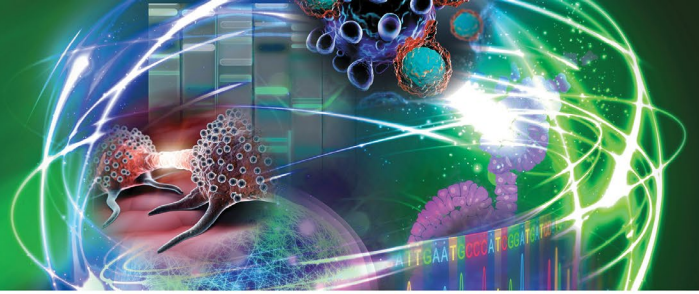
AACR American Association for Cancer Research
ANNUAL MEETING 2021
VIRTUAL #AACR21
APRIL 10-15, 2021 AND MAY 17-21, 2021 ★ AACR.ORG ★ AACR.ORG/AACR2021



BT7480, a novel Nectin-4 dependent agonist of the immune cell costimulatory receptor CD137

Nicholas Keen, M.A., PhD.
Chief Scientific Officer, Bicycle Therapeutics, Lexington MA

Disclosure Information

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Nicholas Keen

I have the following financial relationships to disclose:
Consultant for: HotSpot Therapeutics Inc, Kymera Therapeutics Inc.
Employee of: Bicycle Therapeutics

-and-

I will not discuss off label use and/or investigational use in my presentation.

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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, including that we may not identify and develop additional product candidates for our pipeline, 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, risks associated with our dependence on third-parties, risks regarding the accuracy of our estimates of expenses, risks relating to our capital requirements and needs for additional financing, 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 Annual Report on Form 10-K, filed with the Securities and Exchange Commission (SEC) on March 11, 2021 as well as in other filings Bicycle 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 for addressing intractable challenges

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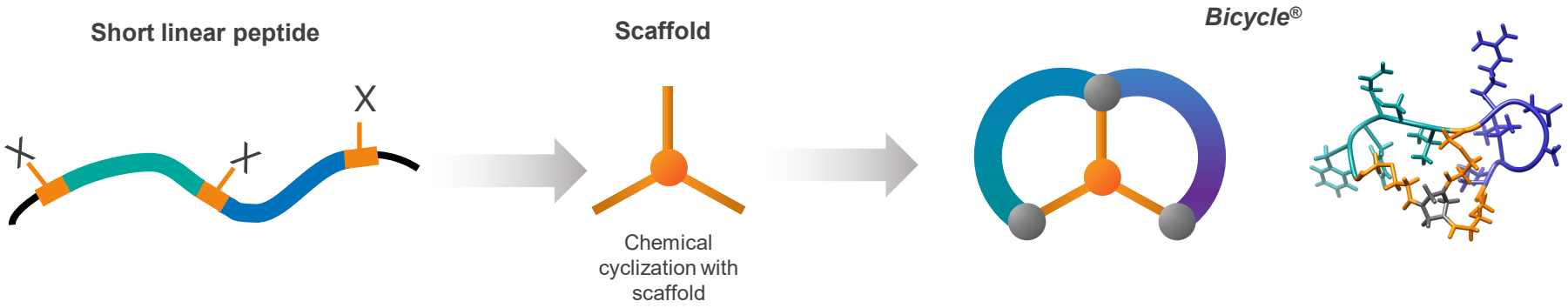

	Chemical synthesis	Rapid tissue distribution	Complex protein targets druggable	Route of elimination
Small molecules	+++	+++	---	Liver
Antibodies	---	+	+++	Liver
Bicycles	+++	+++	+++	Renal

Built-in tolerance to conjugation

- Generalizable approach
- Versatility to adopt multiple formats

Phage-based screening platform

- Nobel Prize-winning technology
- Rapid selection from >10^{17} potential candidates

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

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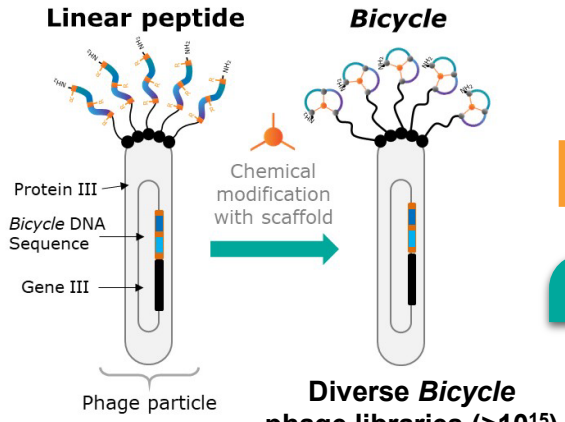
Bicycle Phage Display - Discovery

