The Investigation of GSPT1 as an Off-Target in Targeted Protein Degradation

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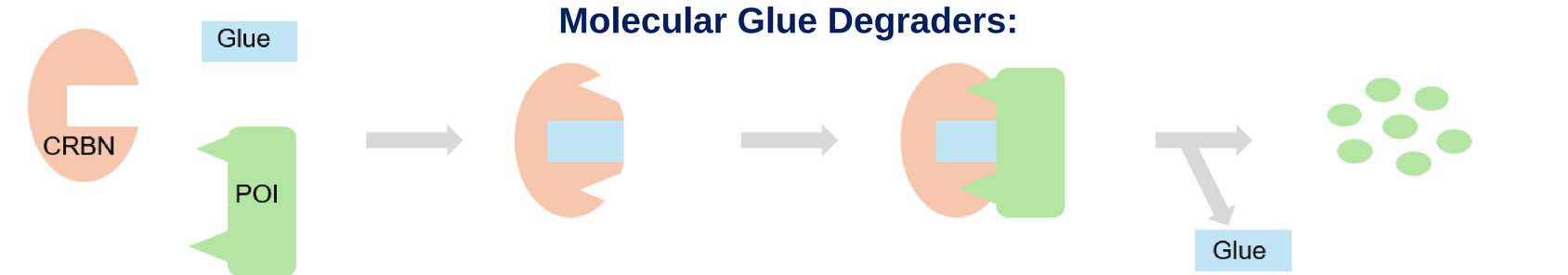
The Importance of Targeted Protein Degradation (TPD) in Drug Discovery

"The potential to target disease-causing proteins previously deemed **undruggable** with small molecule inhibitors"[1]

- The human genome codes for > 20,000 proteins
- Many are "undruggable" with classic small molecule inhibitor drugs
- Many play key roles in cancer

- ✓ Degrade previously "undruggable" targets
- ✓ Completely remove disease-causing proteins from the body
- ✓ Act catalytically – lower doses
- ✓ Potential for oral dosing

Molecular Glue Degraders:



CRBN and POI cannot interact due to a lack of shape complementarity

Molecular glue degrader binds to and modifies the structure of CRBN

CRBN can now bind to the POI, with favourable interactions

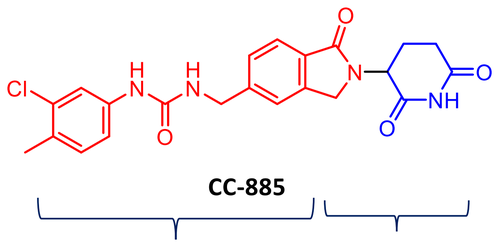
The disease-causing POI is degraded and removed from the body
- Molecular glue released to repeat the cycle

GSPT1 as a Cancer Target and Off-Target in TPD Programmes

1) GSPT1 as a Cancer Target:

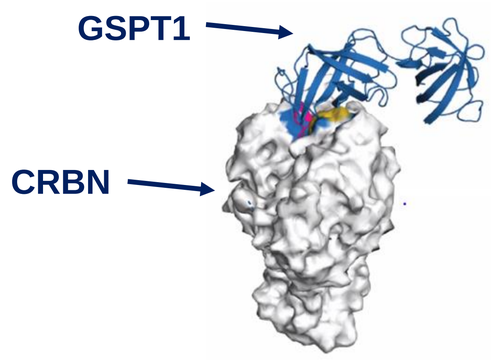
- Over-expressed in human cancers
- Promising therapeutic target for cancer therapy
- Degraded by molecular glue degraders

- GSPT1 degraders have entered clinical trials:



Interacts with GSPT1

Binds to the E3 Ligase Cereblon (CRBN)



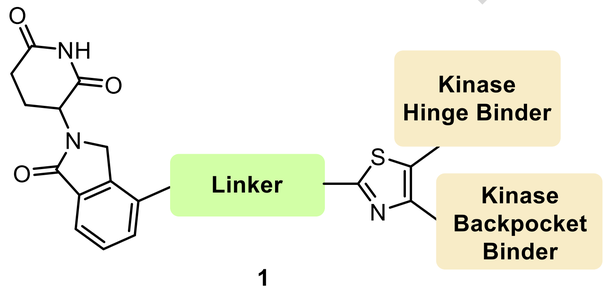
CC-885 in complex with CRBN and GSPT1[2]

pDC_{50} represents the logarithmic concentration of compound required to degrade 50% GSPT1
$Asym_{max}$ represents the percentage of GSPT1 degraded by the compound.

