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ONCOLOGY COOPERATION

# New Targeted Therapies on the Horizon: Protein Degraders

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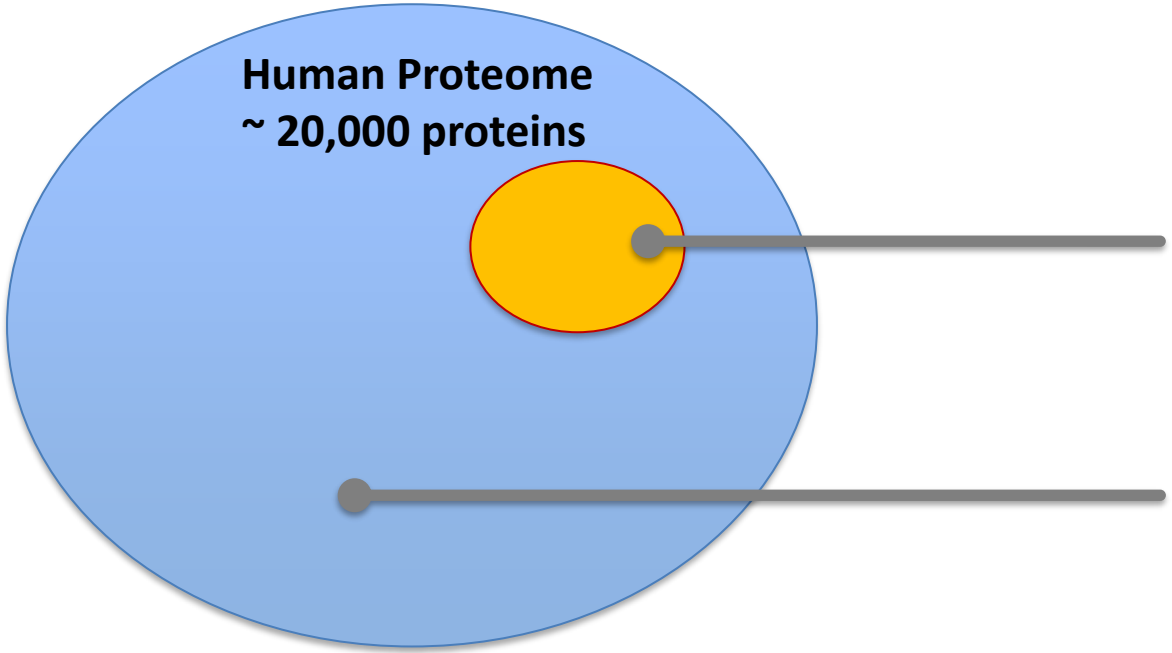
# Disclosures

- **Employment:** Monte Rosa Therapeutics (Chief Medical Officer)
- **Stocks or Options:** Monte Rosa Therapeutics, Cardiff Oncology
- Presented content reflects my expert opinion and is not intended to represent views of Monte Rosa Therapeutics

