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Society for Immunotherapy of Cancer

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A novel fully synthetic dual targeted Nectin-4/4-1BB *Bicycle*® peptide induces tumor localized 4-1BB agonism.

Nicholas Keen, CSO Bicycle Therapeutics

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Conflict of interest statement

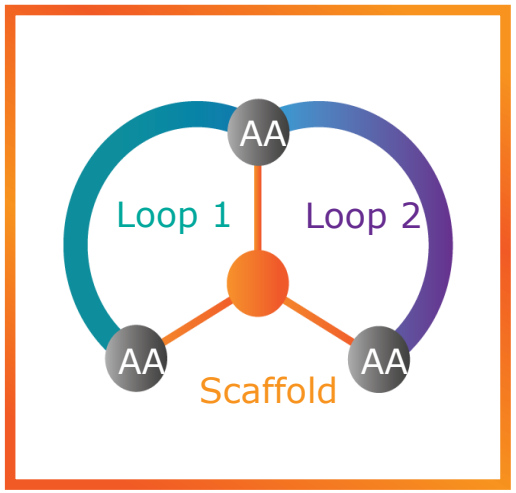
- I am an employee of Bicycle Therapeutics Inc.
- I am a stockholder in Bicycle Therapeutics plc.

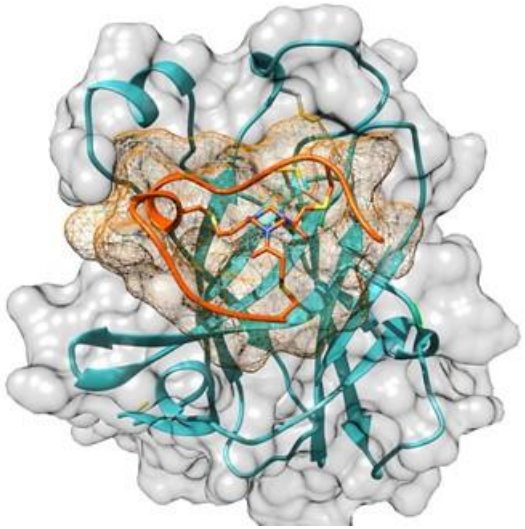
Bicycle Therapeutics

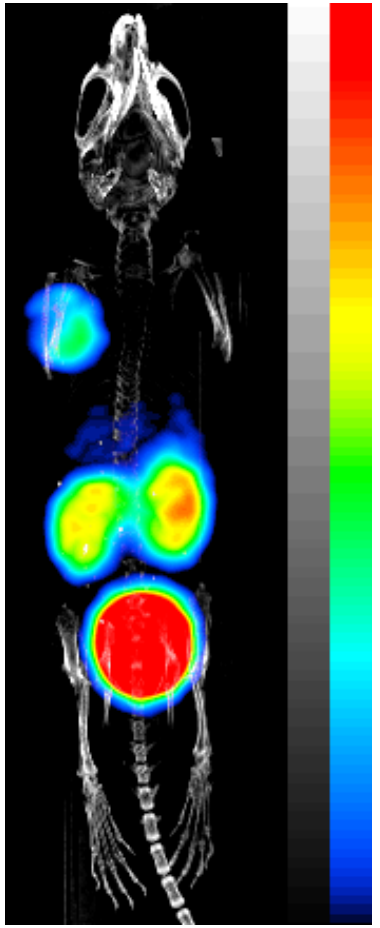
- Founded by Sir Gregory Winter & Prof. Christian Heinis
- UK & US based (Cambridge, UK; Boston, USA)
- Internal focus on Oncology
  - BT1718 – Phase 1/2a (Cancer Research UK)
  - 2nd Generation *Bicycle Toxin Conjugates*® in pre-clinical development
  - ***Bicycle*® immune cell modulators**

Bicycles®: a new therapeutic modality

- Structurally constrained Bicyclic peptides, chemically synthesised, low MWt (1.5-2kDa)
- Large binding footprint allowing targeting of protein-protein interactions
- Small molecule like PK and tumor penetration, renal excretion



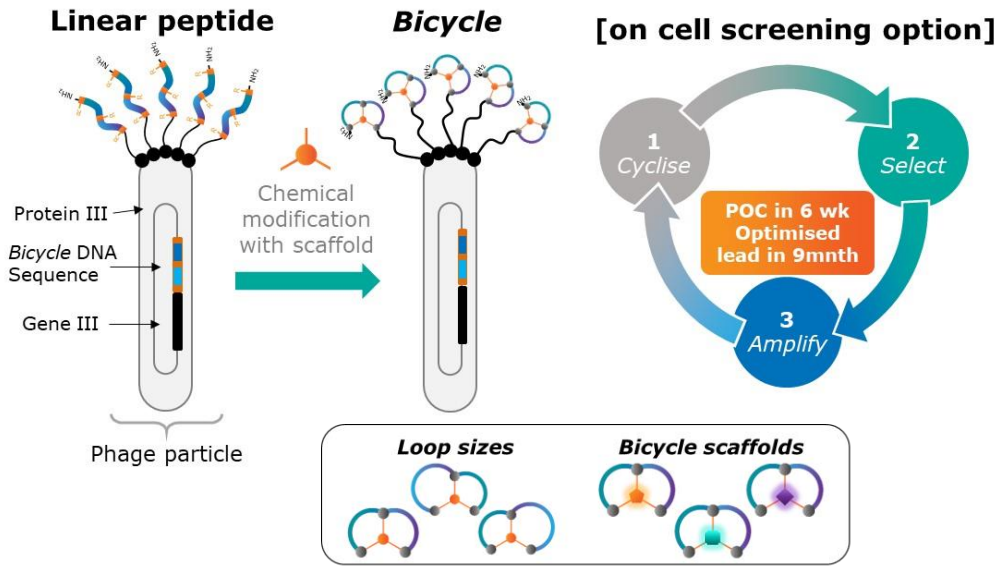




EphA2 binding *Bicycle*

Proprietary screening platform: *Bicycles*® optimised using phage display and medicinal chemistry, informed by structural biology

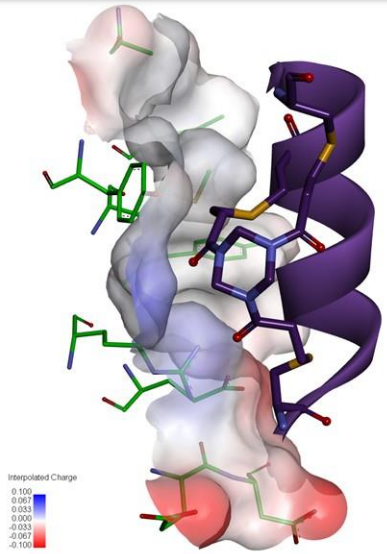
Bicycle Phage Display



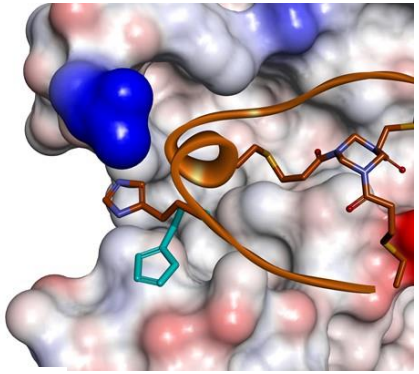
Optimize binder & capture IP

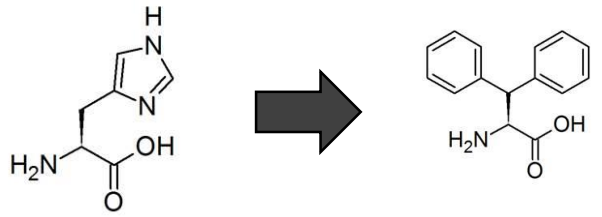
Natural Amino Acids

Structural Biology



Peptide & Medicinal Chemistry





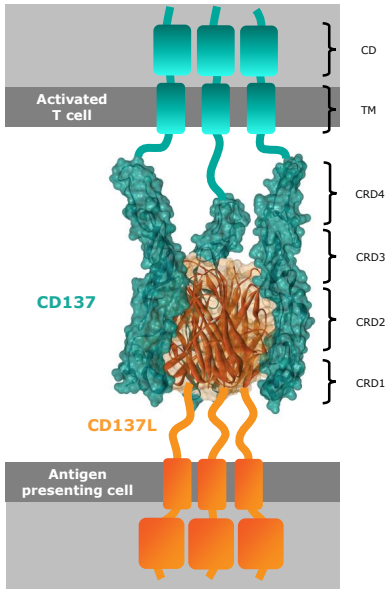
Histidine
Ki=11nM

3,3-diphenylalanine (3,3-DPA)
Ki=0.9nM

Dial in desired drug-like properties and PK profile

Non-natural Amino Acids

CD137 activation leads to potent anti-tumor response through diverse mechanisms



T-cells: Sustained activation, cytokine secretion, induced growth and survival, restoration of effector functions

