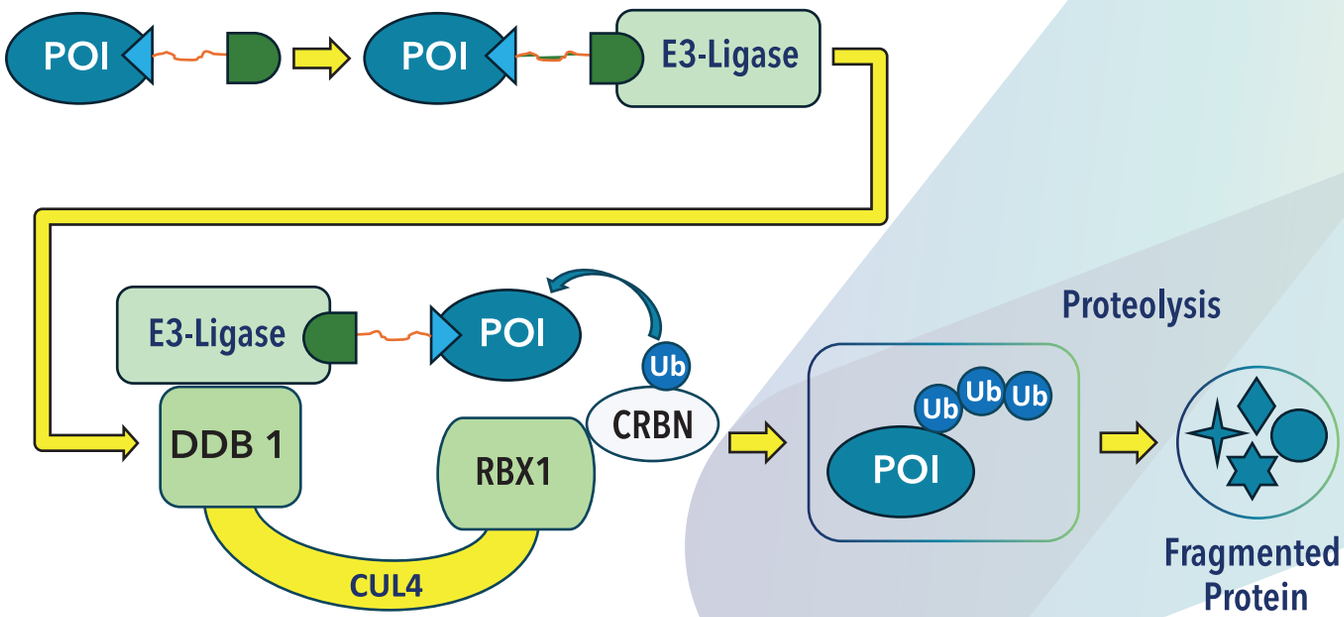
AURIGENE
PHARMACEUTICAL SERVICES



Aurigene PROTAC Research

PROteolysis – TArgeting Chimeras (PROTACs) are hetero-bifunctional molecules that hijack the body's own natural protein disposal system to initiate selective degradation of the protein of interest (POI). Their novel mode of action offers the potential to target the "undruggable" proteome, which comprises of about 85% of human proteins.

The E3 ligand and POI ligand bind to their respective targets, to form a ternary complex. Once bound, an E3 and POI are in proximity, triggering the E3 to transfer multiple ubiquitin molecules from E2 to a lysine residue on the substrate of POI via the formation of a covalent bond.

