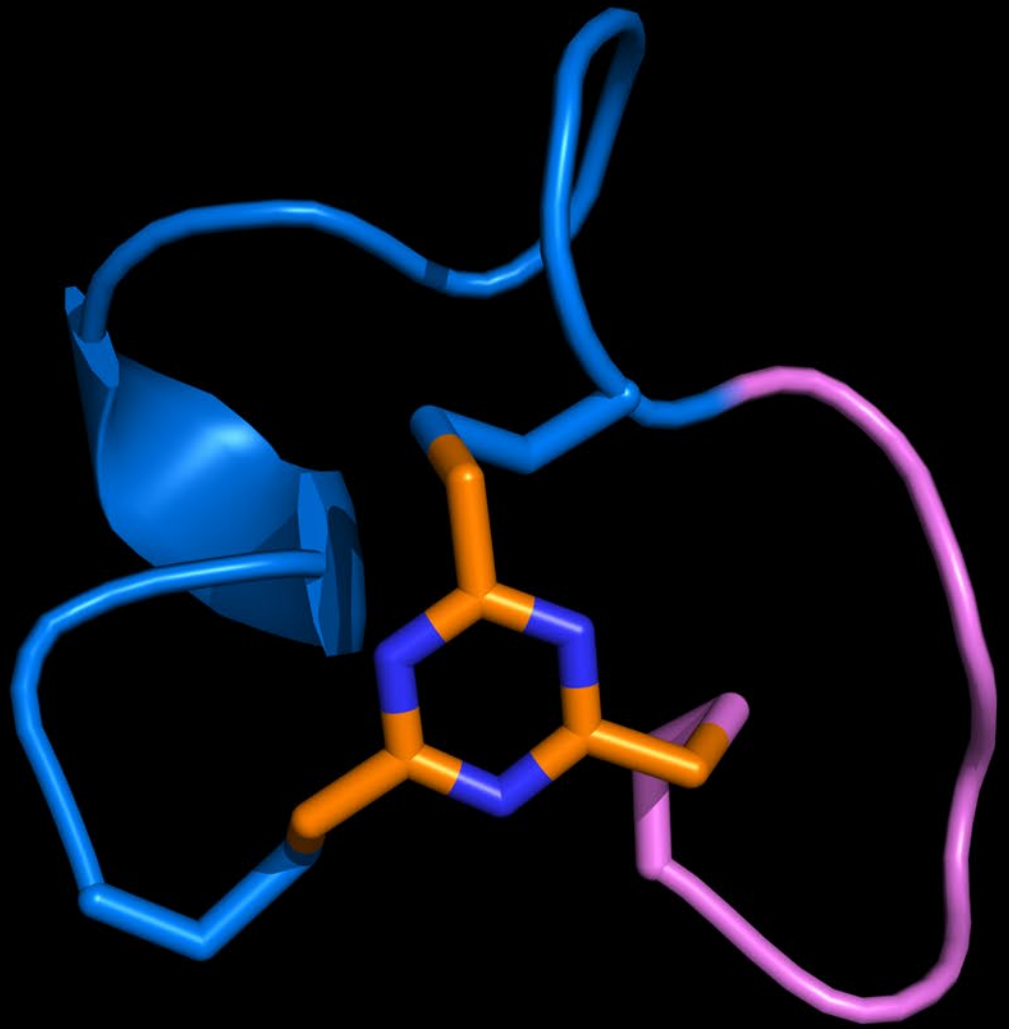
BT7480, a novel and fully synthetic *Bicycle* tumor-targeted immune cell agonist®

Kristen Hurov
Senior Director, Clinical Development

Festival of Biologics, Basel
November 4th, 2022



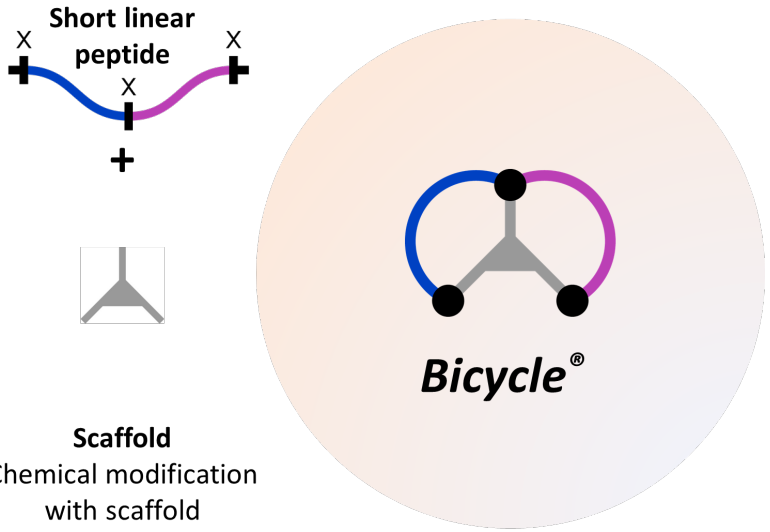
Bicycle®

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.

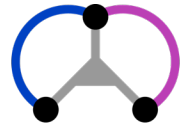
Forward-looking statements are neither historical facts nor assurances of future performance. Instead, they are based on our current beliefs, expectations and assumptions regarding the future of our business, future plans and strategies, our development plans, our preclinical and clinical results, our 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, 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, including that we may not identify and develop additional product candidates for our pipeline, 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 short peptides chemically constrained with a central scaffold

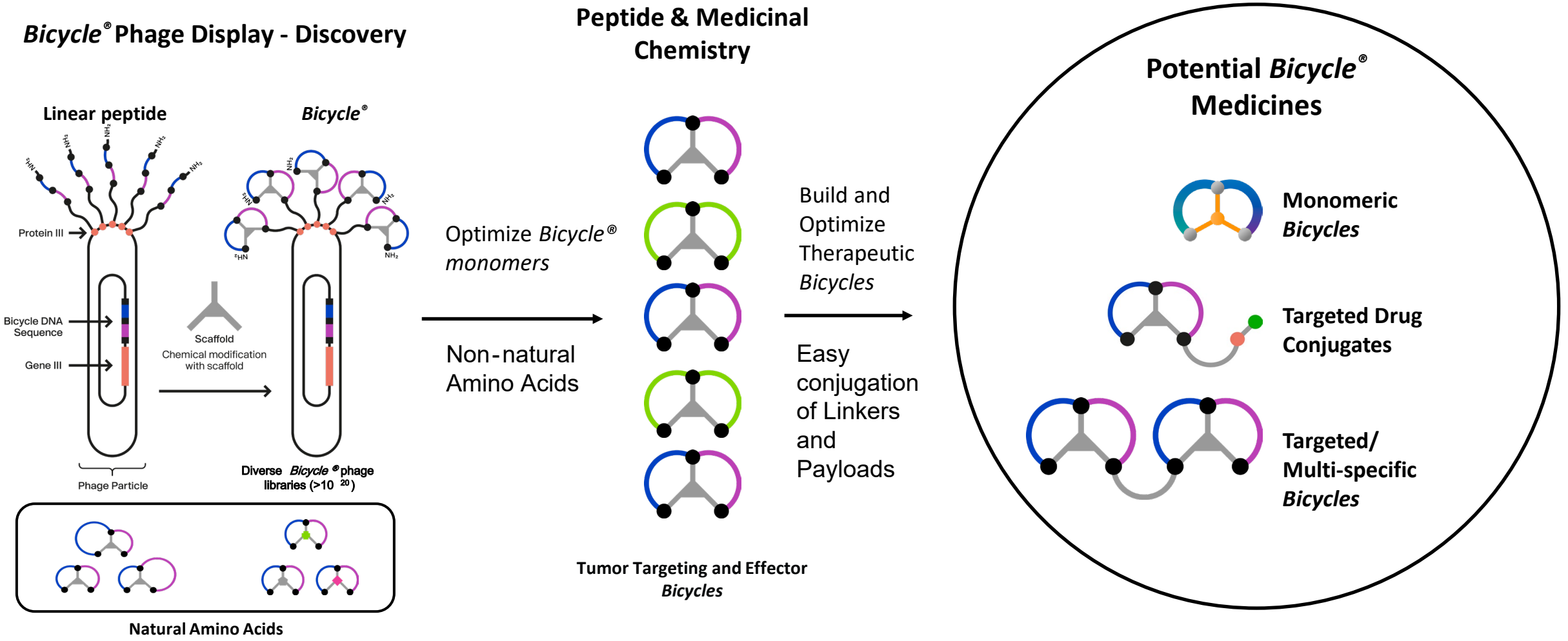


Based on the work of Sir Greg Winter to define the minimal mAb pharmacophore

- 2018 Nobel Prize in Chemistry
- Co-founded Bicycle Therapeutics

	 Bicycle®
Small size	**Yes 1.5 to 2 kDa**
Specificity	**High**
Chemical synthesis (NCEs)	**Yes**
Rapid tissue penetration	**Yes**
Complex protein targets druggable	**Yes**
Route of elimination	**Renal**

Bicycle® platform delivers a toolkit of building blocks to create novel medicines

