Constrained peptides
Unconstrained thinking

July 2020
Forward-looking statements

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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 May 7, 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.
Our goal is to create transformational medicines

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.

- Advancing wholly-owned oncology pipeline of multiple clinical assets
- Developing world’s first fully synthetic immuno-oncology (IO) platform
- Exploring broad potential beyond oncology through partnerships
- Led by world class management team, supported by strong financial foundation

Engineering Bicycles® to solve unique therapeutic challenges
**Bicycles®** are a new therapeutic modality for addressing intractable challenges

**Built-in tolerance to conjugation**
- Generalizable approach
- Versatility to adopt multiple formats

**Phage-based screening platform**
- Nobel Prize-winning technology
- Rapid selection from $>10^{17}$ potential candidates

**Robust patent protection**
- $>90$ patent families
- Expiration into 2030s

<table>
<thead>
<tr>
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<th>Chemical synthesis</th>
<th>Rapid tissue distribution</th>
<th>Complex protein targets druggable</th>
<th>Route of elimination</th>
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<td>Small molecules</td>
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<td>Antibodies</td>
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Internal focus on oncology, partnerships to explore additional applications across therapeutic areas

*Bicycle® Toxin Conjugates*
- Toxin delivery system with unique mechanism of action
- Potentially improved safety & efficacy over other modalities

*Bicycle Immune Cell Agonists*
- Differentiated approach to agonizing immune cells
- May overcome limitations of antibody & biologic therapies
- Multiple formats, e.g. systemic & targeted

- Leverage platform’s versatility
- More efficiently bring novel medicines to patients
# Robust proprietary and partnered pipeline

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<tr>
<th>Product/Target</th>
<th>Therapeutic Interest</th>
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<td><strong>Bicycle® Toxin Conjugates</strong></td>
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<td>BT1718 (MT1-MMP)</td>
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<td>Discovery/ Preclinical</td>
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<td>BT5528 (EphA2)</td>
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<td>BT8009 (Nectin-4)</td>
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<td>Novel CNS targets</td>
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Bicycle®
Toxin Conjugates
**Bicycle® Toxin Conjugates** – designed to be selective tumor targeting therapeutics

- Specific tumor targeting via antigen
- Large amount of cytotoxic payload can be delivered
- Release of toxin directly into tumor via cleavable linker

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

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

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**PET imaging 40-60min**

- **Bicycle**
- **Antibody**

**BTC plasma**

**Toxin tumor**

**Toxin plasma**

[Tissue] (μM)

0 12 24 36 48 60 72

Time (h)
BT1718: Potential first-in-class Bicycle® Toxin Conjugate targeting key tumor antigen

- Highly selective for MT1-MMP (MMP-14)
  - Cell-surface matrix metalloprotease
  - Established role in cell invasion and metastasis
- PhI/IIa open-label, multicenter study in patients with advanced solid tumors is ongoing

Primary objectives of Phase I dose escalation achieved

- BT1718 appeared tolerable, with manageable adverse events
- 20mg/m\(^2\) once-weekly dose selected for Phase IIa
  - Falls within efficacious dose range predicted preclinically (equivalent doses associated with complete responses)

Tumor biopsies show payload selectively delivered & retained in tumor

![Graph showing tumor DM1 and plasma BT1718 concentrations](graph.png)

- [DM1 or BT1718] nM
- LLOQ
- Not detectable

![Graph showing time post end of infusion (1h)](graph2.png)

- 0.5h
- 1.65h
- Patient 1: 15mg/m\(^2\)
- Patient 2: 20mg/m\(^2\)

*Reflecting a data cutoff of August 7, 2019, as reported at ESMO 2019
Clinical data from BT1718 validates Bicycle platform

- Initial analysis reported at ESMO 2019 shows stable disease in 54% of evaluable patients at 8 weeks*

At early doses, anti-tumor activity observed in individual target lesions

One patient with SCLC experienced a partial response of a 68% reduction in a target lesion

*Reflecting a data cutoff of August 7, 2019, as reported at ESMO 2019
BT1718 Phase IIa expansion cohorts in MT1-MMP+ patients

