

# **Stabilizing Proteins; The Future of Breakthrough Drugs – DUBTACs**

**DeUBiquitinating TArgeting Chimeras**

## LifeSensors DUB Capabilities

- Expressed/purified ~40 biologically active DUBs and substrates
- Developed ~25 physiological DUB assays for HTS and validation
- Selectivity panel and compound profiling
- Determine compound MOA, cellular and target tissue PD markers
- Ability to screen ~500,000 compounds

# Business Model

- Help customer discover and characterize DUB ligands, inhibitors, activators, and DUBTACs
- Screen in-house libraries or customer libraries at LifeSensors
- All IP and data belong to the customer
- Work performed under CDA and Master Service Agreement
- Fee for service model, defined milestone-based agreement

# DUB Drug Discovery Program

## Step One

Assay development, optimization, and validation using high-throughput approach

- [Ub-Rh110/Ub-AMC assay](#)
- [CHOP reporter assay](#)
- [Diubiquitin internally quenched fluorescence \(IQF\) assay](#)
- **UbiSensor assay (TR-FRET)<sup>New\*\*\*</sup>**

## Step Two

Hit-to-lead optimization

- Working with medicinal chemistry team
- Selectivity panel, compound profiling

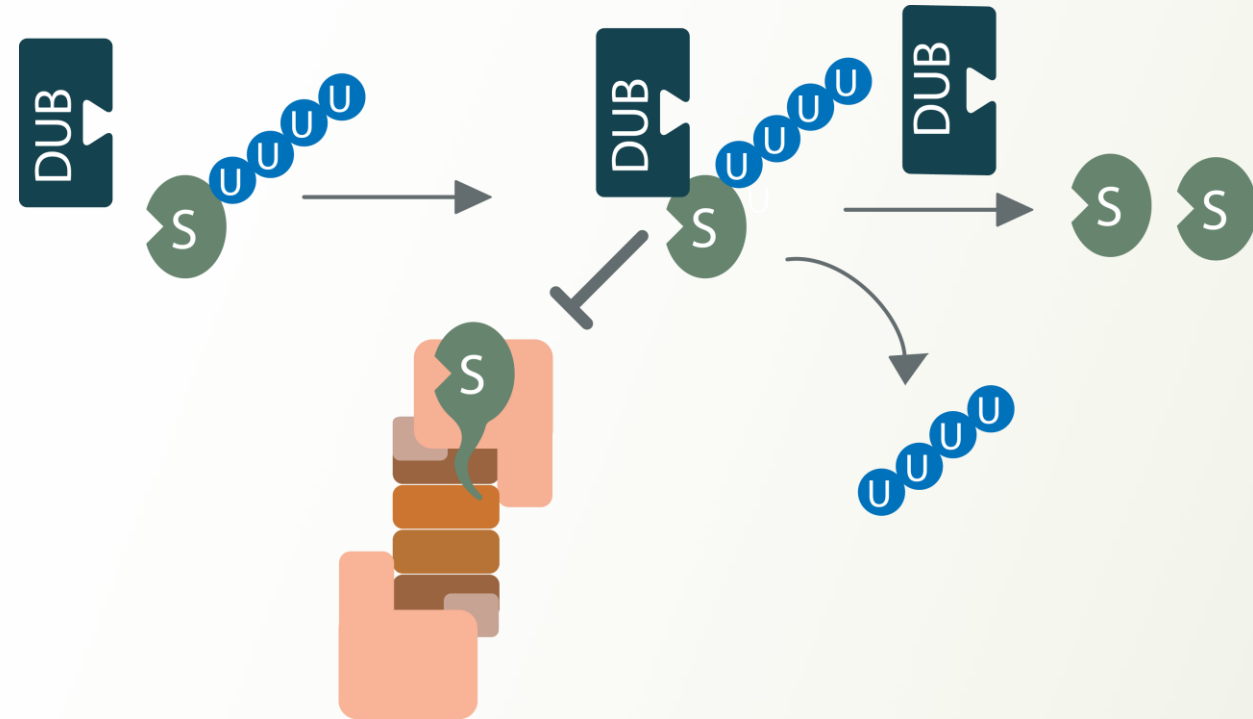
## Step Three

Confirm hits in cellular assays, PD markers

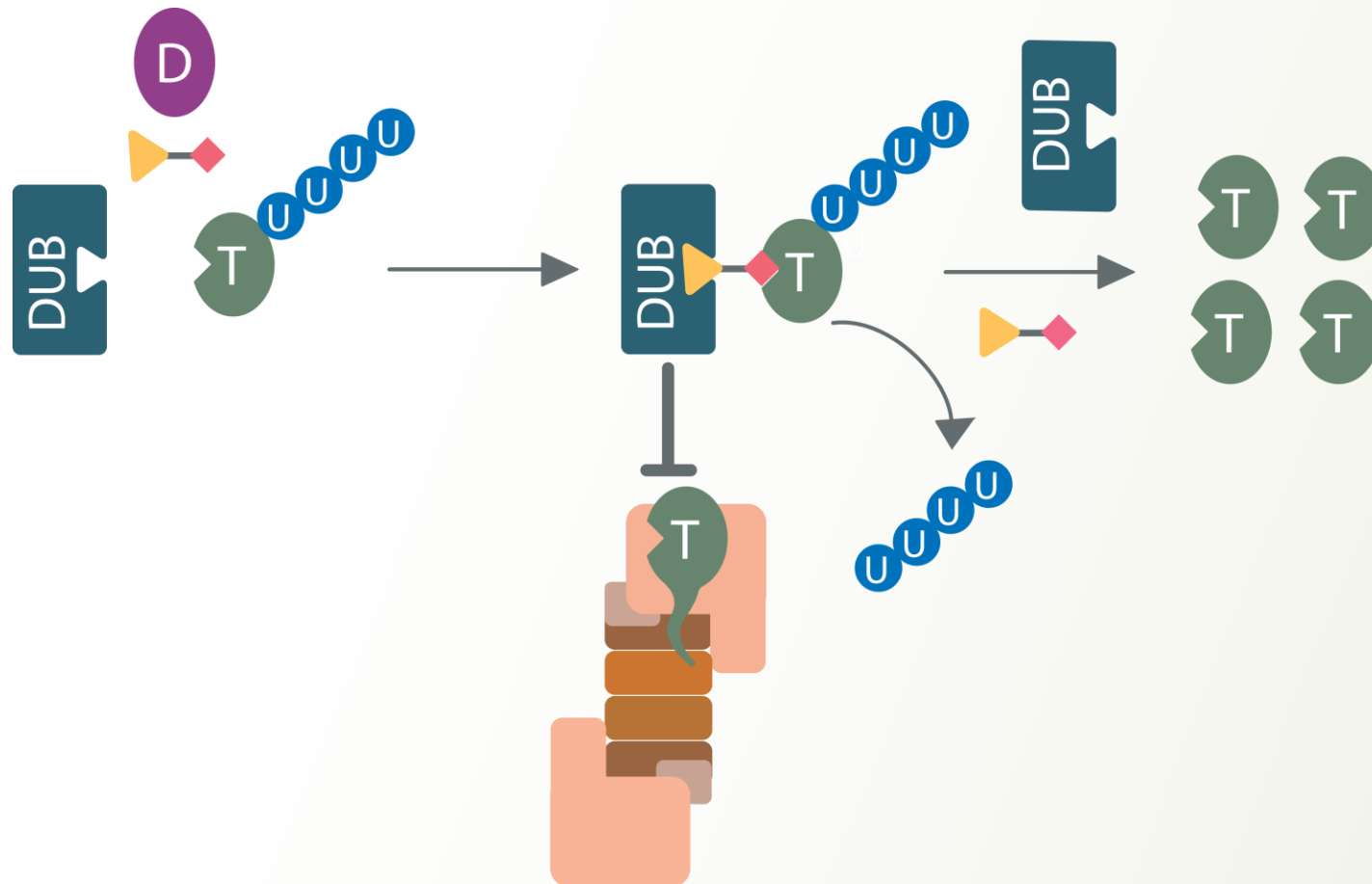
- [UbiQuant S assay \(ELISA / AlphaLISA\)](#)
- [UbiTest \(Immunoblot-based assay\)](#)

