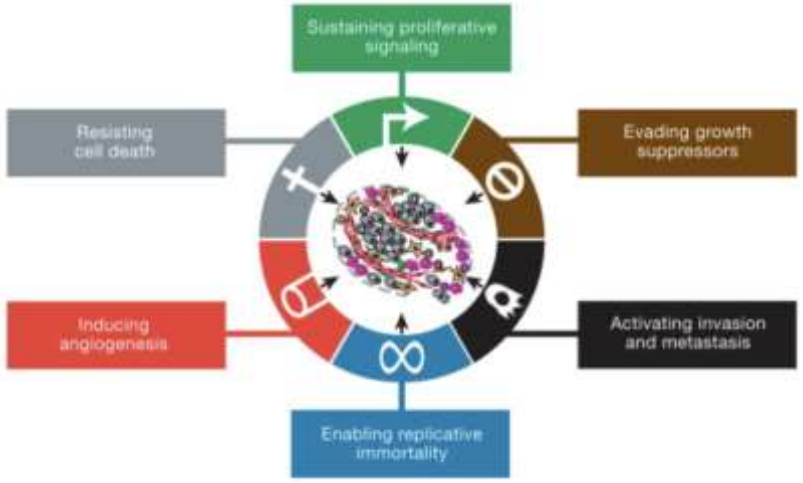
New Opportunities in Undruggable Targets Using Targeted Protein Degradation (TPD)

Ian Churcher, CEO, Janus Drug Discovery

New Modalities in Cancer Drug Development
Cancer Drug Development Forum,
Brussels, 31st March 2025

www.janusdrugdiscovery.com

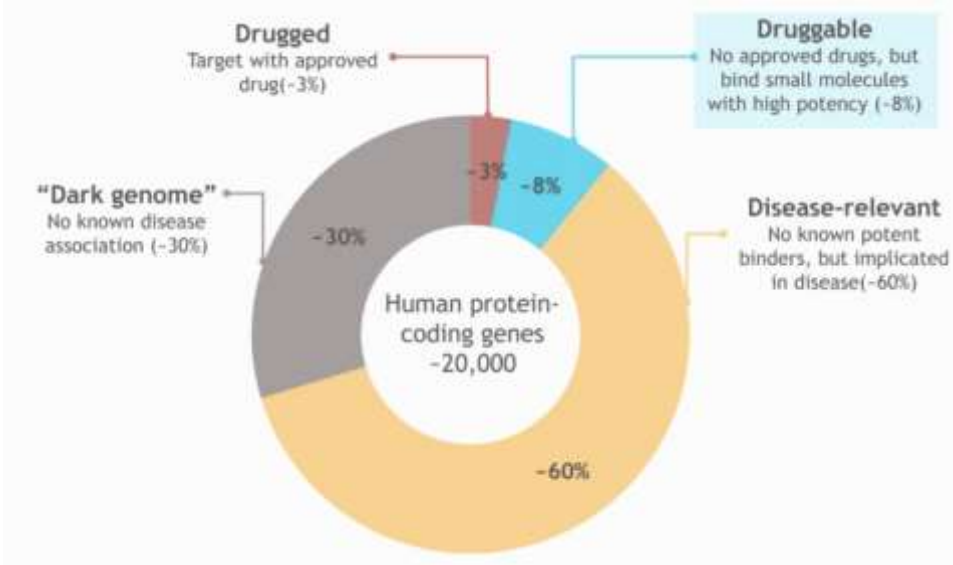
Our Expanding Knowledge of Tumorigenesis Continues to Give Long List of Desirable Drug Targets



Expanding knowledge of cancer biology…

Target validation

CRISPR, RNAi, genome-wide studies, clinical analyses

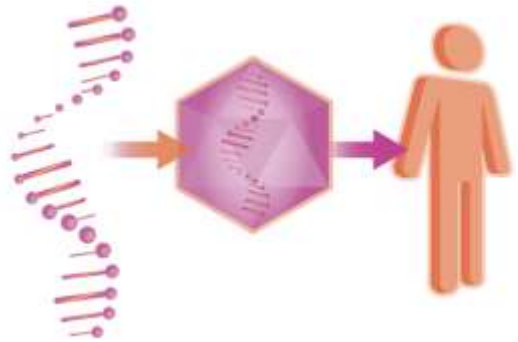


… continues to highlight key drug targets

Large numbers of attractive, intracellular drug targets remain out of reach
The "undruggable" genome remains large