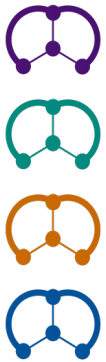


Natural Amino Acids

Peptide & Medicinal Chemistry

Optimize Bicycle monomers

Non-natural Amino Acids



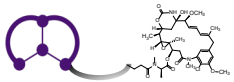
Tumor Targeting and Effector *Bicycles*

Build and Optimize Therapeutic Bicycles

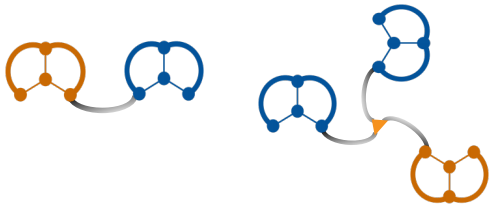
Payloads and Linkers

Bicycle Medicines

Monomeric *Bicycles*



Targeted Drug Conjugates

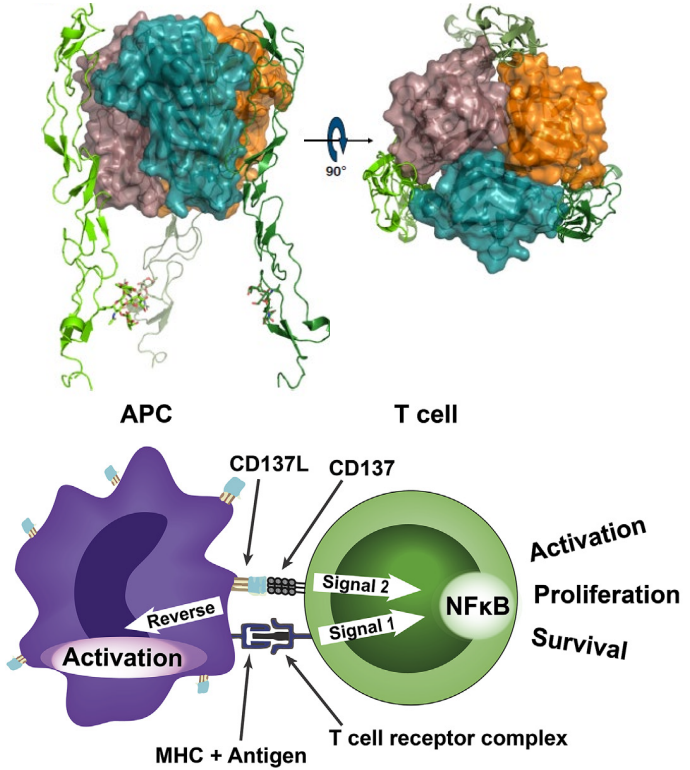


Targeted/Multi-specific *Bicycles*

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

- CD137 is expressed on activated immune cells – signaling enhances function and survival, prevents anergy
- CD137 ligand expressed by APCs provides a co-stimulatory signal to T cells and NK cells – potential in antitumor 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 yet meet fully design goals dictated by the biology**
  - Activity localized to the tumor – potentiate immune activation
  - Rapid onset of action and controllable duration of action
  - No Fc interactions to avoid 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

TICA™: Tumor Targeted Immune Cell Agonists join immune cell and tumor targeting *Bicycles*

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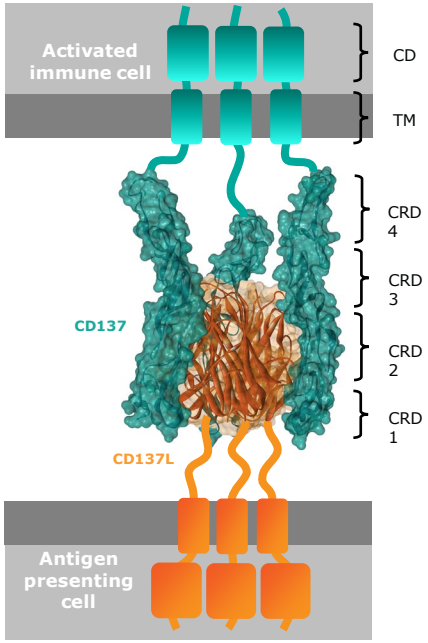
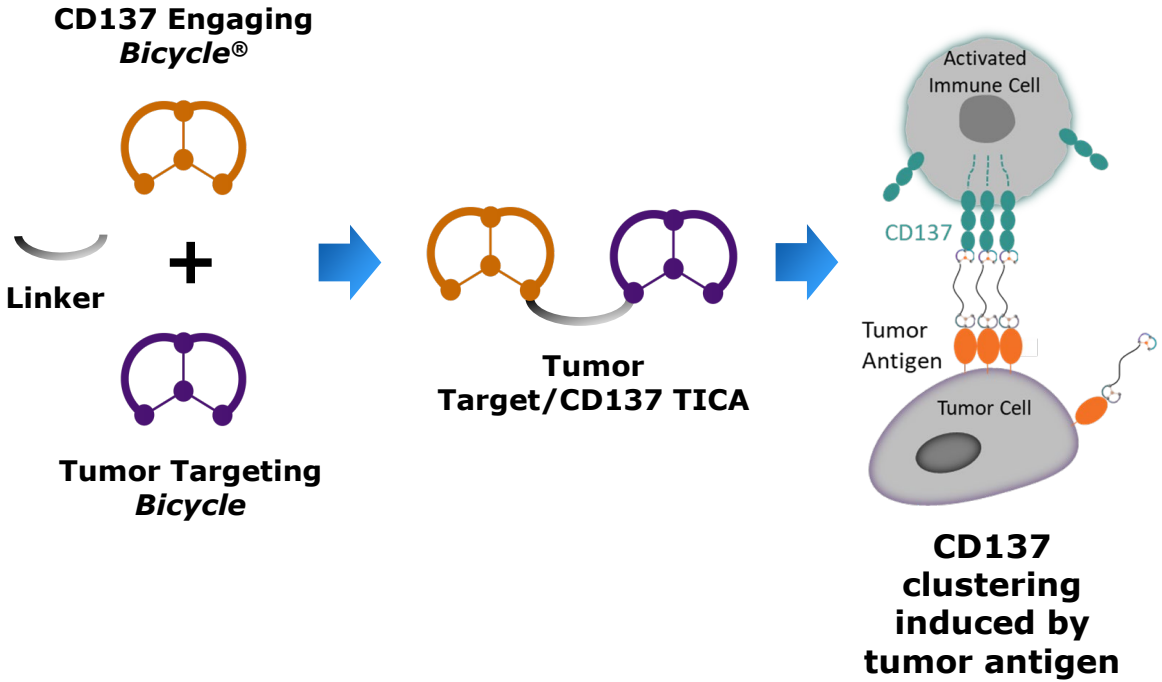
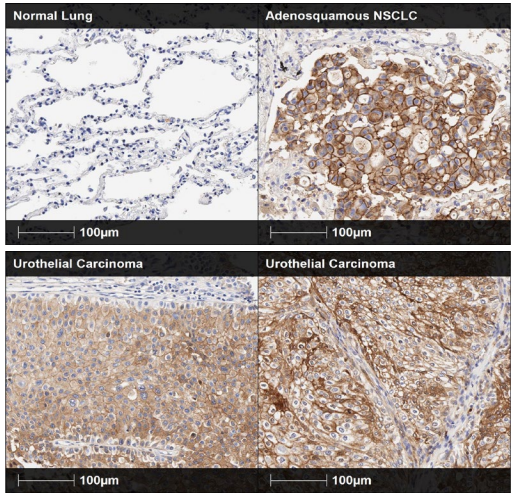


Activation induced by clustering of **CD137** by trimeric **CD137L**



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



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. 2016
[2] **Campbell, et al. AACR. 2021. POSTER #1197**

