BT8009 shows good efficacy in a range of PDX and CDX models, with rapid regression in small and large tumours
  - Efficacy correlates with expression of the Nectin-4 target
  - PK shows retention of toxin in tumour, well in excess of systemic clearance
  - Toxicology studies with BT8009 are progress

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



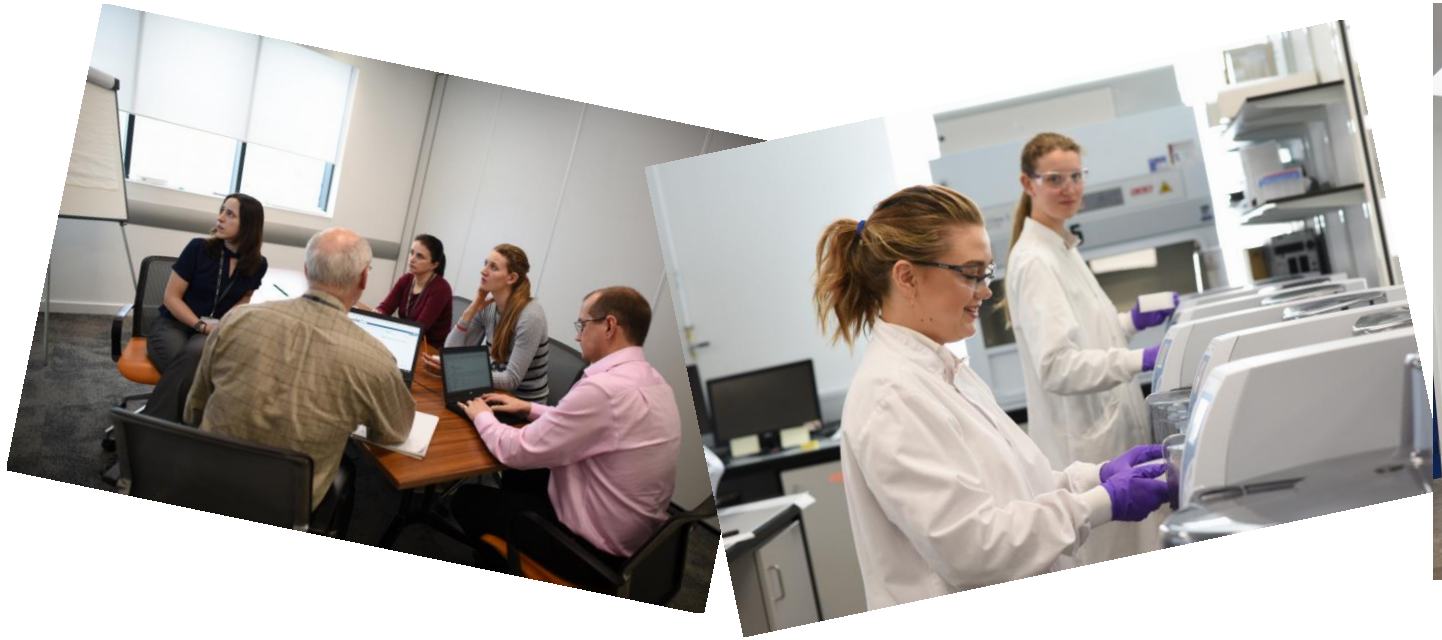
Actively suppress the immune system
- Multimeric immune receptor agonists
- Targeted systemic delivery of innate immune activators

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

- Team at Bicycle UK & US



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#NotWaiting