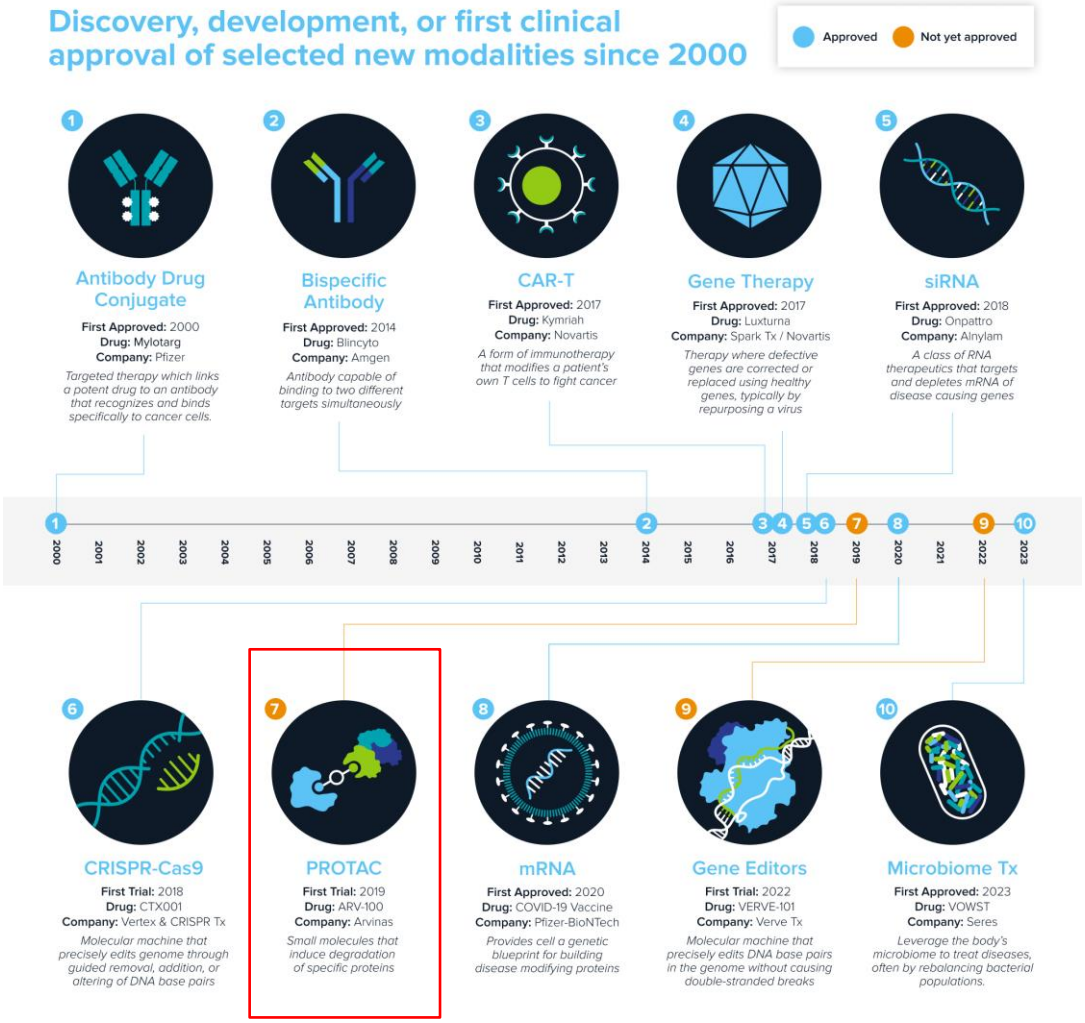
Targeted Protein Degradation (TPD) 101

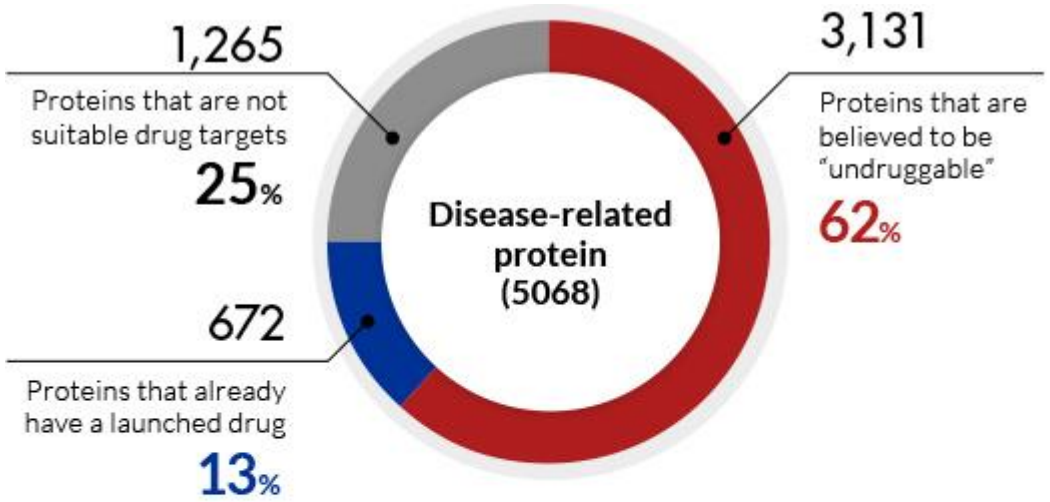
College of Pharmacy
Keimyung University
Kwang-Su Park, PhD

New Modalities



Source: Andreessen Horowitz research.

Unmet Medical Needs



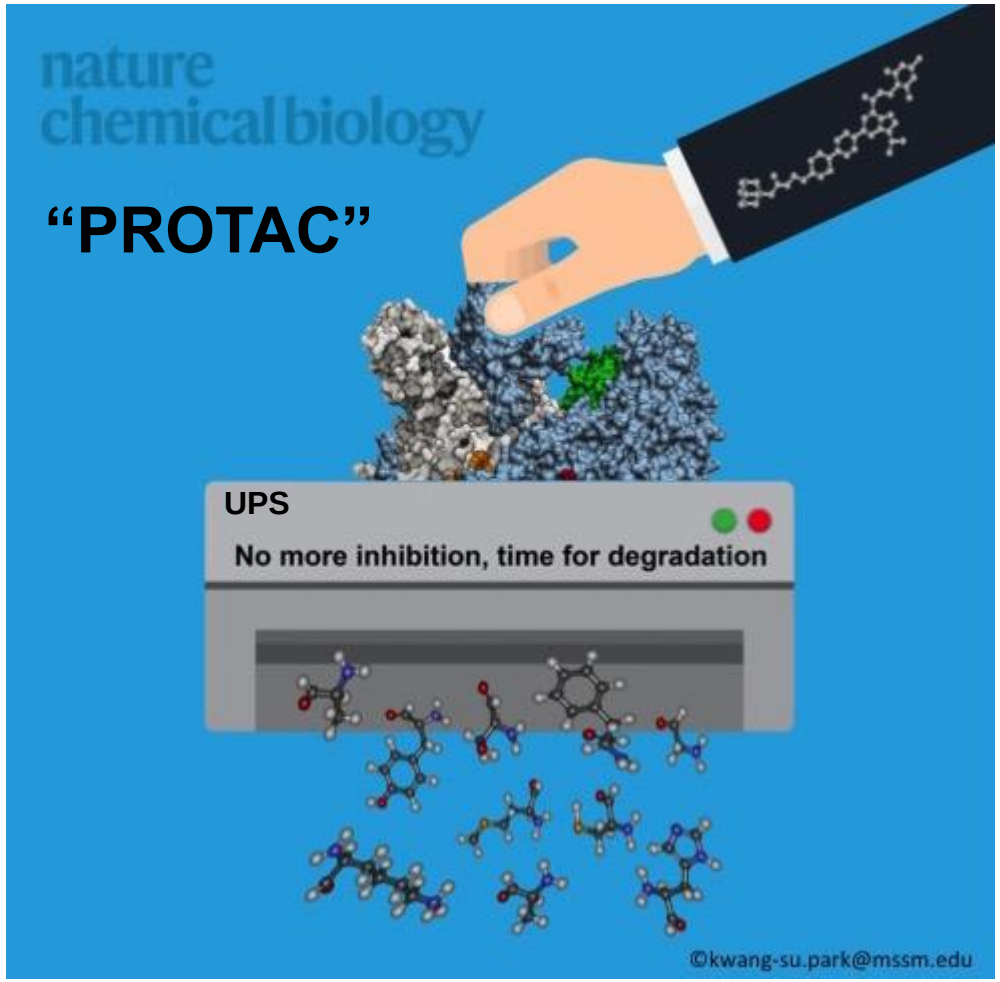
Depletion of druggable proteins

Powered by ibVIS platform consisting of core technologies in RNA informatics and biology, 62% of the disease-related proteins, which corresponds approximately 3,000 proteins in total, can be newly targeted by ASOs and small molecule drugs.

Source: Statistics from ***The Human Protein Atlas***, DrugBank, KS analysis

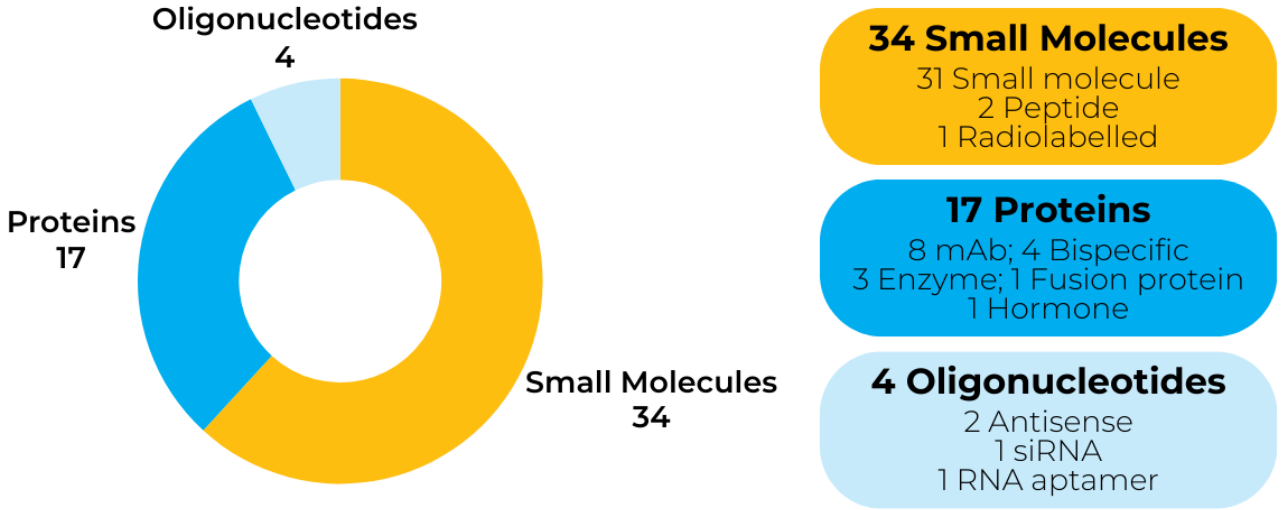
Targeted Protein Degradation (TPD)

