



Leader in Targeted Protein Modulation

# Targeted Protein Degraders As Next Generation Antibody Payloads

*Degrader Antibody Conjugate (DAC) Discovery*

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ADC & Radiopharmaceuticals Pharma & Biotech Partnering Summit  
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Boston, MA

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# Nurix Is a Clinical-Stage Targeted Protein Degradator Company With a Track Record of Successful Discovery Partnerships

- Three wholly-owned protein modulation drugs in clinical development
- Fully integrated research and development organization
- Ability to prosecute a growing internal and partnered pipeline, including three multi-target discovery collaborations with Gilead, Sanofi, and Pfizer

MOA	Oncology program	Target	Therapeutic area	Discovery – Lead Op	IND enabling	Phase 1a	Phase 1b
TPD	NX-5948	BTK	B-cell malignancies	[Progress bar]			
	NX-2127	BTK-IKZF	B-cell malignancies	[Progress bar]			
TPE	NX-1607	CBL-B	Immuno-Oncology	[Progress bar]			
TPD	Multiple	Undisclosed	Undisclosed	[Progress bar]			
	Multiple	Undisclosed	Undisclosed	[Progress bar]			GILEAD
	Multiple	Undisclosed	Undisclosed	[Progress bar]			sanofi
DAC	Multiple	Undisclosed	Oncology	[Progress bar]			Pfizer

MOA	I&I program	Target	Therapeutic area	Discovery – Lead Op	IND enabling	Phase 1a	Phase 1b
TPD	NX-5948	BTK	Inflammation / autoimmune	[Progress bar]			
	NX-0479 / GS-6791	IRAK4	Rheumatoid arthritis and other inflammatory diseases	[Progress bar]			
	STAT6 degrader	STAT6	Type 2 inflammatory diseases	[Progress bar]			sanofi
	Undisclosed	Undisclosed	Inflammation / autoimmune	[Progress bar]			sanofi

TPD: Targeted Protein Degradation; TPE: Targeted Protein Elevation; DAC: Degradator Antibody Conjugate

## San Francisco, CA

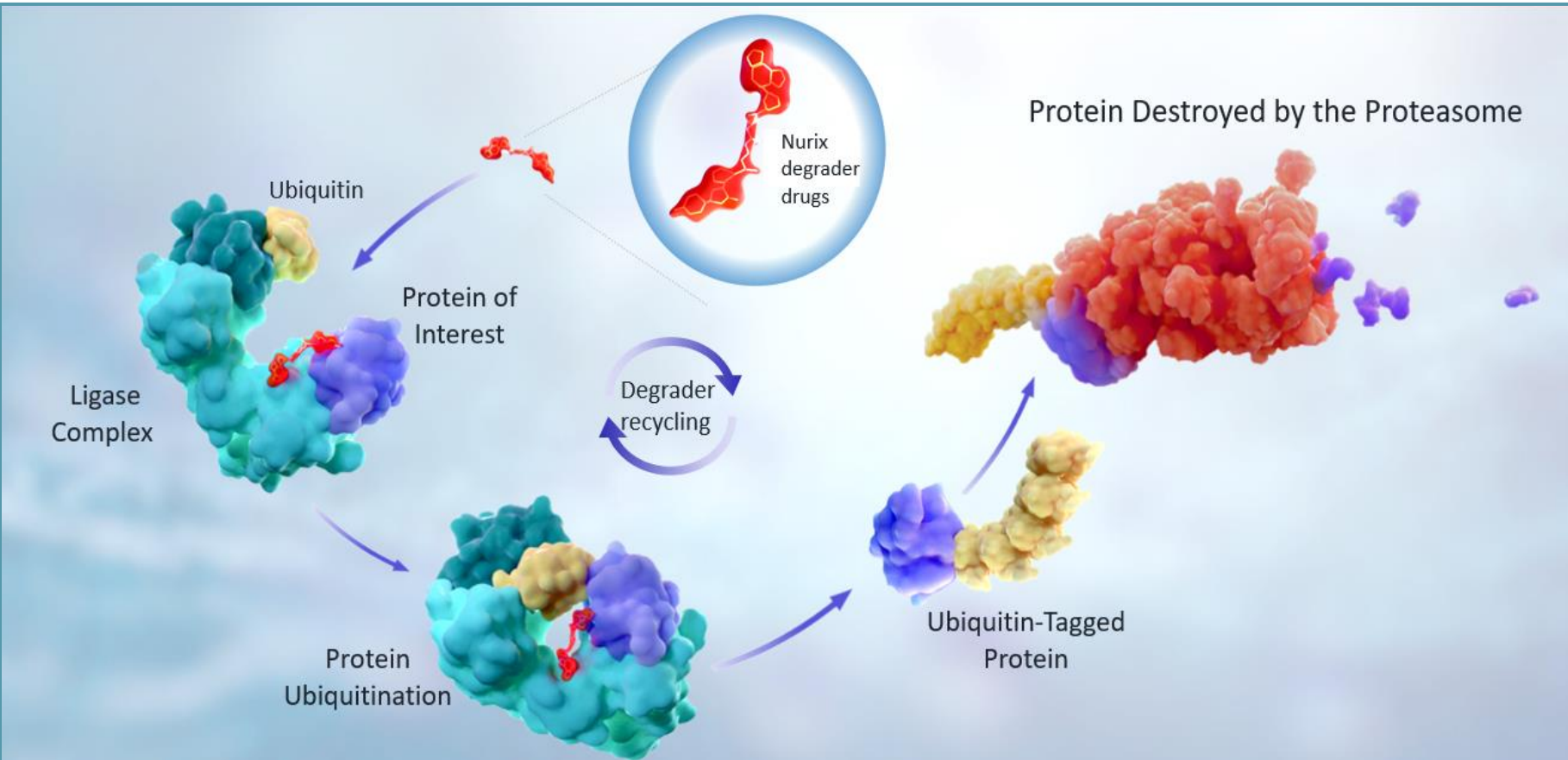


## The Woodlands, TX



# Targeted Protein Degradation

*Harnessing the ubiquitin proteasome system to eliminate disease-causing proteins*

