Constrained peptides
Unconstrained thinking

November 2020

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 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 Quarterly Report on Form 10-Q, filed with the Securities and Exchange Commission (SEC) on November 5, 2020, 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

	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 90 patent families

Versatile platform, immense combinatorial potential

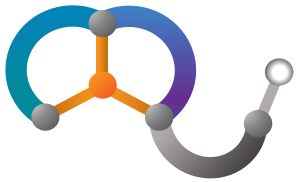
bicycle therapeutics

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	Therapeutic Interest	Preclinical	IND-enabling	Phase 1	Phase 2
***Bicycle*® Toxin Conjugates**						
BT1718 (MT1-MMP)		Oncology				
BT5528 (EphA2)		Oncology				
BT8009 (Nectin-4)		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				

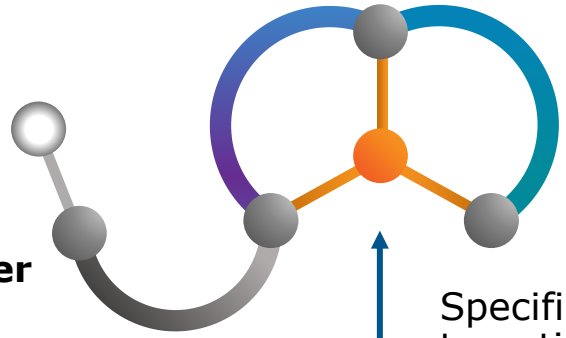
Bicycle® Toxin Conjugates (BTCs)

bicycle therapeutics

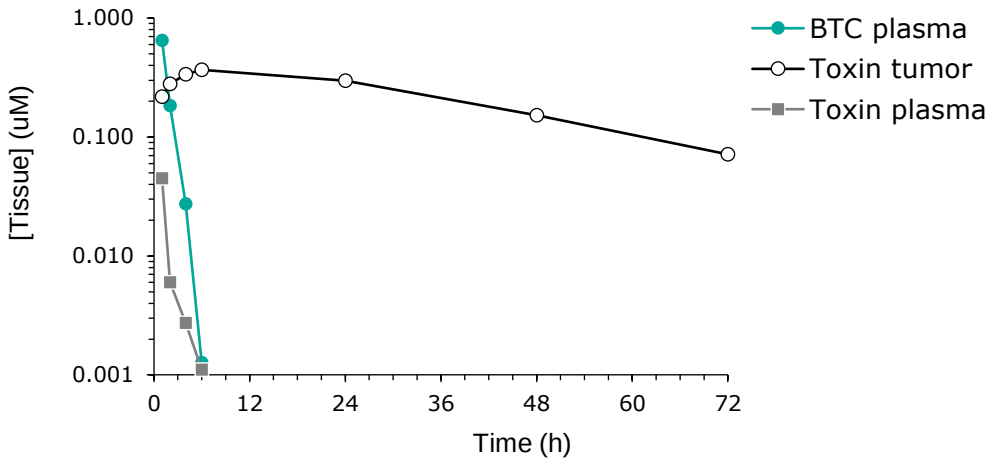
Bicycle® Toxin Conjugates: Designed to be precision targeting therapeutics

Large amount of cytotoxic payload can be delivered → **Toxin**

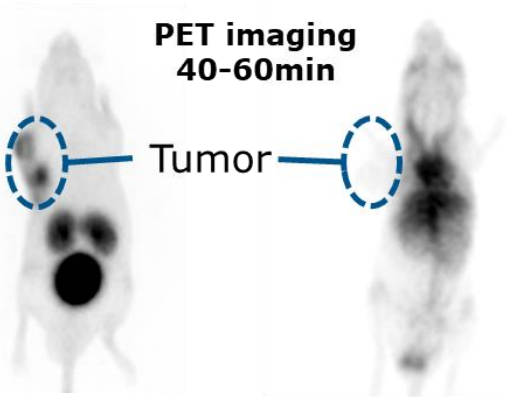
Release of toxin directly into tumor via cleavable linker → **Linker**



