Medicilon

Medicilon Webinars

A.C.E.

America with China Empowerment Seminar Series

Seminar 2: Patent enforcement and clearance for freedom-to-operate in the U.S.

March 4, 2023 09:00-10:00(ET)
March 4, 2023 22:00-23:00 (Beijing)

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Moderator

Karsten Holm , Ph.D.
Director of BD at Medicilon

Welcome Speech Speaker

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Xingquan Ma Ph.D.

SVP of Chemistry

SIOC 1950

Scripps Research

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PROTAC Platform And Its Application Case In Drug Discovery

Xingquan Ma, Ph.D
SVP, Head of Chemistry

Contents

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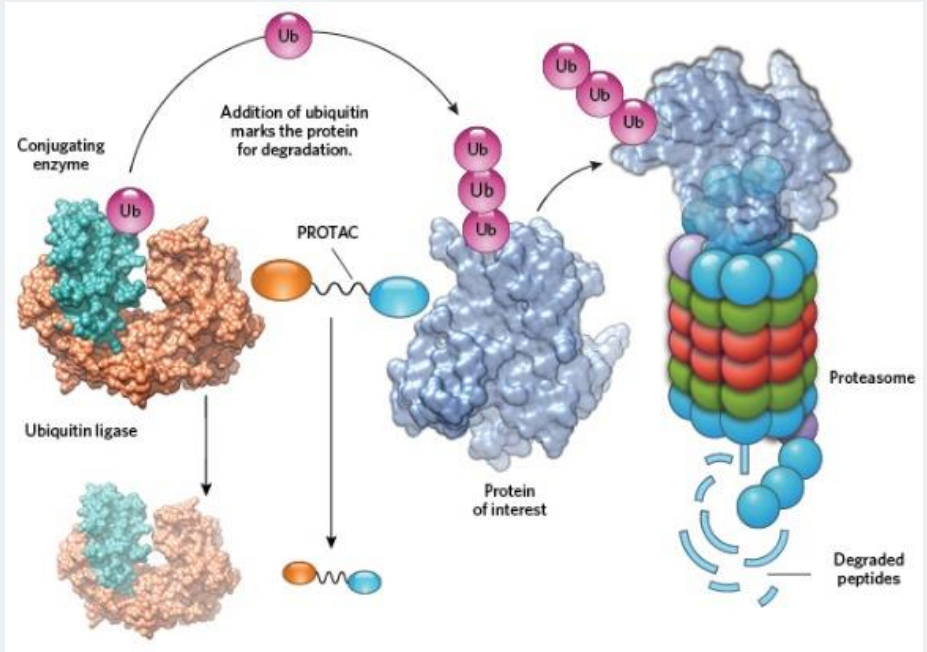
Proteolysis targeting chimeras Technology



Drug Discovery

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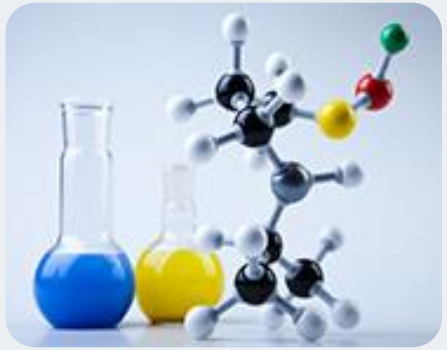
Discovery Chemistry

- **Target Synthesis (single compounds or libraries)**
- Intermediates and building blocks
- Reference compounds
- Final products
- Scaling up preparation
- **Medicinal chemistry**
- Chemical synthesis
- SAR
- CADD

Synthetic Chemistry

- Route design and troubleshooting
- Asymmetric synthesis
- Complex Molecules (e.g. Natural Products)
- Complex Ring Systems (e.g. b-Lactams, Macrolides, Macrocycles)
- Hydrogenation
- Heterocyclic chemistry
- Organoboronchemistry
- Organophosphorouschemistry
- Nucleoside/nucleotide chemistry
- Peptide chemistry
- Carbohydrate Chemistry



Special Expertise in Chemistry

- Heterocyclic chemistry
- Carbohydrate chemistry
- Nucleoside chemistry
- Peptide chemistry
- Antibody Drug Conjugation

New Drug Development Service

- Protein degradation technique (PROTAC and LyTAC)
- siRNA services center
- ADC service platform

Service Models

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Fee For Service (FFS)

- Fixed price quoted for amount of specific synthesis of a molecule, series of molecules, or small library
- Fixed price quoted for a specific service, e.g. chiral separation, fragment-based screening.
- Literature precedent very important for accurate quotation
- CMC work for IND application and IND investigation
- Non-GMP and GMP scale-up, commercial production of API and intermediates

Full Time Equivalent (FTE)

- Dedicated full time employees
- Dedicated teams with well-organized structure
- Flexibility to increase or decrease team size
- Flexibility to reprioritize targets/project direction
- Synthetic chemistry support, medicinal chemistry, and integrated services
- Process chemistry, process R&D, demonstration batch

Integrated Service (INT)

- From Target to IND enabling
- Drug Design and Synthesis
- Drive the project by Medicilon
- Including Hit to Lead to lead optimization to PCC
- Milestone payment
- Dedicated teams of Chemistry, Biology, PK, CMC, pre-clinical
- IND registration in both China and USA
- Risk Sharing

Platform

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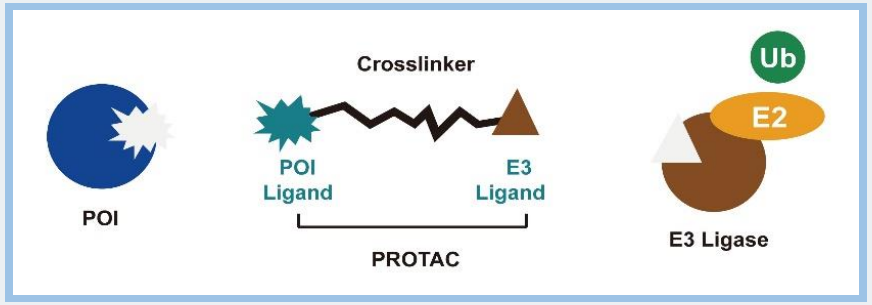
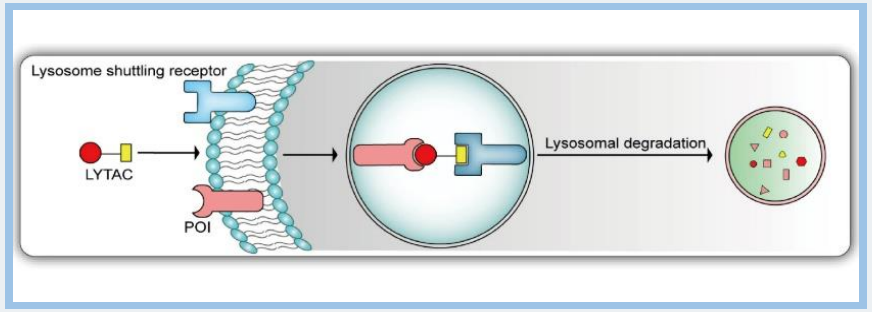
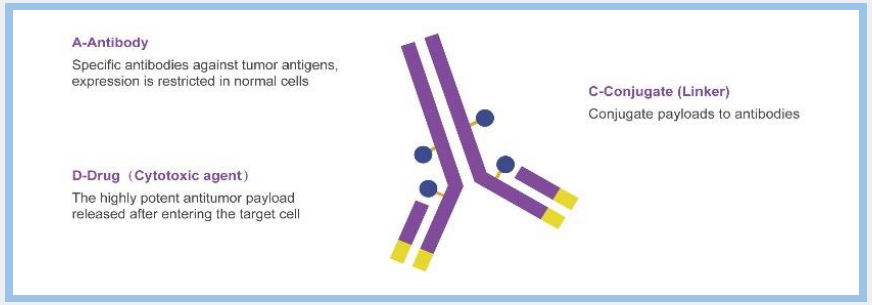


