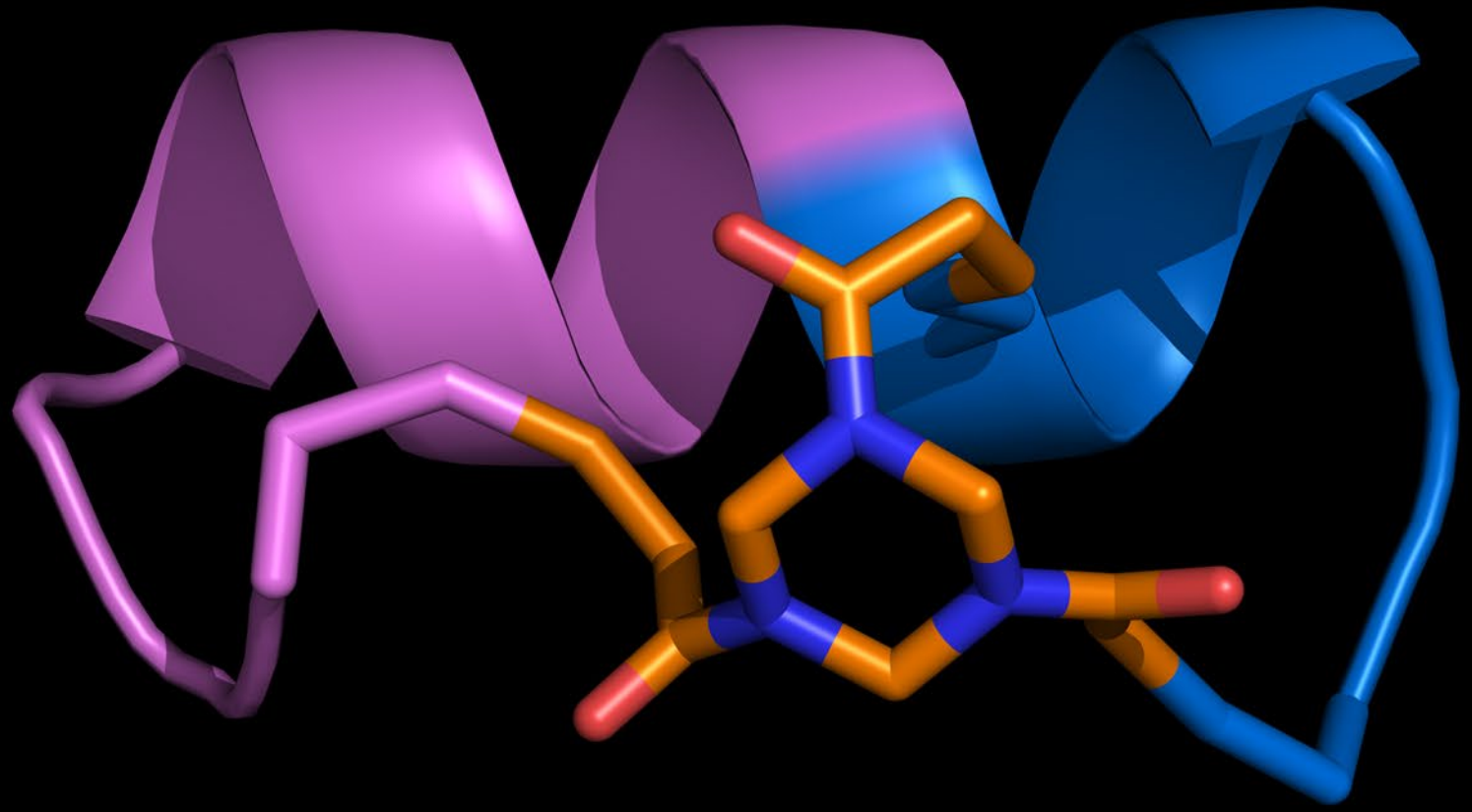
Bicycles as precision guided therapeutics

James Cooke, Associate Director, Discovery



Bicycle®

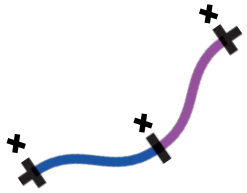
Forward-looking statements and disclaimer

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 current and prospective product candidates, planned clinical trials and preclinical activities, 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 Annual Report on Form 10-K, filed with the Securities and Exchange Commission (SEC) on February 28, 2023, 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.

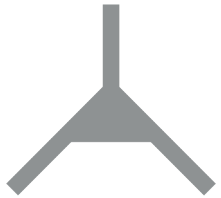
This presentation does not constitute an offer to sell or a solicitation of an offer to buy securities, nor shall there be any sale of any securities in any state or jurisdiction in which such offer, solicitation or sale would be unlawful prior to registration or qualification under the securities laws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