# Unmet Need to Expand the Target Space in Cancer

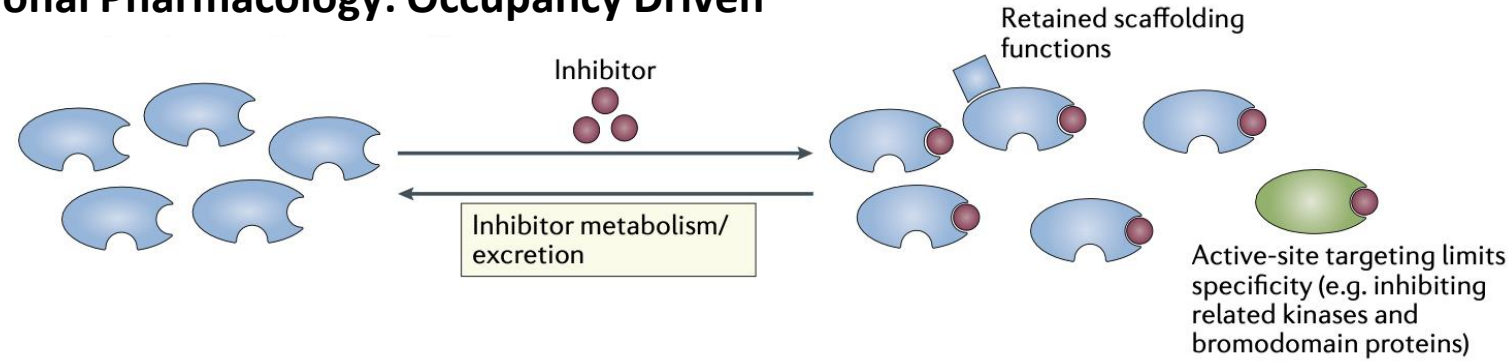



Proteins druggable with molecular inhibitors (5%-10%)

“Undruggable” target space

# Protein Inhibition

**Traditional Pharmacology: Occupancy Driven**



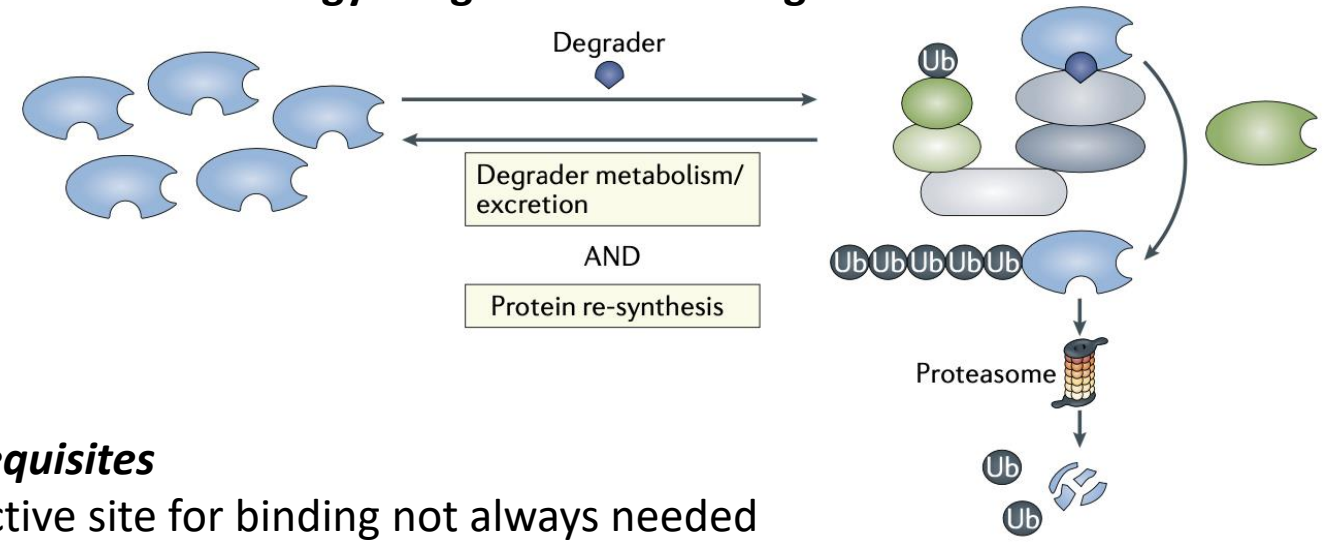

***Prerequisites***

- ✓ Active site for binding
- ✓ Small molecule inhibitor
- ✓ Site occupancy necessary for therapeutic effect
- ✓ One molecule of drug inhibits one target (protein)

*Adapted from Jan M. Nat Rev Clin Oncol 2021*

# Targeted Protein Degradation

**Event-Driven Pharmacology: Targeted Protein Degradation**




***Prerequisites***

- ✓ Active site for binding not always needed
- ✓ Tags protein for degradation
- ✓ Can be selective
- ✓ Catalytic mechanism