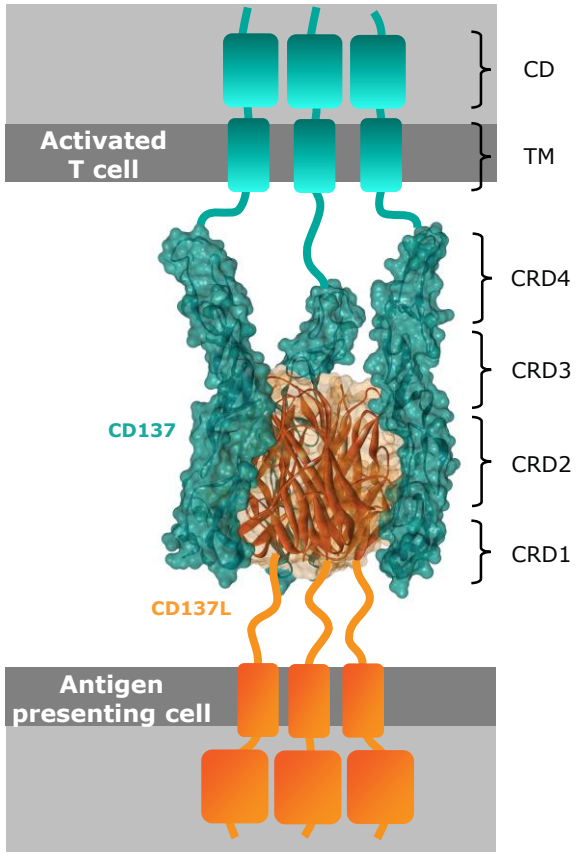
Dendritic cells: Activation and cytokine secretion

Macrophages: Activation and cytokine secretion

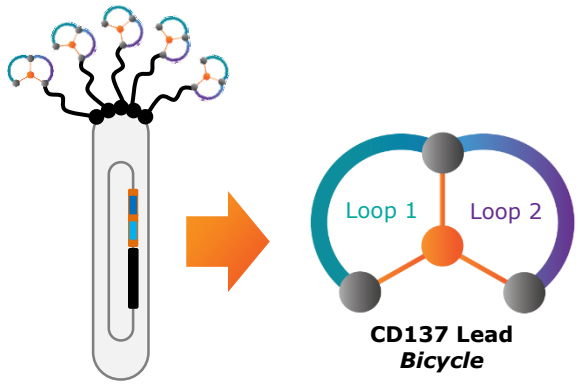
NK cells: Activation and cytokine secretion, increase in ADCC

- Highly validated IO target – roles in key steps in cancer immune cycle
- Expressed on, and stimulates T-cells, NKT, NK, Dendritic cells, Macrophages, B cells and neutrophils
- Urelumab, a superagonistic anti-CD137 mAb effective as a single agent in clinic, but utility limited by hepatotoxicity and long $t_{1/2}$
- A tumor antigen specific agonist could provide efficacy without systemic toxicity

Tumor/CD137 binding *Bicycles*® as tumor-targeted immune cell agonists (TICAs)

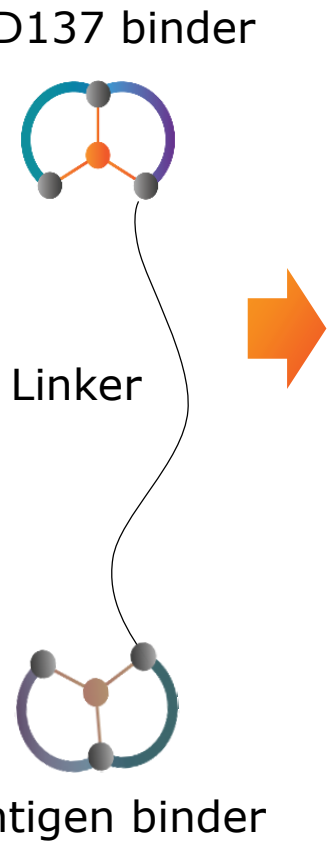


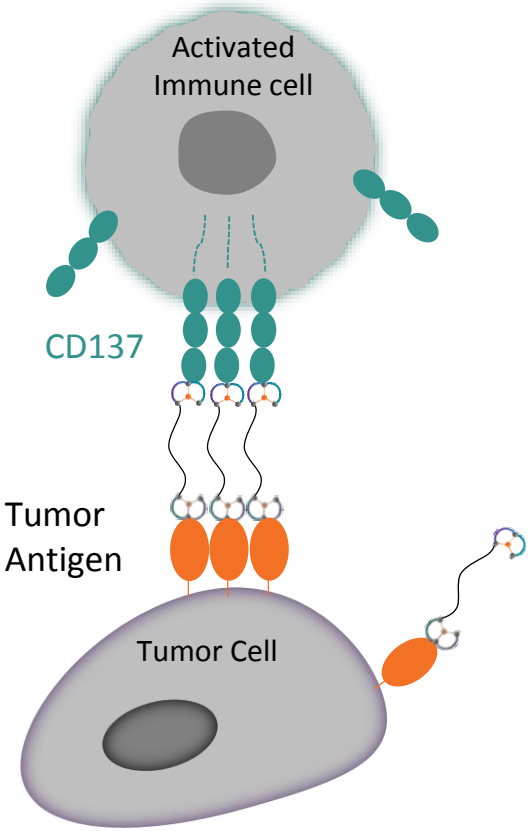
CD137 is member of the TNF superfamily & requires clustering for activation



"All natural" phage peptide
KD = 67nM (Wild Type: WT)

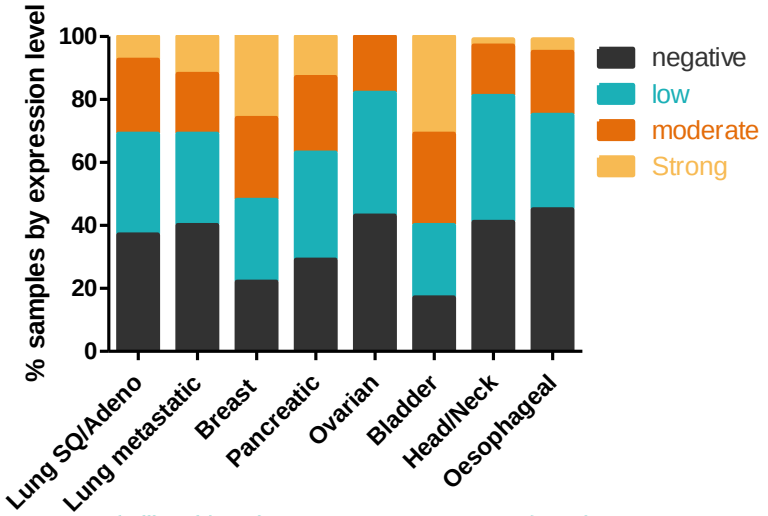
Chemically optimised
KD = 5nM (High Affinity: HA)



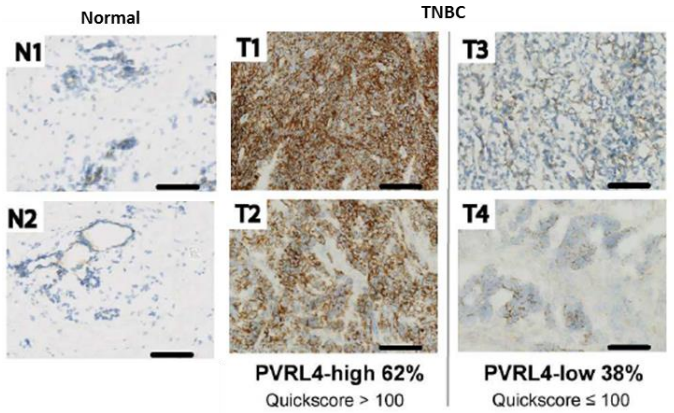


Nectin-4 (PVRL4): Rationale as a tumor antigen

- Nectin-4: cell adhesion molecule; widely expressed during development with restricted expression in adult normal tissue
- Over expressed in numerous tumors of high unmet need; highest frequency in bladder, breast, and pancreatic, but also in lung and esophageal cancers
- Internal work demonstrates co-expression of CD137 in significant subsets of Nectin-4 positive tumors
- Precedented target for bladder cancer; Enfortumab Vedotin (MMAE Nectin-4 ADC) has breakthrough therapy in post platin, post CI bladder cancer
  - ORR 42% (N=125)
- Building internal expression/diagnostic capability