Ongoing Need For General Approach to Silence or Correct Any Disease-causing Protein

Gene therapies

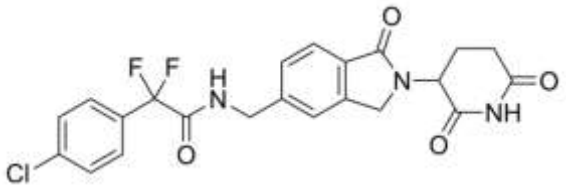


- Great potential but practical & commercial barriers

Genetic knockdown by CRISPR or RNAi

- Regulatory framework now being defined
- Manufacture & delivery can be challenging

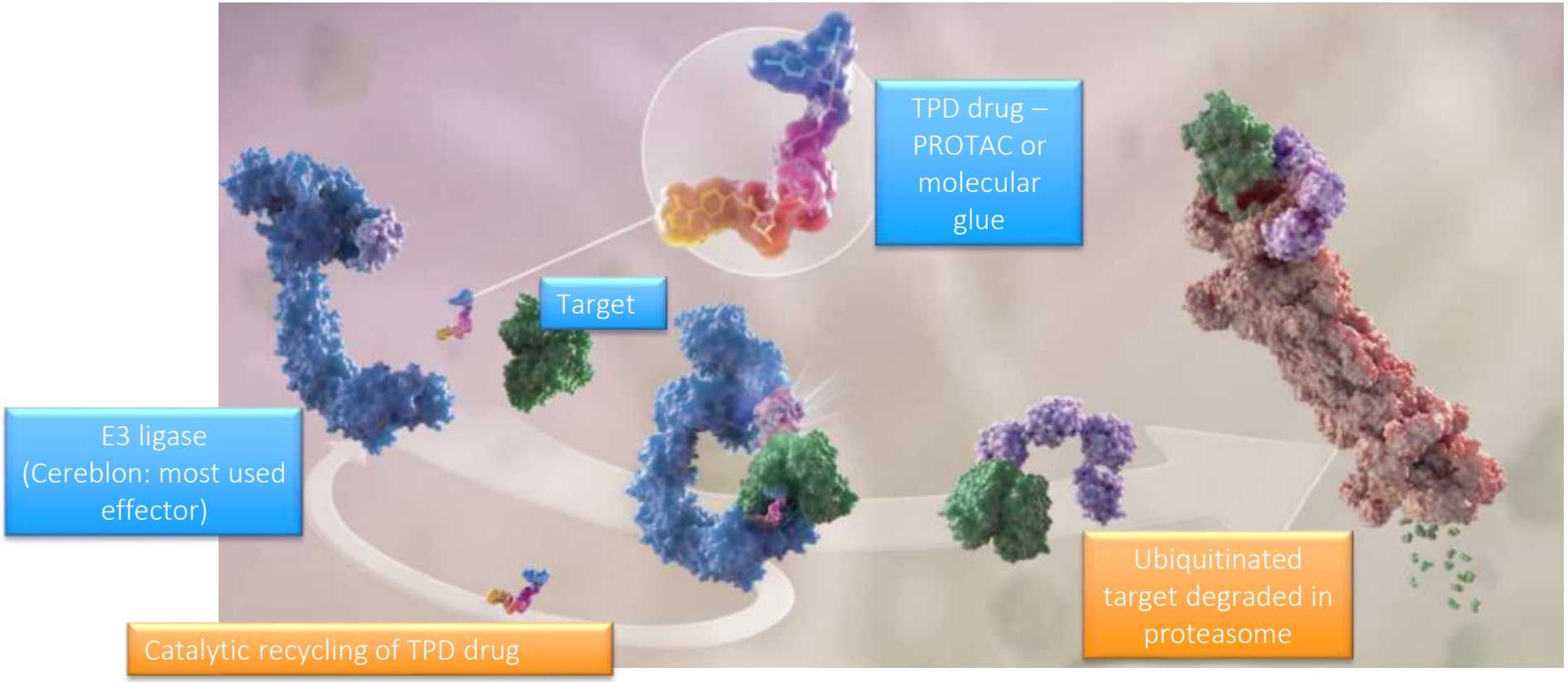
Small molecules



- Well understood regulatory pathway
  - Lower cost of goods
  - Oral dosing potential

