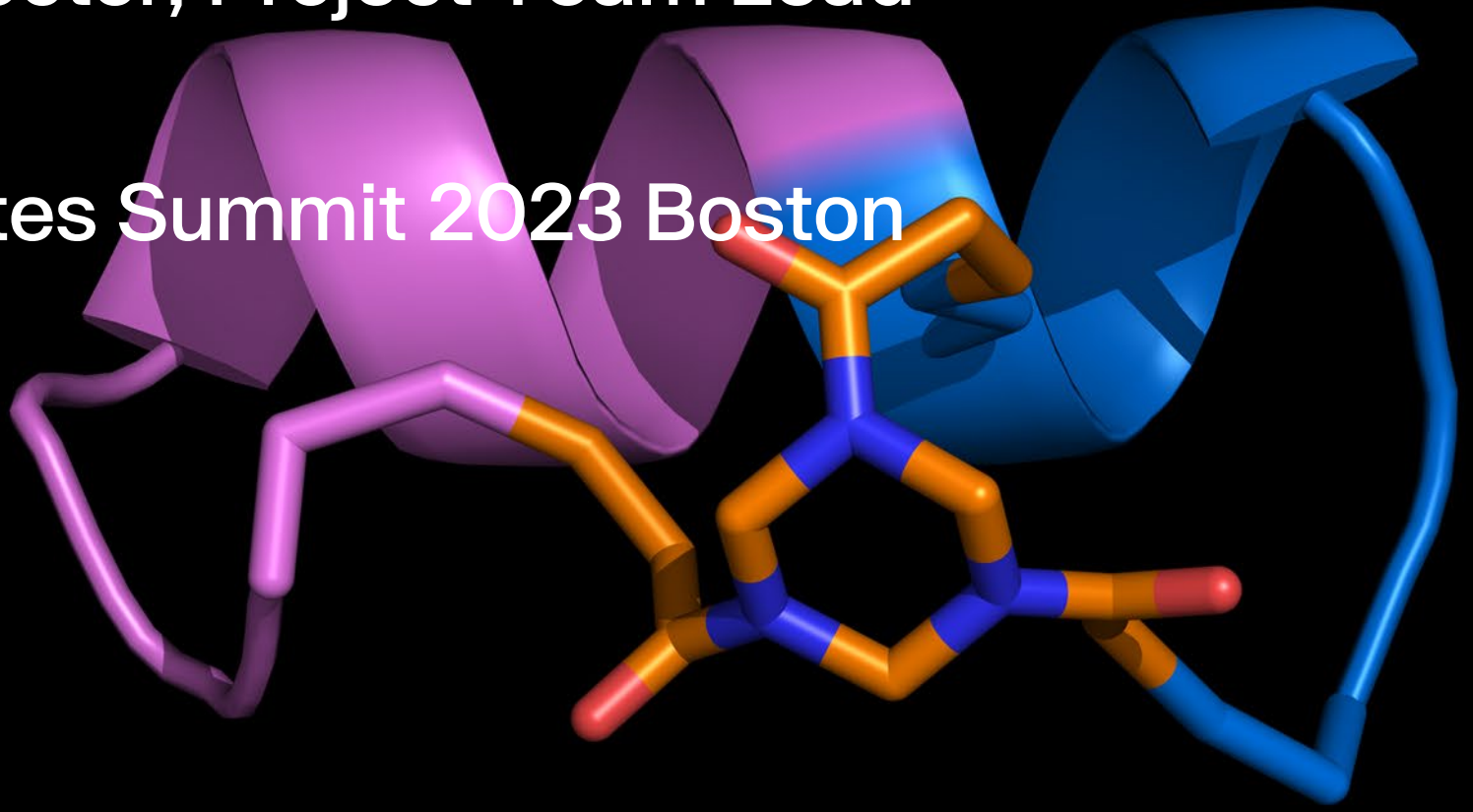
Bicycle Conjugates to Target Solid Tumors

Gavin Bennett, Senior Director, Project Team Lead

Next Generation Conjugates Summit 2023 Boston



Bicycle®

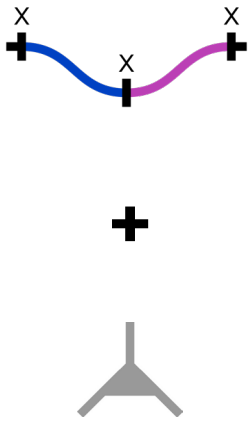
Forward-looking statement

This presentation may contain forward-looking statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. These statements may be identified by words such as "aims," "anticipates," "believes," "could," "estimates," "expects," "forecasts", "goal," "intends," "may" "plans," "possible," "potential," "seeks," "will," and variations of these words or similar expressions that are intended to identify forward-looking statements. All statements other than statements of historical facts contained in this presentation are forward-looking statements, including statements regarding: our future financial or business performance, conditions, plans, prospects, trends or strategies and other financial and business matters; our current and prospective product candidates, planned clinical trials and preclinical activities, current and prospective collaborations and the timing and success of our development of our anticipated product candidates.

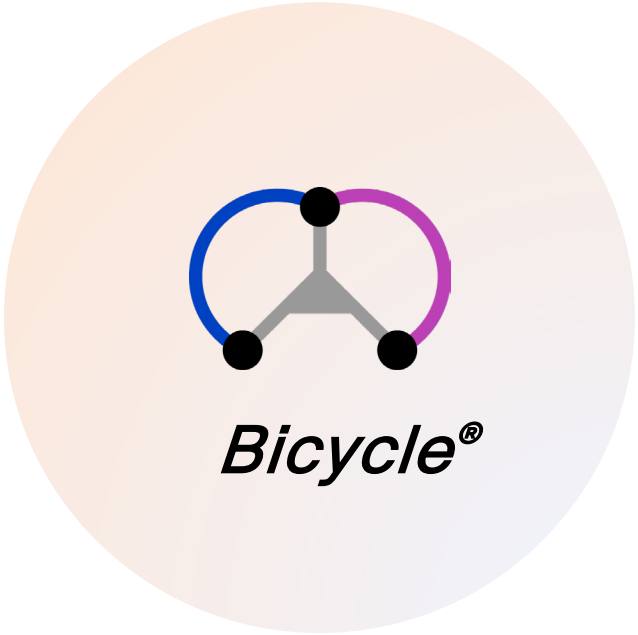
Forward-looking statements are neither historical facts nor assurances of future performance. Instead, they are based on our current beliefs, expectations and assumptions regarding the future of our business, future plans and strategies, our development plans, our preclinical and clinical results, our plans to initiate clinical trials and the designs of the planned trials and other future conditions, and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include, but are not limited to, risks related to the ongoing COVID-19 pandemic, the risk that any one or more of our product candidates will not be successfully developed or commercialized, the risk of cessation or delay of any ongoing or planned clinical trials, the risk that we may not realize the intended benefits of our technology, the risk that we may not maintain our current collaborations or enter into new collaborations in the future, or that we may not realize the intended benefits of these collaborations, the risk that our product candidates or procedures in connection with the administration thereof will not have the safety or efficacy profile that we anticipate, the risk that prior results will not be replicated or will not continue in ongoing or future studies or trials, the risk that we will be unable to obtain and maintain regulatory approval for our product candidates, the risk that the size and potential of the market for our product candidates will not materialize as expected, and risks relating to our ability to obtain and maintain intellectual property protection for our product candidates. For a discussion of these and other risks and uncertainties, and other important factors, any of which could cause our actual results to differ from those contained in the forward-looking statements, see the section entitled "Risk Factors" in our Quarterly Report on Form 10-Q, filed with the Securities and Exchange Commission on November 3, 2022, as well as in other filings we may make with the SEC in the future, as well as discussions of potential risks, uncertainties and other important factors in our subsequent filings with the Securities and Exchange Commission. New risks and uncertainties may emerge from time to time, and it is not possible to predict all risks and uncertainties. Except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise.