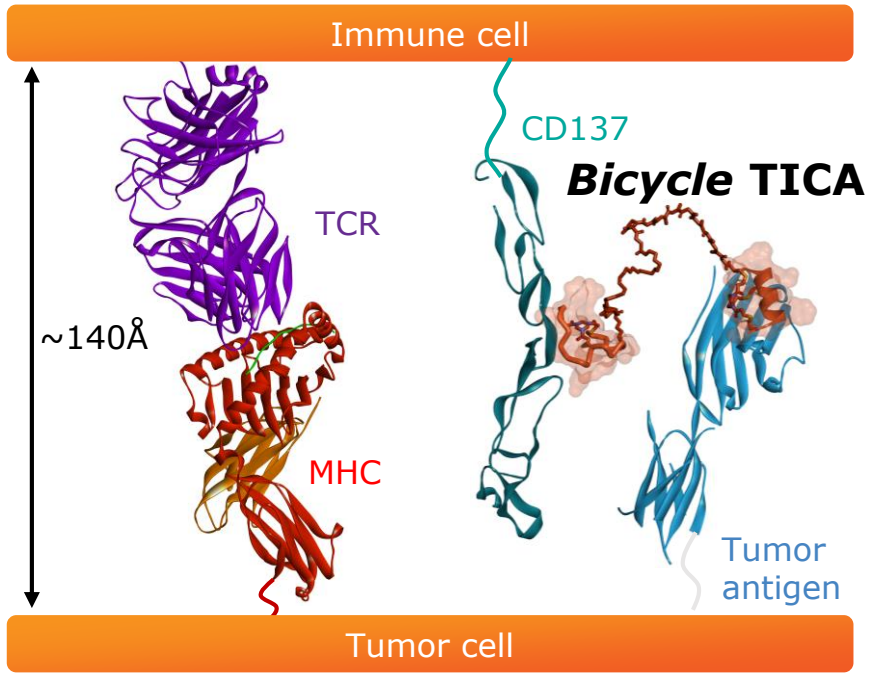


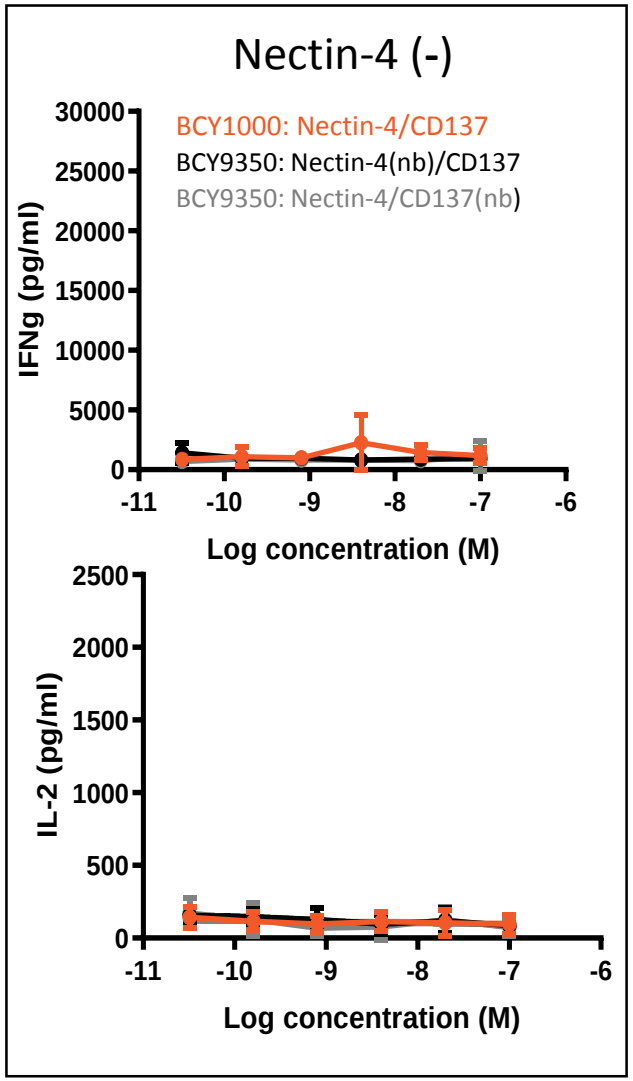
Challita-Eid et al Cancer Res 76: 3003-3013 (2016)

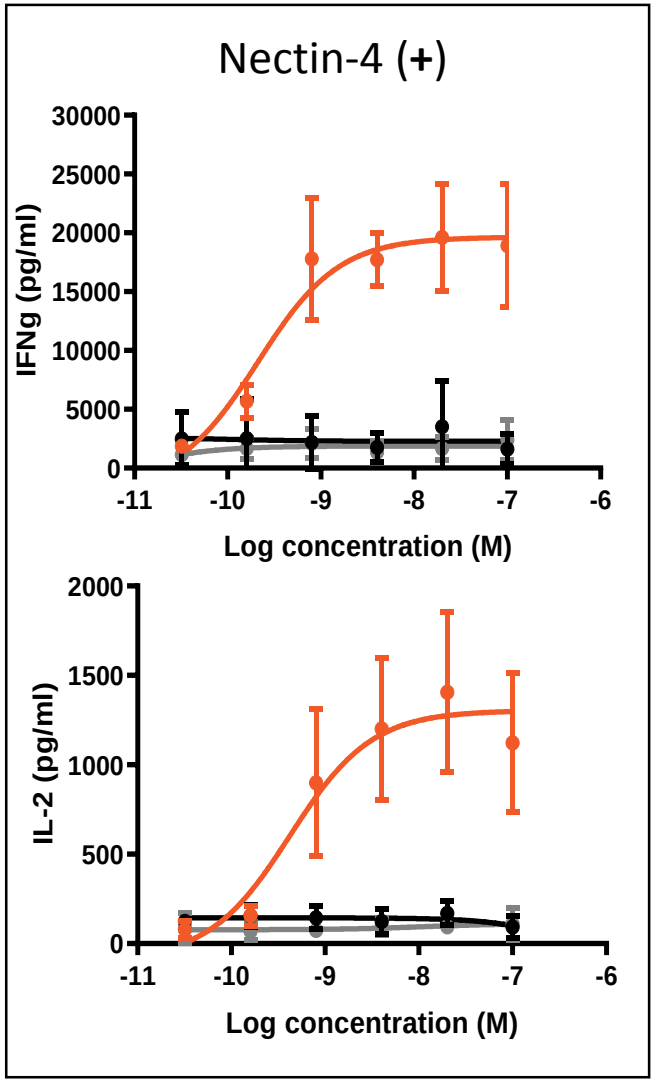


Rabet et al Annals of Oncology 28:769-776 (2017)

Nectin-4/CD137 *Bicycles*® are precisely engineered tumor antigen specific CD137 agonists