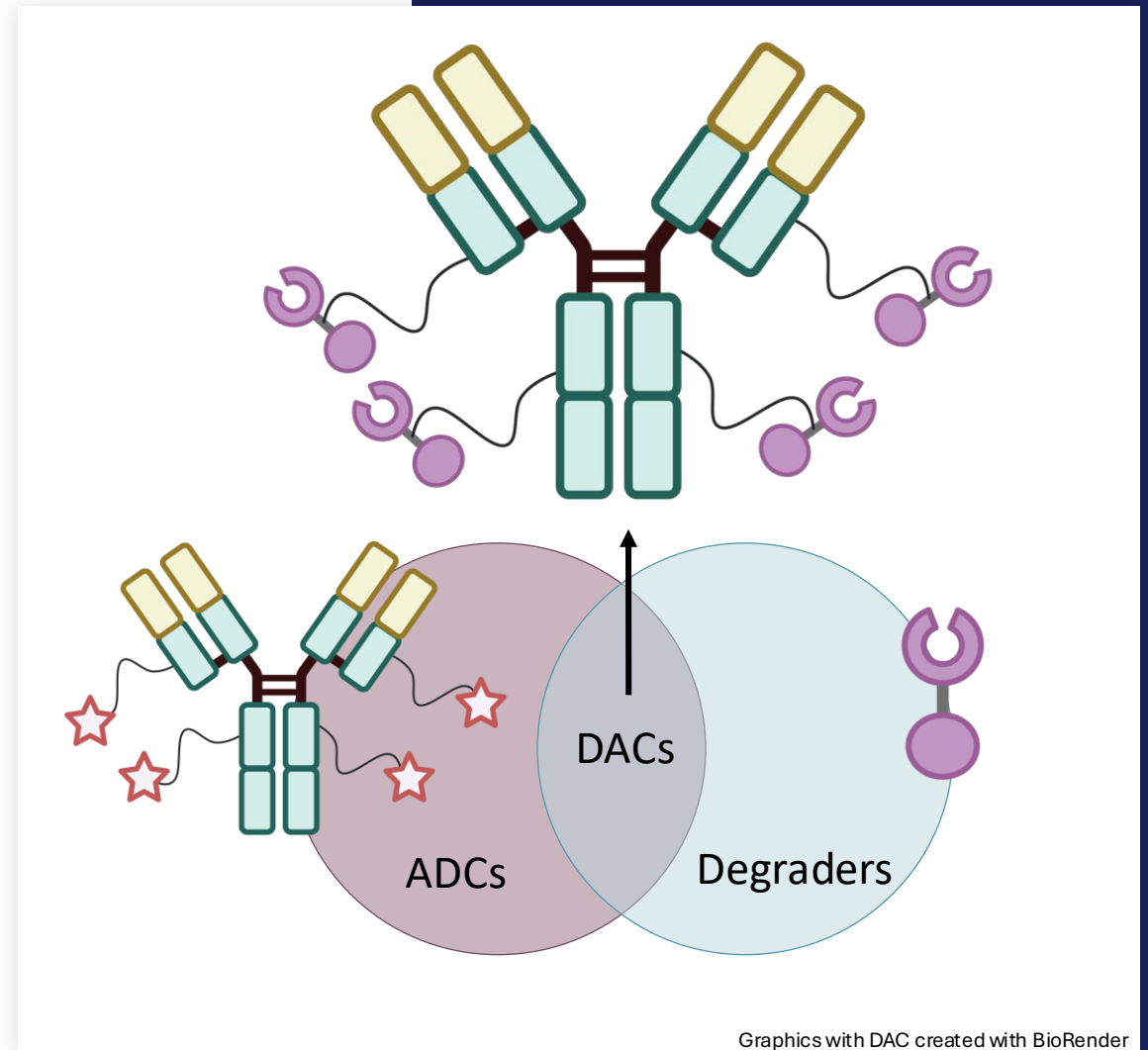


- Degraders target a specific protein or family of proteins
- Degraders catalytically eliminate ALL biological functions of proteins (scaffolding and enzymatic)
- Degradation provides prolonged activity requiring resynthesis of the protein

# Advancing a New Therapeutic Class

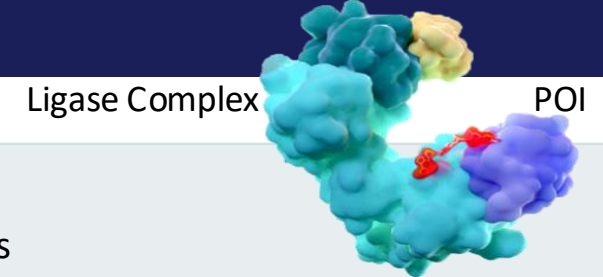
## Degrader Antibody Conjugates (DACs)

- DACs combine the catalytic activity of a Targeted Protein Degradator (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





# Degraders Offer Many Potential Advantages as Antibody Payloads



## Superior potency

- Catalytic, event-driven pharmacology
- One degrader can degrade many protein molecules

## Superior selectivity and safety profile

- Optimization for ternary complex formation and efficient target ubiquitylation allows degraders to achieve enhanced selectivity
- Requires lower drug exposure, avoiding occupancy-driven off-target pharmacology

## Durable coverage

- Protein resynthesis (rather than drug clearance) is required to restore target function

## Broad target opportunities

- Unlike an inhibitor, a degrader can address both the enzymatic and non-enzymatic functions of a protein
- Including targets that are previously thought undruggable

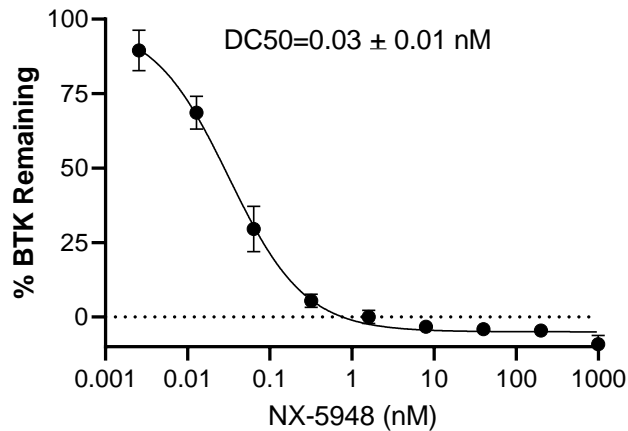
## Ligases offer additional selectivity

- The combination of differential expression and varying activity levels of E3 ligases potentially offers another layer of cell and tissue selectivity