Analysis of historical, primary tumor micro-array (TMA) tissue series indicates squamous cancers as preferred tumor subtype for PhIIa

Primary objectives of Phase IIa study are to evaluate safety and tolerability of BT1718, secondary objectives are to assess preliminary signals of efficacy

Squamous cell carcinoma; n=75

Tumor membrane H-score cutoff to be used to select patients in PhIIa expansion cohorts

Representative image of lung cancer core with corresponding tumor membrane (TM) and tumor stroma (TS) H-scores

Screening → Enrollment

NSCLC cohort (20 mg/m², QW)

Basket cohort (20 mg/m², QW)

Additional cohorts may be initiated based on response
BT5528: EphA2 BTC delivers improved preclinical safety and efficacy over comparator ADCs

- EphA2 is overexpressed in many difficult to treat tumors
- Previous antibody drug conjugate projects, notably MEDI-547, have failed due to bleeding events
- Dosing is underway in Phase I/II study in patients with advanced solid tumors (BT5528 as monotherapy, lagging combo with nivolumab)
  - Doses administered to date appear well-tolerated with manageable adverse events
- Proprietary EphA2 IHC assay developed, demonstrates expression in high value indications including lung, pancreas and bladder

No signs of coagulopathy or bleeding at toxin equivalent of >150x clinical dose of MEDI-547

Displaced superior activity to EphA2 ADC in large tumor xenografts

- Displayed superior activity to EphA2 ADC in large tumor xenografts
- No signs of coagulopathy or bleeding at toxin equivalent of >150x clinical dose of MEDI-547

Doses administered to date appear well-tolerated with manageable adverse events

- Proprietary EphA2 IHC assay developed, demonstrates expression in high value indications including lung, pancreas and bladder

Jul-20
BT5528 Phase I/II study in patients with advanced solid tumors

Key Phase I dose escalation objectives:
- Assess the safety and tolerability of BT5528 in patients with advanced solid tumors associated with EphA2 expression
- Determine a recommended Phase II dose (RP2D)

Phase II dose expansion portion will have primary objective of evaluating the clinical activity of BT5528 in selected tumor indications

Once-weekly infusions; 4 weeks = 1 cycle
BT8009: Nectin-4 BTC fast follower with differentiated profile to clinical ADC

- Nectin-4 is involved in establishing cell-cell contact and tumor cell survival, overexpressed in common types of cancer (e.g. bladder, breast, gastric, lung and ovarian)
- Target validated in the clinic by enfortumab vedotin (Astellas/SeaGen)
- BT8009 designed to avoid hepatic exposure, may overcome stromal barrier in pancreatic cancer, easily manufactured
- IND-enabling studies ongoing; PhI/II initiation expected in 2020

**Impressive selective delivery of toxin to tumor**

**Improved activity over Nectin-4 ADC**

- Time of administration

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**Graphs**

- Graph showing tumor volume over days after start of dosing.
- Graph showing MMAE concentration over time in plasma and tumor.

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Jul-20
Immuno-oncology
Properties of Bicycles® are uniquely suited to IO modulation

**Plug and play for flexible therapeutic design**

- Designed for optimal immune cell engagement
- Rapid tumor penetration
- Renal elimination avoids liver toxicity
- Small molecule COGS
- Short half-life
- Flexible dosing (mono or combo therapy)
- Tuneable PK to vary degree of activation
- Fully synthetic
- Generalizable format

_Bicycle TICAs™_ enable optimum spacing compared to bulkier biologics

_Bicycle_ targeting immune cell agonist receptor

Specific tumor targeting via antigen binding _Bicycle_
Bicycle® Tumor-targeted Immune Cell Agonists are potent and selective modulators of CD137

TICA™ molecules could achieve potent activity through receptor cross-linking across the immune synapse

CD137 provides robust anti-tumor T cell and NK cell effects

Nectin-4/CD137 TICA molecules activate human PBMCs in a Nectin-4 dependent manner
Chemical nature of platform allows rapid “dialing in” of most desirable properties

>90 Nectin-4 TICA molecules synthesized in combinatorial manner

Reporter cell assay data for 30 Nectin-4/CD137 TICAs in co-culture with HT1376

Size of sphere proportional to molecular weight

CD137 Monomers x10
4 Attachment pts

Nectin-4 Monomers x6
2 Attachment pts

Linkers enable various architectures

> 60 TICAs™ synthesized

1:1
1:2
1:3

Loop 1
Loop 2
N-term
C-term

N-term
dLys4

N-term
dLys3

CD137L

1:1 Bicycles®
1:2 Bicycles
1:3 Bicycles

Urelumab
BT7480 leads to robust anti-tumor activity and immune memory in a syngeneic model.