Protein Shredder



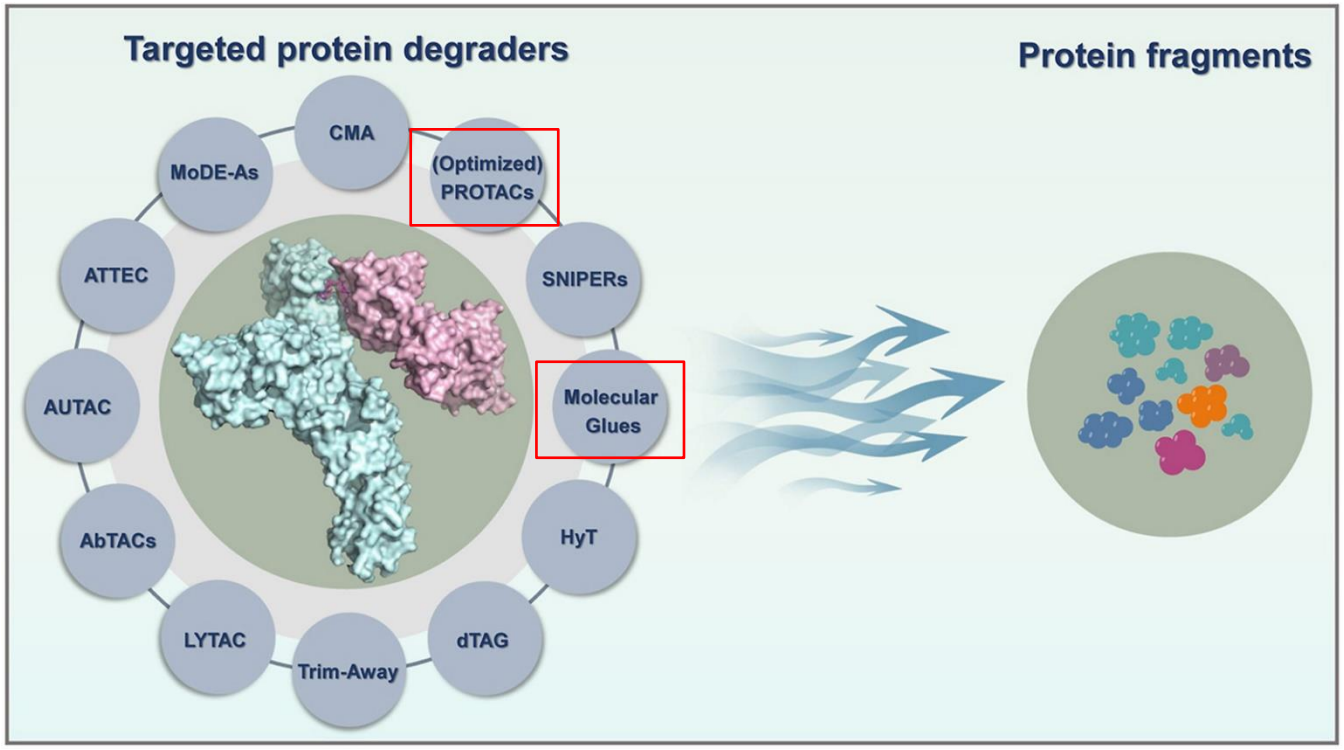
https://labs.icahn.mssm.edu/jinlab/

FDA Novel Drugs Approvals 2023

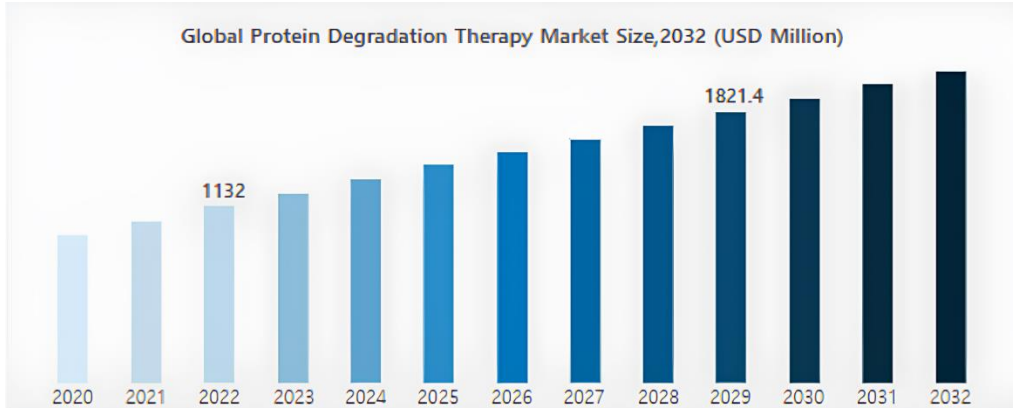


임상 비용! 잠재적 부작용!

Targeted Protein Degradation (TPD)

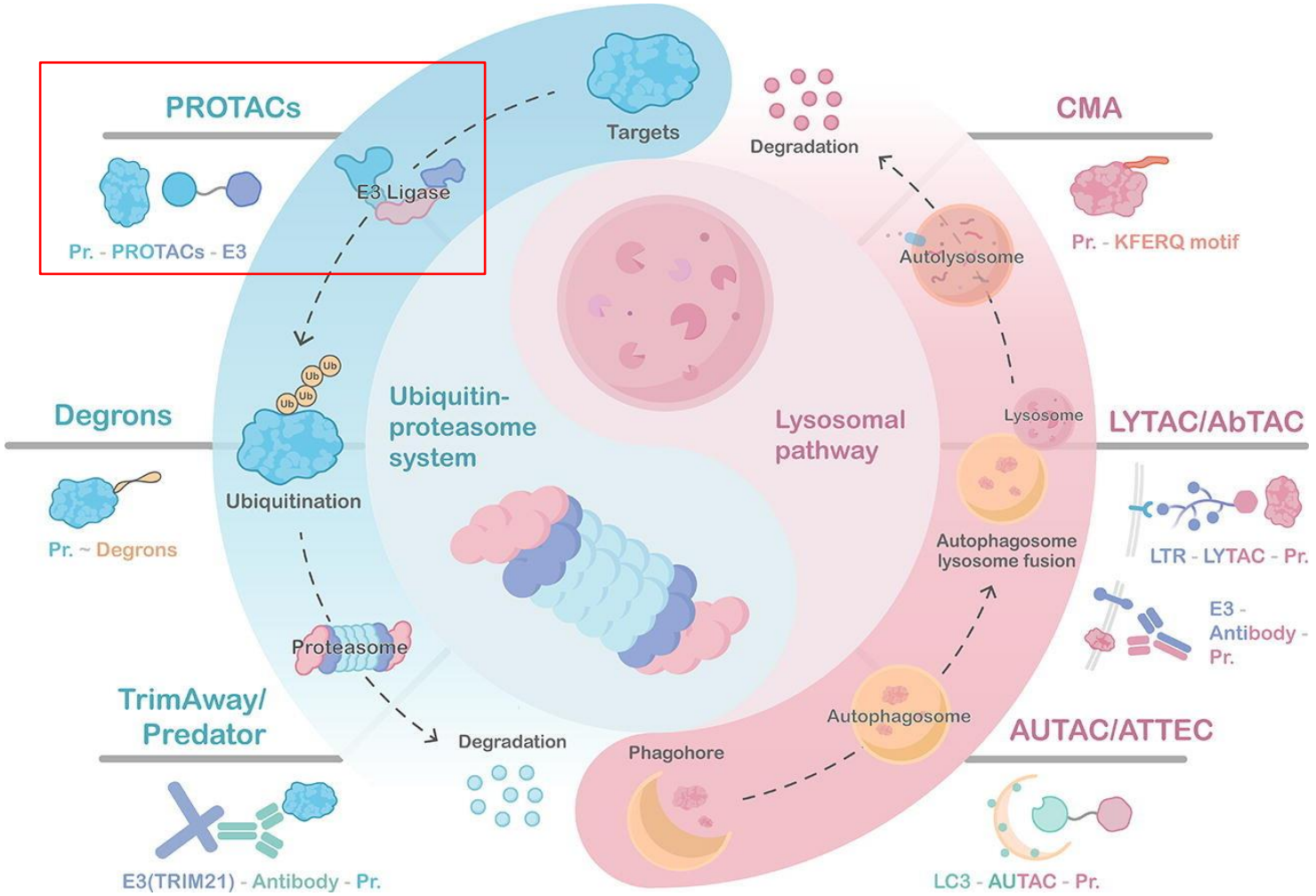


Eur J Med Chem. **2022**, 31, p 114142.



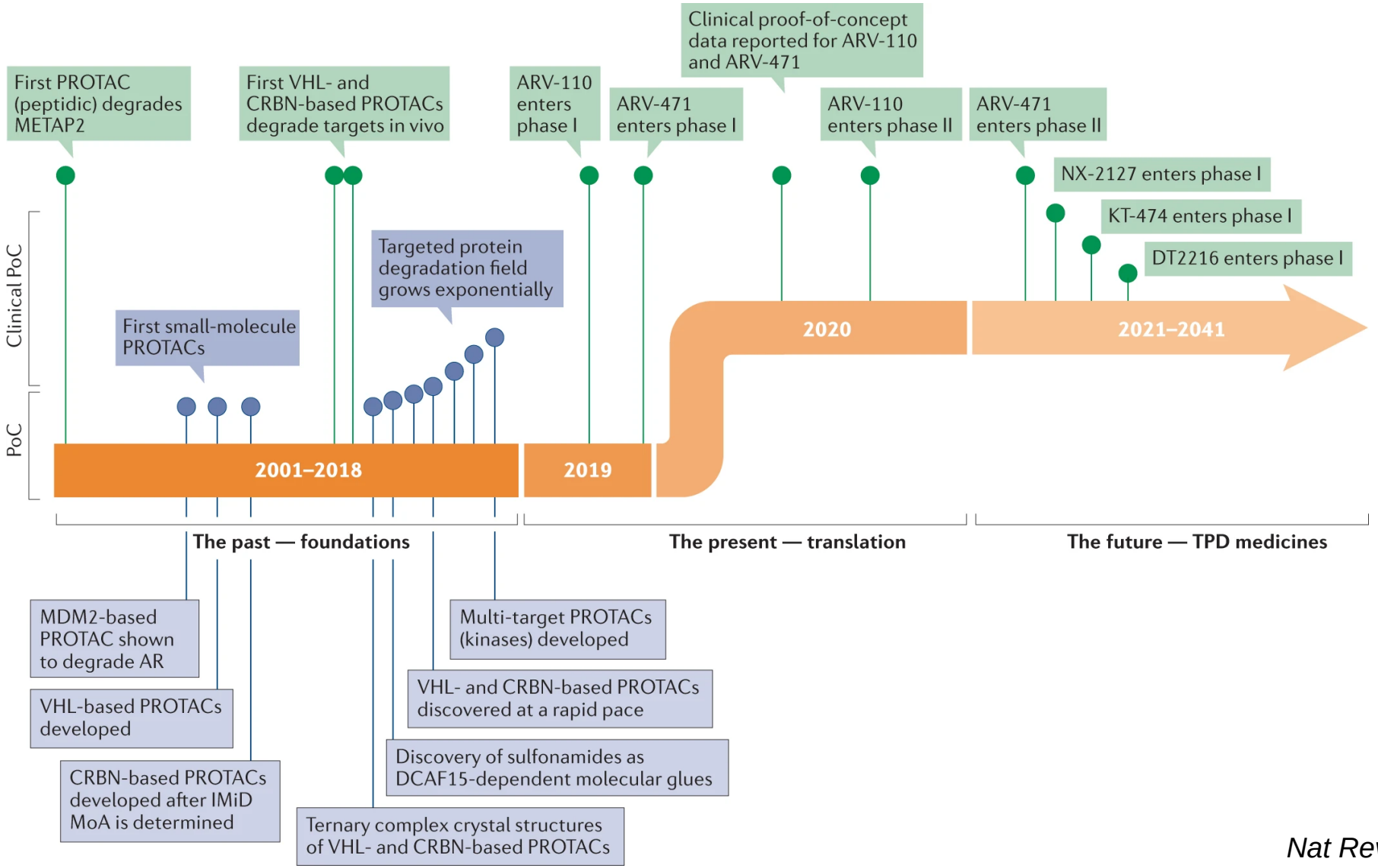
2023년도 Global market size 예측

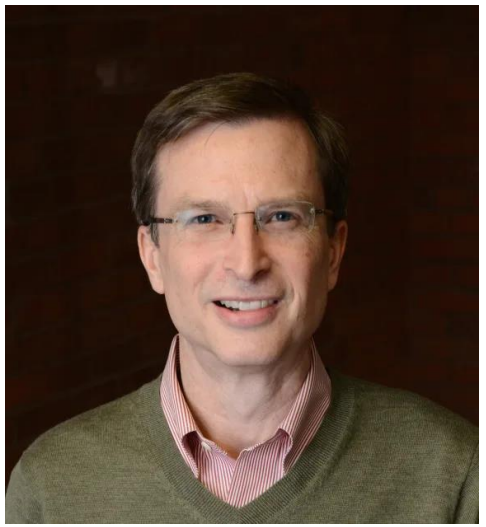
Targeted Protein Degradation (TPD)