# Degraders Provide Many Potential Advantages Over Traditional ADC Payloads

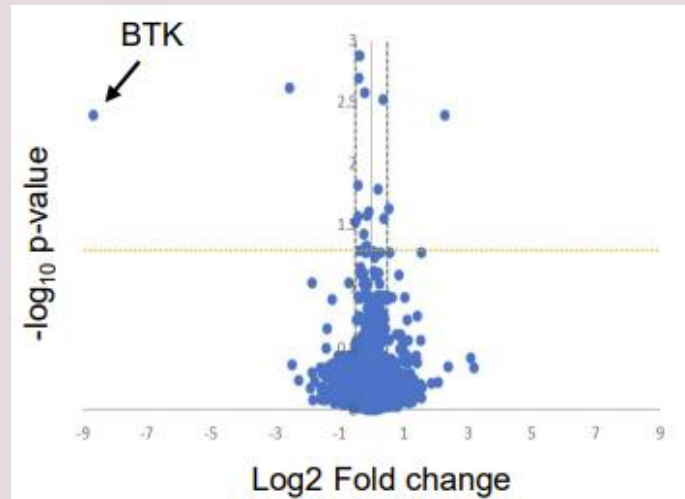
## Picomolar Potency

BTK Degradation in TMD8 Cells



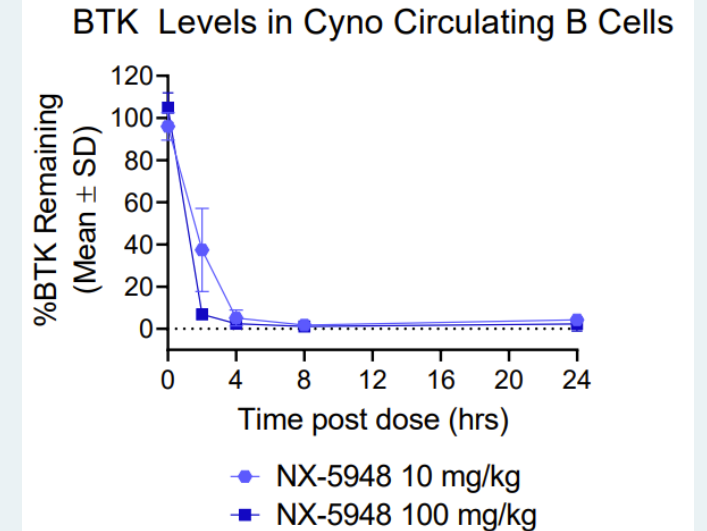
## Exquisite Selectivity

Global Proteomic Analysis



## Prolonged PD

Single Dose Target Suppression

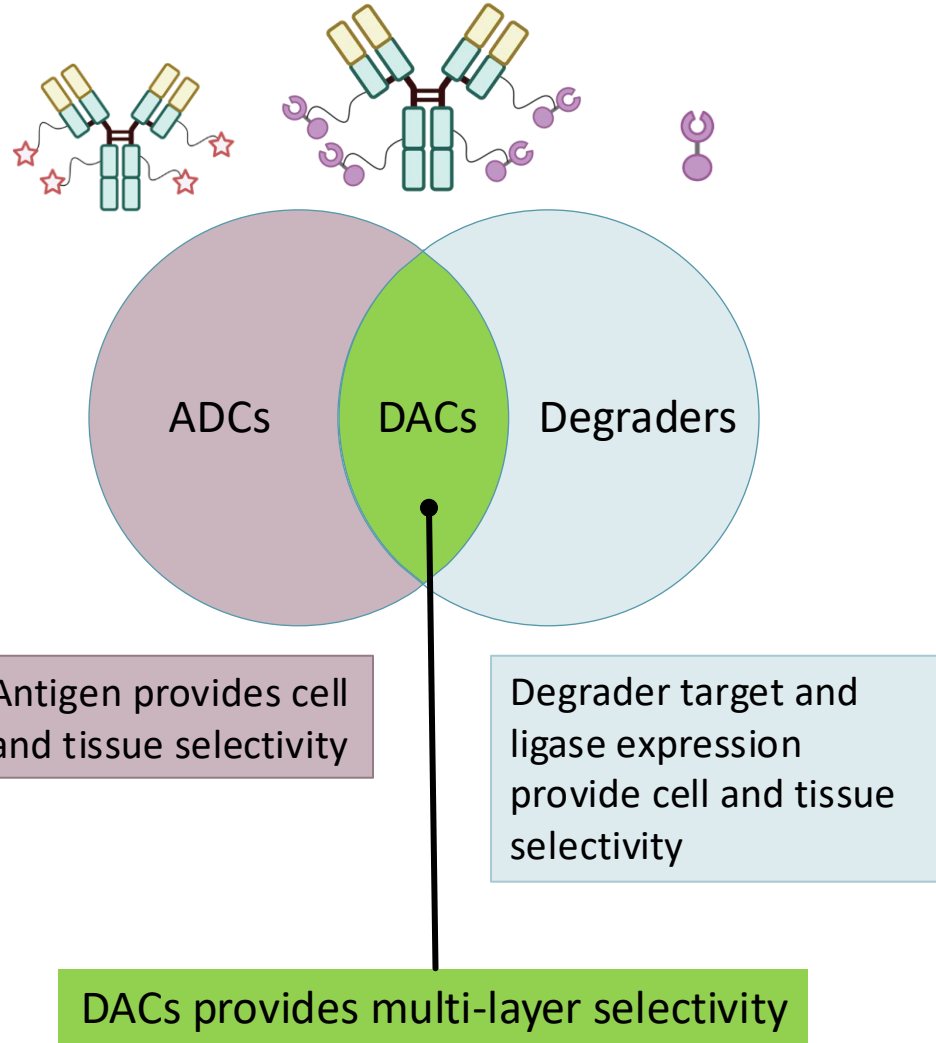


# The DAC Modality Unlocks New Targets, Enhances Selectivity, and Offers the Potential for a Broader Range of Therapeutic Indications

## FDA approved ADCs

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

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



## Growing list of bifunctional degraders in the clinic

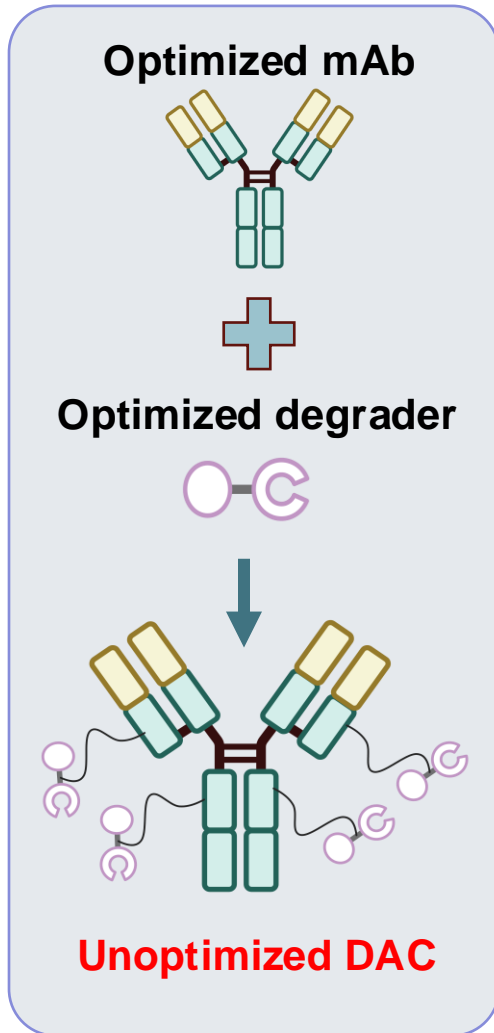
Degrader Name	Target	Indication
ARV-102	LRRK2	Neurology
ARV-471	ER	Oncology
ARV-766	AR	Oncology
ASP3082	KRAS G12D	Oncology
BGB-16673	BTK	Oncology
CC-94676	AR	Oncology
CFT-1946	BRAF V600E	Oncology
CFT-8634	BRD9	Oncology
CG001419	NTRK	Oncology
DT-2216	BCL-xL	Oncology
FHD-609	BRD9	Oncology
GT20029	AR	Oncology
HP518	AR	Oncology
HSK29116	BTK	Oncology
KT-253	MDM2	Oncology
KT-333	STAT3	Oncology
KT-474	IRAK4	Immunology
NX-2127	BTK, IKZF1/3	Oncology
NX-5948	BTK	Oncology / I&I
PRT3789	SMARCA2	Oncology



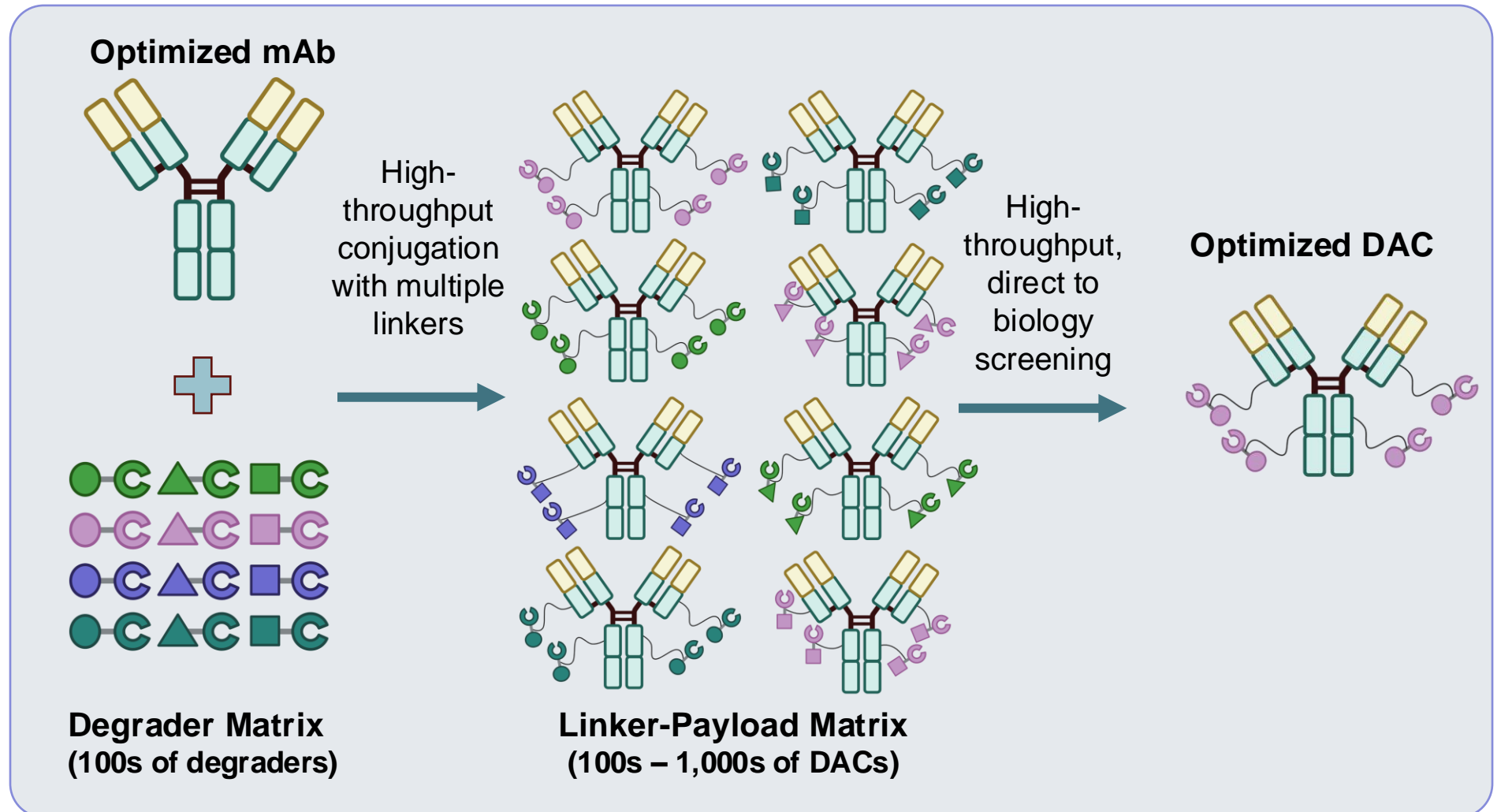
# Next-Generation DAC Design Requires Multi-Parameter Optimization

