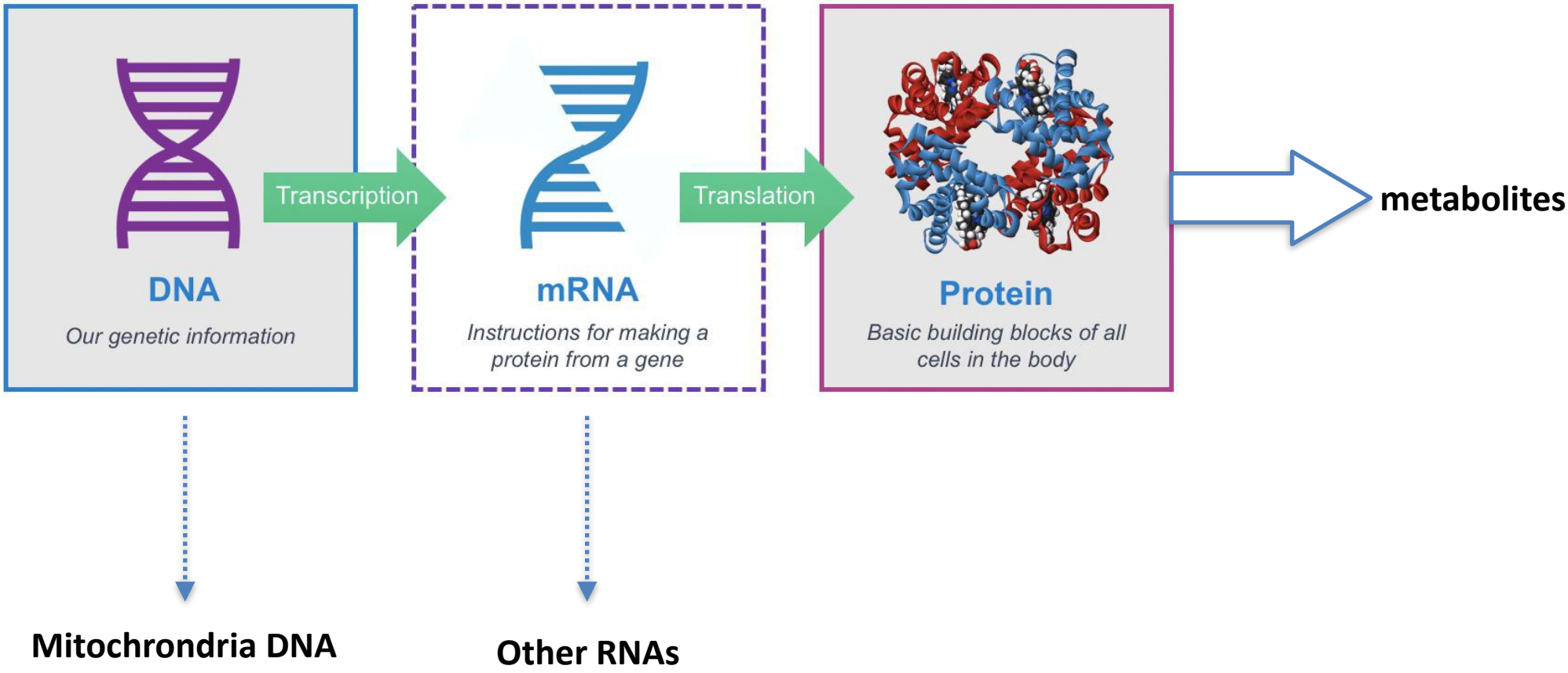
Cancer Therapeutics

1. Small moleules and natural products
2. Peptides
3. Nucleic acids
4. Proteins/antibodies
5. Protein/antibody-drug conjugates
6. Gene therapy
7. PROTACs
8. Cell-based therapies (CAR-T)
9. Nanomedicines
10. Others

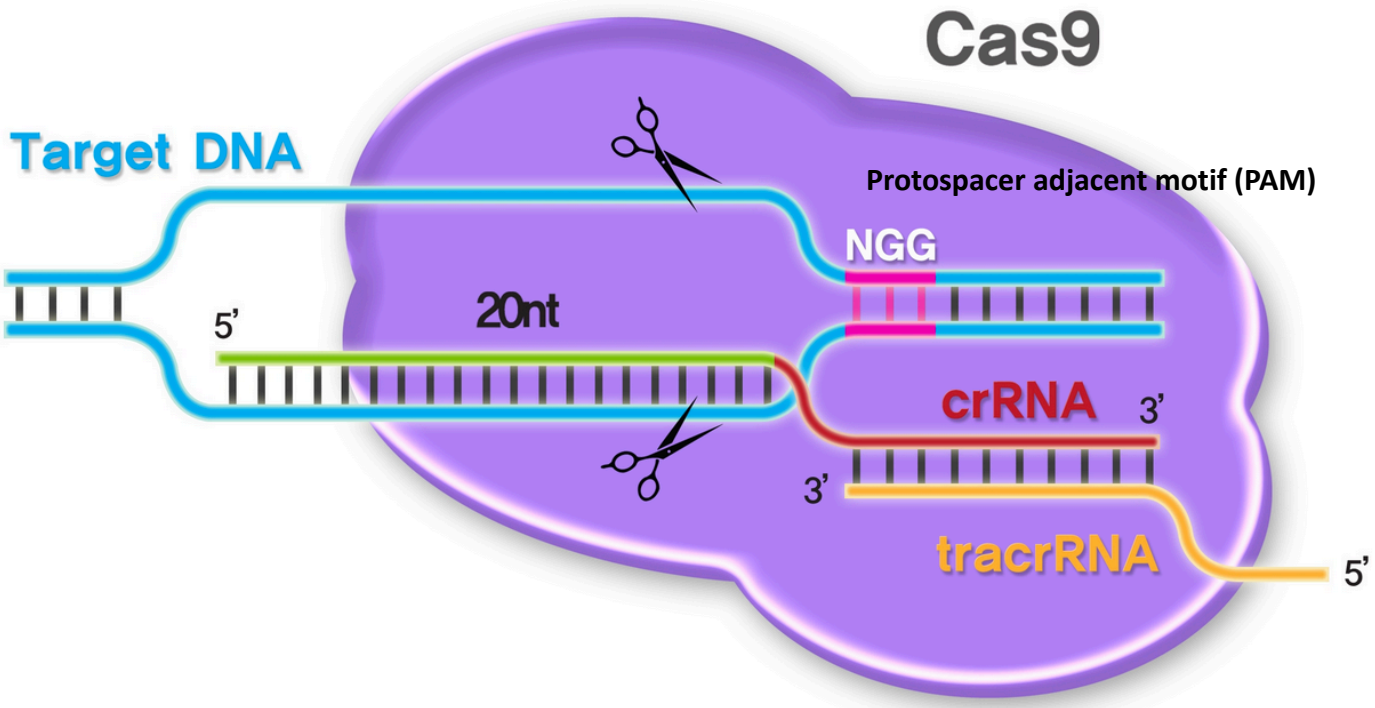
Therapeutic Targets in Cells



Guo, J.; Liu, J.; Wei, W. *Cell Res.* **2019**, *29*, 179–180.

Targeting DNA for Drug Discovery

Genome Editing-CRISPR/Cas9



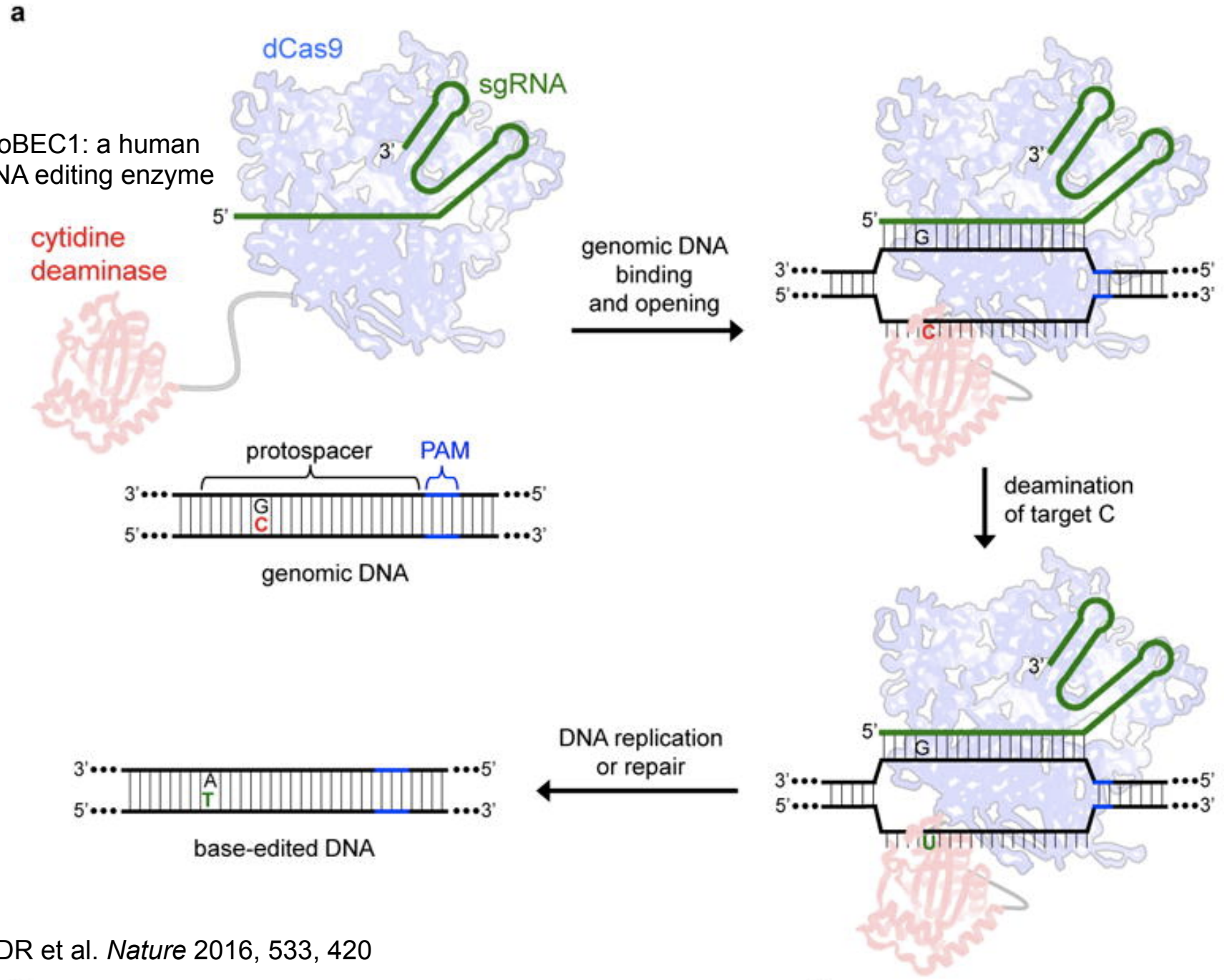
In contrast with other CRISPR system,
Cas9 is the only component in Inference complex in Type II CRISPR system

crRNA and tracrRNA can be merged as sgRNA

Guo, J.; Liu, J.; Wei, W. *Cell Res.* **2019**, *29*, 179–180.

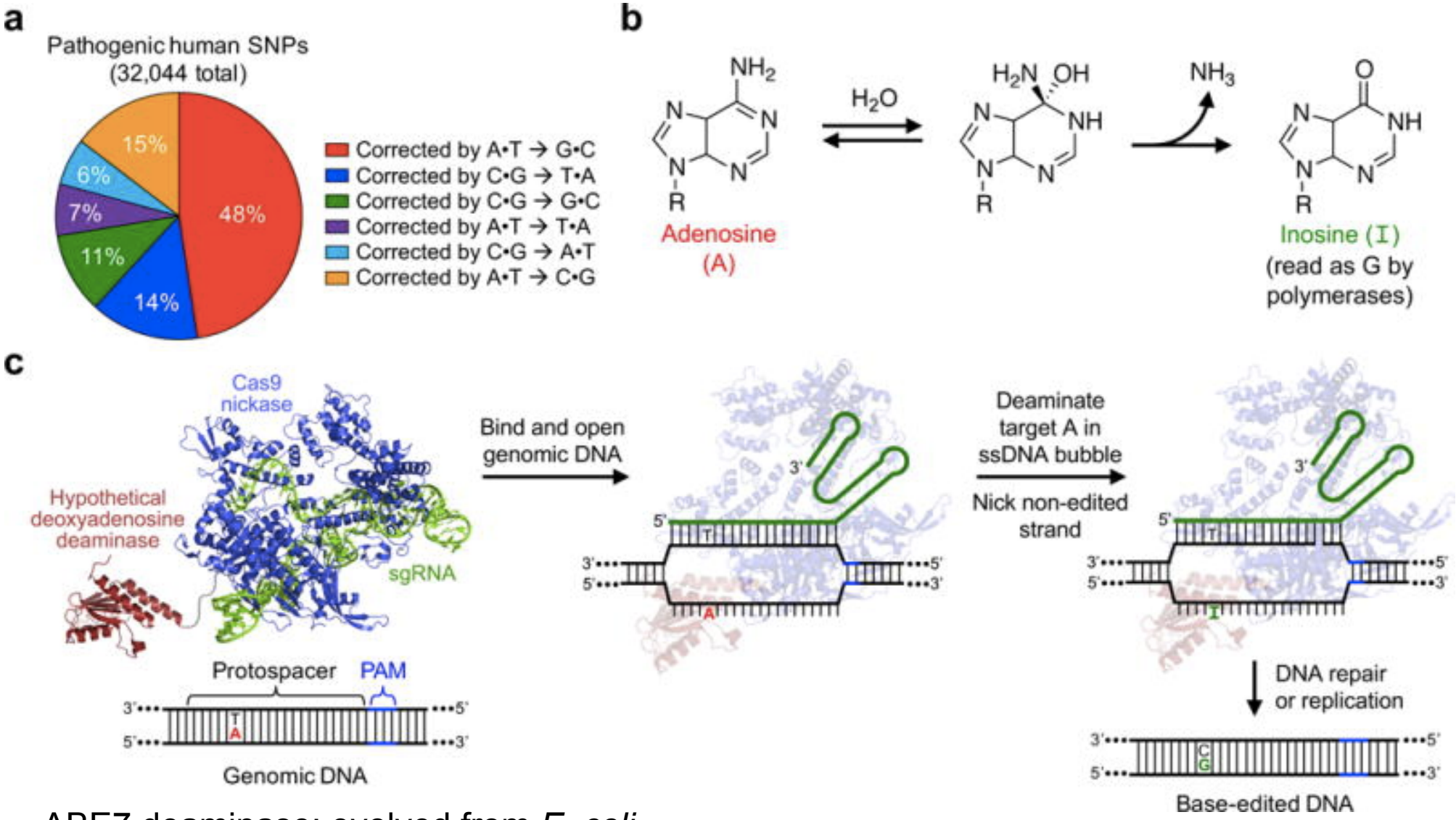
Base Editing C to T (U)