Computational and structural biotechnology journal **2022**, 20, 5477-5489

History of PROTAC discovery



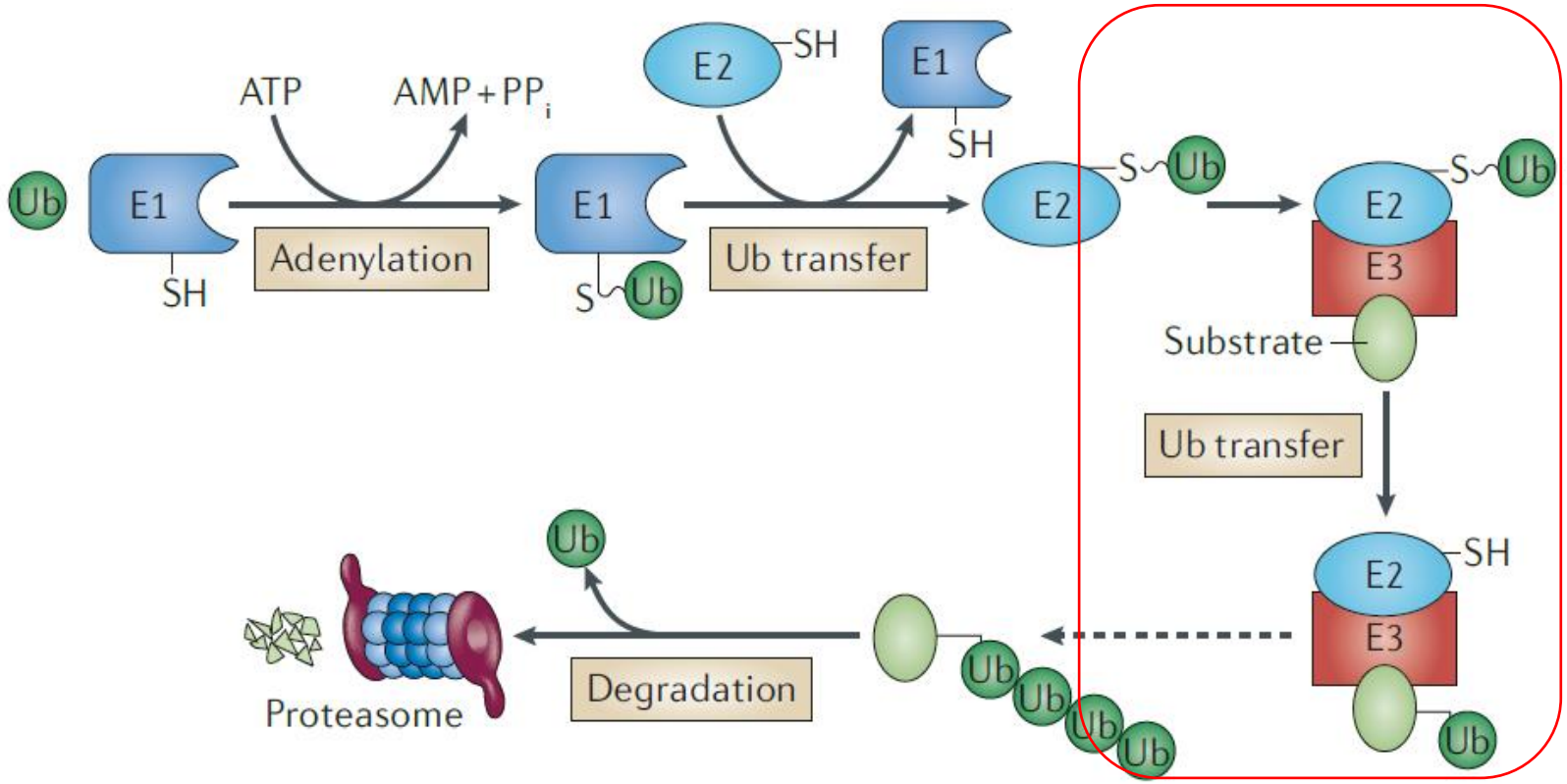


Dr. Craig Crews

Nat Rev Drug Dis 21, 181–200 (**2022**)

PROTAC (PROteolysis-Targeting Chimera)

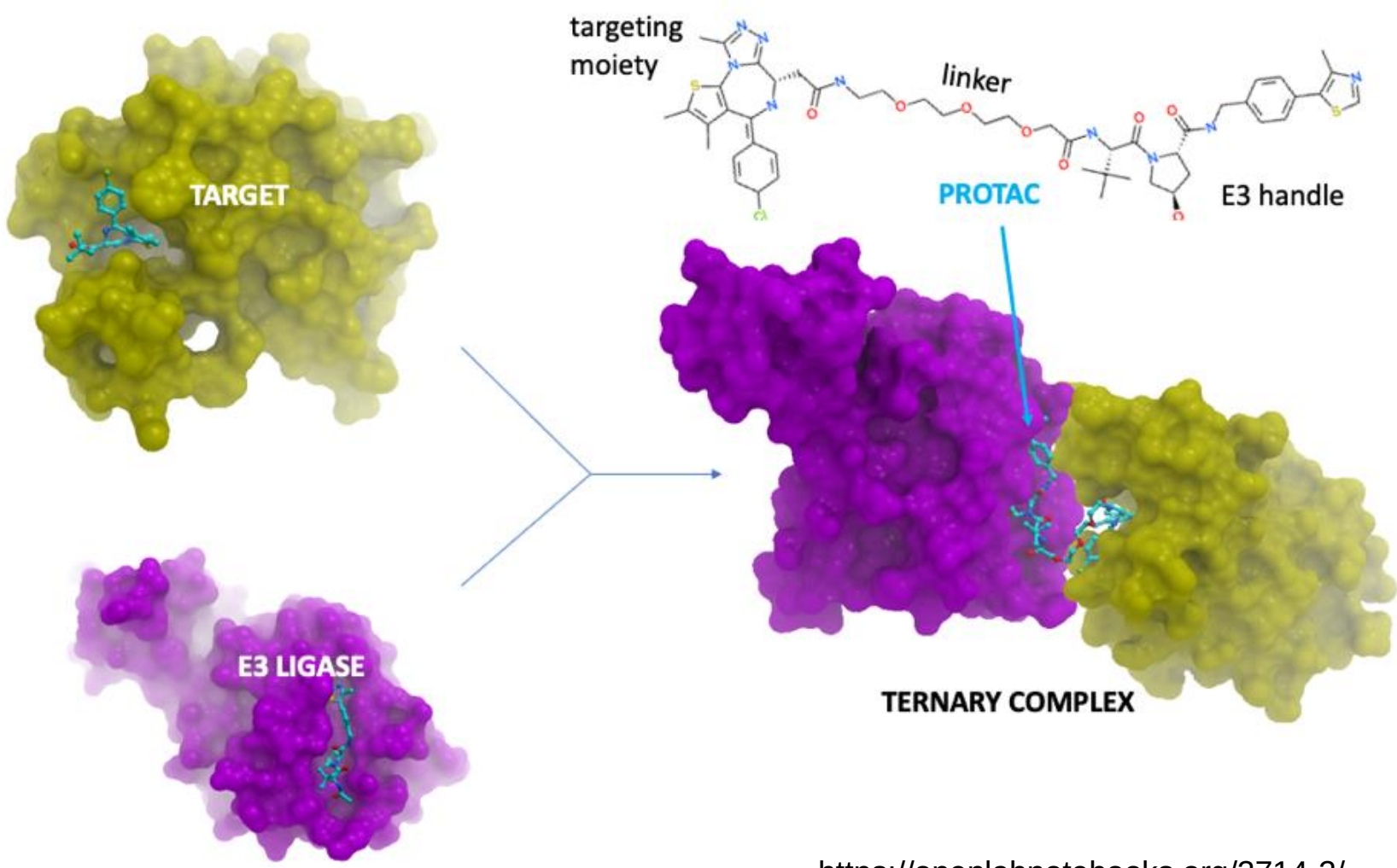
Ubiqutination system



Nat Rev Microbiol 10, 100–111 (**2012**)

PROTAC (PROteolysis-Targeting Chimera)

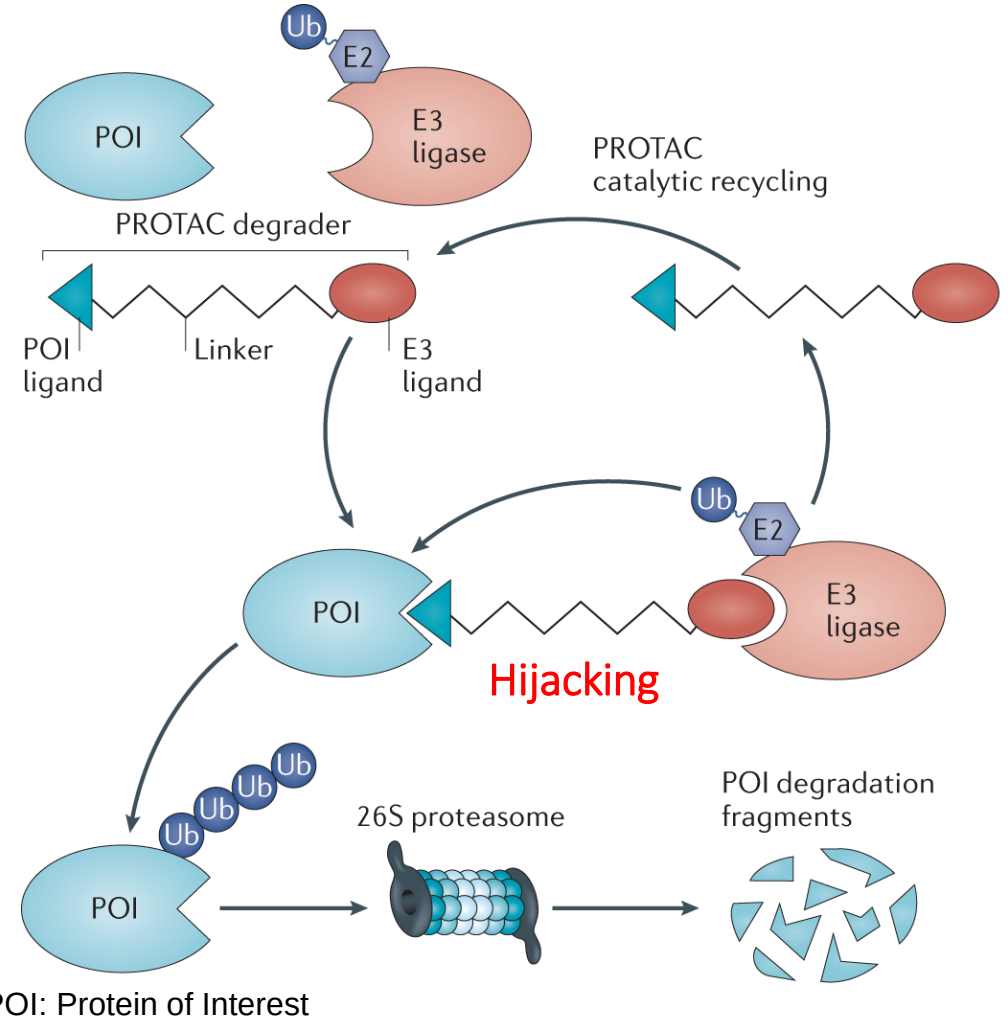
Straight Forward Design



https://openlabnotebooks.org/2714-2/

PROTAC (PROteolysis-Targeting Chimera)

POI: Protein of Interest

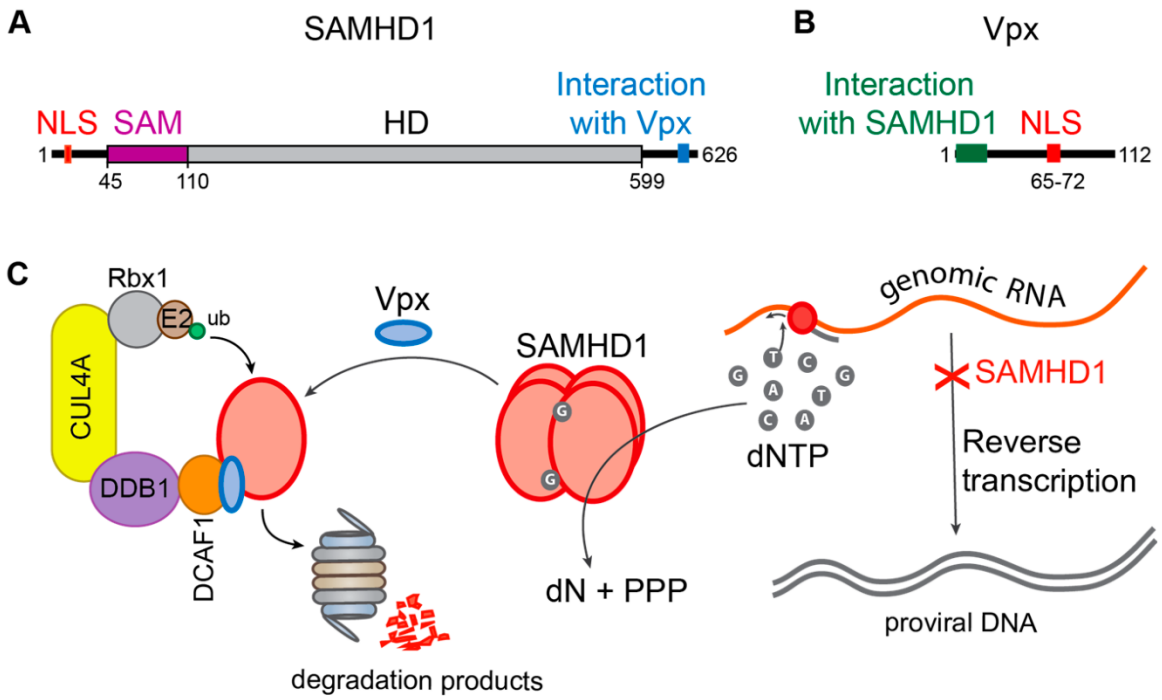


POI: Protein of Interest

Dale B, Cheng M, **Park KS**, et al. *Nat Rev Cancer.* **2021** 21(10):638-654.