*Agnostic assessment of design elements using matrix synthesis and screening*

## Simplistic Approach



## Nurix Approach: Matrixed DAC

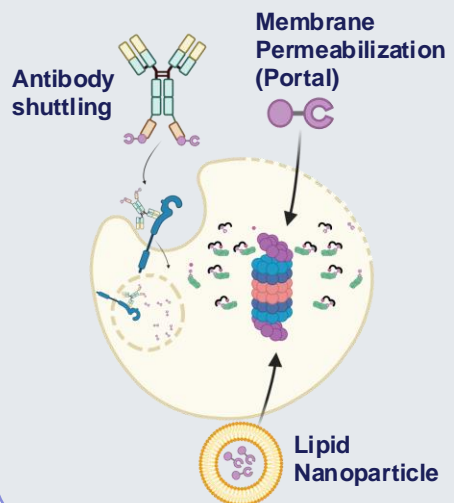


# Fully Integrated Internal DAC Platform

Leveraging lessons learned from automated degrader discovery platform

## Multiple Techniques to Deliver & Screen Payloads

Leveraging cutting-edge technologies to screen and advance degraders for conjugation



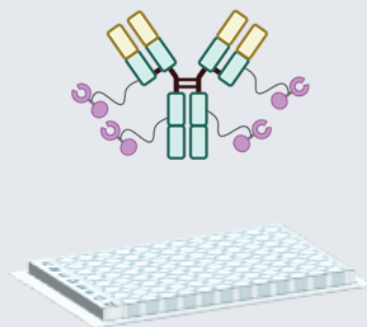
## Linker & Degrader Synthesis

Automated on-DNA & on-resin chemistry platform to generate linker and degrader-linker libraries



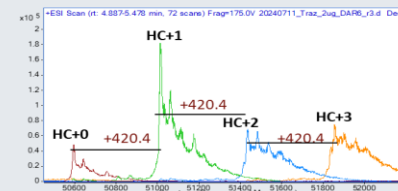
## High-throughput Conjugation

On-bead multi-step HT-conjugation & purification of DACs in a single workflow



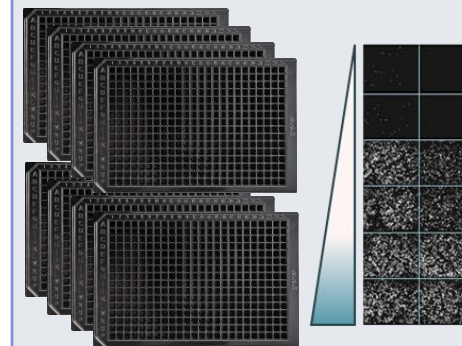
## Analytical Characterization

Robust, plate-based bioanalytical methods to characterize DACs (LCMS, HIC & SEC)

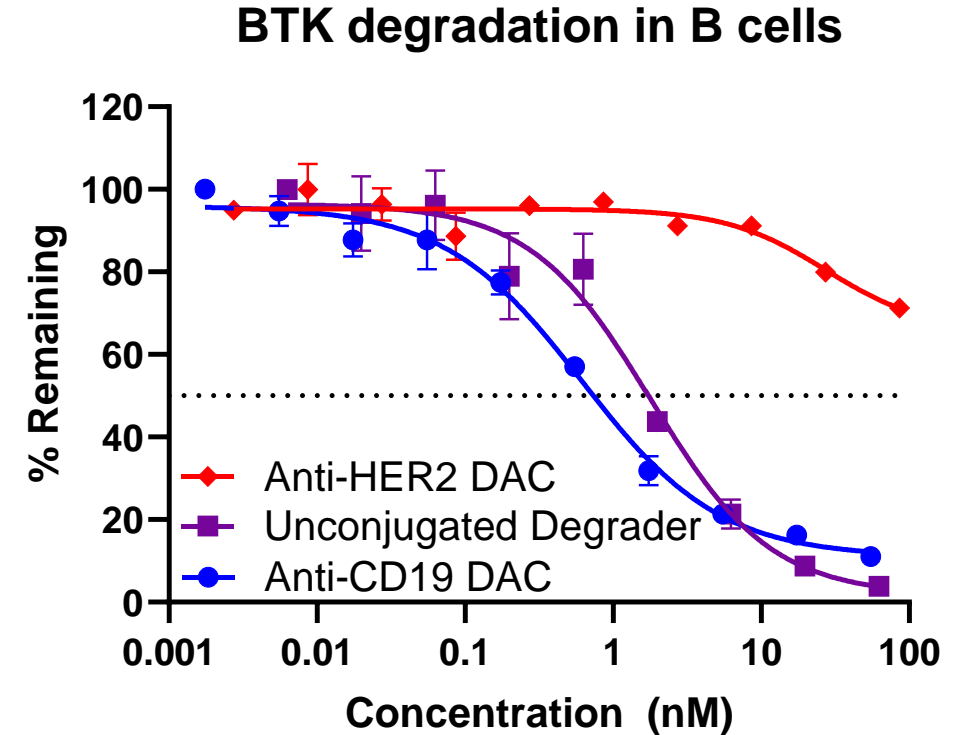
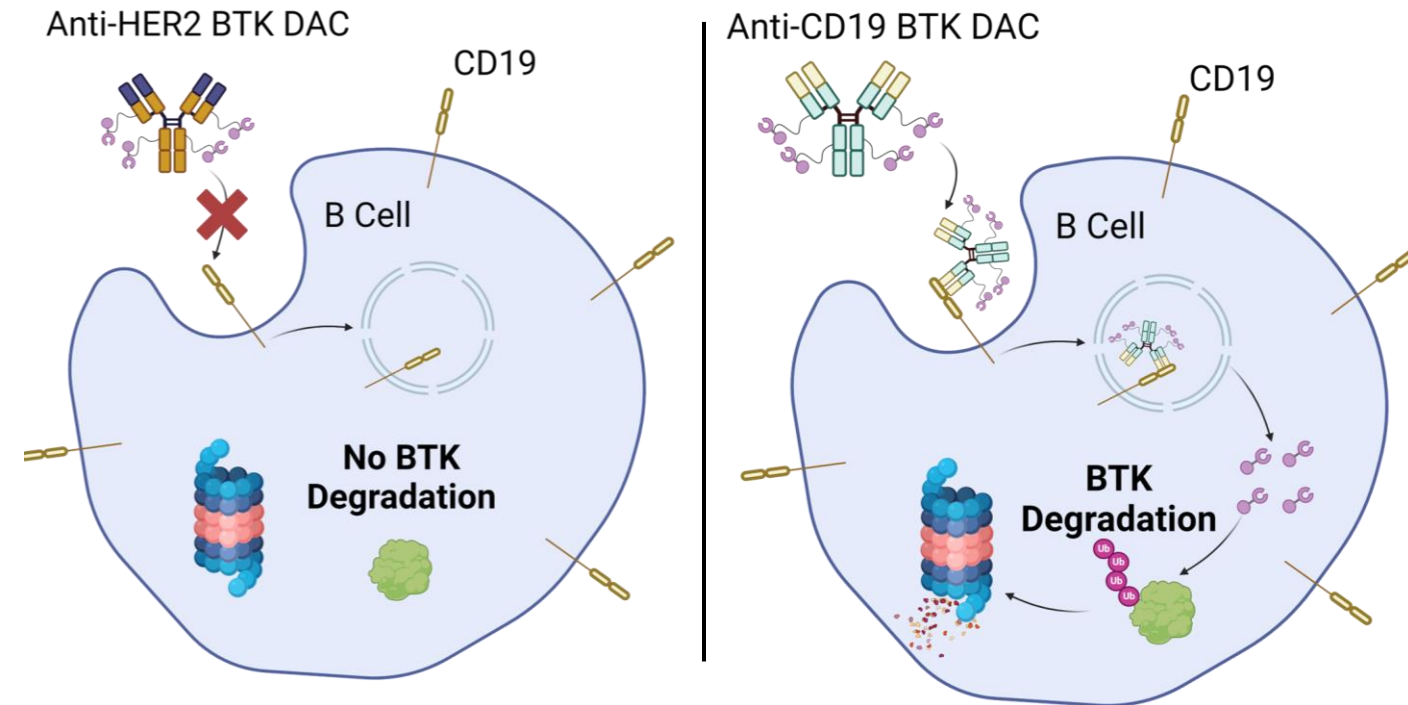


