Enabling and Accelerating Innovative and Emerging Modalities Drug Discovery

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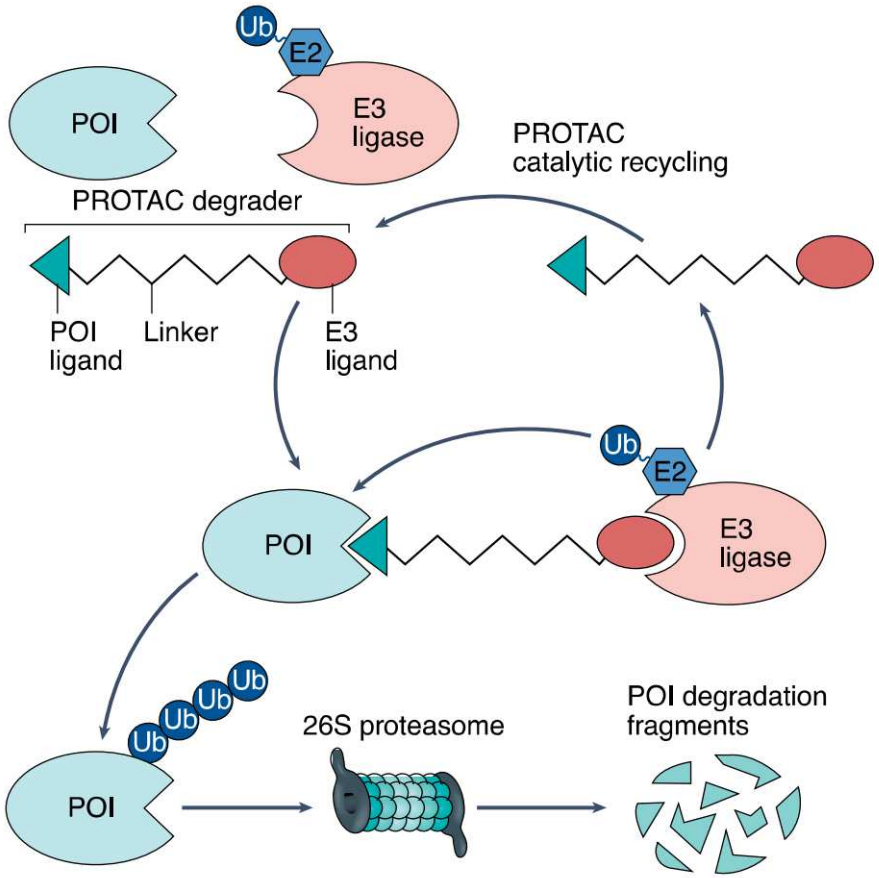
Medicinal Chemistry Strategy Meeting East Coast USA

Topics

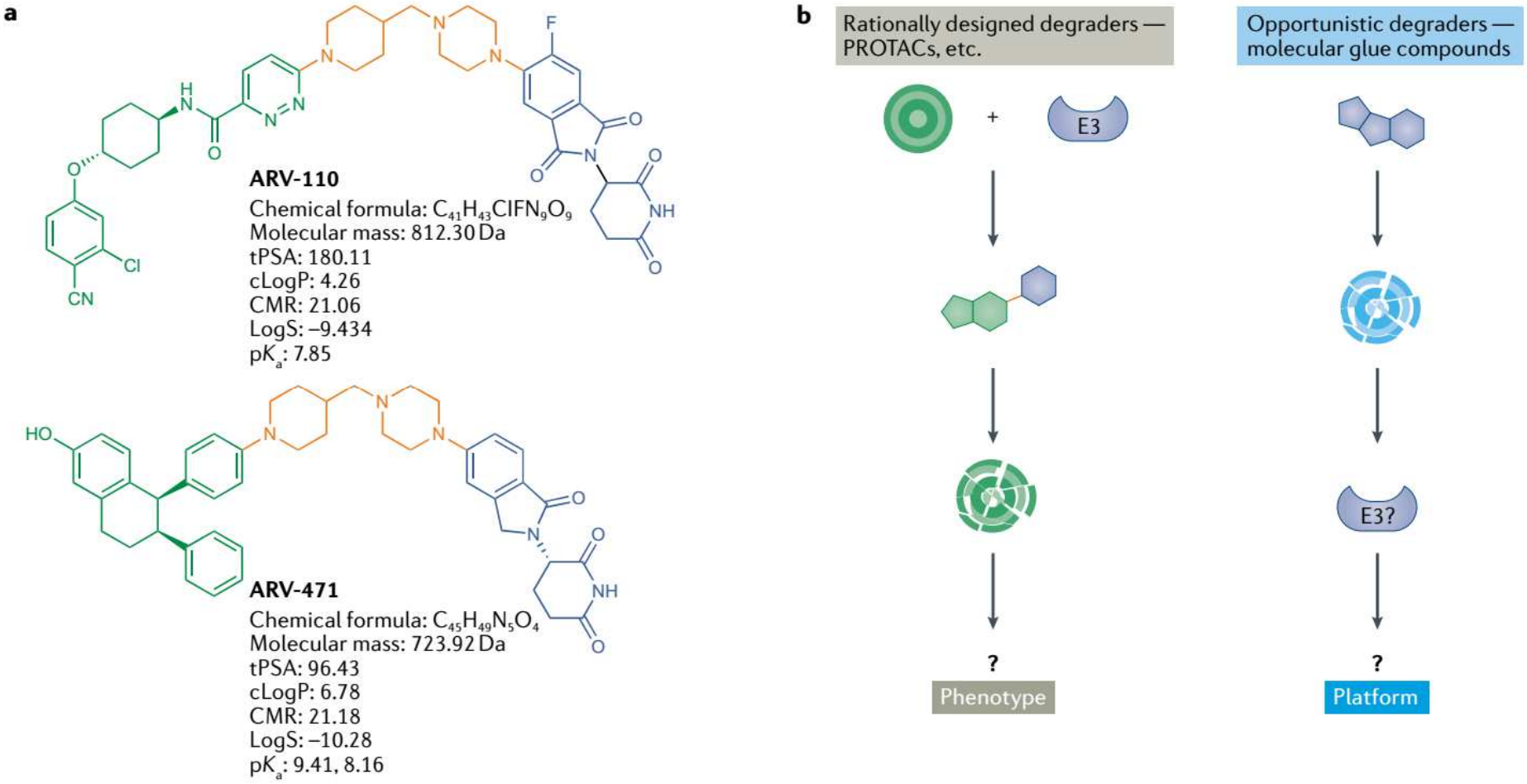
- **Targeted Protein Degraders**
- Targeted Covalent Inhibitors
- Nucleic Acid Therapeutics

Targeted Protein Degraders (TPDs)



Source: The PROTAC gold rush, Ken Garber, *Nature Biotechnology*, 2022, 40, 12-16.

Modalities in Targeted Protein Degradation



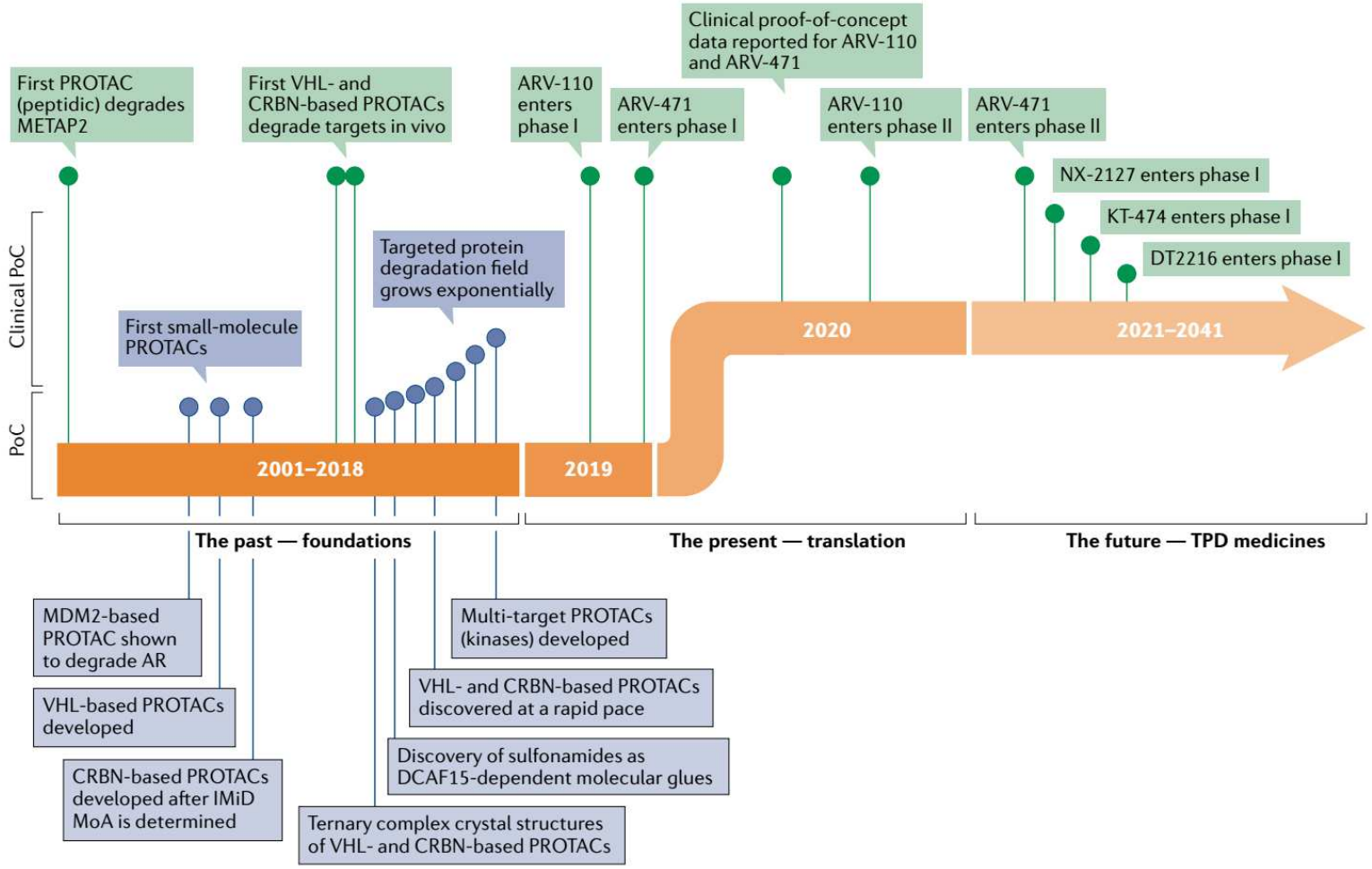
Source: PROTAC targeted protein degraders: the past is prolog, Miklós Békés, et al., *Nature Reviews Drug Discovery*, 2022, 21, 181–200.