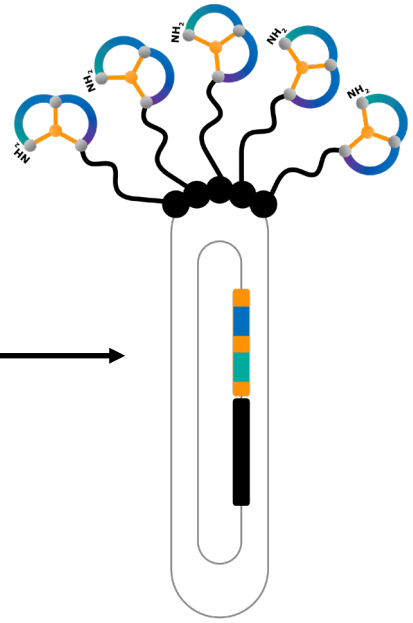
Bicycles are a new therapeutic modality – bicyclic peptides

Short linear peptide

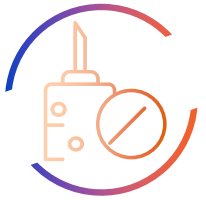


Scaffold
Chemical modification with scaffold



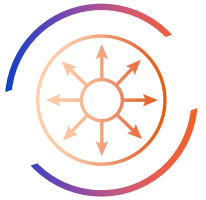


Diverse *Bicycle®* phage libraries (>10^{20})



Powerful/versatile platform
- Immense combinatorial potential
- Combines advantages of both small molecules and antibodies

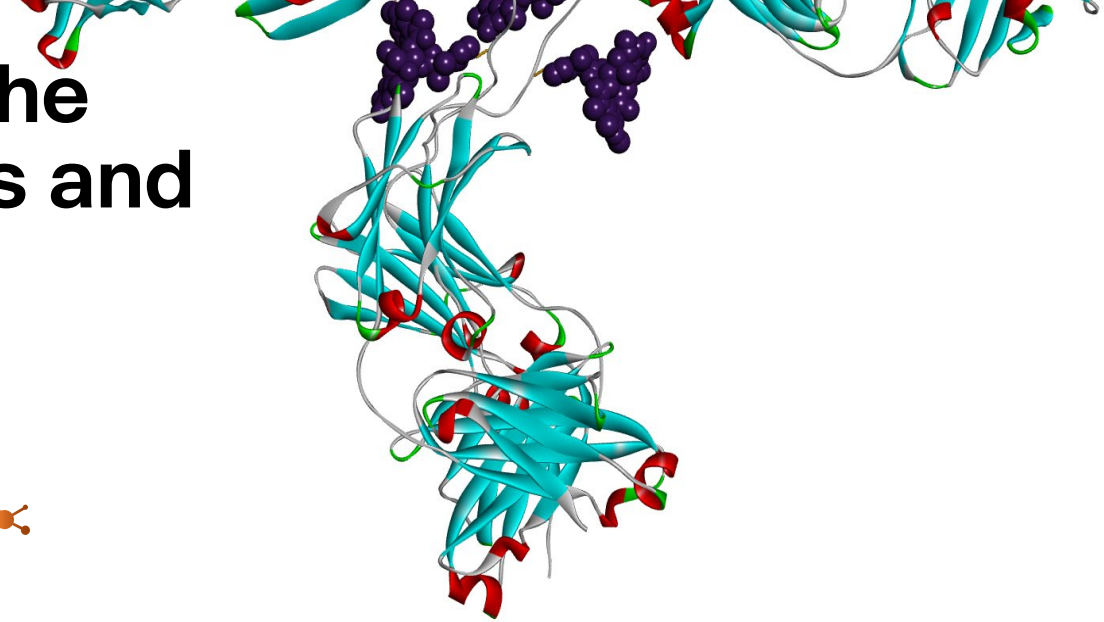
Multi-formats
- Monomeric Bicycles
- Bicycle Toxin Conjugates® (BTCs)
- Tumor-targeted immune cell agonists (*Bicycle* TICAs)



Robust patent protection with 123 patent families*

*As of September 30, 2022

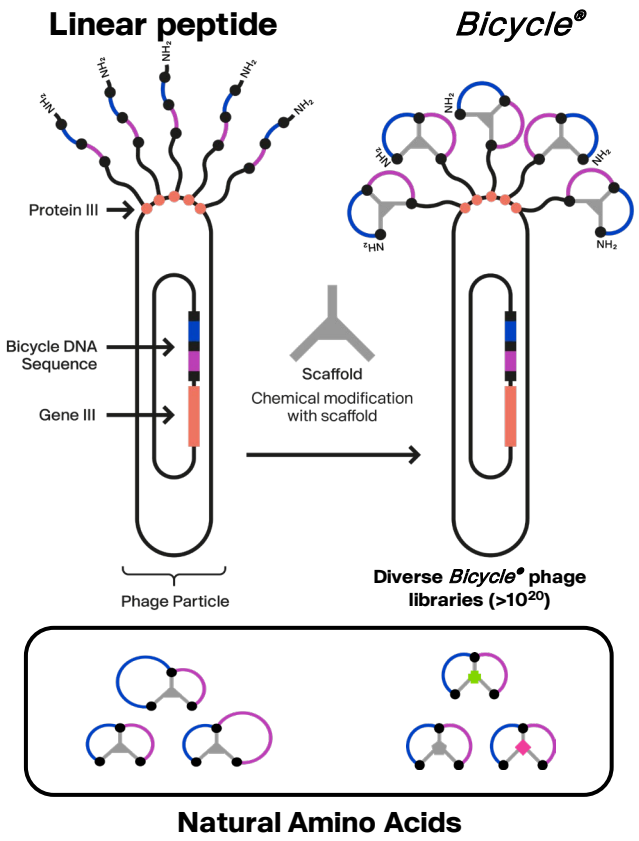
Bicycles are designed to combine the advantages of both small molecules and antibodies



	Bicycle®	Small molecule	Antibody
Small size	**Yes 1.5 to 2 kDa**	Yes <0.8 kDa	No >150 kDa
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® platform delivers a toolkit of building blocks to create novel medicines

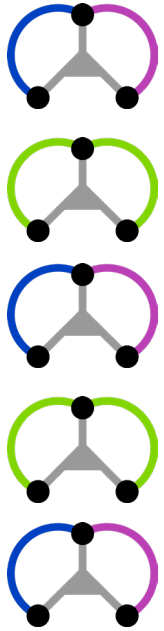
Bicycle® Phage Display - Discovery



Peptide & Medicinal Chemistry

Optimize *Bicycle*® *monomers*

Non-natural Amino Acids

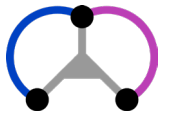


Tumor Targeting and Effector *Bicycles*

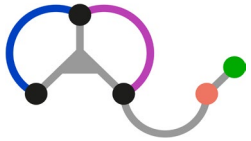
Build and Optimize Therapeutic *Bicycles*

Easy conjugation of Linkers and Payloads

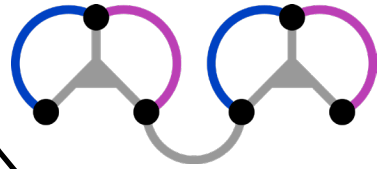
Potential *Bicycle*® Medicines



Monomeric *Bicycles*

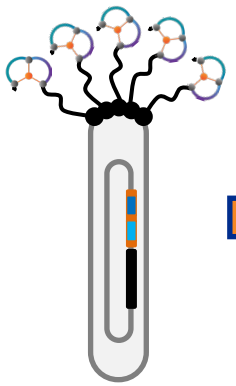


Targeted Drug Conjugates

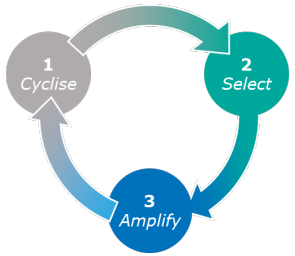


Targeted/ Multi-specific *Bicycles*

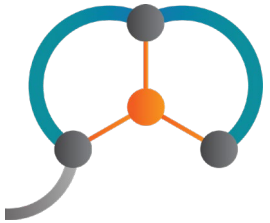
Chemical optimization of a high affinity EphA2 targeting *Bicycle*® with improved properties



2 scaffolds x 10 libraries,
➔ 8 peptide families

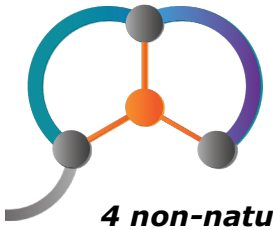


BCY6014

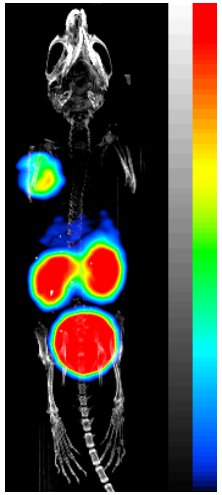


Chemistry Optimisation <40 analogs

BCY6099



4 non-natural amino acids



PET imaging of HT-1080 xenograft at 60 minutes

Modifications (*) to increase polarity, stability and/or potency

BCY6014 Ki = 16 nM – early *Bicycle*

A	R	D	C	P	L	V	N	P	L	C	L	H	P	G	W	T	C	A

BCY6099 Ki = 3 nM – newly optimised *Bicycle*

A	hR	D	C	hyP	L	V	N	P	L	C	L	H	P	dD	W	hR	C	A
	*			*										*		*		

MOLECULAR CANCER THERAPEUTICS | SMALL MOLECULE THERAPEUTICS

MMAE Delivery Using the *Bicycle* Toxin Conjugate BT5528 AC

Gavin Bennett[1], Amy Brown[1], Gemma Mudd[1], Philip Huxley[1], Katerine Van Rietschoten[1], Silvia Pavan[2], Liuhong Chen[1], Sophie Watcham[3], Johanna Lahdenranta[4], and Nicholas Keen[4]