Being Hijacked by Virus

Hijacking E3 ligase by HIV's Vpx protein



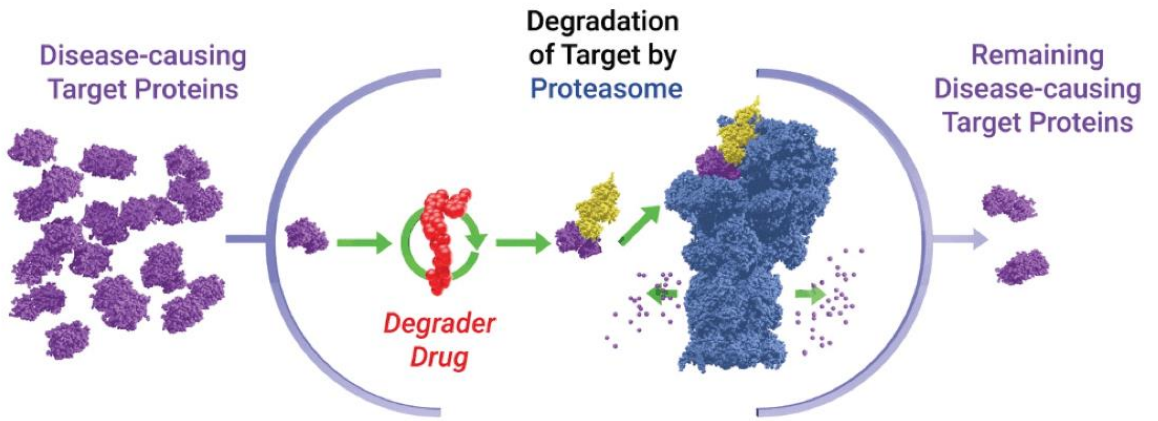
Viruses 9, 322-343.(**2017**)

"The most efficient way to control the host protein"

Conventional Inhibitor VS PROTAC

Degrader

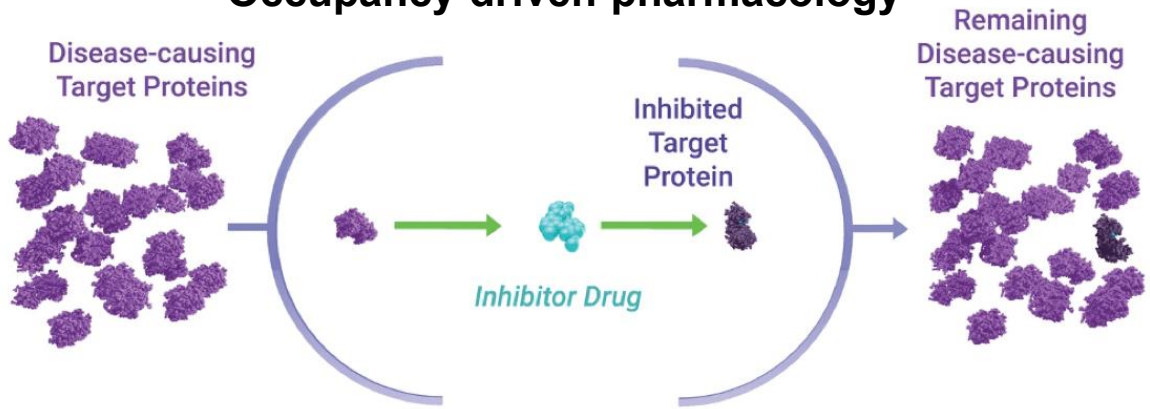
“Event-driven pharmacology”



Relatively low binding affinity binder can be used to design PROTAC

Inhibitor

“Occupancy-driven pharmacology”

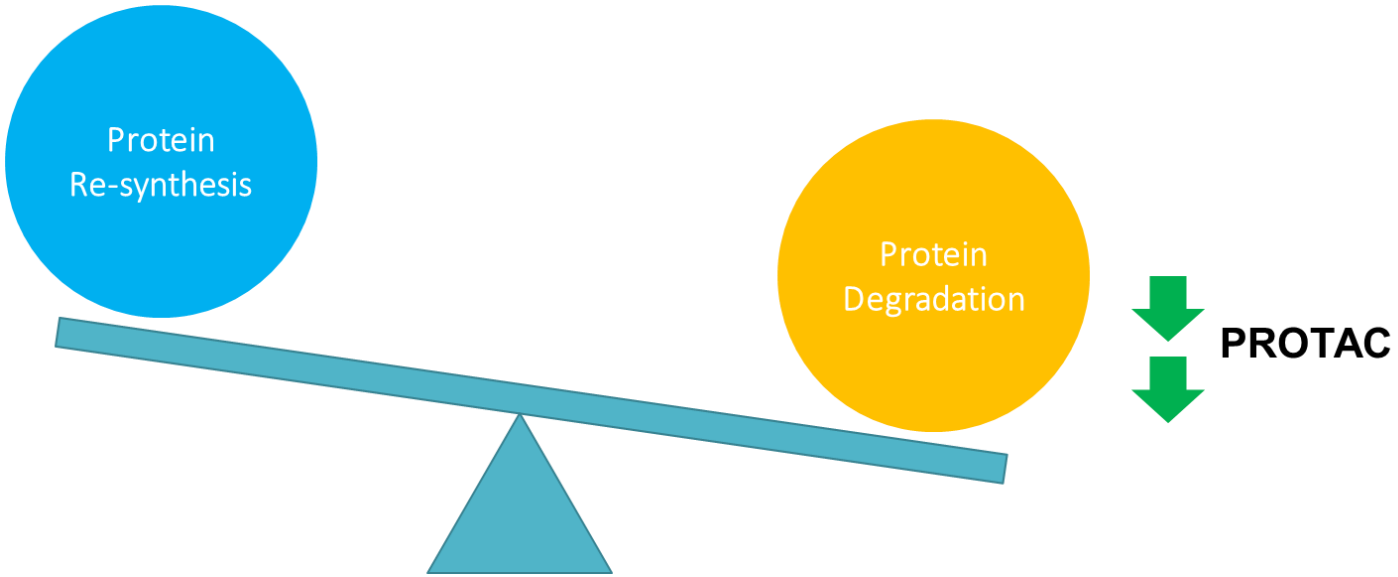


High binding affinity binder is required to design the effective inhibitor

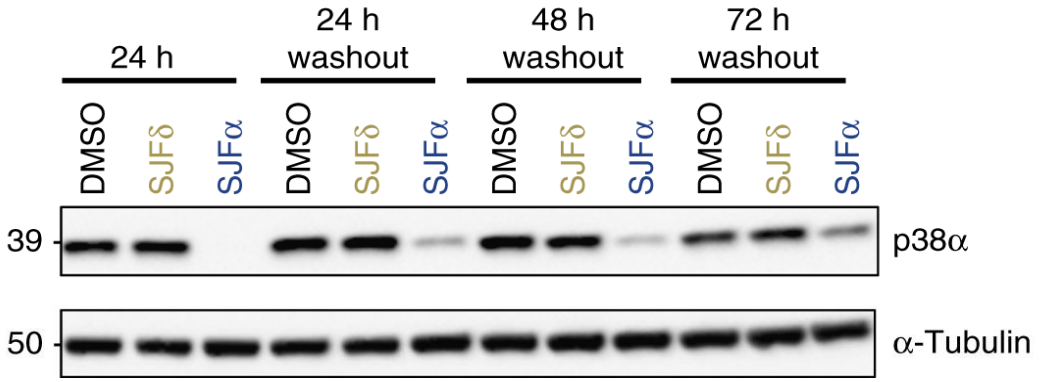
https://c4therapeutics.com/

Protein Homeostasis

Feedback Loop

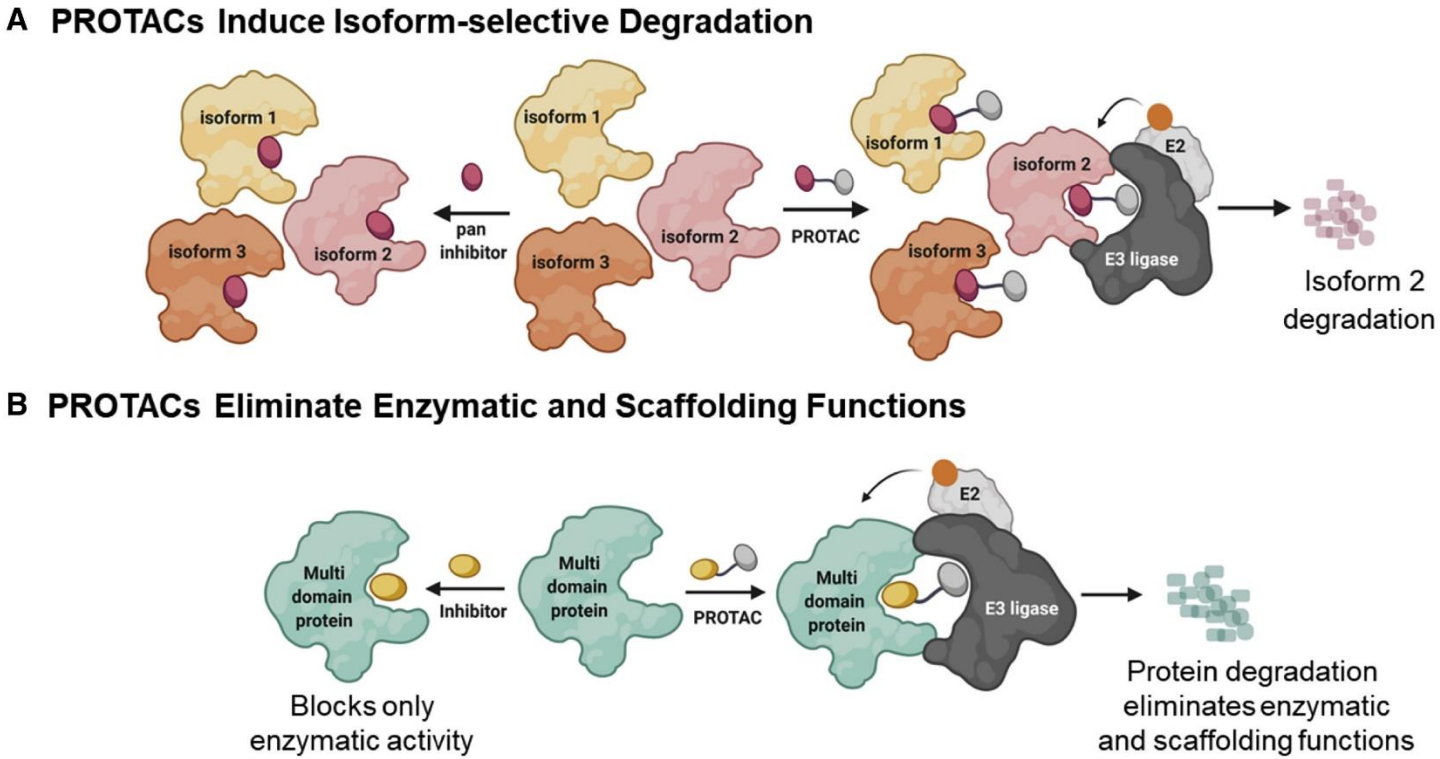


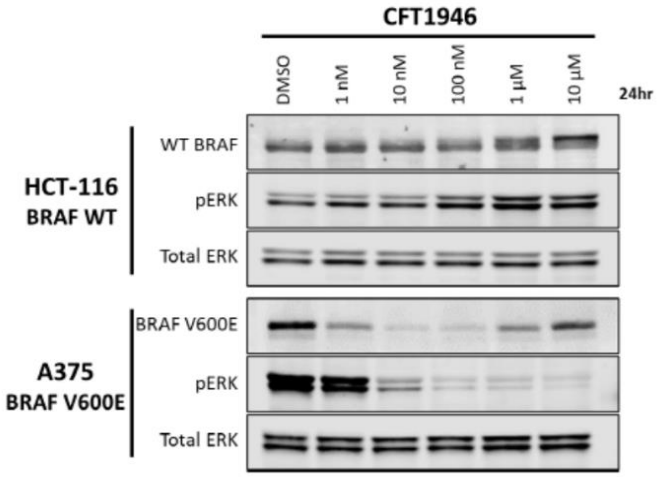
Protein Half-Life



Nat Commun **2019**, 10, p131.