Bicycle® - a unique and disruptive therapeutic modality

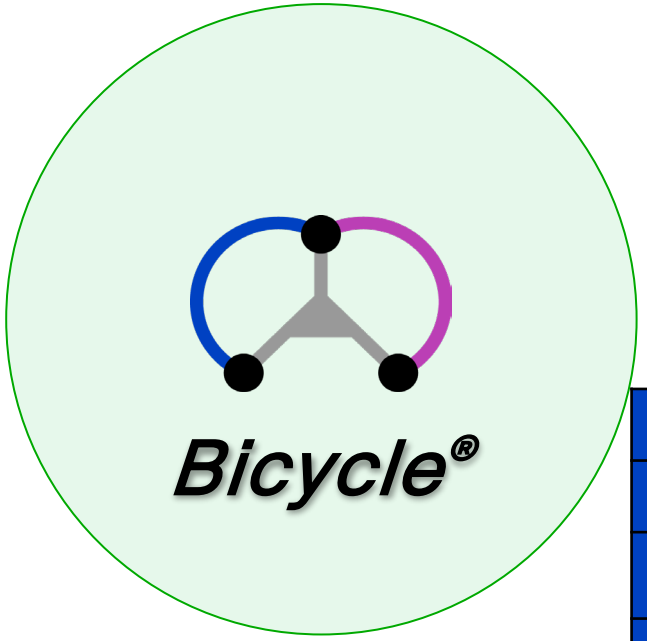


Short linear peptide

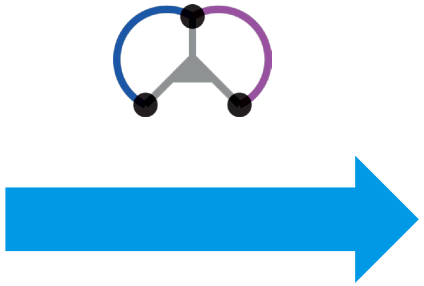
+



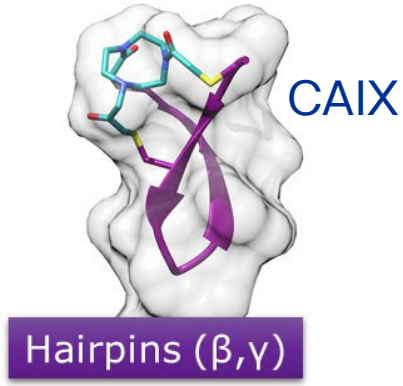
Scaffold

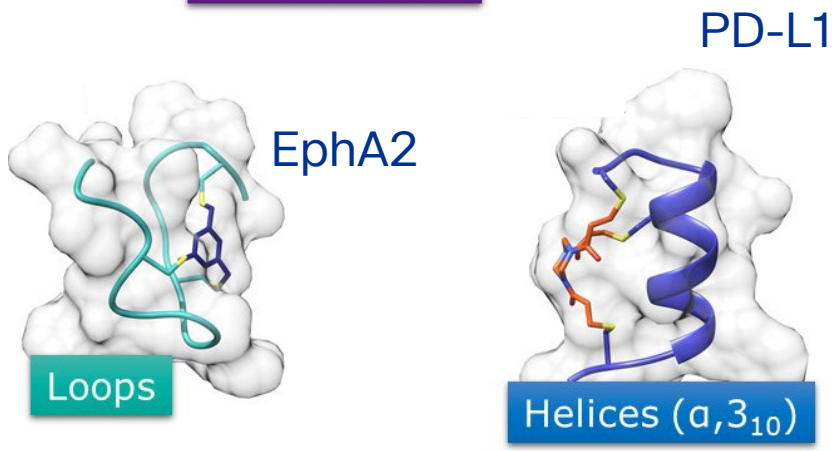


High affinity
Absolute selectivity



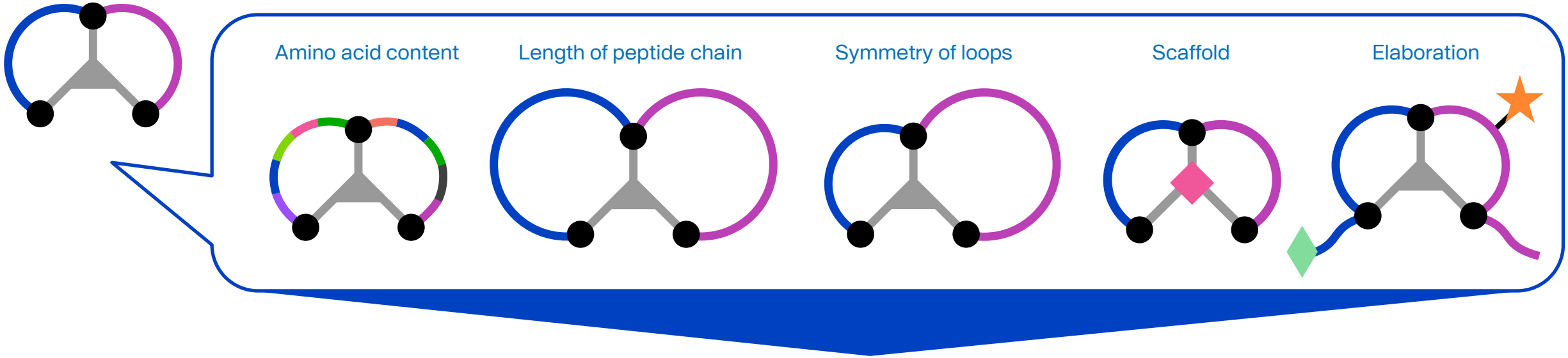
Small size	1.5-2kDa
Specificity	High
Chemical synthesis (NCEs)	Yes
Rapid tissue penetration	Yes
Complex protein targets druggable	Yes
Routes of administration	IV/SQ/IT/IN
Route of elimination	Renal
Immunogenic	No



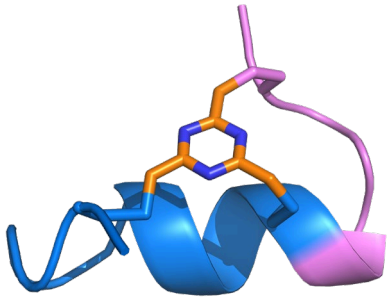


Biologically relevant 3D structures

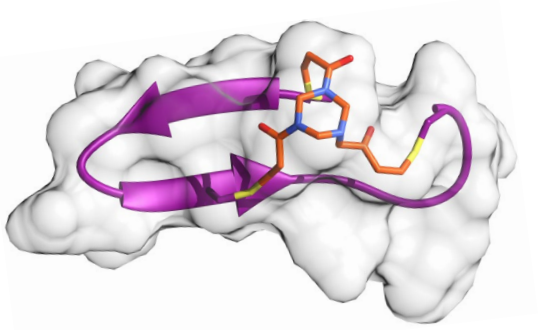
Bicycles have 5 dimensions of variation



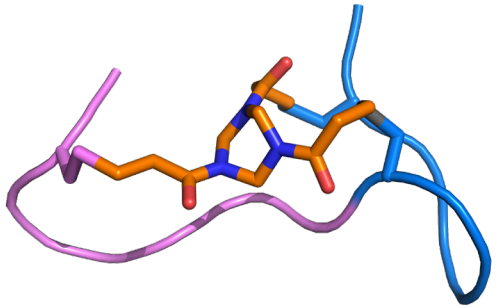
Tremendous structural diversity of molecules to successfully drug targets