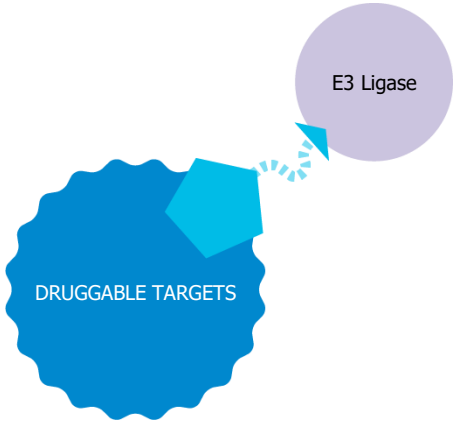
*Adapted from Jan M. Nat Rev Clin Oncol 2021*

# Expanding Target Space through Molecular Glue Degraders (MGDs)

## Inhibitors

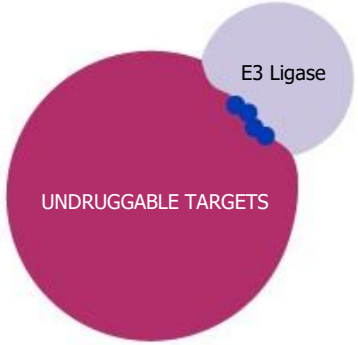

Drugging
the Druggable

## PROTACs




Redrugging
the Druggable

## MGDs




Drugging
the Undruggable

3-10% of Proteome

Uncharted Chemical and Target Space

# The Next Generation of Precision Medicine-based Small Molecule Drugs

Selectively editing the human proteome with rationally designed MGDs

Traditional small molecule inhibitors

Therapeutic Antibodies

MGDs

RNAi, RNA Editing

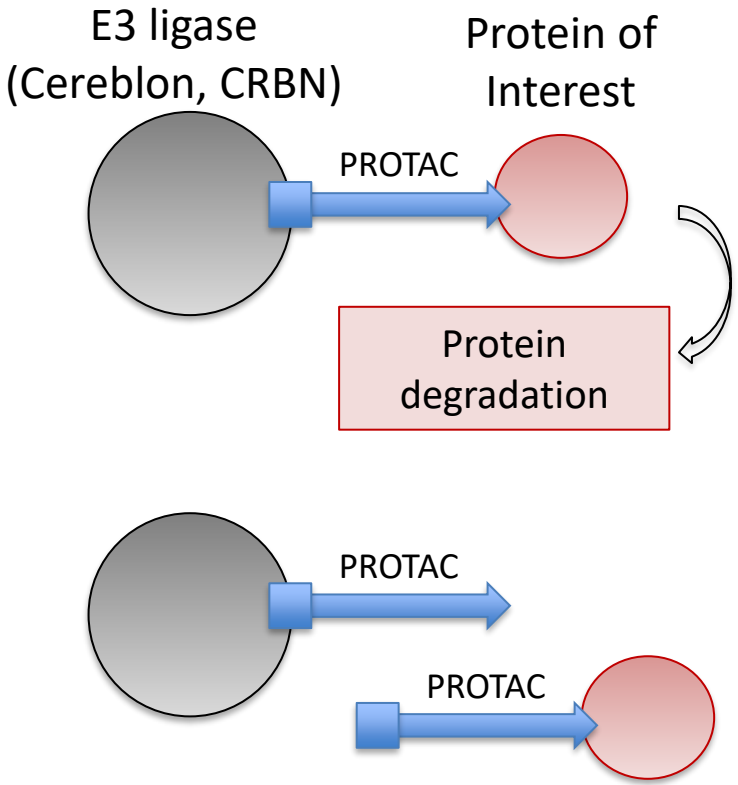
CRISPR/Gene Therapy

| | Traditional small molecule inhibitors | Therapeutic Antibodies | MGDs | RNAi, RNA Editing | CRISPR/Gene Therapy |
|---|---|---|---|---|---|
| Ability to access undruggable space | ✗ | ✓ | ✓ | ✓ | ✓ |
| Cellular permeability | ✓ | ✗ | ✓ | ✓ | ✓ |
| Oral bioavailability | ✓ | ✗ | ✓ | ✗ | ✗ |
| Systemic distribution | ✓ | ✓ | ✓ | ✗ | ✗ |
| CNS Penetration | ✓ | ✗ | ✓ | ✗ | ✗ |
| Manufacturing scalability | ✓ | ✓ | ✓ | ✗ | ✗ |