TPD Drugs Recruit Ubiquitin E3 Ligases

Initiates cascade leading to proteasomal degradation of drug target



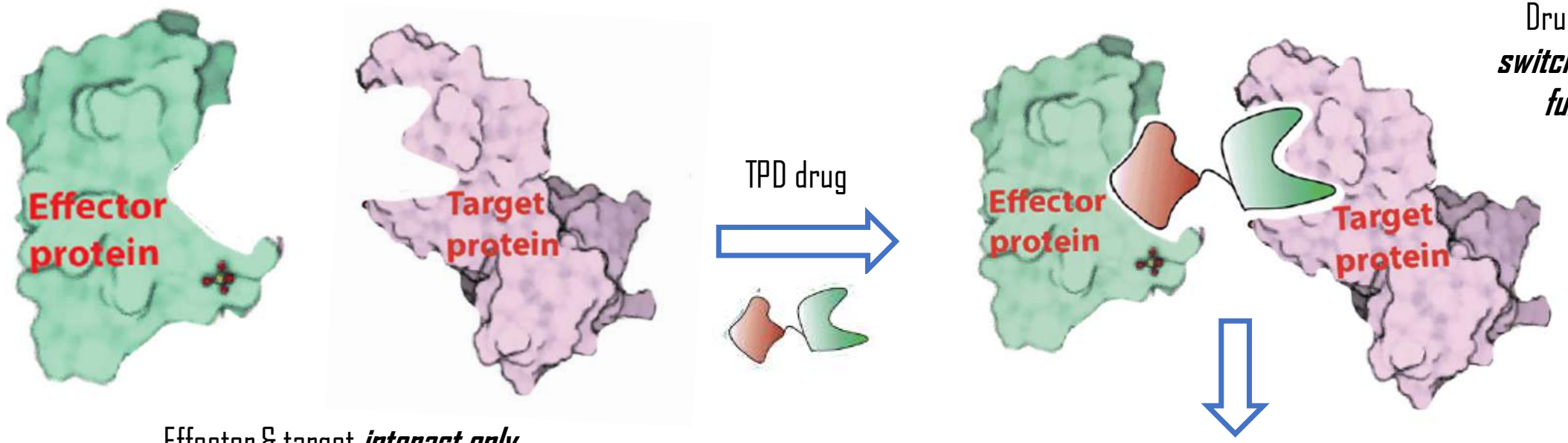
- Step 1: TPD drug induces E3 ligase recruitment to target protein
- Step 2: ubiquitin transferred to target protein
- Step 3: ubiquitylated target protein degraded in proteasome
- Step 4: resultant biological function cf genetic knockdown

- TPD drugs "hijack" function of endogenous cellular protein homeostasis machinery
- Applicable to wide range of cytosolic, membrane-associated & nuclear proteins
- >20 TPD drugs in clinic, first approval (Vepdegestrant, Arvinas/Pfizer expected 2025)