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

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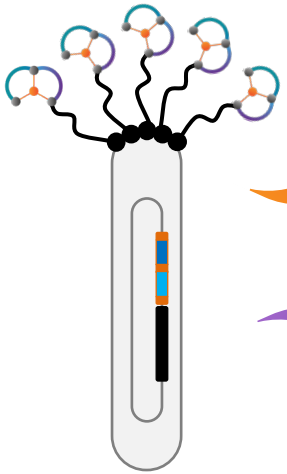


CD137

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

Nectin-4

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

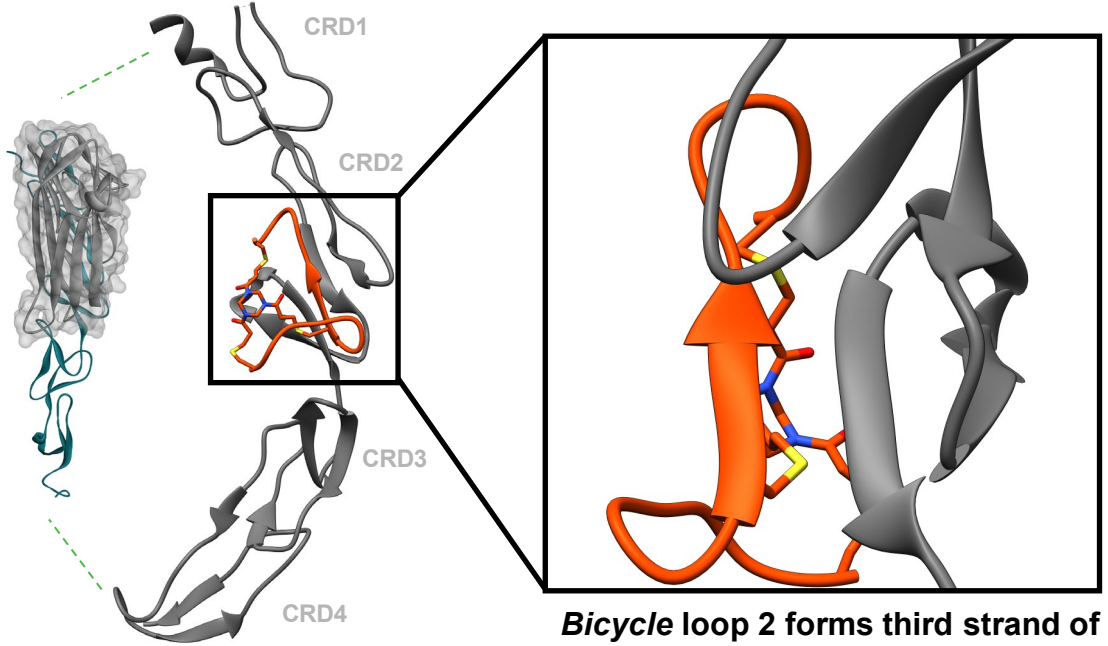
Phage Hits
-ID sequence families
-Define initial pharmacophores

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

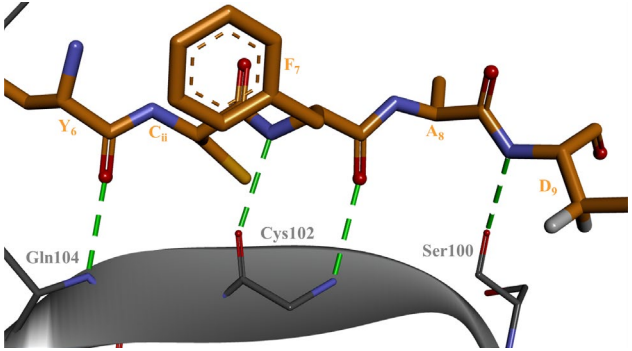
Chemistry Optimized
-Non natural amino acids
-Tune affinity and stability
-Balanced phys chem properties

Bicycle® scaffold nucleates secondary structure with CD137 and provides a pharmacophore

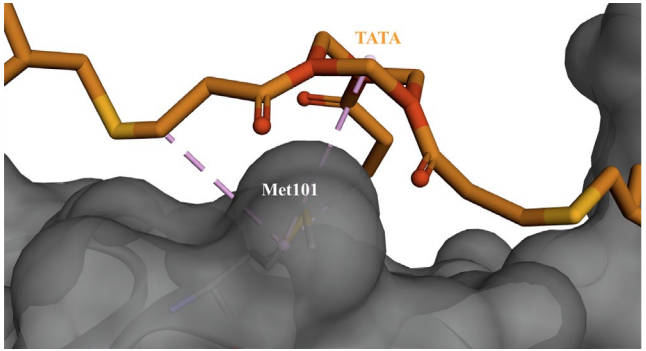
CD137 *Bicycle* binds to epitope common to CD137L



***Bicycle* loop 2 forms third strand of β -sheet with CD137**



Loop 2 antiparallel β-sheet H-bonding



Triazinane ring of TATA scaffold forms close packing interaction with Met101

Bicycles are highly modular and TICAs are built and optimized using medicinal chemistry

