Constrained peptides
Unconstrained thinking

May 2021

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, our plans to initiate clinical trials and the designs of the planned trials 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, risks related to the ongoing COVID-19 pandemic, 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 of 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 Annual Report on Form 10-K, filed with the Securities and Exchange Commission (SEC) on March 11, 2021 as well as in other filings Bicycle may make with the SEC in the future, 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.

We aim to redefine what's possible for people with cancer and other serious diseases by pioneering a new and differentiated class of innovative treatments

Bicycles are a novel modality designed to address therapeutic needs unmet by conventional approaches

Exploring broad potential of novel technology in oncology & beyond through **partnerships**

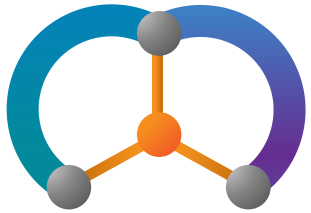
4 assets in Phase I/II trials, represent potential first-in-class / best-in-class medicines for oncology & ophthalmology*

Ophthalmology asset is partnered with Oxurion

Bicycles are a new therapeutic modality wholly-owned by Bicycle Therapeutics

Short linear peptide

Scaffold
Chemical modification with scaffold

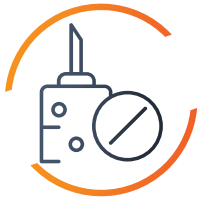


Bicycle®

	Chemical synthesis	Rapid tissue distribution	Complex protein targets druggable	Route of elimination
Bicycles	**+++**	**+++**	**+++**	**Renal**
Small molecules	+++	+++	—	Liver
Antibodies	—	+	+++	Liver

10^{17} molecules in screening platform

Robust patent protection with 103 patent families



Versatile platform, immense combinatorial potential

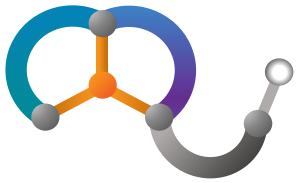
bicycle therapeutics

Business strategy designed to explore full potential of *Bicycle*® technology

Oncology

Bicycles are perfect for solid tumors:

- Selective, controlled delivery to tumor
- Small size
- Drug targets intractable to other modalities
- Renal elimination



Bicycle Toxin Conjugates

Tumor Targeted immune cell agonists (TICAs)

Other serious diseases

Exploring broad application of *Bicycles* beyond oncology through validating partnerships with leading therapeutic experts

AstraZeneca

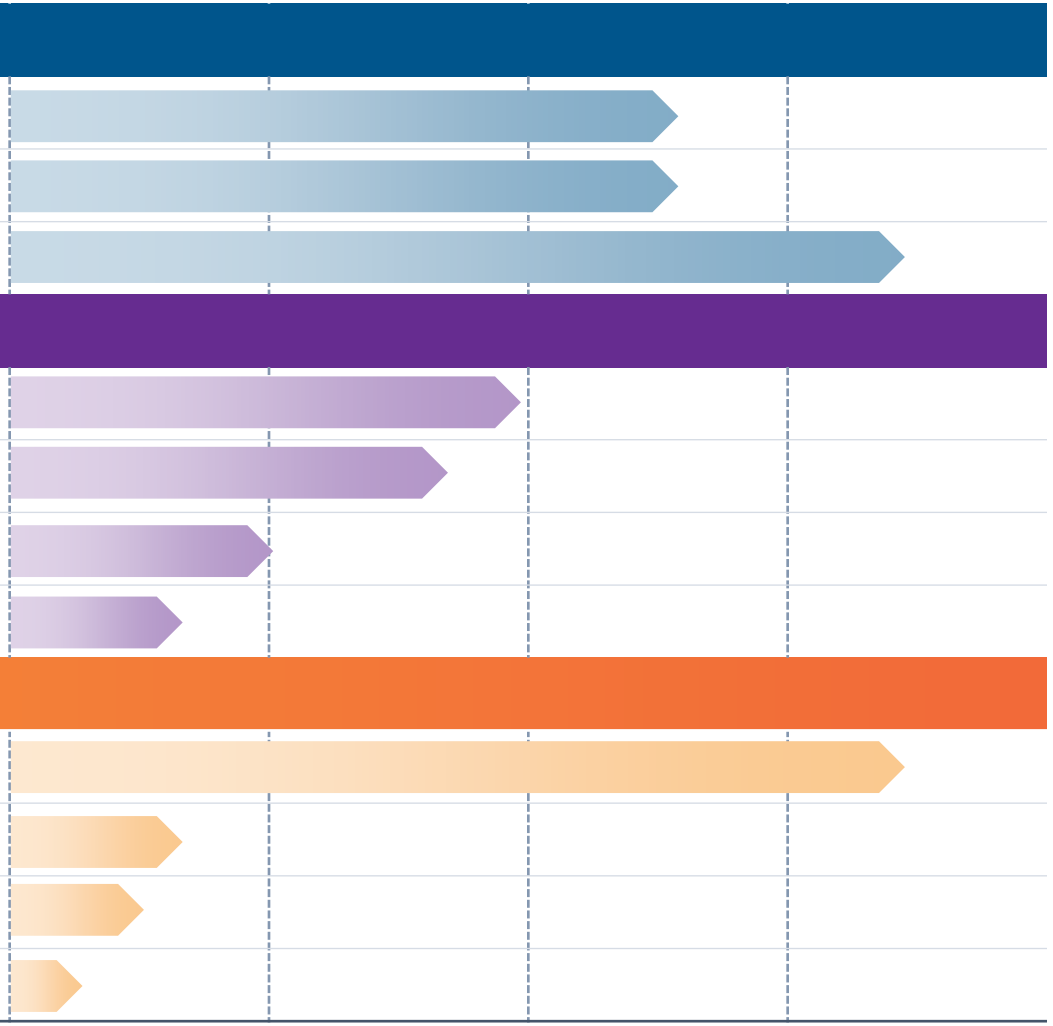
OXURION®

Innovate UK

Dementia Discovery Fund

Robust proprietary and partnered pipeline

Target / Product	Partner / Sponsor	Therapeutic Interest
***Bicycle*® Toxin Conjugates**		
BT5528 (EphA2)		Oncology
BT8009 (Nectin-4)		Oncology
BT1718 (MT1-MMP)	CANCER RESEARCH UK	Oncology
Immuno-oncology		
BT7480 (Nectin-4/CD137 tumor-targeted immune cell agonist, TICA™)		Oncology
BT7455 (EphA2/CD137 TICA)		Oncology
BT7401 (multivalent CD137 systemic agonist)	CANCER RESEARCH UK	Oncology
Undisclosed	Genentech A Member of the Roche Group	Oncology
Partnerships Beyond Oncology		
THR-149 (Kallikrein inhibitor *Bicycle*)	OXURION®	Ophthalmology
Inhaled *Bicycles*	AstraZeneca	Respiratory
Novel anti-infectives	Innovate UK	Anti-infectives
Novel CNS targets	Dementia Discovery Fund	CNS



May-21

bicycle therapeutics

Bicycle Toxin Conjugates® (BTCs)

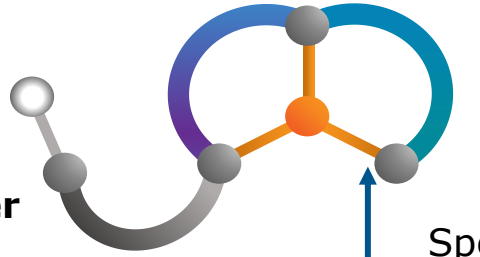
bicycle therapeutics

Bicycle Toxin Conjugates®: Designed to be precision targeting therapeutics

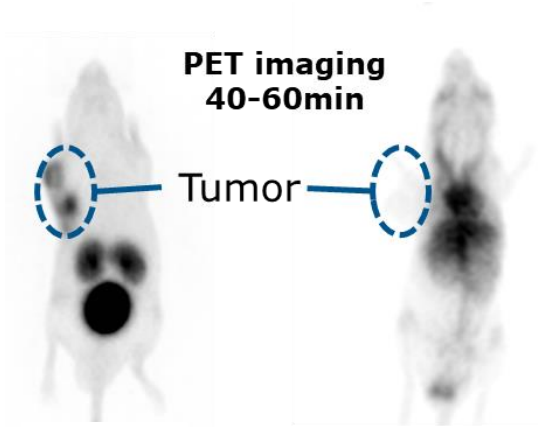
MWt of 1.5-2kDa, 50-100x smaller than antibodies

Large amount of cytotoxic payload can be delivered

Release of toxin directly into tumor via cleavable linker

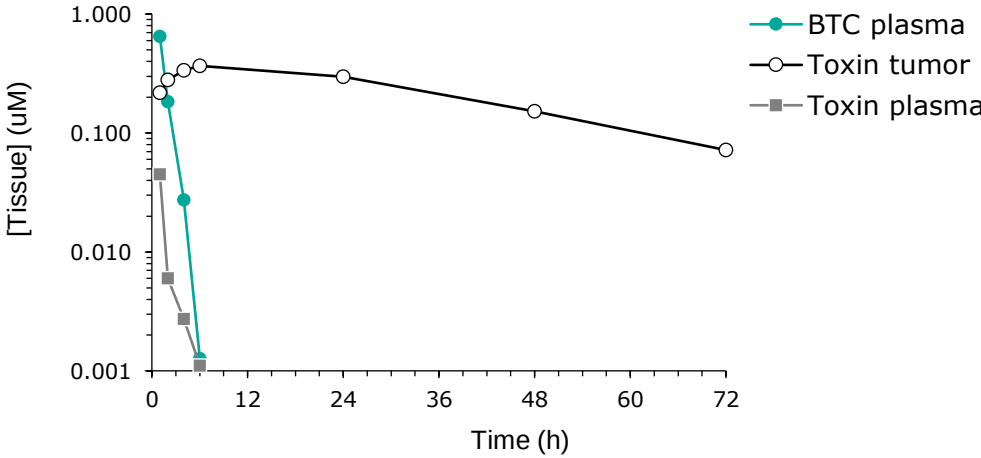


Specific tumor targeting via antigen



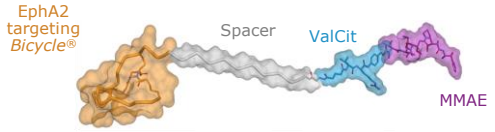
BTCs offer advantages over antibody drug conjugate (ADC) and small molecule approaches

Property	BTC	ADC	Importance
Tumor penetration	✓	?	Access to site of action
Tumor retention	✓	?	Maintenance at site of action, lower total body burden
Short systemic exposure	✓	✗	Minimizes toxicity, enhances combinability
Reduced liver metabolism	✓	✗	Improved safety profile
Renal elimination	✓	✗	Improved safety profile
Flexible dosing	✓	✗	Tailored dosing regimen minimizing toxicity



bicycle therapeutics

BT5528: Exemplifies potential of BTCs to address failed ADC targets



Background

- BT5528 is highly selective for EphA2, which:
  - Regulates cell migration, adhesion, proliferation and differentiation
  - Is overexpressed in many difficult to treat tumors
  - Has been intractable to ADC approaches

Status

- Phase I/II trial ongoing: open-label trial in EphA2(+) solid tumors
- Monotherapy and combination with nivolumab arms continue to enroll
- Patients are selected using proprietary IHC assay
- Topline data expected in 2021

Progress

- Clinically derisked coagulopathy and acute liver toxicity associated with EphA2-targeted ADCs
- Dose escalation ongoing; currently administered doses in the predicted therapeutic range
- Preliminary findings consistent with anti-tumor activity have been observed

Patient Population

- EphA2 is expressed in 52% of pancreatic cases; significant expression (>30%) in NSCLC, gastric, head & neck, and bladder cancers

Sources: SEER Cancer Stats, ECIS Database, 2018 Estimates, all accessed Dec 2019; AstraZeneca Epi Data, Dec 2017 and Feb 2020; industry presentations

