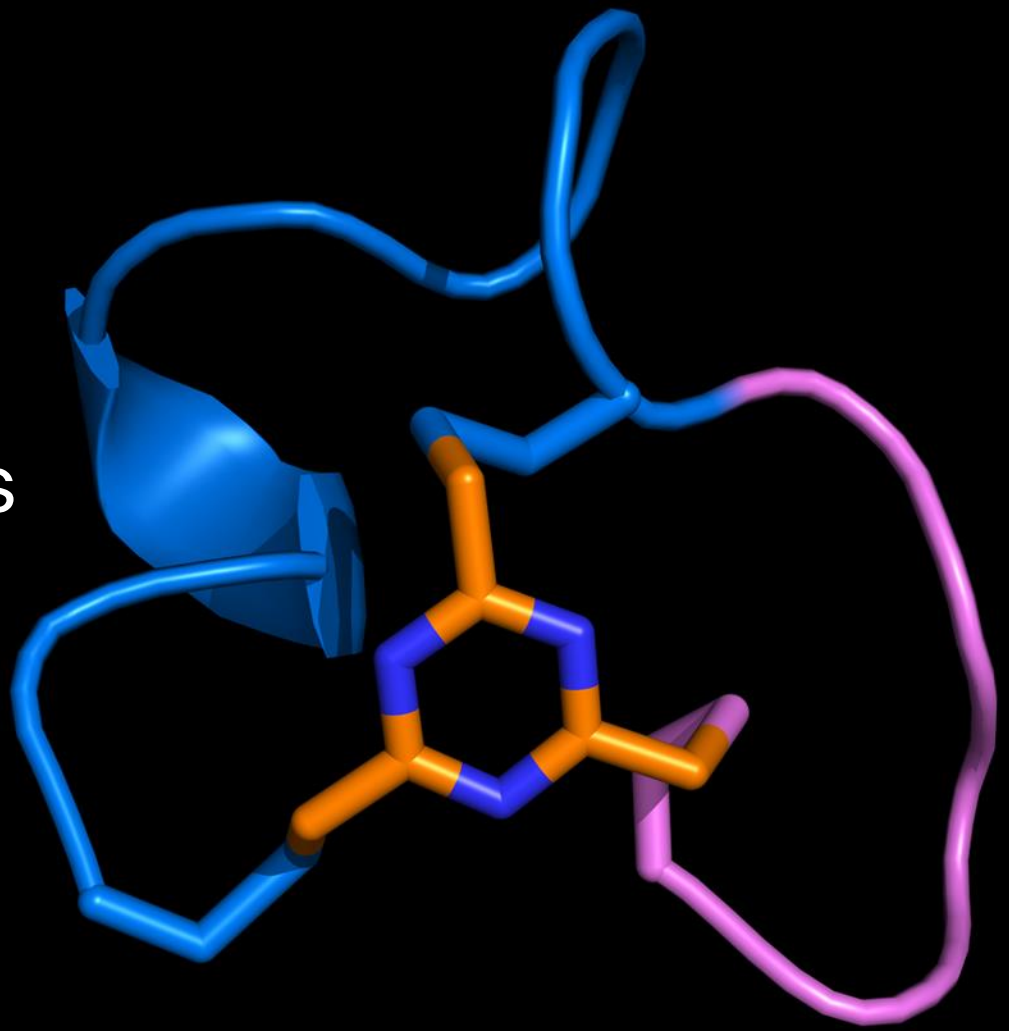
Bicycles - a modality for Tumor-Targeted Immune Cell Agonism

Sandra Uhlenbroich
Associate Director, Discovery

Antibody Engineering & Therapeutics
Amsterdam, June 2023



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 business performance, conditions, plans, prospects, trends or strategies and other 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 and the risk that we will be unable to obtain and maintain regulatory approval 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 May 4, 2023, 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.

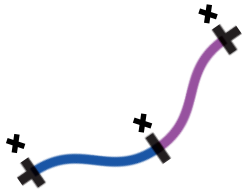
This presentation does not constitute an offer to sell or a solicitation of an offer to buy securities, nor shall there be any sale of any securities in any state or jurisdiction in which such offer, solicitation or sale would be unlawful prior to registration or qualification under the securities laws of any such state or jurisdiction.

Bicycle Therapeutics

- Clinical-stage biopharma company pioneering Bicycles, a new differentiated class of innovative medicines (Founded by Sir Greg Winter & Prof. Christian Heinis)
- Based in Cambridge (UK) & Boston (USA), 236 FTEs (Dec 31 2022)

Target / Product	Partner/Sponsor	Indication	Modality	Preclinical	IND-enabling	Phase I	Phase II/ Expansion	Phase III
Internal Programs								
BT5528 (EphA2)		Oncology	Bicycle® Toxin Conjugate					
BT8009 (Nectin-4)		Oncology	Bicycle® Toxin Conjugate					
BT7480 (Nectin-4/CD137)		Immuno-oncology	Bicycle TICA™					
BT7455 (EphA2/CD137)		Immuno-oncology	Bicycle TICA™					
Undisclosed	dkfz.	Radiopharmaceutical	Bicycle® Radio Conjugate					
Partnered Programs								
THR-149 (Kallikrein inhibitor)	OXURION	Ophthalmology						
BT1718 (MT1-MMP)	CANCER RESEARCH UK	Oncology	Bicycle® Toxin Conjugate					
BT7401 (multivalent CD137 system agonist)	CANCER RESEARCH UK	Immuno-oncology						
Undisclosed	Genentech A Member of the Roche Group	Immuno-oncology						
Novel anti-infectives	Innovate UK	Anti-infectives						
Novel CNS targets	Dementia Discovery Fund IONIS	CNS						
Novel neuromuscular targets	IONIS	Neuromuscular						
Undisclosed	NOVARTIS	Radiopharmaceutical	Bicycle® Radio Conjugate					
Undisclosed	Bayer	Radiopharmaceutical	Bicycle® Radio Conjugate					

Bicycle® - a unique & disruptive therapeutic modality



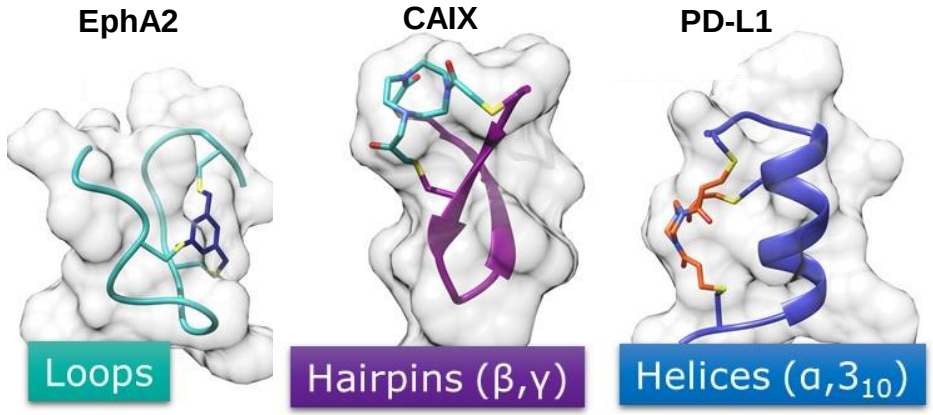
Short linear peptide

+

Scaffold

- **High affinity and selectivity in a small, fully synthetic format**

- **Biologically relevant tertiary structures**

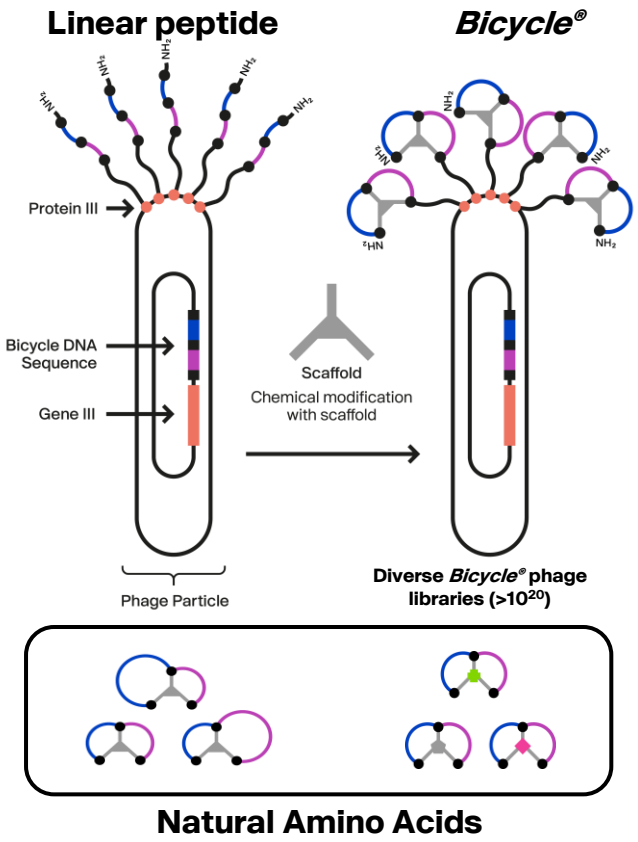


- **Favorable drug-like properties**

Small size (1.5-2 kDa)
High specificity
Chemical synthesis (NCEs)
Rapid tissue penetration
Complex protein targets druggable
Multiple routes of administration
Renal route of elimination
Not immunogenic