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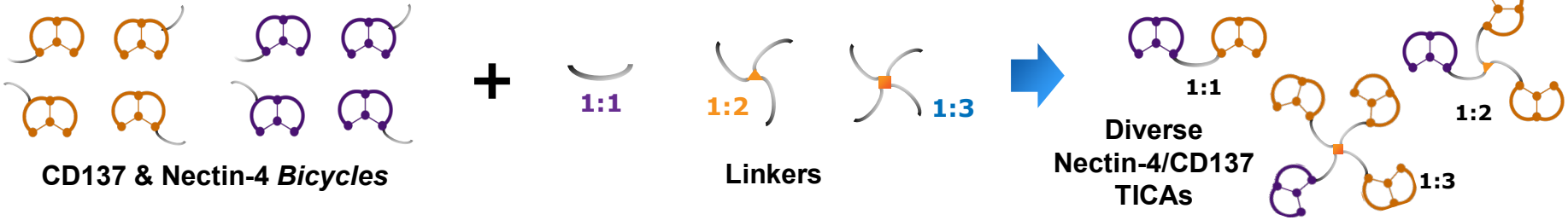
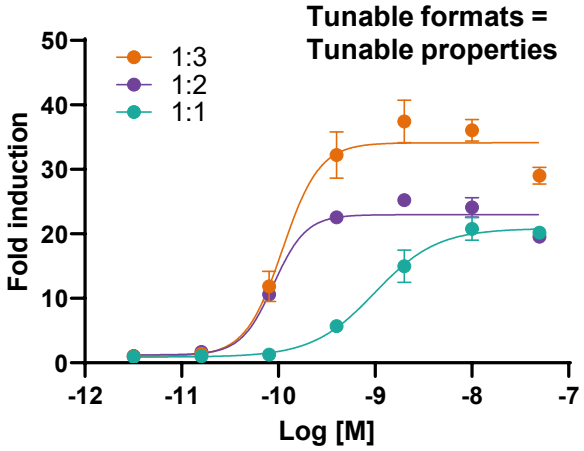
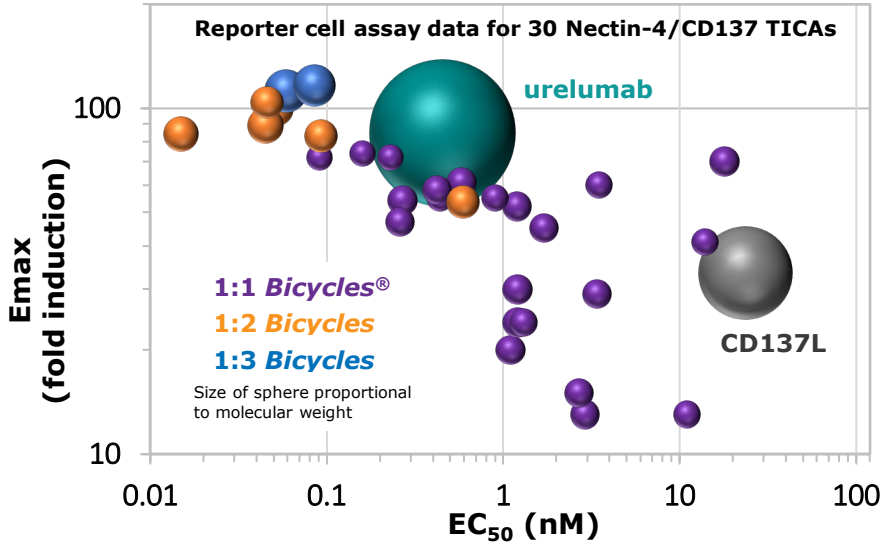


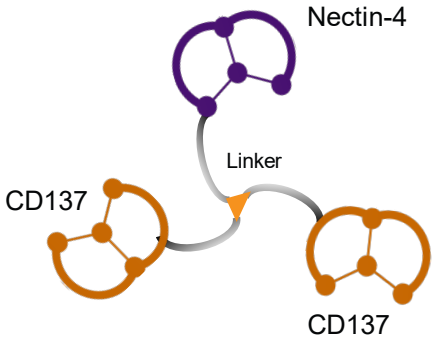


CD137 Jurkat reporter cells in co-culture with HT1376

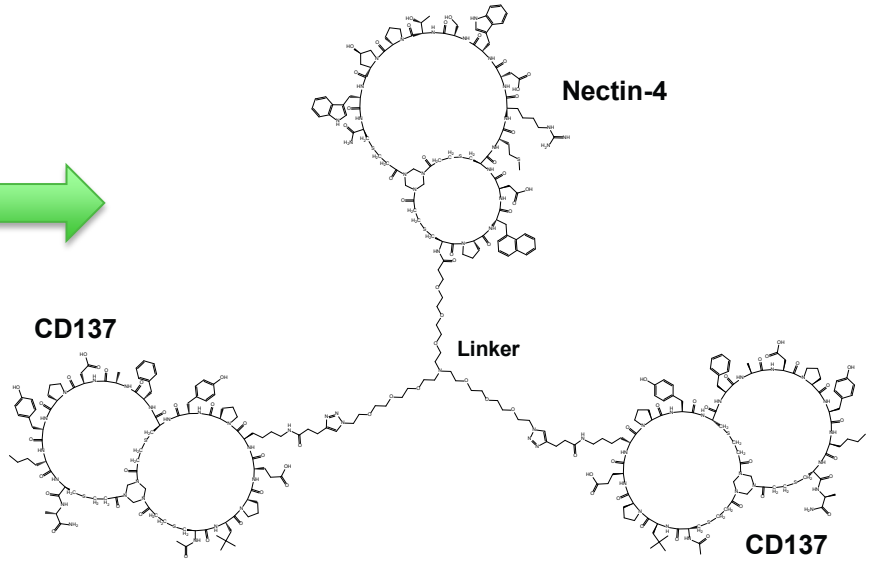


BT7480 is a fully synthetic, heterotrimeric conjugate with 1 Nectin-4 and 2 CD137 *Bicycles*

BT7480 selected as lead TICA™ candidate

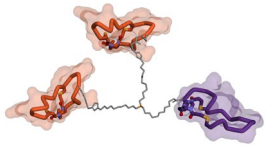


Structure of BT7480
MW = 7.2 kDa



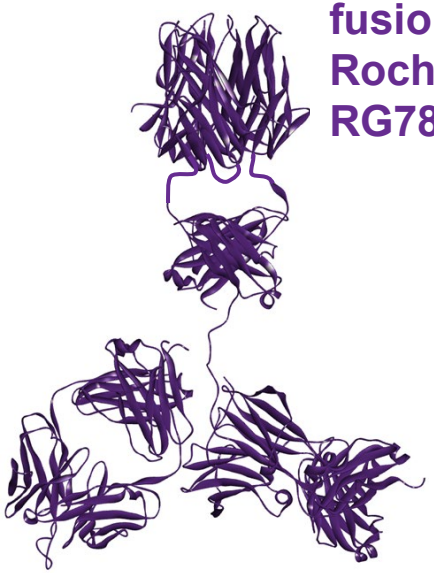
Bicycle® TICAs are ~30x smaller than other targeted agonists

