A novel fully synthetic dual targeted Nectin-4/4-1BB Bicycle® peptide induces tumor localized 4-1BB agonism.

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Conflict of interest statement

• I am an employee of Bicycle Therapeutics Inc.
• I am a stockholder in Bicycle Therapeutics plc.
Bicycle Therapeutics

- Founded by Sir Gregory Winter & Prof. Christian Heinis
- UK & US based (Cambridge, UK; Boston, USA)
- Internal focus on Oncology
  - BT1718 – Phase 1/2a (Cancer Research UK)
  - 2nd Generation Bicycle Toxin Conjugates® in pre-clinical development
  - Bicycle® immune cell modulators
**Bicycles®**: a new therapeutic modality

- Structurally constrained Bicyclic peptides, chemically synthesised, low MWt (1.5-2kDa)
- Large binding footprint allowing targeting of protein-protein interactions
- Small molecule like PK and tumor penetration, renal excretion

![Bicycle Structure](image)

**EphA2 binding Bicycle**
Proprietary screening platform: *Bicycles*® optimised using phage display and medicinal chemistry, informed by structural biology.

**Bicycle Phage Display**

1. **Chemical modification with scaffold**
2. **Cyclise**
   - POC in 6 wk
   - Optimised lead in 9mth
3. **Select**
4. **Amplify**

**Linear peptide**
- Protein III
- Bicycle DNA Sequence
- Gene III

**Bicycle**
- Loop sizes
- Bicycle scaffolds

**Optimize binder & capture IP**

**Natural Amino Acids**

**Peptide & Medicinal Chemistry**

- **Histidine**
  - $K_i = 11 \text{nM}$
- **3,3-diphenylalanine (3,3-DPA)**
  - $K_i = 0.9 \text{nM}$

**Structural Biology**

- **Dial in desired drug-like properties and PK profile**

**Non-natural Amino Acids**

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CD137 activation leads to potent anti-tumor response through diverse mechanisms

- Highly validated IO target – roles in key steps in cancer immune cycle
-Expressed on, and stimulates T-cells, NKT, NK, Dendritic cells, Macrophages, B cells and neutrophils
-Urelumab, a superagonistic anti-CD137 mAb effective as a single agent in clinic, but utility limited by hepatotoxicity and long t₁/₂
-A tumor antigen specific agonist could provide efficacy without systemic toxicity

**T-cells:** Sustained activation, cytokine secretion, induced growth and survival, restoration of effector functions

**Dendritic cells:** Activation and cytokine secretion

**Macrophages:** Activation and cytokine secretion

**NK cells:** Activation and cytokine secretion, increase in ADCC
Tumor/CD137 binding *Bicycles*® as tumor-targeted immune cell agonists (TICAs)

CD137 is member of the TNF superfamily & requires clustering for activation

“All natural” phage peptide

KD = 67nM (Wild Type: WT)

Chemically optimised

KD = 5nM (High Affinity: HA)
Nectin-4 (PVRL4): Rationale as a tumor antigen

- Nectin-4: cell adhesion molecule; widely expressed during development with restricted expression in adult normal tissue
- Over expressed in numerous tumors of high unmet need; highest frequency in bladder, breast, and pancreatic, but also in lung and esophageal cancers
- Internal work demonstrates co-expression of CD137 in significant subsets of Nectin-4 positive tumors
- Precedented target for bladder cancer; Enfortumab Vedotin (MMAE Nectin-4 ADC) has breakthrough therapy in post platin, post CI bladder cancer
  - ORR 42% (N=125)
- Building internal expression/diagnostic capability

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>% samples by expression level</th>
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<tbody>
<tr>
<td>Lung SQ/Adeno</td>
<td>62%</td>
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<tr>
<td>Lung metastatic</td>
<td>60%</td>
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<tr>
<td>Breast</td>
<td>78%</td>
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<tr>
<td>Pancreatic</td>
<td>71%</td>
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<td>Ovarian</td>
<td>57%</td>
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<td>Bladder</td>
<td>83%</td>
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<tr>
<td>Head/Neck</td>
<td>59%</td>
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<tr>
<td>Oesophageal</td>
<td>55%</td>
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</tbody>
</table>

