Combinatorial Optimization of Degrader-Antibody Conjugates Enabled by Automation

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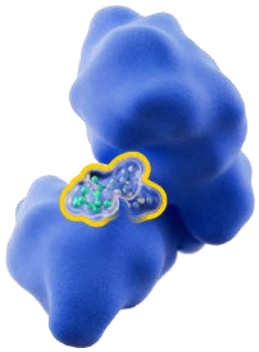
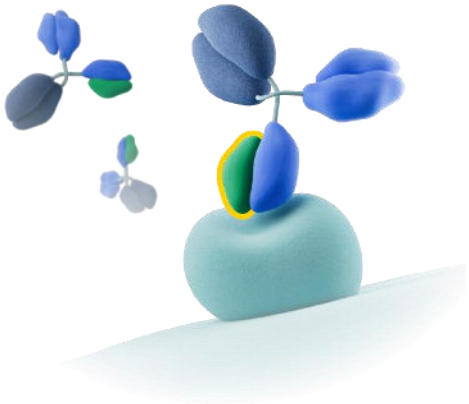
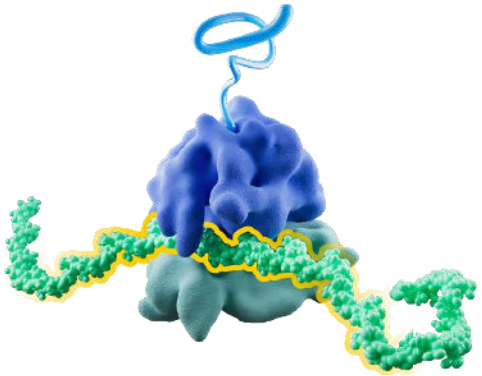
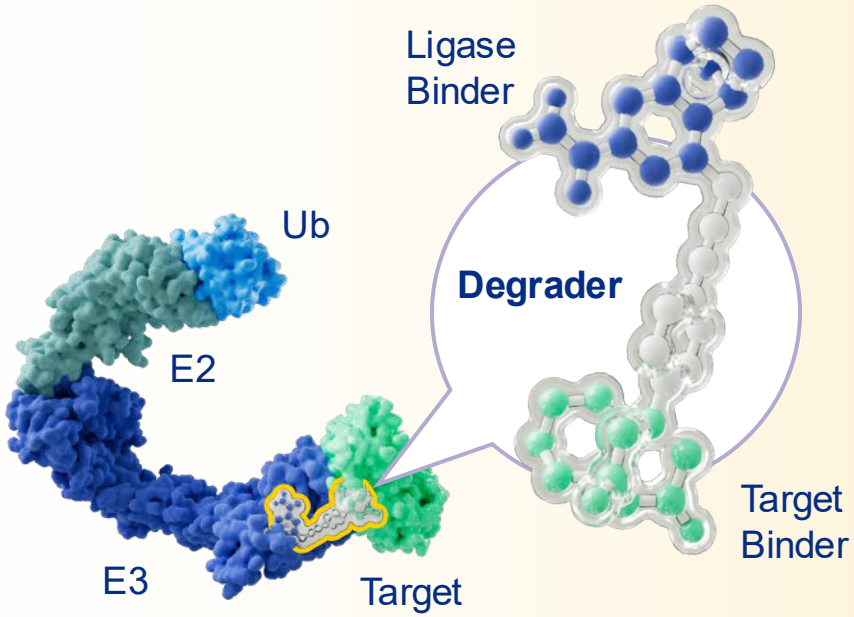
Proximity Therapeutics are the Next Frontier in Drug Development

Target Protein Degradation (TPD)









Small Molecule Inhibitors

Antibodies

Nucleic Acid-based Therapies:
Antisense • RNAi Gene Therapy • CRISPR

Target Protein Degradation Drugs

Evolution of New Therapeutic Modalities

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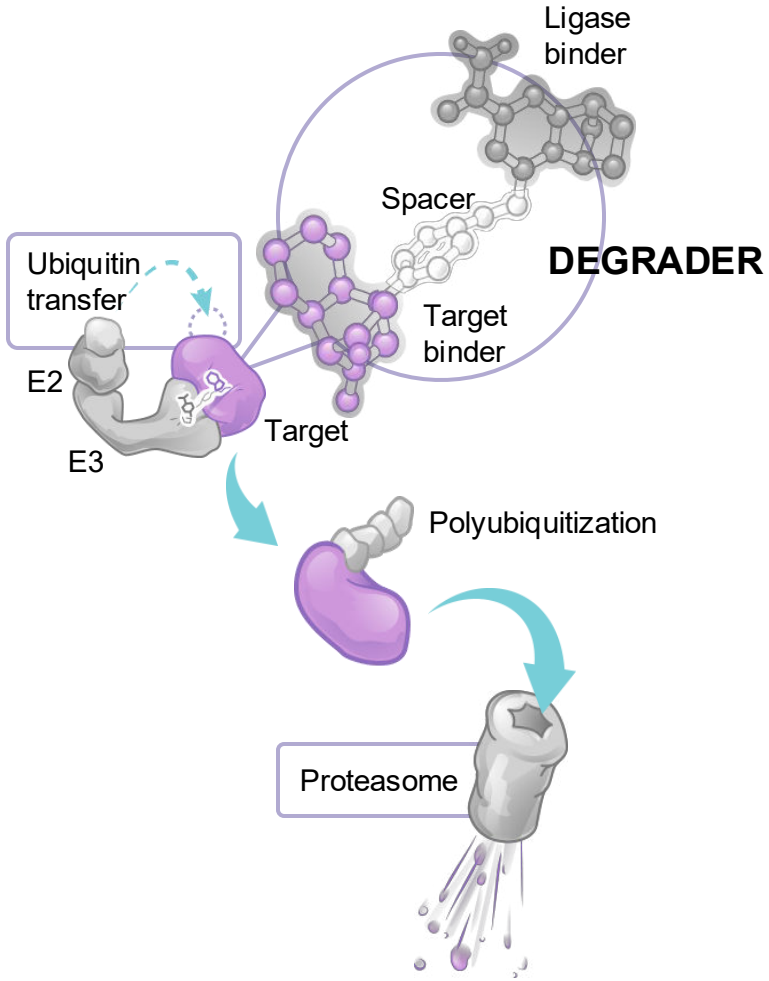
Degraders are Transformative Therapeutics Because they Catalytically Eliminate the Proteins that Drive Disease

Harnessing the ubiquitin proteasome system to eliminate disease-causing proteins



- Degraders target a specific protein or family of proteins
- Degraders catalytically eliminate ALL biological functions of proteins (scaffolding and enzymatic)
- Degradation provides prolonged activity requiring resynthesis of the protein

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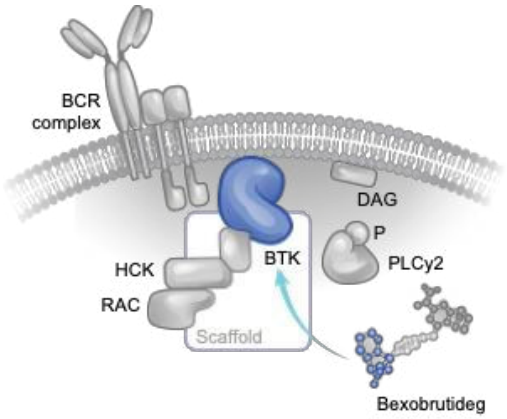
Tackling Key Nodes of Biology, Not Just Undruggable Targets

BTK

B-cell & myeloid cell-driven inflammation

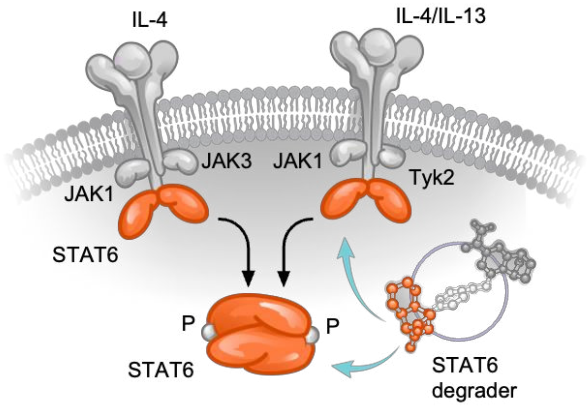


Bexobrutideg

Clinically validated targets where inhibitors fail to address scaffolding and resistance

STAT6

Type 2 inflammation

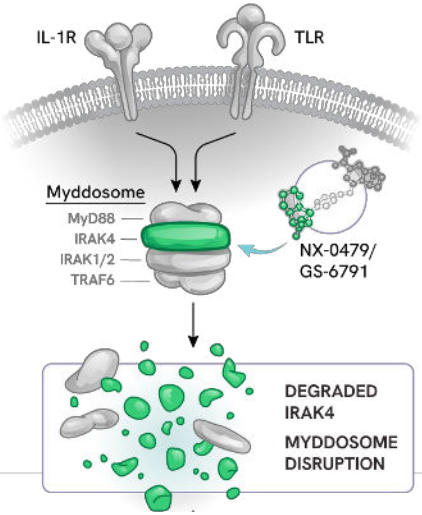


NX-3911

Targeting the ‘Undruggable’

IRAK4

IL-1R/TLR-driven inflammation



NX-0479/GS-6791

Unmet medical need where inhibitors are not sufficient to drive efficacy

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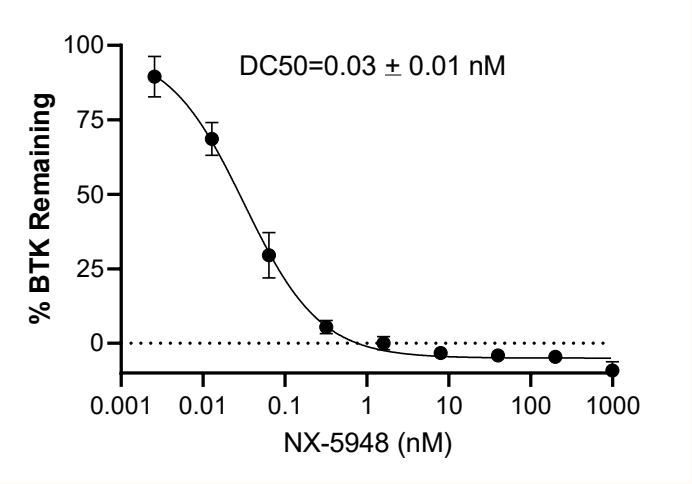
Targeted Protein Degradation is Revolutionizing Precision Therapeutics

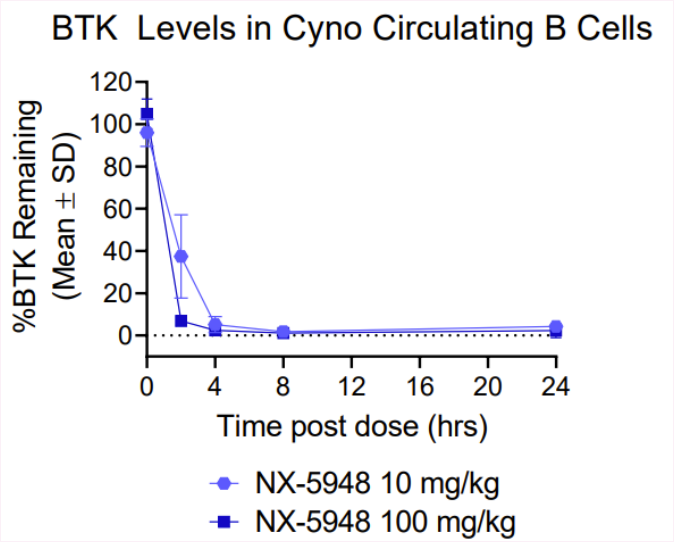
Picomolar Potency

BTK Degradation in TMD8 Cells



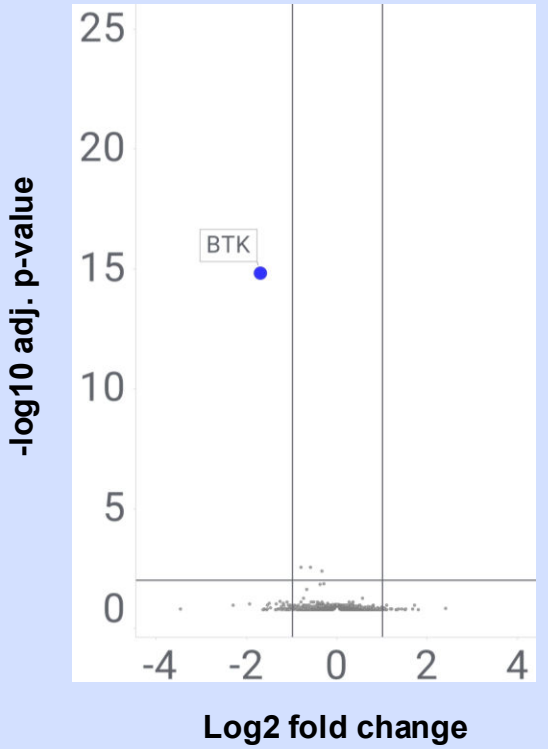
Prolonged PD

Single Dose Target Suppression



Exquisite Selectivity

Global Proteomic Analysis

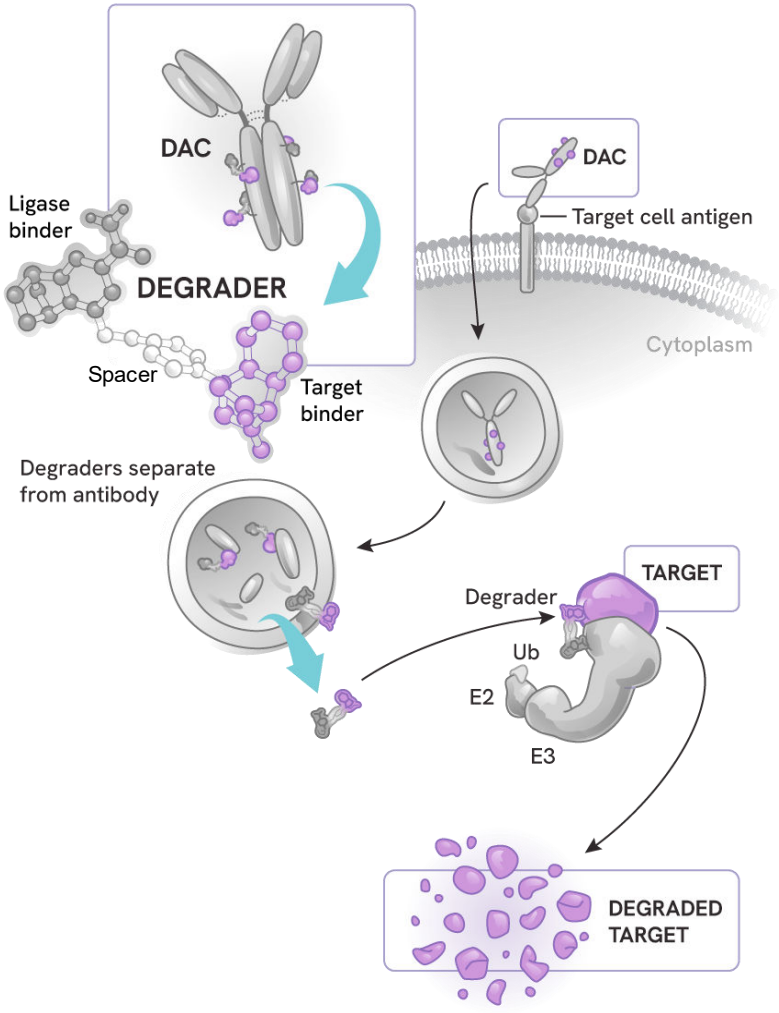


Example from our clinical-stage BTK degrader NX-5948
PD, pharmacodynamics

DACs Represent the Next Wave in Degrader Therapeutics

Degrader Antibody Conjugates

- DACs combine the catalytic activity of a Targeted Protein Degrader (TPD) with the tissue specificity of an antibody
- DACs represent a next generation of antibody drug conjugate (ADC) technology with the potential for enhanced efficacy and improved safety
- Nurix has developed a proprietary linker technology that allows for high throughput synthesis and screening of DACs to speed discovery