Specific tumor targeting via antigen

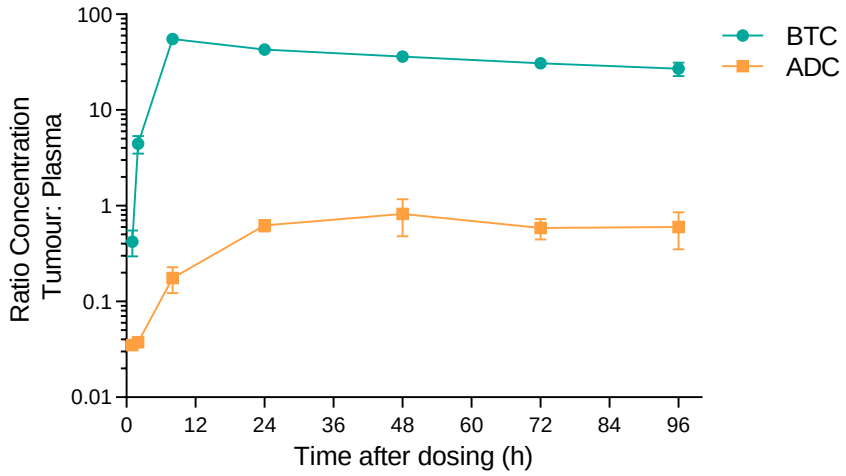


BTCs offer advantages over antibody drug conjugate (ADC) and small molecule approaches



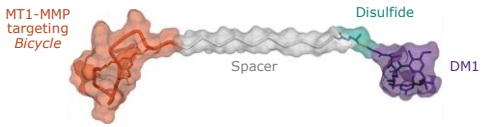
Bicycle **Antibody**

- MWt of 1.5-2kDa, 50-100x smaller than antibodies
- Rapid tumor penetration
- Renal elimination
- Short terminal half-life
- Flexible dosing (mono or combo therapy)



bicycle therapeutics

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



Background

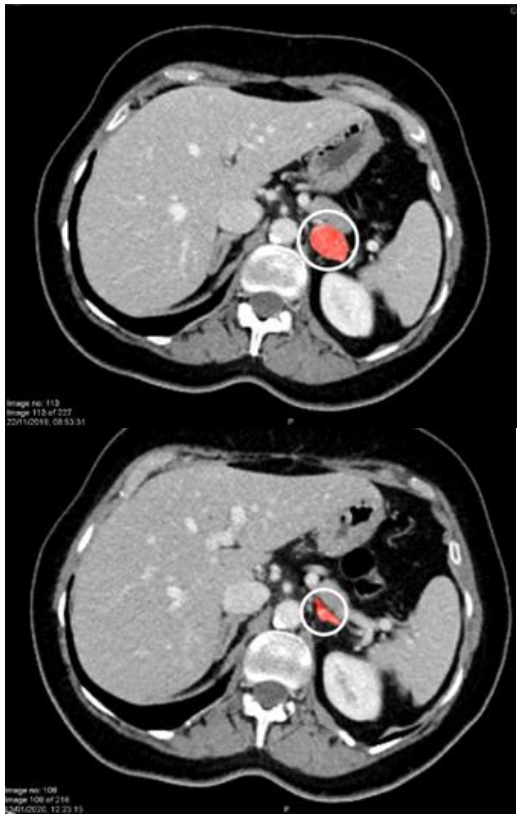
- BT1718 is highly selective for MT1-MMP (MMP-14), which:
  - has established role in cell invasion and metastasis
  - is highly expressed in tumors of squamous cell origin

Status

- Phase II trial initiated: open label, sponsored by CRUK; patients selected based on MT1 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
  - Tolerated at doses delivering >4x toxin delivered by ADCs
  - Early signs of pharmacology in difficult to treat patient population



Baseline

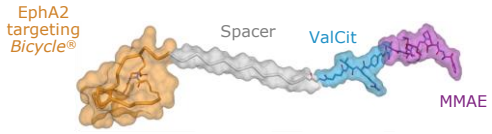
68% reduction in a target lesion (SCLC)

Patient Population

- MT1 is expressed in 58% of NSCLC, 76% of esophageal cases; very highly expressed in bladder and ovarian cancers[1]

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

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

Progress

- Clinically derisked coagulopathy and acute liver toxicity associated with EphA2-targeted ADCs
- Doses administered to date appear tolerable with manageable adverse events

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

Patient Population

- EphA2 is expressed in 52% of pancreatic cases; significant expression (>30%) in NSCLC, gastric, head & neck and bladder cancers[1]