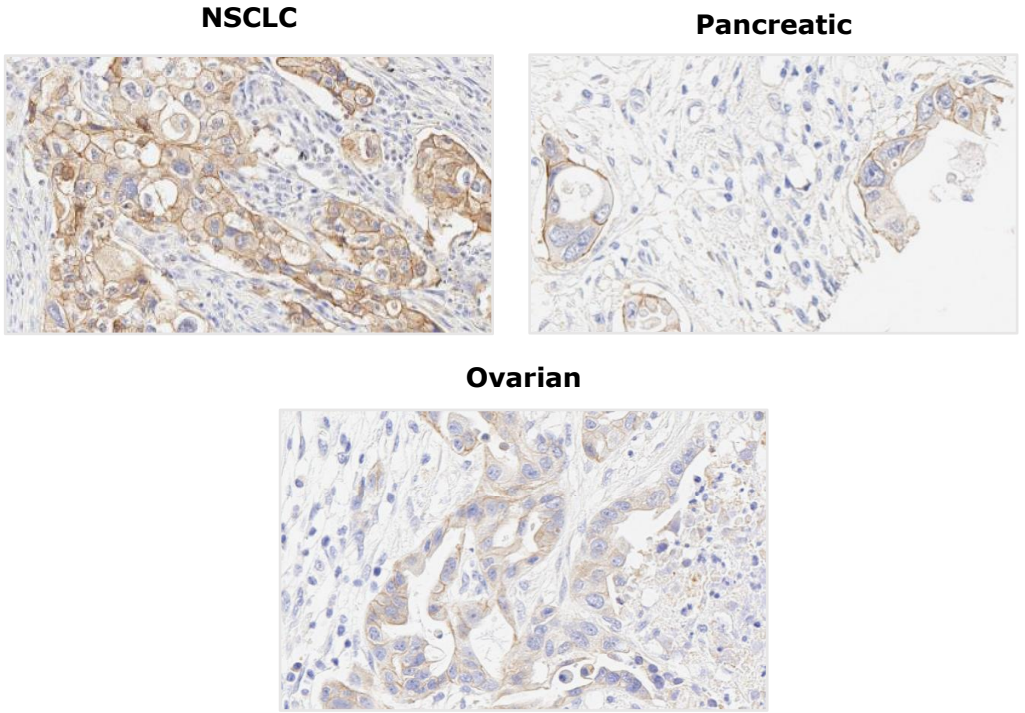
BT5528 clinical experience*

Experience prior to introduction of selection assay

- 19 pts have been dosed between 2.2 and 8.5 mg/m^2, either in combination with nivolumab (N=7) or monotherapy (N=12)
  - *Duration of treatment:* 3-34 weeks. *Tumor types:* pancreatic, ovarian, urothelial, NSCLC, TNBC, upper GI, Ewing's sarcoma
- Dosed up to 8.5 mg/m^2 weekly – reversible neutropenia seen (as predicted from preclinical studies)
- One patient from this group continues on study; retrospective analysis shows moderate EphA2 expression

Patient selection assay

- Proprietary Bicycle IHC assay developed to CAP/CLIA standards
- Measures expression of EphA2 extracellular domain (i.e., *Bicycle*® binding site)
- Multi-indication tumor microarray survey provides guide to frequency of EphA2 patient
- Expression generally increases with stage
- Two patients have been selected by IHC assay
  - Pancreatic (6.5 mg/m^2 Q1W), urothelial (8.5 mg/m^2 Q2W)



Next steps

- Focus initially on monotherapy; optimize dose and frequency

*As of Jan 14, 2021

bicycle therapeutics

BT5528-100: Subject 1 summary

Monotherapy (assigned 8.5 mg/m^2 Q2W); urothelial cancer

- PR seen after 2 cycles; patient failed prior lines of therapies, including pembrolizumab and enfortumab vedotin
- Substantial reductions in non-target lesions were also observed
- Neutropenia resolved within 7 days; patient remains on study, receiving 6.5 mg/m^2 Q2W

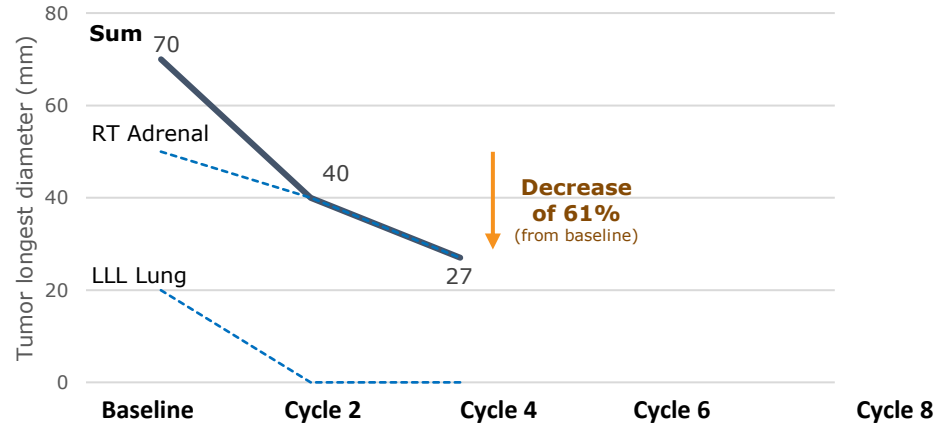
Cycle 1				Cycle 2		Cycle 4	
Day 0	Day 8	Day 15	Day 22	Day 1	Month 2	Day 1	Month 4
8.5 mg/m^2 Q2W	-	Gr3 Neutropenia	SRC review	6.5 mg/m^2 Q2W	43% shrinkage PR	6.5 mg/m^2 Q2W	61% shrinkage PR

76 yo / F
Diagnosis = Urothelial cancer
EphA2 H-Score: *TM=70, TC=80*
Diagnosed March 2017

Prior Treatment – Non-metastatic
1st-Line: MIBC/TURBT (2 months)
2nd-Line: Neoadjuvant cisplatin/gemcitabine (3 months) followed by radical cystectomy ("recurrence free" for 1 year)
Prior Treatment - Metastatic
1st-Line metastatic: pembrolizumab (7 months)
2nd-Line metastatic: enfortumab vedotin x2 cycles complicated with pancreatitis (7 months)
3rd-Line metastatic: Carboplatin/gemcitabine (5 months)
4th-Line metastatic: CNS RXT (2 months)

Course on Study
C1D1: 8.5mg/m^2 Q2W (ie, every two weeks)
C1D15: Dose hold due to Gr3 neutropenia (resolved within 7 days)
C2D1: Lowered to 6.5 mg/m^2 Q2W
RECISTv1.1 best response = Partial Response

Size of target lesions:



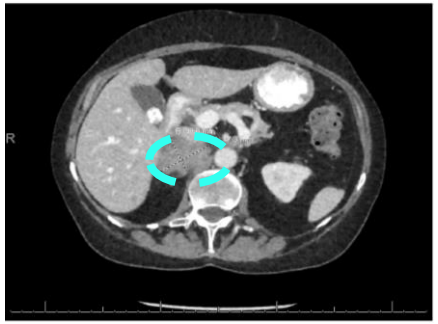
Status of non-target lesions:

Small mediastinal LNs	Present	Decreased			
Small liver mets	Present	Absent			
Retroperitoneal LNs	Present	Decreased			

Subject 1 – pre-treatment and post Cycle 2 scan

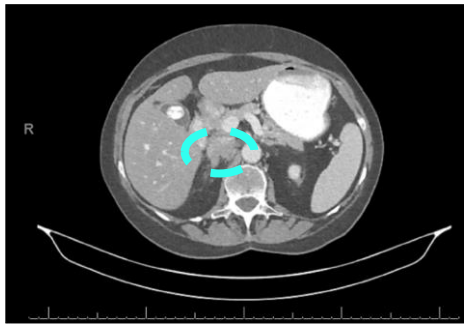
Target lesion – right adrenal nodule

Pre-treatment



50 mm per RECIST

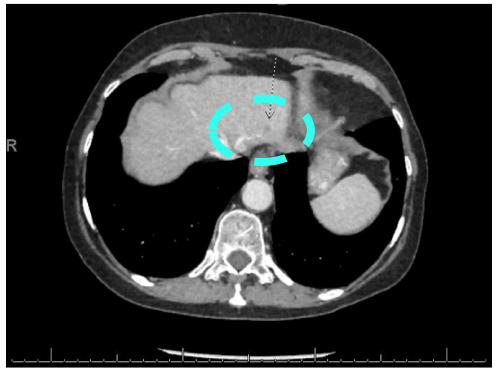
Post-Cycle 2 on BT5528



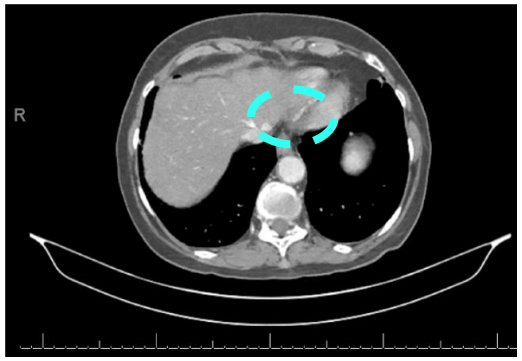
40 mm per RECIST

Non-target lesion – liver lesion

Pre-treatment



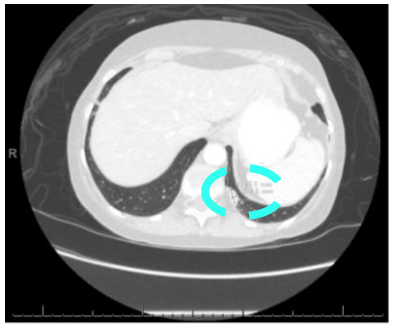
Post-Cycle 2 on BT5528



Absent

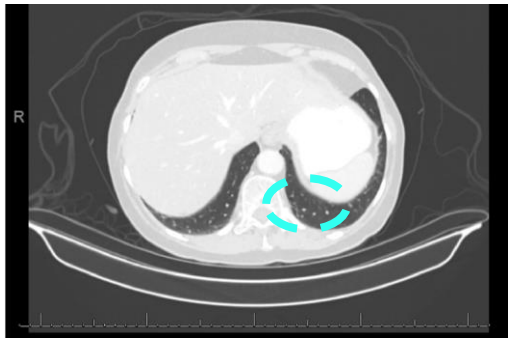
Target lesion – lower left lung nodule

Pre-treatment



20 mm per RECIST

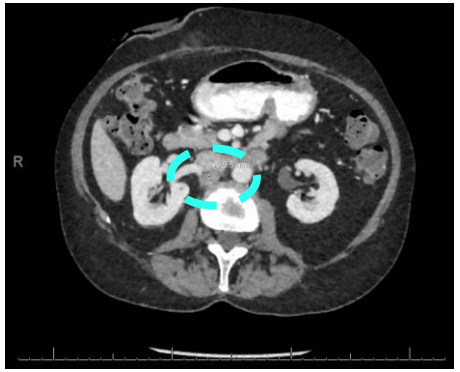
Post-Cycle 2 on BT5528



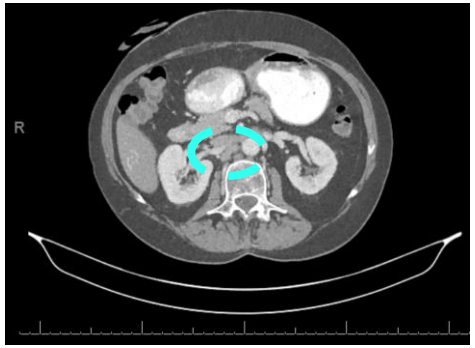
Complete resolution

Non-target lesion – retroperitoneal lymphadenopathy

Pre-treatment



Post-Cycle 2 on BT5528



Decreased

bicycle therapeutics

BT5528-100: Subject 2 summary

Monotherapy (assigned 8.5 mg/m2 Q1W); ovarian cancer

- Tumor shrinkage of 25% in ovarian cancer patient; failed prior lines of therapies, including olaparib and bevacizumab
- Patient started study prior to introduction of selection assay
- Patient in Cycle 11 (first dose May 2020) and remains on study; receiving 4.4 mg/m2 Q1W

Cycle 1				...	...	Cycle 11			
Day 0	Day 8	Day 15	Day 22			Month 10	Day 8	Day 15	Day 22
8.5 mg/m^2 Q1W	8.5 mg/m^2 Q1W	Gr4 Neutropenia	4.4 mg/m^2 Q1W			25% shrinkage			

