Degrader Antibody Conjugates (DACs): Targeted Protein Degraders (TPDs) as Next Generation Antibody Drug Conjugate (ADC) Payloads

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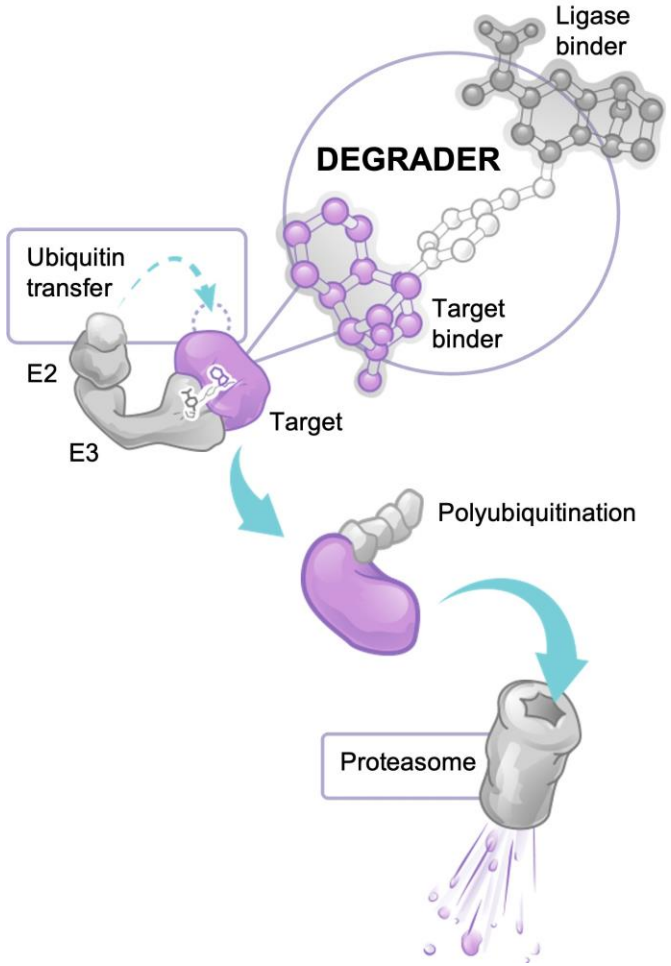
Targeted Protein Degradation

Harnessing the ubiquitin proteasome system to eliminate disease-causing proteins

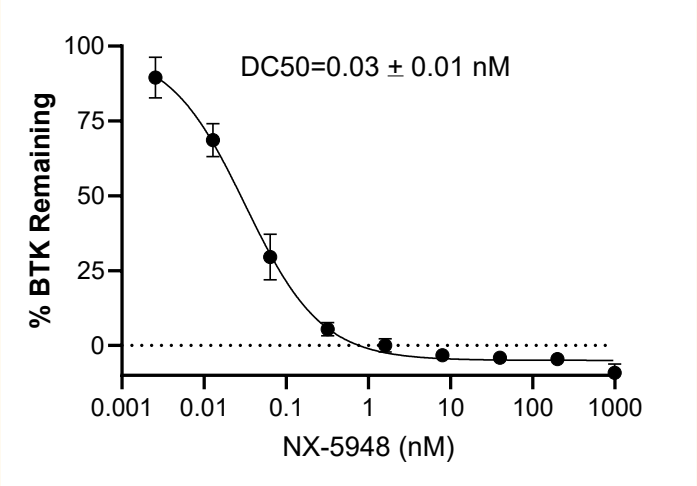


- Degraders target a specific protein or family of proteins
- Degraders catalytically eliminate ALL biological functions of proteins (scaffolding and enzymatic), recapitulating the biology of target “knockout”
- Degradation provides prolonged activity requiring resynthesis of the protein

Degraders Provide Many Potential Advantages Over Traditional ADC Payloads

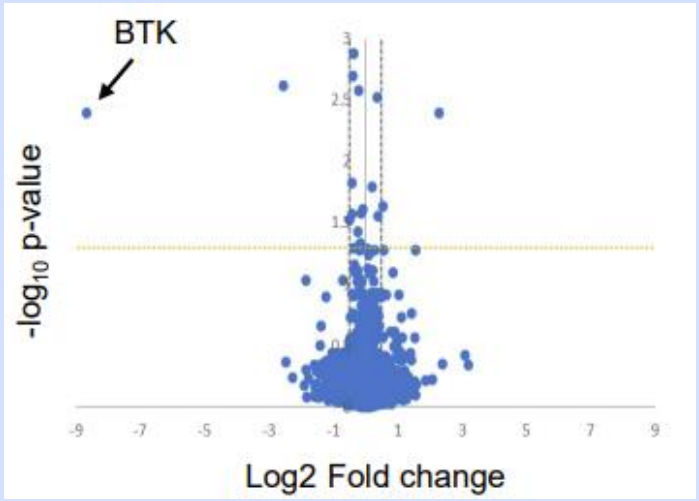
Picomolar Potency

BTK Degradation in TMD8 Cells



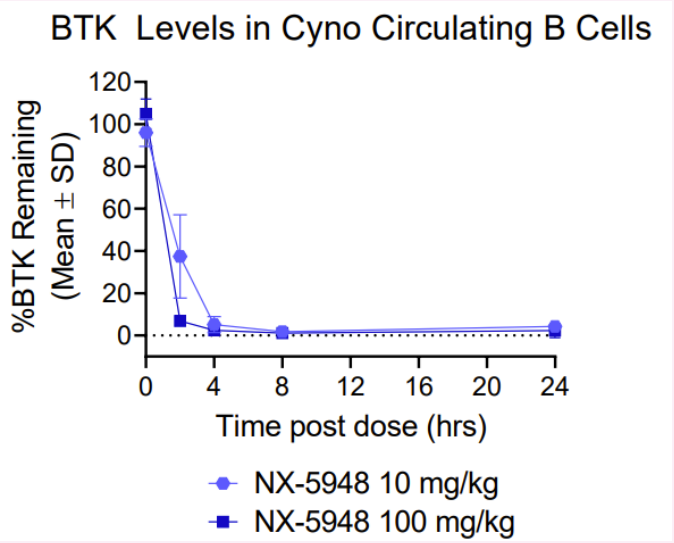
Exquisite Selectivity

Global Proteomic Analysis



Prolonged PD

Single Dose Target Suppression



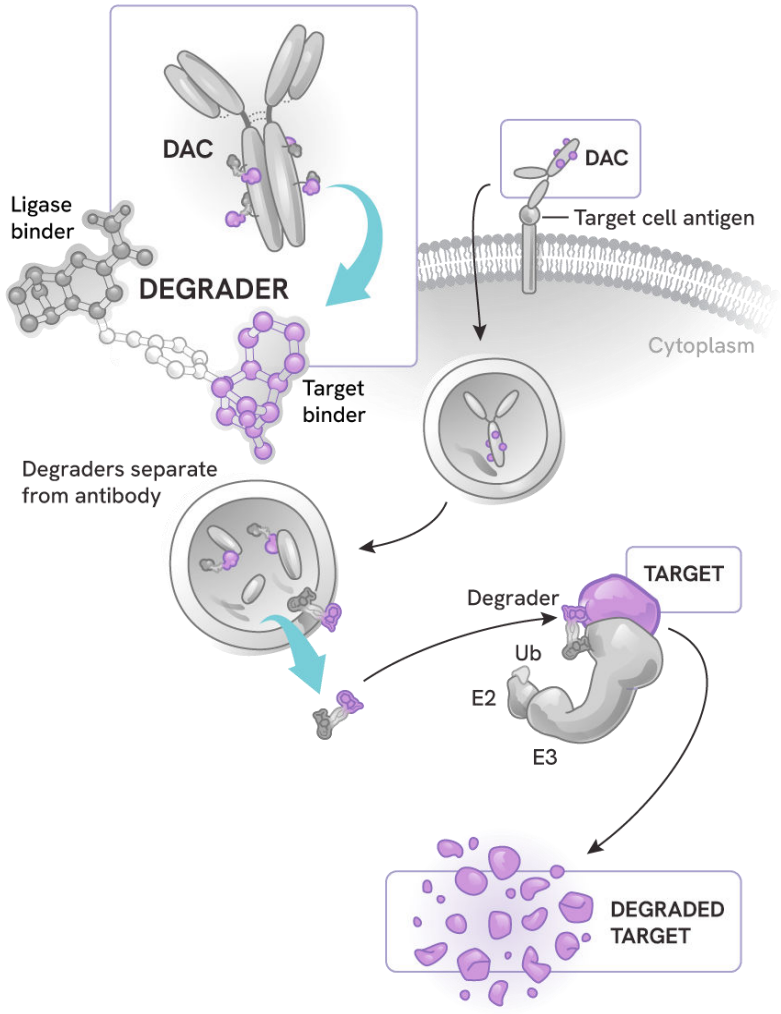
ADC, Antibody Drug Conjugate; BTK, Bruton's Tyrosine Kinase; PD, Pharmacodynamics

