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A New Strategy in Drug Discovery: Protac-Induced Protein Degradation

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25th January 2018

Contemporary Drug Discovery

Small molecule inhibition/antagonism has been a successful therapeutic approach for many decades

Intrinsic limitations of this paradigm:

- Target choice at outset of project is critical for success
- “Occupancy-based” efficacy requires sustained high drug exposure at target
- Inhibition (usually) only affects one function of protein, leaving others intact
Boosting Pharmacodynamic Effects

- Compounds with slow off rates can be designed to achieve extended duration of action
- Ultimate slow off rate strategy is covalency
  - Duration of action driven by protein resynthesis rate
- Alternative approach is to remove protein from cells:
  - Can be achieved indirectly with siRNA, CRISPR and related approaches
  - Key challenges: delivery/selectivity

Cellular Protein Degradation

- Protein degradation is a critical and highly regulated cellular process
- Mainly mediated by the ubiquitin-proteasome system
- Proteins targeted for destruction are tagged with a ubiquitin chain via E1 (activation), E2 (conjugation) & E3 (ubiquitin ligase) enzymes

Can we hijack this process to degrade disease-causing proteins which would otherwise be stable?

Nat. Rev. Drug Disc. 2014, 13, 889
How much do you know about Protac-induced protein degradation?

- I don’t really know much about it at all – this is the first time I’m learning about it
- I’ve read a few papers and I’d like to get more information and detail
- I’d say I’m quite familiar with the area already
- I’m very familiar and already working on protein degradation today

A Protac is a bifunctional small molecule

- Brings target protein and cellular ubiquitinylation machinery into close proximity to initiate degradation cascade
- Effectively upregulates a (non-physiological) PPI

Overall Protac needs:
- Affinity and Selectivity for the target(s) to be degraded
- Good cell uptake, biodistribution, suitable pharmacokinetics
Protac Mode of Action is Catalytic

- Protac allows E3 ligases to recruit neosubstrates
- One Protac molecule removes many protein molecules from cell
- Catalytic action breaks free from receptor occupancy limitations

Steps for Successful Protein Degradation

1) Protac must enter cell and access the target
2) Ternary complex must allow efficient Ub transfer
3) Correct Ub chains should be added to allow recognition by proteasome
4) Ubiquitinated target should not be substrate for deubiquitinases
5) Rate of degradation needs to overcome de novo synthesis rate

A series of complex cellular processes must be orchestrated for efficient protein degradation
Why use Protacs?

• Removing a protein can give additional pharmacology relative to inhibition alone
  - E.g. remove scaffolding function or multiple functions of protein
  - Sustained pharmacological effect, even after drug is cleared

• New approach to undruggable targets
  - An affinity probe only is required - important for proteins where functional site is unligandable (eg PPIs)

• Catalytic MoA gives potential for high potency/low dose
  - Overcomes formulation and toxicity issues often seen with high dose inhibitors

• Greater functional selectivity relative to corresponding inhibitor
  - Additional layer of selectivity with potential to improve safety

Proposed VHL-Protac-Target Active Complex

Constructed from composite of published x-ray structures and docking of Protac (Ian Smith)
What is your current view of the use of Protac-induced protein degradation?

- The whole area could be an interesting chemical biology tool but is very unlikely to have an impact on drug discovery
- It could be useful in a handful of drug discovery applications
- The approach will find increasing use across a wide range of drug discovery applications in coming years
- It has the potential to transform the way drug discovery is carried out
- There’s not yet enough hard data to judge the potential of the area

Which Ubiquitin E3 Ligase to Use?