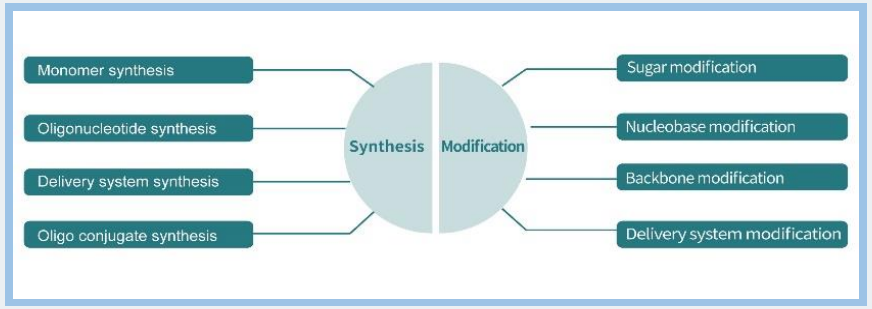
Integrated PROTACs Platform



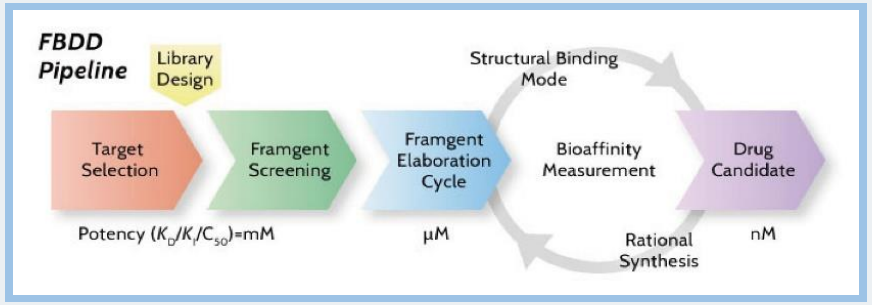
LyTAC Platform



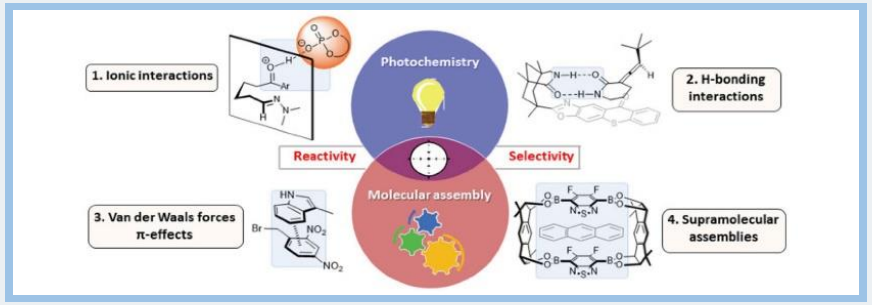
ADC R&D Service Platform



Nucleic Acid Drug R&D Platform



FBDD, SBDD Platform



Photochemistry Platform

PROTACs Platform of Medicilon

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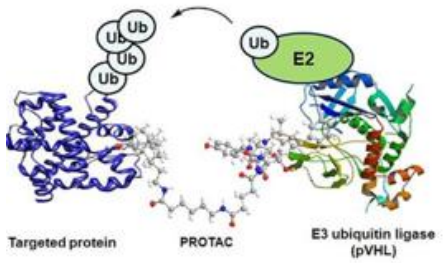
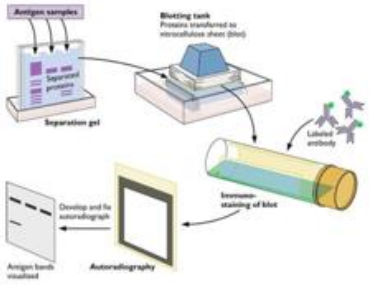


PROTACs Chemistry



PROTACs *In Vitro* Evaluation

PROTACs *In Vivo* Evaluation

Advantage of Medicilon PROTACs Platform

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Challenges in PROTAC Drug Discovery

- Lack of rules and standards
- Chemical/synthetic Complexity
- How to quickly and effectively screen for target protein
- PK
- …

VS

One-stop shop services

- Broad experience in design, synthesis and validation
- Fast turnaround times
- High KPI & Productivity with competitive pricing
- Validated PROTAC targets in Medicilon

  IRAK4, AR, ER, IKZF1, IKZF2, IKZF3, BTK, EGFR, BRD4, BCL-xL, CDK4, CDK6, SMARCA2, SMARCA4, AKT, ALK, STAT3, SHP2, FGFR1, FGFR2, KRAS G12C, KRAS G12D
- API-CMC
- ADME/DMPK
- Pharmacology, toxicity, IND enabling

PROTACs Synthesis Services

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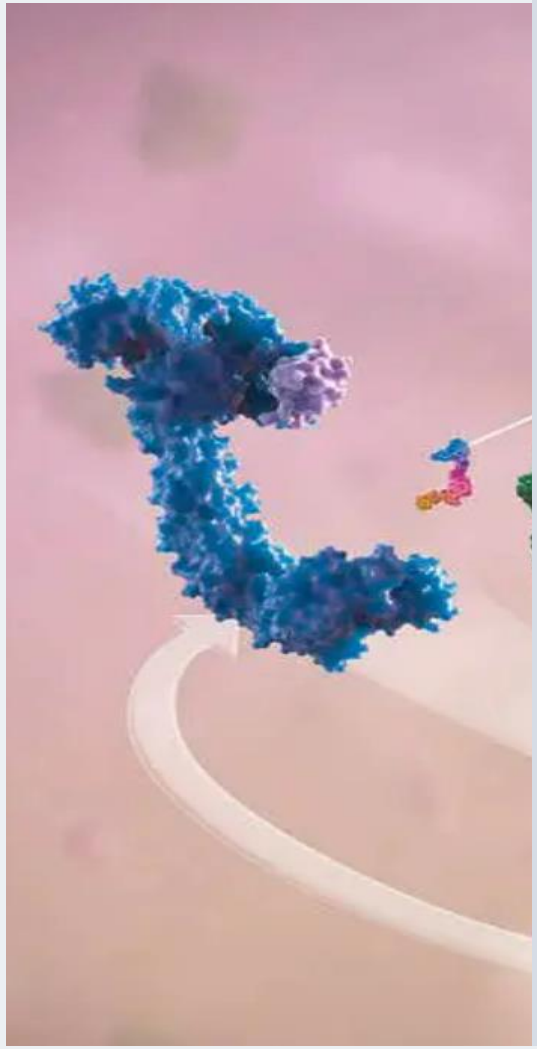

Medicilon has:

- **Know-how: > 6 years** PROTACs experience
- **Comprehensiveness: > 20** ongoing projects
- **Talent: > 300** dedicated well-trained chemists
- **Building Block: > 300** advanced linkers available
- **Scaffold: > 150** E3 ligands available including Cereblon, VHL, MDM2, IAP, etc.

PROTACs Synthesis Services

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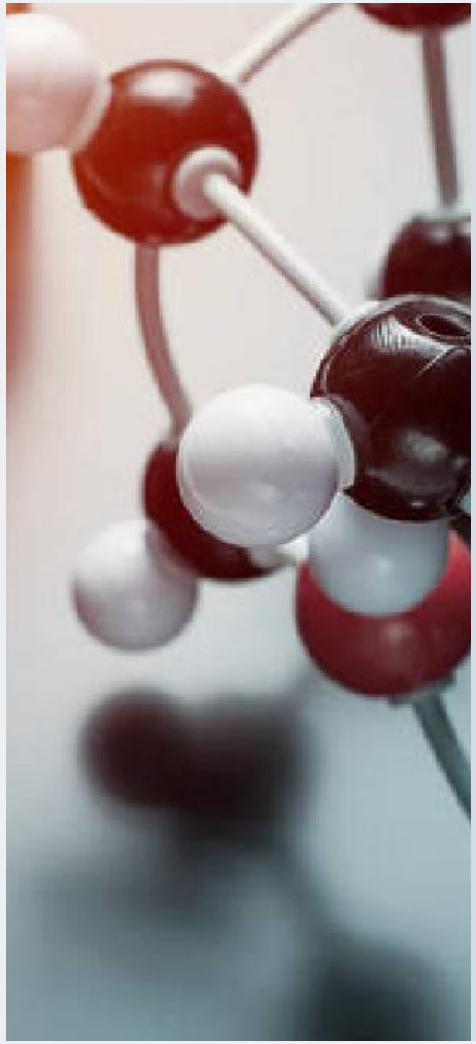


- **Dedicated teams:** chemists and analysts
- **Chromatography**: UPLC, HPLC, LC-MS, GC, IC, SFC
- **Solid analysis**: DSC, TGA, XRPD, PSD, Polarized light microscopy
- **Analysis and identification**: NMR, FT-IR, EA
- **General test**: KF, UV-Vis, Polarimeter
- **Analysis of elements and trace metals**: ICP-MS
- **Process development**

Dedicated Purification team

- **>50** PROTACs purification system
- **>95%** purification success rate
- **>80%** recovery rate
- **<48 h** purification cycle time