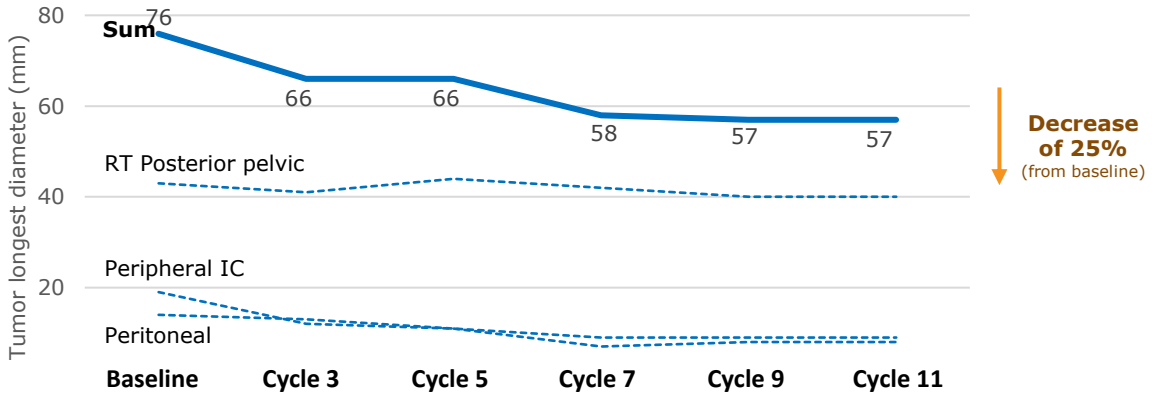
66 yo / F
Diagnosis = Ovarian cancer
EphA2 H-Score: ***TM=32, TC=40***
Diagnosed April 2017, BRCA mutation neg

Prior Treatment
1st-Line: Taxane/carboplatin/olaparib (18 months)
2nd-Line: Carboplatin/gemcitabine/ bevacizumab (7 months)
3rd-Line: Liposomal doxorubicin (6 months)
Surveillance only from Nov 2019 to May 2020 (6 months)

Course on Study
C1D1: 8.5 mg/m^2 Q1W (ie, weekly)
C1D15: Dose hold due to Gr4 neutropenia (resolved within 5 days)
C1D22: Reduce dose to 4.4 mg/m^2 Q1W
- 1 missed dose (missed visit pending Covid-19 test)
- No repeat Gr3 or Gr4 neutropenia (no growth factors)
- Last ANC = 1.3 k/uL (1.3 G/L)= Gr2 Neutropenia

RECISTv1.1 best response = Stable Disease

Size of target lesions:



bicycle therapeutics

BT5528: Mechanistic studies

Achieving efficacious MMAE intra-tumor concentrations

- Tumor concentrations of MMAE sustained after dosing
- MMAE tumor concentrations above those required for preclinical efficacy
- ca. 50 nM at 24h post single dose of 1.5 mg/m^2 BT5528 mouse xenograft study (MED)
- Significantly greater than in vitro cytotoxicity IC_{50}'s (0.2 to 1.3 nM depending on cell line)

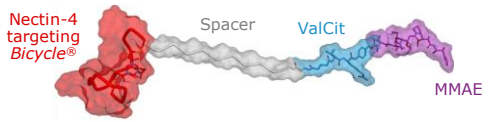
Patient ID	Tumor type	Dose (mg/m^2)	Time post-dose	MMAE Concentration (nM)		
				Tumor	Plasma	Ratio
3000-007	Ewing's sarcoma	4.4	~24h after dose 3	87.5	8.7	**10.1**
3000-009	Ovarian	4.4	~24h after dose 3	197	21.2	**9.3**

Emerging, qualitative metabolic ID data supports the hypothesis that BTCs undergo reduced hepatic metabolism (cf. ADCs) and are renally eliminated

- No circulating metabolites of MMAE have been observed in plasma
  - No evidence of CYP-mediated hepatic metabolism of MMAE
- Significant amounts of MMAE and peptidyl metabolites observed in urine after 24h
  - Contrast with ADCs where ca. 5% of the dose is excreted as MMAE in the urine and 17% in the feces over 7 days

MED = minimally effective dose

BT8009: Nectin-4 BTC fast follower with differentiated profile to approved ADC



Background

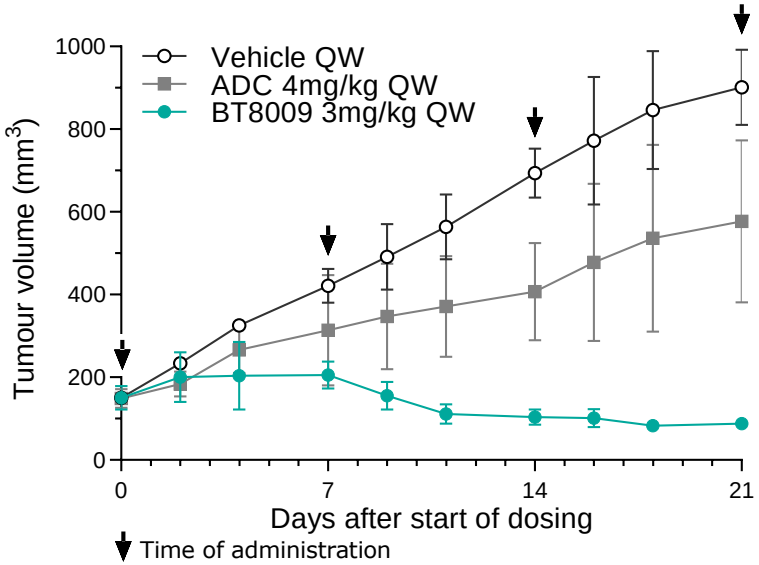
- BT8009 is highly selective for Nectin-4, which:
  - Is believed to play a role in tumor cell growth and proliferation
  - Is overexpressed in common types of cancer
  - Has been validated in the clinic by enfortumab vedotin

Status

- Phase I trial ongoing: open label, multi-center across US & EU, enrolling patients with Nectin-4(+) tumor types (e.g., urothelial)
- Evaluating BT8009 as a monotherapy and in combination with nivolumab
- Topline data expected in 2021

Progress

- Preclinical evidence demonstrates BT8009 has best -in-class potential



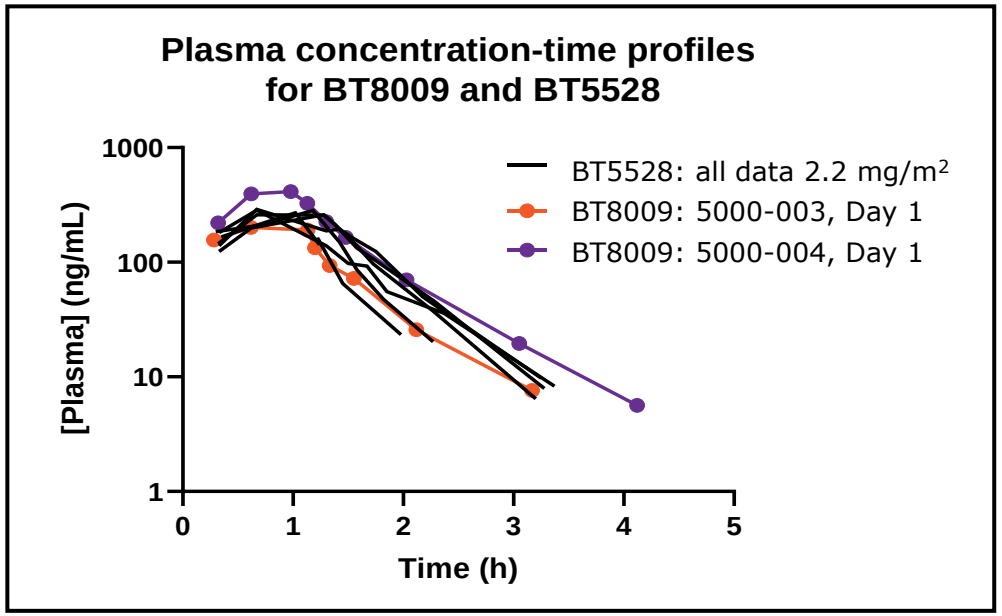
Patient Population

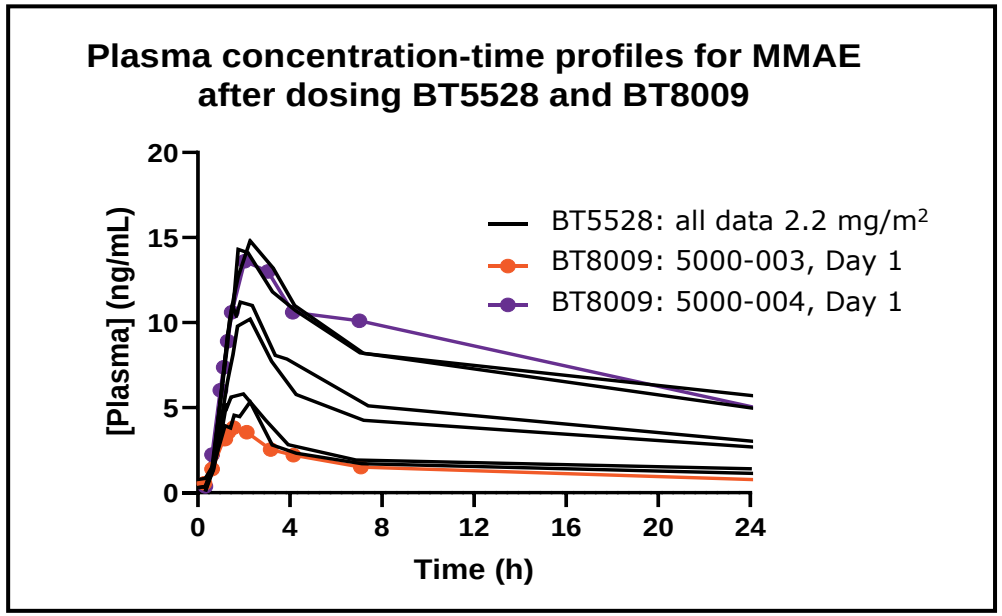
- Nectin-4 is expressed in 98% of bladder, 87% of esophageal and 85% of NSCLC cases

Sources: SEER Cancer Stats, ECIS Database, 2018 Estimates, all accessed Dec 2019; AstraZeneca Epi Data, Dec 2017 and Feb 2020; industry presentations

BT8009 clinical experience*

Compound/Cohort	t½ (h)	Cmax (ng/mL)	AUC∞ (ng.h/mL)	CLp (mL/min/kg)	Vss (L/kg)	MMAE Cmax (ng/mL)	MMAE AUC24 (ng.h/mL)
BT5528 Cohort 1 (2.2 mg/m²)	0.39 ± 0.08	274 ± 13	344 ± 42	2.85 ± 0.32	0.09 ± 0.01	10.3 ± 4.1	114 ± 103
BT8009 5000-003 Day 1 (2.5 mg/m²)	0.500	201	273	3.85	0.12	3.83	34.6
BT8009 5000-004 Day 1 (2.5 mg/m²)	0.572	414	530	2.38	0.09	13.6	193

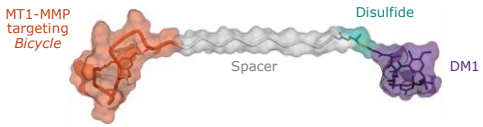




- BT5528 and BT8009 have similar clinical PK profiles
- MMAE has a similar PK profile following administration of either BT5528 or BT8009

*As of Jan 14, 2021

BT1718: Possible first-in-class BTC targeting key tumor antigen



Background

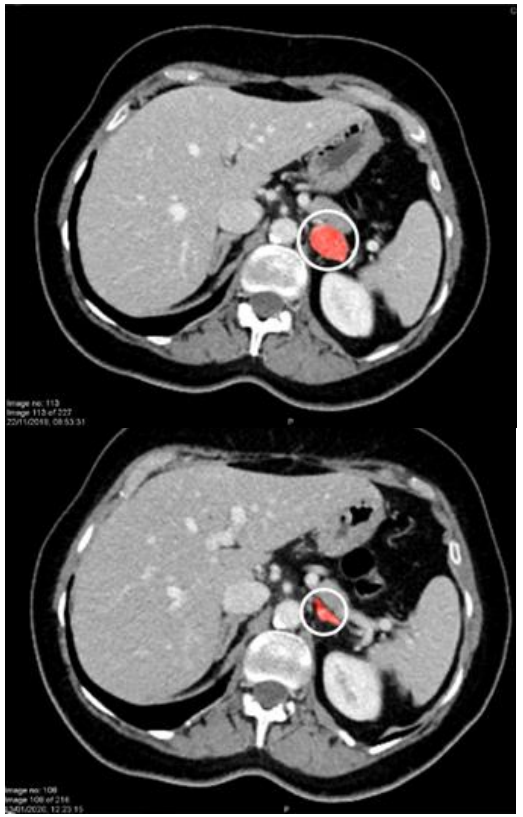
- BT1718 is highly selective for MT1-MMP (MMP-14), which:
  - Has established role in cell invasion and metastasis
  - Is highly expressed in tumors of squamous cell origin

