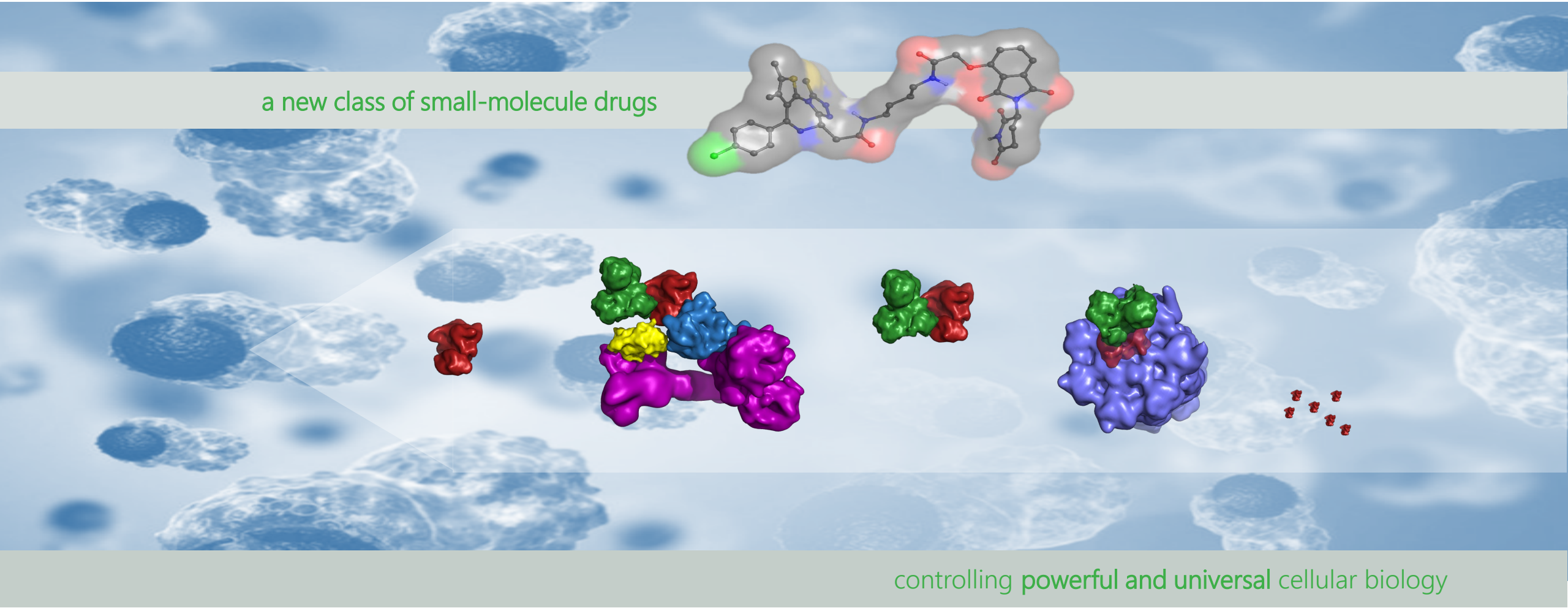


# Degrader Drug Space: What Rules?

Ubiquitin-Induced Targeted Protein Degradation Conference

Virtual Session. August 25, 2020

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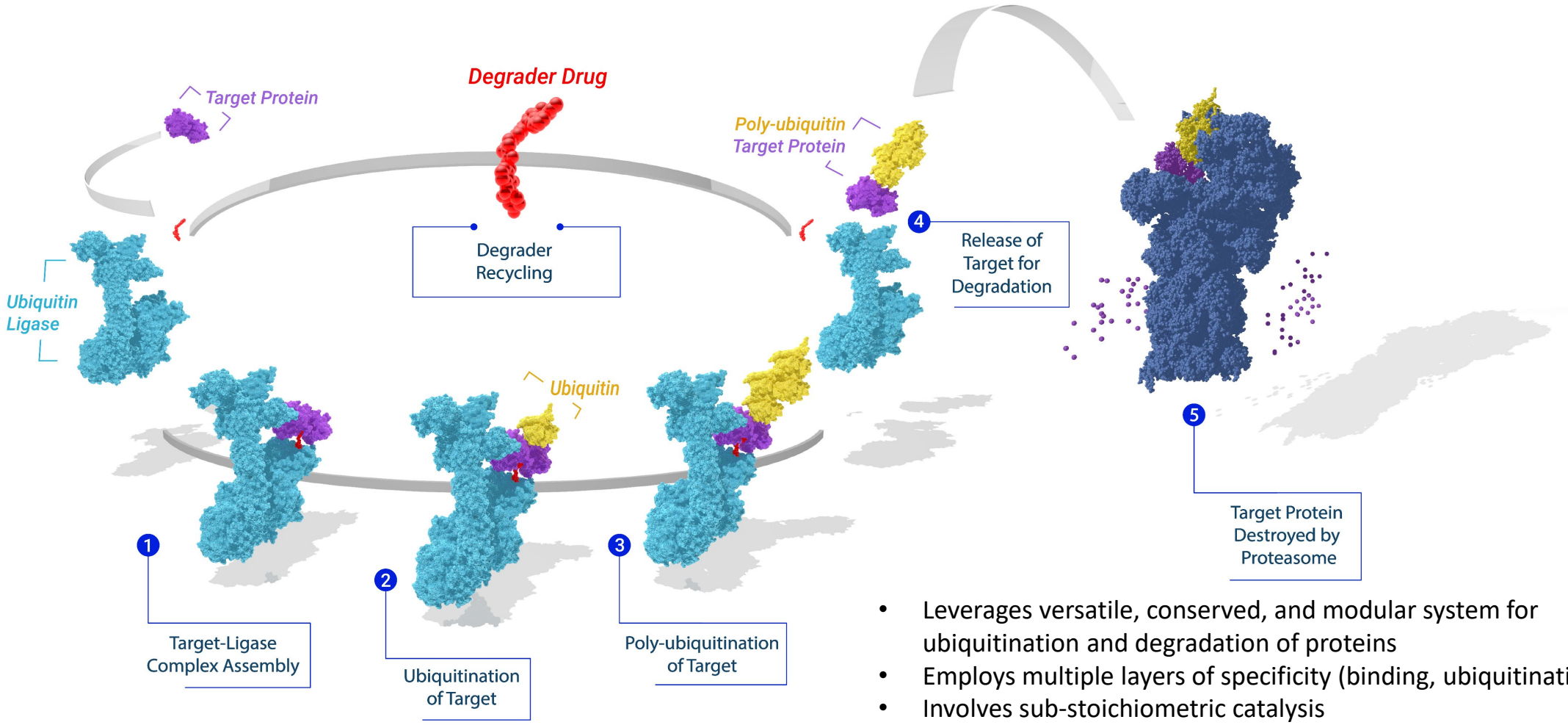
# Degraders Enable a Catalytic Cycle that Destroys Disease-Relevant Proteins