Shimadzu LCMS-2020

Waters UPLC-MS

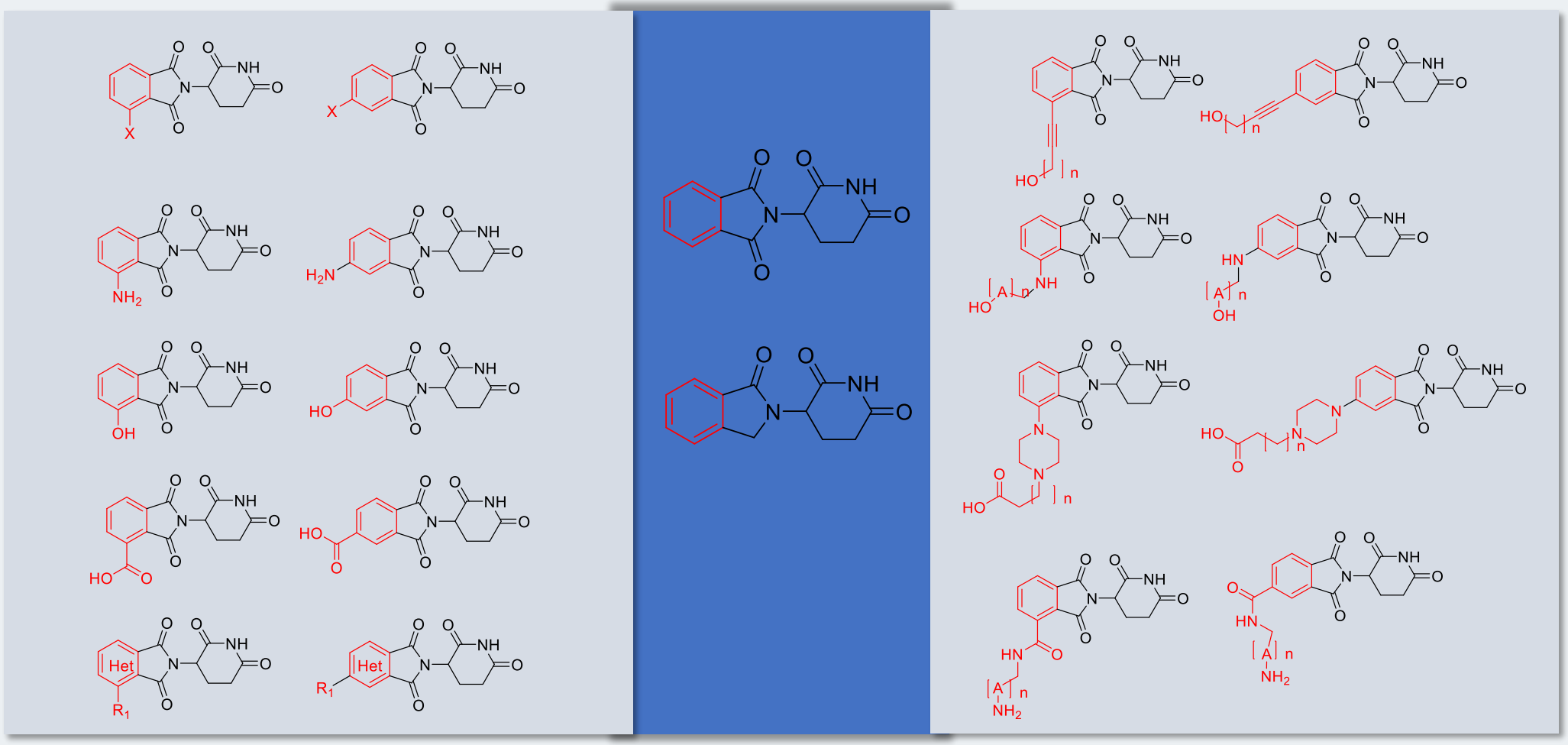
Bruker NMR

Waters SFC

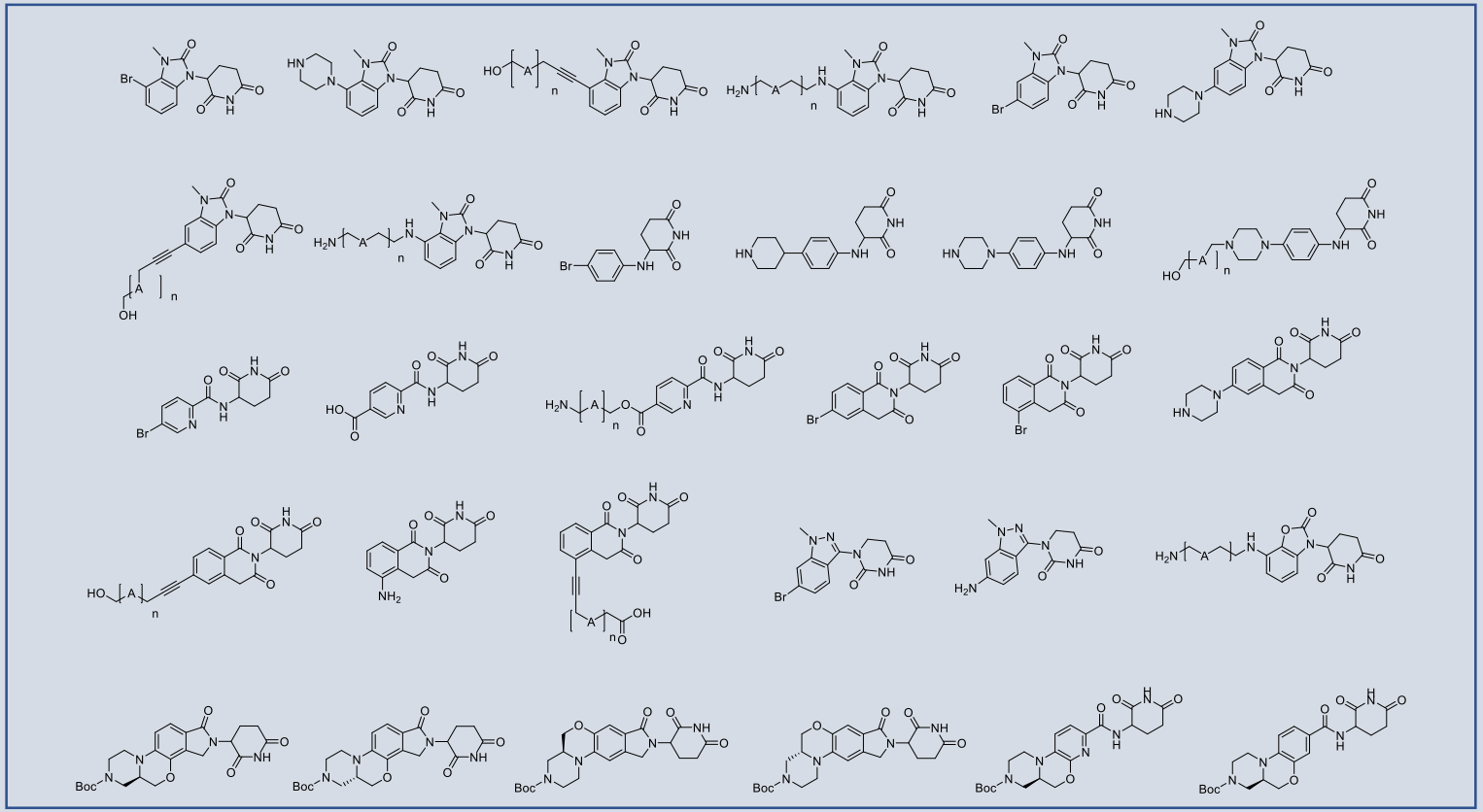
Waters HPLC

Waters Prep-HPLC

Example: Available BBs- E3 ligands (Thalidomide/ Lenalidomide)



Example: Available Building Blocks- Other CRBN Ligands



Example: Available Building Blocks-VHL Ligands

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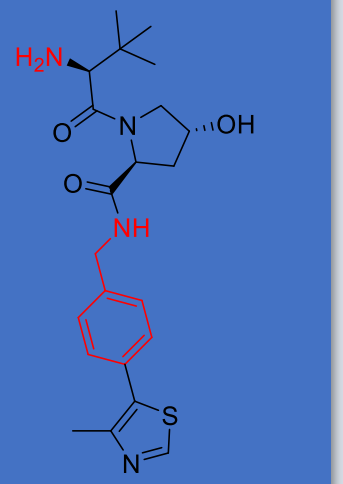

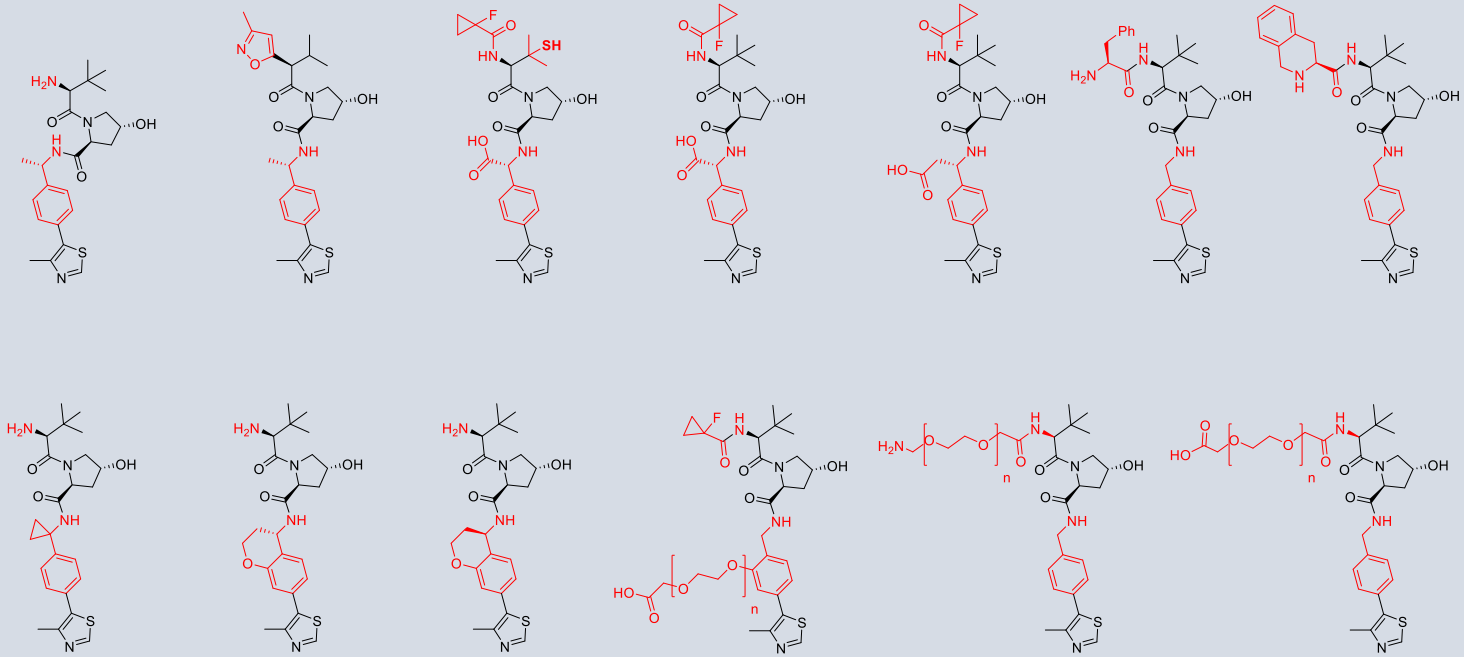

Example: Available Building Blocks-Flexible Linkers

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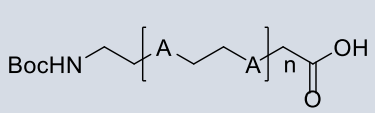
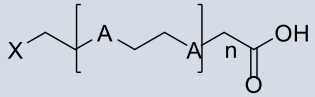
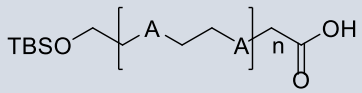
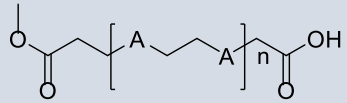
Acid









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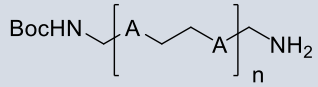
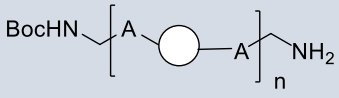
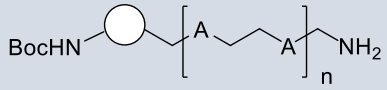
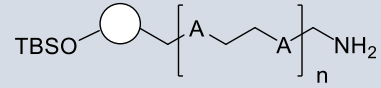
Amine









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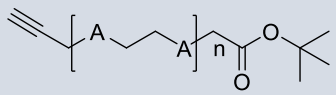
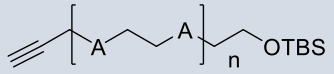
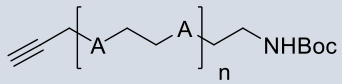
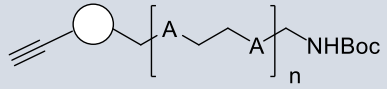
Alkyne









