Key DMPK Attributes of BT7480, a Bicycle Tumor-targeted Immune Cell Agonist™ Targeting Nectin-4 and Agonizing CD137

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Bicycle therapeutics

Founded by Sir Greg Winter & Prof. Christian Heinis

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

- Bicycles are short peptides chemically constrained with a central scaffold
- Bicycles combine the advantages of small molecules and antibodies

<table>
<thead>
<tr>
<th>Bicycles</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>
</tr>
<tr>
<td>Specificity</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Chemical synthesis (NCEs)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Rapid tissue penetration</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Complex protein targets druggable</td>
<td>Yes</td>
<td>Limited</td>
</tr>
<tr>
<td>Route of elimination</td>
<td>Renal</td>
<td>Liver</td>
</tr>
</tbody>
</table>
Bicycle® platform delivers a toolkit of building blocks to create novel medicines

Bicycle® Phage Display - Discovery

Linear peptide

Bicycle DNA Sequence

Gene III

Phage Particle

Bicycle®

Diverse Bicycle® phage libraries (>10²⁰)

Non-natural Amino Acids

Optimize Bicycle® monomers

Peptide & Medicinal Chemistry

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

Natural Amino Acids
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
Target: Nectin-4, CD137
PEG3 linker

Validation

Next-gen BTCs
Different targets, linkers and payloads

Radiopharm

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

NK-TICA™

FIH 2018 2019 2020 2021 2023 and beyond

Targeted ASO/SiRNA delivery
CD137 (4-1BB) is an immune co-stimulatory receptor with high therapeutic potential in cancer

- CD137 is expressed on activated immune cells – signaling enhanced function and survival, prevents anergy
- CD137 ligand expressed by APCs provides a co-stimulatory signal to T cells and NK cells – potential in anti-tumor immunity
- Sustained activation leads to exhaustion and AICD – transient, localized action may be the optimal approach
- Urelumab – anti-CD137 agonist mAb – some clinical activity but liver toxicity precluded development

Many agents in development now – none meets design goals dictated by the biology – we sought to address this by using the Bicycle® platform:
- Activity localized to the tumor – potentiate immune activation
- Rapid onset of action and controllable duration of action
- No Fc interactions to avoid potential liver toxicity

Biologics: not a perfect match for immune agonists

- High MW = low tissue penetration
- Inflexible architecture = difficult “med chem”
- Complex manufacturing = $$$
- Non–tunable PK = not ideal for immune activation (side effects / tox)
- Prone to immunogenicity
**Bicycle TICA™—tumor-targeted immune cell agonists delivers immune agonism to tumors**

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

Immune cell receptor engaging Bicycle® CD137

Tumor Antigen Targeting Bicycle® Nectin-4 or EphA2

CD137 clustering induced by tumor antigen drives stronger immune cell potency
BT7480 (BCY11863) is a fully synthetic, heterotrimeric conjugate with one Nectin-4 and two CD137 Bicycles.
Effect of valency of Nectin-4/CD137 Bicycles: Better activity with higher ratio of CD137 bicycles

Different hinges synthesized for SAR exploration

Hinge 1 (1:2)

Hinge 2 (1:2, 2:1)

Hinge 3 (1:3)

Hinge 4 (2:2)

HT1376/CD137 reporter coculture Assay

Optimization of pharmacokinetics of Bicycle® TICAs via minor structural changes

1:2 Nectin-4/CD137

Structural changes from BCY1 to BCY3

- 1:2 Nectin-4/CD137
- CD137: Ac-Cys → 3-mercaptopropionic acid
- Nectin-4: D-Glu/Glu → D-Asp/Asp
- Nectin-4: 1-2

Optimization of pharmacokinetics of Bicycle® TICAs via minor structural changes

- BCY1
- BCY2
- BCY3

CL (mL/min/kg)

Vdss (L/kg)

Terminal half-life (h)

BT7480 pharmacokinetic profile is conserved across nonclinical species

**NHP PK (BCY 10572 vs BT7480)**

<table>
<thead>
<tr>
<th></th>
<th>BCY10572</th>
<th>BT7480</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL (mL/min/kg)</td>
<td>30</td>
<td>3.3</td>
</tr>
<tr>
<td>Vdss (L/kg)</td>
<td>0.56</td>
<td>0.62</td>
</tr>
</tbody>
</table>