Challita-Eid et al Cancer Res 76: 3003-3013 (2016)
Nectin-4/CD137 Bicycles® are precisely engineered tumor antigen specific CD137 agonists.
**Bicycle**® TICAs enable optimum spacing compared to bulkier biologics

- Typical immune cell receptor complex spacing ~140Å
- Most biologics far larger, meaning significant steric restraints
Bicycle® TICAs are ~30x smaller than other targeted agonists

- Bicycle TICA: ~6kDa
- Anti-FAP IgG-CD137L fusion Roche RG7826: ~185kDa
- Anti-Her2 IgG-anti-CD137 anticalin fusion Pieris PRS-343: ~190kDa
Chemical nature of platform allows rapid “dialing in” of 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

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

Emax (fold induction)

EC\(_{50}\) (nM)

0.01 0.1 1 10 100

>60 TICAs synthesized

Linkers enable various architectures

CD137 Monomers x10
4 Attachment pts

Nectin-4 Monomers x6
2 Attachment pts

N-term
C-term
Lys3
dLys4

N-term
dLys3

C-term
Cs

CD137 Monomers x10
4 Attachment pts

Nectin-4 Monomers x6
2 Attachment pts

N-term
dLys3

C-term
Cs

1:1
1:2
1:3

1:1
1:2
1:3

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PK can be “tuned”

**Predicted human PK parameters**

<table>
<thead>
<tr>
<th>Molecule</th>
<th>EC50 (nM)</th>
<th>$t_{1/2}$ (h)</th>
<th>CLp (mL/min/kg)</th>
<th>Veff (L/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCY10572</td>
<td>0.59</td>
<td>0.83</td>
<td>13</td>
<td>0.91</td>
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<tr>
<td>BT7480</td>
<td>0.47</td>
<td>12</td>
<td>1.2</td>
<td>1.2</td>
</tr>
</tbody>
</table>

50% Target coverage is the line above which [Plasma,u] is maintained over [EC50,u]

(Note: Does not factor tumor retention)

Molecules are selectively retained in Nectin-4 expressing tumors.
Intermittent dosing of BT7480 leads to a robust anti-tumor activity

MC38 #13 in huCD137 C57Bl/6 mice

Vehicle
- BT7480 1 mpk Q3D
- BT7480 1 mpk QD
- BT7480 10 mpk Q3D
- BT7480 10 mpk QD

*** p≤0.0001, 2W-ANOVA with Dunnett’s
** p≤0.01
* p≤0.05

Individual mice, QD dosing

Vehicle
- BT7480 1 mpk QDx15
- BT7480 10 mpk QDx15

Day

Individual mice, Q3D dosing

Vehicle
- BT7480 1 mpk Q3Dx9
- BT7480 10 mpk Q3Dx9

Day

Re-challenge of CR mice with MC38#13 cells

Control huCD137-C57Bl/6 mice (n=5)
- BT7480
- CR mice (n=5)

Days after cell implantation

(Note: Q3D equivalent to QW in human)

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Intermittent dosing of BT7480 leads to an increase in CD8+ T cells without elevations of liver enzymes

- Anti-tumor activity of BT7480 was assessed in Nectin-4 overexpressing (engineered) CT26 syngeneic mouse model
- Several responders in both QD and Q3D dosing groups

- By D15, CD8+ T cell population increases significantly
- By D15, No significant changes in AST, ALT and APHOS

Note: Q3D in mouse equivalent to once per week in human
Summary

- Bicycle are building a new generation of chemically synthetic (NCE) tumor antigen targeted CD137 agonists.
- These are much smaller than biologics, rapidly tumor penetrant, and tailored to the geometry of the immune synapse.
- Potency and pharmacokinetics are “tunable.”
- Our lead Nectin-4/CD137 TICA (BT7480) induces complete regressions and resistance to re-challenge in immune competent models with intermittent dosing.
- Approach is generalizable.

See Posters P782, P794 Saturday!
Thanks!

Bicycle US

Bicycle UK