# Proteolysis-Targeting Chimera (PROTAC)

**PROTAC features**

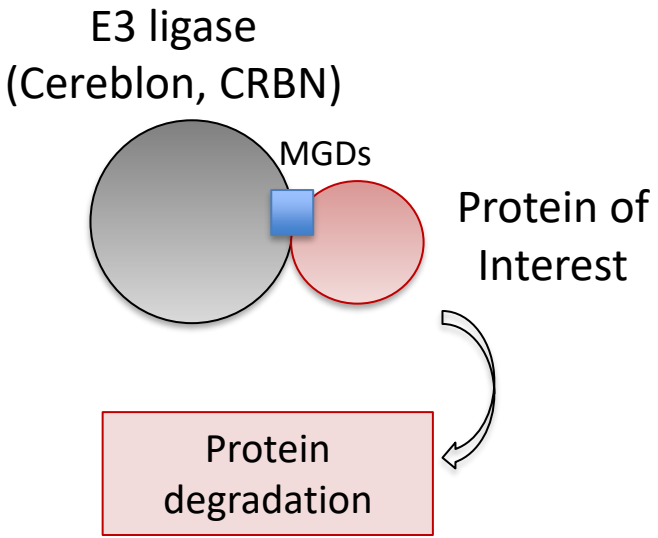
- ❑ Binding pocket required
- ❑ Highly effective catalytic targeted drugs
- ❑ Heterobifunctional molecules
- ❑ High molecular weight
- ❑ Hook-effect



