# Accelerating Targeted Protein Degrader Discovery with Automation and Direct-To-Biology Screening

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## Abstract

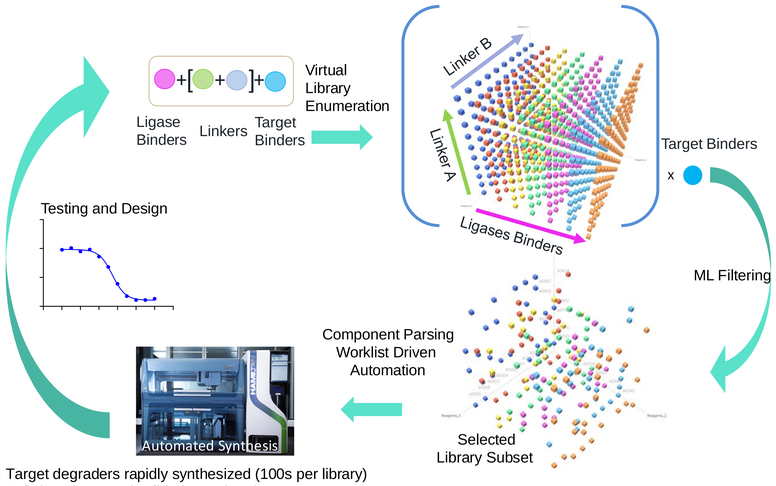
Nurix has established a high-throughput platform that integrates automated chemistry synthesis and biological evaluation to accelerate the discovery of targeted protein degraders. Virtual enumeration of very large libraries of bifunctional degraders containing a combinatorial matrix is filtered through machine learning models. For the direct-to-biology (D2B) platform, selected compounds, predicted to have good activity and developability, undergo synthesis through multi-step and automated solid-phase chemistry. The degradation activity of the crude mixtures are assessed directly in cell-based assays. Potent hits identified are repurified for further studies. The streamlined approach enables the exploration of a broader chemical space, which allows for the discovery of rarely occurring starting material for further optimization.

Here, we demonstrate that the advanced and automated cell screening system provides robust support to assess the biological activities of D2B compounds in a short time frame. In the pilot studies, our results demonstrated a good correlation between crude and purified compounds in the **HiBiT degradation assay** and **CellTiter-Fluor** cell viability assay. In addition, automated system enables the quick identification of ideal target binder and ligase binder. This effort demonstrates Nurix's commitment to pioneering innovative strategies to advance the optimization and discovery of drug therapeutics in the field of targeted protein degradation.

## Introduction

- Ultra-high throughput compound synthesis of large libraries in a plate-based format is followed by direct employment of the crude compounds in biological evaluations (**direct to biology, D2B**)
- Structure-Activity-Relationship (SAR) compound optimization is hindered by the slow pace of compound purification. In contrast, the D2B approach is more time-efficient, saves resources, and reduces the labor intensity associated with the synthesis of large and complex degrader molecules
- The possibility of exploration of diverse binder and linker moieties in a short time enables testing of a larger chemical space, which increases hit finding success
- Direct testing in biological systems enables the discovery of high-quality compounds with developability potential

## Ultra-High Throughput Matrix Synthesis To Maximize Degrader Chemical Space Exploration

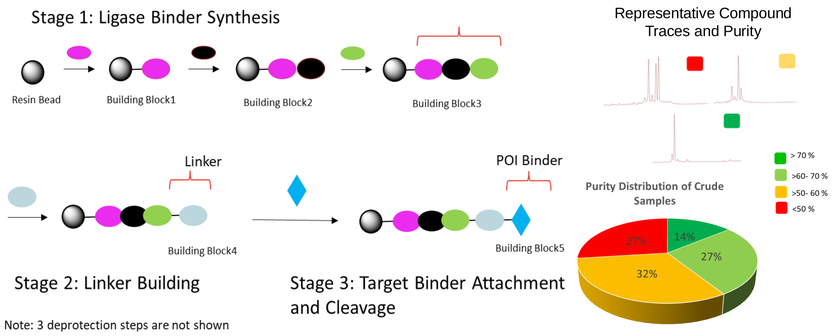



- Target degraders rapidly synthesized (100s per library)
- Solution phase and solid phase chemistry
- On demand linker assembly
- ML driven design enabled