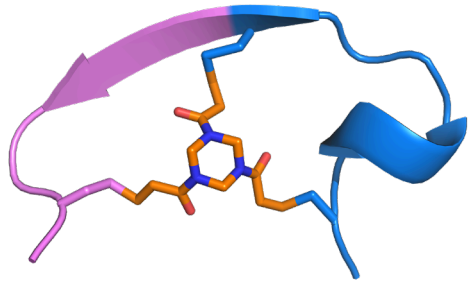
- Helical



- Hairpin



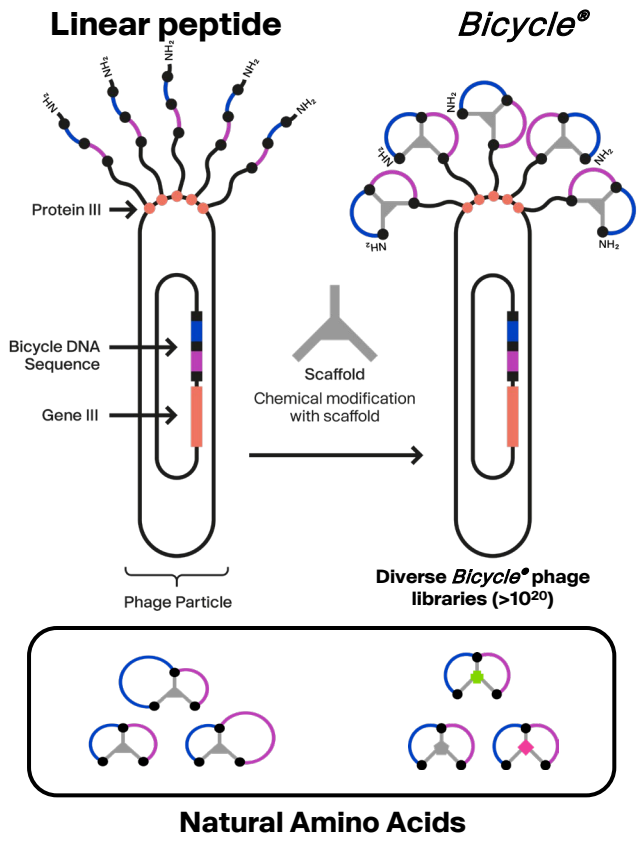
- Extended



- Hybrid

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

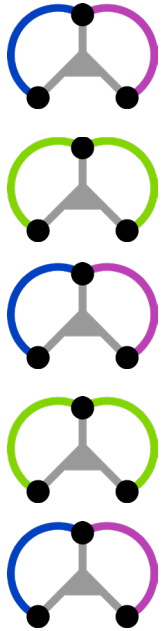
Bicycle® Phage Display - Discovery



Peptide & Medicinal Chemistry

Optimize *Bicycle*® *monomers*

Non-natural Amino Acids

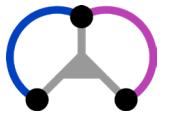


Tumor Targeting and Effector *Bicycles*

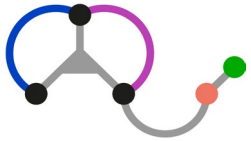
Build and Optimize Therapeutic *Bicycles*