ApoBEC1: a human mRNA editing enzyme



Liu DR et al. *Nature* 2016, 533, 420

Base Editing A to G

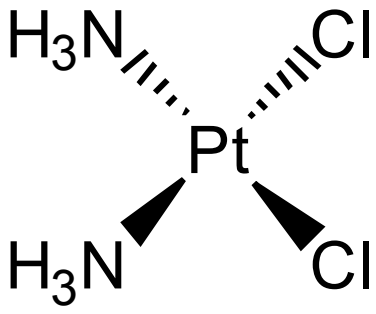


ABE7 deaminase: evolved from *E. coli* TadA, a RNA adenine deaminase

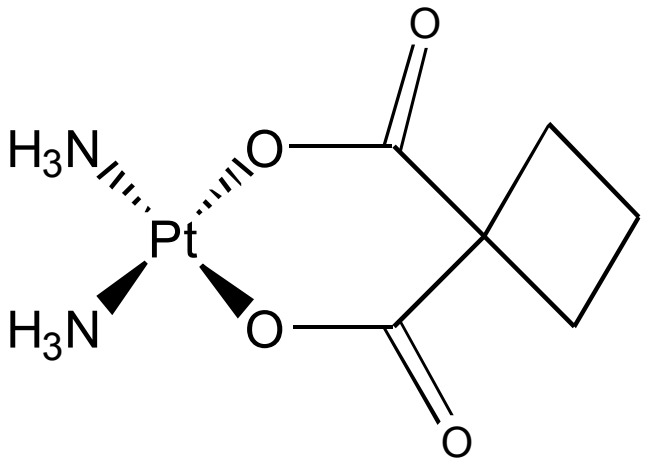
Liu DR et al. *Nature* 2017, 551, 464

Cisplatin: An DNA Chelator and Anticancer Drug

- In 1965 Rosenberg discovered antiproliferative effect of a cisplatin whilst conducting studies on bacteria under in an electric field produced by platinum complexes
- He was able to show that the compound cisplatin was responsible for the effect and this was found to be effective against treating some cancers.
- Cisplatin is now the most used anti-cancer drug

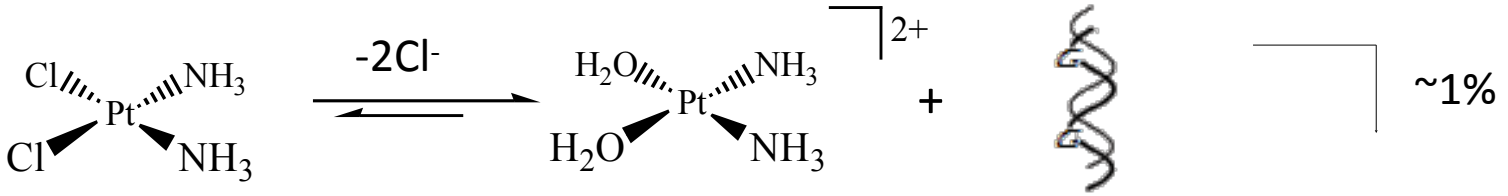


cisplatin

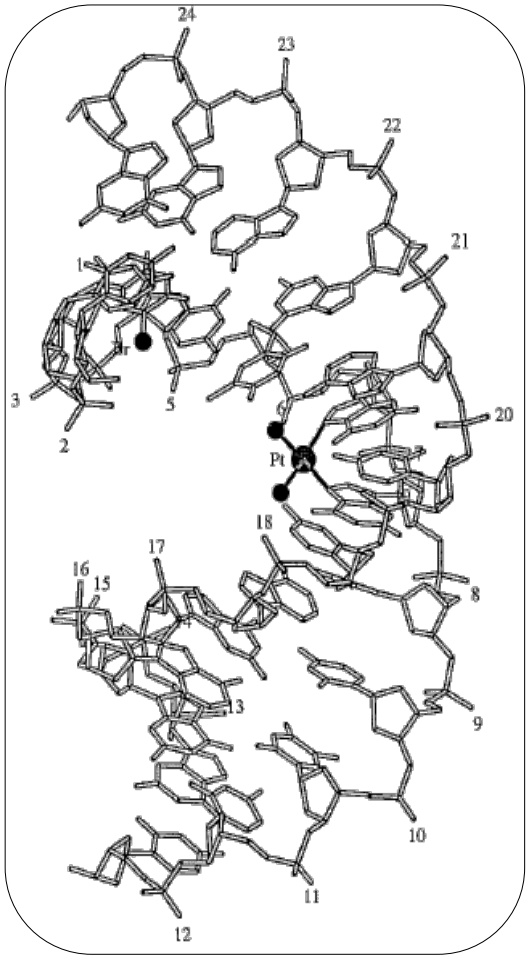


carboplatin

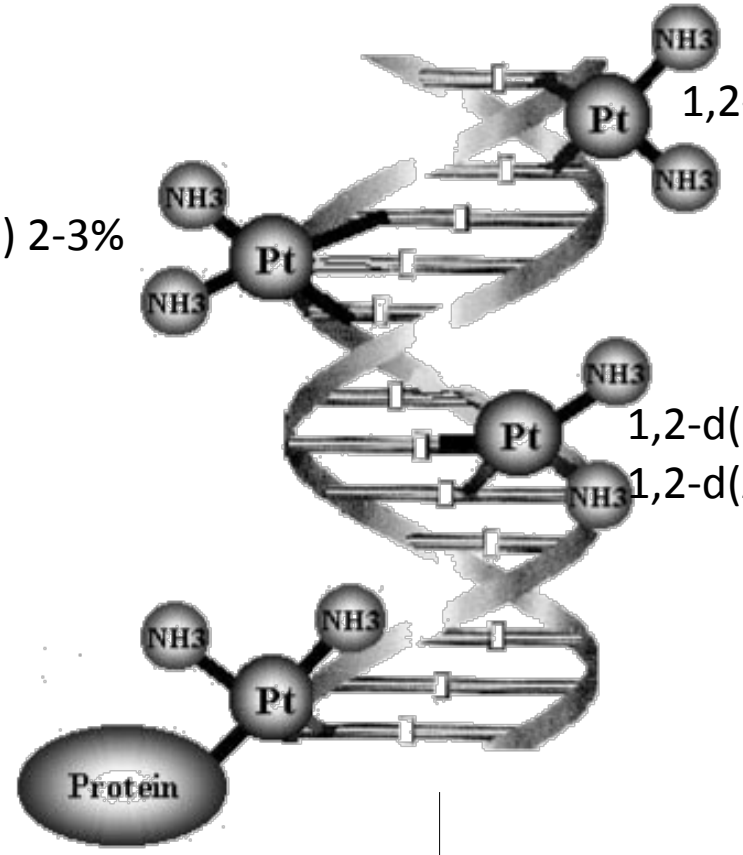
DNA binding



Cisplatin



1,3-d(GXG) 2-3%

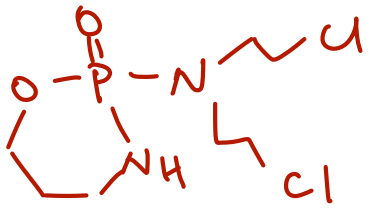


Cell death

Sadler, P. J. et al. *Angew. Chem. Int. Ed.* **1999**, *38*, 1513
Lippard, S. J. et al. *Nature* **1995**, *377*, 649

DNA Alkylating Reagents

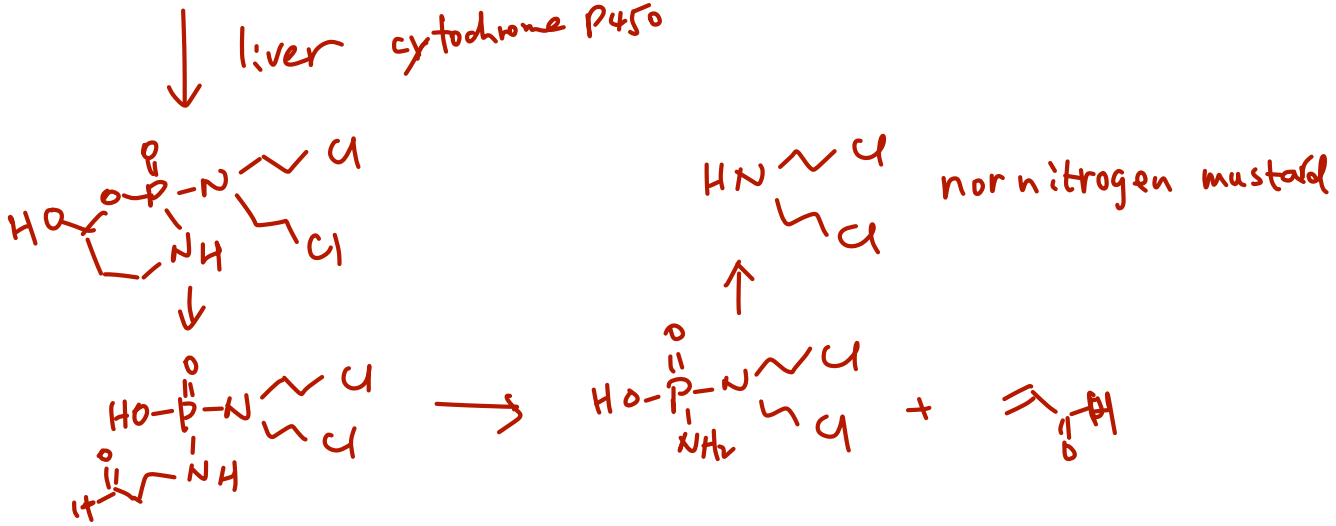
- Nitrogen mustards
- Aziridines
- Alkyl sulfonates
- Nitrosoureas
- Triazenes



Breast cancer, ovarian cancer

Sarcoma, etc.

cyclophosphamide, a prodrug

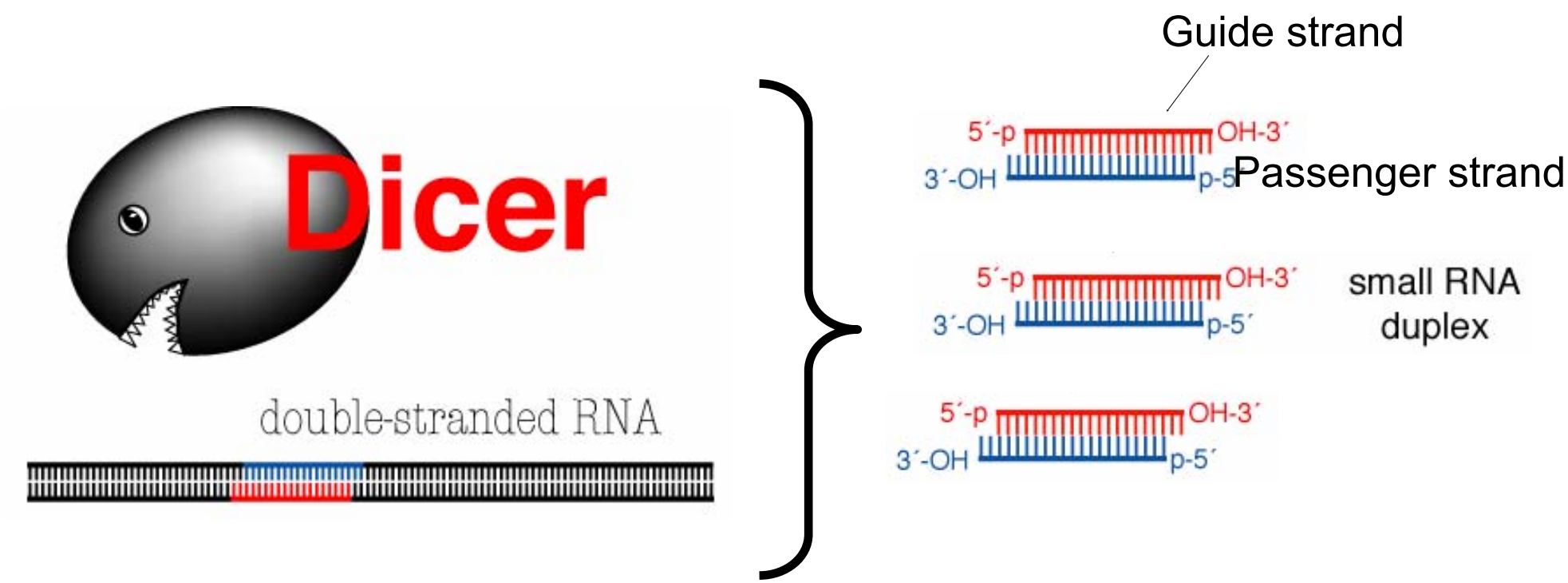


They are excellent anti-tumor reagents

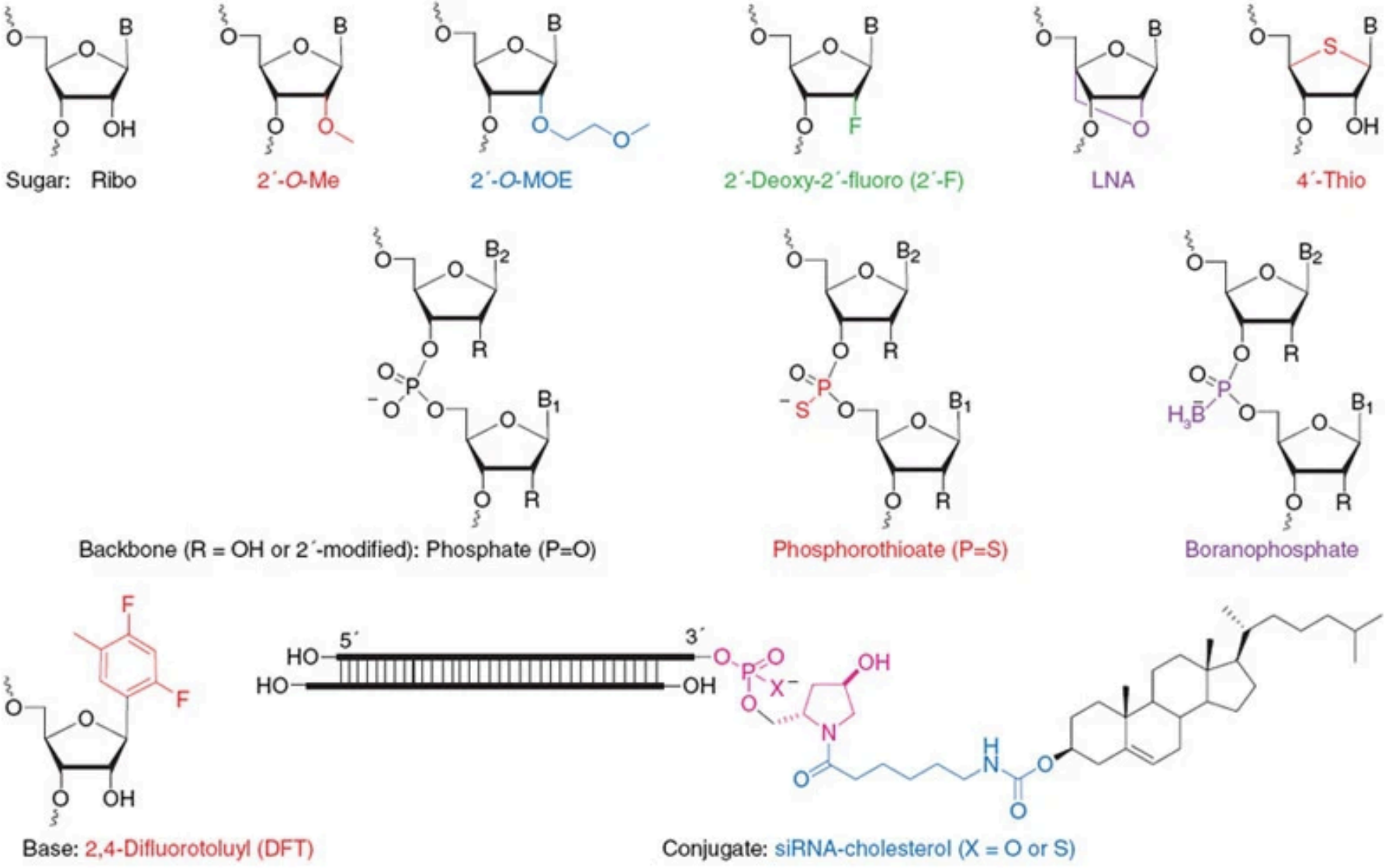
Targeting RNA for Drug Discovery

RNA Interference

- RNA interference (RNAi) is the silencing of gene expression, triggered by the presence of double-stranded RNA homologous to portion of the gene.
- dsRNAs are cleaved into 21-23 nt segments ("small interfering RNAs", or siRNAs) by an enzyme called Dicer