- Leverages versatile, conserved, and modular system for ubiquitination and degradation of proteins
- Employs multiple layers of specificity (binding, ubiquitination)
- Involves sub-stoichiometric catalysis
  (one degrader destroys many copies of target protein)
- Small molecule control of protein level vs. protein function(s)

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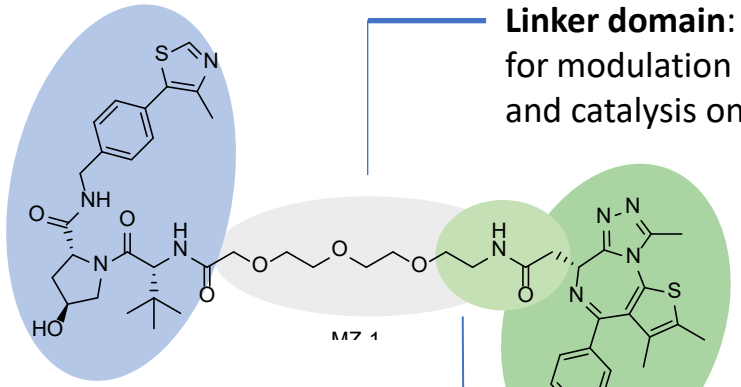
# Dissecting a Degrader

**While many features must be established empirically, frameworks for degrader discovery and optimization are emerging**




**Linker domain**: vast possibilities for chemistries that allow for modulation of properties, ternary complex formation, and catalysis on a case-by-case basis.

**Target-binding:** covalent, orthosteric, and allosteric ligands for targets are known; specific biophysical principles underpinning what is required for effective degradation must be defined on a case-by-case basis.

**Exit vector:** trajectory out of target protein binding pocket; can impact degrader properties and control ternary complex formation.

**E3-ligase binding:** known examples include specific ligands for β-TRCP, MDM2, cIAP, xIAP, VHL, and cereblon. The best ligase for any given target must be defined empirically.

**(put another way: degraders are not simply the sum of their parts)**

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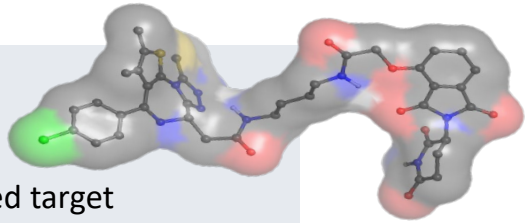
# Degrader Property Space is ‘Drug-like’

**Medicinal chemistry provides degraders with diverse and desirable physicochemical and pharmacological properties**



| | |
|---|---|
| MW | 600-1300 Da |
| Degradation potencies | 50pM (maximum); routinely 0.15-10nM |
| Selectivity* | High. Routinely observe only degradation of desired target |
| Catalytic efficiency | $K_{cat}$ = 6 (high catalysis); $K_{cat}$ = 1 (moderate catalysis) |
| log D | 1 – 4 (experimentally determined) |
| Protein binding | 78 - 99% |
| $V_{dss}$ (L/kg) | 0.13 – 14 L/kg |
| $T_{1/2}$ (h) | 0.3 – 26.7 hour |
| Clearance | 0.14 – 150 ml/min/kg |
| Plasma Stability | 0 – 98% |
| Kinetic Solubility | 0.5 – 500 µM |
| Oral bioavailability | **YES**. F% up to **100%** with examples in all settings where pursued<br>Good oral exposures (AUC/dose >1200 h*ng/ml achieved) |

* Control over degradation of known Cereblon neosubstrates (Ikaros, Aiolos, GSPT1, CK1α, SALL4 etc.) can be achieved by medicinal chemistry

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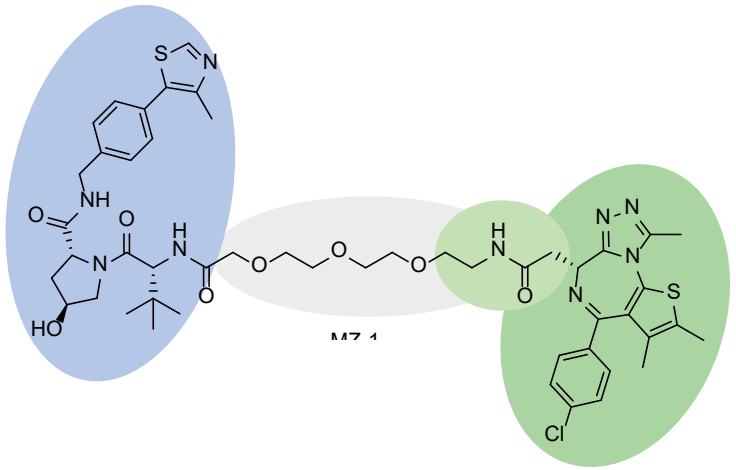
# Degrader Translation to *in vivo* Setting

**While mechanism of action is different, historical learnings point drug discovery teams towards key actions**




- Establish a PK/PD/efficacy relationship
- Establish *in vitro-in vivo* correlation
- Optimize solubility and permeability to enable RoA and exposure level