600+ potential ubiquitin E3 ligases known

- Low druggability: most reports limited to VHL, cerebon & IAP. Mdm2 and a few other reports also.
- Most interact with substrates over large PPI interface, often recognising charged substrates

Von Hippel Lindau (VHL)

- VHL binder (HIF1α mimetic)
- E3 $K_d$ ~0.5μM
- DC$_{50}$ down to low nM

Nat Chem Biol 2015, 11, 611
See also ACS Chem Biol 2015, 10, 1770

Cereblon

- Cereblon binder (thalidomide-based)
- E3 $K_d$ ~1μM
- DC$_{50}$ down to low/sub-nM

Chem & Biol 2015, 22, 755
Science 2015, 348, 1376

Inhibitor of Apoptosis Protein (IAP) Family

- Many cIAP binders identified
- E3 $K_d$ low nM across family
- DC$_{50}$ down to low/sub-nM

Cancer Sci 2013, 104, 1492
J Biol Chem 2017, 292, 4556-70
RIP2 as a Prototypical Degradation Target

- Receptor-interacting protein kinase-2 (RIP2) is an important mediator of innate immune signalling and NF-κB & MAPK activation
  - Dysregulation of NOD2/RIP2 pathway associated with autoinflammatory disease
  - e.g. Hyperactivated in diseases such as Blau Syndrome
- Potent and selective RIP2 binders available

![RIPK2 ligand](image1)

RIPK2 ligand $K_d$ 2nM

![RIPK2 Protacs](image2)

RIPK2 inhibitor from WO 2012122011

Anatomy of a Protac

**Target-Binding Ligand**
- Higher affinity generally better - $<1\mu M K_d$ preferred
- Selective ligand gives selective degradation

**Linker**
- Set up correct geometry of complex
- Secondary interactions
- Tune overall physchem

**E3 Ligase-Recruiting Ligand**
- Can recruit VHL, cereblon, IAP, (+ mdm2, others?)

Overall molecular size 800-1500Da
- Non-traditional space...
A Note on Protac Synthesis

- Syntheses are modular - longest linear sequence 10 steps
- Efficient and scalable

RIP2 can be Degraded by Multiple E3 Ligase Complexes

NB Protacs bind RIPK2 with $K_d \sim 10\text{nM}$ and E3 ligase with $K_d \sim 10-1000\text{nM}$
**“Hook Effect” - Evidence of Ternary Complex**

For comprehensive mathematical analysis of 3 body equilibria, see Spiegel et al J. Am. Chem. Soc. 2013, 135, 6092

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**RIP2 Protein Knockdown is Rapid Across Cell Types**

Knockdown rapid (contrast RNAi)
- Rate of degradation determined by Protac concentration

Broad utility across cell types
- Also T-cells, neutrophils, whole blood
- Degradation rate generally similar across primary cells

Human Primary Blood Mononuclear Cells or THP1 monocytes were treated with Protac_RIP2(IAP) at the indicated concentrations
- RIPK2 levels quantified by Western blot at indicated times post compound addition
Long In vivo Pharmacodynamic Duration of Action

PROTACs show typical small molecule pharmacokinetic profiles
- Long t1/2, moderate volume of distribution
- Oral bioavailability seen in many cases

Protacs give sustained protein knockdown...
RIP2-IAP PROTAC dosed s.c. in rats
RIP2 protein levels in PBMCs analysed by Western Blot

Ex vivo TNFα levels (ELISA) following MDP challenge

...and potent functional efficacy

Protac Degradation is Highly Selective at Proteome Level
- Global expression proteomics shows degradation of 2 proteins from >7000 quantified
- RIPK2 major protein degraded
- Weaker MAPKAPK3 degradation may be secondary effect
- Control Protac shows no effect

RIPK2 ligand binds to 1/371 kinases (Cellzome kinobeads)
Scope of Protein Degradation:

- Using a highly promiscuous ligand to simultaneously assess the degradability of many protein targets
- Diaminopyrimidine ligand below engages 244 kinases with $K_d < 10 \mu M$
- Prepare exemplar Protac for each E3 ligase using “vanilla” 4x ethylene glycol linker

![Promiscuous binder](image1)