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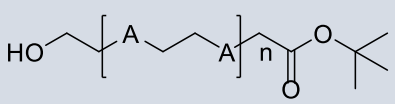
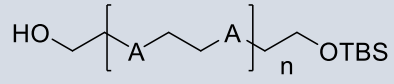
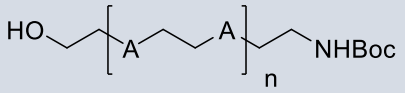
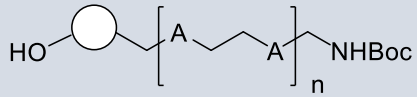
Alcohol









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Example: Available Building Blocks-Linkers with Spiro Cycles

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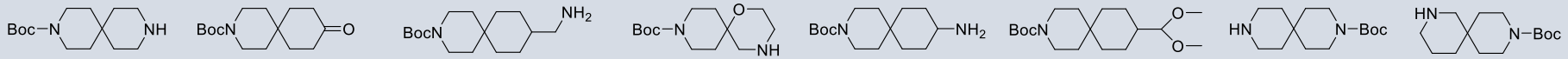
6.6



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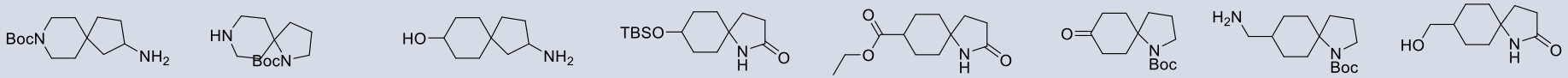
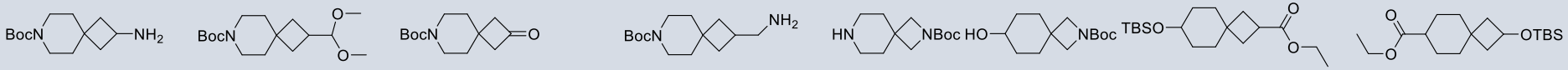
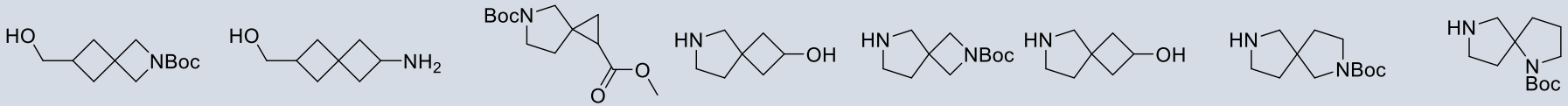


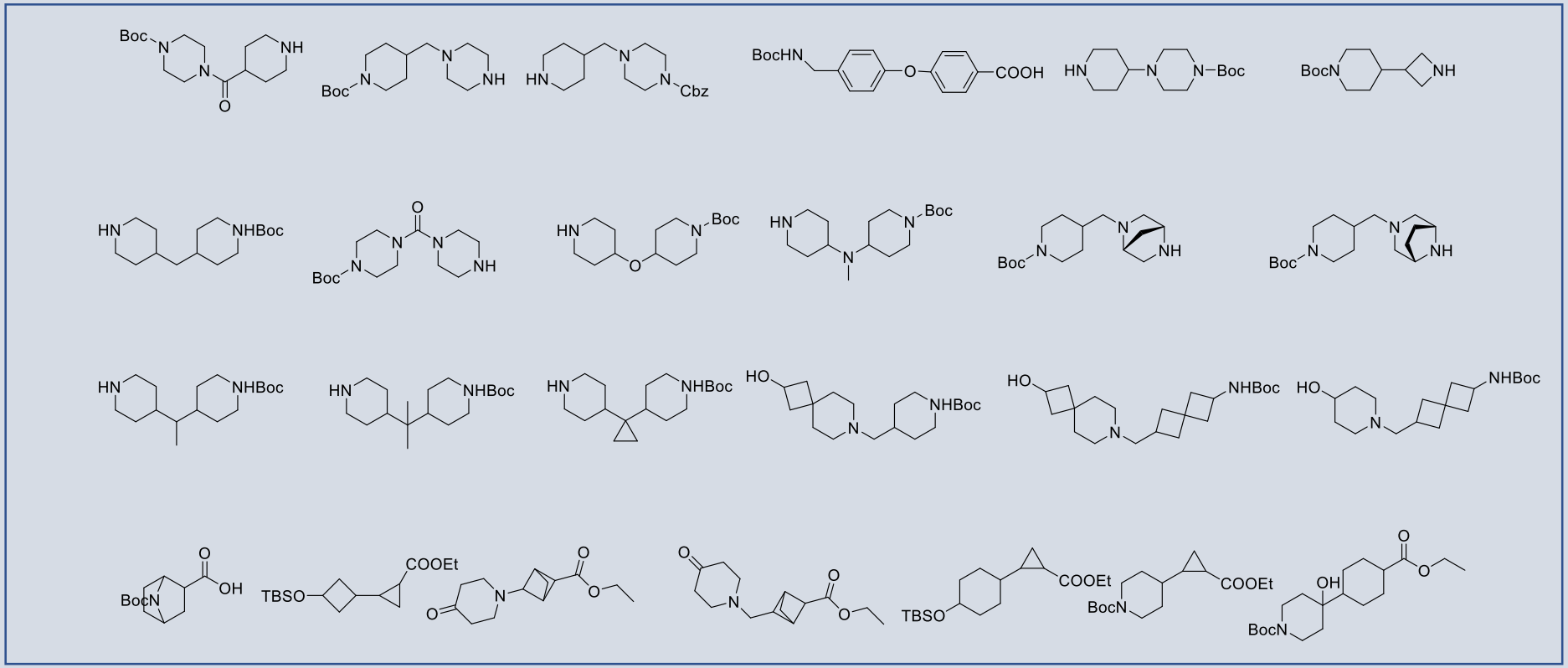
6.4



Others



Example: Available Building Blocks-Other Linkers



Example: Available Building Blocks- Other Ligands

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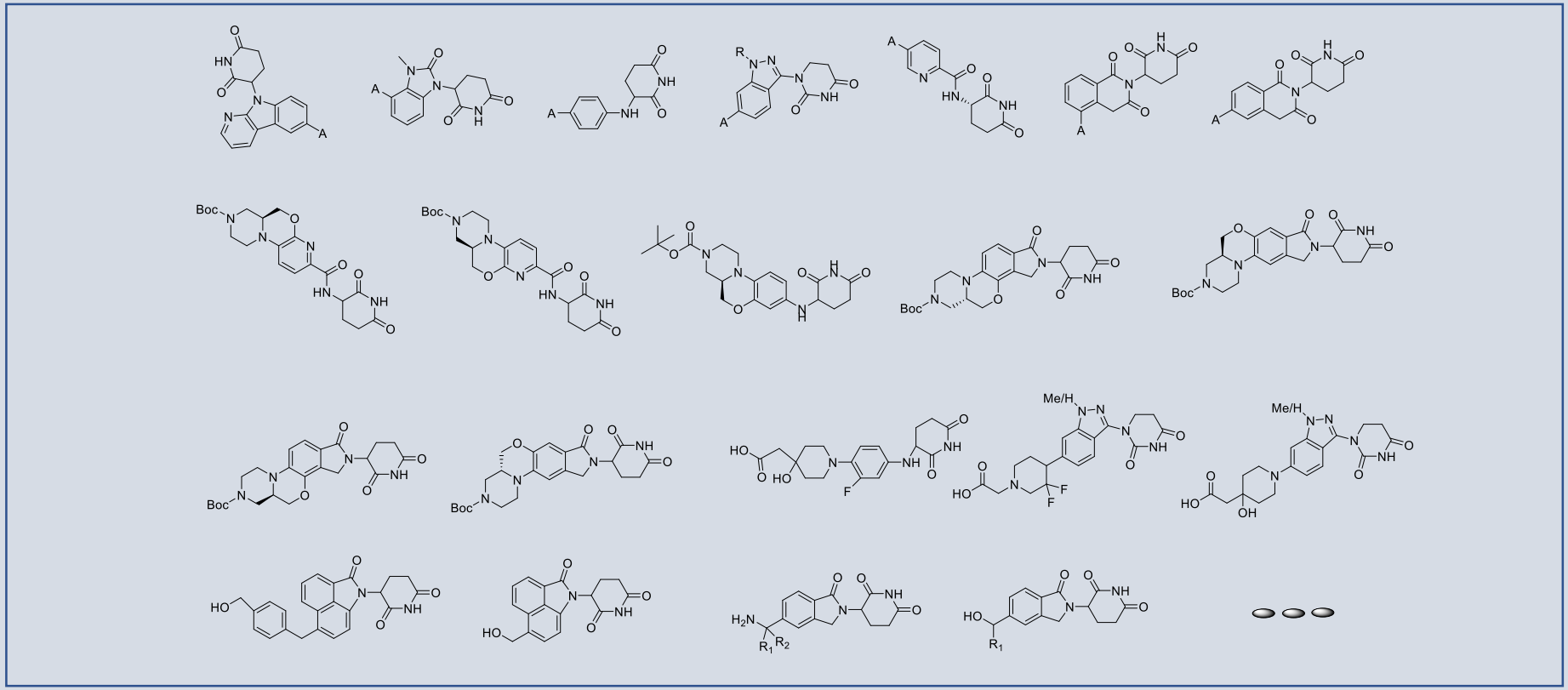