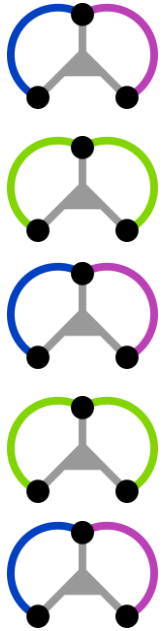
Bicycle® platform delivers a toolkit of building blocks to create novel medicines

Bicycle® Phage Display - Discovery



Optimize *Bicycle*® *monomers*

Peptide & Medicinal Chemistry

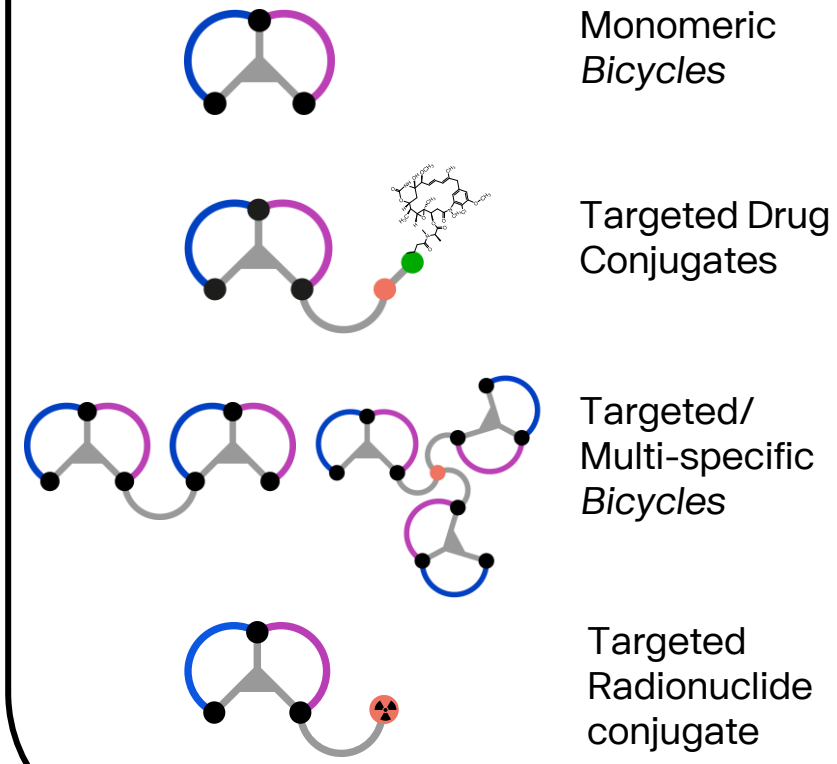


Non-Natural Amino Acids

Build and Optimize Therapeutic *Bicycles*

Easy conjugation of Linkers and Payloads

Potential *Bicycle*® Medicines



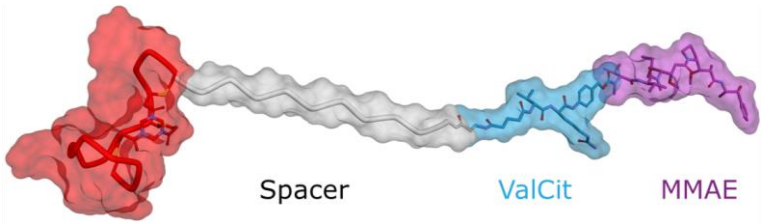
Monomeric *Bicycles*

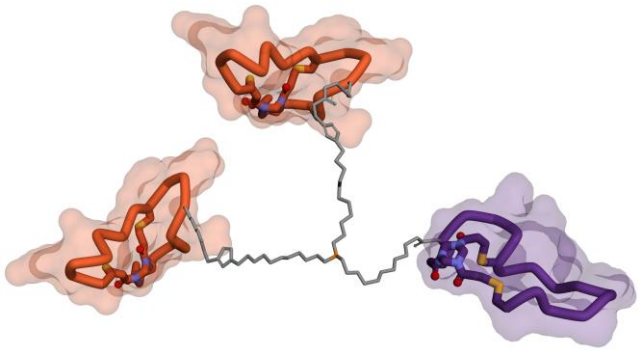
Targeted Drug Conjugates

Targeted/ Multi-specific *Bicycles*

Targeted Radionuclide conjugate

Bicycle Therapeutics – creating versatile new precision-guided medicines with potential to fill major gaps in cancer therapy

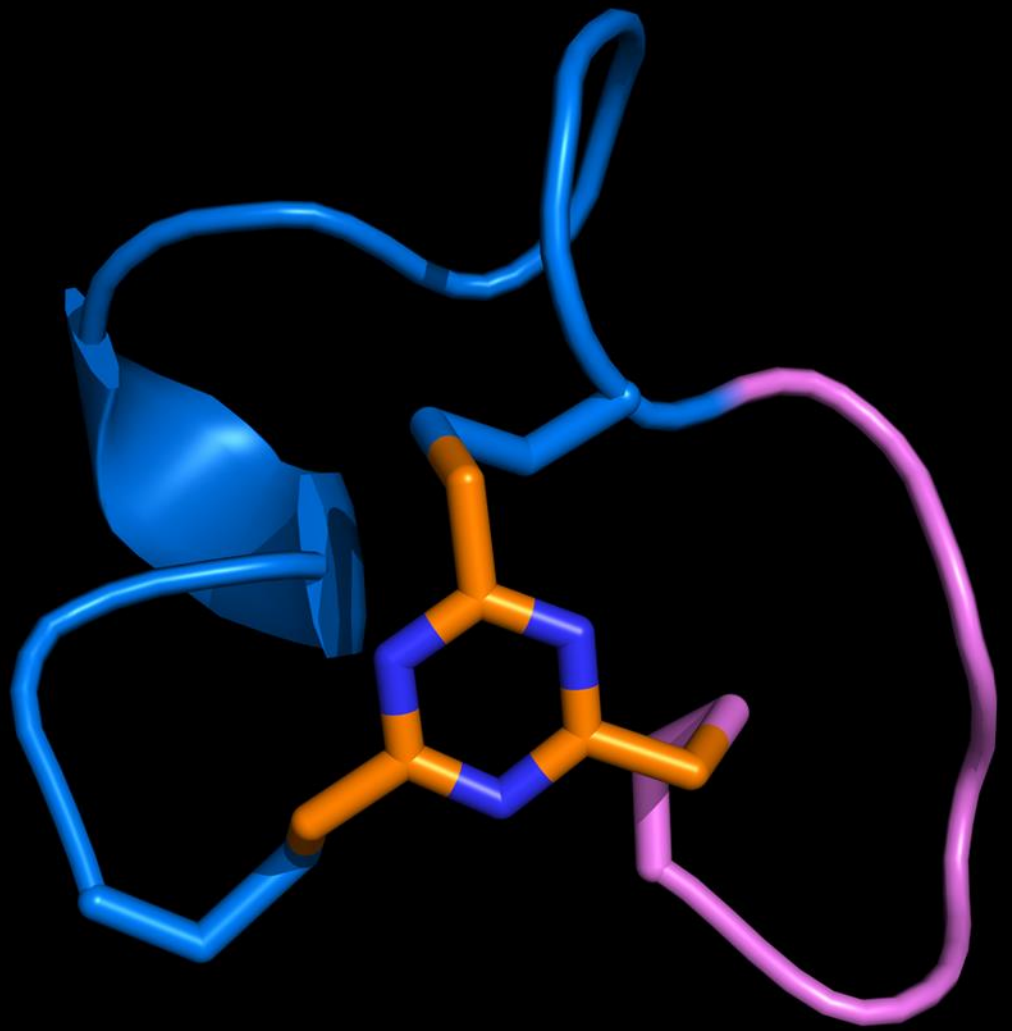




- **Bicycle Toxin Conjugates® (BTCs)**
  - Precision delivery of MMAE - BT8009 & BT5528
  - Fast tissue distribution and clearance
  - Emerging clinical data
- **Bicycle Tumor-Targeted Immune Cell Agonist® (TICAs)**
  - Rapid, local and controlled immune agonism
  - Pathfinder molecule for CD137 – BT7480 in Phase I
  - Pathfinder molecule for NKp46 – preclinical stage

