Syngene

Putting Science to Work

Integrated Solutions for PROTACs

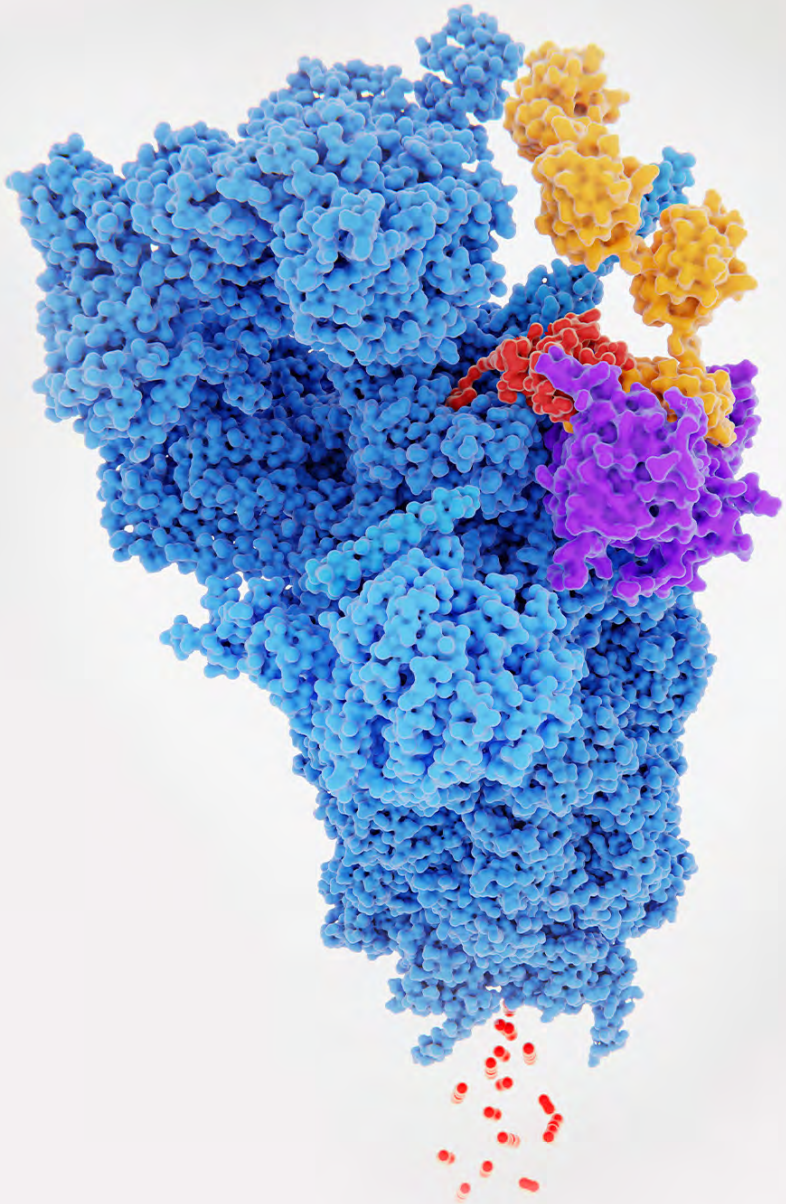
Early proof-of-concept studies to identification of a development candidate

Overview

PROTACs are fast catching on as an effective modality for drugging previously "undruggable" targets. Designing PROTAC molecules calls for an efficient workflow with assay development and mechanistic studies that help enhance understanding of the structure-activity relationship between the PROTAC, its companion enzyme, and the disease-causing protein to be degraded.

At Syngene, we offer integrated solutions (including tools) to seamlessly move your molecule from Target validation to IND. This includes proof-of-concept (POC) studies to validate whether the target is amenable to the targeted protein degradation (TPD) approach, hit PROTAC degrader identification, lead optimization, and clinical candidate selection. Further, we offer Formulation development services to ensure the bioavailability of your PROTAC compounds.

With 200+ dedicated TPD scientists and more than 15 global clients, we have a strong track record in accelerating PROTAC and X-TAC programs for our clients. Our X-TAC programs cover molecular glues, ribonuclease targeting chimeras (RIBOTACs), lysosome-targeting chimeras (LYTACs), and similar induced proximity approaches for "drugging" undruggable targets.



1 Assessing the suitability of a target for TPD approach

We can help you evaluate targets to determine whether they are amenable to degradation using the following approaches.

Informatics-driven approach

We can provide informatics-driven information on the different structural and functional features of potential drug targets where we also highlight a comparative analysis of normal and disease expression (mRNA and protein) of the targets of interest. We specialize in creating informative target dossiers.