PROTAC = Proteolysis targeting chimera

TPD Relies on Induced-Proximity-Based Pharmacology

A "bispecific" small molecule facilitates a protein-protin interaction



Effector & target ***interact only weakly or not at all*** in absence of drug

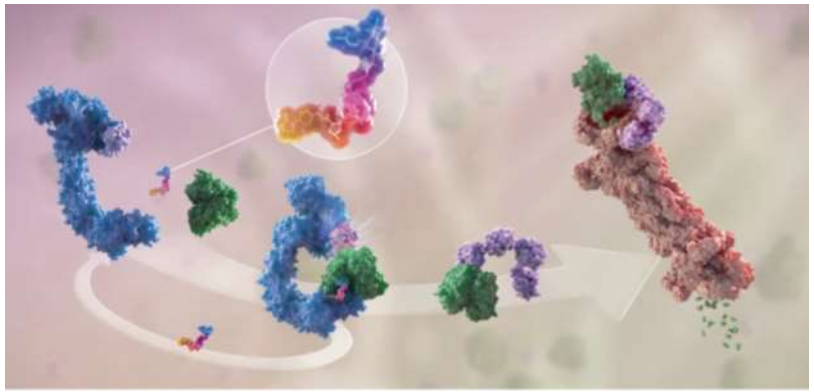
Drug-induced proximity ***switches on or potentiates function*** of complex

Functional benefit eg target ubiquitylation & degradation

Small molecule drug catalyzes a biological process to give highly selective target removal

From ACS Cent Sci 2023, 9, 1269

Advantages of Degradation Over Target Inhibition

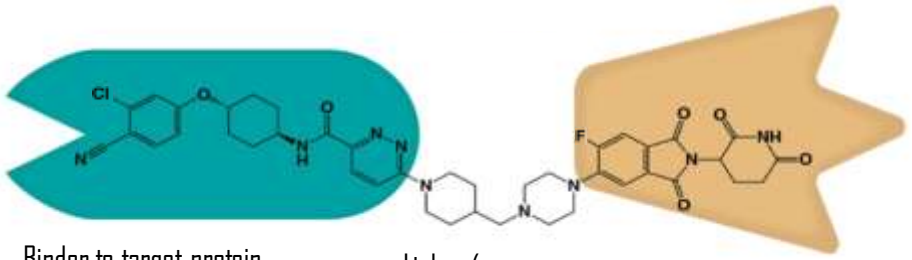


- Degradation **removes ALL functions** of the target (+ scaffolding etc) recapitulating genetic knockdown
- May need **binder to target only** does not need to be functionally active for use in degrader
- **Catalytic mechanism** allows sub-stoichiometric effects (ie higher potency than binding Kd)
- **Long duration of efficacy** possible when protein resynthesized only slowly
- **Selective** degradation can be achieved, even with unselective binding ligands
- Degradation often **potentiates inhibitor-like efficacy** but can also potentiate on-target toxicity!

Image credit, Crews, NRDD

Two main types of degrading molecule
Bifunctional vs monofunctional

"Bifunctional" – often termed PROTACs



Binder to target protein

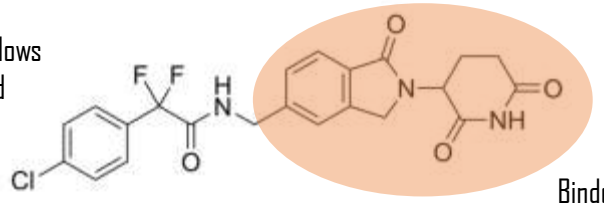
Linker (very important)

Binder to E3 ligase

- Need binder to target protein (from HTS, DEL etc)
- Modular design – work for most targets
- Can recruit different E3 ligases
- Larger molecule but oral dosing often possible

"Monofunctional" – often termed Molecular Glues

Selectivity moiety – allows recruitment of desired target



Binder to E3 ligase

- No binder to target protein needed (opens undruggables)
- May only work for some drug targets – full scope not yet defined
- Limited mainly to one E3 ligase (CRBN)
- Smaller molecule with "typical" drug properties
- MM treatments lenalidomide, pomalidomide are glues

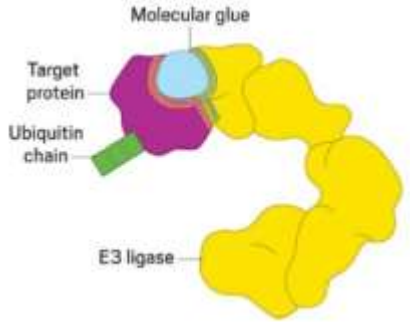
Both PROTACs & glues have shown clinical efficacy
Either approach has unique advantages

