Bicycle Toxin Conjugates® for the treatment of solid tumors

Stephen J. Walsh[1], **Johanna Lahdenranta[2]**, Philip Huxley[1], Gemma E. Mudd[1], Gavin Bennett[1], Amy Brown[1], Katerine van Rietschoten[1], Liuhong Chen[1], Heather Scott[1], Gabriela Ivanova-Berndt[1], Katarzyna Dzionek[1], Mike Rigby[1], Olga Burenkova[2], Phil Jeffrey[1], Paul Beswick[1], Michael Skynner[1], Nicholas Keen[2]

[1]Bicycle Therapeutics, Cambridge, UK; [2]Bicycle Therapeutics, Cambridge, MA, USA

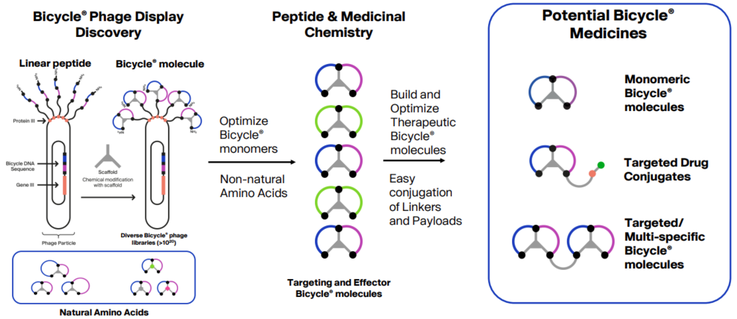
Abstract #

5807

1) Abstract

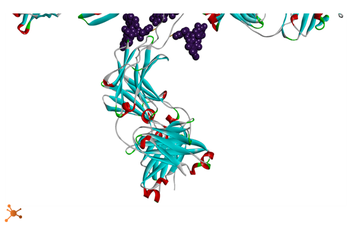
- Bicycle Toxin Conjugates® (BTCs) have potential for the treatment of solid tumors. There are currently two Bicycle Toxin Conjugates® undergoing Bicycle-sponsored clinical studies for a range of solid tumor indications.
- BT8009 is a Nectin-4 targeted BTC® which is currently undergoing a Phase 2/3 clinical study in metastatic urothelial cancer.
- BT5528 is an EphA2 targeted BTC® which is currently undergoing a Phase 1/2 clinical study in solid tumors.
- Here, we present data on BT8009 and BT5528, where we compare the anti-tumor activity of these BTCs to Nectin-4 and EphA2-targeted antibody-drug conjugates (ADCs), respectively, in pre-clinical models.

1) Introduction to Bicycle discovery process



- The discovery of Bicycle® molecules is centered on our phage display platform which can generate high affinity, highly specific molecules against a range of protein targets.[1]
- Phage hits are then optimized and can be incorporated into functional modalities, including Bicycle Toxin Conjugates®.

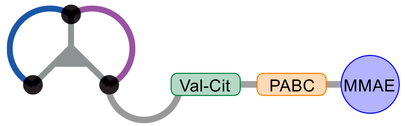
2) Comparison of Bicycle molecules to antibodies and small molecules

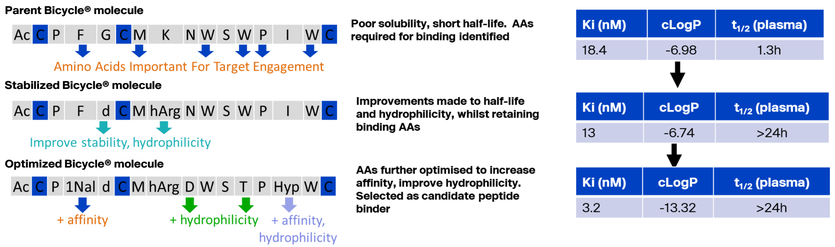


	Bicycle® molecule	Small molecule	Antibody
Small size	Yes – 1.5-2kDa	Yes – <0.8kDa	No – >150kDA
Specificity	High	Low	Multiple
Chemical synthesis (NCEs)	Yes	Yes	No
Rapid tissue penetration	Yes	Yes	No
Complex protein targets druggable	Yes	Limited	Yes
Route of elimination	Renal	Liver	Liver

- Bicycle peptides have antibody-like binding affinities with small molecule-like pharmacokinetics.
- In contrast to both antibodies and small molecules, Bicycle peptides are renally excreted.

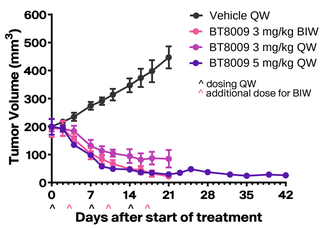
3) BT8009 – A Nectin-4 targeted Bicycle Toxin Conjugate®



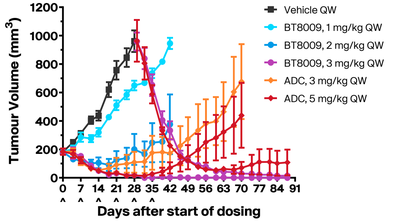


- BT8009 is a Nectin-4 targeted BTC® containing a Val-Cit-PABC-MMAE linker-payload.[2]
- The parent Bicycle® molecule identified from phage display was optimized for affinity, stability and solubility through medicinal chemistry efforts.[3]
- BT8009 is currently undergoing a Phase 2/3 clinical study in metastatic urothelial cancer. See www.bicycletherapeutics.com for more information.