# Molecular Glue Degraders (MGDs)

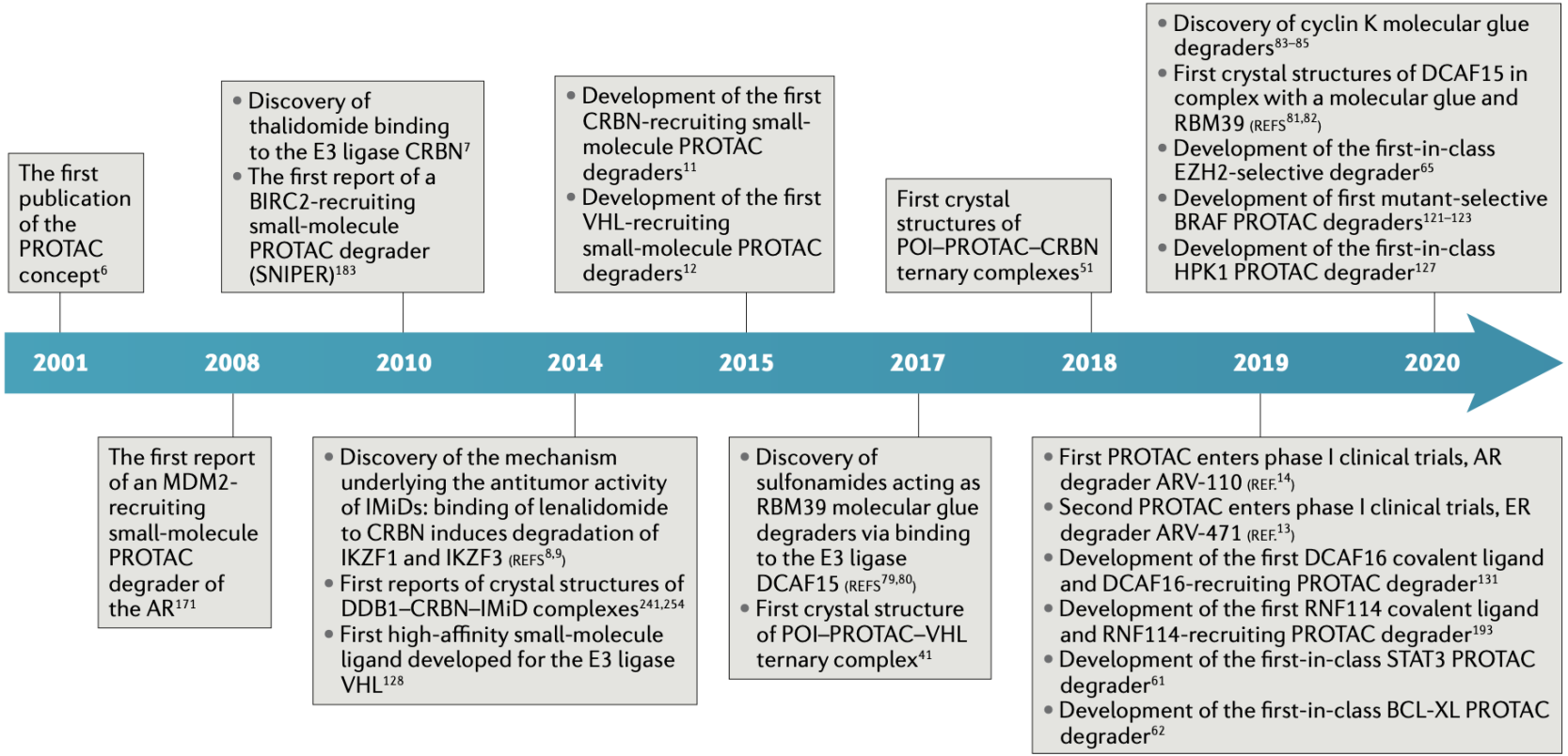
**MGD features**

- ❑ No binding pocket needed
- ❑ Small molecules
- ❑ Clinically validated (lenalidomide)
- ❑ Historically perceived as “hard to discover”



# Targeted Protein Degradation

## Timeline and Milestones

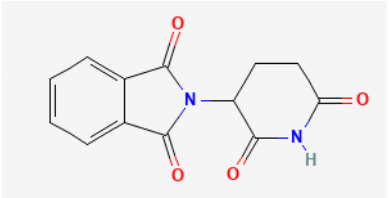



*Dale et al. Nat Rev Cancer 2021*

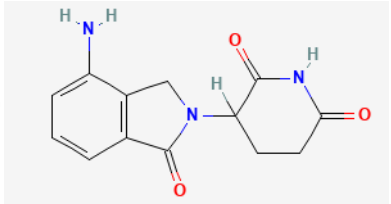
# MGD Evolution: IMiDs

**1961**: Thalidomide confirmed as a cause of birth defects

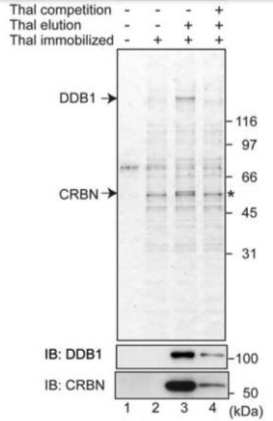
**1990's-2000's**: Thalidomide repurposed as anticancer drug



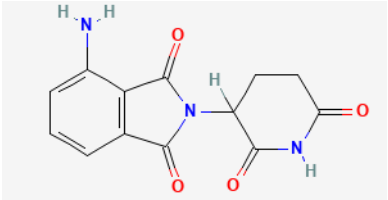
**2005**: Lenalidomide, thalidomide analog approved by FDA



**2010**: CRBN identified as thalidomide interactor




**2013**: Pomalidomide receives accelerated approval



**2014**: Description of CRBN mediated selective degradation of IKZF1/3

# Examples of Molecular Glue Degraders in Clinical Trials

| Drug | Target | Indication | Phase |
|---|---|---|---|
| DKY709 | Helios | Diverse cancers | Phase I |
| CC-90009 | GSPT1 | AML | Phase I |
| CC-92480 | IKZF1/3 | Multiple myeloma | Phase I |
| CC-99282 | IKZF1/3 | NHL | Phase I |
| Iberdomide | IKZF1/2 | Multiple myeloma | Phase III |
| CFTZ7455 | IKZF1/3 | Myeloma, NHL | Phase I |
| BTX-1188 | GSPT1, IKZF1/3 | Diverse cancers | Phase I |