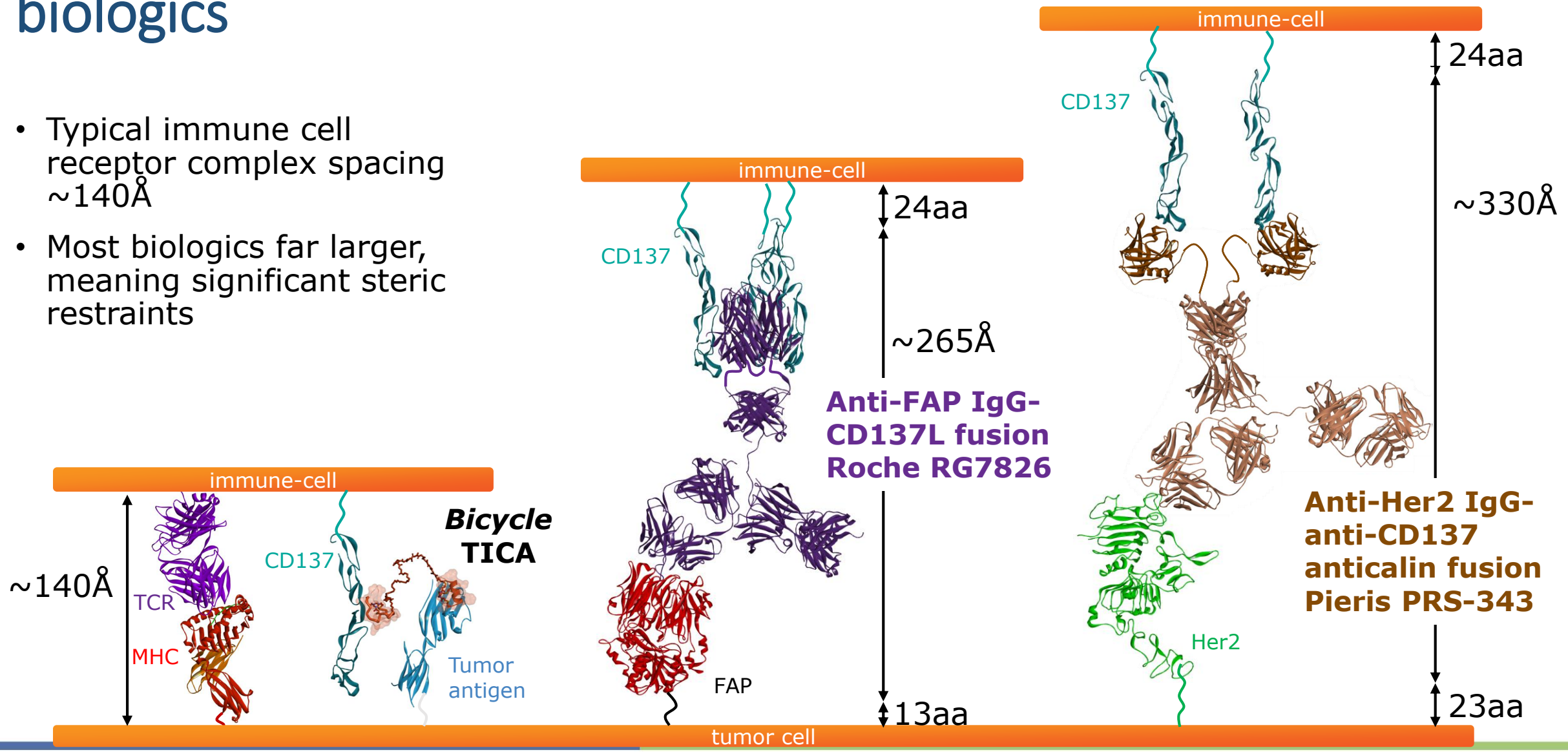




Human PBMC / tumor cell co-culture

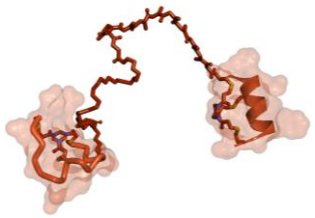
Bicycle® TICAs enable optimum spacing compared to bulkier biologics

- Typical immune cell receptor complex spacing ~140Å
- Most biologics far larger, meaning significant steric restraints



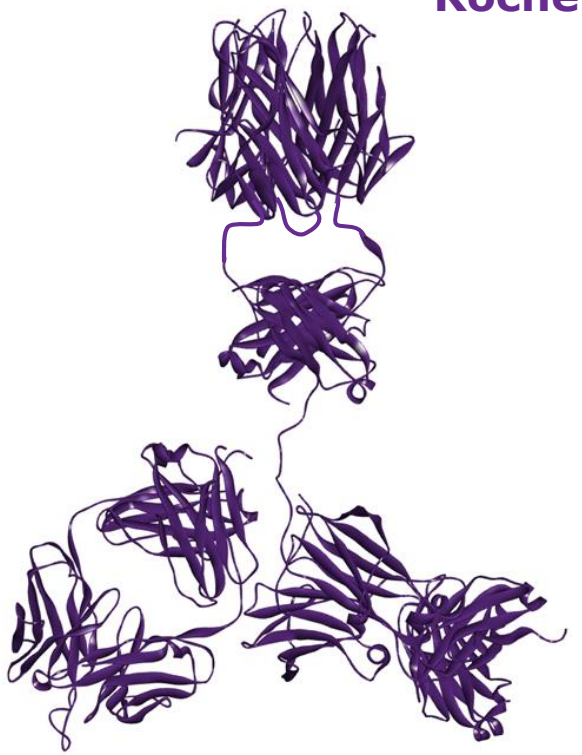
Bicycle® TICAs are ~30x smaller than other targeted agonists