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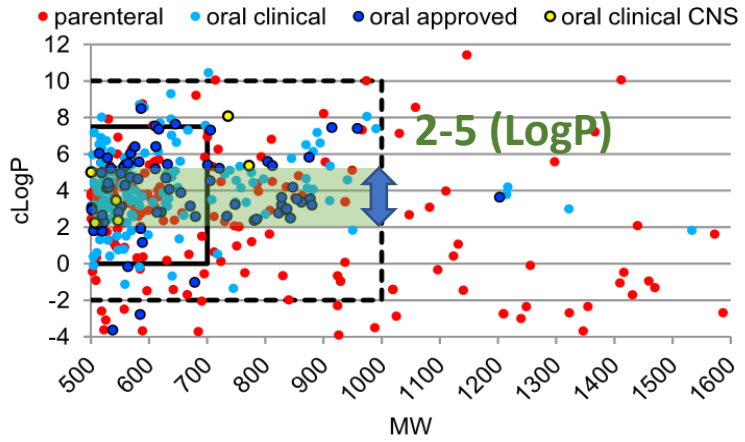
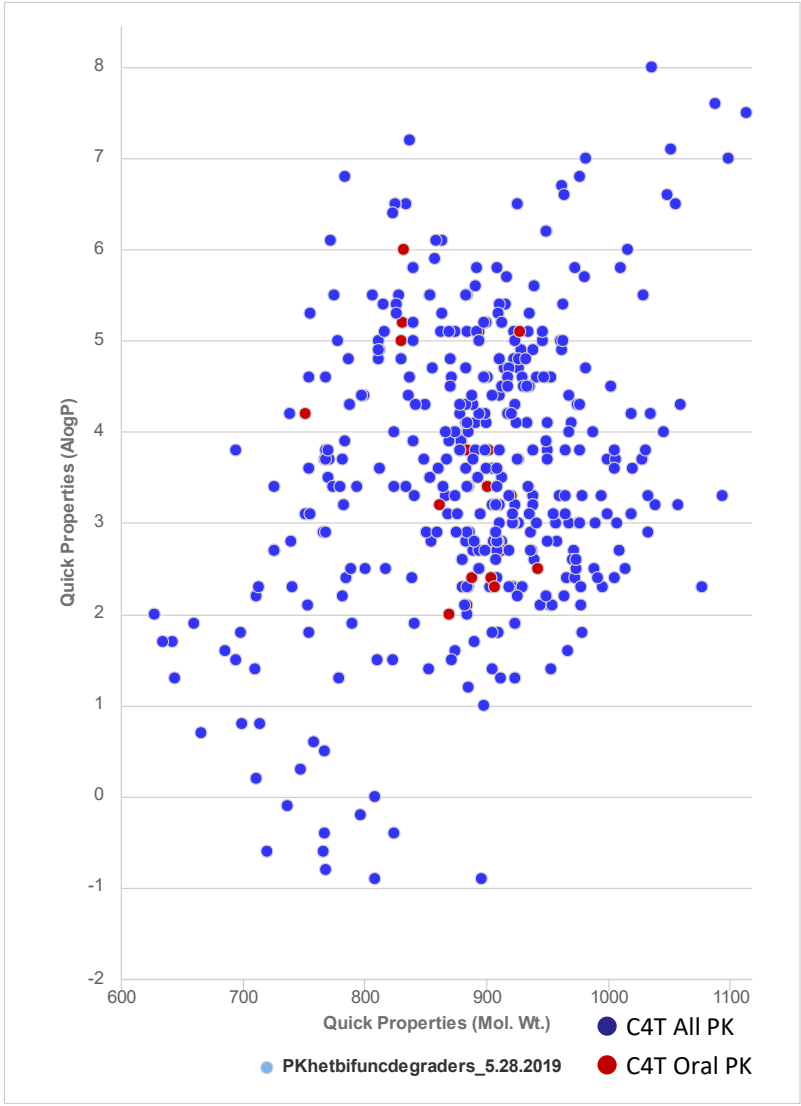
# Beyond 500 Ligand Property Space: cLogP



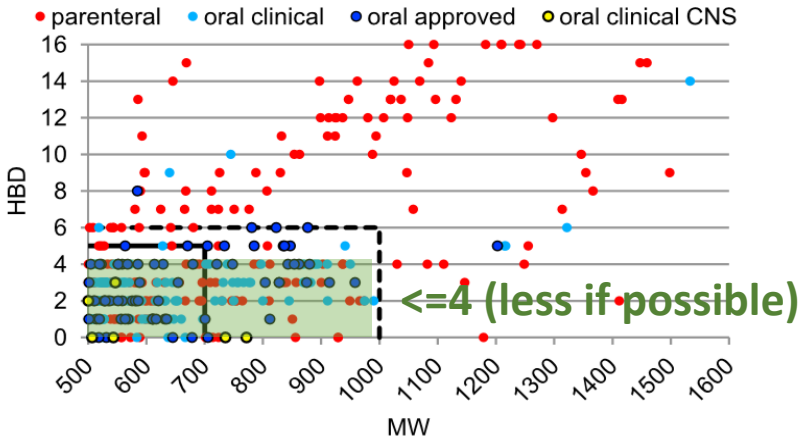

*Chemistry & Biology* **2014**, *21*, 1115.

| | b500 Property Space | C4T Degrader Property Space |
|---|---|---|
| cLogP | -2-9 | ≤ 6 |



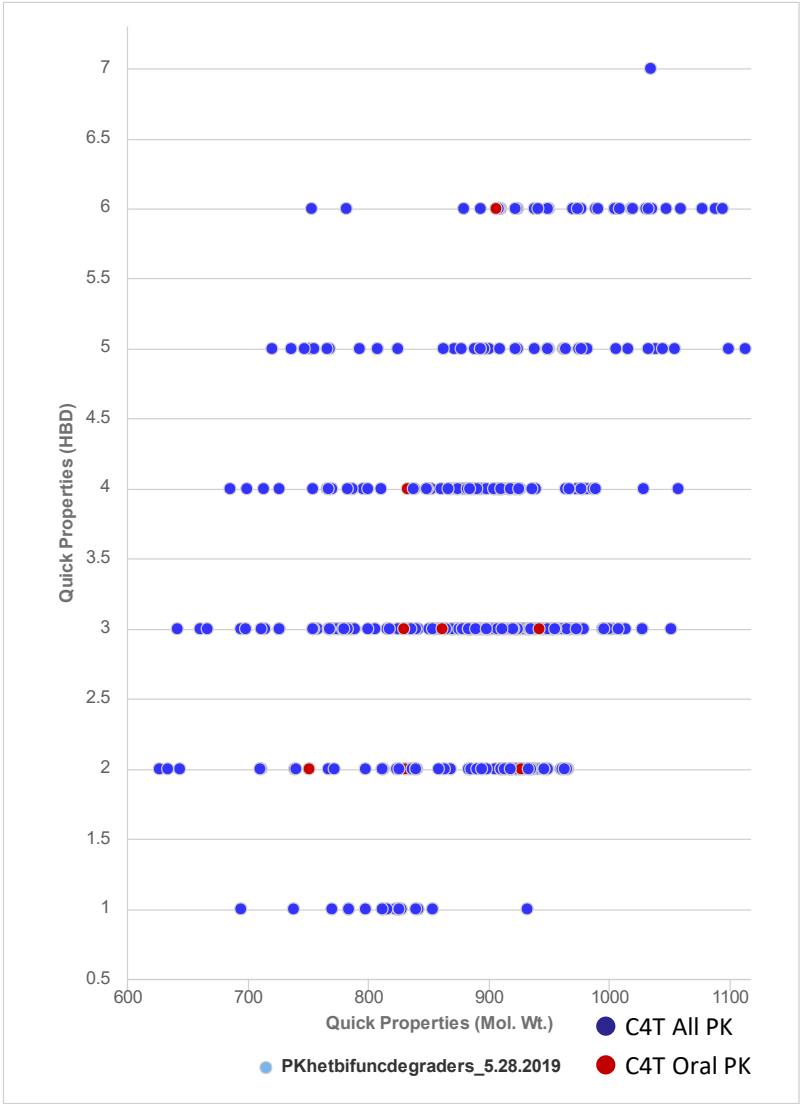

cLogP requirements for orally available b500 ligands and C4T Degraders are different