Journal of Medicinal Chemistry

pubs.acs.org/jmc Article

Identification and Optimization of EphA2-Selective Bicycles for the Delivery of Cytotoxic Payloads

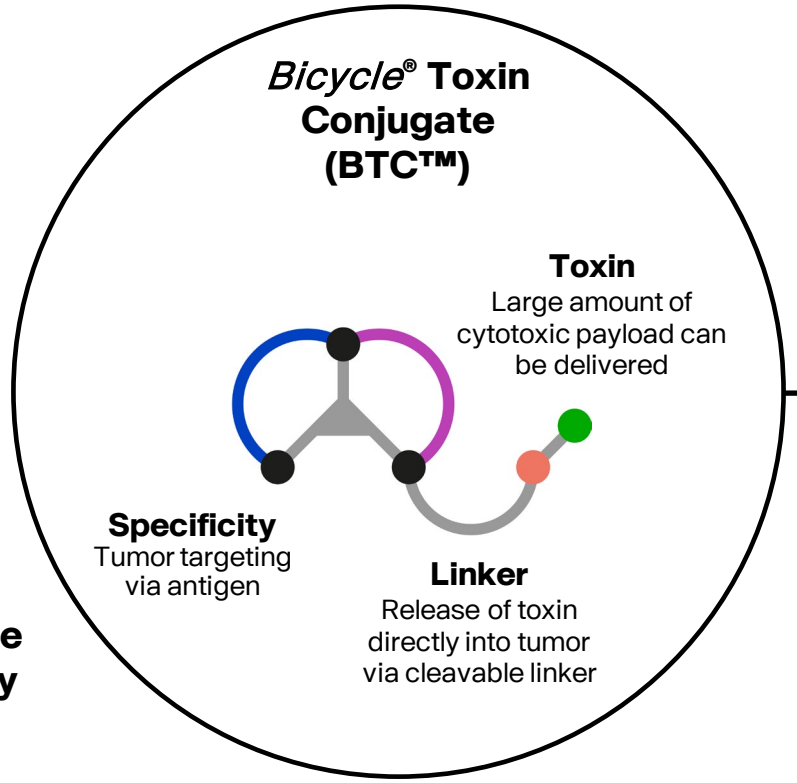
Gemma E. Mudd,* Amy Brown, Liuhong Chen, Katerine van Rietschoten, Sophie Watcham, Daniel P. Teufel, Silvia Pavan, Rachid Lani, Philip Huxley, and Gavin S. Bennett

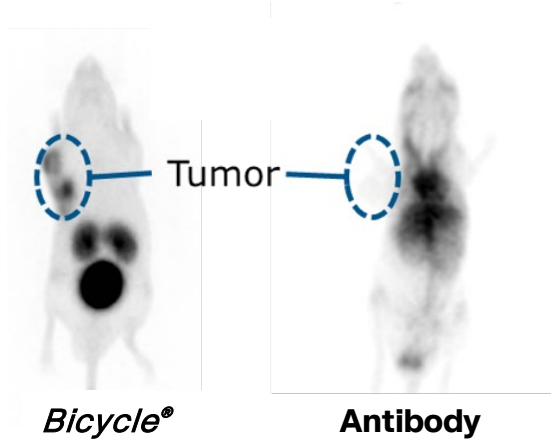
Cite This: https://dx.doi.org/10.1021/acs.jmedchem.9b02129 Read Online

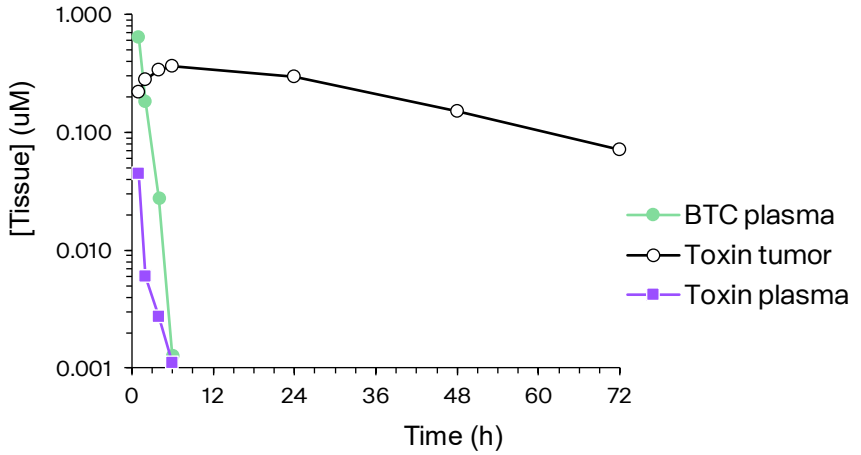
BTCs – preclinical data indicates higher potency and specificity with fewer side effects than ADCs

- **MW of 1.5-2kDa**
- **50-100x smaller than antibodies**

- **High selectivity**
- **Allows more potent toxin to be delivered directly to tumor**







BT5528: EphA2 targeted BTC®

Erythropoietin-producing hepatocellular A2 receptor: member of Eph subfamily of receptor tyrosine kinases

Regulates cell migration, adhesion, proliferation and differentiation

Overexpressed in human cancers and correlates with tumor progression

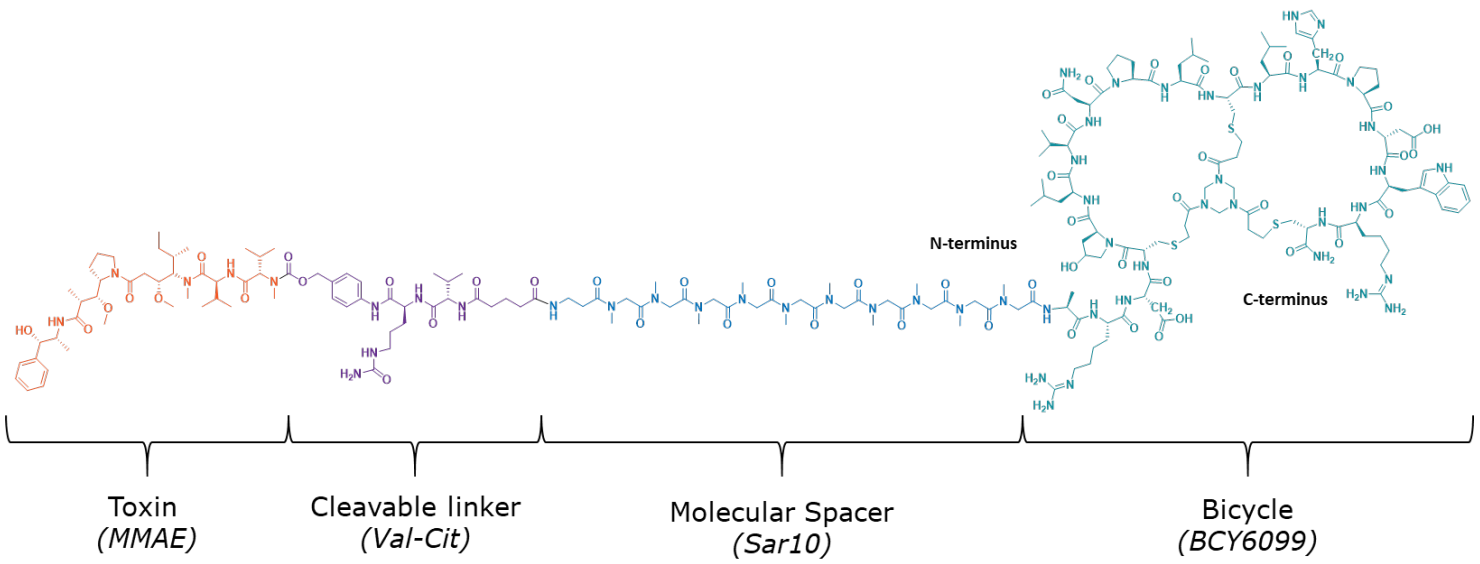
Development of MEDI-547 (MedImmune) in ovarian cancer was halted following serious bleeding events in phase I