Advantages of Protein Degradation

- Hit and run system, less toxic
- Less chance to develop resistance
- Robust, can degrade un-druggable targets
- Minimum amount to achieve efficacy

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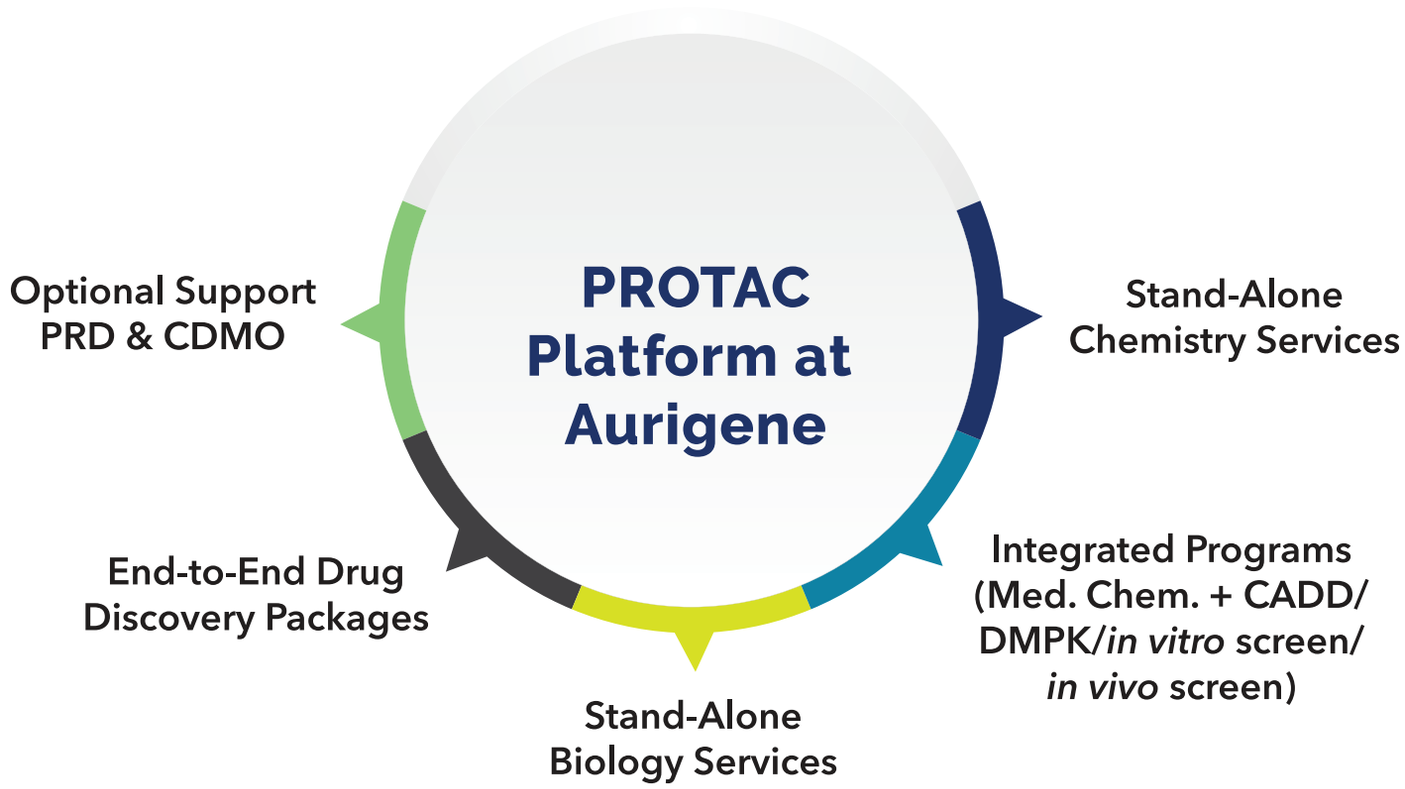
Why Aurigene?