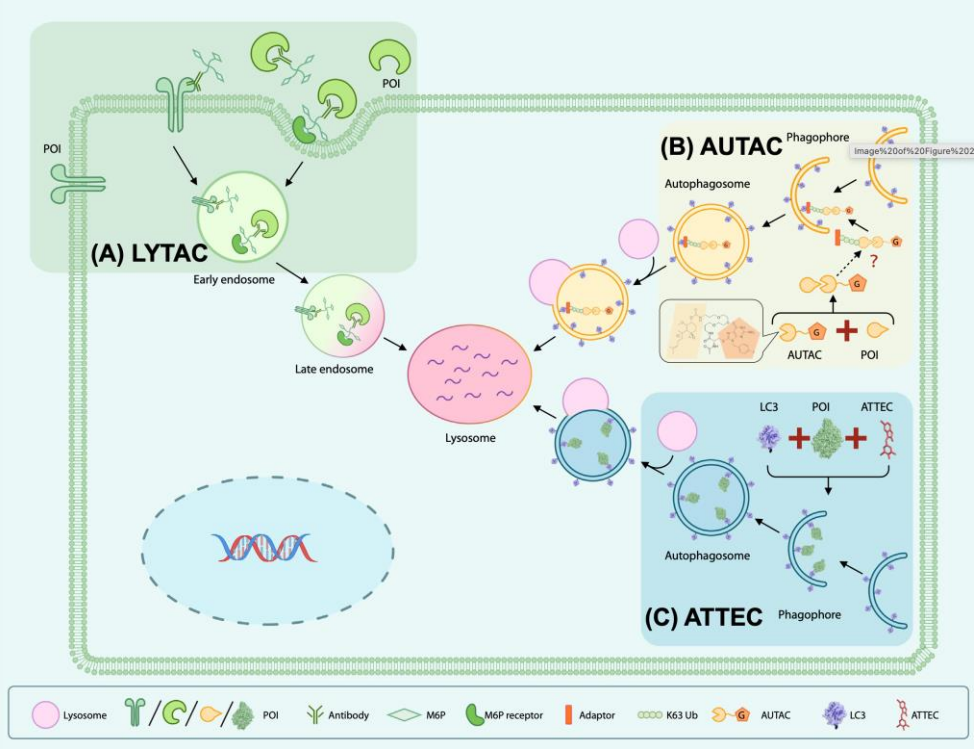
# Examples of PROTAC Degraders in Clinical Trials

| Drug | Target | Indication | Phase |
|---|---|---|---|
| ARV-110 | AR | Prostate cancer | Phase II |
| ARV-471 | ER | Breast cancer | Phase II |
| ARV-766 | AR | Prostate cancer | Phase I |
| DT2216 | BCL-XL | Diverse cancers | Phase I |
| NX-2127 | BTK, IKZF1/2 | B-cell malignancies | Phase I |
| NX-5948 | BTK | B-cell malignancies | Phase I |
| FH-609 | BRD9 | Synovial sarcoma | Phase I |

# Alternative Approaches to Protein Degradation

- **LYTAC** - Lysosome-targeting chimeras
- **AUTAC** - Autophagy-targeting chimera
- **ATTEC** - Autophagosome-tethering compound

