Constrained peptides
Unconstrained thinking

August 2019

bicycle
therapeutics

Forward-looking statements

This presentation may contain forward-looking statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. These statements may be identified by words such as "aims," "anticipates," "believes," "could," "estimates," "expects," "forecasts", "goal," "intends," "may" "plans," "possible," "potential," "seeks," "will," and variations of these words or similar expressions that are intended to identify forward-looking statements. All statements other than statements of historical facts contained in this presentation are forward-looking statements, including statements regarding our future financial or business performance, conditions, plans, prospects, trends or strategies and other financial and business matters; our current and prospective product candidates, planned clinical trials and preclinical activities, current and prospective collaborations and the timing and success of our development of our anticipated product candidates.

Forward-looking statements are neither historical facts nor assurances of future performance. Instead, they are based on our current beliefs, expectations and assumptions regarding the future of our business, future plans and strategies, our development plans, our preclinical and clinical results and other future conditions, and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include, but are not limited to, the risk that any one or more of our product candidates will not be successfully developed or commercialized, the risk of cessation or delay of any ongoing or planned clinical trials, the risk that we may not realize the intended benefits our technology, including that we may not identify and develop additional product candidates for our pipeline, the risk that we may not maintain our current collaborations or enter into new collaborations in the future, or that we may not realize the intended benefits of these collaborations, the risk that our product candidates or procedures in connection with the administration thereof will not have the safety or efficacy profile that we anticipate, the risk that prior results will not be replicated or will not continue in ongoing or future studies or trials, the risk that we will be unable to obtain and maintain regulatory approval for our product candidates, the risk that the size and potential of the market for our product candidates will not materialize as expected, risks associated with our dependence on third-parties, risks regarding the accuracy of our estimates of expenses, risks relating to our capital requirements and needs for additional financing, and risks relating to our ability to obtain and maintain intellectual property protection for our product candidates. For a discussion of these and other risks and uncertainties, and other important factors, any of which could cause our actual results to differ from those contained in the forward-looking statements, see the section entitled "Risk Factors" in our final prospectus for our initial public offering filed with the Securities and Exchange Commission on May 23, 2019, as well as discussions of potential risks, uncertainties and other important factors in our subsequent filings with the Securities and Exchange Commission. New risks and uncertainties may emerge from time to time, and it is not possible to predict all risks and uncertainties. Except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise.

Leadership

Executive Team

Kevin Lee, Ph.D., MBA

Chief Executive Officer

Lee Kalowski, MBA

President and Chief Financial Officer

Nick Keen, Ph.D.

Chief Scientific Officer

Pete Leone, MBA

Chief Business Officer

Michael Skynner, Ph.D.

Chief Operating Officer

Veterans in drug development with executive experience at leading pharmaceutical companies

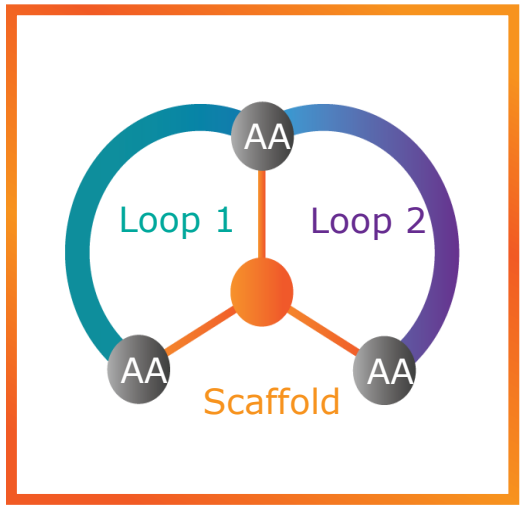
Investment highlights

- Novel class of drug based on innovative science from Nobel laureate Sir Greg Winter and Professor Christian Heinis
- Combines pharmacology of biologics with the manufacturing and pharmacokinetics of small molecules
- Novel and proprietary phage display screening enables rapid identification of candidates
- Proprietary oncology-focused pipeline includes one Phase 1/2a program, two programs in IND-enabling studies and two additional preclinical IO programs
- Several partnerships outside of oncology
- Extensive patent portfolio: 11 platform patent families; 63 bicyclic peptide and related conjugate patent families; 6 indication patent families – one patent expires in 2029, the remainder of the patents expire into the 2030s
- Funded by leading life sciences investors (cash at March 31, 2019 of $59.4m)

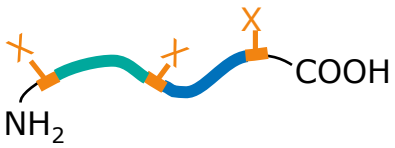
Preliminary Phase 1 data from our proprietary lead compound and Phase 2 start expected in 2H'19

Bicycles®: a new therapeutic modality

- Chemically synthesized, Low MWt (1.5-2kDa)
- Constrained peptide backbone enables high affinity, high selectivity
- Attractive PK and rapid tissue penetration
- Footprint allows targeting of protein-protein interactions
- Renal elimination supports a favorable toxicity profile

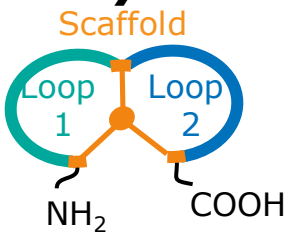


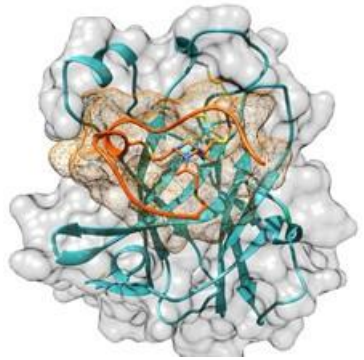
Linear peptide

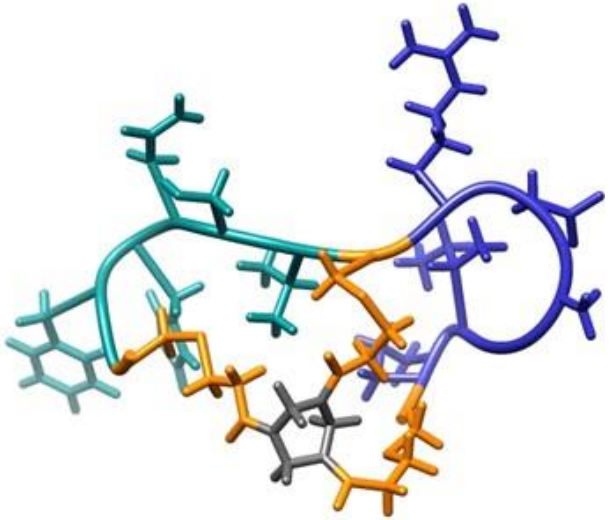


Chemical modification with scaffold

Bicycle



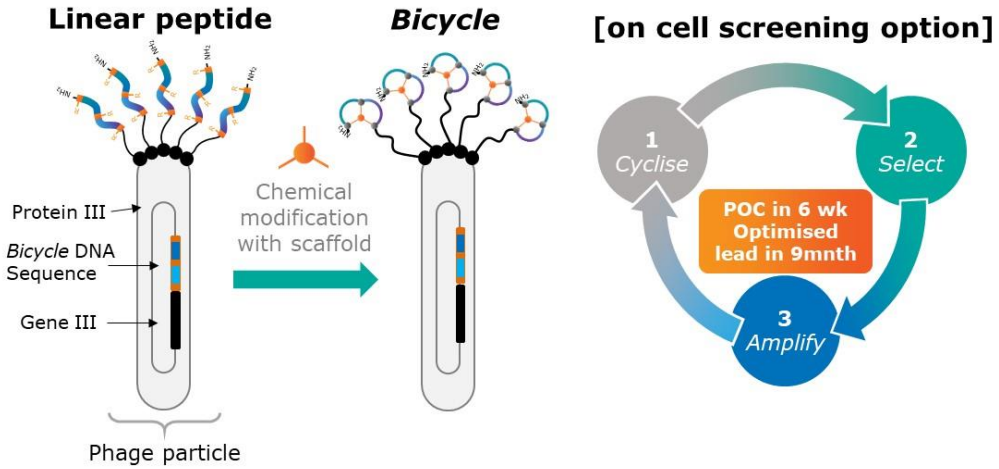




bicycle therapeutics

Proprietary screening platform: *Bicycles*® optimised using phage display and medicinal chemistry, informed by structural biology