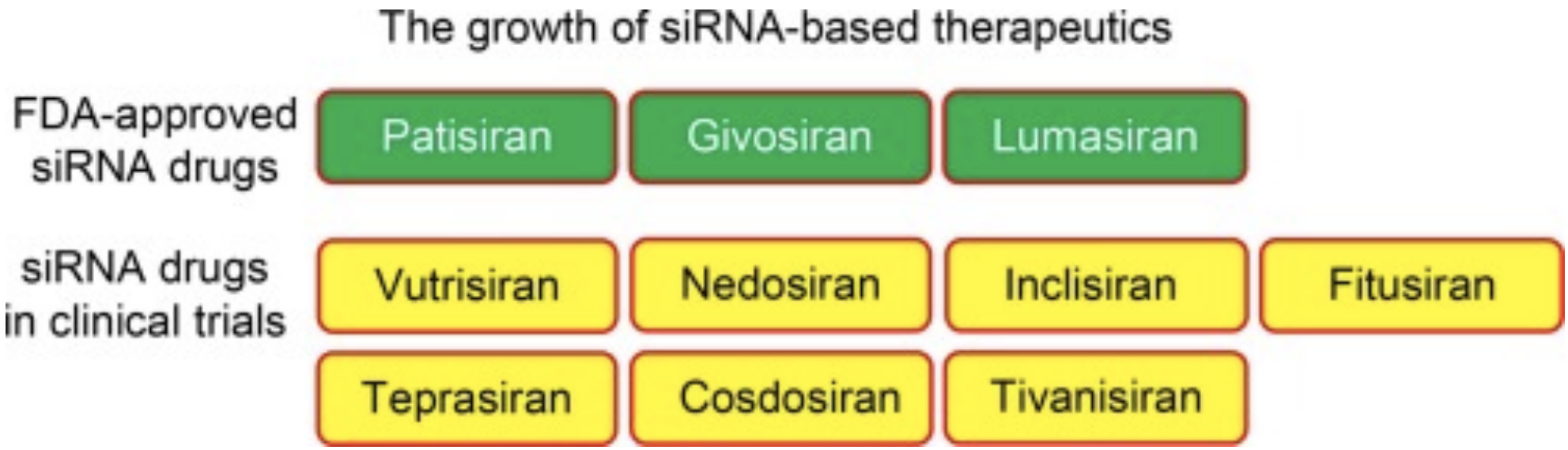


Modified siRNAs



Nat Chem Biol 2006, 711-719

siRNA Drugs



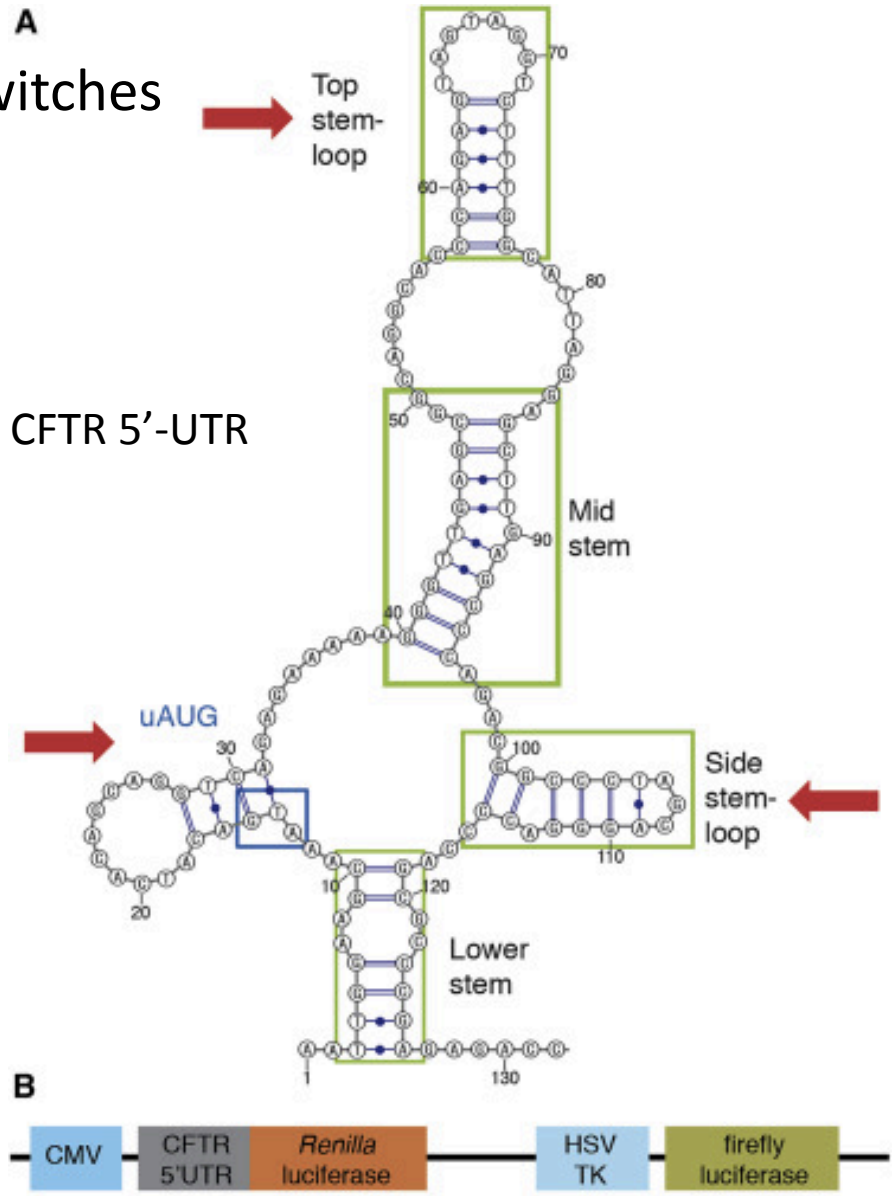
Patisiran: treating polyneuropathy in amyloidosis
Givosiran: treating acute hepatic porphyria
Lumasiran: treating primary hyperoxaluria type 1

Biochem Pharm 2021, 114432

RNA-Targeting Small Molecules

Structural RNAs: tRNAs, rRNAs, mRNA 5’ and 3’-UTRs, and other RNAs

The idea is similar to riboswitches



Mol Ther 2019, 1749-1757.

Targeting Proteins for Drug Discovery

Rational Design of Protein Inhibitors

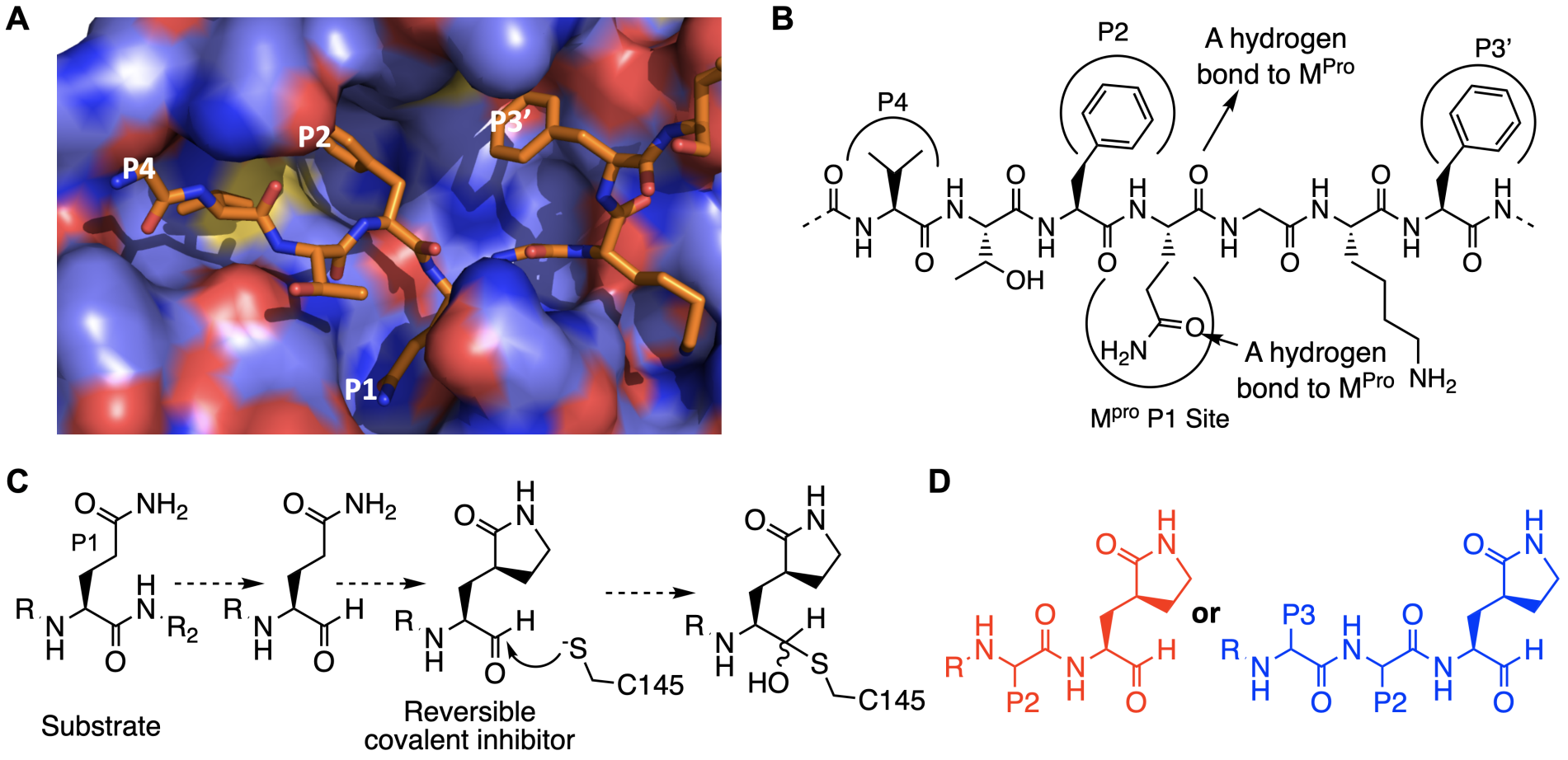
★ A well structured active site.

★ Substrates and low binding ligands as starting points.

★ Chemical manipulation to improve potency, cellular permeability and serum stability.

★ Chemical manipulation to improve pharmacokinetics and pharmacodynamic features (LADME, dose, benefit, adverse effects, etc.).

