# Degradation of Oncoprotien using PROTAC Technology & Validation of Anticancer Efficacy *in Vivo*

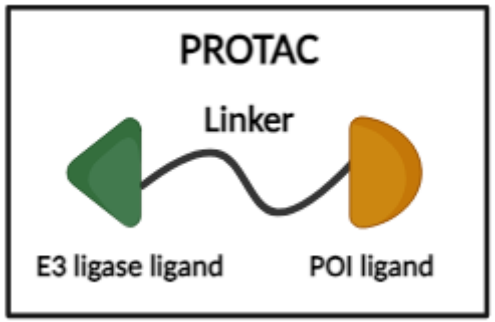
www.sgo.or.kr

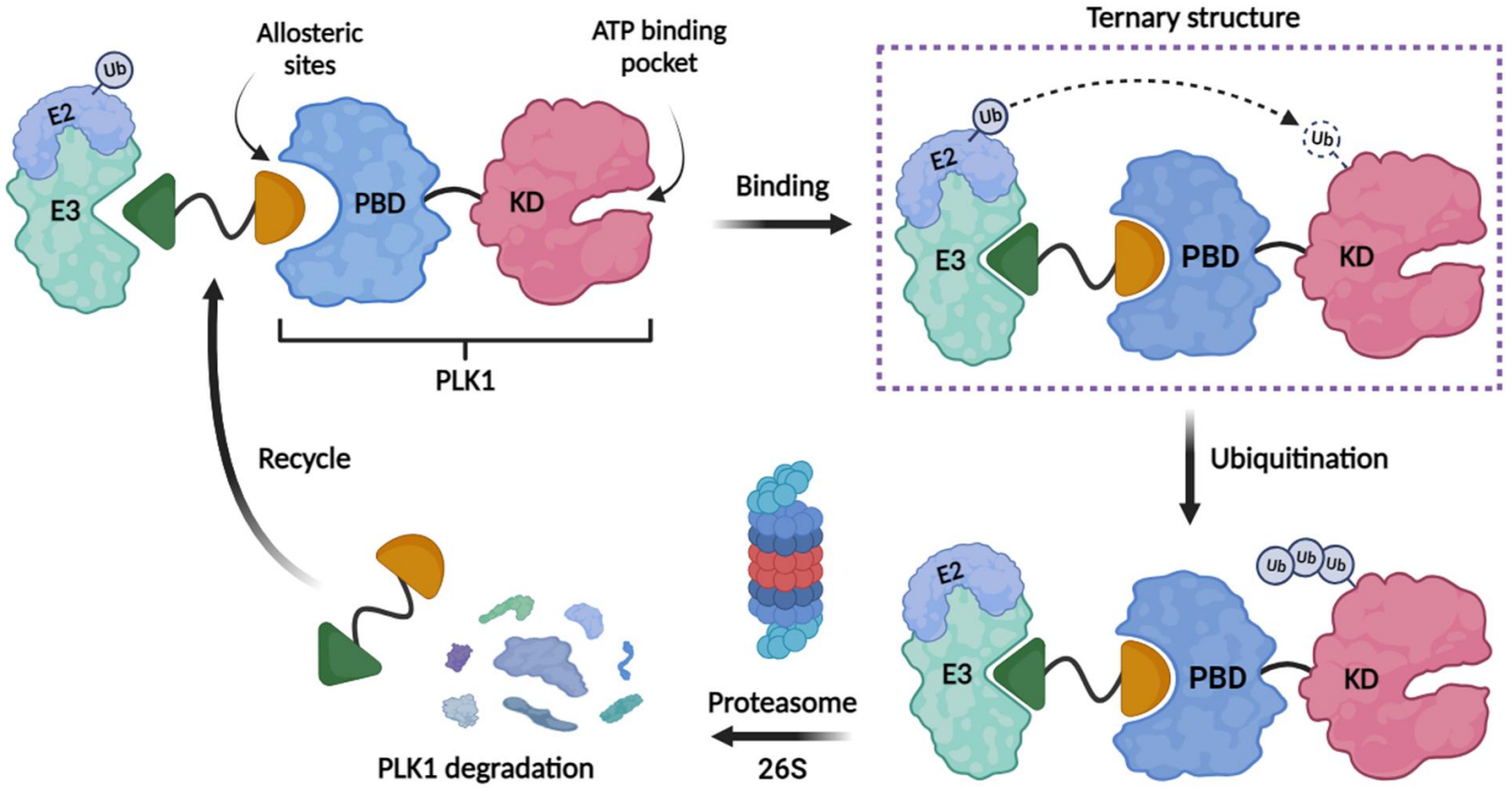


2026. 10. 23

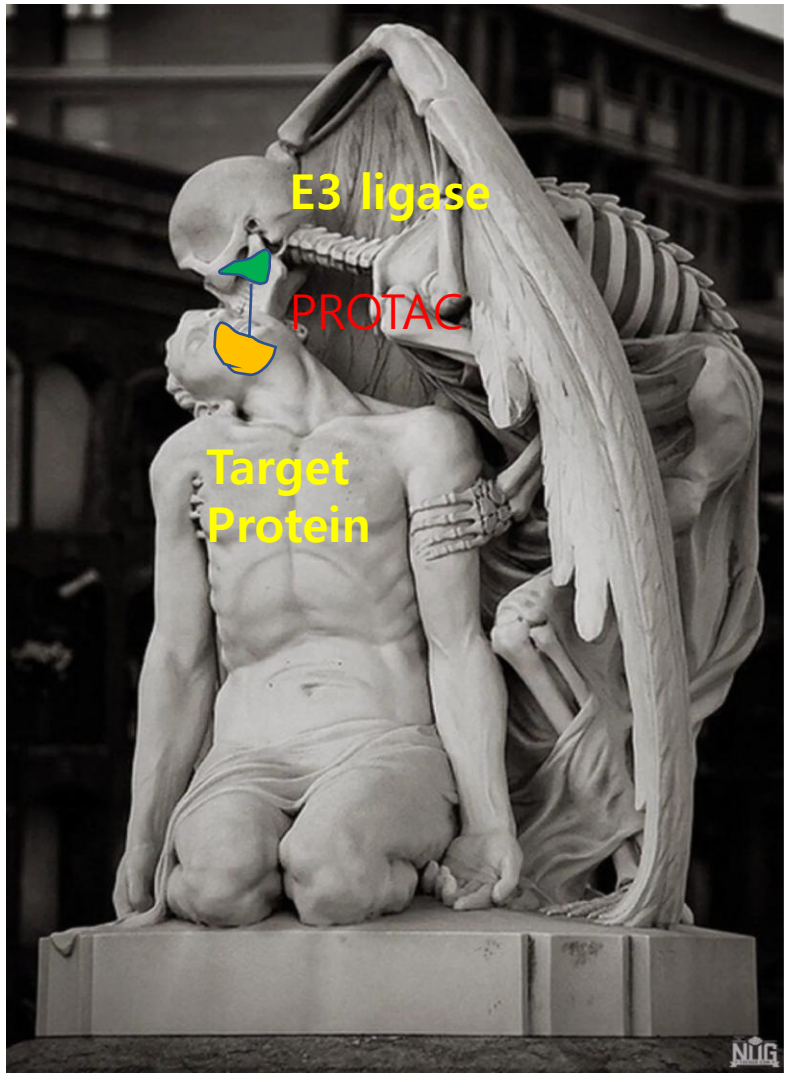
**Jeong Kyu Bang**
(KBSI/ Dandicure Inc.)