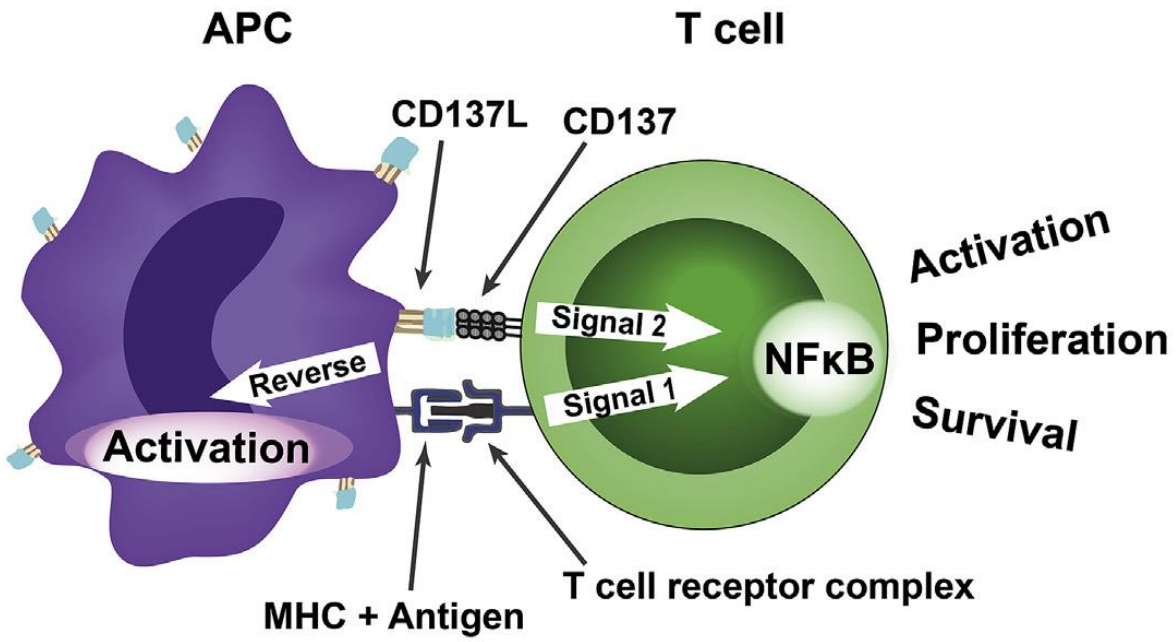
Bicycle® precision-guided immune activation

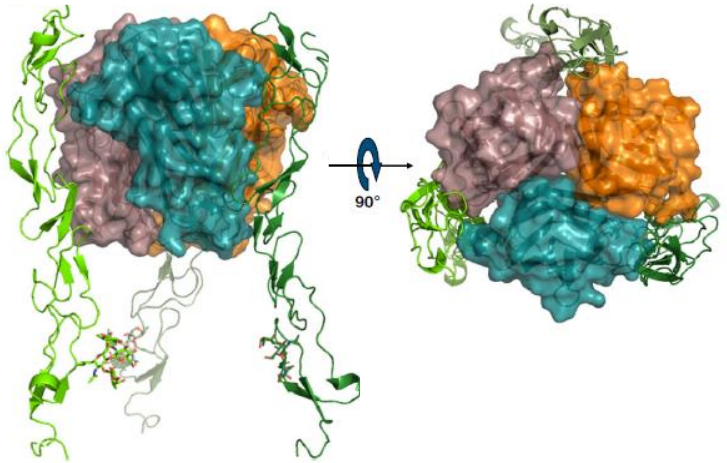
Immune cell receptor = CD137



Bicycle®

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

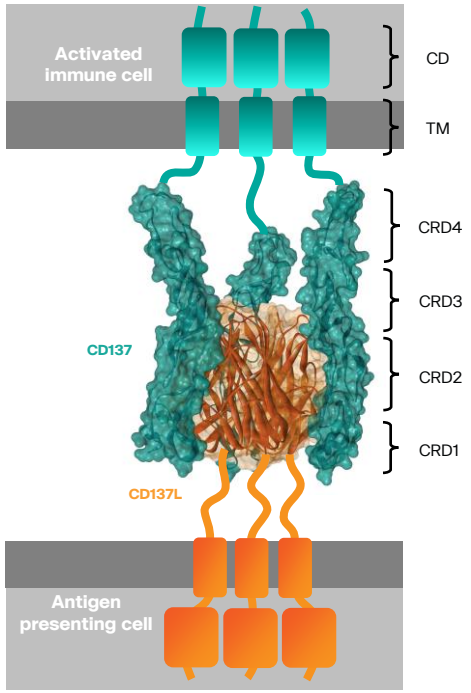




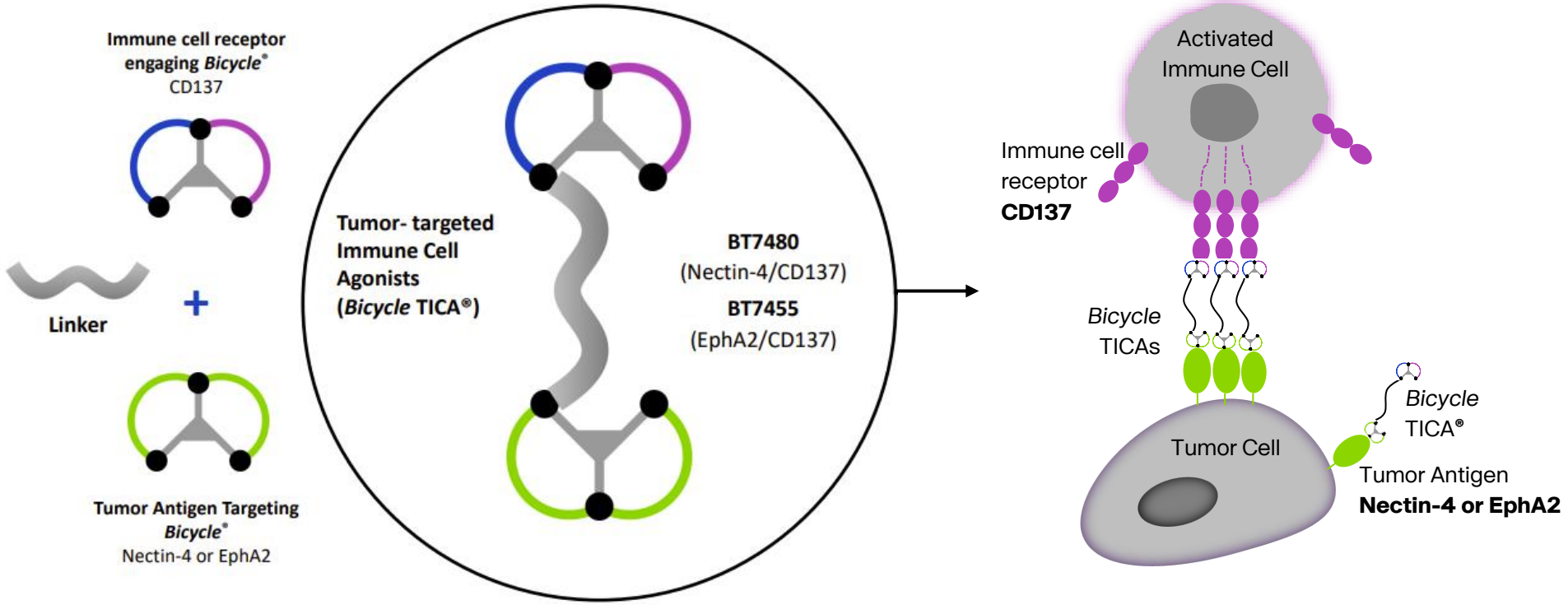
Yonezawa (2015); Melero (2008) TiPS 29, 383; Melero (2007) Nat. Immunol 3, 682; Wilcox (2004) Blood 103, 177; Wilcox (2002) J. Immunol. 169, 4230; Gomes-Silva (2017) Cell Rep. 21, 17; Segal (2016) Clin. Cancer Res. 23, 1929; Zheng – SITC2020 abstract 812; Chin (2018) Nat. Comm. 9, 4679; Soderstrom (2018)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

- Current antibody clinical trials have limited efficacy or reveal hepatic toxicity risks
- Tumor-Targeted Immune Cell Agonist (TICA) approach - meets design goal dictated by biology

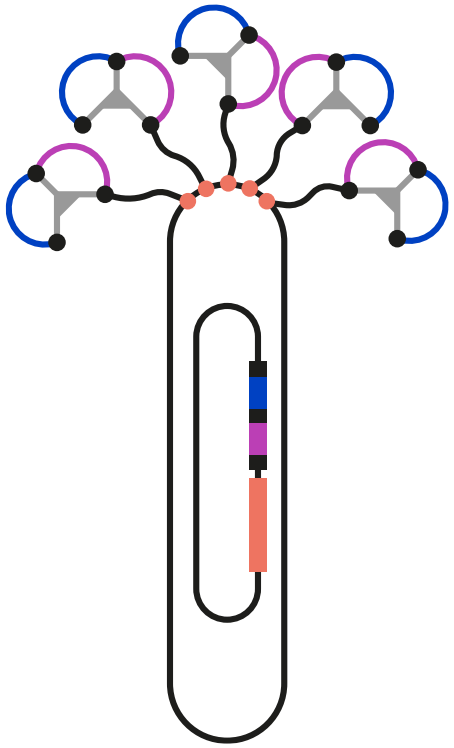
Bicycle TICA®– tumor-targeted immune cell agonists delivers immune agonism to tumors



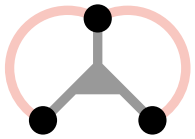
Activation induced by clustering of **CD137** by trimeric **CD137L**



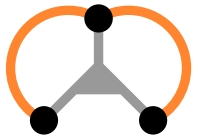
CD137 and Nectin-4 *Bicycles*: discovery and optimization by phage display and chemistry