A SARS-CoV-2 Enzyme as an Example

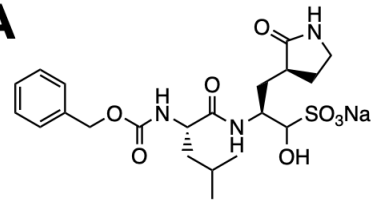


SARS-CoV-2 Main Protease

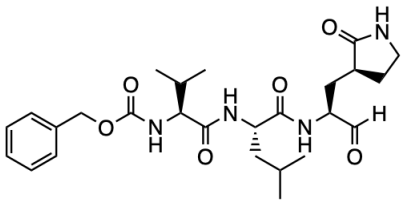
ChemMedChem 2021, 16: 942-948

A SARS-CoV-2 Enzyme as an Example

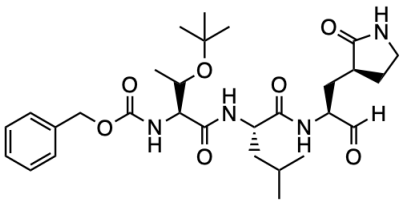
A



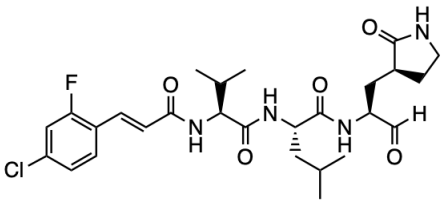
GC376



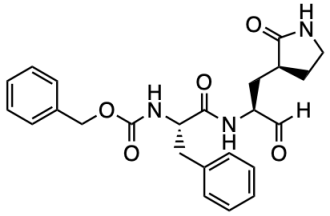
MPI3



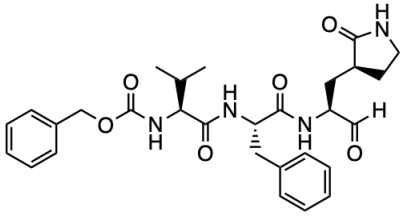
MPI6



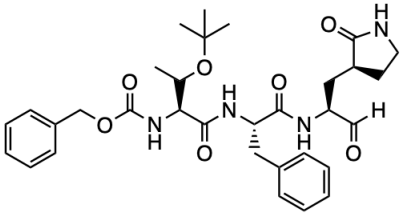
MPI9



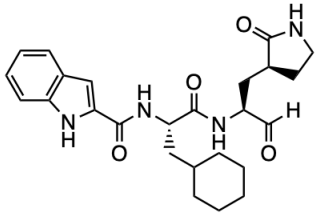
MPI1



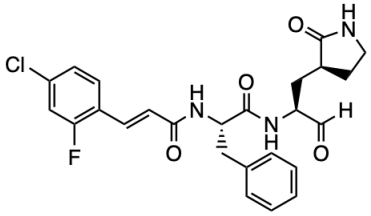
MPI4



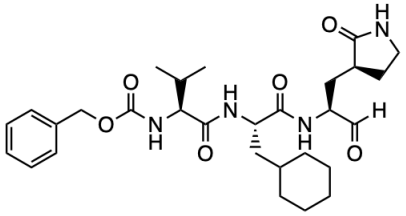
MPI7



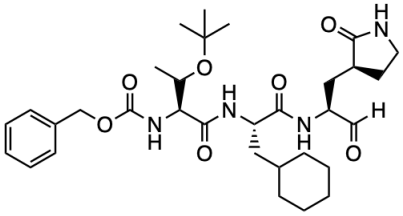
11a



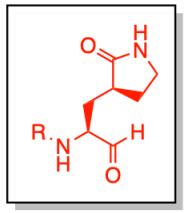
MPI2



MPI5



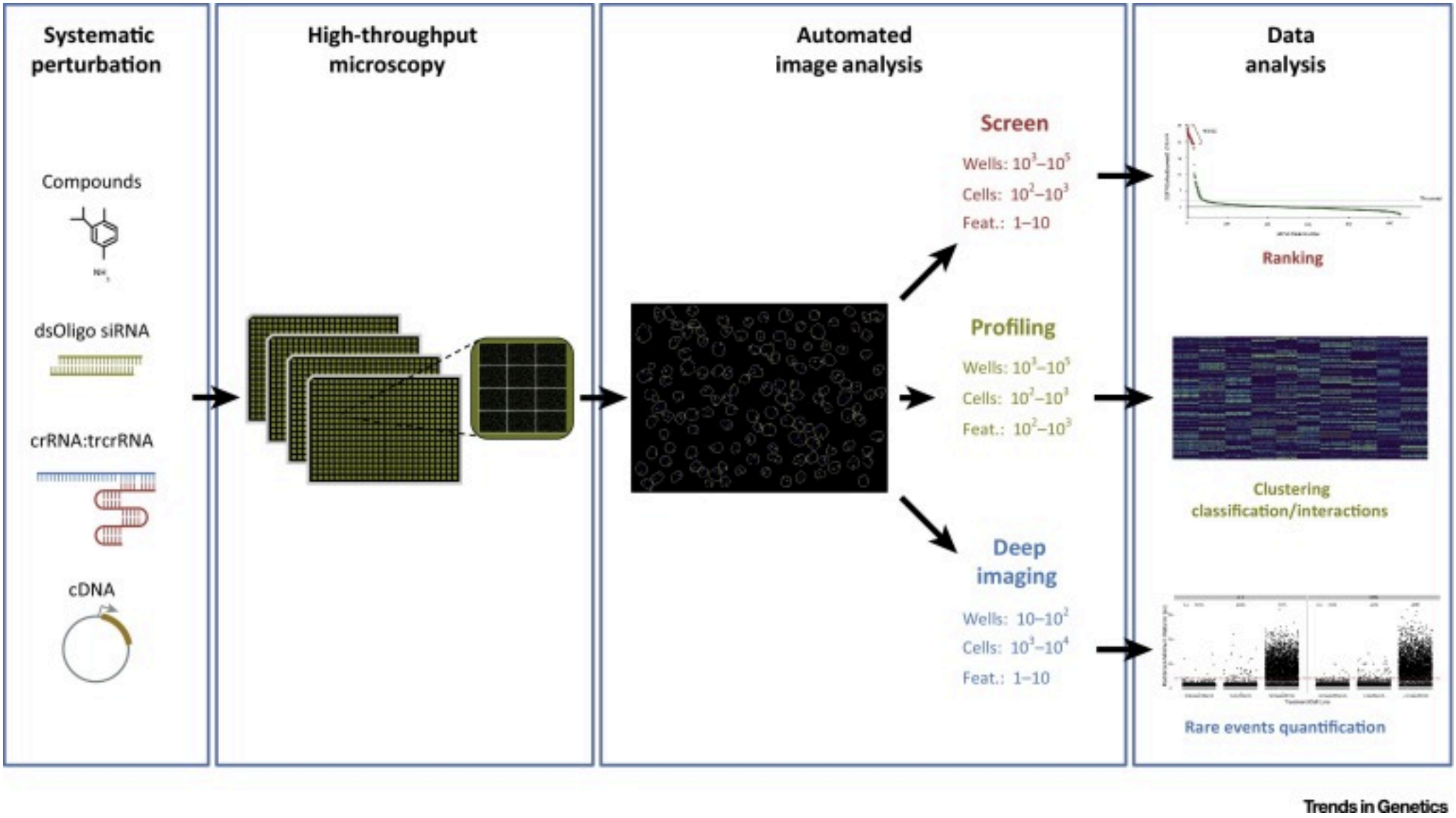
MPI8



Cmp ID	IC50 (nM)	Cmp ID	IC50 (nM)
GC376	81 (14)	MPI6	123 (23)
MPI1	100 (23)	MPI7	118 (11)
MPI2	103 (14)	MPI8	105 (22)
MPI3	8.5 (1.4)		
MPI4	15 (5)		
MPI5	33 (2)		

ChemMedChem 2021, 16: 942-948

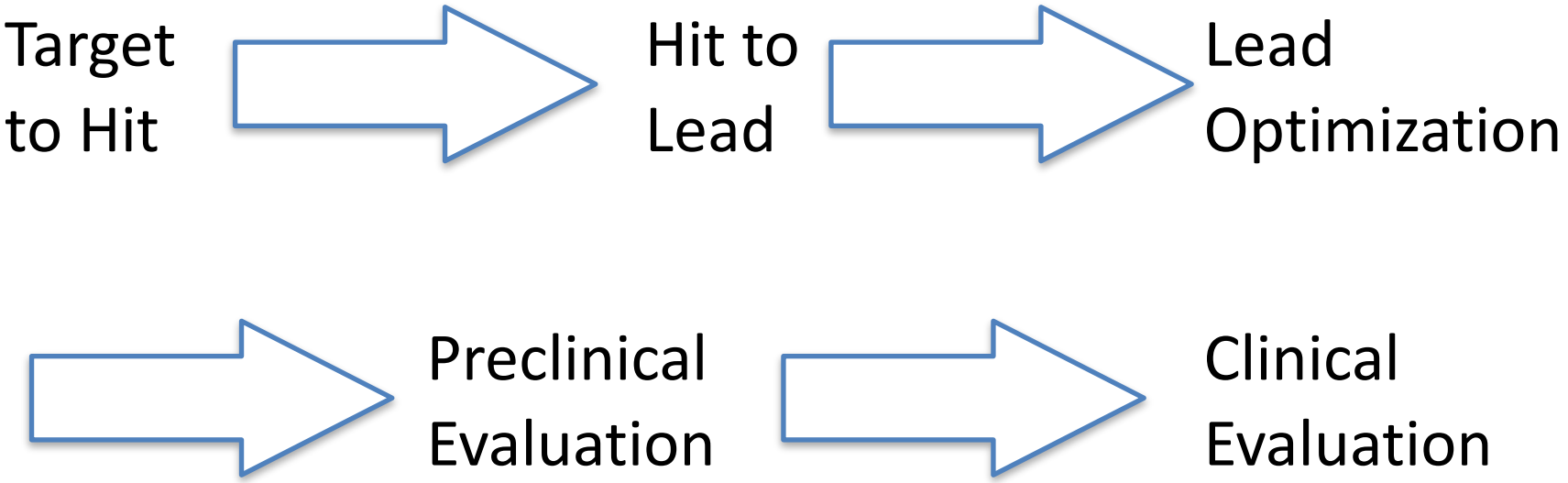
When a Screening Assay is Available



Assay: absorbance, fluorescence, chemiluminescence, fluorescence polarization, etc.

Trend Gen 2017, 33: 604-615

When a Screening Assay is Available



When No HTS Assay is Available

1. In silica based virtual screening

2. AI-based drug discovery

3. Affinity-based selection (folded proteins are available)

Affinity-Based Selection

1. SELEX: systemactic evolution of ligands by exponetntial enrichment (DNA and RNA)
2. Phage display
3. mRNA display
4. One-bead one-compound libraries (peptides or small molecules)
5. DNA-encoded small molecule libraries
6. Other display techniques

Phage Display as an Example

Selection technique based on the presentation of peptides or proteins on the surface of bacteriophages.

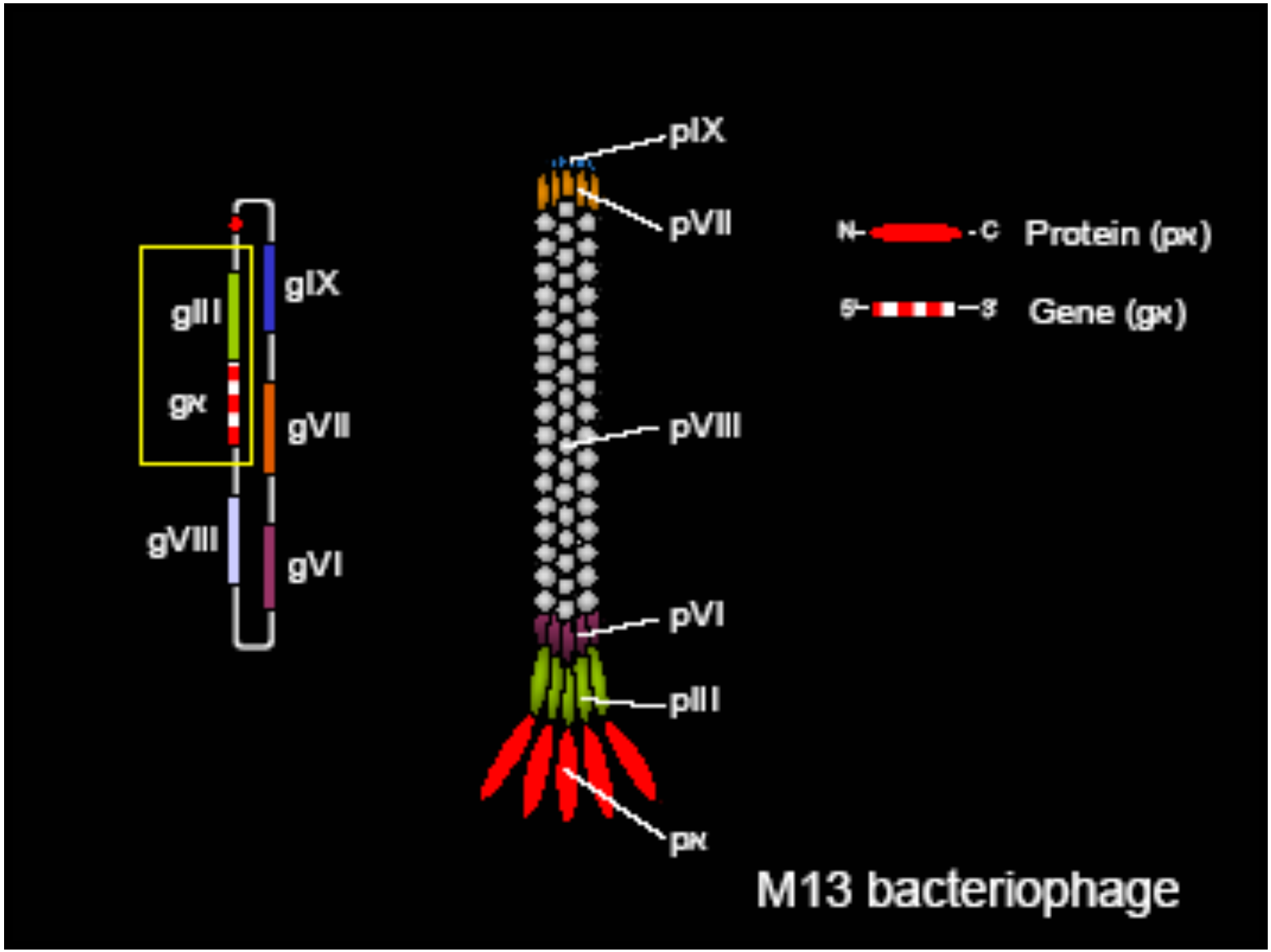
The DNA sequence encoding the peptide is fused to a gene coding for a surface

protein of the phage resulting in physical linkage between DNA sequence and peptide sequence.

This allows easy cloning of DNA sequences for random peptide libraries into a phage vector and rapid identification of selected peptides by sequencing of the DNA encoding the peptide inserts.

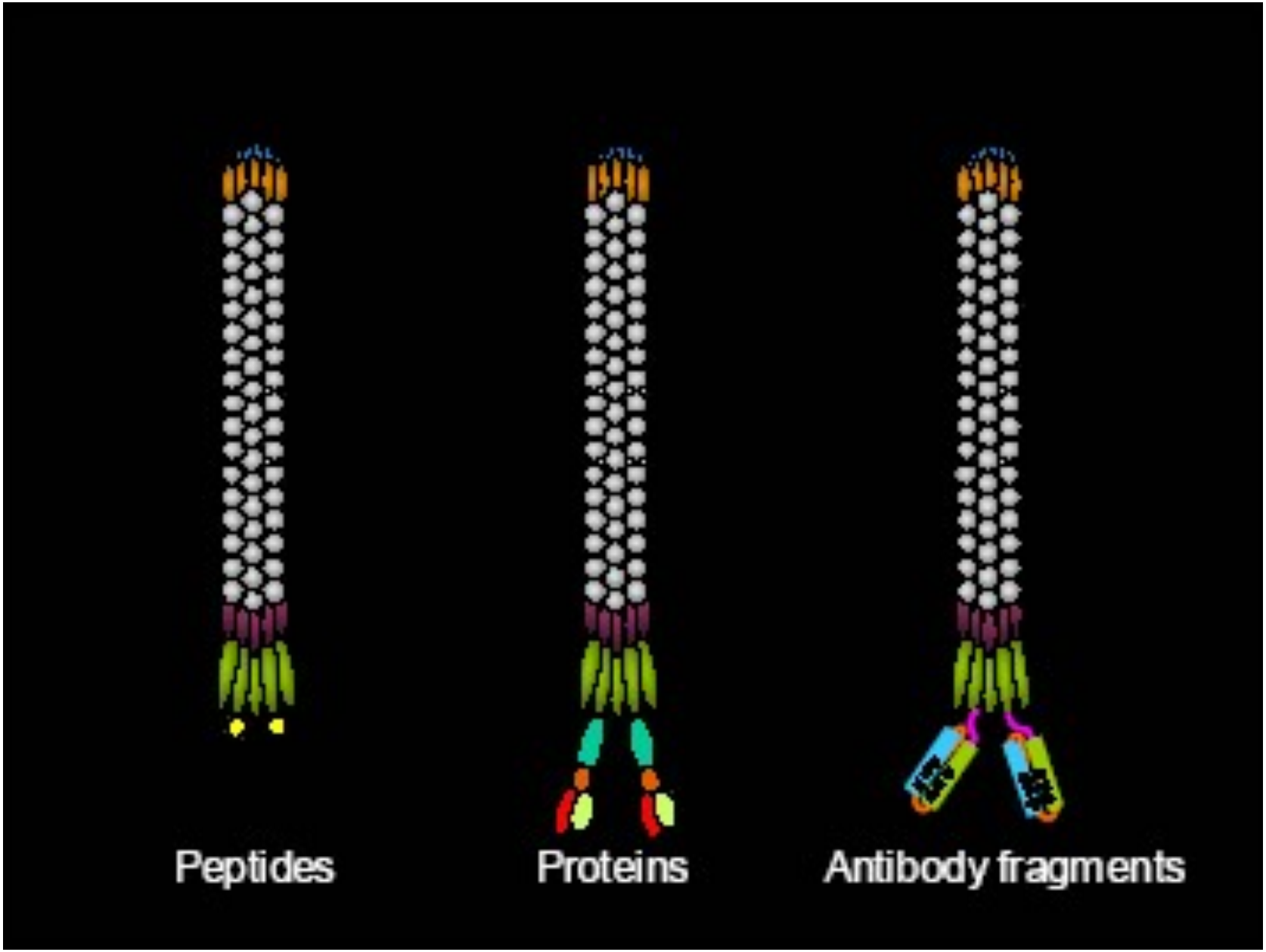
Straightforward enrichment.