MC38 #13 in huCD137 C57Bl/6 mice

Re-challenge of CR mice with MC38#13 cells

Nectin-4-CD137 TICA™ achieves rapid tumor regression.

Rechallenge of “cured” mice with tumor reimplantation shows no tumor growth, implying immunogenic memory.

** **
*** p≤0.0001, 2W-ANOVA with Dunnett's
** p≤0.01
* p≤0.05
Immune cell engaging Bicycles® and tumor antigen engaging Bicycles can be readily interchanged

Potential to rapidly and efficiently generate multiple clinical candidates

Collaboration with Genentech builds on “plug-and-play” capability of Bicycles in IO field
EphA2 / CD137 TICA™ induces dramatic immune response in mouse tumor models

**EphA2 TICA induces a significant change in local immune cell populations when compared to a non-targeted CD137 agonist antibody**

 significan increase in CD8+ cells and macrophage score

MC38 tumors (mEphA2) in hCD137-ECD transgenic mice. 15 mg/kg Q3D EphA2 TICA or control, or 2 mg/kg Q3D Urelumab

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**T Cell Score**

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<thead>
<tr>
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<th>EphA2 TICA</th>
<th>Non Binder</th>
<th>Urelumab</th>
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<td>Score</td>
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**Macrophage Cell Score**

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<tbody>
<tr>
<td>Score</td>
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<td>1000</td>
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</table>

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CD8+ cells in MC38 tumor tissues on D6

**Vehicle**

**EphA2 TICA**

**Non Binder**

**Urelumab**
Beyond Oncology
Partnerships with leading therapeutic experts to explore broad application of *Bicycles®* beyond oncology

Bicycle’s unique technology & deep technical understanding

Development & therapeutic expertise

Differentiated treatments for diseases with high unmet need
THR-149: Novel Pkal inhibitor provides validation of Bicycle® platform for ophthalmological diseases

Phase I trial evaluated safety of a single intravitreal injection of THR-149 at 3 ascending dose levels in 12 patients with visual impairment due to center-involved diabetic macular edema (DME)

- Topline data show that THR-149 was well-tolerated and safe
- Rapid onset of action starting at Day 1
- Activity maintained

No dose-limiting toxicities or drug-related serious adverse events reported

Increasing average improvement in BCVA of up to 7.5 letters at Day 14 following a single injection of THR-149

An average improvement in BCVA of 6.5 letters at Day 90 following a single injection of THR-149

*BCVA = Best Corrected Visual Acuity
Establishing Bicycle as an integrated, top tier biotech company

**ONCOLOGY**

- **BT1718** validates approach, PK, tolerability, tumor accumulation
- Emerging **preclinical data** establishes IO opportunity
- **BTCs validated** as monotherapy option
- **BT7480** establishes translatability of TICA™ approach

**Combination approaches** within and outside Bicycle pipeline to address key unmet needs in oncology

**TODAY**

- Internal programs

**NEAR TERM**

- Collaborations established in key therapeutic areas
- Preclinical and clinical **validation**

**MID TERM**

- Develop **multi-asset portfolio with significant clinical potential**

**LONG-TERM**

- **ONCOLOGY**
- **NON-ONCOLOGY**
Bicycle Therapeutics is led by an experienced team, growth is enabled by robust financial profile

Experts in drug development with executive experience at leading companies

Cash balance of $109.6M* provides runway to support multiple clinical milestones

Clinical data readouts at medical meetings and trial initiations expected in 2020 across BTC, IO and partnered programs

2020 Key Events
- **BT1718** PhIIa start
- **BT5528** interim PhI data
- **BT8009** PhI start
- **BT7480** IND enabling activities

*As of March 31, 2020
Thank you