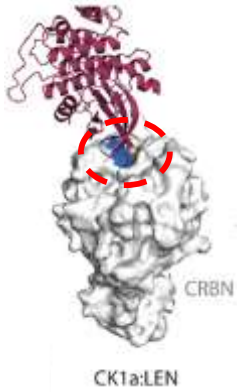
PROTAC = Proteolysis targeting chimera

Designing Molecular Glues

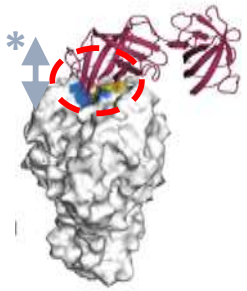
Target space expanding but cannot yet predict which targets will be most "glue-able"

- The E3 ligase-glue complex creates a "neomorphic" surface which can bind the target protein
  - Leads to productive ternary complex which gives target ubiquitylation & subsequent degradation
  - Design increasingly informed by cryo-EM complex structures and computational methods

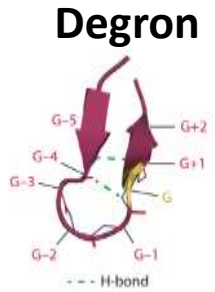




CK1a:LEN



GSPT1:CC885



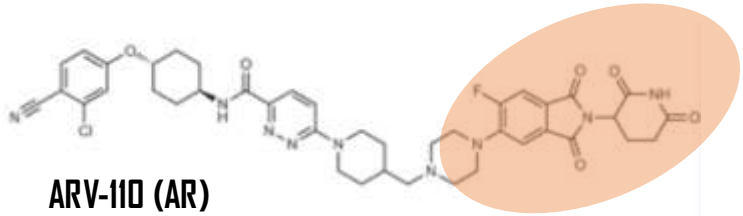
- Usually screen libraries of derivatives of binders to E3 ligase
  - The E3 ligase cereblon is the most used – can potentially be glued to substrates containing a key "degron"
  - Other ligases may also work well – much current effort to identify these
  - NB some binders to drug targets can also act as glues and lead to target degradation

Glues are "typical" small molecules so can be designed to be orally-dosed, CNS penetrant etc

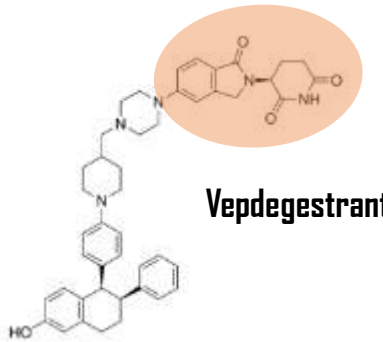
Recent good glue reviews: CellChemBiol 2024; Curr Op Struc Biol Apr2025

Clinical PROTACs Mainly Use "Modular" Design Process

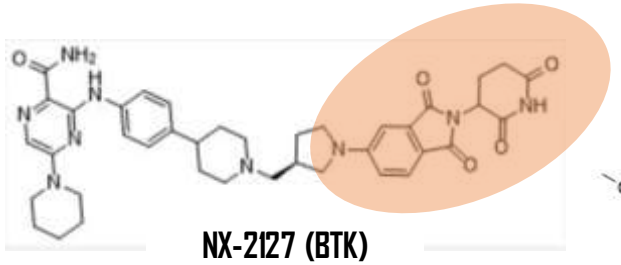
Picking the right linker often critical to get right properties



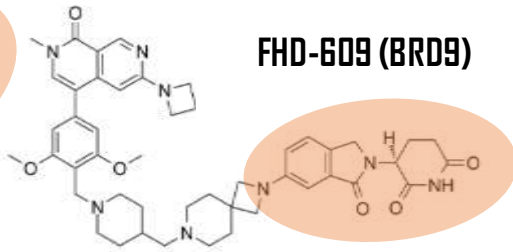
ARV-110 (AR)



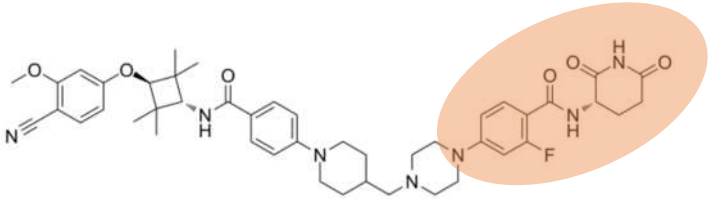
Vepdegestrant (ER)