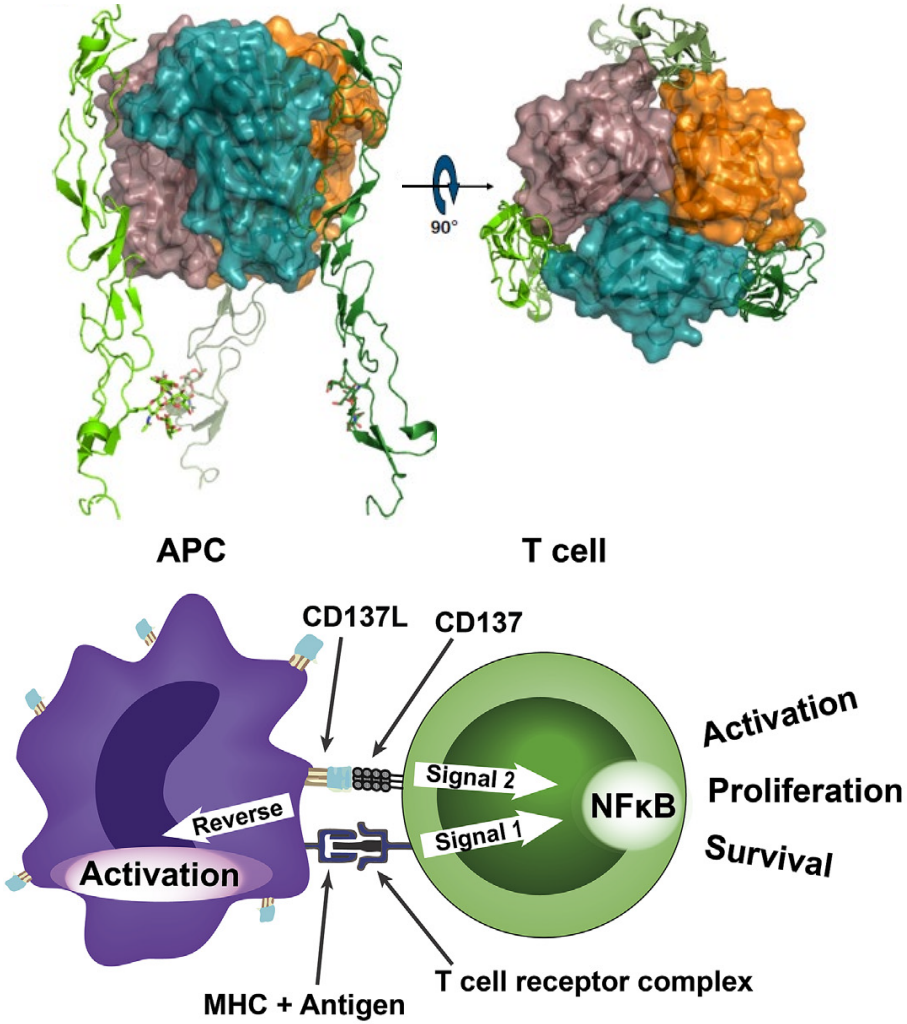


CD137 (4-1BB) is an immune co-stimulatory receptor with high therapeutic potential in cancer

- 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

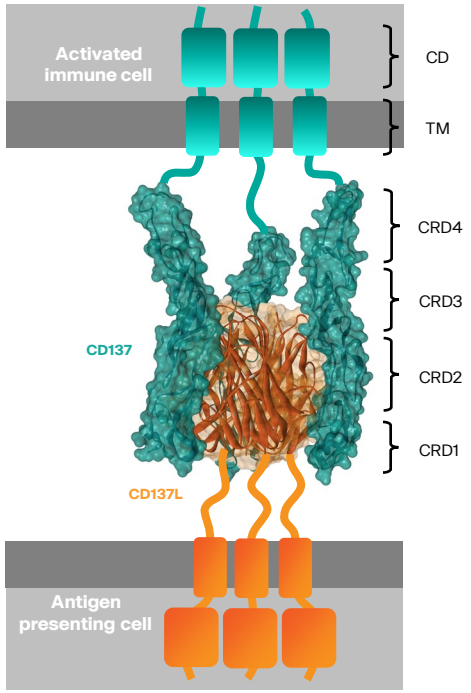
Many agents in development now – none meets design goals dictated by the biology – we sought to address this by using the *Bicycle®* platform:

- 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

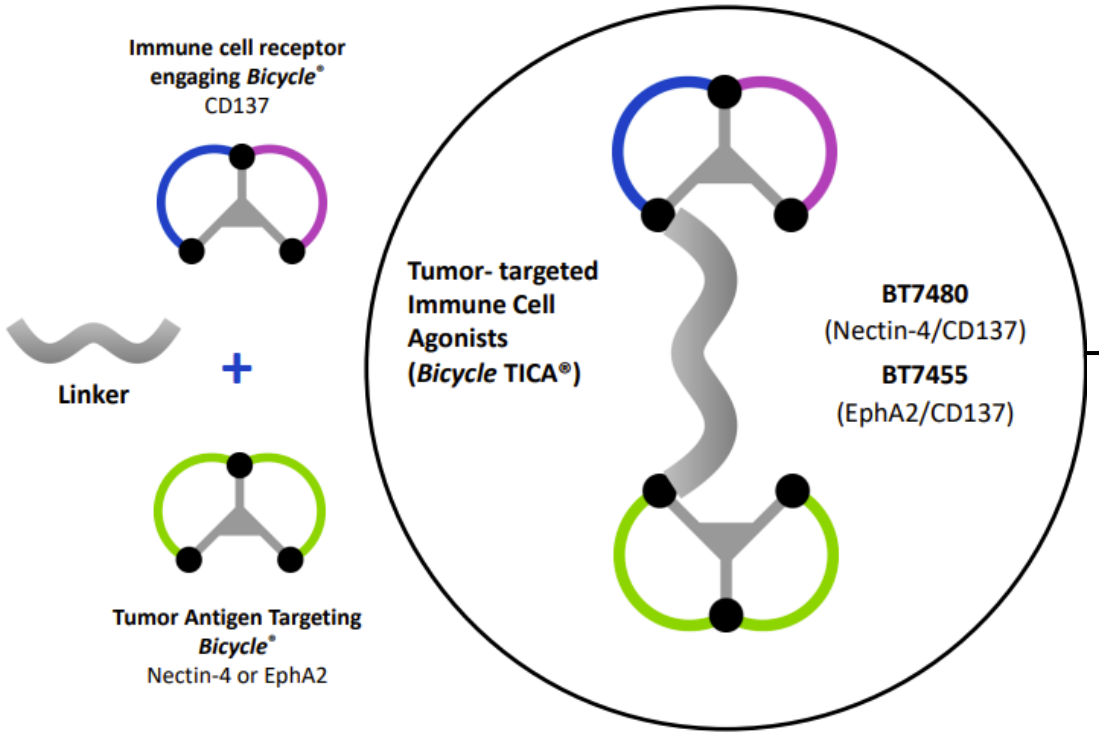


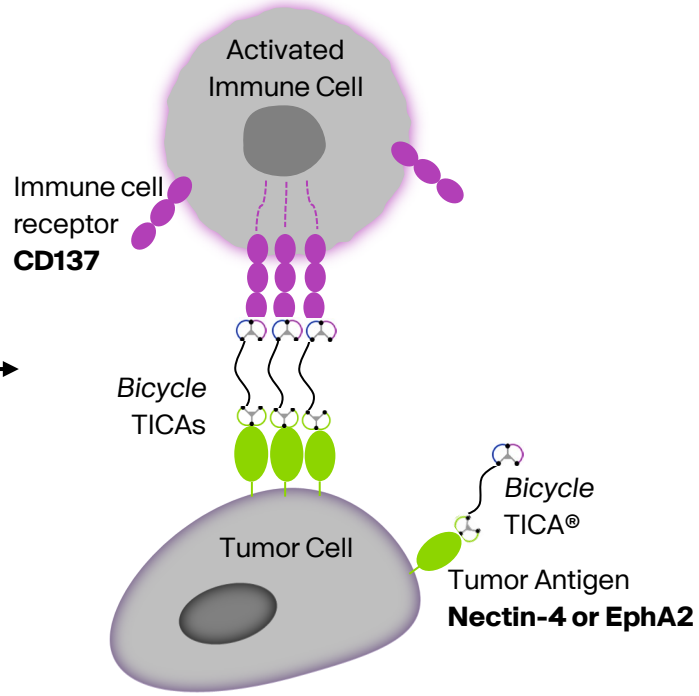
Yonezawa (2015); Melero (2008) TiPS 29, 383; Melero (2007) Nat. Immunol 3, 682; Wilcox (2004) Blood 103, 177; Wilcox (2002) J. Immunol. 169, 4230; Gomes-Silva (2017) Cell Rep. 21, 17; Segal (2016) Clin. Cancer Res. 23, 1929; Zheng – SITC2020 abstract 812; Chin (2018) Nat. Comm. 9, 4679; Soderstrom (2018) Atherosclerosis 272, 66

Bicycle TICA®– tumor-targeted immune cell agonists delivers immune agonism to tumors



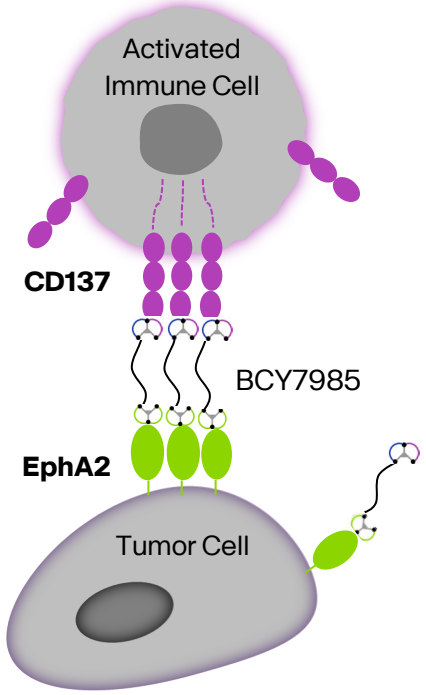
Activation induced by clustering of **CD137** by trimeric **CD137L**



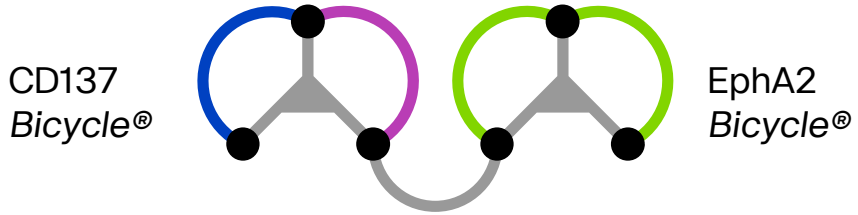


CD137 clustering induced by tumor antigen drives stronger immune cell potency

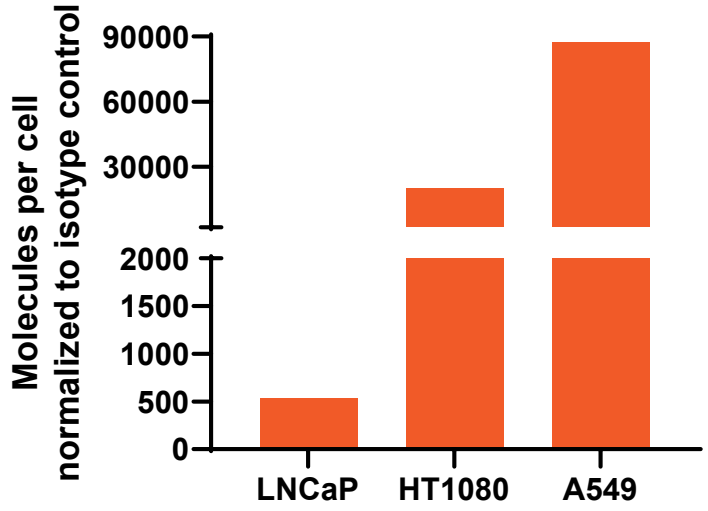
Preclinical in vitro proof of concept with the first EphA2/CD137 molecule