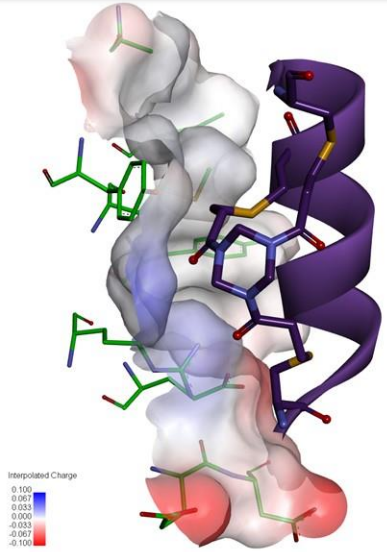
Bicycle Phage Display



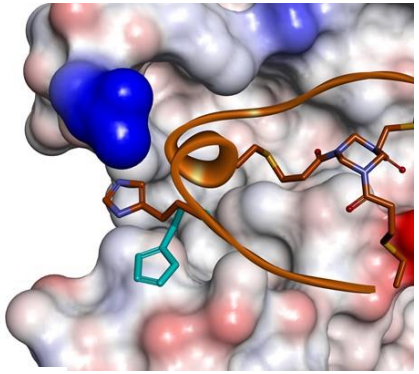
Optimize binder & capture IP

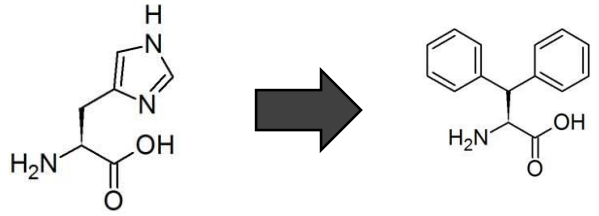
Natural Amino Acids

Structural Biology



Peptide & Medicinal Chemistry





Histidine
Ki=11nM

3,3-diphenylalanine (3,3-DPA)
Ki=0.9nM

Dial in desired drug-like properties and PK profile

Non-natural Amino Acids

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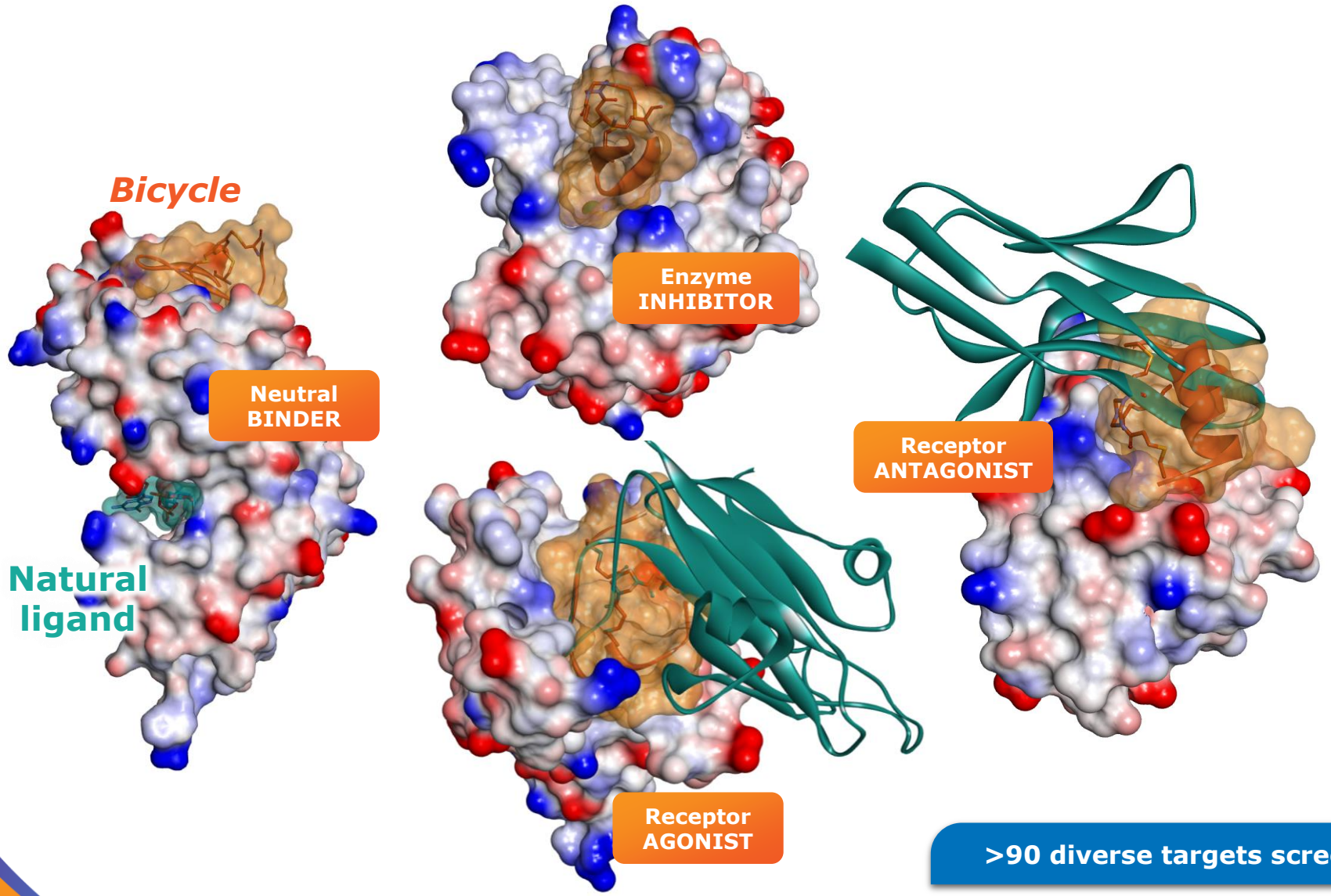
Bicycles® can deliver distinct modes of action

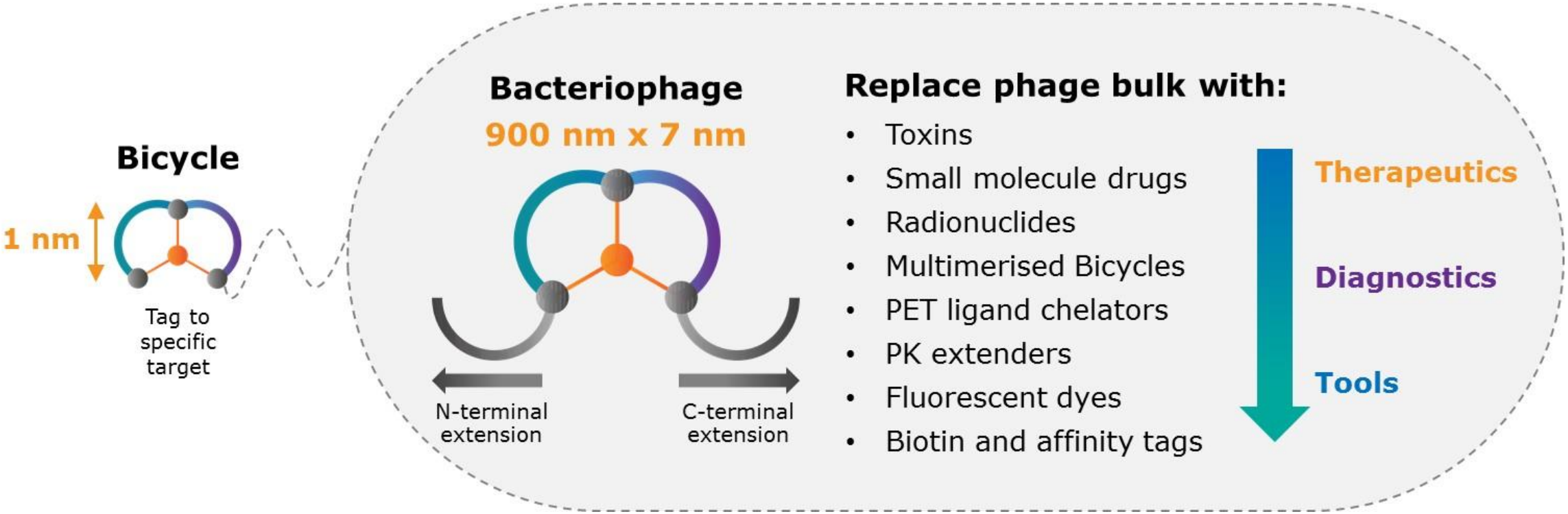


Tractable target classes	
Enzymes	Serine proteases
	Other proteases
	Metalloenzymes
	Matrix metalloproteinases
	Coagulation factors
	Other enzymes
Immune checkpoint	TNFR superfamily members
	IG domain receptors
Signalling	Receptor Tyrosine kinases
	Interleukin receptors
	Interleukins
	Growth Factors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

>90 diverse targets screened

bicycle therapeutics

Bicycles® have built-in tolerance to conjugation



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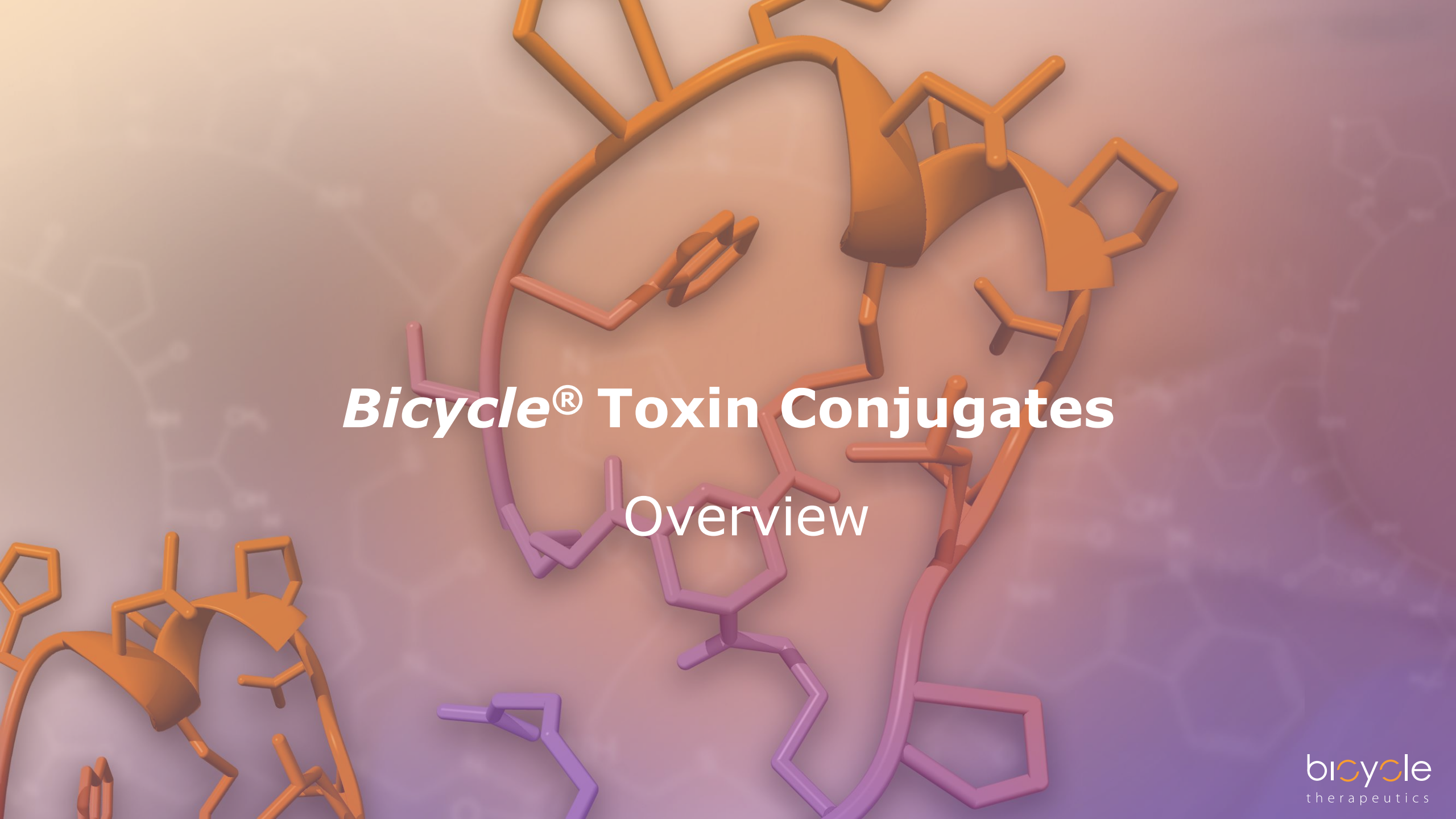
Robust proprietary and partnered pipeline

Product/Target	Interest		Stage
Bicycle Toxin Conjugates			Discovery/Preclinical → Clinical
BT1718 (MT1-MMP)	Oncology	CANCER RESEARCH UK	
BT5528 (EphA2)	Oncology		
BT8009 (Nectin-4)	Oncology		
Bicycle targeted STING activator	Oncology		
T-Cell Modulators			
CD137 *multimers*	Oncology		
CD137 bi-specifics	Oncology		
Beyond Oncology			
THR-149 (Kallikrein inhibitor *Bicycle*)	Ophthalmology (DME)	OXURION	
Inhaled *Bicycles*	Respiratory	AstraZeneca	
Cardiovascular Targeting *Bicycles*	Cardiovascular	AstraZeneca	
Hematology Targeting *Bicycles*	Non malignant hematology	Bioverativ A SANOFI COMPANY	
Novel anti-bacterials	Anti-infectives	Innovate UK	
Novel CNS targets	CNS diseases	Dementia Discovery Fund	



Bicycle® Toxin Conjugates

Overview

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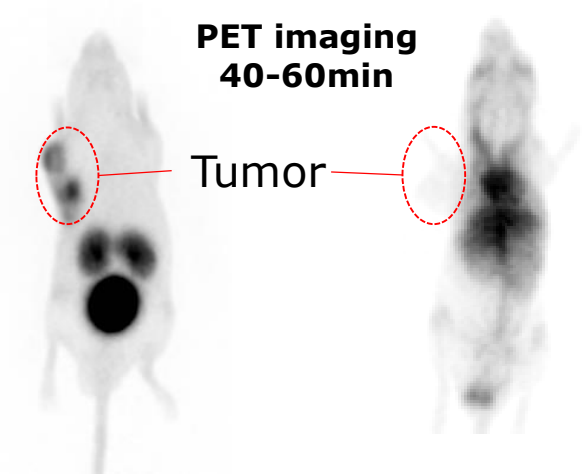
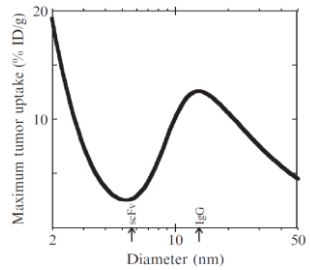
Bicycles® are optimized to be an ideal delivery system in oncology