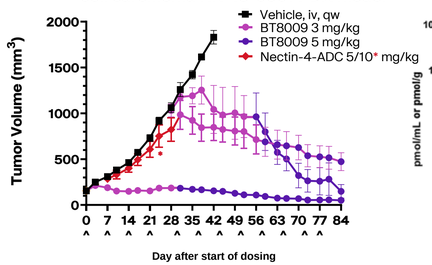
BT8009: Activity in breast adenocarcinoma (MDA-MB468) CDX model



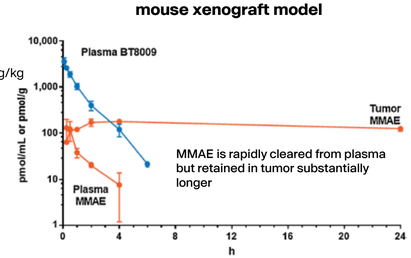
BT8009: Activity in lung cancer LU-01-0412 PDX model



BT8009: Activity in head and neck squamous cell carcinoma HN-13-0001 PDX model

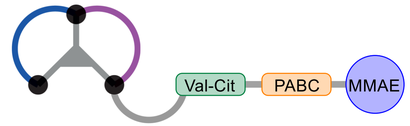


PK profile of BT8009 and MMAE in a mouse xenograft model

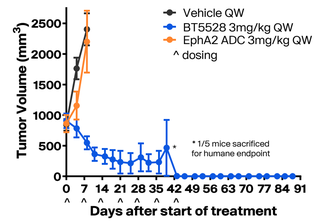


- BT8009 demonstrates robust anti-tumor activity in CDX and PDX pre-clinical models.
- When compared to a DAR 4 Val-Cit-MMAE antibody-drug conjugate (ADC), BT8009 demonstrates favorable anti-tumor activity.
- The PK profile of BT8009 in tumor-bearing animals demonstrated sustained MMAE levels in the tumor after a single dose, and rapid elimination from circulation.

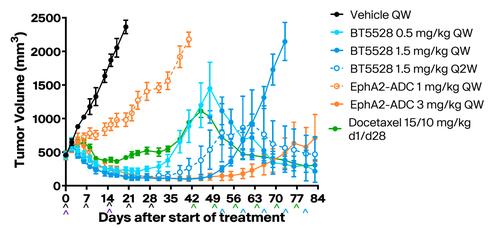
4) BT5528 – An EphA2 targeted Bicycle Toxin Conjugate®

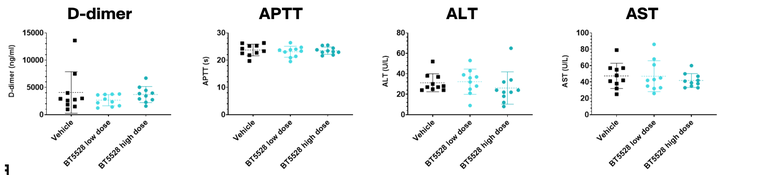


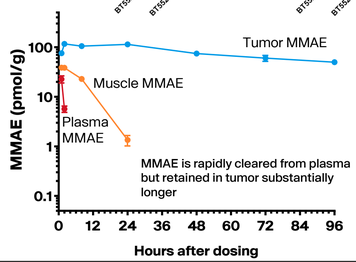
BT5528: Superior activity to EphA2 ADC in large NSCLC LU-01-0046 PDX model



BT5528: Activity in prostate cancer (PC-3) CDX model







- BT5528 is an EpHA2-targeted BTC® which also demonstrated differentiated anti-tumor activity in preclinical tumor models.[1,2]
- No signs of coagulopathy, bleeding or abnormal liver function in preclinical species.
- Sustained delivery of MMAE to tumor while rapid elimination of BT5528 and MMAE from plasma.
- BT5528 is currently undergoing a Phase 1/2 clinical study in solid tumors. See www.bicycletherapeutics.com for more information.

5) Conclusions

- Bicycle Toxin Conjugates® have demonstrated differentiated anti-tumor activity and PK profiles in preclinical species.
- BT8009 (a Nectin-4 targeted BTC®) and BT5528 (an EphA2 targeted BTC®) in certain pre-clinical models have been shown to generate meaningful tumor growth inhibition after ADC administration had proven ineffective, and/or where ADC treatment was ineffective.

6) References

1. Heinis et al, Nat Chem Biol, 2009, 5, 502-507.
2. Rigby et al, Mol Cancer Ther, 2022, 21, 1747-1756.
3. Mudd et al, J Med Chem, 2022, 65, 14337-14347.
4. Bennett et al, Mol Cancer Ther, 2020, 19, 1385-1394.
5. Mudd et al, J Med Chem, 2020, 63, 4107-4116.

BicycleTx Limited
Portway Building
Granta Park, Cambridge
CB21 6GS, UK
T. +44 (0)1223 261503.

Bicycle Therapeutics, Inc.
35 Cambridgepark Drive,
Suite 350
Cambridge, MA 02140
USA
T. +1 617-945-8155

www.bicycletherapeutics.com

Company number 11036101.
Registered in England.