Targeting Tumors with Bicycle Conjugates

Mark Frigerio, VP Chemistry
PEGS Boston - 2023
Forward-looking statement and disclaimer

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 plans, prospects, trends or strategies and other business matters; our current and prospective product candidates, planned clinical trials and preclinical activities, 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, 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 Quarterly Report on Form 10-Q, filed with the Securities and Exchange Commission on May 4, 2023, as well as in other filings we 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.

This presentation does not constitute an offer to sell or a solicitation of an offer to buy securities, nor shall there be any sale of any securities in any state or jurisdiction in which such offer, solicitation or sale would be unlawful prior to registration or qualification under the securities laws of any such state or jurisdiction.
# Bicycle Therapeutics

**Founded by Sir Greg Winter & Prof. Christian Heinis**

**UK & US based (Cambridge, UK; Boston, USA)**

![2018 Nobel Prize in Chemistry](image)

“for the phage display of peptides and antibodies”

<table>
<thead>
<tr>
<th>Target / Product</th>
<th>Partner/Sponsor</th>
<th>Indication</th>
<th>Modality</th>
<th>Preclinical</th>
<th>IND-enabling</th>
<th>Phase I</th>
<th>Phase II/Expansion</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Internal Programs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BT5528 (EphA2)</td>
<td></td>
<td>Oncology</td>
<td>Bicycle* Toxin Conjugate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BT8009 (Nectin-4)</td>
<td></td>
<td>Oncology</td>
<td>Bicycle* Toxin Conjugate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BT7480 (Nectin-4/CD137)</td>
<td></td>
<td>Immuno-oncology</td>
<td>Bicycle TICA™</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BT7455 (EphA2/CD137)</td>
<td></td>
<td>Immuno-oncology</td>
<td>Bicycle TICA™</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MT1-MMP</td>
<td>dkfz</td>
<td>Radiopharmaceutical</td>
<td>Bicycle Radio Conjugate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Partnered Programs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>THIR-149 (Kallikrein inhibitor)</td>
<td>Oxurion</td>
<td>Ophthalmology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BT1718 (MT1-MMP)</td>
<td></td>
<td>Oncology</td>
<td>Bicycle* Toxin Conjugate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BT7401 (multivalent CD137 system agonist)</td>
<td>Cancer Research Institute</td>
<td>Immuno-oncology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undisclosed</td>
<td></td>
<td>Immuno-oncology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple targets</td>
<td></td>
<td>Cardio, metabolic, resp</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novel anti-infectives</td>
<td>Innovate UK</td>
<td>Anti-infectives</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novel CNS targets</td>
<td>IONIS</td>
<td>CNS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novel neuromuscular targets</td>
<td>IONIS</td>
<td>Neuromuscular</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undisclosed</td>
<td>NOVARTIS</td>
<td>Radiopharmaceutical</td>
<td>Bicycle Radio Conjugate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Bicycle** platform delivers a toolkit of building blocks to create novel medicines

*Bicycle*® Phage Display - Discovery

- Linear peptide
- *Bicycle*®
- Protein III
- Bicycle DNA sequence
- Gene III
- Phage particle
- Diverse *Bicycle*® phage libraries (>10^20)

**Peptide & Medicinal Chemistry**

- Optimize *Bicycle*® monomers
- Non-natural Amino Acids

**Potential *Bicycle*® Medicines**

- Monomeric *Bicycles*
- Targeted Drug Conjugates
- Targeted/ Multi-specific *Bicycles*

**Tumor Targeting and Effector *Bicycles***

Build and Optimize Therapeutic *Bicycles*

Easy conjugation of Linkers and Payloads

PEGS Boston, 2023
Structural constraints create *Bicycle®* advantage

<table>
<thead>
<tr>
<th>MT1-MMP affinity (FP competition)</th>
<th>BCY00009863 (MT1-MMP) $K_i$ (nM)</th>
<th>BCY00009862 (MT1-MMP) $K_i$ (nM)</th>
<th>BCY00009520 (MT1-MMP) $K_i$ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;10000 (n=2)</td>
<td>$115.1 \pm 22.9$ (n=2)</td>
<td>$1.15 \pm 0.07$ (n=2)</td>
</tr>
</tbody>
</table>
**Bicycles** are designed to combine the advantages of both small molecules and antibodies.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Bicycle®</th>
<th>Small molecule</th>
<th>Antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small size</td>
<td>Yes – 1.5-2kDa</td>
<td>Yes – &lt;0.8kDa</td>
<td>No – &gt;150kDa</td>
</tr>
<tr>
<td>Specificity</td>
<td>High</td>
<td>Low</td>
<td>Multiple</td>
</tr>
<tr>
<td>Chemical synthesis (NCEs)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Rapid tissue penetration</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Complex protein targets druggable</td>
<td>Yes</td>
<td>Limited</td>
<td>Yes</td>
</tr>
<tr>
<td>Route of elimination</td>
<td>Renal</td>
<td>Liver</td>
<td>Liver</td>
</tr>
</tbody>
</table>
BTCs – preclinical data indicates higher potency and specificity with fewer side effects than ADCs