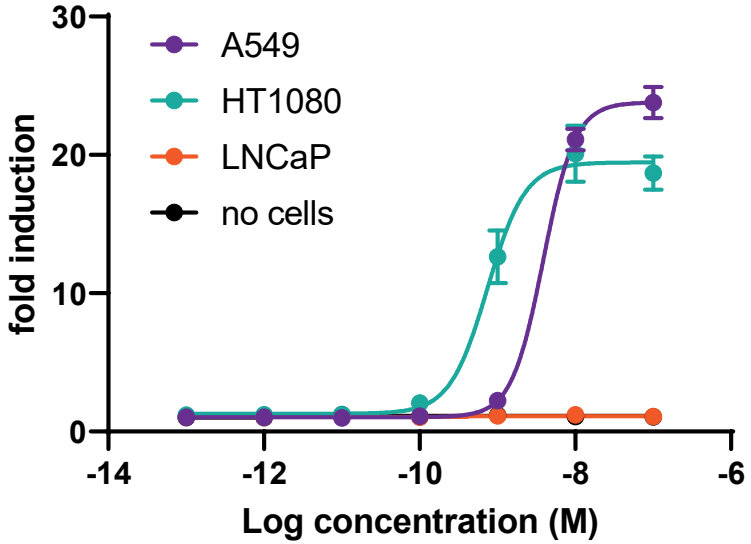
Cancer cells expressing high levels of EphA2



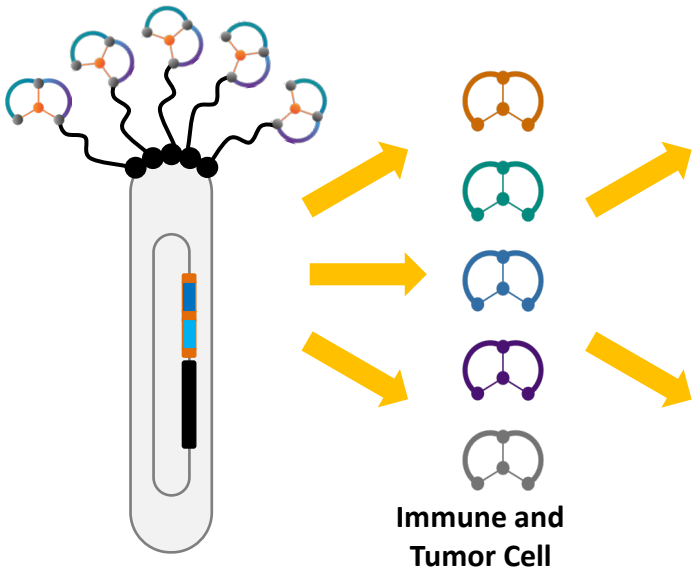
EphA2 expression



BCY7985: CD137 reporter assay in co-culture with EphA2 cells

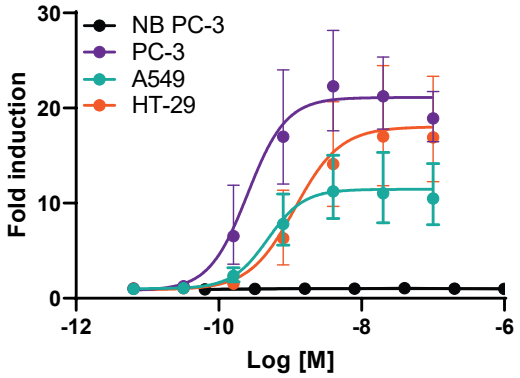


Bicycle TICA® is a generalizable concept

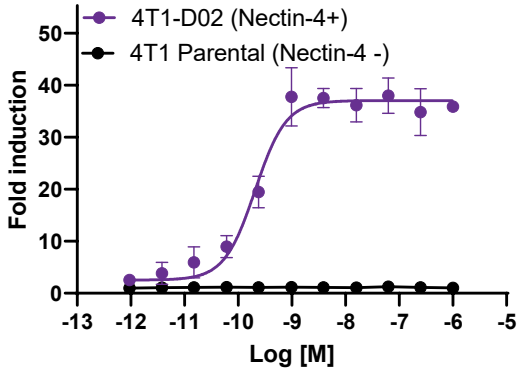


Diverse *Bicycle®* phage libraries (>10^{20})

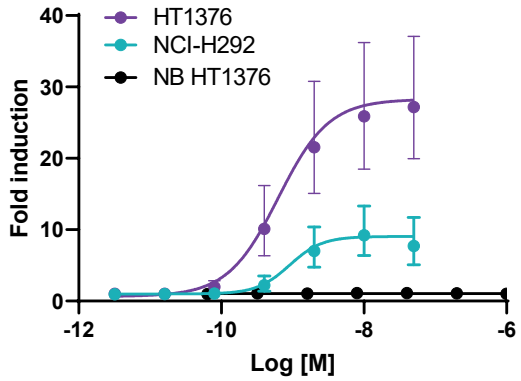
Immune and Tumor Cell Targeting *Bicycles*



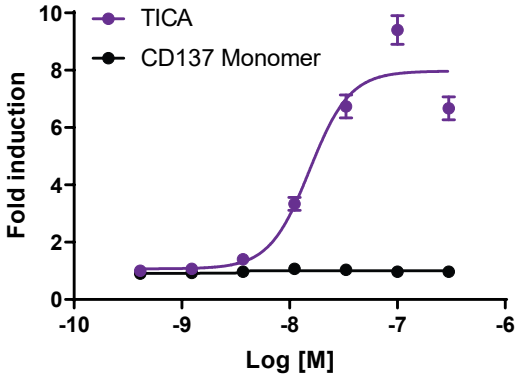
EphA2/CD137 1:1



Nectin-4/OX40 1:1



Nectin-4/CD137 1:1



PD-L1/CD137 1:1

Journal for ImmunoTherapy of Cancer

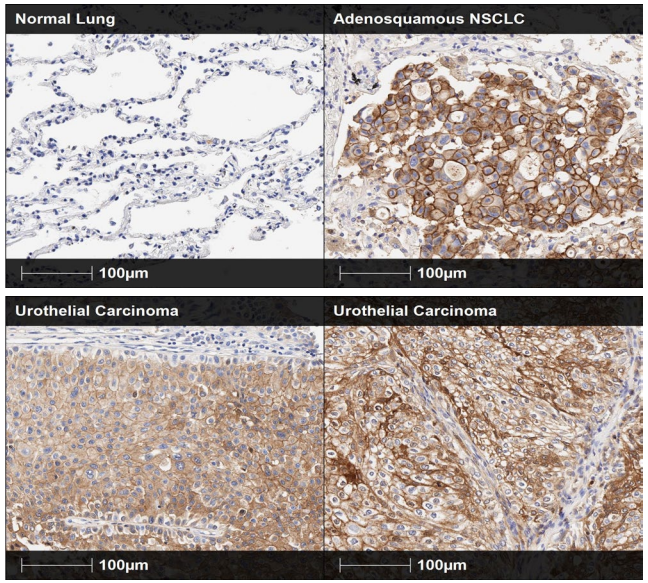
Anticancer immunity induced by a synthetic tumor-targeted CD137 agonist

Punit Upadhyaya,[1] Johanna Lahdenranta,[1] Kristen Hurov,[1] Sailaja Battula,[1] Rachel Dods,[2] Eric Haines,[1] Marianna Kleyman,[1] Julia Kristensson,[2] Jessica Kublin,[1] Rachid Lani,[2] Jun Ma,[1] Gemma Mudd,[2] Elizabeth Repash,[1] Katerine Van Rietschoten,[2] Tom Stephen,[1] Fanglei You,[1] Helen Harrison,[2] Liuhong Chen,[2] Kevin McDonnell,[1] Philip Brandish,[1] Nicholas Keen [1]

Immune effector and tumor targeting *Bicycles* can be combined in a modular fashion to construct a pipeline of *Bicycle®* tumor-targeted immune cell agonists

Nectin-4 – targeting and scaffolding for a CD137 *Bicycle®*

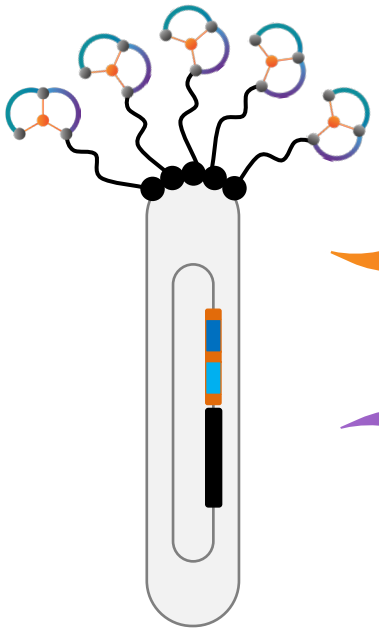
- Cell adhesion molecule, widely expressed during development, restricted in adult normal tissue
- Highly expressed in a wide range of solid tumor indications including breast, bladder, head & neck, esophageal, ovarian, and lung cancer[1,2]
- Nectin-4 and CD137 co-expressed in variety of human tumors[3,4]



Indication	Total cores (N)	% Nectin-4+ (H-score > 20)
Breast (all)	225	80
TNBC	*141*	*86*
Bladder	142	78
Esophagus	140	55
Head & Neck	69	58
Lung	157	39
Ovarian	89	45
Pancreas	96	19
Stomach	131	4

[1] Challita-Eid, et al., *Cancer Res* 2016; 76(10):3003-13
[2] Campbell, et al., AACR; *Cancer Res* 2021; 81(13_Suppl):Abstract nr 1197
[3] Hurov, Lahdenranta, et al., *JITC* 2021; 9(11):e002883
[4] Cohen, et al., SITC; *JITC* 2021; 9 (Issue Suppl 2): Abstract nr 2

CD137 and Nectin-4 *Bicycles*: discovery and optimization by phage display and chemistry