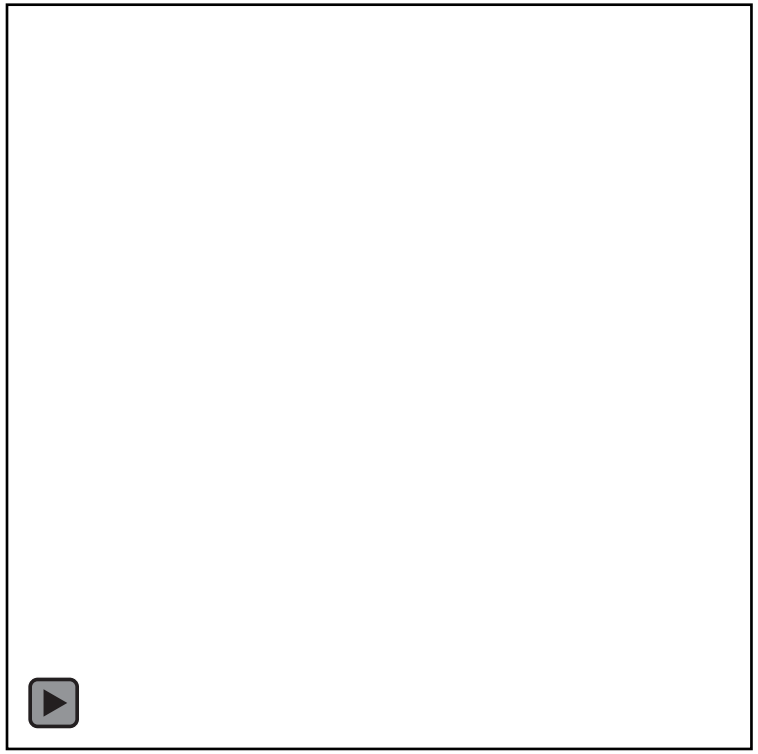
Internal	Target	Modality	Pre-clinical	IND-enabling	Phase I	Phase II
Bicycle®	EphA2	*Bicycle*® Toxin Conjugate				

- BT5528-100: Phase I/II multi-center first-in-human study in patients with advanced solid tumors associated with EphA2 expression
- NCT04180371 Study ongoing

1. Annunziata, Christina M., et al. "Phase 1, open-label study of MEDI-547 in patients with relapsed or refractory solid tumors." *Investigational new drugs* 31.1 (2013): 77-84.

BT5528: structure and profile

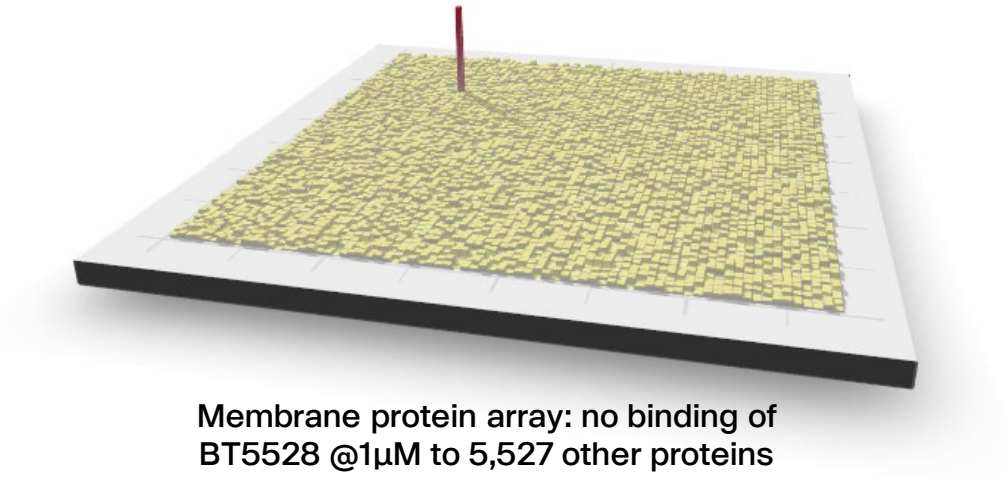




High affinity binding to EphA2 protein across species and on cells. Species cross-reactivity, high selectivity.

BT5528 affinity	Human	Mouse	Rat	NHP
FP comp (K_i, nM)	1.9 ± 0.9 n=29	5.2 ± 1.9 n=16	1.9 ± 1.3 n=10	
SPR (K_D, nM)	0.9 ± 0.4 n=2	2.0 ± 0.8 n=2	2.7 ± 0.4 n=2	1.0 n=1
Cell binding by HCS ($K_{b\,app}$, nM)	14.8 ± 10.5			

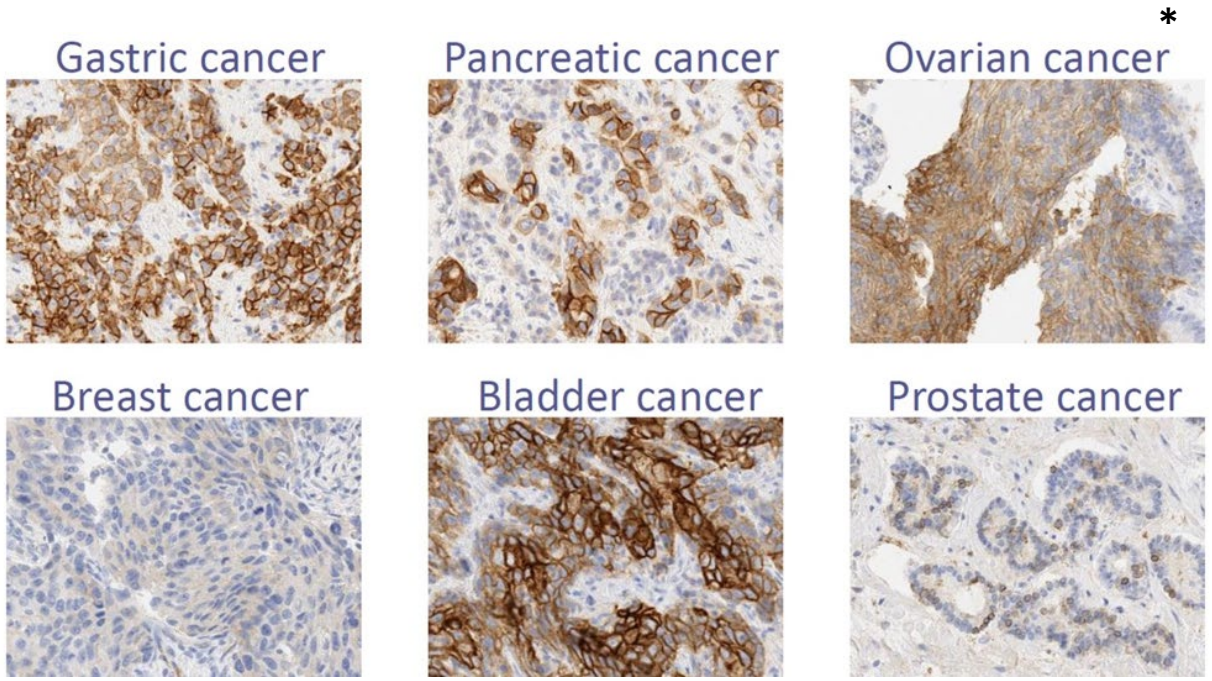
BT5528 only binds EphA2



Membrane protein array: no binding of BT5528 @1µM to 5,527 other proteins

EphA2 is a high value target for the treatment of cancer

- EphA2, a member of Eph subfamily of receptor tyrosine kinases
- Regulates cell migration, adhesion, proliferation and differentiation
- Highly expressed in many human cancers and correlates with tumor progression
  - Ovarian
  - Urothelial
  - NSCLC
  - Head & Neck
  - Gastric
  - TNBC



*

*Kamoun, et al, Nanoliposomal Targeting of Ephrin Receptor A2 (EphA2): Clinical Translation, Merrimack Pharmaceuticals

Multiple approaches targeting EphA2-expressing tumors have failed

- MEDI-547 (MedImmune) ADC: halted following first dose-cohort coagulopathy[1]
- DS-8895a (Daiichi) antibody: limited efficacy in EphA2+ gastric and esophageal cancer, significant infusion reactions. Discontinued because of poor risk-benefit profile[2]
- MM-310 (Merrimack) antibody-targeted nanoliposome: terminated - “unable to reach optimal therapeutic index”[3]