1. ~ 20 years of proven expertise in both Drug Discovery and Med. Chem. CRO
2. Thorough understanding (~11 years) of PROTAC-related Med. Chem. space
3. In-House library of Partial PROTACs (~500 no.) for rapid synthesis of analogues
4. Synthetic capability to rapidly progress from mg to gm scale and beyond
5. Experience with AUTACs, ATTECs, RIBOTACs etc.
6. Experience with molecular glues

Flexible Business Models



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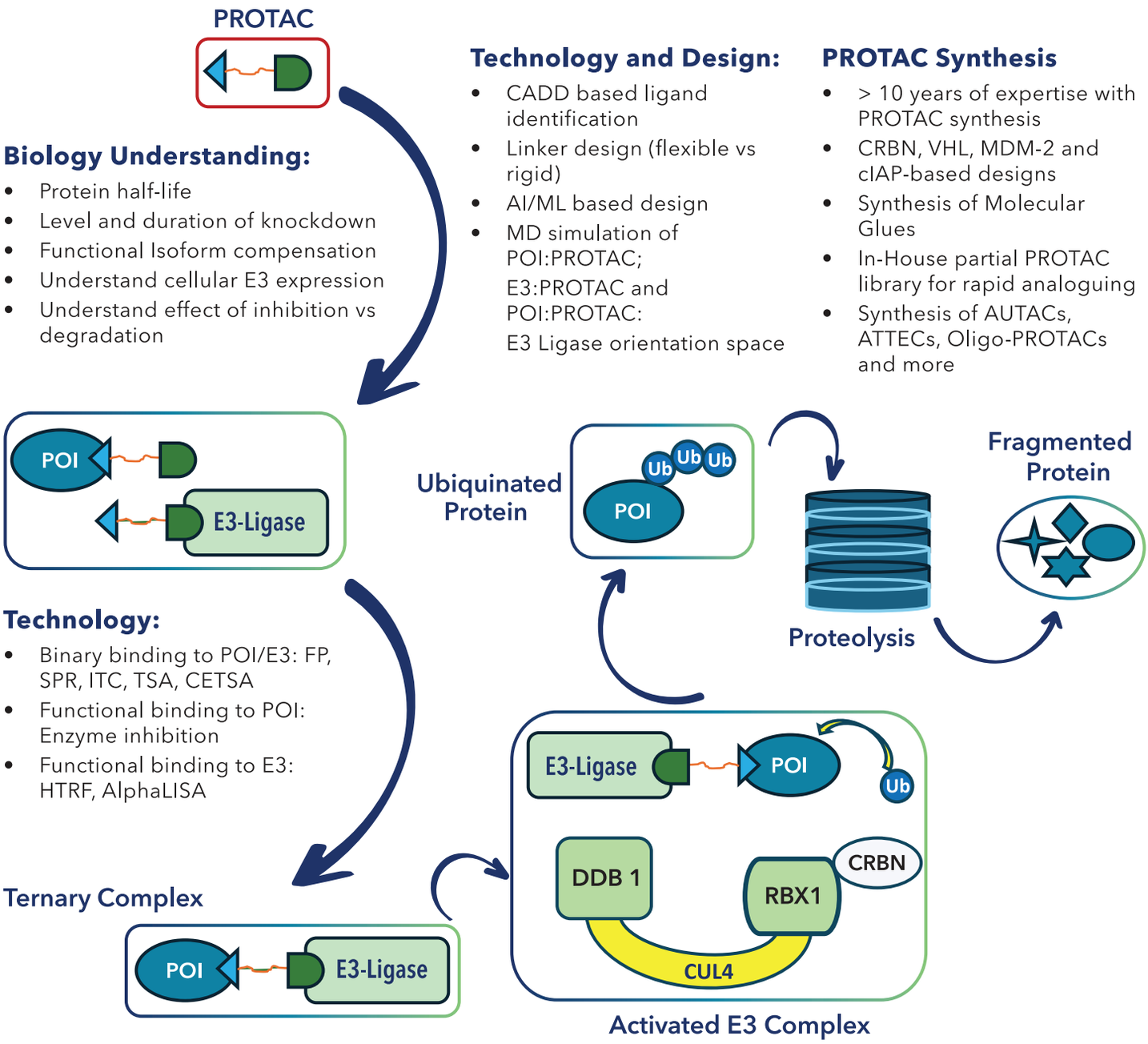
PROTAC Discovery at Aurigene