# PROTAC(Proteolysis-Targeting Chimera, 표적 단백질 분해 기술)

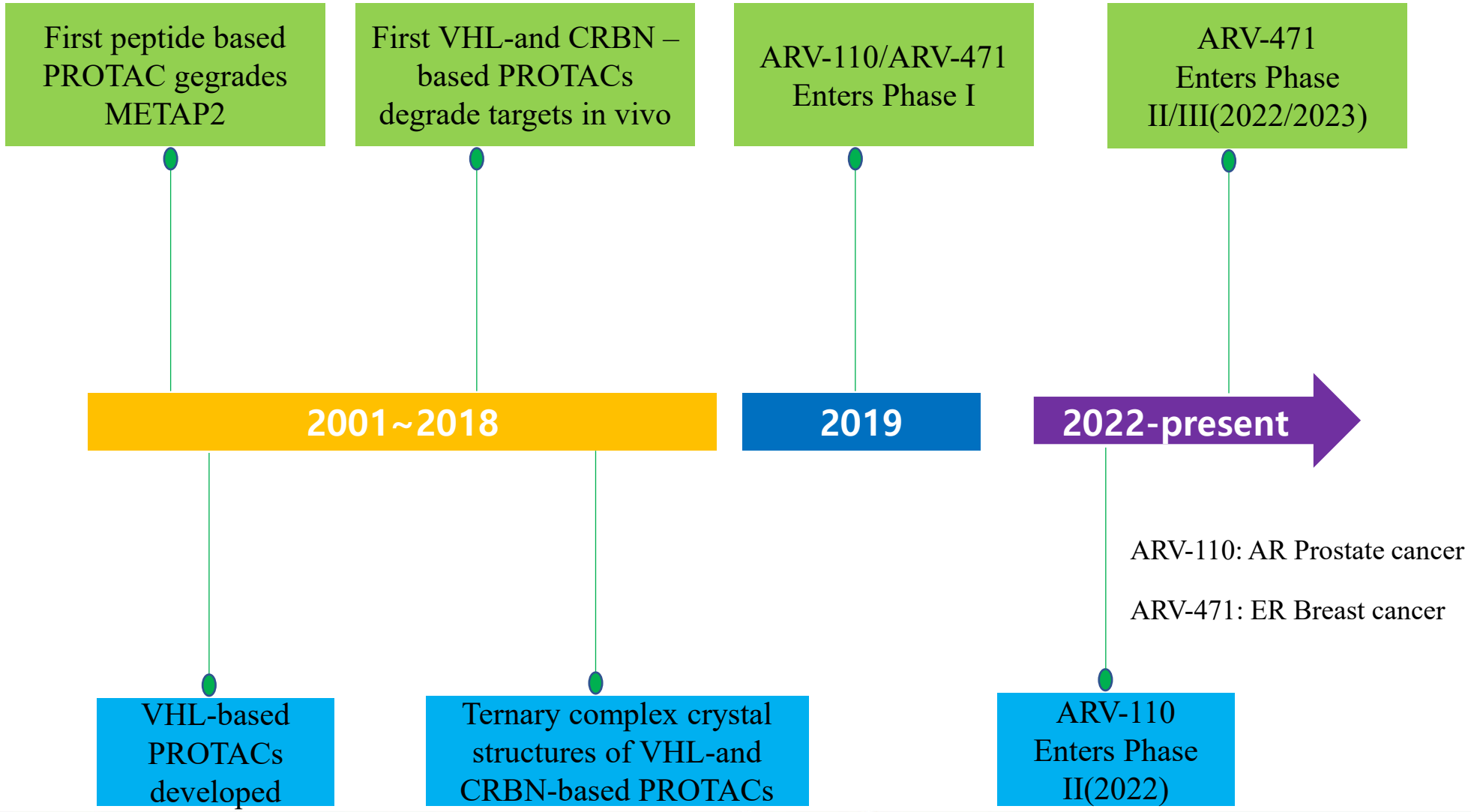


# PROTACs : The Kiss of Death



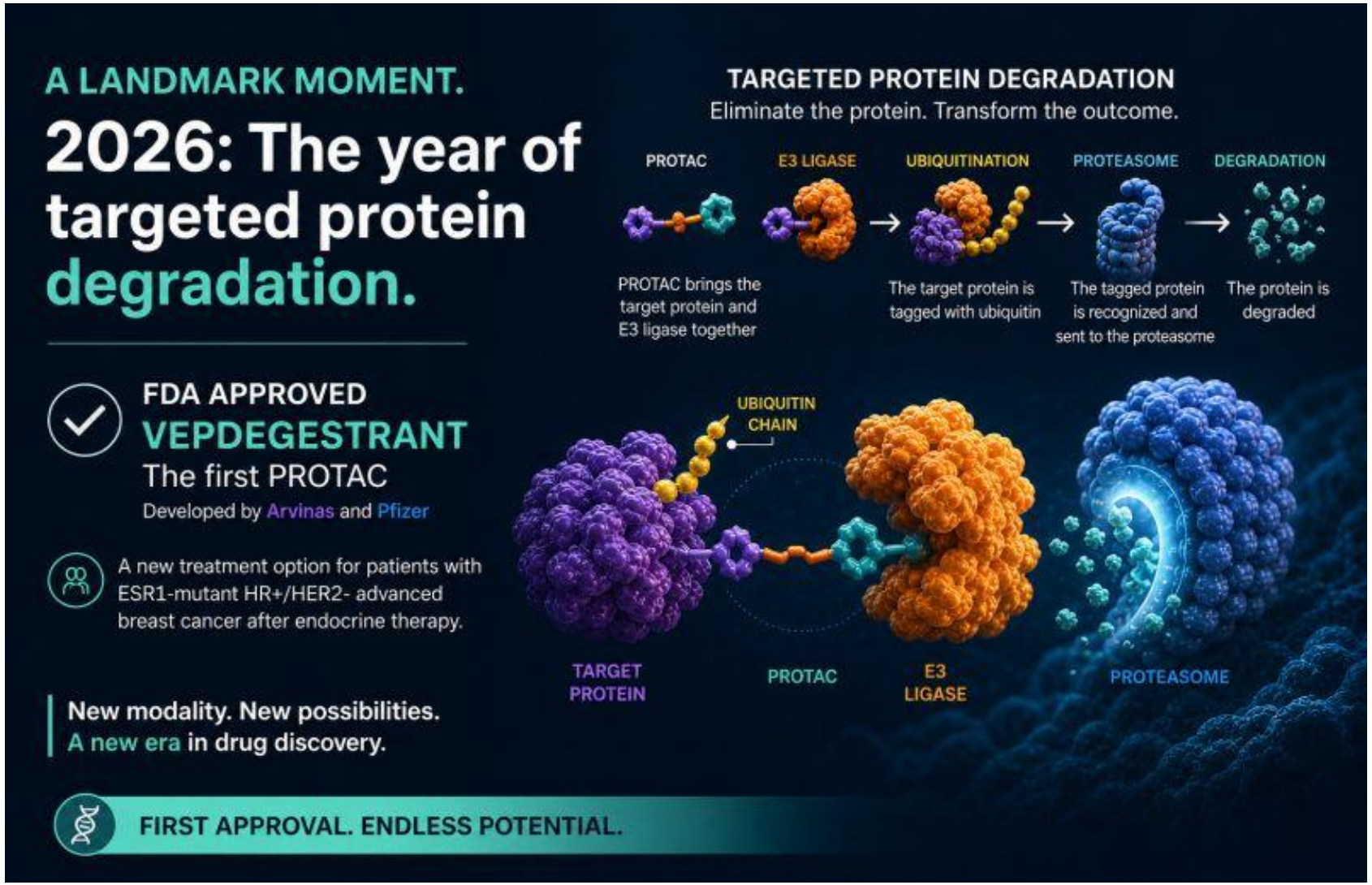
# Timetable: PROTACs



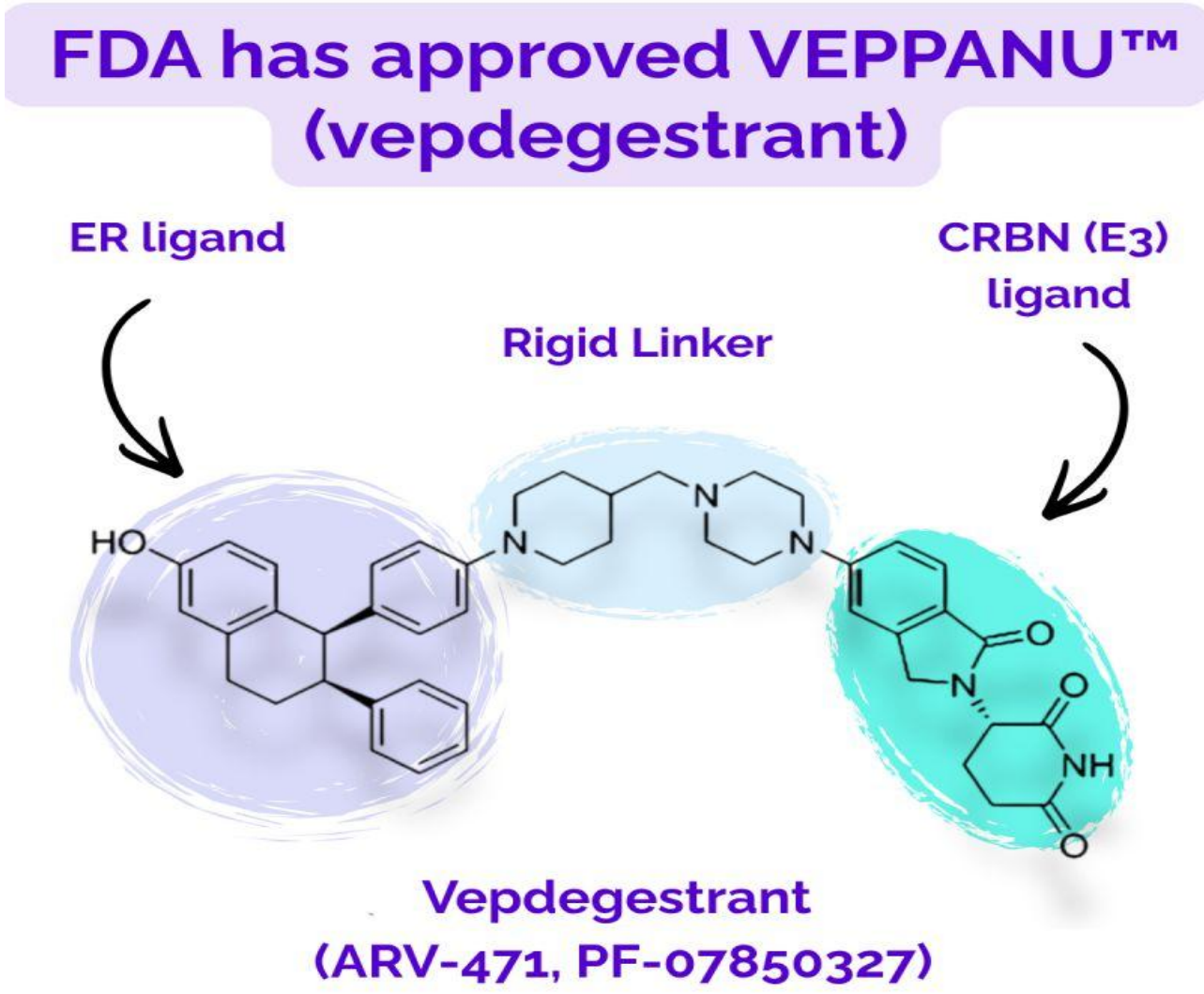
# Timetable: PROTACs

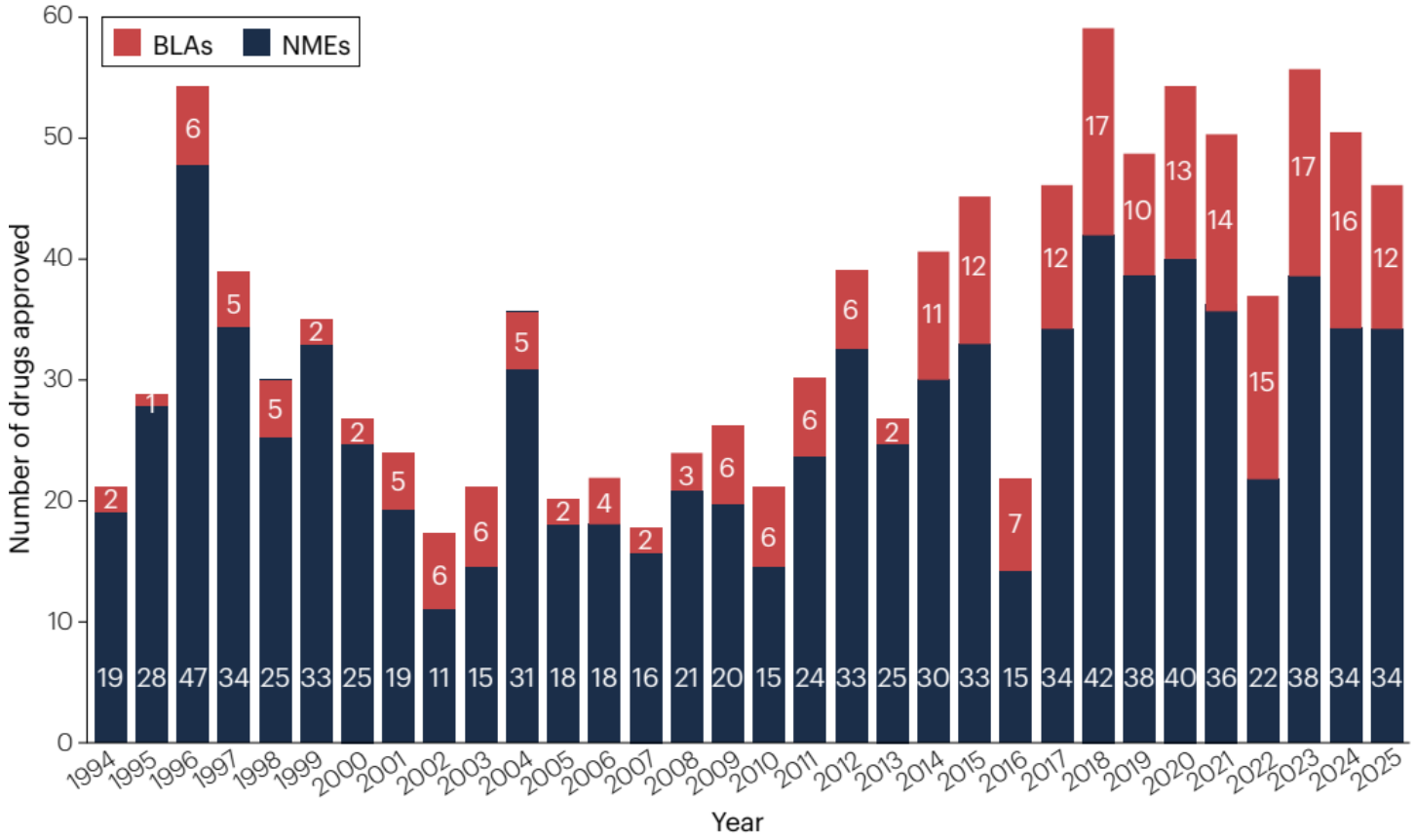


# Timetable: PROTACs

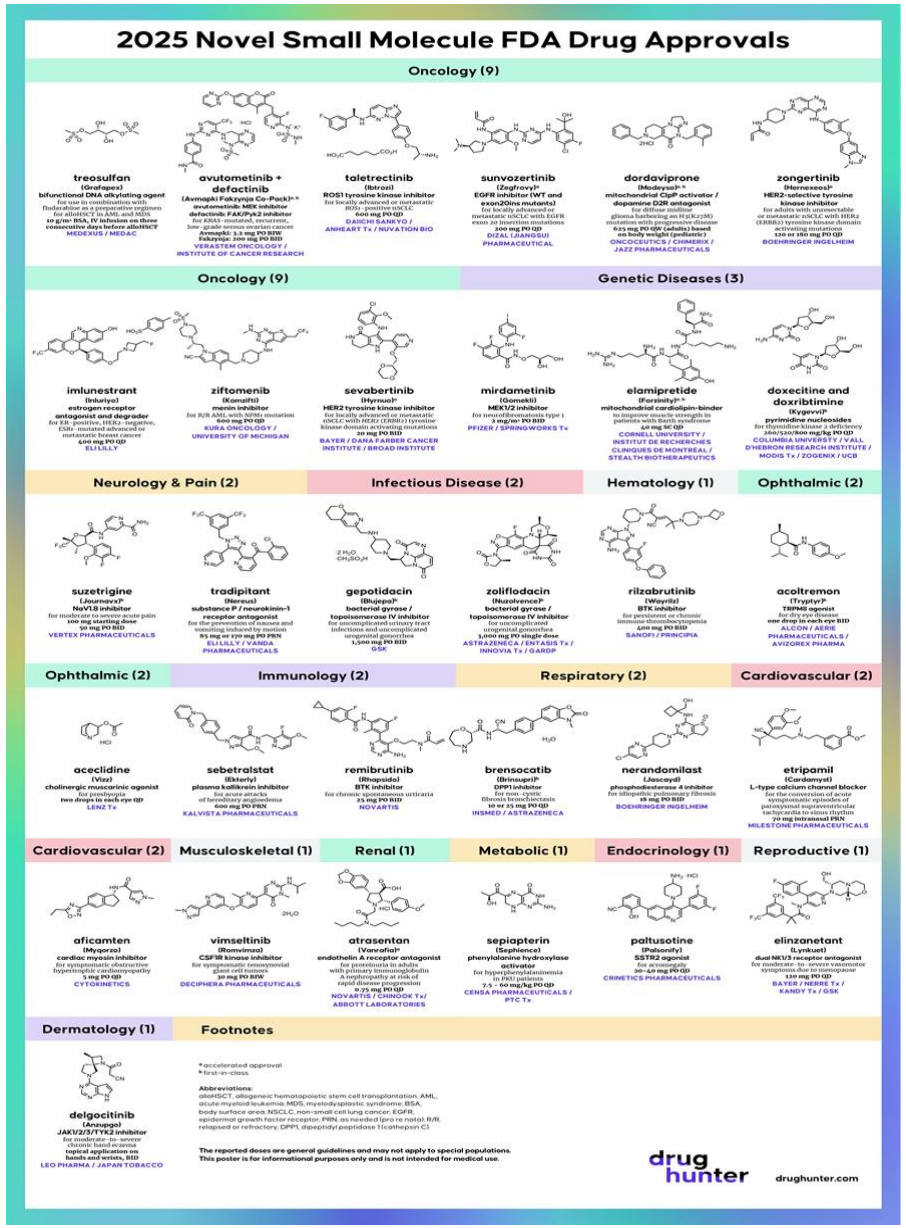


# First PROTAC Drug: VEPPANU

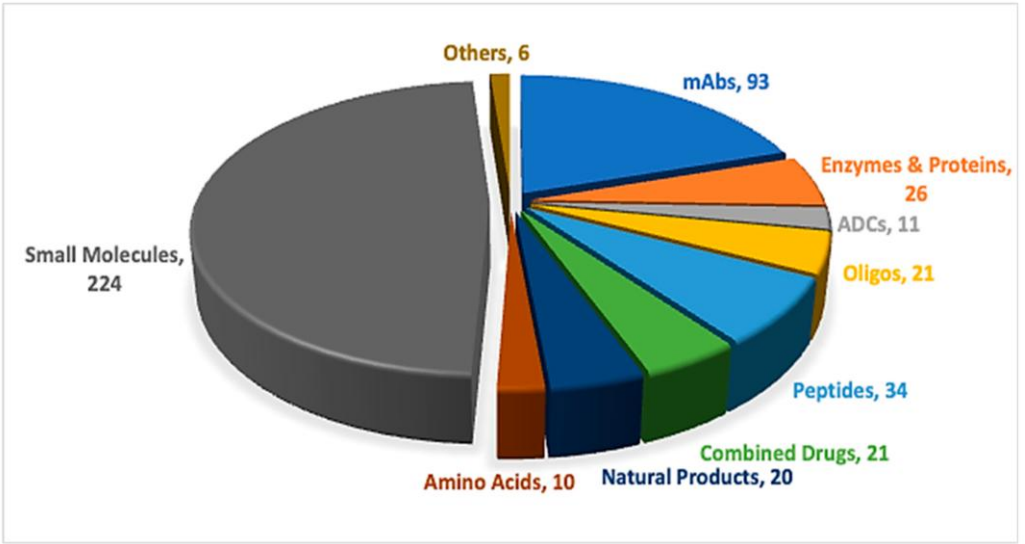





Novel FDA approvals since 1993. Annual numbers of new molecular entities (NMEs) and biologics license applications (BLAs) approved by the FDA's CDER. See Table 1 for new approvals in 2025. Products approved by CBER, including vaccines and gene therapies, are not included in this drug count (Table 2). Source: FDA.




# FDA Approve between 2016 and 2025

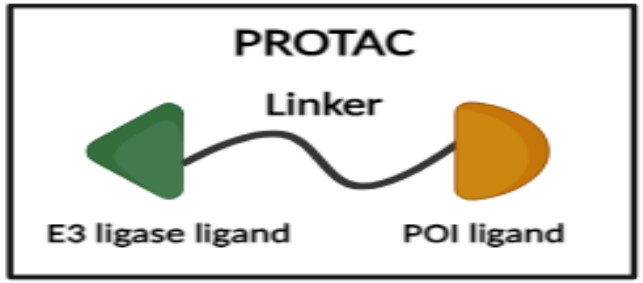



A total of 466 new drugs were approved by the Food and Drug Administration (FDA) between 2016 and 2025 .