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

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

Background

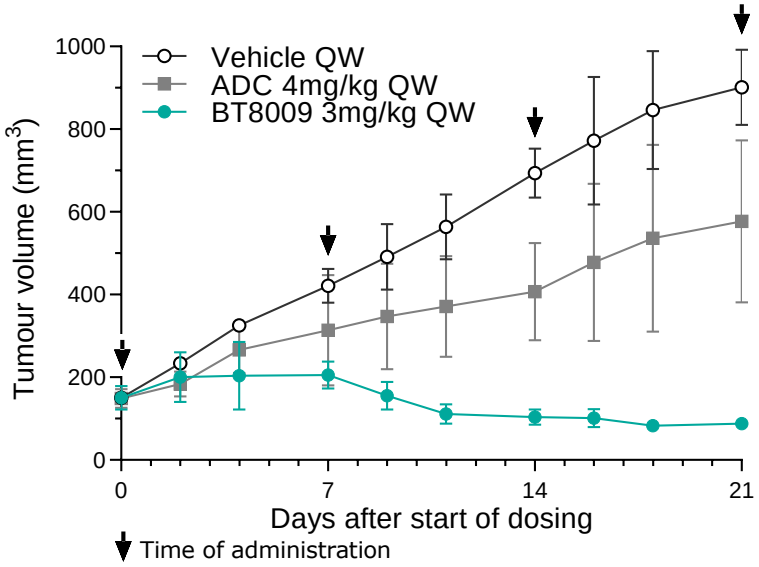
- BT8009 is highly selective for Nectin-4, which:
  - is believed to play a role in tumor cell growth and proliferation
  - is overexpressed in common types of cancer
  - has been validated in the clinic by enfortumab vedotin (Padcev: Astellas/SeaGen)

Status

- Phase I trial ongoing: open label, multi-center across U.S. & EU, enrolling patients with Nectin-4-positive 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[1]

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

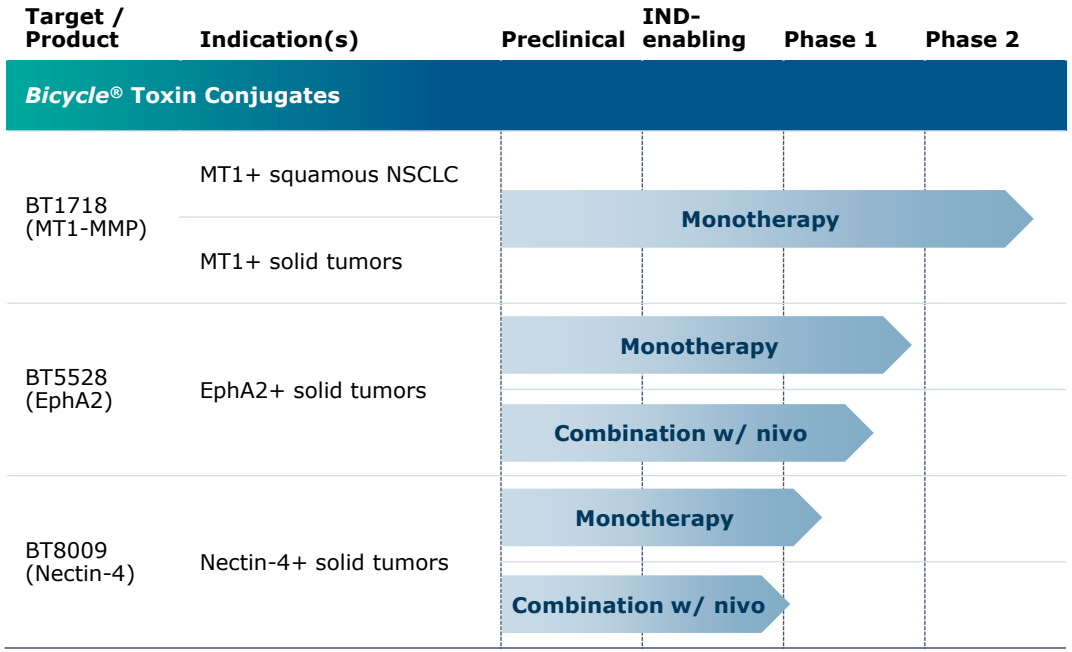
Bicycle® Toxin Conjugates represent possible next-generation cancer therapeutics with broad potential

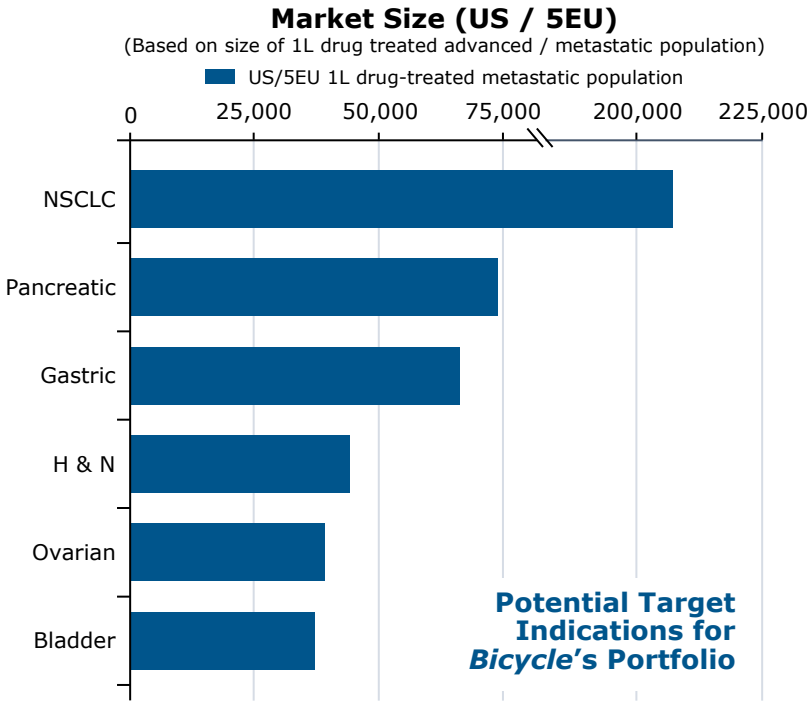
First-in-class or best-in-class opportunities