2) GSPT1 as an Off-Target – "False" Degradation Results:

- GSPT1 degradation prevents the resynthesis of other cancer targets
- Leads to deceptively false degradation results of the target protein
- Monumental issue in TPD field – has occurred at GSK and other organisations[3]

GSK kinase X* project



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$GSPT1: pDC_{50} = 9.43, asym_{max} > 99\%$

- ✓ Binds desired kinase
- ■ False kinase degradation observed
- ■ GSPT1 molecular glue degrader

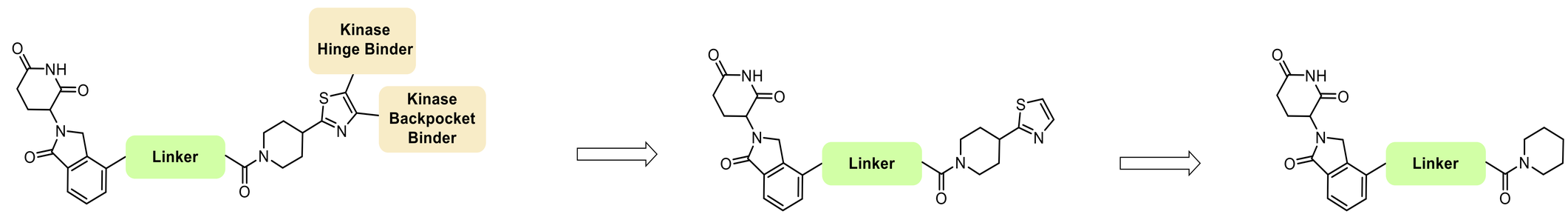
GSPT1 Structure Activity Relationship (SAR) Study – A Two-Pronged Approach

Project Aims: Two–Pronged Approach

- **GSPT1 as a Cancer Target** – optimise GSPT1 degraders to more drug like space
- **GSPT1 as an Off-Target** – determine chemical space to be avoided / incorporated to avoid GSPT1

Key Results:

1) Terminal ring required for strong degradation – kinase binders less critical



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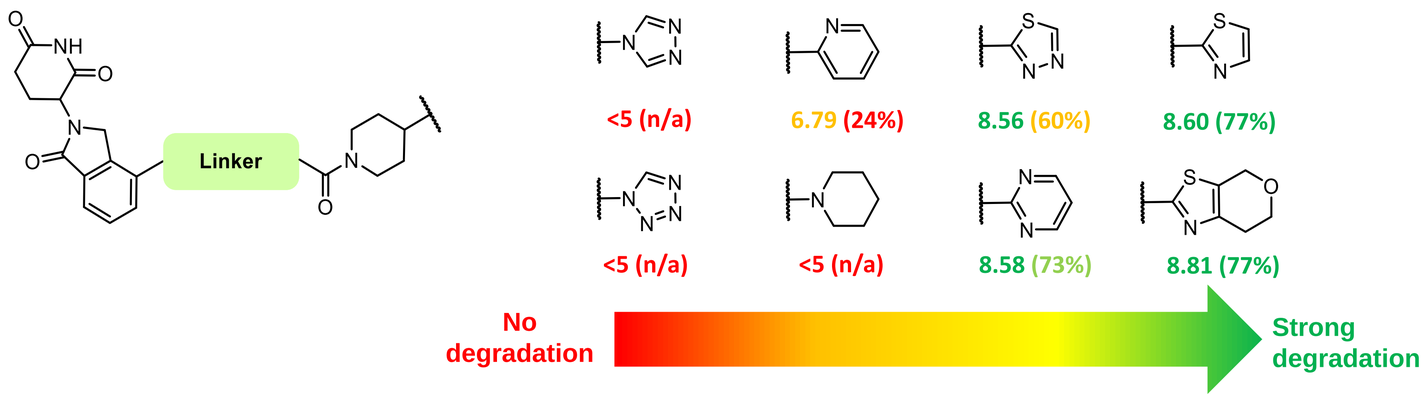
pDC_{50} ($asym_{max}$):	9.43 (>99%)	8.60 (77%)	7.63 (24%)

2) Changes to terminal ring highly sensitive:



- ✓ Full SAR Study completed in first 18 months of PhD
- ✓ Synthesised >100 molecular glue degraders
- ✓ Wide range of GSPT1 degradation potencies achieved with clear SAR trends
- ✓ Manuscript for publication in preparation

References

(1) Sakamoto, K. M. *et al. Proc. Natl. Acad. Sci. U S A,* **2001**, 98, 8554-8559.
(2) Matyskiela, M. E. *et al.* Nature **2016**, 535, 252-257.
(3) Vetma, V. *et al*. *ACS Chem. Bio.* **2024**, 19, 1484 – 1494.

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