TPDs in Clinical Development

Company	Degrader	Target	Indications	E3 ligase	ROA	Highest phase	Clinical trial no. (if applicable)
Arvinas	ARV-110	AR	Prostate cancer	CRBN	Oral	Phase II	NCT03888612
Arvinas/Pfizer	ARV-471	ER	Breast cancer	CRBN	Oral	Phase II	NCT04072952
Accutar Biotech	AC682	ER	Breast cancer	CRBN	Oral	Phase I	NCT05080842
Arvinas	ARV-766	AR	Prostate cancer	Undisclosed	Oral	Phase I	NCT05067140
Bristol Myers Squibb	CC-94676	AR	Prostate cancer	CRBN	Oral	Phase I	NCT04428788
Dialectic Therapeutics	DT2216	BCL-x_L	Liquid and solid tumours	VHL	I.v.	Phase I	NCT04886622
Foghorn Therapeutics	FHD-609	BRD9	Synovial sarcoma	Undisclosed	I.v.	Phase I	NCT04965753
Kymera/Sanofi	KT-474	IRAK4	Autoimmune diseases (e.g., AD, HS, RA)	Undisclosed	Oral	Phase I	NCT04772885
Kymera	KT-413	IRAK4	Diffuse large B cell lymphoma (MYD88-mutant)	CRBN	I.v.	Phase I	
Kymera	KT-333	STAT3	Liquid and solid tumours	Undisclosed	Undisclosed	Phase I	
Nurix Therapeutics	NX-2127	BTK	B cell malignancies	CRBN	Oral	Phase I	NCT04830137
Nurix Therapeutics	NX-5948	BTK	B cell malignancies and autoimmune diseases	CRBN	Oral	Phase I	NCT05131022
C4 Therapeutics	CFT8634	BRD9	Synovial sarcoma	CRBN	Oral	IND-e	
C4 Therapeutics	CFT8919	EGFR-L858R	Non-small-cell lung cancer	CRBN	Oral	IND-e	
Cullgen	CG001419	TRK	Cancer and other indications	CRBN	Oral	IND-e	

Source: PROTAC targeted protein degraders: the past is prolog, Miklós Békés, et al., *Nature Reviews Drug Discovery*, 2022, 21, 181–200.

The Past and Future of TPDs

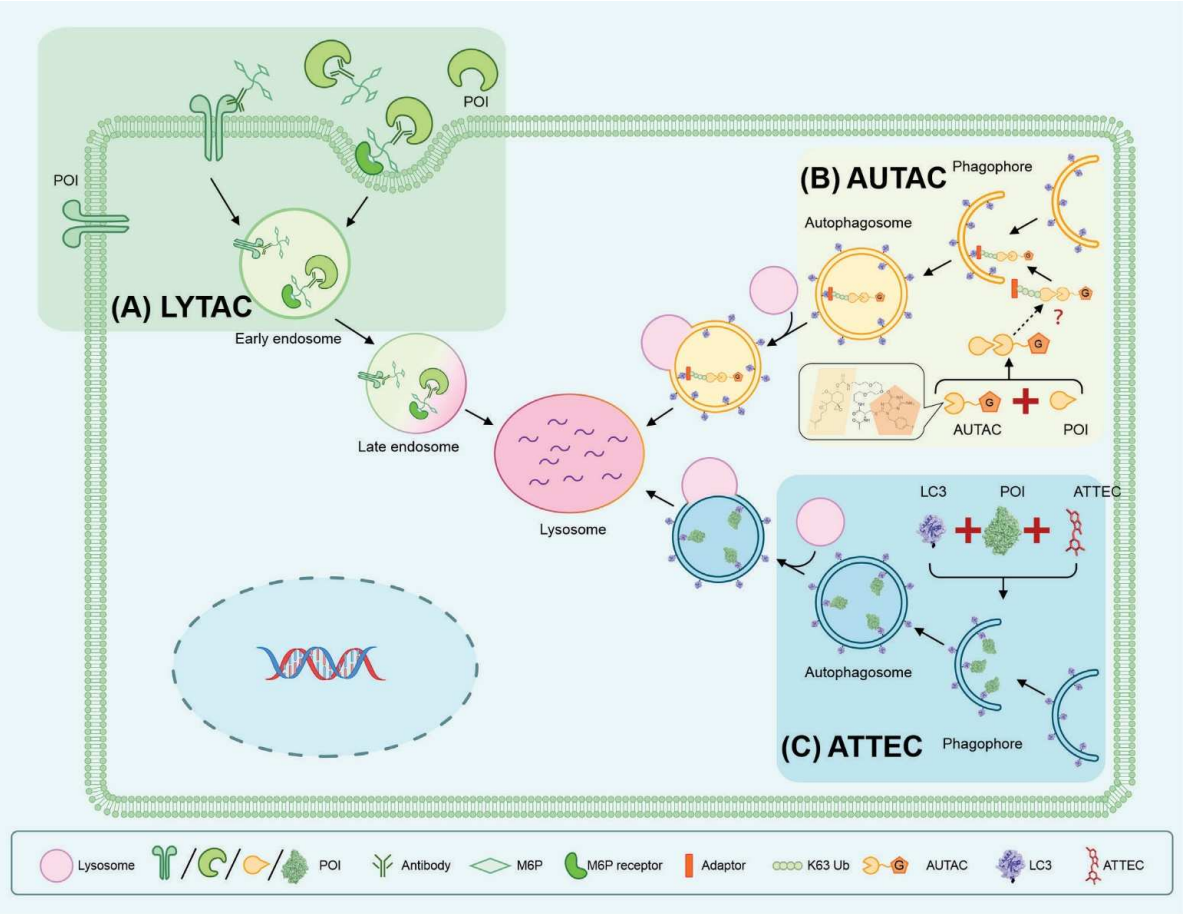


Source: PROTAC targeted protein degraders: the past is prolog, Miklós Békés, et al., *Nature Reviews Drug Discovery*, 2022, 21, 181–200.

Novel Concepts Employing Lysosomal Degradation Pathway

The lysosome is a major degradation pathway utilized by cells to degrade extracellular and intracellular content

- **LYTAC** (lysosome targeting chimera) technology exploits the endosome/lysosome pathway to degrade POIs.
- **AUTAC** (autophagy-targeting chimera) functions via ubiquitination by triggering K48 polyubiquitination which is recognized by the selective autophagy pathway, leading to degradation of the target POI.
- **ATTEC** (autophagosome-tethering compound) tether the POI to the autophagosomes by direct binding to the POI and the key autophagosome protein LC3.



Source: Emerging New Concepts of degrader technology, Yu Ding, et al., *Trends in Pharmacological Sciences*, 2020, 41, 464-474.

Characteristics of TPDs

Therapeutic modality	PROTACs/ molecular glues	Small-molecule inhibitors	Gene-based strategies	bioPROTAC	oligoTAC	LYTAC	ATTEC	AUTAC	abTAC
Target scaffolding functions	✓		✓	✓	✓	✓	✓	✓	✓
Potential to treat undruggable proteins	✓		✓	✓	✓	✓	✓	✓	✓
Iterative mechanism of action	✓		✓	✓	✓	✓	✓	✓	
Broad tissue penetration	✓					✓	✓	✓	
Orally bioavailable	✓	✓							
Ease of manufacturing	✓	✓		✓	✓	✓	✓	✓	
Preclinical validation, proof-of-concept established	✓	✓	✓	✓	✓	✓	✓	✓	✓
Clinical validation	✓ (Phase II for PROTACs)	✓	✓						

Source: PROTAC targeted protein degraders: the past is prolog, Miklós Békés, et al., *Nature Reviews Drug Discovery*, 2022, 21, 181–200.

Challenges for TPD Discovery

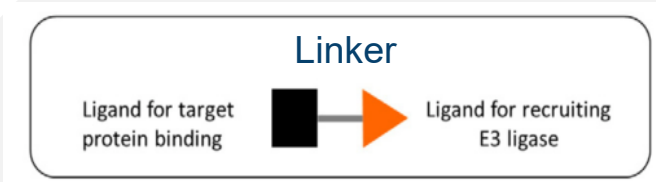
- TPDs are harder to synthesize and purify than traditional small molecules.
- TPD design remains largely empirical as target binding affinity does not predict activity, and many compounds need to be synthesized and tested to find functionally active degraders.
- TPDs are “beyond the rule of 5” molecules, and many compounds need to be synthesized and tested in animal studies to find orally bioavailable degraders.