Advancing a New Therapeutic Class

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



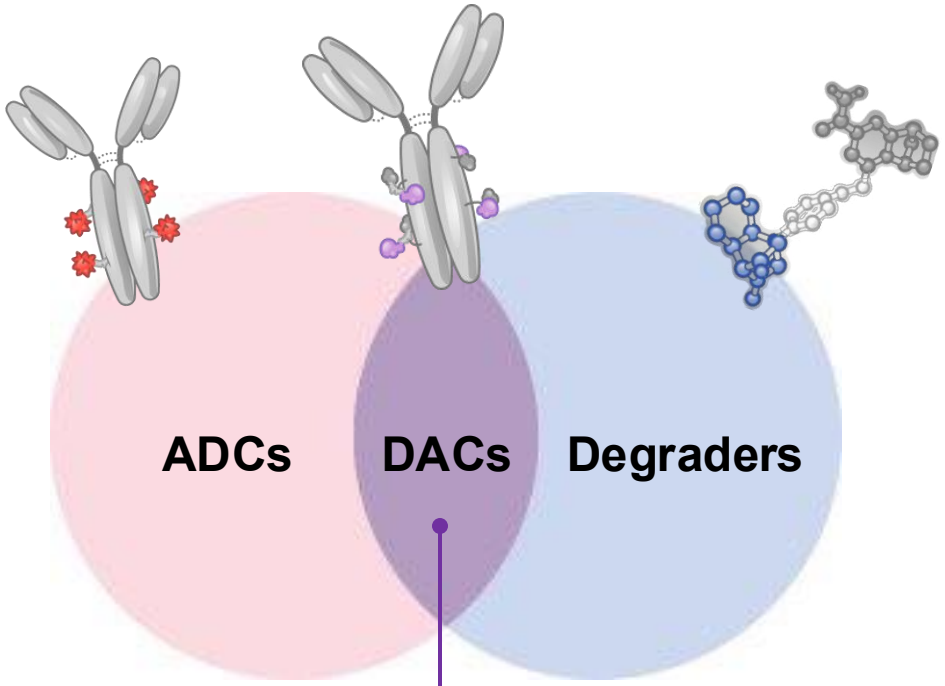
DAC, Degrader Antibody Conjugate

DACs Can Unlock New Targets, Enhance Selectivity, and Enable Access to a Broader Set 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 Aidixi 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 bifunctional degraders in the clinic

Degrader Name	Target	Indication
ARV-102	LRRK2	Neurology
ARV-471	ER	Oncology
ARV-766	AR	Oncology
ASP3082	KRAS G12D	Oncology
BGB-16673	BTK	Oncology
CC-94676	AR	Oncology
CFT-1946	BRAF V600E	Oncology
CFT-8634	BRD9	Oncology
CG001419	NTRK	Oncology
DT-2216	BCL-xL	Oncology
FHD-609	BRD9	Oncology
GT20029	AR	Oncology
HP518	AR	Oncology
HSK29116	BTK	Oncology
KT-253	MDM2	Oncology
KT-333	STAT3	Oncology
GS-6791/NX-0479	IRAK4	Immunology
NX-2127	BTK, IKZF1/3	Oncology
NX-5948	BTK	Oncology / I&I
PRT3789	SMARCA2	Oncology

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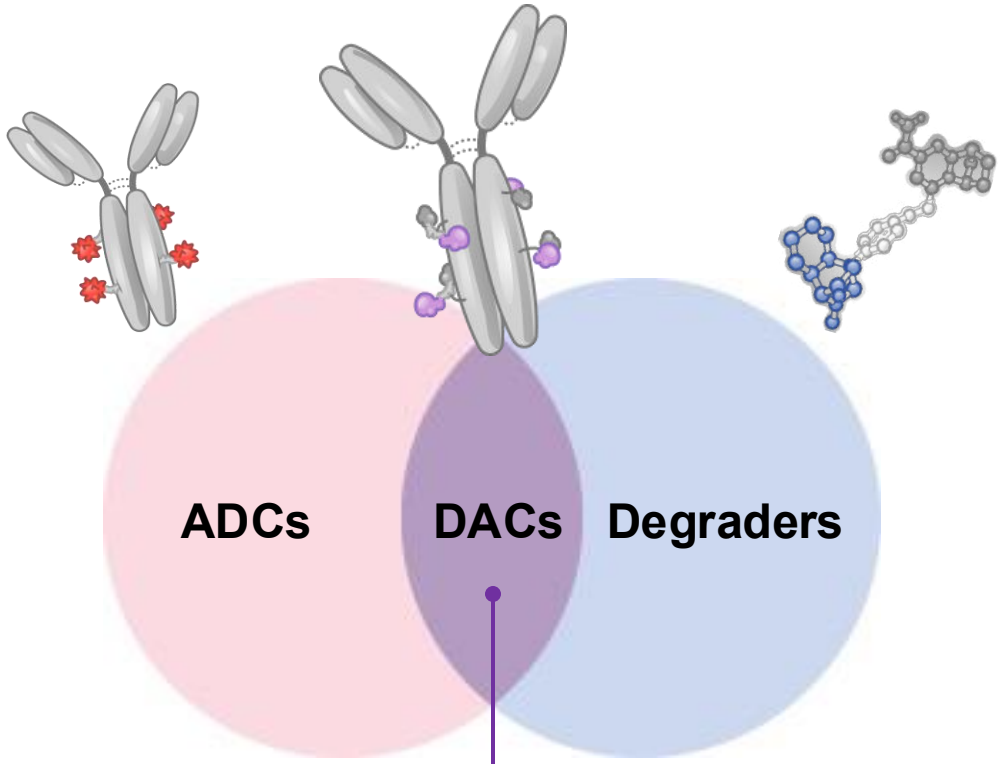
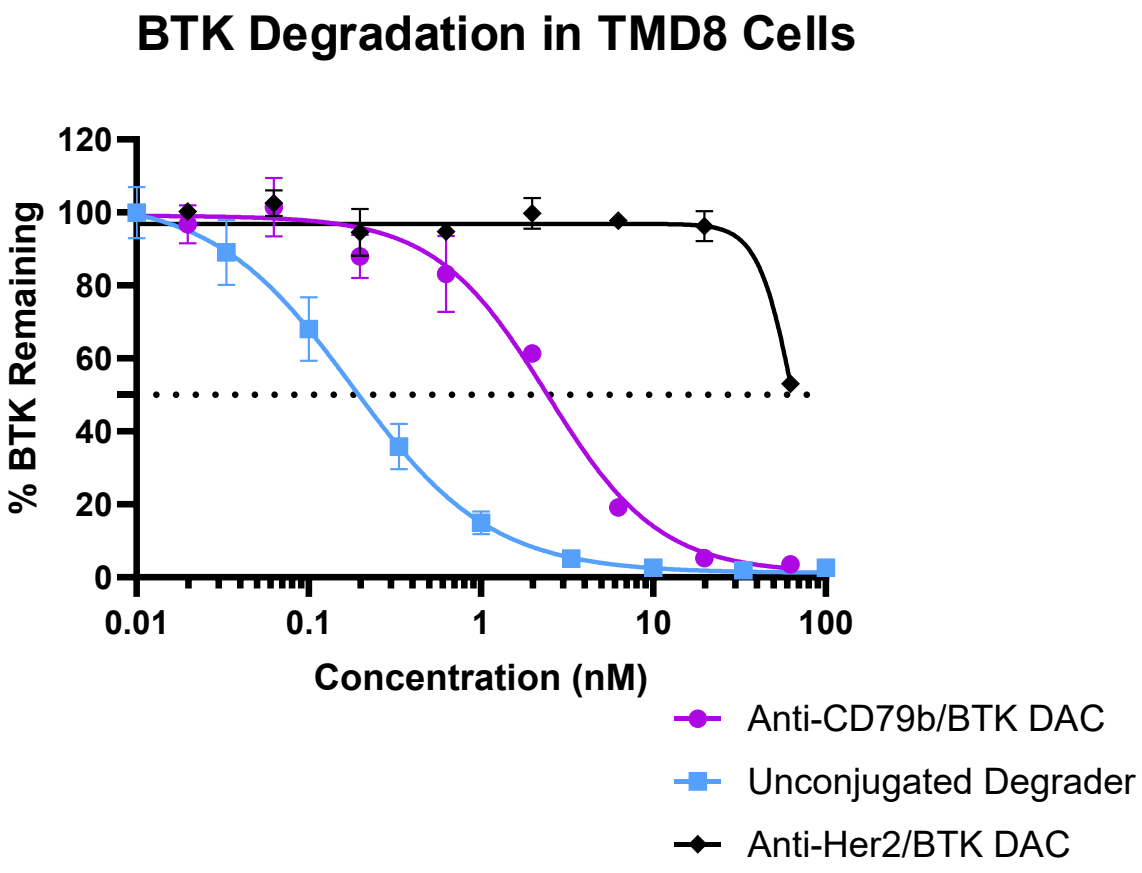
A BTK Degrader Conjugated to a CD79b Antibody Demonstrates Antigen-Selective Delivery and Degradation



Antigen provides cell and tissue selectivity

Degrader target and ligase expression provide cell and tissue selectivity

DAC provides multi-layer selectivity



TMD8 cells are CD79b(+) and Her2 (-)