Contents

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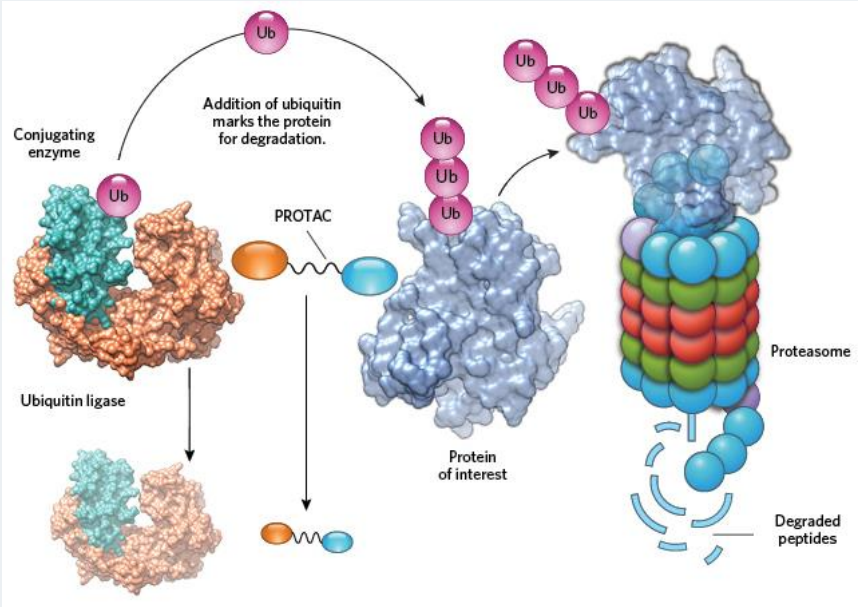
Proteolysis targeting chimeras Technology

☐ EGFR-PROTAC



Non Small Cell Lung Cancer (NSCLC) & EGFR-TKI

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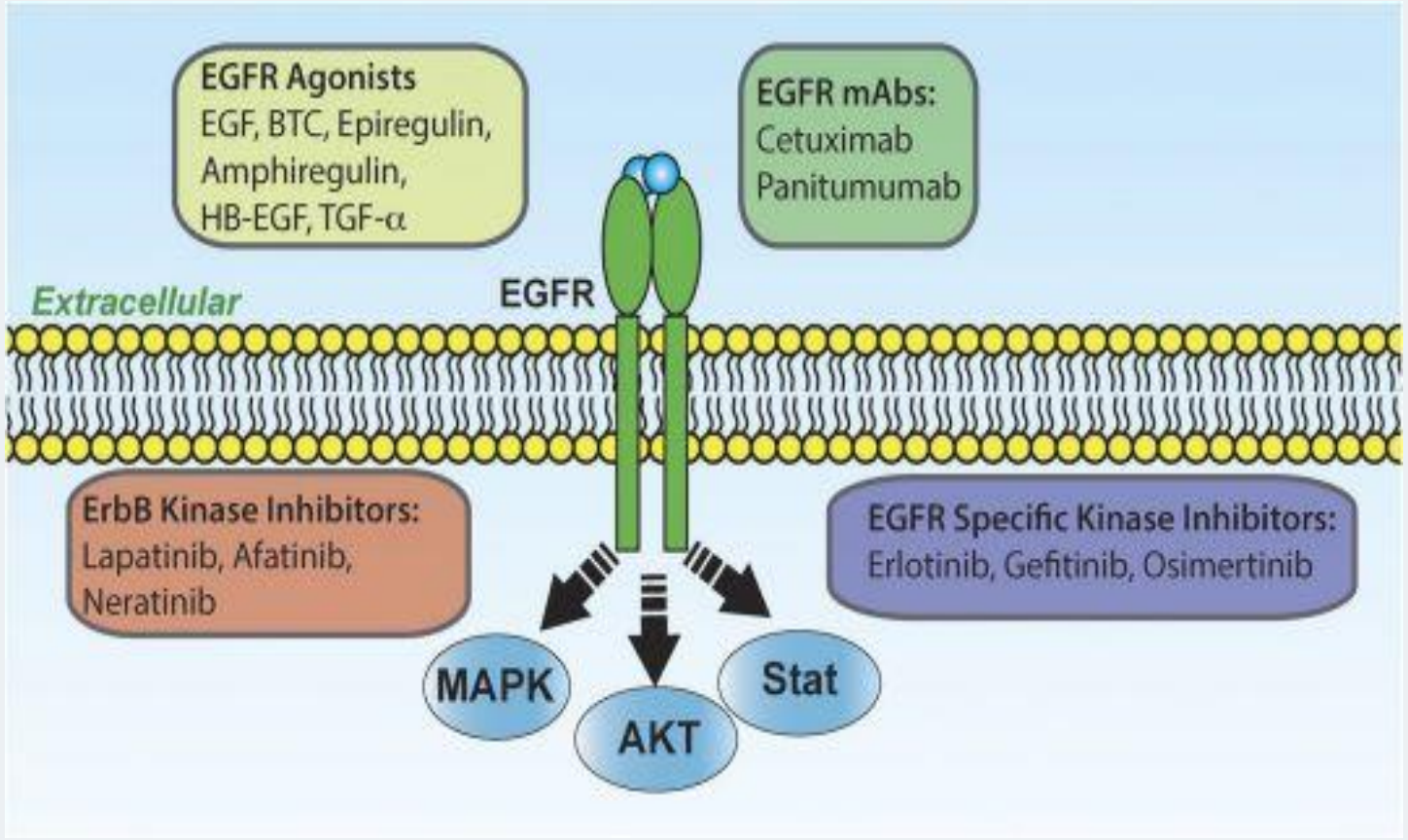

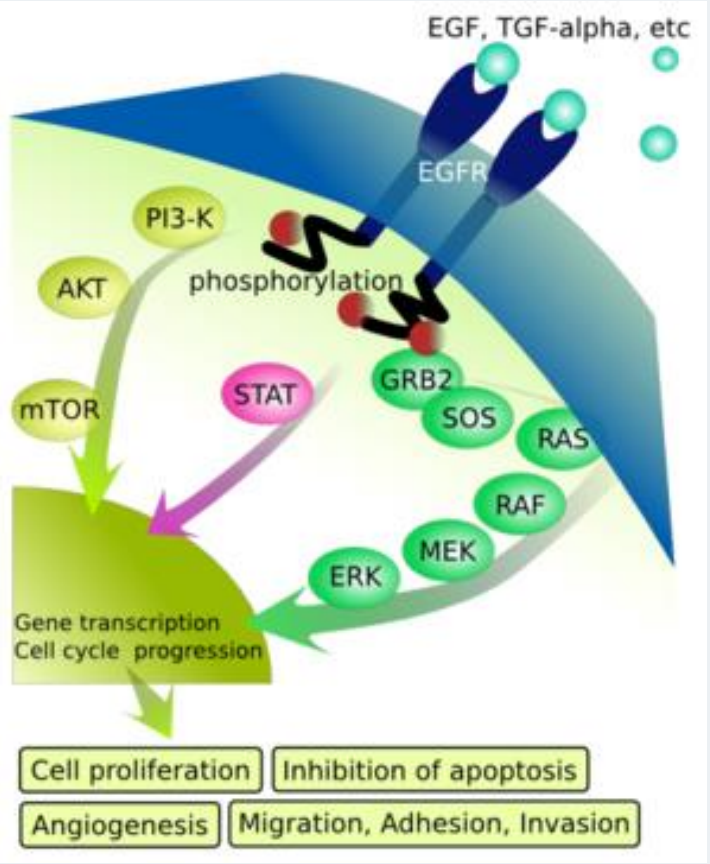

Some disagreement

Process In Different Stage

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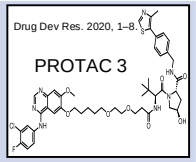
Assays	Synthesis of compounds	Excellent screening of in *vitro* PD	LMS/DMPK/hERG/CYP/Plasma Excellent screening	Excellent screening of in *vivo* PD	Safety evaluation/ toxicology	Alternative PCC

 Drug Dev Res. 2020, 1–8. PROTAC 3 **5 tool/Ref. cmpds**	• 10-15 FTEs
	• 258 cmpds made
	  • Warhead: 5
	  • E3 ligand: 8
	  • Linker: >60
		G1 to G4:
		• Enzyme IC_{50}
		• Cell IC_{50}
		• DC_{50}
		WB => Hibit
		45 compounds
			• 43 cmpds mice PK
			• 15 cmpds rat PK
			• 9 cmpds dog PK
			• 3 cmpds monkey PK
				• 5 in *vivo* PD models
				• 8 times in *vivo* PD study
				• 10 cmpds, completed (HCC827 model done 3 times; Del19-T790M-C797S model done 2 times; PC-9, NCI-H1975 and T790M-L858R-C797S models all done 1 time)
					2 cmpds (TB015, DRF, mice and dog)	• TB015 (preferred)
						• TB043 (back up)

10 months

Profile Data *In Vitro* （TB015 ）

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Compound ID	Gefitinib（G1）	Osimertinib（G3）	EGFR-IN-7（G4，TQB3804）	MB-TB015（PCC candidate）
MW / LogP	446.9	499.61	694.6	779.91/2.1
IC_{50}s on EGFR WT (nM)	0.3478	8.444		4.157
IC_{50}s on EGFR L858R (nM)	0.3687	4.686		3.181
IC_{50}s on EGFR L858R/T790M (nM)	140.1	2.653	13.77	81.48
IC_{50}s on EGFR L858R/T790M/C797S (nM)	299.7	354.9	3.771	119.3
IC_{50}s on EGFR Del19/T790M/C797S (nM)	169.9	169.9	3.818	17.85
IC_{50}s on L858R/T790M/C797S (nM)	**82.59**		**11.18/98.08**	**61.22/97.56**
IC_{50}s on Del19/T790M/C797S (nM)	**169.9**		**24.5/98.0**	**18.5/99.2**
HCC827 IC_{50} (nM)/Imax (%)	**11.61/82.95**	**8.23/86.84**	**286.5/95.26**	**2.08/85.17**
HCC827 DC_{50}(nM) /DCmax (%)				1.83/76.4
PC-9 IC_{50} (nM)	**10.4**	**2.279**	**113.6**	**5.864**
NCI-H1975 cells IC_{50} (nM）/Imax(%)	**25800**	**7.5/67.40**	**97.81/94.80**	**35.52**
NCI-H1975 DC_{50} (nM) /DCmax (%)				54.82