M13 Phage

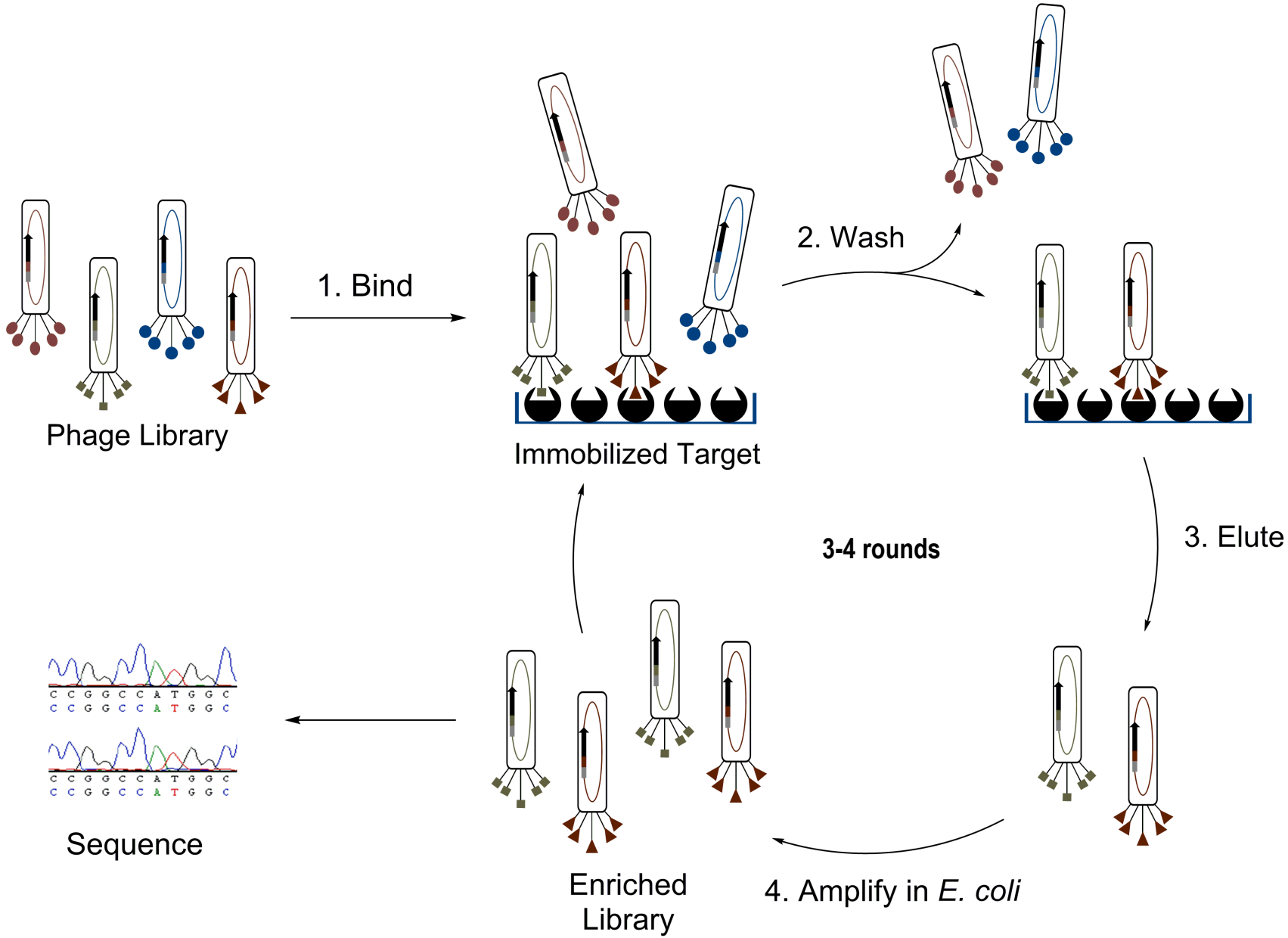


G.P. Smith, 1985

Different Displays



Directed Evolution of Phage-Displayed Peptides



Chem. Rev. **1997**, *97*, 391-410.

Novel Drug Discovery Concepts

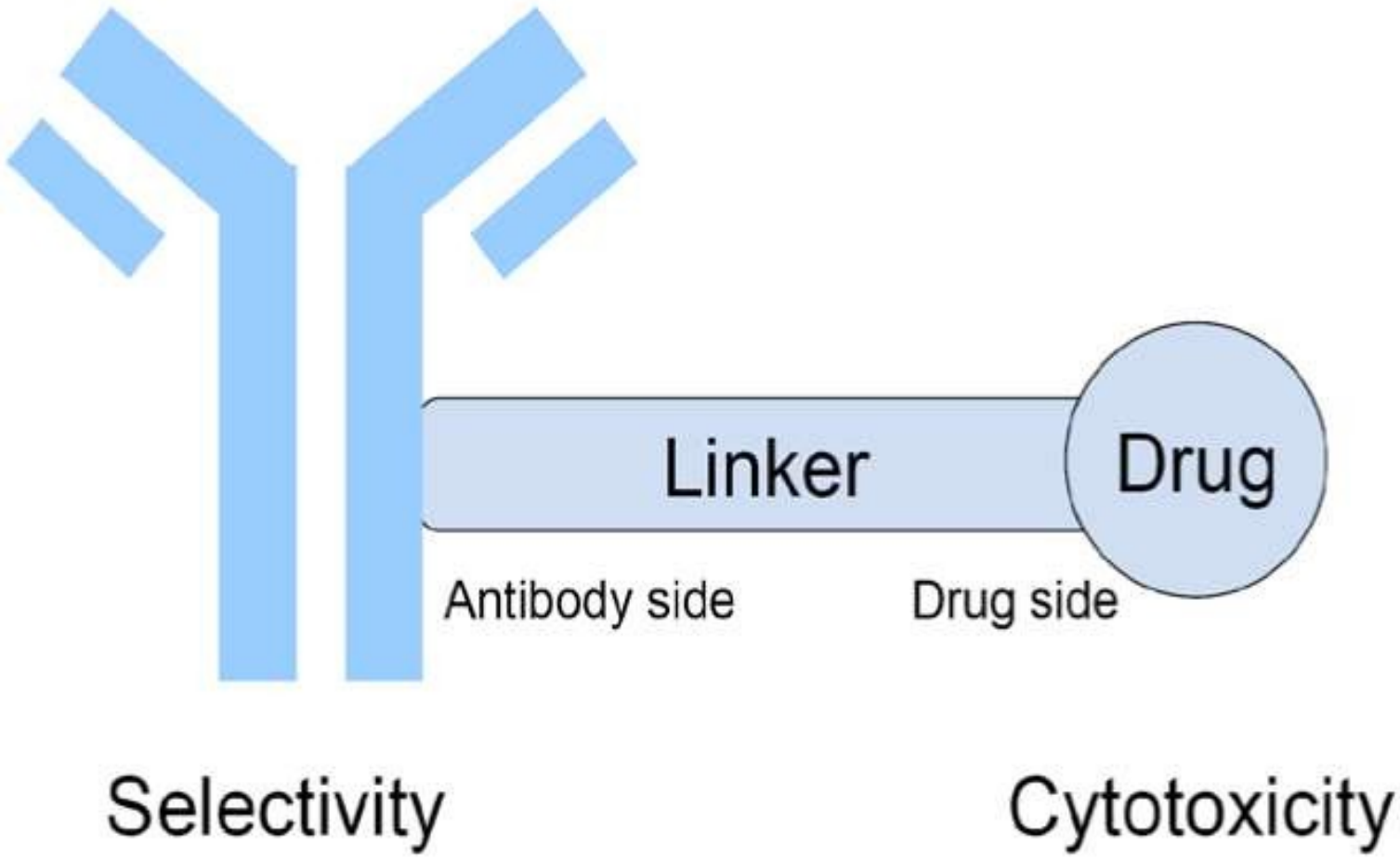
1. Antibody-drug conjugates (more than a decade old)

2. Covalent inhibitors (long existant but not appreciated)

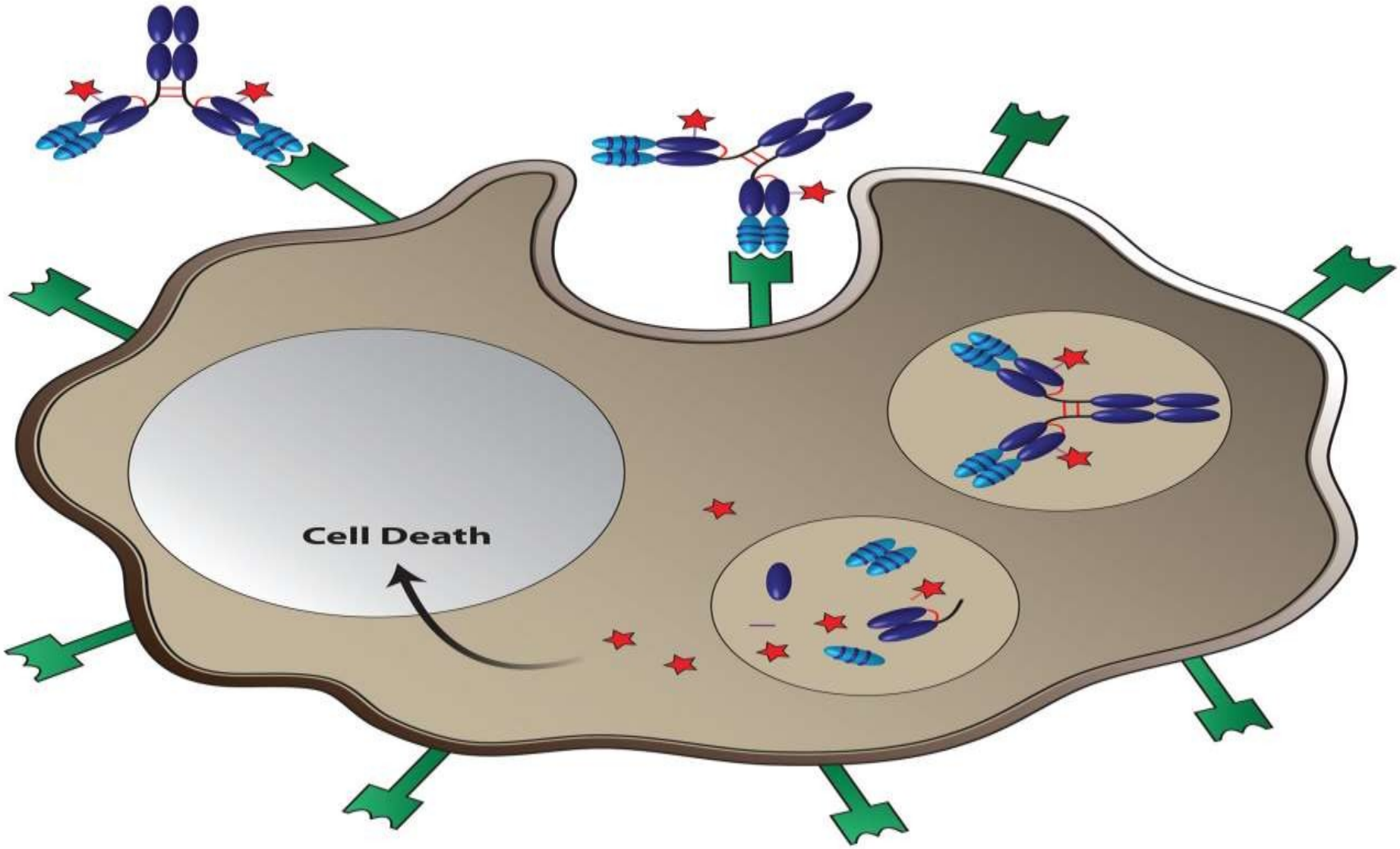
3. PROTACs (more than a decade old and all of sudden popular)