# DUB Functions

- DUBs are a large group of proteases that remove ubiquitin from proteins
- Rescue ubiquitylated proteins from proteasome attack
- Antagonize E3 ligase activity
- Regulate protein trafficking, autophagy
- Epigenetic chromatin remodeling; DUBs are “erasers”

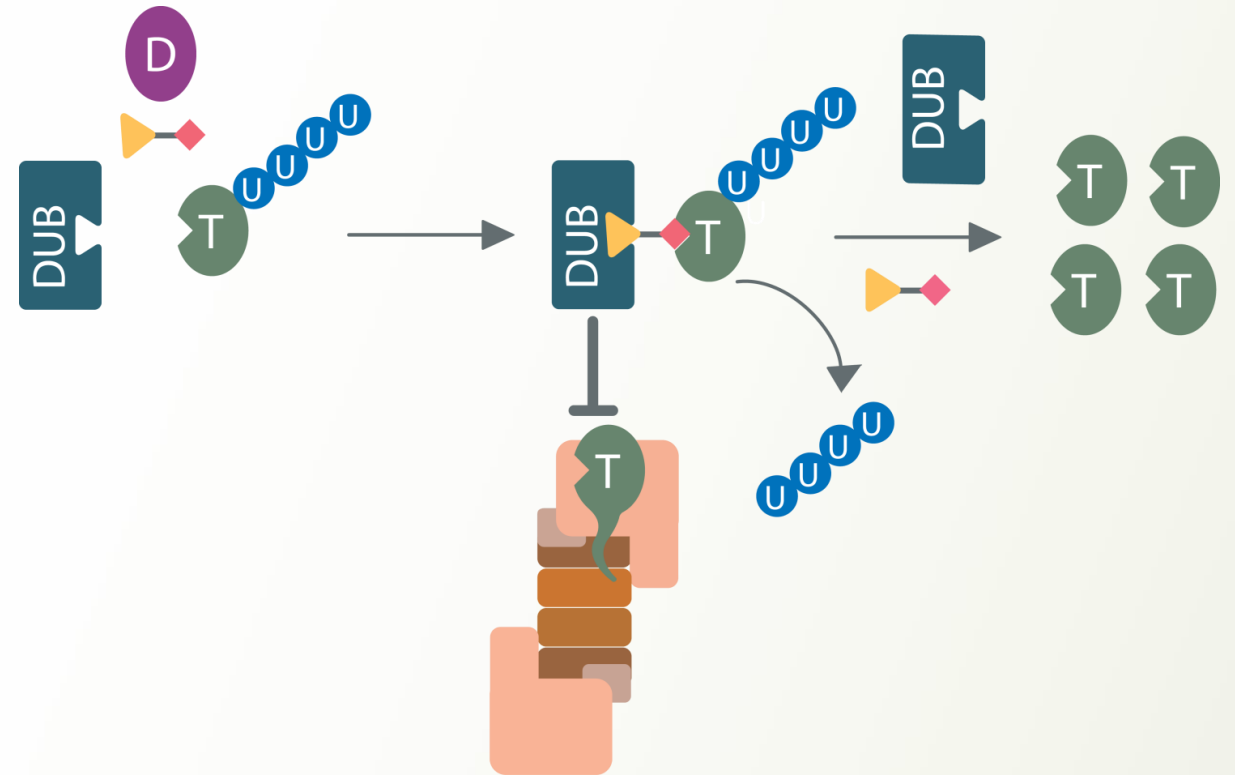


DeUBiqu<sup>ti</sup>inating  
TArgeting  
Chimeras:  
DUBTACs



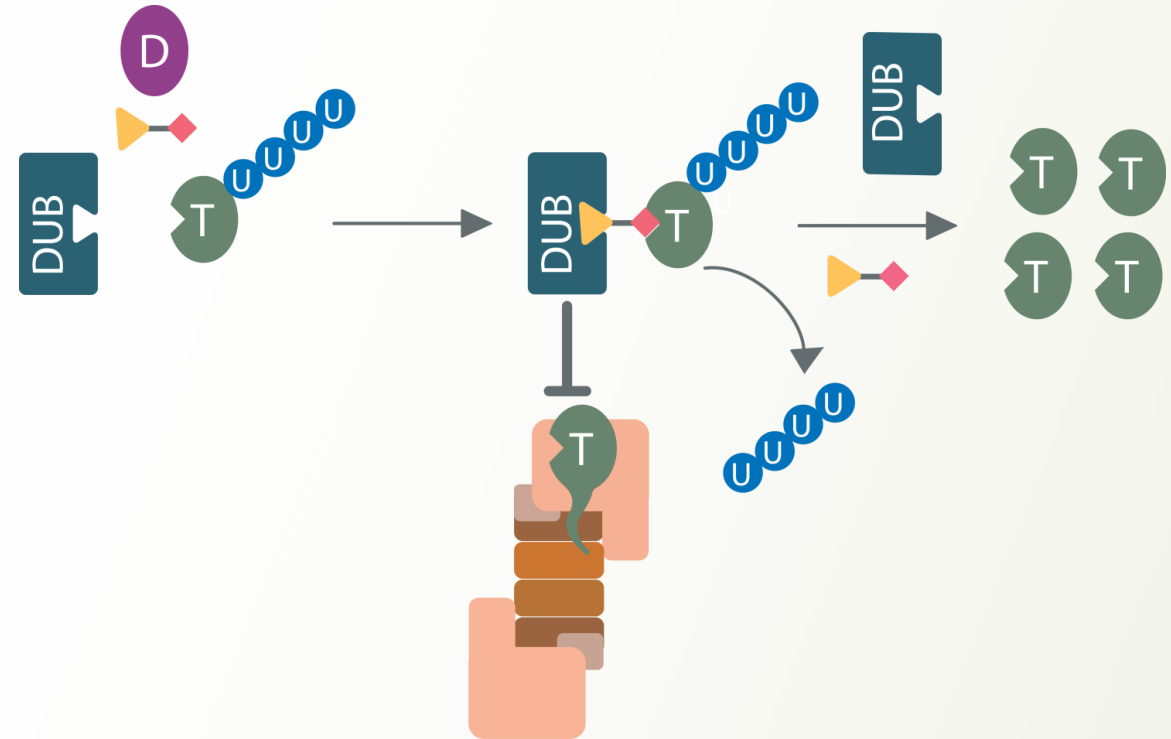
# DUBTAC: An Emerging Therapeutic

- DUBTACs recruit DUBs to a target protein and remove ubiquitin chains, resulting in stabilization of target proteins
- DUBTACs consist of three components:
  - DUB recruiter
  - Target protein binder
  - Linker connecting both entities



# Harnessing DUBs for Targeted Protein Stabilization

- Traditional PROTACs promote *degradation* of target proteins, whereas DUBTACs *stabilize* target proteins
- DUBTACs restore protein levels, function, and rescue target proteins from degradation via the proteasome





# LifeSensors' Approach to DUBTAC Drug Discovery

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## Validation of DUBTAC Ligands for Stabilizing Activity rather than Inhibition

- [Ub-Rh110/Ub-AMC assay](#)
- [CHOP reporter assay](#)
- [Diubiquitin internally quenched fluorescence \(IQF\) assay](#)
- [UbiSensor assay \(TR-FRET\)<sup>New\\*\\*\\*\\*</sup>](#)

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## Cellular Validation & DUBTAC Activity