## *In Vitro* Characterization

High throughput cell-based platforms to characterize DAC molecules

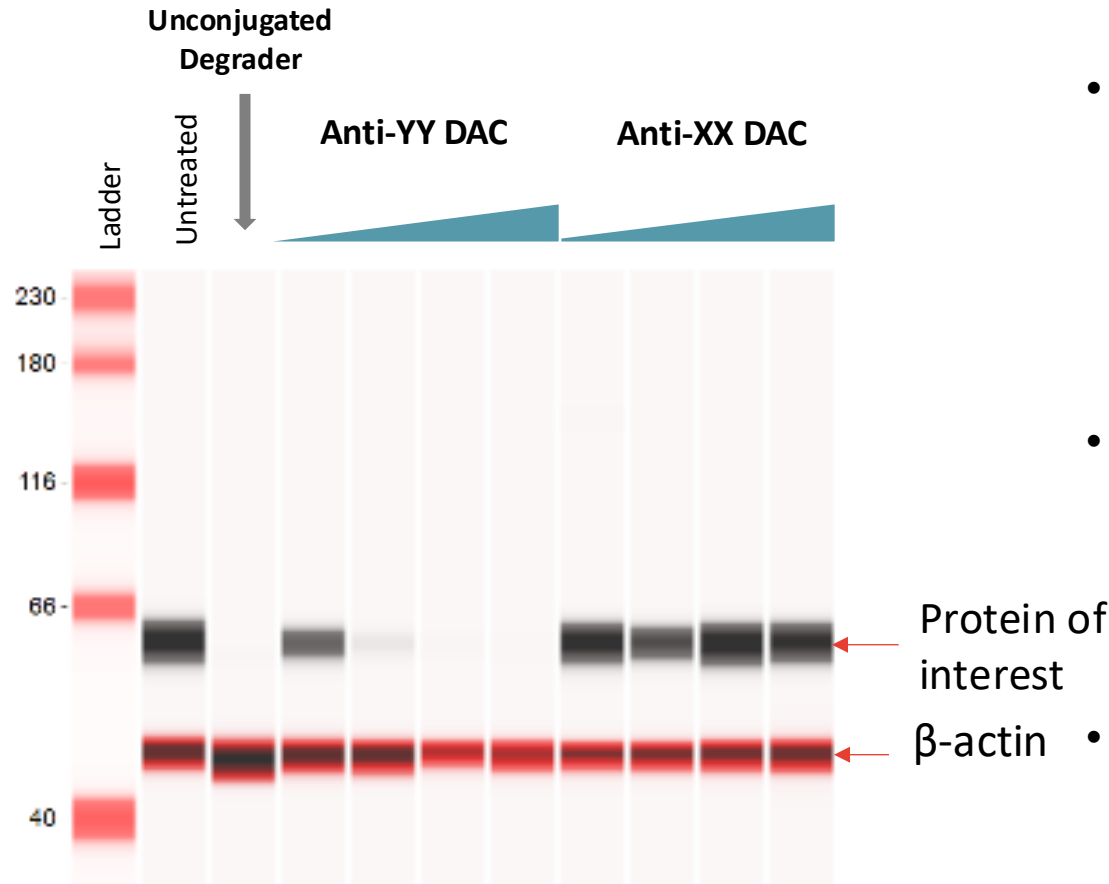
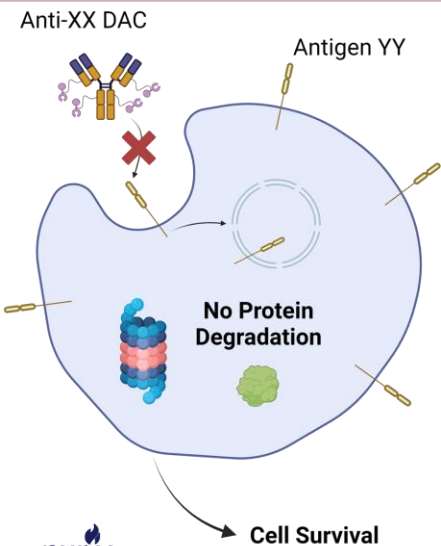
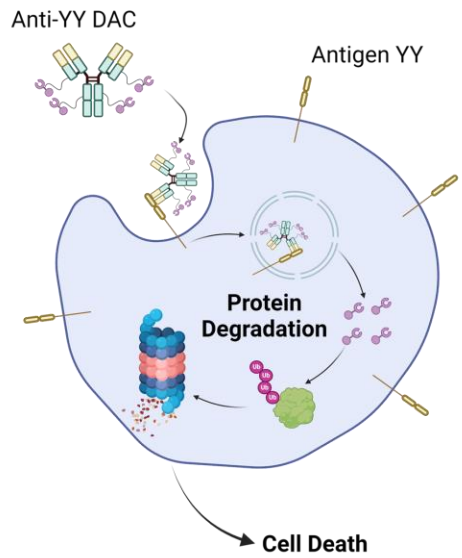


# Conjugation of a BTK Degradator to an Anti-CD19 Antibody Results in Highly Specific Degradation in CD19<sup>+</sup> B Cells