Expression Proteomics - IAP Protac

- Recruitment of IAP also results in kinase degradation, however in a more selective manner
- The IAP Protac degrades 6/12 kinases engaged $pIC_{50} > 6$
- IAP Protac allows degradation of more weakly bound targets ($pIC_{50} = 5-6$)
  - E.g. BTK $K_d \approx 5 \mu M$, $DC_{50} \approx 300 nM$ (confirmed below)
• The promiscuous Cereblon PROTAC induces **significant** kinase degradation
• **15/30** kinases targets engaged with a pIC\(_{50} > 6\) were found to be degradable
• Trend towards greater degradation with increasing kinase binding potency
  – No kinases with a pK\(_d\) < 6 were significantly degraded
• Demonstration of selective degradation even in the absence of binding selectivity

---

• VHL Protac induced **modest** kinase degradation only
• Protein knockdown relatively weak compared to use of Cereblon or IAP
• Kinases shown to be degradable using other ligases appear “undegradable” using VHL
• Factors underlying degradation efficiency/selectivity can include:
  – Geometry of ternary complex
  – Role of linker in facilitating complex formation
  – Availability of suitable ubiquitinylation sites on substrate
**Summary: Protacs - Solved Problems**

- **High potency - low nM-pM cellular pharmacology routinely achieved**
  - Catalytic mode of action gives potential for low doses

- **Wide range of targets degraded**
  - 100s-1000s protein targets likely degradable by this mechanism
  - High selectivity easily achieved

- **Range of E3 ligases utilized**
  - Small but growing list of E3 ligases gives flexibility

- **Potent in vivo effects**
  - Despite untraditional molecules, designing desired pharmacokinetics is not an issue, and may even be easier

- **[Dogma overturned...?]**

**Where Next for Protacs?**

- **Picking best Protac target proteins - which will give most clinically useful pharmacology?**
  - Which proteins are most degradable?
  - Where will degradation have most benefit/lowest potential for undesirable effects?

- **Designing better Protacs, faster**
  - Matching the right E3 ligase to the right degradation target
  - Best linkers for efficacy, desired selectivity & druglike properties
  - Achieving more predictable pharmacokinetic profiles including routine oral availability

- **Better understanding of E3 ligases**
  - Expanding E3 ligases used including tissue-specific E3 ligases

- **Demonstrated long term safety and tolerability leading to clinical efficacy**
What is the biggest outstanding challenge Protacs need to overcome to have impact on drug discovery?

- Chemical synthesis, scale-up and formulation may lead to high cost of goods
- The optimisation process and matching E3 ligase to target protein will be complex and unpredictable
- This complex mechanism of action will suffer poor safety and tolerability
- Difficulties in achieving oral bioavailability will limit attractive clinical dosing regimens.
- The approach will only be useful for a small range of therapeutic targets

The Allure of Undruggable Targets...

- Protacs need only affinity probes and not functional inhibitors
- It should be easier to find an affinity probe than a functional inhibitor...
- Many ways to identify such ligands now exist
  - Biophysical screening (SPR, NMR etc)
  - DNA-encoded library screening
- Despite this, still few examples of degradation of truly undruggable targets to appear
Summary

• Protacs are now established as a novel drug discovery approach which deliver pharmacology impossible through other means

• Clinical testing expected soon

• Protac-based medicinal chemistry has the potential to be more complex, or simpler, than current strategies
  - A new, multi-parameter optimisation challenge?

• Emerging data will start to clarify the true scope of the approach

Acknowledgements & Further Information

- John Harling et al
- Craig Crews et al
- Marcus Bantscheff et al

And all the other scientists across industry and academia who have helped advance this new field
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Senior Principal Scientist,
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- Donna M. Hugyn, University of Pittsburgh's School of Pharmacy
- Erika Viera Araujo, Bristol-Myers Squibb
- Annetze Bai, Asia Zeneca

What You Will Learn
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- A day in the life of each panel member highlighting their roles and responsibilities in their specific functions
- The technical and soft skills ideal for each panelists' position within drug discovery and development

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