4. CAR-T (chimeric antigen receptor T cell therapy)

Antibody-Drug Conjugates

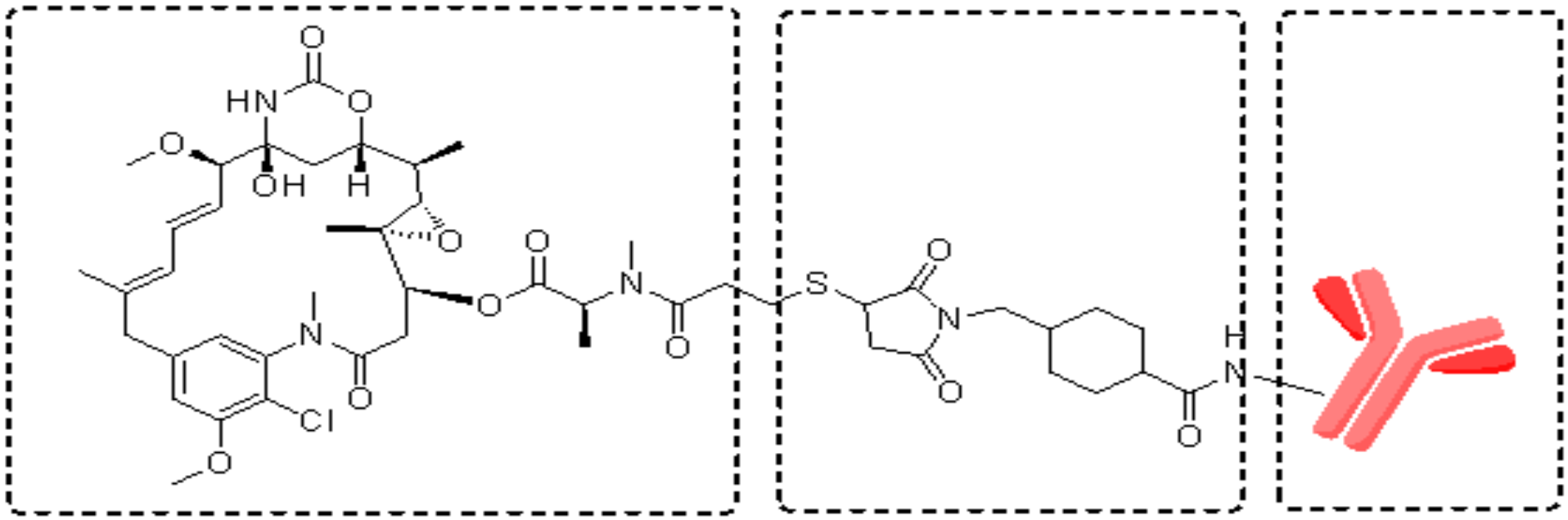


Antibody-Drug Conjugates

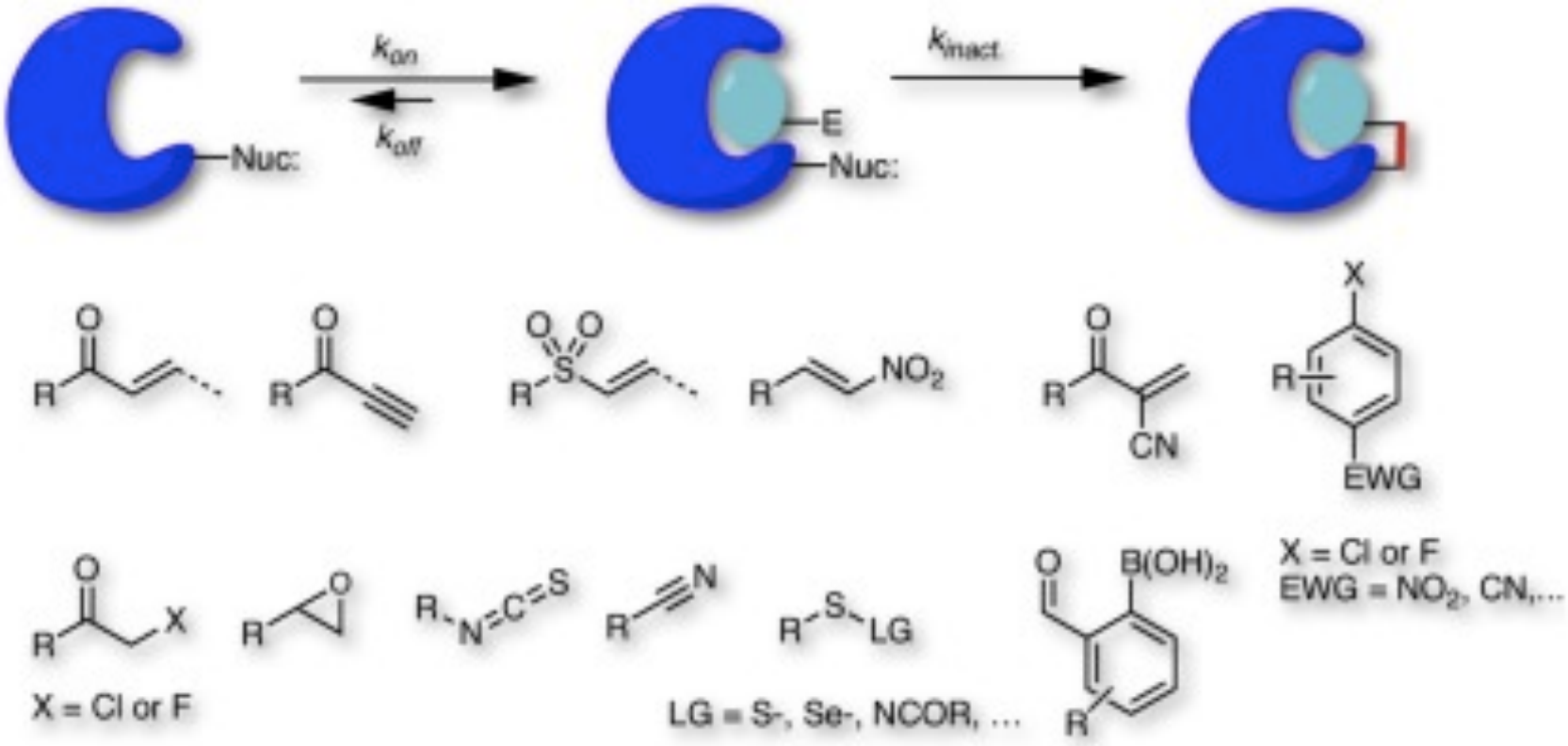


Mechanism of Action

Antibody-Drug Conjugates

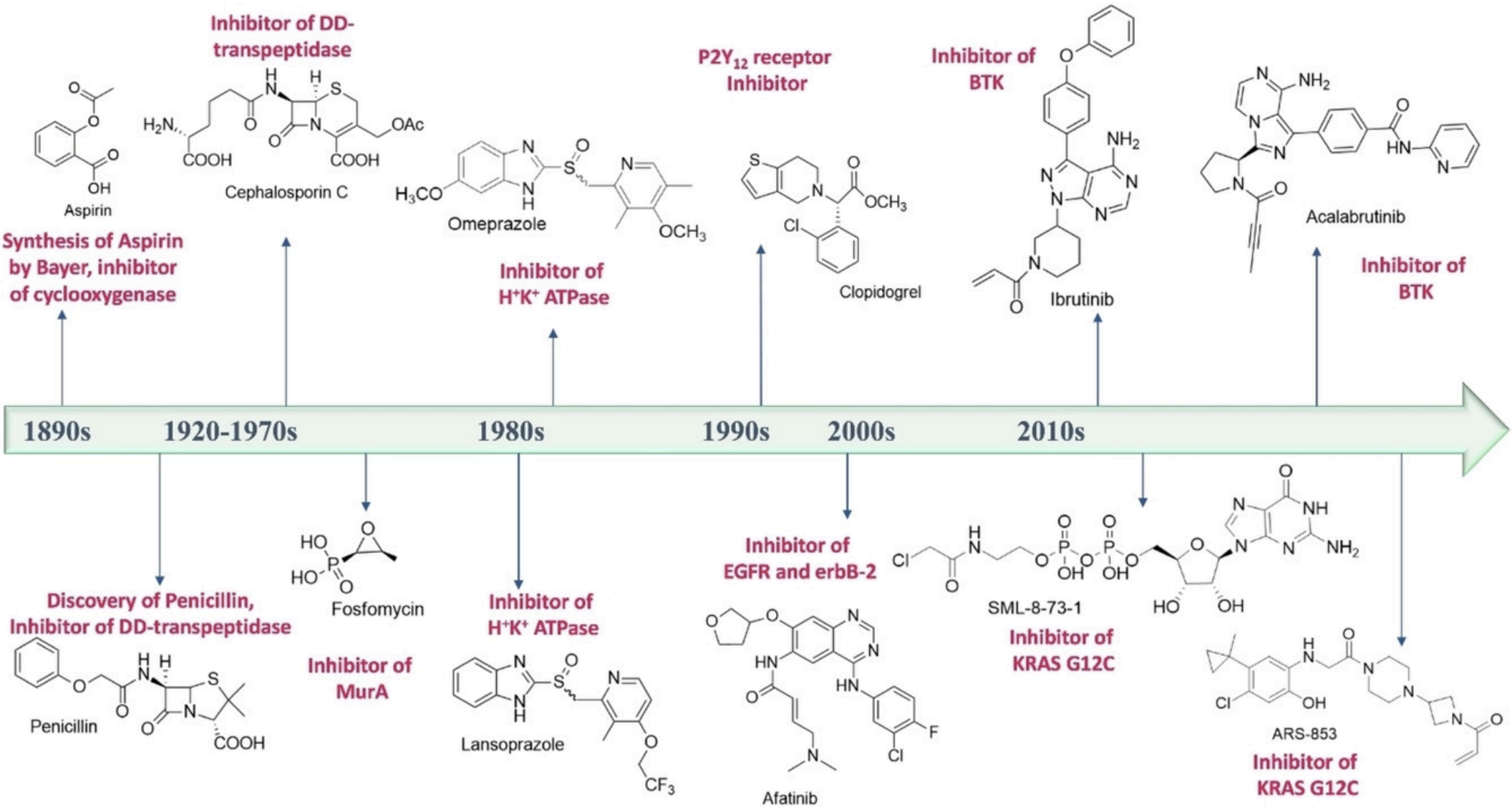


Covalent Inhibitors



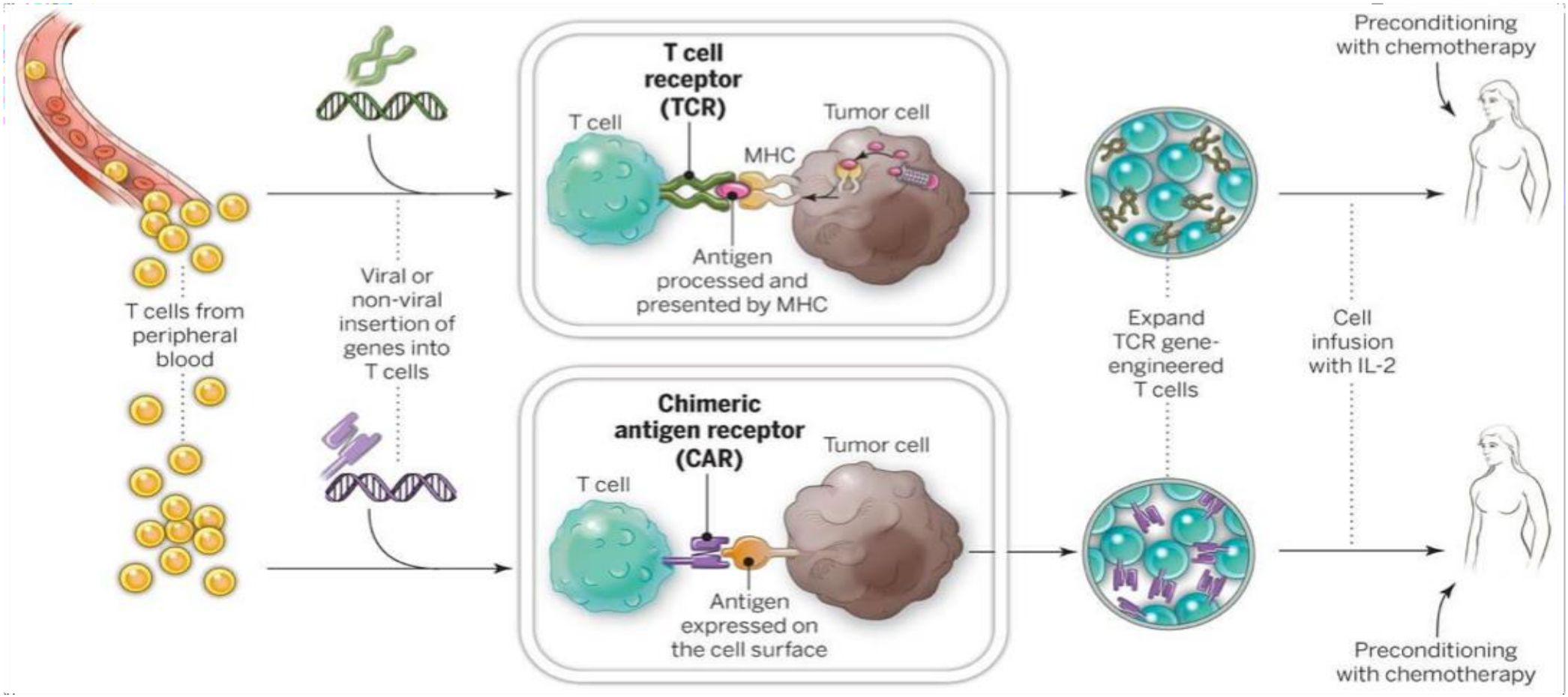
Curr Opin Chem Biol 2017, 39: 54-63

Covalent Inhibitors



ChemMedChem 2019, 14: 889-906

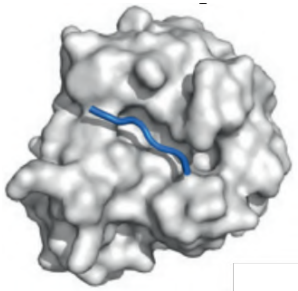
Chimeric Antigen Receptor T Cell Therapy



Approved CAR-T therapies: Kymriah for lymphoma, Yescarta for lymphoma, etc.

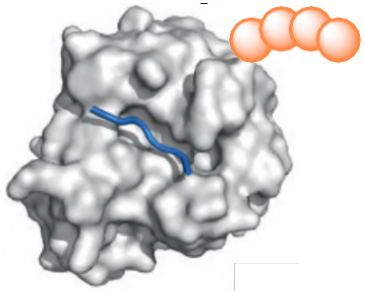
Proteolysis Targeting Chimera (PROTAC)

Ubiquitin–proteasome system

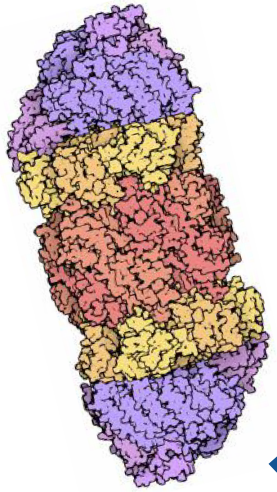


Target protein

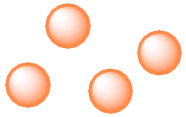
Ubiquitination by
E1, E2, E3 ligases



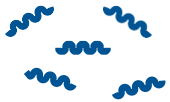
Ubiquitinated protein



Proteasome

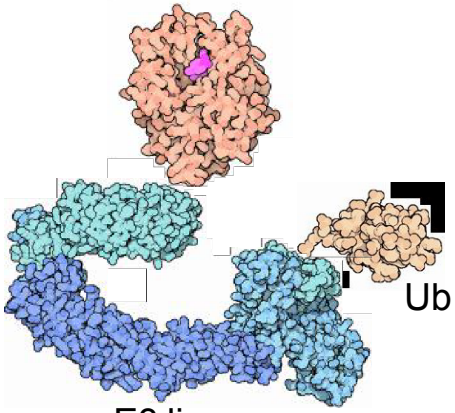


Ubiquitin

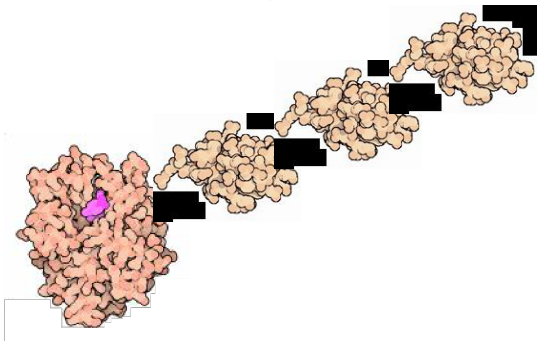


Small peptide

Target protein



E3 ligase

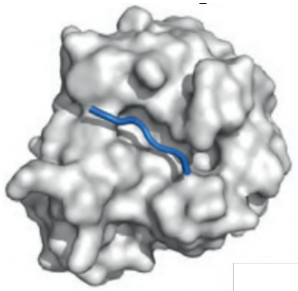


Polyubiquitinated protein

Can we induce artificial interaction between E3 ligase and POI?