Invest New Drugs (2013) 31:77–84
DOI 10.1007/s10637-012-9801-2

PHASE I STUDIES

Phase 1, open-label study of MEDI-547 in patients with relapsed or refractory solid tumors

Christina M. Annunziata · Elise C. Kohn · Patricia LoRusso · Nicole D. Houston · Robert L. Coleman · Manuela Buzoianu · Gabriel Robbie · Robert Lechleider

Investigational New Drugs
https://doi.org/10.1007/s10637-022-01237-3

PHASE I STUDIES

A phase 1 safety and bioimaging trial of antibody DS-8895a against EphA2 in patients with advanced or metastatic EphA2 positive cancers

Hui K. Gan[1,2,3] · Sagun Parakh[1,2,3] · F. T. Lee[1] · Niall C. Tebbutt[3] · Malaka Ameratunga[3] · Sze Ting Lee[1,2,4,5] · Graeme J. O'Keefe[1,4] · Sylvia J. Gong[1,4] · Christine Vanrenen[3] · Jaren Caine[3] · Mara Giovannetti[6] · Carmel Murone[1] · Fiona E. Scott[1,2] · Nancy Guo[1] · Ingrid J. G. Burvenich[1,2] · Cameron Paine[4] · Mary J. Macri[6] · Masakatsu Kotsuma[7] · Giorgio Senaldi[7] · Ralph Venhaus[6] · Andrew M. Scott[1,2,4,5]

Clinical Trial · J Immunother Cancer. 2019 Aug 14;7(1):219. doi: 10.1186/s40425-019-0679-9.

Safety, tolerability, pharmacokinetics, and pharmacodynamics of the afucosylated, humanized anti-EPHA2 antibody DS-8895a: a first-in-human phase I dose escalation and dose expansion study in patients with advanced solid tumors

Kohei Shitara [1], Taroh Satoh [2], Satoru Iwasa [3], Kensei Yamaguchi [4], Kei Muro [5], Yoshito Komatsu [6], Tomohiro Nishina [7], Taito Esaki [8], Jun Hasegawa [9], Yasuyuki Kakurai [9], Emi Kamiyama [9], Tomoko Nakata [9], Kota Nakamura [9], Hayato Sakaki [9], Ichinosuke Hyodo [10]

merrimack

Merrimack Discontinues Development of MM-310

April 4, 2019

-- Safety update shows Phase 1 study unable to reach optimal therapeutic index for MM-310 due to continued observation of cumulative peripheral neuropathy --

-- Company expects to reduce workforce reflective of narrowed preclinical development pipeline; continues to prudently advance programs while completing the assessment of its strategic alternatives --

1. Annunziata et al, Invest New Drugs. 2013 Feb;31(1):77-84
2. Shitara et al, Journal for ImmunoTherapy of Cancer. 2019 7: 219-230 (Ph1 study); Gan et al, Invest New Drugs. 2022 40(4) 747-755
3. Merrimack Pharmaceuticals Inc., press release April 4, 2019

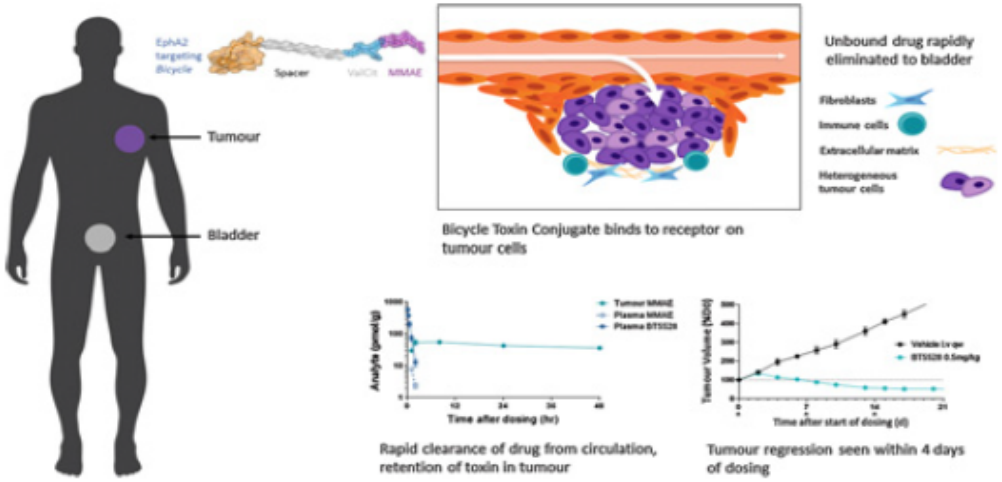
MMAE Delivery Using the *Bicycle* Toxin Conjugate BT5528 AC

Gavin Bennett[1], Amy Brown[1], Gemma Mudd[1], Philip Huxley[1], Katerine Van Rietschoten[1], Silvia Pavan[2], Liuhong Chen[1], Sophie Watcham[3], Johanna Lahdenranta[4], and Nicholas Keen[4]

ABSTRACT

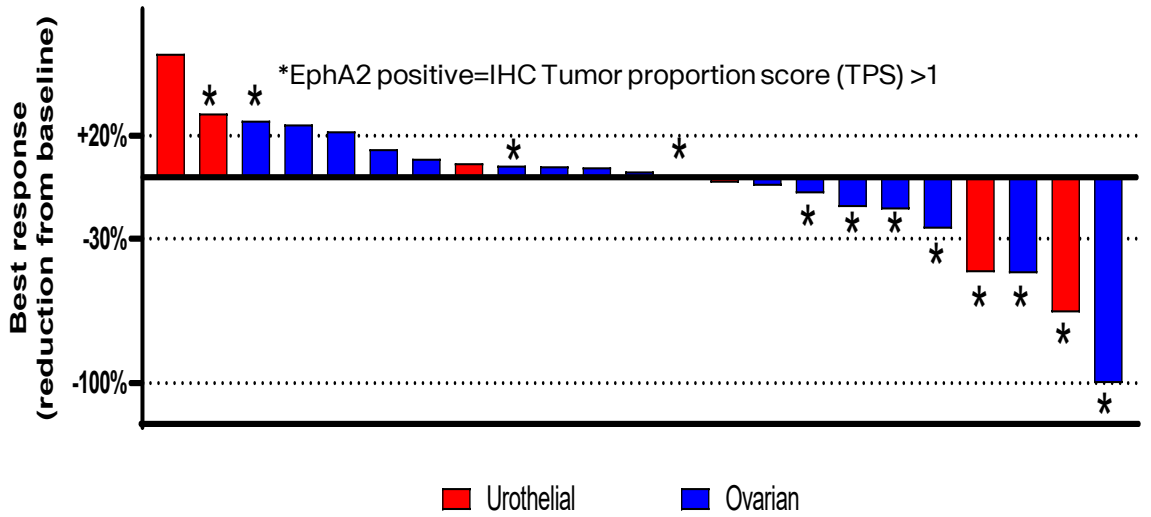
The EphA2 receptor is found at high levels in tumors and low levels in normal tissue and high EphA2 expression in biopsies is a predictor of poor outcome in patients. Drug discovery groups have therefore sought to develop EphA2-based therapies using small molecule, peptide, and nanoparticle-based approaches (1–3). However, until now only EphA2-targeting antibody–drug conjugates (ADC) have entered clinical development. For example, MEDI-547 is an EphA2-targeting ADC that displayed encouraging antitumor activity in preclinical models and progressed to phase I clinical testing in man. Here we describe the development of BT5528, a bicyclic peptide ("*Bicycle*") conjugated to the auristatin derivative maleimidocaproyl-monomethyl auristatin E to generate the *Bicycle* toxin conjugate BT5528. The report compares and contrasts the Pharmacokinetics (PK) characteristics of antibody and *Bicycle*-based targeting systems and discusses how the PK and payload characteristics of different delivery systems impact the efficacy—toxicity trade off which is key to the development of successful cancer therapies. We show that BT5528 gives rise to rapid update into tumors and fast renal elimination followed by persistent toxin levels in tumors without prolonged exposure of parent drug in the vasculature. This fast in, fast out kinetics gave rise to more favorable toxicology findings in rats and monkeys than were observed with MEDI-547 in preclinical and clinical studies.

Graphical Abstract: http://mct.aacrjournals.org/content/molcanther/19/7/1385/F1.large.jpg.