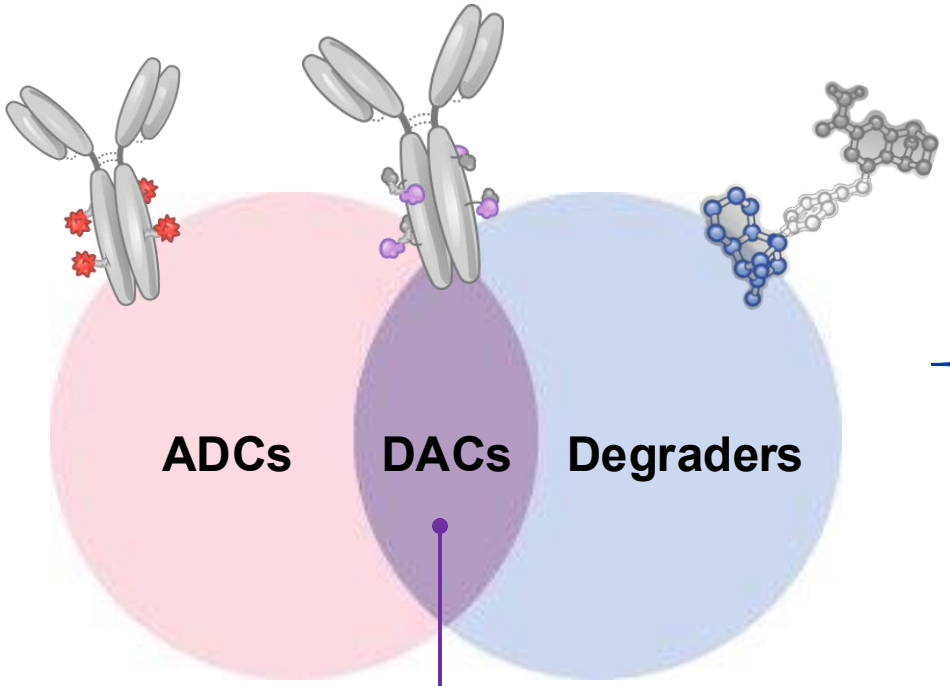
DAC, Degrader Antibody Conjugate

By Enhancing Degrader Selectivity, the DAC Modality Unlocks New Targets and Offers the Potential for a Broader Range of Therapeutic Indications

FDA approved ADCs

ADC	Payload	Payload MOA
Mylotarg Besponsa Enhertu Trodelvy Zynlonta	calicheamicin calicheamicin topoisomerase topoisomerase PBD dimer	**DNA damage**
Adcetris Kadcyla Padcev Polivy Tivdak Blenrep Aldixi Elahere	MMAE emtansine MMAE MMAE MMAE MMAF MMAE DM4	**Microtubule inhibition**
Lumoxiti Akalux	bacterial toxin photosensitizer IR700	**Other**

Adapted from: Senior, M. Cancer-targeting antibody–drug conjugates drive dealmaking frenzy. Nat Biotechnol 42, 362–366 (2024).



Antigen provides cell and tissue selectivity

Degrader target and ligase expression provide cell and tissue selectivity

DAC provides multi-layer selectivity

Growing list of clinical degraders

Degrader Name	Target	Indication
bexobrutideg	BTK	Oncology / I&I
zelebrudomide	BTK, IKZF1/3	Oncology
gridegalutamide	AR	Oncology
vepdegestrant	ER	Oncology
luxdegalutamide	AR	Oncology
setidegrasib	KRAS G12D	Oncology
tacabrutideg	BTK	Oncology
NX-0479/GS-6791	IRAK4	I&I
ARV-102	LRRK2	Neurology
ARV-393	BCL6	Oncology
CC-94676	AR	Oncology
CG001419	NTRK	Oncology
DT-2216	BCL-xL	Oncology
GT20029	AR	Oncology
HP518	AR	Oncology
HSK29116	BTK	Oncology
KT-621	STAT6	I&I

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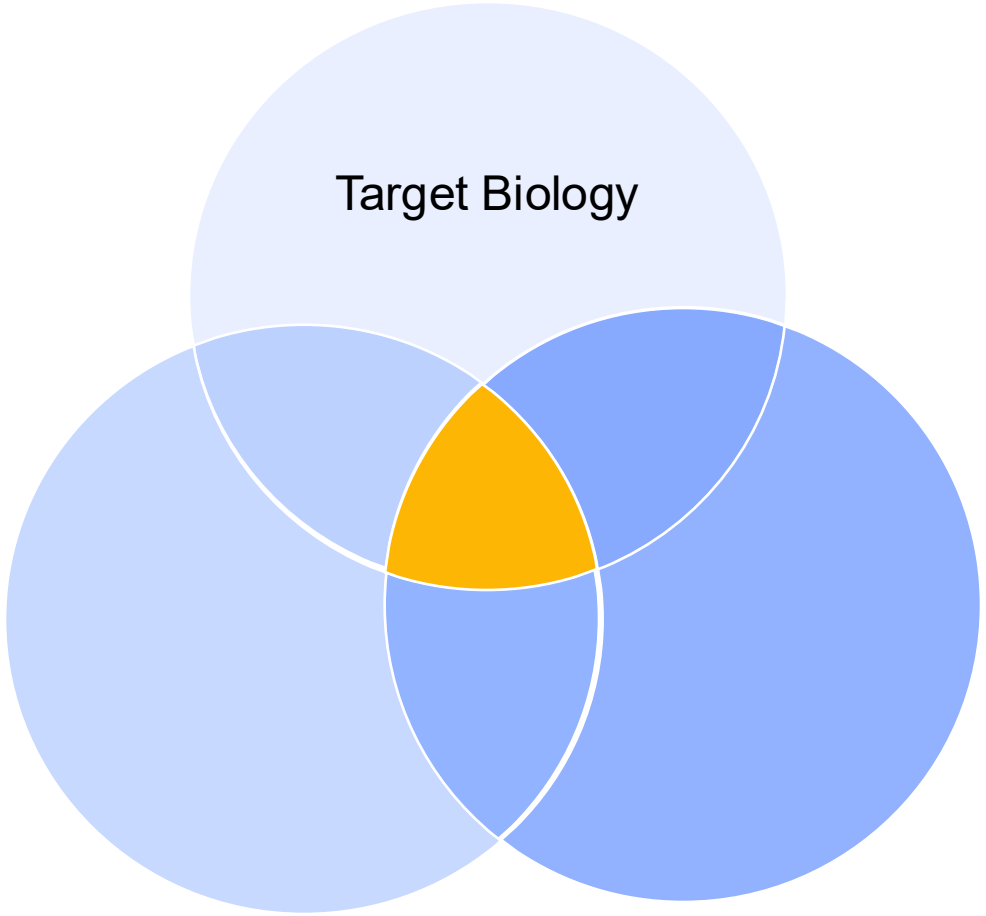
Integration of Target Biology, Antigen, and Antibody for DAC Therapeutics



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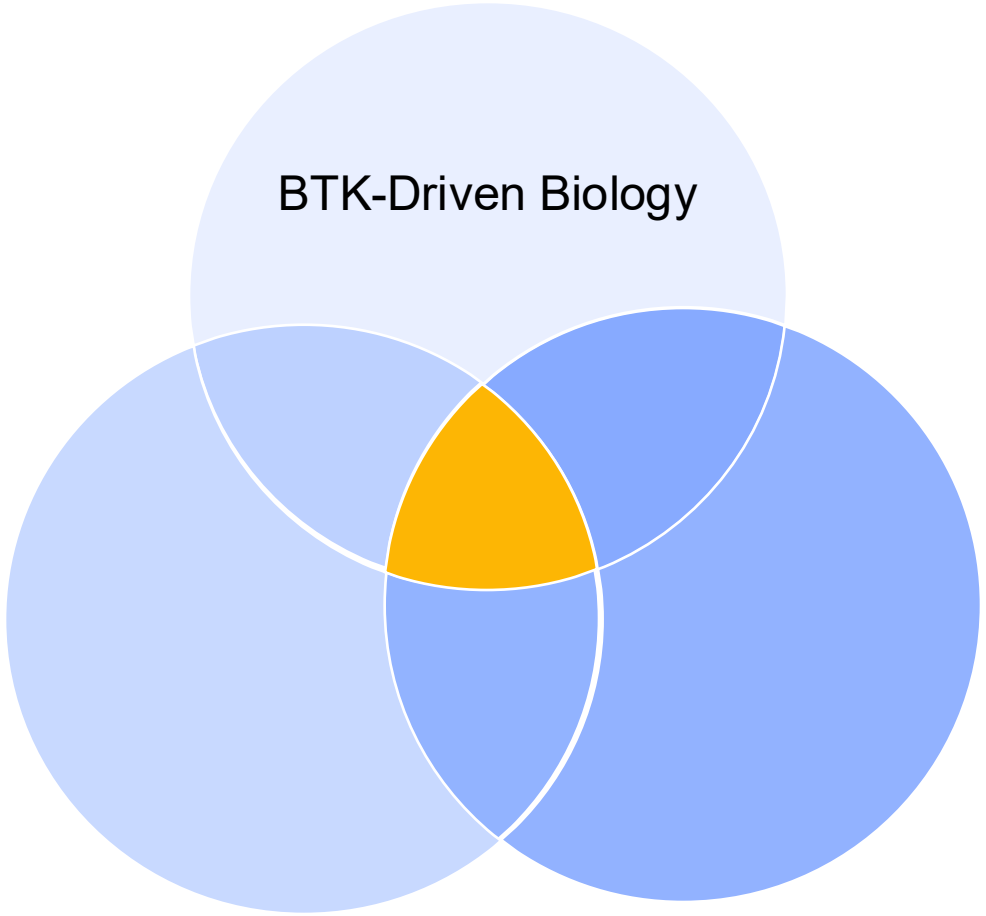

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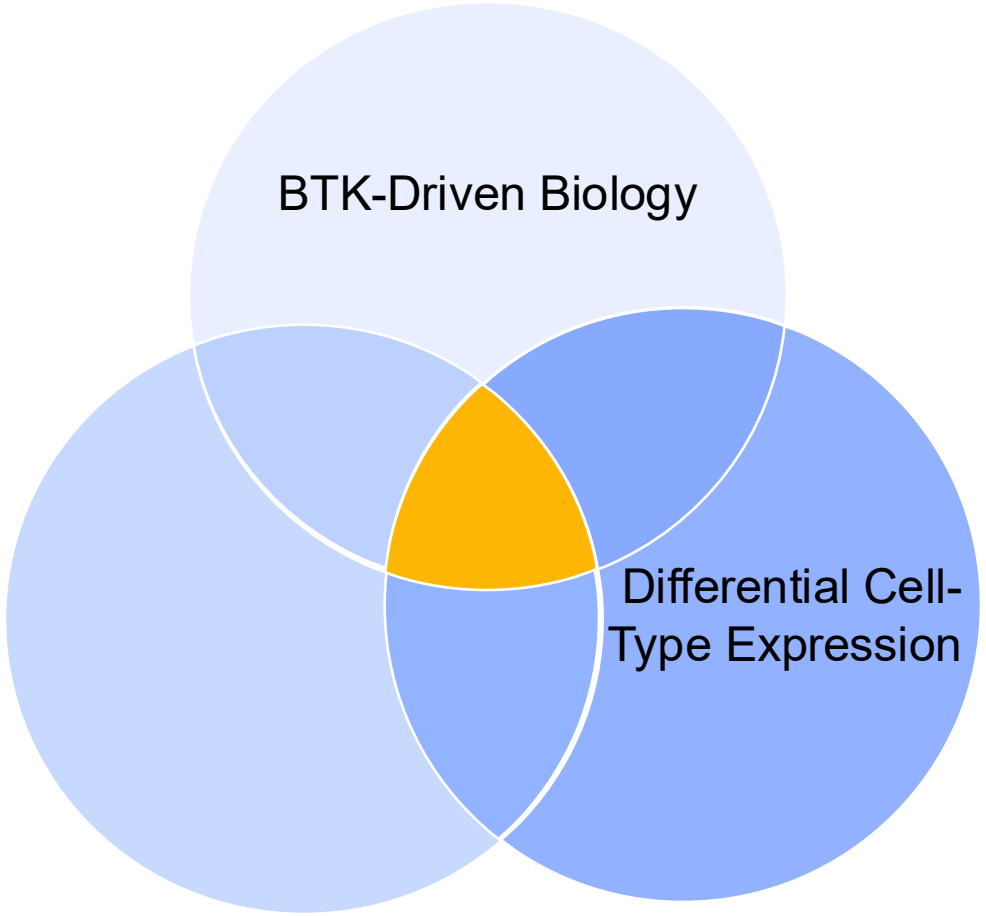

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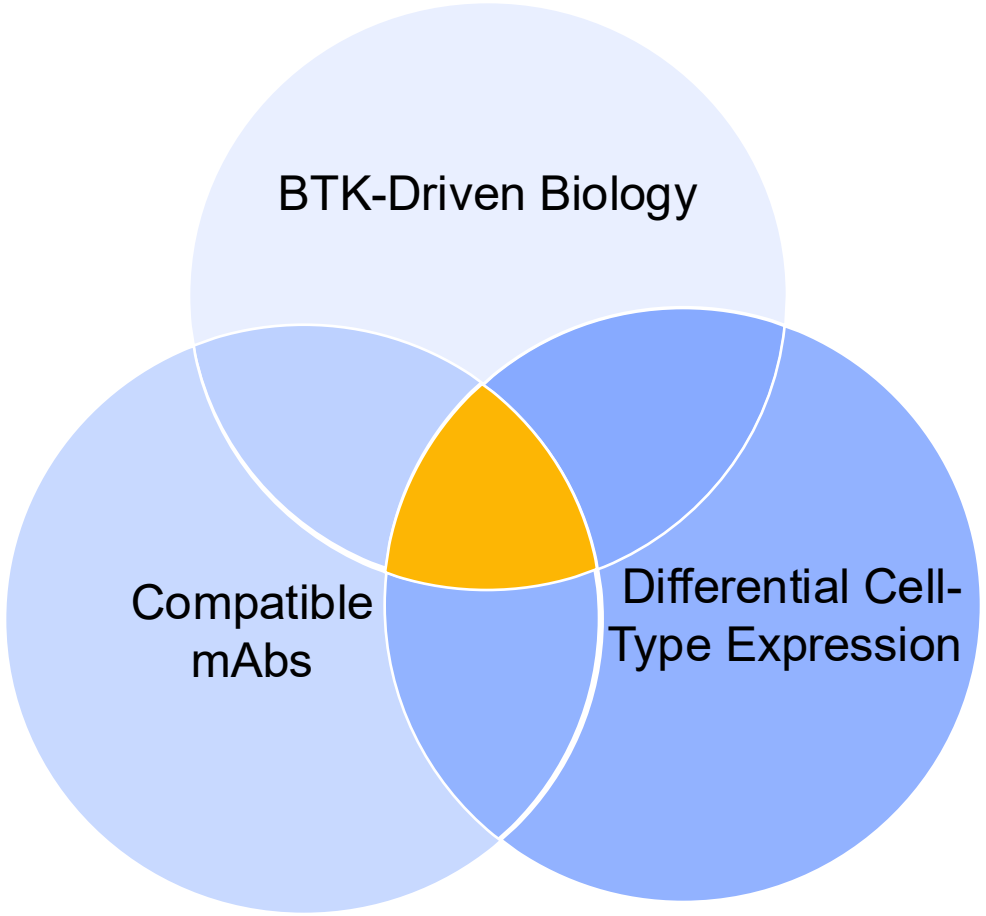