- MW of 1.5-2kDa
- 50-100x smaller than antibodies

- High selectivity
- Allows more potent toxin to be delivered directly to tumor

**Bicycle® Toxin Conjugate (BTC™)**

- **Toxin**
  - Large amount of cytotoxic payload can be delivered
- **Linker**
  - Release of toxin directly into tumor via cleavable linker
- **Specificity**
  - Tumor targeting via antigen

**Graph:**
- BTC plasma
- Toxin plasma
- Tissue (uM)
- Time (h)
EphA2 is a high value target for the treatment of cancer

- EphA2, a member of Eph subfamily of receptor tyrosine kinases

- Regulates cell migration, adhesion, proliferation and differentiation

- Highly expressed in many human cancers and correlates with tumor progression
  - Ovarian
  - Urothelial
  - NSCLC
  - Head & Neck
  - Gastric
  - TNBC

*Kamoun, et al, Nanoliposomal Targeting of Ephrin Receptor A2 (EphA2): Clinical Translation, Merrimack Pharmaceuticals
Multiple approaches targeting EphA2-expressing tumors have failed

- MEDI-547 (MedImmune) ADC: halted following first dose-cohort coagulopathy\(^1\)

- DS-8895a (Daiichi) antibody: limited efficacy in EphA2+ gastric and esophageal cancer, significant infusion reactions. Discontinued because of poor risk-benefit profile\(^2\)

- MM-310 (Merrimack) antibody-targeted nanoliposome: terminated - “unable to reach optimal therapeutic index”\(^3\)

1. Annunziata et al, Invest New Drugs. 2013 Feb;31(1):77-84
BT5528 is a first-in-class BTC-targeting EphA2

- BT5528 has potential to penetrate solid tumors; approximately 40X smaller than an ADC

- Toxin is released and retained in tumor cells, resulting in tumor cell death and bystander killing

- PK profile distinct from ADCs; renally eliminated, bypassing liver metabolism

- Recently completed dose escalation of Phase I clinical study
BT5528: Emerging relationship between EphA2 expression and response in ovarian and urothelial cancers

- Waterfall plot showing best response among urothelial and ovarian cancer patients in first in human study
- Immunohistochemistry data suggest EphA2 positive patients more likely to respond to BT5528
- Scan showing complete responder with ovarian cancer
BT5528: structure and profile

High affinity binding to EphA2 protein across species and on cells. Species cross-reactivity, high selectivity.

<table>
<thead>
<tr>
<th>BT5528 affinity</th>
<th>Human</th>
<th>Mouse</th>
<th>Rat</th>
<th>NHP</th>
</tr>
</thead>
<tbody>
<tr>
<td>FP comp ($K_i$, nM)</td>
<td>1.9 ± 0.9</td>
<td>5.2 ± 1.9</td>
<td>1.9 ± 1.3</td>
<td>1.9 ± 1.3</td>
</tr>
<tr>
<td></td>
<td>n=29</td>
<td>n=16</td>
<td>n=10</td>
<td></td>
</tr>
<tr>
<td>SPR ($K_D$, nM)</td>
<td>0.9 ± 0.4</td>
<td>2.0 ± 0.8</td>
<td>2.7 ± 0.4</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>n=2</td>
<td>n=2</td>
<td>n=2</td>
<td>n=1</td>
</tr>
<tr>
<td>Cell binding by HCS ($K_{app}$, nM)</td>
<td>14.8 ± 10.5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Membrane protein array: no binding of BT5528 @1μM to 5,527 other proteins
Chemical optimization of a high affinity EphA2 targeting *Bicycle*® with improved properties

2 scaffolds x 10 libraries, ➔ 8 peptide families

**BCY6014**

Chemistry Optimisation <40 analogs

**BCY6099**

4 non-natural amino acids

Modifications (*) to increase polarity, stability and/or potency

**BCY6014 Ki = 16 nM** – early *Bicycle*

ARDCLVPNPLCLHPGWTCA

**BCY6099 Ki = 3 nM** – newly optimised *Bicycle*

AhRDChyPLVNPLCLHPdDWhRCAC

* * *

PET imaging of HT-1080 xenograft at 60 minutes
**BT5528: activity in difficult-to-treat xenograft models**

