ACS Webinars
CLICK • WATCH • LEARN • DISCUSS

ACS Chemistry for Life®

Have Questions?

Type them into questions box!

"Why am I muted?"
Don't worry. Everyone is muted except the presenter and host. Thank you and enjoy the show.

Contact ACS Webinars ® at acswebinars@acs.org

1

ACS Webinars
CLICK • WATCH • LEARN • DISCUSS

ACS Chemistry for Life®

Have you discovered the missing element?

http://bit.ly/benefitsACS

Find the many benefits of ACS membership!

2

ACS Webinars
CLICK • WATCH • LEARN • DISCUSS

ACS Chemistry for Life®

Benefits of ACS Membership

Chemical & Engineering News (*C&EN*)
The preeminent weekly digital and print news source.

NEW! ACS SciFinder
ACS Members receive 25 complimentary SciFinder® research activities per year.

NEW! ACS Career Navigator
Your source for leadership development, professional education, career services, and much more.

http://bit.ly/benefitsACS

3

Let's get Social…post, tweet, and link to ACS Webinars during today's broadcast!

ACS Chemistry for Life®

facebook.com/acswebinars

@acswebinars

Search for "acswebinars" and connect!

4

How has ACS Webinars® benefited you?

ACS Chemistry for Life®

"This was an awesome webinar presentation addressing how pharmaceutical chemistry and drug development can be used to correct the complex autoimmune disease of SLE using a combination of and interaction between self molecules within the diseased patient and specific inhibitors made in the lab to hit the right combination of targets to stop the symptoms of autoimmunity."

http://bit.ly/DDDSlupus

Fan of the Week

Rafael Álvarez González, PhD
Editorial Board Member of Cáncer Investigation and CEO of ÁGORA Scientific Services, LLC

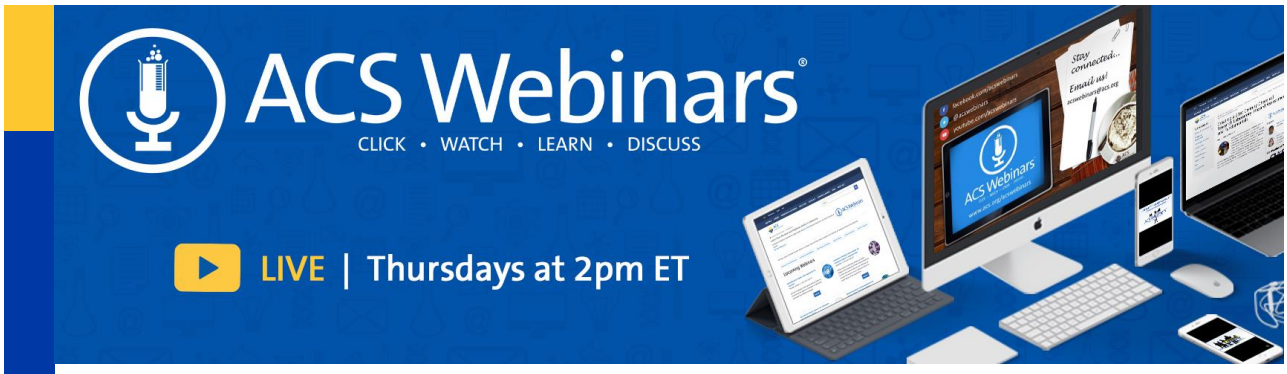
Be a featured fan on an upcoming webinar! Write to us @ acswebinars@acs.org

5

ACS Webinars® CLICK • WATCH • LEARN • DISCUSS

ACS Chemistry for Life®

6



Learn from the best and brightest minds in chemistry! Hundreds of webinars on diverse topics presented by experts in the chemical sciences and enterprise.

Recordings are an exclusive ACS member benefit and are made available to registrants via an email invitation once the recording has been edited and posted.

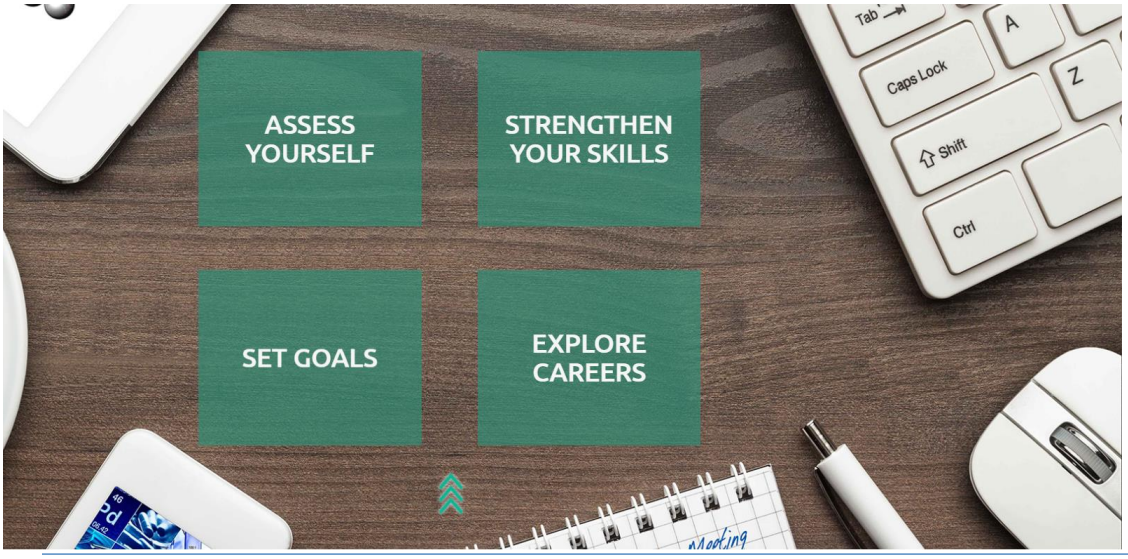
Live Broadcasts of ACS Webinars® continue to be available to the general public every Thursday from 2-3pm ET!

www.acs.org/acswebinars

7

An individual development planning tool for you!

ACS Chemistry for Life®



ChemIDP.org

8

Celebrating 4 years & 40 Drug Discovery Webinars!

http://bit.ly/acsDrugDiscoveryArchive

ACS Chemistry for Life®

2014

1. **Drug Discovery Series #1 - Current Drug Discovery and Development Process**
(DDS #1) Watch this overview of the drug discovery and development process to learn the stages and challenges in every step.
2. **Primer in Drug Target Classes**
(DDS #2) Listen in on a discussion on the big four druggable families and the difference between small molecule and biotherapeutic targets.
3. **Key Concepts in Identifying Drug Leads**
(DDS #3) Discover how drug-likeness is a deceiving concept, explore the Rule of Five, and show how lessons from the past may guide the present.
4. **Lead Optimization – Building Efficacy & Safety**
(DDS #4) Learn strategies on how to effectively optimize small molecule hits and rapidly assess your findings.
5. **Tips for Filing IND and Starting your Clinical Trials**
(DDS #5) What do you need to know when filing for Investigational New Drug submissions to the United States Food and Drug Administration?
6. **The Role of Chemistry in Clinical Trials: The Big Expense & Lessons Learned**
(DDS #6) Learn how the properties of the candidate impact decisions in the discovery process.
7. **Pharmacoeconomics and IP Strategies in Drug Development**
(DDS #7) Review the basic principles of Pharmaco-economics in drug development strategies as well as its role in determining health insurance coverage of drug products.
8. **Future of Drug Discovery - Challenges, Risks and Rewards**
(DDS #8) Explore how how risks and challenges will be dealt with in the future and the key skill sets required of future medicinal chemists.