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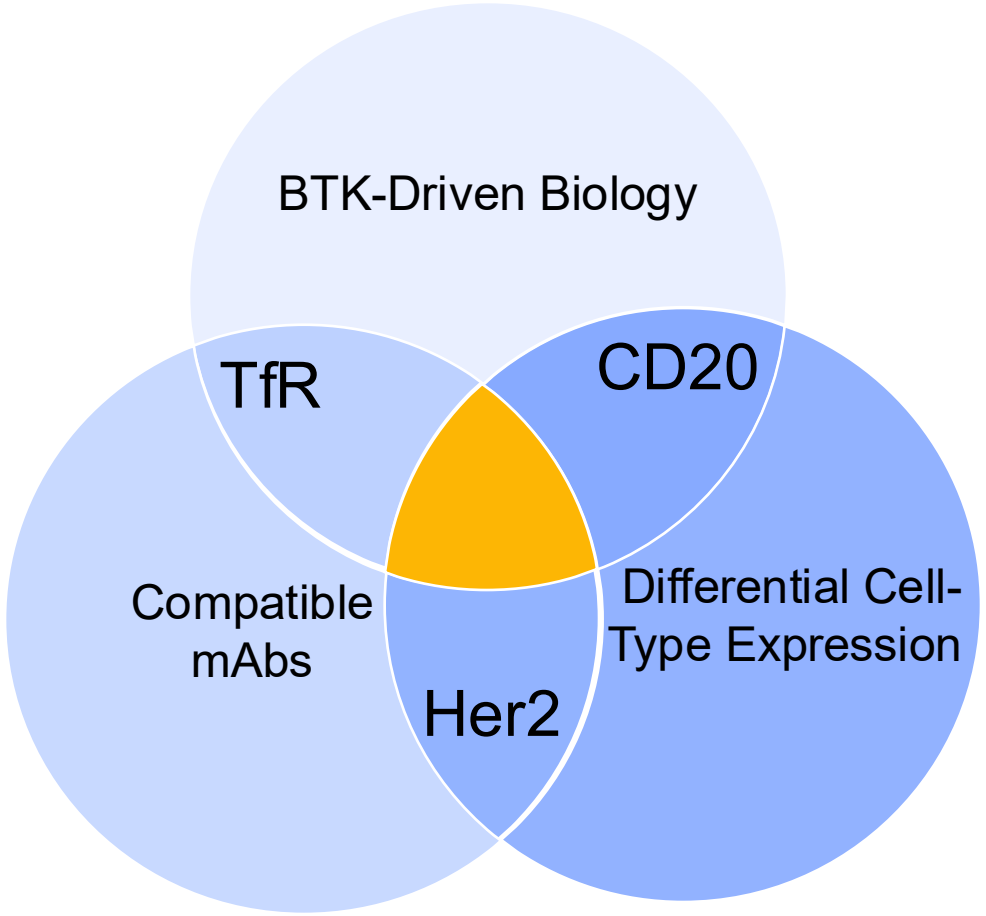

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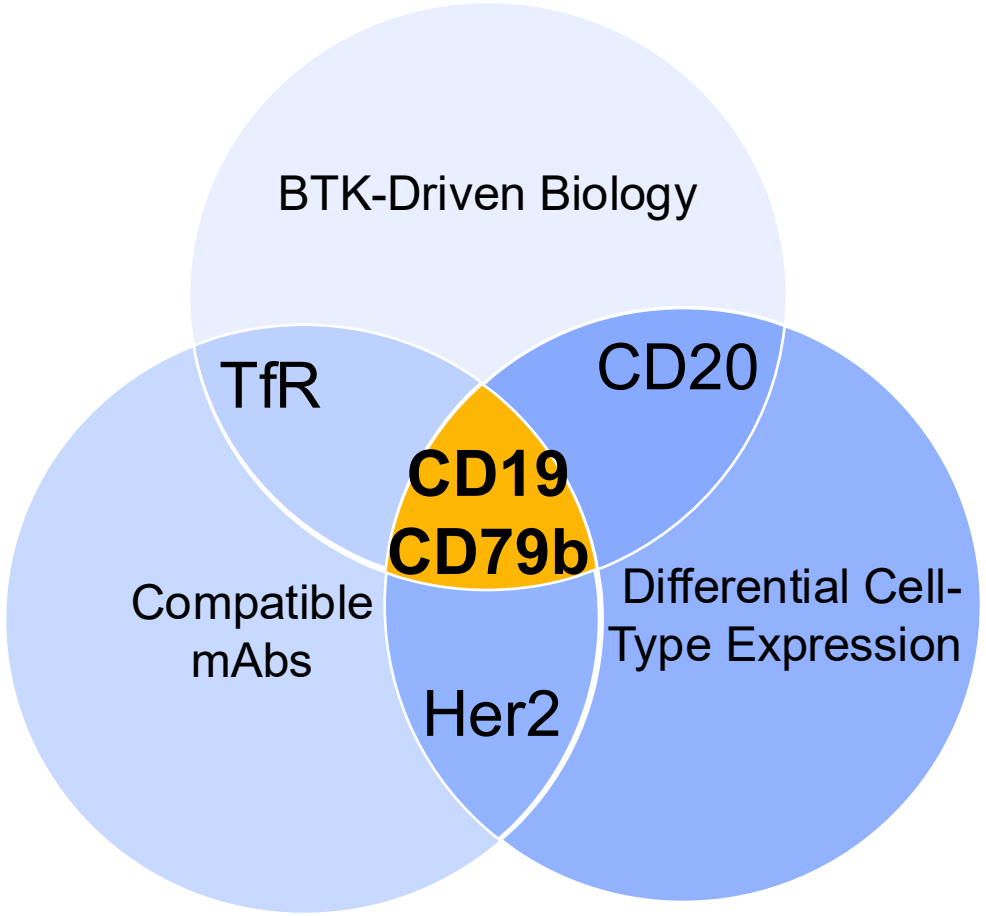
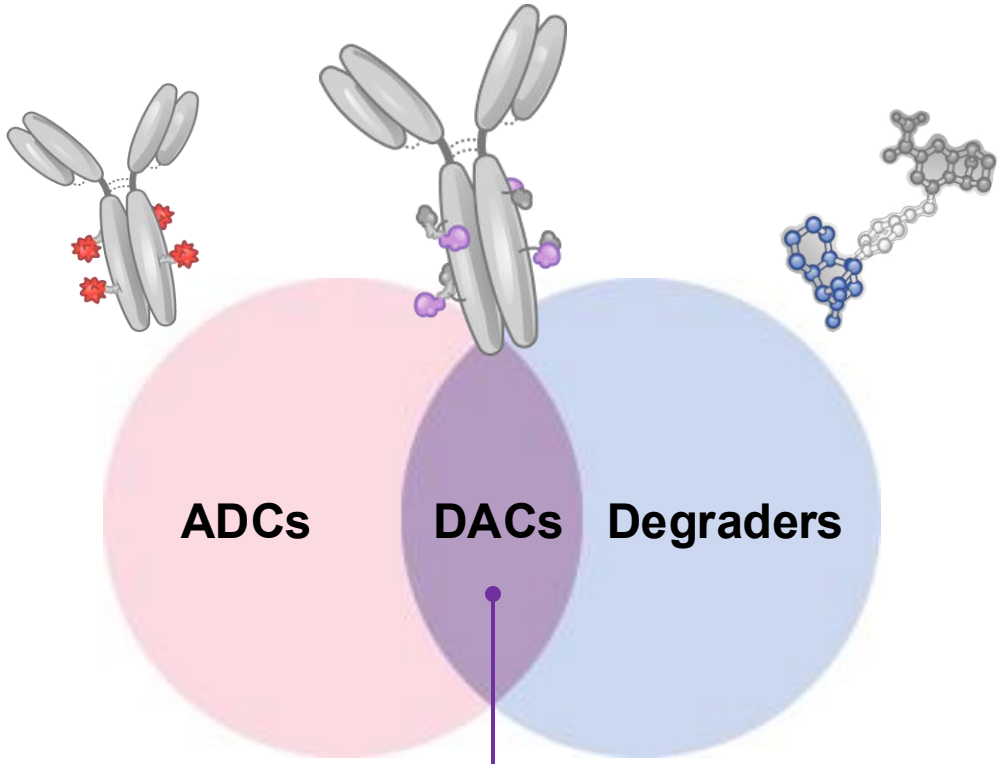


Questions Posed at the Program Outset

- Could we achieve cell-type selective delivery through a compatible antigen-antibody pair?
- Can we deliver enough degrader intracellularly to cover the target?
- Does that target coverage confer to cell-selective biological effect?

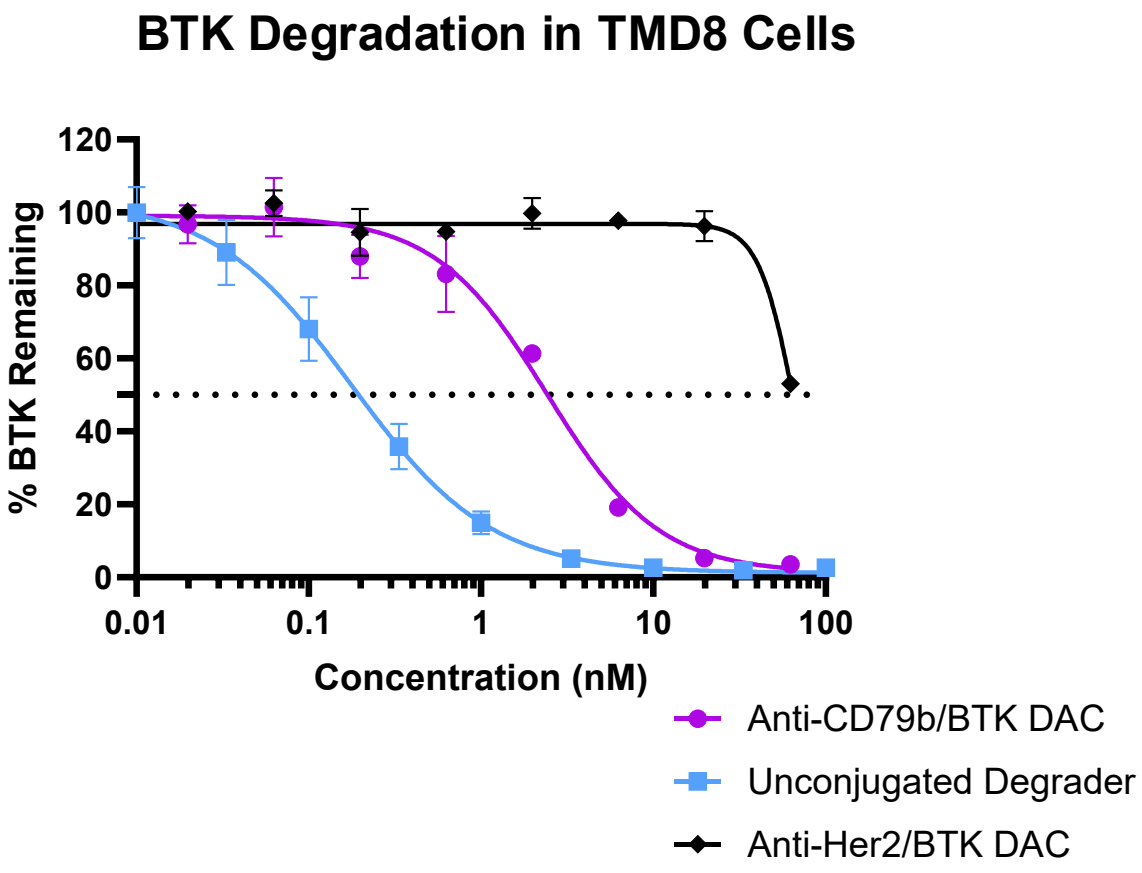
A BTK Degrader Conjugated to a CD79b Antibody Selectively Degrades BTK in CD79b+ TMD8 Cells



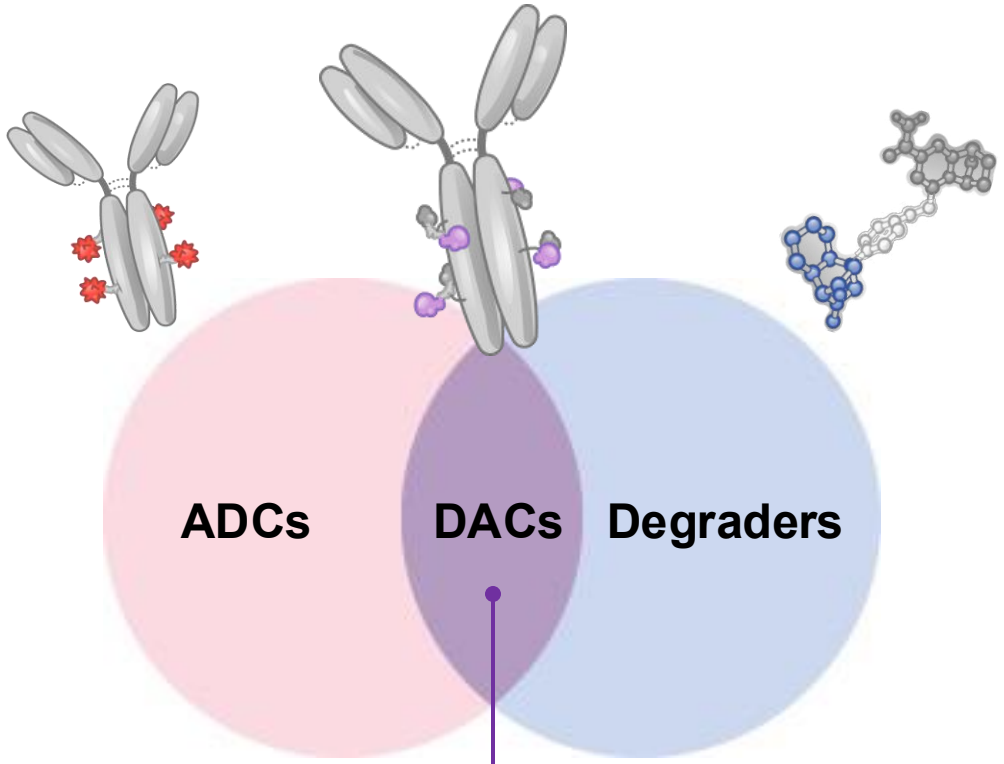
Antigen provides cell and tissue selectivity