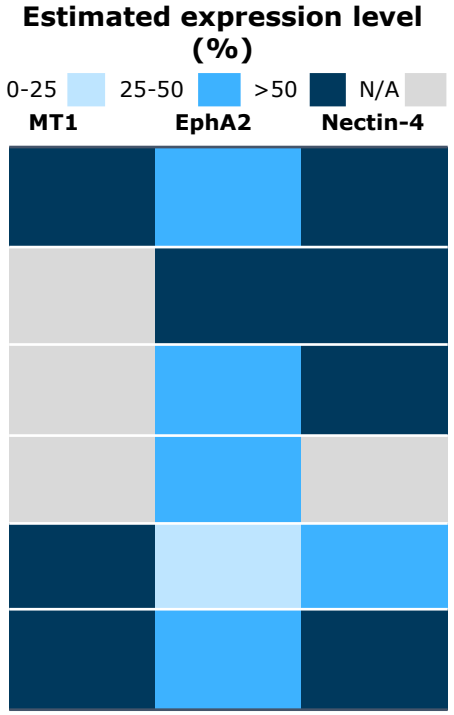
Based on novel technology, designed to overcome ADC failure and other limitations

Potential for internal/ external combinations

Represent future of tumor-targeted cytotoxic payload delivery







Nov-20

bicycle therapeutics

Immuno-oncology

bicycle therapeutics

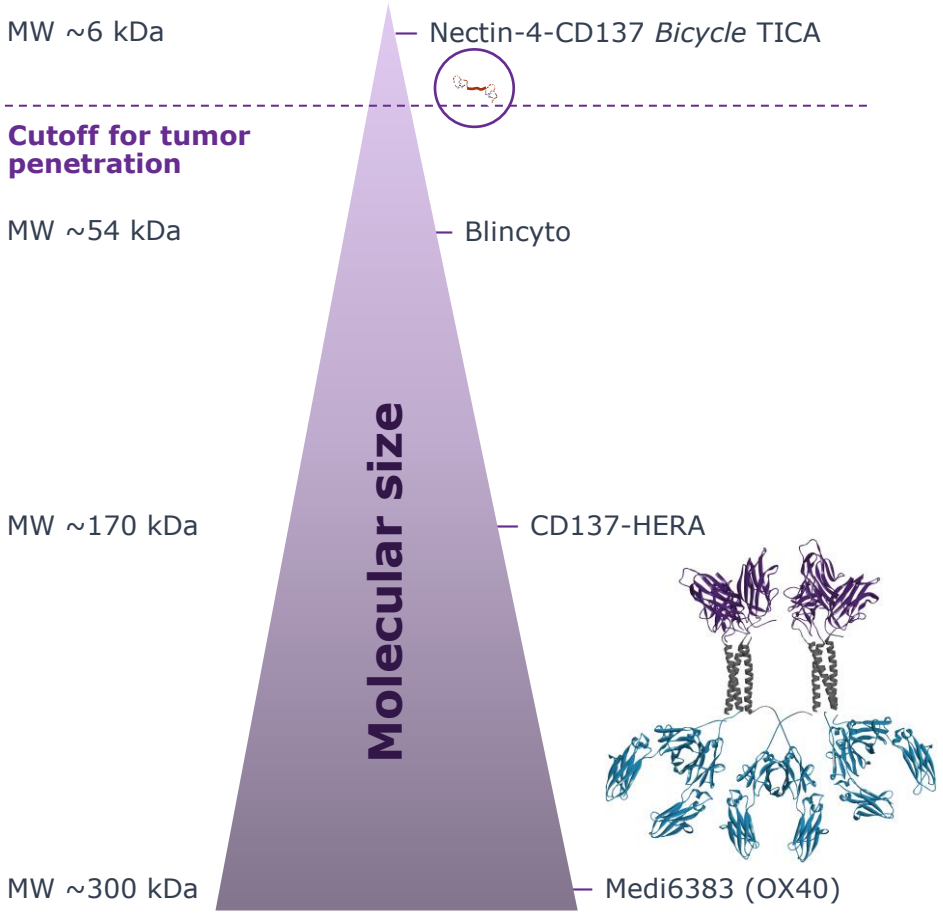
Bicycles® are a new class of IO therapies that could overcome limitations of existing approaches

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
- No immunogenicity
- Generalizable approach
- Chemically synthetic so easy to "tune" properties
- Simple peptide manufacturing



bicycle therapeutics

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

Why CD137?