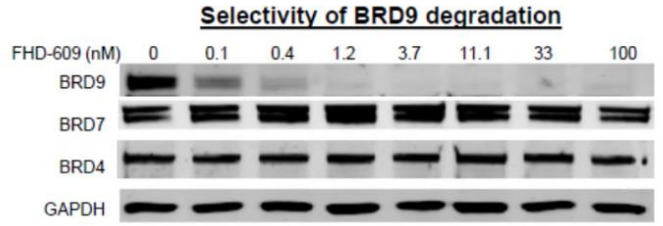
Interesting Features of PROTACs





Mutant Specific degradation by PROTAC

From C4 Thx

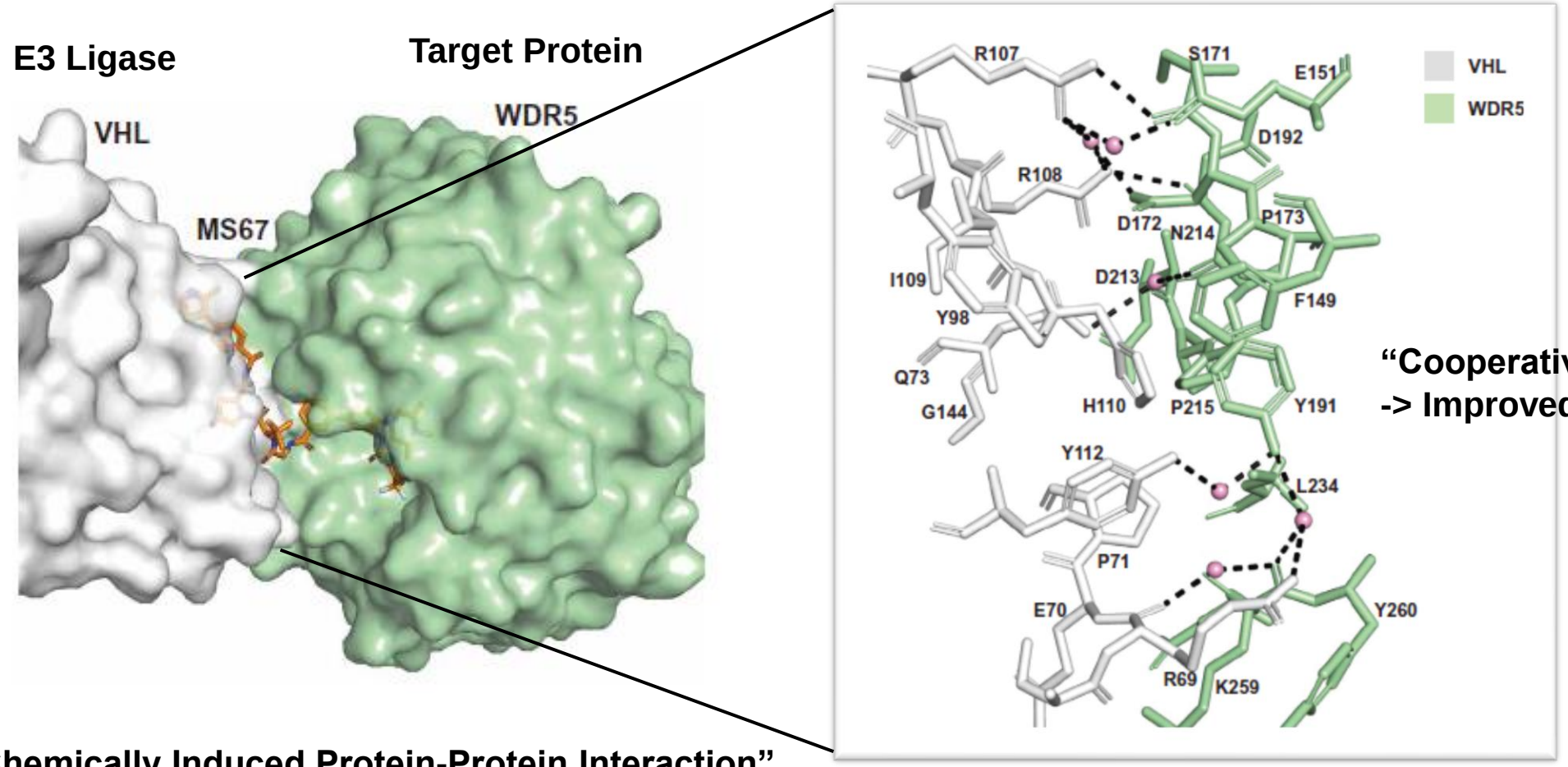


From Foghorn Thx

Cell Chemical Biology 27, **2020,** p998

New Protein-Protein Interaction

Protein-Protein Interaction energy + PROTAC Binding energy



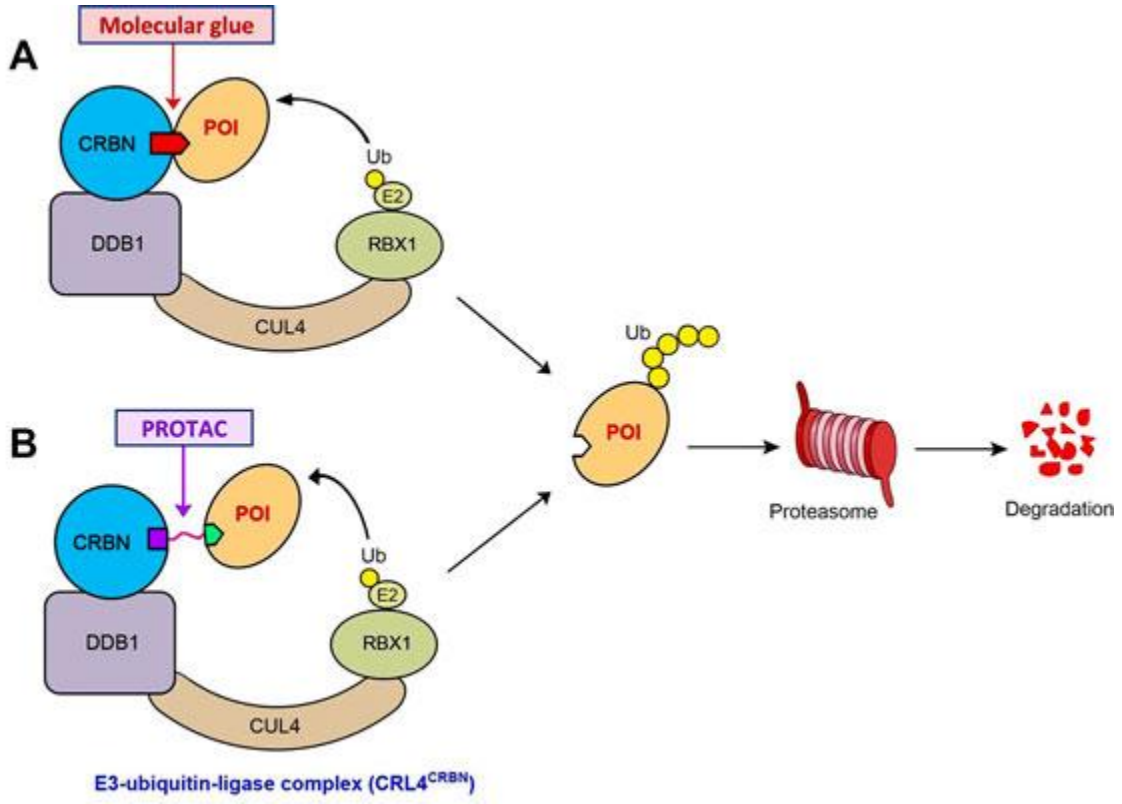
"Cooperative Interaction"
-> Improved Selectivity

"Chemically Induced Protein-Protein Interaction"

Yu X, Li D, Kottur J, Shen Y, Kim HS, **Park KS**, Tsai YH, Gong W, Wang J, Suzuki K, Parker J, Herring L, Kaniskan HÜ, Cai L, Jain R, Liu J, Aggarwal AK, Wang GG, Jin J. *Sci Transl Med.* **2021** Sep 29;13(613):eabj1578.

PROTAC vs Molecular Glue

	Molecular glues	PROTACs
Feature	Monovalent	Bivalent
Linker	No	Yes
Molecular weight	<500 Da	700-1000 Da
Lipinski's rule of 5	Within	Defy
Target	To be determined	Predictable
Binding pocket	Not required	Required
Binding affinity	Weak binding affinities for either E3 ligase or target protein is needed, display an event driven catalytic mechanism of action.	Strong binding to E3 ligase and the target protein, two ligands are connected by a linker.



Biochemistry **2023** 62 (3), 601-623

Clinical Trials

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	

AD, atopic dermatitis; AR, androgen receptor; BCL-x_L, B cell lymphoma-extra large; BRD9, bromodomain-containing protein 9; BTK, Bruton's tyrosine kinase; CRBN, cereblon; EGFR, epidermal growth factor receptor; ER, oestrogen receptor; HS, hidradenitis suppurativa; IND-e, in IND-enabling preclinical studies; IRAK4, interleukin-1 receptor-associated kinase 4; i.v., intravenous; PROTAC, proteolysis-targeting chimera; RA, rheumatoid arthritis; ROA, route of administration; STAT3, signal transducer and activator of transcription 3; TRK, tropomyosin receptor kinase; VHL, von Hippel–Lindau.

Nature reviews. Drug discovery, **2022**, 21 (3), p.181-200

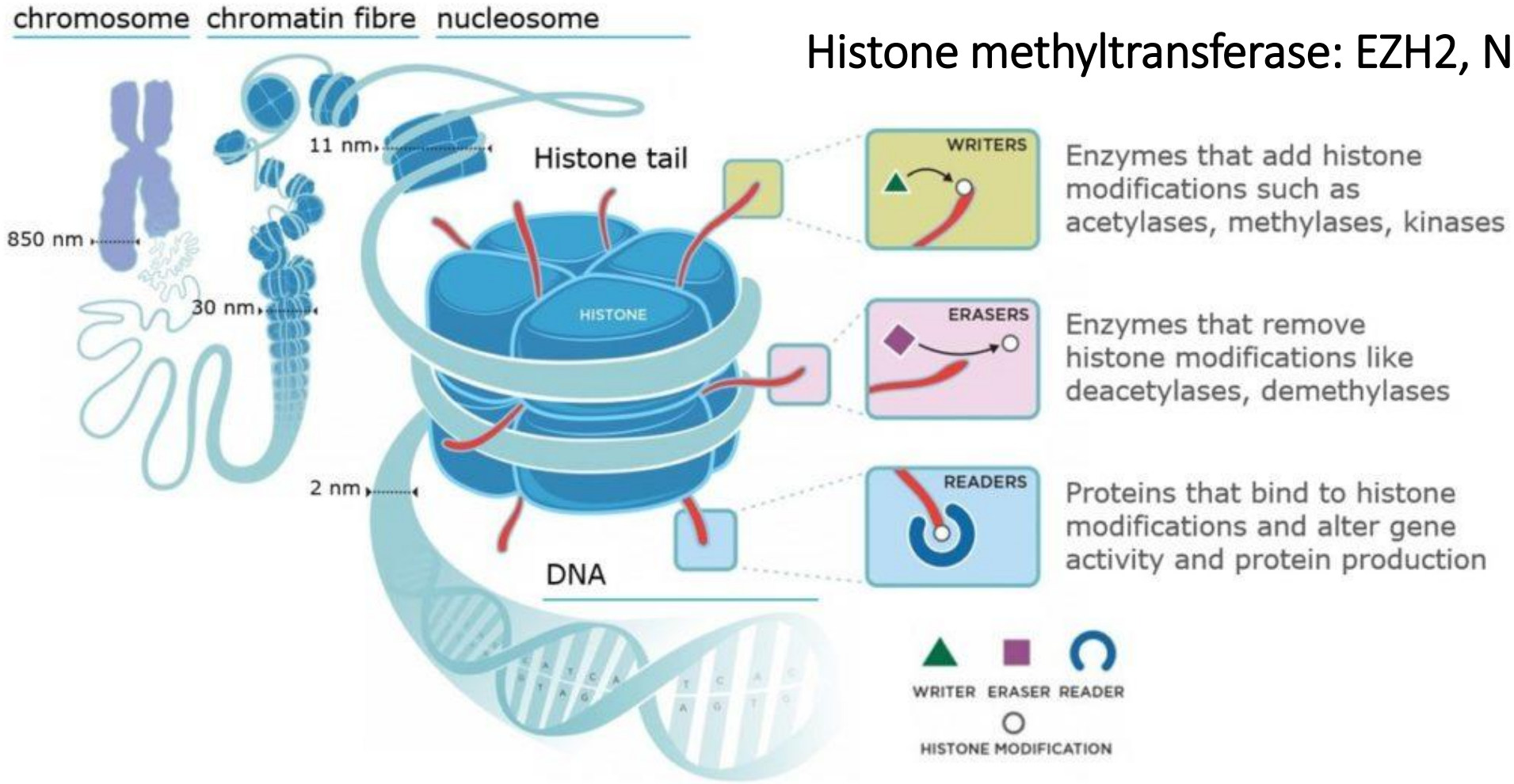
Table 1 | Selected protein degraders being tested in clinical trials