- When a BTK degrader is conjugated to an anti-HER2 antibody and tested in CD19<sup>+</sup>/HER2<sup>-</sup> B cells, the DAC is **inactive**
- When a BTK degrader is conjugated to an anti-CD19 antibody and tested in CD19<sup>+</sup>/HER2<sup>-</sup> B cells, the DAC is **as active as the free degrader**

# Antibody Delivery Confers Cell-Type Selective Protein Degradation

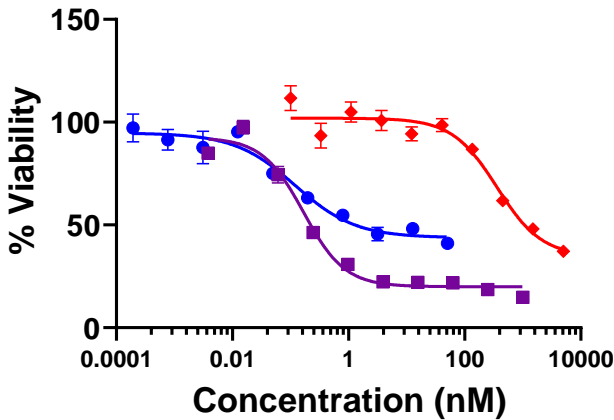


Note: Antibody range: 78-2000 ng/ml  
Unconjugated degrader tested at 100 nM

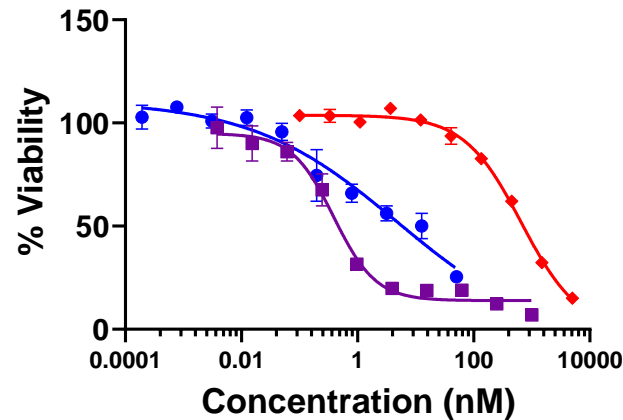
- Cells express the antigen YY but not XX, allowing assessment of antigen-specific delivery of degrader conjugates
- Unconjugated degrader potently eliminates the protein from cells (unconjugated degrader lane)
- Only the Anti-YY DAC shows degradation of the protein in this cell type

# Cell-Type Selective DAC Demonstrates Superior Cell-Killing When Compared to an Approved Inhibitor

Tumor Cell Line A Viability



Tumor Cell Line B Viability



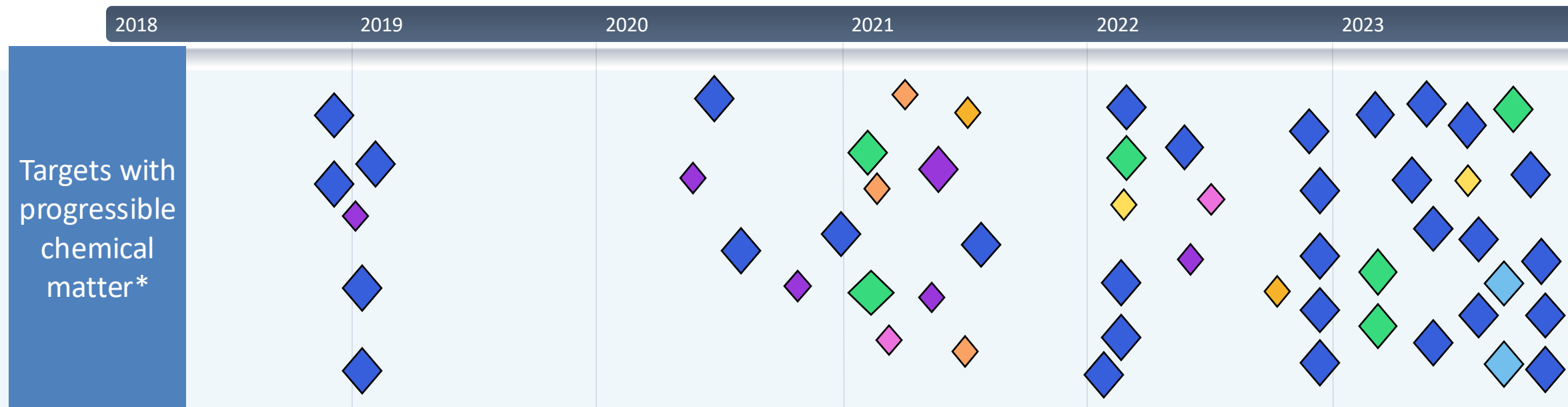
- ◆ FDA Approved Inhibitor
- Anti-YY DAC
- Unconjugated Degrader

Compound	Tumor Cell Line A Cell killing IC <sub>50</sub> (nM)	Tumor Cell Line B Cell killing IC <sub>50</sub> (nM)
FDA Approved Inhibitor	1071	713
Anti-YY DAC	1.3	5.9
Unconjugated Degrader	0.22	0.47

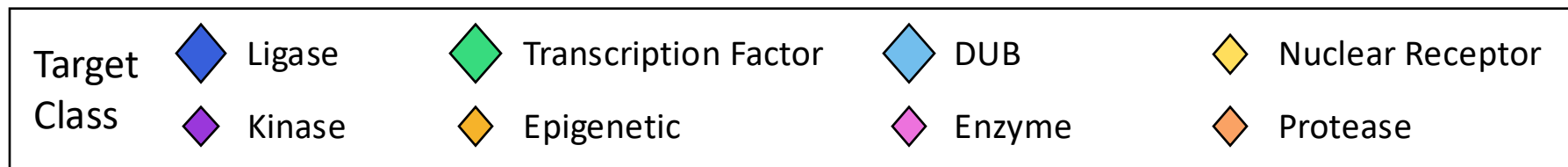
Cell viability measured using CellTiter-Glo assay.

- Unconjugated degrader and DAC show more potent cell killing in both tumor cell lines
- The DAC molecule is >800- and >100-fold more potent than the approved target inhibitor in tumor cells line A and B, respectively

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



\*All series validated by  $\geq 2$  orthogonal assays



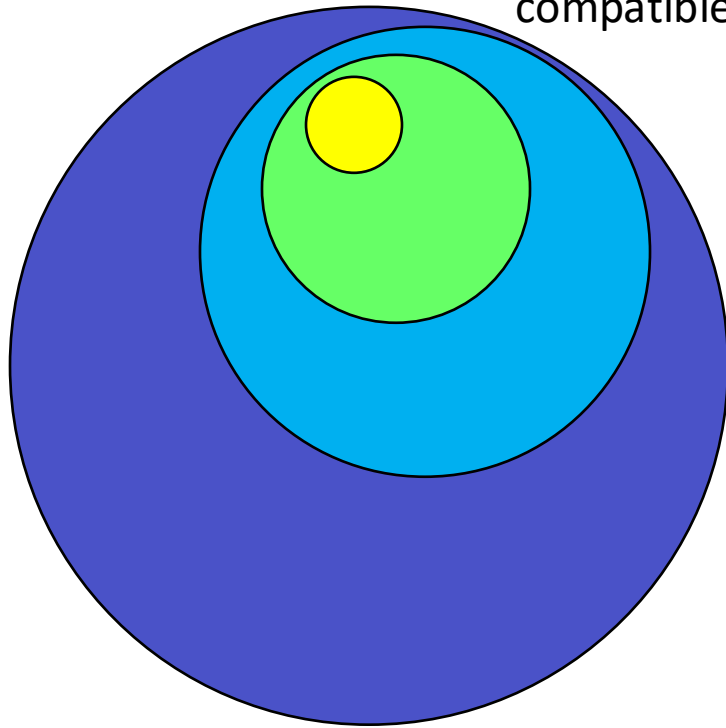


# Enhancing Tissue Selectivity Through Broader Access of Ligase Space

Nurix Ligases with Optimized Libraries of binders (14)