Status

- Phase IIa trial initiated: open label, sponsored by CRUK*; patients selected based on MT1-MMP expression using proprietary IHC assay
  - Initial cohorts include squamous non-small cell lung cancer (NSCLC) and basket; further cohorts may be added
- Topline data expected in 2021

Progress

- Achieved primary objectives of Phase I trial in patients with advanced solid tumors
  - PK in line with preclinical predictions
  - Delivering >4x toxin delivered by ADCs
  - Early signs of activity in difficult to treat patient population



Baseline

68% reduction in a target lesion (SCLC)

Patient Population

- MT1-MMP is expressed in 58% of NSCLC, 76% of esophageal cases; very highly expressed in bladder and ovarian cancers§

* Sponsored by Cancer Research UK Centre for Drug Development

§ *Sources:* SEER Cancer Stats, ECIS Database, 2018 Estimates, all accessed Dec 2019; AstraZeneca Epi Data, Dec 2017 and Feb 2020; industry presentations

Emerging clinical data support BTCs as a next-generation tumor-targeted delivery platform

Property	BTC	ADC	Importance
Tumor penetration	✓	?	Access to site of action
Tumor retention	✓	?	Maintenance at site of action, lower total body burden
Short systemic exposure	✓	✘	Minimizes toxicity, enhances combinability
Reduced liver metabolism	✓	✘	Improved safety profile
Renal elimination	✓	✘	Improved safety profile
Flexible dosing	✓	✘	Tailored dosing regimen minimizing toxicity

Precision Targeting & Efficacy

Maximal Therapeutic Window

Optimal Patient Experience

We believe that the unique properties of BTCs, which are now being demonstrated clinically, will lead to superior clinical outcomes for patients

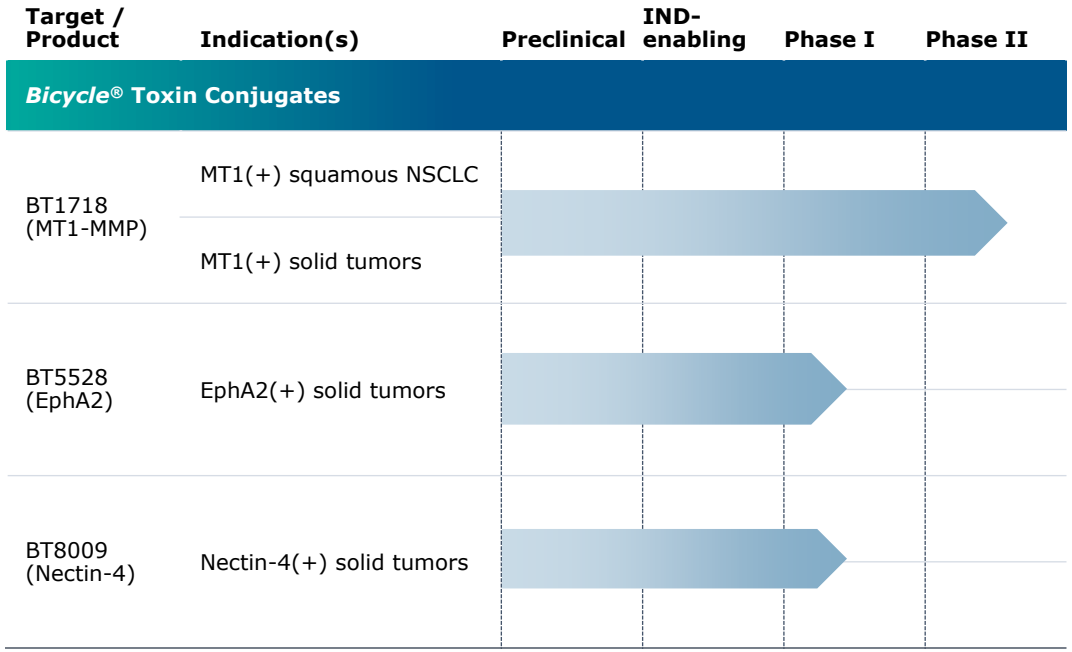
Bicycle Toxin Conjugates® represent potentially differentiated next-generation cancer therapeutics

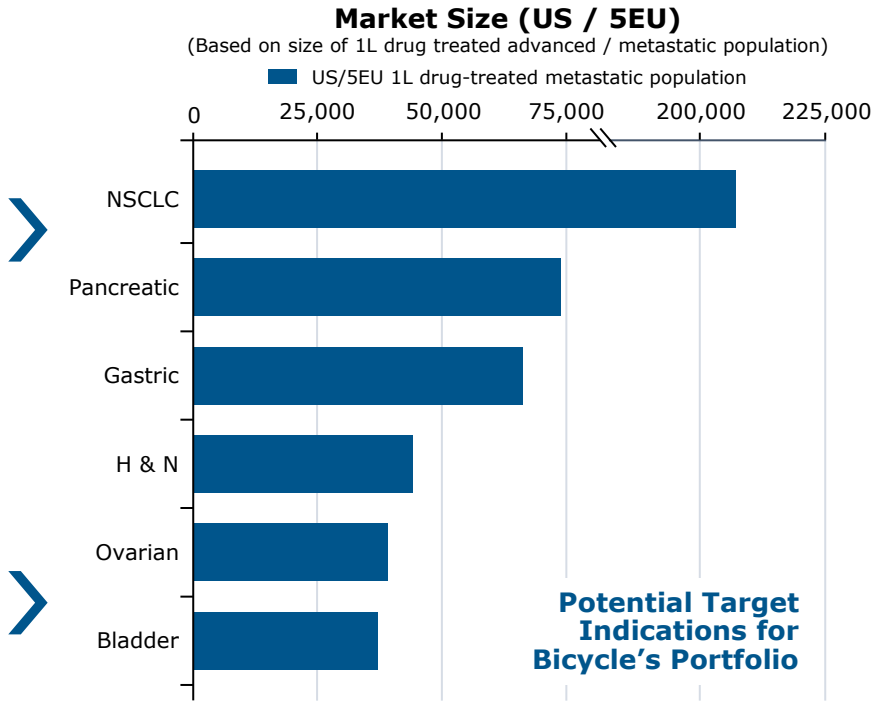
First-in-class or best-in-class opportunities

Based on novel technology, designed to overcome ADC failure and other limitations

Potential for internal/ external combinations

Represent future of tumor-targeted cytotoxic payload delivery





bicycle therapeutics

Immuno-oncology

bicycle therapeutics

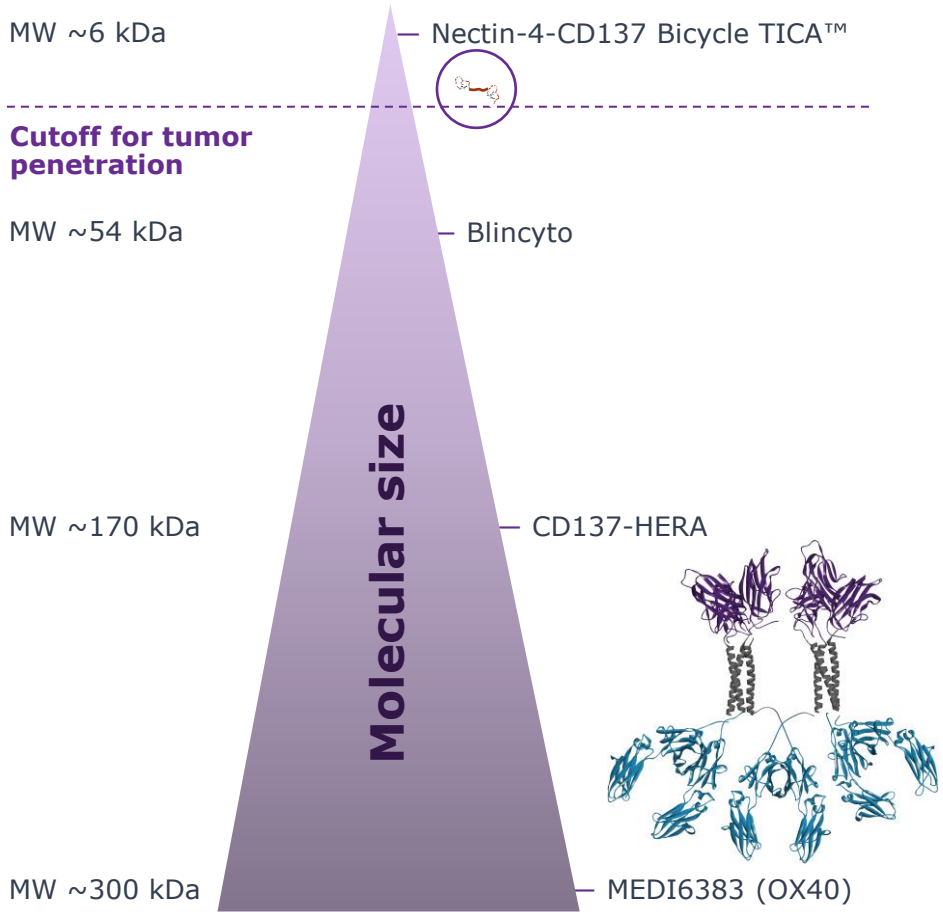
Bicycles are a new class of IO therapies that could overcome limitations of existing approaches

Disadvantages of biologics in IO

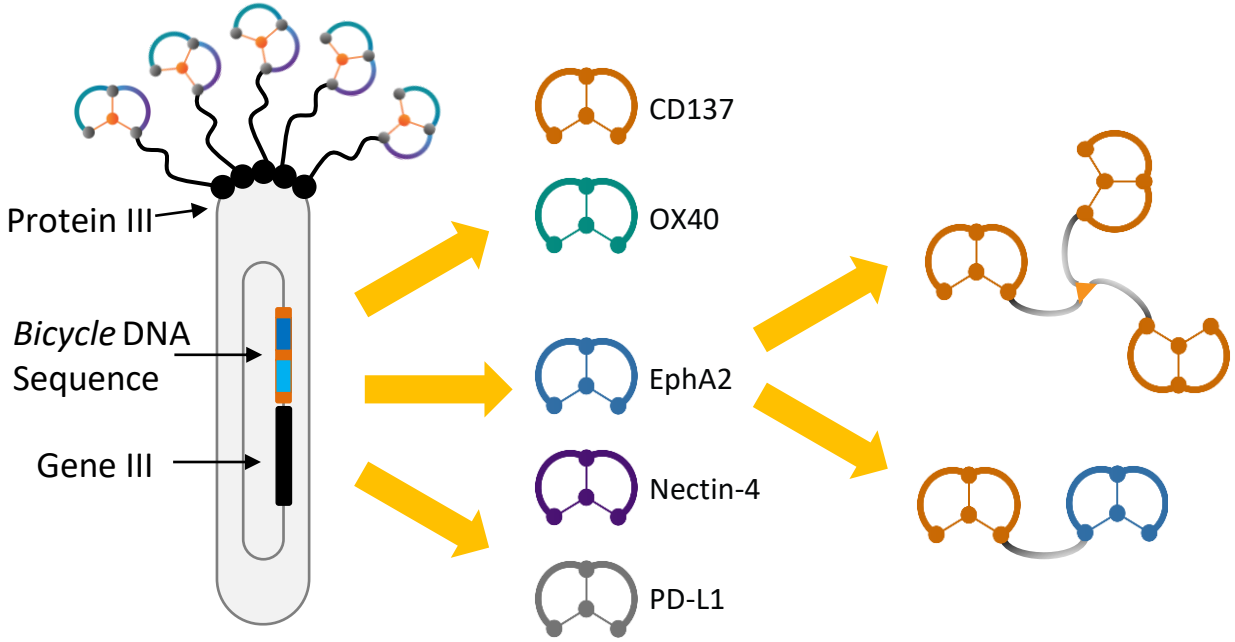
- Very large and complex molecules, poor tumor penetration
- High chance for immunogenicity
- Approach often not generalizable
- Little opportunity to "tune" properties and mitigate toxicities
- Complex, expensive and risky manufacturing