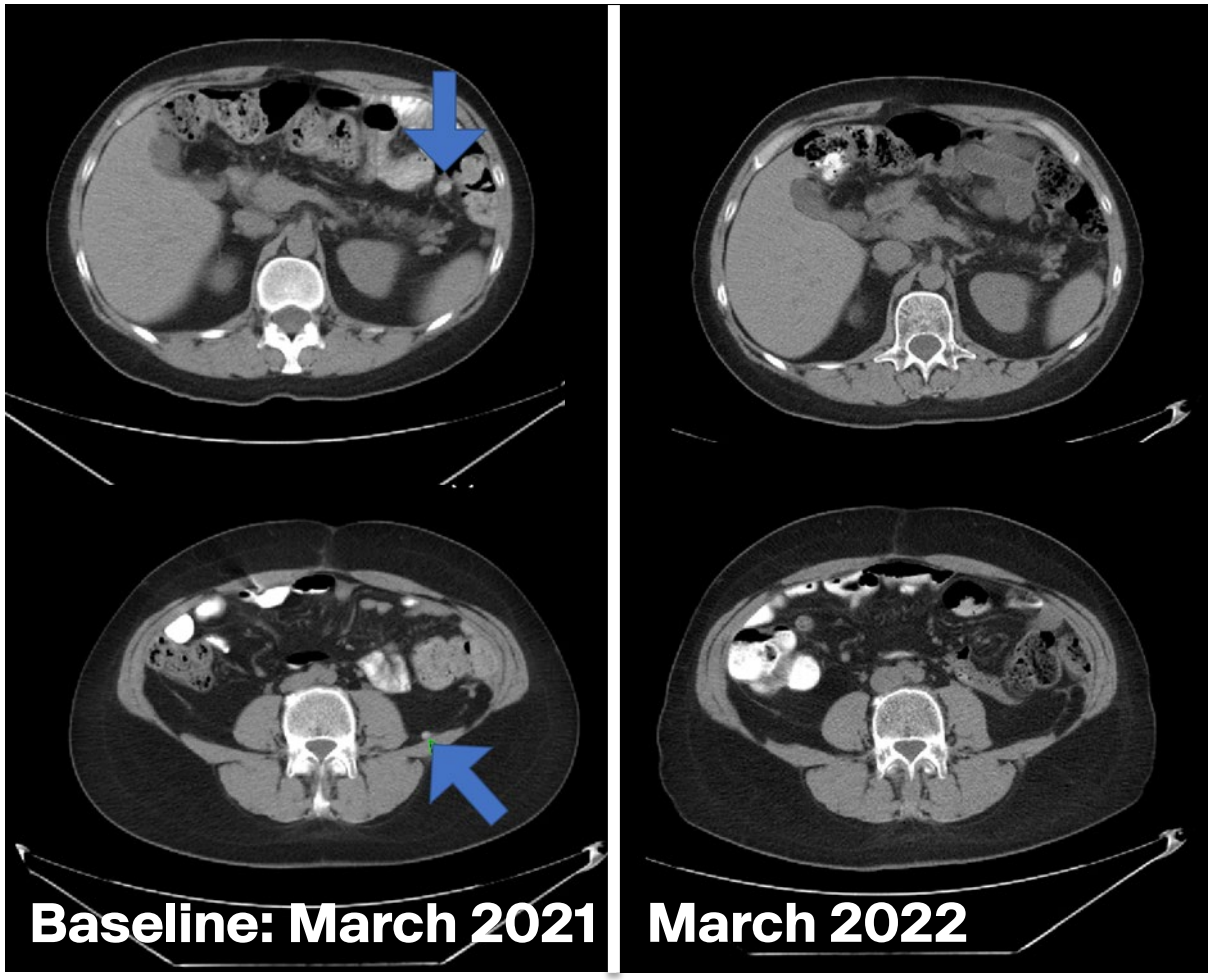
BT5528: Emerging relationship between EphA2 expression and response in ovarian and urothelial cancers

Best response by RECIST in response evaluable patients



- Waterfall plot showing best response among urothelial and ovarian cancer patients in first in human study
- Immunohistochemistry data suggest positive patients more likely to respond to BT5528
- Scan showing complete responder with ovarian cancer
- *For more information, please visit www.bicycletx.com*

CT scans-abdomen. First in human dose escalation trial.



BT5528

- BT5528 demonstrates anti-tumor activity in highly refractory ovarian and urothelial cancer patients
- Emerging safety profile distinguishes it from other EphA2-targeted molecules
- Dosing at recommended Phase II dose of 6.5 mg/m ^{2} q2w in expansion cohorts is ongoing
- Full Phase I dose escalation trial results to be published in 2023
- For more information, please visit www.bicycletx.com

BT8009: Nectin-4 targeted BTC

Nectin-4:

A cell adhesion molecule and one of four members of the nectin family

All nectins share the same overall structure defined by three extracellular immunoglobulin domains, a single transmembrane helix and an intracellular domain

Overexpressed in human cancers and correlated with tumor progression

Solid tumors with high levels of Nectin-4 expression are urothelial, TNBC, ovarian, head & neck and NSCLC

Internal	Target	Modality	Pre-clinical	IND-enabling	Phase I	Phase II
Bicycle®	Nectin-4	*Bicycle*® Toxin Conjugate				

- BT8009-100: Phase I/II Study of the Safety, Pharmacokinetics, and Preliminary Clinical Activity of BT8009 in Patients With Nectin-4 Expressing Advanced Malignancies
- NCT04561362
- Study ongoing
- BT8009 Phase I trial results released at ASCO GU Feb 2023
- For more information, please visit www.bicycletx.com

Bicycle TICA™ – Tumor-targeted Immune Cell Agonists join immune cell-engaging and tumor-targeting Bicycles

Immune cell receptor engaging *Bicycle*®
CD137

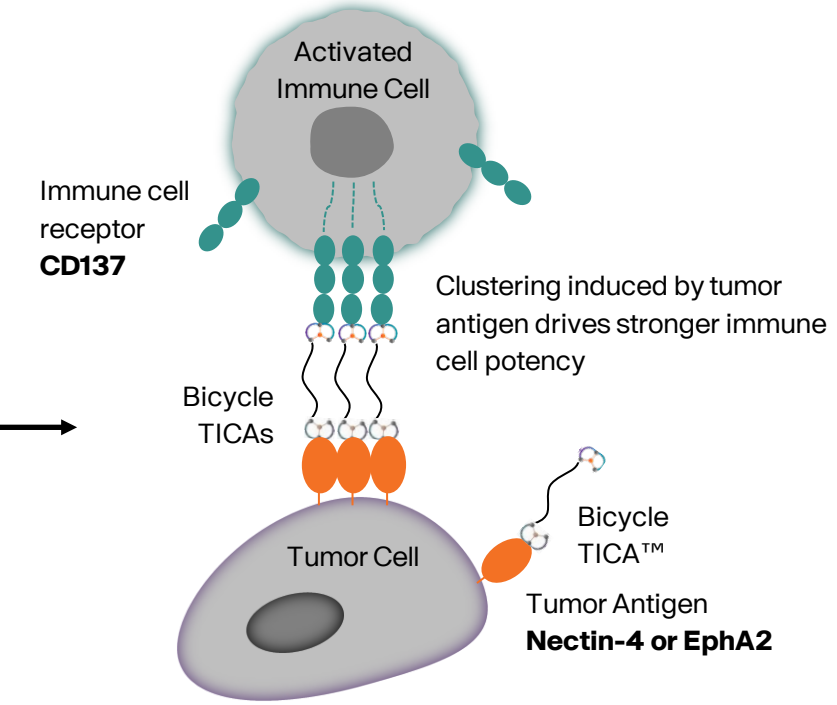
Linker

Tumor Antigen Targeting *Bicycle*®
Nectin-4 or EphA2

Tumor-targeted Immune Cell Agonists (*Bicycle* TICA™)

BT7480
(Nectin-4/CD137)

BT7455
(EphA2/CD137)



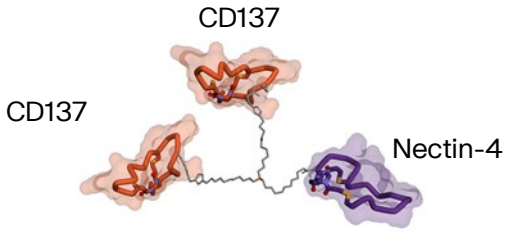
CD137 validated target
Signal 2 costimulatory receptor – drives T-cell function and survival, also expressed on NK cells and myeloid cells

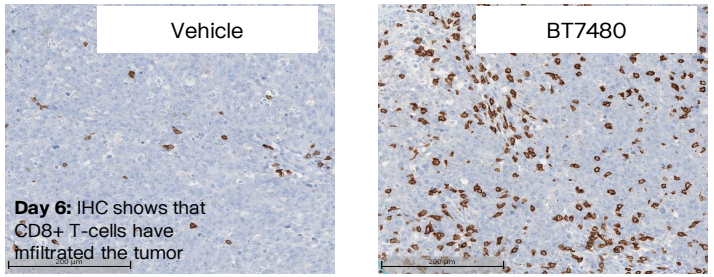
BT7480 entered clinic Q4 2021

Nectin-4 and CD137 co-expressed in a variety of human tumors

- BT7480 binds to Nectin-4 (across species) and CD137 (human, non-human primates) with high affinity. Exquisite selectivity observed in pre-clinical studies – no binding seen with >5,000 other membrane proteins.