***Bicycle* TICA**



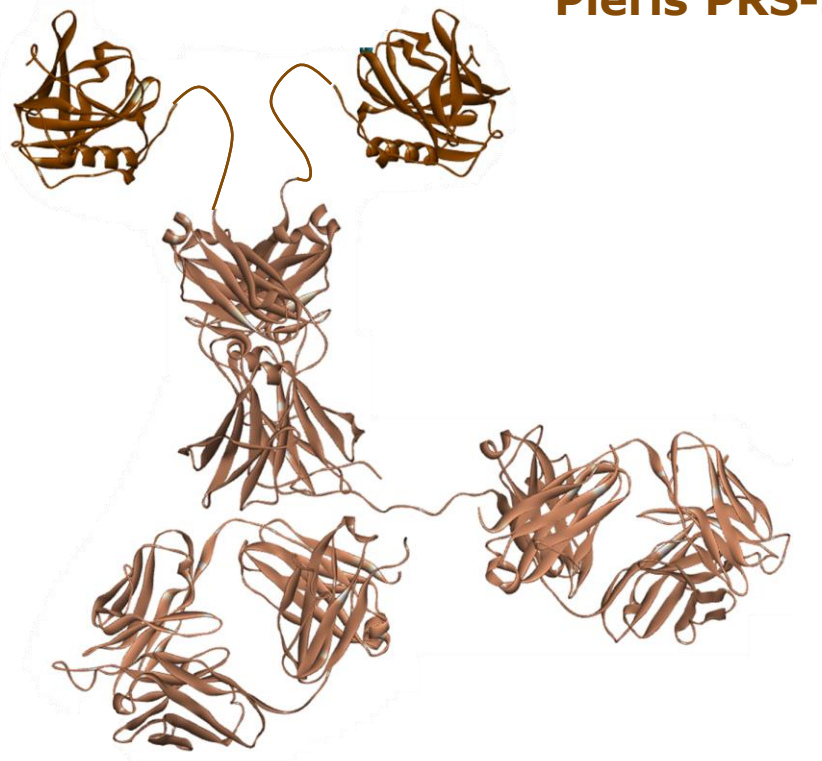
~6kDa

Anti-FAP IgG-CD137L fusion Roche RG7826



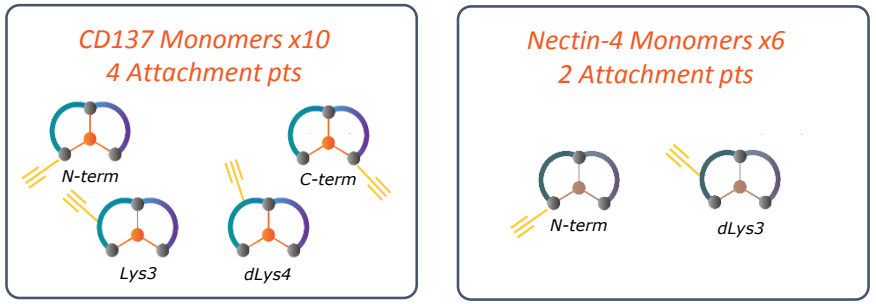
~185kDa

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



~190kDa

Chemical nature of platform allows rapid "dialing in" of properties



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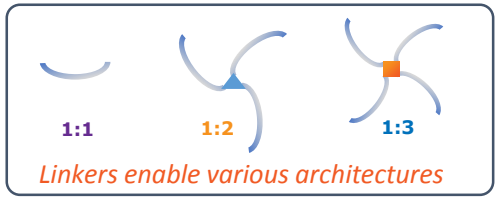
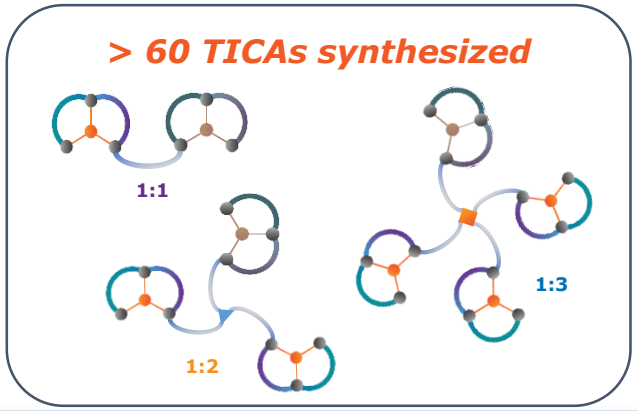
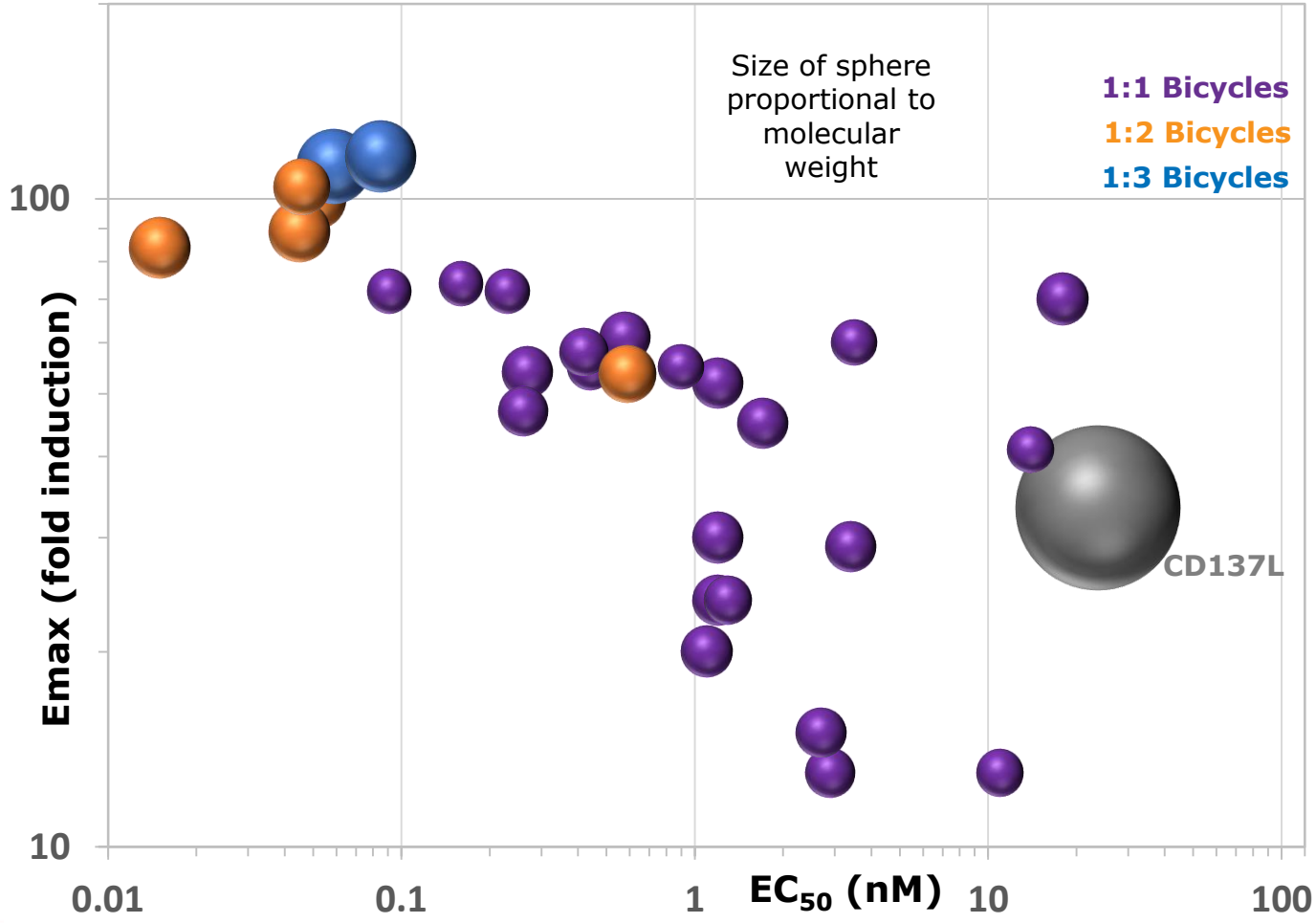


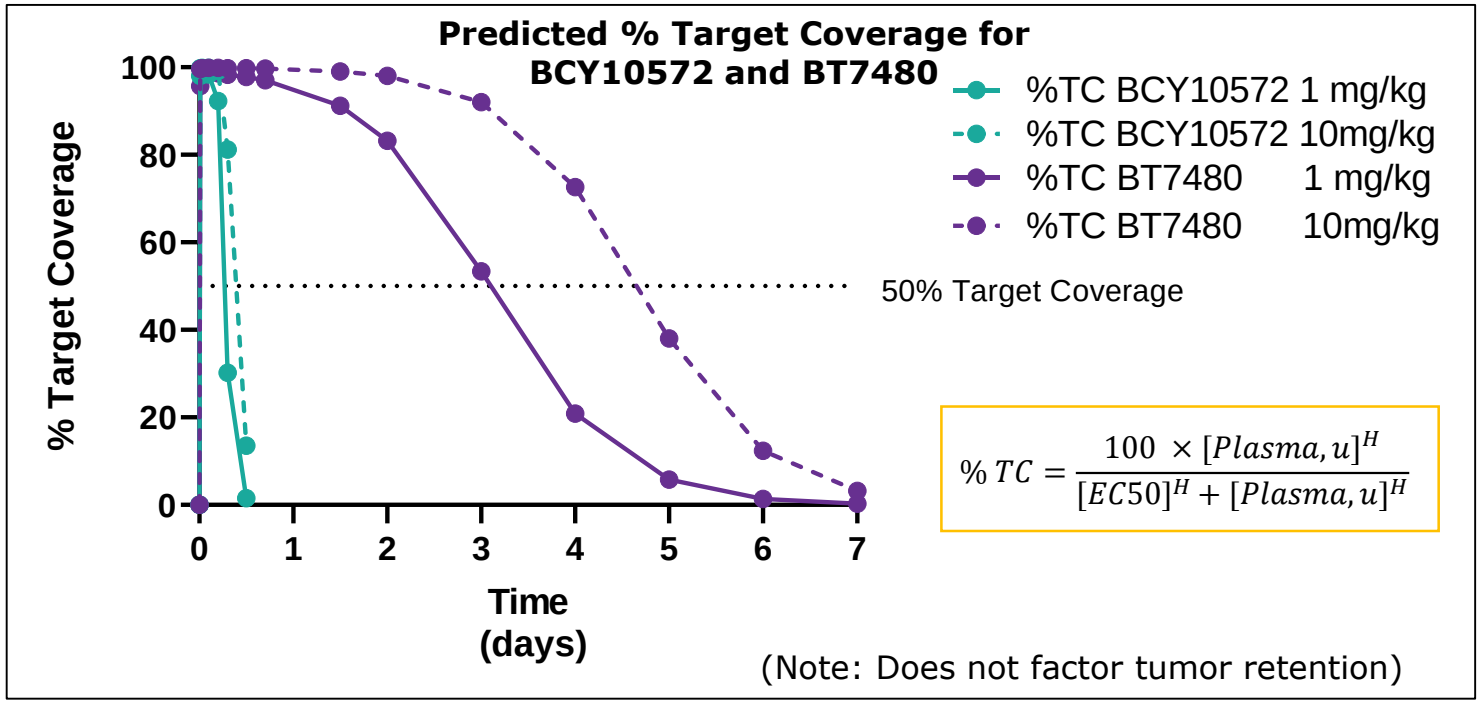


>90 Nectin-4 TICA molecules synthesized in combinatorial manner

Reporter cell assay data for 30 Nectin-4/CD137 TICAs in co-culture with HT1376

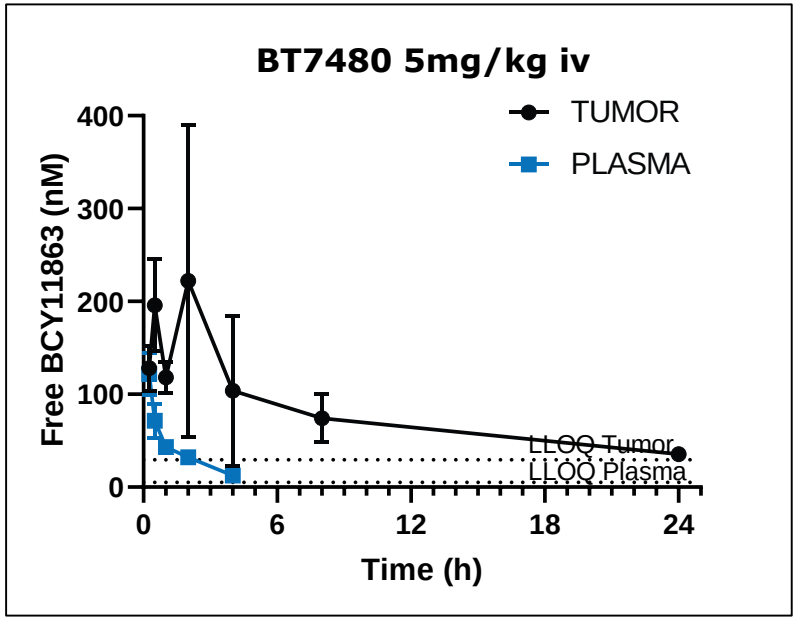


PK can be "tuned"



