Figure 1: MT1 over-expression in triple negative breast cancer (TNBC) (Rosse et al., PNAS 111: E1872-1879) and
• type 1-matrix metalloprotease (MT1-MMP/MMP14/MT1) is a promising
Therapeutics has developed a proprietary phage display platform technology
• is implicated in the invasion and metastasis of many cancers (Zarrabi
Design of bicyclic peptide and linker selection
1) Cyclise
2) Select
3) Hit identification – sequencing and
4) Hit optimisation
The functional small molecule scaffold
library with 6 amino acids in each loop. Output clones were characterised using
Bicycle Drug Conjugate
17-69-07
BT17BDC21 SMCC-Lys DM-1 N/A Not
HT-1080 cells
DM-4 30 24 0.6 0.2
Human MT3-MMP ectodomain 64% >> 500 (n=5) >10000 (n=1)
Human/cyno MT1 PEX 100% 1.6 ± 1.1 (n=20) 2.6 ± 0.4 (n=3)
Human/cyno MT1 catalytic domain N/A >> 100 (n=3) Not tested
Table 2: Structure, relative stability and affinity of Bicycle
BDC Linker Toxin Relative DTT
Ka (nM)
Stability
Plasma stability >>20hrs
Increasing stability of the disulphide bond was achieved by introducing methyl groups on
Stability: High
D in nM ± SD) (Biacore™)
In vitro
cytotoxicity:
Efficacy measured
Tumour Volume (mm3)
Days after start of dosing
Days after start of dosing
In vivo efficacy: Treatment with BDC containing the most labile linkers (BT17BDC17 or
BT1718) showed rapid and complete tumour clearance (ERC1 cells), while BDCs containing more
stabilised linkers showed comparatively reduced efficacy (fig. 5) suggesting that target
interation is not the sole mechanism driving BDC efficacy and that extracellular
drainage and release of toxin within the local tumour environment likely also contribute
only. The most labile BDC17BDC21 contained significant toxicity (17 ± 5.7 body weight loss); all
others were well tolerated (<50% body weight loss at 10mg/kg iv). Optimistic therapeutic
index was achieved with BT1718, testing of BT1718 in different dosing regimens in an
additional model (HT-1080 cells) also demonstrated excellent tumour regression, with 10mg/kg
b.i.w leading to complete tumour clearance in all 3 animals within 23 days and no re-growth out to
70-days.

Bicycle Therapeutics will be presenting further data on posters 1167/2 & 3719/4
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Bicycle Therapeutics® A successful targeted delivery modality

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Conclusions
• Bicycle demonstrates high efficacy for the tumour target MT1 and excellent selectivity against
other MMPs
• Correlation of N24 to CKM via a range of dissectable linkers produced a panel of Bicycle
Drug Conjugates which maintain high efficacy for MT1 and demonstrate in vivo efficacy,
exemplifying proof of concept for an exciting new targeted delivery modality
• Optimal therapeutic index was achieved using a mono-linked indole disulphide bond (BT1718)
• BT1718 has demonstrated efficacy in a wide range of MT1 positive cell and patient derived
xenografts and is currently progressing well through pre-clinical studies
• BT1718 showcases the great potential of Bicycle Therapeutics’ platform for the development
of novel and transformational drugs for the treatment of a wide range of cancers

References
1. Zarrabi N et al., Cancer Res. 2011, Bioconjugate Chemistry, 22, 717-727. Affinity for target was