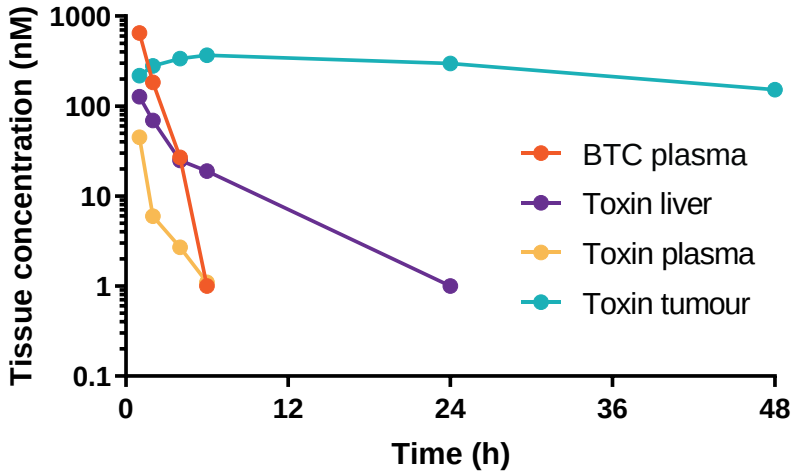
Favorable distribution



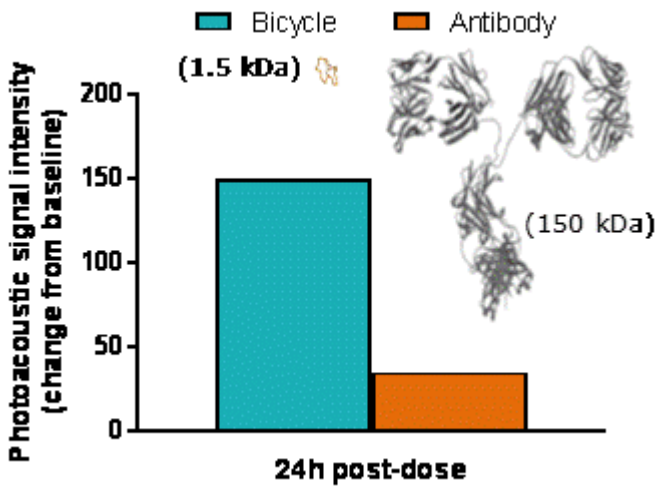


Wittrup, et al., (2012) *Meth. Enzymol.* **503**, 255–68

Minimal systemic exposure



Penetration & retention

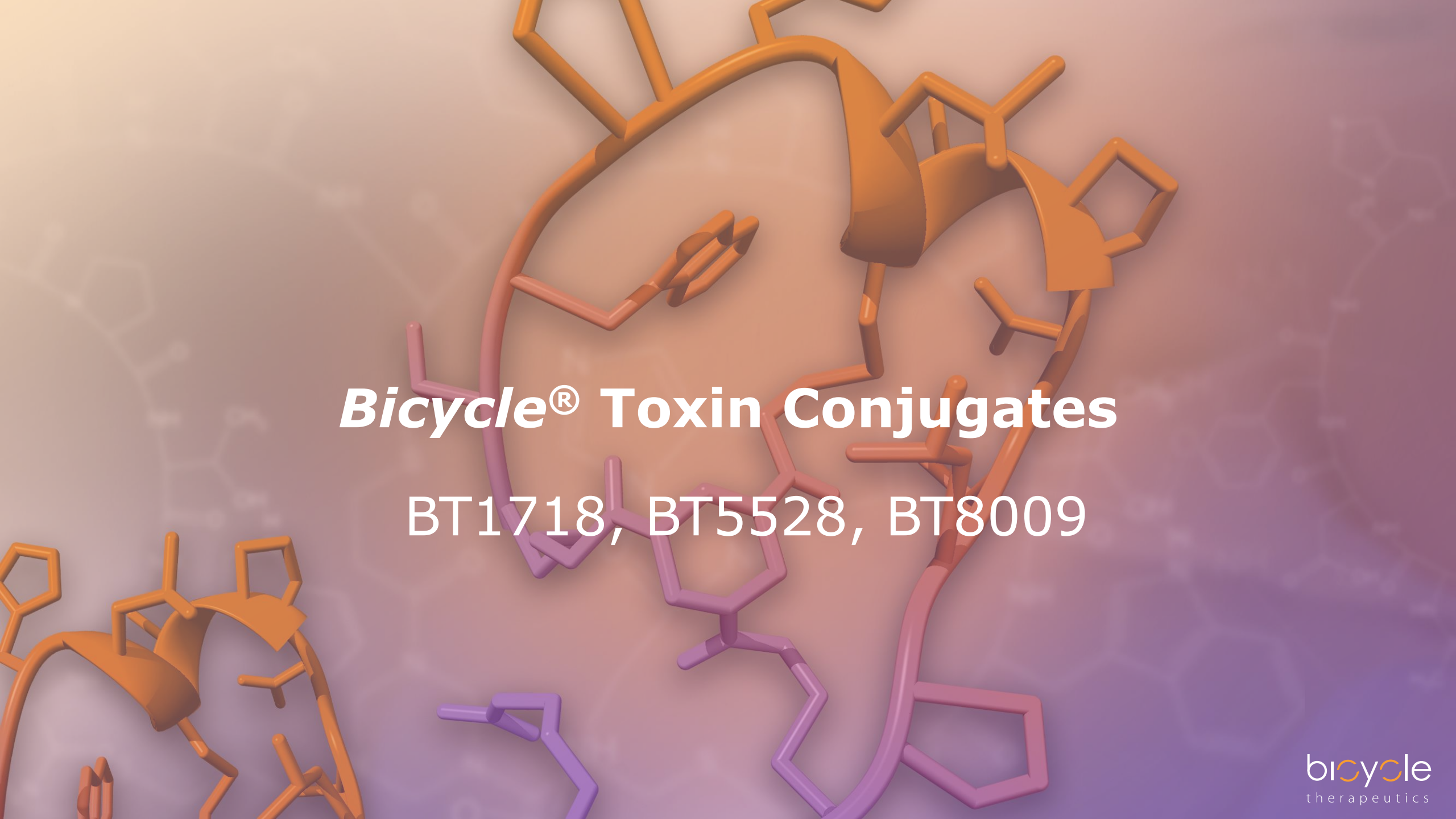


Favorable activity & toxicity

bicycle therapeutics

Bicycle® Toxin Conjugates

Extensive & rapid tumor penetration	• BTCs penetrate tumors more rapidly and exhibit increased penetration to poorly perfused regions of the tumor
Retention in tumors	• In preclinical studies a tumor antigen targeting *Bicycle* was observed to be retained in the tumor for 24 hours after dosing
Short systemic half-life & renal elimination	• Short systemic half-life of approximately 20-30 minutes • Due to their small size, *Bicycles* are able to exit the tissue rapidly and are excreted through the kidneys rather than the liver
No requirement for internalization	• BTCs do not require internalization into the cell and therefore potentially can target a wider range of tumor antigens
Access to non-expressing tumor cells	• Toxin in BTCs is liberated in the extracellular space, enabling cell-killing adjacent cells that do not express the specific target through a toxin bystander effect
Larger toxin payload	• BTCs are able to carry a larger dose of toxin per unit mass than a comparator ADC
Manufacturing	• Fully synthetic manufacturing process facilitates ease and consistency of manufacturing and improved formulation



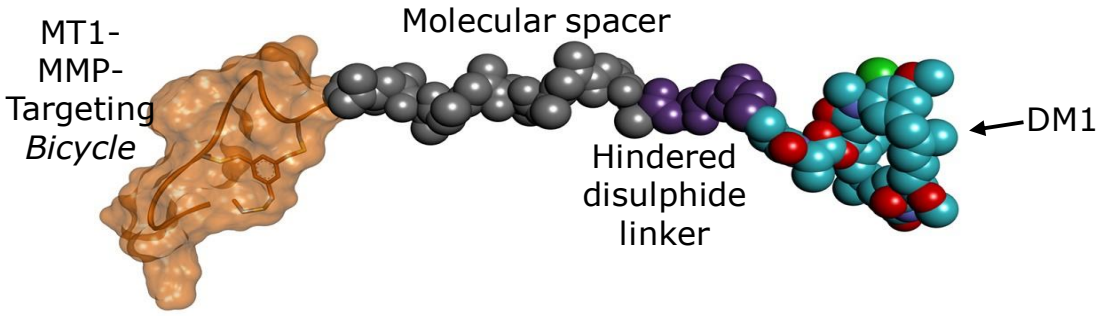
Bicycle® Toxin Conjugates

BT1718, BT5528, BT8009

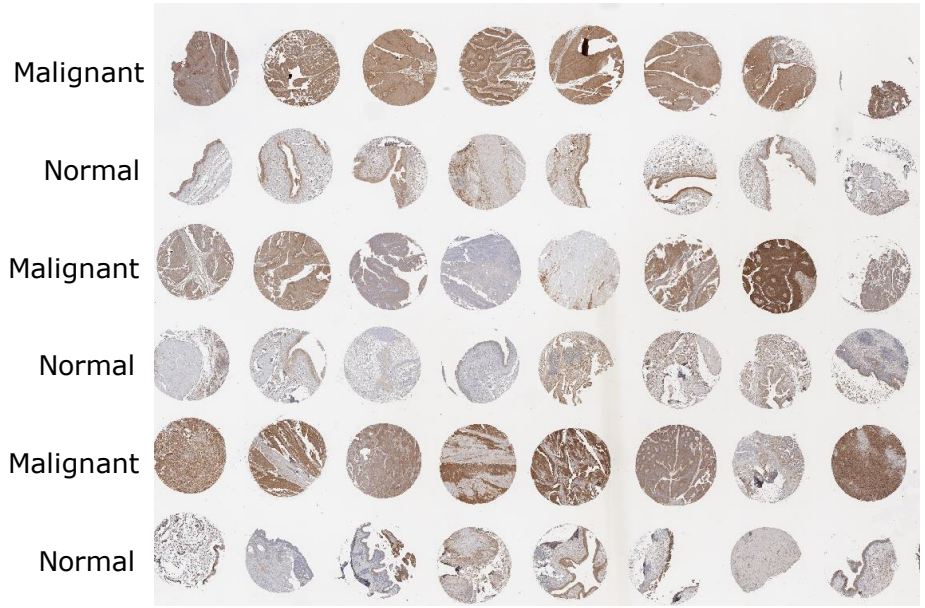
bicycle therapeutics

BT1718: MT1-MMP targeting *Bicycle*® toxin conjugate

- Highly selective for MT1-MMP (MMP-14), a cell-surface matrix metalloprotease with an established role in cell invasion and metastasis
- MT1-MMP is overexpressed in many tumor types eg lung, breast, bladder, gastric, head and neck, fibrosarcoma