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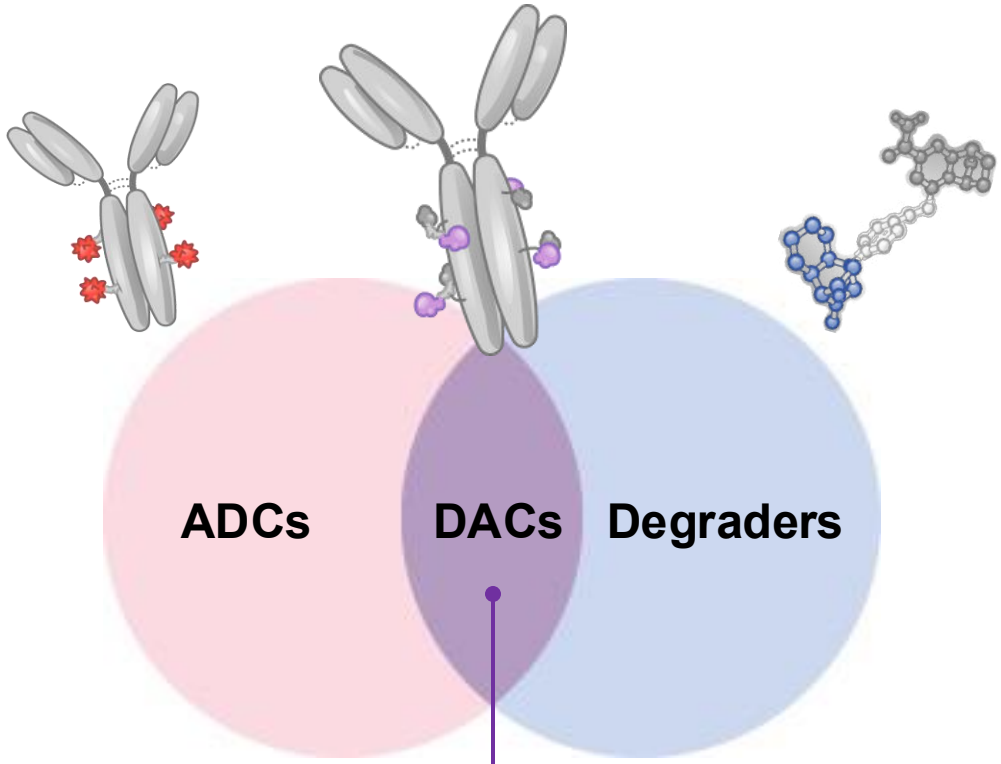
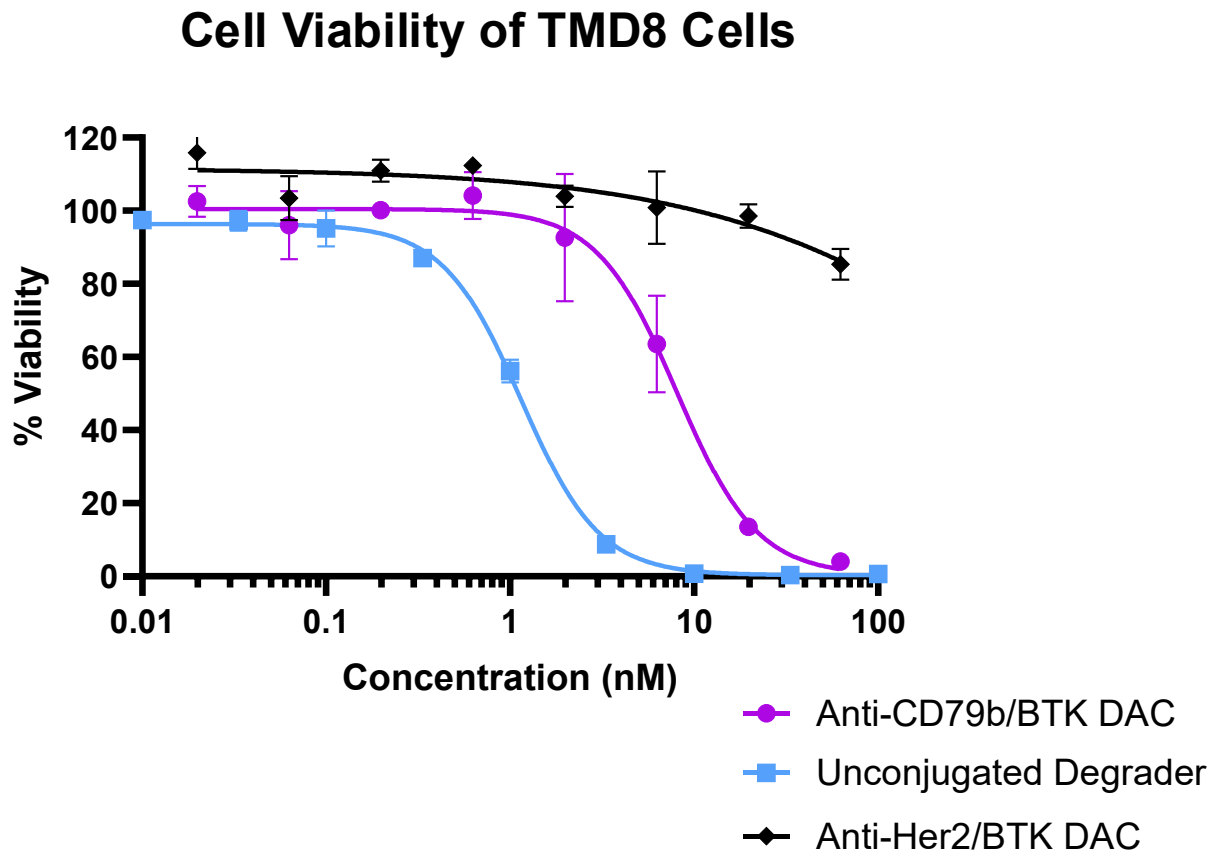
A BTK Degrader Conjugated to a CD79b Antibody Demonstrates Potent Antigen-Selective Delivery and Cell Killing

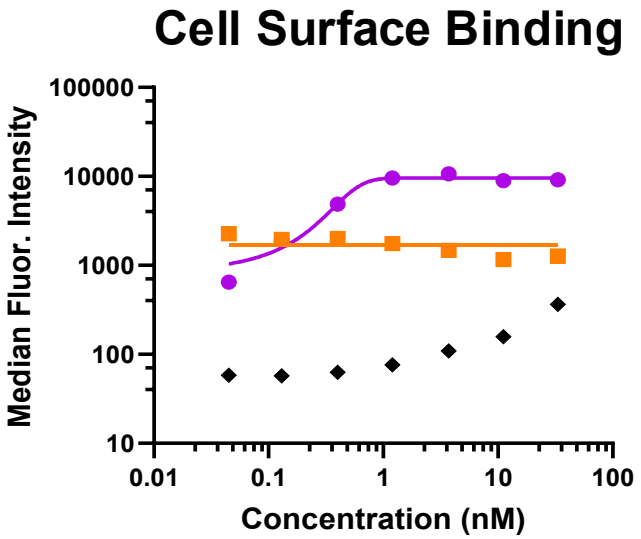


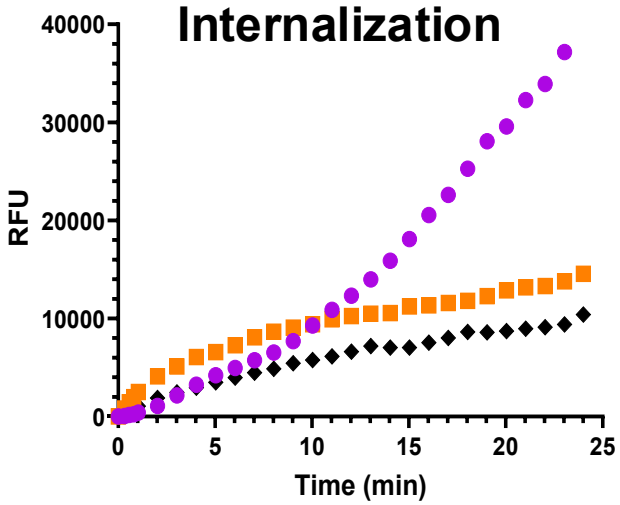


TMD8 cells are CD79b(+) and Her2 (-)

TMD8 cells are CD79b^{+} and Her2^{-}

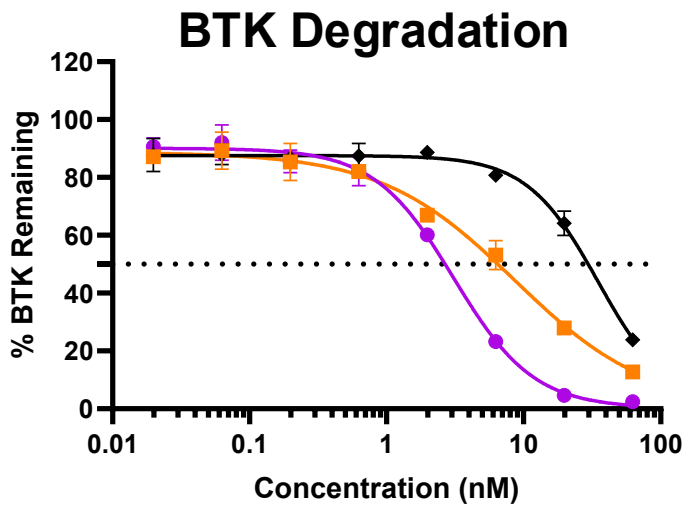
Cell Surface Binding and Internalization Strongly Impacts DAC Activity