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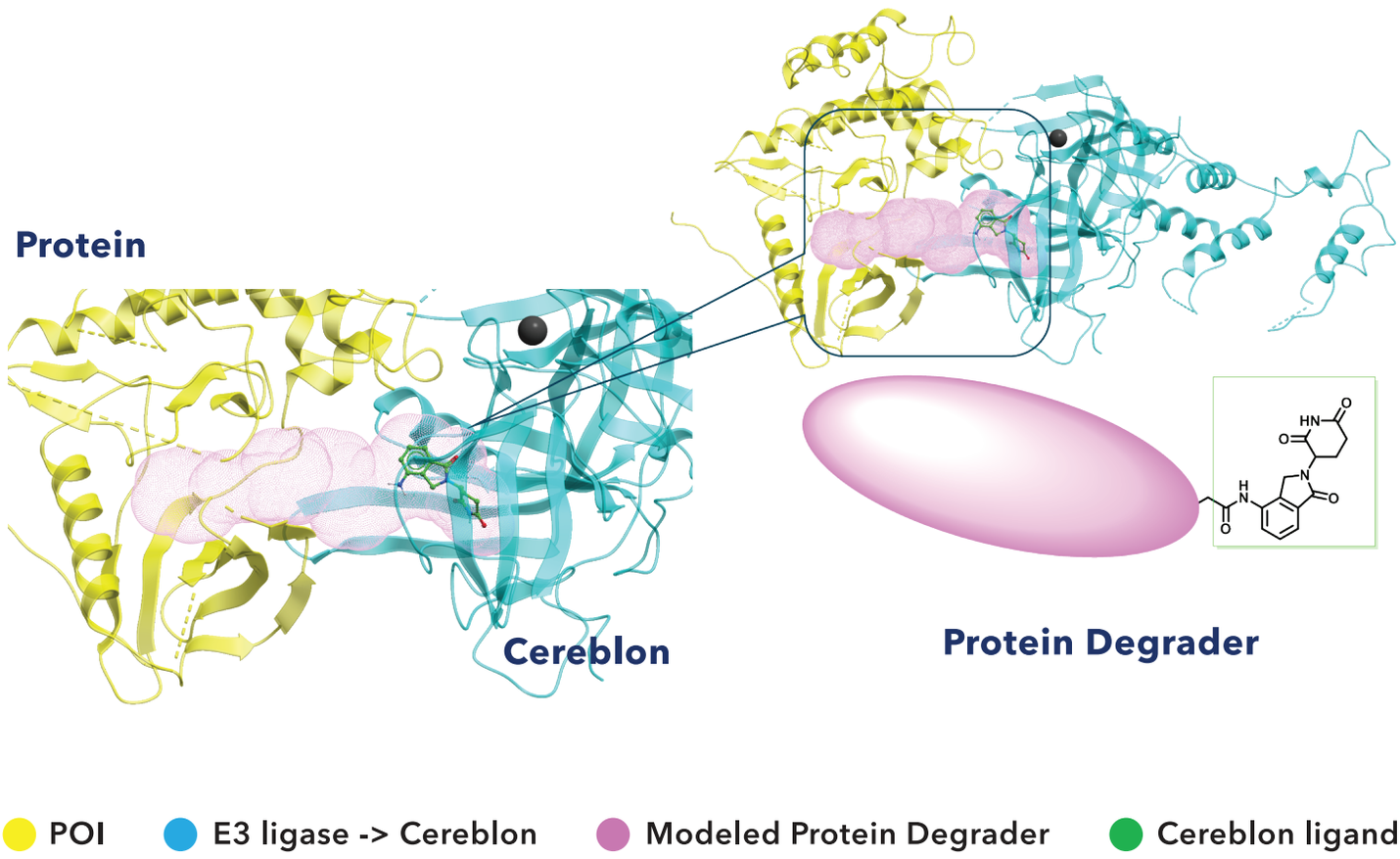
Novel CADD-Based TPD Designs