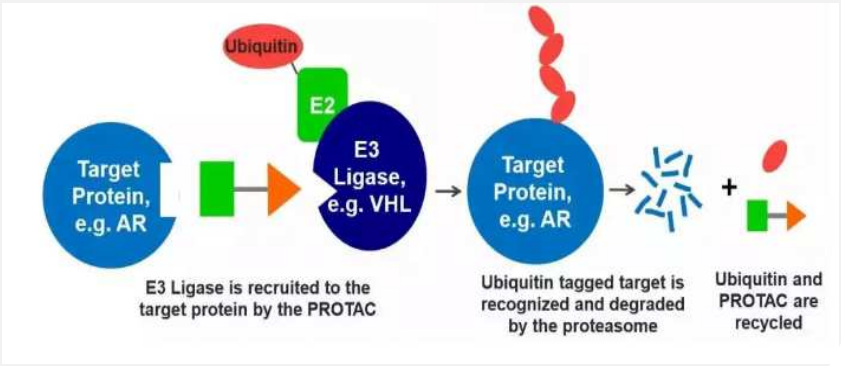
Our Targeted Protein Degraders Discovery Chemistry Platform

Synthesis, Analysis, and Purification

- **>1000** discovery chemists, with strong experiences in the linkers, E3 ligase ligands and target protein ligands synthesis since 2016
- **>100** clients/collaborations

- **>1,000** diverse linkers successfully synthesized
- Novel linker synthesis with high productivity, quality, speed, and reliability





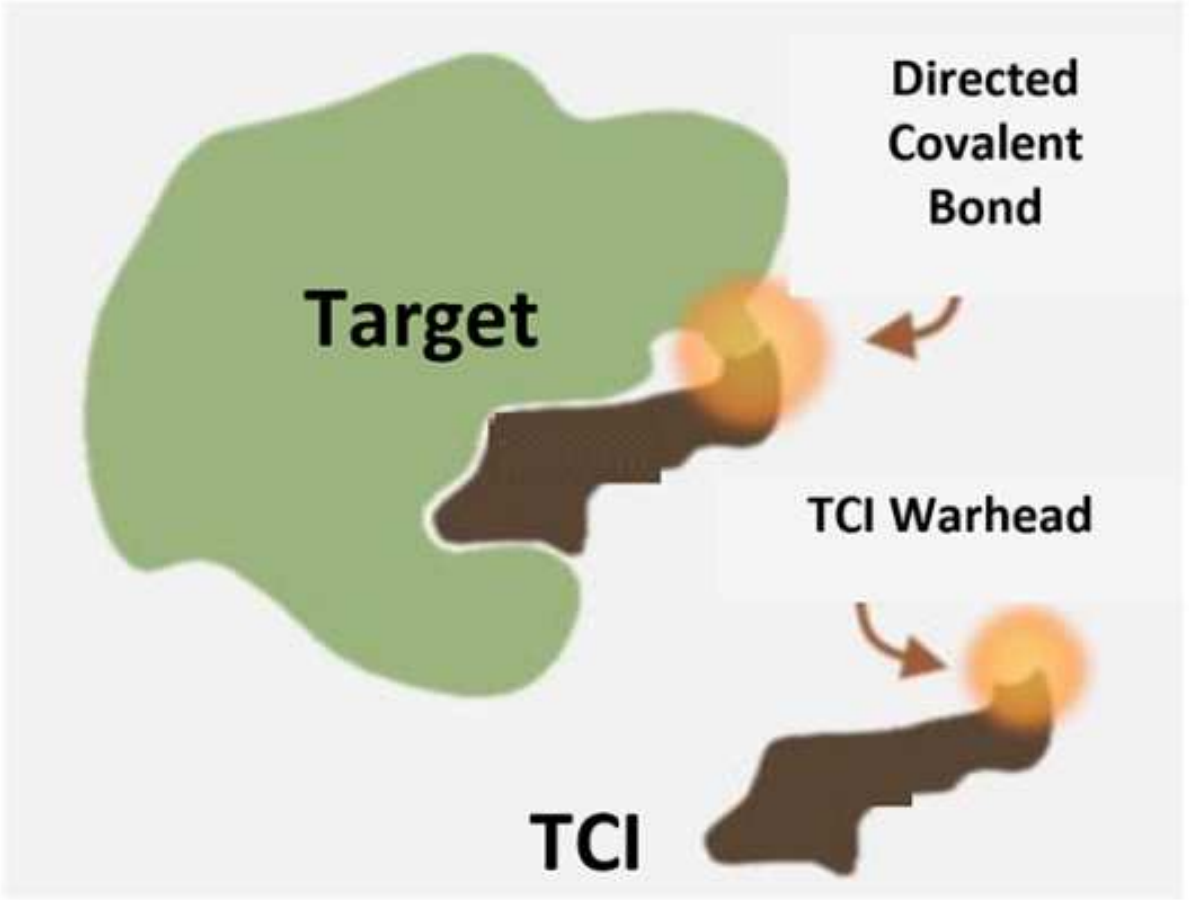
- **>100** novel E3 ligase ligands
- **>60** series of target protein ligands pre-coupled with various linkers

- **>200** methods of Prep-HPLC and chiral-SFC analysis and purification
- **>70,000** Targeted Protein Degraders successfully delivered

Topics

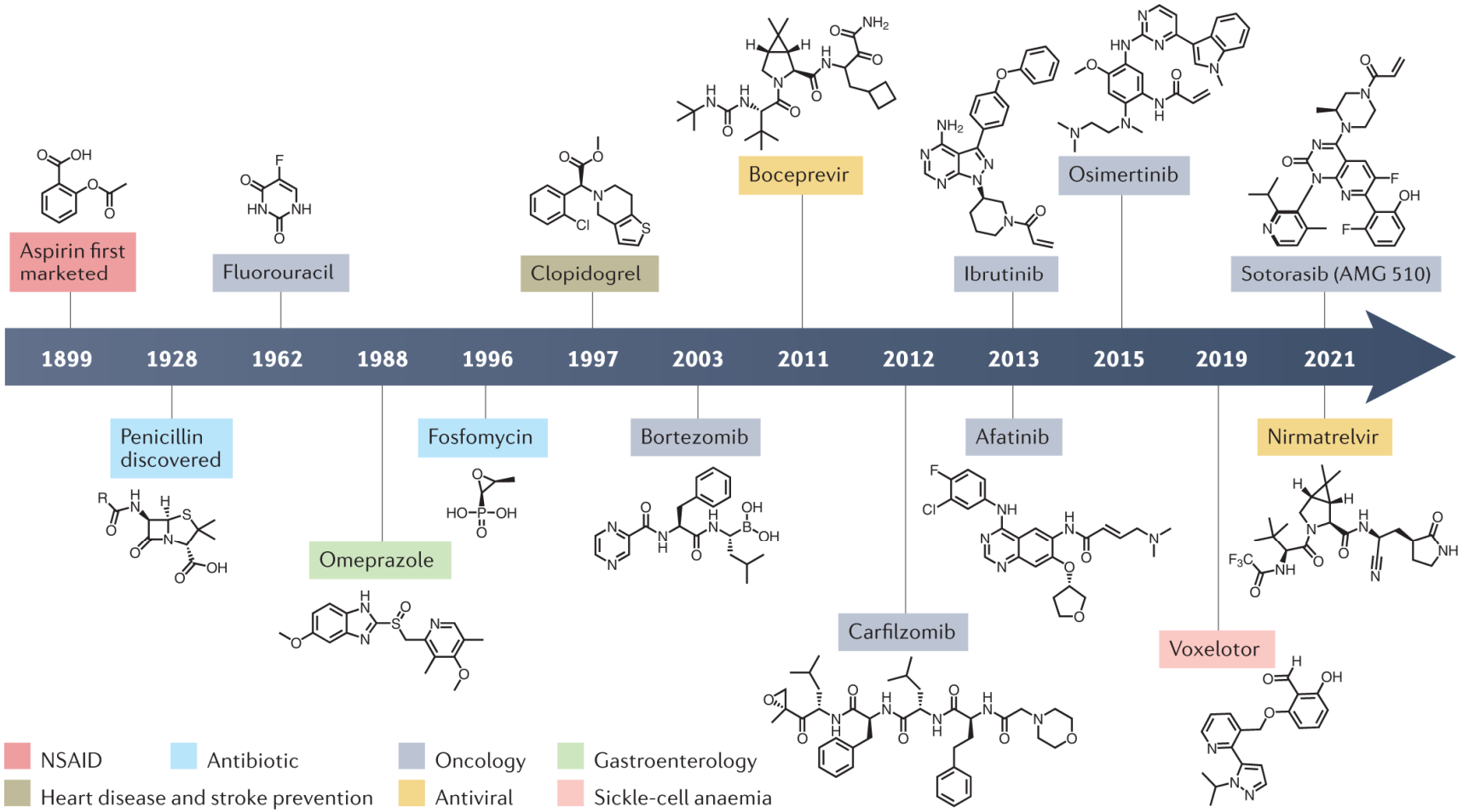
- Targeted Protein Degraders
- **Targeted Covalent Inhibitors**
- Nucleic Acid Therapeutics

Targeted Covalent Inhibitor (TCI)



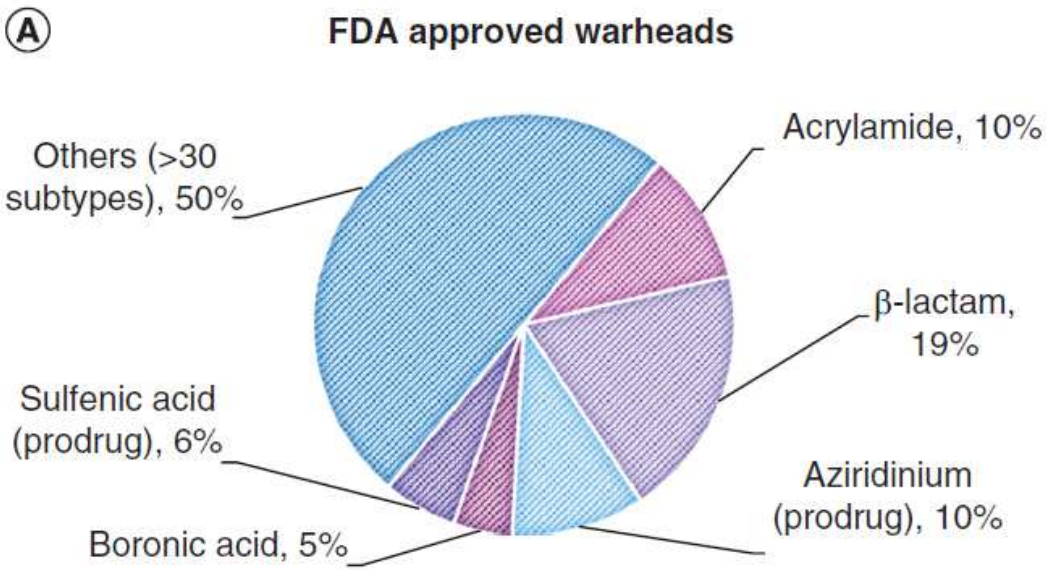
Source: The Ascension of Targeted Covalent Inhibitors, Juswinder Singh, *J Med Chem,* 2022, 65, 8, 5886–5901.