Co-Produced By

aaps American Association of Pharmaceutical Scientists | Division of Medicinal Chemistry

2015

1. **Designing Better Drug Candidates**
(January) Learn various factors that can be used to improve candidate quality from Dr. Paul Leeson.
2. **Strategies to Improve Solubility of Drug Candidates**
(February) Learn a number of different strategies for improving drug solubility through structural modification.
3. **Fragment-Based Drug Design Strategies**
(March) Finding the right drug target is becoming increasingly difficult. Learn how focusing on the smaller picture can have big results.
4. **Screening Strategies**
(April) Learn the pros and cons of different screening strategies.
5. **Avoiding PAINS (pan-assay interference compounds)**
(May) Jonathan Baell shares some tips on how to avoid the dead ends of drug discovery.
6. **Accelerating CNS Positron Emission Tomography (PET) Ligand Discovery**
(June) Join Lei Zhang as he lays out a set of preferred parameters for which has yielded successful PET ligands and reduced resources and timelines.
7. **X-ray Crystallography in Drug Discovery**
(July) Jon Mason and Miles Congreve describe what protein-ligand X-ray data can do for you.
8. **Choices and Trends in Solid Dosage Form Selection**
(August) Discover the pros and cons of the different solid state forms and what to consider when selecting.
9. **Delivery Options to Support Dose Escalation in Preclinical Toxicology and Pharmacodynamic Activity Studies**
(September) Gain an understanding of acceptable drug delivery approaches to support preclinical dose escalation.
10. **Pharmacokinetic Considerations in Drug Design and Development**
Learn about key pharmacokinetic concepts including clearance, volume of distribution, half life and protein binding.
11. **Prodrugs in Drug Discovery**
(November) John Higgins shares the utility of prodrugs, their general properties and prerequisites for optimal performance.

2016

- I - Time: The Fourth Dimension in Drug Discovery
  1. The Importance of Drug-Target Kinetics in Drug Design — Robert Copeland - Epizyme, Inc; Dan Bramson - Camtot Therapeutics
  2. Long-Acting Injectable Medications: Strategies and Mechanistic Considerations — Jules Remenar - Alkermes; Annette Bak - Merck
  3. Modified Release Formulations for Solubility Starved Compounds — Mengwei Hu - Merck; John Morrison - BMS
  4. The Medicinal Chemist of Tomorrow (Special Topic) — Joel Barrish - Achillion; Ravi Nargund - Merck; Marty Schmid - Tech Coast Angels
- II - Beyond Traditional Small Molecules
  5. Design of Deliverable Macrocycles — Scott Lokey - UC Santa Cruz; Nicholas Meanwell - BMS
  6. Dreaming Big and Thinking Small: Applying Medicinal Chemistry Strategy to Antibody-Drug-Conjugates — L. Nathan Tumey - Pfizer; Peter Senter - Seattle Genetics
  7. Nucleic Acids Therapeutics: Making Sense of Antisense Oligonucleotides — Punit Seth - Ionis; Richard Olson - BMS
  8. Crystallography as a Drug Design and Delivery Tool (Special Topic) — Robert Wenslow - Crystal Pharmatech; Vincent Stoll - AbbVie; Andrew Brunskill - Merck
- III - Pharmacology Revisited
  9. Dealing with Reactive Drug Metabolites in Drug Discovery: Can We Predict Toxicities of Drug Candidates that form Reactive Metabolites? — Deepak Dalvie - Pfizer; Frederick Peter Guengerich - Vanderbilt University
  10. Rational Design of Small Molecules Targeting RNA — Matt Disney - Scripps Rl Florida; Amanda Garner - University of Michigan
  11. Cell Penetrating Peptides to Improve Cellular Drug Uptake — Dehua Pei - The Ohio State University; Scott Hart - Bristol-Myers Squibb

2017

- I - Fighting Cancer
  1. Fighting Cancer: Targeting CNS Malignancy with Kinase Inhibitors — Timothy P. Heffron - Genentech; Mark Witzman - Bristol-Myers Squibb
  2. Fighting Cancer: Epigenetic targets for Oncology — Stuart Conway - Oxford; Sharan Bagal - AstraZeneca
  3. Fighting Cancer: Allostery and Targeting Cancer Cell Metabolism — Stefan Gross - Agios; Scott Edmundson - AstraZeneca
- Special Broadcast
  4. Cystic Fibrosis: Discovery of CFTR Modulators — Peter Grootenhuis - Vertex; Nick Meanwell - Bristol-Myers Squibb
- II - Anti-Infectives
  5. Anti-Infectives: Rational Approaches to the Design and Optimization — Jason Sello - Brown University; Courtney Aldrich - University of Minnesota
  6. Tuberculosis: An Introduction for Medicinal Chemists — Carl Nathan - Weill Cornell Medicine; Christopher Boyce - Merck
  7. Viral Hepatitis: The Search for a Cure — Mike Sofia - Arbutus Biopharma; Stephen Mason - CaroGen Corporation
- Special Broadcast
  8. Spinal Muscular Atrophy — Kevin Hodgetts - Harvard Medical School; Alyson Weidmann - ACS Publications
- III - Immunology
  9. Psoriasis: Treatment and Novel Approaches — Frank Narjes - AstraZeneca; John Morrison - Bristol-Myers Squibb
  10. Lupus: Treatment and Novel Approaches — Laurence Menard - Bristol-Myers Squibb; Mary Struthers - Bristol-Myers Squibb

9

Upcoming ACS Webinars

www.acs.org/acswebinars

ACS Chemistry for Life®

Thursday, February 1, 2018

***Navigating My Research Career**: How to Manage US Immigration & Visa Opportunities*

Co-produced with the ACS Graduate & Postdoctoral Scholars Office

Experts

Brendan Delaney
Frank & Delaney Immigration Law, LLC

Joerg Schlatterer
American Chemical Society

Thursday, February 8, 2018

***Networking without Saying a Single Word:** Silent but Deadly*

Experts

Matt Grandbois
Dow Chemical

Patricia Simpson
University of Illinois at Urbana-Champaign

Contact ACS Webinars ® at acswebinars@acs.org

10

Chemical Entity and Biomolecule Scientific Program Tracks:

- **Preclinical** (including Discovery)
- **Bioanalytical**
- **Clinical Pharmacology**
- **Manufacturing & Bioprocessing**
- **Formulation & Quality**

YouTube video:
https://www.youtube.com/watch?v=1DOxLBg0Ouw

Website: www.aapspharmsci360.org

Join the ACS Division of Medicinal Chemistry Today!