Treatment	Organization(s)	Target	Phase	Lead indication
Vepdegestrant (ARV-471)	Arvinas and Pfizer	Estrogen receptor	3	Metastatic breast cancer
ARV-766	Arvinas and Novartis	Androgen receptor	3	Metastatic castration-sensitive and castration-resistant prostate cancer
Bavdegalutamide (ARV-110)	Arvinas	Androgen receptor	1/2	Metastatic castration-resistant prostate cancer
ARV-102	Arvinas	LRRK2	1	Parkinson's disease
KT-474	Kymera Therapeutics	IRAK4	2	Hidradenitis suppurativa and atopic dermatitis
KT-333	Kymera Therapeutics	STAT3	1a/b	Refractory leukemias and lymphomas
NX-5948	Nurix Therapeutics	BTK	1a/b	B cell cancers
NX-2127	Nurix Therapeutics	BTK and IKZF	1b	B cell cancers

2024 updated version

Application Example – Targeting Epigenetic Regulators

Epigenetic Regulators



Histone methyltransferase: EZH2, NSD2/3, G9a/GLP

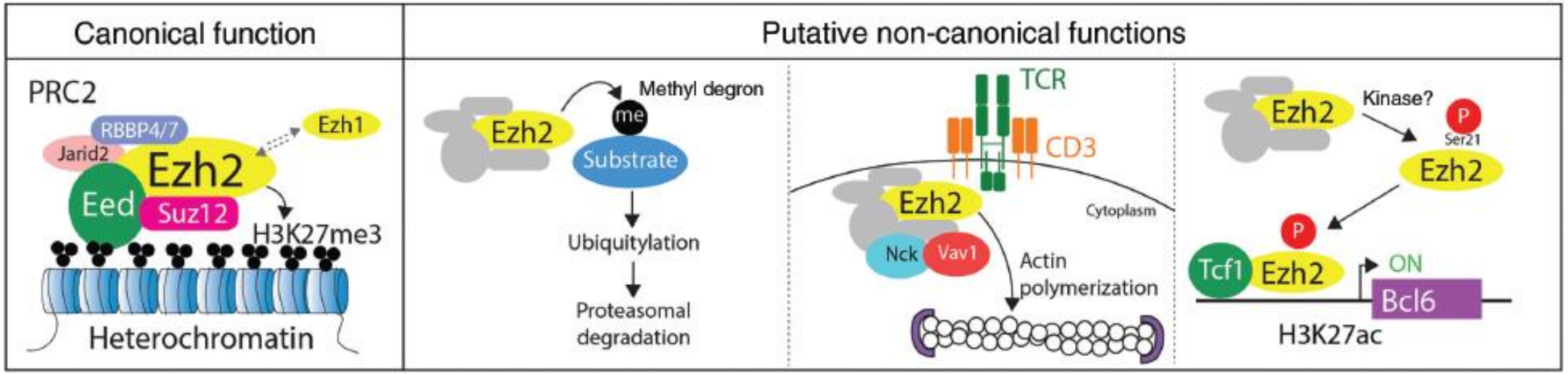
Role of EZH2 in Cancer

Biological importance

PRC2 Status	Associated Cancer Type
EZH2 overexpression	Hematological malignancies [5] Pancreatic cancer [7,8] Chronic Pancreatitis [10] Prostate cancer [11] Breast cancer [13,14] Bladder carcinoma [15–17] Gastric cancer [20] Lung cancer [22,23] Hepatocellular carcinoma [26–28] Glioblastoma multiforme [31] Cervical Cancer [33,34] Ovarian cancer [35] Melanoma [36] Soft Tissue Sarcoma [39,40] Lymphoma, Mantle-Cell [41] Colorectal cancer [42–44] Retinoblastoma [45] Tongue cancer [46,47]

Mol Cancer Ther (2018) 17 (3): 591–602.

Role of PRC2 Complex



Biol. Chem. **2020**; 401(8): 933–943

"Canonical function"
&
"Non-Canonical function"

Discovery of EZH2 Degraders

ARTICLES
https://doi.org/10.1038/s41589-019-0421-4
nature chemical biology

Discovery of a first-in-class EZH2 selective degrader

Anqi Ma[1,5], Elias Stratikopoulos[2,5], Kwang-Su Park[1,5], Jieli Wei[1], Tiphaine C. Martin[2], Xiaobao Yang[1], Megan Schwarz[2], Violetta Leshchenko[3], Alexander Rialdi[2], Brandon Dale[1], Alessandro Lagana[4], Ernesto Guccione[1,2], Samir Parekh[2,3], Ramon Parsons[2*] and Jian Jin[1,2*]

Published online 27 October 2022

Nucleic Acids Research, 2022, Vol. 50, No. 19 10929–10946
https://doi.org/10.1093/nar/gkac861

A cryptic transactivation domain of EZH2 binds AR and AR's splice variant, promoting oncogene activation and tumorous transformation

Jun Wang[1,2,†], Kwang-Su Park[3,†], Xufen Yu[3], Weida Gong[1], H. Shelton Earp[1,4,5], Gang Greg Wang[1,2,4,*], Jian Jin[3,*] and Ling Cai[1,6,*]

ARTICLES
https://doi.org/10.1038/s41556-022-00850-x
nature cell biology

EZH2 noncanonically binds cMyc and p300 through a cryptic transactivation domain to mediate gene activation and promote oncogenesis

Jun Wang[1,2,8], Xufen Yu[3,8], Weida Gong[1], Xijuan Liu[1], Kwang-Su Park[3], Anqi Ma[3], Yi-Hsuan Tsai[1], Yudao Shen[3], Takashi Onikubo[4], Wen-Chieh Pi[5], David F. Allison[1,2], Jing Liu[3], Wei-Yi Chen[5], Ling Cai[1,6], Robert G. Roeder[4], Jian Jin[3] ✉ and Gang Greg Wang[1,2,7] ✉

ACS Pharmacology & Translational Science

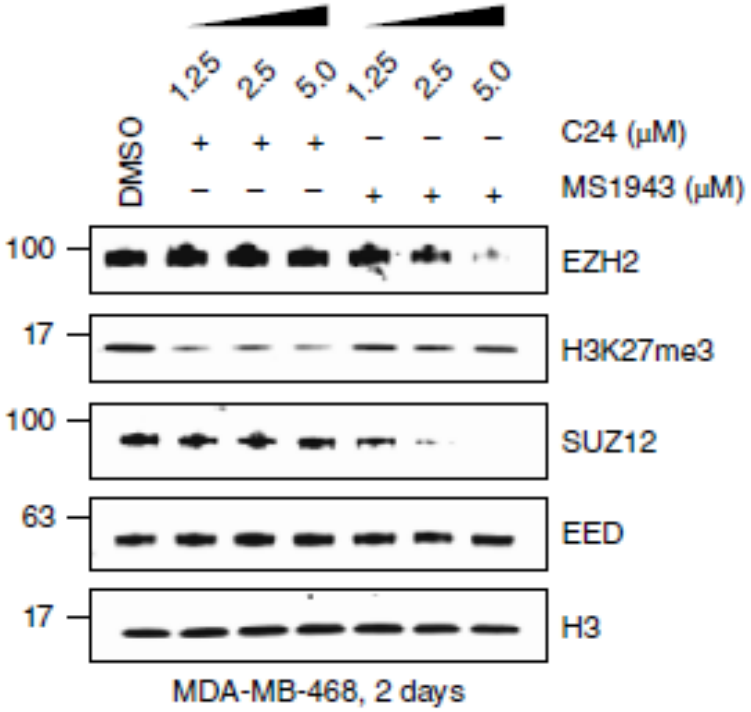
pubs.acs.org/ptsci Article

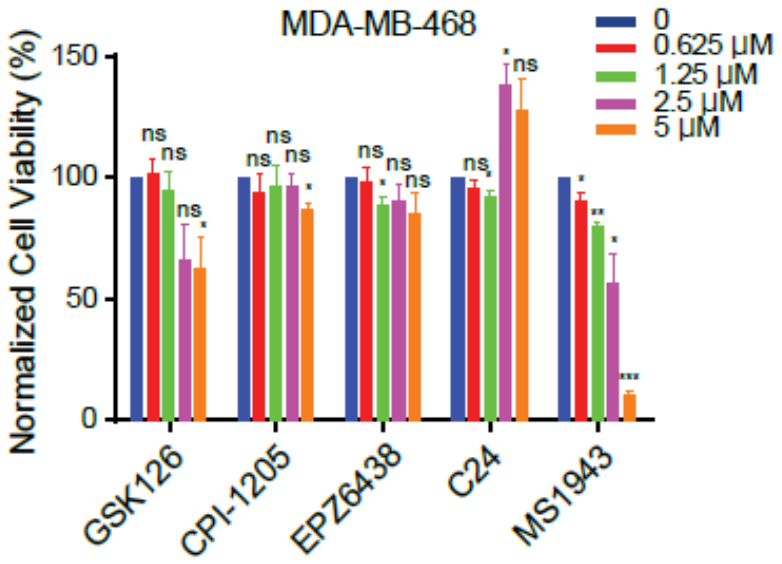
Targeting Triple-Negative Breast Cancer by a Novel Proteolysis Targeting Chimera Degrader of Enhancer of Zeste Homolog 2

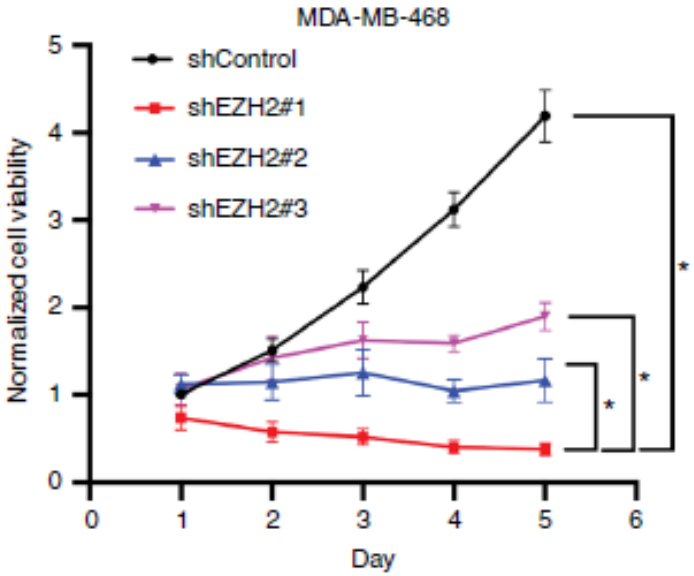
Published as part of the ACS Pharmacology & Translational Science virtual special issue "New Drug Modalities in Medicinal Chemistry, Pharmacology, and Translational Science".