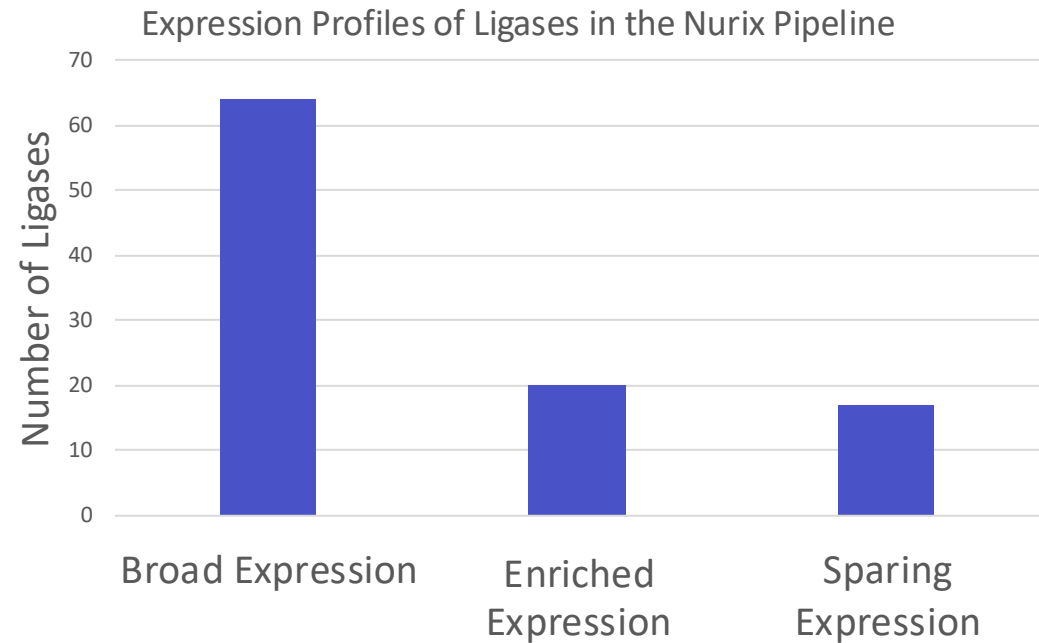
Ligases in the clinic (2)

Nurix Ligases with Harness compatible for DAC (25)



Ligases in Nurix Discovery pipeline (>100)

Our broad collection of ligases gives us access to novel biology



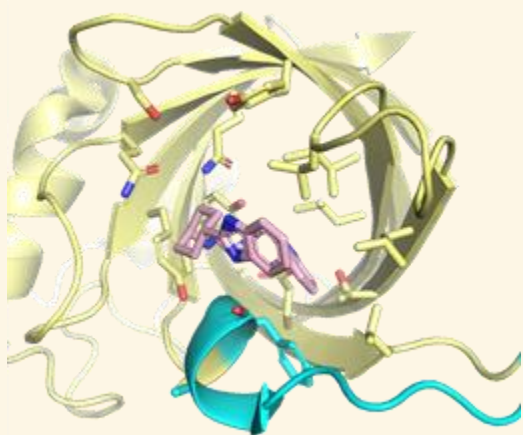
Ligase levels elevated in a single tissue relative to others.  
e.g., Tumor specific ligases for improved specificity

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

# Conferring Platelet Sparing Profile to Novel DACs Through DEL Discovery

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

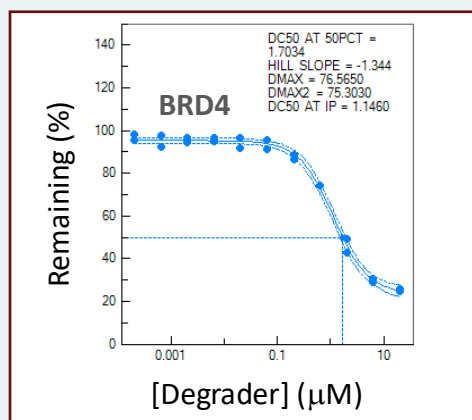
No degradation of BRD4 observed with literature GID4 binder PFI-7



PFI-7 bound structure

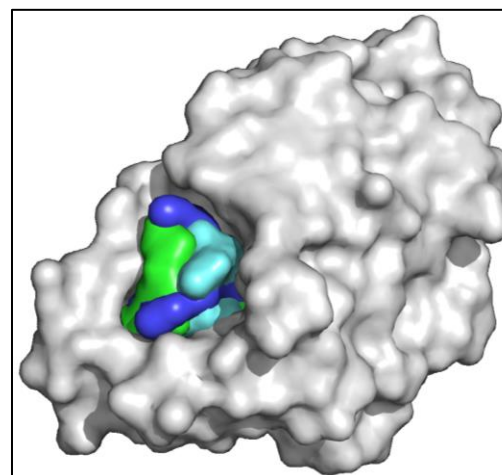
Nurix DEL Screens identified a series that bind in a conformation distinct from substrate bound receptor & PFI-7

Nurix GID4 binders induce BRD4 degradation suggesting conformation is amenable to degradation

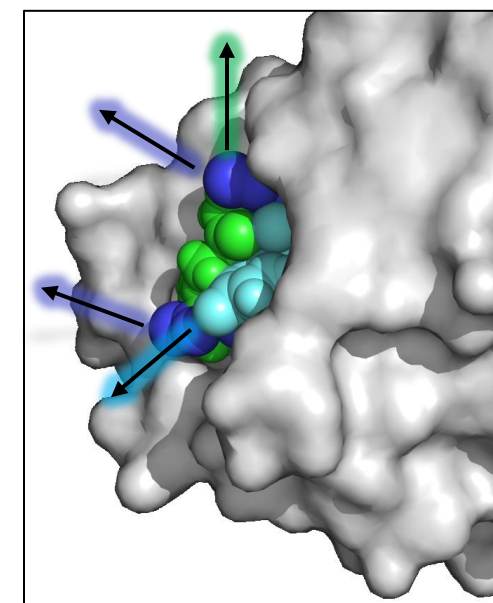


- *GID4 is broadly active on diverse targets with Pro/N-degrons\**
- *Tissue sparing expression profile*
- *GID4 Degraders could spare platelets to further augment antibody selectivity, improving therapeutic index of DAC*

Multiple DEL series confirmed in active binding conformation



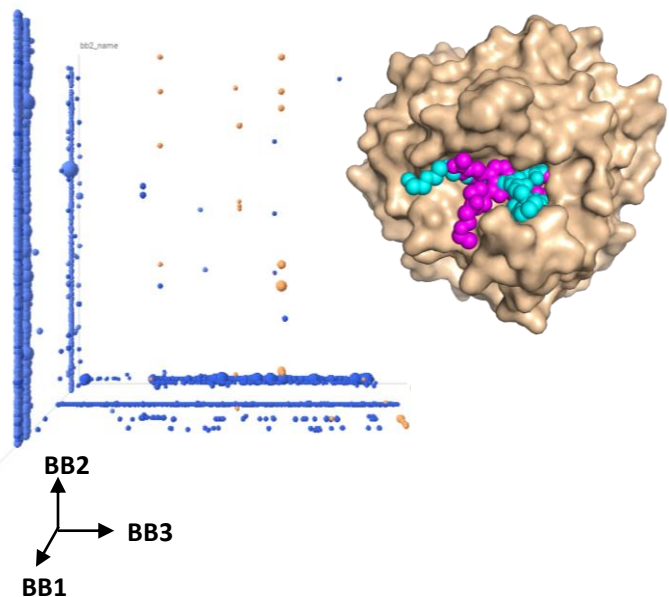
Second generation designs explore & optimize alternate linker attachment vectors while maintaining active conformation