ACS Chemistry for Life®

Division of Medicinal Chemistry

For $25 ($10 for students)**, You Will Receive:**

- A free copy of our annual medicinal chemistry review volume (over 600 pages, $160 retail price)
- Abstracts of MEDI programming at national meetings
- Access to student travel grants and fellowships

Find out more about the ACS MEDI Division! www.acsmedchem.org

12

Women in Drug Discovery and Development: How to Succeed as a Female in Academia and Industry

ACS Chemistry for Life®

February 22, 2018 @ 2-3pm ET

Session 2 of the 2018 Drug Design and Delivery Symposium

"Life is not easy for any of us...We must have perseverance and above all confidence in ourselves. We must believe that we are gifted for something and that this thing must be attained." Marie Curie is an inspiration for all scientists and for good reason as she was a true pioneer and the first scientist to be awarded a Nobel Prize in two different categories. With more young women than ever opting to study within the STEM field, we look to answer just what it takes to create a rewarding and successful career within academia or the pharmaceutical industry as a female. We will explore insights from those in the field today to understand the technical and soft skills necessary to flourish.

Register For Free!

Experts


Nurulain Zaveri
Astraea Therapeutics


Erika Vieira Araujo
Bristol-Myers Squibb


Donna M. Huryn
University of Pittsburgh's School of Pharmacy


Annette Bak
Astra Zeneca

Co-Produced By

aaps American Association of Pharmaceutical Scientists

Division of Medicinal Chemistry

What You Will Learn

- Insight and real life experiences from successful females in drug discovery and development from academia to industry
- 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 panelist's position within drug discovery and development

http://bit.ly/WomenDDD

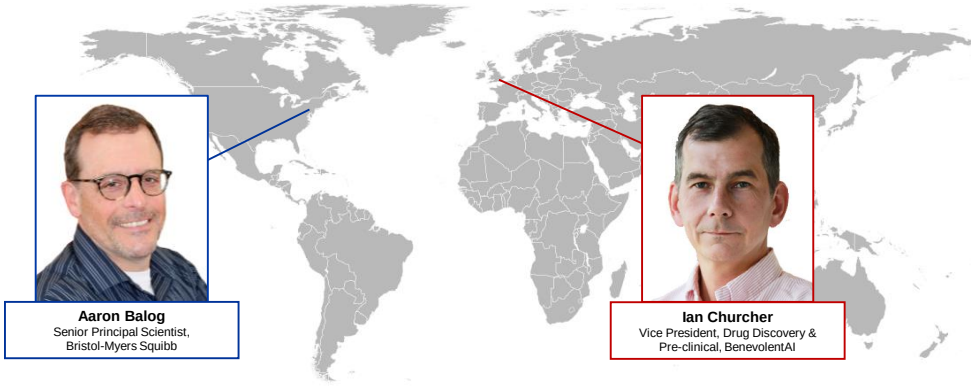
13

ACS Webinars CLICK • WATCH • LEARN • DISCUSS

ACS Chemistry for Life®

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

Session 1 of the 2018 Drug Design and Delivery Symposium



Aaron Balog
Senior Principal Scientist,
Bristol-Myers Squibb

Ian Churcher
Vice President, Drug Discovery &
Pre-clinical, BenevolentAI

Slides available now and an invitation to view the recording will be sent when available.

www.acs.org/acswebinars

This ACS Webinar is co-produced with the ACS Division of Medicinal Chemistry and the American Association of Pharmaceutical Scientists

14

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

Ian Churcher
VP, Drug Discovery & Pre-clinical, BenevolentAI
Ian.churcher@benevolent.ai

25th January 2018

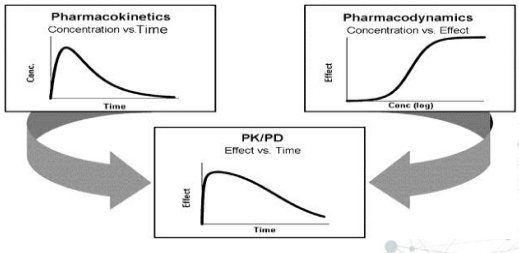
Contemporary Drug Discovery

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

Hypothesis: inhibition of drug target affects disease phenotype → Find high affinity functional inhibitor → Optimise pharmacokinetics/ residence time in target tissue → In vivo/clinical efficacy

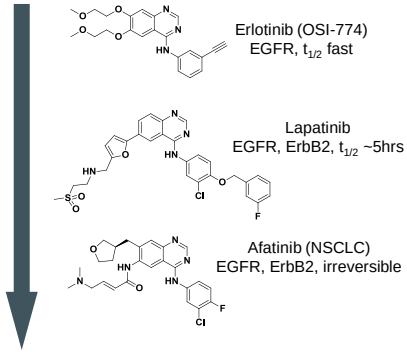
Intrinsic limitations of this paradigm:

- 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:

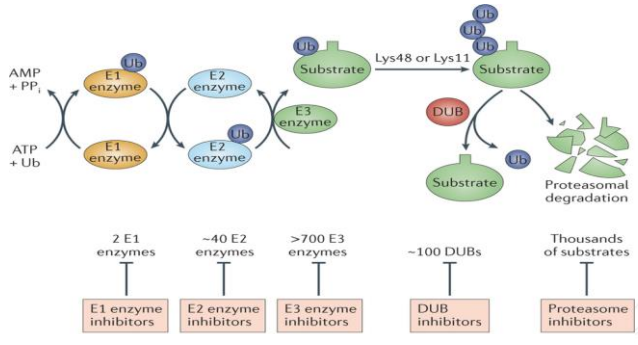
Can be achieved indirectly with siRNA, CRISPR and related approaches

- **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

Audience Challenge Question

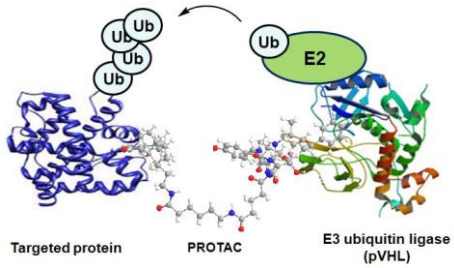
ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

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

19

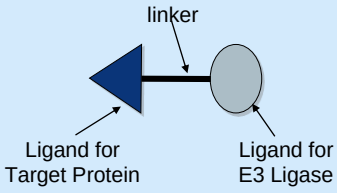
Proteolysis-Targeting Chimeras: Fundamentals of Protac Action



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**

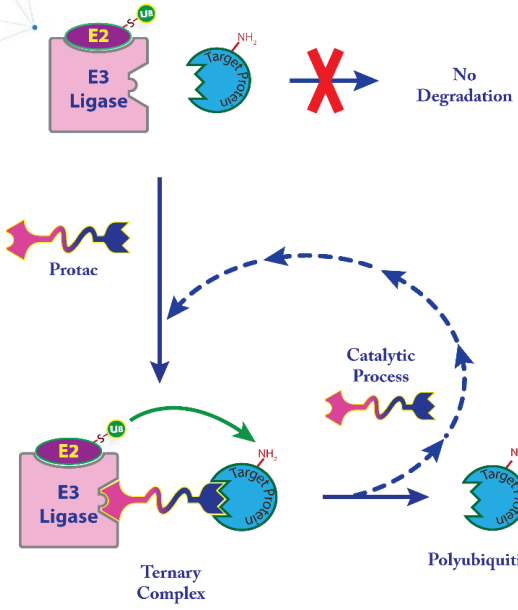
Protacs contain 3 "domains"