Easy conjugation of Linkers and Payloads

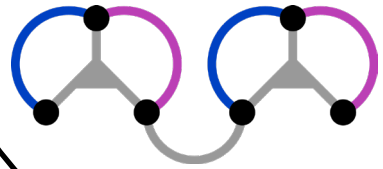
Potential *Bicycle*® Medicines



Monomeric *Bicycles*

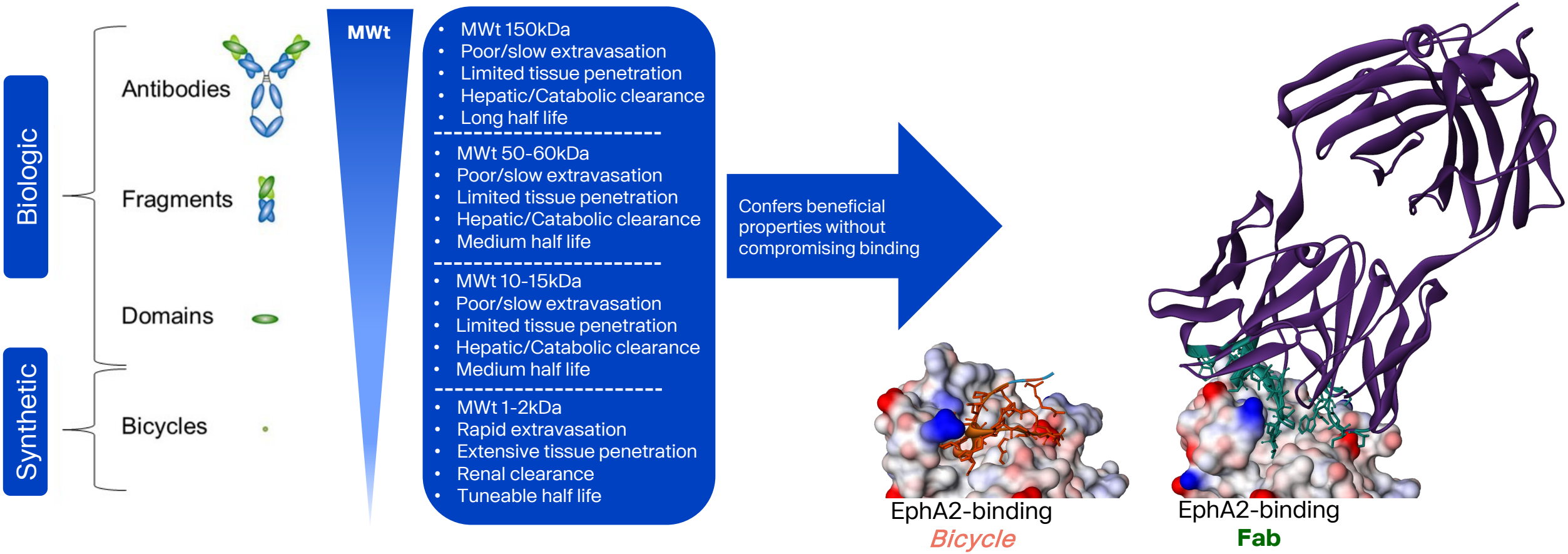


Targeted Drug Conjugates

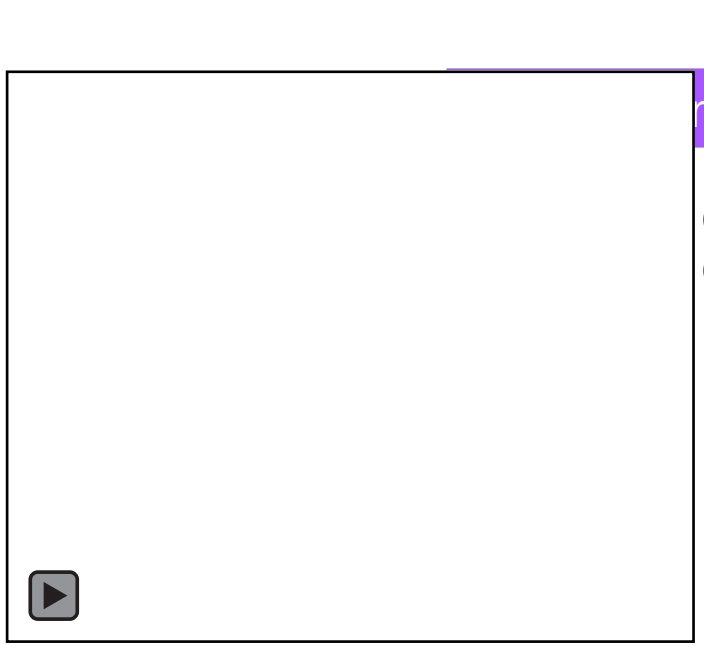


Targeted/ Multi-specific *Bicycles*

What are Bicycles and why are they different from biologics?

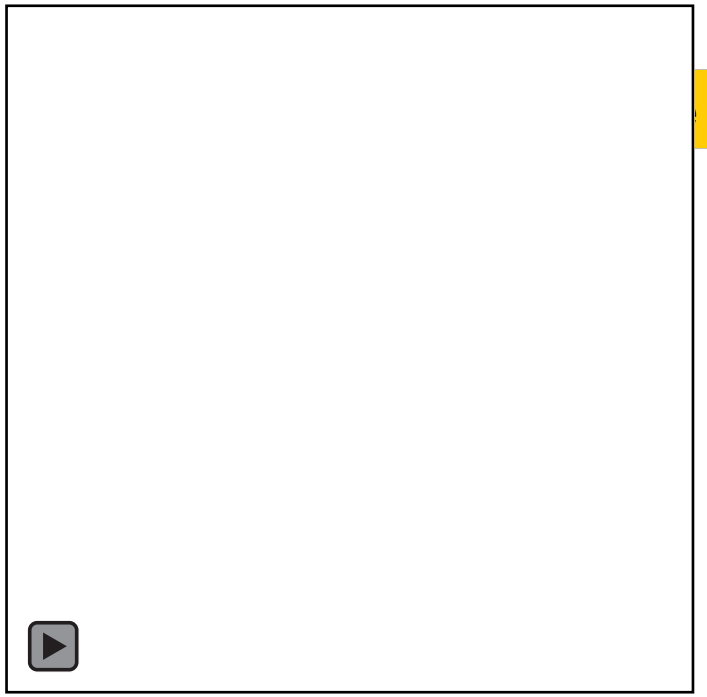


.....and why are they different from small molecules?



mide

CA IX K_i = 25 nM
CA XII K_i = 6 nM



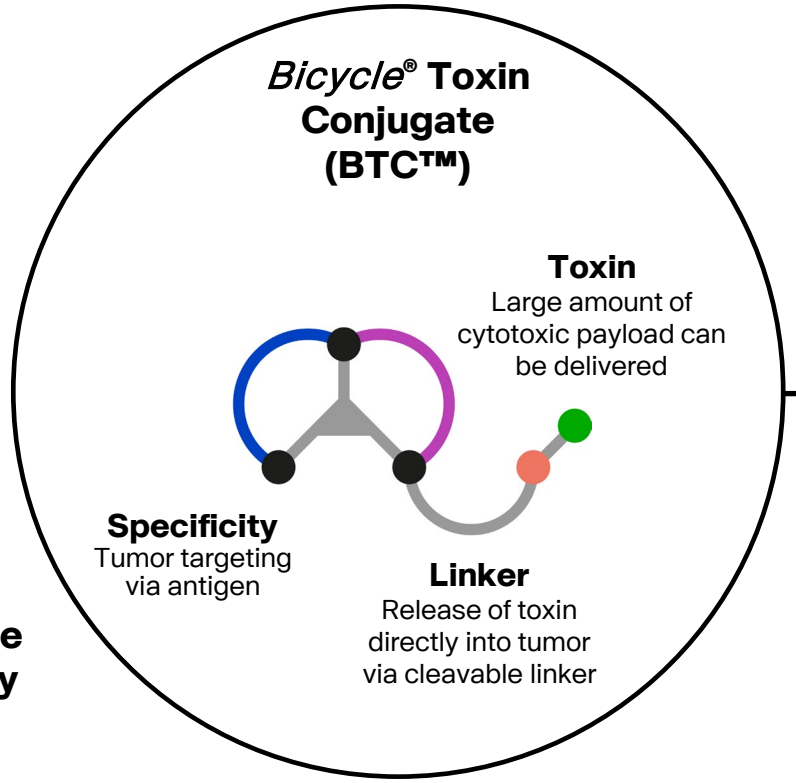
CA IX K_i = 7.5 nM
CA XII K_i > 2000 nM

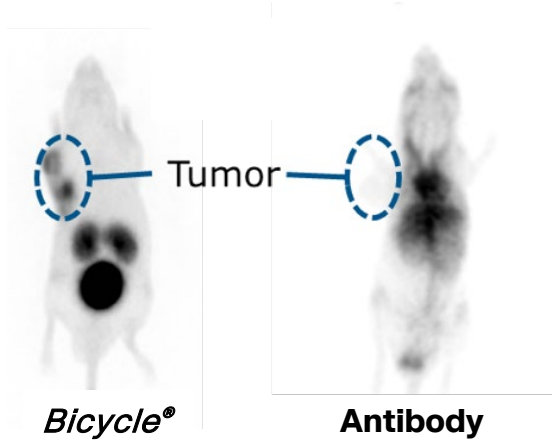
large molecular footprint drives affinity and selectivity between close homologues