Example of Tissue Microarray:
MT1-MMP expression in bladder cancer

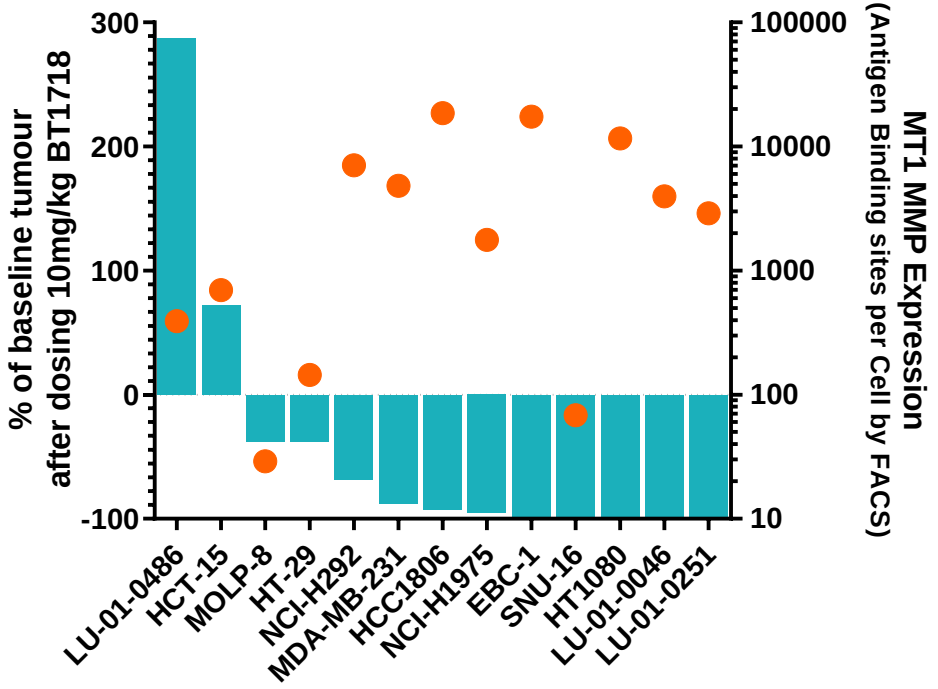


Tumor Type	Number of cases tested	MT1-MMP positive*
Endometrial cancer	15	**100%**
Ovarian cancer	312	**96%**
Bladder cancer	22	**95%**
Triple negative breast cancer	41	**76%**
Non-small cell lung cancer	151	**58%**
Esophageal cancer	191	Pending

*MT1-MMP expression was determined using IHC performed with in house validated antibody, positive cases were defined as H-score ≥ 50 in either tumor cell membrane or in stroma

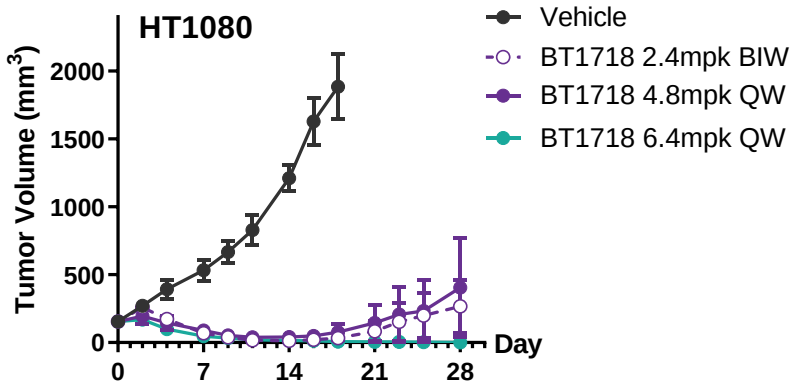
BT1718 reduces tumor volume when dosed in combination or as monotherapy

Broad activity in MT1-MMP expressing xenografts

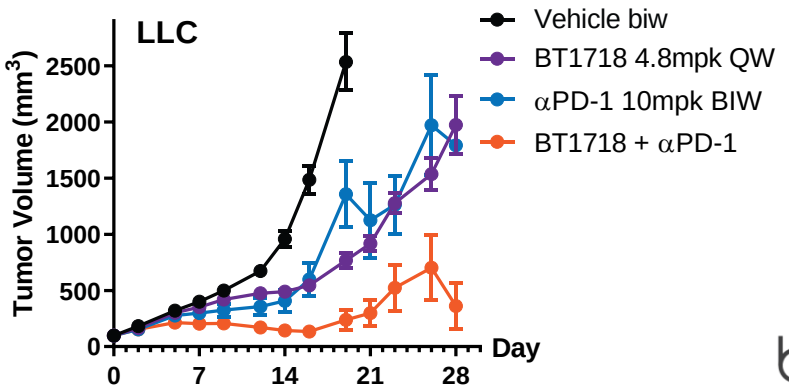


Mouse dose	Human equivalent dose
4.8 mpk	14.4 mg/m^2
6.4 mpk	19.2 mg/m^2
9.6 mpk	28.8 mg/m^2

Minimal dose for full activity in xenografts is 6.4mg/kg ow



Synergistic activity with CPI's



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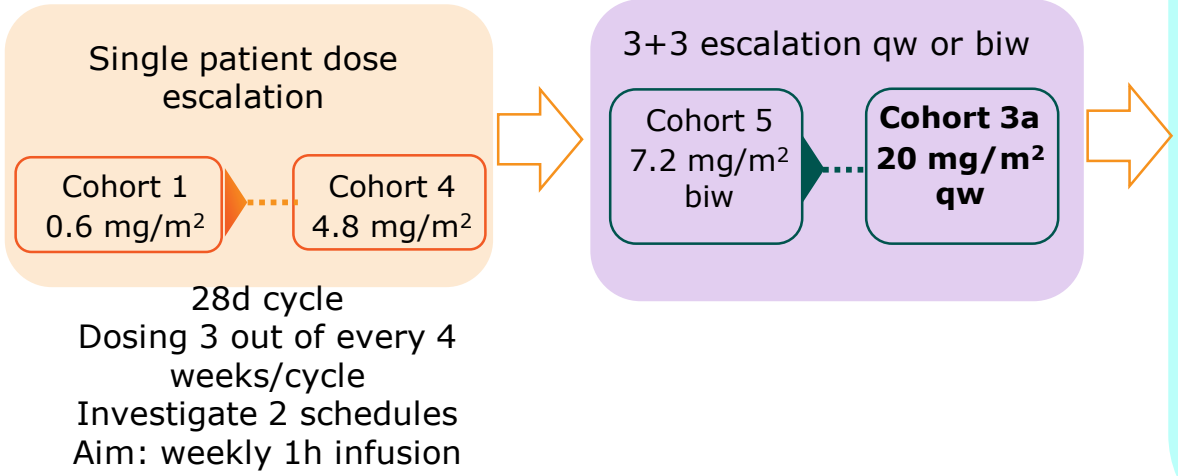
BT1718 is achieving its Phase 1 objectives

Phase 1 objectives: safety, determine Phase 2 dose, PK, platform validation in non preselected advanced stage solid tumors



For weekly dose schedules, tolerability was generally favorable. As of May 9, 2019:

9.6 mg/m² qw: Two patients left the study due to disease progression and one patient continues to have stable disease through completion of cycle 6

15 mg/m² qw: 2/3 patients had stable disease at end of cycle 2. One patient of three continues to have stable disease through cycle 4

20 mg/m² qw: 2/2 patients had stable disease at end cycle 2. One patient subsequently left study due to disease progression

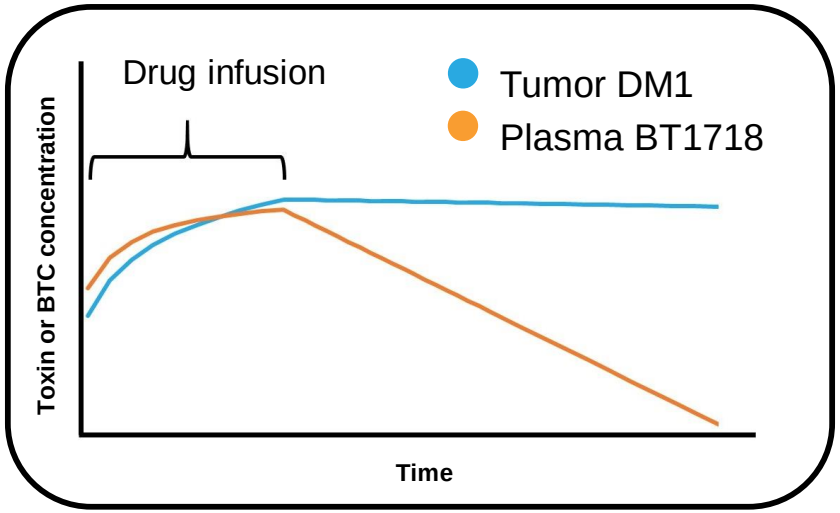
Platform Validation

- $T_{1/2}$ as predicted ✓
- V_D as predicted ✓
- PK linear over time ✓
- DM1 delivered >4X ADC ✓
- No dose limiting liver/GI toxicity ✓
- No renal toxicity ✓
- Serum biomarker response ✓
- Selective tumor accumulation ✓

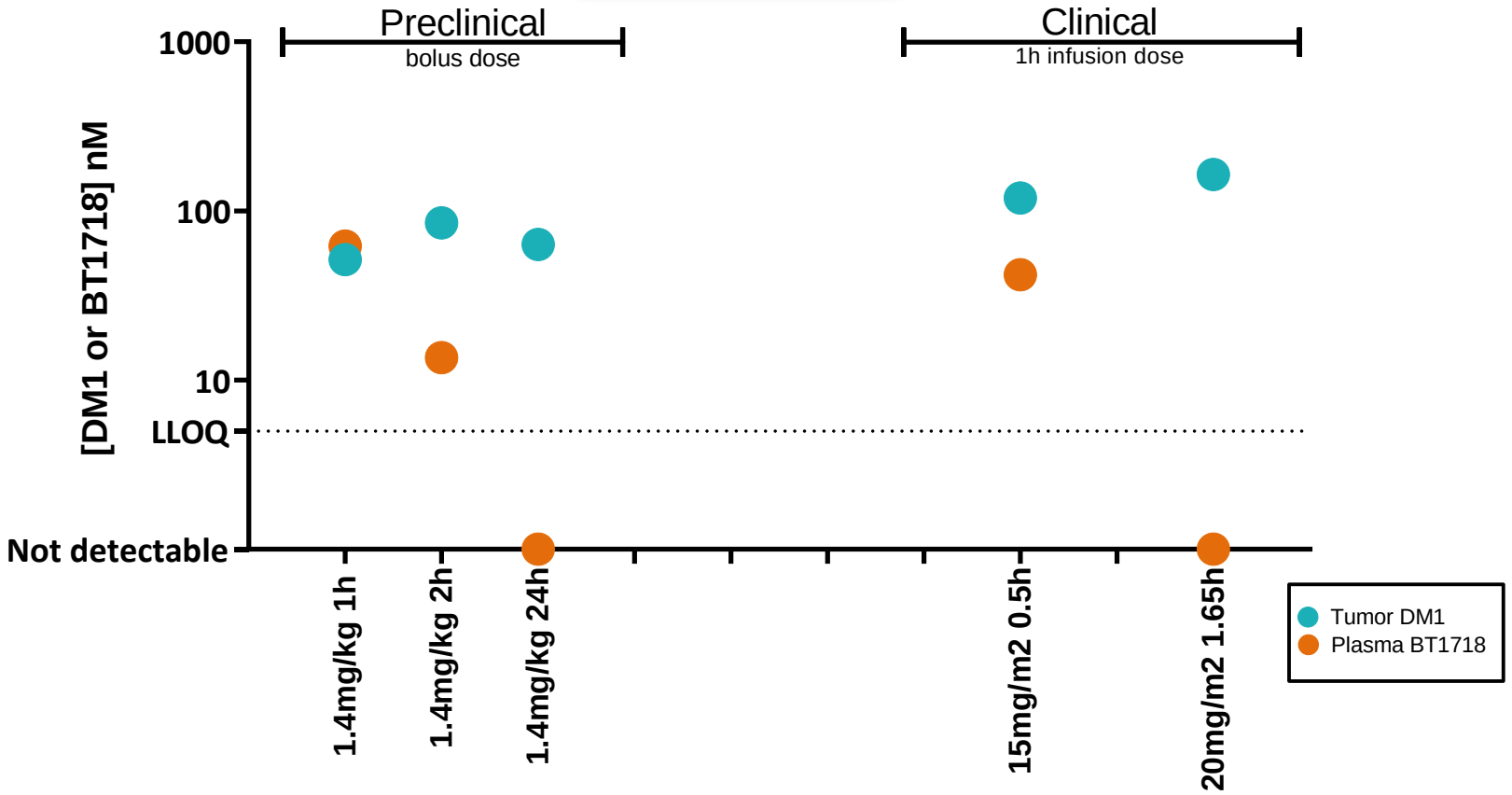
- RP2D ongoing
- Tumor selection ongoing