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

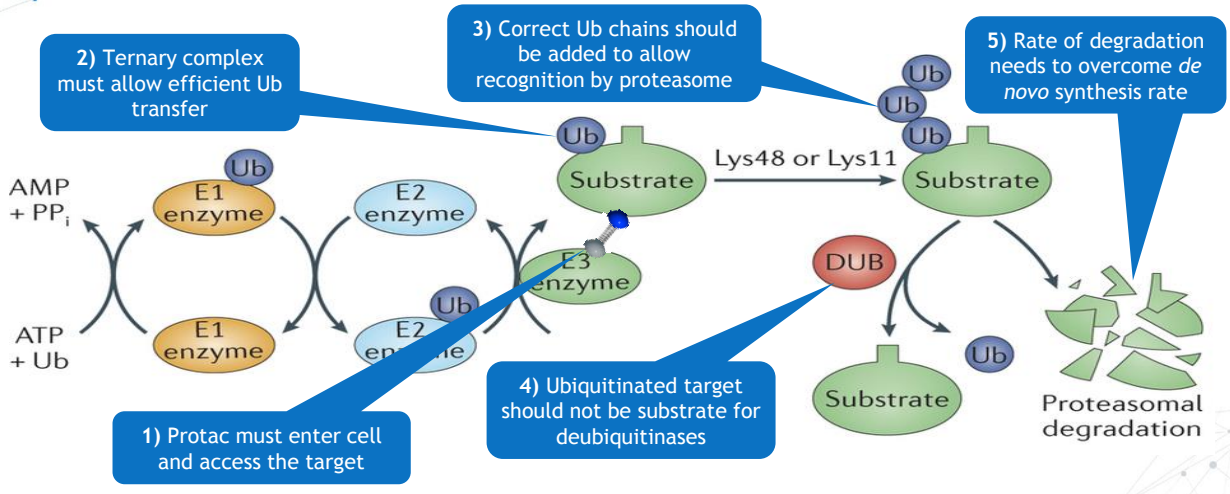


Protac allows E3 ligases to recruit neosubstrates

One Protac molecule removes many protein molecules from cell

Catalytic action breaks free from receptor occupancy limitations

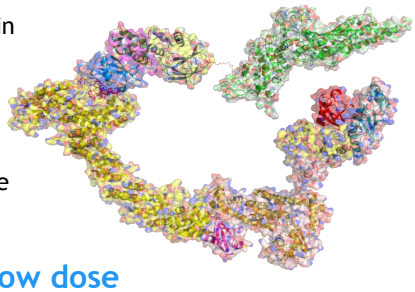
Steps for Successful Protein Degradation



A series of complex cellular processes must be orchestrated for efficient protein degradation

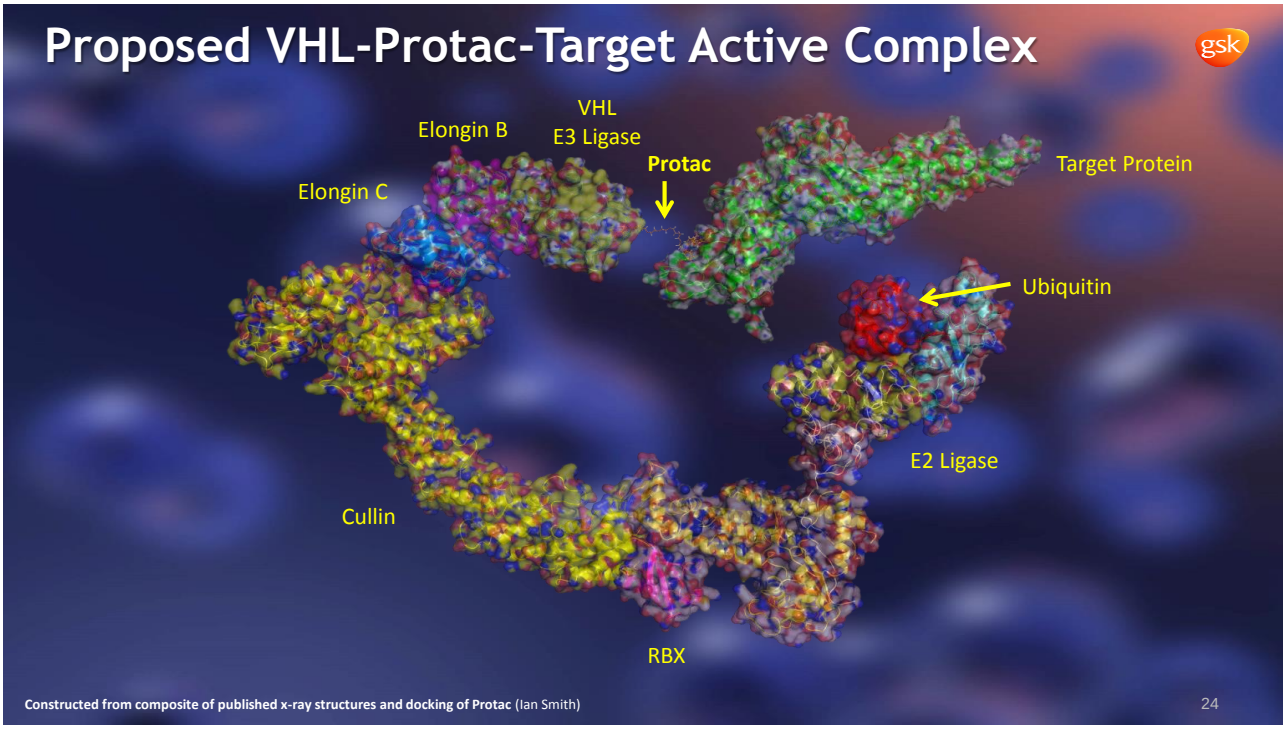
Why use Protacs?

- **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)

Audience Challenge Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

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

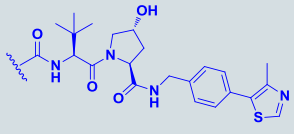
25

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

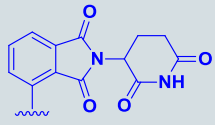
Von Hippel Lindau (VHL)



- **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

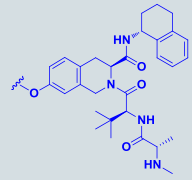
cereblon



- **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

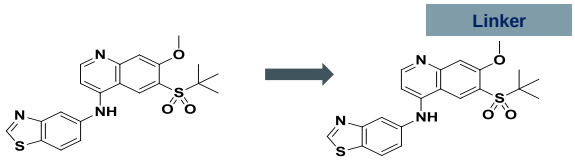


- **Many cIAP binders identified**
- **E3 K_d low nM across family**
- **DC_{50} down to low/sub-nM**