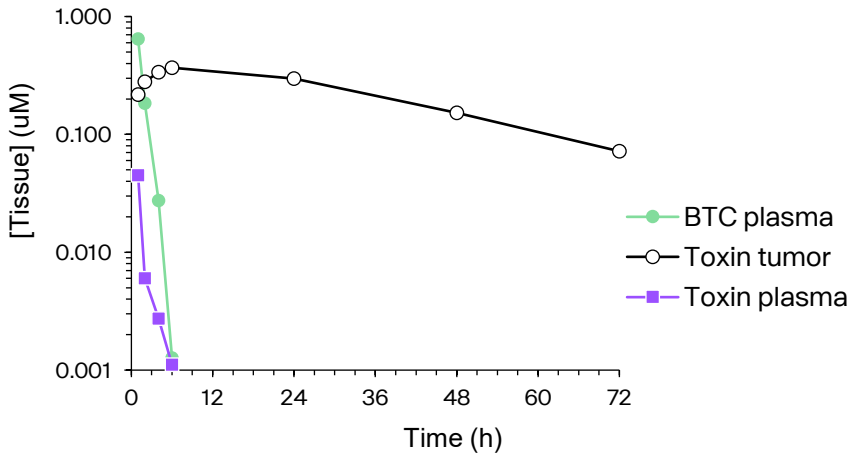
BTC™ preclinical data – effective delivery of toxin payload to tumors

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

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







The properties that make *Bicycles* ideal for toxin delivery also make them ideal for immune agonism, but for different reasons

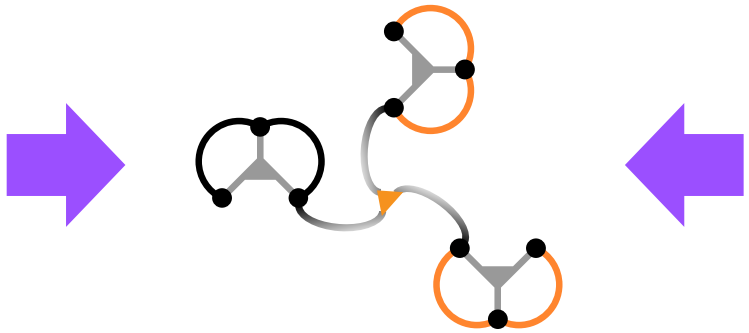
- In the body, activating signals (agonists) are local, rapid, and then stop
  - Cytokines, neurotransmitters, stress hormones
- Sustained (pathologic) signaling can lead to desensitization and dysregulation

Bicycles match the biology

precision-guided (local)
distribute quickly (rapid)
cleared rapidly (stop)

Localize action to the tumor

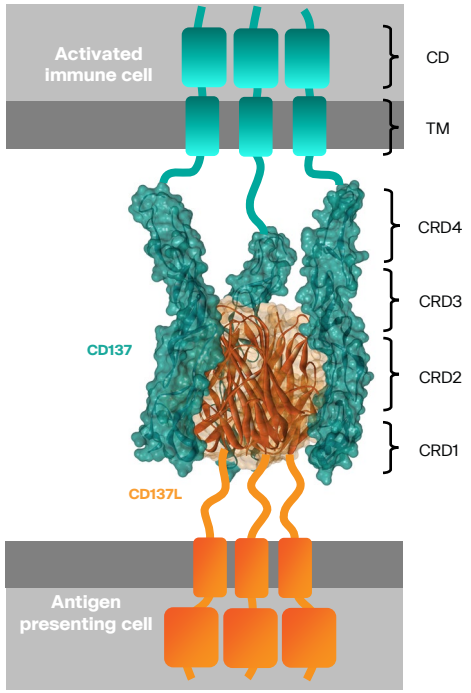
We choose targets that are present in solid tumors not well-served by current therapies