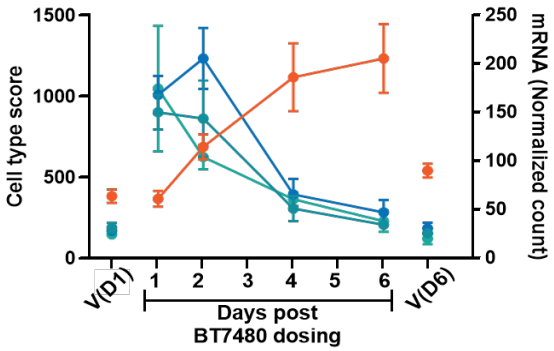
Internal	Target	Modality	Pre-clinical	IND-enabling	Phase I	Phase II
Bicycle	Nectin-4 /CD137	Bicycle TICA™				

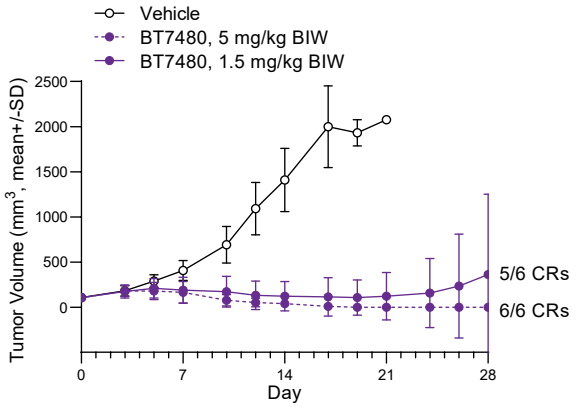




- BT7480 well-tolerated in preclinical species, with no liver tox
- BT7480 is ca. 30x smaller than comparator biologics
- US IND cleared 17Sept21
  - 9 sites selected
  - qw dosing initially with dosing adjustment to q2w

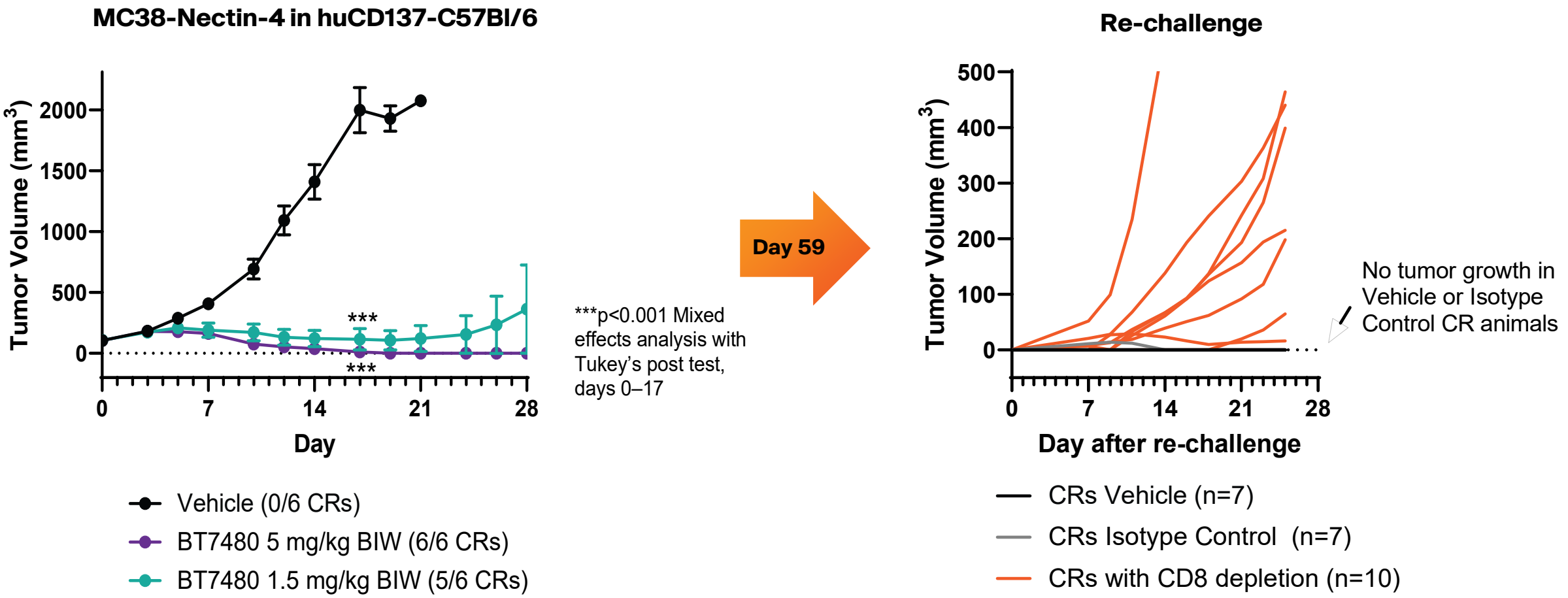
Entered clinic Q4 2021





Bicycle®

BT7480 induces complete responses and memory *in vivo* in a syngeneic mouse model



CRs=Complete Responders

NK-TICAs to engage NK cells

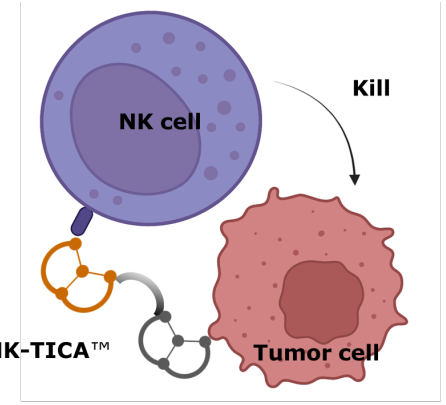
Prototype NK cell engagers developed

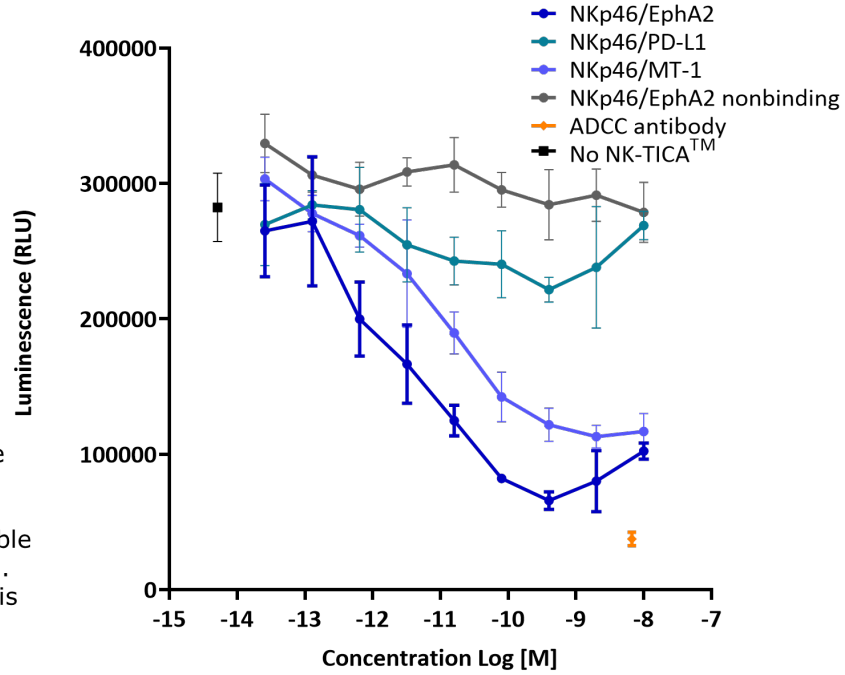
Building on CD137 Bicycle® TICAs

NK-TICAs drive NK cell-mediated tumor cell killing and cytokine production *in vitro*

Bicycle's NK-TICA™ molecules are designed to engage NK cells in a tumor antigen dependent manner to kill and drive adaptive immunity in solid tumors.

