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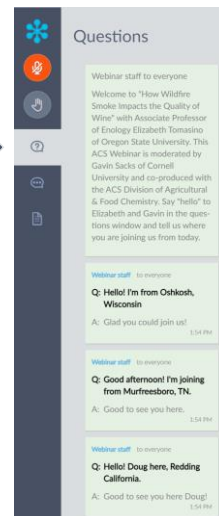


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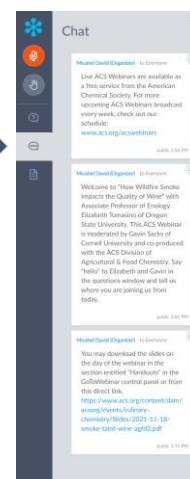
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Announcements and hyperlinks from our team



2

2

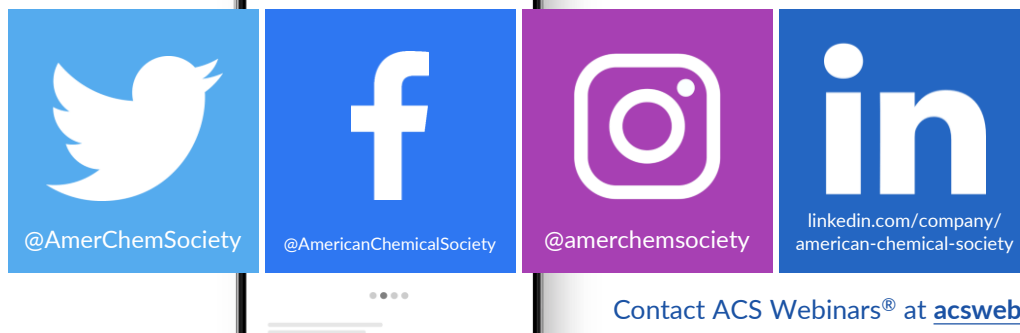


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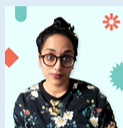
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A Career Planning Tool For Chemical Scientists



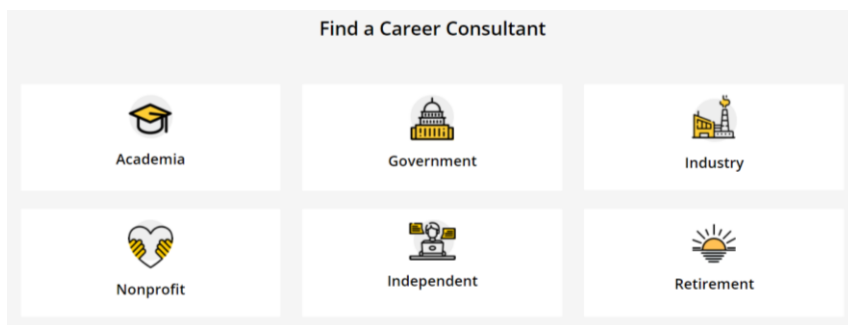
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Career Consultant Directory

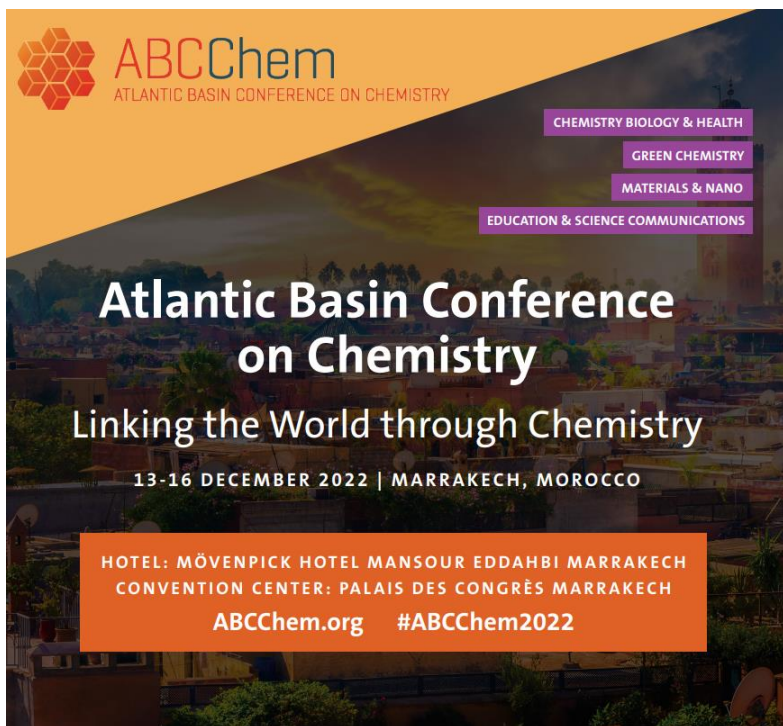


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ACS Scholar Adunoluwa Obisesan