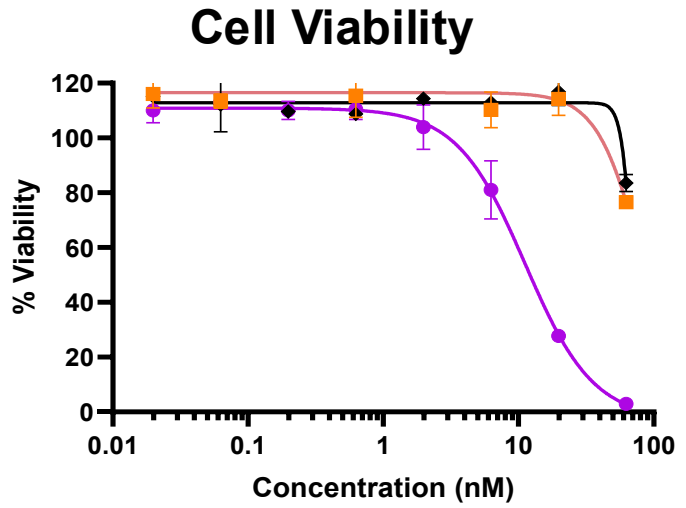




Anti-CD79b/BTK DAC
Anti-CD19/BTK DAC
Anti-Her2/BTK DAC

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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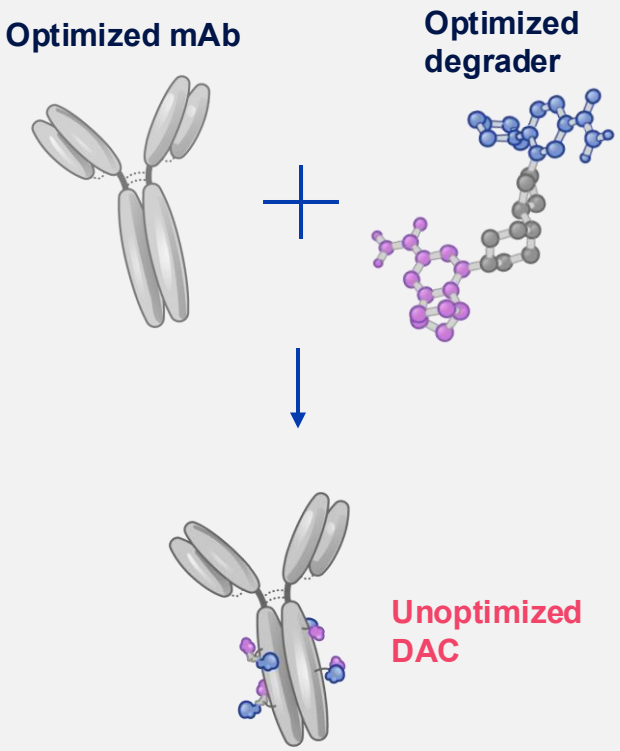
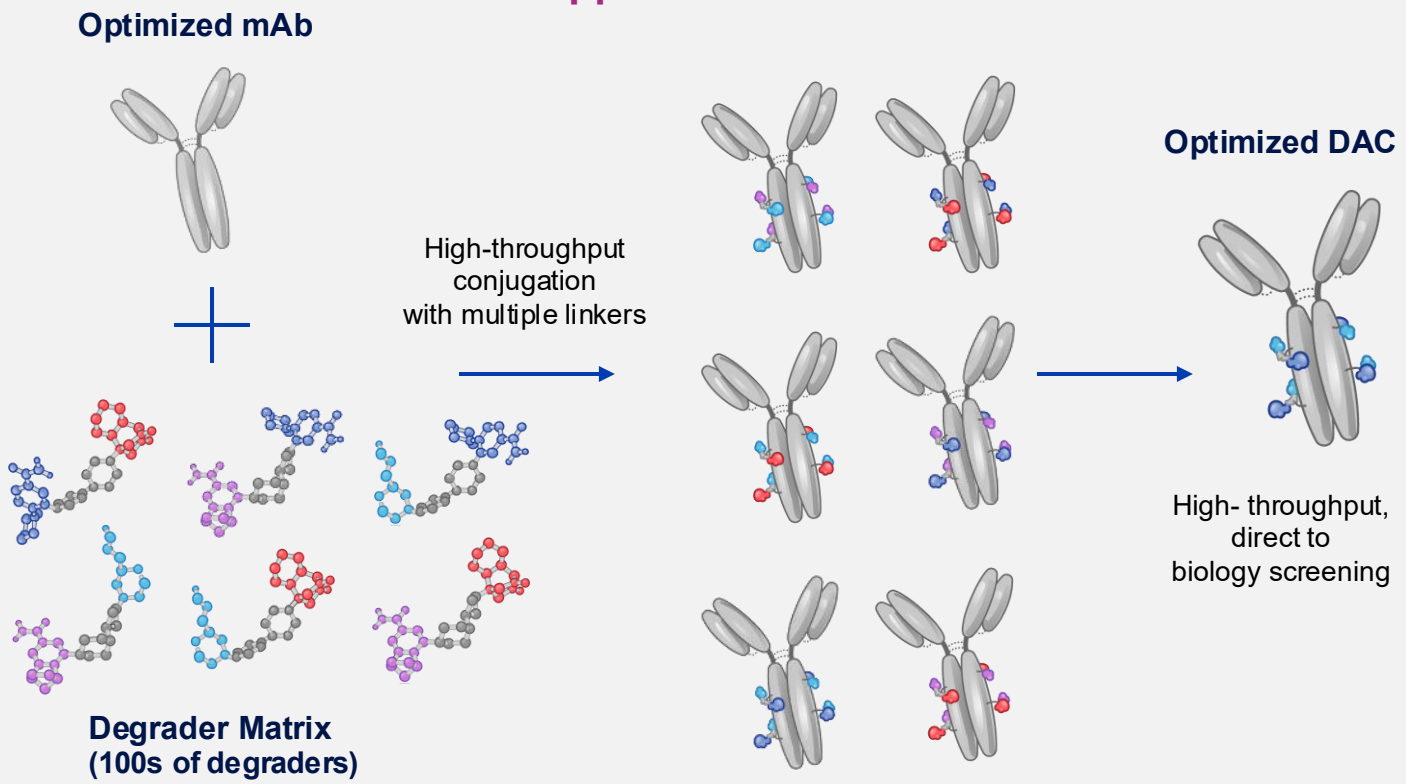
Next-Generation DAC Design Requires Multi-Parameter Optimization