# Beyond 500 Ligand Property Space: HBD




*Chemistry & Biology* **2014**, *21*, 1115.

| | b500 Property Space | C4T Degrader Property Space |
|---|---|---|
| cLogP | 2-9 | ≤ 6 |
| HBD | HBD ≤ 6 | HBD ≤ 6 |




HBD requirements for orally available b500 ligands and C4T Degraders are similar

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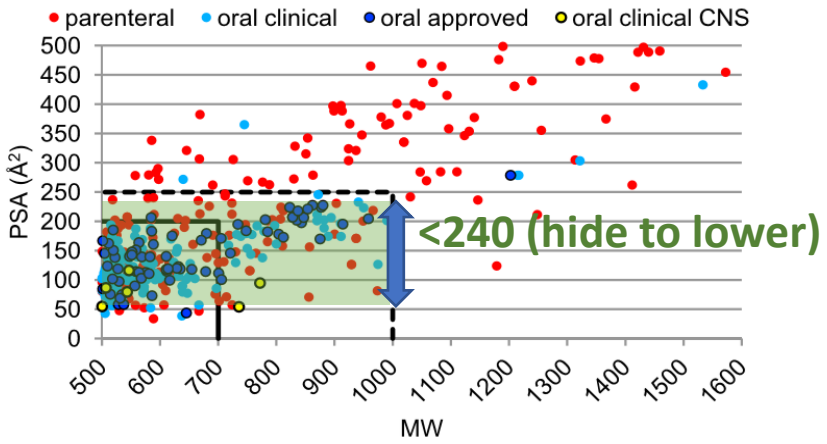
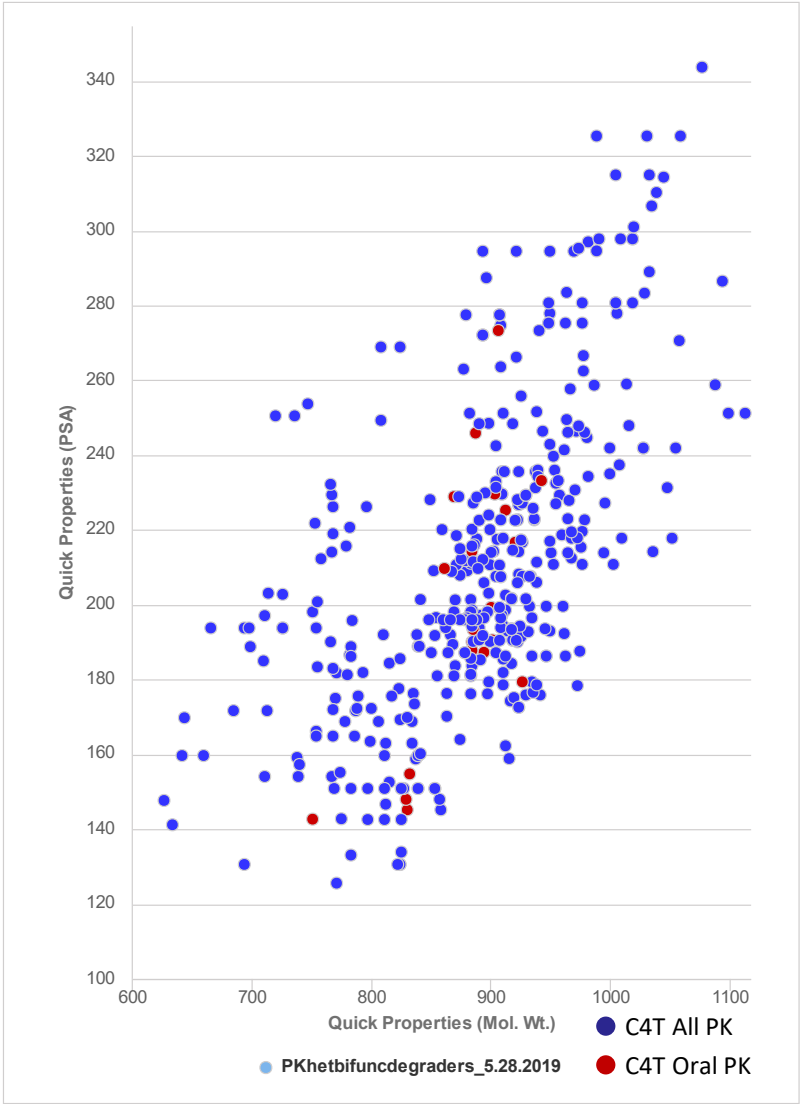
# Beyond 500 Ligand Property Space: PSA




*Chemistry & Biology* **2014**, *21*, 1115.

| | b500 Property Space | C4T Degrader Property Space |
|---|---|---|
| cLogP | 2-9 | ≤ 6 |
| HBD | HBD ≤ 6 | HBD ≤ 6 |
| PSA | tPSA ≤ 240 | tPSA ≤ 273 |




PSA requirements for orally available b500 ligands and C4T Degraders are different