Early clinical biopsy data validates the *Bicycle*® platform as a vehicle for selective delivery of payload to tumors

Predicted



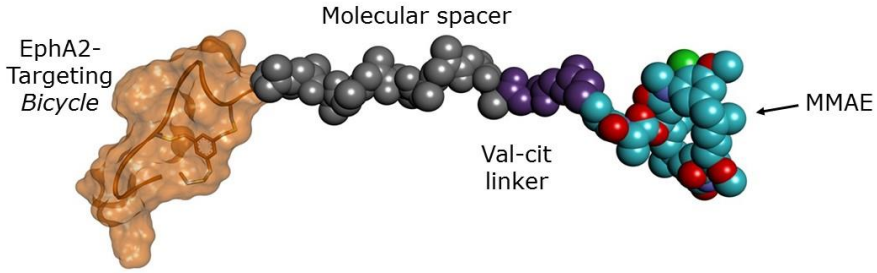
Observed



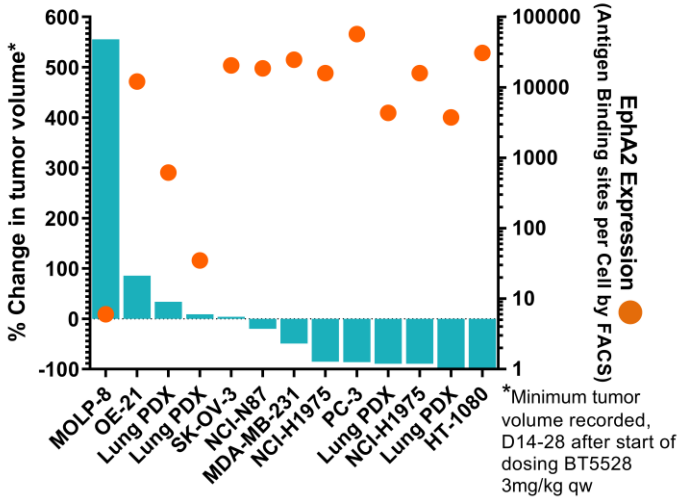
bicycle therapeutics

BT5528 offers a differentiated approach to EphA2

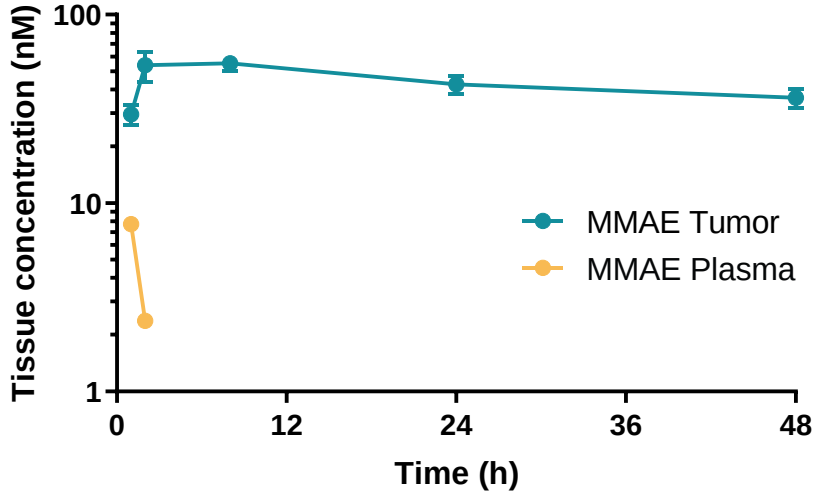
- Highly attractive target
  - Multiple antibody projects have failed due to toxicity
- EphA2 regulates cell migration, adhesion proliferation and differentiation
- Overexpression in many difficult to treat tumors (e.g. lung, breast, bladder, ovarian, endometrial, cervical, melanoma, glioma). Elevated EphA2 is often correlated with poor prognosis and/or treatment resistance



Broad activity in EphA2 expressing xenografts



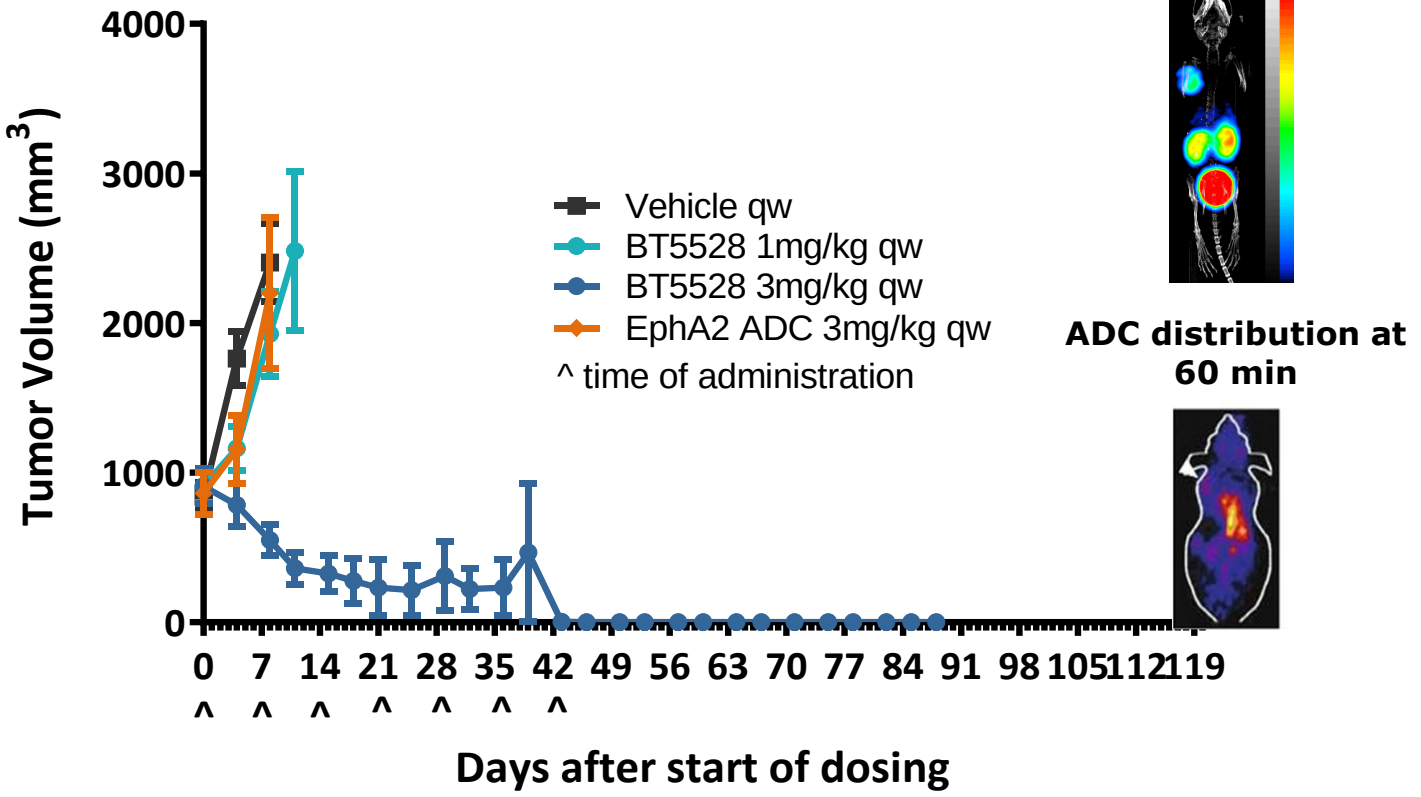
Efficiently delivered MMAE to tumor



bicycle therapeutics

BT5528 showed activity in difficult to treat xenograft models

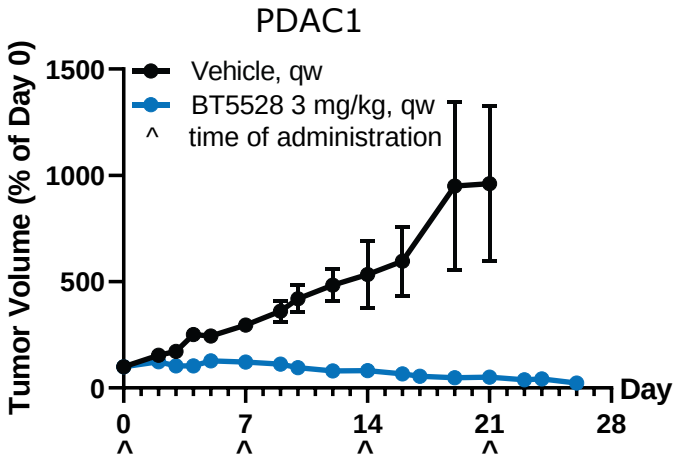
Displayed superior activity to EphA2 ADC in large tumor xenografts

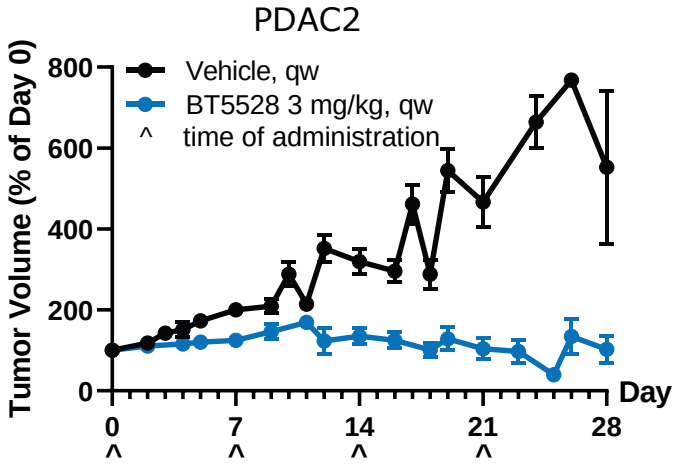


***Bicycle* distribution at 60 min**

ADC distribution at 60 min

Activity in pancreatic xenograft models





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Toxicology studies support EphA2 as a target that can be addressed in the *Bicycle*® format

Findings from MEDI-547 Phase 1 study

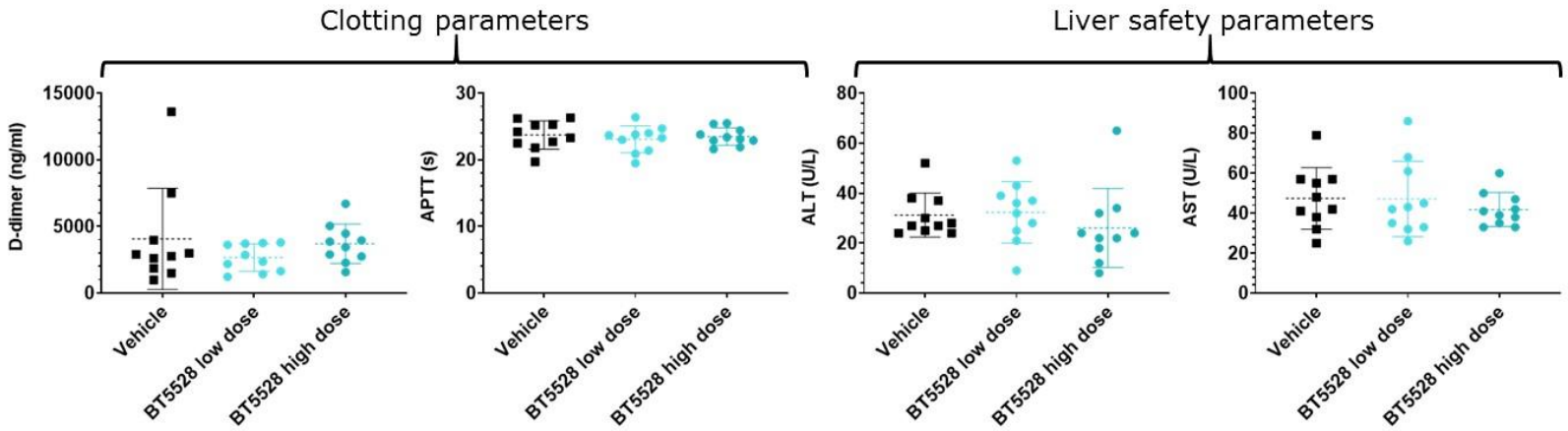
Phase 1, open-label study of MEDI-547 in patients with relapsed or refractory solid tumors