Agnostic assessment of design elements using matrix synthesis and screening

Simplistic Approach



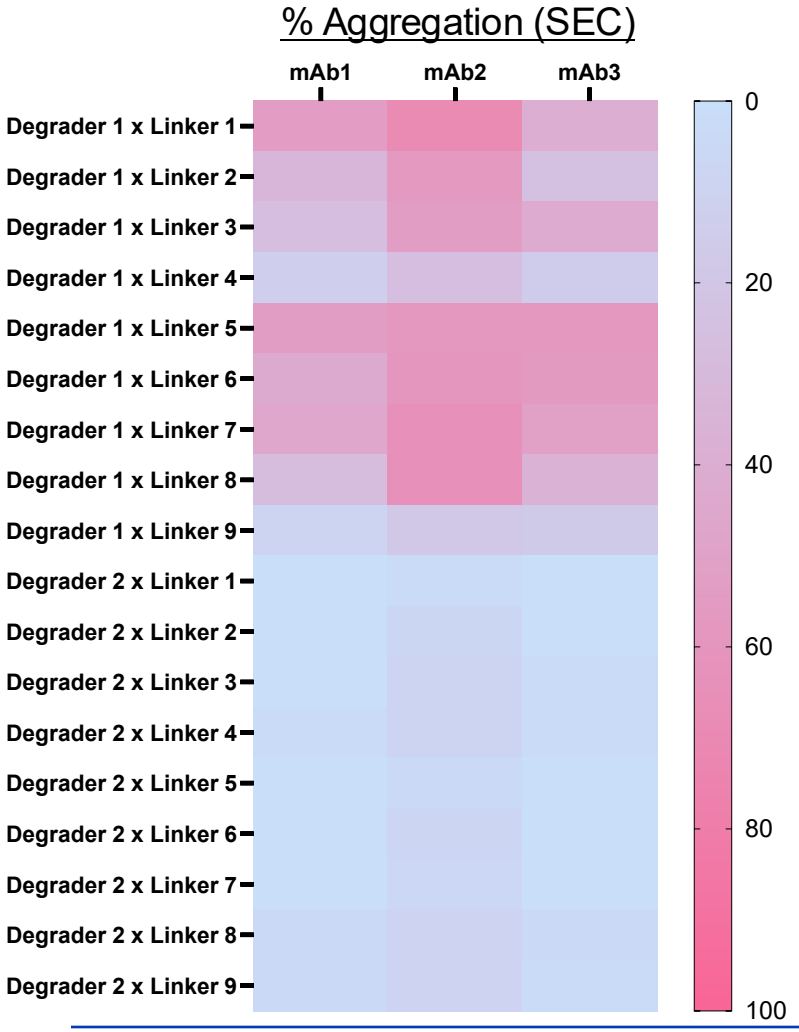
Nurix Approach: Matrixed DAC



DAC 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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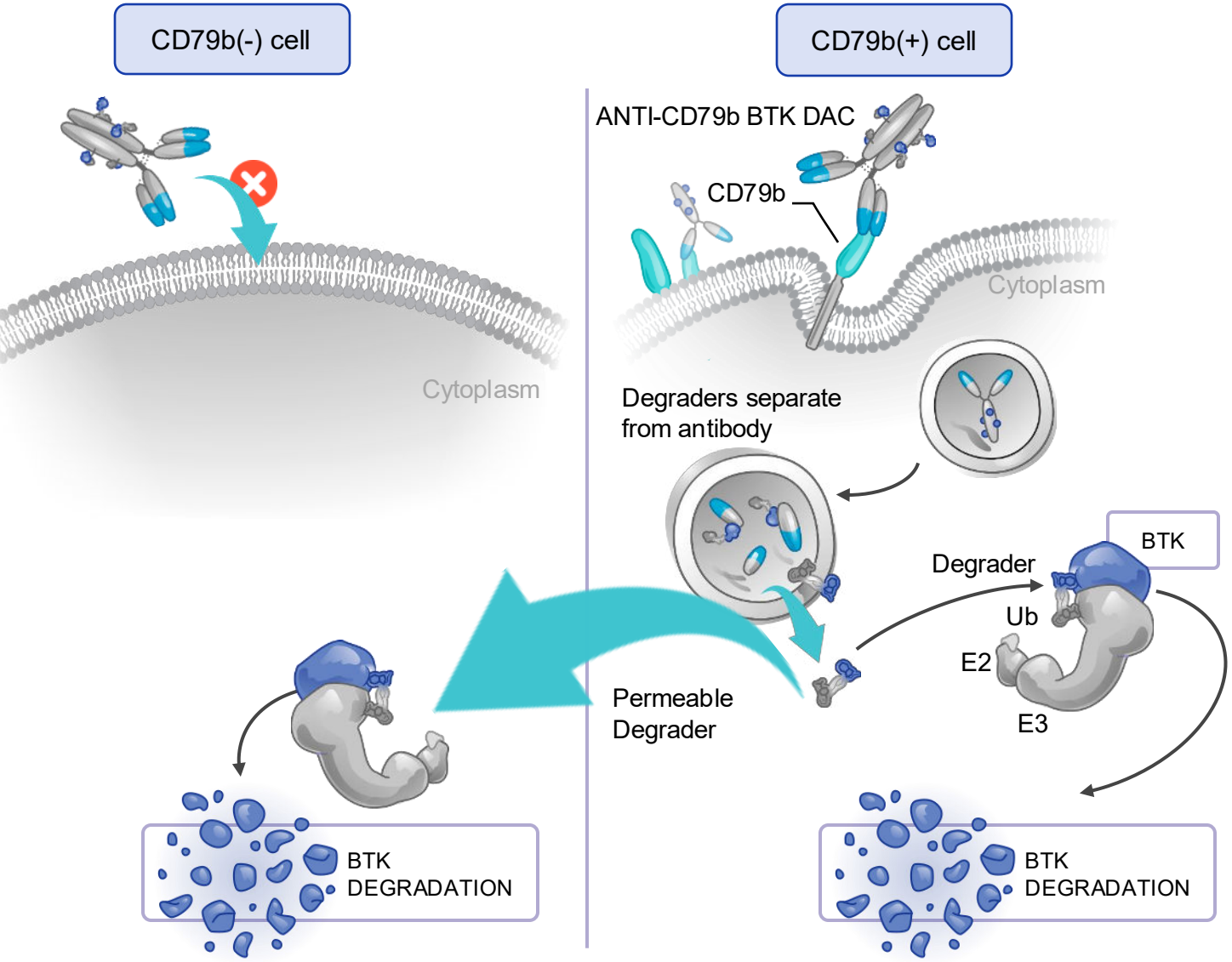
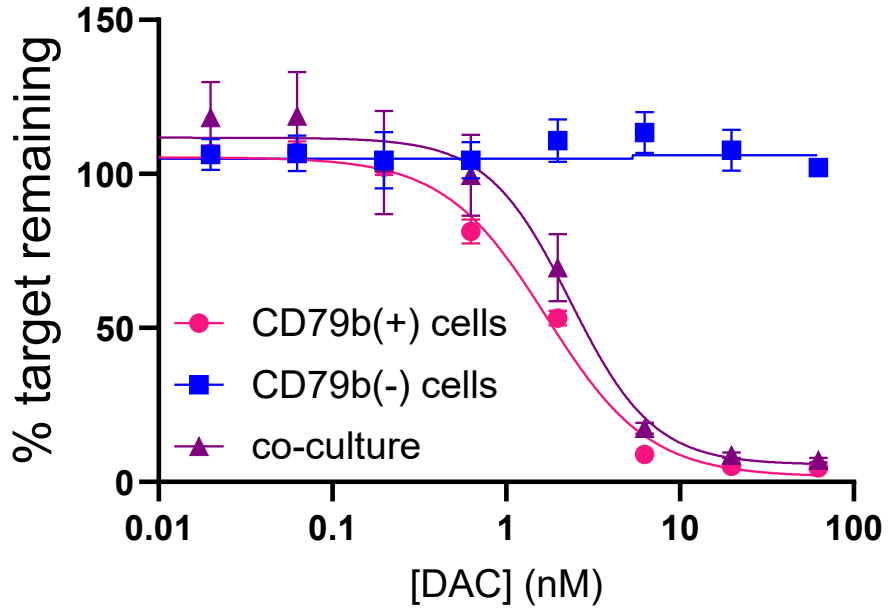
DAC Payload Properties Can be Tailored to Their Indication



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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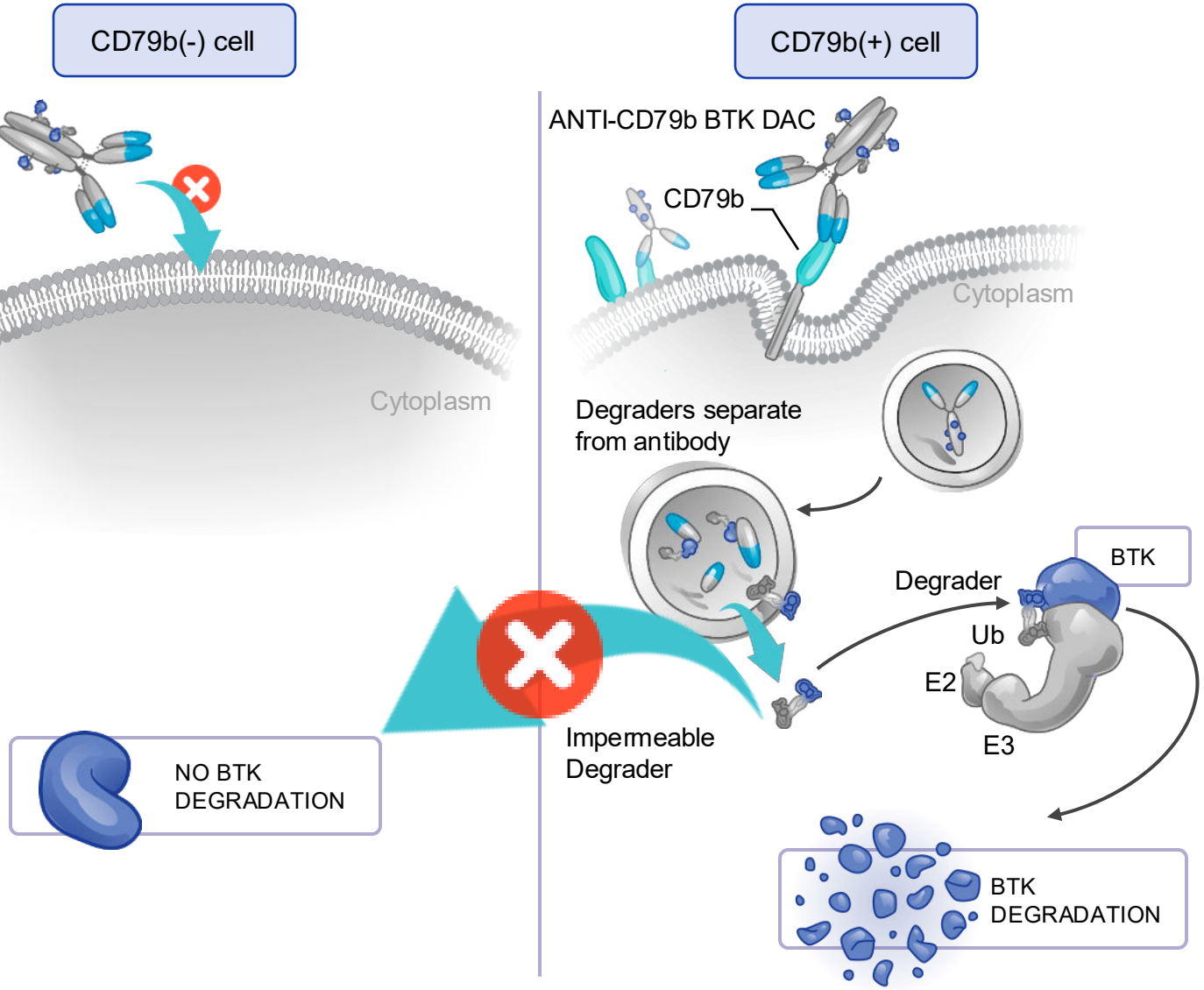
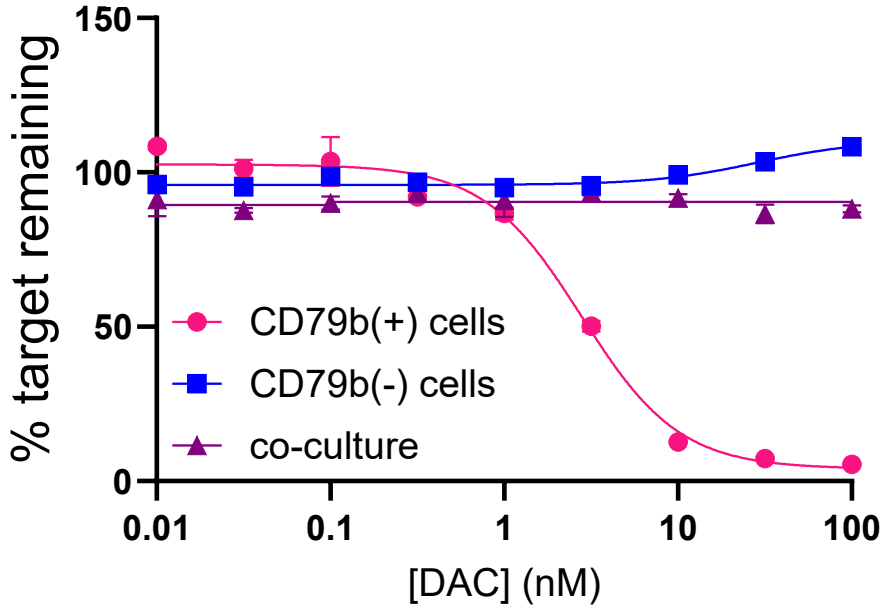
DAC Payload Properties Can be Tailored to Their Indication