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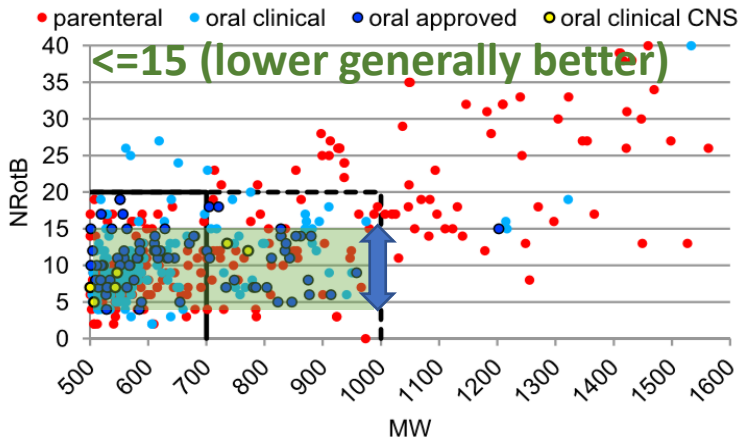
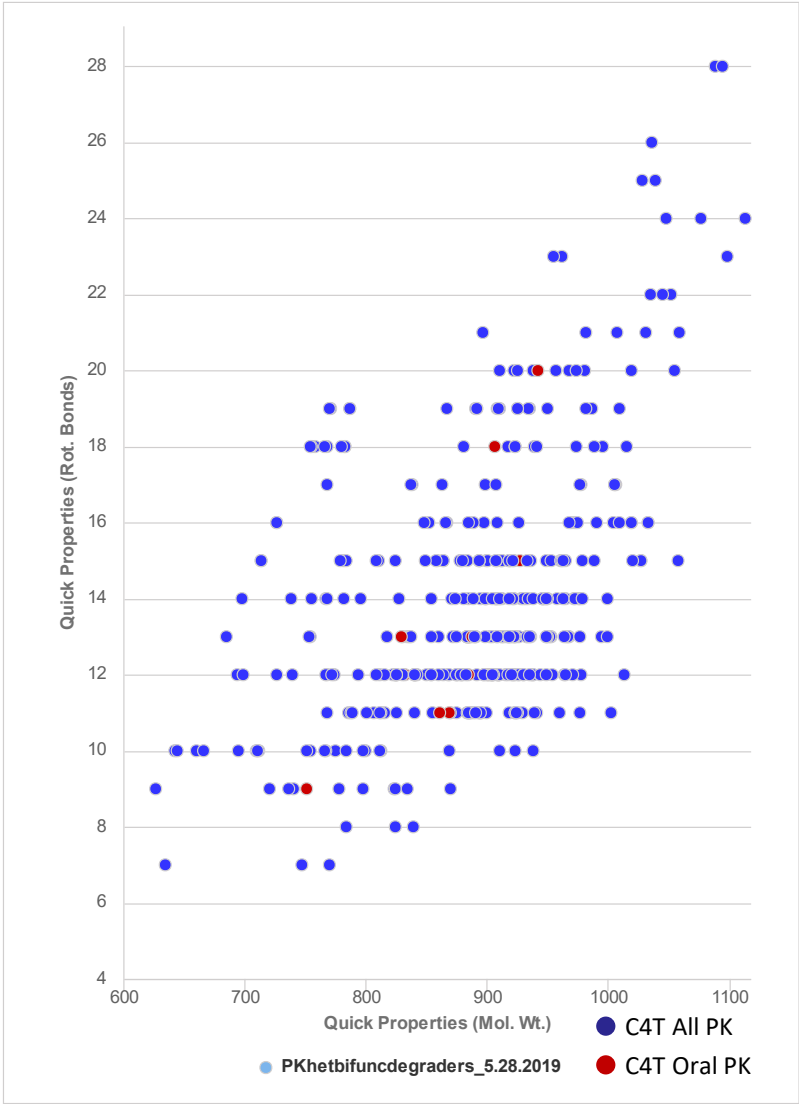
# Beyond 500 Ligand Property Space: NRotB




*Chemistry & Biology* **2014**, *21*, 1115.

| | b500 Property Space | C4T Degrader Property Space |
|---|---|---|
| cLogP | 2-9 | ≤ 6 |
| HBD | HBD ≤ 6 | HBD ≤ 6 |
| PSA | tPSA ≤ 240 | tPSA ≤ 273 |
| NRotB | ≤ 15 | ≤ 20 |




NRotB requirements for orally available b500 ligands and C4T degraders are different

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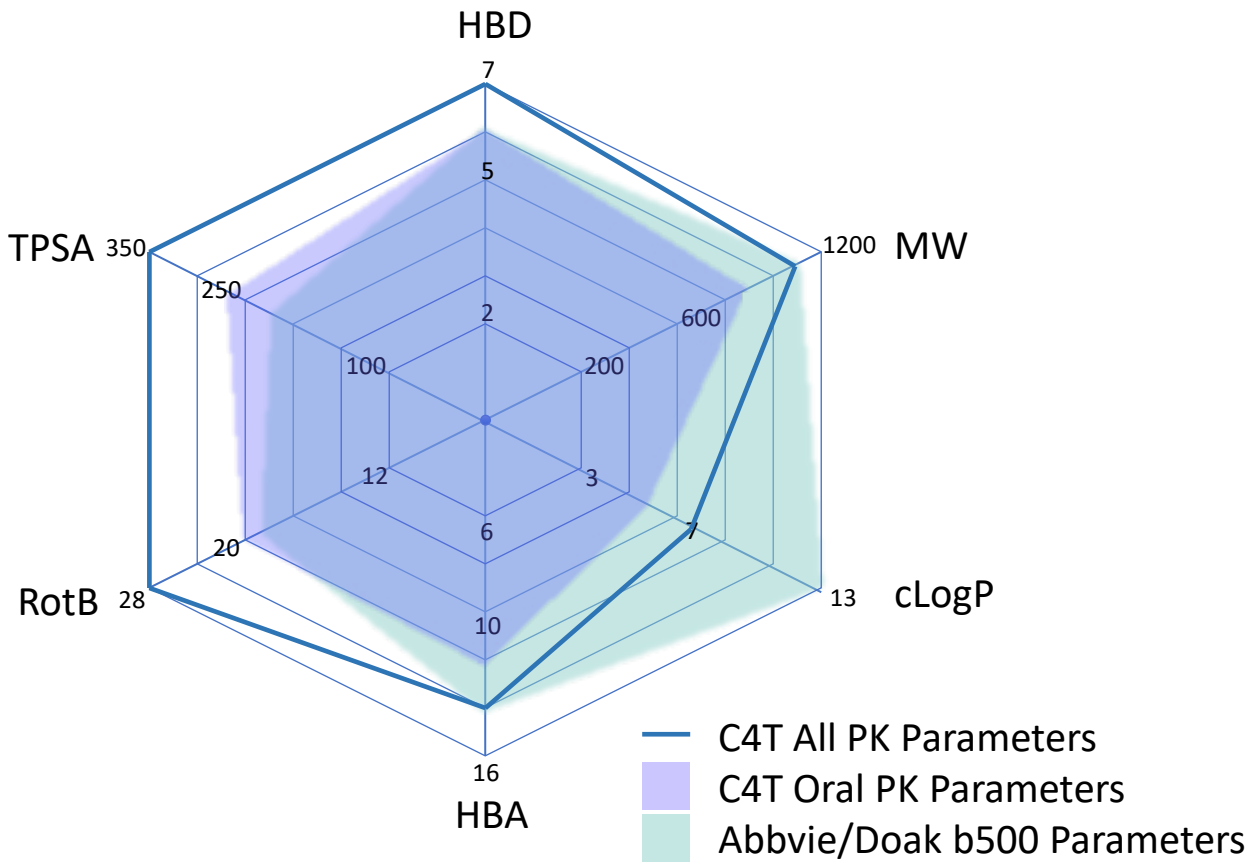
# Beyond 500 vs Degraders: Property Space