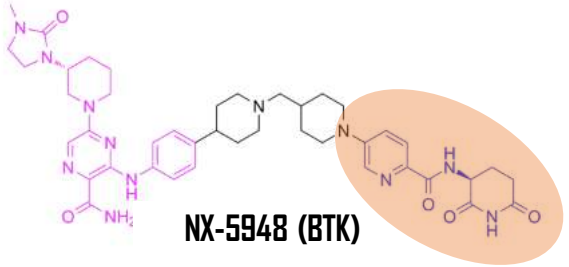
NX-2127 (BTK)



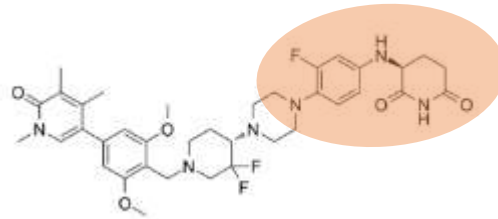
FHD-609 (BRD9)



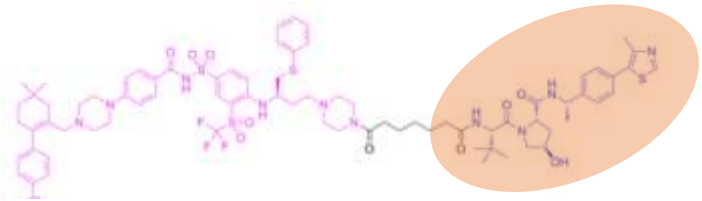
ARV-776 (AR)



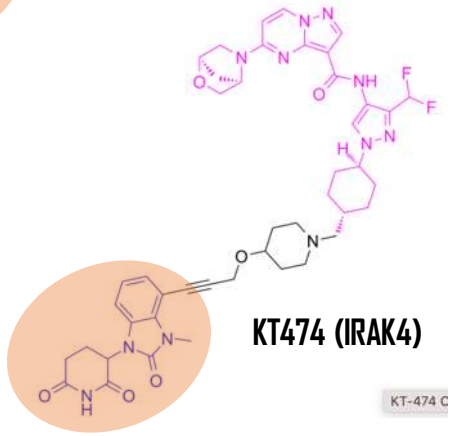
NX-5948 (BTK)



CFT8634 (BRD9)

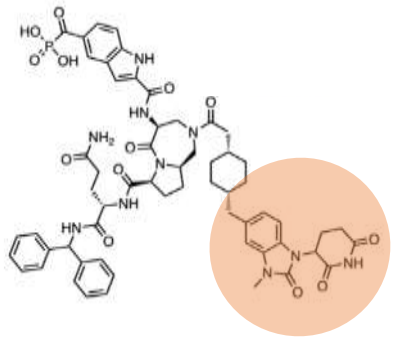


DT-2216 (Bcl-xl)
Iv dosed



KT474 (IRAK4)

KT-333 (STAT3)
Iv-dosed



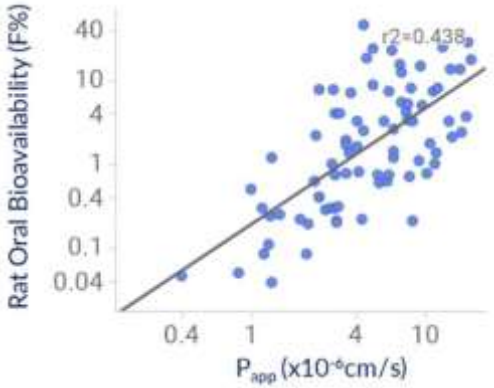
Medicinal chemists have quickly learnt how to optimize these larger "beyond rule of 5" agents