50% Target coverage is the line above which [Plasma,u] is maintained over [EC50,u]

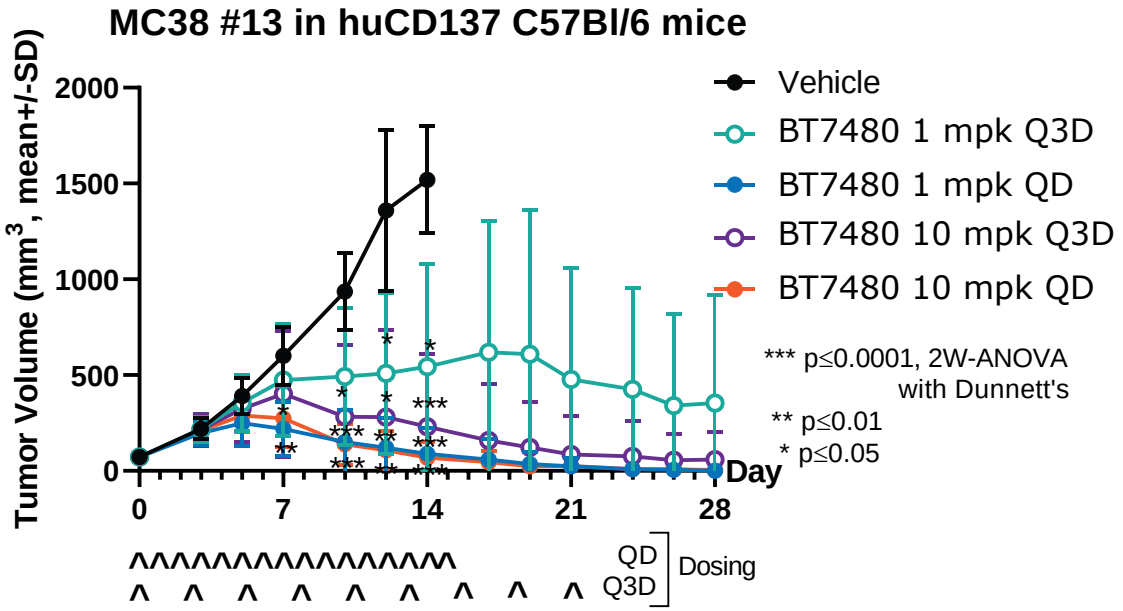
Molecules are selectively retained in Nectin-4 expressing tumors.

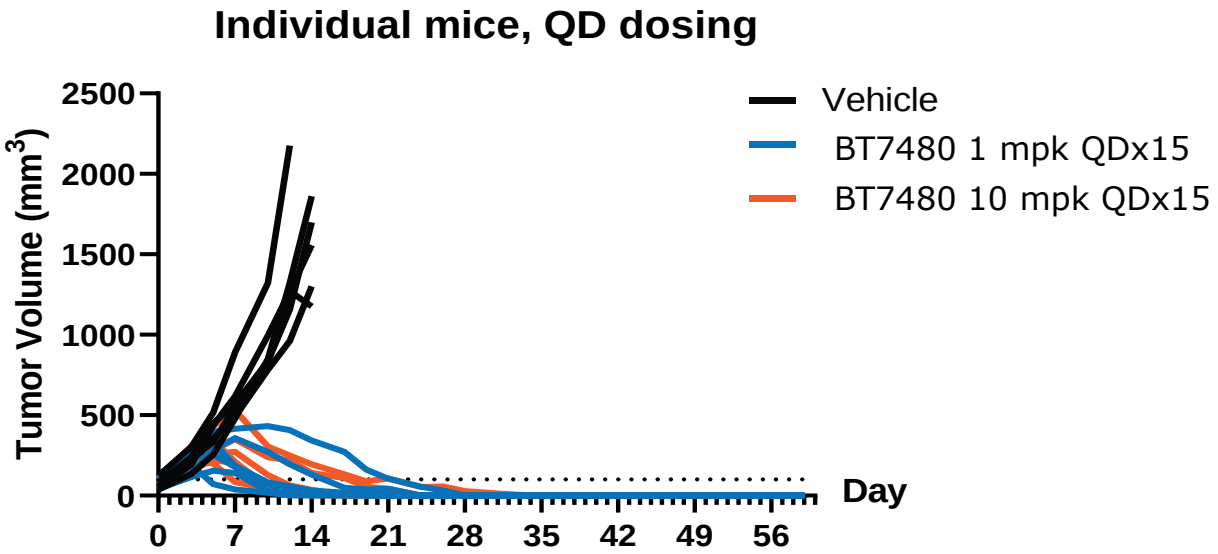


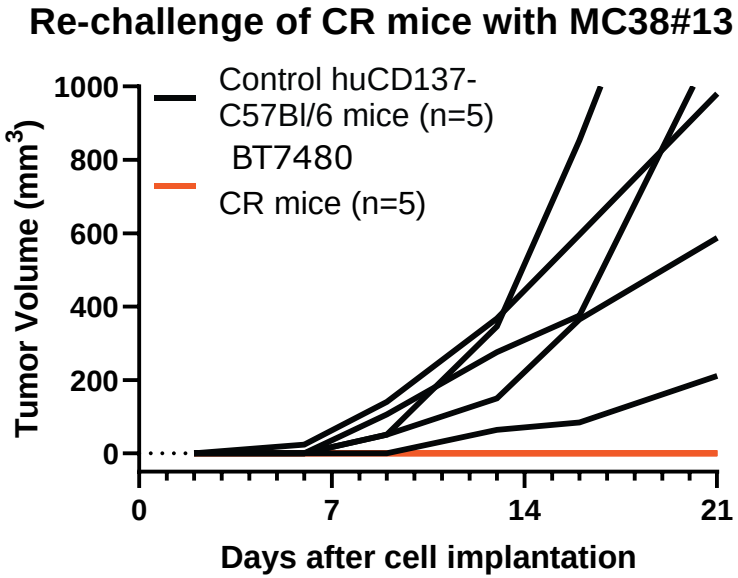
Predicted human PK parameters

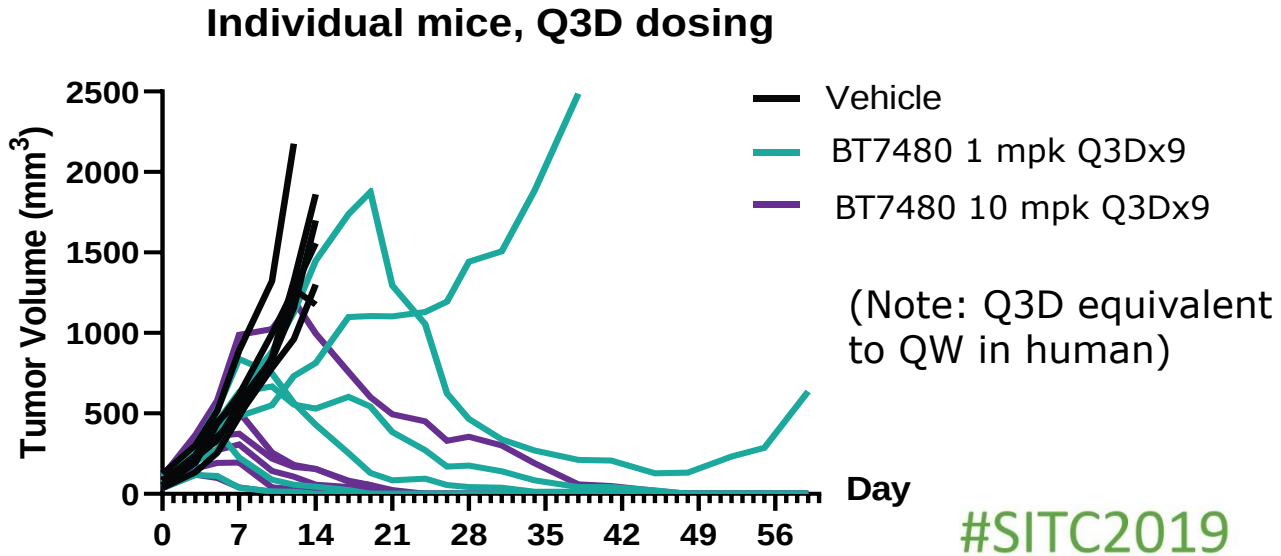
BCY	in vitro EC50(nM)	$t_{1/2}$(h)	CLp (mL/min/kg)	Veff (L/kg)
BCY10572	0.59	0.83	13	0.91
BT7480	0.47	12	1.2	1.2