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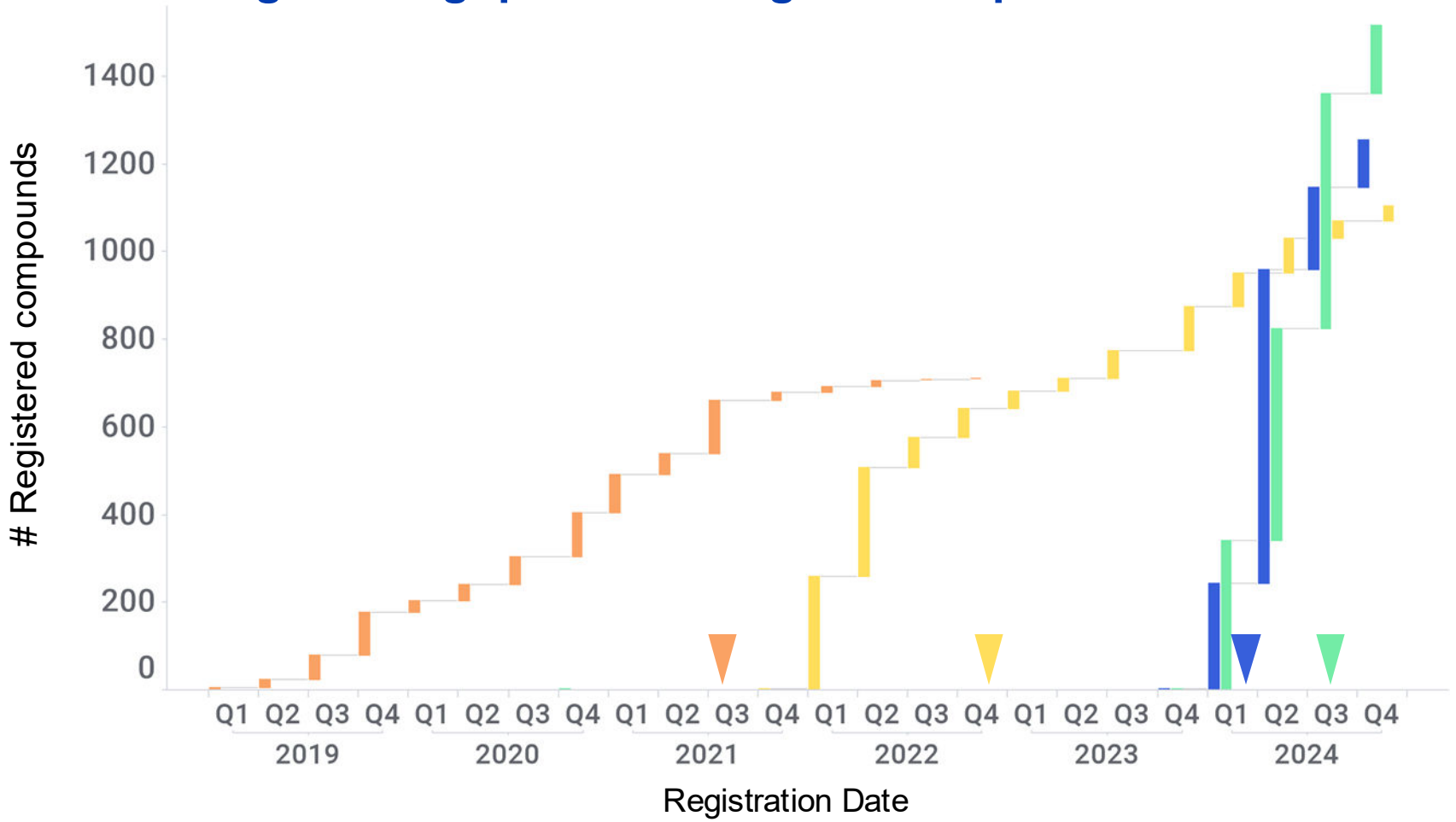
Automation Drives Our Ability to Scale Degrader and DAC Discovery, Drastically Shortening the Time to Identify Potent Leads

High-throughput screening with bespoke libraries



Target A; Manual Synthesis

Target B; Semi-automated Synthesis

Target C

Target D

Automated Synthesis

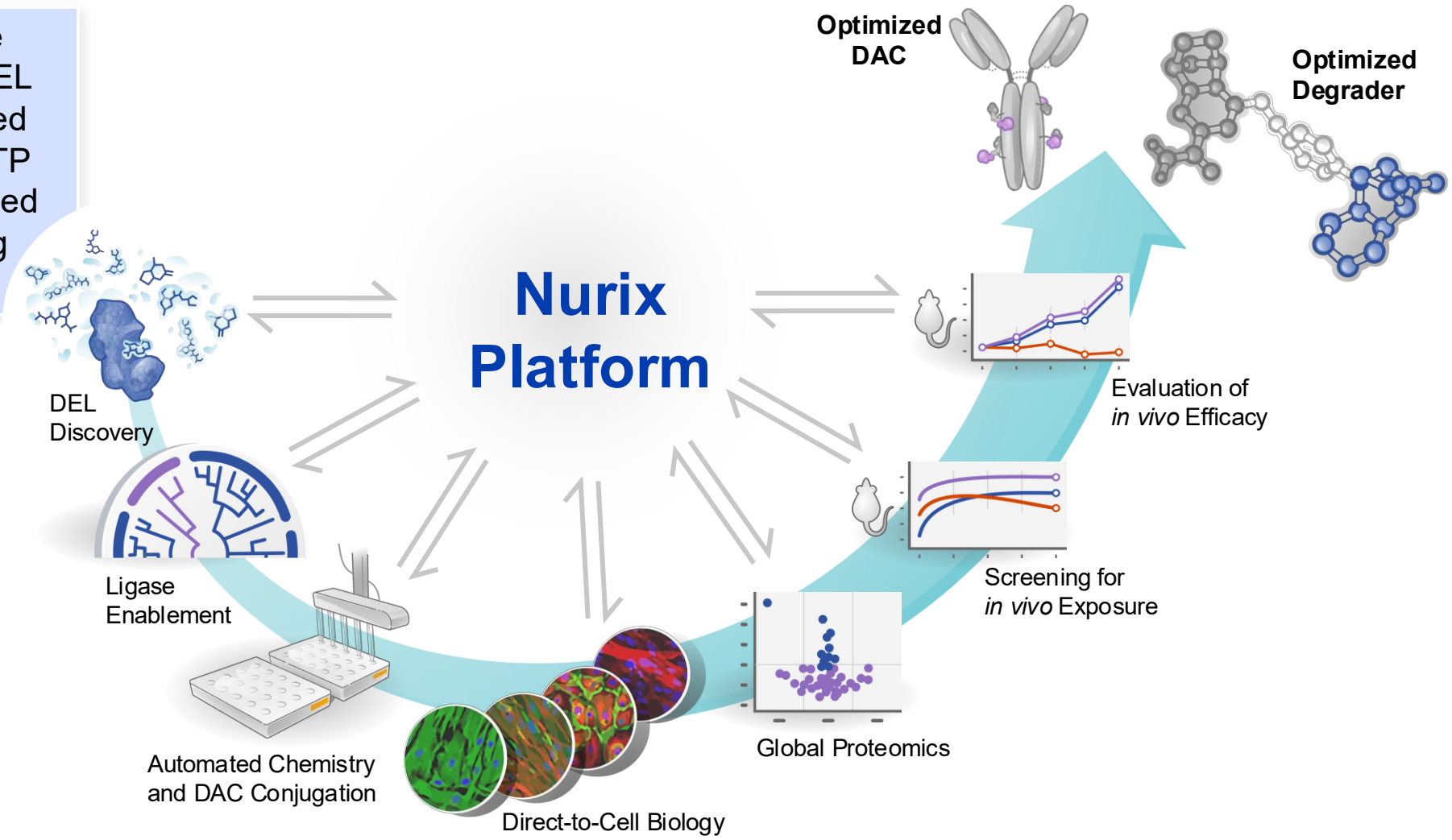
▼ nM degrader synthesized

Targets C&D achieved <10 nM DC_{50} in ≤6 months from optimized binders.