CD137

K_D = 1400 nM → K_D = 67 nM → K_D = 5 nM

Phage Hits
-ID sequence families
-Define initial pharmacophores

Phage Optimized
-Focused libraries
-Optimize natural AAs
-Scaffold/Loop symmetry

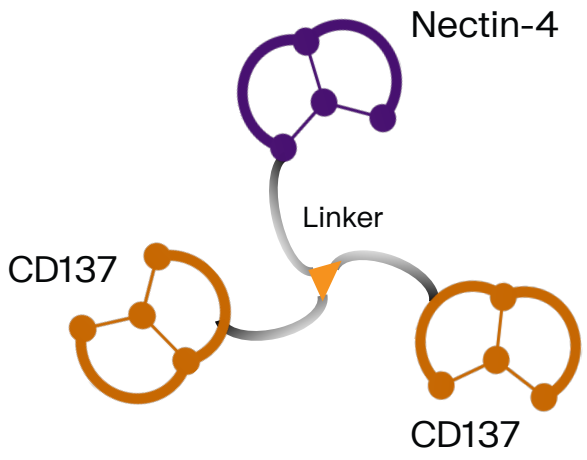
Chemistry Optimized
-Non natural amino acids
-Tune affinity and stability
-Balanced phys chem properties

Nectin-4

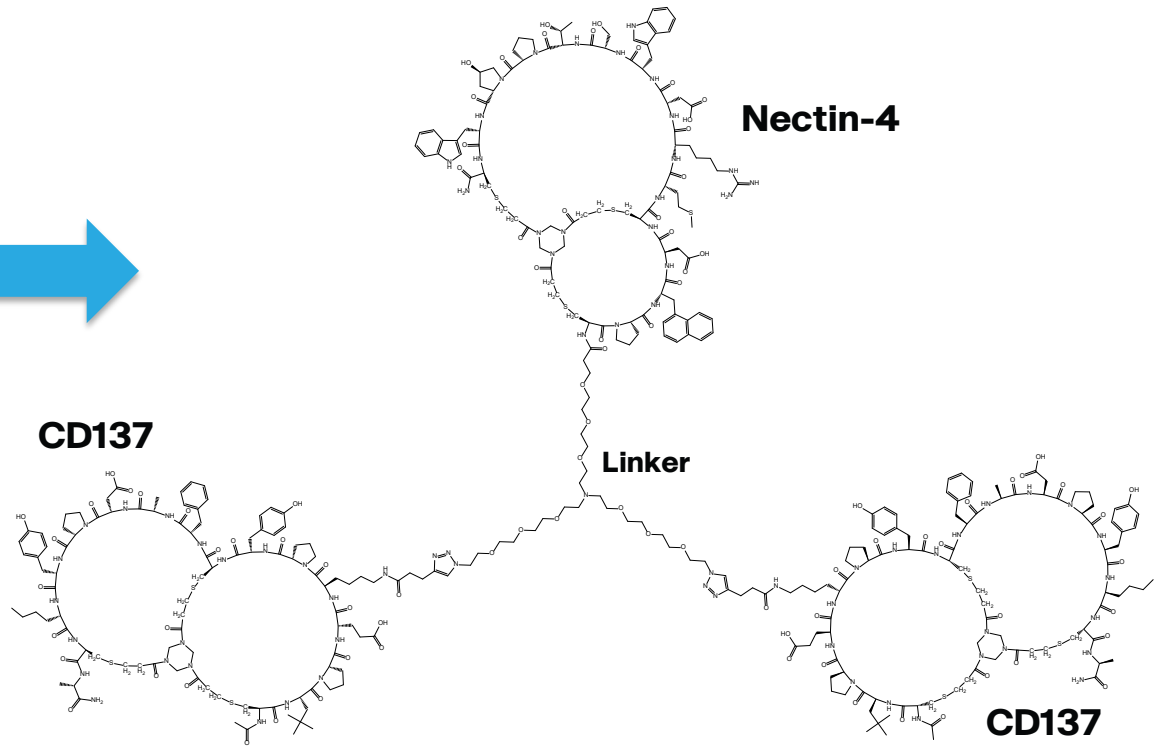
K_D = 508 nM → K_D = 80 nM → K_D = 1 nM

BT7480 is a fully synthetic, heterotrimeric conjugate with 1 Nectin-4 and 2 CD137 *Bicycles*

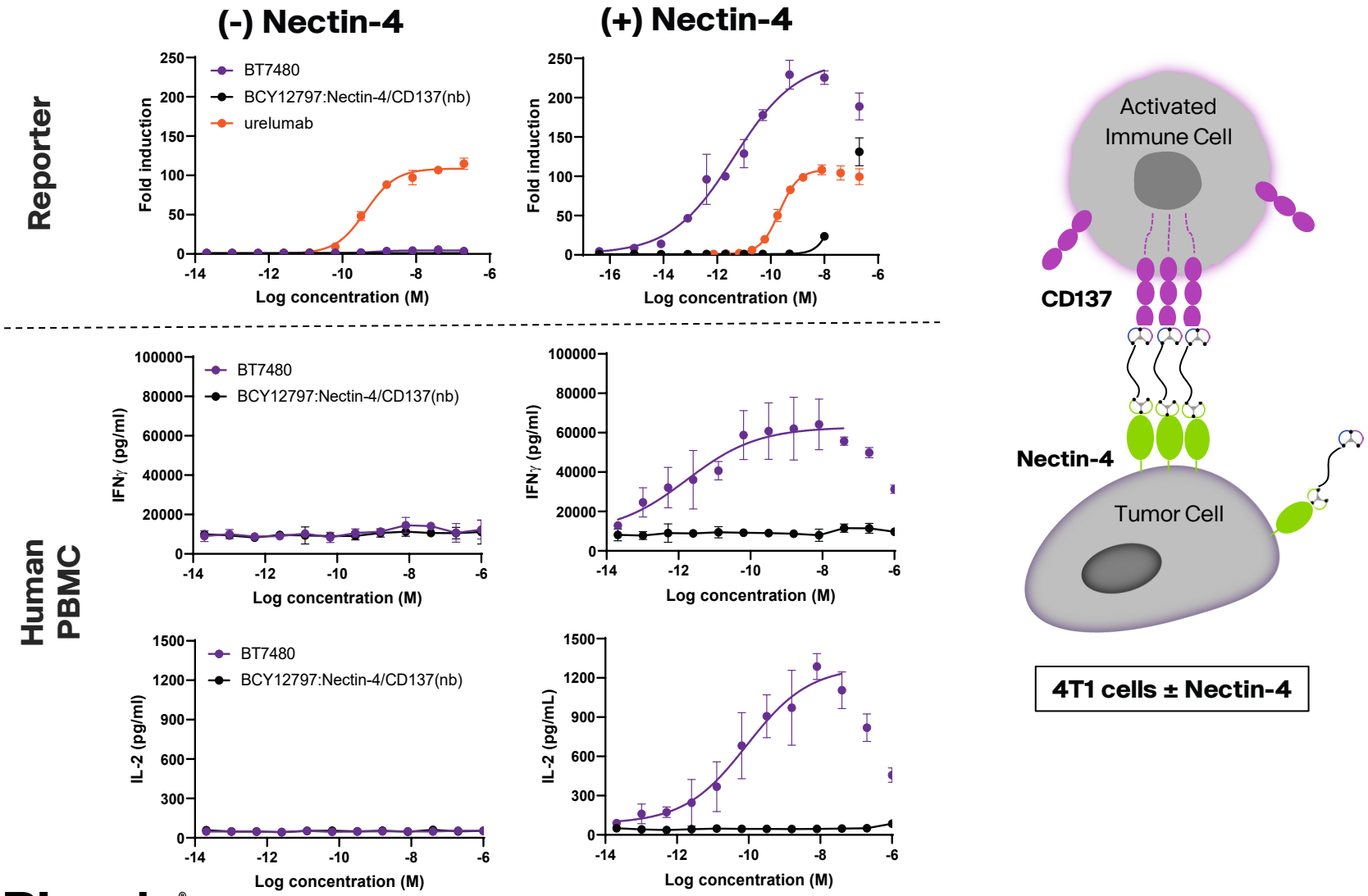
BT7480 selected as lead *Bicycle* TICA™ candidate



Structure of BT7480
MW = 7.2 kDa

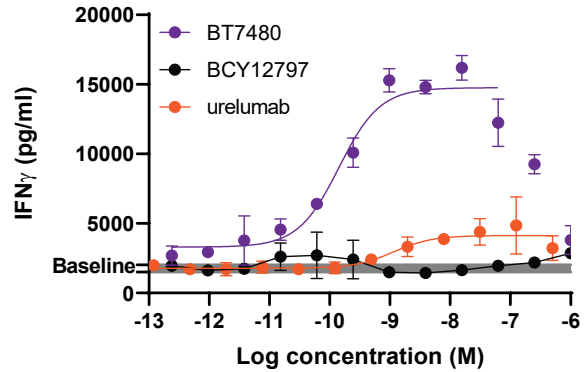


BT740 functional activity is dependent on Nectin-4 in cell-based assays *in vitro*