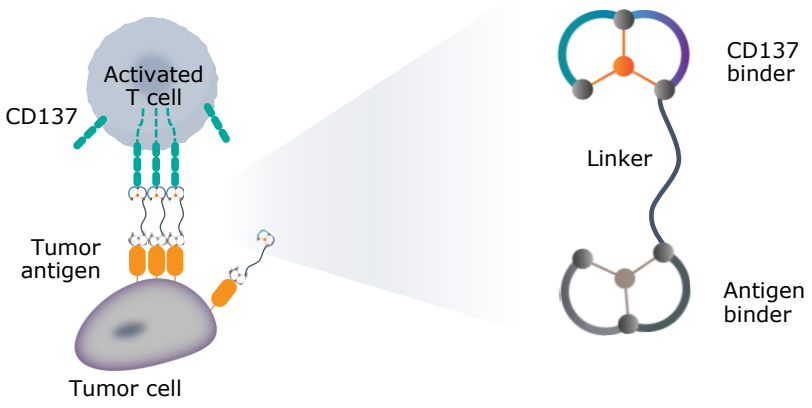
- Validated target, limited by toxicity
- Unlike CD3, expressed on multiple immune cell types
- Transient agonism may be superior to prolonged agonism induced by biologics

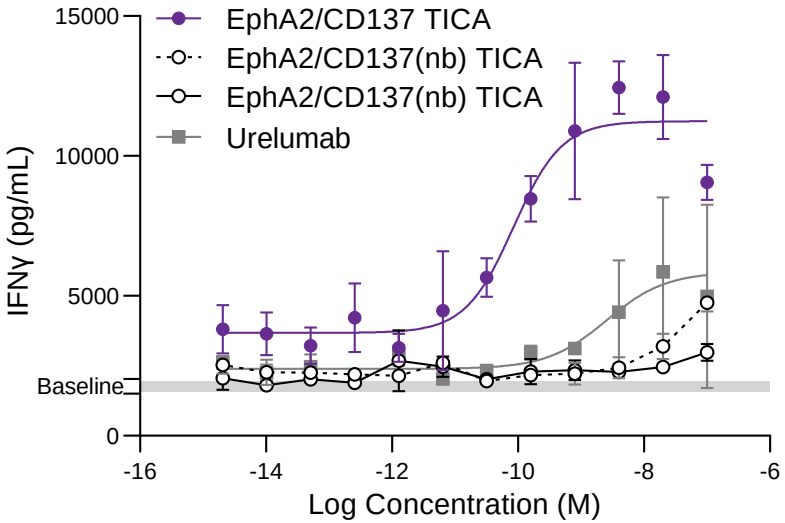
Flexibility in tumor targeting

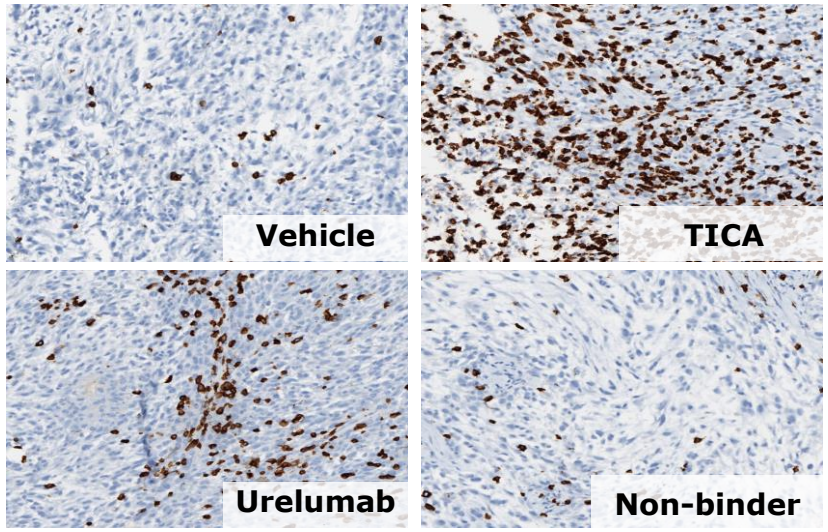
- Tumor antigen binding *Bicycles*® can be easily swapped, a true product platform
- Nectin-4, EphA2 build on BTC platform and establish franchise
- Enables novel internal combinations