All dosed orally in clinic unless otherwise stated

PROTACs Can be Dosed Orally or via Long-acting Formulations

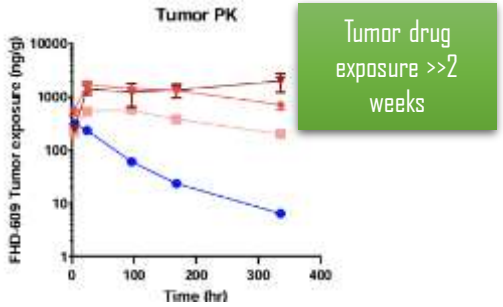
- Advanced PROTACs often competing with inhibitors as SoC, all of which are oral

Design guides for oral now understood

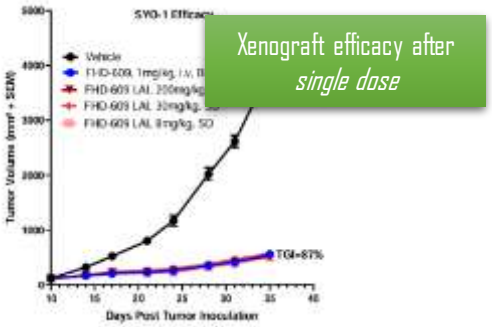


- Requires careful control of chemical properties including polarity and conformational flexibility

Foghorn iv dosed BRD9 PROTAC



Tumor drug exposure >>2 weeks



Xenograft efficacy after *single dose*

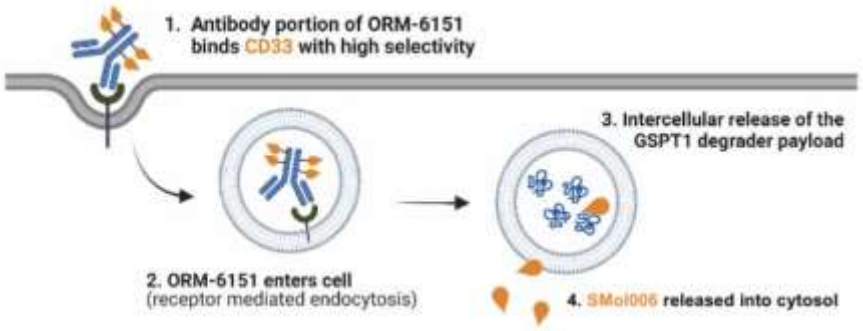
- Bifunctional agents are known to show long residence times in target tissues
- Efficacy seen even after drug metabolized if slow resynthesis of target protein

Cereblon gives best potential for orally available PROTACs
Other ligases more difficult for oral dosing but "biologic-like" injectable profiles accessible

Ref: oral PK guide Kymera, ACS meeting, August 2022, BRD9: Foghorn Therapeutics, AACR presentation

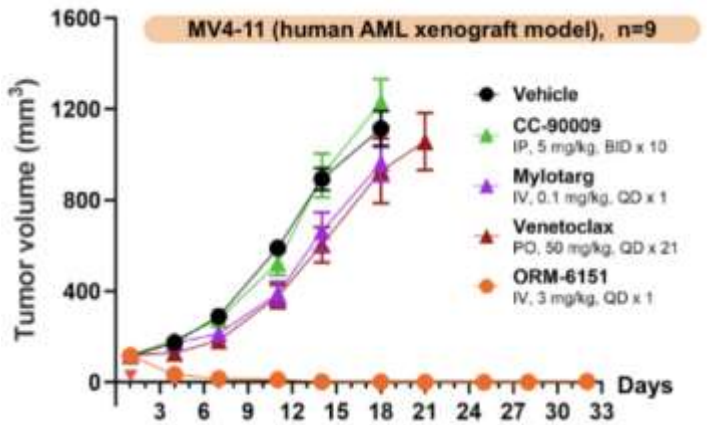
Harnessing the Power of Degraders: Degrader-Antibody Conjugates