Intermittent dosing of BT7480 leads to a robust anti-tumor activity

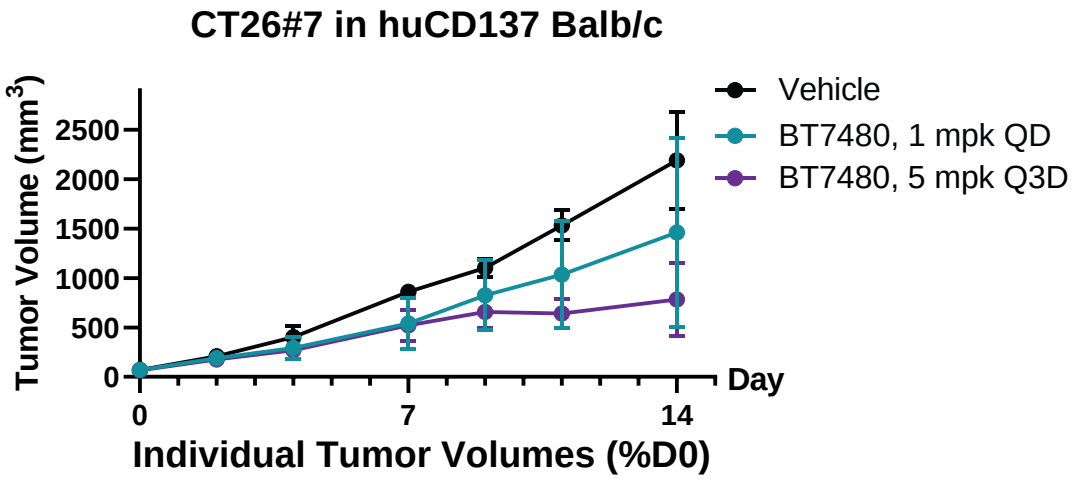


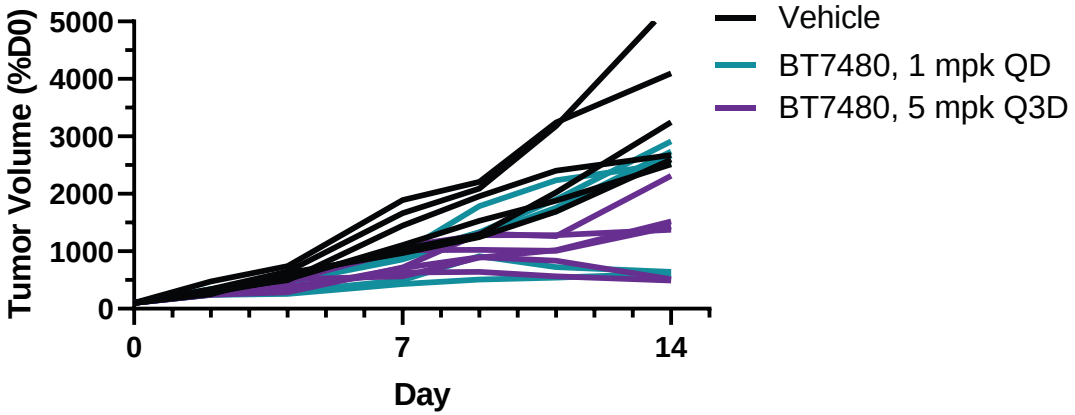


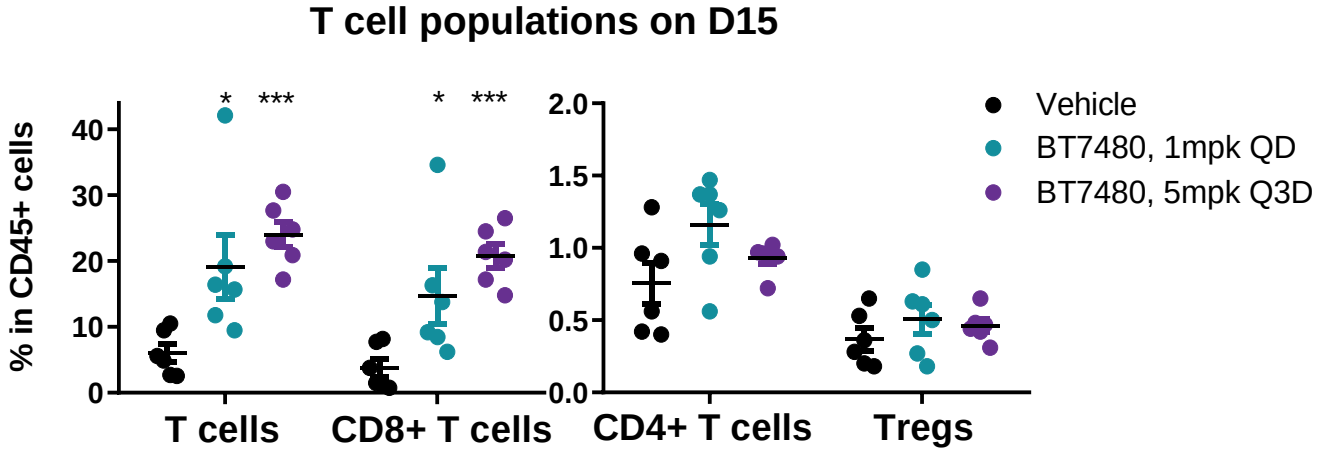


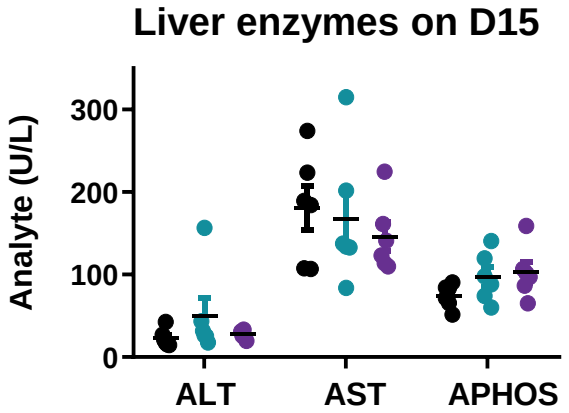


Intermittent dosing of BT7480 leads to an increase in CD8+ T cells without elevations of liver enzymes









