Bicycles as precision guided therapeutics

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**Bicycle®** - a unique and disruptive therapeutic modality

- **Small size**: 1.5-2kDa
- **Specificity**: High
- **Chemical synthesis (NCEs)**: Yes
- **Rapid tissue penetration**: Yes
- **Complex protein targets druggable**: Yes
- **Routes of administration**: IV/SQ/IT/IN
- **Route of elimination**: Renal
- **Immunogenic**: No

Biologically relevant 3D structures:
- CAIX
- PD-L1
- EphA2
- Hairpins (β, γ)
- Loops
- Helices (α, 3₁₀)

**Scaffold**

**Short linear peptide**

**Bicycle®**

High affinity
Absolute selectivity

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Bicycles have 5 dimensions of variation

Amino acid content  Length of peptide chain  Symmetry of loops  Scaffold  Elaboration

Tremendous structural diversity of molecules to successfully drug targets

- Helical
- Hairpin
- Extended
- Hybrid
**Bicycle**® platform delivers a toolkit of building blocks to create novel medicines

**Bicycle**® Phage Display - Discovery

- Linear peptide
- Bicycles
- Bacteriophage DNA Sequence
- Gene III
- Diverse Bicycle® phage libraries (>10^12)
- Protein III
- Scaffold
- Chemical modification with scaffold

**Peptide & Medicinal Chemistry**

- Optimize Bicycle® monomers
- Non-natural Amino Acids
- Build and Optimize Therapeutic Bicycles
- Easy conjugation of Linkers and Payloads
- Tumor Targeting and Effector Bicycles

**Potential Bicycle® Medicines**

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

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What are Bicycles and why are they different from biologics?

Biologicals:
- Antibodies
- Fragments
- Domains

Bicycles:
- MWt 1-2kDa
- Rapid extravasation
- Extensive tissue penetration
- Renal clearance
- Tuneable half life

MWt 150kDa
- Poor/slow extravasation
- Limited tissue penetration
- Hepatic/Catabolic clearance
- Long half life

MWt 50-60kDa
- Poor/slow extravasation
- Limited tissue penetration
- Hepatic/Catabolic clearance
- Medium half life

MWt 10-15kDa
- Poor/slow extravasation
- Limited tissue penetration
- Hepatic/Catabolic clearance
- Medium half life

Confers beneficial properties without compromising binding
large molecular footprint drives affinity and selectivity between close homologues
BTC™ preclinical data – effective delivery of toxin payload to tumors

- 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 tumor
- Toxin plasma

**Time (h)**: 0 12 24 36 48 60 72

**[Tissue] (µM)**: 0.001 0.010 0.100 1.000

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The properties that make *Bicycles* ideal for toxin delivery also make them ideal for immune agonism, but for different reasons.

- In the body, activating signals (agonists) are **local**, **rapid**, and then **stop**
  - Cytokines, neurotransmitters, stress hormones

- Sustained (pathologic) signaling can lead to desensitization and dysregulation

*Bicycles* match the biology
- precision-guided (local)
- distribute quickly (rapid)
- cleared rapidly (stop)

**Localize action to the tumor**
We choose targets that are present in solid tumors not well-served by current therapies

**Cause activation of immune cells**
We choose targets where knowledge of human biology says that activation is likely to help, and where other drug technologies, like antibodies, aren’t working
Bicycle TICA™—tumor-targeted immune cell agonists deliver immune agonism to tumors.

Tumor Antigen: Nectin-4 or EphA2

Immune cell receptor: CD137

Activated Immune Cell

Tumor Cell

CD137 clustering induced by tumor antigen drives stronger immune cell potency.

Activation induced by clustering of CD137 by trimeric CD137L.

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Preclinical in vitro proof of concept with the first EphA2/CD137 molecule

Cancer cells expressing high levels of EphA2

Activated Immune Cell
CD137
EphA2

Tumor Cell

CD137 Bicycle®
EphA2 Bicycle®

EphA2 expression

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

Molecules per cell normalized to isotype control

Log concentration (M)

fold induction

A549
HT1080
LNCaP
no cells

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Bicycles have demonstrated preliminary clinical anti-tumor activity delivering cytotoxic payloads and appear ideally suited to delivering radionuclide payloads.

- **Bicycle Toxin Conjugates® (BTCs)**
  - Baseline
  - Follow-up 1
  - Follow-up 2
  - BT8009 complete responder

- **Bicycle Radionuclide Conjugates (BRCs)**
  - Differentiated MOA (DNA damage)
  - Highly potent payloads
  - Potentially effective in different patient populations / cancers
  - Portfolio risk diversification

Tumor cell death
MT1-MMP targeting BRC shows far superior tumor uptake and contrast versus mAb in mouse model

- MT1-MMP overexpressed in variety of cancers (non–small cell lung, gastric and breast)
Summary and looking to the future

BT1718  Target: MT1-MMP  DM1 payload

BT5528  Target: EphA2  MMAE payload

BT8009  Target: Nectin-4  MMAE payload

BT7480  Targets: Nectin-4, CD137

Validation

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

Validation

Next-gen BTCs  Different targets, linkers and payloads

Radiopharm

FIH  2018  2019  2020  2021  2023 and beyond

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Thank you