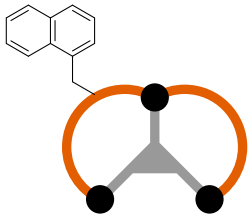
CD137



K_D = 1400 nM



K_D = 67 nM



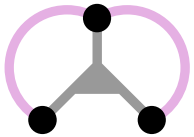
K_D = 5 nM

Phage Hits
- ID sequence families
- Define initial pharmacophores

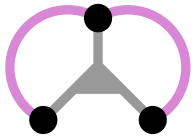
Phage Optimization
- Focused libraries
- Optimize natural AAs
- Scaffold/Loop symmetry

Chem Optimization
- Non natural amino acids
- Tuned affinity and stability
- Balanced phys. chem properties

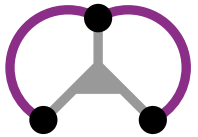
Nectin-4



K_D = 508 nM

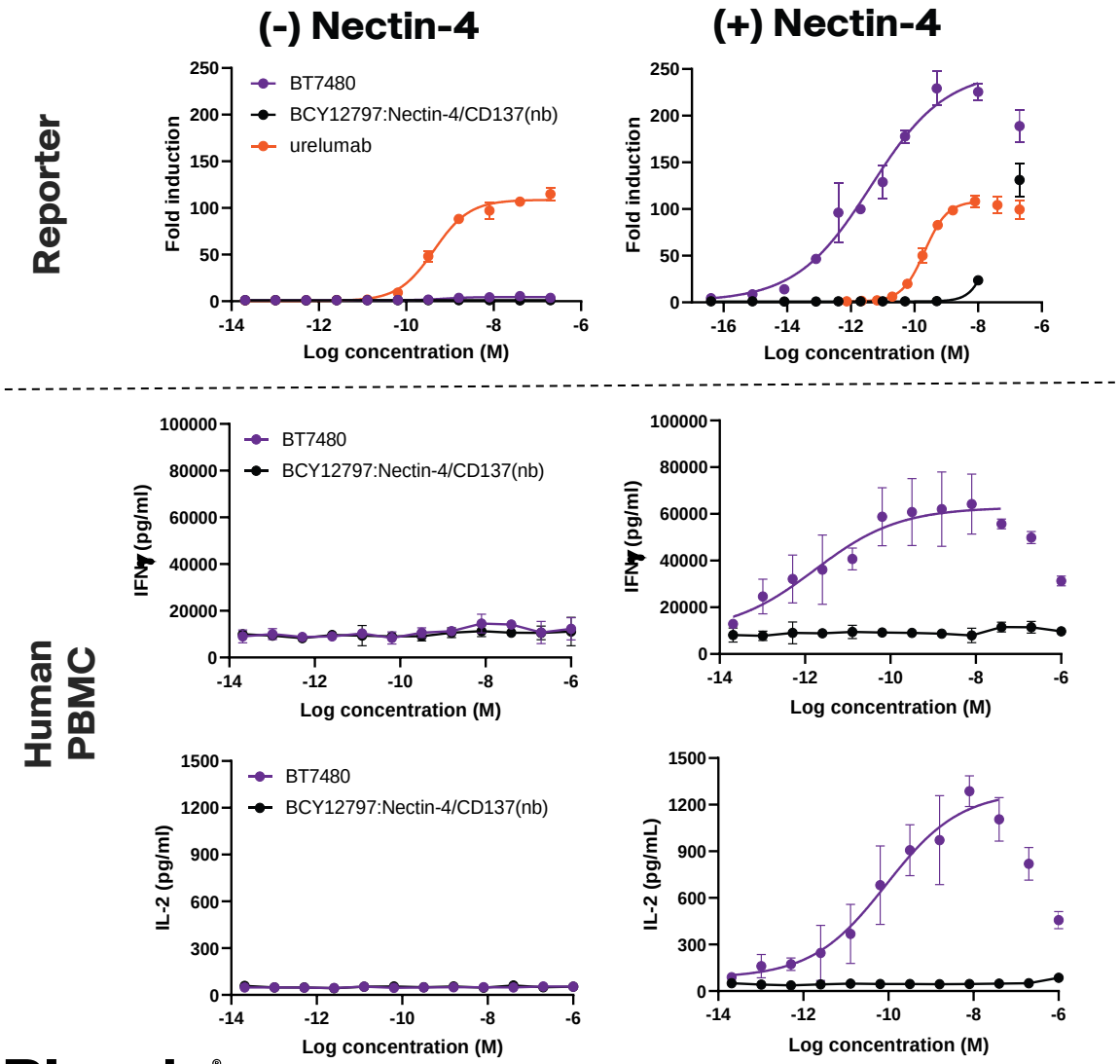


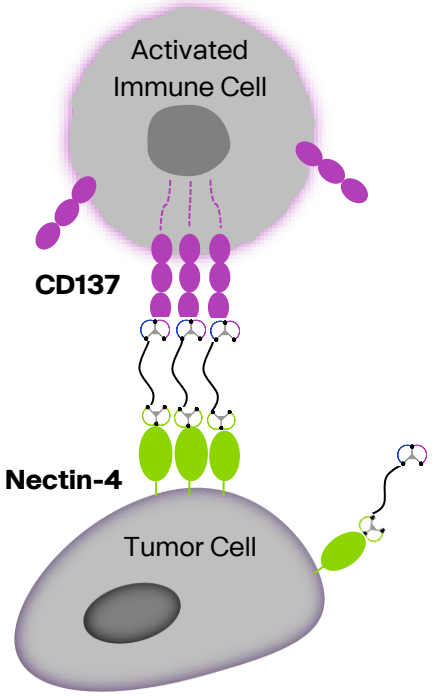
K_D = 80 nM



K_D = 1 nM

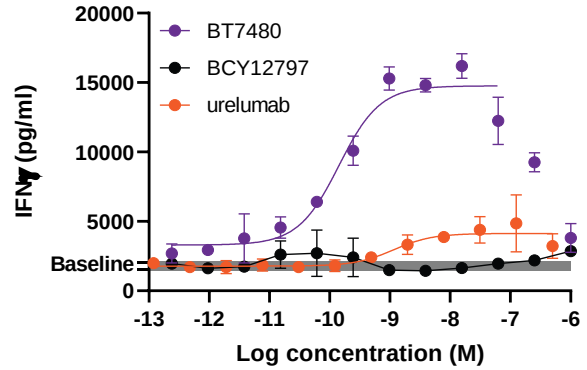
BT7480 functional activity is dependent on Nectin-4 in cell-based assays *in vitro*