PK Study In Mice & Rat

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Group 2 Number	Method	Dose mg/kg	$T_{1/2}$ h	T_{max} h	C_{max} ng/mL	$AUC_{(0-t)}$ h*ng/mL	$AUC_{(0-\infty)}$ h*ng/mL	$MRT_{(0-t)}$ h	$MRT_{(0-\infty)}$ h	F %
201	PO	10.0	5.89	4.00	2375.90	37757.05	37923.31	9.21	9.41	48.14
202	PO	10.0	4.00	4.00	2280.40	49041.78	49152.77	13.37	13.46	62.53
203	PO	10.0	5.37	6.00	2155.80	28406.76	28483.58	7.54	7.67	36.22
n		3	3	3	3	3	3	3	3	3
Mean value		10.0	5.09	4.67	2270.70	**38401.87**	38519.89	10.04	10.18	48.96
Standard deviation		0.0	1.0	1.2	110.4	10332.6	10347.5	3.0	3.0	13.17

Mice (TB015, Free Base)

Group 6 Number	**Method**	**Dose** mg/kg	$T_{1/2}$ h	T_{max} h	C_{max} ng/mL	$AUC_{(0-t)}$ h*ng/mL	$AUC_{(0-\infty)}$ h*ng/mL	$MRT_{(0-t)}$ h	$MRT_{(0-\infty)}$ h	F %
601	PO	10.0	5.26	6.00	132.75	1404.01	1416.46	8.68	8.99	6.18
602	PO	10.0	4.36	6.00	118.94	1271.75	1311.15	6.98	7.68	5.59
603	PO	10.0	6.16	6.00	215.27	2109.29	2144.14	9.61	10.18	9.28
n		3	3	3	3	3	3	3	3	3
Mean value		10.0	5.26	6.00	155.65	1595.02	1623.91	8.42	8.95	7.02
Standard deviation		0.0	0.90	0.00	52.09	450.26	453.60	1.33	1.25	1.98

Rat (TB015, Formate)

PK Study In Dog & Monkey

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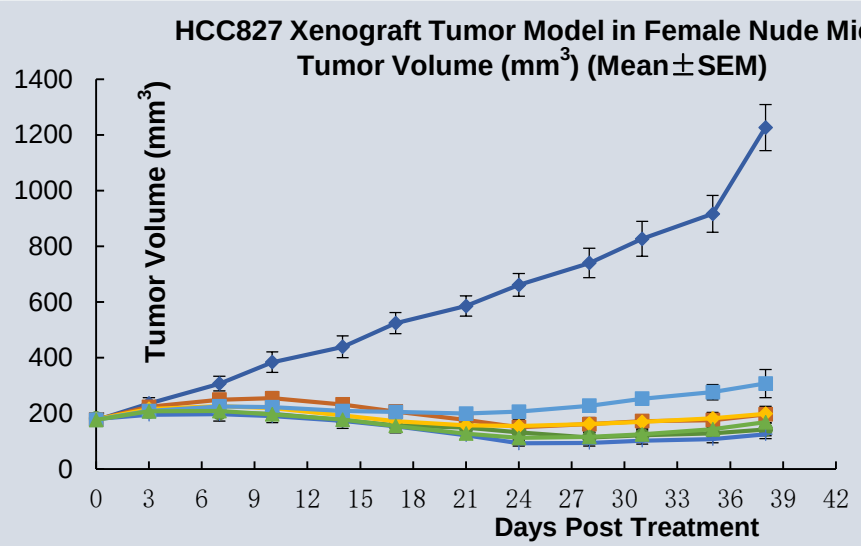
Group 1 Number	Method	Dose mg/kg	$T_{1/2}$ h	T_{max} h	C_{max} ng/mL	$AUC_{(0-t)}$ h*ng/mL	$AUC_{(0-\infty)}$ h*ng/mL	$MRT_{(0-t)}$ h	$MRT_{(0-\infty)}$ h	F %
101	PO	25.0	13.06	6.00	131.99	2638.24	2880.53	15.92	20.20	9.07
102	PO	25.0	14.01	6.00	178.75	4233.68	4706.35	17.09	22.22	14.56
103	PO	25.0	14.62	6.00	123.76	2405.82	2660.24	14.79	19.99	8.27
n		3	3	3	3	3	3	3	3	3
Mean value		25.0	13.9	6.0	144.8	3092.6	3415.7	15.9	20.8	10.64
Standard deviation		0.0	0.8	0.0	29.7	995.0	1123.1	1.1	1.2	3.42

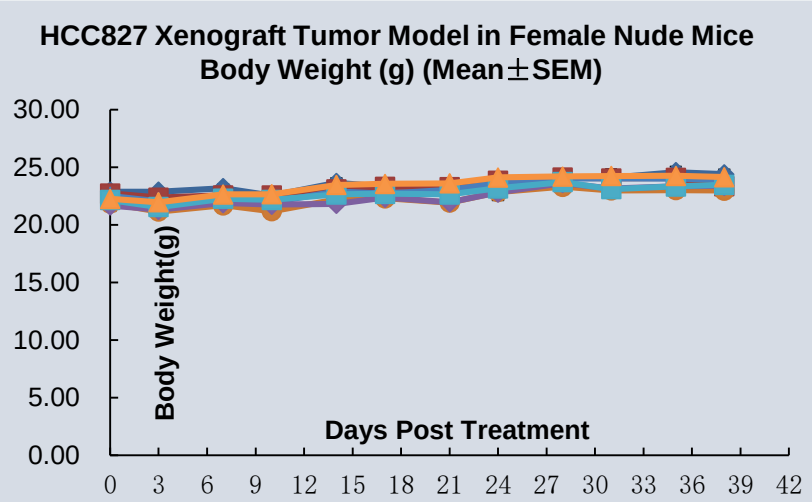
Dog (TB015 , Free Base)

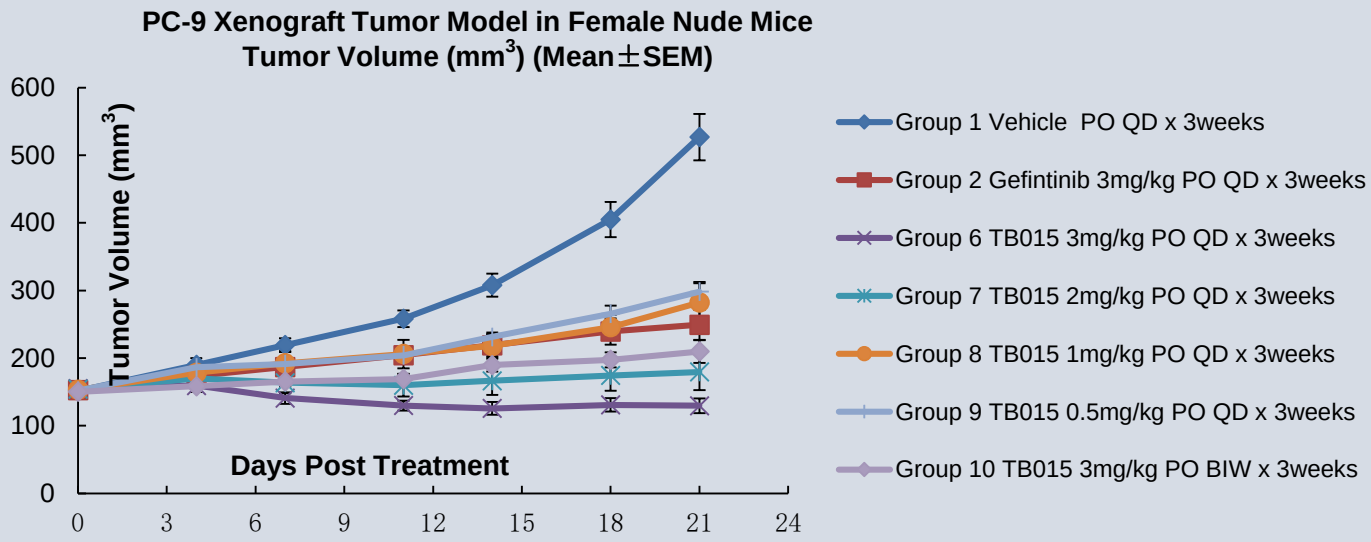
Group 2 Number	Method	Dose mg/kg	$T_{1/2}$ h	T_{max} h	C_{max} ng/mL	$AUC_{(0-t)}$ h*ng/mL	$AUC_{(0-\infty)}$ h*ng/mL	$MRT_{(0-t)}$ h	$MRT_{(0-\infty)}$ h	F %
201	PO	5.0	12.22	8.00	27.16	708.36	793.74	18.34	23.42	4.92
202	PO	5.0	13.74	6.00	60.43	988.86	1064.35	13.14	17.02	6.87
203	PO	5.0	19.88	8.00	44.86	858.64	1023.77	16.04	25.82	5.96
n		3	3	3	3	3	3	3	3	3
Mean value		5.0	15.28	7.33	44.15	851.96	960.62	15.84	22.09	5.92
Standard deviation		0.0	4.06	1.15	16.65	140.37	145.94	2.60	4.55	0.97

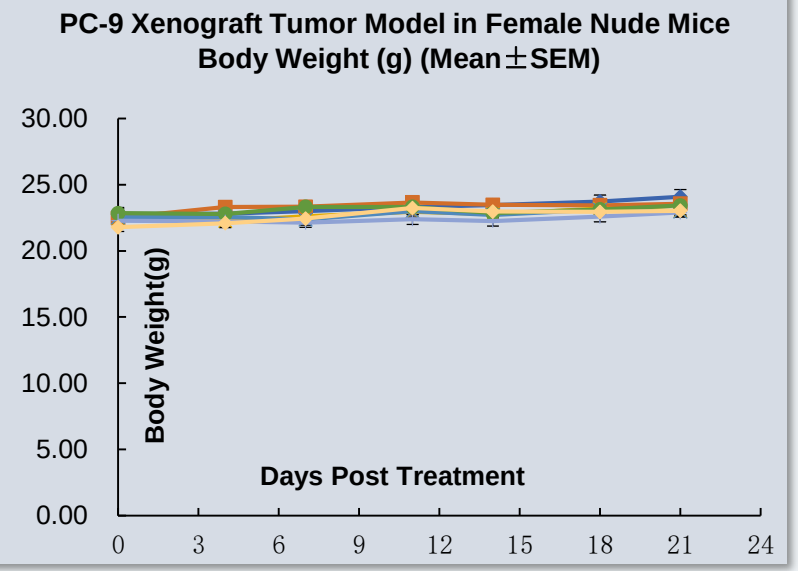
Monkey (TB015, Free Base)