Tumor dependent super-agonism

- Highly potent (>urelumab)
- Completely dependent on presence of tumor antigen







bicycle therapeutics

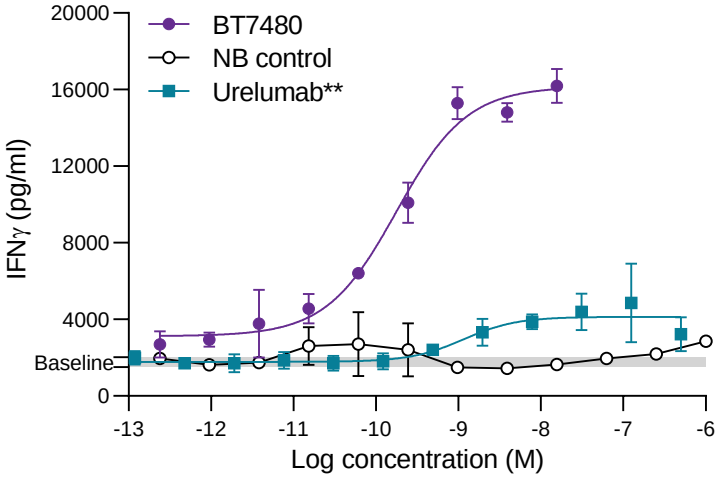
BT7480: Potential first-in-class, highly potent Nectin-4-targeted CD137 agonist

Background & Status

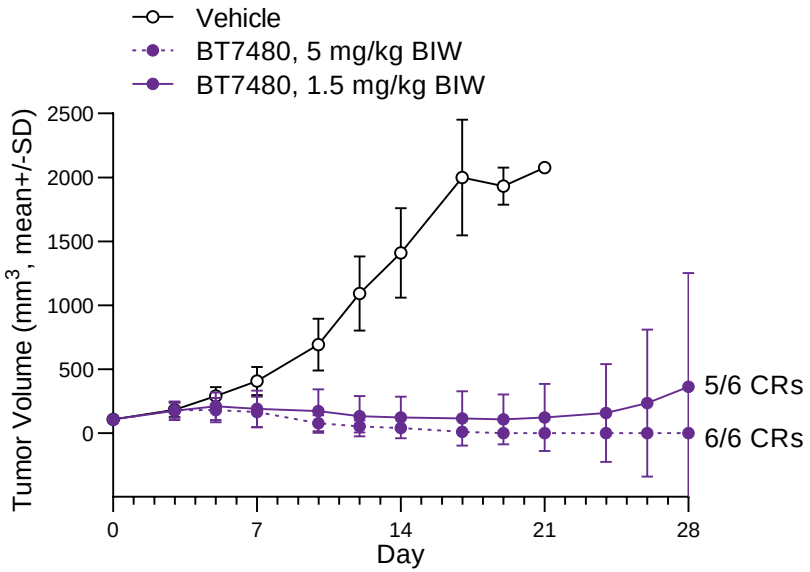
- More potent than urelumab in Nectin-4 expressing tumors
- Fully synthetic, 30x smaller than antibodies
- Short half life, compatible with intermittent dosing
- Ideal combination partner
- IND-enabling studies ongoing
- Phase I initiation expected in 2021

Progress

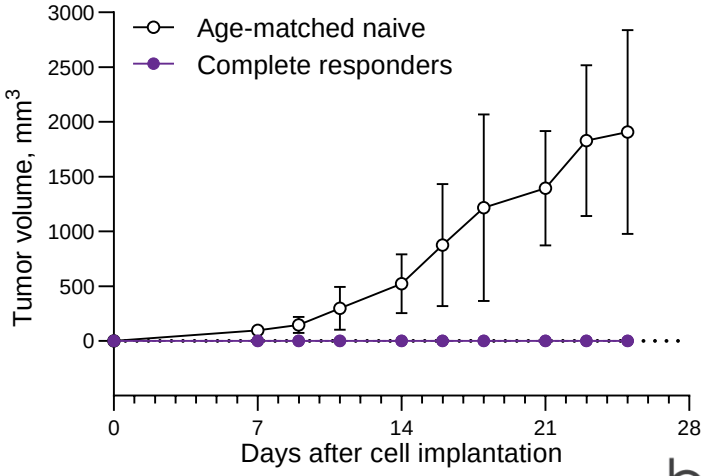
- BT7480 is a more potent and targeted agonist than urelumab