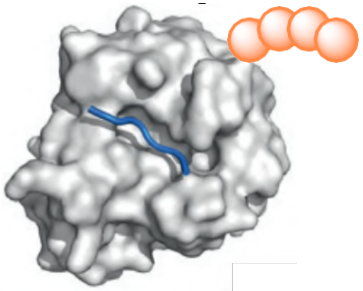
Proteolysis Targeting Chimera (PROTAC)

Ubiquitin–proteasome system

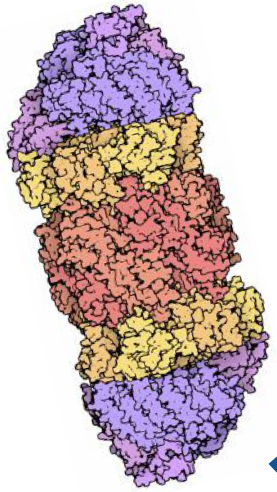


Target protein

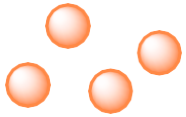
Ubiquitination by
E1, E2, E3 ligases



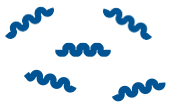
Ubiquitinated protein



Proteasome



Ubiquitin



Small peptide

PROTAC

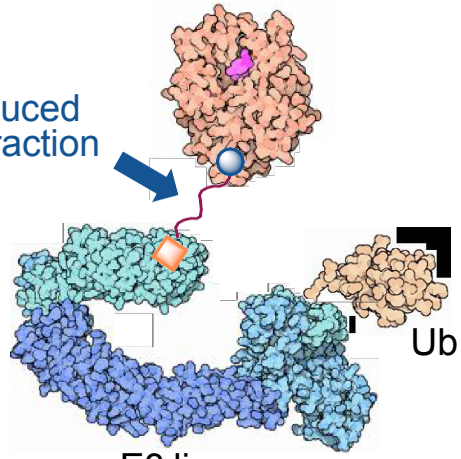
linker

E3 ligase
ligand

Target protein
ligand

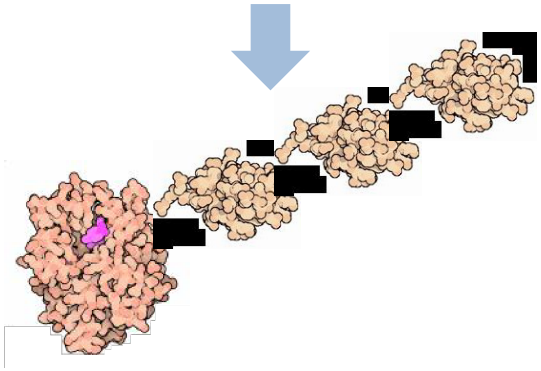
Target protein

Induced
interaction



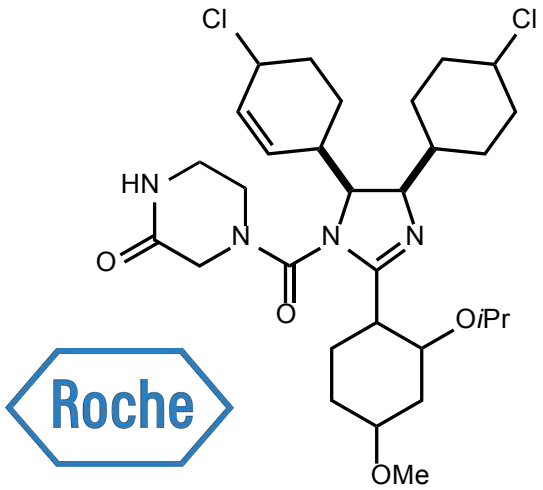
Ub

E3 ligase



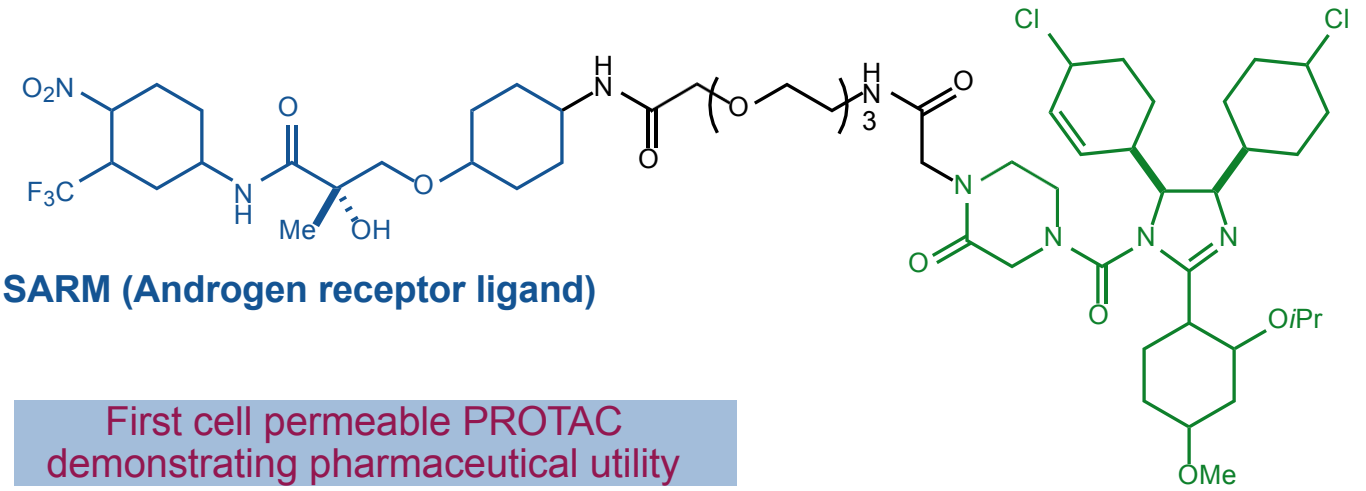
Polyubiquitinated protein

Small Molecule PROTACs



Roche

Nutlin-3 (MDM2 E3 ligase inhibitor)
Science **2004**, 844.



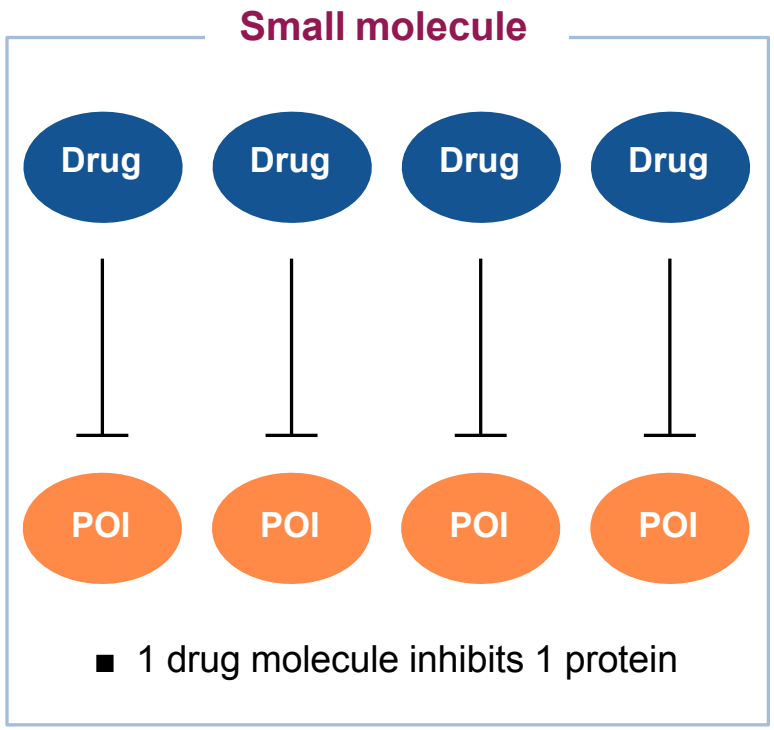
SARM (Androgen receptor ligand)

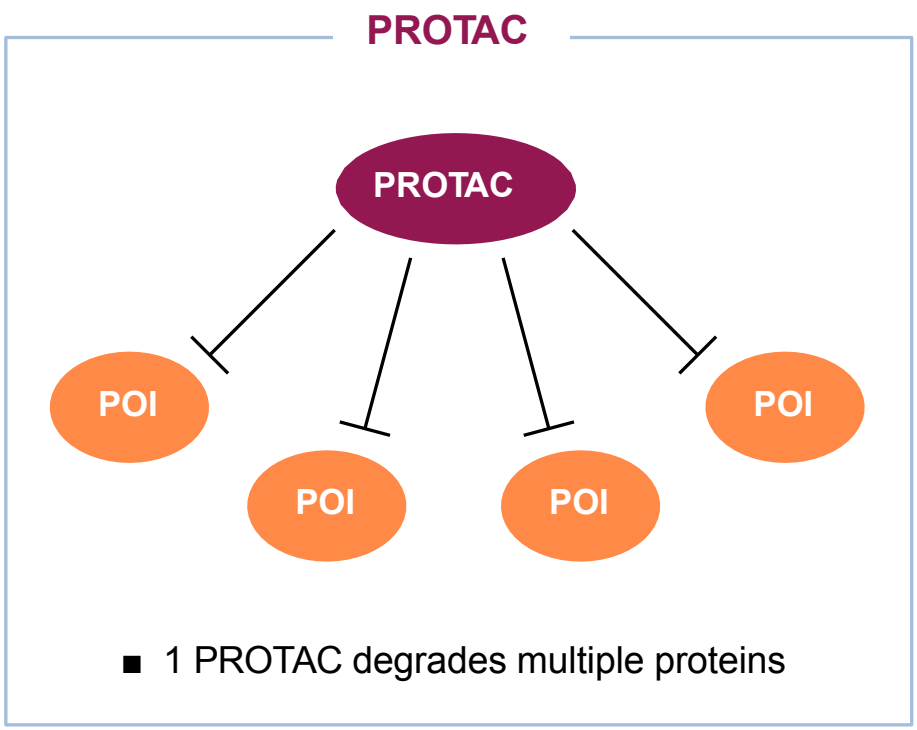
Nutlin-3 (MDM2 ligand)

First cell permeable PROTAC demonstrating pharmaceutical utility

Schneekloth, A.R.; Pucheault, M.; Tae, H.S.; Crews, C.M. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5904–5908.

Small Molecule Drugs v.s. PROTACs



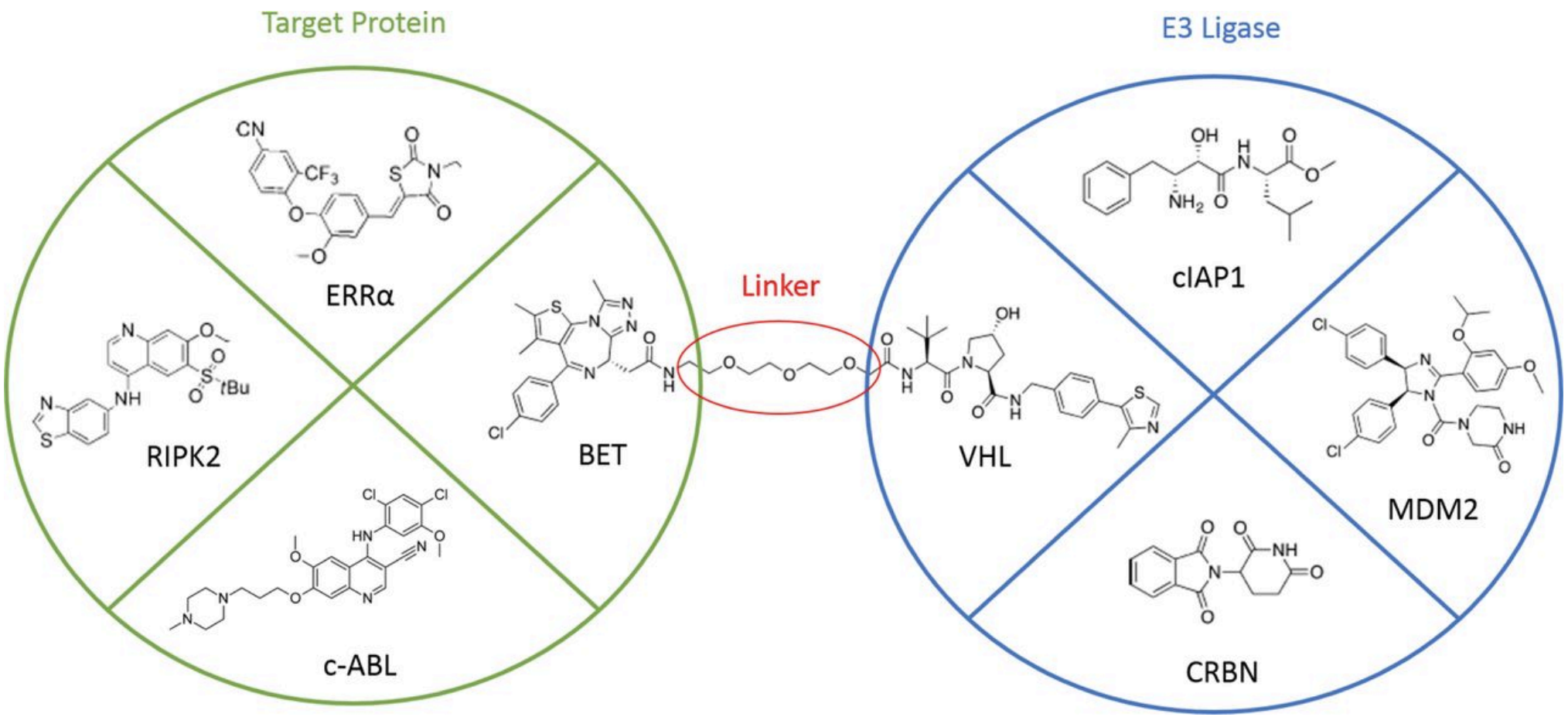


Catalytic mode of action can provide high potency and selectivity

Only affinity probes are required – no need to be inhibitors

Removal of a protein instead of inhibition can provide additional therapeutic effects such as selectivity

E3 Ligands

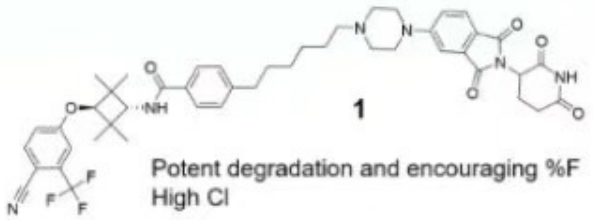

Target Protein
ERRα
BET
RIPK2
c-ABL
Linker
E3 Ligase
cIAP1
MDM2
VHL
CRBN

PROTACs on Clinical Trials (Arvinas)

Evolution of AR Degrading PROTACs Leading to ARV-110

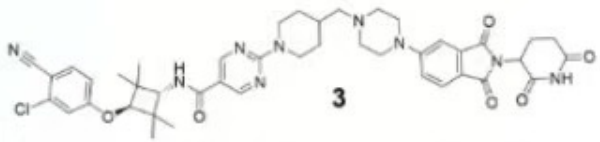
American Association for Cancer Research
FINDING CURES TOGETHER

Early Discovery Efforts
Multiple E3 recruiting ligands
Multiple AR binders



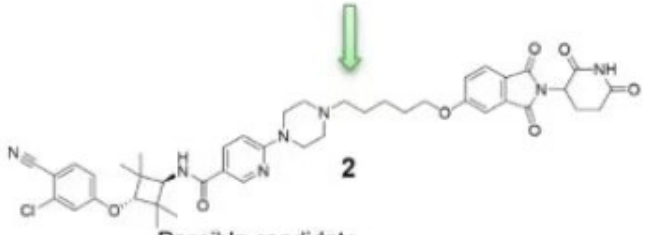
1

Potent degradation and encouraging %F
High Cl



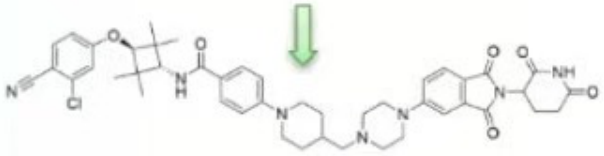
3

Good in vitro degradation potency
Possible autoinduction signal
AR ligand by itself agonist
In vivo potency superseded by **4**