Bicycle TICA™
BT7480



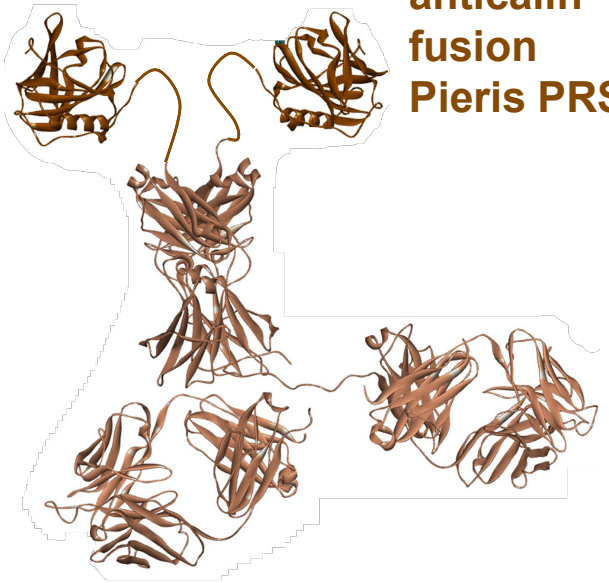
7.2kDa

Anti-FAP IgG-CD137L fusion Roche RG7826



~185kDa

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



~190kDa

BT7480: a Nectin-4/CD137 TICA™ clinical development candidate

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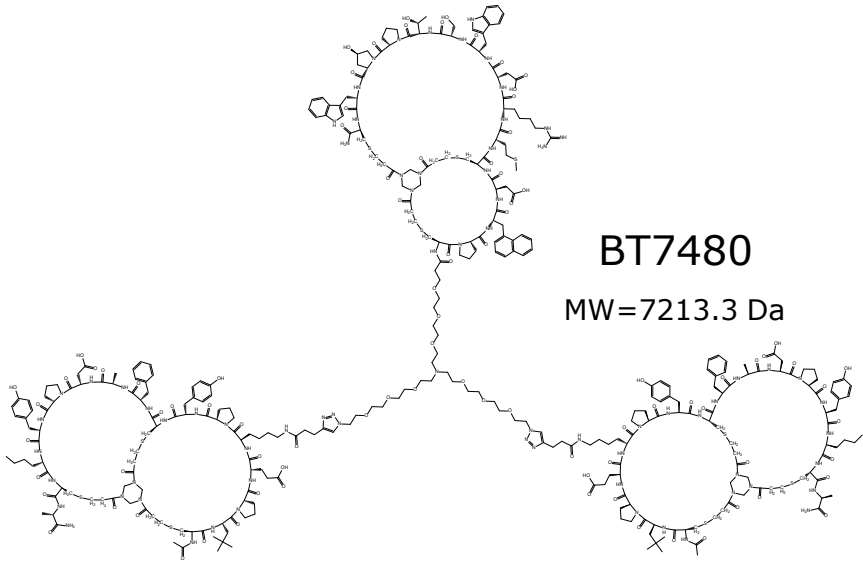
Assay	Target Value	BT7480
Primary Immune Cell Assay (EC_{50})[1]	< 2 nM	0.37±0.23 nM (IL-2) 0.22±0.12 nM (IFNγ)
CD137 dependent activity	Require CD137	CD137 dependent
Tumor antigen dependent activity	Require Nectin-4	Nectin-4 dependent
Immune target selectivity (Vs OX40/CD40)	>10 fold	Selective[2]
Tumor target selectivity (Vs other Nectin family members)	>10 fold	Selective
Define species selectivity (CD137)	Define for tox species	Human, NHP specific[2]
Define species selectivity (Nectin-4)	Define for tox species	Cross Reactive
POC in vivo activity (syngeneic or engraftment model)	Anti-tumor activity	Achieved
Rodent IV-PK ($t_{1/2}$, h)	>1	2.6 (mouse); 4.1 (rat)
NHP IV-PK ($t_{1/2}$, h)[3]	>5	5.3
Thermodynamic Solubility (mg/ml)	>10	>50
Tractable synthesis / CMC Risk	Low Risk	Synthesis scaled to >300g
Cytokine Release Syndrome Assay	Low Risk	Inactive[4]
Safety margin vs predicted human efficacious dose	>50-fold margin	Achieved



BT7480

MW=7213.3 Da

[1]Human PBMC/HT-1376 tumor cell co-culture; average of 13 donors
[2]Demonstrated using biotinylated version of BT7480
[3]Scaling consistent with desired human profile
[4]No cytokine release in unstimulated human whole blood

BT7480 binds potently and specifically to its targets

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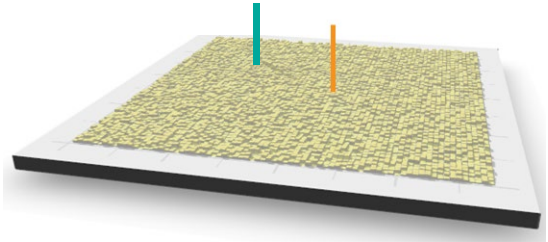
- BT7480 binds to Nectin-4 (across species) and CD137 (human, NHP) with high affinity
- BT7480 binds both targets simultaneously by SPR assay
- Exquisite selectivity, no binding seen to >5000 other membrane proteins
- No interactions seen in CYP and hERG channel inhibition assays

Paralog screening	BT7480 (SPR, K_D (nM))
Nectin-1	>200 (n=3)
Nectin-2	>200 (n=3)
Nectin-3	>200 (n=3)
Necl-1	>200 (n=3)
Necl-2	>200 (n=3)
Necl-3	>200 (n=3)
Necl-4	>5000 (n=3)
Necl-5	> 200 (n=3)
OX40*	>100 (n=2)
CD40*	> 100 (n=2)

BT7480 only binds **Nectin-4** and **CD137**



Retrogenix membrane protein array: no binding of biotinylated-BT7480 @1μM to 5,482 other proteins

BT7480 SPR affinity (nM)	Human	Mouse	Rat	NHP
Nectin-4	5.6 ± 2.4 (n = 11)	4.6 ± 2.1 (n = 9)	15 ± 1 (n = 6)	27 ± 15 (n = 9)
Nectin-4 (simultaneous)	12 ± 2 (n = 4)	6.7 ± 1.7 (n = 3)	25 ± 2 (n = 3)	28 ± 5 (n = 3)
CD137 (simultaneous)	6.3 ± 0.7 (n = 4)	>100 (n = 2)	>100 (n = 2)	18 ± 6 (n = 3)