ADCs, antibody–drug conjugates; mAbs, monoclonal antibodies; Oligos, oligonucleotides.

***Pharmaceuticals*** **2026,** ***19*****(2), 244**

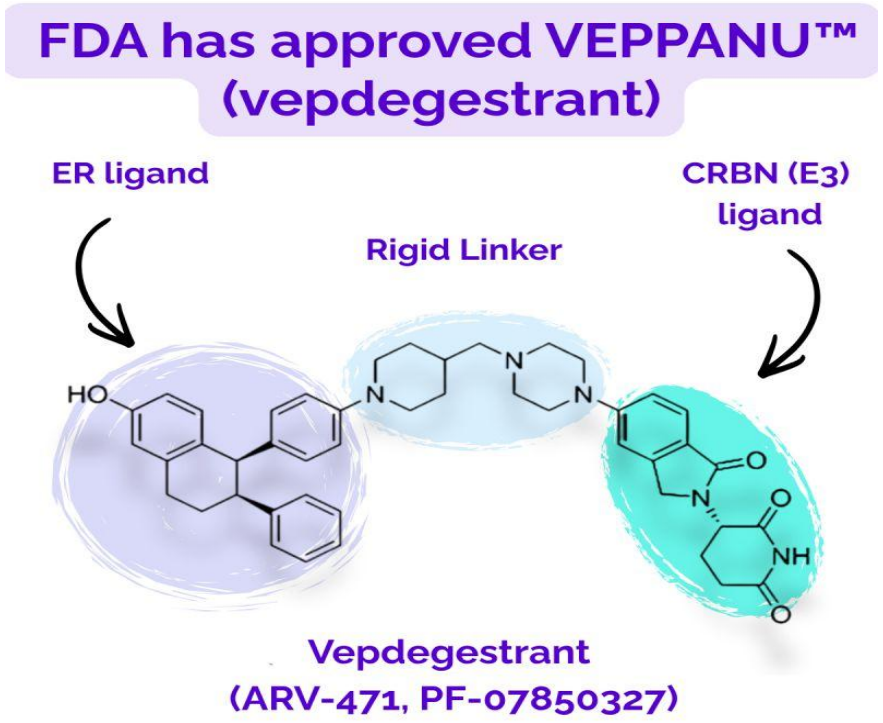
# Why PROTAC ?



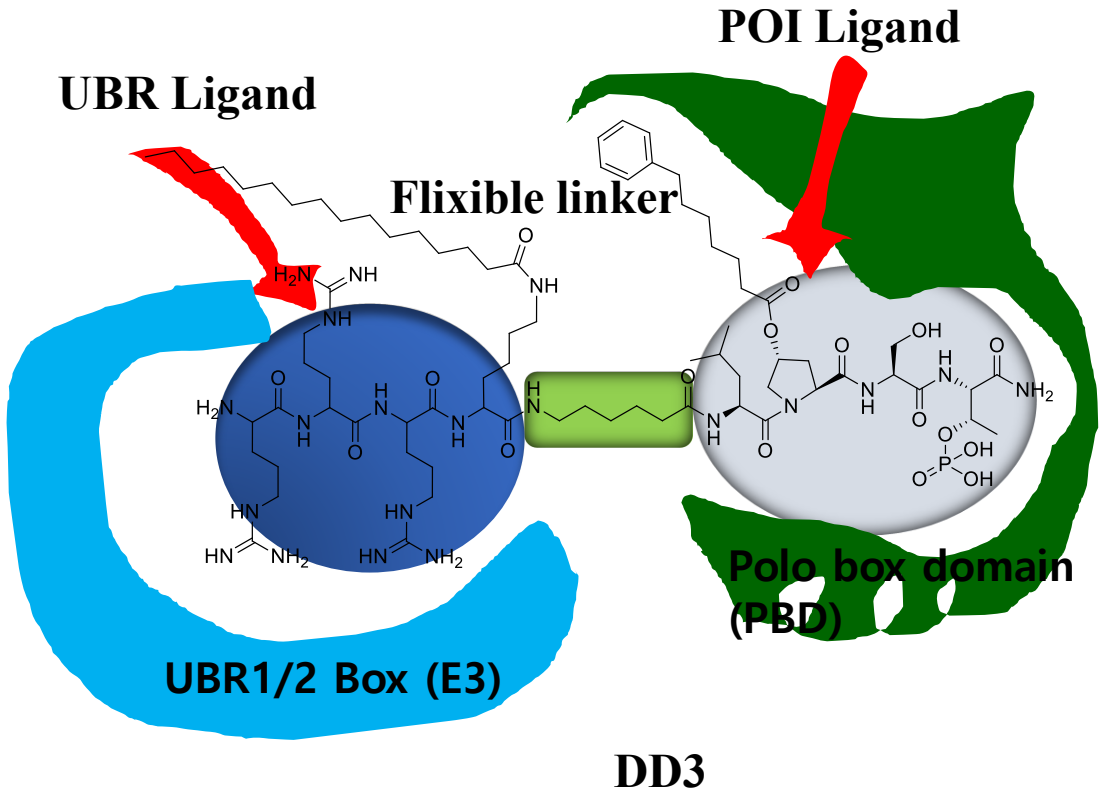

| | Small Molecule | Antibody | RNAi | Cell Therapy | PROTAC |
|---|---|---|---|---|---|
| Removing Disease-Causing Protein(Drug resistanace) | X | X | ● | X | ● |
| Undruggable Target(no binding pocket:Tau/β-amyloid etc) | X | X | ● | ● | ● |
| Oral Bioavailability | ● | X | X | X | ● |
| Cell Permeability | ● | X | X | X | ● |
| Easy to Manufacture | ● | X | X | X | ● |
| Recycle(low dose, high activity) | X | X | X | X | ● |

# DandiCure PROTAC Drug

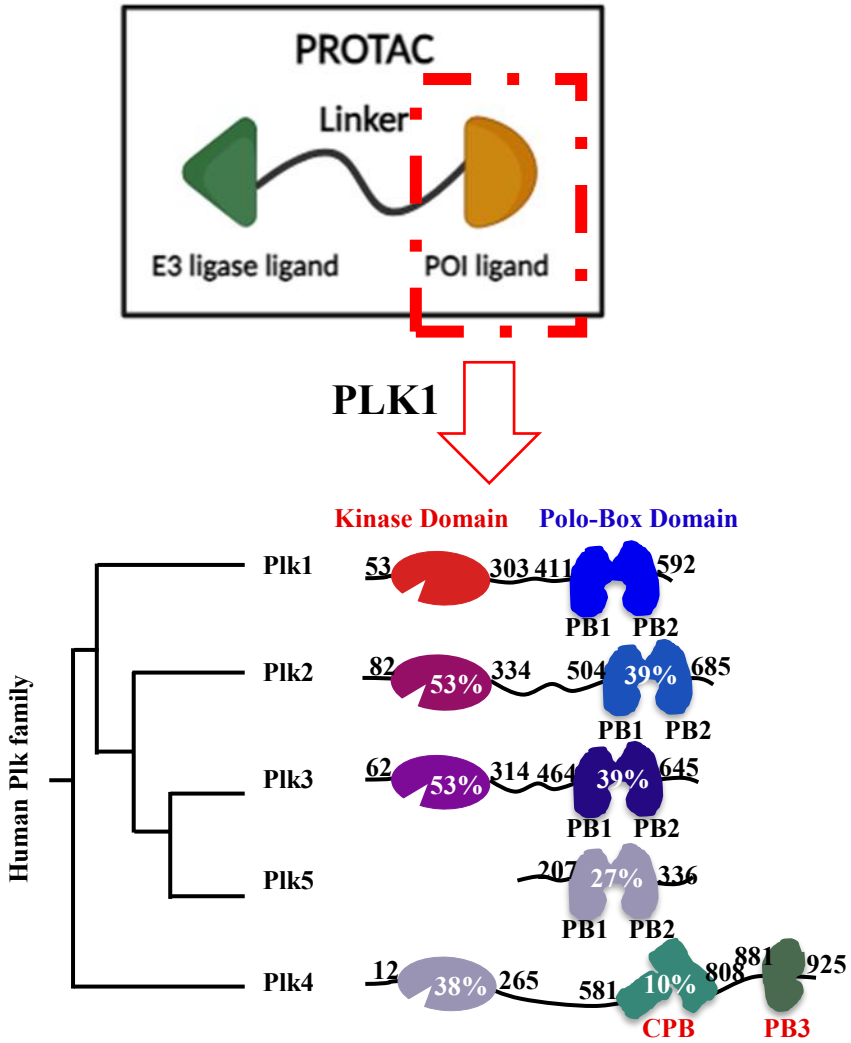
## Arvinas PROTAC




## Dandicure PROTAC



# Polo-like Kinase 1(Plk1) As POI

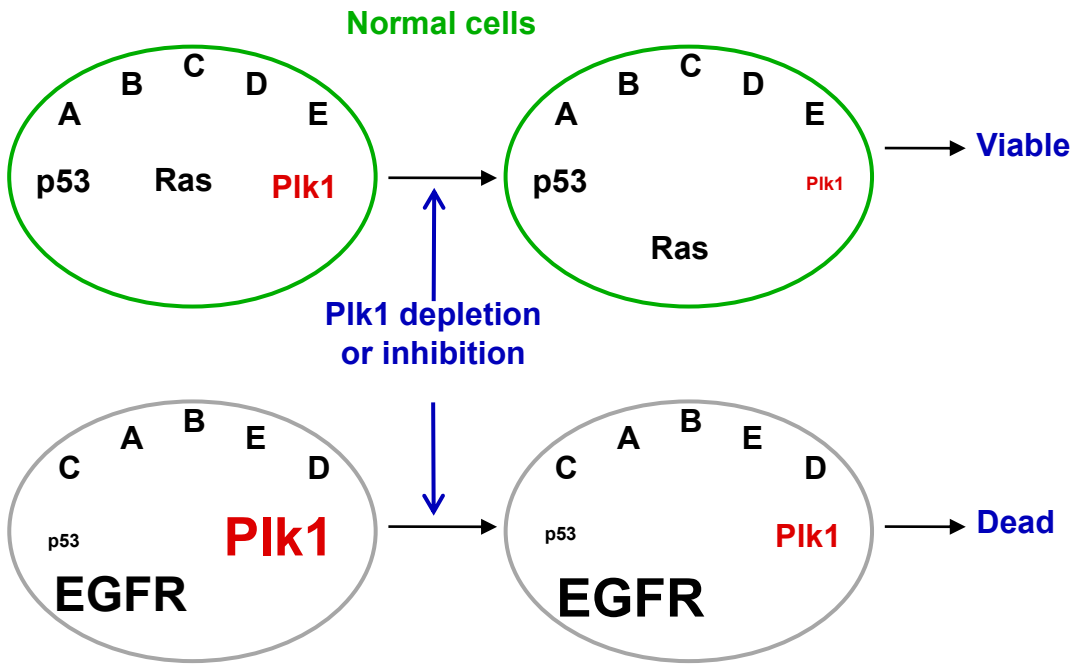



- Ser/Thr protein kinase
- N-term; Kinase domain(KD)
- C-term; Polo-box domain (PBD)
- Multiple form of Plks; Plk1, Plk2, Plk3, Plk4, Plk5
- Plk1/Plk2/Plk3 high homology
- Plk1: overexpression in a broad range of human tumors (~ 80%)
- Plk2, Plk3 : genetic stability and prevent oncogenic trans-formation

**Polo-box domain (PBD): a critical protein-protein interaction domain**

- Binds to various S-pS or S-pT motif-containing proteins
- Essential for subcellular location and mitotic function of Plk1