- *RNA degradation (e.g. RIBOTAC)*

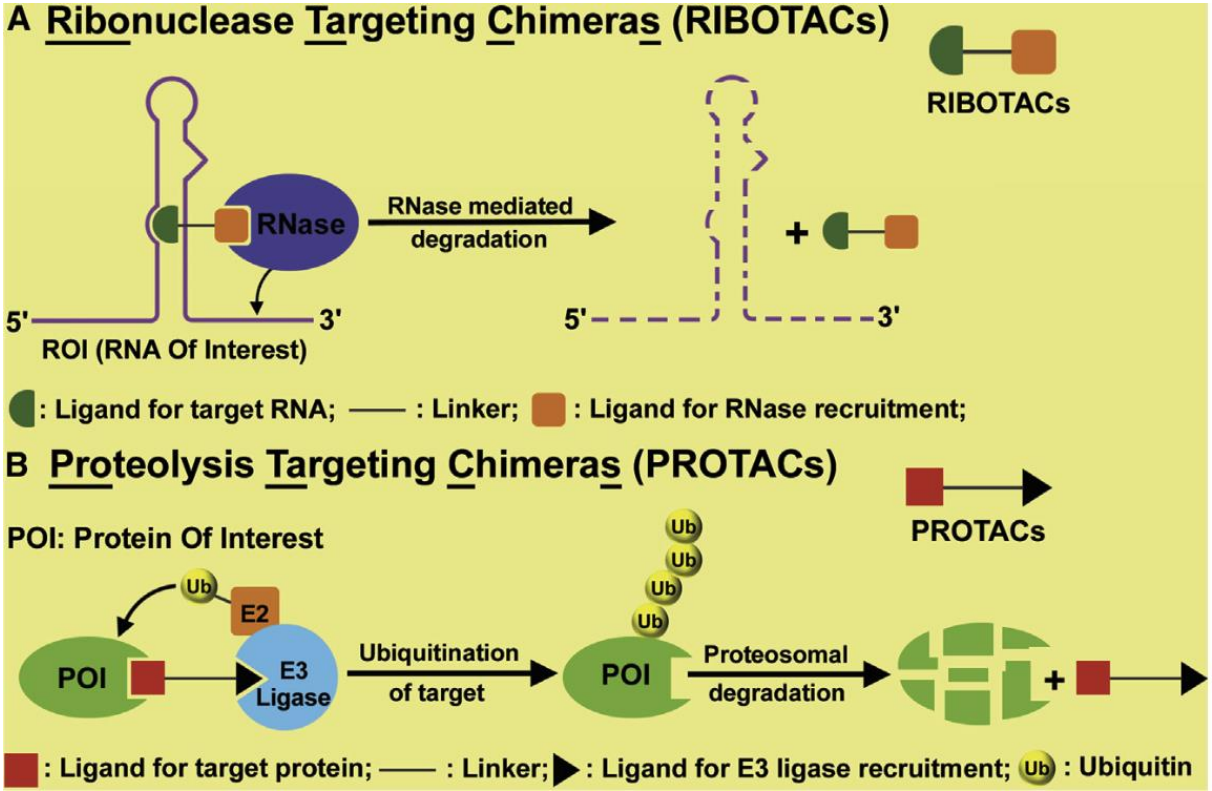



*Ding et al. Trends Pharmacol Sci 2020*

# MGDs, PROTACs vs. Emerging Approaches

| Tx | Degradation | Targets | Advantages | Limitations |
|---|---|---|---|---|
| **MGD** | Proteasome | Intracellular proteins | Established, selectivity, catalytic | Dependent on E3, ubiquitination and proteasome, discovery |
| **PROTAC** | Proteasome | Intracellular proteins | Established, selectivity, catalytic | Dependent on E3, ubiquitination and proteasome, complex molecules |
| **LYTAC** | Endosome/ lysosome | Extracellular, transmembr. proteins | Extracellular, transmembrane proteins; independent of ubiquitination and proteasome | Large molecular weight and poor permeability; possible induction of immune response in vivo |
| **AUTAC** | Autophagy | Intracellular proteins; organelles | Target spectrum; proteasome-independent; can degrade mitochondria | Understanding MOA; dependent on K63 ubiquitination; possible influence on selective autophagy |
| **ATTEC** | Autophagy | Intracellular proteins; non-protein autoph. substrates | Target spectrum; direct targeting to the degradation machinery | The LC3-bound chemical moieties need to be solved; lack of studies on designed chimeras |

# Protein vs. RNA Degradation




*Dey Cell Chemical Biology 2019*

# Targeted Protein Degradation: Beyond Cancer

- Neurological disorders
- Inflammatory and autoimmune disorders
- Cardiovascular disorders
- Metabolic disorders
- Hemoglobinopathies

# Conclusions

- Targeted Protein Degradation can have more potent inhibitory effect than classical inhibition
- Targeted Protein Degradation with MGDs can unravel additional “undruggable” space such as transcription factors
- Targeted Protein Degradation has therapeutic potential similar to gene editing technologies, with less complexity