*Determined using biotinylated-BT7480
All data are mean ± SD and n= number of replicates

BT7480 functional activity is dependent on Nectin-4 in cell-based assays *in vitro*

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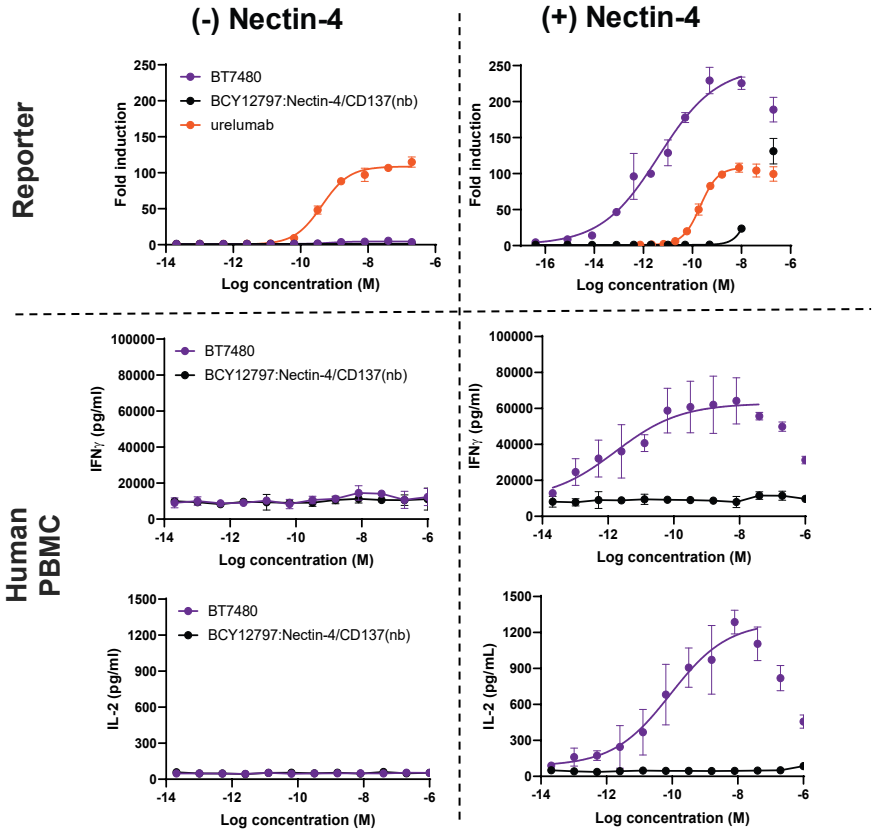
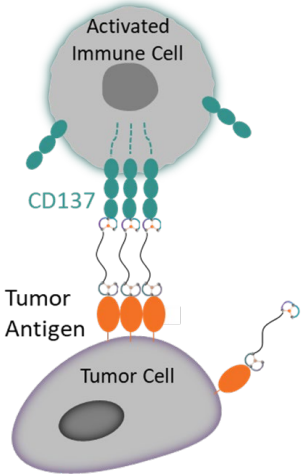
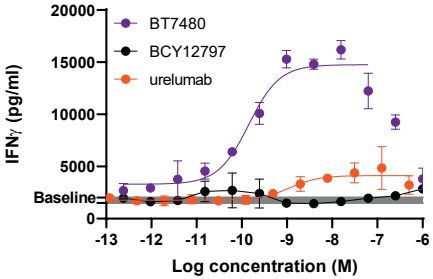