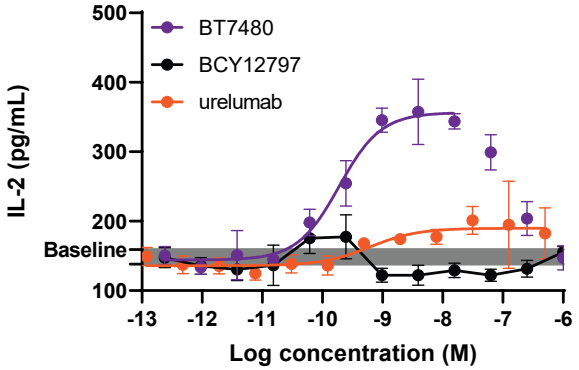


4T1 cells ± Nectin-4

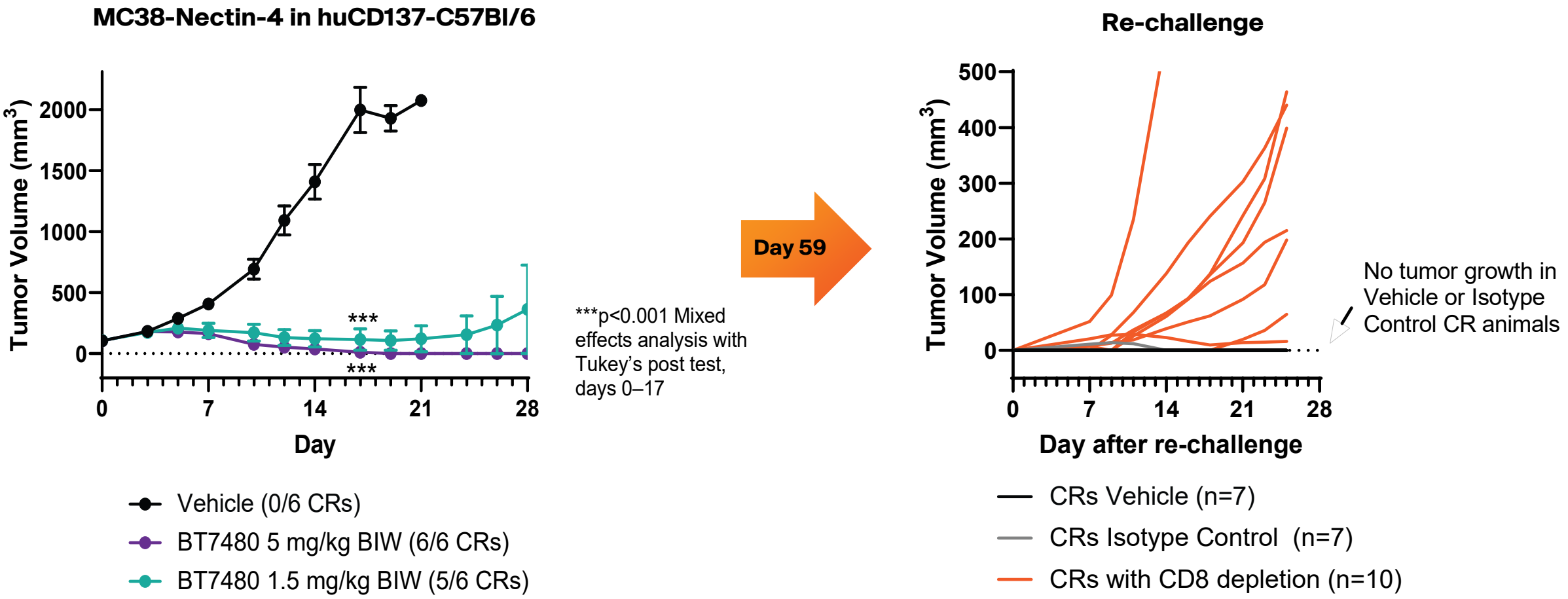
HT1376 bladder tumor cells



EC_{50}
0.37±0.23 nM (IL-2)
0.22±0.12 nM (IFNγ)

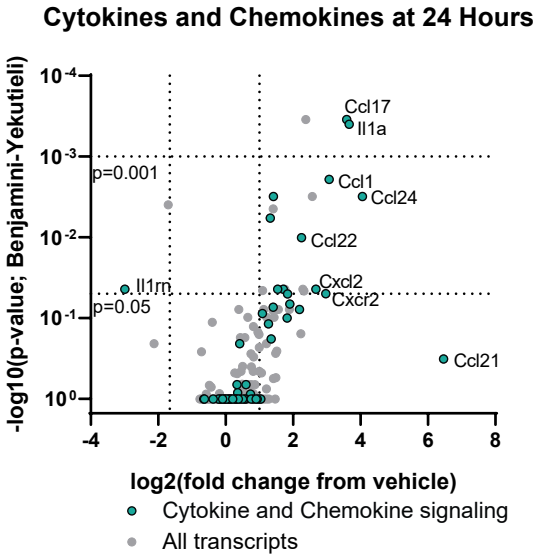


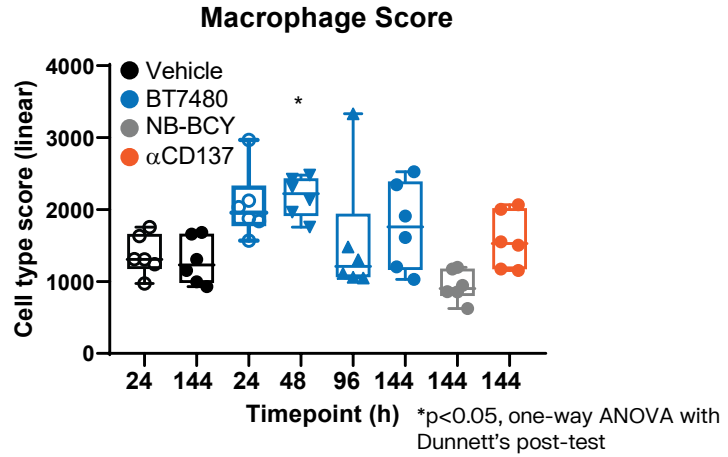
BT7480 induces complete responses and memory *in vivo* in a syngeneic mouse model

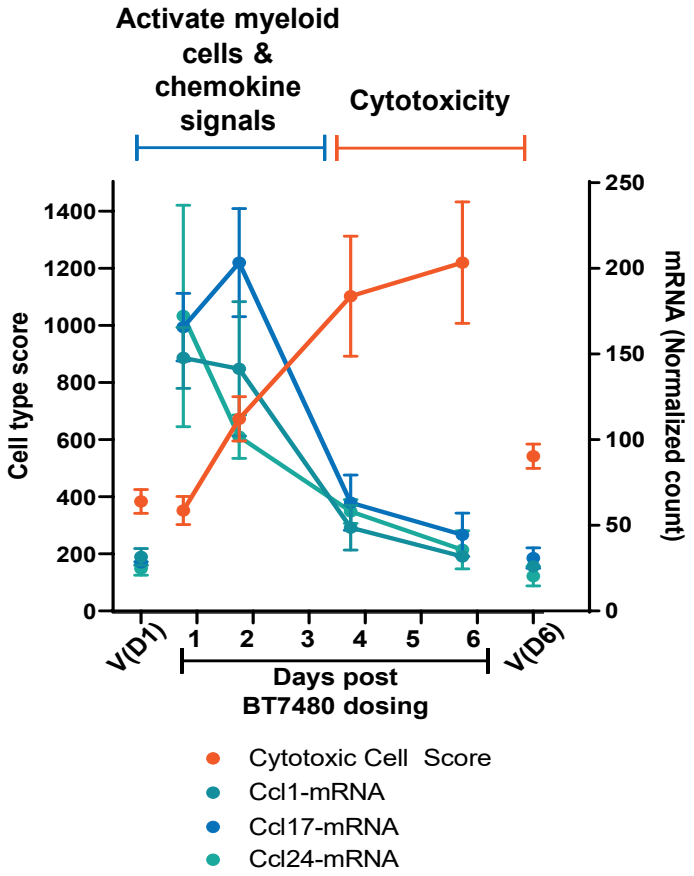


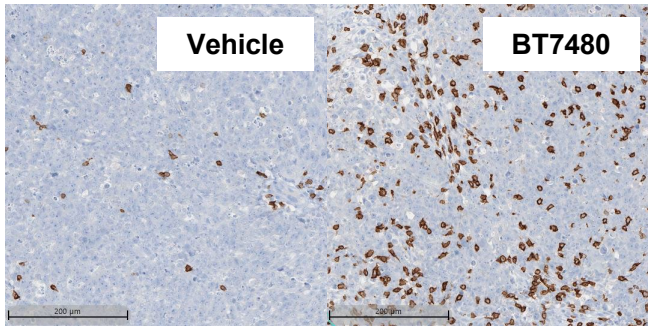
CRs=Complete Responders

Transcriptional analysis in mouse MC38 tumor model revealed an unanticipated, rapid burst of T cell chemotactic cytokine production





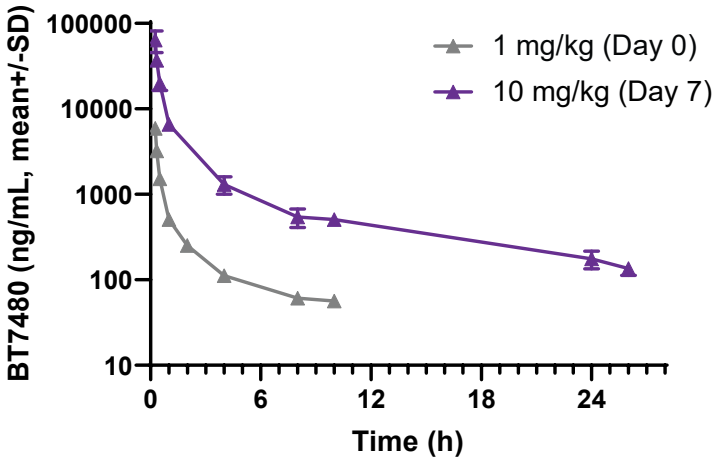




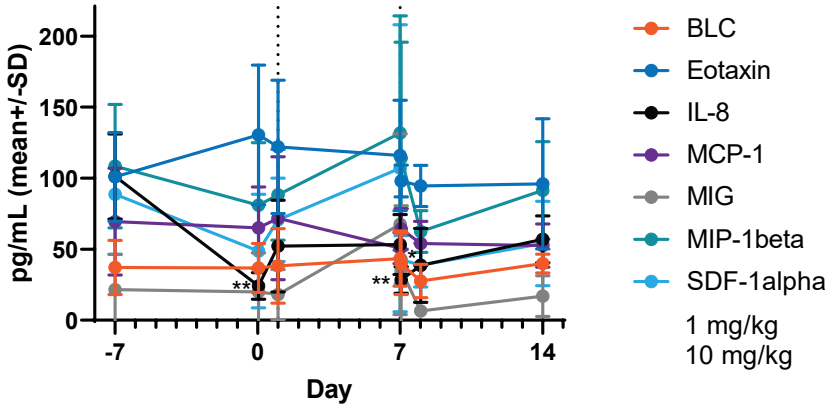
- BT7480 leads to an early increase in cytokine gene expression in tumor
- BT7480 leads to increase in CD8+ cell infiltration, cytotoxic and macrophage cell scores in tumor
- BT7480 induces significant changes in local immune cell populations

BT7480 is well-tolerated in preclinical species, with no evidence of liver effects

NHP (Cynomolgus monkey) PK



Serum cytokines



Species^	Dose (mg/kg)	C_{max} (µg/mL)	AUC_{last} (µg•h/mL)
Rat	30	42	47
	100	174	230
	300	716	953
NHP	30	146	88.3
	100	717	484
	300	3630	3040