Brandon Dale,[#] Chris Anderson,[#] Kwang-Su Park, H. Ümit Kaniskan, Anqi Ma, Yudao Shen, Chengwei Zhang, Ling Xie, Xian Chen, Xufen Yu,* and Jian Jin*

Discovery of EZH2 degrader in Breast Cancer







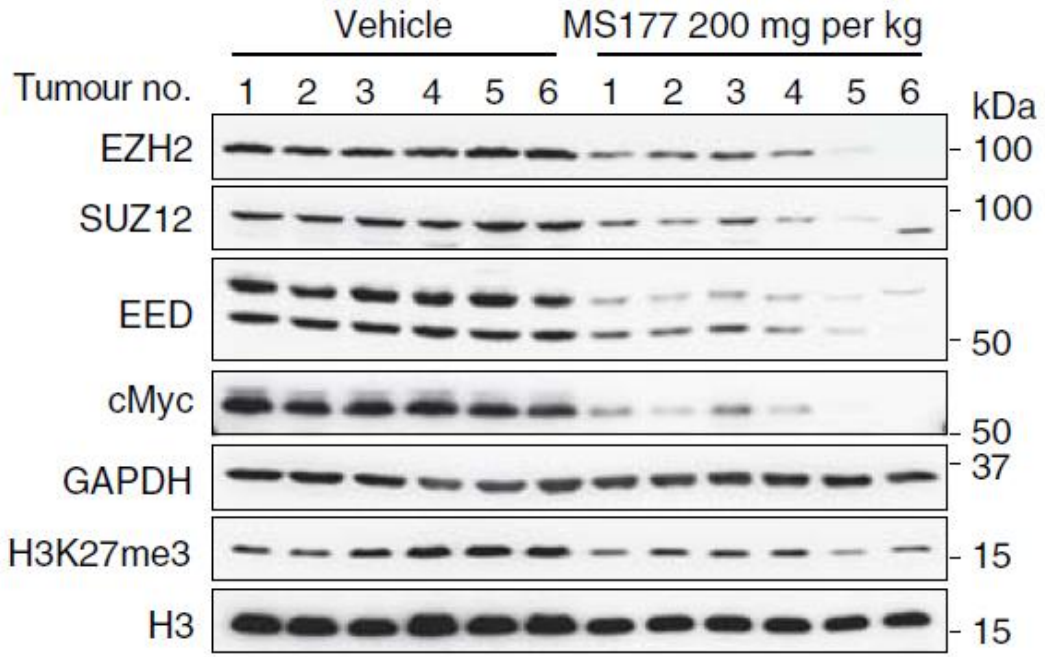
Tazemetostat - AML

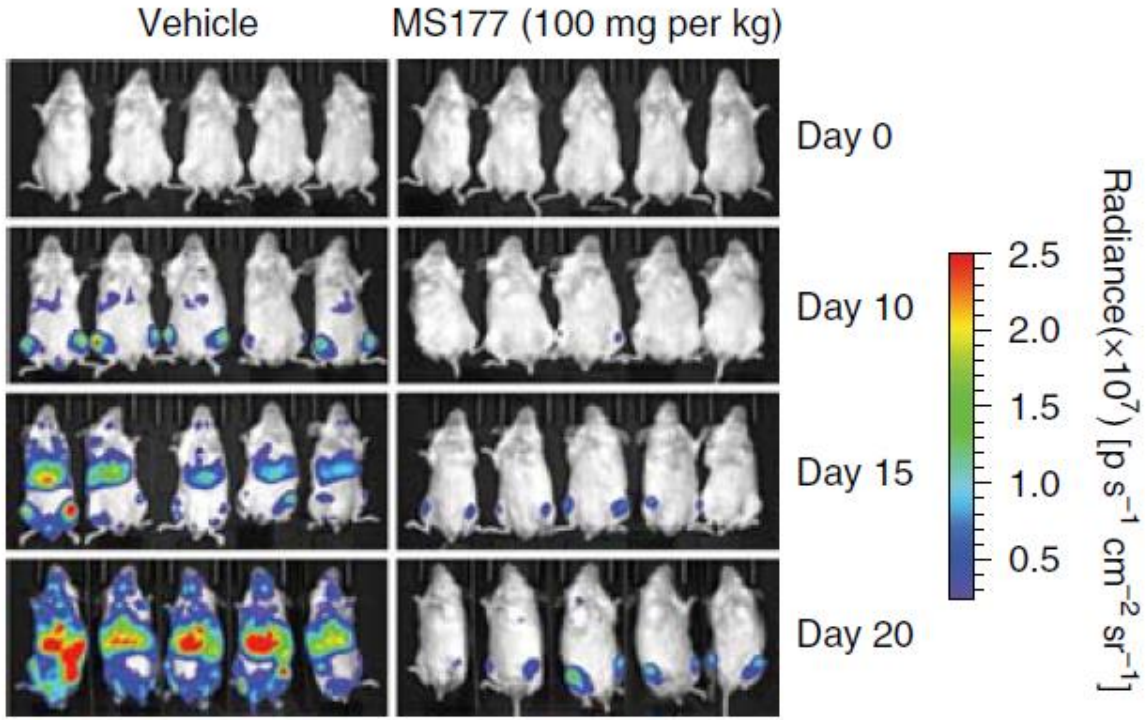
"Non canonical function"
(or non enzymatic function)

Degrader can abolish not only enzymatic activity but also protein-protein interactions

Ma A*, Stratikopoulos E*, **Park KS***, Wei J, Martin TC, Yang X, Schwarz M, Leshchenko V, Rialdi A, Dale B, Lagana A, Guccione E, Parekh S, Parsons R, Jin J. Discovery of a first-in-class EZH2 selective degrader. ***Nat Chem Biol***.,16(2), p214-222 (**2020**).

Discovery of EZH2 degrader in Blood Cancer

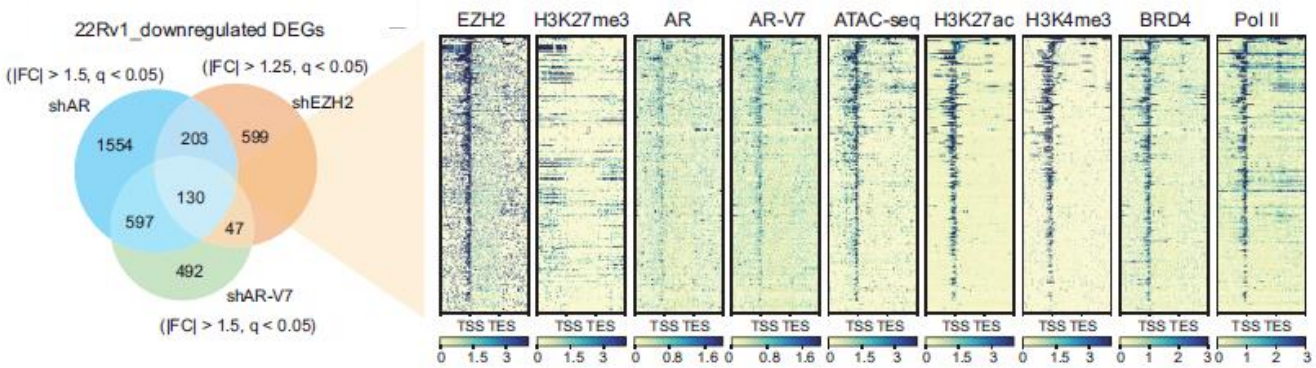




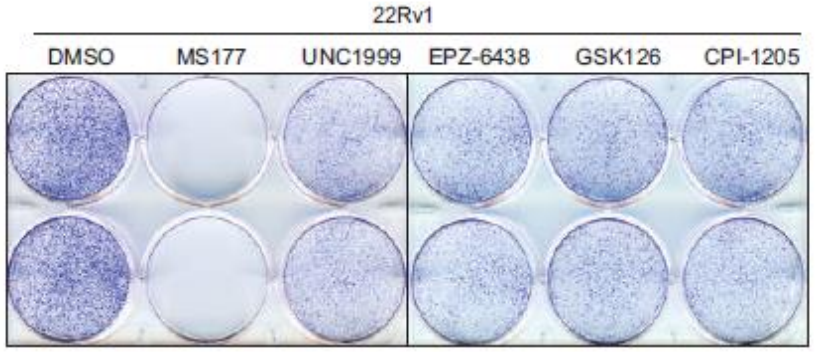
Wang J, Yu X, Gong W, Liu X, **Park KS**, Ma A, Tsai YH, Shen Y, Onikubo T, Pi WC, Allison DF, Liu J, Chen WY, Cai L, Roeder RG, Jin J, Wang GG. EZH2 noncanonically binds cMyc and p300 through a cryptic transactivation domain to mediate gene activation and promote oncogenesis. ***Nat Cell Biol.***, 24(3), p384-399 (**2022**).

Discovery of EZH2 degrader in Prostate Cancer

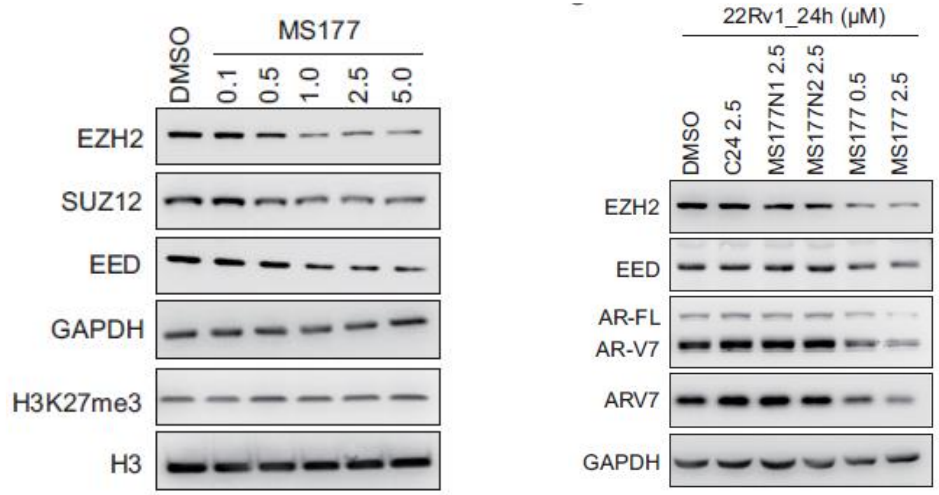
RNA-Seq analysis for the cooperative down regulation of EZH2/AR