Creation of Target dossier

- Disease driving MOA-target association
- Sequence, function, and structural homology -gene & protein
    - Homology across orthologs to identify the pre-clinical study species
    - Paralog information to understand the off-target effects associated with safety and efficacy
    - Protein domain analysis - sequence & critical residues, PTMs including prediction of ubiquitination sites
    - Genetic alterations -SNPs and CNVs and their disease association
- Small molecules competitive landscape – pharma players, molecule profile, clinical trials, identifying conservation of binding sites in different species
- A comprehensive SWOT analysis

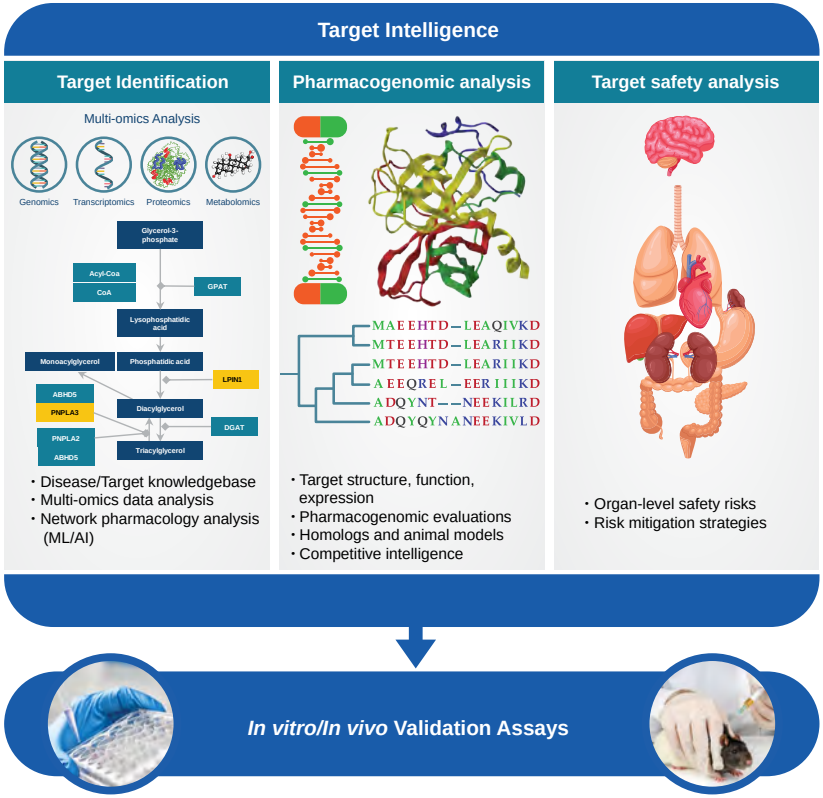


Figure 1: Target Intelligence services

Approaches used in Chemistry and Biology

- **WES/ICW for estimating Target protein expression and its kinetics in the cell line/s of interest**
  We provide a quantitative estimation of the target protein expression kinetics – a crucial first step in the PROTAC strategy for TPD – to determine endogenous degradation of the target of interest.
  For advanced studies supporting the regular screening of compounds at higher throughputs, we perform target degradation assays using HiBiT or Nano-Luc tag-based approaches.
- **dTAG** approach
  To evaluate the suitability of the target, we use a generalized tag-based strategy called degradation TAG (dTAG system). The system evaluates the effects of rapid and selective degradation of protein targets in time scales not possible with traditional genetic approaches.

2 Hit degrader identification to *in vivo* proof-of-concept

Computer-aided design for PROTAC

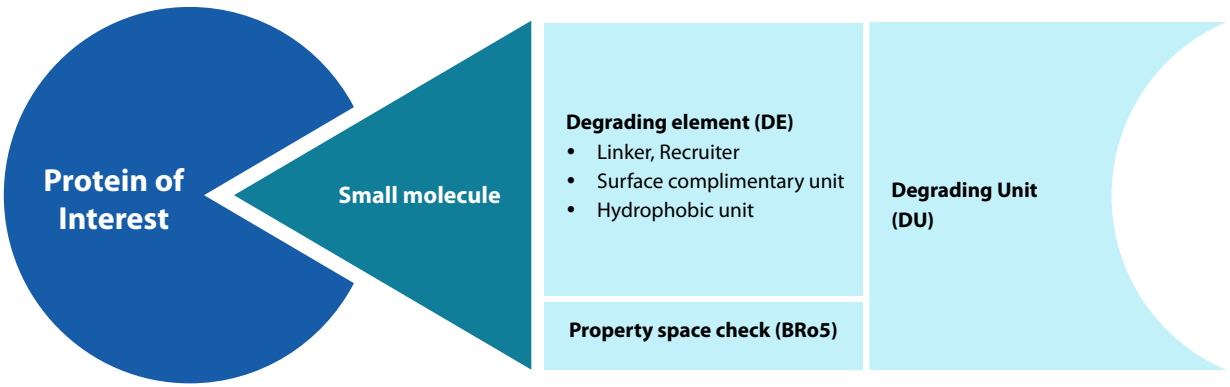


Figure 2: Designing a PROTAC molecule

We offer computer-aided design (CADD) services to assist you in identifying hit degraders based on your target of interest. These are as follows:

Establishing the binding mode of the inhibitor into the protein target of interest (POI) in the absence of X-ray structure

- Docking and molecular dynamics-based CADD protocol for identification of vectors in a core for linker exploration

Ligand + Degrading element (DE) library enumeration

- Docking-based establishment of ternary complex (POI +DE and DU): Multiple approaches needs to be applied

Refinement of Ternary complex (POI+DE+DU)

Calculation of Phys-chem properties relevant for TPD

- 3D-PSA, conformational flexibility, inter molecular hydrogen bonding (IMHB), LogD, etc.

Cheminformatics support for property-based optimization (multi-parameter optimization (MPO))

Biology and DMPK/Druggability services

We provide high-quality *in vitro* assay data with a quick turnaround time, enabling you to make informed decisions for structure-activity relationships (SAR) and medicinal chemistry-related iterations to advance your R&D programs.

Our Assay Biology group has expertise in selecting the right assay using the right platforms and approaches based on the target and E3 ligase to enable quick Identification of Hits. We evaluate the compounds for their biochemical and cell-based assay potencies for *in vitro* ranking. This is followed by DMPK (solubility, permeability, stability, mouse/rat PK) and *in vivo* studies for PROTAC screening as per the screening cascade. Our experts help establish PK-PD correlation and test the lead PROTACs to understand their efficacy or need for optimization.

3

Lead optimization to candidate selection

Syngene offers all services in the drug discovery pipeline to efficiently advance your PROTAC molecule from bench to bedside. Our services include the following:

Informatics-driven approach

- Medicinal chemistry
- Assay biology
- DMPK
- *In vivo* pharmacology
- Safety assessment
- Toxicology

4 Formulation Development services

PROTAC molecules pose a number of challenges in terms of molecular weight (MW 700-1200), labile peptide bonds, poor cell penetration/ low cell permeability, low solubility/low aqueous solubility, and high potency. However, we have many Formulation approaches to ensure the bioavailability of your PROTAC compounds.

Our Formulation approaches for improving poor permeability and poor solubility issues are as follows:

- Polymer formulations: Conventional tablets/capsules with drug or granules filled into bottles and capsules, micellar systems based on surfactants or phospholipids, hydrogels, microparticles, microspheres, lipid nanoparticles, microemulsions, and self-micro emulsifying drug delivery systems (SMEDDS)
- Particle size reduction using micronization and nanosuspensions
- Solid dispersions using spray drying

Our formulation work plan is as follows:

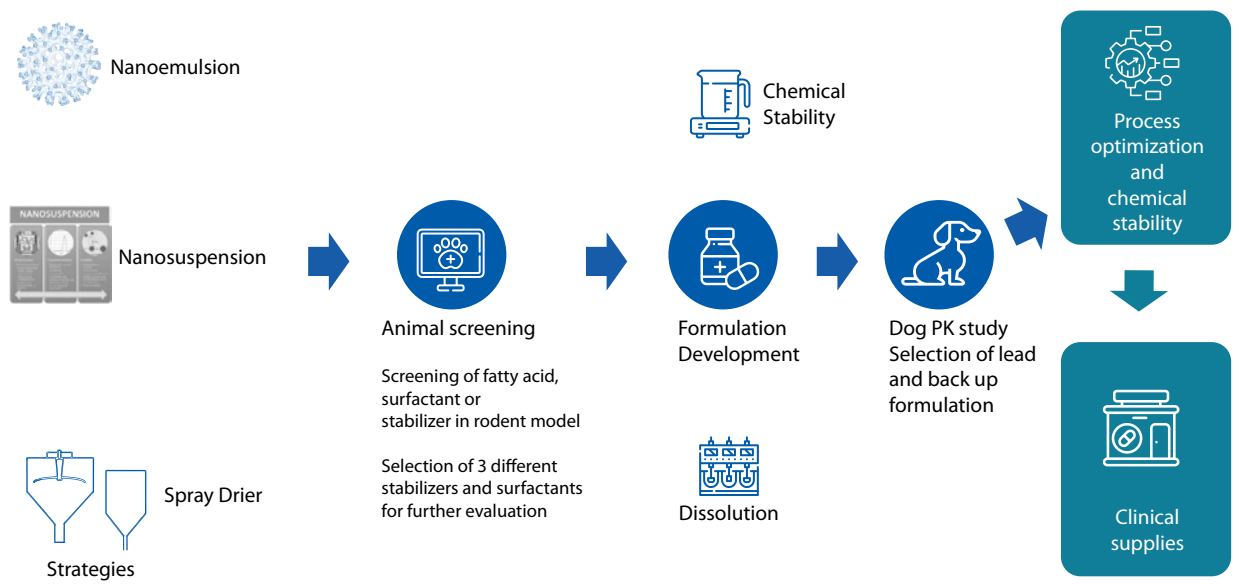
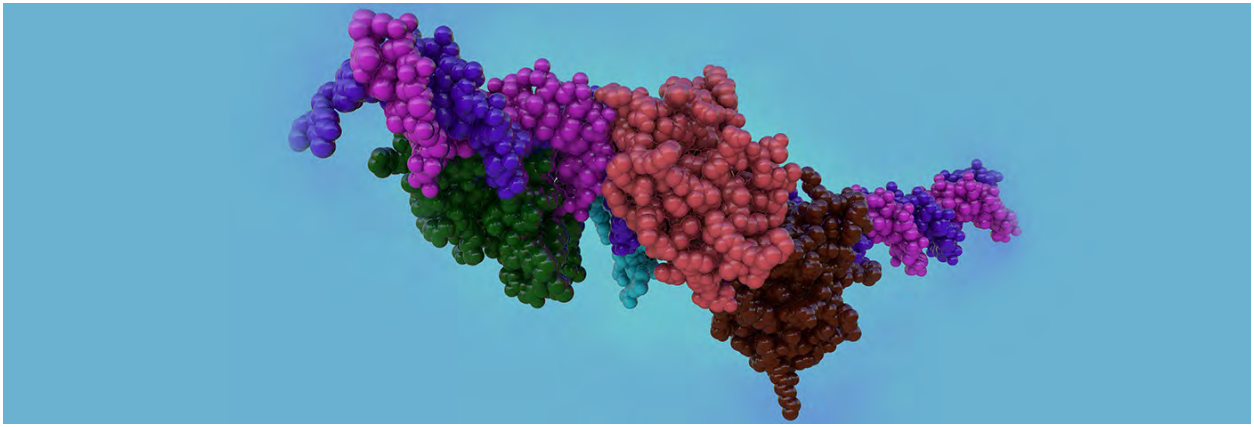


Figure 3: Formulation work plan

Factors we consider while selecting the formulation design:

- Desired target area for the PROTAC when administered orally — local/systemic action
- Physicochemical properties specific to the molecule — e.g., particle size, stability, solubility, etc.
- Recommended predefined dosage levels — this helps in designing formulation with the desired drug
- Whether the compounds are hydrolytic in nature — ensuring solution stability if hydrolytic in nature; developing platforms using co-solvents/lipids with no water in the formulation
- Whether cell permeability data is specific to the molecule (e.g., CaCO2 cell permeability *in vitro*)



The Syngene Advantage for PROTACs

- Informatics-driven identification, selection, analysis, and prioritization of potential drug targets for PROTACs to reduce late-stage attrition
- Integrated drug discovery services across medicinal chemistry, assay biology, DMPK, and *in vivo* pharmacology, enabling seamless progression of your PROTAC molecules
- Assay Biology unit equipped with automation and state-of-the-art instruments to enable assay optimization and effective screening flow
- Availability of all assay formats for cell-free and cell-based assays for target engagement, ternary complex formations, and target degradation. This includes fluorescent polarization (FP), AlphaLISA, NanoBRET, time-resolved fluorescence (TR-FRET), HiBiT, Western, InCell Westerns (WES/ICW) platforms for various screening cascade assays to identify PROTACs from hit to lead to candidate degrader selection across drug discovery programs
- Availability of *in vivo* models in various therapeutic areas, including oncology, inflammation, central nervous system (CNS) disorders, and metabolic disorders, to support PK-PD and efficacy studies
- Diverse Formulation approaches to ensure bioavailability of PROTAC compounds

To know more about our PROTAC services or to contact our experts, please, click here

Syngene
Putting Science to Work

About Syngene

Syngene International Ltd. (BSE: 539268, NSE: SYNGENE, ISIN: INE398R01022) is an integrated research, development and manufacturing services company serving the global pharmaceutical, biotechnology, nutrition, animal health, consumer goods and specialty chemical sectors. Syngene's more than 4700 scientists offer both skills and the capacity to deliver great science, robust data management and IP security and quality manufacturing at speed to improve time-to-market and lower the cost of innovation. With a combination of dedicated research facilities for Amgen, Baxter and Bristol-Myers Squibb, as well as 2 Mn sq. ft of specialist discovery, development and manufacturing facilities, Syngene works with biotech companies pursuing leading-edge science as well as multinationals, including GSK and Merck KGaA.

For more details, visit www.syngeneintl.com or write to us at bdc@syngeneintl.com

Stay Connected