BS, Massachusetts Institute of Technology, June 2021
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Advancing ACS' Core Value of Diversity, Equity, Inclusion and Respect

Resources

<p>Inclusivity Style Guide Designed to help staff and members use language and images that respect diversity in all its forms.</p> <p>→</p>	<p>ACS Webinars on Diversity Covering diversity and inclusion at the workplace</p> <p>→</p>
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<p>C&EN Trailblazers C&EN highlights scientists from different backgrounds who are making an impact in chemistry.</p> <p>→</p>	<p>NEW! Download DEIR Educational Resources Download this educational guide for additional recommendations on videos, articles, books, podcasts, and more on diversity, inclusion, and related topics.</p> <p>→</p>
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**Adapted from definitions from the Ford Foundation Center for Social Justice:

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Seeks to ensure fair treatment, equality of opportunity, and fairness in access to information and resources for all. We believe this is only possible in an environment built on respect and dignity. Equity requires the identification and elimination of barriers that have prevented the full participation of some groups.

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Inclusion**

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Ensures that each person is treated with professionalism, integrity, and ethics underpinning all interpersonal interactions.

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Thurs., Oct. 6, 2022 | 2:00pm–3:15pm ET

Reproductive Health in the Lab

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Molecular Glues in Drug Discovery: Solutions that Stick for the Undruggable



JANET SASSO, MPH

Information Scientist, CAS, a division
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BENJAMIN EBERT, MD, PhD

Chair of Medical Oncology,
Dana-Farber Cancer Institute



PHILIP CHAMBERLAIN, PhD

Co-Founder, President, and CEO,
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Angela Zhou, PhD

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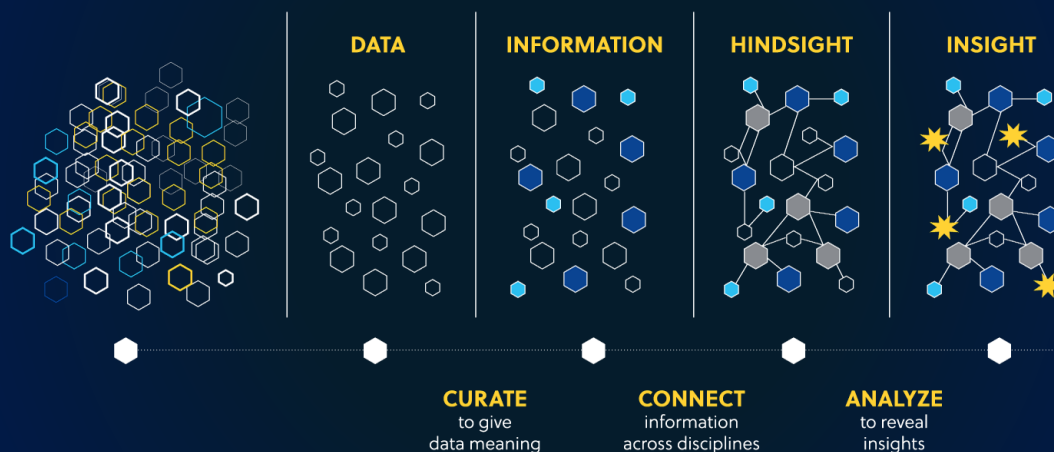
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Data is valuable only when it is transformed into insight



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A landscape view

MOLECULAR GLUES AND TARGETED PROTEIN DEGRADATION

Janet Sasso, Information Scientist

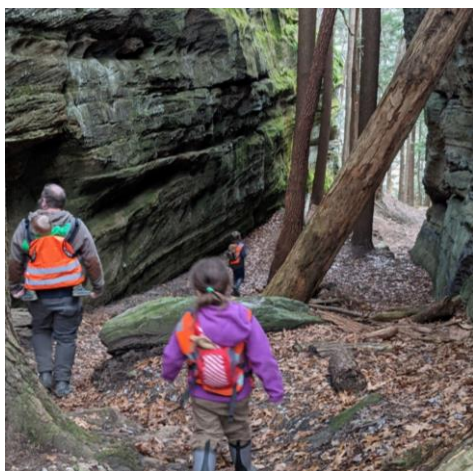
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The why behind our research