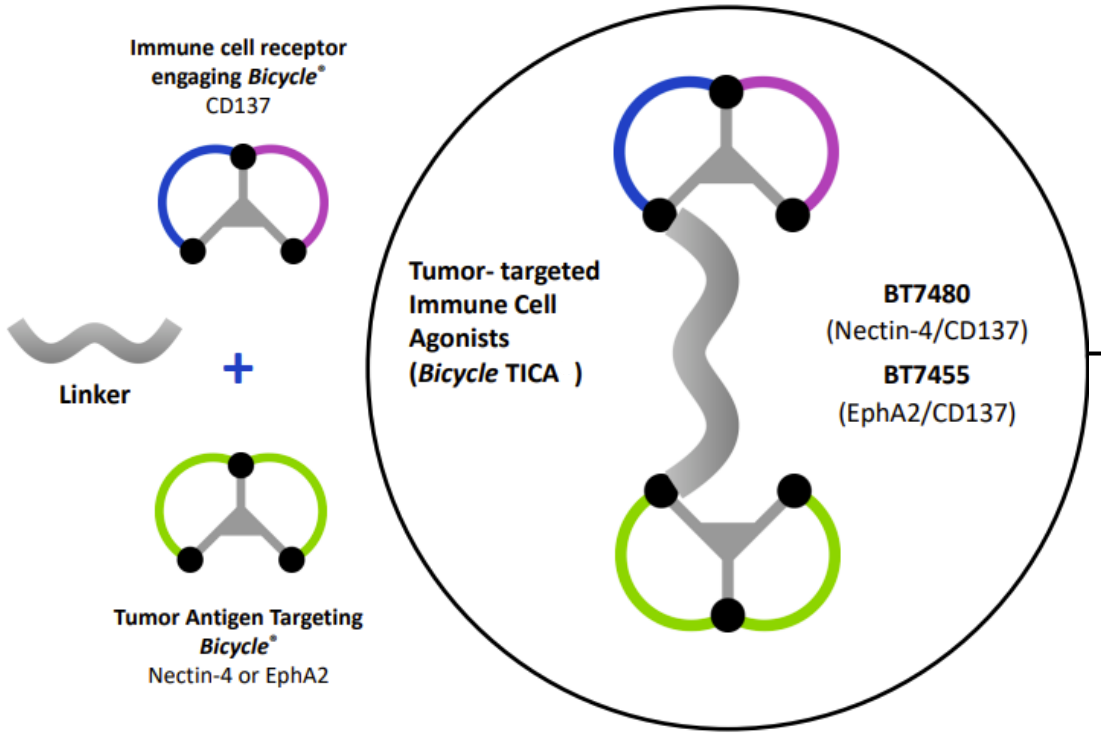
Cause activation of immune cells

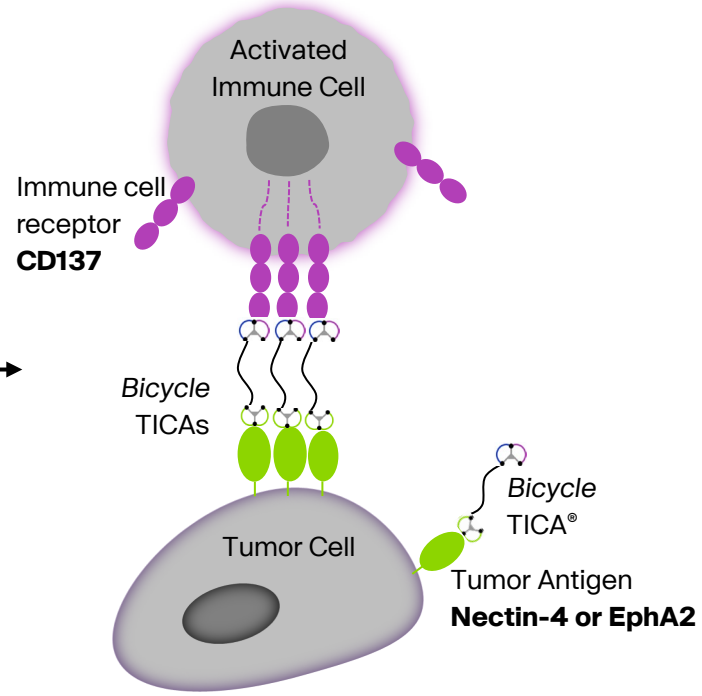
We choose targets where knowledge of human biology says that activation is likely to help, and where other drug technologies, like antibodies, aren't working

Bicycle TICA™– tumor-targeted immune cell agonists deliver immune agonism to tumors



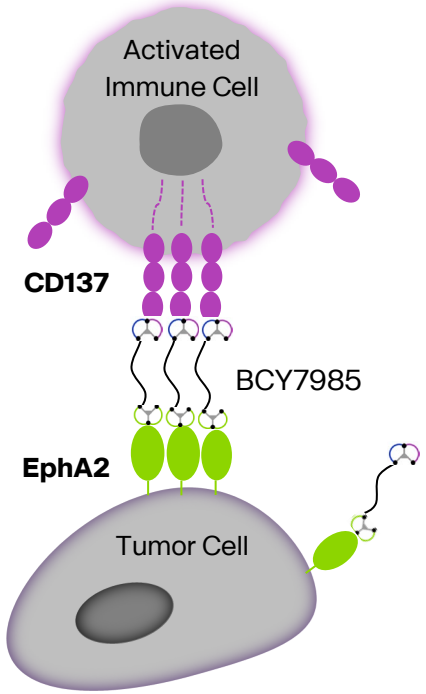
Activation induced by clustering of **CD137** by trimeric **CD137L**



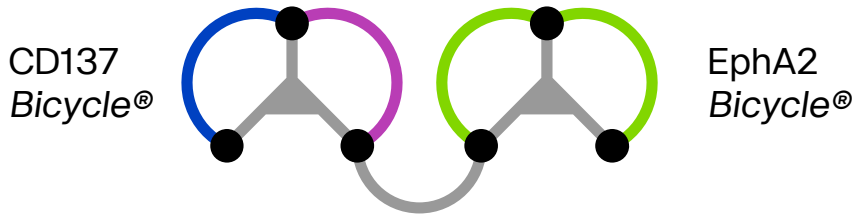


CD137 clustering induced by tumor antigen drives stronger immune cell potency

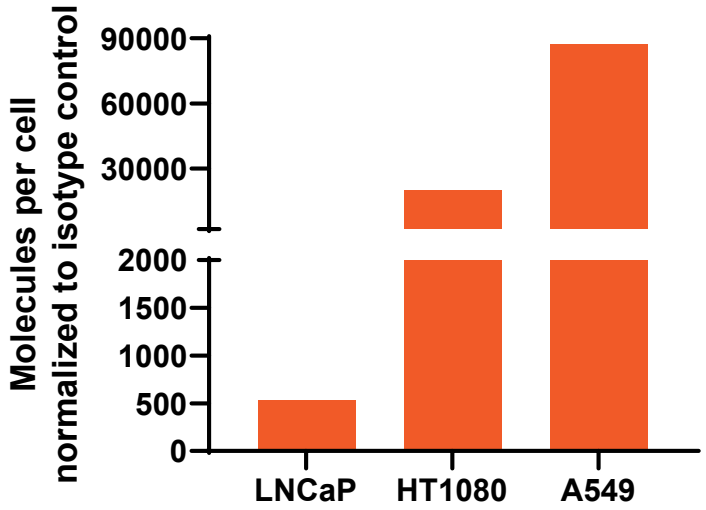
Preclinical in vitro proof of concept with the first EphA2/CD137 molecule



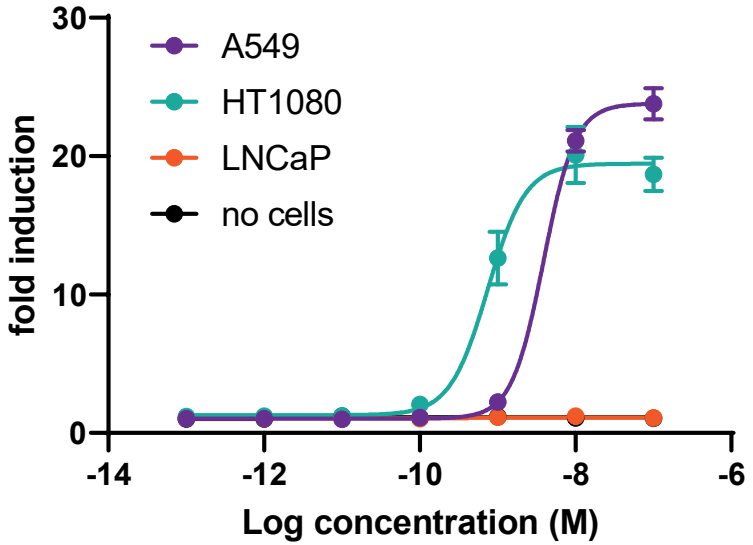
Cancer cells expressing high levels of EphA2