# Correlation between Cancer and PLK1




Cancer cell-selective killing by the reversal of Plk1 addiction

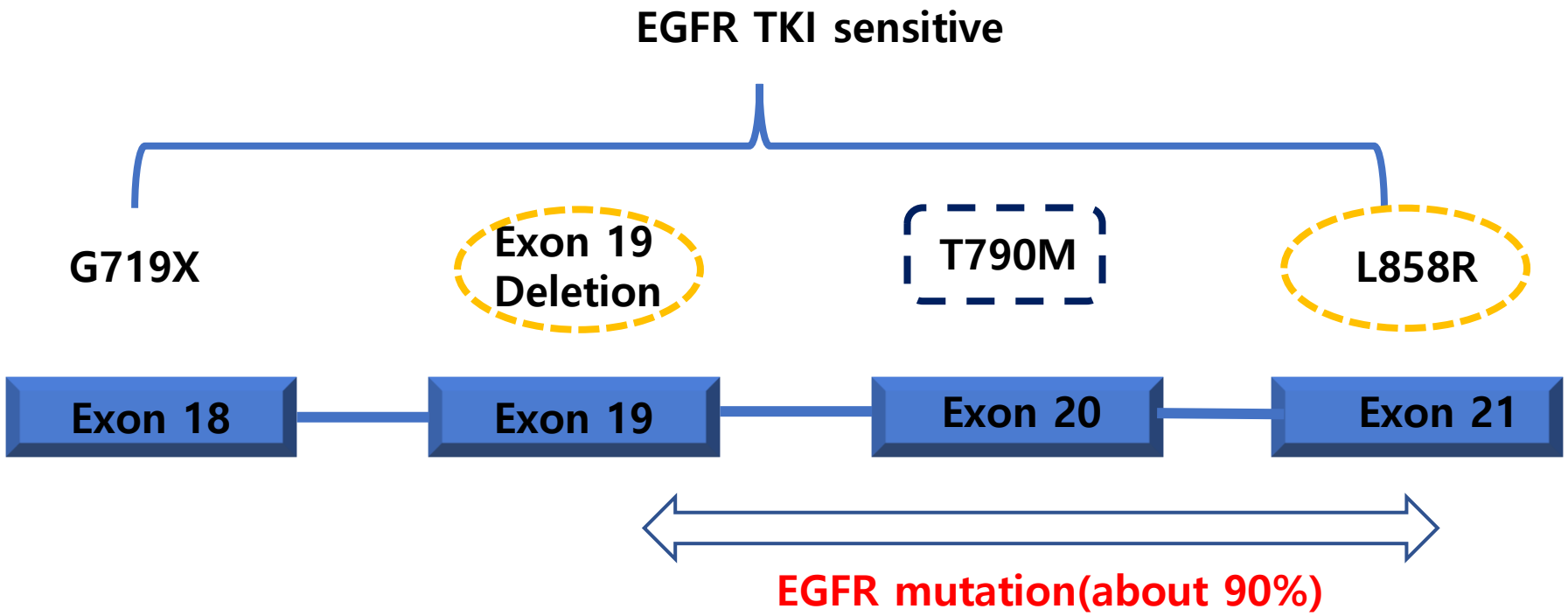
# PLK1 expression in Cancers

**PLK1 expression in cancers**

| Cancer Type | Full Name | P Value | Fold Change* |
|---|---|---|---|
| **LUSC** | **Lung squamous cell carcinoma** | **7.41E-157** | **20.8** |
| **BRCA** | **Breast invasive carcinoma** | **5.88E-126** | **11.3** |
| LUAD | Lung adenocarcinoma | 1.18E-63 | 9.7 |
| KIRC | Kidney renal clear cell carcinoma | 2.33E-55 | 6.1 |
| HNSC | Head and neck squamous cell carcinoma | 6.52E-50 | 4.2 |
| **LIHC** | **Liver hepatocellular carcinoma** | **3.59E-40** | **11.7** |
| **UCEC** | **Uterine corpus endometrial carcinoma** | **1.96E-36** | **21.3** |
| COAD | Colon adenocarcinoma | 5.97E-33 | 2.5 |
| STAD | Stomach adenocarcinoma | 8.45E-27 | 4.8 |
| ESCA | Esophageal carcinoma | 9.52E-27 | 10.2 |
| BLCA | Bladder urothelial carcinoma | 4.96E-26 | 9.1 |
| PRAD | Prostate adenocarcinoma | 1.29E-22 | 3.3 |
| KIRP | Kidney renal papillary cell carcinoma | 6.76E-22 | 4.7 |
| **CHOL** | **Cholangiocarcinoma** | **6.97E-14** | **24.3** |
| **GBM** | **Glioblastoma multiforme** | **5.63E-12** | **12.4** |
| KICH | Kidney chromophobe 1.63E-06 3.3 | 1.63E-06 | 3.3 |
| READ | Rectum adenocarcinoma | 1.06E-05 | 2.3 |
| PAAD | Pancreatic adenocarcinoma | 0.04 | 2.2 |

* Mean PLK1 expression in cancers/mean PLK1 expression in normal tissue.

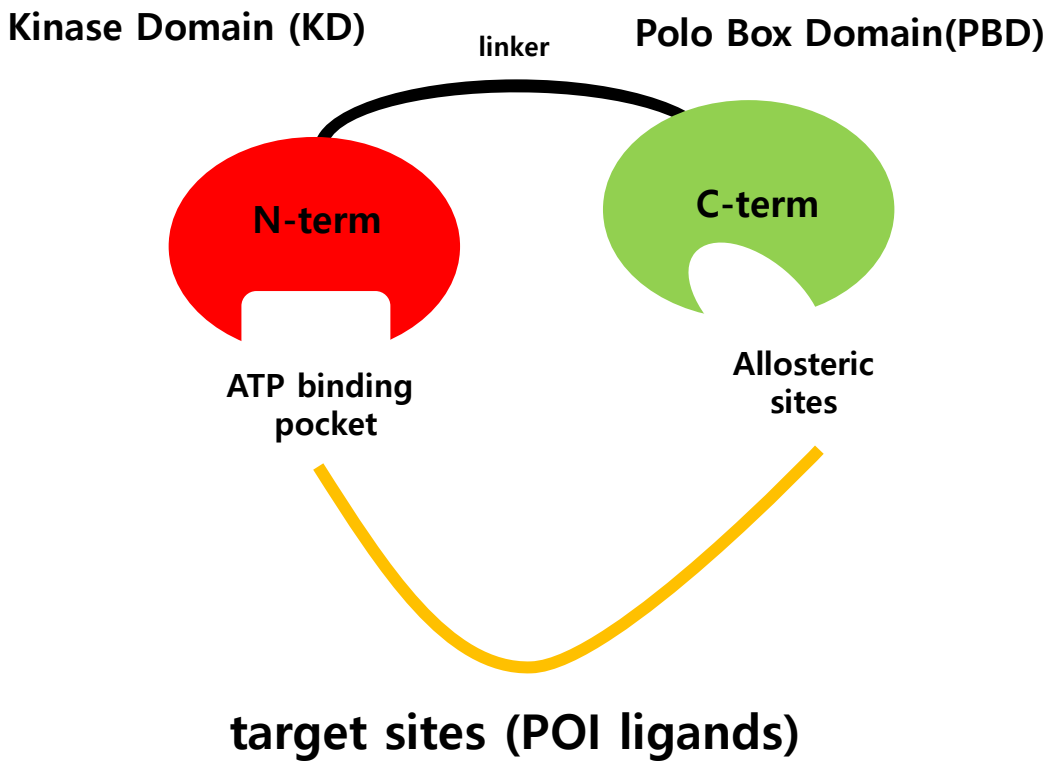
# Types and Proportion of EGFR mutations in NSCLC

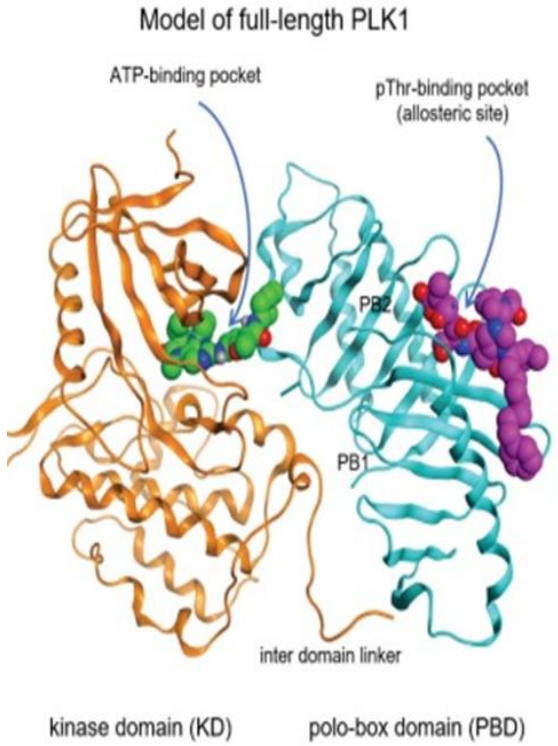



**Proportion of EGFR mutation in NSCLC**
**US: 10%**
**East Asia: 35%**

**Many drugs** have been developed targeting T790M and L858R. However, drug development using **PROTAC targeting PLK1** has not been reported yet.

# Drug Target Sites of PLK1




PLK1 has two POI ligand binding sites:
-ATP binding site located at the N-terminus
-POLO Box Domain(PBD) at the C-terminus

# Drugs targeting the PLK1 ATP site and their side effects in NSCLC patients

| Compound | Company | Mode of action | Target structure | PLK1 IC50 | Clinical trial DLT | Status |
|---|---|---|---|---|---|---|
| BI 2536 | Boehringer Ingelheim | ATP-competitive | PLK1, PLK2, PLK3 | 0.8 nM | Neutropenia, neutropenic infection, GIT | On hold |
| BI 6727 (Volasertib) | Boehringer Ingelheim | ATP-competitive | PLK | 0.87 nM | Neutropenia, thrombocytopenia | Ongoing in solid and hemat. malignancies |
| GSK461364A | Glaxo-Smith-Kline | ATP-competitive | PLK1, PLK2, PLK3 | 2.2 nM | Neutropenia, thrombocytopenia | On hold |
| ON01910.Na (Rigosertib) | Onconova Therapeutics | non ATP-competitive | PLK1, PLK2, PI3K, Abl, Flt-1, PDGFR | 9 nM | Neutropenia, hyponatriemia, delirium, urinary symptoms, pelvic pain | Ongoing in hemat. malignancies |
| MK-1496 | Merck | ATP-competitive | PLK1 | n/a | Neutropenia, thrombocytopenia, anemia | |
| NMS-1,286,937 | Nerviano Medical Sciences | ATP-competitive | PLK1 | 2 nM | Neutropenia, thrombocytopenia, hypokaliemia | On hold |
| TAK-96 | Takeda | ATP-competitive | PLK1, PLK2 | 0.8 nM | Not reported | Clinical trial was terminated, on hold |
| HMN-214 | Nippon Shinyaku Co. Ltd. | Not reported | PLK1 | 0.12 μM | GIT, arthralgia, myalgia | On hold |

**Abbreviations:** PLK, Polo-like kinases; GIT, gastrointestinal toxicity; ATP, adenosine triphosphate.

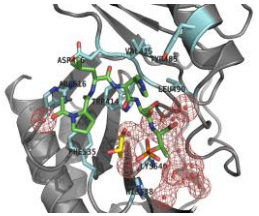
**Serious side effect when targeting ATP binding sites because of selectivity issues**

**Neutropenia**

**Thrombocytopenia**

**Polo-Box Domain (PBD)**

# Our research group's PLK1 PBD ligand development timetable



PLHSpT

$IC_{50}$ 36 uM

Yun SM. *et al., Nat.Struct. Mol. Biol.*

2009

2011

2013

2014

2015

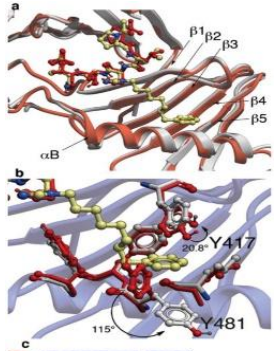
2017

2021

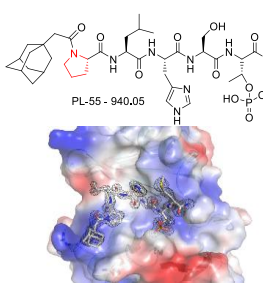
2024

4J

$IC_{50}$ 2 nM



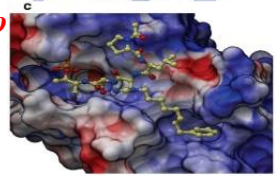
Liu F. *et al., Nature Chem. Bio*
(Terrence R Burke Jr. NCI)



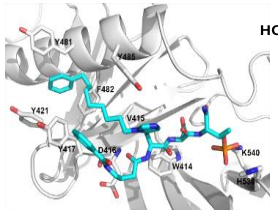
PL-55 - 940.05

Ravi. . *et al., PloS ONE*

Ravi. . *et al.,*
*Bioorg.Med.Chem*



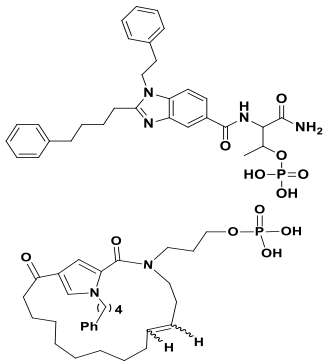
Rao. *et al., PloS ONE*



AB-103-5

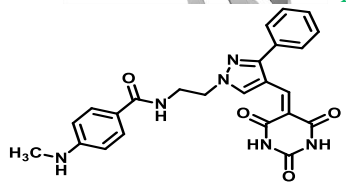
$IC_{50}$ 4 nM

Ahn *et al., J. Med. Chem.* 2015



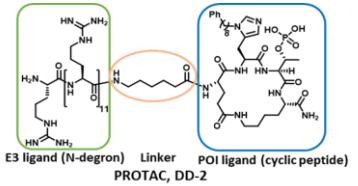


Guna . *et al., Chemedchem*



Guna . *et al., J.MED.CHEM*





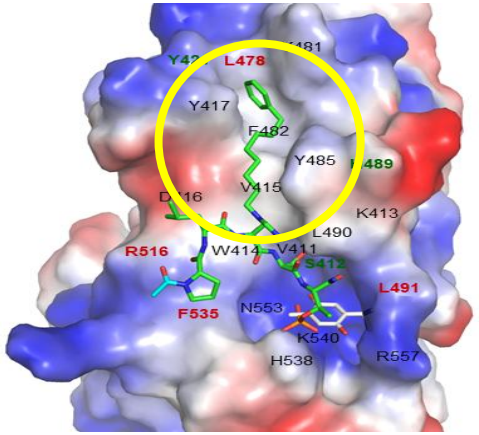
E3 ligand (N-degron) Linker POI ligand (cyclic peptide)
PROTAC, DD-2

Guna . *et al., J.MED.CHEM*

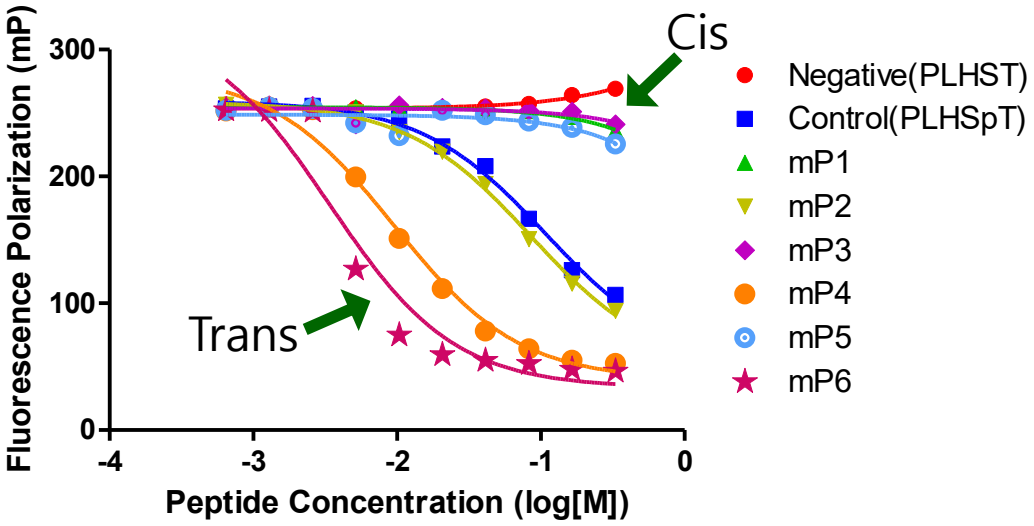


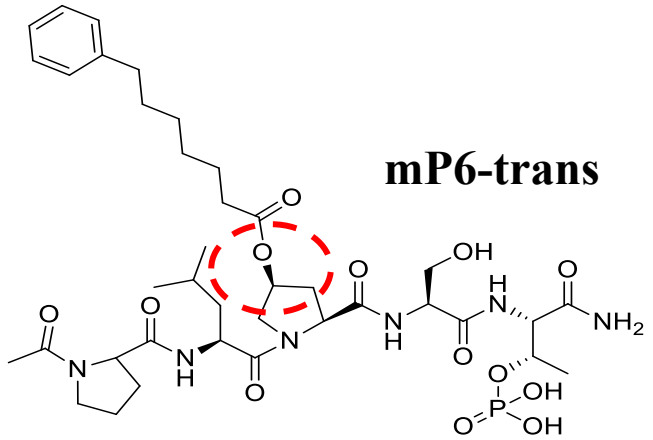
# POI Ligand: Cis/Trans binding affinity