- ORM-6151 – GSPT1 glue conjugated to aCD33 antibody



CD33-Positive Cells				CD33-Negative Cells			
Cell Line	ORM-6151 IC_{50} (M)	CC-90009 IC_{50} (M)	Mylotarg IC_{50} (M)	Cell Line	ORM-6151 IC_{50} (M)	CC-90009 IC_{50} (M)	Mylotarg IC_{50} (M)
MV-4-11	9.00E-11	1.20E-08	7.00E-11	RS4;11	>2.00E-08	4.50E-09	5.60E-10
ML-2	9.00E-11	9.10E-09	2.00E-11	CCRF-CEM	>2.00E-08	8.04E-09	8.56E-09
HL-60	1.10E-10	7.84E-09	9.00E-11	TALL-1	>2.00E-08	4.12E-09	2.92E-09
SKNO-1	1.60E-10	4.94E-09	4.00E-11	NALM-16	>2.00E-08	9.60E-09	8.02E-09
F-36P	2.00E-10	3.69E-09	>2.00E-08	Molt-4	>2.00E-08	1.13E-08	4.30E-10
Kasumi-6	3.40E-10	>2.00E-08	>2.00E-08	LC4-1	>2.00E-08	1.31E-08	1.47E-09
OCI-AML-4	3.60E-10	8.26E-09	1.00E-10	Reh	>2.00E-08	1.37E-08	5.80E-10
Molm-13	3.60E-10	>2.00E-08	3.00E-11	Loucy	>2.00E-08	4.07E-09	3.31E-09
AML-193	4.30E-10	9.59E-09	>2.00E-08	SUP-B15	>2.00E-08	>2.00E-08	1.78E-09
EoL-1	5.20E-10	1.18E-08	3.00E-11	THP-1	>2.00E-08	>2.00E-08	2.57E-09
HNT-34	1.01E-09	1.33E-09	5.20E-10	SKM-1	>2.00E-08	>2.00E-08	4.50E-10
Kasumi-3	1.12E-08	1.16E-09	>2.00E-08	Kopn-8	>2.00E-08	>2.00E-08	4.10E-10
OCI-AML-1	>2.00E-08	6.44E-09	9.00E-11	CMK-86	>2.00E-08	8.01E-09	>2.00E-08
KG-1a	>2.00E-08	1.27E-08	>2.00E-08	CMK-11-5	>2.00E-08	5.74E-09	>2.00E-08
				KU812	>2.00E-08	1.49E-08	>2.00E-08
				TF-1a	>2.00E-08	8.15E-09	>2.00E-08
				GDM-1	>2.00E-08	6.91E-09	>2.00E-08

- Delivers highly cytotoxic GSPT1 glue selectively to cytosol of CD33 high expressing tumor cells
  - Large window over effects in CD33 –ve & non-tumor cells
- *Single dose* complete responses in xenograft
- In Phase I. Acquired by BMS for $100M upfront in 2023

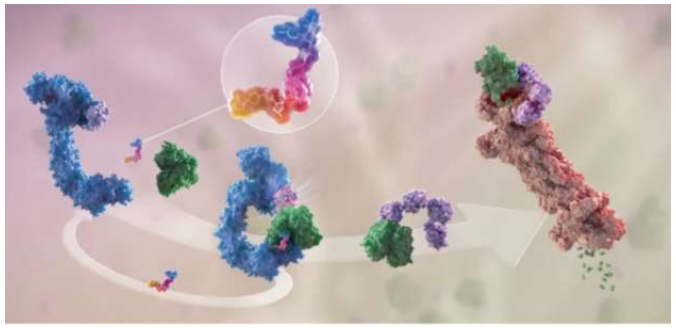


TPD agents now key part of pharmacologic toolbox with many applications

Ref Orum: ASH 2022 presentation

Targeted Protein Degradation – Key Messages

- New small molecule modality uses well understood regulatory pathway to approval
  - Gives genetic knockdown efficacy but with oral-dosing potential
  - First of "new" wave of TPD drugs likely to be approved in 2025
- Two available strategies: PROTACs & molecular glues
  - PROTACs need binder (not inhibitor) of target
  - Glues do not even need binder to target so can open undruggable targets
- Applicable to wide range of intracellular drug targets
  - Rational design possible in many cases



TPD agents have changed the way we think about using small molecule drugs

If you would like a copy of these slides or to discuss any of these areas further, please contact me at ian.churcher@janusdrugdiscovery.com or send me a note on LinkedIn