Degrader target and ligase expression provide cell and tissue selectivity

DAC provides multi-layer selectivity



A BTK Degrader Conjugated to a CD79b Antibody Demonstrates Selective and Potent Antigen-Specific Cell Killing in CD79b+ TMD8 Cells



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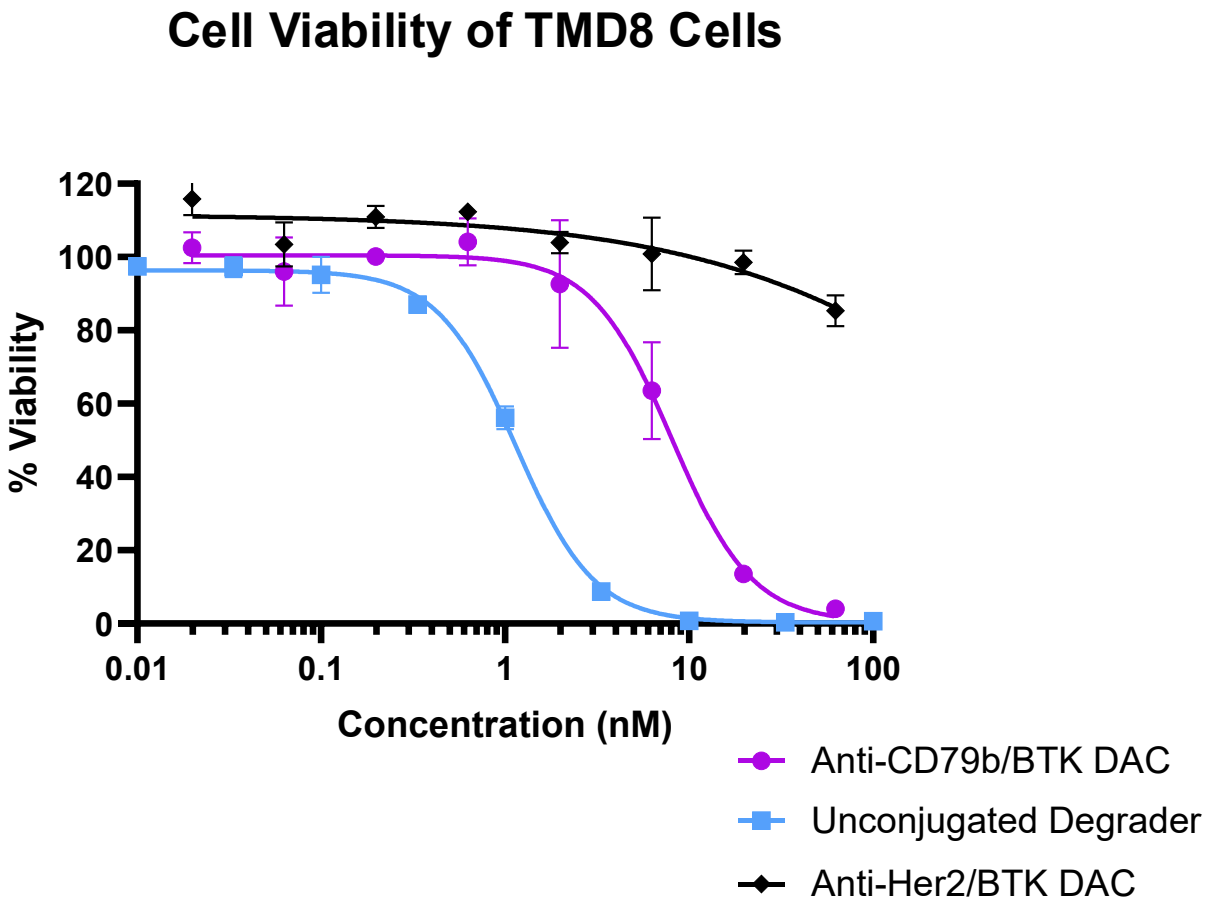
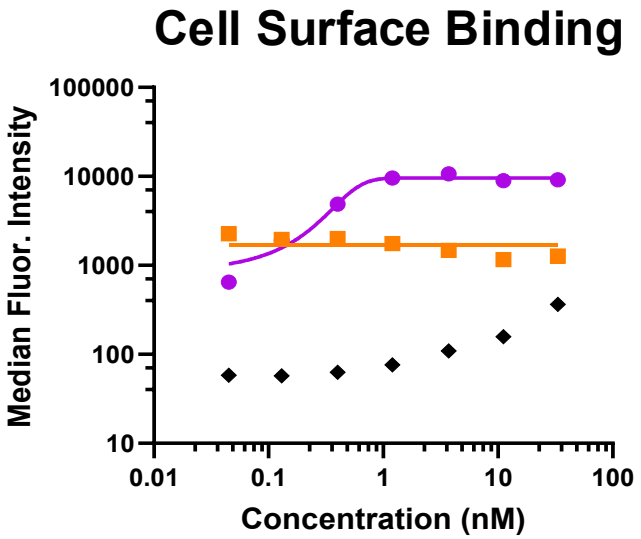
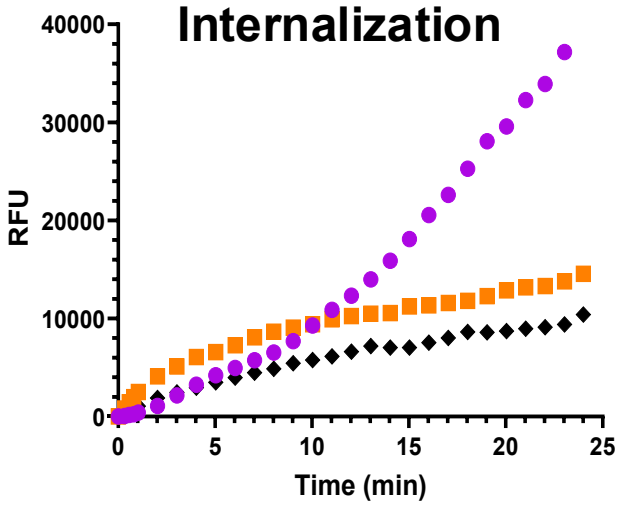
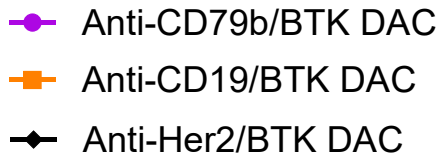


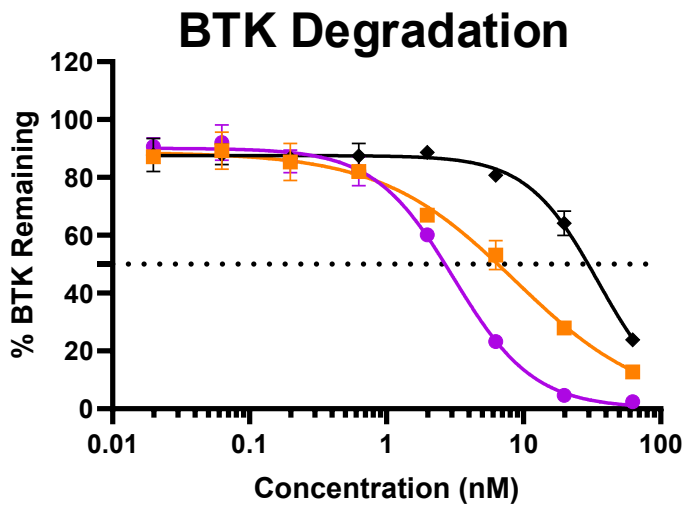
Cell Surface Binding and Internalization Strongly Impacts DAC Activity

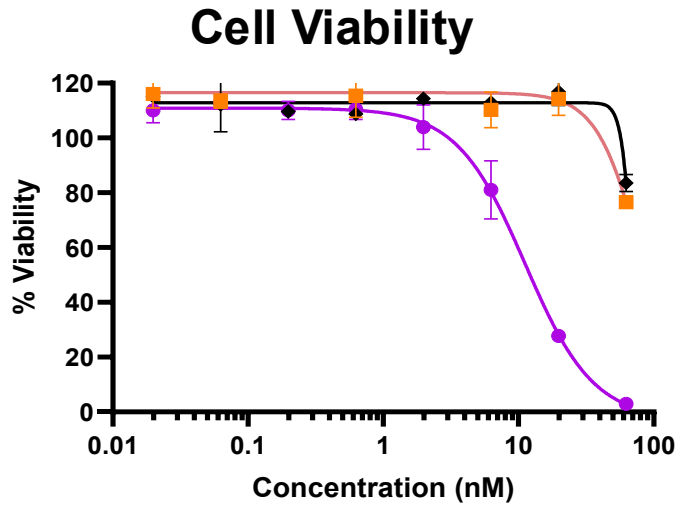






BTK DAC	DAR	% Monomer
Anti-CD79b	4	94
Anti-CD19	4	97
Anti-Her2	4	98





All data measure in TMD8 cells. 50 nM DACs used for the internalization assay

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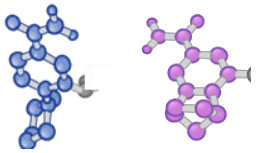
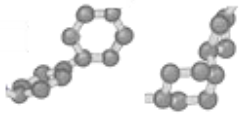
The Nurix Approach: Combinatorial Synthesis of Degraders

Combinatorial assembly of degraders allows for scaled empiricism

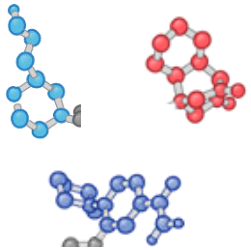
POI Binders



Spacers



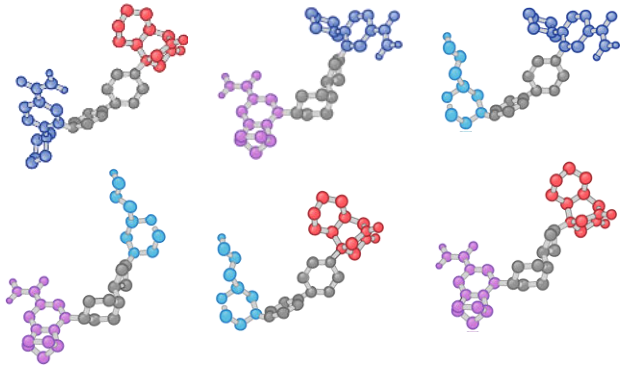
Ligase Binders



Reagent/Building Block Inventory
Automated Liquid Handling

Purified or D2B

Matrix of Degraders



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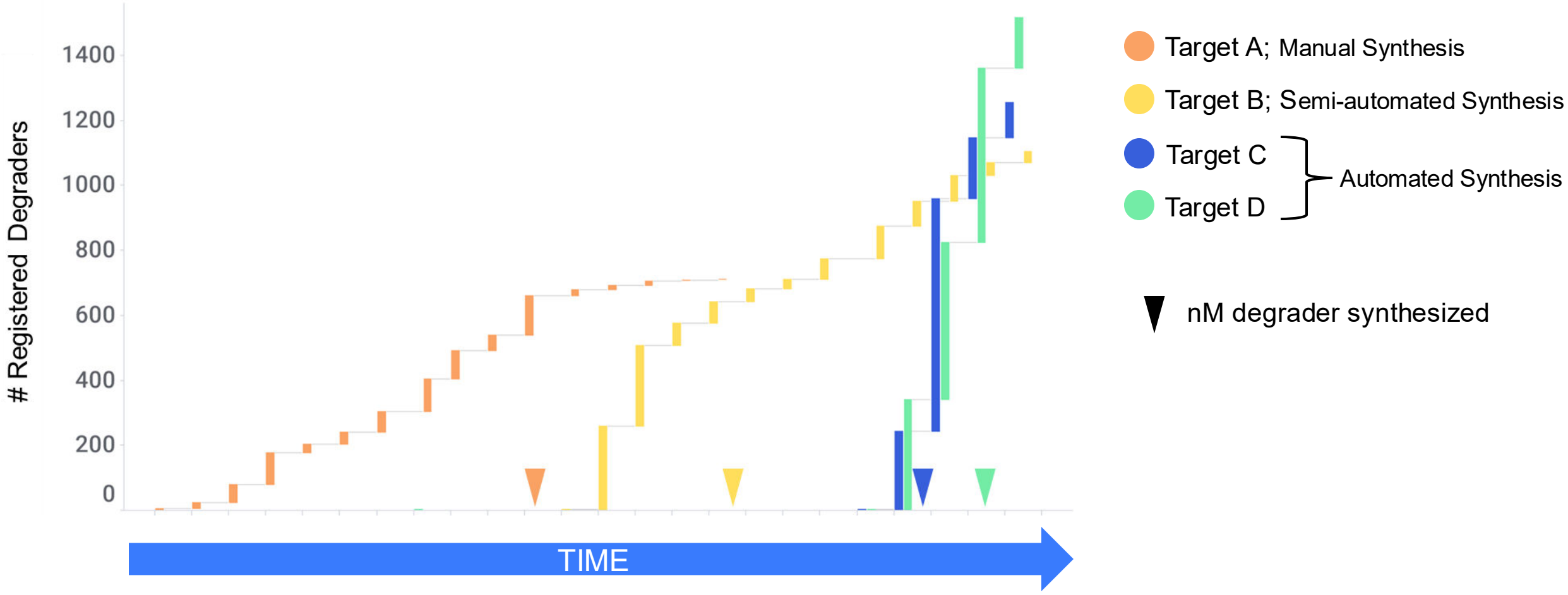
Automation Drives Our Ability to Scale Degrader Discovery, Shortening the Time to Identify Potent Leads

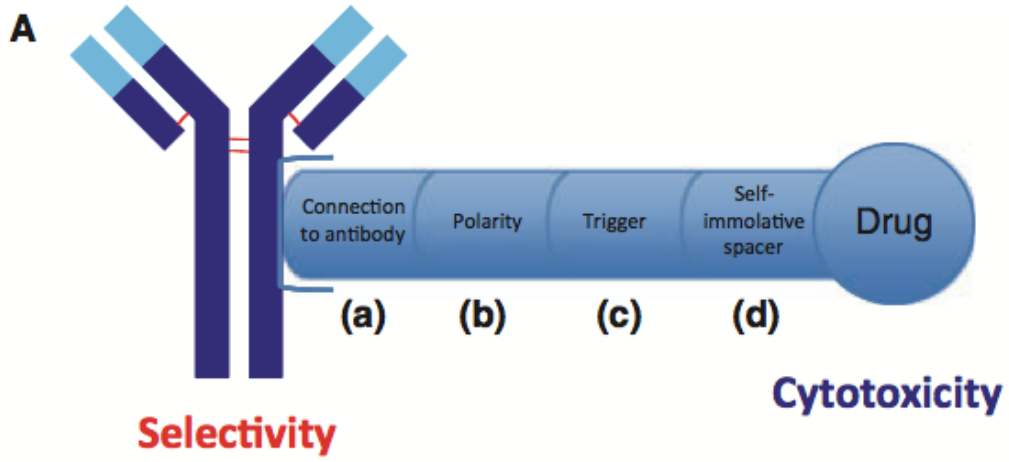
High-throughput screening with bespoke libraries



Plot of timeline to achieve potent lead compounds for 4 programs from Nurix pipeline

Challenges in ADC Discovery

The components of the ADC cannot be optimized independently, so there is a combinatorial explosion in the number of potential molecules to test.



mAB X Linker X Drug

It's an antibody project multiplied by a linker project, multiplied by a toxin project, cubing the complexity of the problem.