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



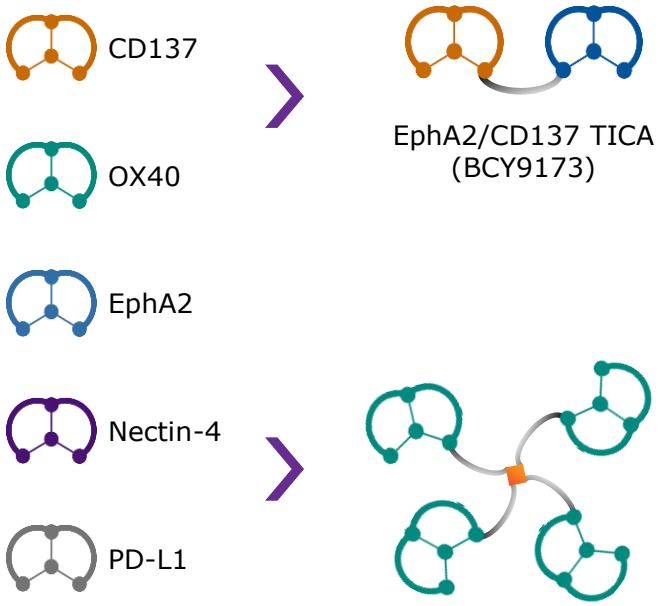
- Evidence of immunogenic memory in syngeneic mouse model



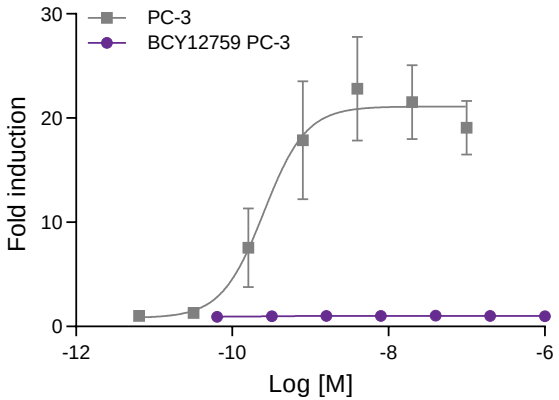
Bicycle® TICAs: A modular & generalizable platform

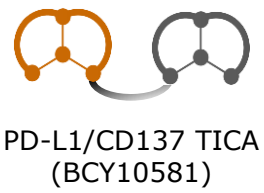
Immune cell and tumor targeting Bicycles *can be rapidly combined and chemically optimized*

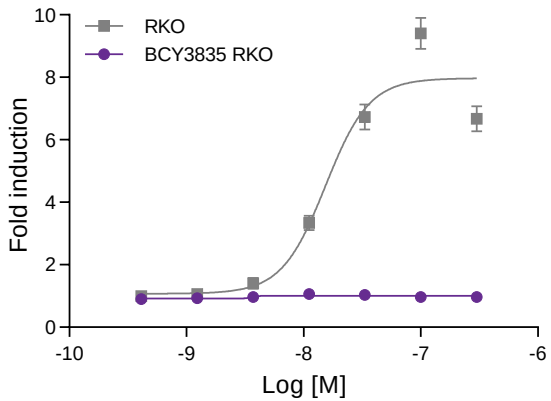
Immune and Tumor Cell Targeting *Bicycles*

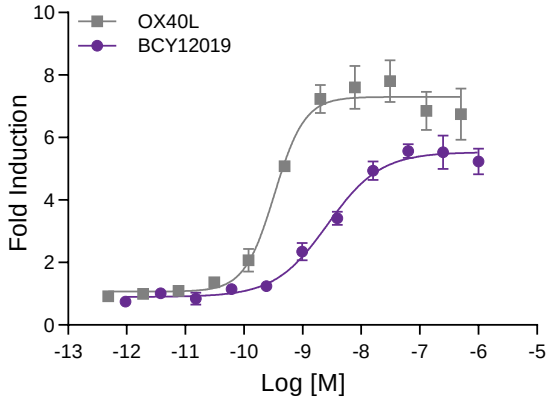


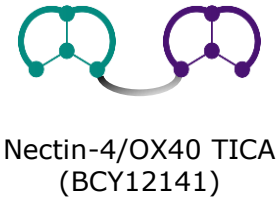
CD137 or OX40 reporter cell assay data (Promega) alone or in co-culture with tumor cells