**BT7480 PK Parameters (CL, V, t_{1/2}) in preclinical species**

<table>
<thead>
<tr>
<th>Species</th>
<th>CLp (mL/min/kg)</th>
<th>Vss (L/kg)</th>
<th>Terminal half-life (t_{1/2}, h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>16</td>
<td>2.3</td>
<td>2.3</td>
</tr>
<tr>
<td>Rat</td>
<td>8.5</td>
<td>1.5</td>
<td>3.6</td>
</tr>
<tr>
<td>NHP</td>
<td>4.0</td>
<td>0.88</td>
<td>6.2</td>
</tr>
<tr>
<td>Pred. Human</td>
<td>1.7</td>
<td>1.3</td>
<td>8.9</td>
</tr>
</tbody>
</table>

NHP: nonhuman primate

BT7480 demonstrated rapid tumor penetration and renal uptake

- **In vitro distribution:**
  - BT7480 does not distribute to red blood cells and is restricted to plasma.
  - BT7480 is subject to relatively low protein-binding.

<table>
<thead>
<tr>
<th></th>
<th>Mouse</th>
<th>Rat</th>
<th>NHP</th>
<th>Human</th>
</tr>
</thead>
<tbody>
<tr>
<td>B/P</td>
<td>0.61</td>
<td>0.53</td>
<td>0.33</td>
<td>0.50</td>
</tr>
<tr>
<td>PPB (% bound)</td>
<td>61.4</td>
<td>78.9</td>
<td>67.6</td>
<td>74.3</td>
</tr>
</tbody>
</table>

B/P: blood-to-plasma ratio; PPB: plasma protein binding; NHP: nonhuman primate

- **In vivo distribution:**
  - Rapid tumor penetration: $T_{\text{max}} = 2$ h
  - Colocalization in tumor: AUC ratio =10.6:1 (tumor: plasma)

**BCY11863 Mean PK Parameters in Plasma and Tumors, BALB/c Mice (IV injection, 5 mg/kg)**

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Plasma</th>
<th>Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>3865</td>
<td>4149</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL or ng/g)</td>
<td>---</td>
<td>2.0</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>---</td>
<td>2.0</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>1.65</td>
<td>13.4</td>
</tr>
<tr>
<td>$T_{\text{last}}$ (h)</td>
<td>4</td>
<td>24</td>
</tr>
<tr>
<td>AUC$_{0-\text{last}}$ (ng.h/mL or ng.h/g)</td>
<td>3196</td>
<td>33775</td>
</tr>
<tr>
<td>AUC$_{0-\text{inf}}$ (ng.h/mL or ng.h/g)</td>
<td>3760</td>
<td>46568</td>
</tr>
<tr>
<td>AUC$_{\text{Extra}}$ (%)</td>
<td>15.0</td>
<td>27.5</td>
</tr>
<tr>
<td>AUC Ratio</td>
<td>---</td>
<td>10.6</td>
</tr>
</tbody>
</table>

AUC: Area under curve; AUC Ratio = Tumor AUC$_{0-\text{last}}$ / Plasma AUC$_{0-\text{last}}$

**In vivo disposition of EphA2 binding Bicycle in tumor, kidney and bladder**

PET imaging of HT-1080 xenograft @ 60 min

PET: positron emission tomography
BT7480 underwent extensive extrahepatic metabolism and renal elimination

- Extensive renal metabolism and excretion
- No apparent to minimal hepatic metabolism and excretion, consistent with minimal metabolism in microsome/hepatocyte in vitro

BT7480 Metabolites in Plasma, Kidney, Urine and Bile from the bile duct cannulated rat (IV infusion for 3 h, 100 mg/kg/h)

<table>
<thead>
<tr>
<th>ID</th>
<th>Proposed Transformation</th>
<th>Plasma</th>
<th>Kidney</th>
<th>Urine</th>
<th>Bile</th>
</tr>
</thead>
<tbody>
<tr>
<td>BT7480</td>
<td>Parent compound (dominated)</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>BT7480 +18 amu</td>
<td>Hydrolytic ring opening</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 3000 amu</td>
<td>Hydrolysis (dominated)</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1600 amu</td>
<td>Hydrolysis</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BT7480 In Vitro Stability