**PBD-Peptide Complex structure**



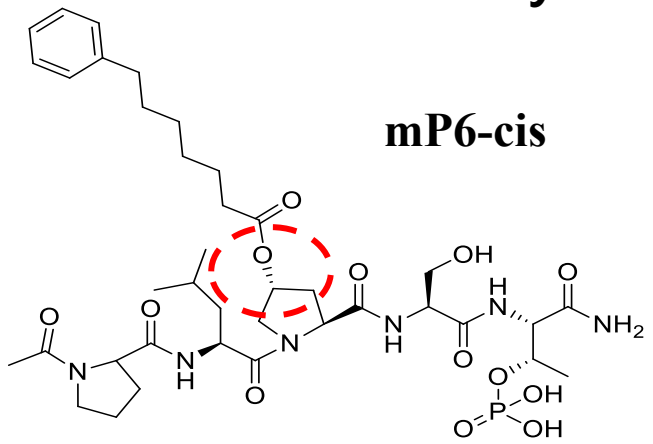

**Fluorescence Polarization(FP) Assay**




$Ac\text{-}PLmP_6SpT\text{-}NH_2$

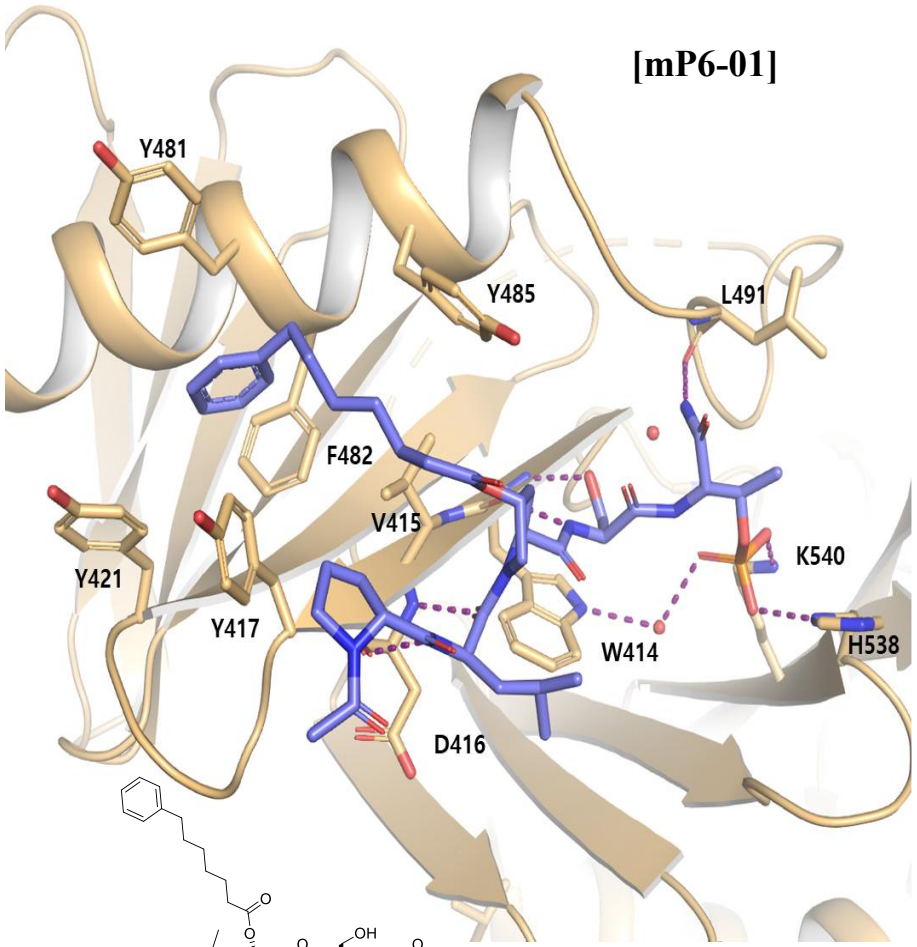
**Cis POI: No activity**



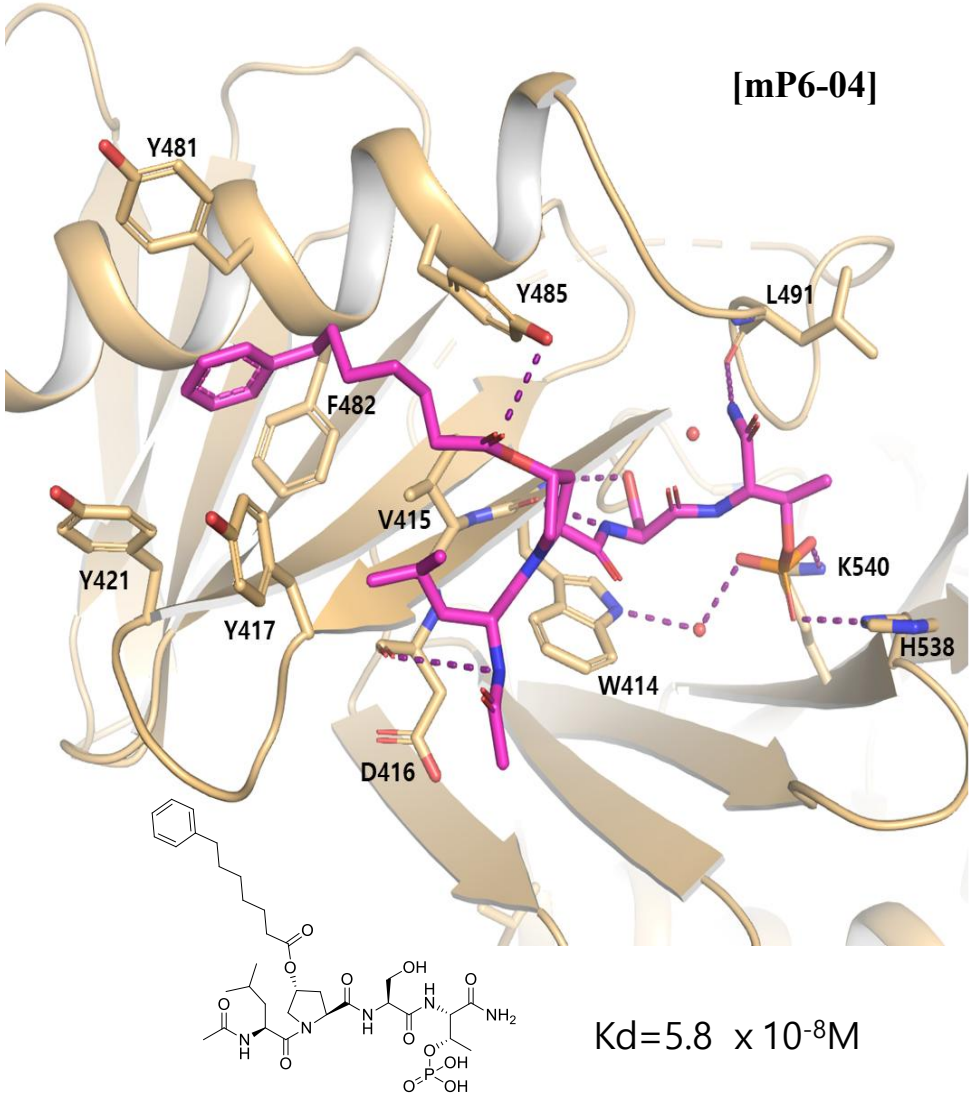

$Ac\text{-}PLmP_6SpT\text{-}NH_2$

**Trans Trans: High activity**

# X-ray structure and binding affinity

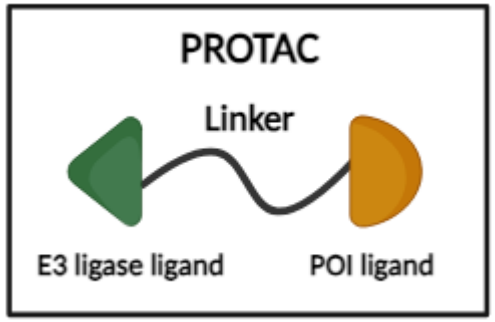



Kd=1.4 x $10^{-7}$M

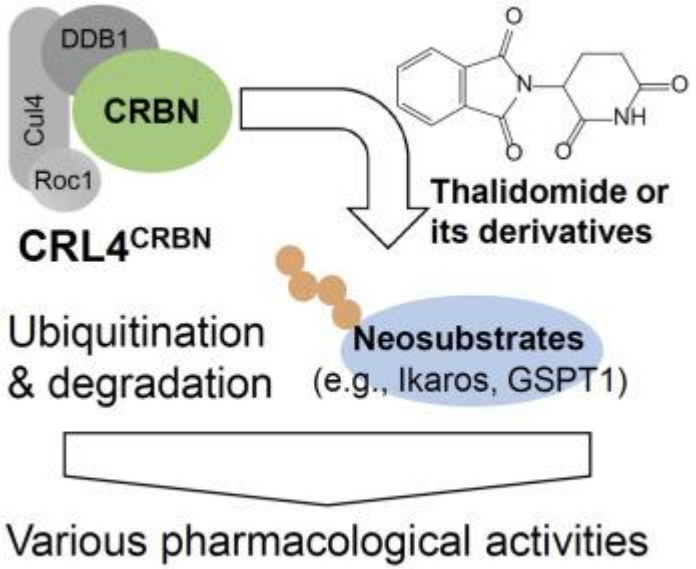



Kd=5.8 x $10^{-8}$M

# E3 Ligase Ligand



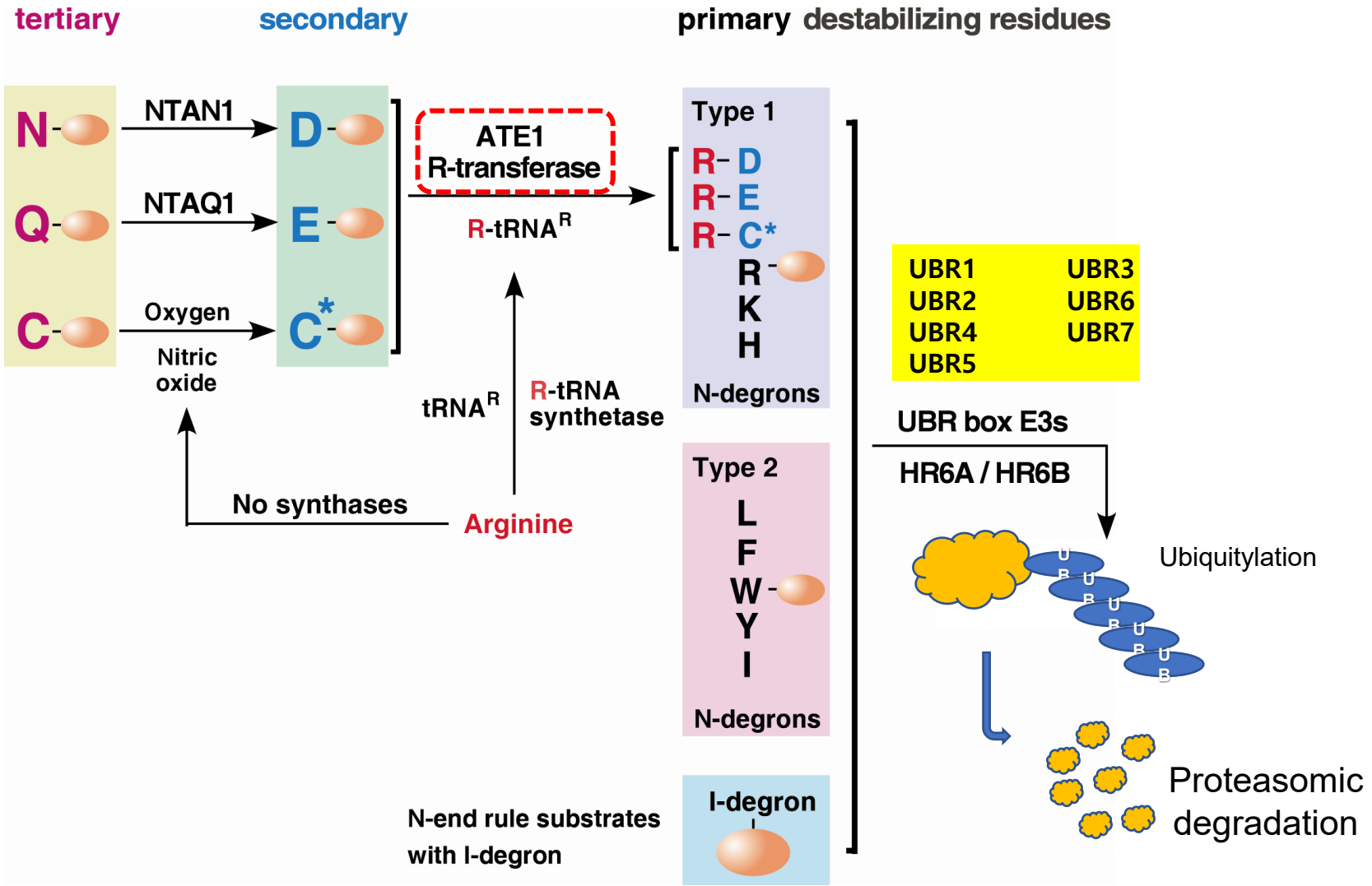

-Small size(oral available)
-High stability
-Most popular




-Low expression level
-Low solubility
-Low permeability
-High toxicity

Ito *et. al*., Cell chemical biology, ***2021***

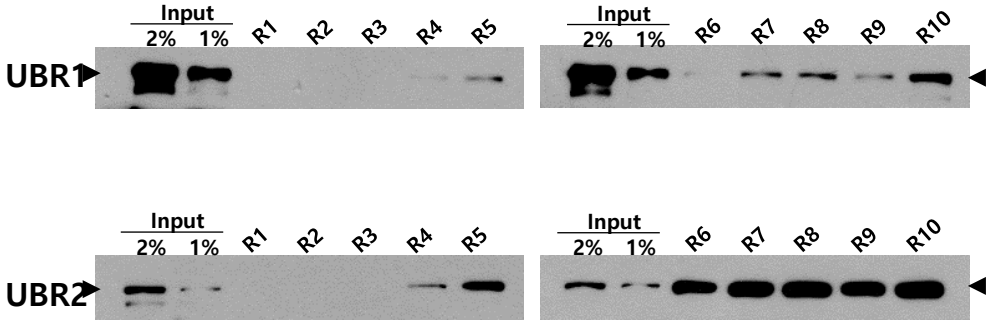
# Novel E3 Ligase Ligand :Arg/N-end rule pathway