Molecular glues over conventional drugs



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85%

of the human proteome is considered to be “undruggable”

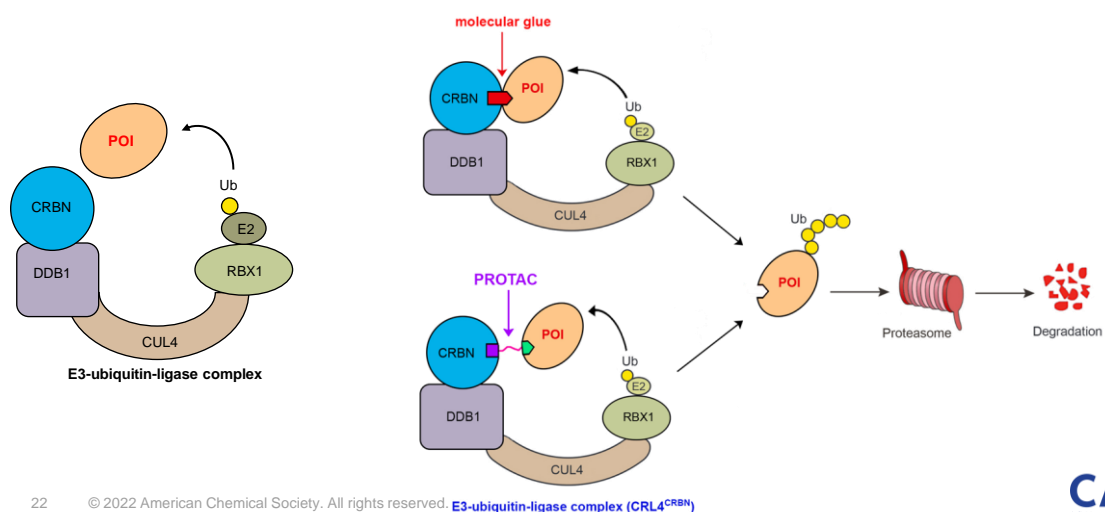


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What is protein degradation?

Targeted protein degradation and induced proximity



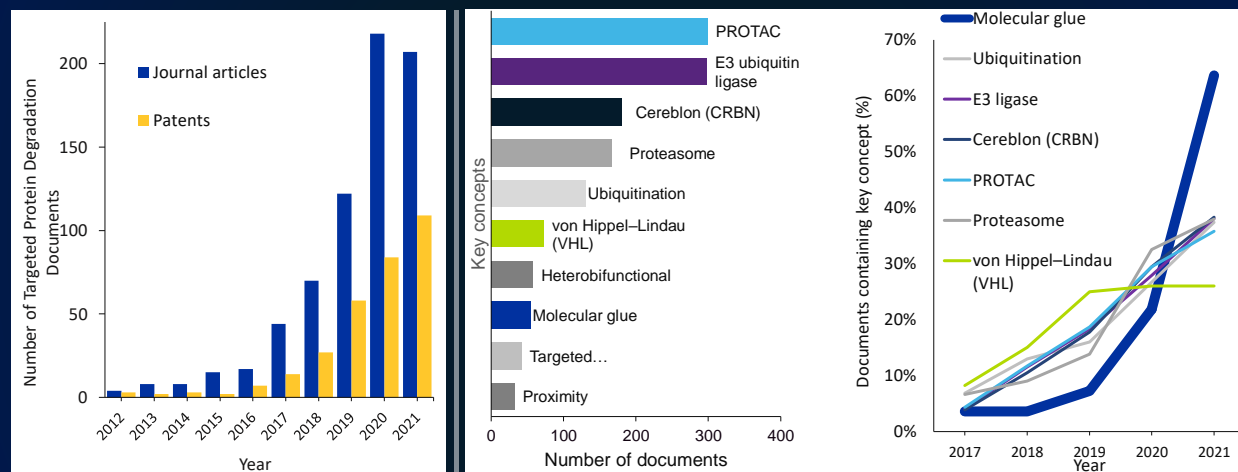
22 © 2022 American Chemical Society. All rights reserved. E3-ubiquitin-ligase complex (CRL4^{CRBN})