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

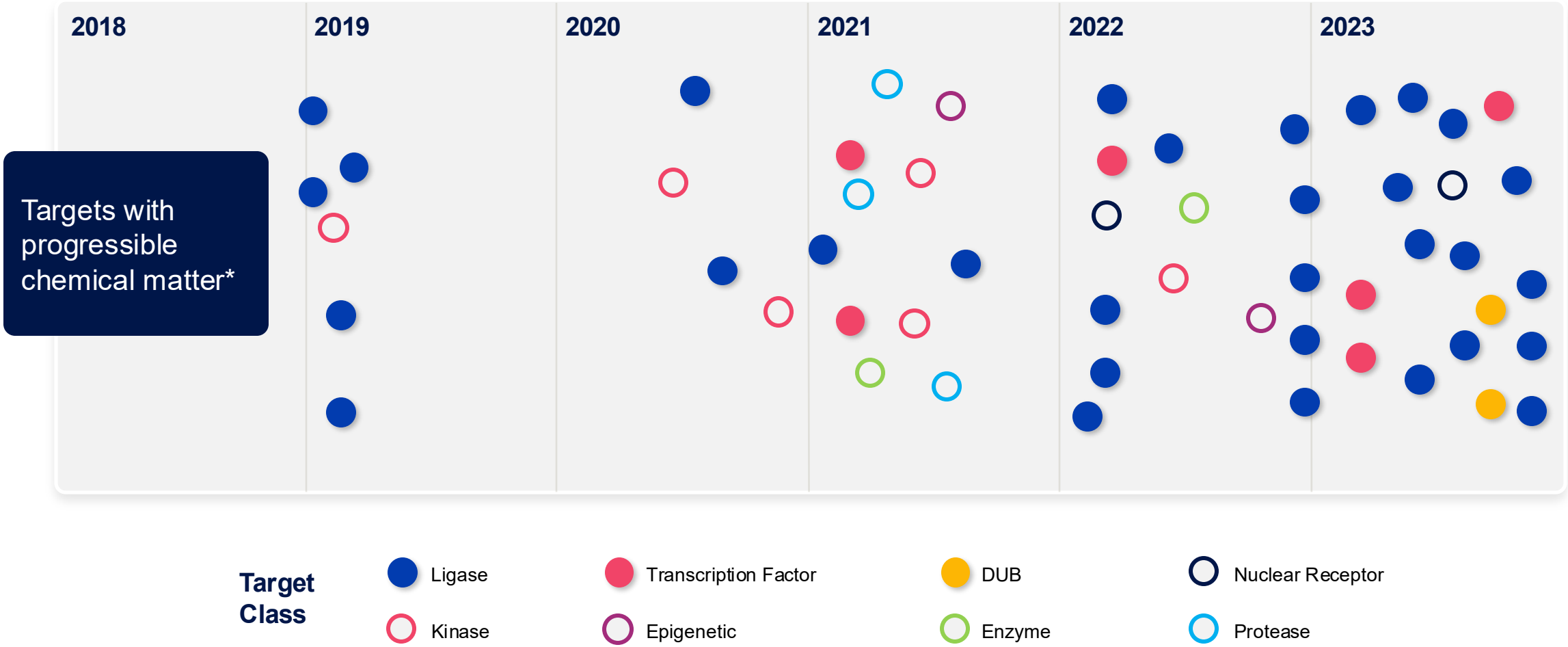
Industry Leading Discovery Engine for TPD and DAC Drug Discovery

Our discovery engine leverages the combined power of our data-rich DEL ligand-finding capabilities, automated chemistry and DAC conjugation, HTP cell and *in vivo* biology, and advanced machine learning to accelerate drug discovery



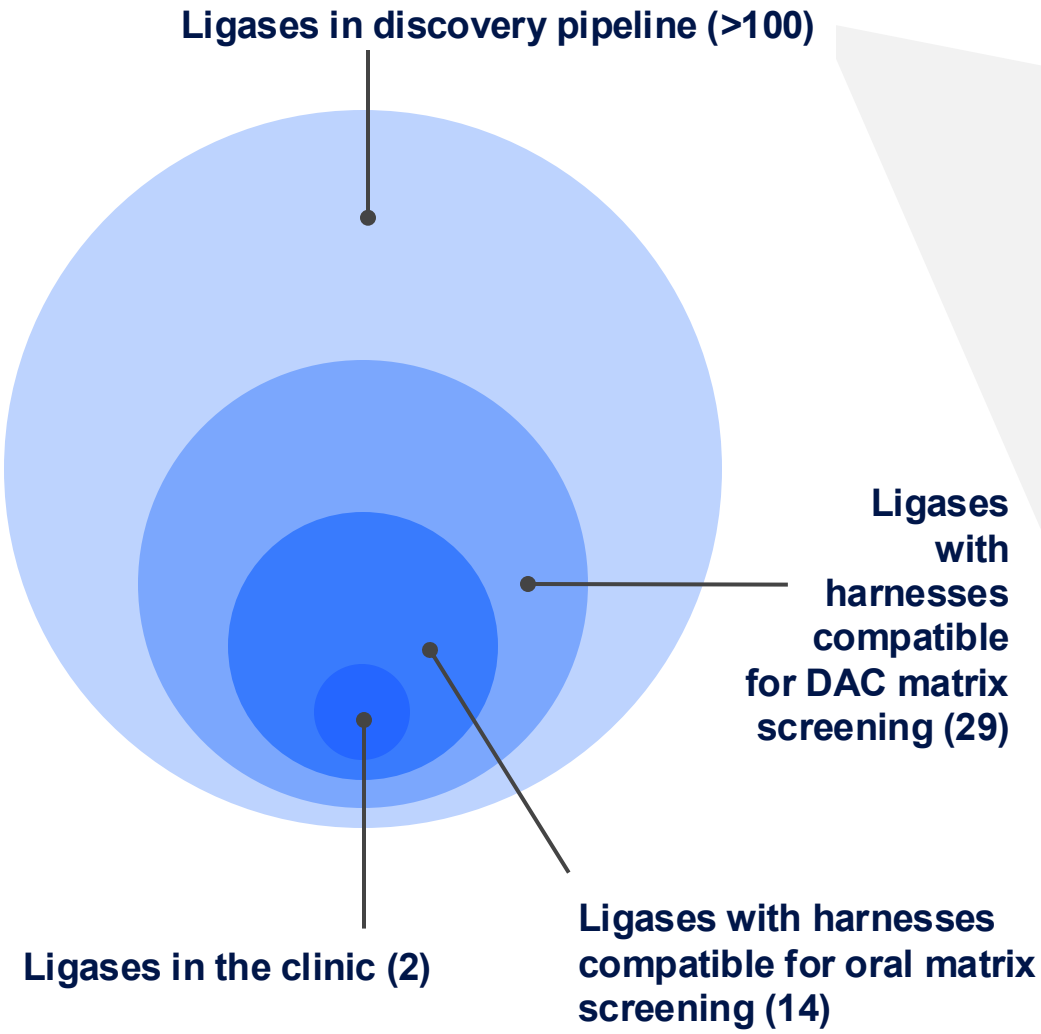
TPD, targeted protein degradation; DEL, DNA encoded library

Nurix's Platform Enables Efficient Discovery of Ligands for Many Challenging to Drug Proteins, Including E3 Ligases

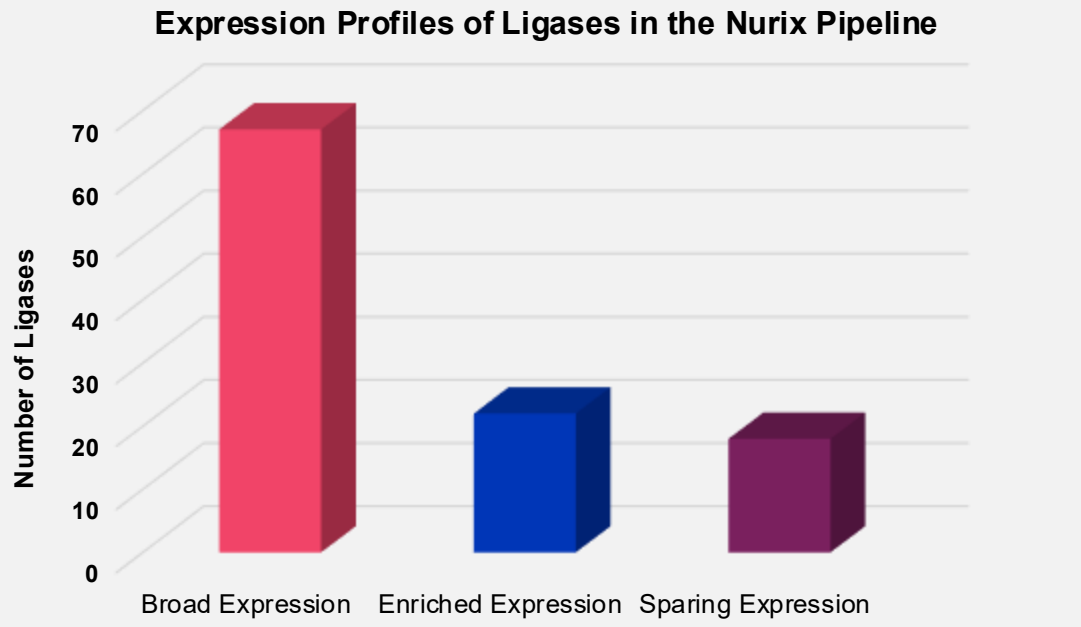


All series validated by more than 2 orthogonal assays
** binders with IC_{50} or K_D < 10 µM*

Our Evolving Ligase Pipeline is Expanding the Reach of Targeted Protein Degradation



Our broad collection of ligases gives us access to novel biology



Ligase levels elevated in a single tissue relative to others. e.g., Tumor specific ligases for improved specificity

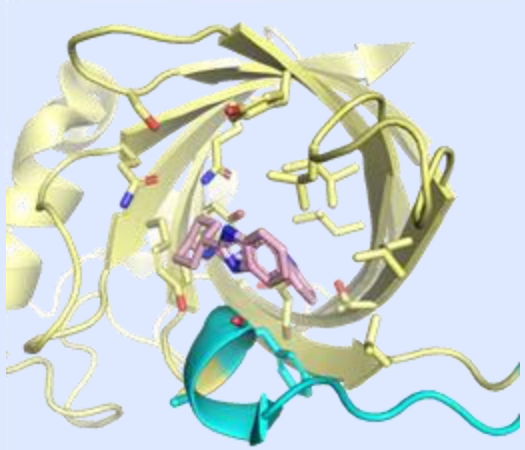
Ligase levels undetectable in a tissue and broadly expressed otherwise. e.g., Heart sparing for reduced toxicity