Advantages of *Bicycles*

- Smaller than the smallest monovalent antibody, primed for rapid tumor penetration
- Generalizable approach to multiple immune cell receptors
- Chemically synthetic, so easy to "tune" properties
- Simple peptide manufacturing



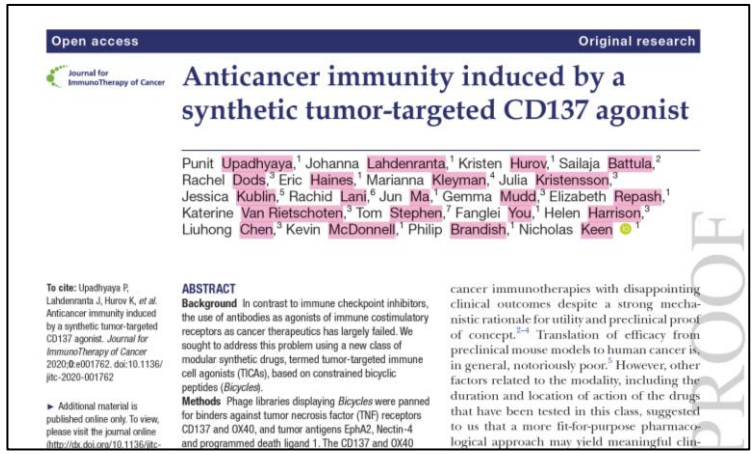
Bicycles platform is delivering a tool kit of building blocks to create novel IO agonists



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

Immune and tumor cell targeting *Bicycles*

Multimeric and tumor targeted agonists


Open access Original research

Journal for ImmunoTherapy of Cancer

Anticancer immunity induced by a synthetic tumor-targeted CD137 agonist

Punit Upadhyaya,[1] Johanna Lahdenranta,[1] Kristen Hurov,[1] Sailaja Battula,[2] Rachel Dods,[3] Eric Haines,[1] Marianna Kleyman,[4] Julia Kristensson,[3] Jessica Kublin,[5] Rachid Lani,[6] Jun Ma,[1] Gemma Mudd,[3] Elizabeth Repash,[1] Katerine Van Rietschoten,[3] Tom Stephen,[7] Fanglei You,[1] Helen Harrison,[3] Liuhong Chen,[3] Kevin McDonnell,[1] Philip Brandish,[1] Nicholas Keen[1]

To cite: Upadhyaya P, Lahdenranta J, Hurov K, *et al*. Anticancer immunity induced by a synthetic tumor-targeted CD137 agonist. *Journal for ImmunoTherapy of Cancer* 2020;**0**:e001762. doi:10.1136/jitc-2020-001762

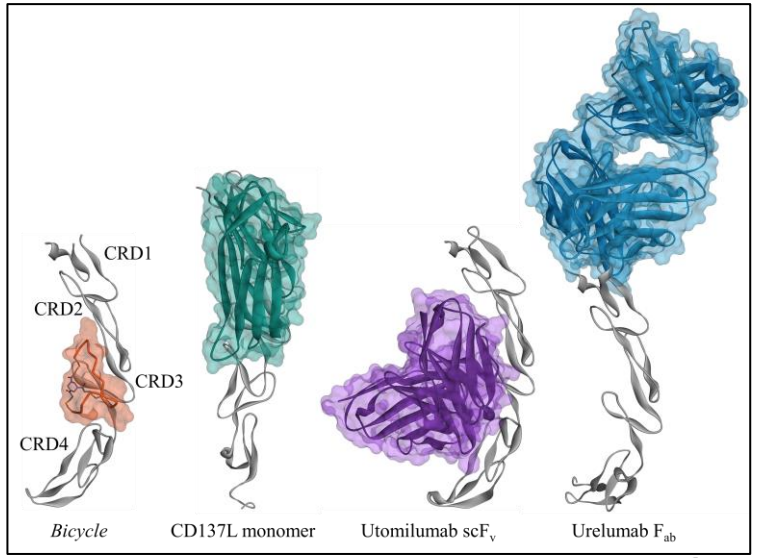
► Additional material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jitc-

ABSTRACT

Background In contrast to immune checkpoint inhibitors, the use of antibodies as agonists of immune costimulatory receptors as cancer therapeutics has largely failed. We sought to address this problem using a new class of modular synthetic drugs, termed tumor-targeted immune cell agonists (TICAs), based on constrained bicyclic peptides (*Bicycles*).

Methods Phage libraries displaying *Bicycles* were panned for binders against tumor necrosis factor (TNF) receptors CD137 and OX40, and tumor antigens EphA2, Nectin-4 and programmed death ligand 1. The CD137 and OX40

cancer immunotherapies with disappointing clinical outcomes despite a strong mechanistic rationale for utility and preclinical proof of concept.[2–4] Translation of efficacy from preclinical mouse models to human cancer is, in general, notoriously poor.[5] However, other factors related to the modality, including the duration and location of action of the drugs that have been tested in this class, suggested to us that a more fit-for-purpose pharmacological approach may yield meaningful clin-



Why CD137?

- Validated target, limited by toxicity
- Unlike CD3, expressed on multiple immune cell types
- Urelumab (BMS), efficacious, but trials halted due to dose-limiting liver toxicity, utomilumab (Pfizer), safe, but inactive

May-21

bicycle therapeutics

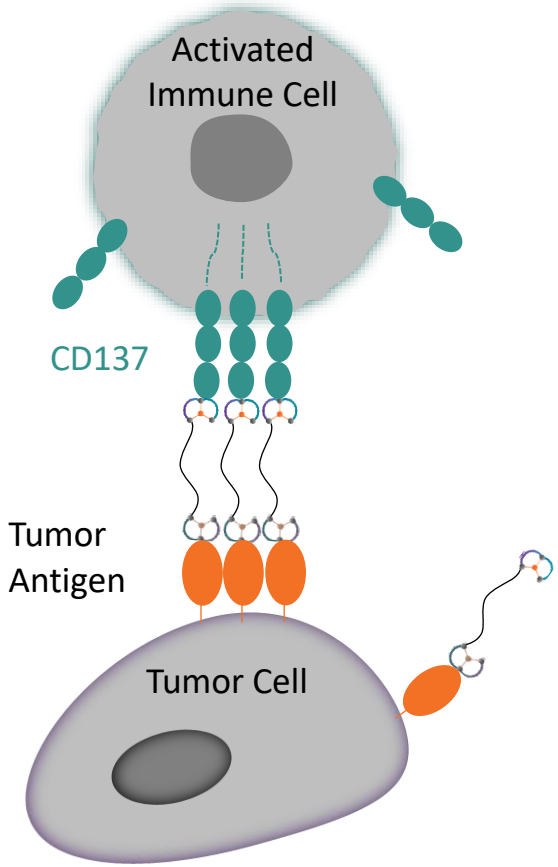
Tumor-targeted immune cell agonists (TICA™): Next-generation IO modulators for oncology

- Simple bivalent (or multivalent) molecules using tumor antigens as a scaffold to assemble CD137 signaling complexes *in-trans*

- Tumor antigen binder arm = **Nectin-4 binder**
  - Expression in range of solid tumors including bladder, lung and breast

- Immune activator effector arm = **CD137 binder**
  - Signal 2 costimulatory receptor – drives T-cell function and survival, also expressed on NK cells and myeloid cells

BT7480



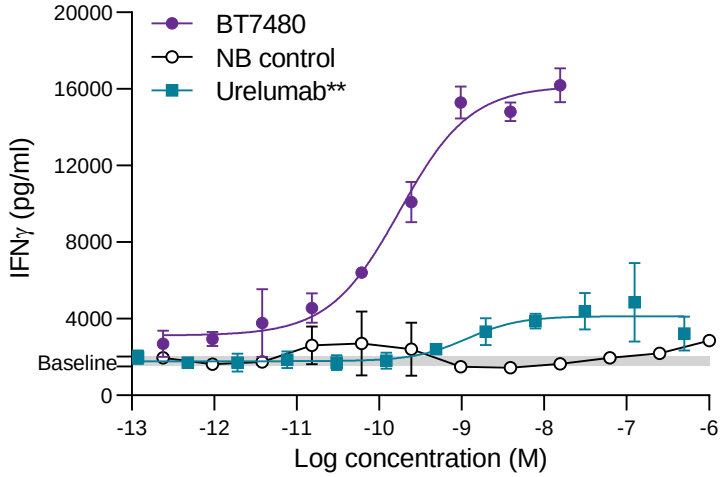
BT7480: Potential first-in-class, highly potent Nectin-4-targeted CD137 agonist

Background & Status

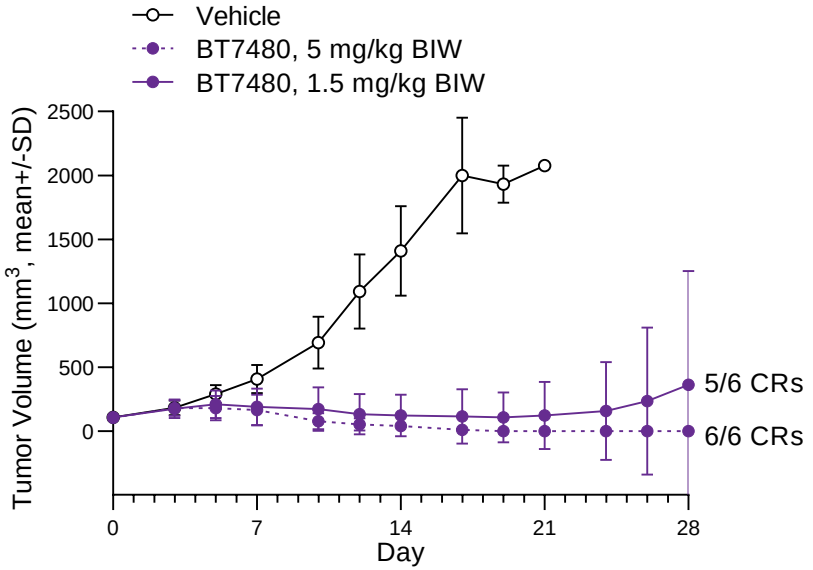
- More potent than urelumab in Nectin-4 expressing tumors
- Fully synthetic, 30x smaller than antibodies
- Short half life, compatible with intermittent dosing
- Ideal combination partner
- IND-enabling studies ongoing
- Phase I initiation expected in 2H 2021

Progress

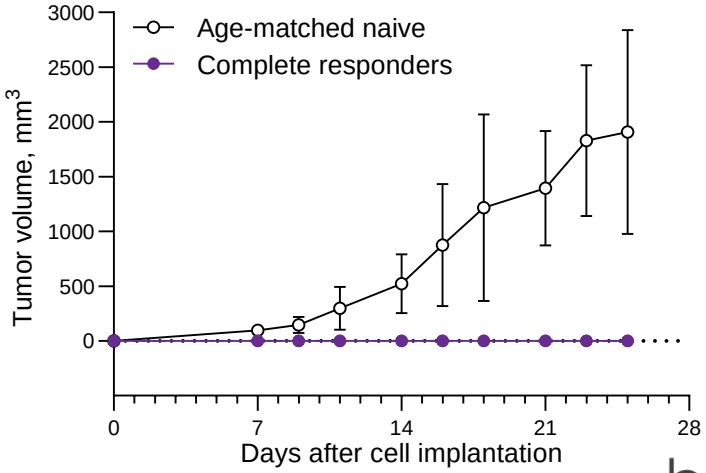
- BT7480 is a more potent and targeted agonist than urelumab**



- Dramatic anti-tumor responses observed preclinically and on a dosing schedule consistent with intermittent dosing in humans