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Protein degradation publications has increased over time

Research in molecular glues is outpacing all others



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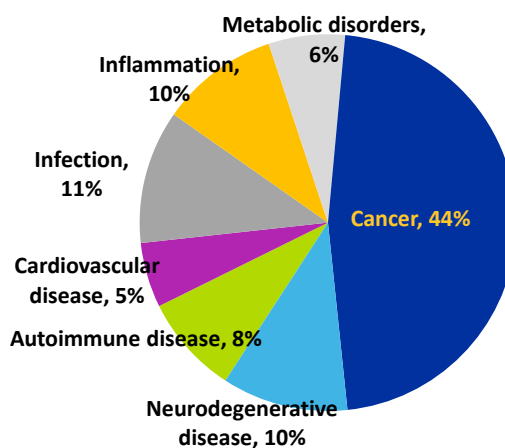
23

Most researched E3 ligases

Showcases the focus and impact this may have in oncology

E3 ligase / subunit	Number of records	Cancer	All Others
CRBN	309	20.1%	9.3%
VHL	207	12.6%	4.3%
MDM2	189	2.6%	1.8%
SCF	86		
RNF	63		
SKP	55		
clAP	50		
DDB1	47		
KEAP1	31		
FBXO	23		
UBR2	19		
β-TRCP	9		
DCAF	8		
SIAH1	4		
STUB1	4		
ASB6	2		
CDC34A	1		
UBE4A	1		

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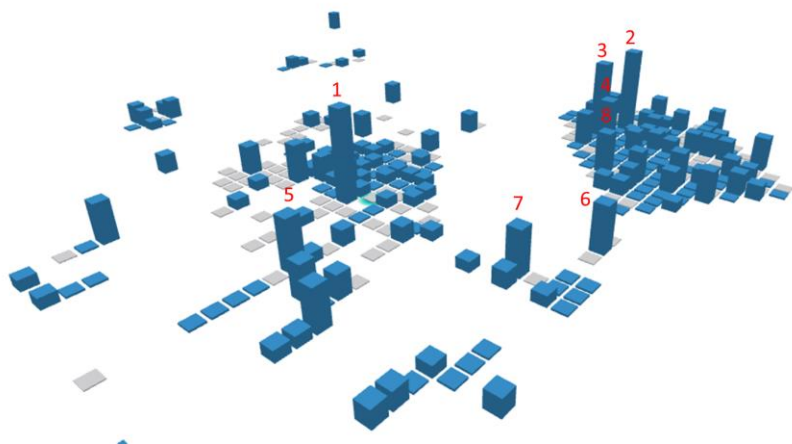










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From serendipity to data driven discoveries

Chemscape analysis for Thalidomide

Chemscape map of compounds within 90% similarity limit to thalidomide used as protein degraders (SciFinder®)



	Compound CAS #	Structure	Number of patents
1	50-35-1 (thalidomide)		1,060
2	191732-72-6 (lenalidomide)		962
3	19171-19-8 (pomalidomide)		496
4	5054-59-1		104
5	64567-60-8		39
6	1061604-41-8		28
7	191732-76-0		24
8	191732-70-4		23

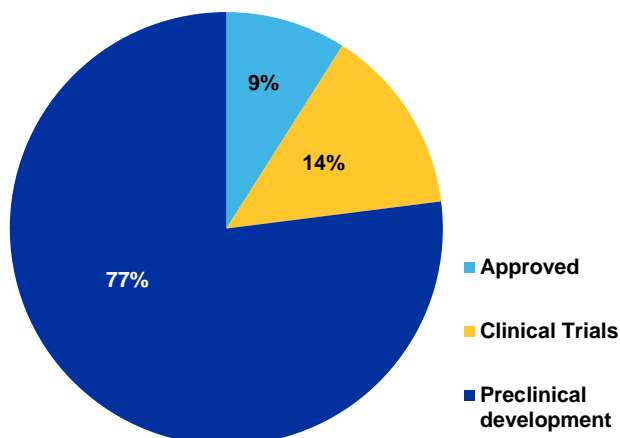
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Molecular glues in the clinical development pipeline

Preclinical Development, in Clinical Trials, and Approved



Approved Molecular Glues	Therapeutic Focus
Thalidomide	Cancer/Inflammatory
Lenalidomide	Cancer
Pomalidomide	Cancer
Rapamycin	Cancer/Immune
Cyclosporin A	Immune
Mekinist	Cancer
FK506	Immune
Lupkynis	Immune/Inflammatory