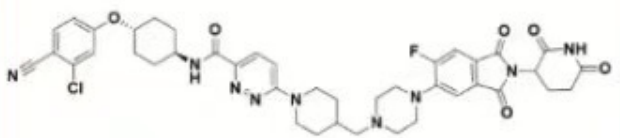
2

Possible candidate
In vivo potency suboptimal
Crystallized to high melting solid



4

Possible candidate
Dose escalation exposure suboptimal



ARV-110

PROTACs on Clinical Trials

ARV-110 is a Potent and Selective Degrader of AR in Vcap Cells

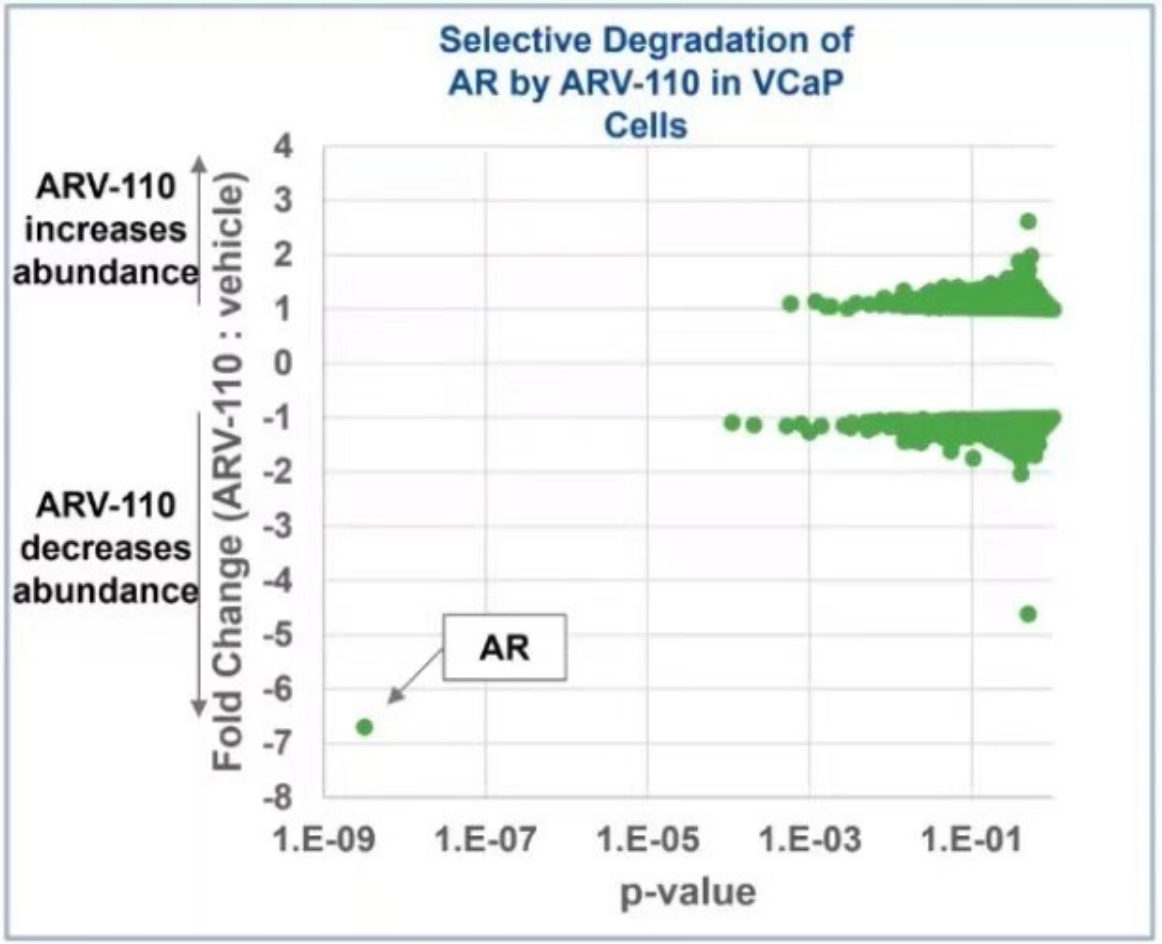
American Association for Cancer Research
FINDING CURES TOGETHER

Orally bioavailable androgen receptor-targeted PROTAC protein degrader

- ARV-110 is in development for the treatment of men with mCRPC who have progressed on abiraterone and/or enzalutamide
- Appears to overcome mechanisms of resistance to current standards of care
- **DC_{50} = 1 nM** in VCaP cells[1]

ARV-110 Selectively Degrades AR

- After 8 hours of treatment of VCaP cells with 10 nM ARV-110 *in vitro*, AR was the only degraded protein among the nearly 4,000 proteins measured
  - 85% D_{max}[2]
  - p-value: $3x10^{-9}$



1 VCaP, Vertebral Cancer of the Prostate
2 D_{max}, maximal degradation

PROTACs on Clinical Trials

ARV-110 Demonstrates Efficacy and Plasma PSA Reduction in an Enzalutamide-Insensitive PDX Model

AACR American Association for Cancer Research
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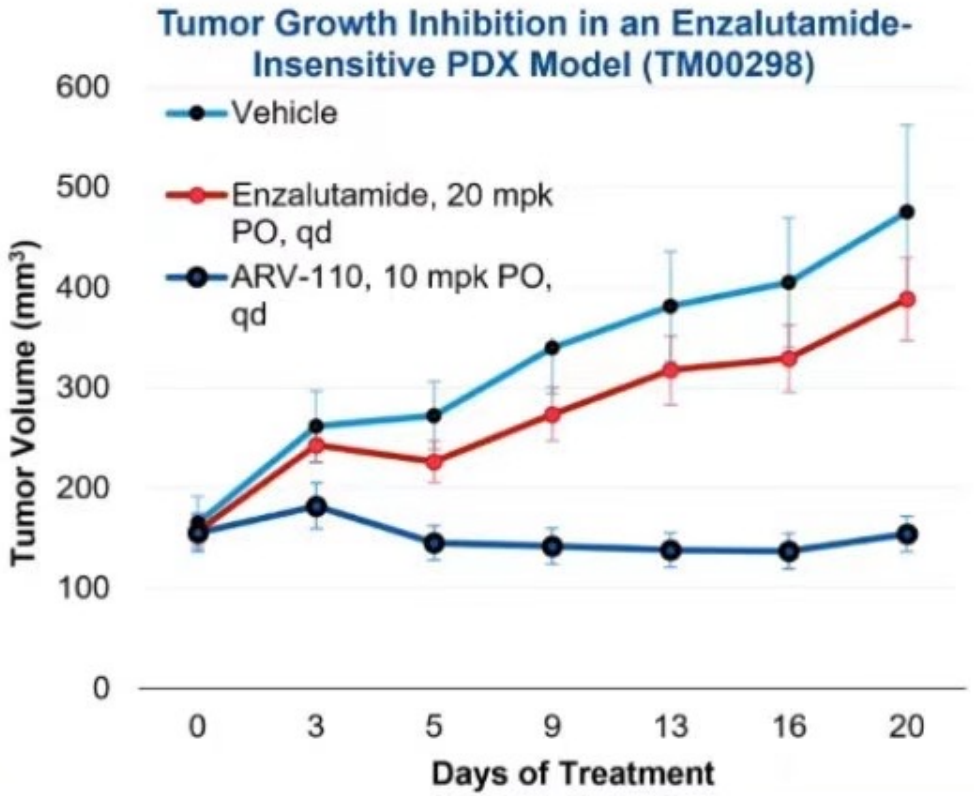
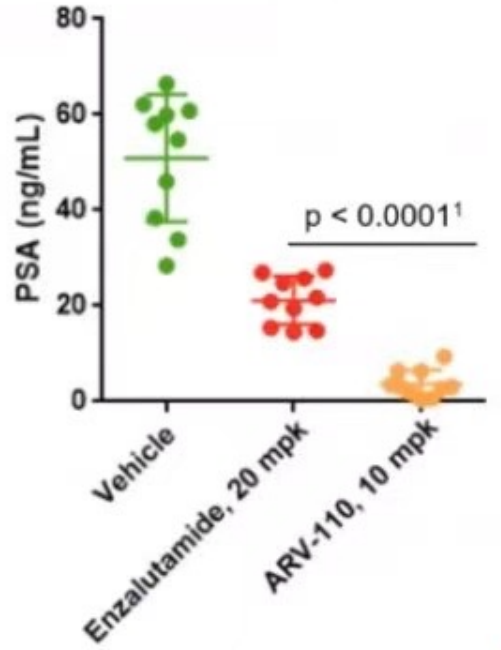
- Orally delivered ARV-110 significantly inhibited tumor growth in these enza-insensitive tumors (TGI: 100%)



- Plasma PSA levels following ARV-110 treatment significantly decreased vs. mice treated with vehicle or enzalutamide



1 p value refers to ARV-110 vs. enzalutamide

ARVINAS

PROTACs on Clinical Trials

Medicinal Chemistry Driven Evolution Leading to ARV-471

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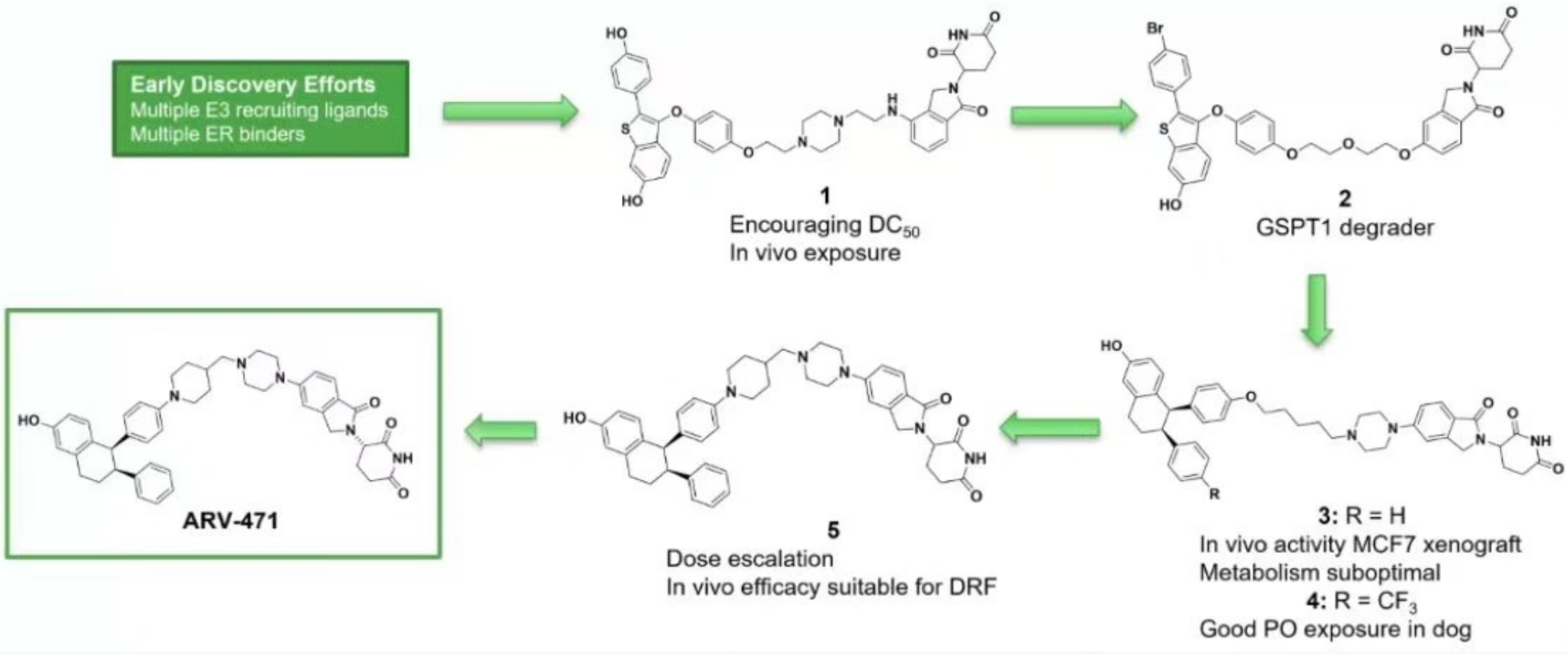

PROTACs on Clinical Trials

In Combination with Palbociclib, ARV-471 Exhibits Superior Tumor Shrinkage Versus Fulvestrant

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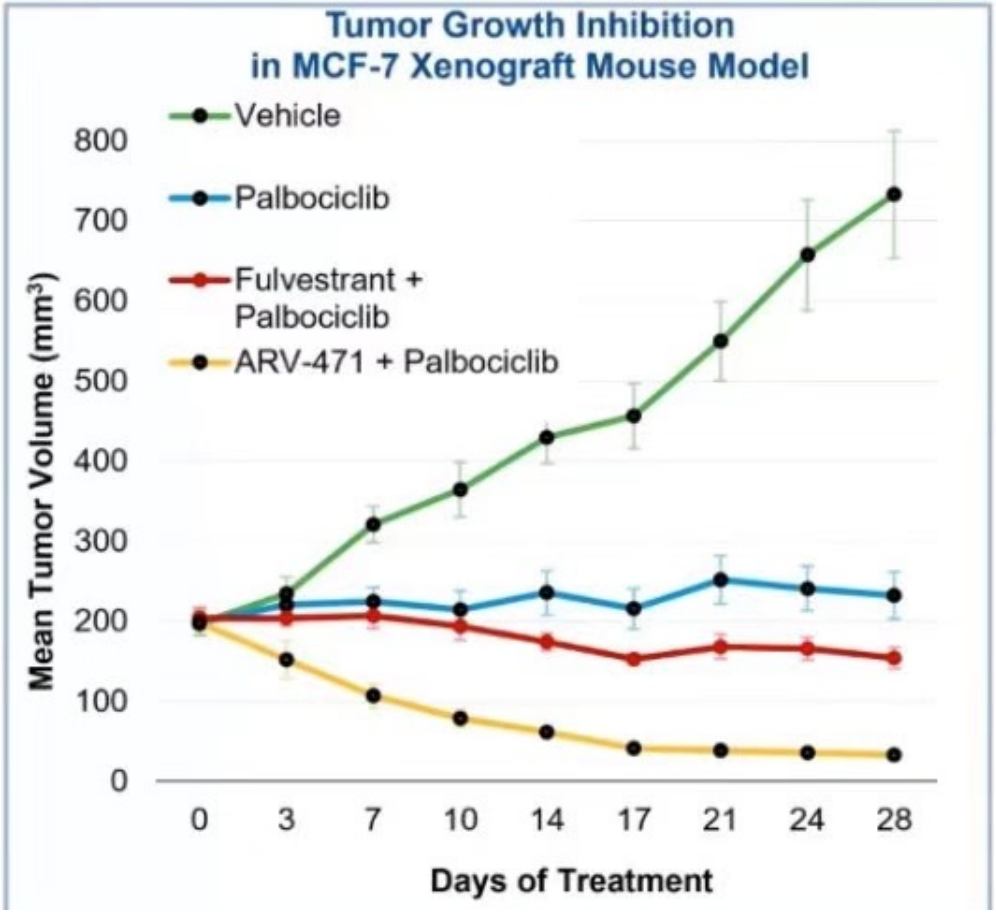
ARV-471 *In Vivo* Preclinical Development

- Achieved significant tumor shrinkage in combination with palbociclib (131% TGI)
  - In all 10 mice in experiment, tumors reduced by >80%
- Superior tumor shrinkage (in combination with palbociclib) compared to fulvestrant (108% TGI)



-Palbociclib arm: 60 mpk po qd; 94% TGI.
-Fulvestrant + Palbociclib arm: Fulvestrant 200 mpk sc biwx 2, qwx 3 + palbociclib 60 mpk po qd; 108% TGI
-ARV-471 + Palbociclib arm: ARV-471 30 mpk po qd + palbociclib 60 mpk po qd; 131% TGI