*Literature on "Degrader bRo5 Space" see:*
*Bioorg. Med. Chem. Lett.* **2019**, *29(13)*, 1555-1564

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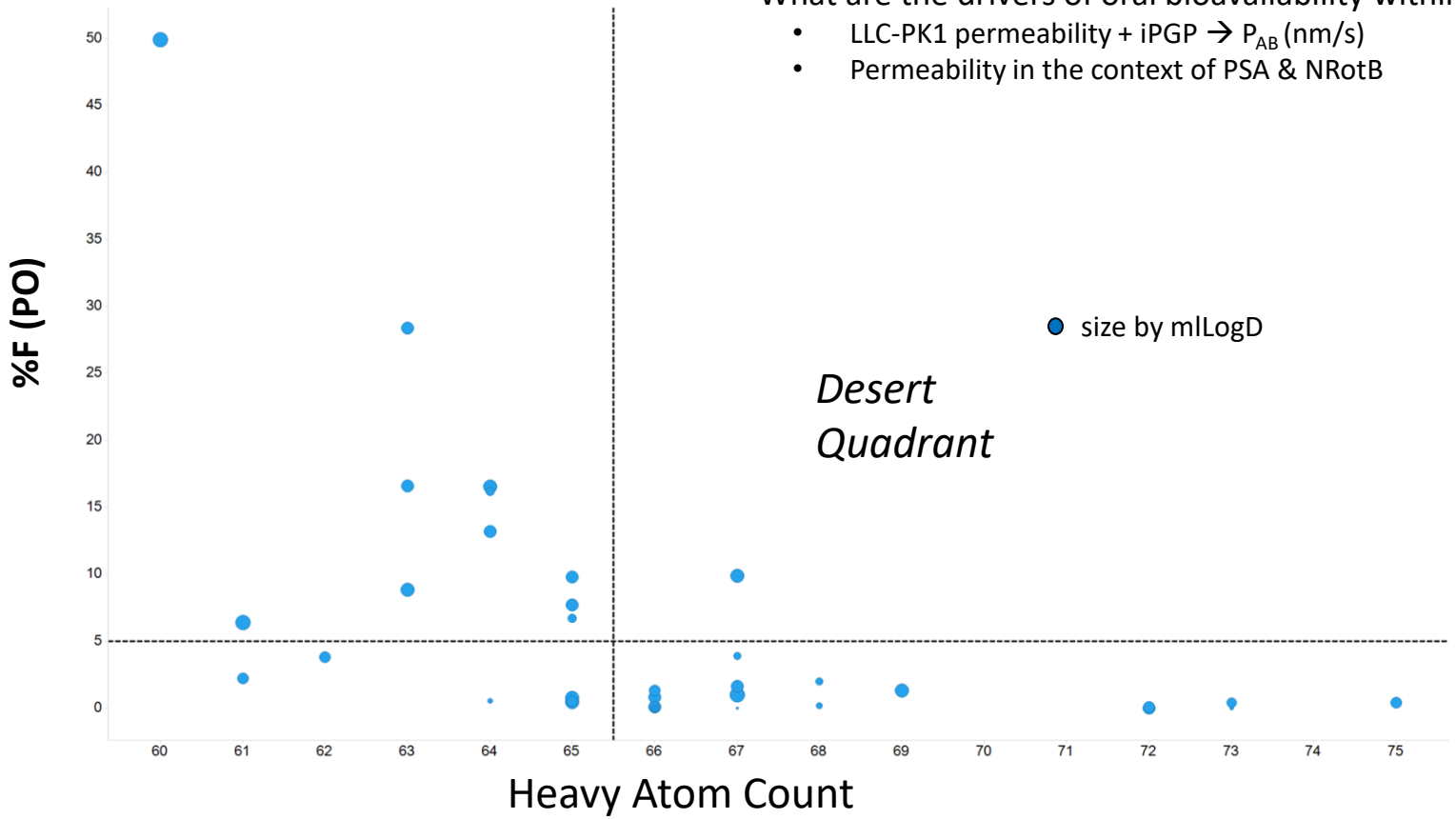
# Degrader Oral Bioavailability: What are the Drivers?

- Data from a single project – 36 degraders, >5% F for 11/36
- Suggests MW is the primary driver of oral bioavailability – not true!
- What are the drivers of oral bioavailability within this degrader set?
  - LLC-PK1 permeability + iPGP → $P_{AB}$ (nm/s)
  - Permeability in the context of PSA & NRotB

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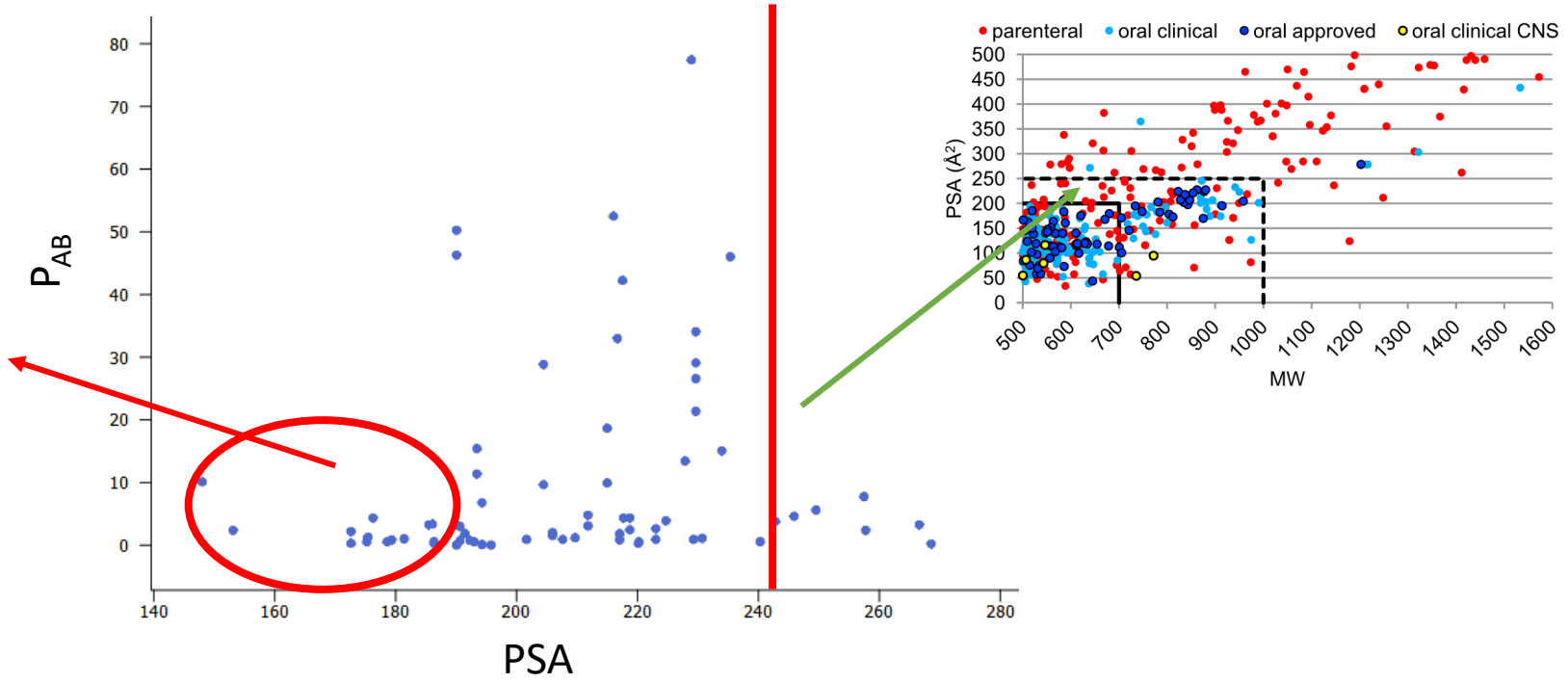
# Degrader Polar Surface Area

