Bicycles - a modality for Tumor-Targeted Immune Cell Agonism

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Antibody Engineering & Therapeutics
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**Bicycle Therapeutics**

- Clinical-stage biopharma company pioneering Bicycles, a new differentiated class of innovative medicines (Founded by Sir Greg Winter & Prof. Christian Heinis)
- Based in Cambridge (UK) & Boston (USA), 236 FTEs (Dec 31 2022)

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<th>Target / Product</th>
<th>Partner/Sponsor</th>
<th>Indication</th>
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**Bicycle®** - a unique & disruptive therapeutic modality

- **High affinity and selectivity in a small, fully synthetic format**
- **Biologically relevant tertiary structures**
  - EphA2
  - CAIX
  - PD-L1
  - Loops
  - Hairpins ($\beta, \gamma$)
  - Helices ($\alpha, 3_{10}$)
- **Favorable drug-like properties**
  - Small size (1.5-2 kDa)
  - High specificity
  - Chemical synthesis (NCEs)
  - Rapid tissue penetration
  - Complex protein targets druggable
  - Multiple routes of administration
  - Renal route of elimination
  - Not immunogenic
**Bicycle® platform delivers a toolkit of building blocks to create novel medicines**

**Bicycle® Phage Display - Discovery**
- Linear peptide
- Diverse Bicycle® phage libraries (>10^20)
- Natural Amino Acids

**Peptide & Medicinal Chemistry**
- Optimize Bicycle® monomers
- Build and Optimize Therapeutic Bicycles
- Easy conjugation of Linkers and Payloads
- Non-Natural Amino Acids

**Potential Bicycle® Medicines**
- Monomeric Bicycles
- Targeted Drug Conjugates
- Targeted/Multi-specific Bicycles
- Targeted Radionuclide conjugate

Antibody Engineering & Therapeutics
Bicycle Therapeutics – creating versatile new precision-guided medicines with potential to fill major gaps in cancer therapy

- **Bicycle Toxin Conjugates® (BTCs)**
  - Precision delivery of MMAE - BT8009 & BT5528
  - Fast tissue distribution and clearance
  - Emerging clinical data

- **Bicycle Tumor-Targeted Immune Cell Agonist® (TICAs)**
  - Rapid, local and controlled immune agonism
  - Pathfinder molecule for CD137 – BT7480 in Phase I
  - Pathfinder molecule for NKp46 – preclinical stage
$Bicycle^\textregistered$ precision-guided immune activation

Immune cell receptor = CD137
CD137 (4-1BB) is an immune co-stimulatory receptor with high therapeutic potential in cancer

- Current antibody clinical trials have limited efficacy or reveal hepatic toxicity risks
- Tumor-Targeted Immune Cell Agonist (TICA) approach - meets design goal dictated by biology

**Bicycle TICA®**—tumor-targeted immune cell agonists delivers immune agonism to tumors
CD137 and Nectin-4 *Bicycles*: discovery and optimization by phage display and chemistry

**Phage Hits**
- ID sequence families
- Define initial pharmacophores

**Phage Optimization**
- Focused libraries
- Optimize natural AAs
- Scaffold/Loop symmetry

**Chem Optimization**
- Non natural amino acids
- Tuned affinity and stability
- Balanced phys. chem properties

**CD137**
- $K_D = 1400\, \text{nM}$
- $K_D = 67\, \text{nM}$
- $K_D = 5\, \text{nM}$

**Nectin-4**
- $K_D = 508\, \text{nM}$
- $K_D = 80\, \text{nM}$
- $K_D = 1\, \text{nM}$
BT7480 functional activity is dependent on Nectin-4 in cell-based assays *in vitro*
BT7480 induces complete responses and memory *in vivo*

**MC38-Nectin-4 in huCD137-C57Bl/6**

- **Vehicle (0/6 CRs)**
- **BT7480 5 mg/kg BIW (6/6 CRs)**
- **BT7480 1.5 mg/kg BIW (5/6 CRs)**