Christina M. Annunziata · Elise C. Kohn · Patricia LoRusso · Nicole D. Houston · Robert L. Coleman · Manuela Buzoianu · Gabriel Robbie · Robert Lechleider

Treatment related adverse events	# events (% of patients) n of total
ALT increased	3 (50) 3/6
Haemorrhage	6 (83.3) 5/6

MEDI-547 was originally developed by MedImmune LLC and development was abandoned

Findings from BT5528 Primate GLP toxicology study



- Dosing: no bleeding events in primates at toxin equivalent doses >150 fold higher than the clinical dose of MEDI-547 used in patients
- No significant effect on clotting parameters
- No evidence of abnormal liver function

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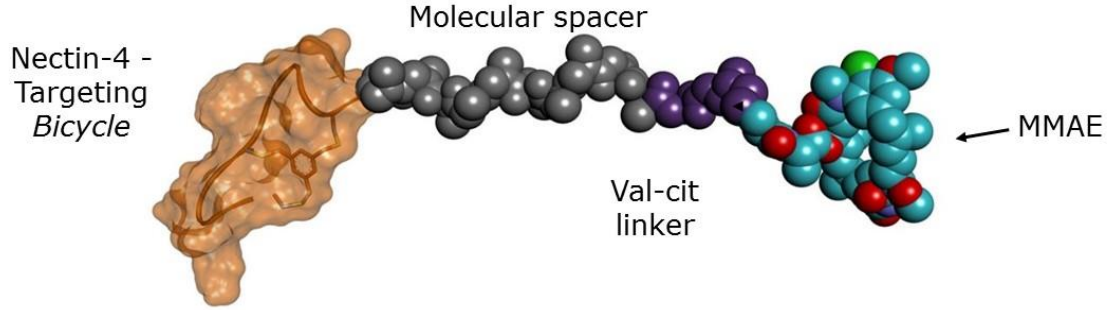
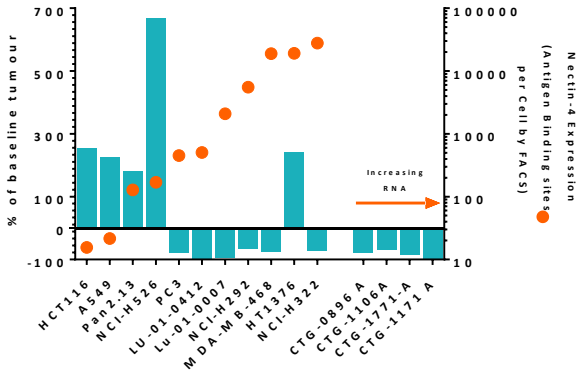
BT8009 targets Nectin-4

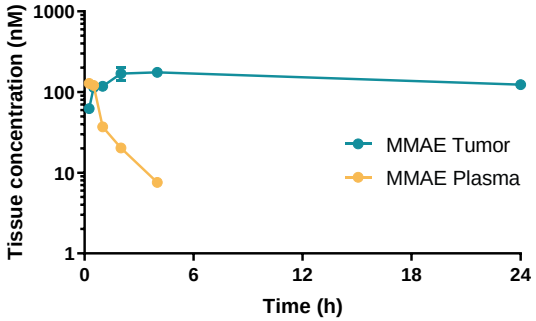
- Highly attractive target
  - POC provided by enfortumab vedotin (Astellas/SeaGen) MMAE containing ADC awarded "breakthrough designation" for metastatic urothelial cancer (now Phase 3)
- Overexpression in several human cancers (e.g. bladder, breast, gastric, lung and ovarian), involved in establishing cell-cell contact and tumor cell survival. Often correlated with poor prognosis



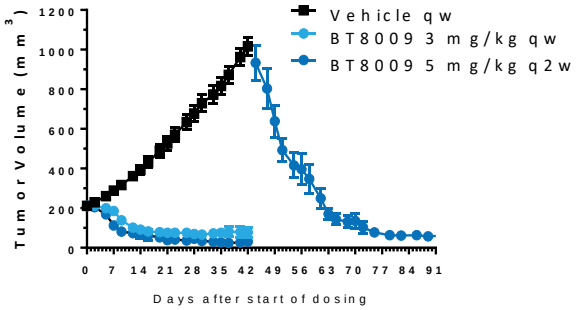
Broad spectrum of activity



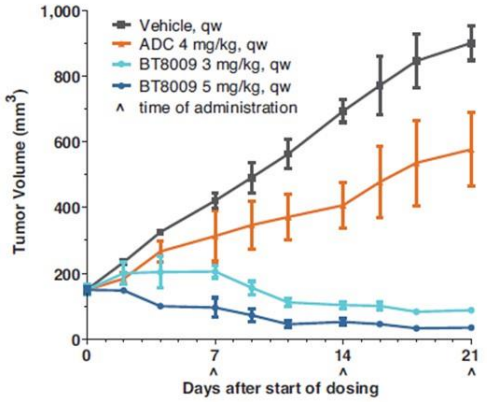
Efficient toxin delivery to tumor

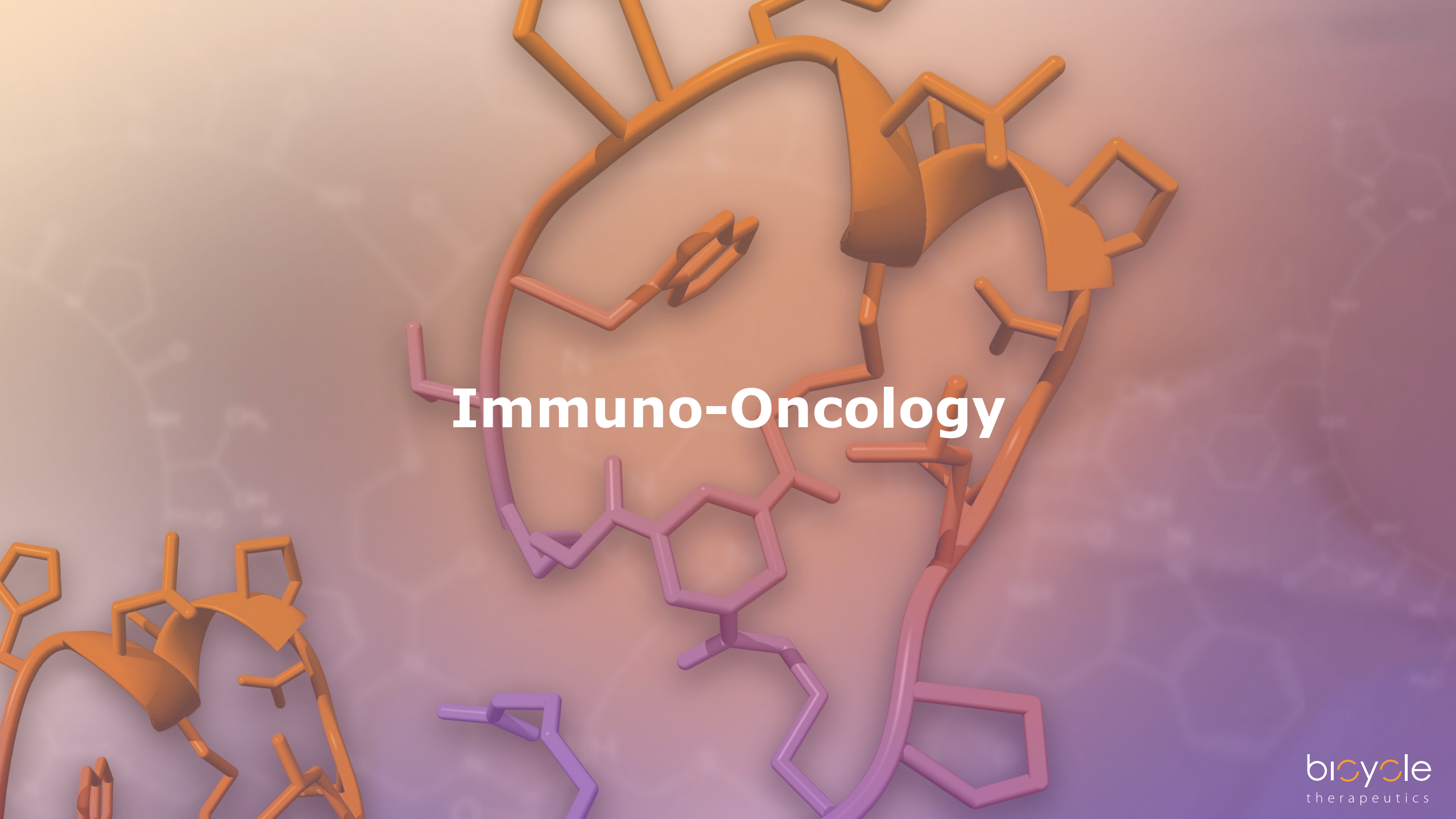


Active against large tumors



Improved activity over Nectin-4 ADC





bicycle
therapeutics

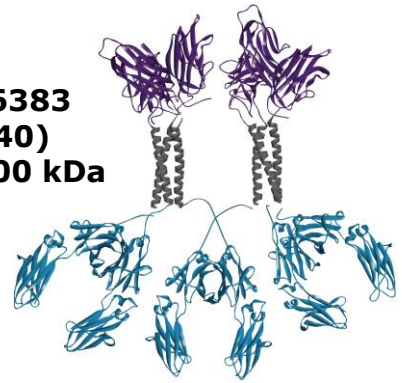
Bicycles® are the ideal modality to modulate T-cells

- We believe we are the **only** company that has fully chemically synthetic CD137 agonists

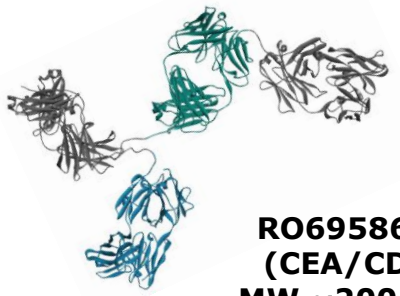
- We believe we are the **only** company that has fully chemically synthetic bi-specifics, can produce them rapidly, and apply the power of medicinal chemistry to them

- We believe this is generalizable and has the potential to generate multiple programs

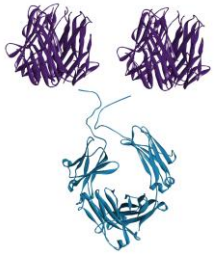
Bicycles® vs. biologics as T-cell modulators