## References

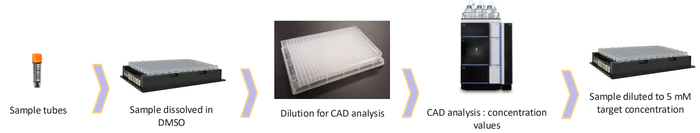

- Bush, J. T., *Chem. Sci.* **2021**, *12*, 12098-12106
- Hendrick, C. E., *ACS Med. Chem. Lett.* **2022**, *13*,1182
- Harling, J. D., *J. Med. Chem.* **2023**, *66*,15437-15452
- Chen, X. H., *Adv. Sci.* **2024**, *11*, 2400594


## 8 Step Solid-Phase Synthesis with 5 Diverse Elements




- Bank of ligase binder-linker conjugates can be prepared in bulk, ready for various target binders to be incorporated in a single step
- Compatible with optimizations of target binder, E3 ligase binder, and linker

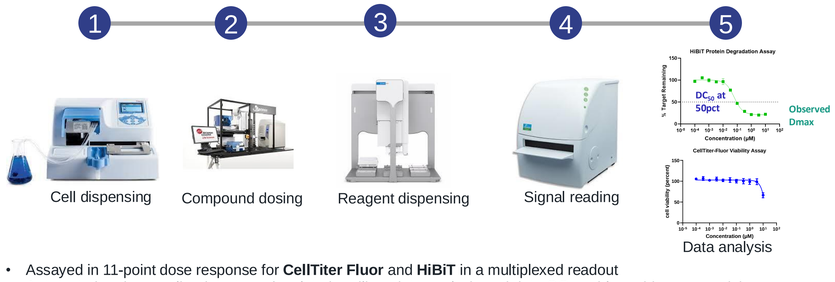
## High Throughput QC and Normalization




Fully automated and validated process on the Hamilton Vantage

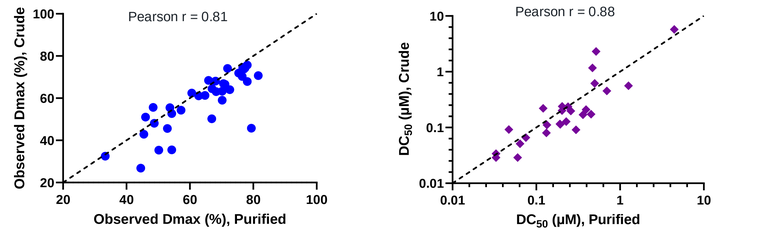
- **Individual dilution of each sample based on concentration**
- **Normalization to the same product concentration**

## High Throughput Cell Based HiBiT Screening



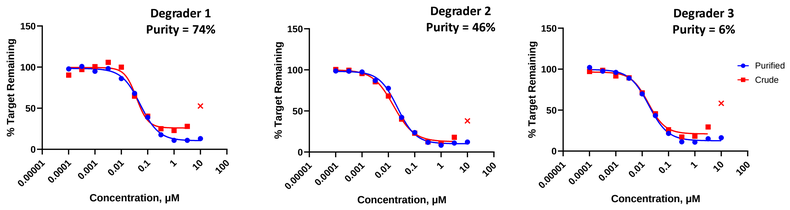

- Assayed in 11-point dose response for **CellTiter Fluor** and **HiBiT** in a multiplexed readout
- Automated and streamlined systems for plate handling, data analysis and data QC enable rapid turnaround times

## High Correlation Observed Between Crude and Purified Compounds



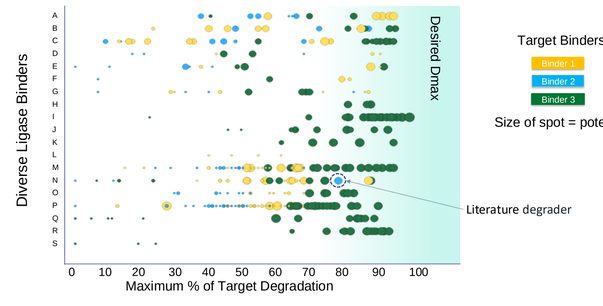

- Crude compounds showed robust correlation with purified compounds in Observed Dmax and $DC_{50}$ at 50pct

**High correlation of degradation pattern observed between D2B compounds at various purities and purified compounds in HiBiT degradation assay and viability assay**




- A range of highly pure and crude compounds show robust and reproducible degradation

## Automation Combined with D2B Quickly Identifies Ideal Design Space




## Conclusions

- Nurix has established and developed an advanced direct-to-biology platform by integrating computational chemistry, automated solid-phase chemistry, and high-throughput biological evaluation
- Automation significantly enhances the efficiency and productivity of D2B process
- The platform offers an efficient way for exploring the chemical space and compound optimization
- Pilot studies demonstrated good correlation between crude and purified compounds, which validates the platform's capability to accurately assess compound activity