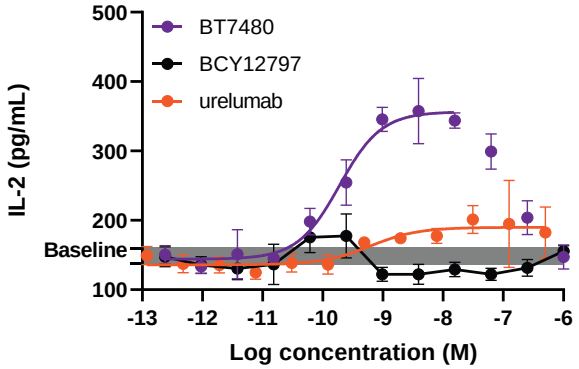


4T1 cells ± Nectin-4

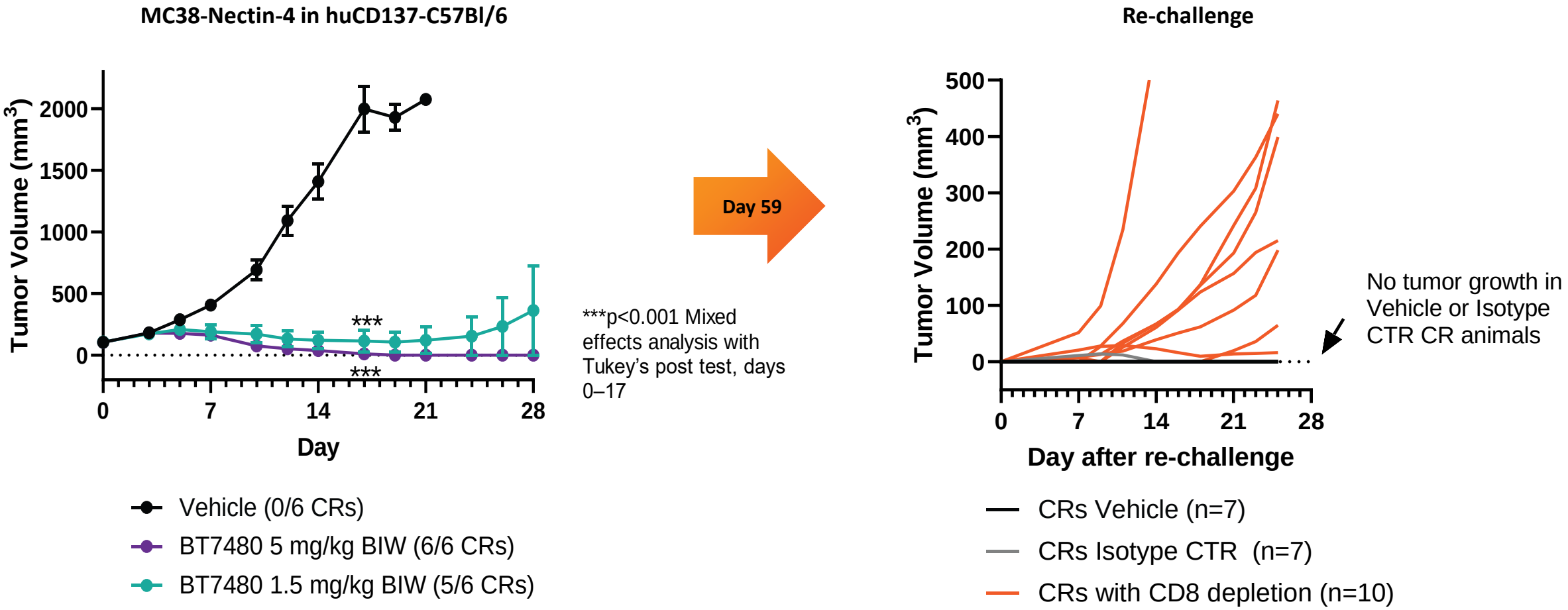
HT1376 bladder tumor cells



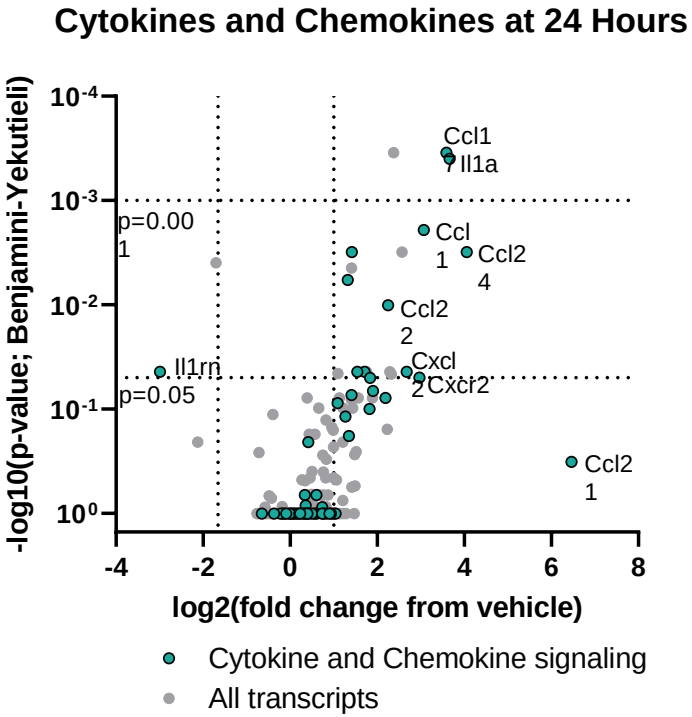
EC_{50}
0.37±0.23 nM (IL-2)
0.22±0.12 nM (IFNγ)

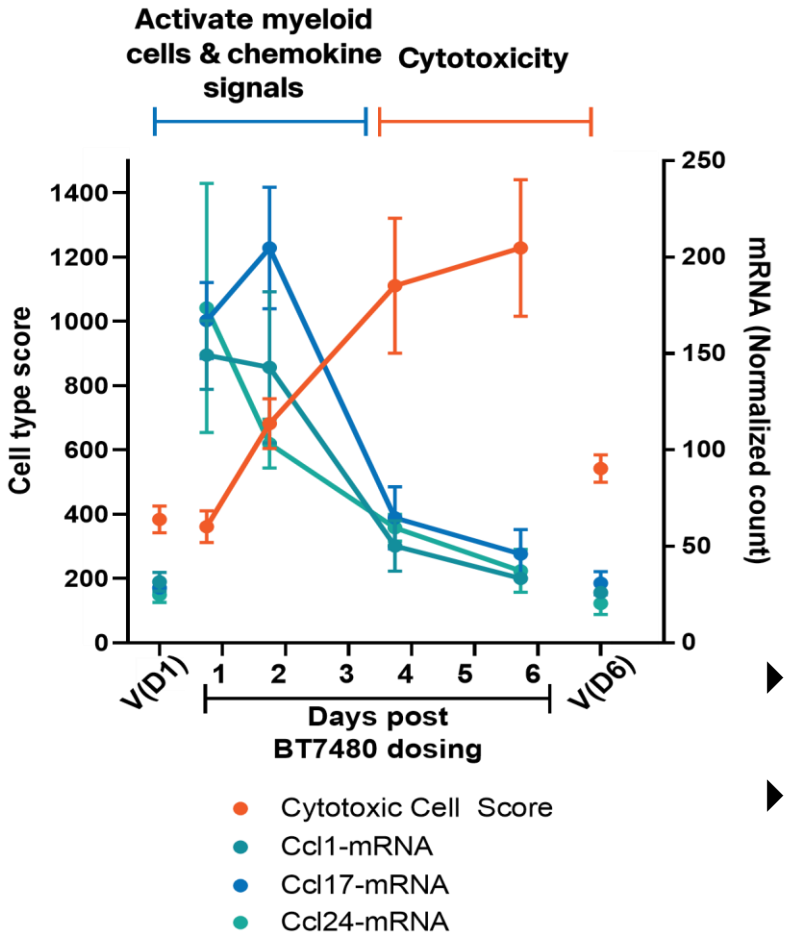


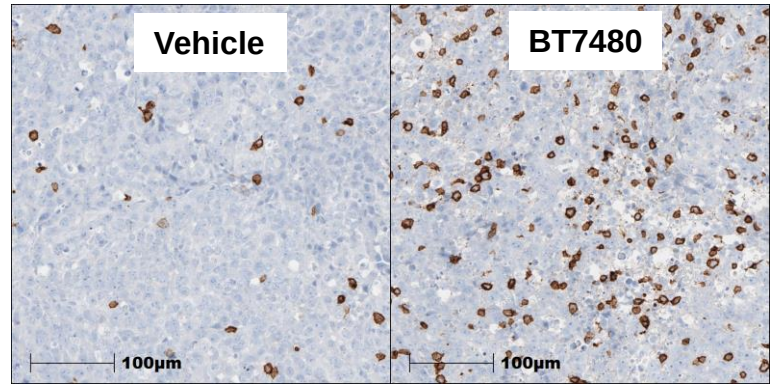
BT7480 induces complete responses and memory *in vivo*



BT7480 has a unique and differentiated mechanism of action



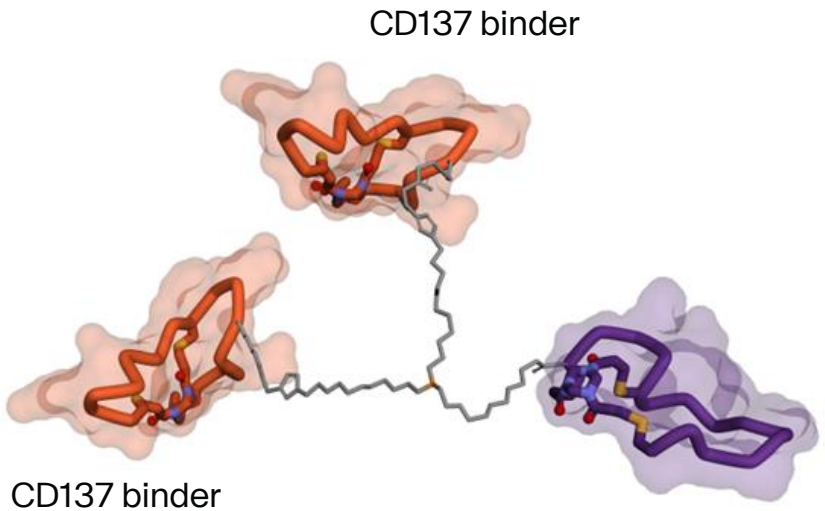




- BT7480 leads to a tumor localized early increase in cytokine gene expression
- BT7480 leads to increase in CD8+ cell infiltration, cytotoxic and macrophage cell scores in tumor

BT7480 meets rationale design goals for a locally acting immune agonist

- CD137 agonism dependent on ligation to tumor specific antigen
- Robust anti-tumor activity with only intermittent dosing observed *in vivo*
- Early increase in cytokine production precedes CD8+ T cell infiltration into the tumor
- Well-tolerated in preclinical safety species
- Entered Phase I clinical trial in November 2021