^Rat: Wistar Han; NHP: Cynomolgus monkey

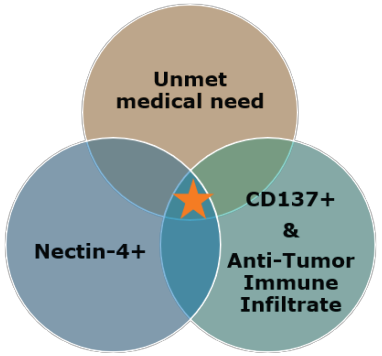
Species^	Dose (mg/kg)	Clinical observations	Hematology findings*	Clinical chemistry findings*
Rat	30	None	None	None
	100	None	None	None
	300	None	None	None
NHP	30	None	None	None
	100	None	None	None
	300	None	None	None

Day 7 after BT7480 administration

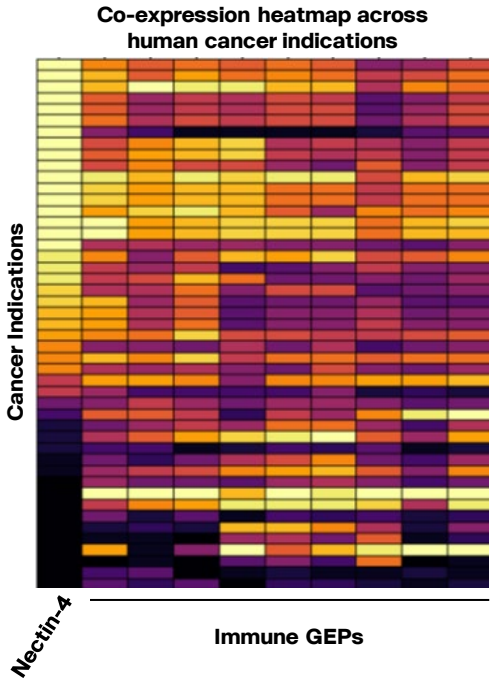
*Noteworthy treatment related findings

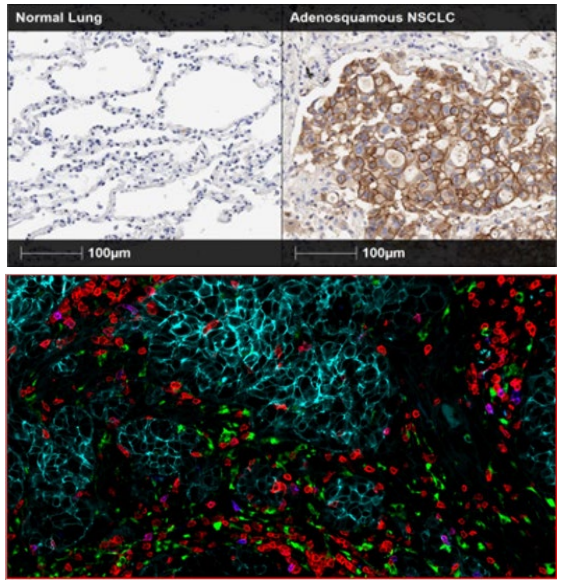
Which patients are most likely to benefit from BT7480?

Biomarker-driven approach to identifying indications that co-express Nectin-4 and CD137



Bicycle TICA™ Translational Infrastructure & Informatics Pipeline → Patient Enrichment → Target Expression & Immune Profiling → Patient Selection





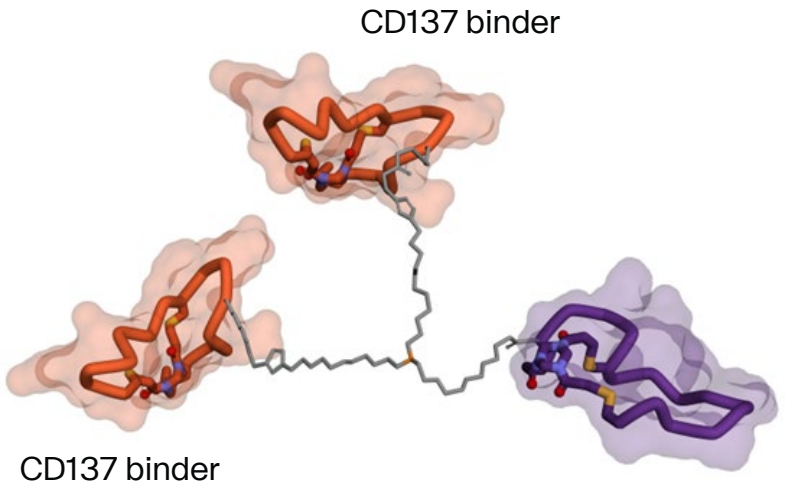
CD137 CD3 CD68 Nectin-4 Human TNBC sample

Indications more likely to benefit include:
>50% of breast, head & neck, ovarian and esophageal cancers

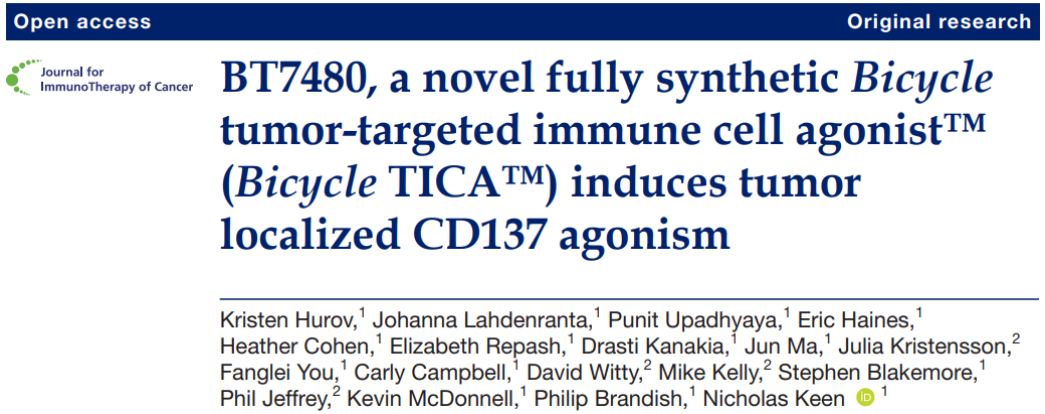
Cohen H, et al., SITC Annual Meeting 2021, Abstract #2; Hurov K, Lahdenranta J, et al., *J Immunother Cancer*, 2021

BT7480 – the first chemically synthetic, conditionally active targeted CD137 activator

- Activity of the CD137 agonist arm is dependent on ligation of the Nectin-4 arm, leading to tumor specificity
- Causes complete regressions and anti-tumor activity with only intermittent dosing in syngeneic mouse models
- Causes an early increase in chemotactic cytokine production that precedes an increase in CD8+ T cell infiltration into the tumor
- Is well-tolerated in preclinical safety species
- Entered phase 1 clinical testing in November 2021



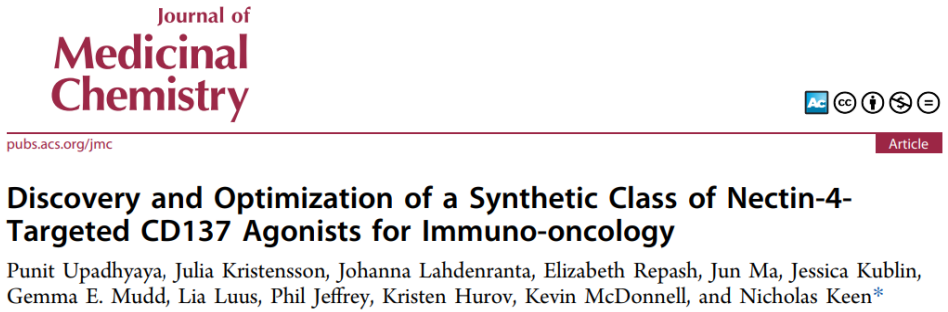
BT7480
MW = 7213.3 Da


Open access Original research

Journal for ImmunoTherapy of Cancer

BT7480, a novel fully synthetic *Bicycle* tumor-targeted immune cell agonist™ (*Bicycle* TICA™) induces tumor localized CD137 agonism

Kristen Hurov,[1] Johanna Lahdenranta,[1] Punit Upadhyaya,[1] Eric Haines,[1] Heather Cohen,[1] Elizabeth Repash,[1] Drasti Kanakia,[1] Jun Ma,[1] Julia Kristensson,[2] Fanglei You,[1] Carly Campbell,[1] David Witty,[2] Mike Kelly,[2] Stephen Blakemore,[1] Phil Jeffrey,[2] Kevin McDonnell,[1] Philip Brandish,[1] Nicholas Keen [1]


Journal of Medicinal Chemistry

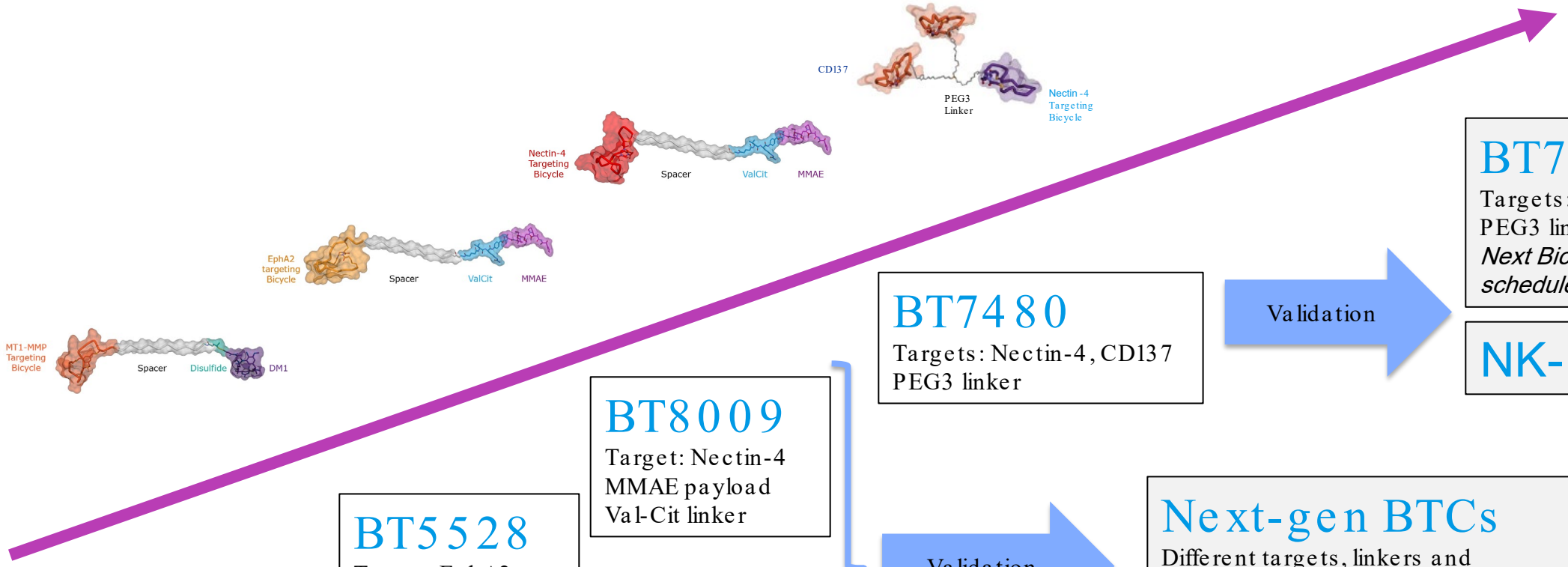
pubs.acs.org/jmc Article

Discovery and Optimization of a Synthetic Class of Nectin-4-Targeted CD137 Agonists for Immuno-oncology