Cancer Sci **2013**, *104*, 1492
J Biol Chem **2017**, *292*, 4556-70

RIP2 as a Prototypical Degradation Target

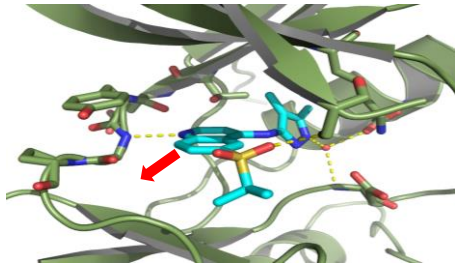
- **Receptor-interacting protein kinase-2** (RIP2) **is an important mediator of innate immune signalling and NF-κB & MAPK activation**
  - Dysregulation of NOD2/RIP2 pathway associated with autoinflammatory disease
  - e.g. Hyperactivated in diseases such as Blau Syndrome
- **Potent and selective RIP2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

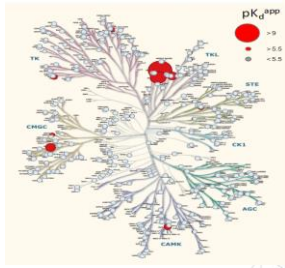


RIPK2 ligand
K_d 2nM

RIPK2 Protacs

RIPK2 inhibitor from WO 2012122011





Selectivity profiling (Cellzome Kinobeads) of RIPK2 ligand vs 371 kinases

Anatomy of a Protac

Target-Binding Ligand

Higher affinity generally better - <1μM K_d preferred

Selective ligand gives selective degradation

Linker

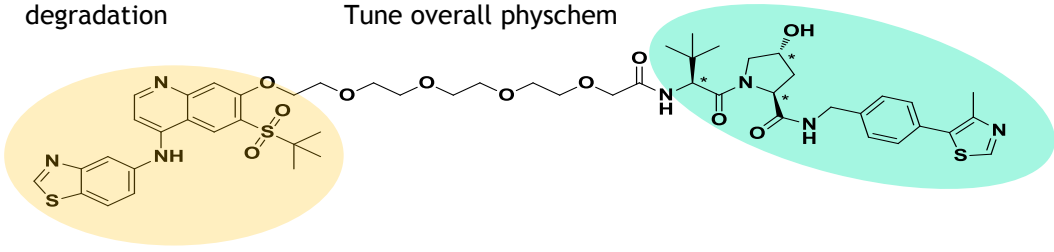
Set up correct geometry of complex

Secondary interactions

Tune overall physchem

E3 Ligase-Recruiting Ligand

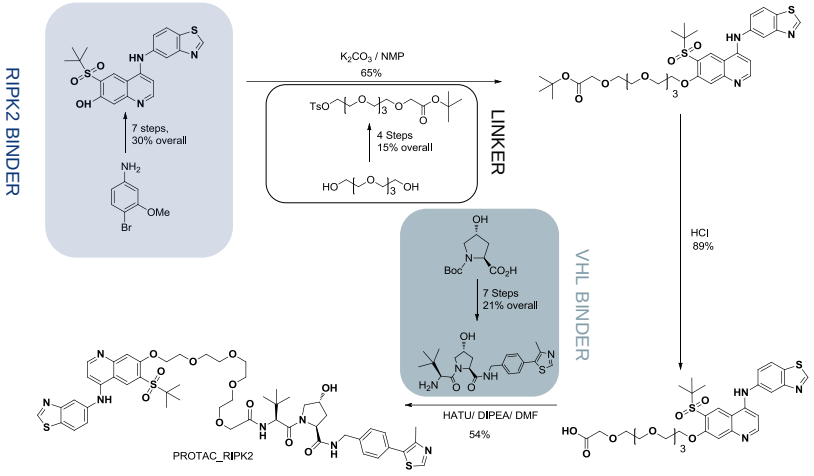
Can recruit VHL, cereblon, IAP, (+ mdm2, others?)



Overall molecular size 800-1500Da

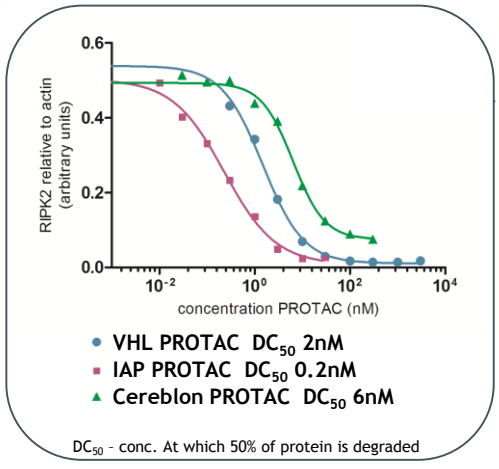
Non-traditional space…

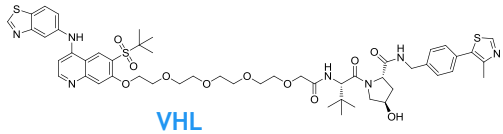
A Note on Protac Synthesis

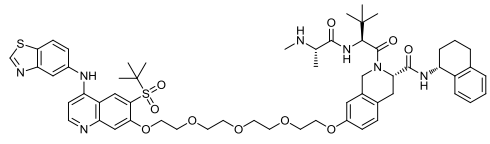


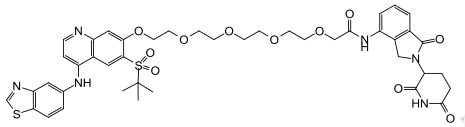
- Syntheses are modular – longest linear sequence 10 steps
- Efficient and scalable

RIP2 can be Degraded by Multiple E3 Ligase Complexes



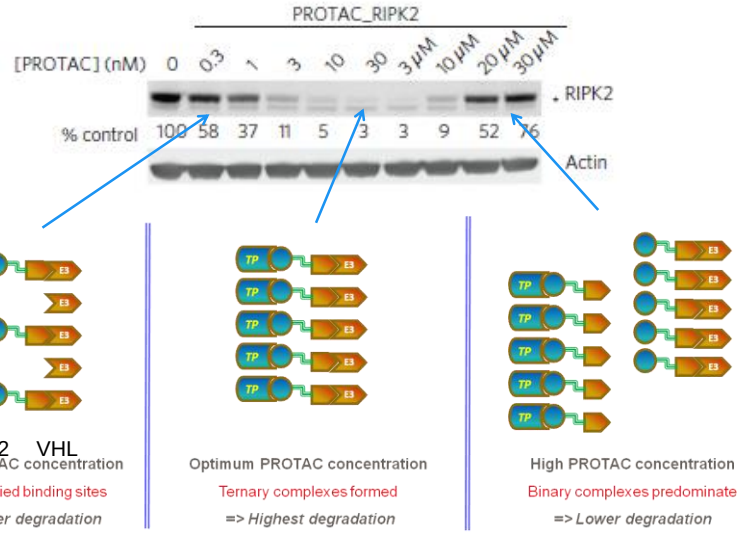

VHL


IAP


Cereblon

NB Protacs bind RIPK2 with K_d~10nM and E3 ligase with K_d~10-1000nM

"Hook Effect" - Evidence of Ternary Complex

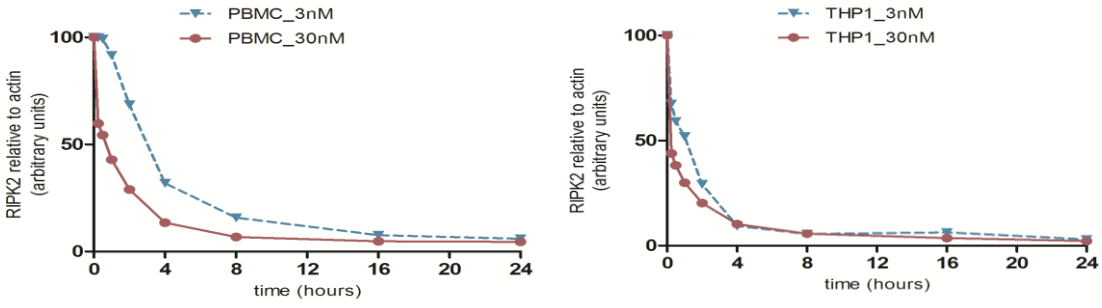


For comprehensive mathematical analysis of 3 body equilibria, see Spiegel et al *J. Am. Chem. Soc.* 2013, 135, 6092