**Superior activity to EphA2 ADC in large NSCLC xenograft models**

- Bicycle distribution at 60 min
- ADC distribution at 60 min

**Activity in pancreatic xenograft models**

- PDAC1
- PDAC2

---

**Tumor Volume (mm$^3$)**

- Vehicle qw
- BT5528 3mg/kg qw
- EphA2 ADC 3mg/kg qw

**Days after start of dosing**

\[0\, 7\, 14\, 21\, 28\, 35\, 42\, 49\, 56\, 63\, 70\, 77\, 84\, 91\, 98\]
BT5528 offers a differentiated approach to EphA2

EphA2 has been viewed as a "difficult" target

Clinical trial of EphA2-targeting ADC, MEDI-547, terminated after bleeding & liver effects seen at starting dose

BT5528 PK/PD profile offers pre-clinical anti-tumor activity without prolonged vascular exposure

Treatment related adverse events

<table>
<thead>
<tr>
<th>Event</th>
<th># events (% of patients)</th>
<th>n of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT increased</td>
<td>3 (50)</td>
<td>3/6</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>6 (83.3)</td>
<td>5/6</td>
</tr>
</tbody>
</table>

BT5528 toxicology study

- No signs of coagulopathy or bleeding in preclinical species
- No evidence of abnormal liver function
- Dosing to toxin equivalent doses >100x dose of MEDI-547 used in patients
MMAE Delivery Using the *Bicycle* Toxin Conjugate

**BT5528**

Gavin Bennett¹, Amy Brown¹, Gemma Mudd¹, Philip Huxley¹, Katerine Van Rietschoten¹, Silvia Pavan², Liuhong Chen¹, Sophie Watcham³, Johanna Lahdenranta⁴, and Nicholas Keen⁴

**ABSTRACT**

The EphA2 receptor is found at high levels in tumors and low levels in normal tissue and high EphA2 expression in biopsies is a predictor of poor outcome in patients. Drug discovery groups have therefore sought to develop EphA2-based therapies using small molecule, peptide, and nanoparticle-based approaches (1–3). However, until now only EphA2-targeting antibody–drug conjugates (ADC) have entered clinical development. For example, MEDI-547 is an EphA2-targeting ADC that displayed encouraging antitumor activity in preclinical models and progressed to phase I clinical testing in man. Here we describe the development of BT5528, a bicyclic peptide ("Bicycle") conjugated to the auristatin derivative maleimidocaproyl-monomethyl auristatin E to generate the *Bicycle* toxin conjugate BT5528. The report compares and contrasts the Pharmacokinetics (PK) characteristics of antibody and *Bicycle*-based targeting systems and discusses how the PK and payload characteristics of different delivery systems impact the efficacy— toxicity trade off which is key to the development of successful cancer therapies. We show that BT5528 gives rise to rapid update into tumors and fast renal elimination followed by persistent toxin levels in tumors without prolonged exposure of parent drug in the vasculature. This fast in, fast out kinetics gave rise to more favorable toxicology findings in rats and monkeys than were observed with MEDI-547 in preclinical and clinical studies.

**Graphical Abstract:** http://mct.aacrjournals.org/content/molcanther/19/7/1385/F1.large.jpg.
BT5528: EphA2 targeted BTC™

Erythropoietin-producing hepatocellular A2 receptor: member of Eph subfamily of receptor tyrosine kinases

- Regulates cell migration, adhesion, proliferation and differentiation
- Overexpressed in human cancers and correlates with tumor progression
- Development of MEDI-547 (MedImmune) in ovarian cancer was halted following serious bleeding events in phase I

<table>
<thead>
<tr>
<th>Internal</th>
<th>Target</th>
<th>Modality</th>
<th>Pre-clinical</th>
<th>IND-enabling</th>
<th>Phase I</th>
<th>Phase II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bicycle</td>
<td>EphA2</td>
<td>Bicycle® Toxin Conjugate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- BT5528-100: Phase I/II multi-center first-in-human study in patients with advanced solid tumors associated with EphA2 expression
- NCT04180371 Study ongoing
- Clinical update presented by Dr Meredith McKean at AACR-NCI-EORTC Triple Meeting Oct 7 2021
- Topline data from escalation phase released Sep 2022
- Further BT5528 update in 2023

**BT8009: Nectin-4 targeted BTC™**

**Nectin-4:**
A cell adhesion molecule and one of four members of the nectin family

All nectins share the same overall structure defined by three extracellular immunoglobulin domains, a single transmembrane helix and an intracellular domain