Following are some examples to illustrate these points.

Flygare, J. et al. 2012 https://doi.org/10.1111/cbdd.12085

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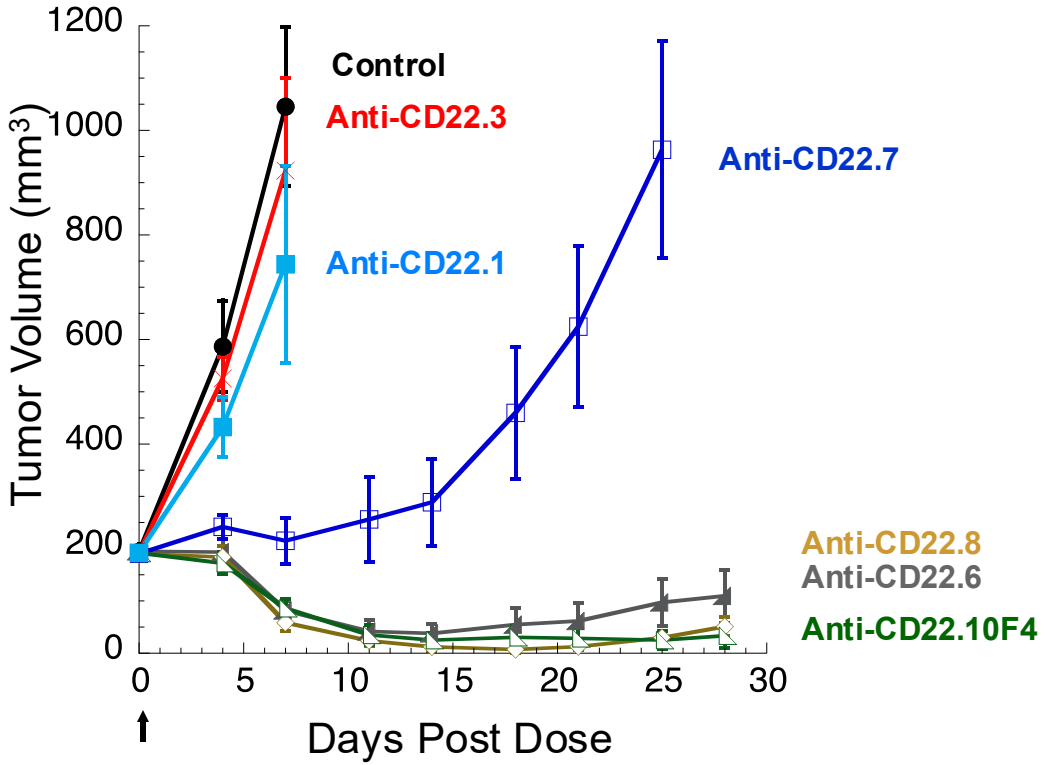
The Nature of the mAB Matters

Anti-CD22 MCC DM1 (DAR 3– 4)

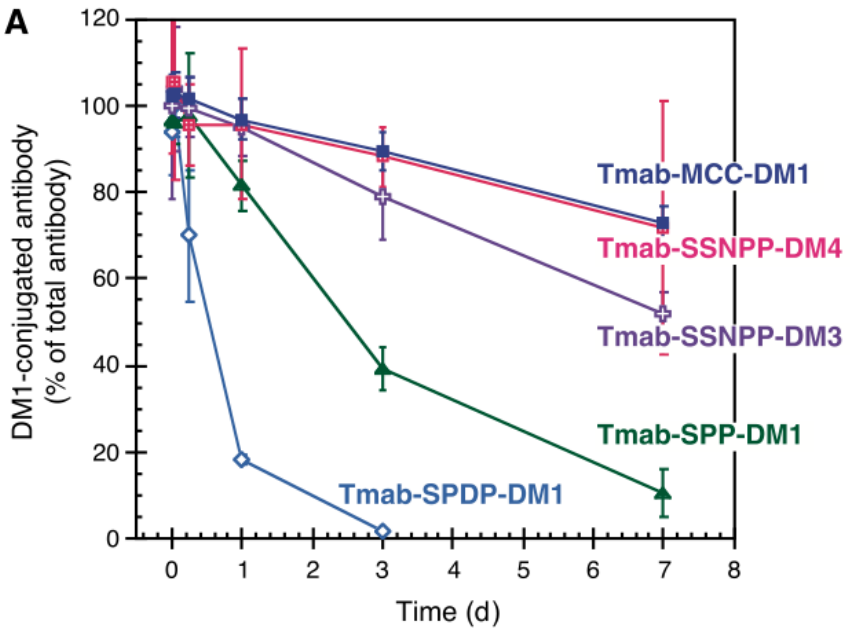
Antibody	Isotype	Affinity	Epitope
Anti-CD22.1	msIgG1	4.1	2
Anti-CD22.2	msIgG2a	1.2	ND
Anti-CD22.3	huIgG1	3.4	5-7
Anti-CD22.4	msIgG1	2.9	2
Anti-CD22.5	huIgG1	2.0	1,2
Anti-CD22.6	msIgG1	ND	2,3
Anti-CD22.7	huIgG1	21.8	5-7
Anti-CD22.8	huIgG1	ND	1,2
Anti-CD22.10F4	msIgG1	14.3	1,2

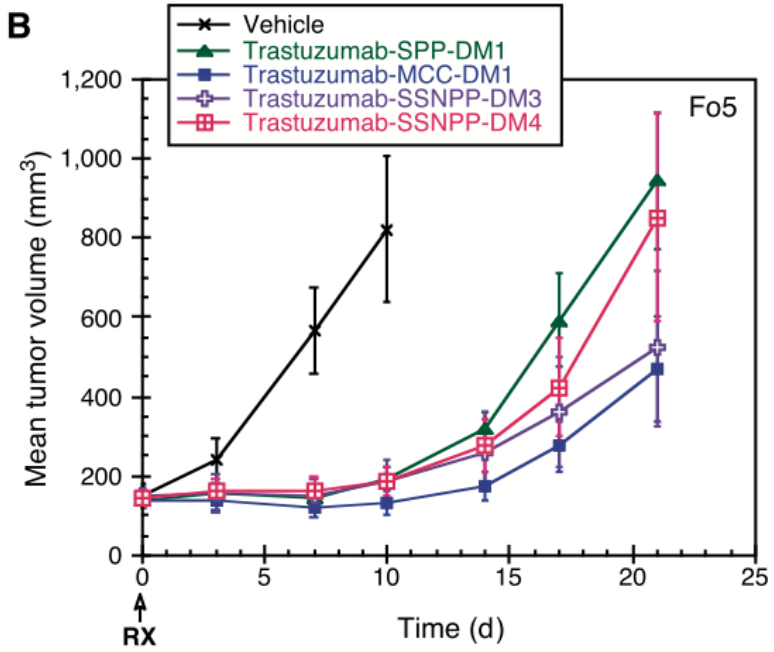


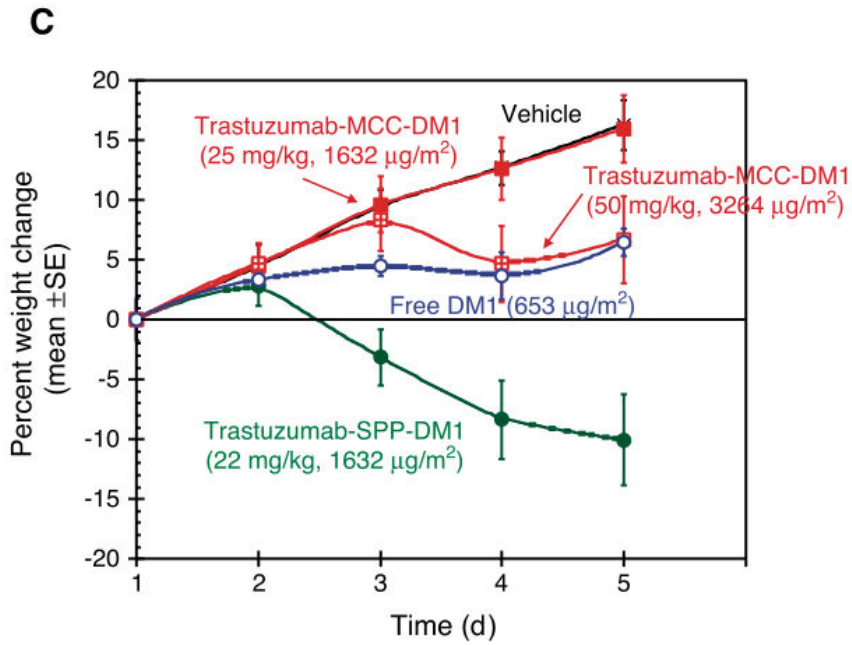
For one mAB-linker-drug series, there is no apparent correlation between affinity and efficacy.

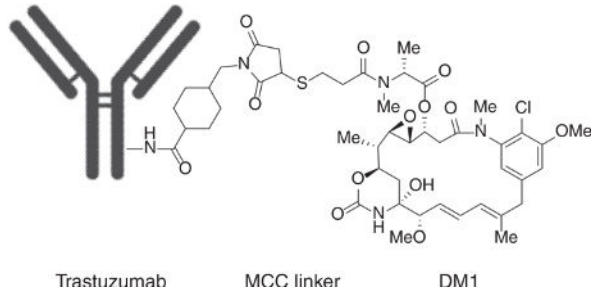
https://doi.org/10.1038/leu.2010.141 Polson, et al 2010

Cleavable vs Uncleavable Linkers: HER2







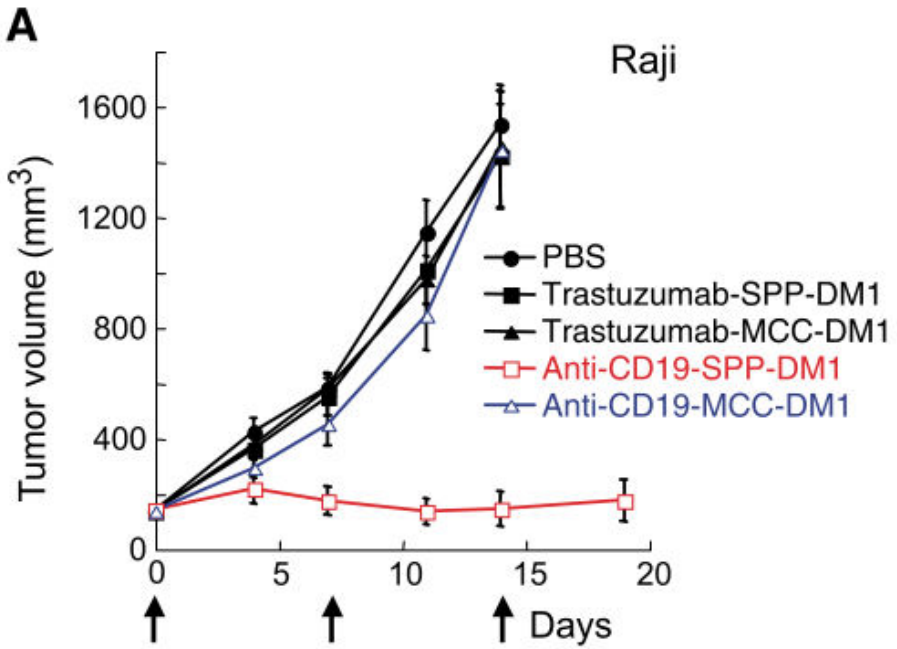


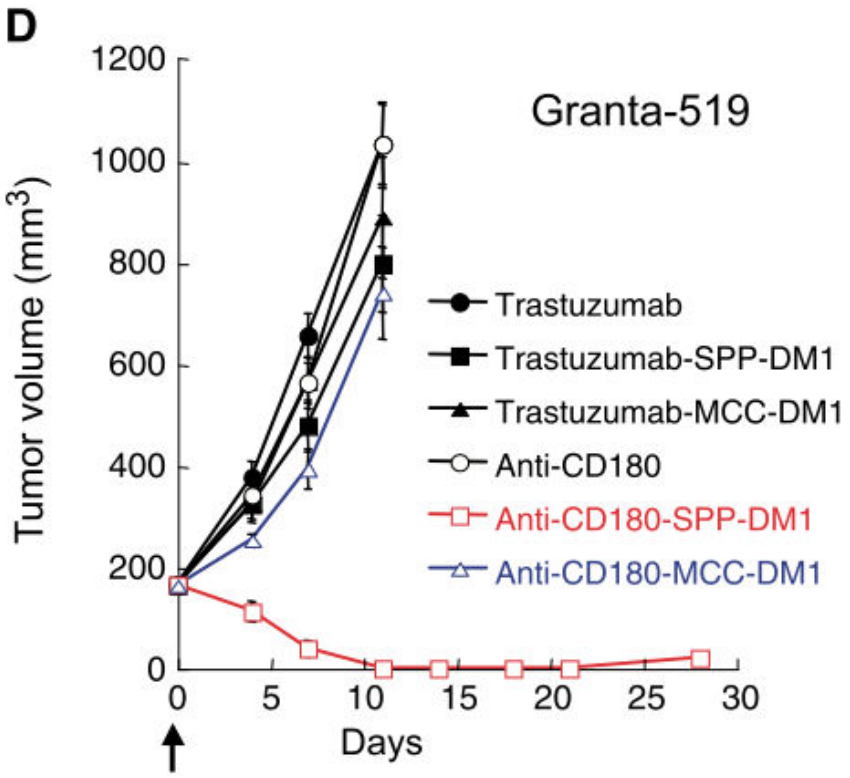
For anti-HER2, stable MCC linker more efficacious, better PK and safer than reducible SPP linker.