***p<0.001 Mixed effects analysis with Tukey’s post test, days 0–17**

**Day 59**

**No tumor growth in Vehicle or Isotype CTR CR animals**

**Re-challenge**

- **CRs Vehicle (n=7)**
- **CRs Isotype CTR (n=7)**
- **CRs with CD8 depletion (n=10)**
BT7480 has a unique and differentiated mechanism of action

- BT7480 leads to a tumor localized early increase in cytokine gene expression
- BT7480 leads to increase in CD8+ cell infiltration, cytotoxic and macrophage cell scores in tumor
BT7480 meets rationale design goals for a locally acting immune agonist

- CD137 agonism dependent on ligation to tumor specific antigen
- Robust anti-tumor activity with only intermittent dosing observed in vivo
- Early increase in cytokine production precedes CD8+ T cell infiltration into the tumor
- Well-tolerated in preclinical safety species
- Entered Phase I clinical trial in November 2021

Hurov K, Lahdenranta J, et al., 2021, J Immunother Cancer,
Upadhyaya, et al., 2022, J Med Chem
Bicycle® precision-guided NK cell activation

NK cell receptor = NKp46
Natural killer (NK) cells have emerged as important early drivers of the adaptive anti-tumor immune response

- Traditional understanding: NK cells kill tumor cells through direct cytotoxic mechanisms
- New science: role for NK cells in orchestration of adaptive immunity catalysis
- NK cell therapy is emerging as an important new approach to cancer
- NKp46 as NK-TICA™ target - an activating receptor specifically and constitutively expressed on NK cells

Bald et al., (2020) Nat. Immunol. 21, 835
NKp46 *Bicycles*: discovery and optimization by phage display and chemistry

**NKp46**

- **Phage Hits**
  - PD-L1: $K_D = 5$ nM
  - MT-1: $K_D = 15$ nM
  - EphA2: $K_D = 1.7$ nM

- **Phage Optimization**
  - $K_D = 35$ nM

- **Chem Optimization**
  - $K_D < 5$ nM

NK-TICA™
NKp46 *Bicycles* coupled to multiple antigen targets drive potent tumor cell killing

- Potential to create NK-TICA™ to address multiple solid tumor indications
NK-TICA™ enhances NK cytokine production in the presence of tumor antigen expressing cell lines

- NK cells secrete IFNγ and TNFα in the presence of NK-TICA™
- Cytokine secretion is dependent on binding to tumor antigen
**NK-TICA™ enhances NK cell secretion of FLT3L**

- NK-TICA™ causes FLT3L production by primary NK cells co-cultured with tumor cells
- FLT3L is a clinically validated driver of cDC1 maturation and anti-tumor responses

Additional Information:

- Allen F et al. Oncoimmun 2018
- Bottcher et al. Cell, 2018
- Holmes et al. PNAS 2014
- Zhou, Y. et al. Mol Cancer 2023
- Salmon H et al. Immunity 2016
- Barry et al. Nat Med 2018
First series of chemically synthetic, conditionally active, targeted NKp46 activators

- NK-TICA™
  - Tumor antigen-dependent NK cell engagers
  - Potent tumor cell killing
  - Potential to drive adaptive anti-tumor immunity

- NK-TICA™ have the potential to catalyze durable anti-tumor immunity in tumor types not well served by current therapies

Dufort et al., AACR 2022
Diversifying the Bicycle® platform

- **BT1718**: Target: MT1-MMP, DM1 payload, Disulfide linker (FIH 2018)
- **BT5528**: Target: EphA2, MMAE payload, Val-Cit linker (2019)
- **BT8009**: Target: Nectin-4, CD137, PEG3 linker (2020)
- **BT7480**: Targets: Nectin-4, CD137, PEG3 linker (Validation)
- **BT7455**: Targets: EphA2, CD137, PEG3 linker, Next Bicycle TICA™ scheduled for clinic (Validation)
- **NK-TICA™**: Next-generation BTCs (2021)
- **Radiopharm**: Different targets, linkers, and payloads (2021)
- **2023 and beyond**: Diverseplatforms

Antibody Engineering & Therapeutics
Thank you