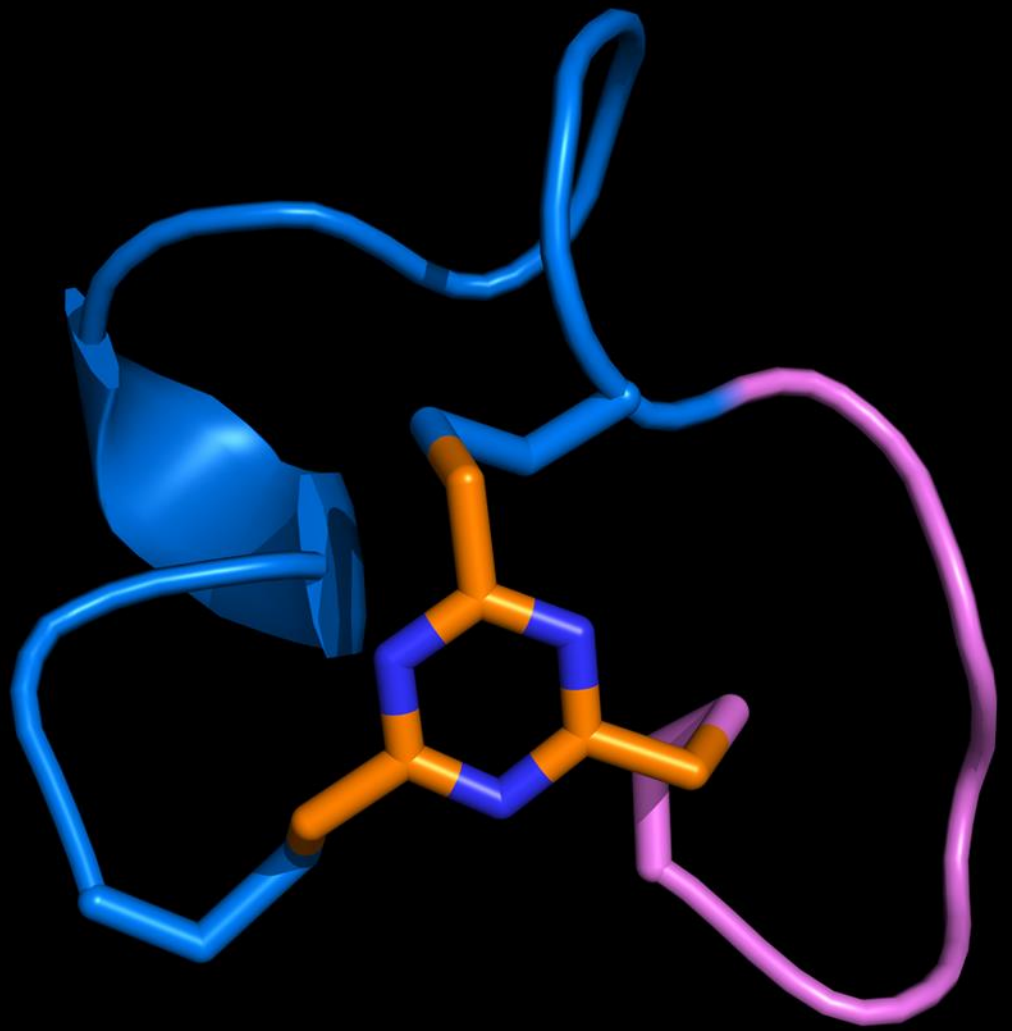


BT7480
MW = 7213.3 Da

Hurov K, Lahdenranta J, et al., 2021, *J Immunother Cancer*,
Upadhyaya, et al., 2022, *J Med Chem*

Bicycle® precision-guided NK cell activation

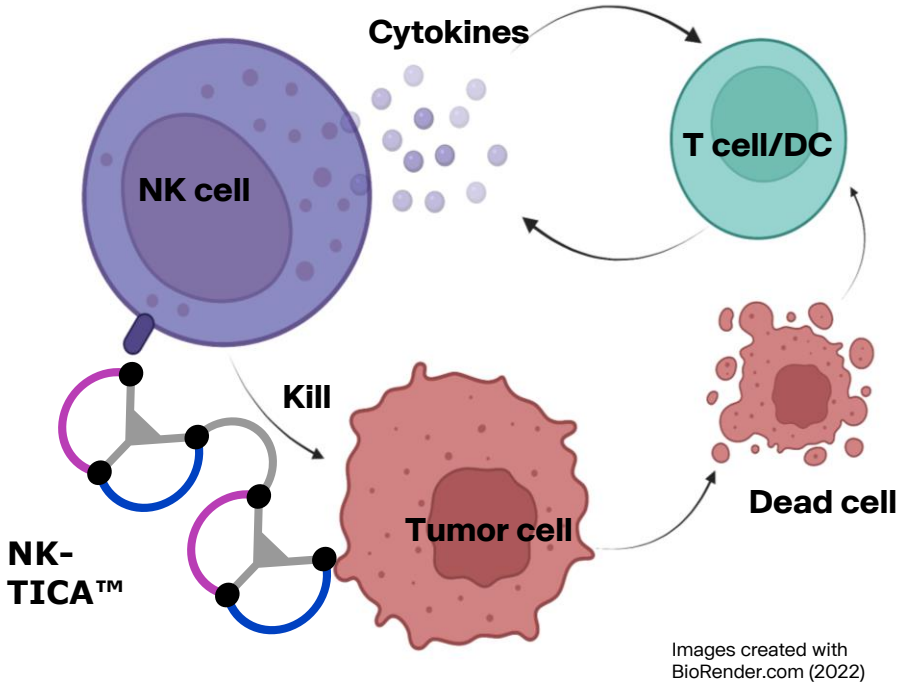
NK cell receptor = NKp46



Bicycle®

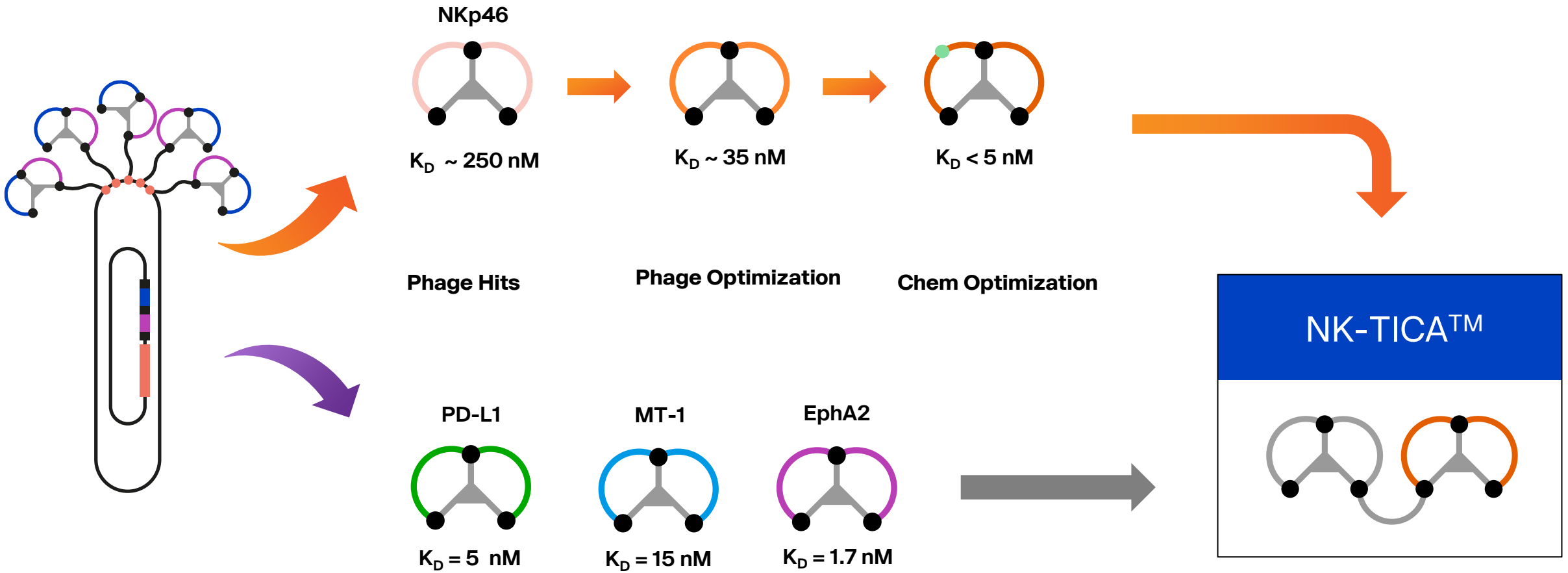
Natural killer (NK) cells have emerged as important early drivers of the adaptive anti-tumor immune response

- Traditional understanding: NK cells kill tumor cells through direct cytotoxic mechanisms
- New science: role for NK cells in orchestration of adaptive immunity catalysis
- NK cell therapy is emerging as an important new approach to cancer
- NKp46 as NK-TICA™ target - an activating receptor specifically and constitutively expressed on NK cells