RIP2 Protein Knockdown is Rapid Across Cell Types

Knockdown rapid (contrast RNAi)

- Rate of degradation determined by Protac concentration



Broad utility across cell types

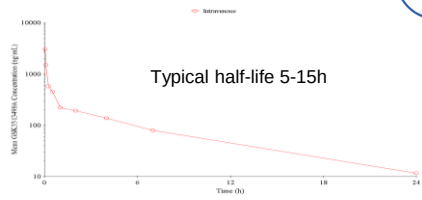
- Also T-cells, neutrophils, whole blood
- Degradation rate generally similar across primary cells

– 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

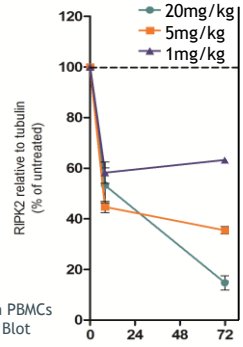
- Long $t_{1/2}$, moderate volume of distribution
- Oral bioavailability seen in many cases



Typical half-life 5-15h

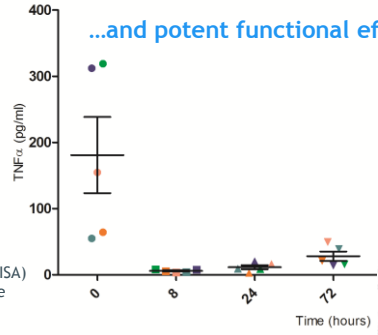
Protacs give sustained protein knockdown…

RIP2-IAP PROTAC dosed s.c in rats



RIP2 protein levels in PBMCs analysed by Western Blot

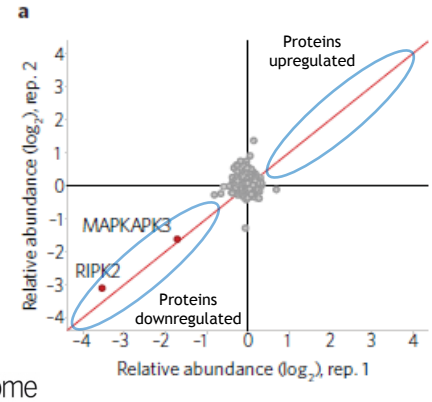
…and potent functional efficacy



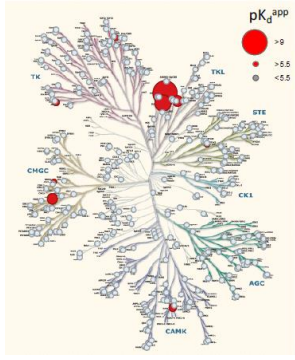
Ex-vivo TNFα levels (ELISA) following MDP challenge

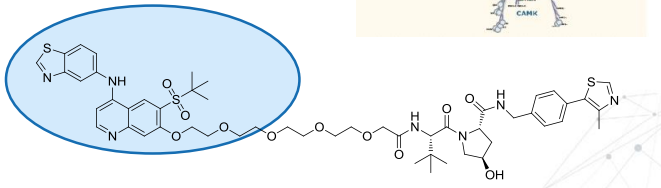
Protac Degradation is Highly Selective at Proteome Level

- **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)



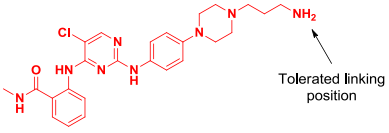


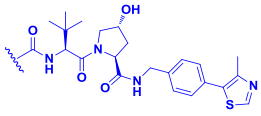
cellzome A GSK company

Scope of Protein Degradation:

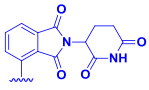
- Using a highly promiscuous ligand to simultaneously assess the degradability of many protein targets
- Diaminopyrimidine ligand below engages 244 kinases with K_d < 10 µM
- Prepare exemplar Protac for each E3 ligase using "vanilla" 4x ethylene glycol linker

Ligand only
K_d<10 µM
@244 kinases

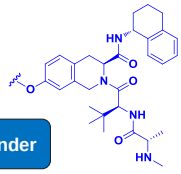




VHL Protac
K_d < 10 µM maintained
96/244 kinases



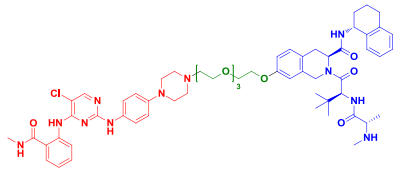
Cereblon Protac
K_d < 10 µM maintained
144/244 kinases

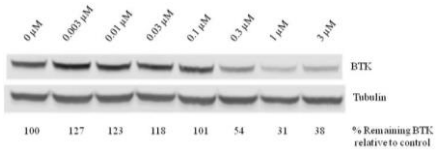


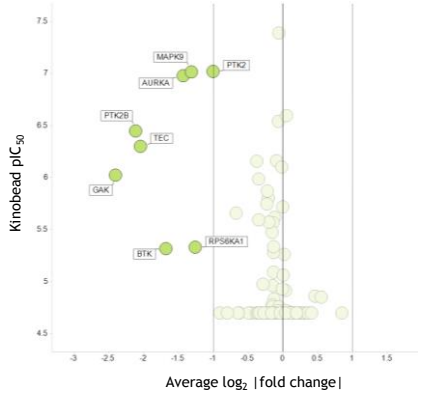
IAP Protac
K_d < 10 µM maintained
66/244 kinases

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 ~5µM, DC_{50} ~300nM (confirmed below)