In Vivo PD : First Generation

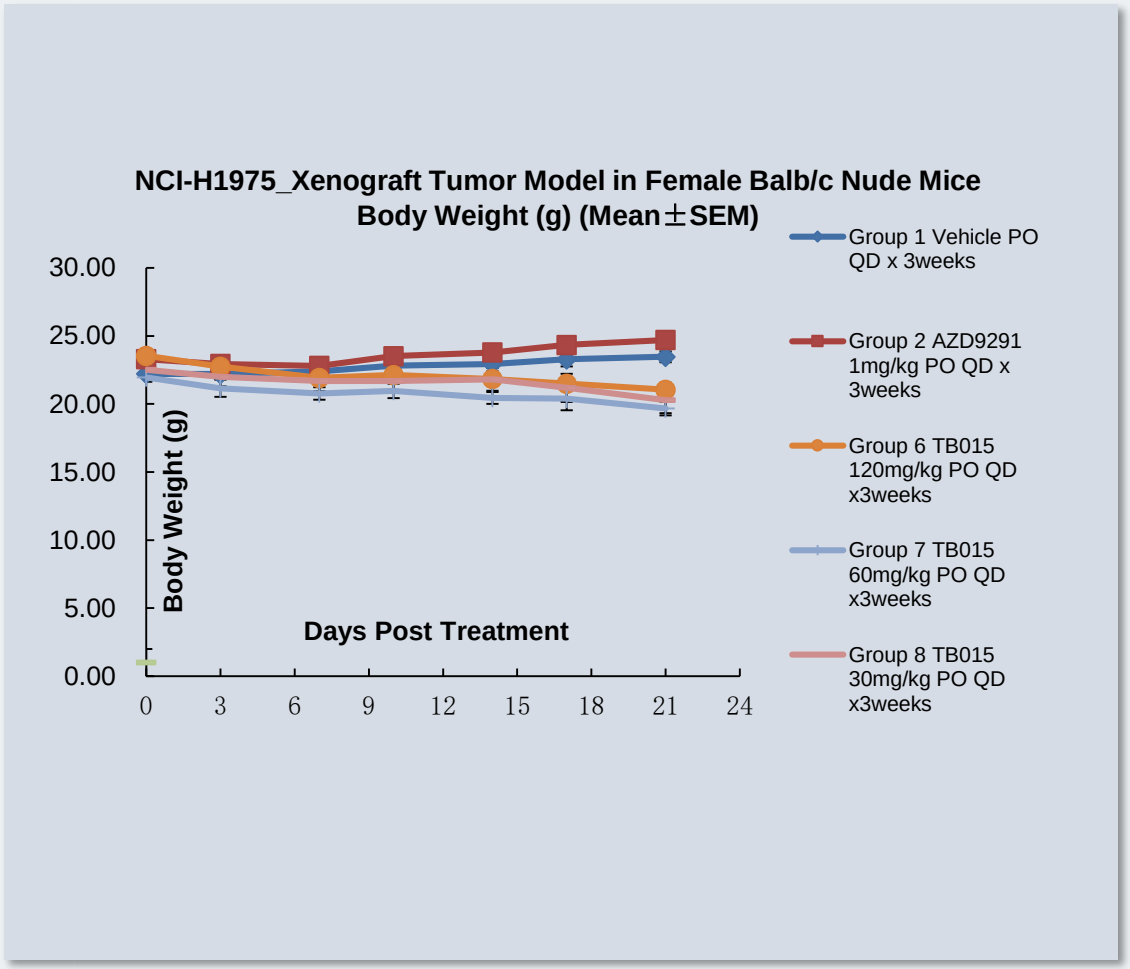


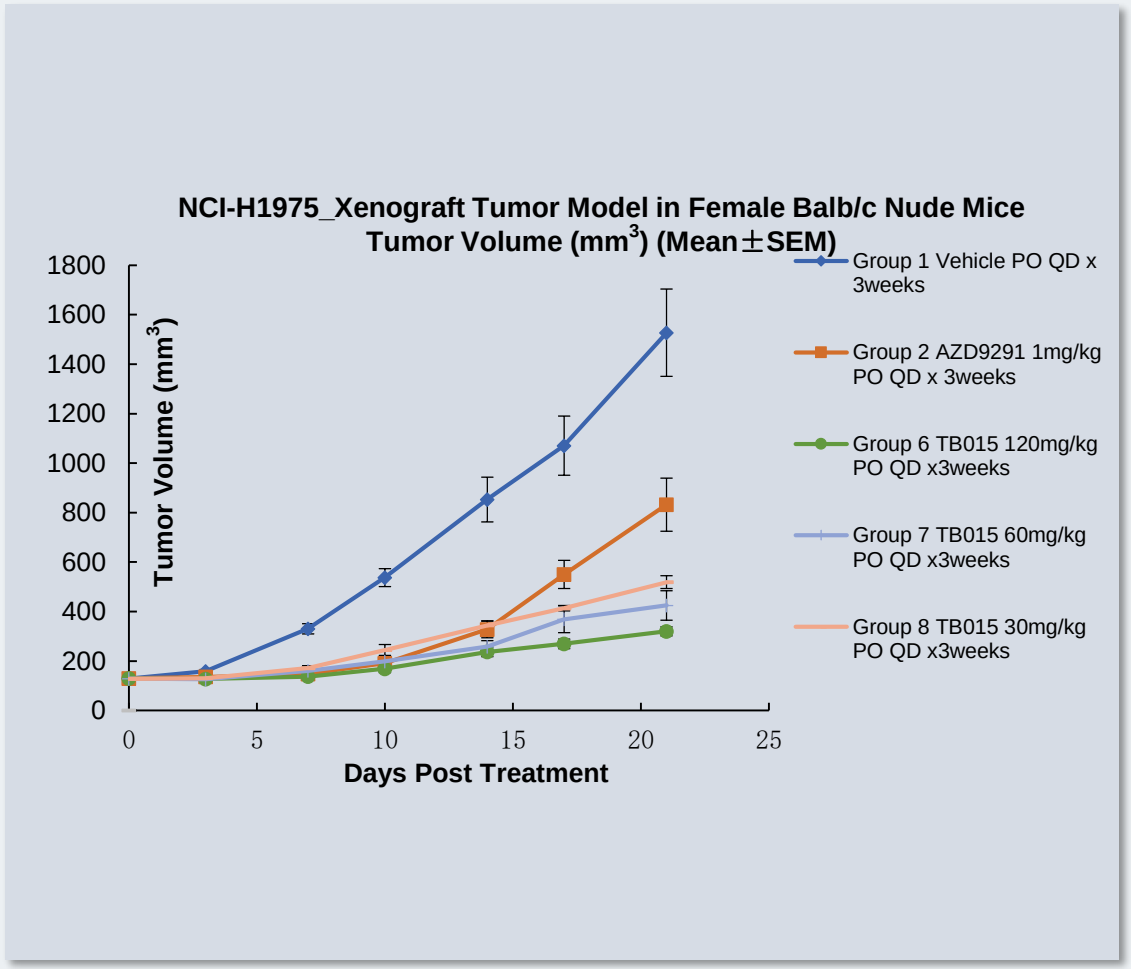






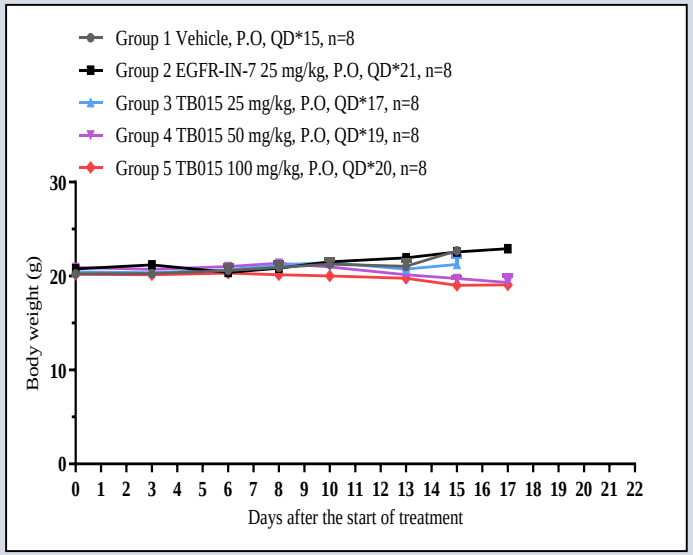
In Vivo PD : Third Generation

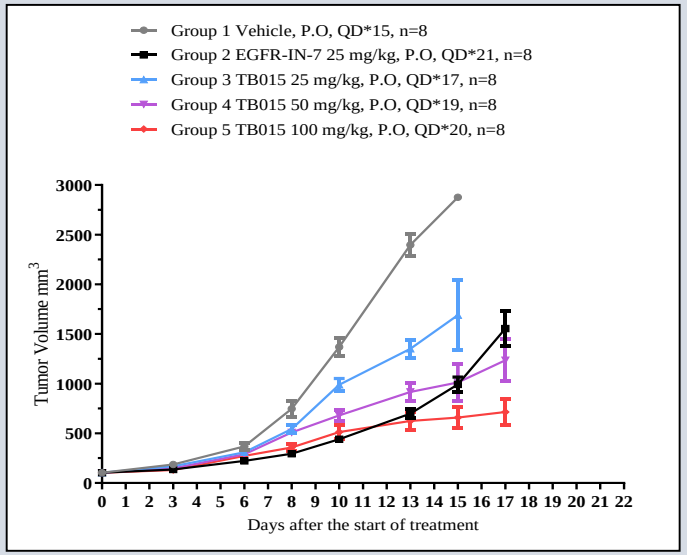




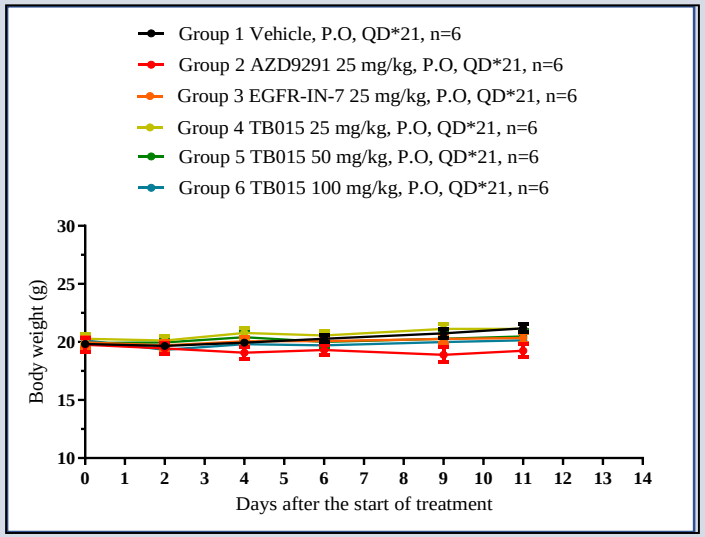
positive control Osmertinib

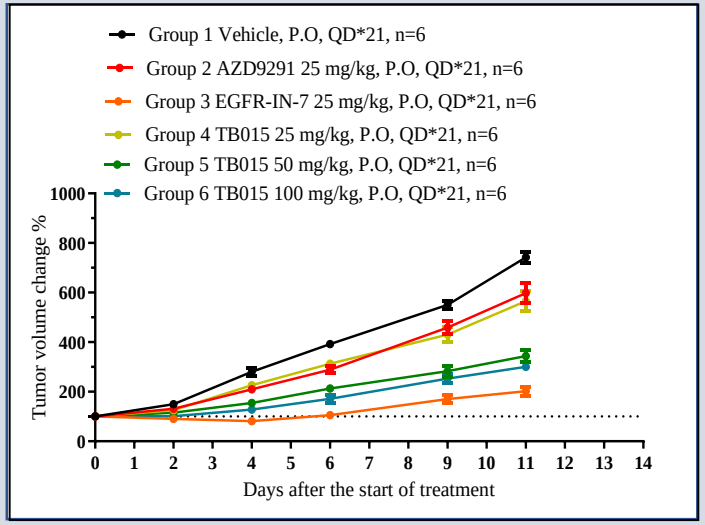
In Vivo PD : Fourth Generation





T790M-L858R-C797S model (TB015 & positive control EGFR-IN-7)





Del19-T790M-C797S model (TB015 & positive control EGFR-IN-7)

MetID (TB015)

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In vitro

Met NO.	RT (min)	m/z	UV and HRMS Peak area percentage										Metabolic pathway
			In vitro										
			MsLM		RLM		DLM		MkLM		HLM		
			UV	HRMS	UV	HRMS	UV	HRMS	UV	HRMS	UV	HRMS	
M1	9.48	########	ND	ND	ND	ND	3.61%	9.38E+06	1.57%	1.42E+06	7.19%	6.48E+06	Mono-oxidation (P+O)
Parent	10.70	########	100%	2.29E+08	100%	2.13E+08	96.39%	1.54E+08	98.43%	2.28E+08	92.81%	1.96E+08	n/a
nn/a: Not applicable; +: Only detected in MS; ND: Only detected at trace level or not detected.； *: normalized percentage of UV absorption peak area (%) = 100* UV absorption of parent or metabolites / UV absorption of all drug-related;													

In vivo

Met NO.	RT (min)	m/z	UV and HRMS Peak area percentage								Metabolic pathway
			In vivo plasma								
			Mouse		Rat		Dog		Monkey		
			UV	HRMS	UV	HRMS	UV	HRMS	UV	HRMS	
M1	9.37	#####	+	2.80E+06	+	1.14E+06	ND	ND	ND	ND	Mono-oxidation (P+O)
M1-1	9.61	#####	+	3.45E+06	12.88%	2.04E+07	3.33%	6.23E+07	ND	ND	Mono-oxidation (P+O)
M2	10.74	#####	ND	ND	ND	ND	ND	3.56E+06	ND	ND	Mono-oxidation+Methylation (P+CH_2+O)
Parent	10.94	#####	100.00%	5.10E+08	87.12%	4.09E+08	96.67%	8.74E+07	100.00%	8.42E+07	n/a
nn/a: Not applicable; +: Only detected in MS; ND: Only detected at trace level or not detected.； *: normalized percentage of UV absorption peak area (%) = 100* UV absorption of parent or metabolites / UV absorption of all drug-related;											