Case Study: Ligase with Potential for Platelet Sparing Degradation Profile

- GID4 is broadly active on diverse targets with Pro/N-degrons*
- Tissue sparing expression profile**
- GID4 Degraders could spare platelets to further augment antibody selectivity, improving therapeutic index of DAC

Substrate-bound and PFI-7 ligand bound structures share a common conformation*

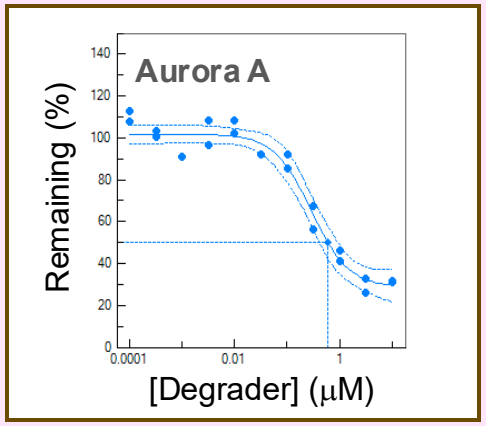
No degradation of BRD4 observed with literature GID4 binder PFI-7



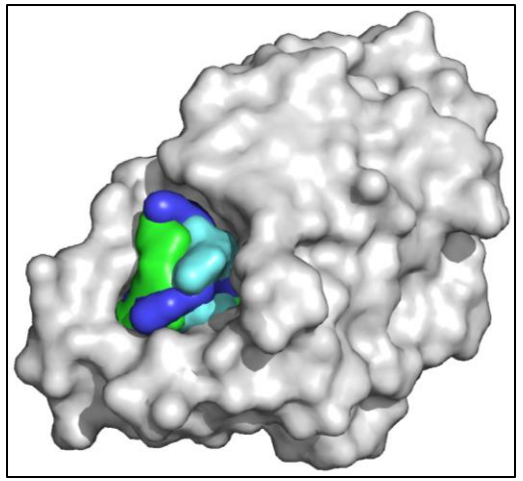
PFI-7 bound structure

Nurix DEL Screens identified a series that binds in a confirmation distinct from substrate bound receptor & PFI-7

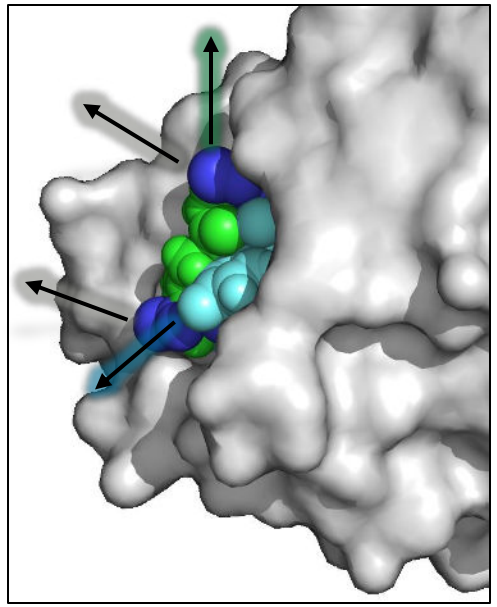
Nurix GID4 binders induce Aurora A degradation suggesting conformation is amenable to degradation



Multiple DEL series confirmed in active binding conformation



Second generation designs explore & optimize alternate linker attachment vectors while maintaining active conformation



GID4-mediated degradation of BRD4 also confirmed

*Owens, D. D. G. et al. Nat Chem Bio (2024)
** Best, M. G. et al. Cancer Cell (2017)

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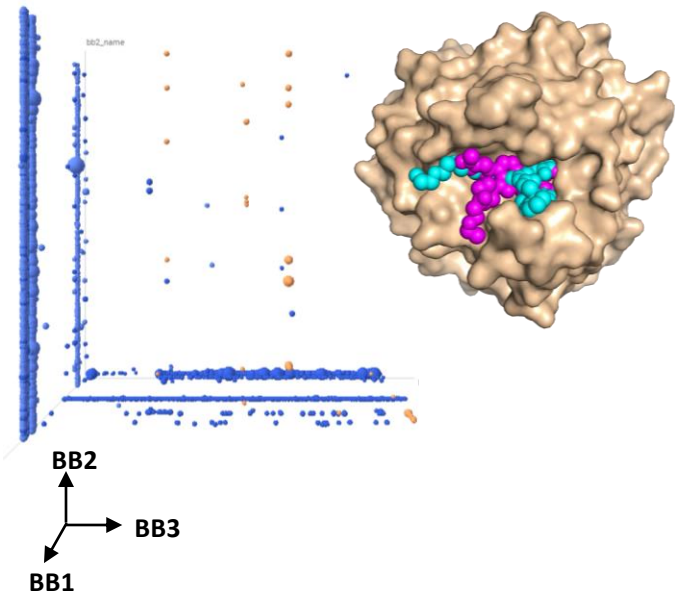
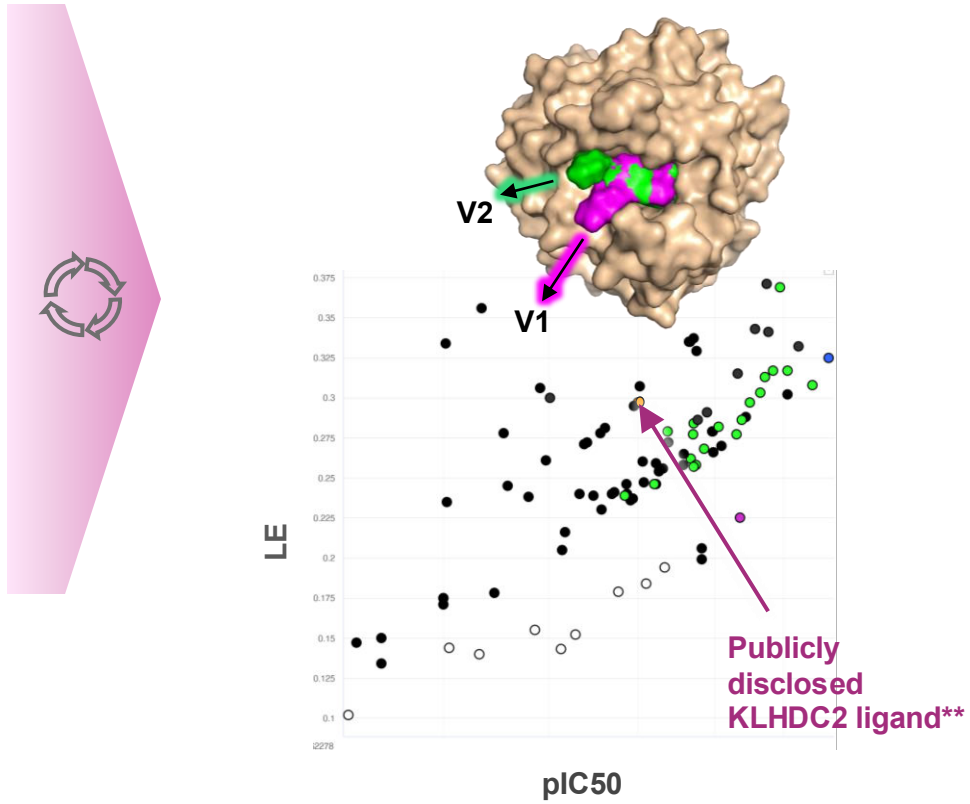
Case Study: Ligase with Potential to Enhance Cellular PK of DAC Payload

- The KLHDC2 ligase degrades a broad spectrum of cellular proteins by recognizing a Gly-Gly C-end degron*
- Nurix's KLHDC2 binders contain a free carboxylic acid and improved ligand efficiency vs published binders
- As a DAC payload, KLHDC2 degraders may show enhanced cellular PK and reduced bystander effect, desirable properties for I&I indications and some cancer indications

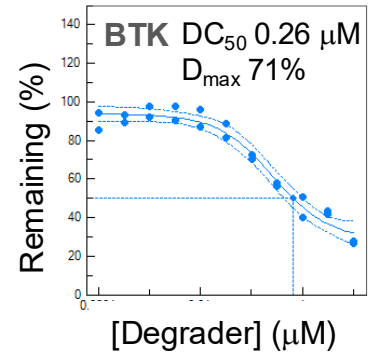
4 distinct DEL chemical series
IC_{50} < 550 nM



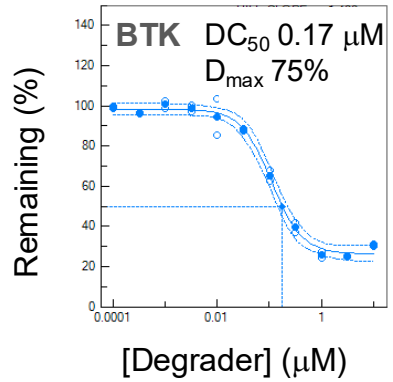
Structure guided optimization improves potency



Vector 1
IC_{50} = 4 nM



Vector 2
IC_{50} = 2 nM



** Timms, R. T. et al. Nat. Cell Biol. 1–11 (2023)*
*** Hickey, C. M. et al. Nat Struct Mol Biol. 31, 311-322 (2024)*

PK, pharmacokinetics
I&I, Immunology and inflammation

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The DAC Advantage and Keys to Design

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
- Next-gen DAC design requires multi-parameter optimization and unbiased evaluation through matrix synthesis and screening
- Proper ligase selection has the potential to provide an additional layer of tissue selectivity
- Nurix’s expansive collection of ligase binders enables an industry-leading discovery engine for TPDs and DACs


NURIX™