- Advance modelling tools predicted binary (POI and E3 ligase) and ternary complex (POI, E3 ligase and TPD)
- Deep Neural Network (DNN) model predicted degradation potential of DC50 <= 100 nM, Dmax >= 80%



POI E3 ligase -> Cereblon Modeled Protein Degrader Cereblon ligand

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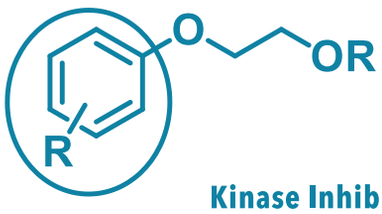
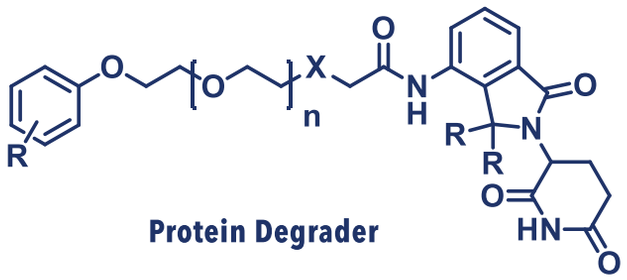
In vitro Biology: Inhibitor vs Degrader



Kinase Inhibitor

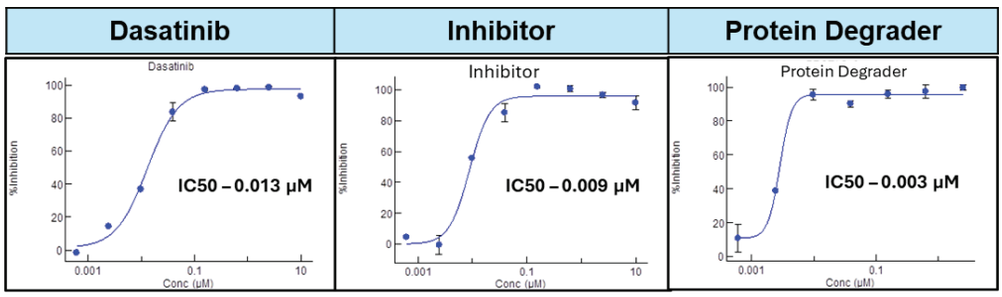


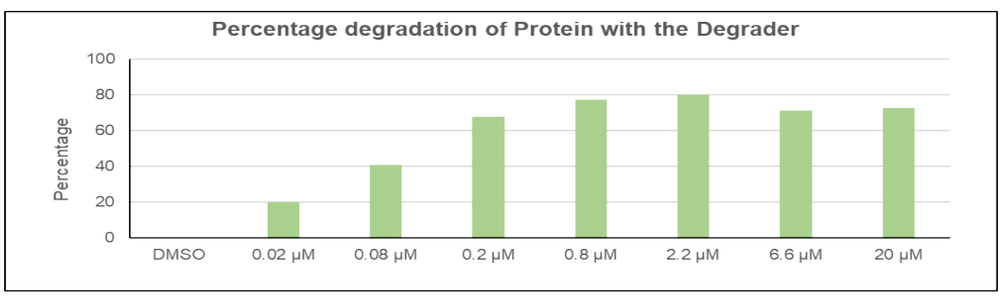
Protein Degrader

	IC50 / DC50 (µM)		
	ADP Glo	Protein NanoBRET	Western Blot
Inhibitor	0.009	0.67	>20
Degrader	0.003	1.85	0.11

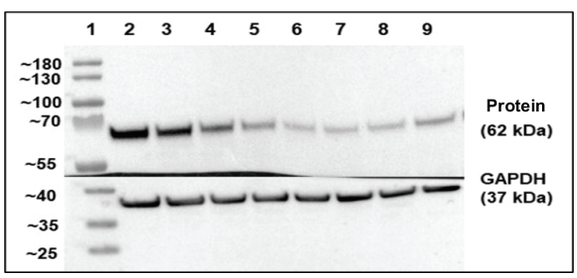
	% Inhibition / degradation at top conc.		
	ADP Glo	Protein NanoBRET	Western Blot
Inhibitor	92	93	5
Degrader	100	84	73