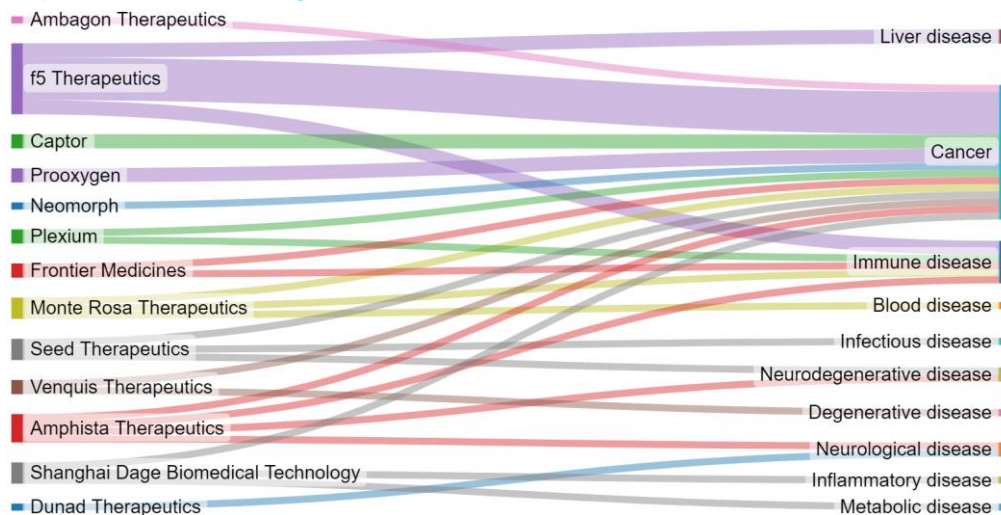
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Molecular Glue Research in Preclinical Stages

Companies and their targeted diseases



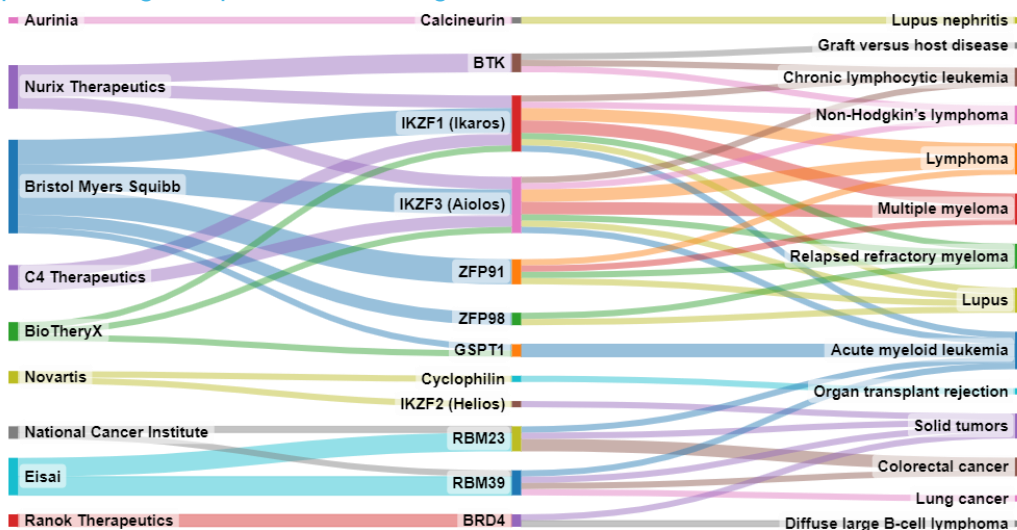
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Molecular Glue Research in Clinical Trials

Companies, targeted proteins, and targeted diseases



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Targeted protein degradation for the treatment of cancer