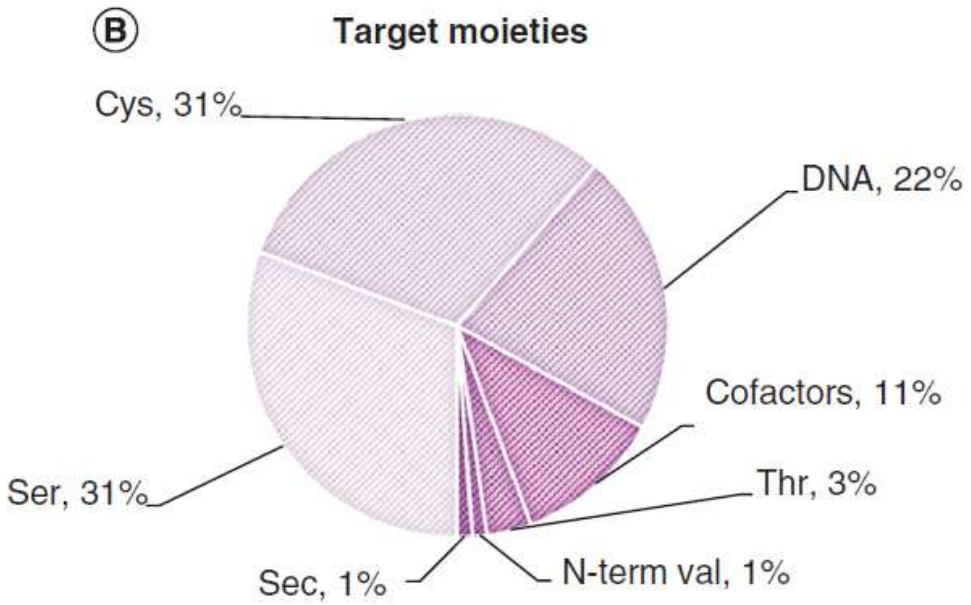
Timeline of the Development of Major Covalent Drugs



Source: Advances in covalent drug discovery, Lydia Bioke, et al., *Nature Reviews Drug Discovery,* August 25, 2022, https://doi.org/10.1038/s41573-022-00542-z.

Types of Warheads of FDA-Approved TCI and Target Moieties





Source: 10 years into the resurgence of covalent drugs, Elena De Vita, *Future Med Chem,* 2021, 13(2), 193–210.

Collection of Warheads for TCI Design

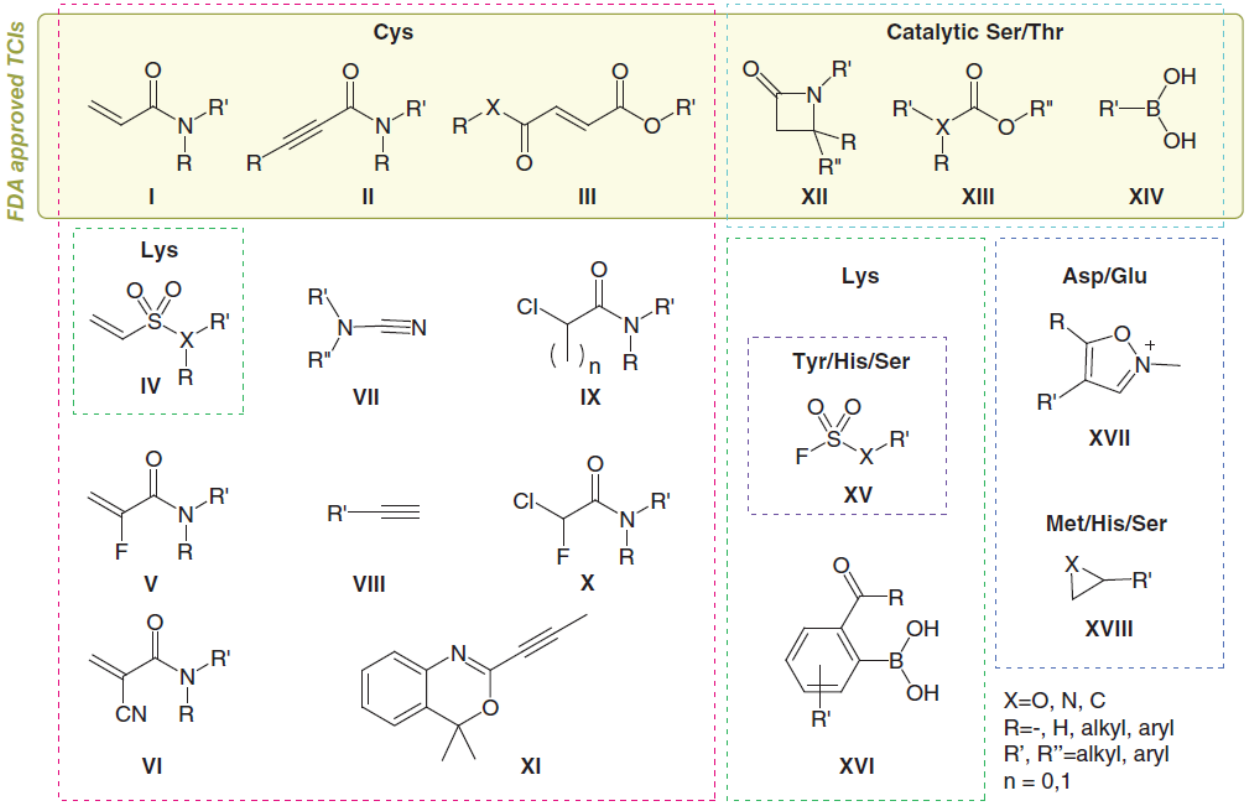
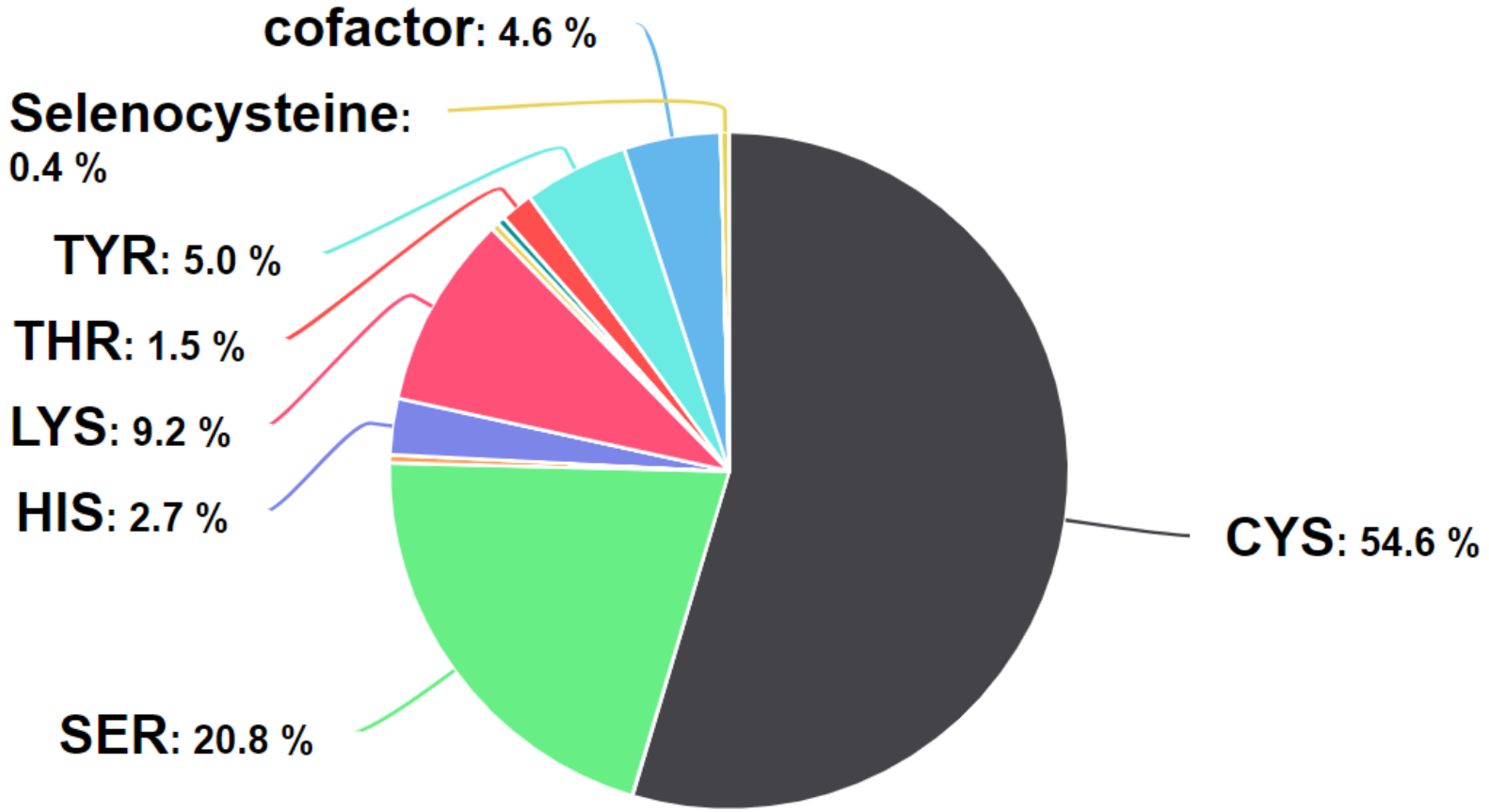


Figure 4. Nonexhaustive collection of warheads used for TCI design. The warheads are grouped in panels by target residues (Cys, pink; catalytic Ser/Thr, cyan; Lys, green; Tyr/His/Ser, purple; Asp/Glu, blue; His/Ser, orange). Some warheads may be used to target multiple residues.