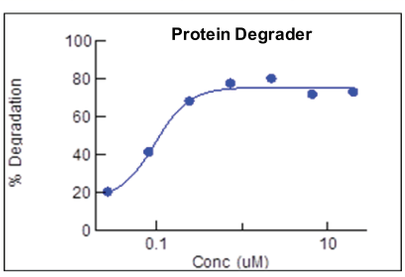
- The inhibitor and protein degrader showed nanomolar potency in ADP Glo Assay.
- The small molecule showed IC50 of 670 nM in cell based NanoBRET Target Engagement Assay, where as the protein degrader demonstrated an IC50 of 1.85 µM.
- The degrader showed dose dependent degradation of Protein in THP-1 cell line for 16 h. However, the small molecule was inactive. The tested concentrations are non cytotoxic (data supported by Cell Titer Glo assay).





Gel Loading Sequence								
1	2	3	4	5	6	7	8	9
Ladder	DMSO	0.02uM	0.08uM	0.2uM	0.7uM	2.2uM	6.6uM	20uM





Bottleneck

- Low permeability and metabolic stability
- Suboptimal PK parameters (Low AUC & T12/, High Cl)

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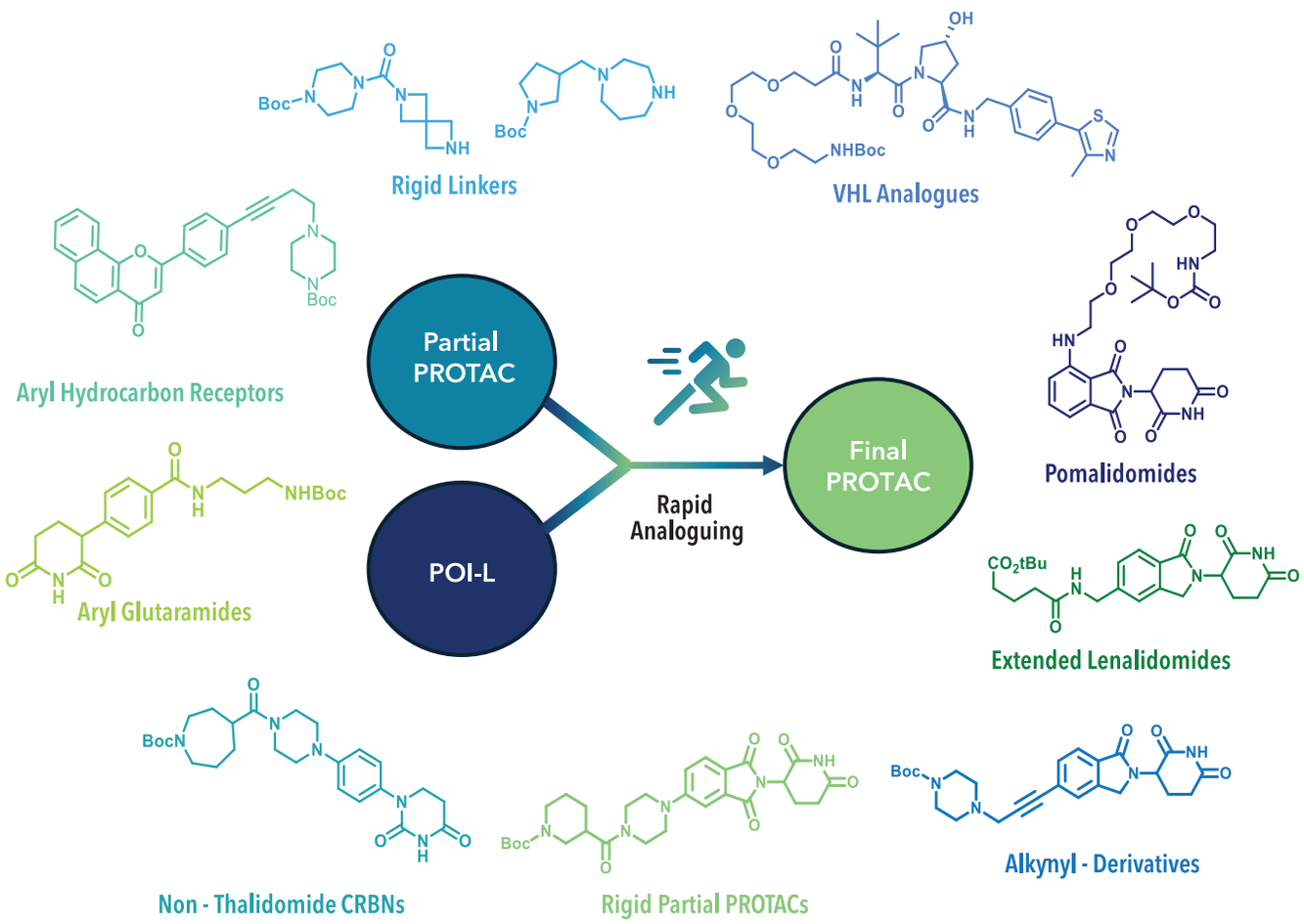
PROTAC Design using Aurigene's Partial PROTAC Library