Punit Upadhyaya, Julia Kristensson, Johanna Lahdenranta, Elizabeth Repash, Jun Ma, Jessica Kublin, Gemma E. Mudd, Lia Luus, Phil Jeffrey, Kristen Hurov, Kevin McDonnell, and Nicholas Keen*

Hurov K, Lahdenranta J, et al., 2021, *J Immunother Cancer*, **9**(11):e002883; Upadhyaya, et al., 2022, *J Med Chem*, **65**(14):9858-72

Elevating 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
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

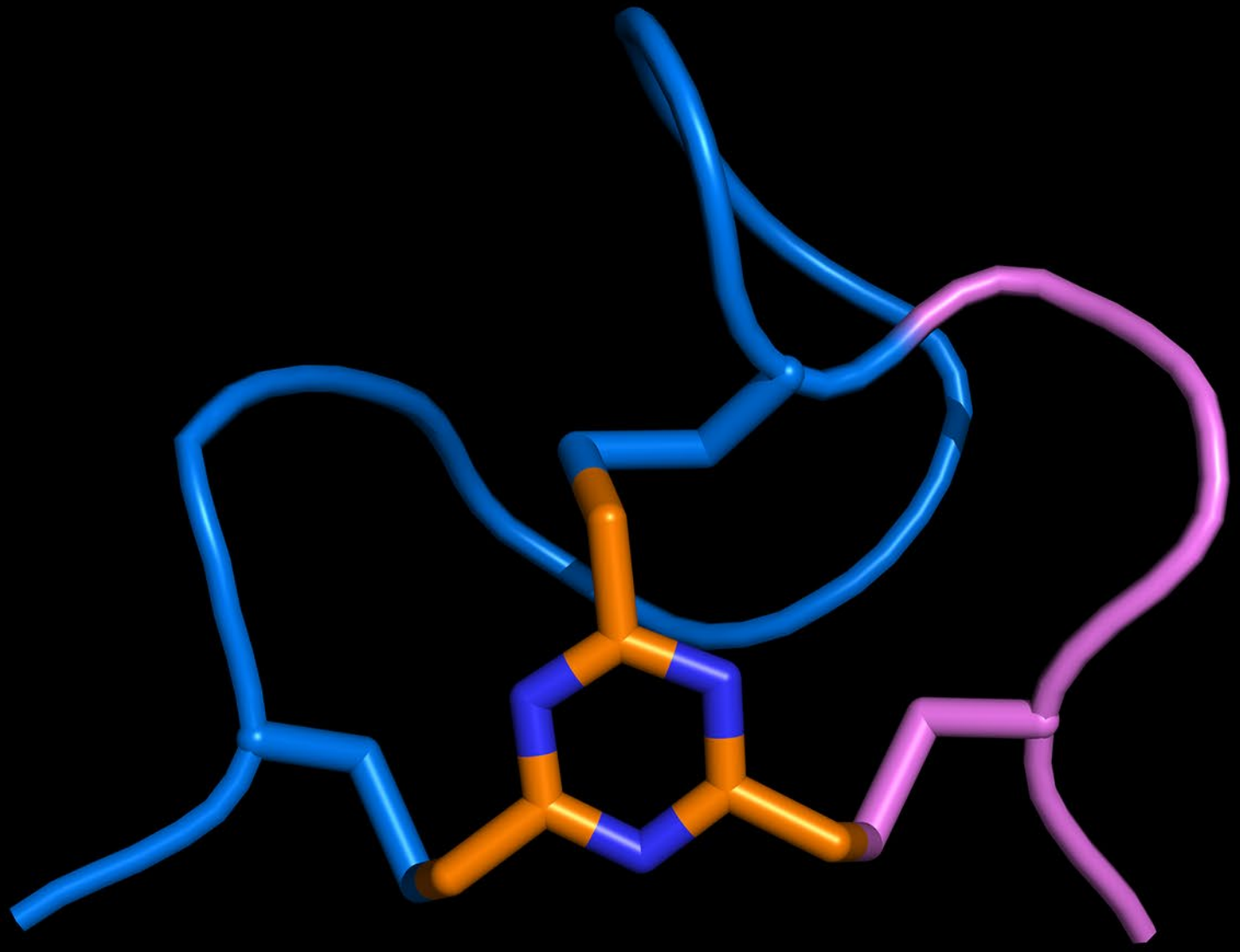
Radiopharm

FIH 2018 2019 2020 2021 2023 and beyond

Thank you

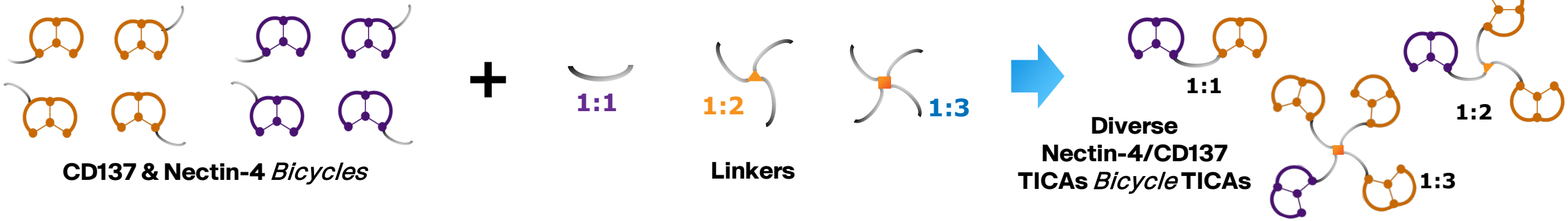
Bicycle®

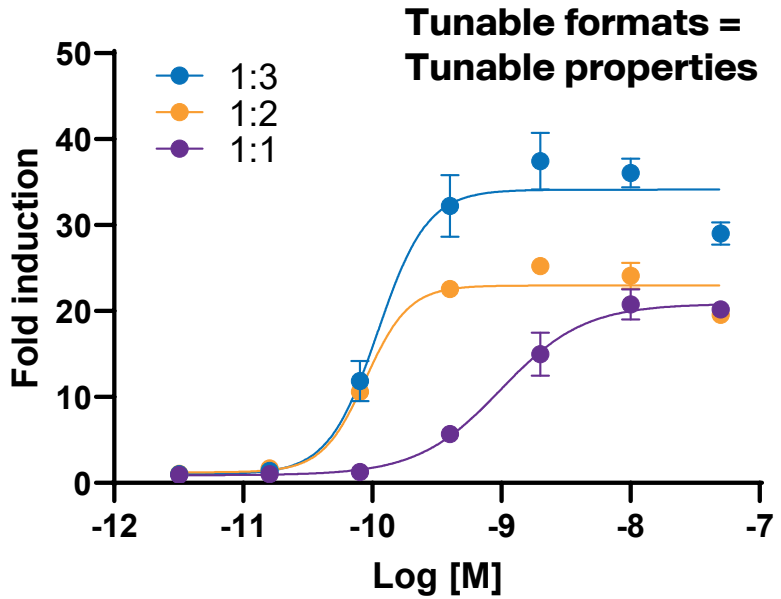
Backups



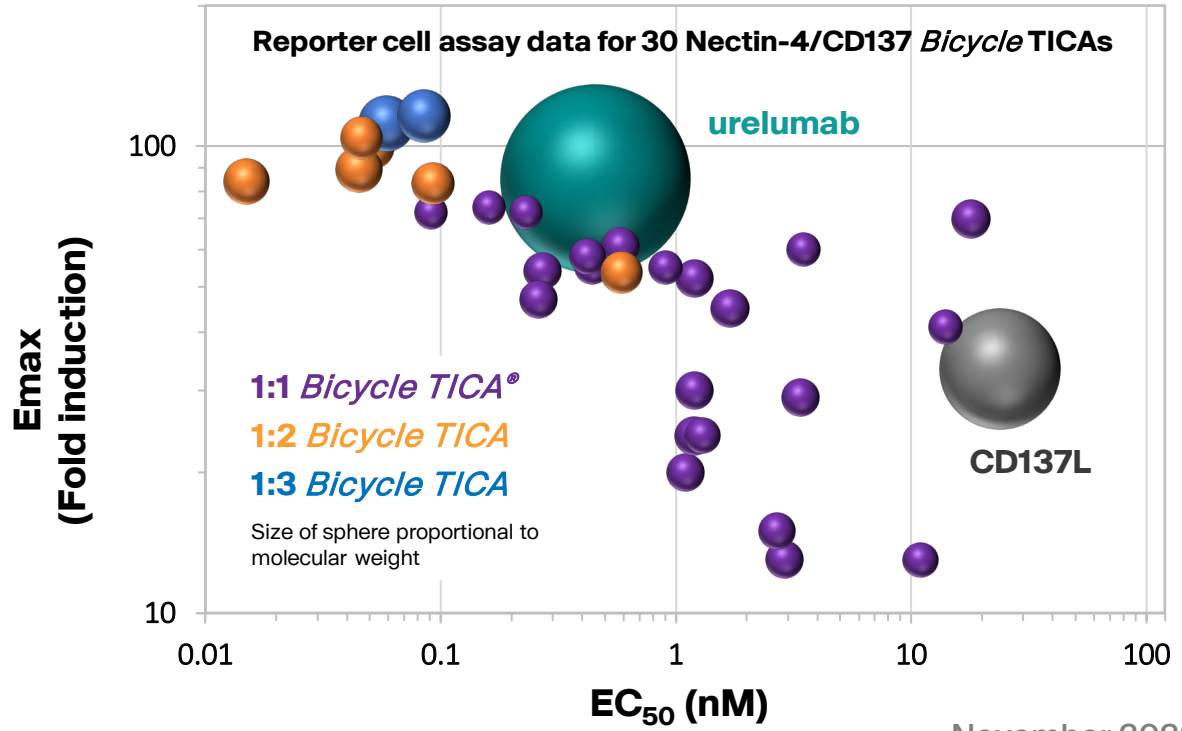
Bicycle®

Bicycles are highly modular and *Bicycle®* TICAs are built and optimized using medicinal chemistry