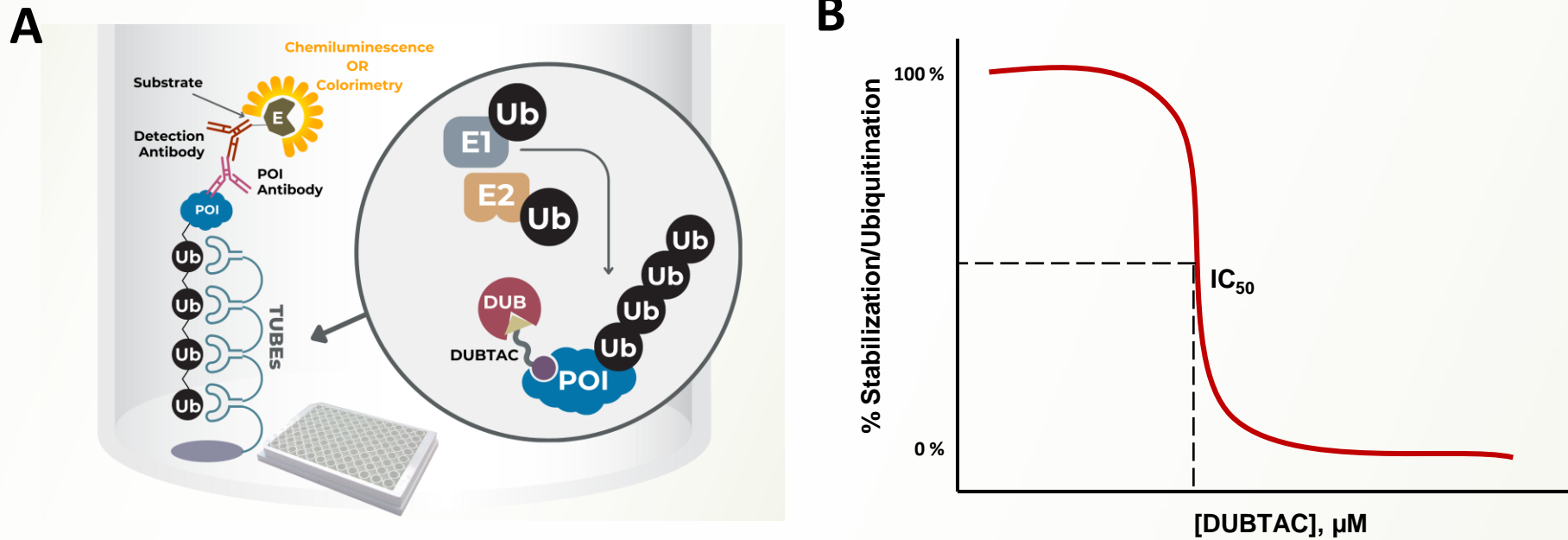
- [UbiTest Assay](#)
- [UbiQuant ELISA](#)

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## Specificity Studies

- TUBE-based mass-spectrometry studies

# UbiQuant ELISA for Cellular Validation of DUBTAC Activity



**(A)** UbiQuant ELISA to study ubiquitination and subsequent de-ubiquitination in presence of DUBTAC that represents stabilization of protein of interest. UbiQuant ELISA uses TUBE technology to estimate and accurately quantitate ubiquitinated proteins of interest with sub-nanomolar affinity. **(B)** A dose response study with DUBTAC suggests loss in basal ubiquitination on target protein with increase in DUBTAC dose representing successful protein stabilization.

# A New Perspective to the Ubiquitin Proteasome System

Adaptation of the Ubiquitin Proteasome System (UPS) presents an abundant space for drug discovery

DUBs have been implicated in many regulatory mechanisms and biological functions, where they play a role in a plethora of clinical disease

LifeSensors helps you study these DUBs to make breakthrough discoveries and pave the way to novel therapeutics

# Thank You

We are your partner in UPS, **DUBs**, E3s, PROTAC, Mol Glue, Protein Expression, CAR-T/Gene therapy and vaccine development

## Contact Us!

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