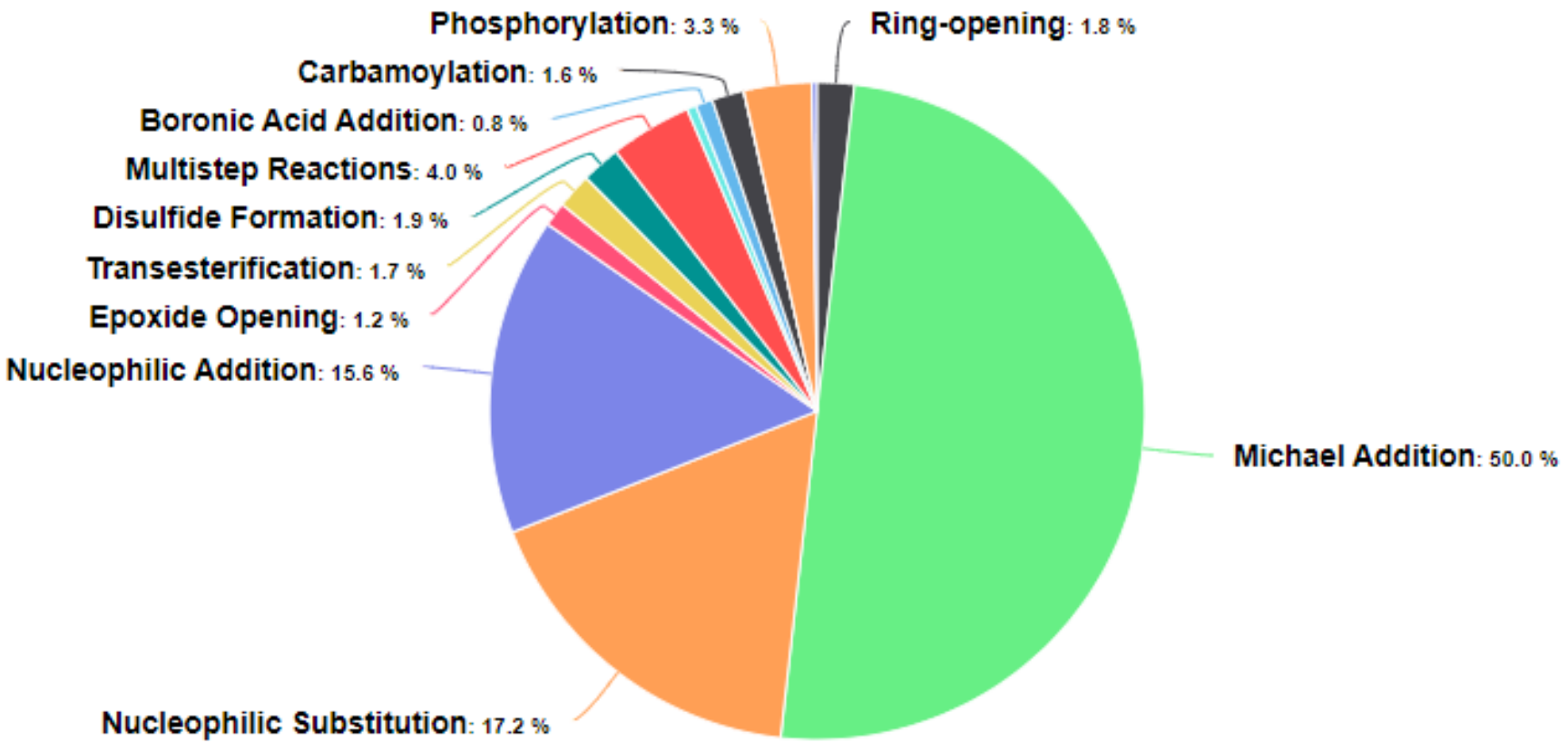
Source: 10 years into the resurgence of covalent drugs, Elena De Vita, *Future Med Chem,* 2021, 13(2), 193–210.

The Distributions of Residues Forming Covalent Bonds



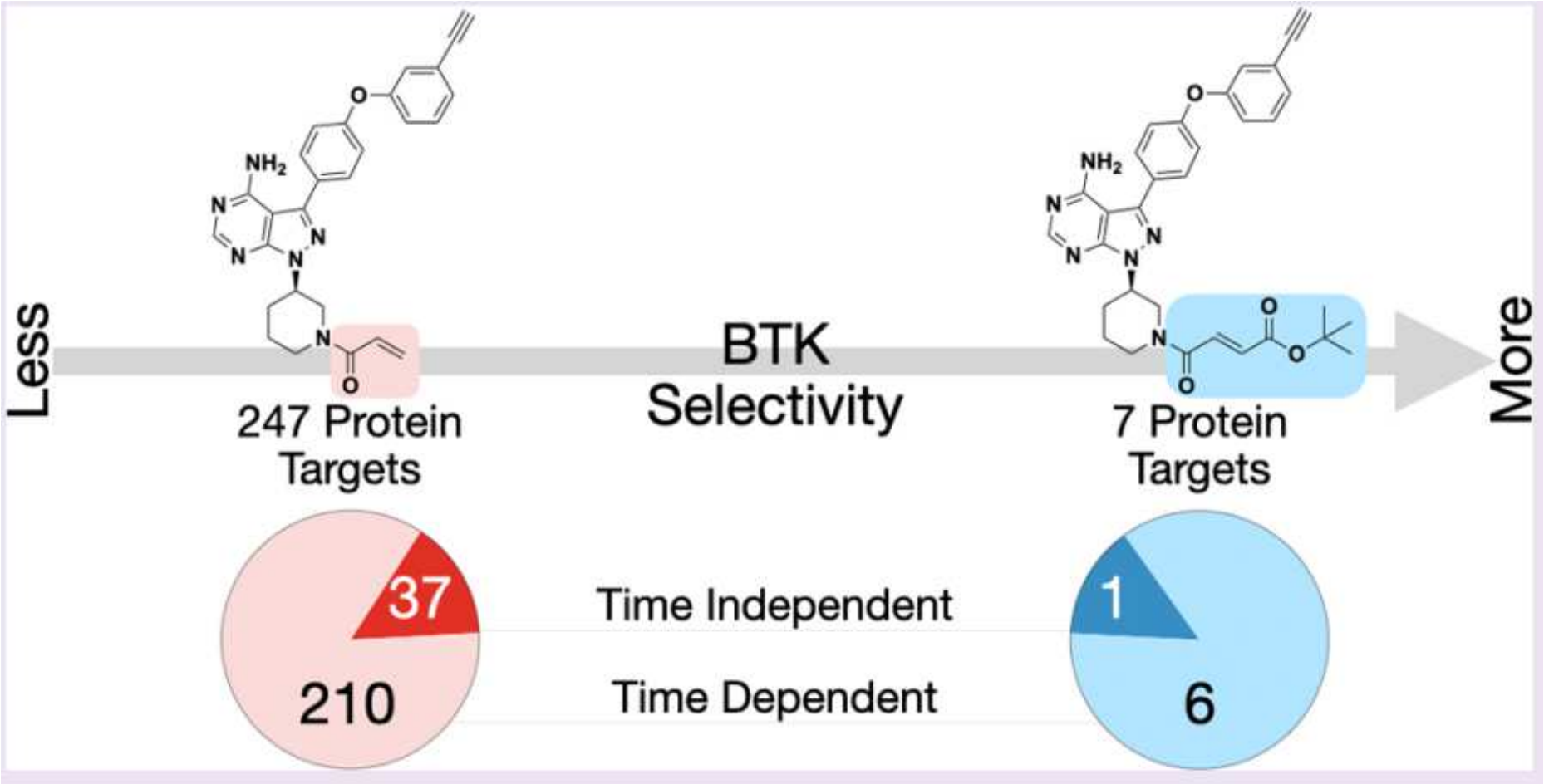
Source: CovalentInDB: a comprehensive database facilitating the discovery of covalent inhibitors, Hongyan Du, et al., *Nucleic Acids Research,* 2021, Vol. 49, D1122–D1129. (CovalentInDB is freely accessible at http://cadd.zju.edu.cn/cidb/)

Statistics of Reaction Mechanism



Source: CovalentInDB: a comprehensive database facilitating the discovery of covalent inhibitors, Hongyan Du, et al., *Nucleic Acids Research,* 2021, Vol. 49, D1122–D1129. (CovalentInDB is freely accessible at http://cadd.zju.edu.cn/cidb/)

Warhead Optimization to Improve Selectivity



Source: Improved Electrophile Design for Exquisite Covalent Molecule, Jose L. Montano, et al., *ACS Chem Biol,* 2022, 17, 6, 1440–1449.

Challenges for TCI Discovery

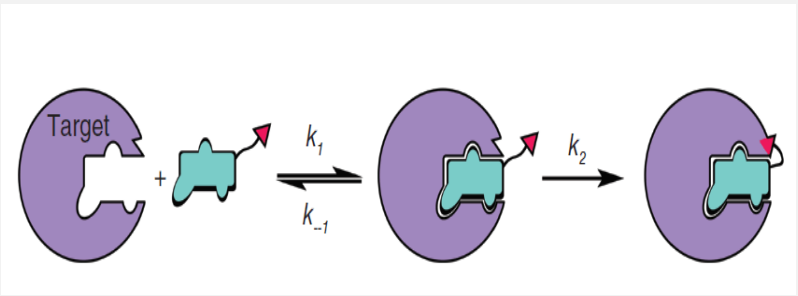
- TCIs are harder to synthesize and purify than traditional small molecules.
- TCI design remains largely empirical as the fine balance between reactivity and stability needs to be achieved, and many compounds need to be synthesized and tested to find the right molecules.
- TCI optimization to improve selectivity of target inhibition over off-target inhibition requires many compounds to be synthesized and tested (often in vivo) to find the candidates.