- Overexpressed in human cancers and correlated with tumor progression
- Solid tumors with high levels of Nectin-4 expression are urothelial, TNBC, ovarian and NSCLC

<table>
<thead>
<tr>
<th>Internal Target Modality</th>
<th>Pre-clinical</th>
<th>IND-enabling</th>
<th>Phase I</th>
<th>Phase II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bicycle Nectin-4 Bicycle® Toxin Conjugate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- BT8009-100: Phase I/II Study of the Safety, Pharmacokinetics, and Preliminary Clinical Activity of BT8009 in Patients With Nectin-4 Expressing Advanced Malignancies
- NCT04561362
- Study ongoing
- BT8009 Phase I trial results released at ASCO GU Feb 2023
- For more information, please visit www.bicycletx.com
Nectin-4 Bicycle® optimization from lead to BT8009

Parent Bicycle
Ac C P F G C M K N W S W P I W C
Amino Acids Important For Target Engagement

Stabilised Bicycle
Ac C P F d C M hArg N W S W P I W C
Improve stability, hydrophilicity

Optimised Bicycle
Ac C P 1Nal d C M hArg D W S T P Hyp W C
+ affinity + hydrophilicity + affinity, hydrophilicity

BT8009
MW=4173.8

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

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

AAs further optimised to increase affinity, improve hydrophilicity. Selected as candidate peptide binder

<table>
<thead>
<tr>
<th>Ki (nM)</th>
<th>cLogP</th>
<th>t_{1/2} (plasma)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.4</td>
<td>-6.98</td>
<td>1.3h</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ki (nM)</th>
<th>cLogP</th>
<th>t_{1/2} (plasma)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>-6.74</td>
<td>&gt;24h</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ki (nM)</th>
<th>cLogP</th>
<th>t_{1/2} (plasma)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.2</td>
<td>-13.32</td>
<td>&gt;24h</td>
</tr>
</tbody>
</table>

MW=4173.8
BT8009: Nectin-4 targeted BTC™

**Discovery of BT8009: A Nectin-4 Targeting Bicycle Toxin Conjugate for the Treatment of Cancer**

Gemma E. Mudd, Heather Scott, Liuhong Chen, Katerine van Rietschoten, Gabriela Ivanova-Berndt, Katarzyna Dzioniak, Amy Brown, Sophie Watcham, Lewi White, Peter U. Park, Phil Jeffrey, Mike Rigby, and Paul Beswick

---

**Human Nectin-4 KD (nM)**

<table>
<thead>
<tr>
<th>Human Nectin-4 KD (nM)</th>
<th>plasma protein binding (%)</th>
<th>In vitro plasma stability</th>
<th>mouse pharmacokinetics 3 mg/kg, IV (bolus)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>Human</td>
<td>mouse</td>
<td>human</td>
</tr>
<tr>
<td>2.50</td>
<td>88.2</td>
<td>4.4</td>
<td>&gt;57.8</td>
</tr>
</tbody>
</table>

**Activity in breast adenocarcinoma (MDA-MB468) CDX model**

Vehicle: IV qw
- BT8009: 3mg/kg qw
- BT8009: 3mg/kg bw
- BT8009: 5mg/kg qw

Tumour Volume [mm^3]

Days after start of dosing
The percentage of change from initial tumor volume and Nectin-4 expression, assessed by IHC, in 14 NSCLC PDX models.

A clear association between degree of tumor regression and level of Nectin-4 expression observed.

MMAE is rapidly cleared from plasma but retained in tumor substantially longer.
Bicycle TICA™—tumor-targeted immune cell agonists delivers immune agonism to tumors

Activation induced by clustering of **CD137** by trimeric **CD137L**

CD137 clustering induced by tumor antigen drives stronger immune cell potency
Preclinical in vitro proof of concept with the first EphA2/CD137 molecule

Cancer cells expressing high levels of EphA2

EphA2 expression

BCY7985: CD137 reporter assay in co-culture with EphA2 cells

Molecules per cell normalized to isotype control

Log concentration (M) vs. fold induction

- A549
- HT1080
- LNCaP
- no cells

PEGS Boston, 2023
**Bicycle TICA™ is a generalizable concept**

Diverse Bicycle® phage libraries (>10^{20})

Immune and Tumor Cell Targeting Bicycles

Anticancer immunity induced by a synthetic tumor-targeted CD137 agonist

Immune effector and tumor targeting Bicycles can be combined in a modular fashion to construct a pipeline of Bicycle® tumor-targeted immune cell agonists