Highly flexible & too basic




Results consistent with beyond 500 data

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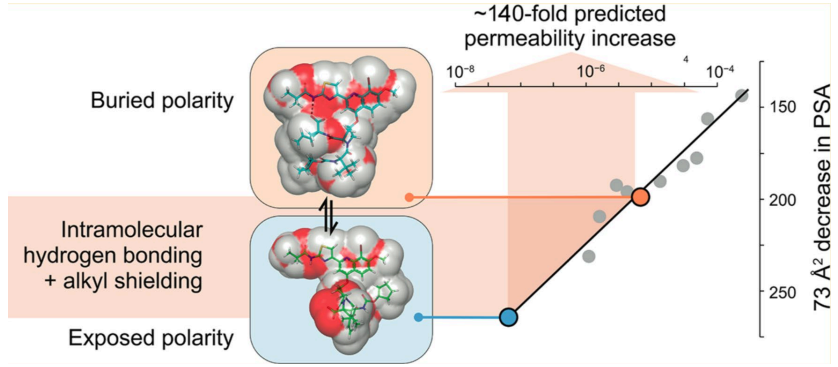
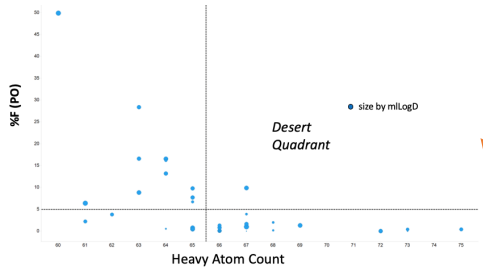
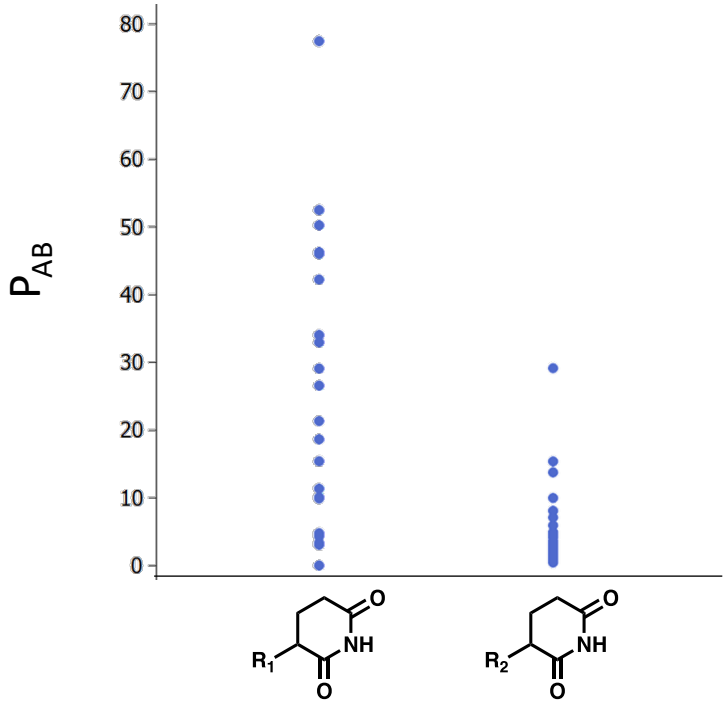
# Strategy to Improve Permeability



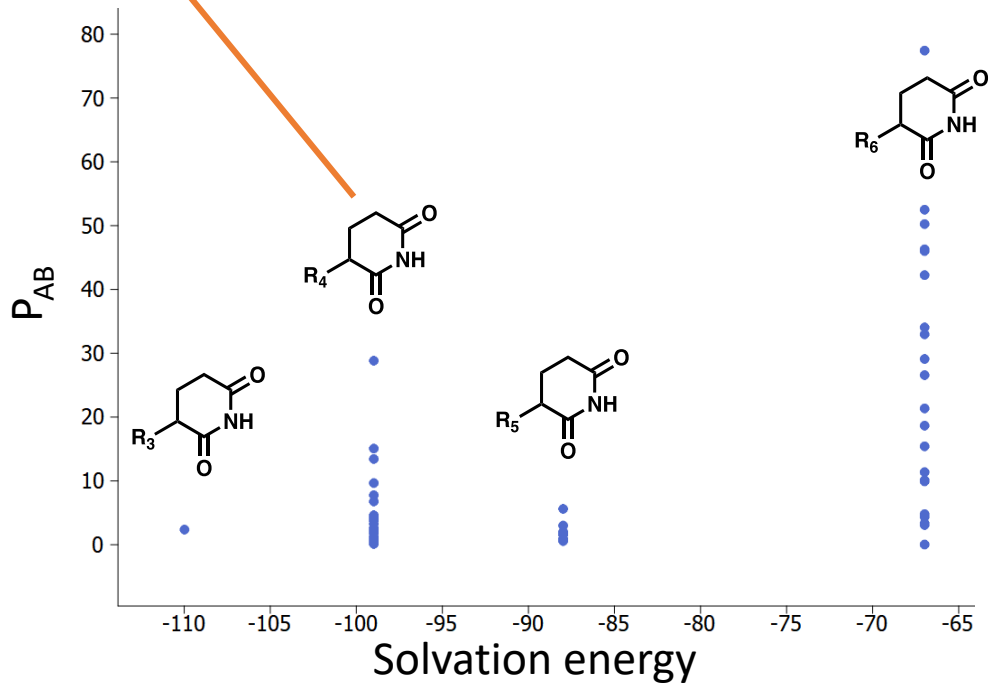

*J. Med. Chem.* **2018**, *61(9)*, 4189.