<table>
<thead>
<tr>
<th>Stability</th>
<th>Mouse</th>
<th>Rat</th>
<th>NHP</th>
<th>Human</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole blood (heparin) (t1/2, h)</td>
<td>5.5</td>
<td>15.7</td>
<td>15.9</td>
<td>&gt;57.8</td>
</tr>
<tr>
<td>Microsome (CLint, mL/min/g liver)</td>
<td>&lt; 0.43</td>
<td>&lt; 0.43</td>
<td>&lt; 0.43</td>
<td>&lt; 0.43</td>
</tr>
<tr>
<td>Hepatocyte (CLint, mL/min/g liver)</td>
<td>&lt; 0.86</td>
<td>&lt; 0.75</td>
<td>&lt; 0.77</td>
<td>&lt; 0.89</td>
</tr>
</tbody>
</table>

NHP: nonhuman primate
Low DDI risk is expected at clinically relevant concentrations

- **Low DDI RISK associated with BT7480 as the perpetrator of CYP inhibition, CYP induction, and transporter inhibition**
  - IC$_{50}$ values > 50 μM for inhibition of CYPs 1A2, 2C9, 2C19, 2D6, and 3A4
  - No significant induction of CYPs 1A2, 2B6, or 3A4 up to 10 μM
  - Not an inhibitor of MDR1 or BCRP transporters up to 10 μM
  - No or low inhibition of MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, and OCT2 transporters up to 10 μM

- **Low DDI potential as the victim of CYP enzymes**
  - Low substrate potential for CYP enzymes given the low Cl$_{int}$ in microsomes and hepatocytes across species

IC$_{50}$: half maximal inhibitory concentration
Continuous systemic exposure not required for maximal anti-tumor activity with Bicycle® TICAs

MC38-Nectin-4+ syngeneic mouse model in huCD137-C57Bl/6 mice (BT7480)

**Simulated PK**

**3 mg/kg/week**

- 0.43 mg/kg QD
- 1.5 mg/kg BIW

**Anti-Tumor Activity**

- Vehicle
- QD
- BIW

**10 mg/kg/week**

- 1.43 mg/kg QD
- 5 mg/kg BIW
Preclinical PK/PD model projects target coverage at the efficacious dose in the mouse disease model

- A target coverage of 20% for 2 days over 7 days is required for robust anti-tumor activity, e.g., complete anti-tumor activity at 5 mg/kg (0, 24 h) (weekly dose of 10 mg/kg)

Where \([Cp,u]\) is unbound concentration of BT7480 in plasma, EC50\(_u\) is the unbound EC50 from the in vitro coculture assay and \(H\) is Hillslope.
Preclinical PK/PD model projects efficacy in humans with weekly dosing

- Human PK parameters was predicted using single species scaling from the NHP physiological parameters by the semi-PBPK modeling approach.
- A weekly human efficacious dose is projected to achieve the target coverage of 20% for 2 days.

**NHP PK**
- Two-compartmental Phoenix model
- Allometric exponent of 0.75 (CL) and 1 (V)
- Corrected for protein binding

**Predicted Human PK**
(based on 1 hour zero-order IV infusion)

**In vitro functional activity (human)**

**Projected target coverage in human vs mouse**

Where $[C_{p,u}]$ is unbound concentration of BT7480 in plasma, $EC50,u$ is the unbound EC50 from the in vitro coculture assay and H is Hillslope.

PBPK: Physiologically based pharmacokinetic
Summary

- **DMPK profiles** along with pharmacology and toxicology data **supports the clinical development of BT7480** for the treatment of solid tumors associated with Nectin-4 expression.
  - PK profiles is consistent across the nonclinical species.
  - Protein binding is relatively low.
  - Drug is localized in tumor vs plasma (drug concentration asymmetry in tumor/plasma).
  - The major metabolic pathway is extrahepatic (e.g., renal).
  - The major elimination pathway is renal.

- **Human dose projection** by the integrated PK/PD modeling approach suggested **weekly dosing**

- **Low DDI risk** is expected with BT7480 at clinically relevant concentrations based on existing *in vitro* CYP/transporter studies.
Thank you

Johanna Lahdenranta
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