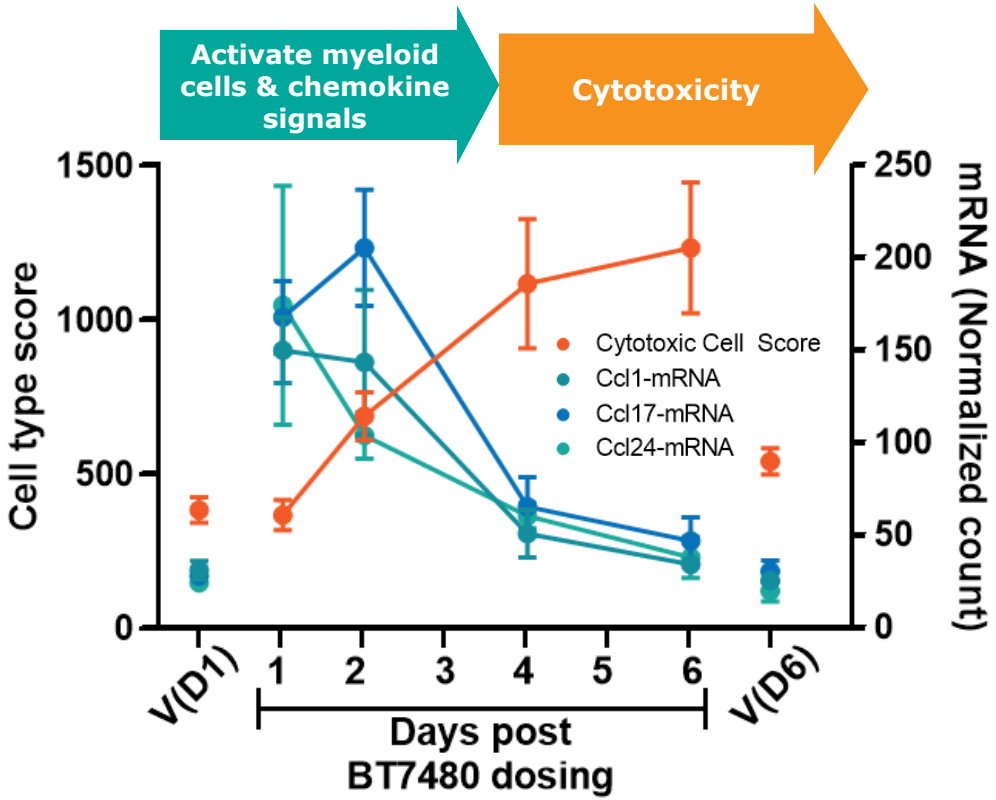
- Evidence of immunogenic memory in syngeneic mouse model



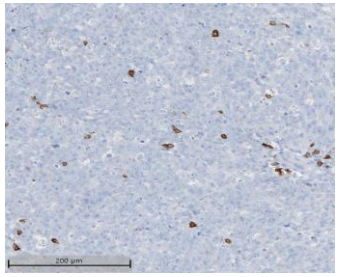
** Commercially available analog was used

bicycle therapeutics

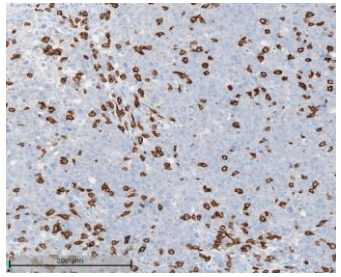
BT7480 has a unique and differentiated mechanism of action



Day 6: IHC shows that CD8+ T-cells have infiltrated the tumor



Vehicle

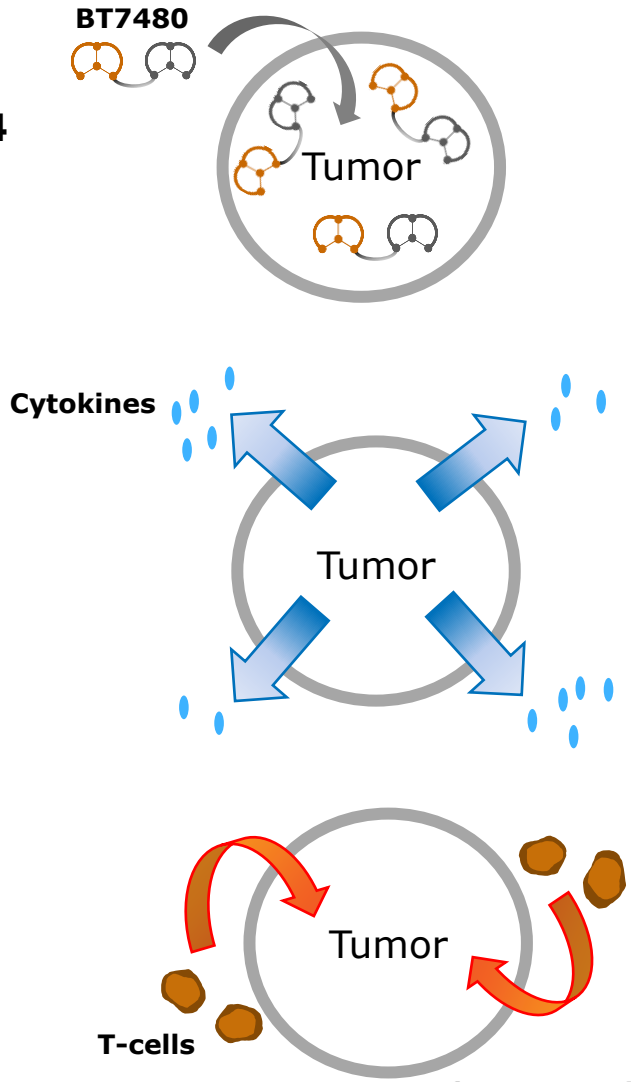


BT7480

BT7480 binds Nectin-4 in tumor

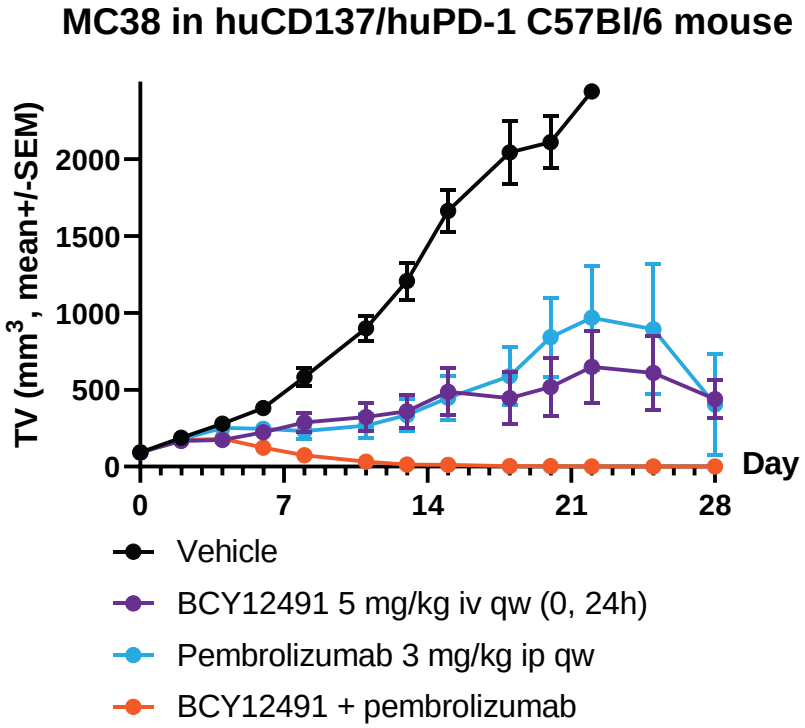
Myeloid cells activated, "shout for help"