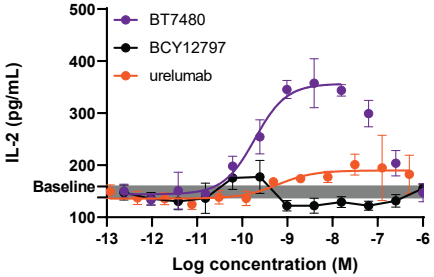


4T1 cells ± Nectin-4

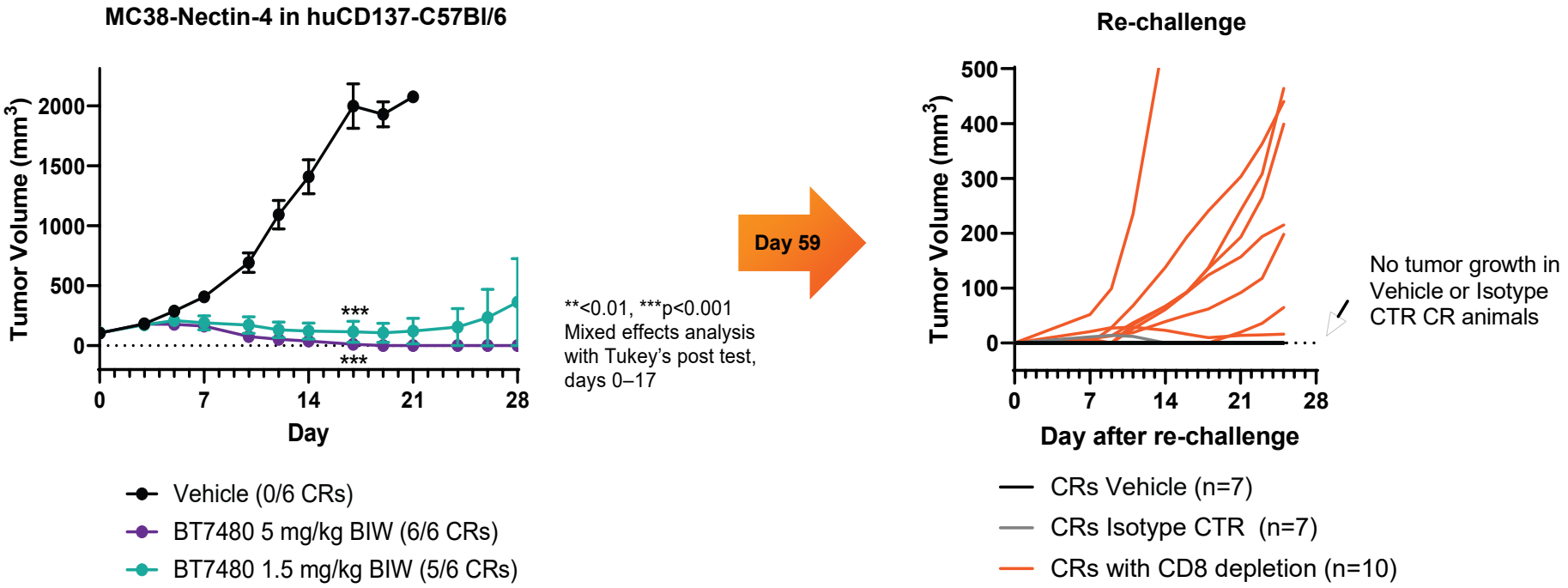
HT1376 bladder tumor cells



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



BT7480 induces complete responses and memory *in vivo*



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

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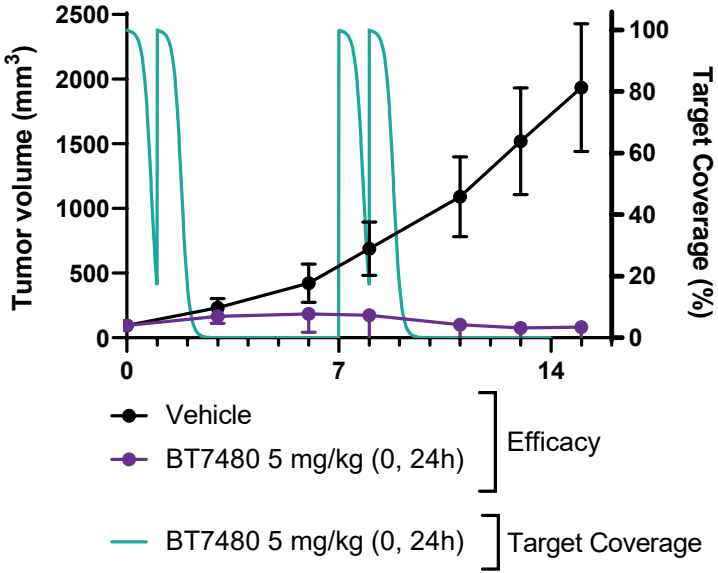
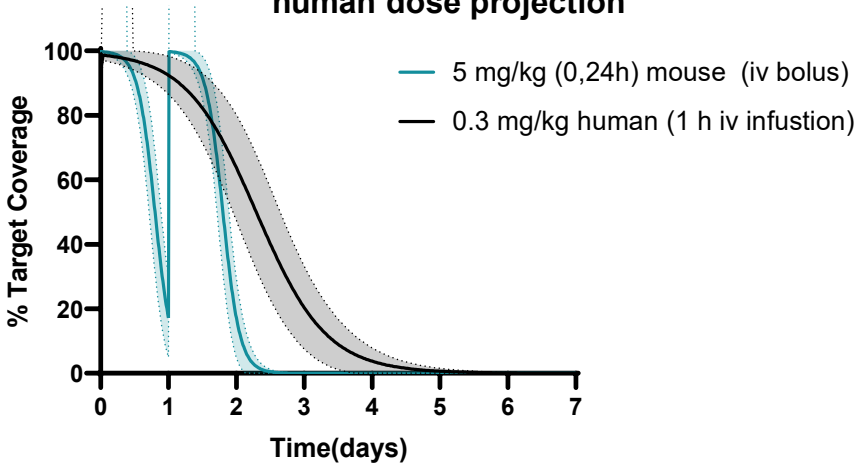
- Data suggest that continuous target coverage is not needed for robust efficacy
- Once weekly or less frequent dosing is predicted to be efficacious in humans

MC38-Nectin-4 in huCD137-C57Bl/6 mice



Simulation of target coverage for human dose projection



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

BT7480 has a unique and differentiated mechanism of action

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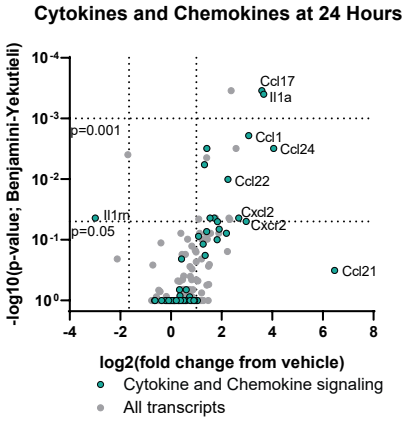
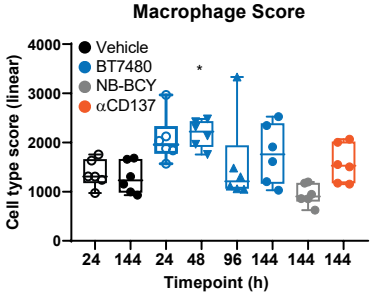
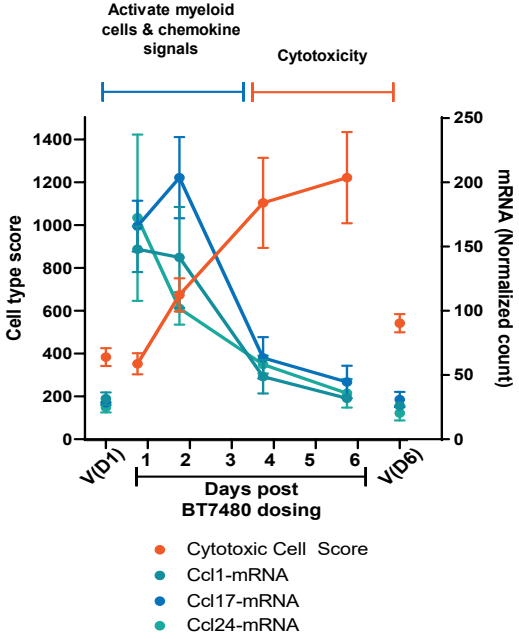
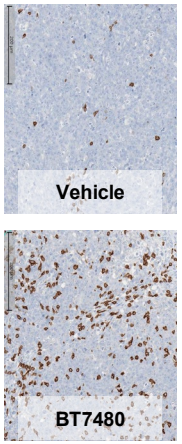
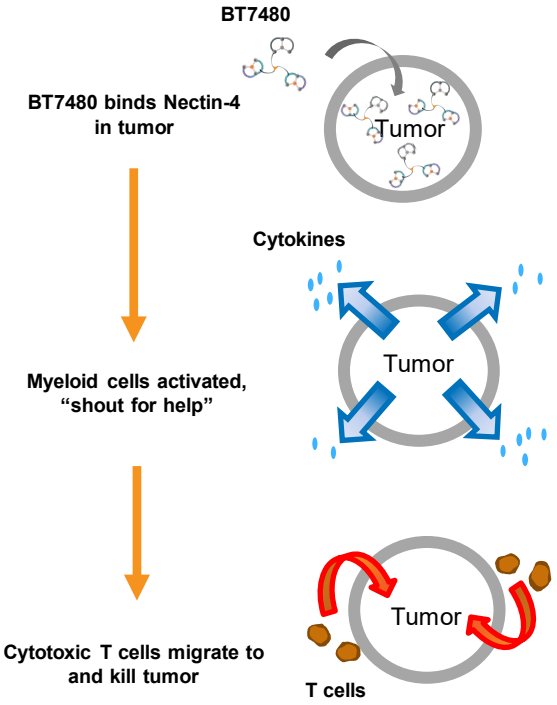