*Dominated by Ligase Binder




Ligase binder substructure




Improve permeability: Bury polarity/HBD/HBA within the structure via local or longer-range intramolecular interactions

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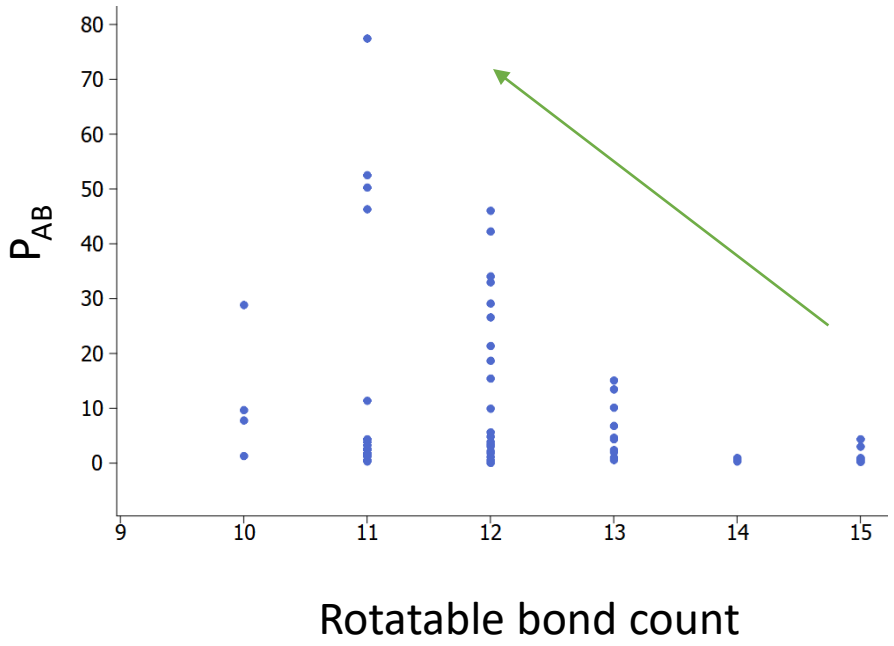
# Degrader Conformational Flexibility




- Signal observed with flexibility defined as rotatable bond count
- Flexibility – increased opportunity for optimal interactions with each surface or component of a membrane that is encountered

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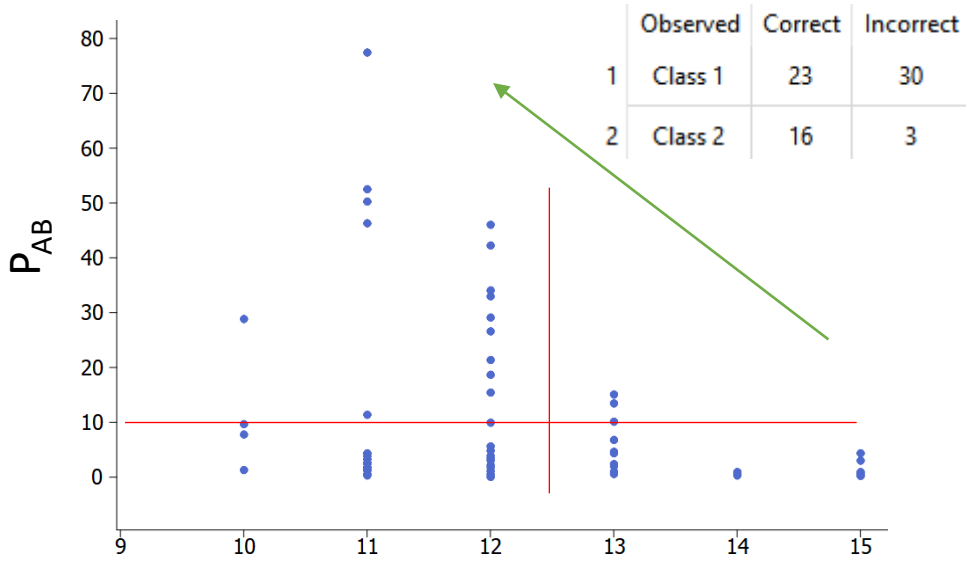
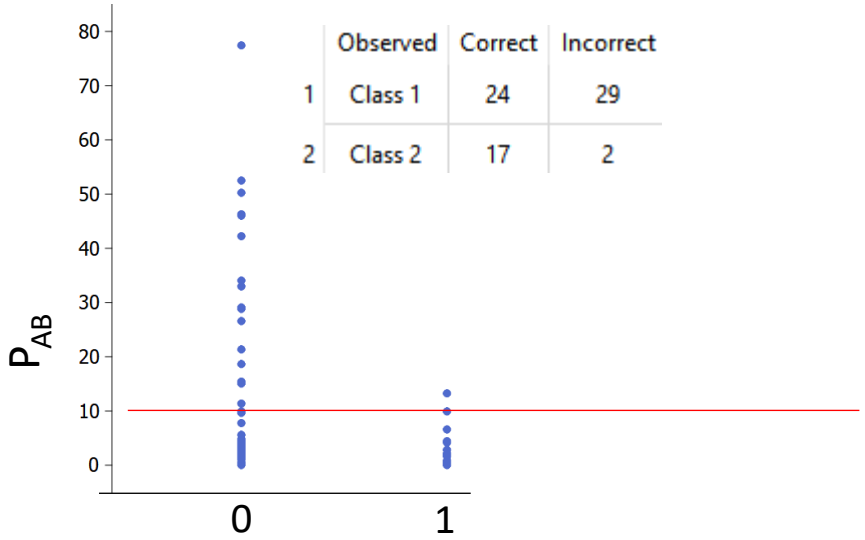
# Strategy to Improve Permeability




| | Observed | Correct | Incorrect |
|---|---|---|---|
| 1 | Class 1 | 23 | 30 |
| 2 | Class 2 | 16 | 3 |

Rotatable bond count




| | Observed | Correct | Incorrect |
|---|---|---|---|
| 1 | Class 1 | 24 | 29 |
| 2 | Class 2 | 17 | 2 |

Presence of unsubstituted propyl in compound


Improve permeability: Rigidification of linker/reduction of accessible conformations

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# Summary and Closing Thoughts

- 'Drug-Like Chemical Space' and Degrader Design Concepts
  - Property space of degraders and data are not that different from beyond 500 space
  - LogP/D, HBD count, PSA and conformational flexibility are emerging as important design areas for accessing oral bioavailable space for degraders
  - Focus on the property trends, not molecular weight

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# Acknowledgments: The C4T Team

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