Bicycles® - An entirely new class of therapeutics

Paul Beswick
Bicycle Therapeutics
The challenges in treating cancer

- Can be hard to access
- Tumours can be “silent”
- Are difficult to differentiate from normal tissue
- Actively suppress the immune system
- Diverse set of diseases
- Heterogeneous and evolving

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Overview

• Bicyclic peptides: A completely new, disruptive therapeutic modality

• Sir Greg Winter technology, platform derisked, industrialized, reduced to practice and validated

• Internal oncology pipeline, multiple therapeutic themes, BT1718 in Ph1: funded by CRUK. Partnered outside oncology

• UK /US presence, world class team & strong clinical / scientific collaborations

• >£65M Series B funded
Highly constrained: high affinity, exquisite selectivity, excellent stability

Large binding footprint: disrupt protein-protein interactions

Fully synthetic: NCE classification and synthetic control

Highly flexible modality: modular building blocks retain pharmacology

Adjustable PK: excellent tissue penetration, renal elimination, tuneable $T_{1/2}$
# Comparison of therapeutic modalities

<table>
<thead>
<tr>
<th></th>
<th>Antibody</th>
<th>ScFv (fragment)</th>
<th>Bicycle</th>
<th>Small molecule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mw (kDa)</td>
<td>150</td>
<td>28</td>
<td>1.5-2</td>
<td>&lt;0.8</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>Low (vascular)</td>
<td>Intermediate</td>
<td>Whole body</td>
<td>Typically whole body</td>
</tr>
<tr>
<td>t₁/₂</td>
<td>Days to weeks</td>
<td>Minutes to days</td>
<td>Min to hours (tunable). Days possible²</td>
<td>Hours (tunable)</td>
</tr>
<tr>
<td>Clearance</td>
<td>hepatic</td>
<td>Renal, hepatic</td>
<td>Renal</td>
<td>Renal, hepatic</td>
</tr>
<tr>
<td>Tumour penetrance</td>
<td>Low (outer rim only)</td>
<td>Low (poor exposure)</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Target classes</td>
<td>Many, small pockets restricted</td>
<td>Many, small pockets restricted</td>
<td>All tested successful, PPI trivial</td>
<td>Small pockets, PPI rare</td>
</tr>
<tr>
<td>Selectivity</td>
<td>Highly</td>
<td>Highly</td>
<td>Highly</td>
<td>Poor</td>
</tr>
<tr>
<td>Modularity</td>
<td>Low (bi-specifics)</td>
<td>Possible, difficult</td>
<td>Trivial (&quot;Lego like&quot;)</td>
<td>Low</td>
</tr>
<tr>
<td>Synthesis</td>
<td>Complex biologic</td>
<td>Complex biologic</td>
<td>Chemical, trivial</td>
<td>Chemical, trivial</td>
</tr>
<tr>
<td>Immunogenicity</td>
<td>Possible</td>
<td>Frequent</td>
<td>None detected</td>
<td>None</td>
</tr>
</tbody>
</table>

(to scale)
Current generation of peptidic imaging agents & approved drugs all inspired by nature

Peptide imaging agents in the clinic based on:

Human
- RGD (fibronectin)
- Vasoactive intestinal peptide
- Somatostatin-14

Other species
- Exendin-4 (GLP-1 homologue)
- Bombesin (GRP homologue)
- Venoms & toxins

64Cu-DOTA-TATE

111In-DTPA-Octreotide
The Bicycle platform can deliver novel tumour targeting peptides

**Linear peptide**

Protein III

Bicycle DNA Sequence

Gene III

Phage particle

Chemical modification with scaffold

**Bicycle**

**Diverse Bicycle phage libraries (>10^{15})**

Evolution driven, informed selection

1. **Cyclise**
   - POC in 6 wk
   - Optimised lead in 9mnth

2. **Select**

3. **Amplify**

**Extremely large and diverse chemical library**

**Low synthetic burden**

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Bicycles®: many shapes to drug many targets