Our Targeted Covalent Inhibitors Discovery Chemistry Platform

Synthesis, Analysis, and Purification

- **>750** discovery chemists, with strong experiences in targeted covalent inhibitor synthesis
- **>50** clients/collaborations

- **>12** types of warheads, including Acrylamide, Chloroacetamide, 2-Chloropropionamide and Vinyl Sulfone class of compounds



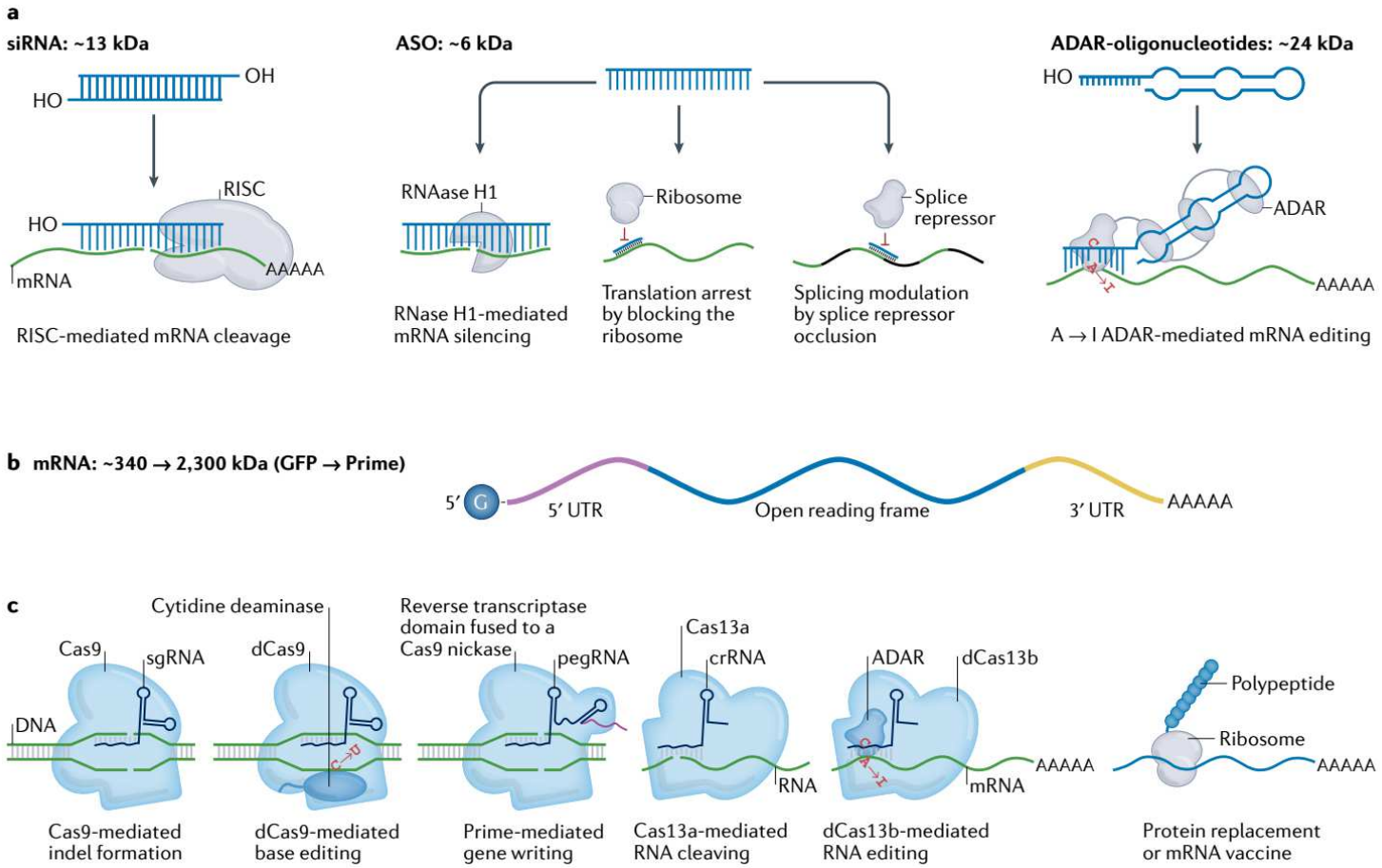
- **>36,000** Covalent compounds successfully delivered from 2021 to 2022H1

- **7** PCCs delivered to clients in 2022H1
- **1** NDA filed by client

Topics

- Targeted Protein Degraders
- Targeted Covalent Inhibitors
- **Nucleic Acid Therapeutics**

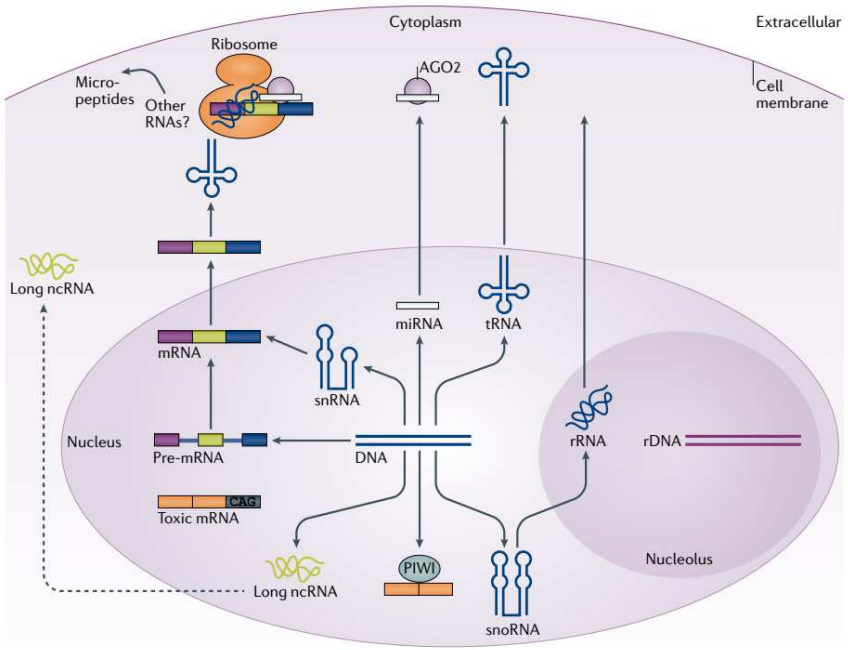
Nucleic Acid Therapeutics



Source: Drug delivery systems for RNA therapeutics, Kalina Paunovska, et al., *Nature Reviews Genetics,* 2022, 23, 265–280.

ASO Drug Discovery

Occupancy-mediated degradation	Occupancy only	
Downregulation	**Downregulation**	**Upregulation**
1. RNase-H1-mediated degradation 2. AGO2-mediated degradation 3. Nonsense-mediated decay 4. No-go decay	5. Translational arrest 6. 5′ Cap inhibition 7. Altering polyadenylation site	1. Splicing modulation 2. Inhibition of miRNA function 3. Modulating uORF and TIE utilization 4. Inhibition of nonsense-mediated decay 5. RNA activation

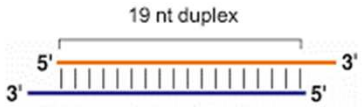


Source: Antisense technology: an overview and prospectus, Stanley T. Crooke, et al., *Nature Reviews Drug Discovery,* 2021, 20, 427–453.

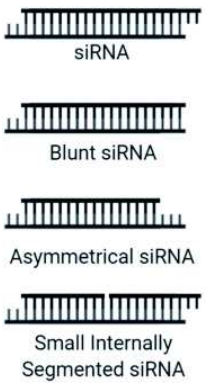
siRNA Drug Discovery

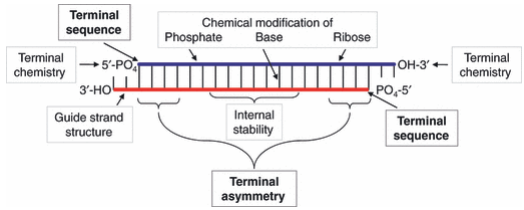
Sequence Selection | Topology | Modifications | Targeting and Delivery

Sense strand

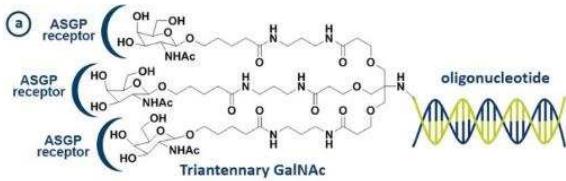


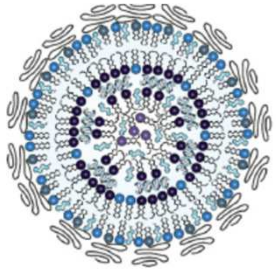
Antisense strand

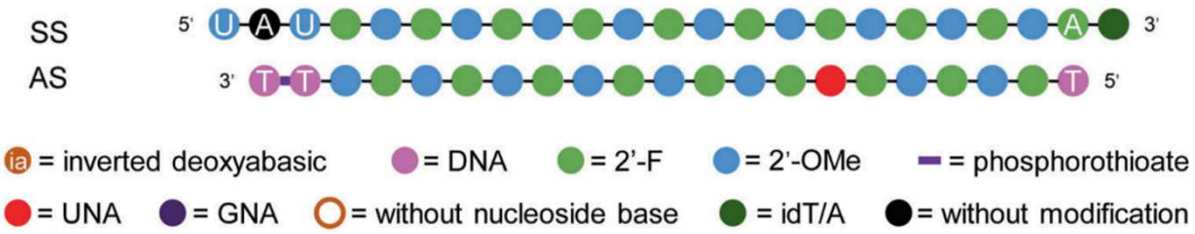




- *Ribose modifications*
- *Backbone modifications*
- *Base modifications*
- *Chirality*