CD8+ T cells on Day 6



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

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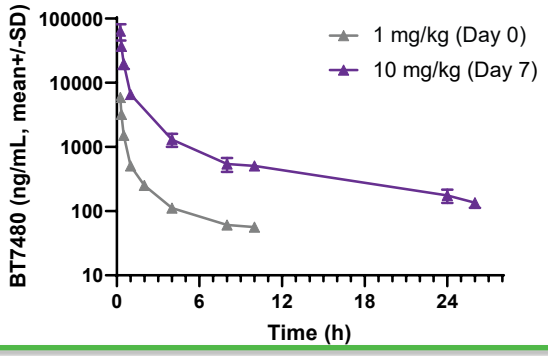
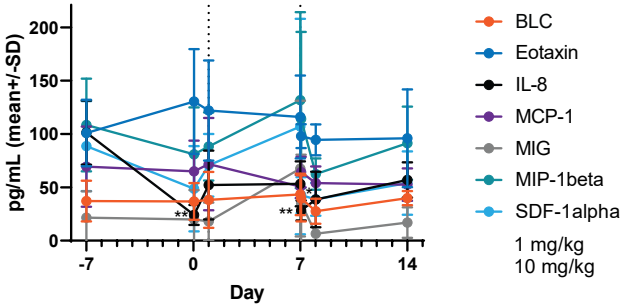
NHP (Cynomolgus monkey) PK



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

*Noteworthy treatment related findings

Day 7 after BT7480 administration

What patients are most likely to benefit from BT7480?

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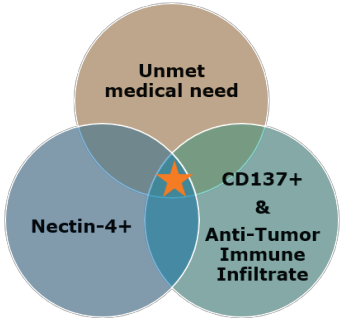
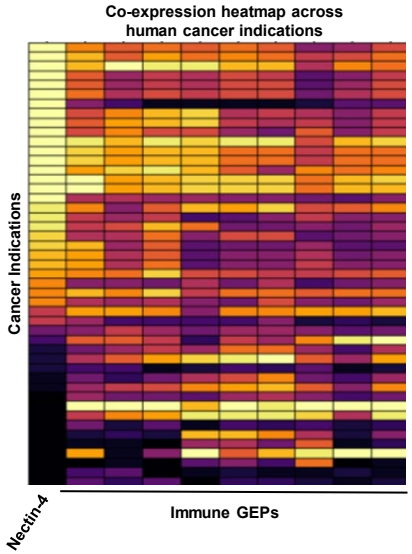
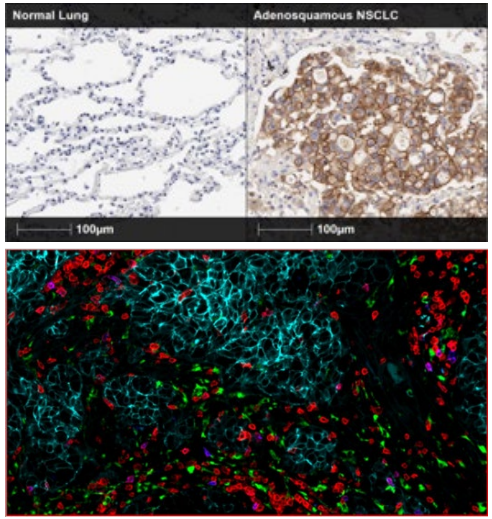
Biomarker-driven approach to identifying indications that co-express Nectin-4 & CD137



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



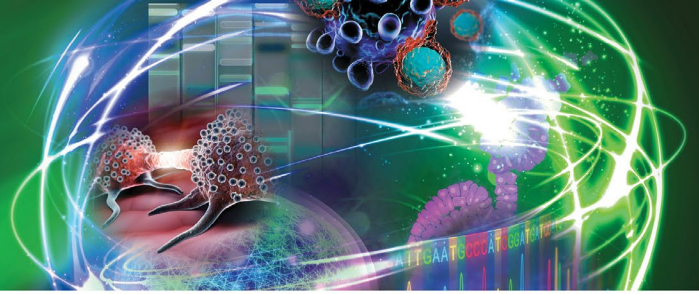


Human TNBC sample

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

Summary

- BT7480 is a novel, fully synthetic, tumor antigen (Nectin-4) dependent CD137 agonist with high biological potency (ca. 300pM EC_{50} in *in-vitro* assays)
- BT7480 is ca. 30x smaller than comparator biologics
- BT7480 induces robust anti-tumor responses to Nectin-4 expressing tumors in immune competent mouse models. BT7480 induces immunologic memory to those tumors
- BT7480 has a benign profile in preclinical safety evaluation with no liver effects observed
- BT7480 exhibits a unique mechanism in preclinical models
- Tumors that may benefit include >50% of breast, head & neck, ovarian and esophageal cancer patients
- BT7480 will be entering human trials in 2021



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