Tractable target classes

<table>
<thead>
<tr>
<th>Enzymes</th>
<th>Immune checkpoint</th>
<th>Signalling</th>
<th>Adhesion</th>
<th>GPCRs</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serine proteases</td>
<td>TNFR superfamily members</td>
<td>Receptor Tyrosine kinases</td>
<td>Integrins</td>
<td>Chemokine receptors</td>
<td>Heat shock proteins</td>
</tr>
<tr>
<td>Other proteases</td>
<td>IG domain receptors</td>
<td>Interleukin receptors</td>
<td>Other cell adhesion proteins</td>
<td>Adrenergic receptors</td>
<td>Serum proteins</td>
</tr>
<tr>
<td>Metalloenzymes</td>
<td>Coagulation factors</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Matrix metalloproteinases</td>
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<tr>
<td>Other enzymes</td>
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</tr>
</tbody>
</table>

>90 diverse targets screened
80% success rate
**Bicycle** – large molecular footprint drives affinity and selectivity between close homologues

<table>
<thead>
<tr>
<th>Bicycle inhibitors</th>
<th>Human Kallikrein $K_i$ (nM)</th>
<th>Rat Kallikrein $K_i$ (nM)</th>
<th>Thrombin $K_i$ (nM)</th>
<th>Plasmin $K_i$ (nM)</th>
<th>Factor Xla $K_i$ (nM)</th>
<th>Factor Xlla $K_i$ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exemplar 1</td>
<td>0.8</td>
<td>17.6</td>
<td>&gt;10,000</td>
<td>&gt;15,000</td>
<td>&gt;50,000</td>
<td>&gt;10,000</td>
</tr>
<tr>
<td>Exemplar 2</td>
<td>0.2</td>
<td>3.7</td>
<td>&gt;10,000</td>
<td>&gt;35,000</td>
<td>15,000</td>
<td>&gt;10,000</td>
</tr>
<tr>
<td>Homologue active site sequence identity</td>
<td>85%</td>
<td>92%</td>
<td>100%</td>
<td></td>
<td></td>
<td>85%</td>
</tr>
</tbody>
</table>

**CA IX**
- $K_i = 25$ nM
- $K_i = 7.5$ nM

**CA XII**
- $K_i = 6$ nM
- $K_i > 2000$ nM

**Exemplar 1**
- Acetazolamide
  - CA IX: $K_i = 25$ nM
  - CA XII: $K_i = 6$ nM

**Exemplar 2**
- Acetazolamide
  - CA IX: $K_i = 7.5$ nM
  - CA XII: $K_i > 2000$ nM
Tolerance to conjugation is built-in

**Bacteriophage**

900 nm x 7 nm

- Small molecule drugs
- Other Bicycles (tandems)
- Chelated radionuclides
- Fluorescent dyes
- Affinity tags
- PK extenders

**Phage bulk readily replaced without compromising binding**

**In vitro tools**

- Fluorescent probe

**In vivo tools/diagnostics**

- 68Ga DOTA

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Case Study: MT1-MMP Targeting BTC – BT1718
Proven tumour delivery with *Bicycle* Toxin Conjugates: targeting MT1-MMP

- Membrane type 1 matrix metalloproteinase
- Low expression in normal adult
- Strong correlation with invasiveness in cancer cells

*Bicycle* binder to MT1-MMP:

<table>
<thead>
<tr>
<th>Human MT1-MMP $K_d$ (nM)</th>
<th>Mouse MT1-MMP $K_d$ (nM)</th>
<th>MT2-MMP $K_d$ (nM)</th>
<th>MT3-MMP $K_d$ (nM)</th>
<th>MT5-MMP $K_d$ (nM)</th>
<th>MMP1 $K_d$ (nM)</th>
<th>MMP2 $K_d$ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.6</td>
<td>1.8</td>
<td>&gt;10000</td>
<td>&gt;10000</td>
<td>&gt;2000</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
</tr>
</tbody>
</table>

Rosse *et al.*, 2014, PNAS 111, pp1872–1879
Bicycles® are retained in tumours and rapidly cleared from systemic circulation

Ideal distribution for imaging

68Ga MT1-MMP Bicycle
Coronal slices 0.8 mm ROI: tumor
maximum intensity
Projection (MIP)

68Ga MT1-MMP Antibody

Tumour Heart Liver

High tumour retention

Photoacoustic signal intensity (change from baseline)

Bicycle show superior retention in tumours and lower background vs antibodies
Bicycle® radio conjugate - kinetics of distribution and clearance

Figure 22. Whole-body coronal slices (0.8 mm) from μPET imaging 0-20 min p.i. (A), 20-40 min p.i. (B), and 40-60 min p.i. (C).