Cytotoxic T-cells migrate to and kill tumor

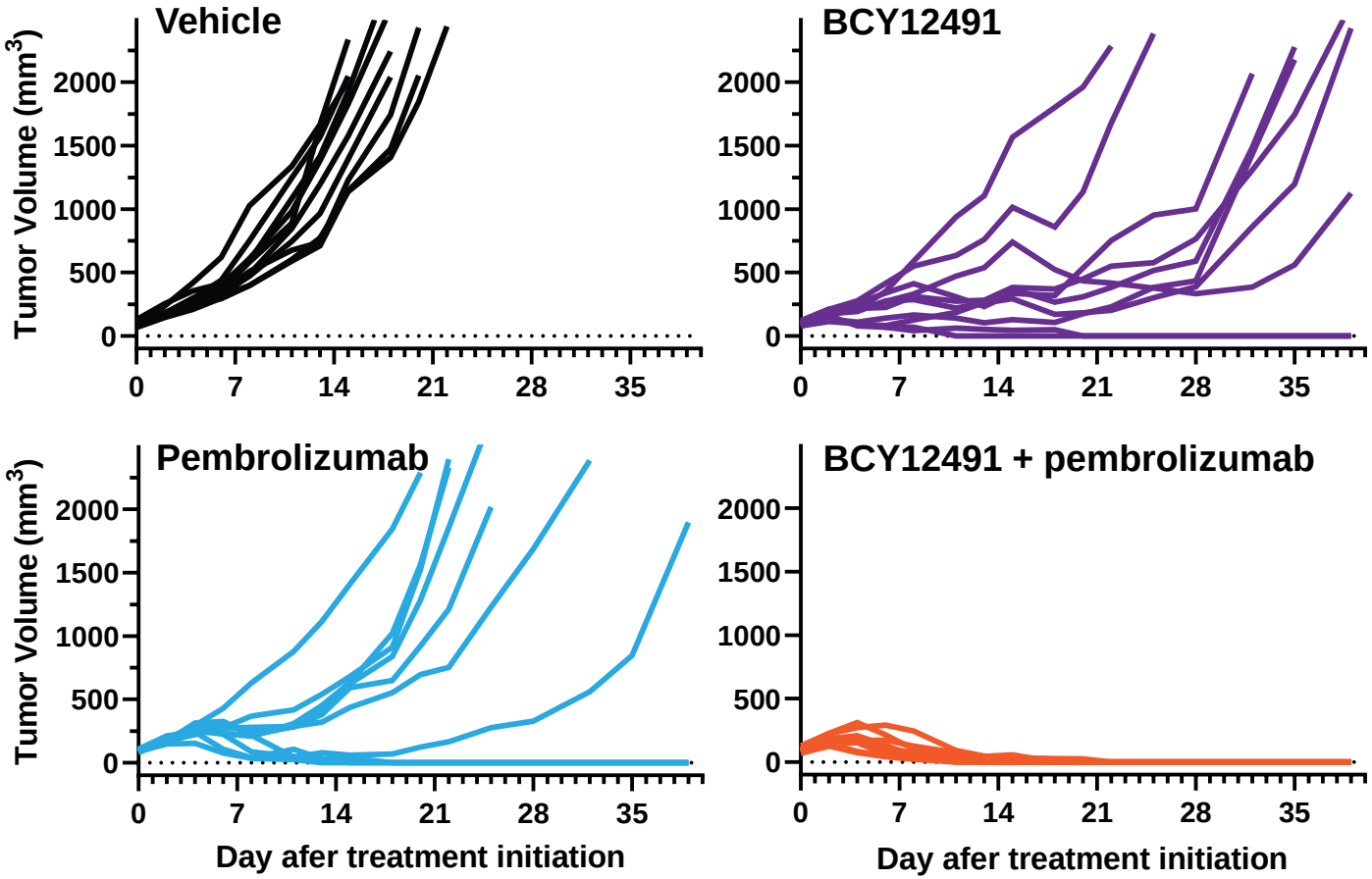


bicycle therapeutics

100% complete response rate with model CD137 TICA™+ pembrolizumab combination



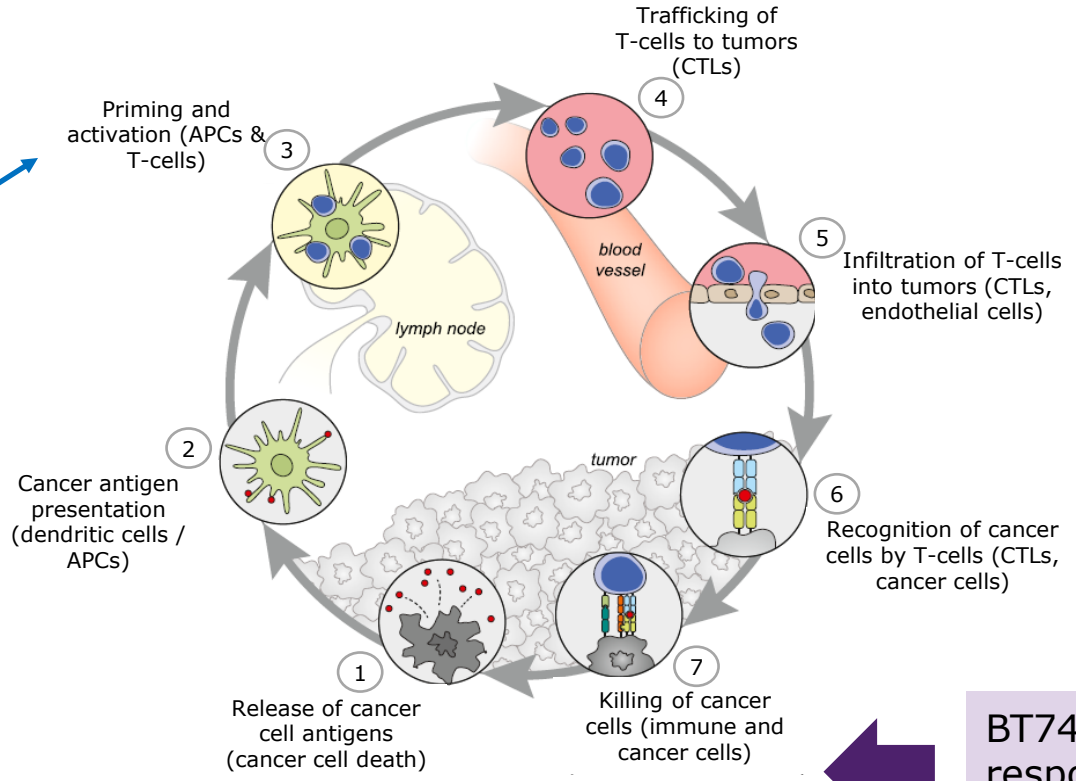
Test Agent	CRs on D39
Vehicle	0/10
BCY12491	2/10
Pembrolizumab	3/10
BCY + pembrolizumab	10/10



bicycle therapeutics

BT7480 has the potential to both drive and sustain tumor immunity via targeted agonism of CD137

PD-1/PD-L1 blockers work here (may be the primary site of action)



BT7480: initiate and invigorate the anti-tumor immune response by causing recruitment of T-cells to the tumor, perhaps via myeloid cells

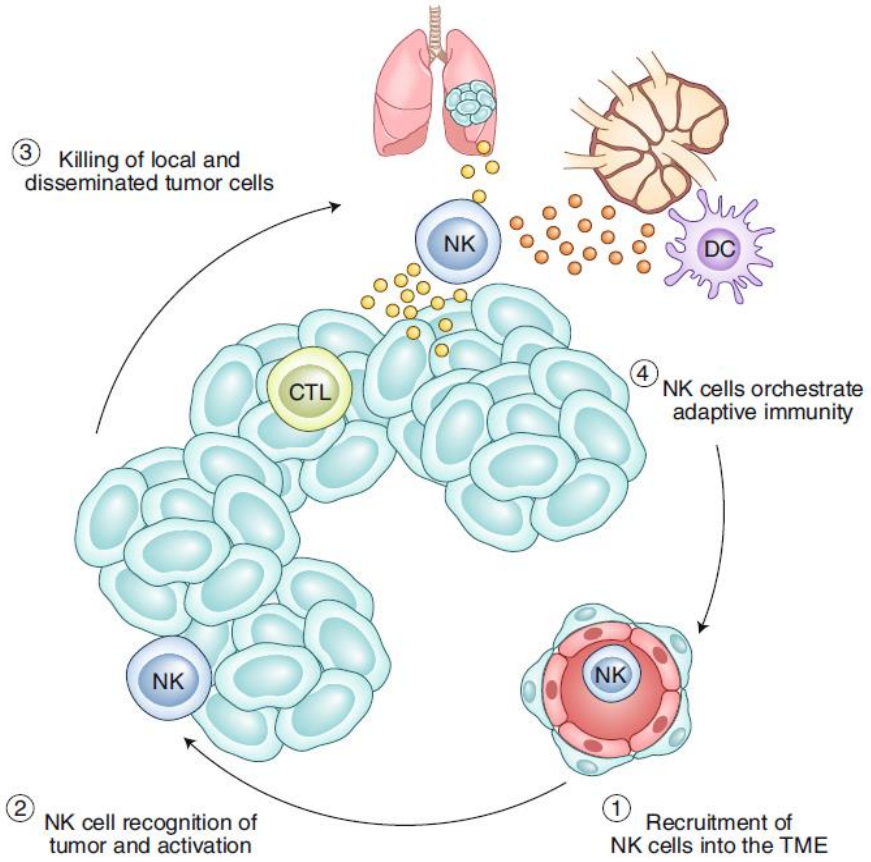
BT7480: sustains the anti-tumor T-cell response by promoting T-cell survival and memory

PD-1/PD-L1 blockers work here

Chen DS & Mellman I. *Immunity* 39, 1-10 (2013)

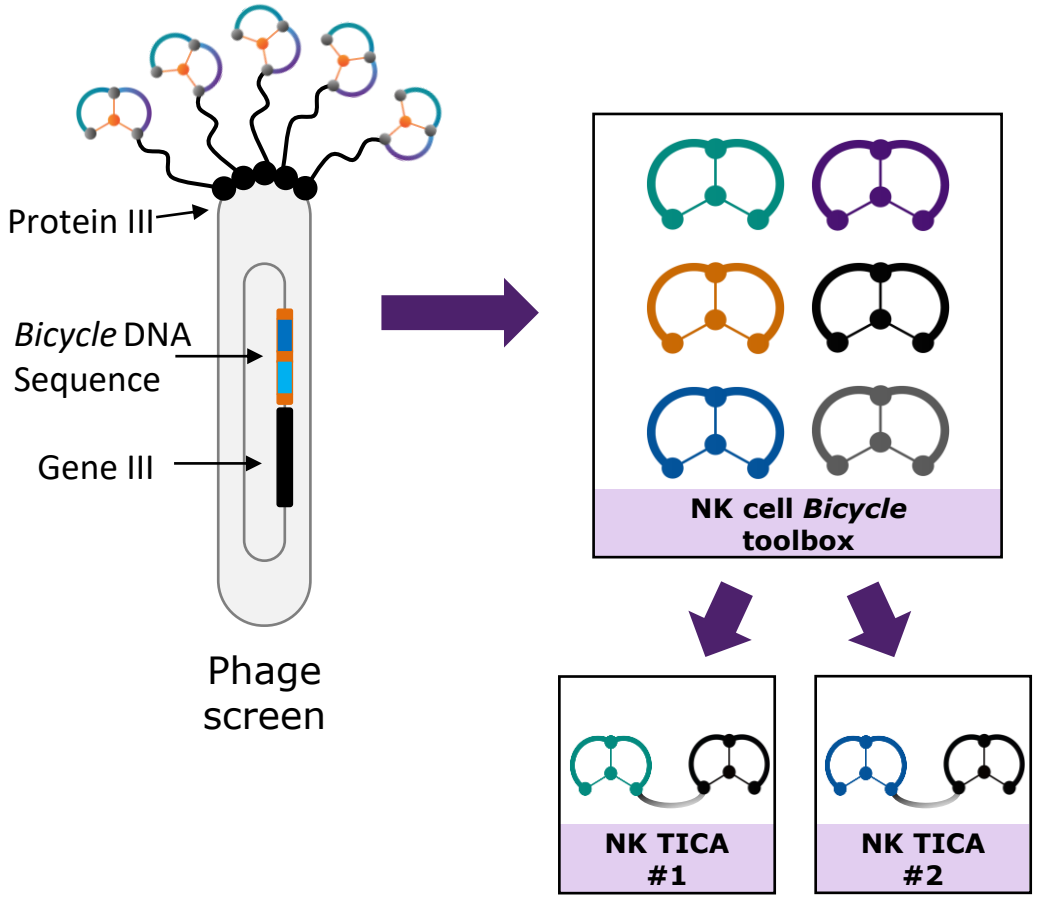
Natural killer (NK) cells are emerging key players in anti-tumor immunity

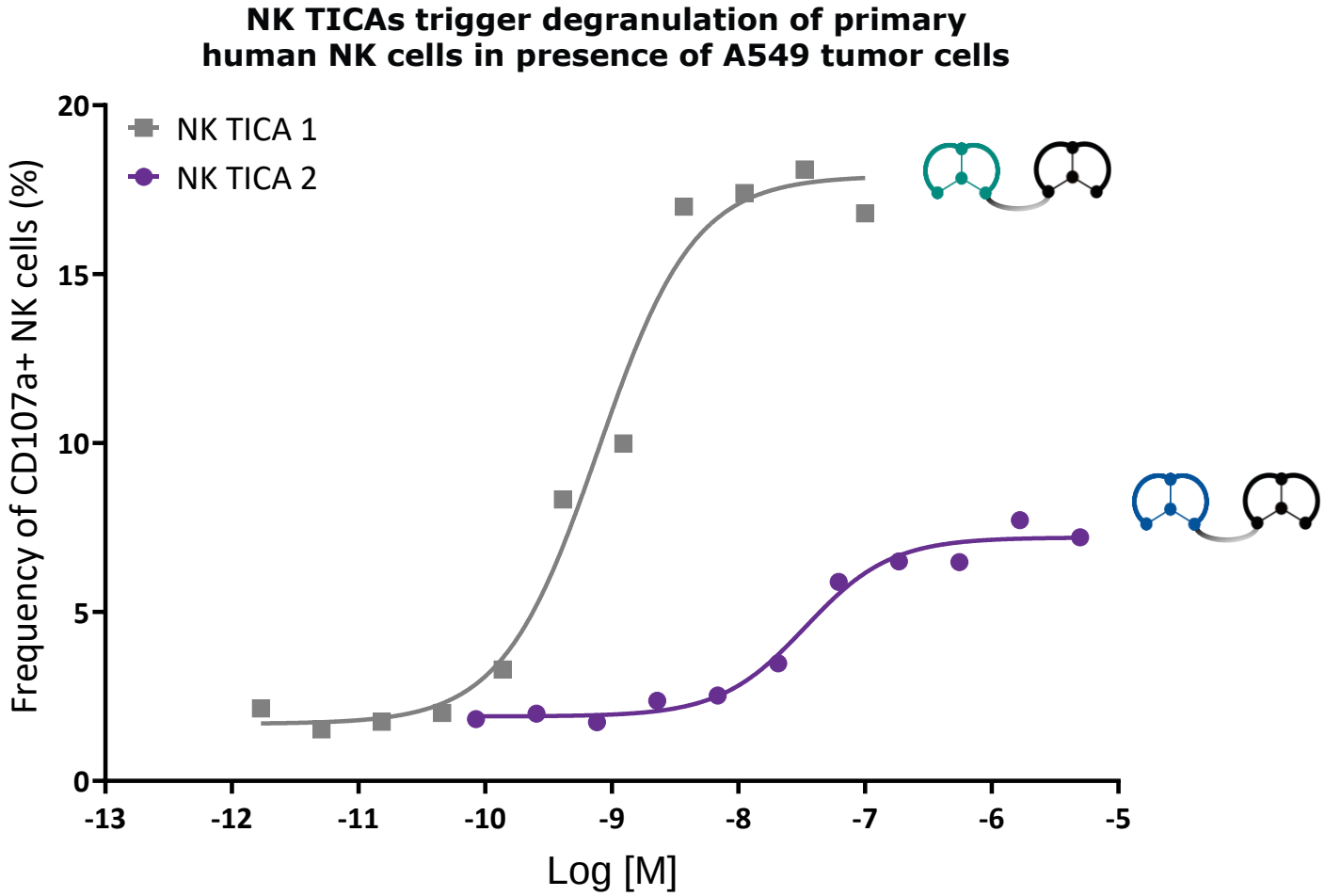
- NK cells kill tumor cells through direct cytotoxic mechanisms
- New published science has revealed a role for NK cells in orchestrating adaptive tumor immunity
- NK cells are activated through surface receptors – excellent opportunity for tumor-targeted *Bicycles*