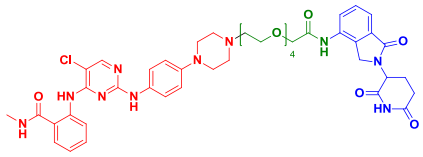


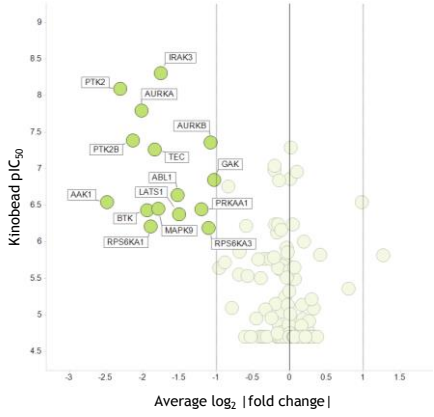


Protac dosed to cells @1uM/24h

Expression Proteomics - Cereblon Protac

- 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

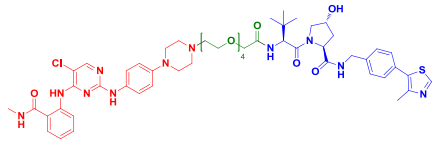


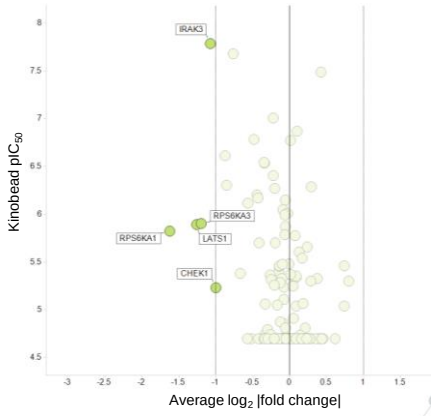


Protac dosed to cells @1uM/24h

Expression Proteomics - VHL Protac

- 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**

Audience Challenge Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

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

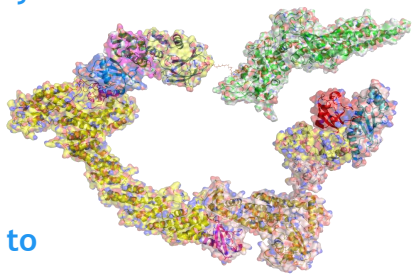
41

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

GlaxoSmithKline

- John Harling et al

Yale University

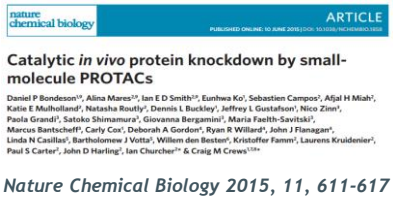
- Craig Crews et al

cellzome
A GSK company

- Marcus Bantscheff et al

BenevolentAI

And all the other scientists across industry and academia who have helped advance this new field



nature chemical biology — ARTICLE

Catalytic *in vivo* protein knockdown by small-molecule PROTACs

Daniel P Bondeson[1,9], Alina Mares[2,9], Ian E D Smith[2,3], Eunhwa Ko[1], Sebastien Campos[2], Afjal H Miah[2], Katie E Mulholland[2], Natasha Routly[2], Dennis L Buckley[1], Jeffrey L Gustafson[1], Nico Zinn[2], Paola Grandi[3], Satoko Shimamura[3], Giovanna Bergamini[3], Maria Faelth-Savitski[3], Marcus Bantscheff[3], Carly Cox[1], Deborah A Gordon[4], Ryan R Willard[4], John J Flanagan[4], Linda N Casillas[5], Bartholomew J Votta[5], Willem den Besten[6], Kristoffer Famm[7], Laurens Kruidenier[2], Paul S Carter[2], John D Harling[2], Ian Churcher[2]* & Craig M Crews[1,8]*

Nature Chemical Biology 2015, 11, 611-617

Journal of Medicinal Chemistry — Perspective

Cite This: J. Med. Chem. XXXX, XXX, XXX−XXX — pubs.acs.org/jmc

Protac-Induced Protein Degradation in Drug Discovery: Breaking the Rules or Just Making New Ones?

Ian Churcher*

BenevolentBio, 40 Churchway, London NW1 1LW, U.K.

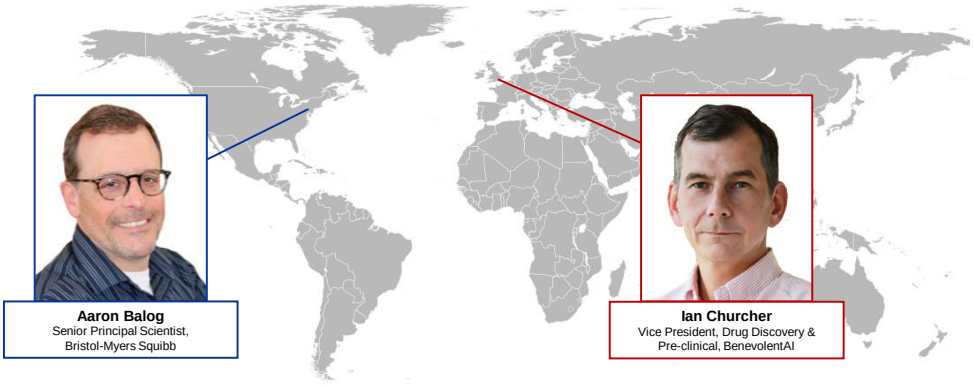
J. Med. Chem., **Just Accepted Manuscript**
DOI: 10.1021/acs.jmedchem.7b01272

ACS Webinars
CLICK • WATCH • LEARN • DISCUSS

ACS Chemistry for Life®

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

Session 1 of the 2018 Drug Design and Delivery Symposium



Aaron Balog
Senior Principal Scientist,
Bristol-Myers Squibb

Ian Churcher
Vice President, Drug Discovery &
Pre-clinical, BenevolentAI

Slides available now and an invitation to view the recording will be sent when available.

www.acs.org/acswebinars

This ACS Webinar is co-produced with the ACS Division of Medicinal Chemistry and the American Association of Pharmaceutical Scientists

45

Women in Drug Discovery and Development: How to Succeed as a Female in Academia and Industry

ACS Chemistry for Life®

February 22, 2018 @ 2-3pm ET

Session 2 of the 2018 Drug Design and Delivery Symposium

"Life is not easy for any of us...We must have perseverance and above all confidence in ourselves. We must believe that we are gifted for something and that this thing must be attained." Marie Curie is an inspiration for all scientists and for good reason as she was a true pioneer and the first scientist to be awarded a Nobel Prize in two different categories. With more young women than ever opting to study within the STEM field, we look to answer just what it takes to create a rewarding and successful career within academia or the pharmaceutical industry as a female. We will explore insights from those in the field today to understand the technical and soft skills necessary to flourish.

Register For Free!

Experts


Nurulain Zaveri
Astraea Therapeutics


Erika Vieira Araujo
Bristol-Myers Squibb


Donna M. Huryn
University of Pittsburgh's School of Pharmacy


Annette Bak
Astra Zeneca

Co-Produced By

aaps American Association of Pharmaceutical Scientists

Division of Medicinal Chemistry

What You Will Learn

- Insight and real life experiences from successful females in drug discovery and development from academia to industry
- 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 panelist's position within drug discovery and development

http://bit.ly/WomenDDD

46

Upcoming ACS Webinars
www.acs.org/acswebinars

ACS Chemistry for Life®

Thursday, February 1, 2018

***Navigating My Research Career**: How to Manage US Immigration & Visa Opportunities*

Co-produced with the ACS Graduate & Postdoctoral Scholars Office

Experts

Brendan Delaney
Frank & Delaney Immigration Law, LLC

Joerg Schlatterer
American Chemical Society

Thursday, February 8, 2018

***Networking without Saying a Single Word:** Silent but Deadly*

Experts

Matt Grandbois
Dow Chemical

Patricia Simpson
University of Illinois at Urbana-Champaign

Contact ACS Webinars ® at acswebinars@acs.org

47

ACS Webinars
CLICK • WATCH • LEARN • DISCUSS

ACS Chemistry for Life®

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

Session 1 of the 2018 Drug Design and Delivery Symposium

Aaron Balog
Senior Principal Scientist,
Bristol-Myers Squibb

Ian Churcher
Vice President, Drug Discovery &
Pre-clinical, BenevolentAI

Slides available now and an invitation to view the recording will be sent when available.