# Arg/ N-end rule pathway

## Pull down assay

**UBR1/UBR2 overexpressed HEK293T cell lysate**
**+ Rn-biotin-streptavidin bead**




**Poly-Arg Peptide**

1. R1: RK-biotin
2. R2: RRK-biotin
3. R3: RRRK-biotin
4. R4: RRRRK-biotin
5. R5: RRRRRK-biotin
6. R6: RRRRRRK-biotin
7. R7: RRRRRRRK-biotin
8. R8: RRRRRRRRK-biotin
9. R9: RRRRRRRRRK-biotin
10. R10: RRRRRRRRRRK-biotin

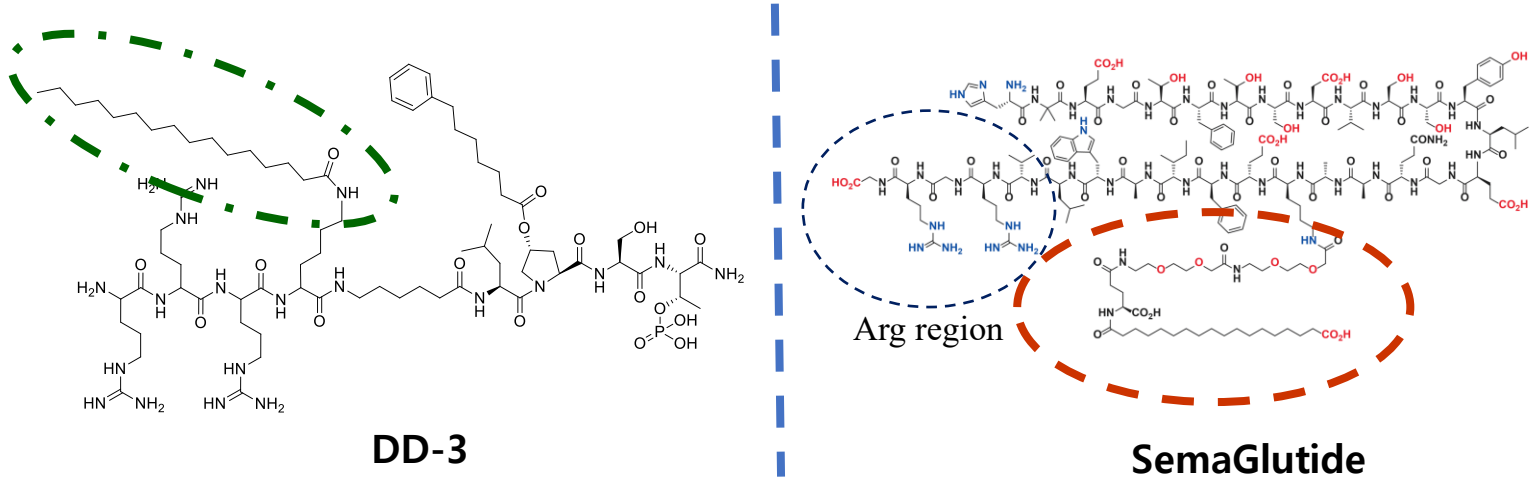
***The role of poly-arg:**

**1.Ubr1/Ubr2 ligase ligand(E3 ligase ligand)**

**2. cell penetration (CPP)**

# New E3 ligase ligand



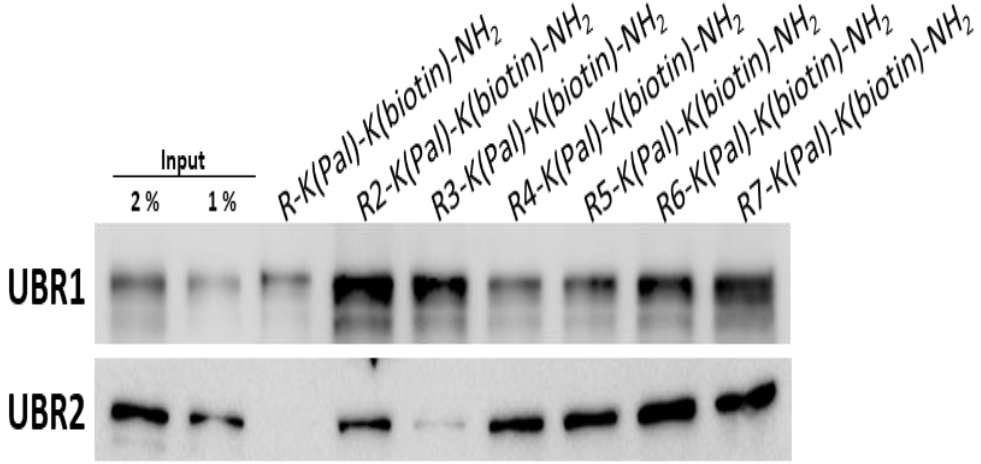



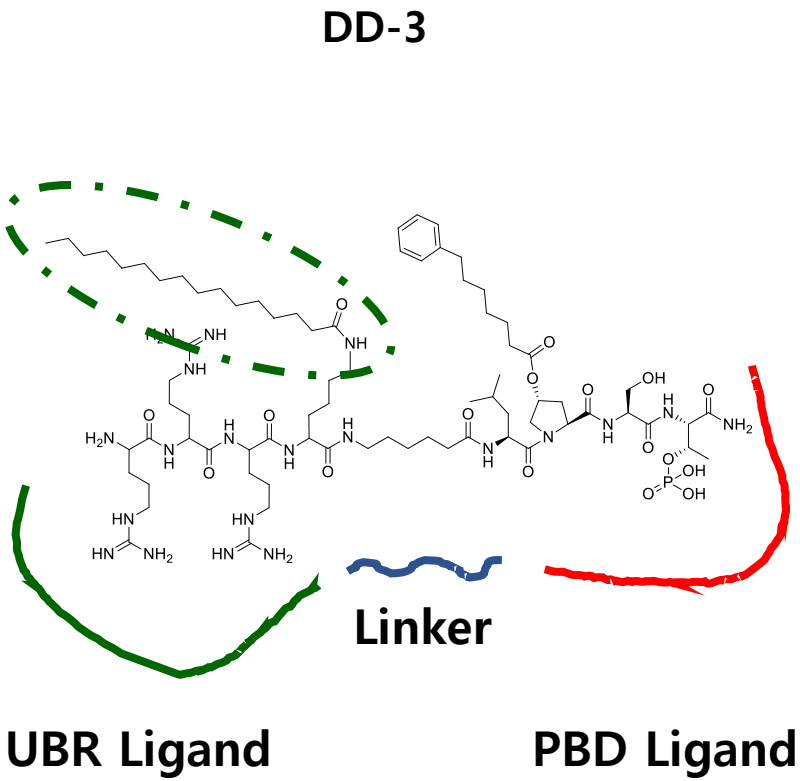

DD-3

SemaGlutide

-No lipid in the Lys side chain, the half-life is within 10 minutes,
-but the half-life increases to one week through the introduction of lipid
-Based on these results, we also intend to increase the stability of PROTAC by introducing lipids into the side chain of Lys.

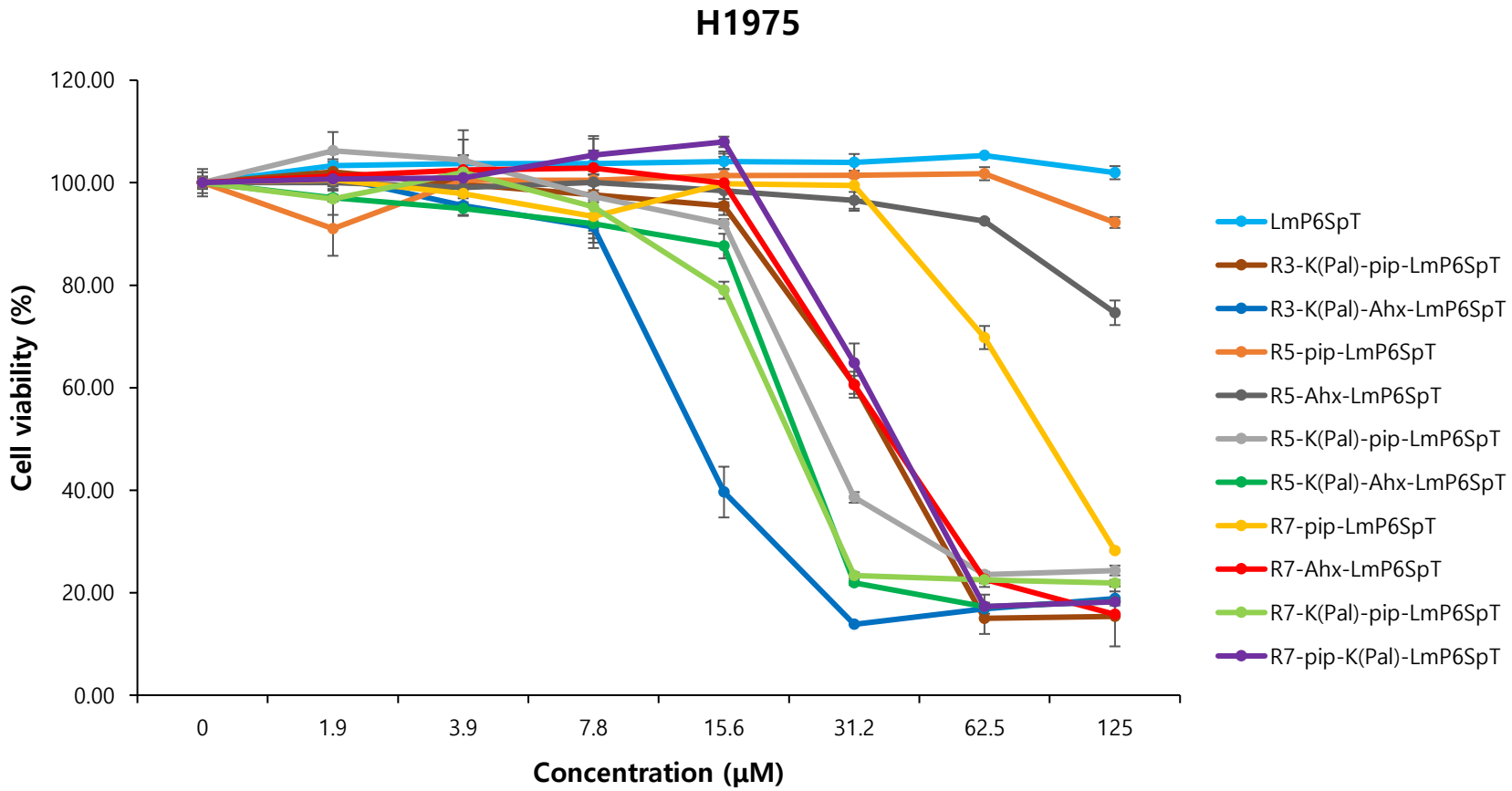
# Two or Three Arg are enough…



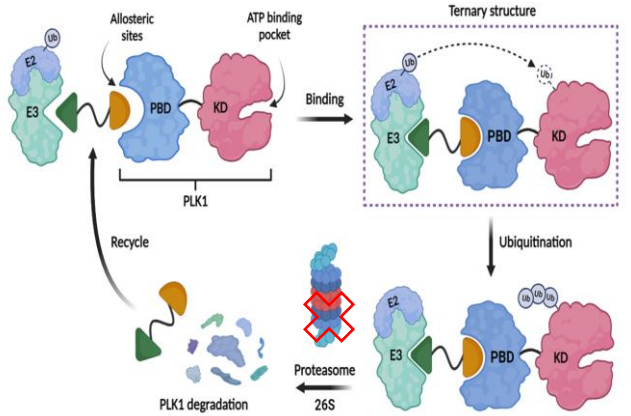




-Lipid-introduced Arg and check the binding with UBR1/UBR2.
-To bind the UBR1/UBR2, **only one or two Arg is enough**. In particular, strong binding was observed even when 2 or 3 Args were present.
-This result is different from that 5 or more Arg are required to bind to UBR1/UBR2 in the **absence of lipids**.
-Synthesized **the DD3 which has lipid attached Arg E3 ligand**.