68Ga conjugated MT1-MMP targeting Bicycle
**Bicycle®** toxin conjugates show profound efficacy

**BT1718**: MT1-MMP targeting Bicycle Drug Conjugate

- **DM1 Toxin**
- **Cleavable linker**
- **Spacer**
- **Targeting Bicycle**

**Antigen mediated cell killing**

**Clears heterogenous PDXs**

**Cell-derived xenografts**

**Patient-derived xenografts**

**Large 1000mm³ CDX (EBC1)**

- **Vehicle**
- **BT1718 10mg/kg biw**

**Large 1000mm³ PDX (Lu-01-0046)**

- **Vehicle**
- **BT1718 10mg/kg biw**
- **Docetaxel 20mg/kg qw**
- **BT1718 10mg/kg, biw**

** Days after start of dosing**

**Tumour Volume (mm³)**

**Vehicle, iv, biw**

**BT1718 3mg/kg, biw**

**BT1718 10mg/kg, biw**

**Vehicle, day 14**

**BT1718, day 28**

**Vehicle, day 7**

**BT1718, day 28**
Case Study: EphA2 Targeting BTC - BT5528
**EphA2: Biological rationale**

- Erythropoietin-producing hepatocellular A2 receptor
- Member of Eph subfamily of receptor tyrosine kinases
- Regulates cell migration, adhesion proliferation and differentiation
- Overexpression in human cancers, correlates with tumour progression
- Key area for pharma companies, multiple programs in discovery, and clinical stages

**Zelinski et al**
Cancer Res 61: 2301-2306 (2001)
Biodistribution of $^{68}$Ga labelled Bicycle® shows excellent tumour targeting

PET imaging of HT-1080 xenograft at 60 minutes

Physicochemical properties of Bicycles have profound effect on distribution
BT5528: Rapid discovery of EphA2 targeted Bicycle® Toxin Conjugate

- Matrix of ~70 conjugates synthesized and screened
- Identify optimal toxin, cleavable linker, molecular spacer
- BT5528 identified as candidate BTC

Phage hit → Candidate selection: 1 year

Matrix of ~70 conjugates synthesized and screened
Identify optimal toxin, cleavable linker, molecular spacer
BT5528 identified as candidate BTC

Targeting Bicycle BCY6099

Val-Cit cleavable linker

MMAE

huEphA2 $K_d$ (nM)  |  moEphA2 $K_d$ (nM)  |  ratEphA2 $K_d$ (nM)  |  huEphA1 $K_d$ (nM)  |  huEphA3 $K_d$ (nM)  |  huEphA4 $K_d$ (nM)  |  huEphA5 $K_d$ (nM)
--- | --- | --- | --- | --- | --- | ---
1.2  | 2.5  | 3  | >5000  | >5000  | >5000  | >25000
Extensive tumour penetration maintains efficacy even in very large PDX model

- BT5528 maintains efficacy seen in CDX models even in large PDX
  - Patient-derived xenograft
    - Lung adenocarcinoma
  - Heterogeneous tumour
  - 1000mm$^3$ at dosing start
- Significant regression of tumour after 21d dosing 3mg/kg qw
- ADC shows no efficacy
  - Dosed 3mg/kg qw
- PET imaging shows rapid penetration of Bicycle conjugate into tumour
  - ADC data shows largely vascular distribution
- BT5528 in pre-clinical development


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Bicycles® can meet many of the challenges in oncology

**Can be hard to access**
- Size and PK accesses tumours efficiently

**Tumours can be “silent”**
- Large toolkit of novel probes

**Are difficult to differentiate from normal tissue**
- Highly selective to tumour target
- Combine in bispecifics tandem etc.

**Actively suppress the immune system**
- Multimeric immune receptor agonists
- Targeted systemic delivery of innate immune activators

**Diverse set of diseases**
- Companion diagnostics to stratify patients

**Heterogeneous and evolving**
- Superior penetration & bystander effect kills whole tumour
- Extensive arson of different anti-cancer targeting agents
Acknowledgements

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- Team at Bicycle UK & US

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Twitter (@Bicycle_tx)
#NotWaiting