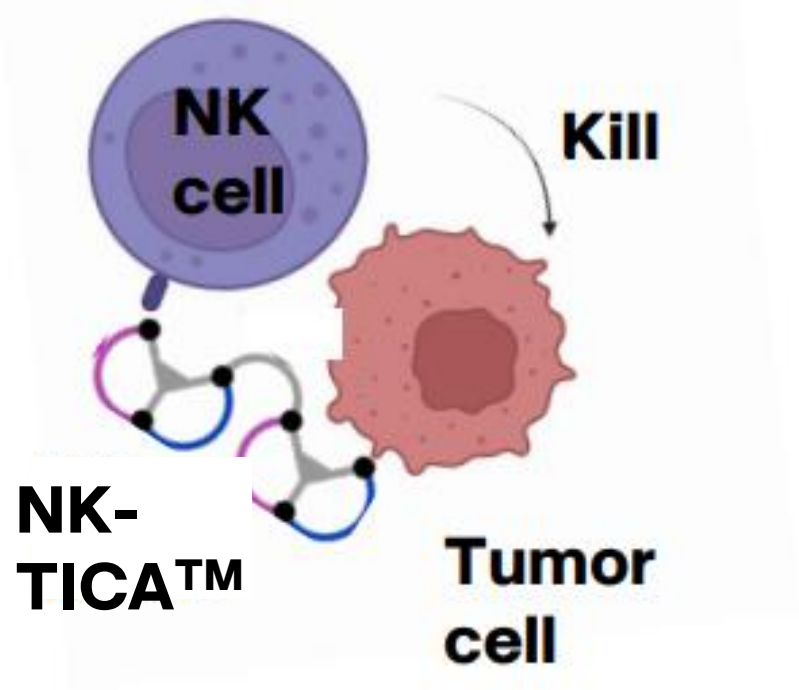


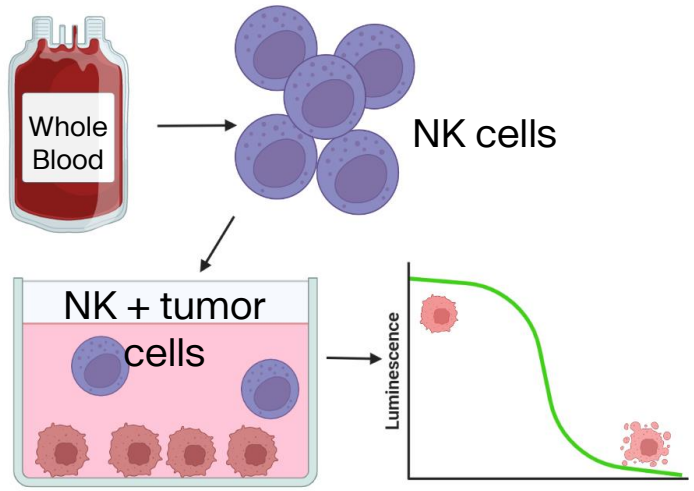
Chiossone et al., (2018) Nat. Rev. Immunol. 18, 672
Huntington et al., (2020) Nat. Rev. Cancer 20, 437
Bald et al., (2020) Nat. Immunol. 21, 835

NKp46 *Bicycles*: discovery and optimization by phage display and chemistry

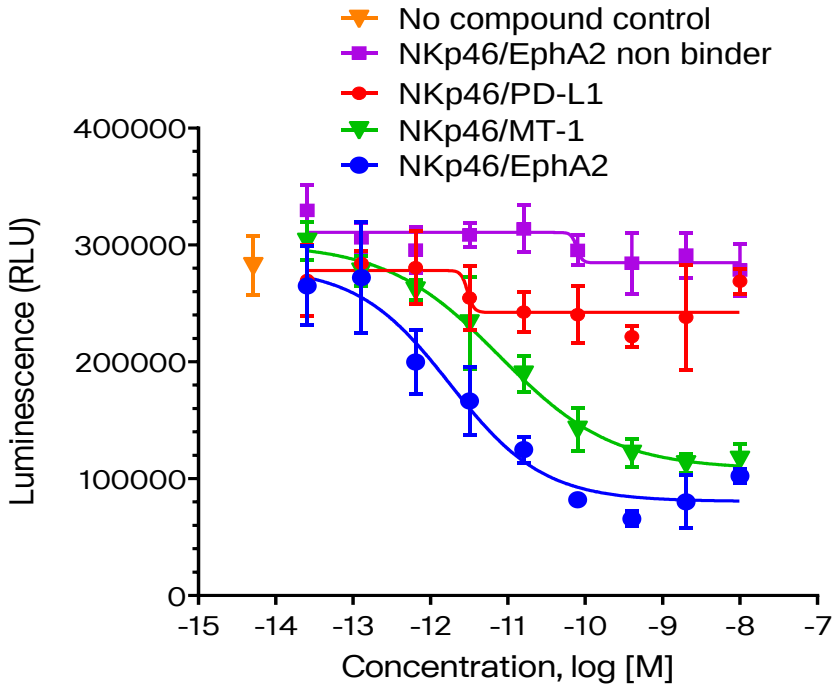


NKp46 *Bicycles* coupled to multiple antigen targets drive potent tumor cell killing



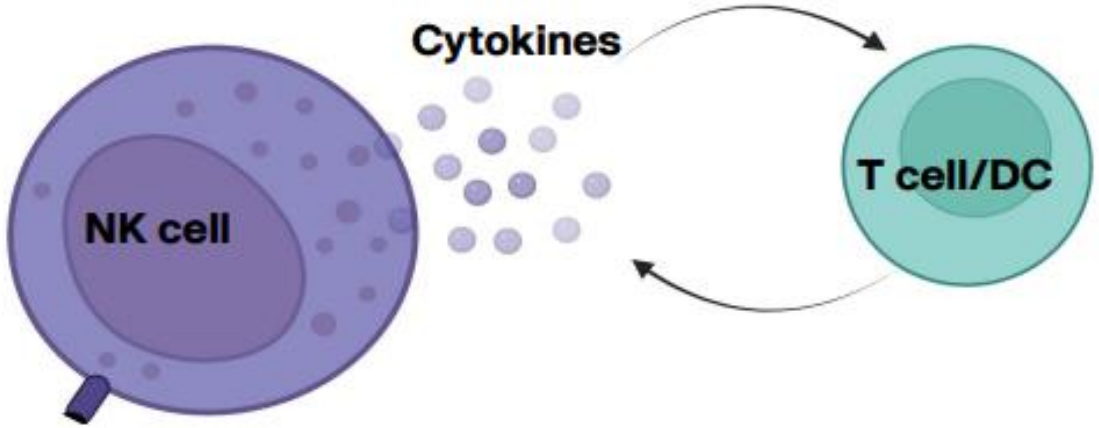


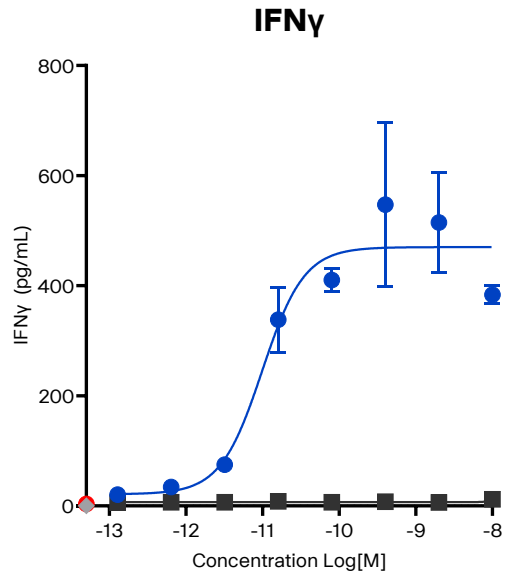
Images created with BioRender.com (2022)

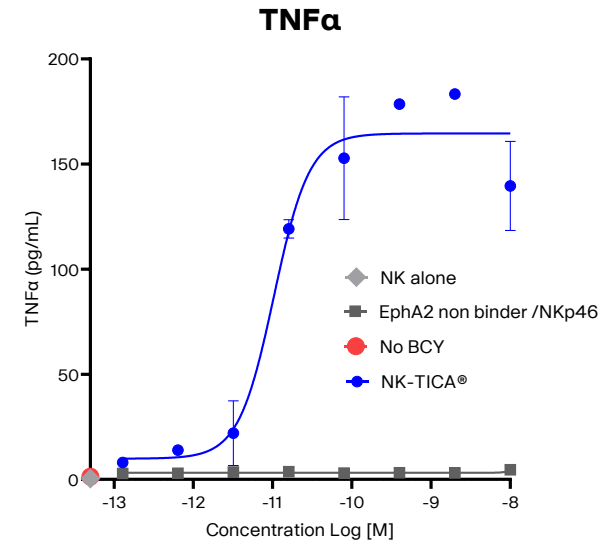


- Potential to create NK-TICA™ to address multiple solid tumor indications

NK-TICA™ enhances NK cytokine production in the presence of tumor antigen expressing cell lines