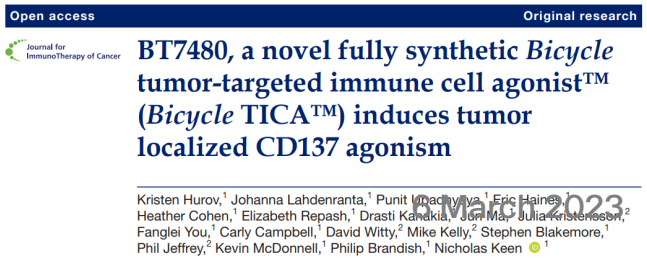


EphA2 expression



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



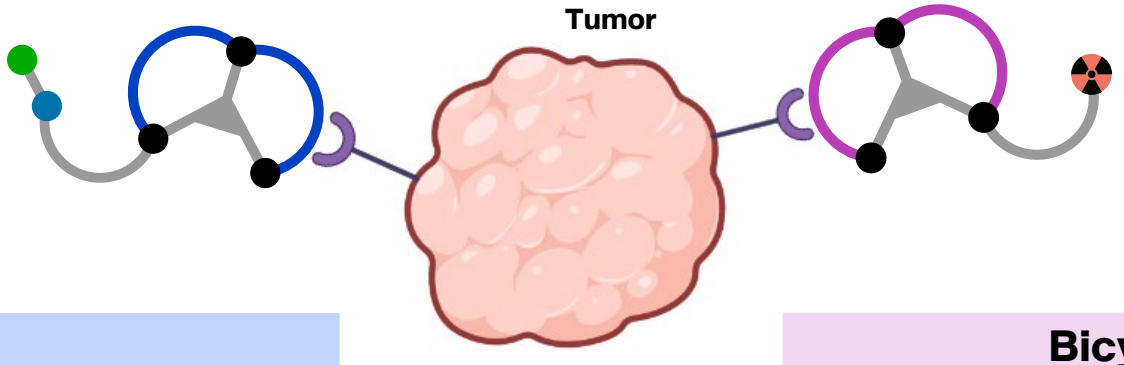

Open access Original research

Journal for ImmunoTherapy of Cancer

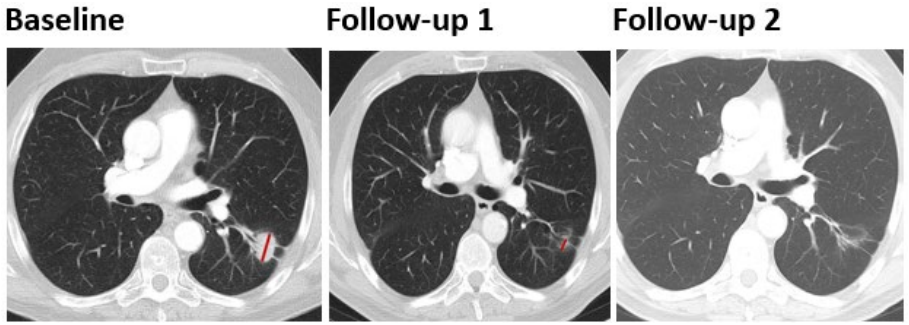
BT7480, a novel fully synthetic *Bicycle* tumor-targeted immune cell agonist™ (*Bicycle* TICA™) induces tumor localized CD137 agonism

Kristen Hurov,[1] Johanna Lahdenranta,[1] Punit Upadhyaya,[1] Eric Haines,[1] Heather Cohen,[1] Elizabeth Repash,[1] Drasti Kankia,[1] Jon Ma,[1] Julia Kristensen,[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]

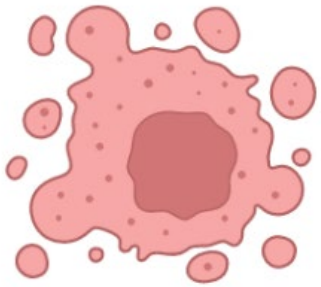
Bicycles have demonstrated preliminary clinical anti-tumor activity delivering cytotoxic payloads and appear ideally suited to delivering radionuclide payloads



Bicycle Toxin Conjugates® (BTCs)