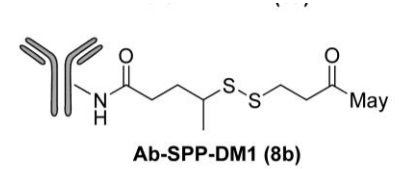
In vitro potency not related to final choice.
(data not shown)

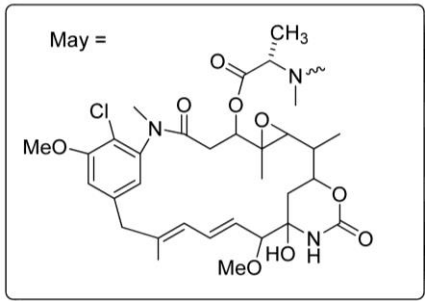
10.1158/0008-5472.CAN-08-1776 Phillips 2008

Cleavable vs Uncleavable Linkers: NHL Targets









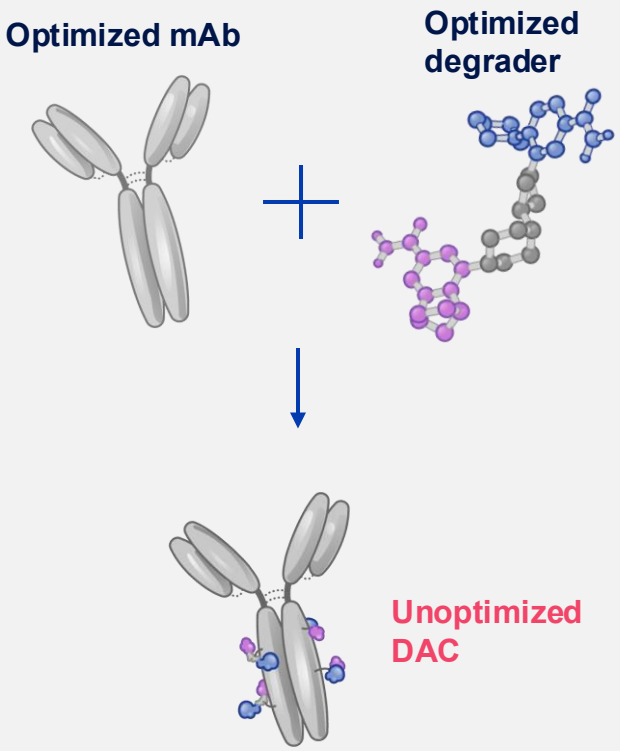
For anti-CD19 and anti-CD180, cleavable SPP linker is more efficacious than stable MCC

10.1158/0008-5472.CAN-08-2250 Polson 2009; J. Med. Chem. 2014, 57, 16, 6949-6964

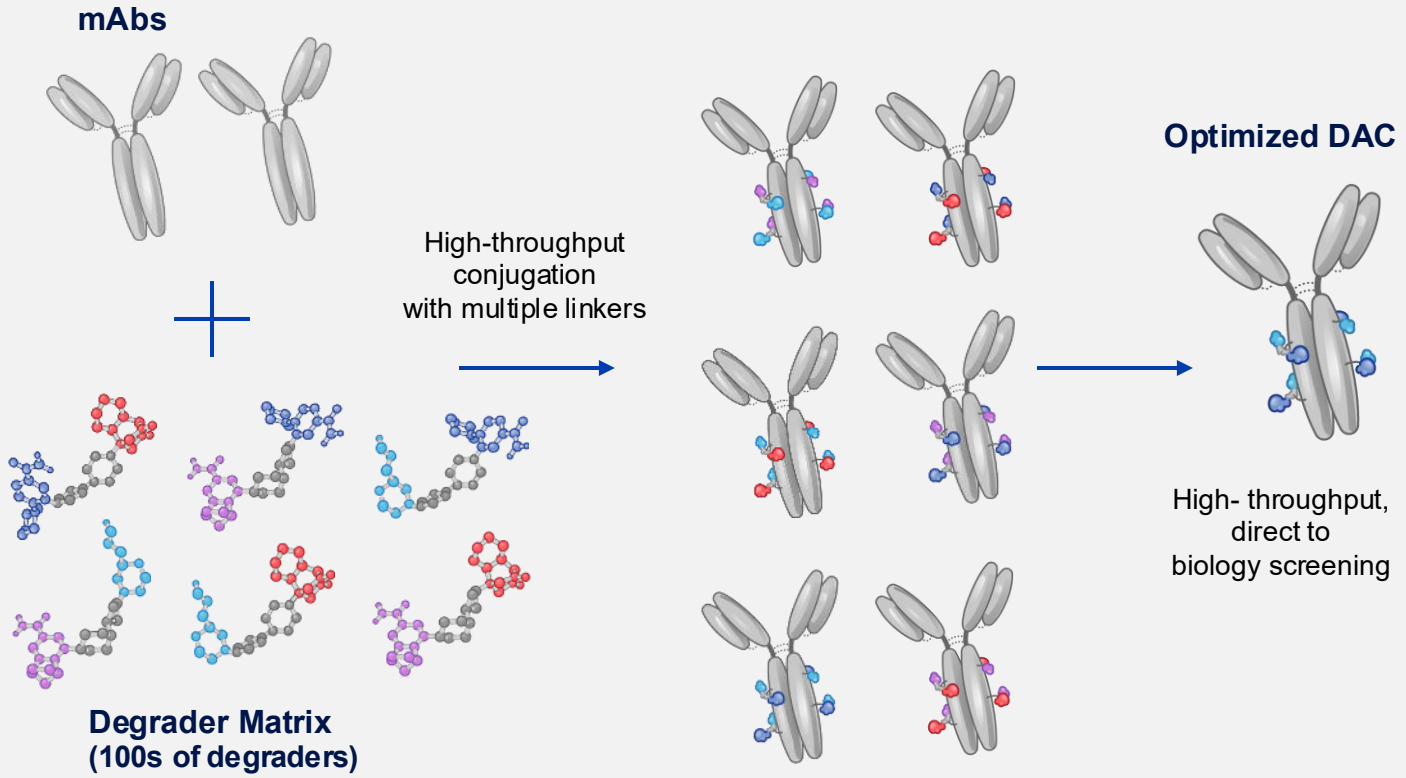
Next-Generation DAC Design Requires Multi-Parameter Optimization

Agnostic assessment of design elements using matrix synthesis and screening

Simplistic Approach



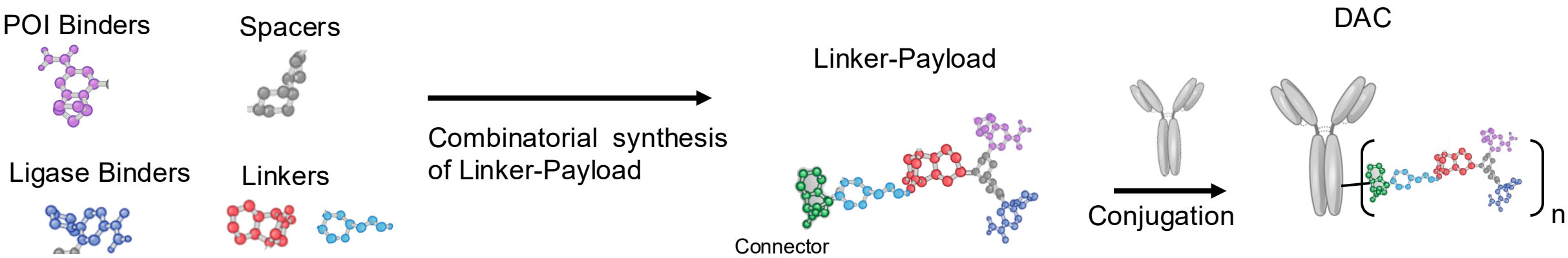
Nurix Approach: Matrixed DAC



***DAC**, degrader antibody conjugate; mAb, monoclonal antibody*

Nurix's Approach to Synthesis, Screening and Optimization of DACs

Proprietary linker/spacer technology that enables *high throughput automated synthesis of DACs*

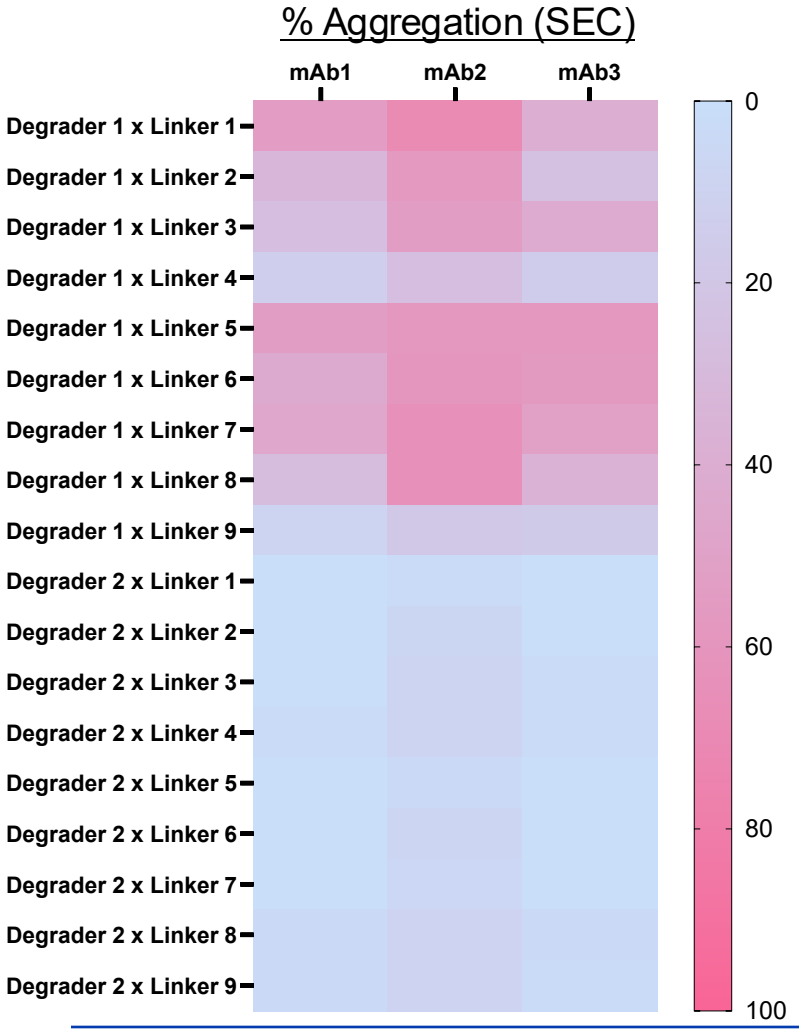


- Up to 15 synthetic steps with automated liquid handling
- Diversity at each component: True combinatorial chemistry
- One compound/well
- Chemistry validated for multiple targets enabling diversification of both POI and Ligase binder

DAC Optimization is Multi-Factorial, Requiring Empirical Screens + Matrix Design

Aggregation cannot be predicted by the properties of the component parts

2 Degraders *x* 9 Linkers *x* 3 mAbs = 54 DACs



Assessment of two degraders with highly optimized cell-based potency for the same target (DC_{50} = < 5 nM) and similar property profiles

	mwt	ALogP	PSA	HBD	HBA	#ArRing
Degrader 1	818	3.55	198	4	9	3
Degrader 2	807	3.45	202	5	9	3

- DAC aggregation is undesirable and difficult to predict from degrader properties alone
- Degrader 2 DACs show much lower tendency to aggregate despite having a nearly identical property profile to Degrader 1
- Similar to degraders, empirical screening of DACs is required to guide optimization

mAbs used are clinically validated therapeutic mAbs

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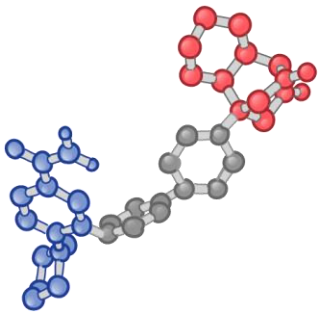
DACs Can Possess Superior Activity Compared to Unconjugated Degrader

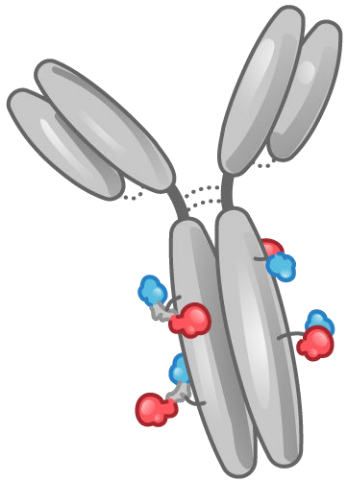
Degraders that appear to have poor potency as free compounds can be potent DAC payloads