Bald T et al. *Nat Immunol.* 21, 835-847 (2020); Barry K et al. *Nat Med*. 24, 1178-1191 (2018); Böttcher B et al. *Cell*. 172, 1022-1037 (2018)

Key NK cell receptors are amenable to *Bicycle*® technology and can rapidly be assembled into NK-TICAs





bicycle therapeutics

Bicycle® TICA™: a modular & generalizable platform

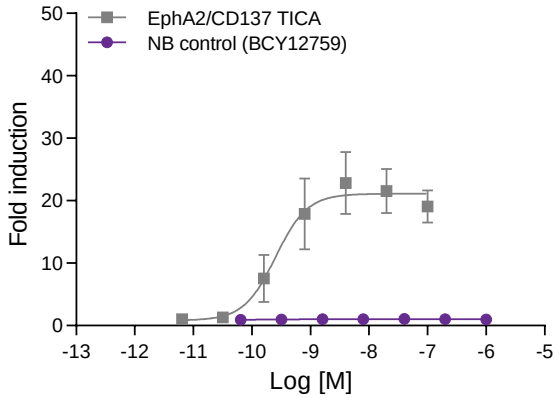
Immune cell and tumor targeting *Bicycles* can be rapidly combined and chemically optimized
Extending beyond T-cell into multiple immune cell receptor classes

Immune and Tumor Cell Targeting *Bicycles*

- CD137
- OX40
- NK receptor 1
- NK receptor 2
- EphA2
- Nectin-4
- PD-L1

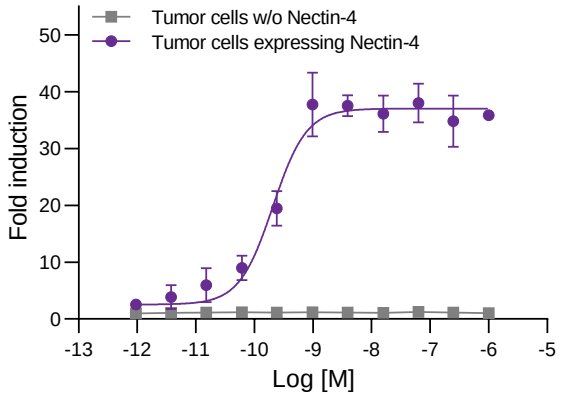
EphA2/CD137 TICA
(BCY9173)

Promega reporter assay / co-culture with PC-3 tumor cells



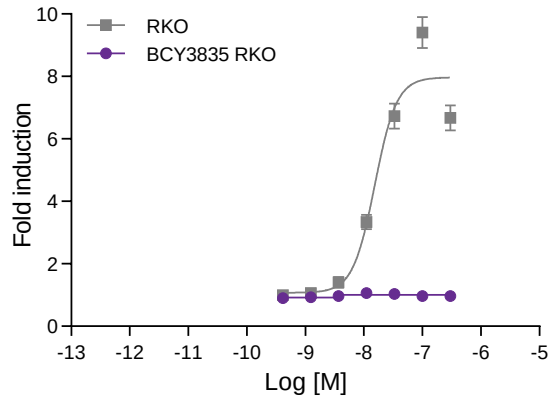
Nectin-4/OX40 TICA
(BCY12141)

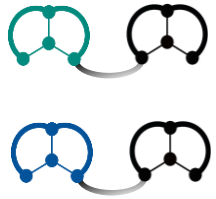
Promega reporter assay / co-culture with 4T1 tumor cells



PD-L1/CD137 TICA
(BCY10581)

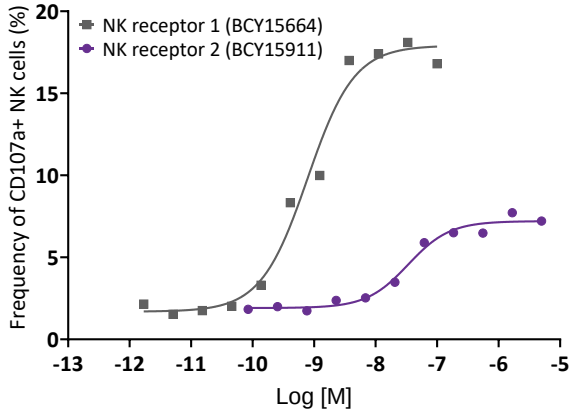
Promega reporter assay / co-culture with RKO tumor cells





NK cell receptors
(undisclosed)

Primary human NK cells in co-culture with A549 tumor cells



Genentech
A Member of the Roche Group

Collaboration with Genentech builds on "plug-and-play" capability of *Bicycles* in IO

bicycle therapeutics

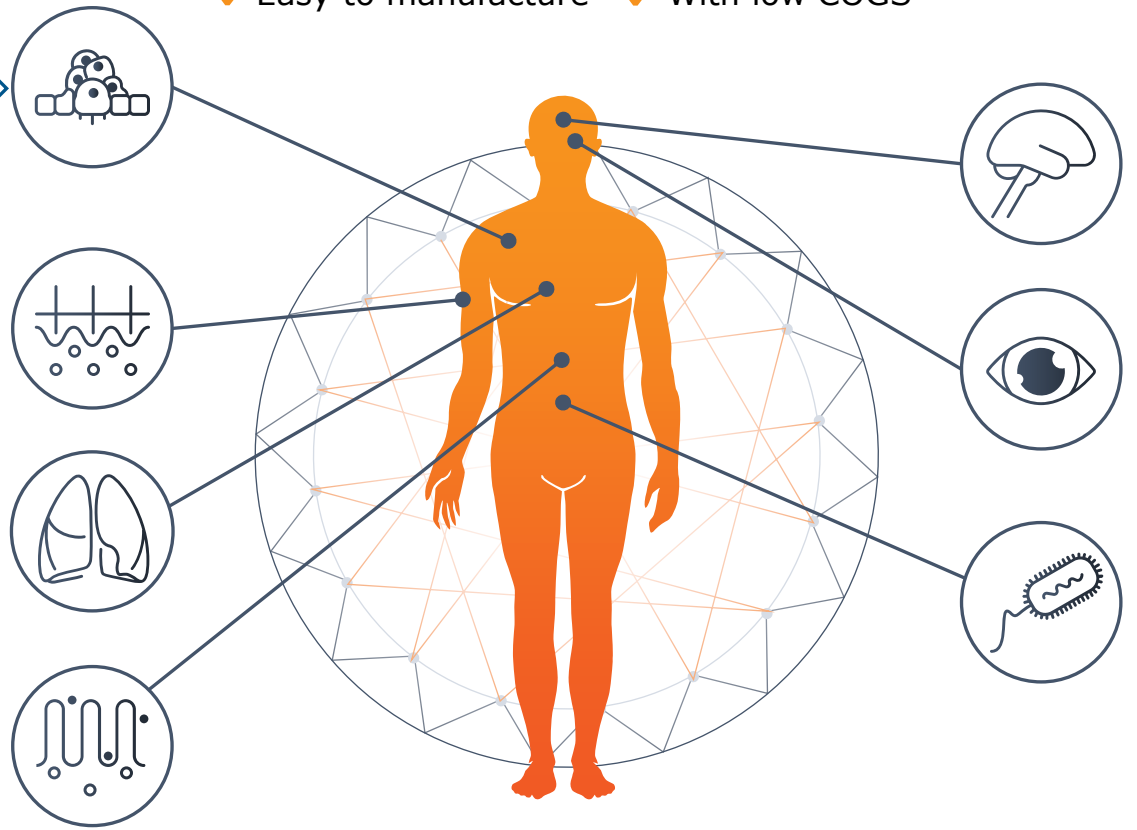
Partnerships

bicycle
therapeutics

Potential of *Bicycle*® technology is unconstrained

***Bicycles* are ideally suited for a broad range of therapeutic interventions and are:**

✓ Easy to manufacture ✓ With low COGS



Oncology
Genentech — A Member of the Roche Group

- Ideally suited for solid tumor delivery
- Preclinical & clinical evidence of precision targeting

Dermatology
- Capable of skin penetration
- Able to potently modulate key inflammatory pathways

Respiratory
- Rapid lung penetration and retention
- Potent modulation of key inflammatory pathways

AstraZeneca

Gastrointestinal
- Gut stable, potent immunomodulation
- Intraluminal modulation of GI disease

Neurodegeneration
- CNS delivery
- Potential next-generation medicines for CNS diseases

Dementia Discovery Fund

Ophthalmology
- Potential for long term modulation
- Proof of concept achieved with clinical evidence of durable activity

OXURION

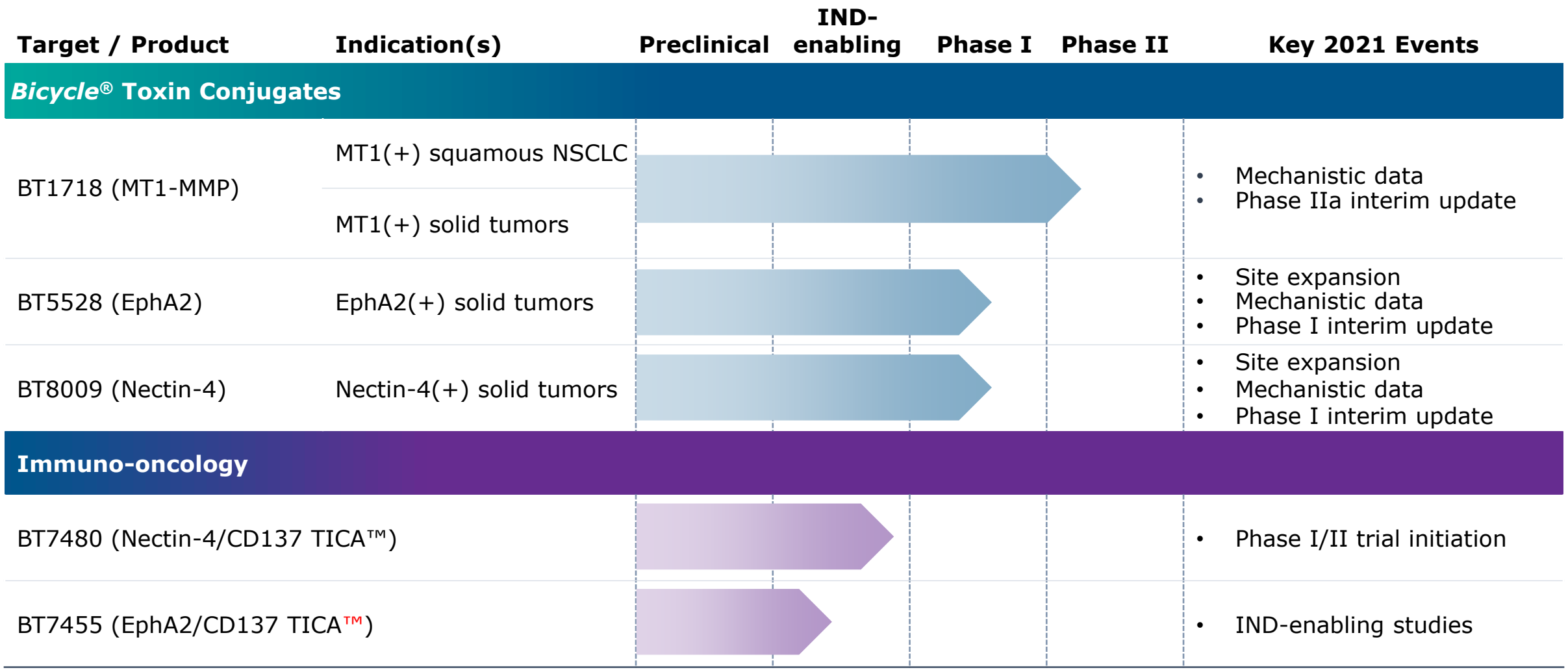
Infectious disease
- Modulation key prokaryotic pathways

Innovate UK

Upcoming Milestones

bicycle therapeutics

Multiple milestones expected across pipeline of wholly-owned clinical & near-clinical assets



May-21

bicycle therapeutics

We aim to redefine what's possible for people with cancer and other serious diseases by pioneering a new and differentiated class of innovative treatments

Leadership team with **deep expertise in drug development**

Robust clinical pipeline of first-in-class / best-in-class medicines with **potential to treat millions of patients**

Cash balance of $195.6M* provides runway to support multiple clinical milestones

as of March 31, 2021