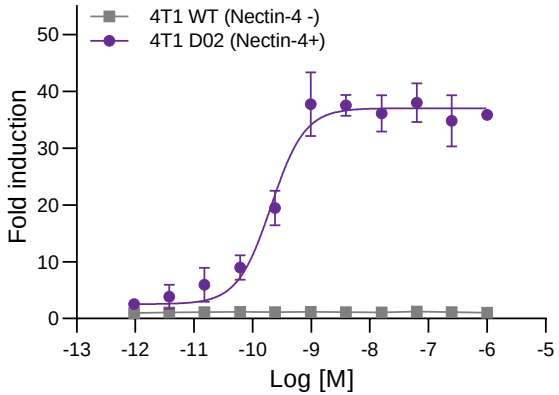












Genentech
A Member of the Roche Group

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

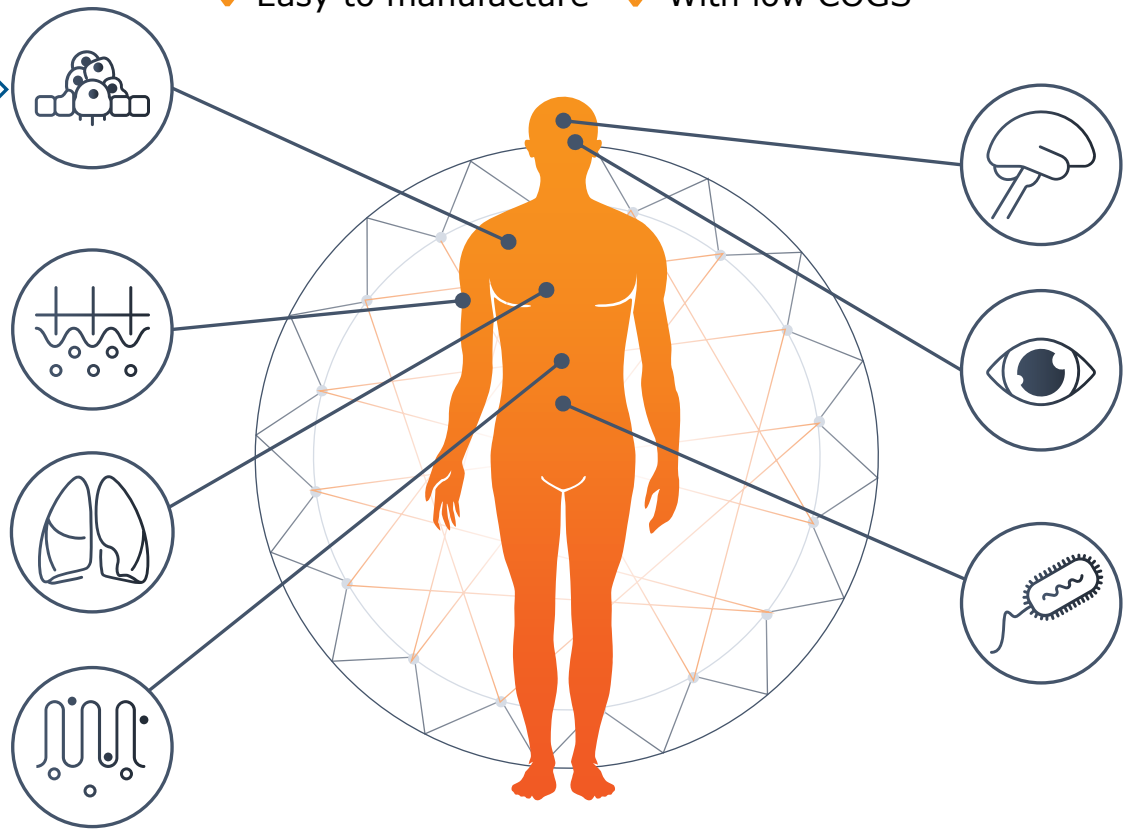
Respiratory

- 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

Partners have contributed $60M (30%) of total capital raised & $2bn+ in potential milestones

Upcoming Milestones

bicycle
therapeutics

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

Target / Product	Indication(s)	Preclinical	IND-enabling	Phase 1	Phase 2	Key 2021 Events
***Bicycle*® Toxin Conjugates**						
BT1718 (MT1-MMP)	MT1+ squamous NSCLC MT1+ solid tumors	Monotherapy				• Phase II interim update
BT5528 (EphA2)	EphA2+ solid tumors	Monotherapy Combination w/ nivo				• RP2D for mono & combo arms • Initiation of Phase II study
BT8009 (Nectin-4)	Nectin-4+ solid tumors	Monotherapy Combination w/ nivo				• Phase I interim update
Immuno-oncology						
BT7480 (Nectin-4/CD137 TICA™)						• Phase I/II trial initiation
BT7455 (EphA2/CD137 TICA)						• IND-enabling studies

Nov-20

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**

NOVARTIS AstraZeneca Pfizer Bristol-Myers Squibb gsk

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

Cash balance of $149.8M* provides runway to support multiple clinical milestones

*As of September 30, 2020