BTK Degrader

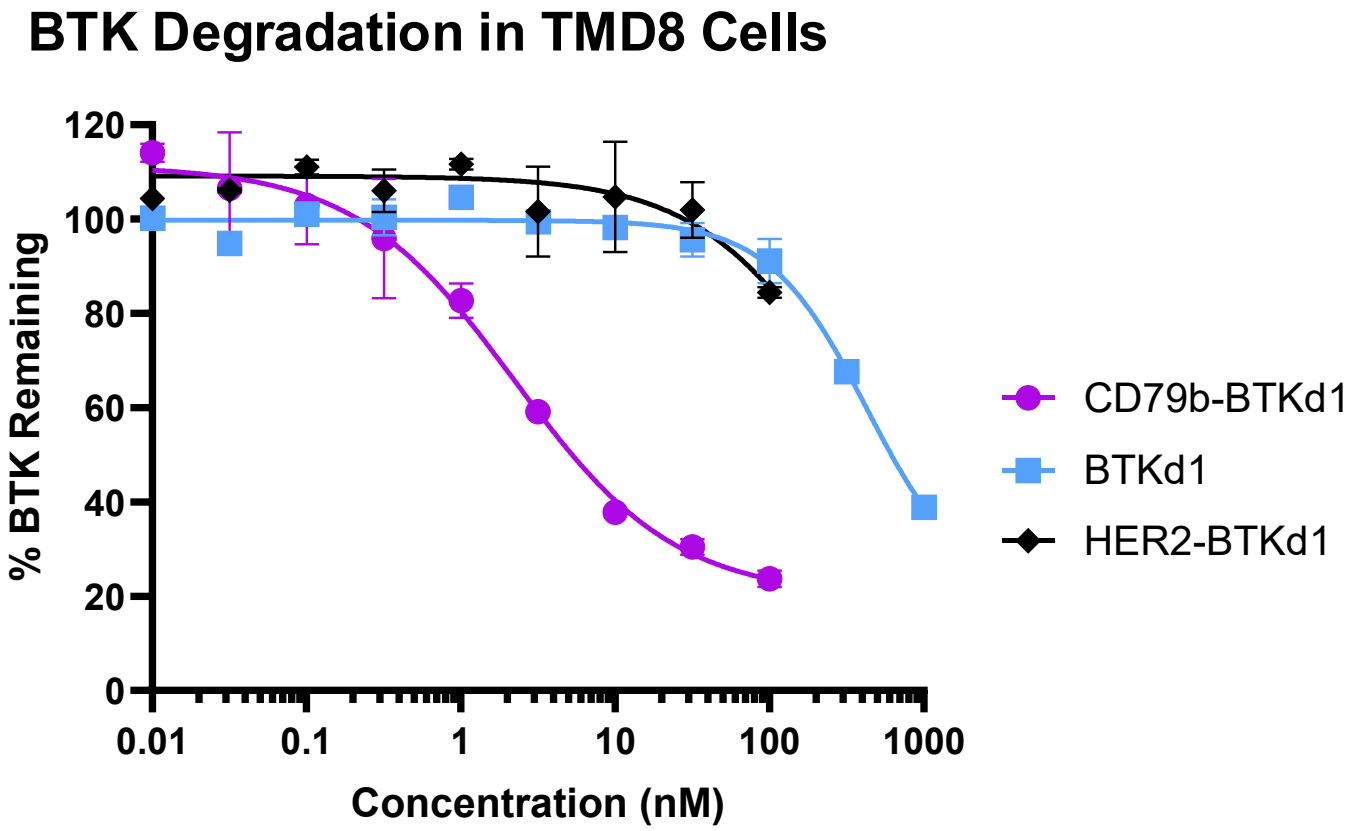


NRX-1

BTK DAC



Ab-conjugated NRX-1



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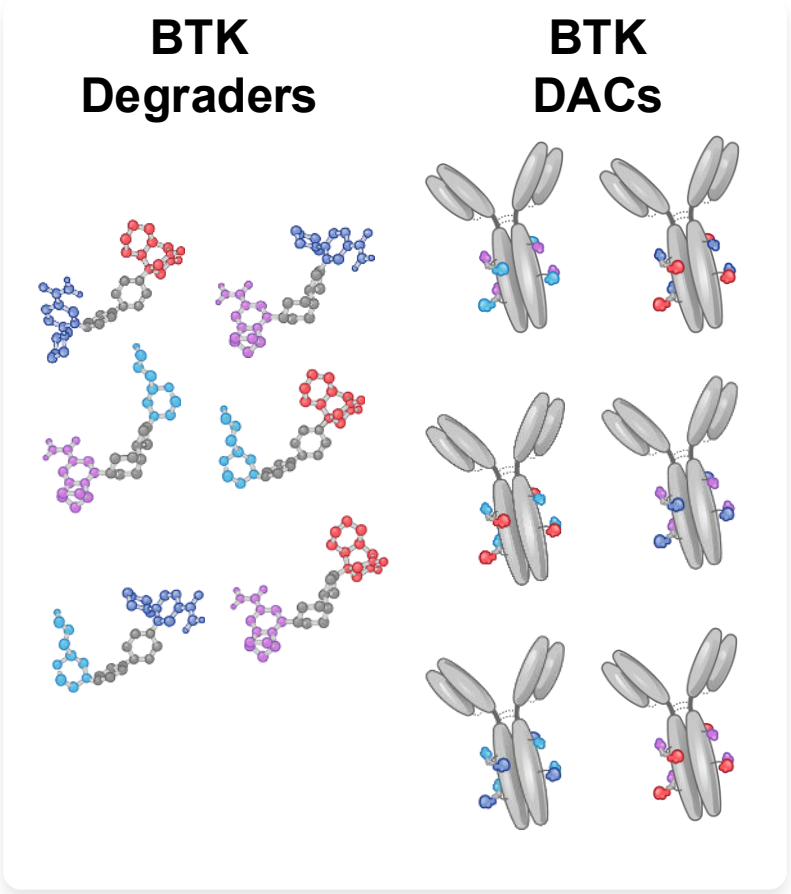
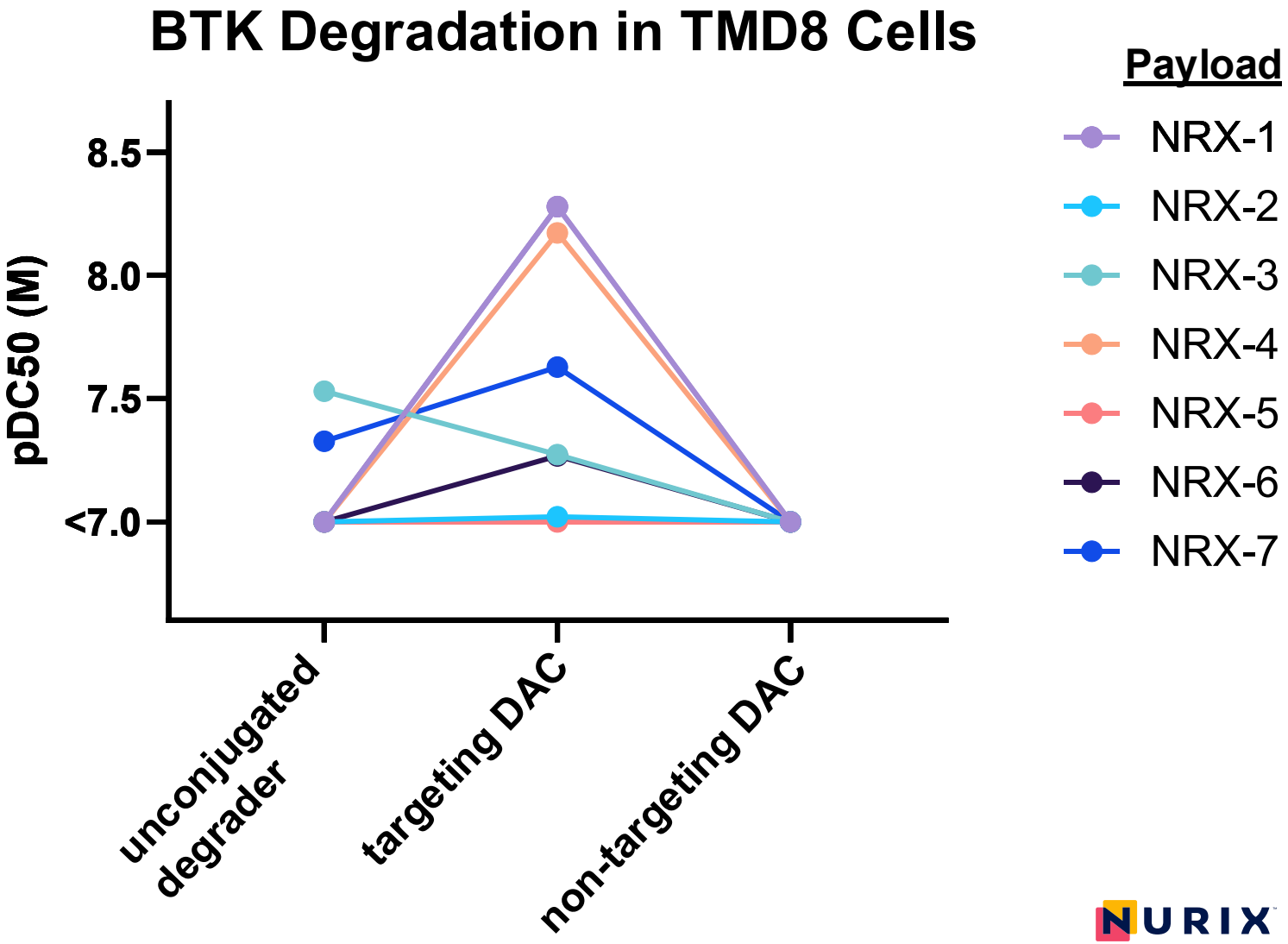
DACs Can Possess Superior Activity Compared to Unconjugated Degrader

Not all degraders show the same pattern of behavior as DACs





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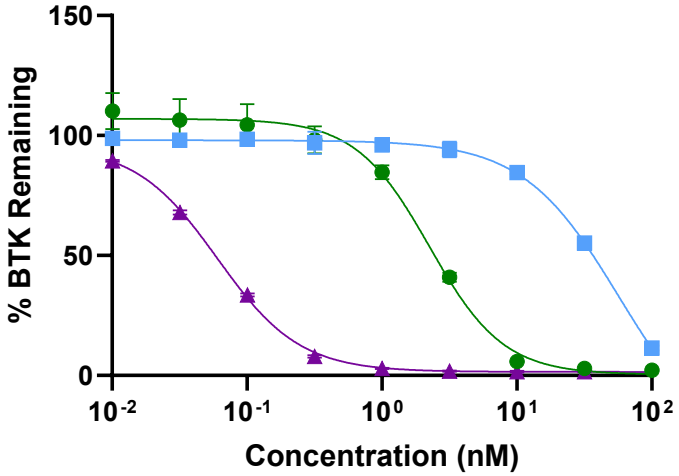
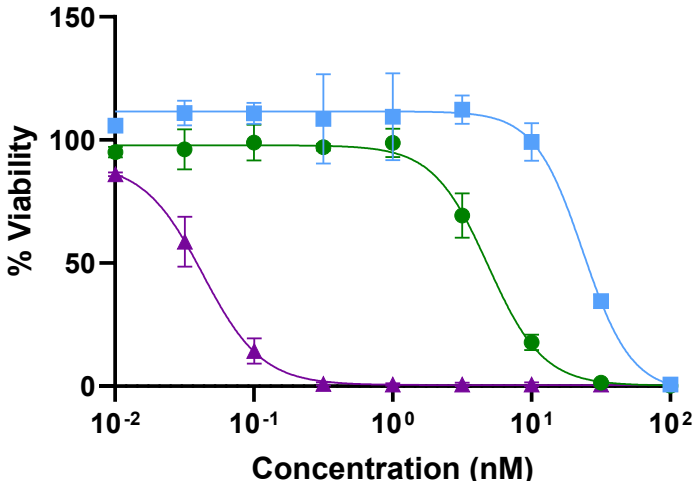
BTK-DAC Affords BTK Degradation, Cell Killing and Plasma Stability

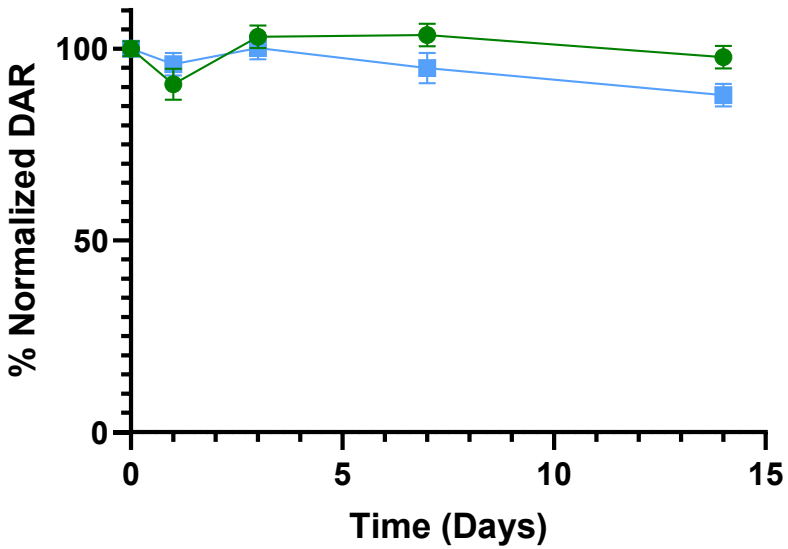
TMD8 Degradation (24h)



TMD8 Viability (4d)



Mouse Plasma Stability



CD79b-BTKd3

HER2-BTKd3

BTKd3

The BTKd3 payload is a BTK-targeted degrader with pM activity

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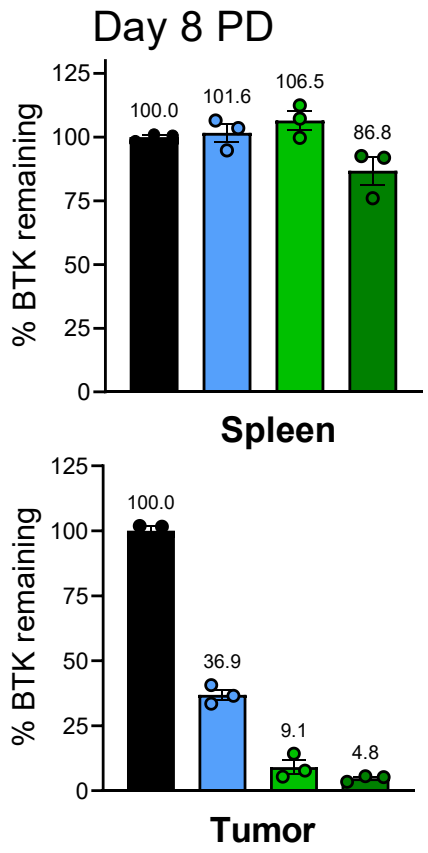
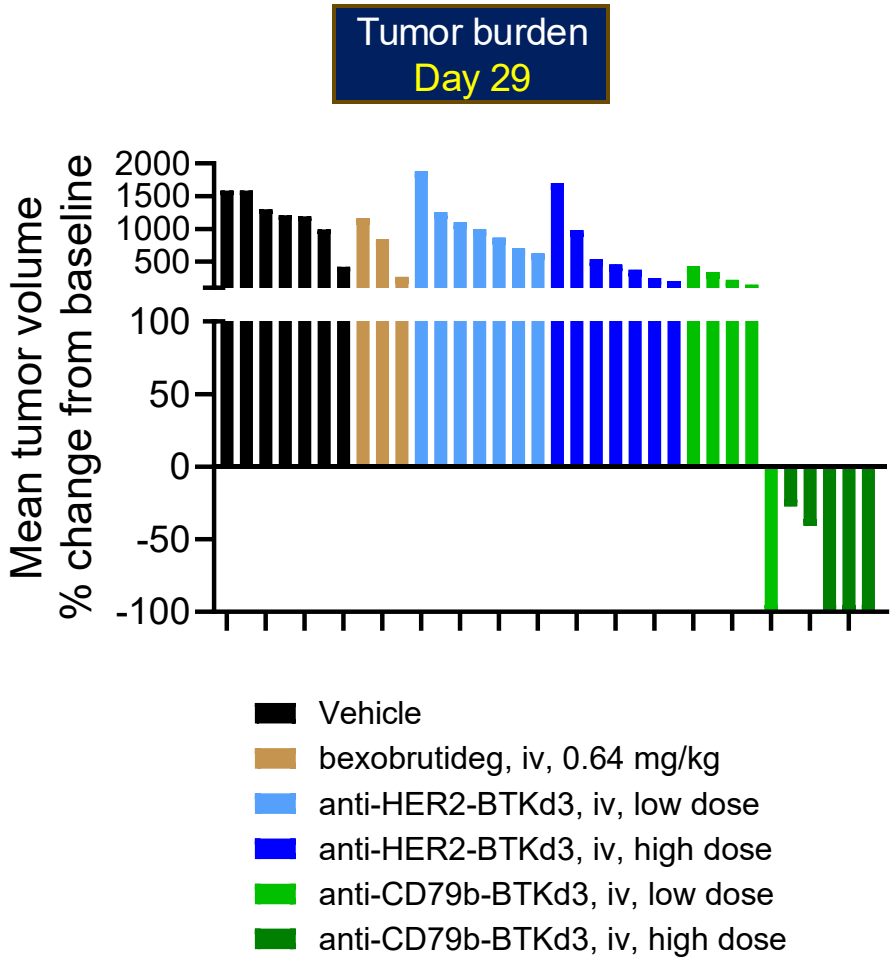
Stable BTK-DAC Affords Extended PD and Single-Dose Efficacy

TMD8 PD/efficacy study in mice; Single dose on day 1



Human-specific CD79b mAb allows selective tissue delivery



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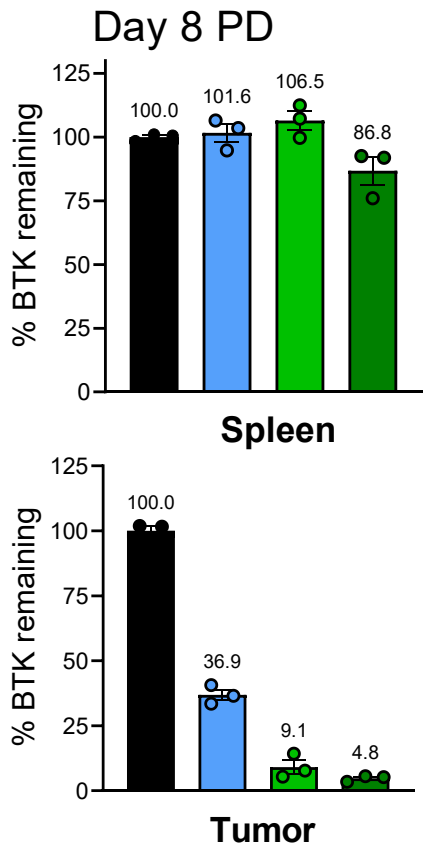