NK cells can be directed to kill tumor cells by NKp46 NK-TICAs employing multiple different tumor antigens: EphA2, MT-1 and PD-L1





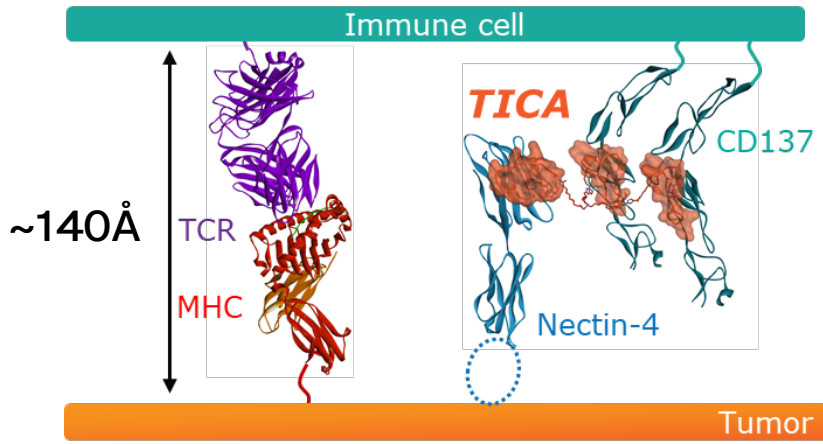
NK cells co-cultured with HT1080-luc cells in the presence of NKp46 NK-TICAs of varying tumor binding arms: EphA2 (BCY17226), MT-1 (BCY18604), or PD-L1 (BCY18603). ADCC-capable anti-EGFR antibody was used as positive control. Luminescence values for no NK-TICA™ addition is arbitrarily shown as 5 x 10^{-15} M.

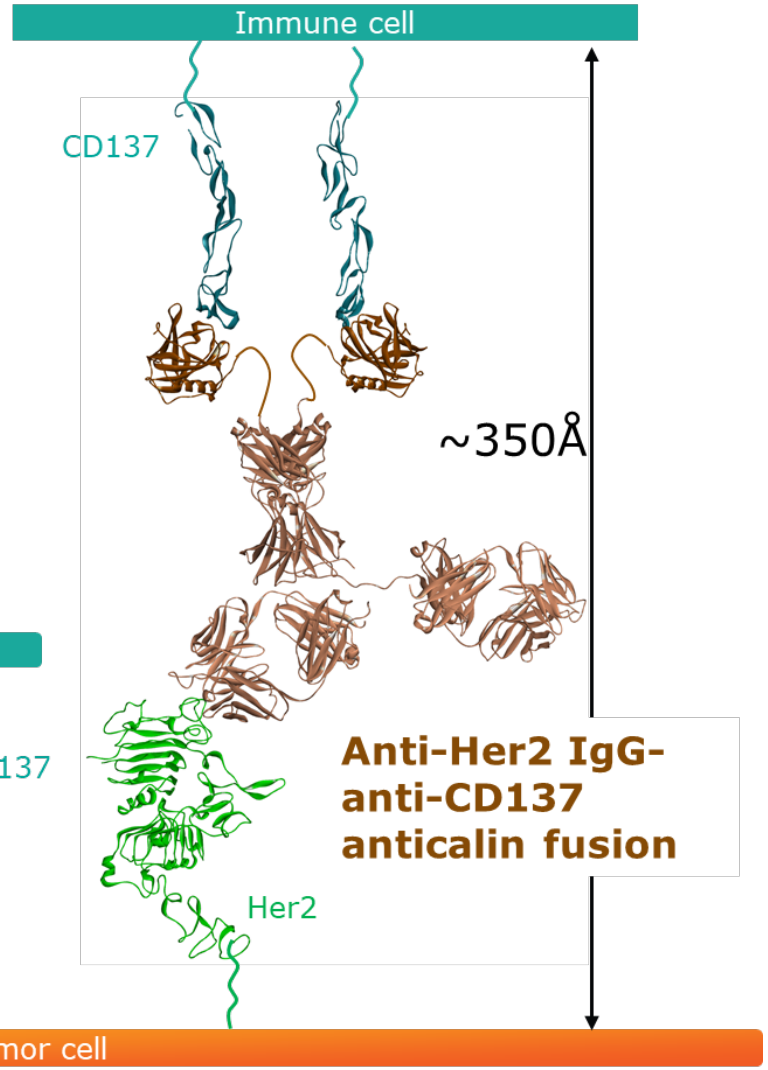
Dufort *et al*, Abstract 4233, AACR 2022

Bicycle TICA™
Potential to be immuno-oncology medicines

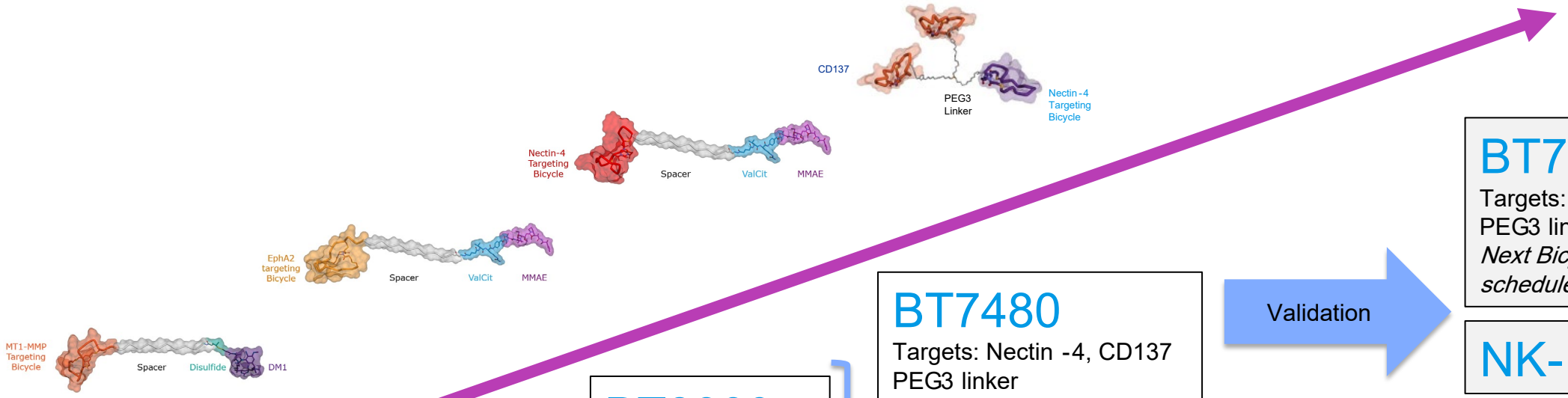
Target / Product	Partner/ Sponsor	Preclinical	IND-enabling	Phase I	Phase II
Immuno-oncology					
BT7480 (Nectin-4/CD137 tumor-targeted immune cell agonist, *Bicycle* TICA)					
BT7455 (EphA2/CD137 *Bicycle* TICA)					
BT7401 (multivalent CD137 systemic agonist)	CANCER RESEARCH UK				
Undisclosed	Genentech A Member of the Roche Group				

- Synthetic & tunable properties
- PK and physical size believed to be a good match for immune agonism
- Potent and tumor specific





Elevating the 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
Targets: Nectin -4, CD137
PEG3 linker

Validation

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

NK-TICA™

Validation

Next-gen BTCs
Different targets, linkers and payloads

Radiopharm

FIH 2018 2019 2020 2021 2023 and beyond

Summary

Bicycles offer a potential new modality for oncology therapeutics

- Antibody-like affinity and selectivity in a small molecule
- Chemically synthesized
- Rapid distribution to solid tumors, elimination via renal route

Bicycle TICAs show promise for targeted stimulation of immune cells in tumors

- BT7480 entered the clinic Q4 2021
- BT7455 (EphA2-CD137 Bicycle TICA™) in IND-enabling stage
- NK-TICA™ programs targeting natural killer (NK) cells identified and moving into lead optimization

Bicycle Toxin Conjugates® progressing in clinical studies

3 conjugates in clinical trials

- Clinical PK profile consistent with preclinical prediction
- Preliminary signs of anti-tumor activity seen
- Emerging safety profile supports potential of Bicycle platform

Thank you

Bicycle®