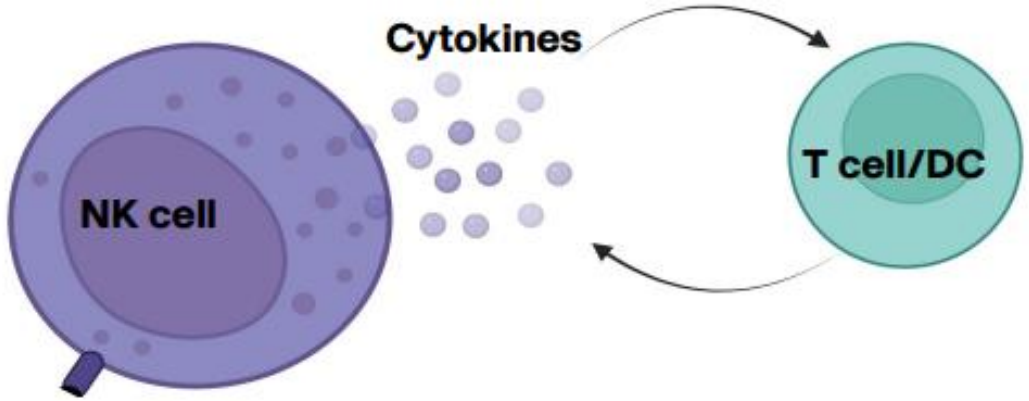


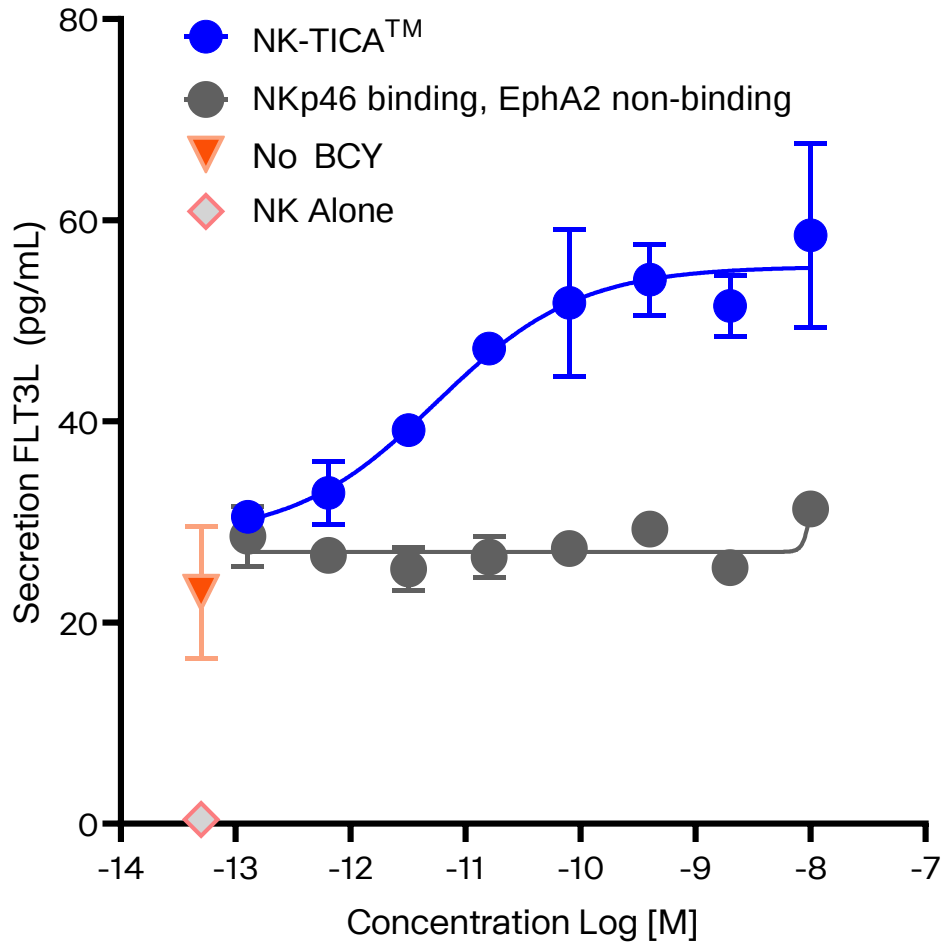


- NK cells secrete IFNγ and TNFα in the presence of NK-TICA™
- Cytokine secretion is dependent on binding to tumor antigen

NK-TICA™ enhances NK cell secretion of FLT3L

- NK-TICA™ causes FLT3L production by primary NK cells co-cultured with tumor cells
- FLT3L is a clinically validated driver of cDC1 maturation and anti-tumor responses



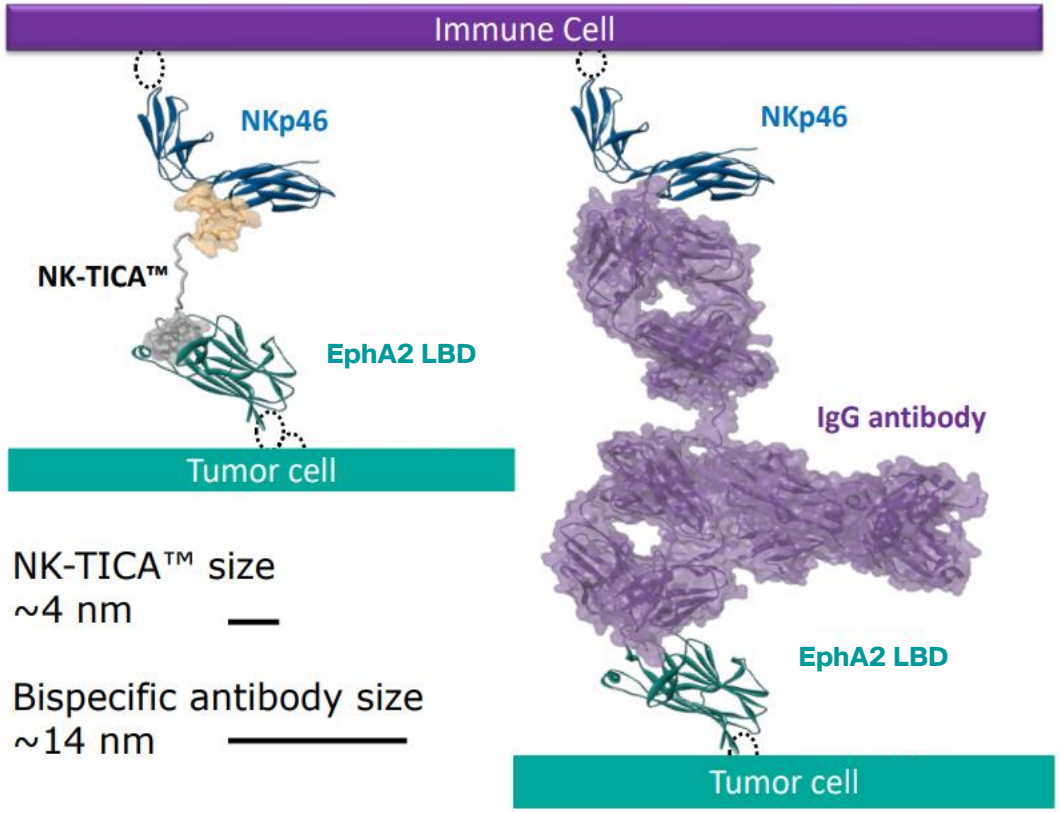


Wculek et al. Nat Rev Immunol. 2020, Allen F et al. Oncoimmun 2018, Bottcher et al. Cell, 2018 , Holmes et al. PNAS 2014
Zhou, Y. et al. Mol Cancer 2023, Salmon H et al. Immunity 2016 Barry et al. Nat Med 2018

First series of chemically synthetic, conditionally active, targeted NKp46 activators

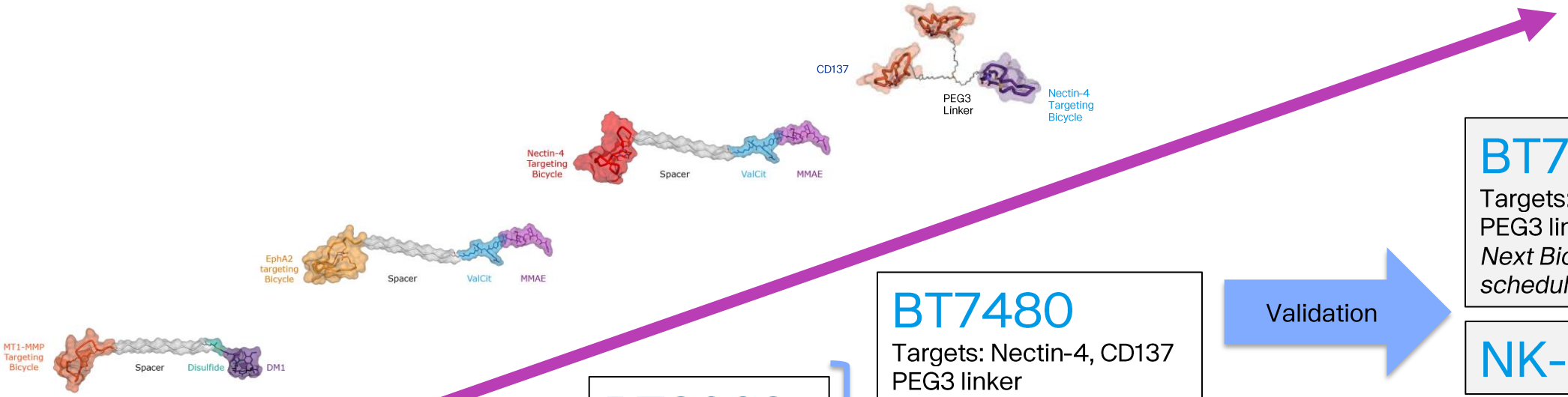
- NK-TICA™
  - Tumor antigen-dependent NK cell engagers
  - Potent tumor cell killing
  - Potential to drive adaptive anti-tumor immunity

- NK-TICA™ have the potential to catalyze durable anti-tumor immunity in tumor types not well served by current therapies



Dufort et al., AACR 2022

Diversifying 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

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