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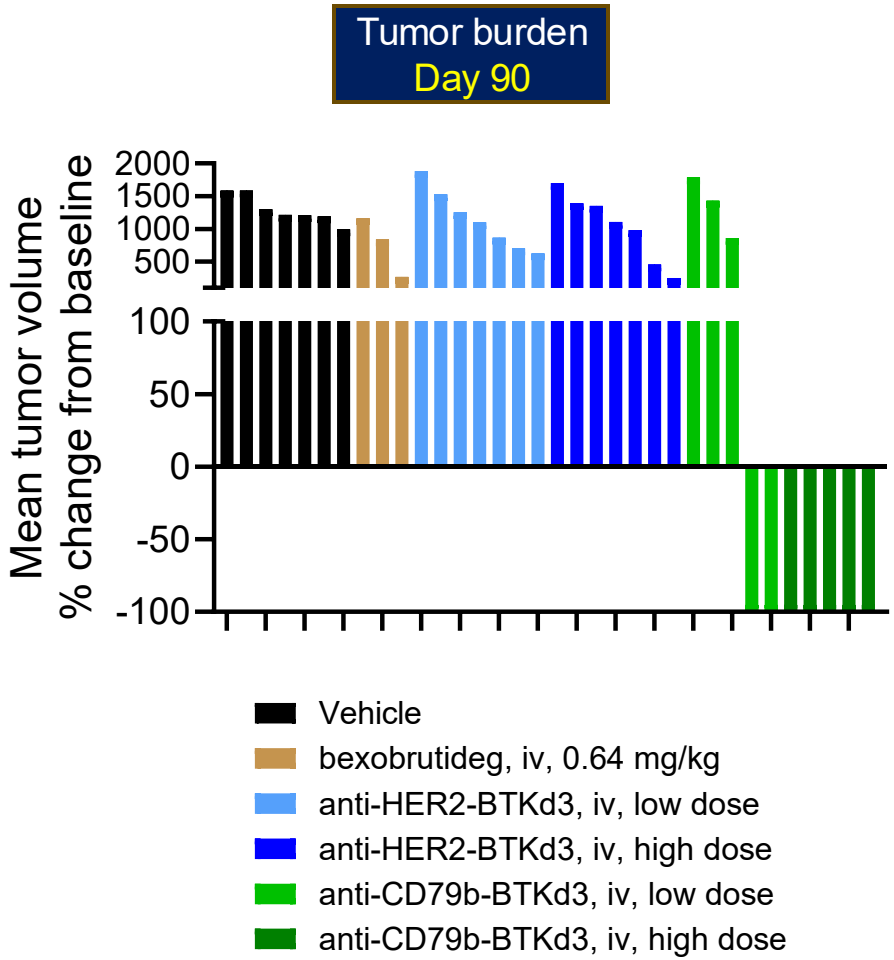

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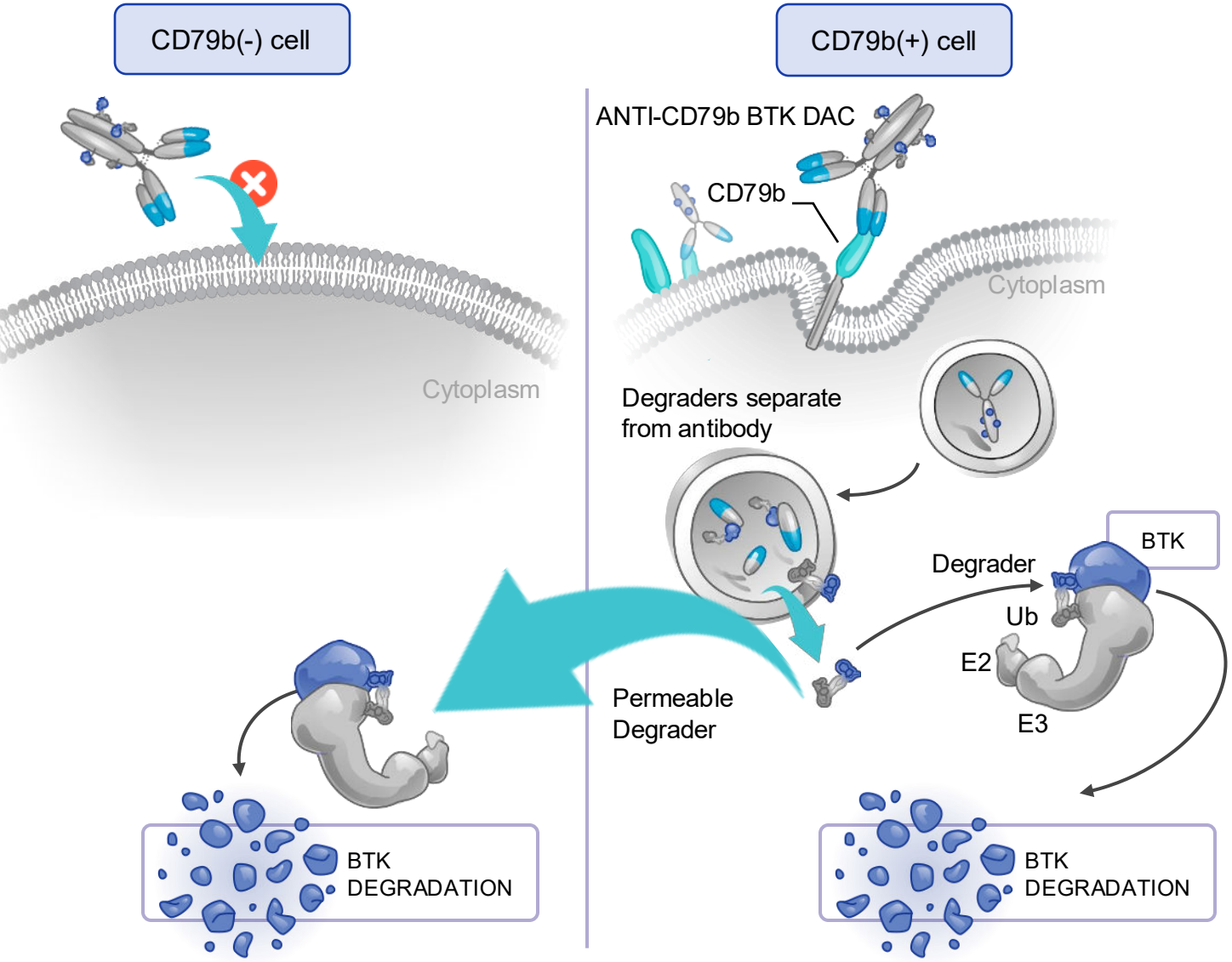
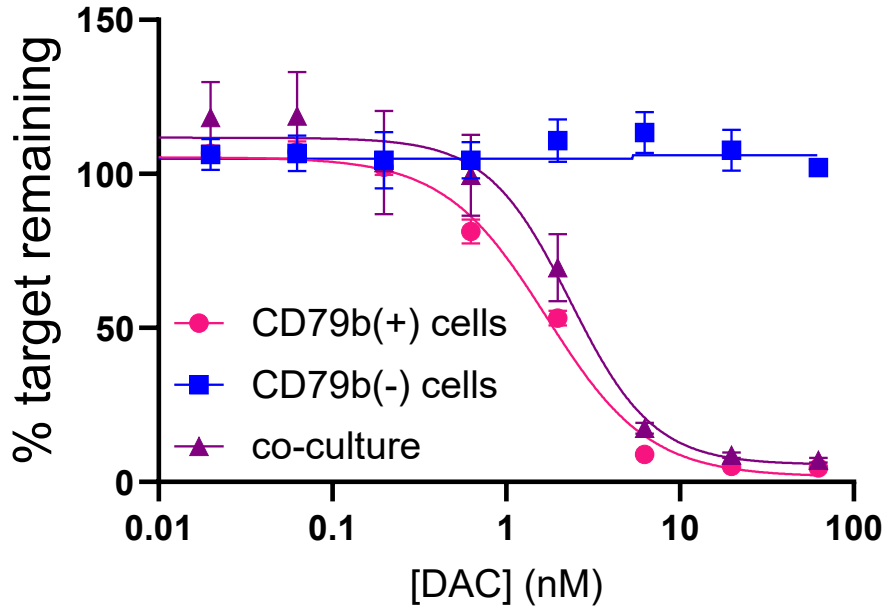
DAC Payload Properties Can be Tailored to Their Indication



DAC utilizing a permeable degrader shows bystander activity



- DACs with efficient bystander effects enable robust target modulation in all cell types within proximity of the antigen positive cells (such as solid tumors)

Note: co-culture uses antigen-negative cells with HiBiT-tagged BTK combined with antigen positive cells with untagged BTK

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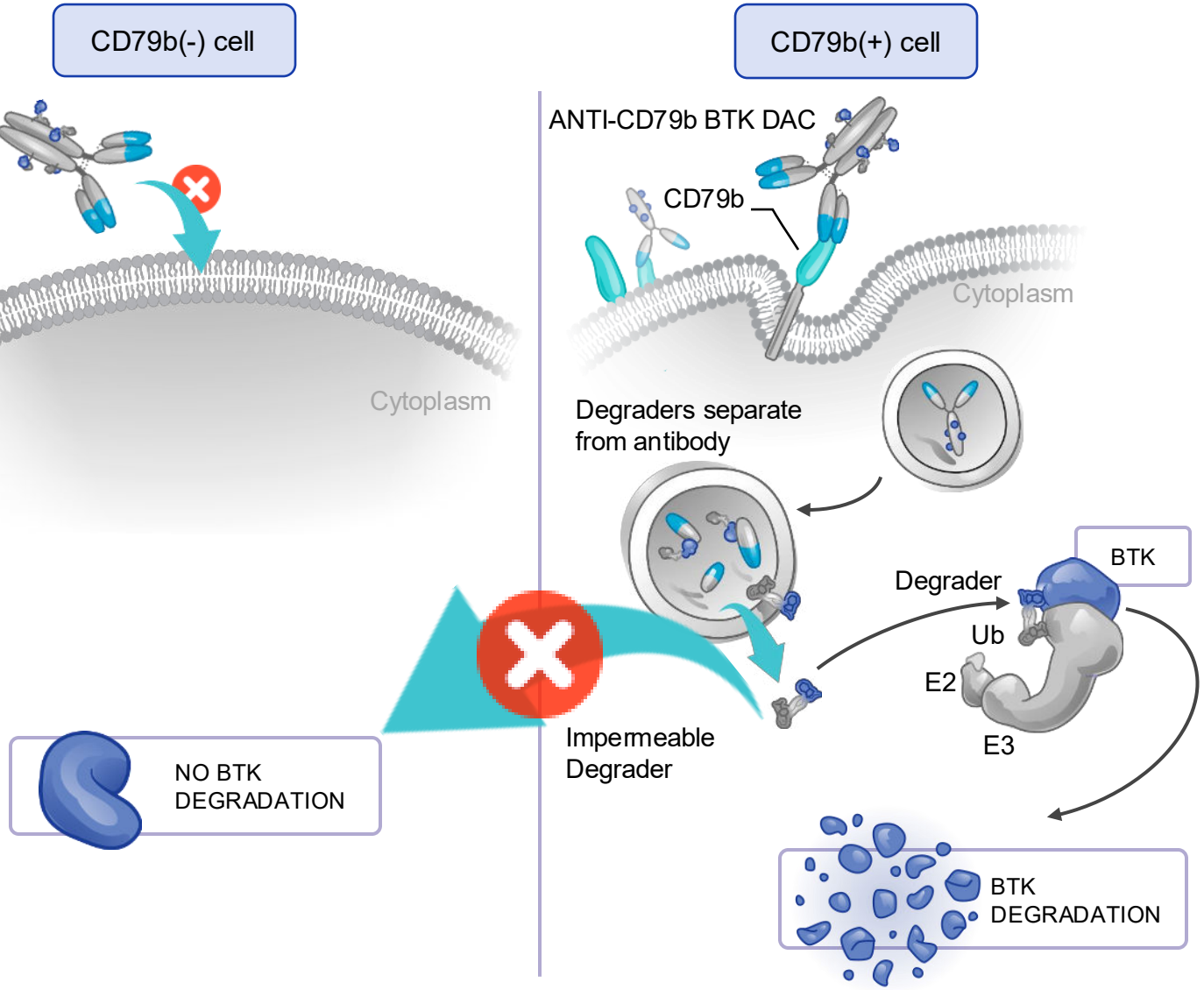
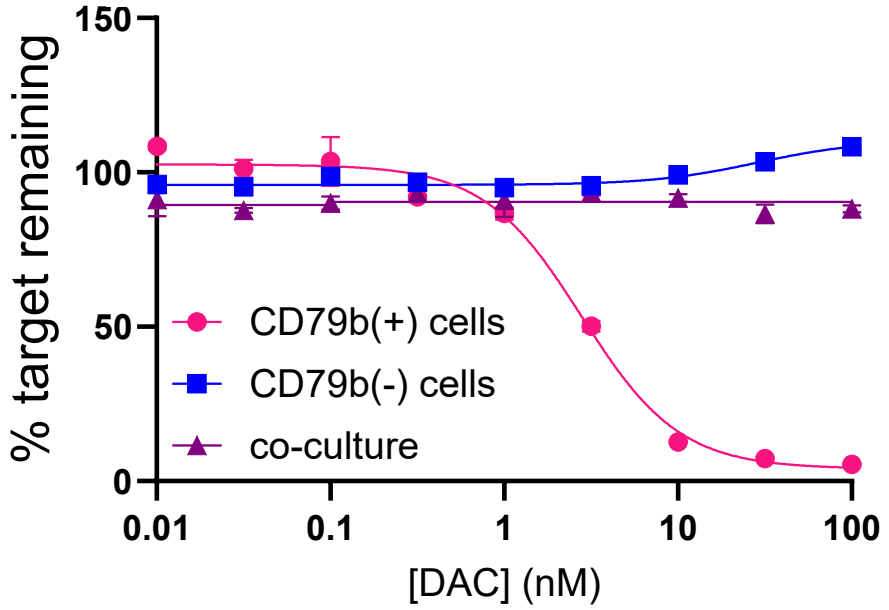
DAC Payload Properties Can be Tailored to Their Indication



DAC utilizing an impermeable degrader avoids bystander activity



- DACs with cell-specific delivery enable precise modulation of pathogenic cell types (such as inflammatory immune cells)

Note: co-culture uses antigen-negative cells with HiBiT-tagged BTK combined with antigen positive cells with untagged BTK

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DACs Represent the Next Frontier in Targeted Protein Degradation

Combining targeted degradation with the specificity of antibodies

- Pairing exquisitely targeted “knockout” biology with the cell-type and tissue selectivity of antibodies
- Potential for improved therapeutic index and broader applicability than standard ADCs
- Moving beyond oncology to tackle potentially any protein target in any tissue
- DAC discovery requires multi-parameter optimization and unbiased evaluation through matrix synthesis and screening
- DACs may enable new ligases for TPD with differentiated properties

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