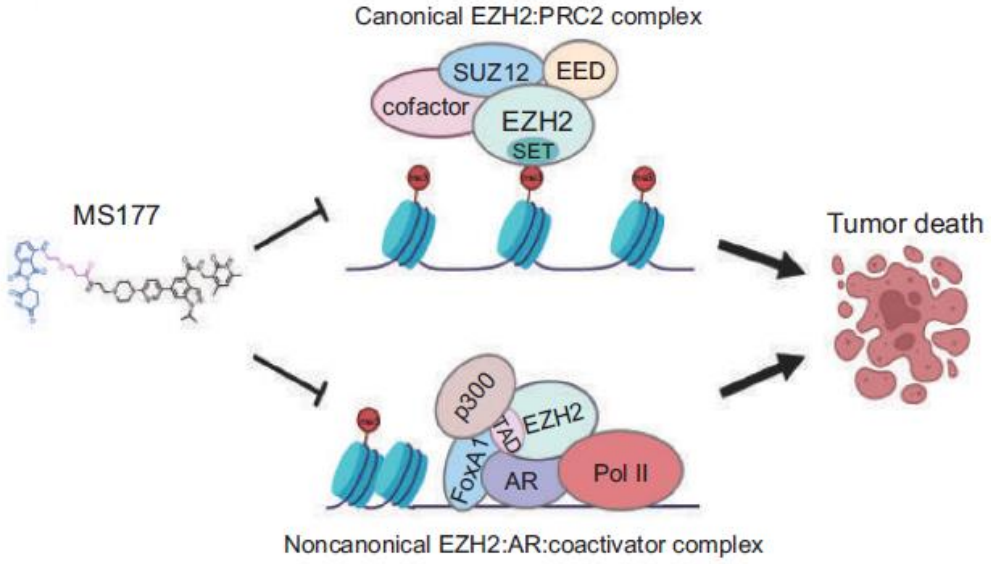


Clonogenic assay for MS177



Degradation profile of MS177 in prostate cancer

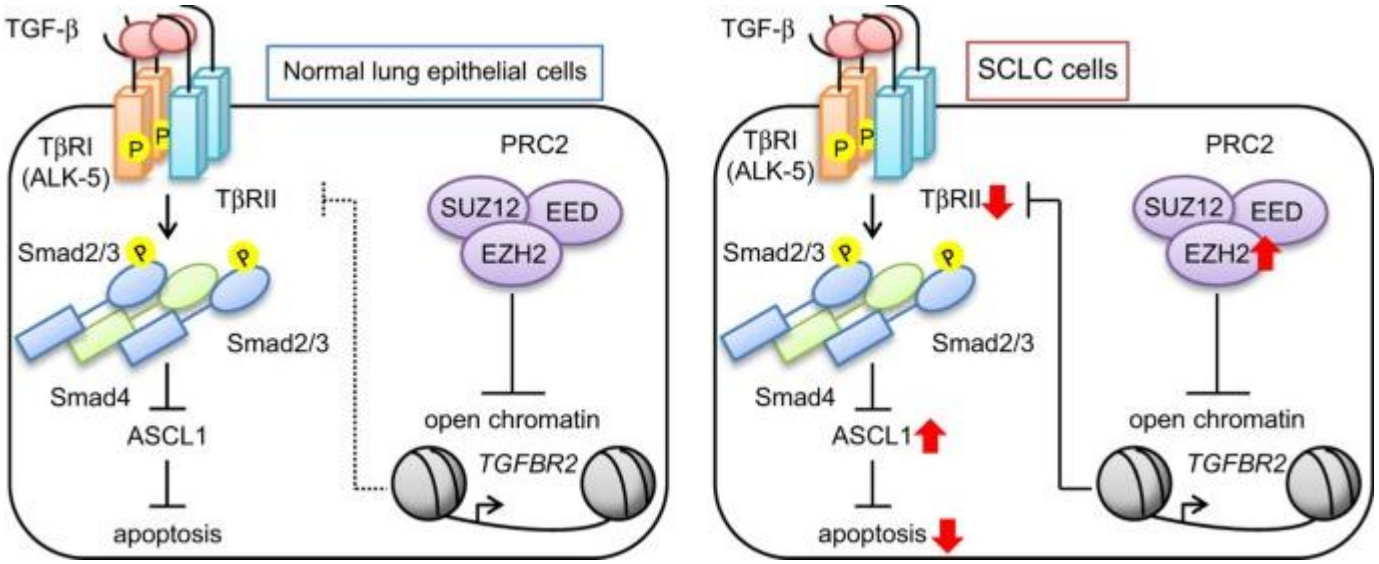




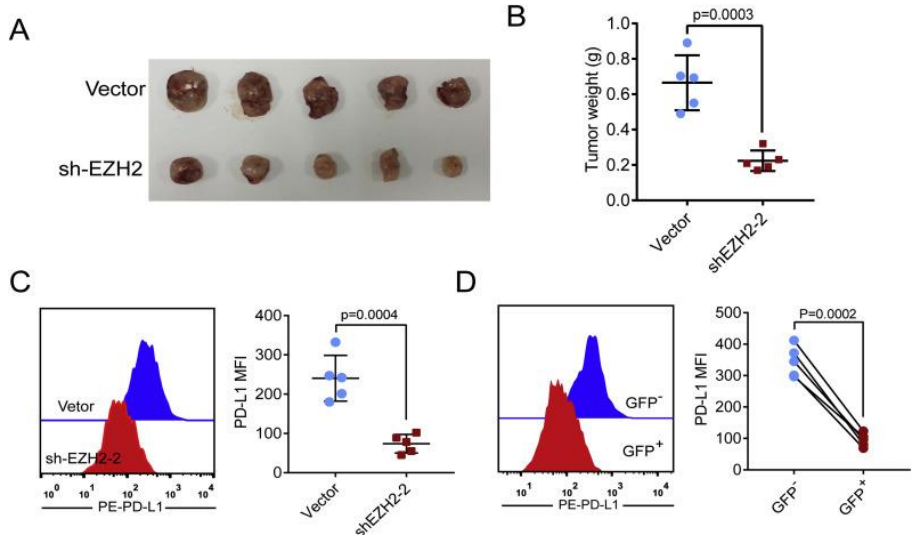
Wang J*, **Park KS***, Yu X, Gong W, Earp HS, Wang GG, Jin J, Cai L. A cryptic transactivation domain of EZH2 binds AR and AR's splice variant, promoting oncogene activation and tumorous transformation. ***Nucleic Acids Res***., 50(19), p10929-10946 (**2022**).

Role of EZH2 in Lung Cancer

In SCLC



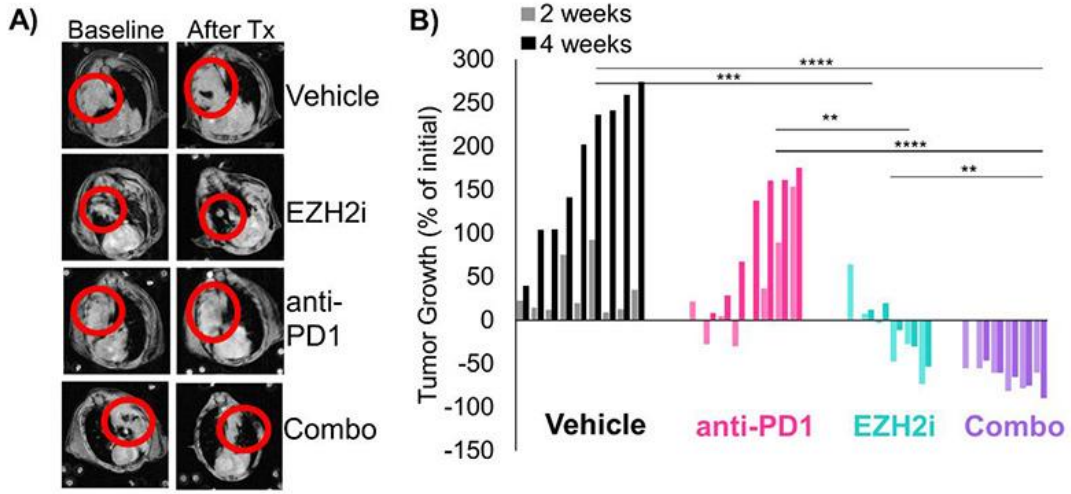
In NSCLC



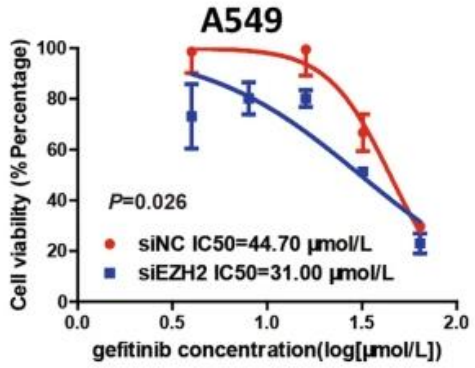
Cell Discov **2015**, 1, 15026.

Biochem Biophys Res Commun. **2019** 517(2):201-209.

In Lung squamous cell carcinoma (LSCC)

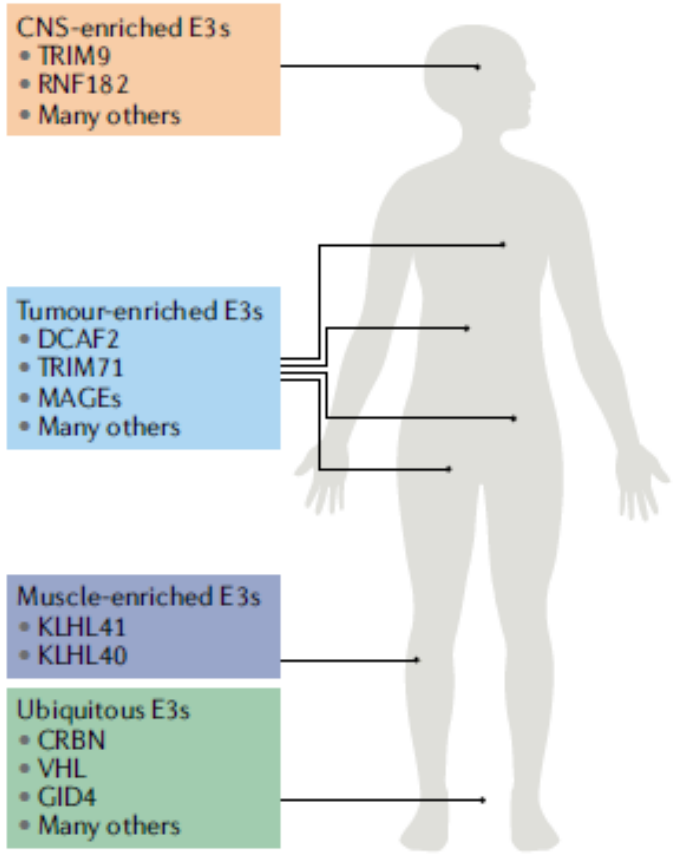


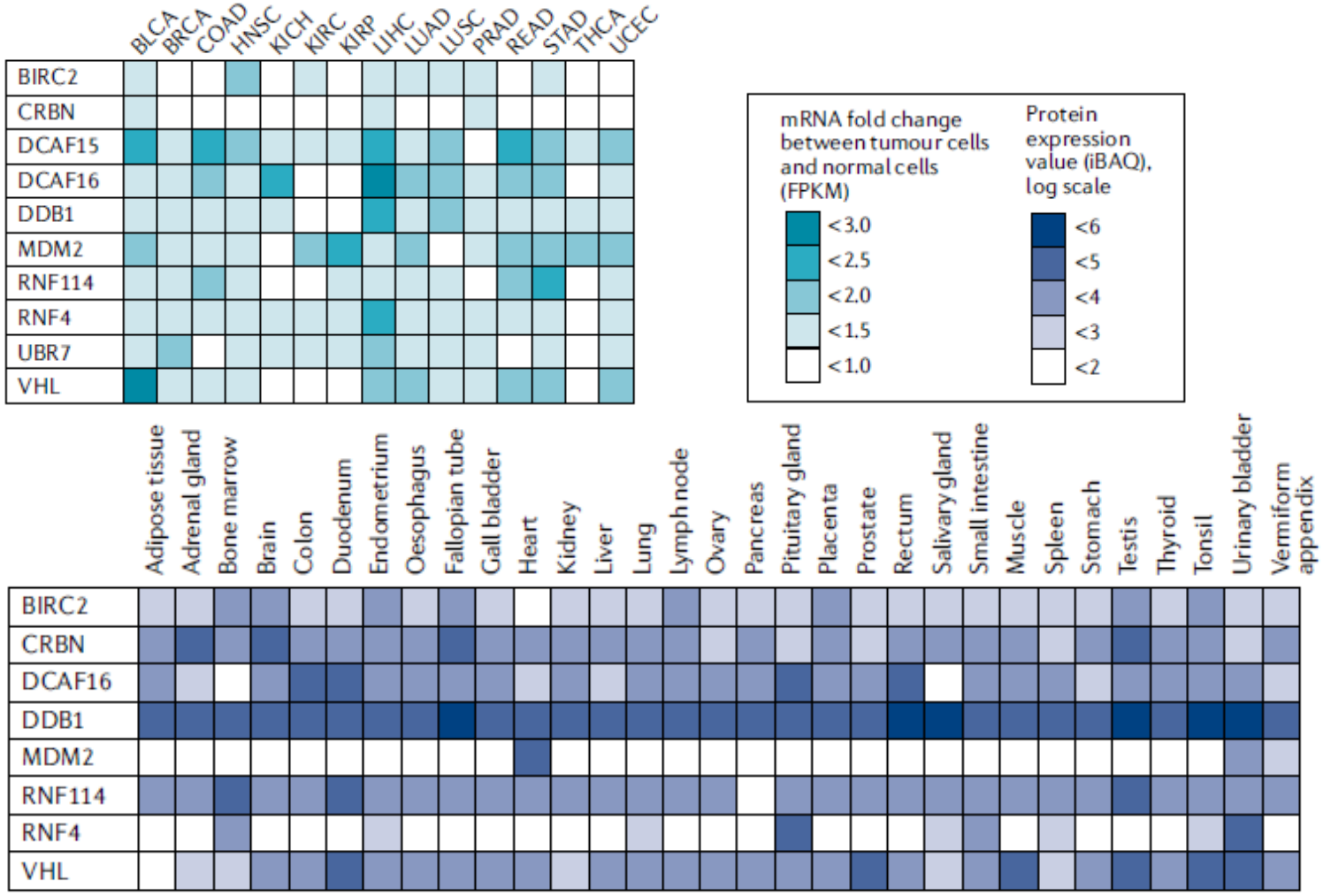
Cancer Research Communications **2024**, 4 (2): 388–403.



BMC Cancer **2020**, 20, 1189.

Future Directions





Nature reviews. Drug discovery, **2022**, 21 (3), p.181-200

Dale B, Cheng M, **Park KS**, et al. *Nat Rev Cancer.* **2021** 21(10):638-654.

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All lab members

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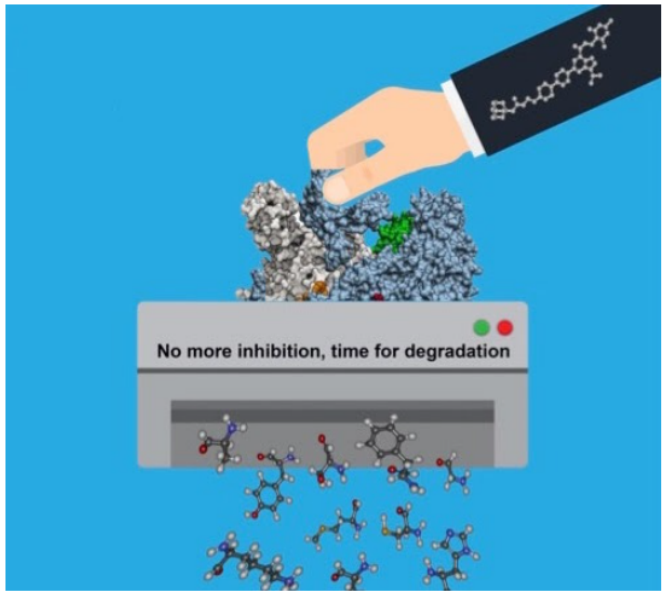

Unlocking the Future of Modulating Disease Proteins

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BRL Team

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기초연구실 (BRL)
신진연구자 인프라 구축 사업

Thank you for your attention!!