Case Study: CADD-based design, synthesis and testing (*in vitro*, degradation, ADME & PK) of a small library in <2 months



- Linker-ligase library (~500 No)
- Rapid library synthesis
- Parallel purifications using Mass-based prep. HPLCs

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Improvement of Physicochemical Parameters

Route	Dose (mg/Kg)	C0 (ng/mL)	Cmax (ng/mL)	AUC last (h*ng/mL)	AUC INF_Obs (h*ng/mL)	T1/2 (h)	MRT (h)	Cl_obs (mL/min/Kg)	%F
i.v.	1	559	-	59.5	60.1	0.15	0.09	278.7	-
SC	5	-	456	573	582	0.49	0.76	-	≥ 100

Route	Dose (mg/Kg)	C0 (ng/mL)	Cmax (ng/mL)	AUC last (h*ng/mL)	AUC INF_Obs (h*ng/mL)	T1/2 (h)	MRT (h)	Cl_obs (mL/min/Kg)	%F
i.v.	1	1236	-	276.5	280	1.54	0.65	59.9	-
SC	5	-	1348	1960	1990	5.72	2.57	-	≥ 100

Code	Metabolic Stability: T1/2 (min)			IC50(μM)		Protein Degradation
	MLM	RLM	HLM	ADP Glo	NanoBRET	% Degradation
Protein Degrader	3.16	< 2.0	< 2.0	0.009	1.85	DC50 = 0.11 μM
NB1-033-P	22.97	9.95	6.80	0.014	0.040	59% @ 0.078 μM, Hook Effect observed at higher concentrations

Improved stability and PK parameters were observed in case of NB1-033-P. Further studies to improve the degradation potential are in progress.

The Aurigene Advantage

Truly Integrated Services

- Integrated discovery chemistry & Biology services (Small & large molecules)
- Early discovery to commercialization with Global regulatory & quality expertise
- Pre-formulation & formulation services, analytical & purification expertise

Quality

- Our R&D site is US FDA inspected
- cGMP sites have multiple accreditations across globe
- All our labs are GLP approved, animal facilities are AAALAC accredited

Intellectual Property Safety

- Your IPs stay with you! All IP generated through projects belong to our clients

Information security

- We are ISO27001 ISMS certified

Flexible Business Models

- Stand-Alone Chemistry Services, Mix-and Match programs (e.g. Med. Chem. + DMPK)
- End-to-End Drug Discovery Packages, Optional Support PRD & CDMO and more

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