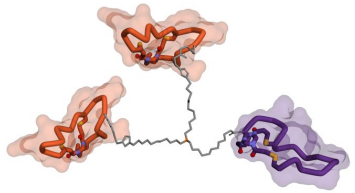


CD137 Jurkat reporter cells in co-culture with HT1376



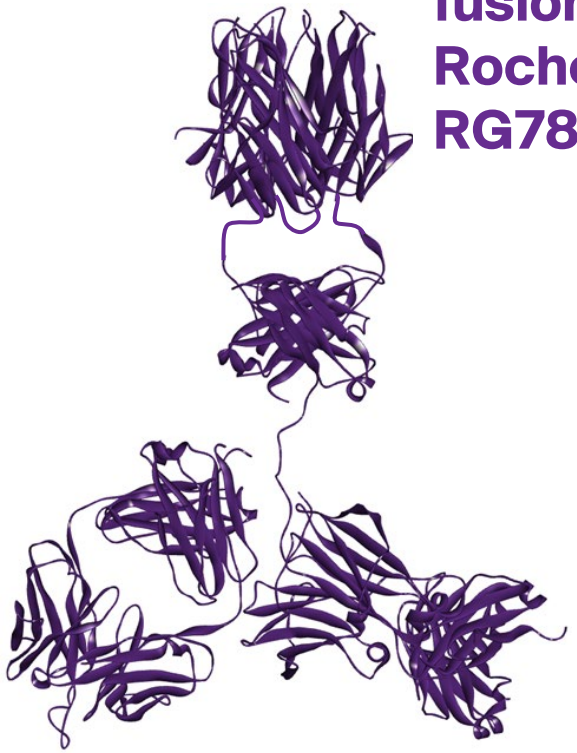
Bicycle® TICAs are ~30x smaller than other targeted CD137 agonists

Bicycle TICA®
BT7480



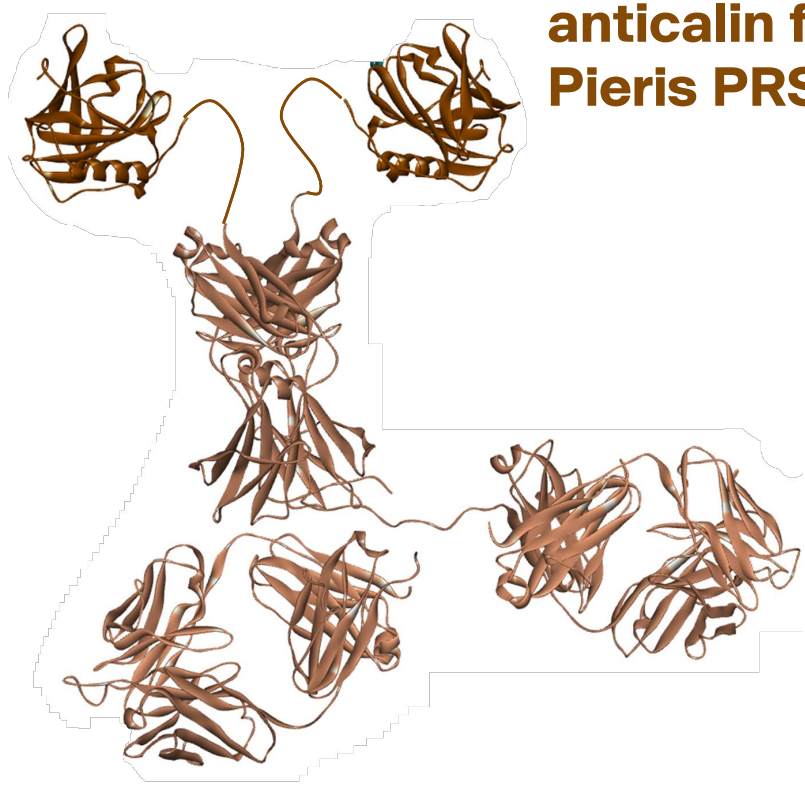
7.2kDa

Anti-FAP IgG-CD137L fusion Roche RG7826



~185kDa

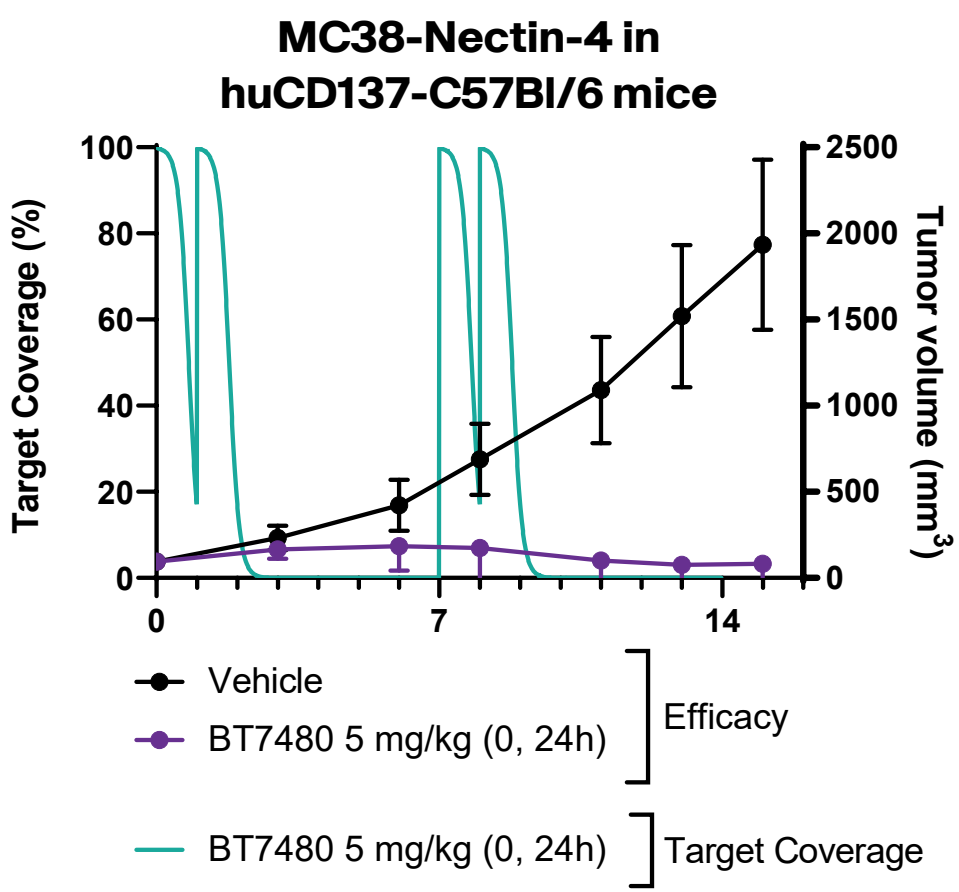
Anti-Her2 IgG-anti-CD137 anticalin fusion Pieris PRS-343

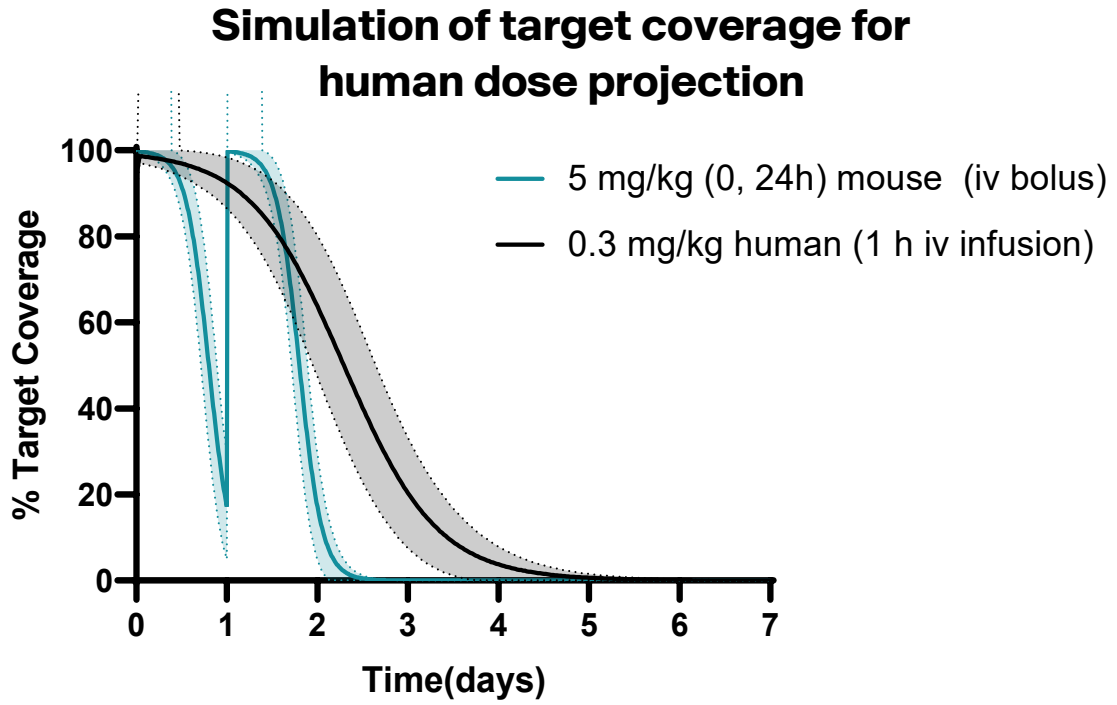


~190kDa

PK and *in vivo* modeling predicts potential target coverage and efficacy in humans with QW dosing

- Data suggest that continuous target coverage is not needed for robust efficacy
- Once weekly or less frequent dosing is predicted to be efficacious in humans





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