# MTT assay in H1975

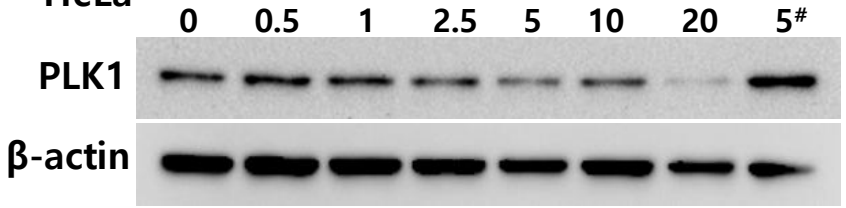


# PLK1 Degradation in HeLa and A549

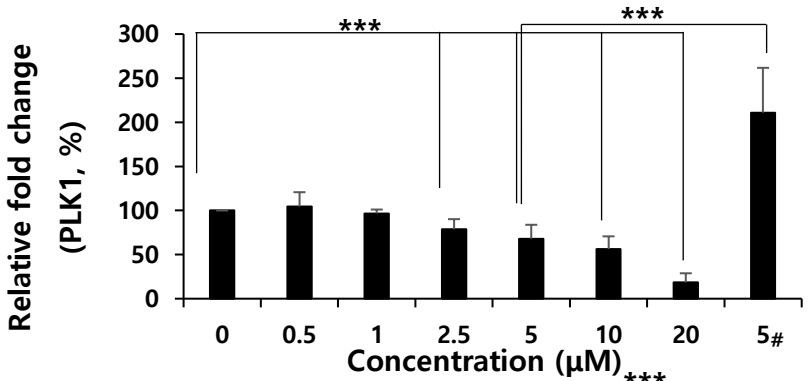



(A)

HeLa

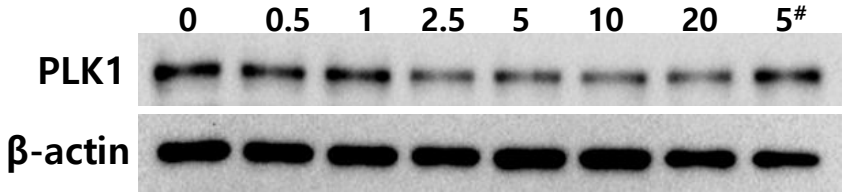



# MG132 was added

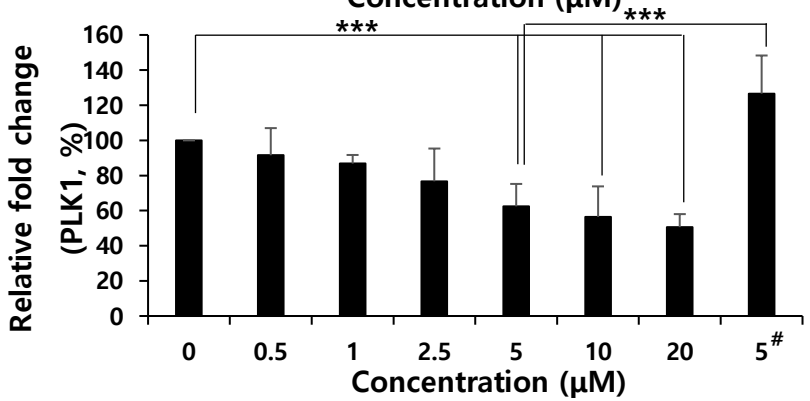



(B)