www.acs.org/acswebinars

This ACS Webinar is co-produced with the ACS Division of Medicinal Chemistry and the American Association of Pharmaceutical Scientists

48

Celebrating 4 years & 40 Drug Discovery Webinars!

http://bit.ly/acsDrugDiscoveryArchive

ACS Chemistry for Life®

2014

1. Drug Discovery Series #1 - Current Drug Discovery and Development Process
(DDS #1) Watch this overview of the drug discovery and development process to learn the stages and challenges in every step.
2. Primer in Drug Target Classes
(DDS #2) Listen in on a discussion on the big four druggable families and the difference between small molecule and biotherapeutic targets.
3. Key Concepts in Identifying Drug Leads
(DDS #3) Discover how drug-likeness is a deceiving concept, explore the Rule of Five, and show how lessons from the past may guide the present.
4. Lead Optimization – Building Efficacy & Safety
(DDS #4) Learn strategies on how to effectively optimize small molecule hits and rapidly assess your findings.
5. Tips for Filing IND and Starting your Clinical Trials
(DDS #5) What do you need to know when filing for Investigational New Drug submissions to the United States Food and Drug Administration?
6. The Role of Chemistry in Clinical Trials: The Big Expense & Lessons Learned
(DDS #6) Learn how the properties of the candidate impact decisions in the discovery process.
7. Pharmacoeconomics and IP Strategies in Drug Development
(DDS #7) Review the basic principles of Pharmaco-economics in drug development strategies as well as its role in determining health insurance coverage of drug products.
8. Future of Drug Discovery - Challenges, Risks and Rewards
(DDS #8) Explore how how risks and challenges will be dealt with in the future and the key skill sets required of future medicinal chemists.

Co-Produced By

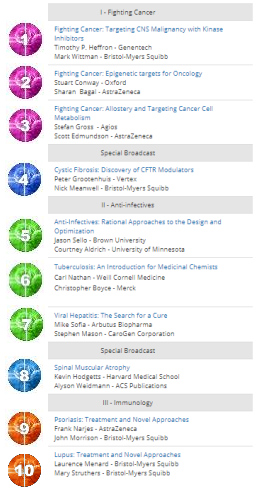
aaps American Association of Pharmaceutical Scientists | Division of Medicinal Chemistry

2015

- Designing Better Drug Candidates
(January) Learn various factors that can be used to improve candidate quality from Dr. Paul Leeson.
- Strategies to Improve Solubility of Drug Candidates
(February) Learn a number of different strategies for improving drug solubility through structural modification.
- Fragment-Based Drug Design Strategies
(March) Finding the right drug target is becoming increasingly difficult. Learn how focusing on the smaller picture can have big results.
- Screening Strategies
(April) Learn the pros and cons of different screening strategies.
- Avoiding PAINS (pan-assay interference compounds)
(May) Jonathan Baell shares some tips on how to avoid the dead ends of drug discovery.
- Accelerating CNS Positron Emission Tomography (PET) Ligand Discovery
(June) Join Lei Zhang as he lays out a set of preferred parameters for which has yielded successful PET ligands and reduced resources and timelines.
- X-ray Crystallography in Drug Discovery
(July) Jon Mason and Miles Congreve describe what protein-ligand X-ray data can do for you.
- Choices and Trends in Solid Dosage Form Selection
(August) Discover the pros and cons of the different solid state forms and what to consider when selecting.
- Delivery Options to Support Dose Escalation in Preclinical Toxicology and Pharmacodynamic Activity Studies
(September) Gain an understanding of acceptable drug delivery approaches to support preclinical dose escalation.
- Pharmacokinetic Considerations in Drug Design and Development
Learn about key pharmacokinetic concepts including clearance, volume of distribution, half life and protein binding.
- Prodrugs in Drug Discovery
(November) John Higgins shares the utility of prodrugs, their general properties and prerequisites for optimal performance.

2016

2017



49

Chemical Entity and Biomolecule Scientific Program Tracks:

- **Preclinical** (including Discovery)
- **Bioanalytical**
- **Clinical Pharmacology**
- **Manufacturing & Bioprocessing**
- **Formulation & Quality**

YouTube video:
https://www.youtube.com/watch?v=1DOxLBg0Ouw

Website: www.aapspharmsci360.org

Join the ACS Division of Medicinal Chemistry Today!

ACS Chemistry for Life®

Division of Medicinal Chemistry

For $25 ($10 for students)**, You Will Receive:**

- A free copy of our annual medicinal chemistry review volume (over 600 pages, $160 retail price)
- Abstracts of MEDI programming at national meetings
- Access to student travel grants and fellowships

Find out more about the ACS MEDI Division! www.acsmedchem.org

51

How has ACS Webinars® benefited you?

ACS Chemistry for Life®

"This was an awesome webinar presentation addressing how pharmaceutical chemistry and drug development can be used to correct the complex autoimmune disease of SLE using a combination of and interaction between self molecules within the diseased patient and specific inhibitors made in the lab to hit the right combination of targets to stop the symptoms of autoimmunity."

http://bit.ly/DDDSlupus

Fan of the Week

Rafael Álvarez González, PhD
Editorial Board Member of Cáncer Investigation and CEO of ÁGORA Scientific Services, LLC

52

Be a featured fan on an upcoming webinar! Write to us @ acswebinars@acs.org

ACS Webinars
CLICK • WATCH • LEARN • DISCUSS

ACS Chemistry for Life®

53

ACS Webinars
CLICK • WATCH • LEARN • DISCUSS

ACS Chemistry for Life®

Benefits of ACS Membership

Chemical & Engineering News (*C&EN*)
The preeminent weekly digital and print news source.

NEW! ACS SciFinder
ACS Members receive 25 complimentary SciFinder® research activities per year.

NEW! ACS Career Navigator
Your source for leadership development, professional education, career services, and much more.

http://bit.ly/benefitsACS

54

ACS Webinars®

CLICK • WATCH • LEARN • DISCUSS

ACS Chemistry for Life®

ACS Webinars® does not endorse any products or services. The views expressed in this presentation are those of the presenter and do not necessarily reflect the views or policies of the American Chemical Society.

Upcoming ACS Webinars

www.acs.org/acswebinars

ACS Chemistry for Life®

Thursday, February 1, 2018

***Navigating My Research Career**: How to Manage US Immigration & Visa Opportunities*

Co-produced with the ACS Graduate & Postdoctoral Scholars Office

Experts

Brendan Delaney
Frank & Delaney
Immigration Law, LLC

Joerg Schlatterer
American Chemical Society

Thursday, February 8, 2018

***Networking without Saying a Single Word:** Silent but Deadly*

Experts

Matt Grandbois
Dow Chemical

Patricia Simpson
University of Illinois at Urbana-Champaign