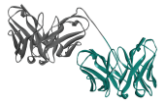
Medi6383 (OX40) MW ~300 kDa



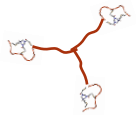
RO6958688 (CEA/CD3) MW ~200 kDa



CD137-HERA MW ~170 kDa



Blincyto MW ~54 kDa



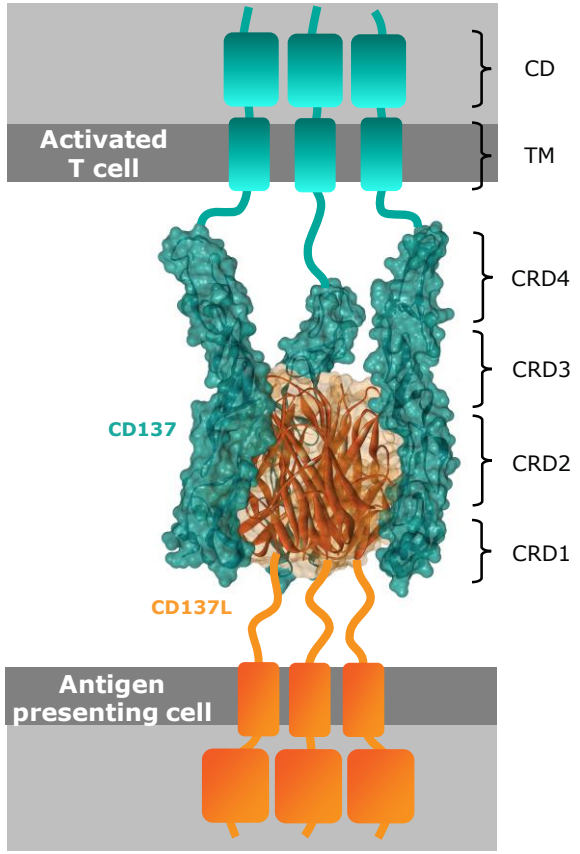
CD137 Bicycle trimeric agonist MW ~10 kDa

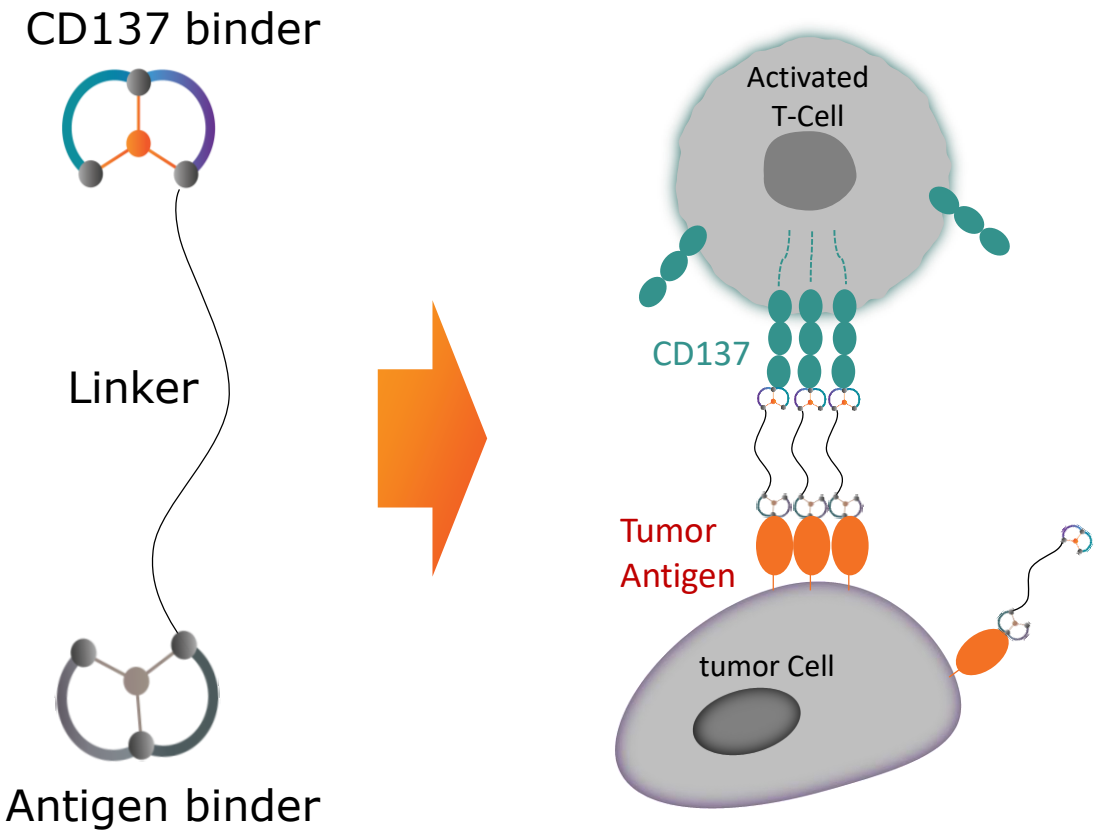
Nectin-4-CD137 Bicycle bi-specific MW ~6 kDa

Limitations of multivalent and bi-specific biologics	*Bicycles* potentially overcome these limitations
Pharmacology	
• Very large molecules: (~150-350 kDa) for multimeric; ~40-200 kDa for bi-specific • Limits on presentation of binding domain to the target results in fixed orientation • Difficult to make a molecule bind to more than two targets • High chance for immunogenicity as the size and complexity increase	• Very small: (~9-15 kDa) for multimeric; ~3.5-5 kDa for bi-specific • Linkage through various sites of attachment allows presentation of binder in various orientations • Easy to make tri- and tetrameric molecules • Immunogenicity unlikely—multimeric molecules are still smaller than smallest monovalent antibody
Manufacturing	

• Low yield (even for research scale ~10 mg)
  • Requires another optimization of the molecule even if the parent molecules are fully optimized
• Increase in heterogeneity
  • Requires more controls and stringent potency assays
	• Simple chemical synthesis
	• Chemically defined, new chemical entity

Bi-specific tumor/CD137 binding *Bicycles*® are potent and targeted immune cell activators

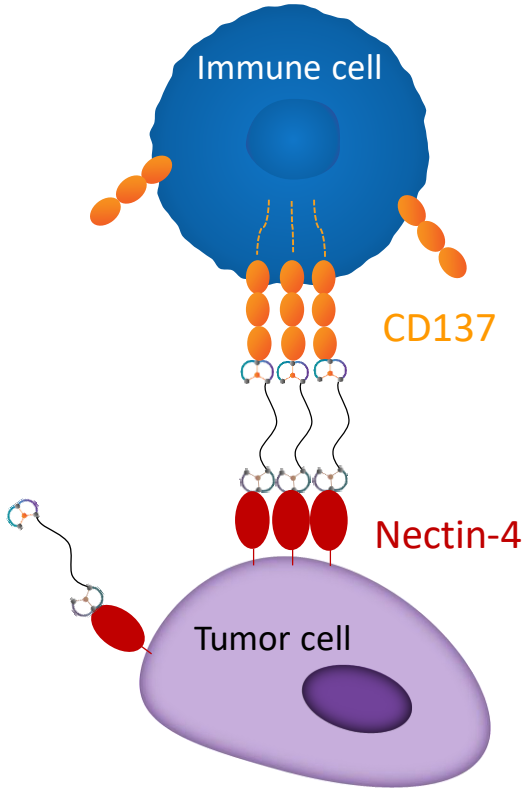




CD137 is a member of TNF superfamily & requires clustering for activation

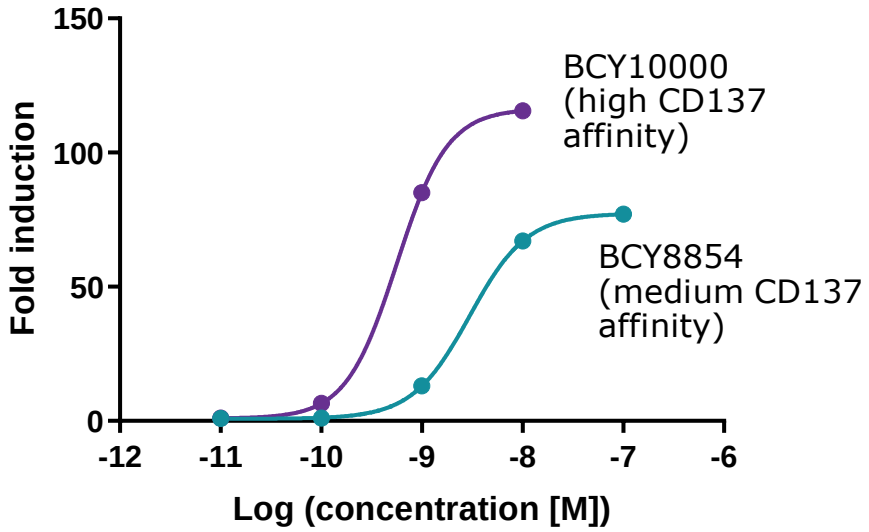
Fully synthetic molecules comprising CD137 and tumor antigen targeting *Bicycles*® could achieve potent CD137 activity through receptor cross-linking across the immune synapse