A549

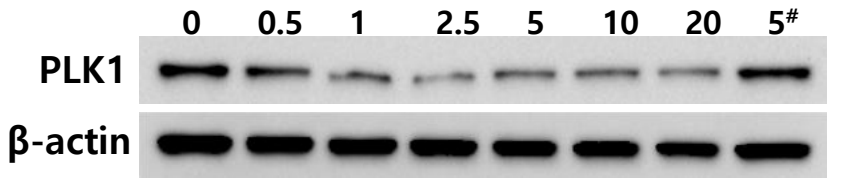



# MG132 was added



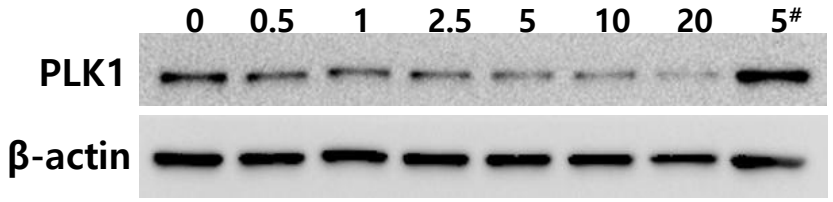
# PLK1 Degradation in PC9 and H1975

PC9

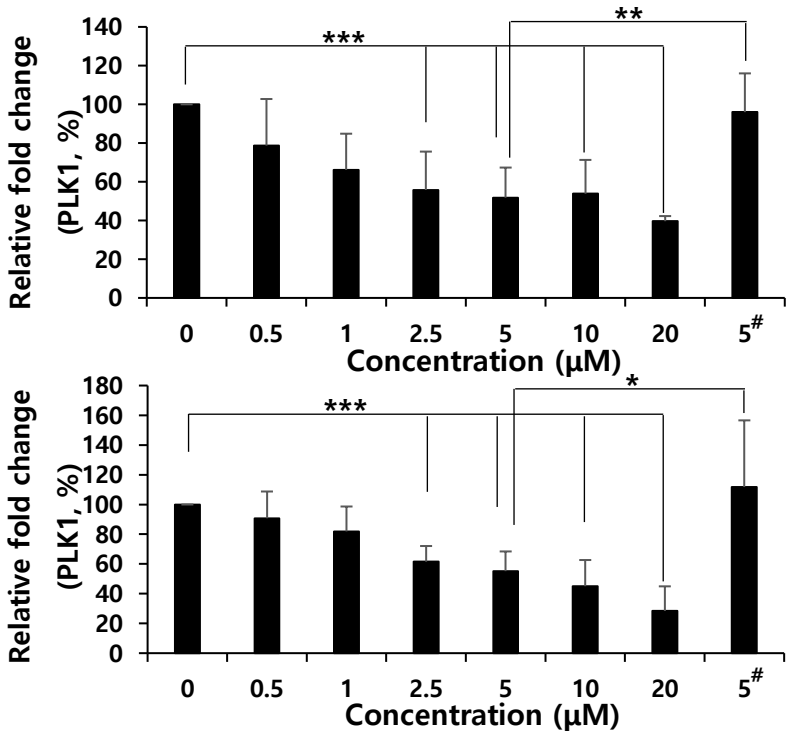



# MG132 was added

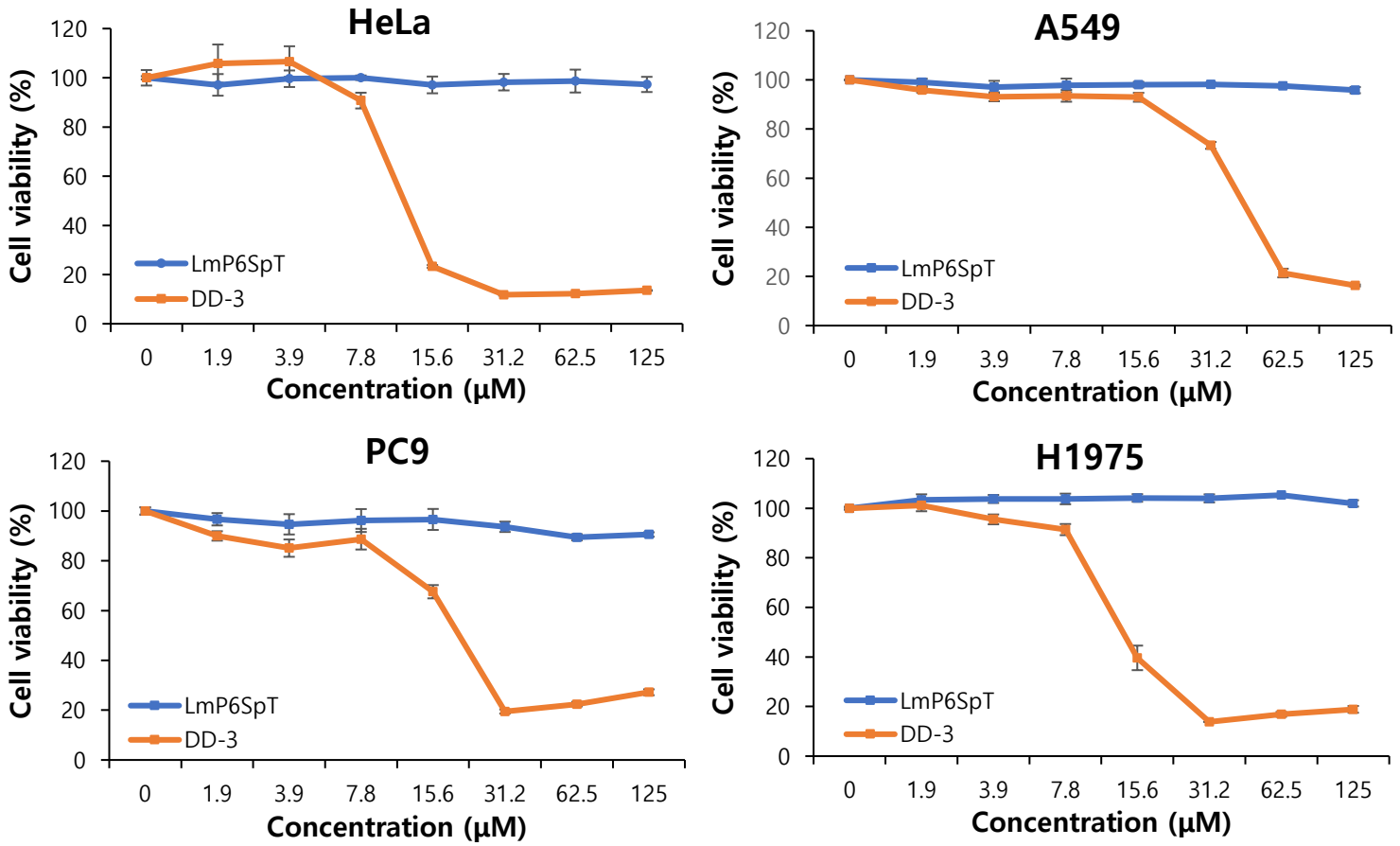
H1975



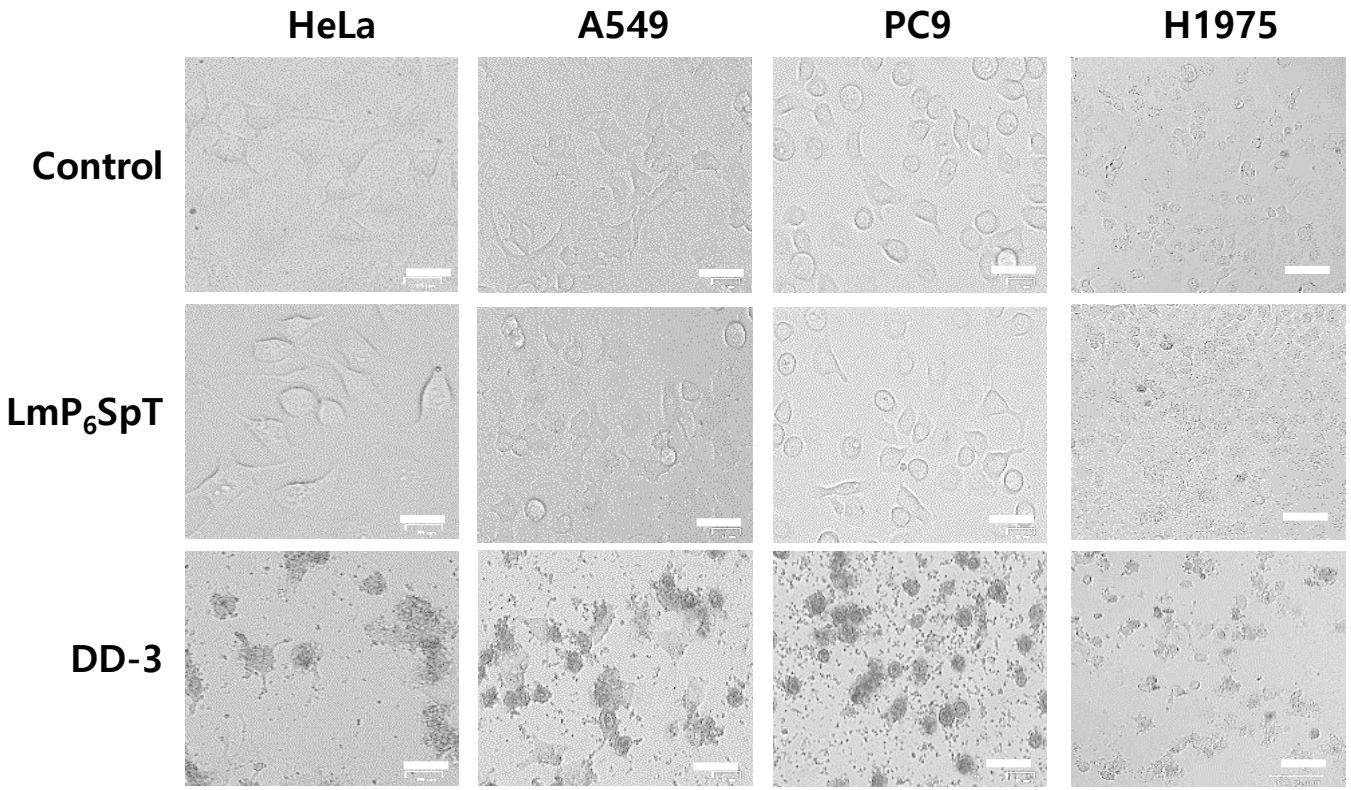

# MG132 was added

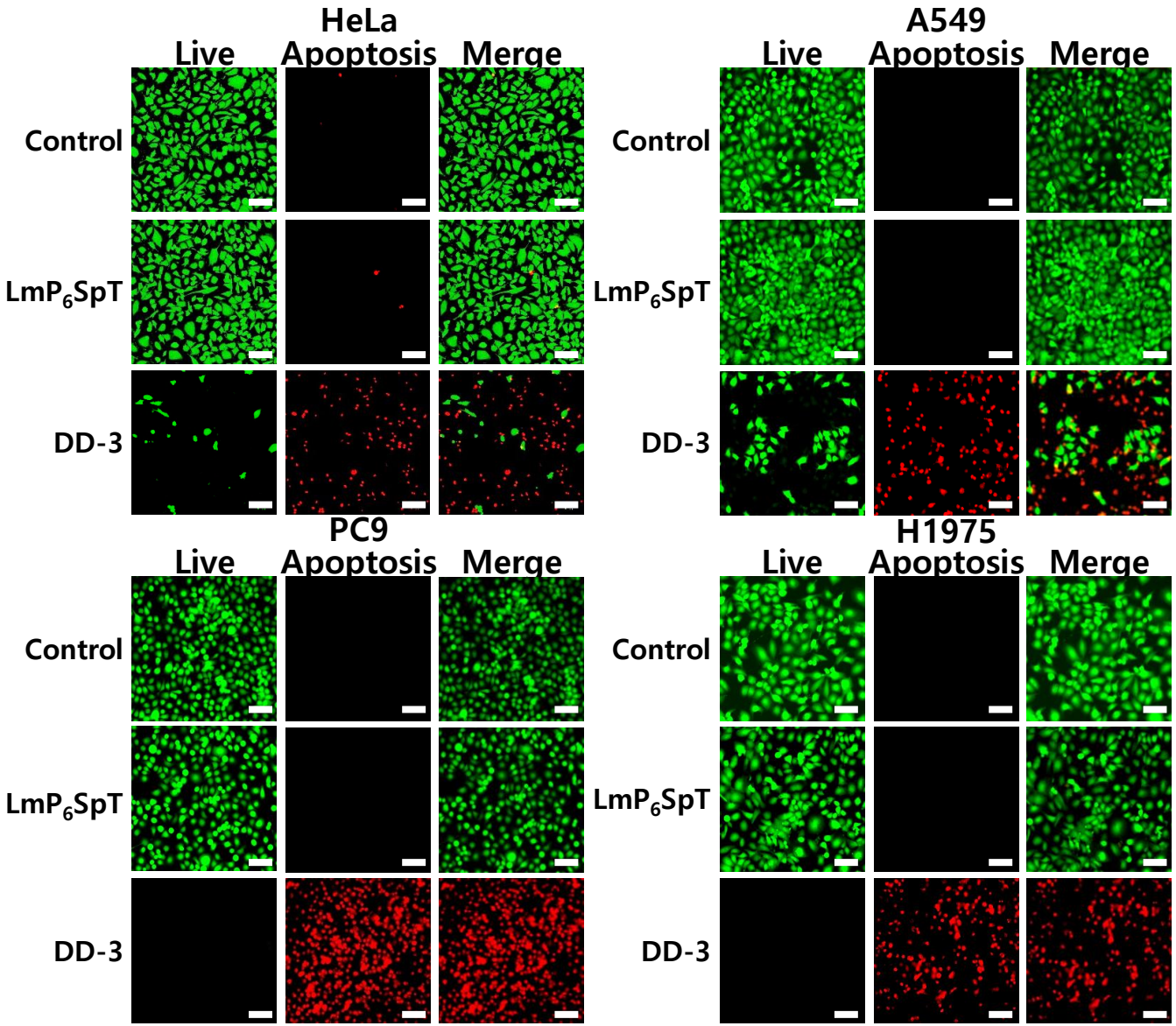


# Cell Viability in HeLa/A549/PC9/ H1975

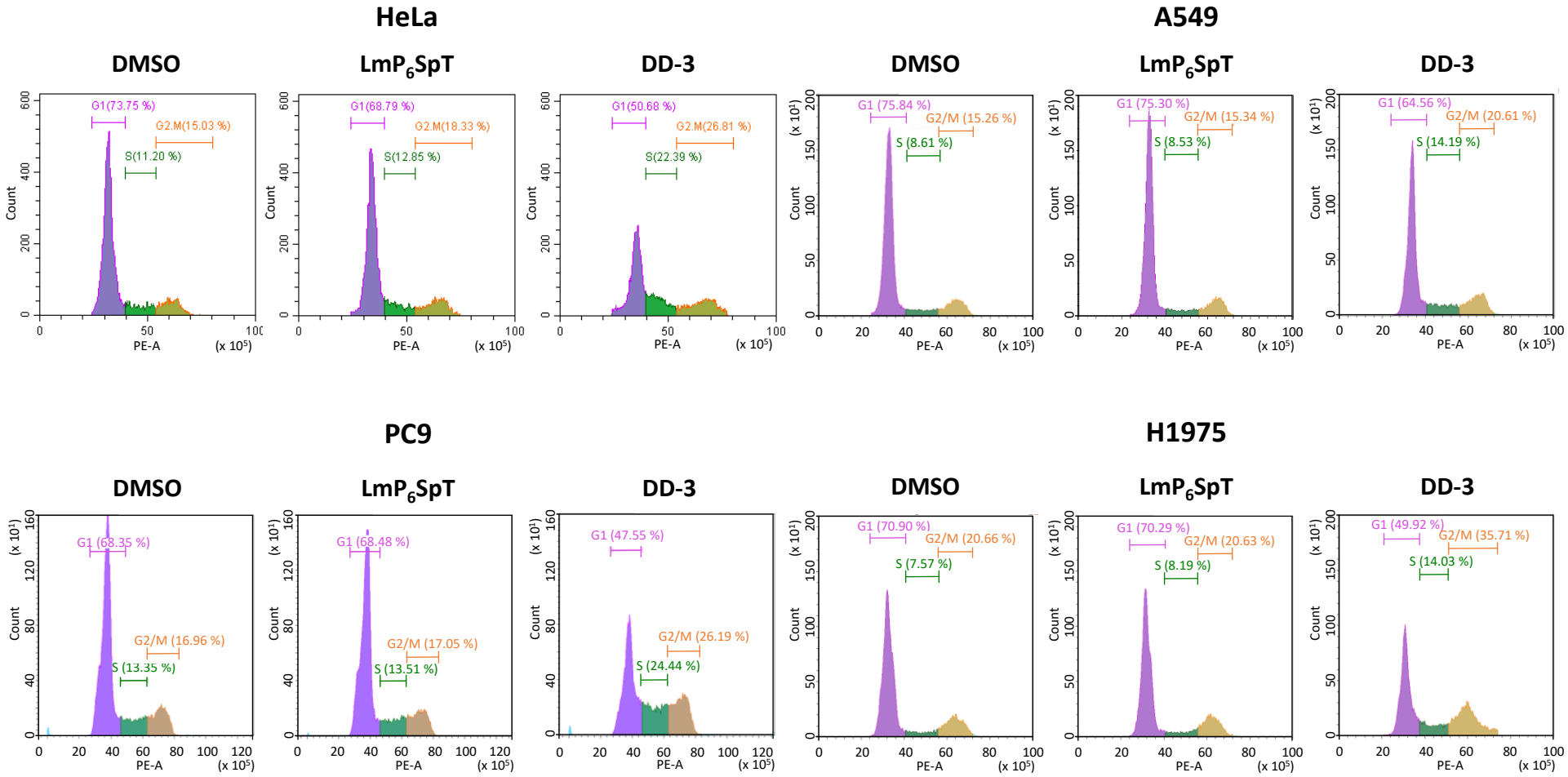


# Cell Viability in HeLa/A549/PC9/ H1975

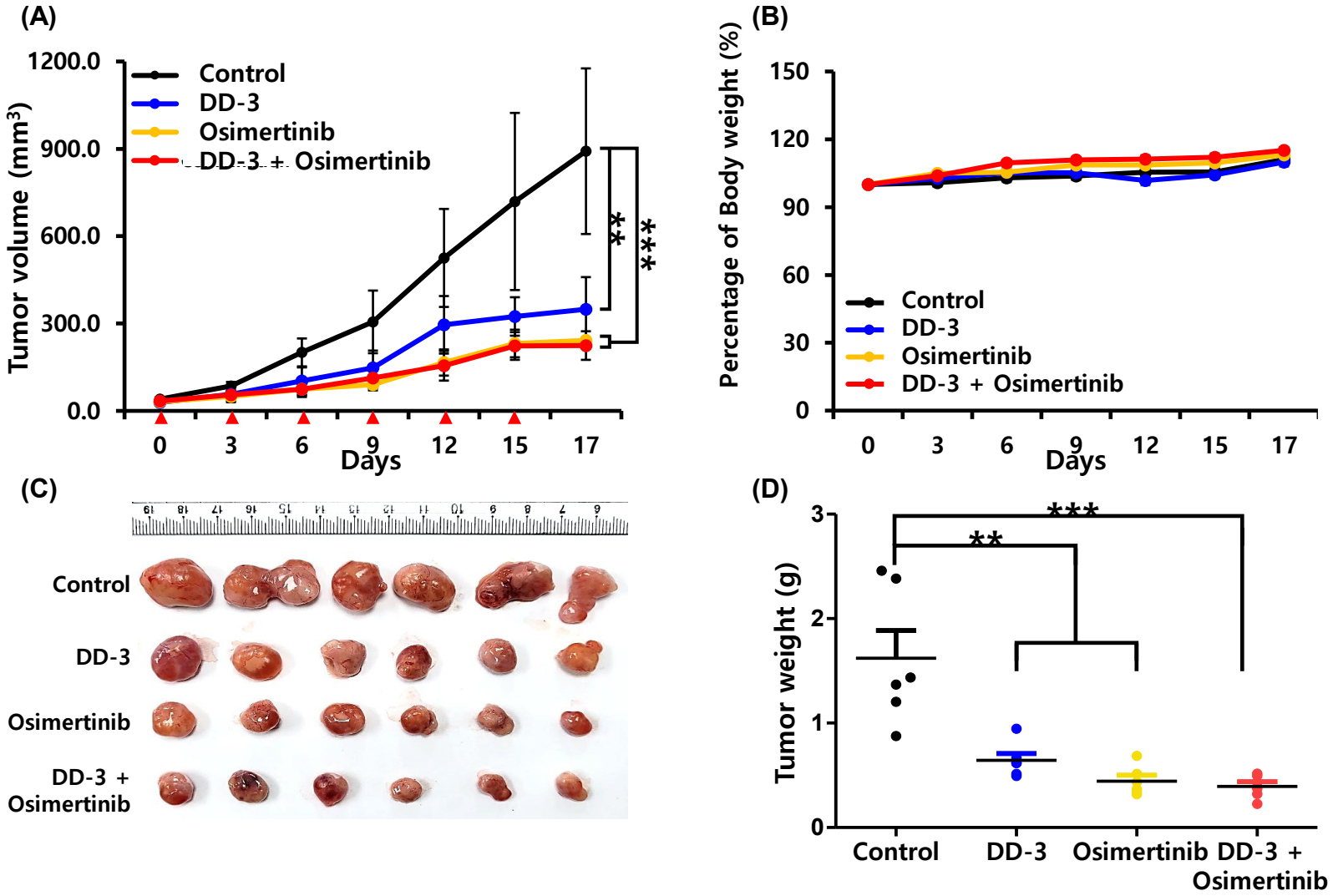



HeLa
Live
Apoptosis
Merge
Control
LmP6SpT
DD-3
A549
Live
Apoptosis
Merge
Control
LmP6SpT
DD-3
PC9
Live
Apoptosis
Merge
Control
LmP6SpT
DD-3
H1975
Live
Apoptosis
Merge
Control
LmP6SpT
DD-3

# Cell Cycle Arrest



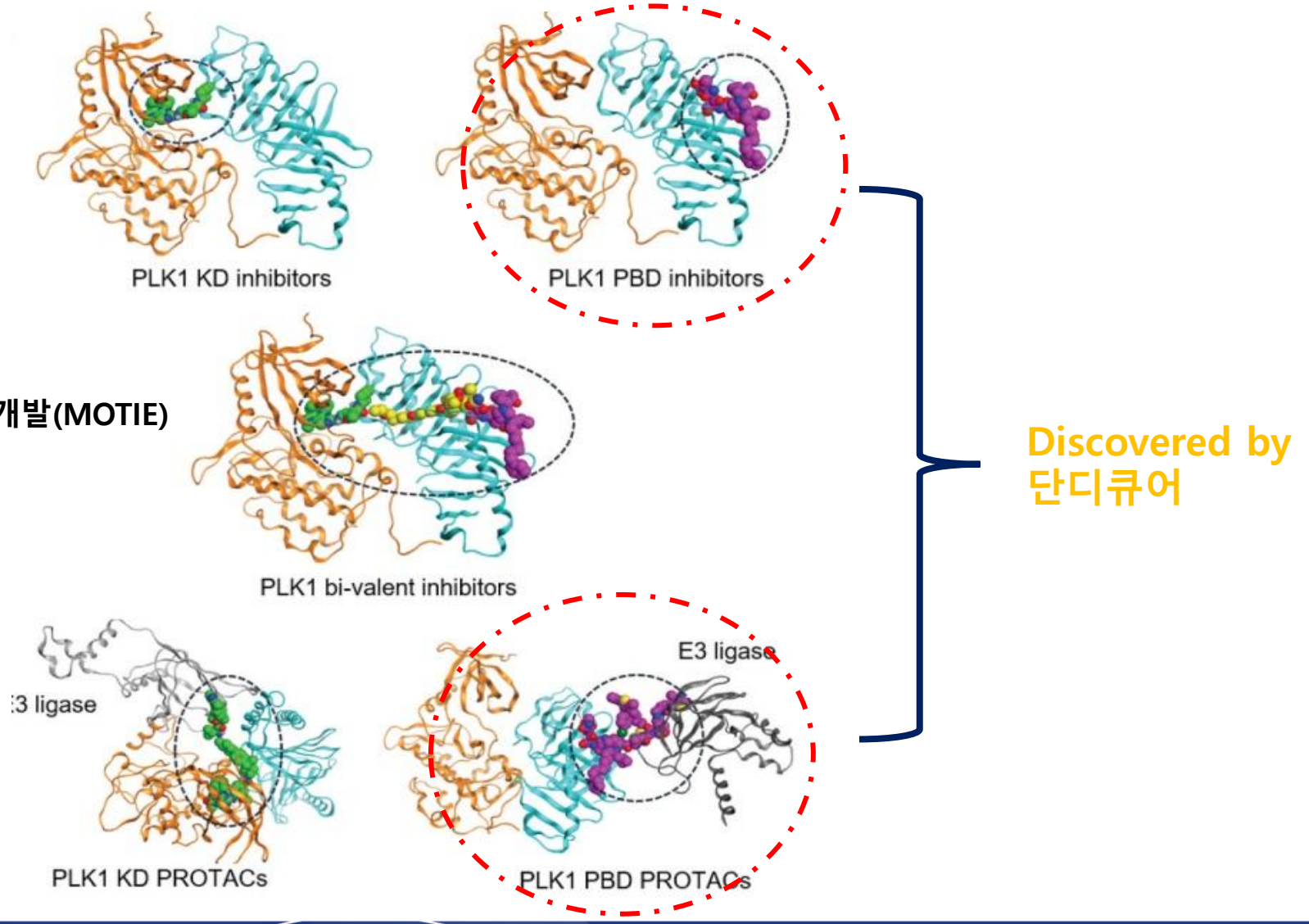
# *In vivo* Efficacy of PROTAC



# Summary: Strategies to Develop PLK1 Inhibitors or Degraders


## GRANTS

1.바이오·의료기술개발(NRF)
과제번호 : RS-2024-00401422
2.멀티오믹스기반난치암맞춤형진단치료상용화기술개발(MOTIE)
과제번호 : RS-2024-00400101
3.소재부품기술개발(MOTIE)
과제번호 : RS-2024-00439224
4.바이오·의료기술개발(NRF)
과제번호 : RS-2026-25520326

울지 않는 새를 울게 하는 방법

1.울도록 만든다(조조/토요또미 히데요시)

2.울어 달라고 애원한다(유비/오다 노무나가)

3. 울때까지 기다린다(사마의/ 토쿠가와 이에야스)

# 경청해 주셔서 감사 합니다




# 2026년
# 대한부인종양학회
# 제31차 추계 심포지엄

2026.10. 23. (금) - 24. (토)

정부세종컨벤션센터 / 세종 코트야드 바이 메리어트

대한부인종양학회
Korean Society of Gynecologic Oncology