- BT8009 complete responder

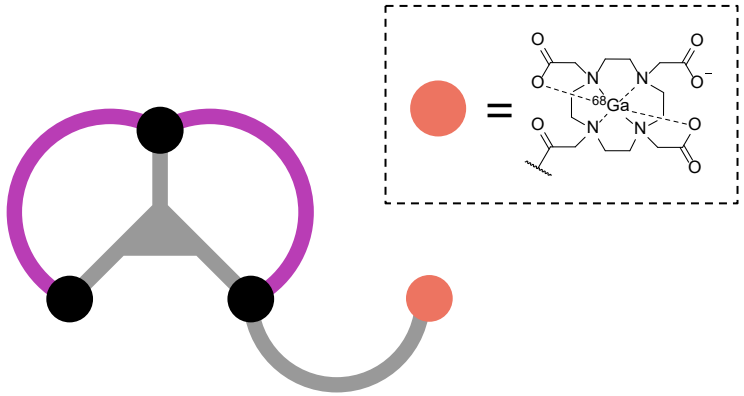


Tumor cell death

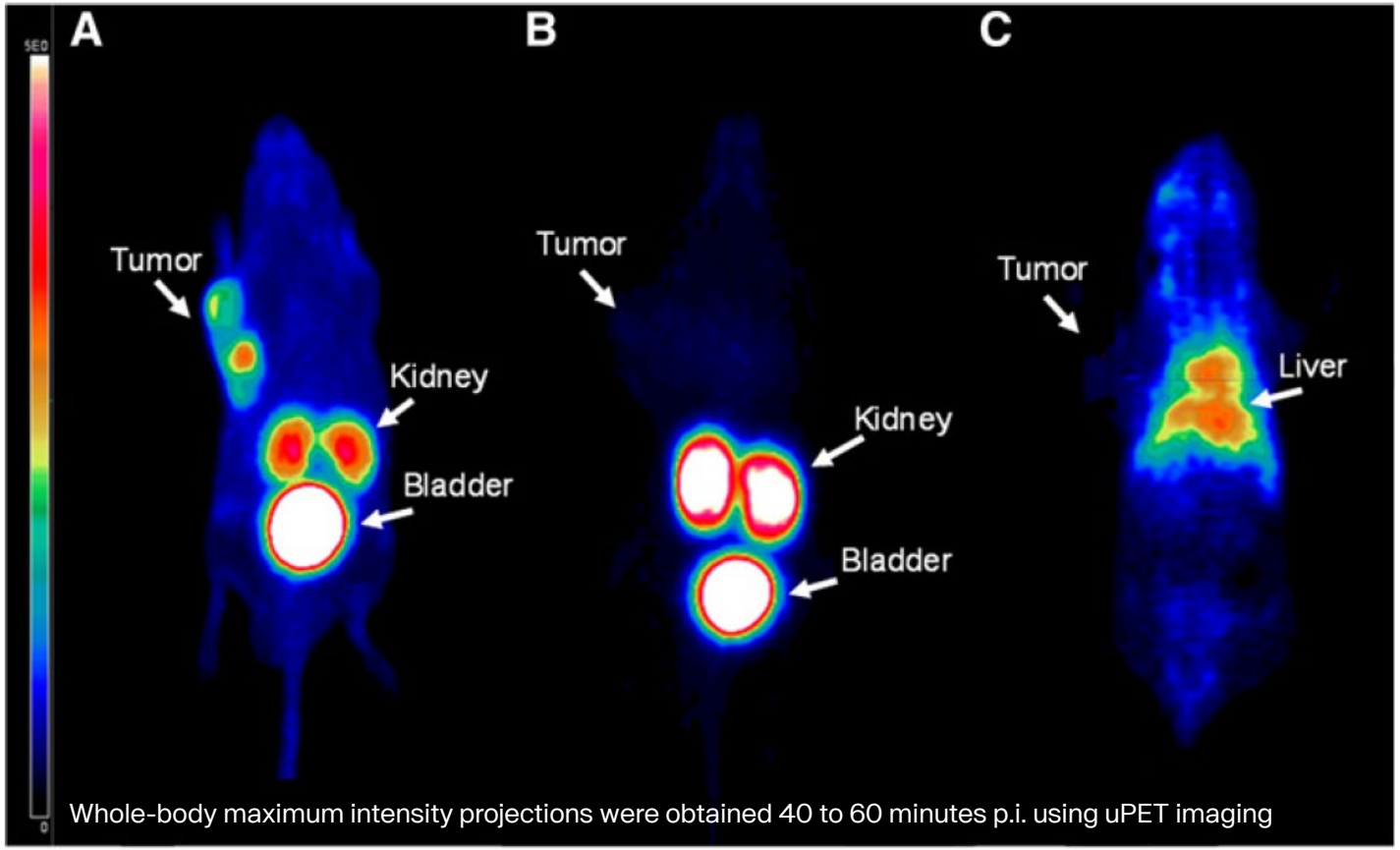
Bicycle Radionuclide Conjugates (BRCs)

- Differentiated MOA (DNA damage)
- Highly potent payloads
- Potentially effective in different patient populations / cancers
- Portfolio risk diversification

MT1-MMP targeting BRC shows far superior tumor uptake and contrast versus mAb in mouse model



- MT1-MMP overexpressed in variety of cancers (non–small cell lung, gastric and breast)

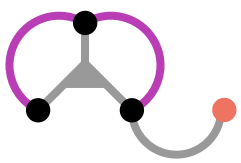


Convergence and Technologies

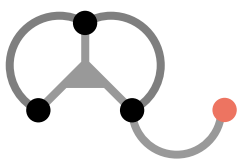
Cancer Research

Bicyclic Peptides as a New Modality for Imaging and Targeting of Proteins Overexpressed by Tumors

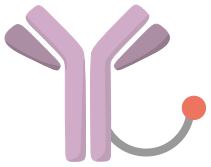
Matthias Eder[1,2], Silvia Pavan[3], Ulrike Bauder-Wüst[4], Katerine van Rietschoten[3], Ann-Christin Baranski[1,2], Helen Harrison[3], Spencer Campbell[3], Catherine L. Stace[3], Edward H. Walker[3], Liuhong Chen[3], Gavin Bennett[3], Gemma Mudd[3], Ursula Schierbaum[5], Karin Leotta[5], Uwe Haberkorn[5,6], Klaus Kopka[4], and Daniel P. Teufel[3]



MT1-MMP targeting BRC

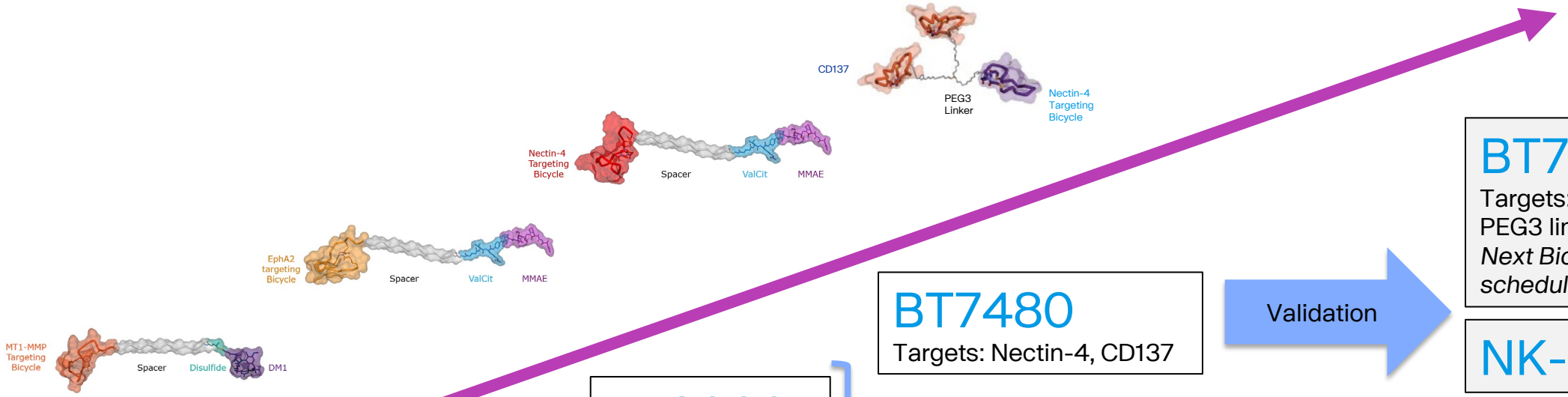


Non-binding BRC



MT1-MMP targeting mAb conjugate

Summary and looking to the future



BT1718
Target: MT1-MMP
DM1 payload

BT5528
Target: EphA2
MMAE payload

BT8009
Target: Nectin-4
MMAE payload

BT7480
Targets: Nectin-4, CD137

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®