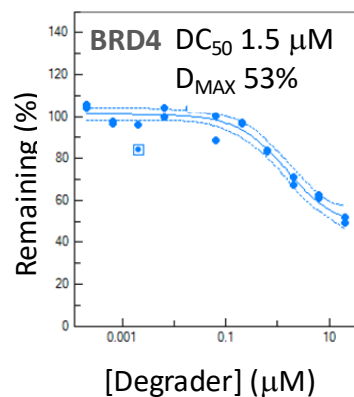
# Expanding Ligase Toolbox for Degraders Could Enhance DAC Payload PK

- 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
- As a DAC payload, KLHDC2 degraders may show enhanced cellular PK, further improving the therapeutic index of DAC

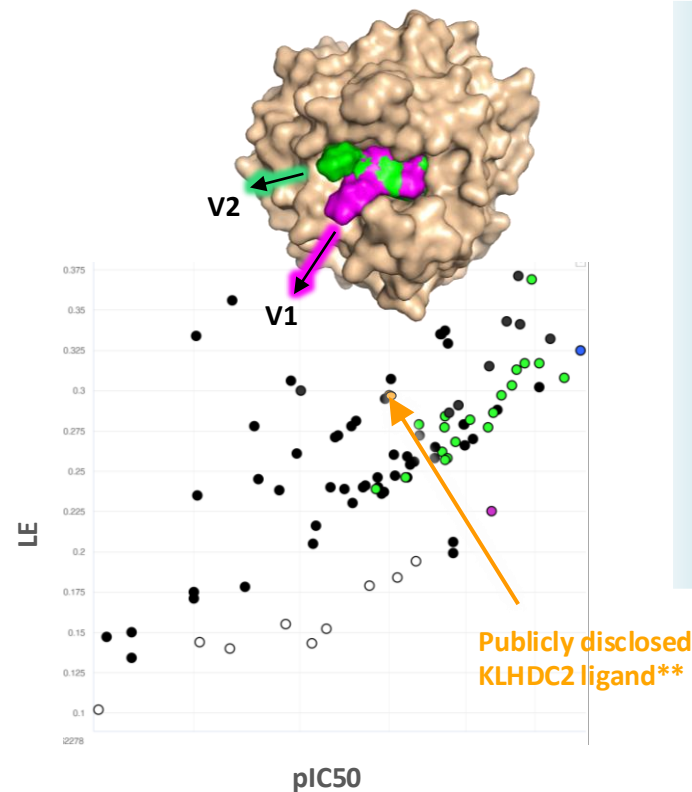
4 distinct DEL chemical series  
< 550 nM



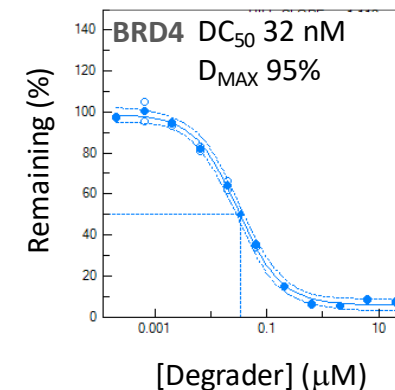
Modest Degradation  
using Initial Hit  
IC50 = 4 nM



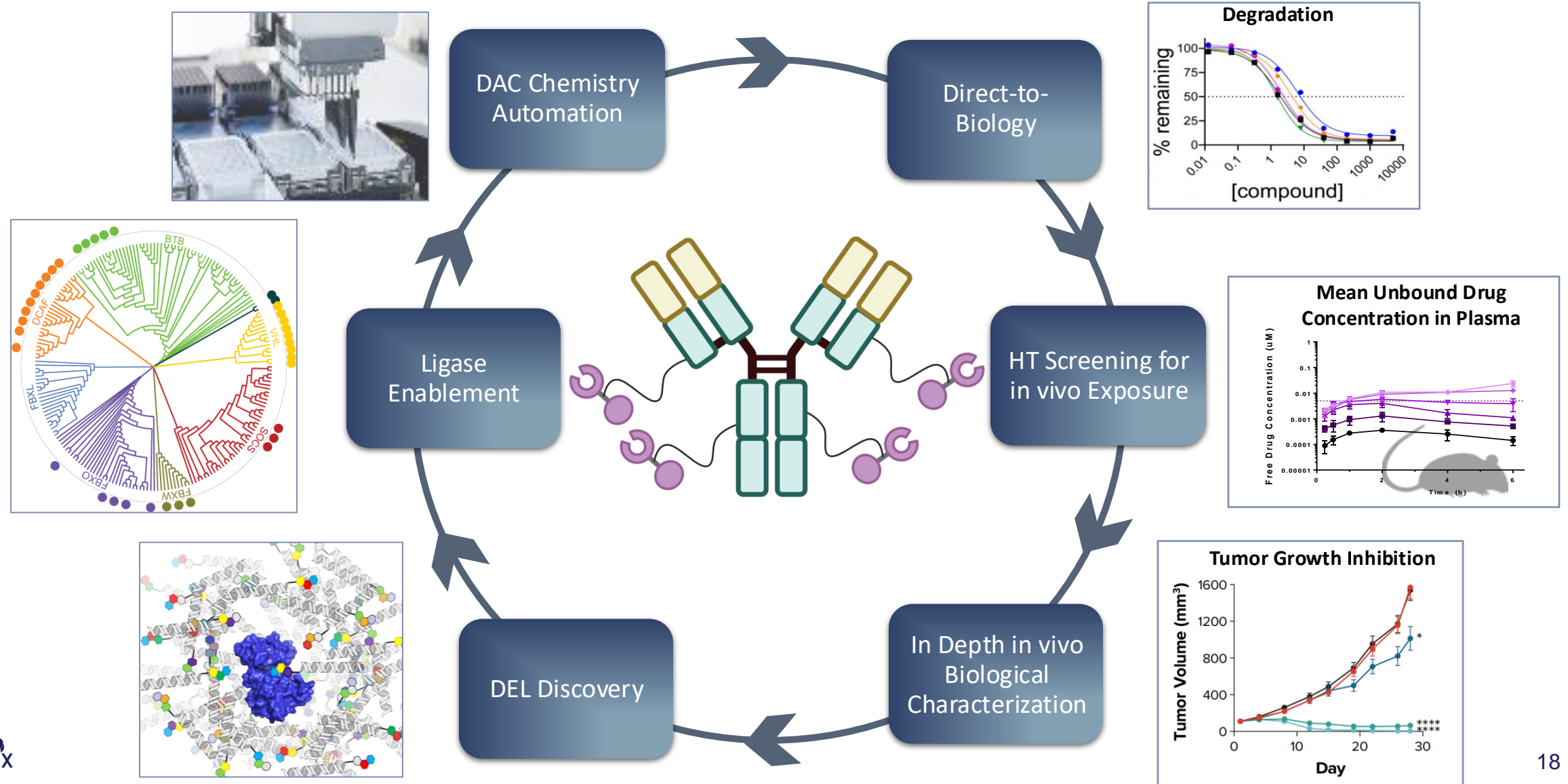
Structure guided optimization improves potency



Potent Degradation using  
Optimized Hit  
IC50 = 0.2 nM



# Our Integrated Discovery Platform is Helping us Learn the Rules of DAC Design to More Rapidly Create Next-Generation Conjugate Drugs



# The DAC Advantage

- 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