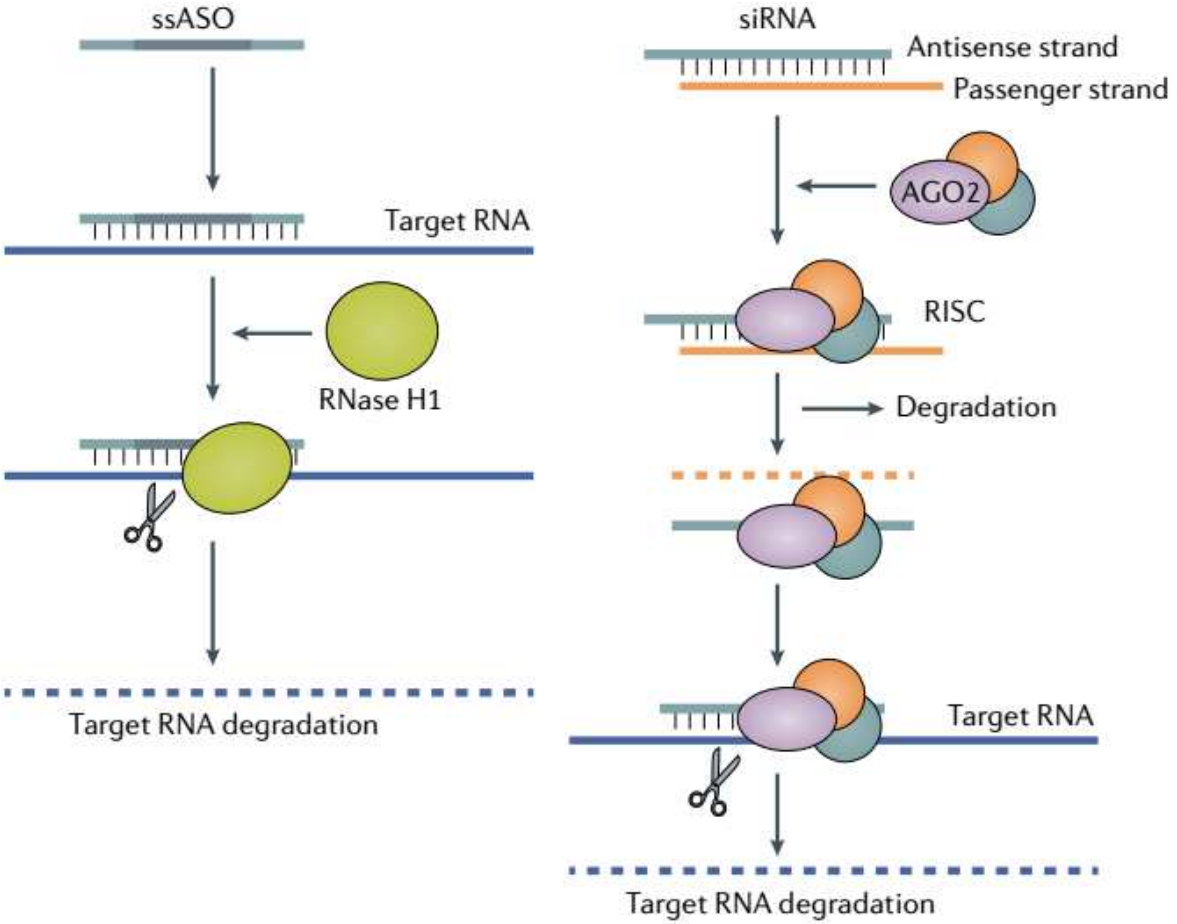






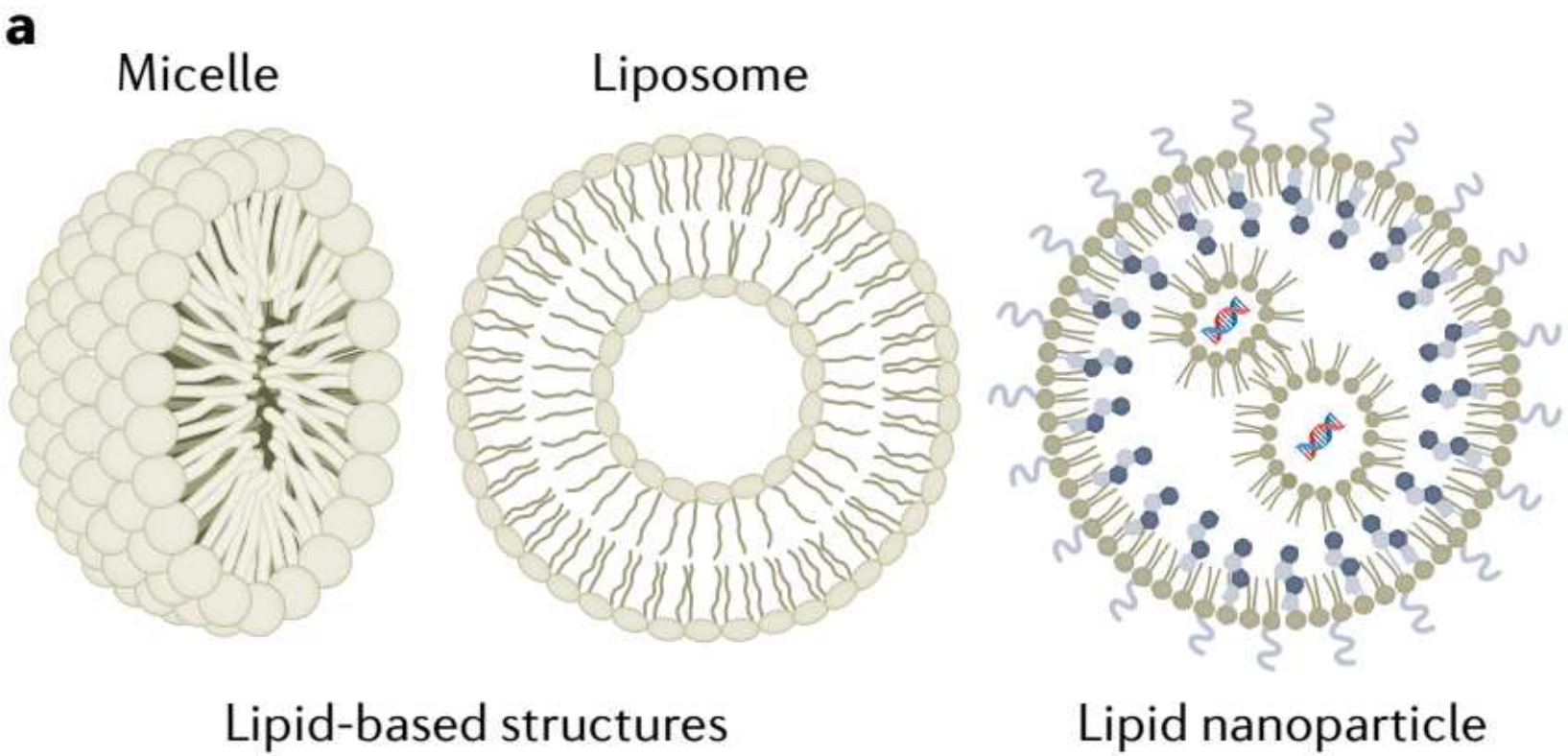
- *GalNAc conjugation*
- *Lipid nanoparticle formulation*
- *Peptide conjugation*
- *Aptamer conjugation*

ASO and siRNA Comparison



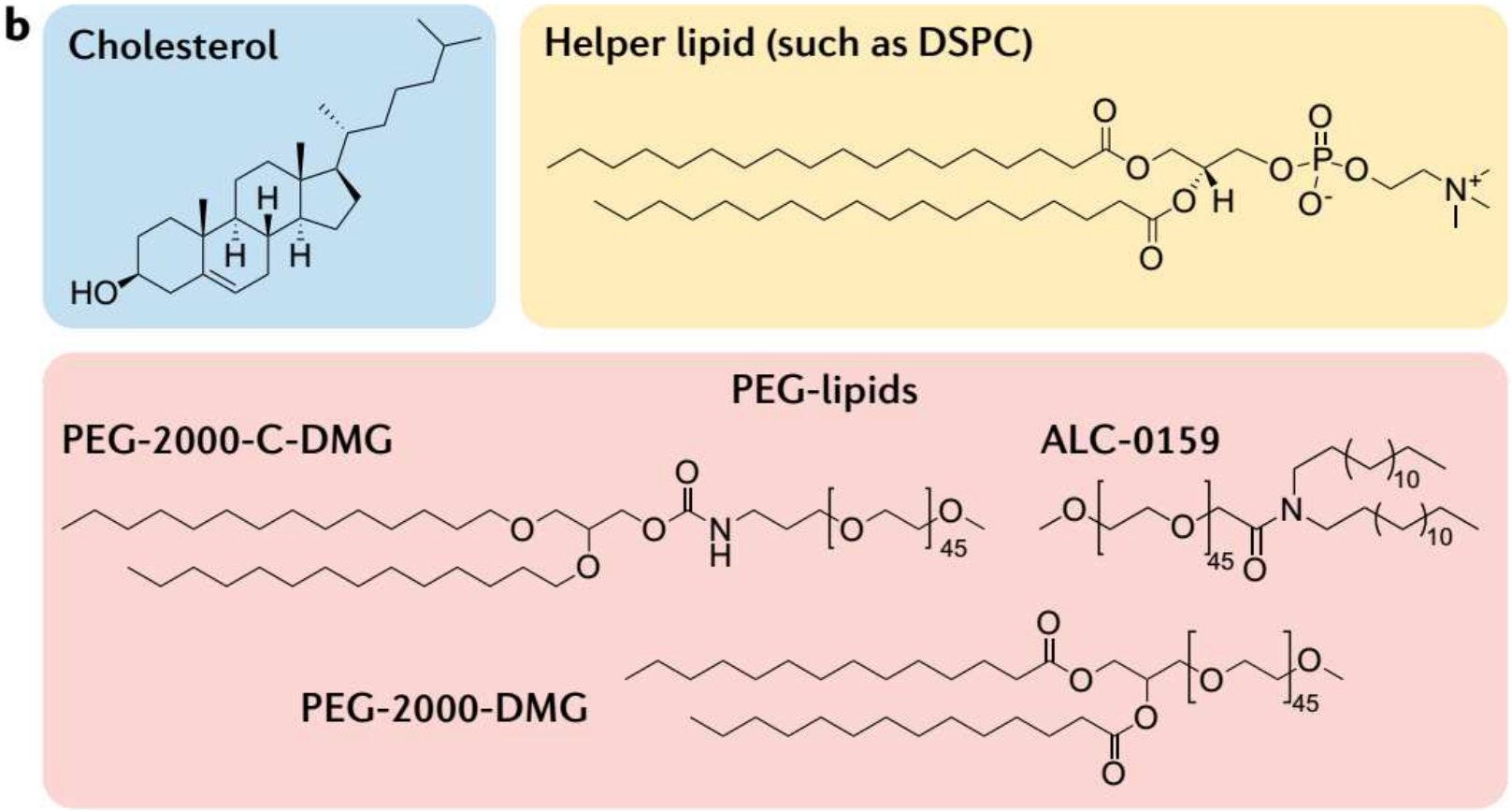
Source: Antisense technology: an overview and prospectus, Stanley T. Crooke, et al., *Nature Reviews Drug Discovery,* 2021, 20, 427–453.