On balance, dogs and mice were preferred as the relevant species

Therapeutic Window (Compound TB015)

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Study Type	Dose (mg/kg)	Equivalent dose to human body& (mg/kg)	Therapeutic window (multiple, calculatied based on dose)	AUC $_{(0\text{-}t)}$ (h*ng/ml)	Therapeutic window (multiple, calculated based on exposure)
In *vivo* PD study of SCID mice (PC-9 model，%TGI: 60.98)	MED = 0.5	0.04	/	899.06	/
In *vivo* PD study of SCID mice (HCC827 model，%TGI: 87.68)	MED = 0.2	0.02	/	/	/
14-day toxicology study in mice (non-GLP)	STD_{10} = 200	17.84	**446**	98875.36	**110**
14-day toxicology study in dog (non-GLP)	HNSTD = 10	5.81	**145**	21879.73	**24**

Note: & Human Equivalent Dose (mg/kg): MED /11.21 (mouse conversion factor); STD_{10} /11.21 (mouse conversion factor); HNSTD /1.72 (canine conversion factor)

MED：Minimum Effect Dose，minimum effective dose；
STD10：Severely toxic dose to 10% of the animals，10% of animals showed severe toxic reaction dose；
HNSTD：Highest Non-Severly Toxic Dose，maximum non-severe toxic dose。

TB015 preclinical toxicology studies have shown it to have a good safety profile with a higher toxic dose than the lowest starting dose and a large range of therapeutic window of up to 24 times or more.

EGFR-TKI PROTAC Summary

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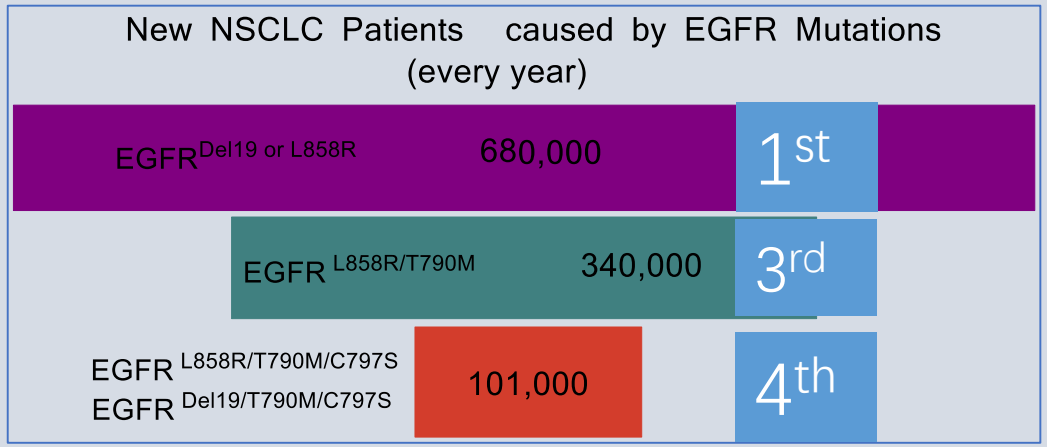


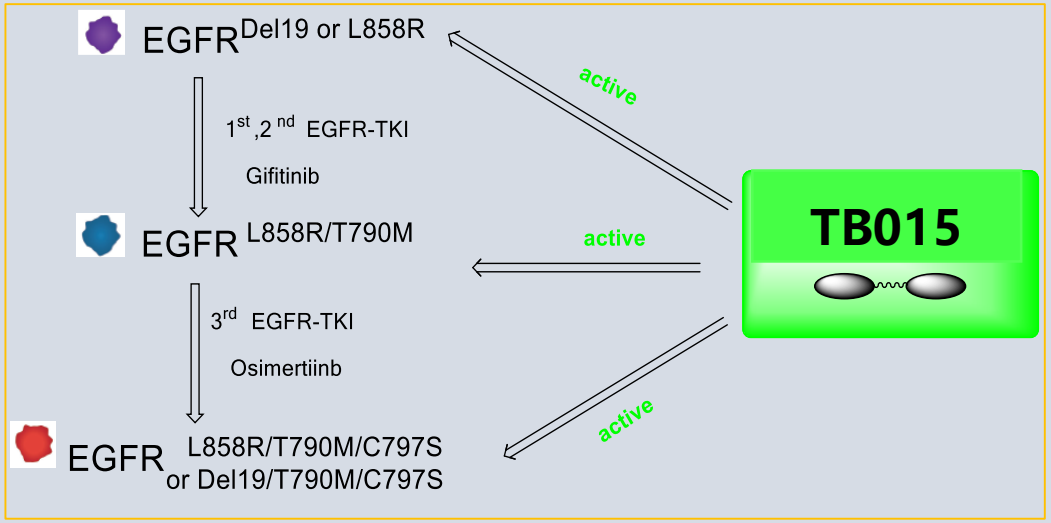
1st of treatment with PROTAC ,
Reduced greatly
the mutation to 3rd & 4th

The First-Line Clinical Drugs for NSCLC:
Gifitinib
Osimertinib

TB015 Effective

For Various Mutations

As 1st~4th gen EGFR-TKIs



Patent enforcement and clearance for freedom-to-operate in the U.S.

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