Nectin-4/CD137 bi-specifics are highly active in model systems

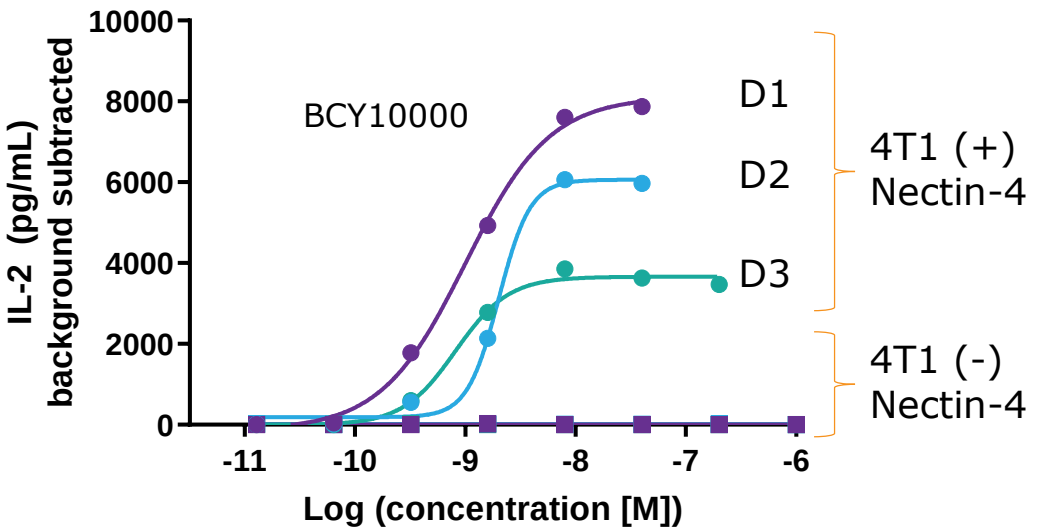


Cancer cell expressing high levels of Nectin-4

Reporter cell assay

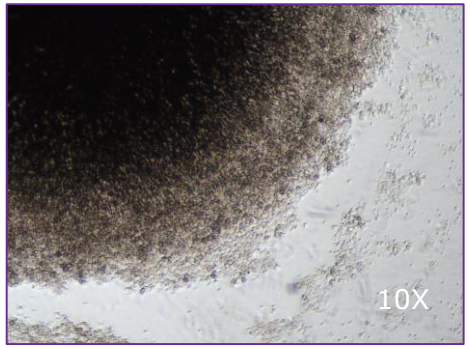


Primary human cell assay



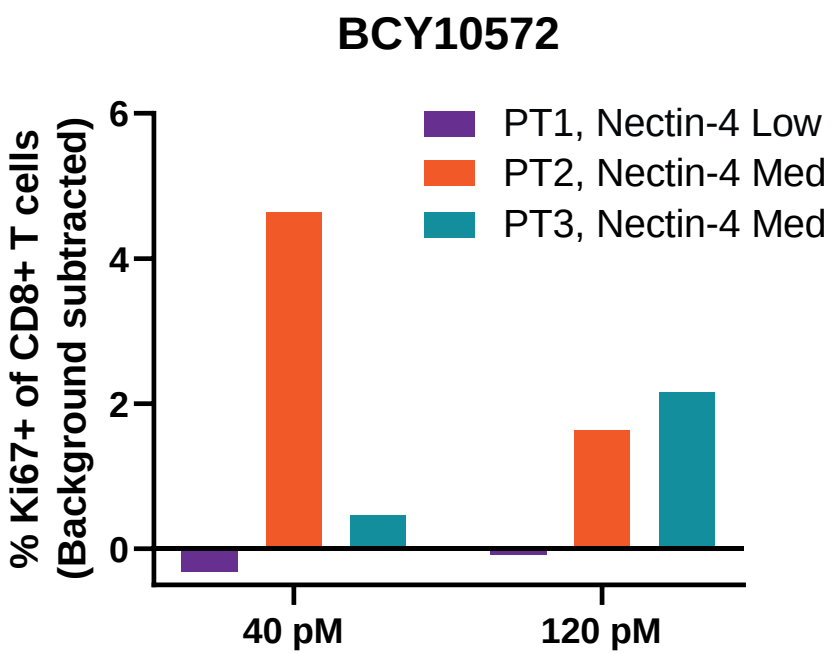
bicycle therapeutics

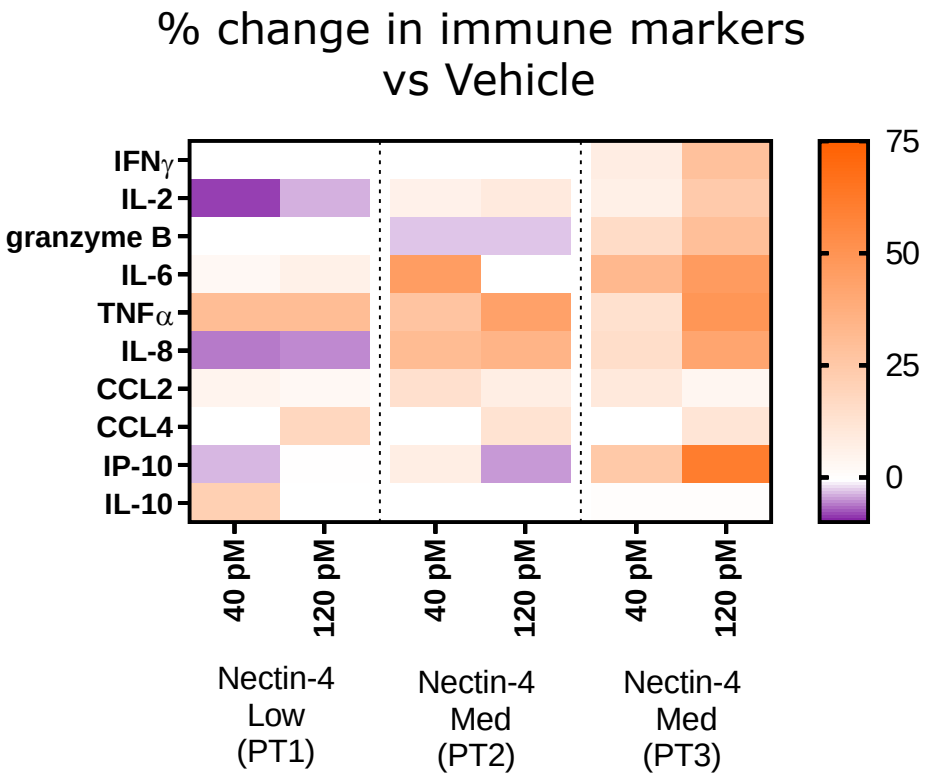
Nectin-4/CD137 bi-specific *Bicycles*® induce target dependent cytokine release in *ex-vivo* cultures of patient-derived lung tumors



ex vivo patient derived tumor cells form 3D spheroids within 4h in culture

	CD137+ T cells (%)	Nectin-4+ cells (%)
PT1	19.8	4.4
PT2	15.1	25.8
PT3	30.0	15.1

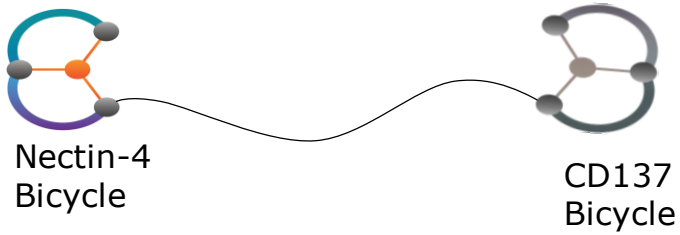




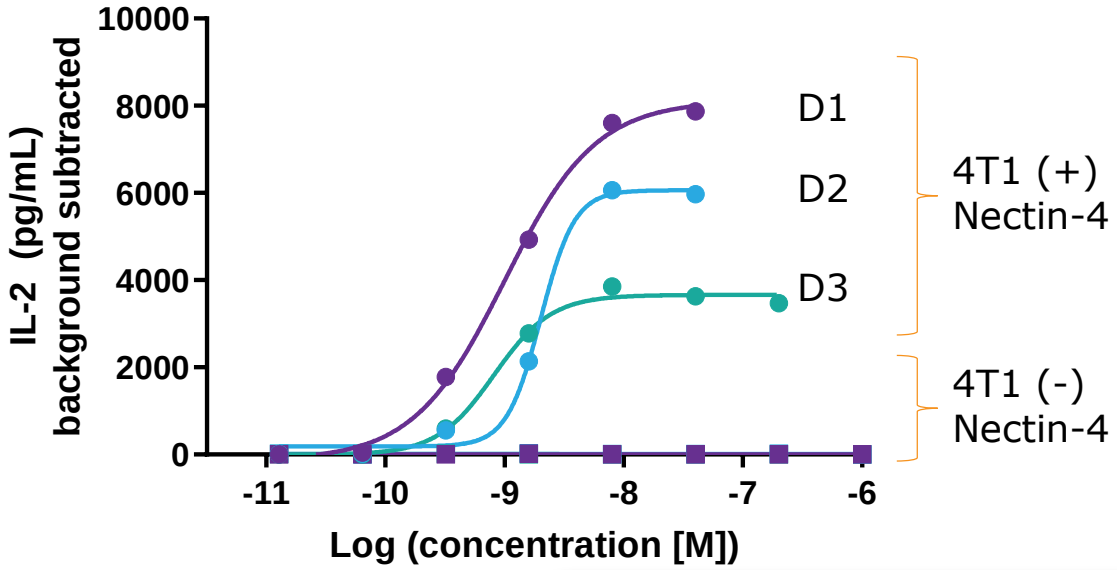
bicycle therapeutics

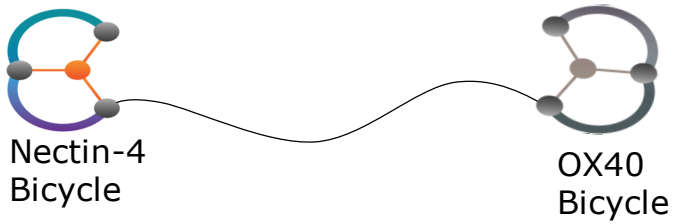
The approach is truly generalizable

Immune cell engaging *Bicycles*® and tumor antigen engaging *Bicycles*® can be readily switched

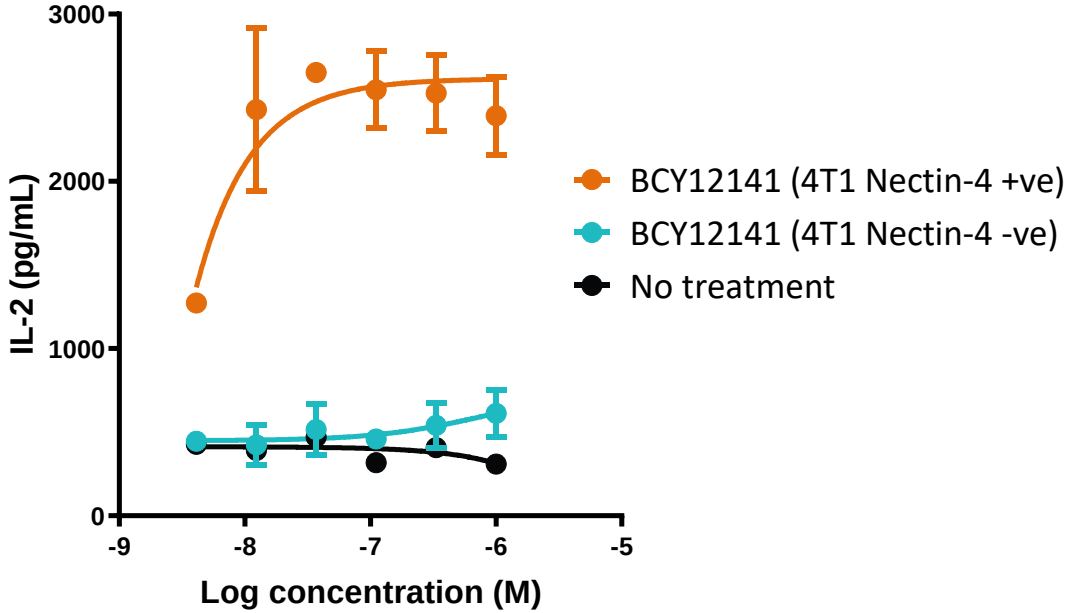


CD137 Bi-specific (BCY10000)





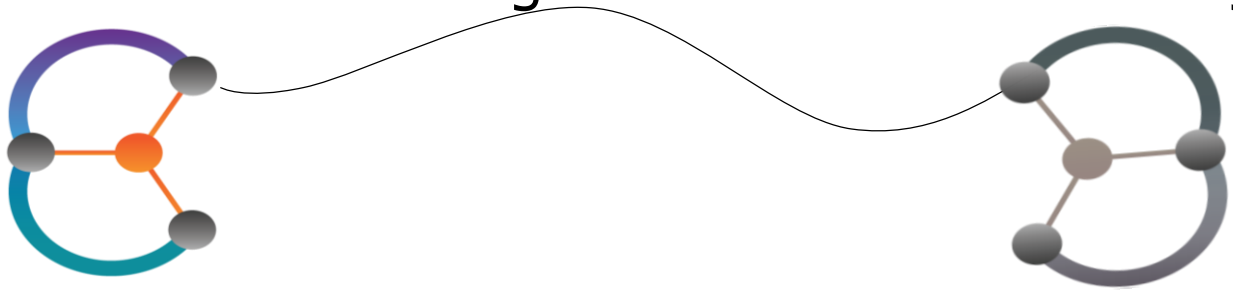
OX40 Bi-specific (BCY12141)



This has the potential to rapidly and efficiently generate multiple clinical candidates

Fully synthetic bi-specific platform enable a diverse pipeline with strong competitive advantages

- First focus on CD137 bi-specifics with pre-existing Nectin-4, PD-L1 and EphA2 tumor targeting *Bicycles*®
- New immune and tumor cell targets accessible and being screened



Immune Cell Targets
CD137*
OX40*
FCgRIIIA**
NKp46**
CD28
CD3
HVEM
GITR

Tumor Targets
Nectin-4*
PSMA*
PD-L1*
EphA2*
DLL3*
GCC**
Trop2*
EDNRB
NAPI2B
PTK7

*Fully developed Bicycle®
**screening initiated or ready to start

Aug 2019

bicycle therapeutics

Investment highlights

- Novel class of drug based on innovative science from Nobel laureate Sir Greg Winter and Professor Christian Heinis
- Combine pharmacology of biologics with the manufacturing and pharmacokinetics of small molecules
- Novel and proprietary phage display screening enables rapid identification of candidates
- Proprietary oncology-focused pipeline includes one Phase 1/2a program, two programs in IND-enabling studies and two additional preclinical IO programs
- Several partnerships outside of oncology
- Extensive patent portfolio: 11 platform patent families; 63 bicyclic peptide and related conjugate patent families; 6 indication patent families – one patent expires in 2029, the remainder of the patents expire into the 2030s
- Funded by leading life sciences investors (cash at March 31, 2019 of $59.4m)

Preliminary Phase 1 data from our proprietary lead compound and Phase 2 start expected in 2H'19