PEGS Boston, 2023
MT1-MMP targeting BRC™ shows superior tumor uptake and contrast versus mAb in mouse model

MT1-MMP overexpressed in variety of cancers (non–small cell lung, gastric and breast)

Whole-body maximum intensity projections were obtained 40 to 60 minutes p.i. using uPET imaging

Bicyclic Peptides as a New Modality for Imaging and Targeting of Proteins Overexpressed by Tumors

Bicycles Fikszczak, Fikszczak, and Palacios

MT1-MMP targeting BRC
Non-binding BRC
MT1-MMP targeting mAb conjugate

PEGS Boston, 2023
Targeted alpha therapy of a Lead-212 labelled MT1-MMP targeting Bicycle Radionuclide Conjugate™ (BRC)

MT1-MMP targeting Bicycle
- High affinity (5 nM) binding to target antigen
- Allows precision targeting of BRC™ to tumor cells

Half-life extending (HLE) moiety
- Reversible albumin binding motif
- Prolongs circulating half-life of conjugate

Lead-212
- Potent radioisotope causes dsDNA break through alpha emission

212Pb-MT1-BRC shows tumor activity levels of >45% ID/g 24 hrs post 10μCi injection

- In vivo distribution of 212Pb-BRC in mice with HT1080 tumors shows a favorable biodistribution profile
- 10μCi of 212Pb-MT1-BRC administered and organs collected at 1 hour, 4 hours and 24 hours post injection, with tissue uptake expressed as %ID per gram (n=5)
- A tumor to kidney ratio of >1 was achieved at this dose
Targeted alpha therapy of a Lead-212 labelled MT1-MMP targeting Bicycle Radionuclide Conjugate™ (BRC)

- Alpha imaging of tumor sections at 1- and 4- hours post injection shows that a Lead-212 labelled MT1-MMP-BRC is rapidly accumulated in the tumor with homogeneous distribution.

- In comparison, a Lead-212 labelled MT1-MMP targeting antibody shows very low, heterogeneous uptake in the tumor at the same timepoints.

Alpha-imaging of $^{212}$Pb-MT1-BRC and $^{212}$Pb-MT1-mAb with microdistribution in cryosectioned HT1080 xenograft tissue samples with equivalent contrast.
Potent anti-tumor activity of a Lead-212 labelled MT1-MMP targeting Bicycle Radionuclide Conjugate™

- Anti-tumor activity of a $^{212}$Pb-MT1-BRC in an HT1080 mouse model efficacy study
- Doses of 1x5 µCi, 1x10 µCi, 3x5 µCi or 3x10 µCi (2 weeks apart) (N= 8-10)
- $^{212}$Pb-MT1-BRC is well tolerated up to 40µCi in single dose mouse model DRF studies and shows potent anti-tumor activity
- Administration of $^{212}$Pb-MT1-BRC led to increased survival at all doses tested, with complete tumor regressions observed at the highest dose.

Survival plot with median survival increases for each dosing group and 90% survival for the highest dose group (3 cycles of 10 µCi $^{212}$Pb-MT1-BRC every two weeks).
Diversifying the Bicycle® platform

**BT1718**
- Target: MT1-MMP
- DM1 payload
- Disulfide linker

**BT5528**
- Target: EphA2
- MMAE payload
- Val-Cit linker

**BT8009**
- Target: Nectin-4
- MMAE payload
- Val-Cit linker

**BT7480**
- Targets: Nectin-4, CD137
- PEG3 linker

**BT7455**
- Targets: EphA2, CD137
- PEG3 linker
- Next Bicycle TICA™ scheduled for clinic

**NK-TICA™**
- Next-gen BTCs
- Different targets, linkers and payloads

---

**Validation**

**Radiopharm**

**FIH 2018**

**2019**

**2020**

**2021**

**2023 and beyond**

PEGS Boston, 2023
Bicycles offer a potential new modality for oncology therapeutics
• Antibody-like affinity and selectivity in a small molecule
• Chemically synthesized
• Rapid distribution to solid tumors, elimination via renal route

Bicycle TICAs show promise for targeted stimulation of immune cells in tumors
• BT7480 entered the clinic Q4 2021
• BT7455 (EphA2-CD137 Bicycle TICA™) in IND-enabling stage
• NK-TICA™ programs targeting natural killer (NK) cells identified and moving into lead optimization

Bicycle Toxin Conjugates® progressing in clinical studies
• 3 conjugates in clinical trials
• Preliminary signs of anti-tumor activity seen
• Emerging safety profile supports potential of Bicycle platform