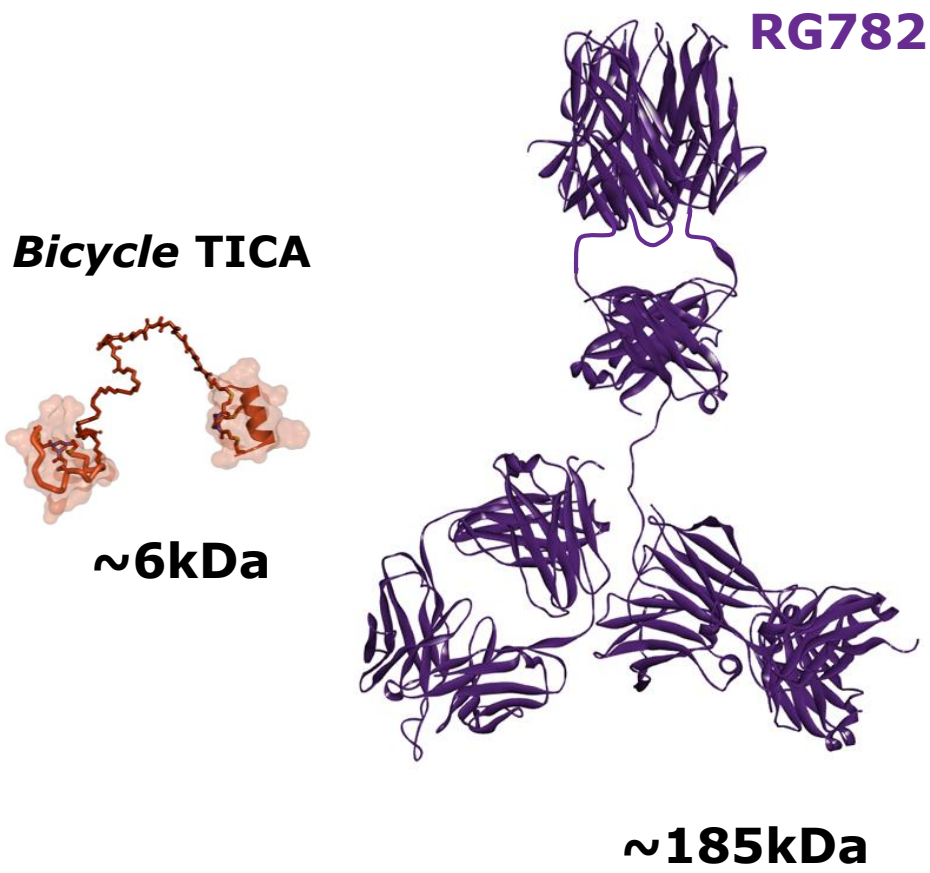
Note: Q3D in mouse equivalent to once per week in human

- Anti-tumor activity of BT7480 was assessed in Nectin-4 overexpressing (engineered) CT26 syngeneic mouse model
- Several responders in both QD and Q3D dosing groups

- By D15, CD8+ T cell population increases significantly
- By D15, No significant changes in AST, ALT and APHOS

Summary

- Bicycle are building a new generation of chemically synthetic (NCE) tumor antigen targeted CD137 agonists.
- These are much smaller than biologics, rapidly tumor penetrant, and tailored to the geometry of the immune synapse .
- Potency and pharmacokinetics are “tunable.”
- Our lead Nectin-4/CD137 TICA (BT7480) induces complete regressions and resistance to re-challenge in immune competent models with intermittent dosing.
- Approach is generalizable.



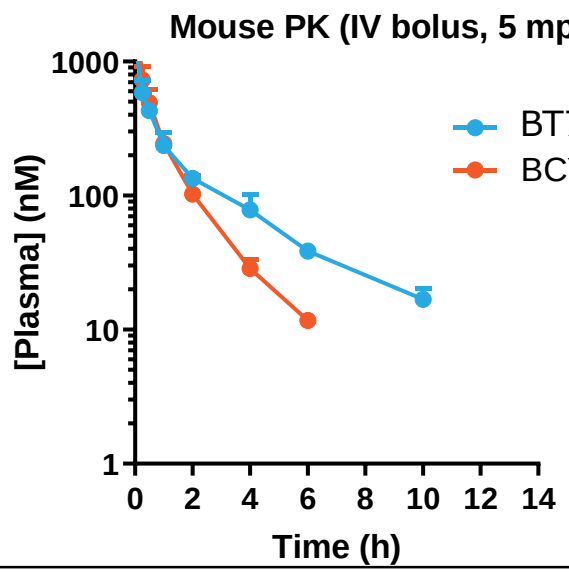
See Posters **P782**, **P794 Saturday!**

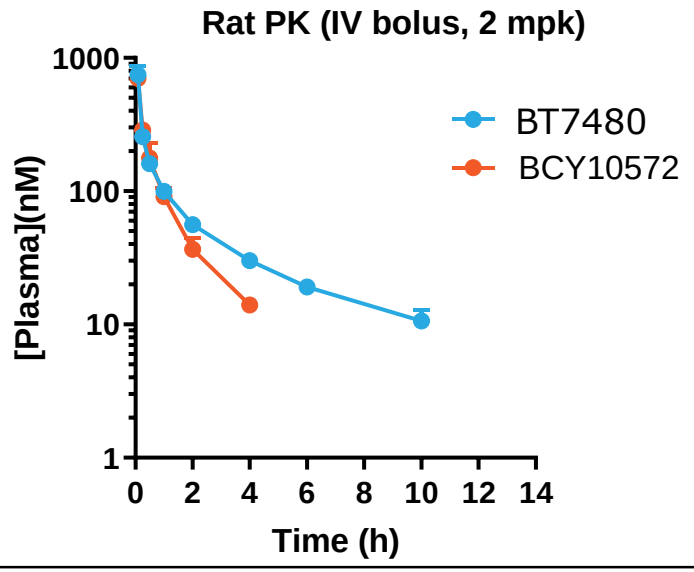
Thanks!

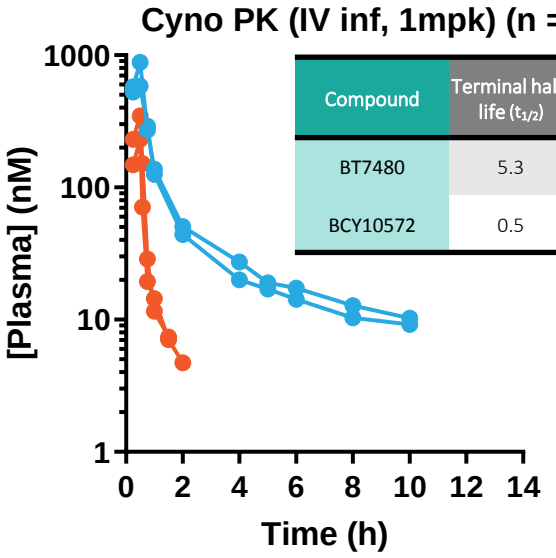
Bicycle US

Bicycle UK

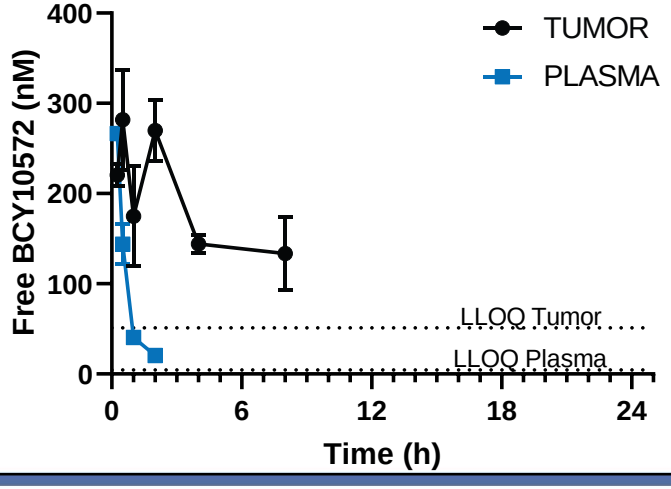
Pharmacokinetics can be readily "tuned"

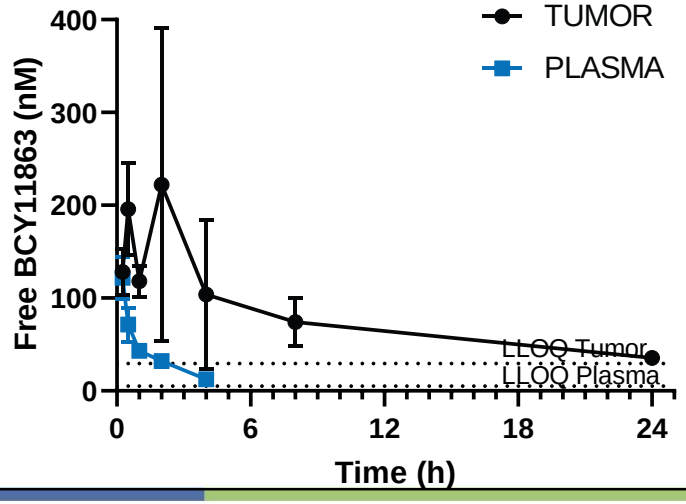






Compound	Terminal half-life ($t_{1/2}$)	CLp (mL/min/kg)	Vss (L/kg)
BT7480	5.3	3.3	0.62
BCY10572	0.5	30	0.56





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