Delivery via Lipid Nanoparticle (LNP)



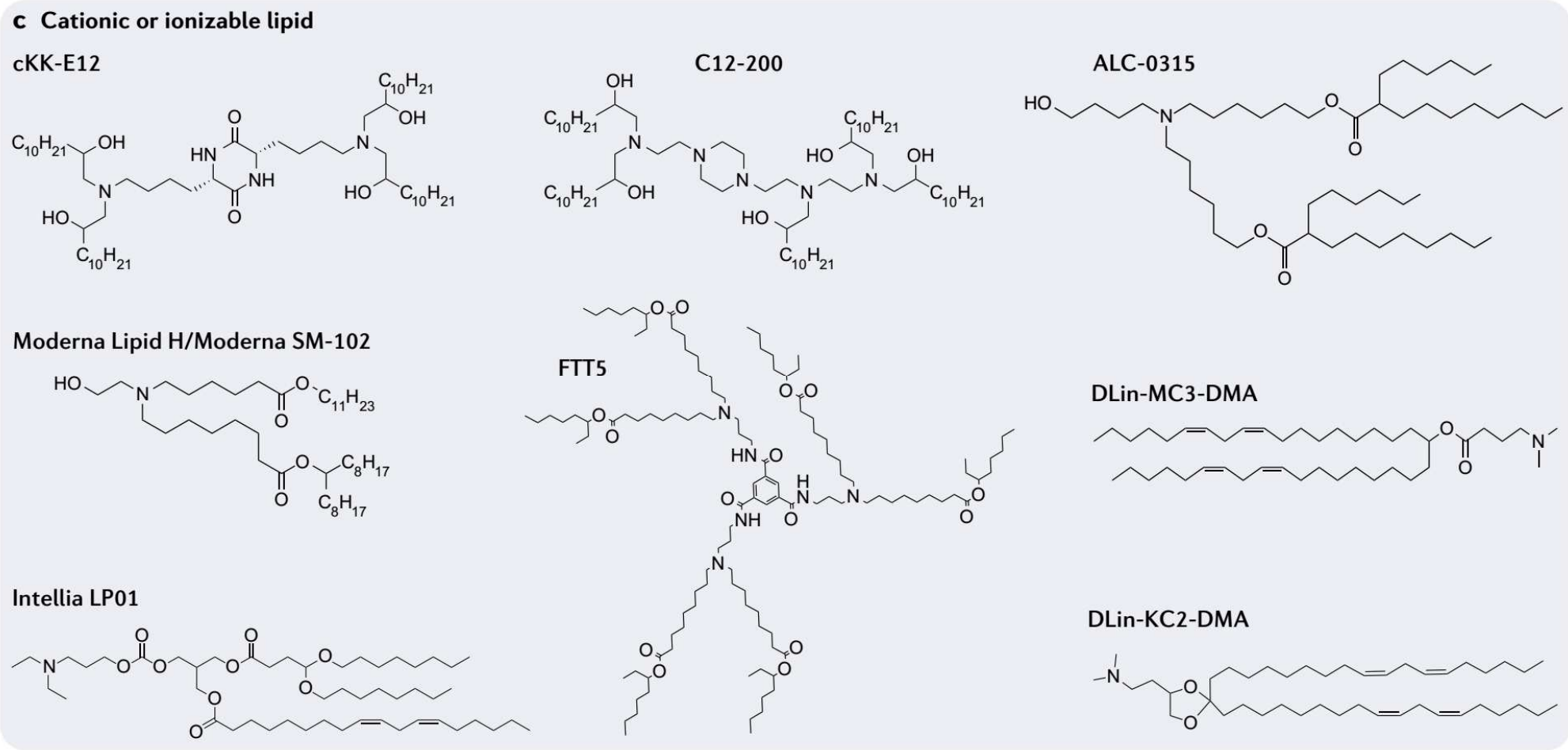
Source: Drug delivery systems for RNA therapeutics, Kalina Paunovska, et al., *Nature Reviews Genetics,* 2022, 23, 265–280.

LNP Component: 1. Cholesterol, 2. Helper Lipid, 3. PEG-Lipid



Source: Drug delivery systems for RNA therapeutics, Kalina Paunovska, et al., *Nature Reviews Genetics,* 2022, 23, 265–280.

LNP Component: 4. Cationic or Ionizable Lipid



Source: Drug delivery systems for RNA therapeutics, Kalina Paunovska, et al., *Nature Reviews Genetics,* 2022, 23, 265–280.

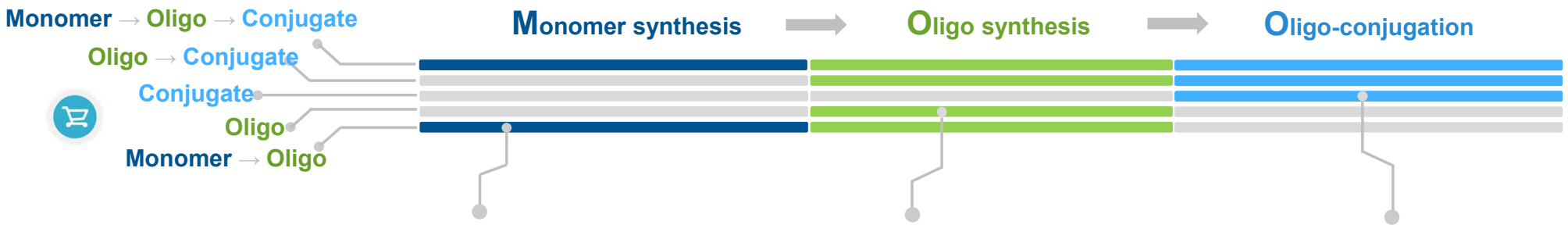
Challenges for Nucleic Acid Therapeutics Discovery

- Nucleic Acid Therapeutics need stabilization chemistry with modifications including 2'-F, 2'-OMe, 2'-OMOE, LNA, UNA, GNA, PS, PMO, etc., and the synthesis of many sequences are needed to identify the right combination.

- Nucleic Acid Therapeutics targeting often needs special conjugation synthesis, e.g., liver targeting through GalNAc conjudate.

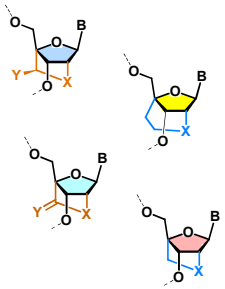
- Nucleic Acid Therapeutics delivery is very challenging, requiring LNP assistance. The design, synthesis, and the right mix of LNP are largely empirical, requiring the synthesis and testing of many lipids.

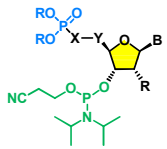
Our Nucleic Acid Therapeutics Discovery Chemistry Platform

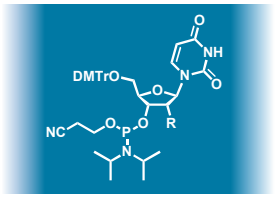


Special Monomer Synthesis

- ☑ Bridged Nucleic acid
- ☑ 2' and 5'-modification
- ☑ Nucleobase Modification
- ☑ GalNAc Ligand
- ☑ Lipid and Spacer Amidite
- ☑ Stereodefined Amidite
- ☑ PMO Monomers

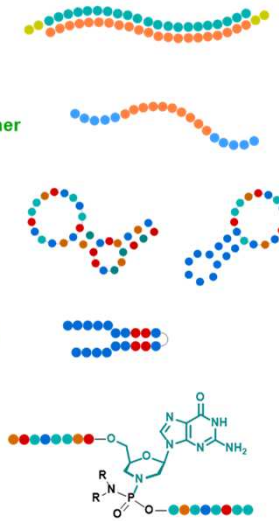




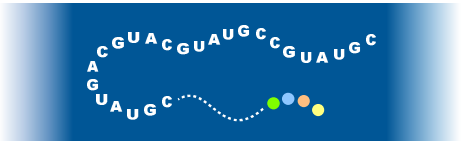


Oligonucleotide Synthesis

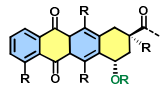
- ☑ siRNA
- ☑ ASO/gapmer
- ☑ Aptamer
- ☑ CpG ODN
- ☑ PMO



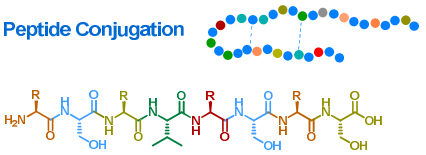
Oligo-conjugate Synthesis for Delivery



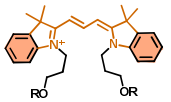
- ☑ Small Molecule



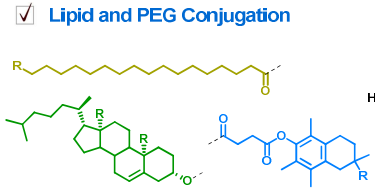
- ☑ Peptide Conjugation

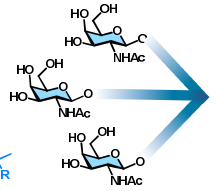


- ☑ Fluorescent Tag



- ☑ Lipid and PEG Conjugation





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