Benjamin Ebert

ACS/CAS webinar
October 05, 2022



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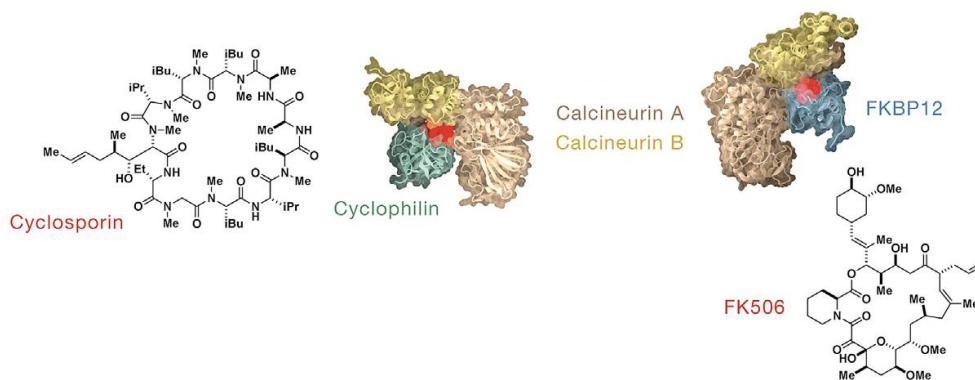
Disclosures

- **Founder and scientific advisory board:** Neomorph, TenSixteen Bio
- **Scientific advisory board:** Skyhawk Therapeutics, Exo Therapeutics
- **Research funding:** Celgene, Deerfield, Novartis, Calico

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Molecular glues



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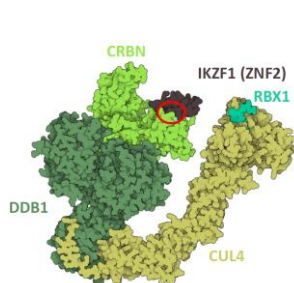
Schreiber, *Cell*, 2021

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Molecular glues causing protein degradation

Thalidomide analogs

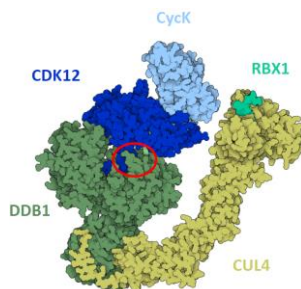
CRBN – neosubstrate glue



Kronke et al. *Science* (2014)
Lu et al. *Science* (2014)
Ghandi et al. *Br J. Hematol* (2014)

CR8 and other molecules

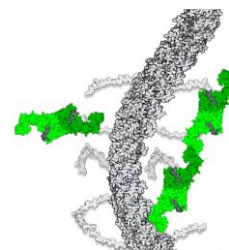
DDB1 - neosubstrate receptor glue



Slabicki, Kozicka, Petzold et al. *Nature* (2020)
Mayor-Ruiz et al. *Nat Chem Biol*, (2020)
Lv et al. *Elife* (2020)

BI-3802

BCL6 "glued" to itself

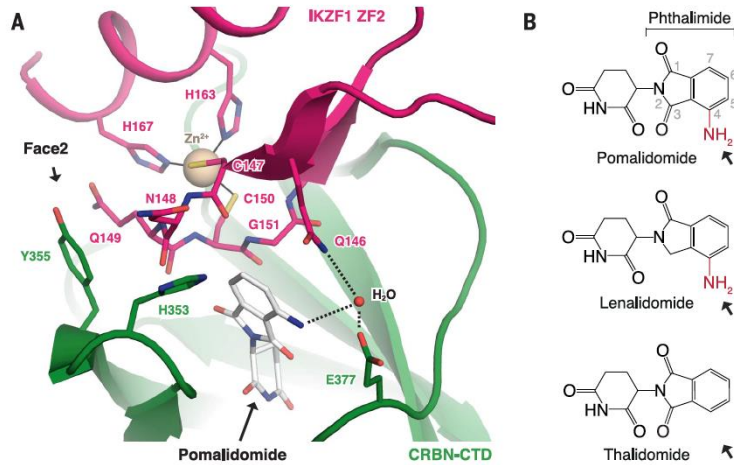


Slabicki, Yoon, Koepffel et al., *Nature* (2020)

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Structure of zinc finger – pomalidomide - CRBN

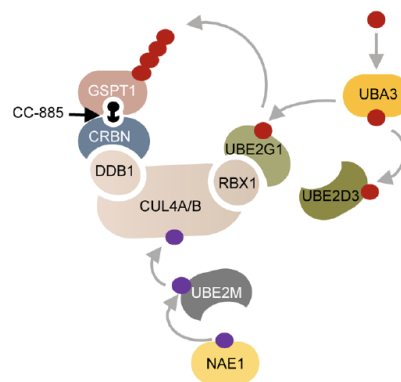
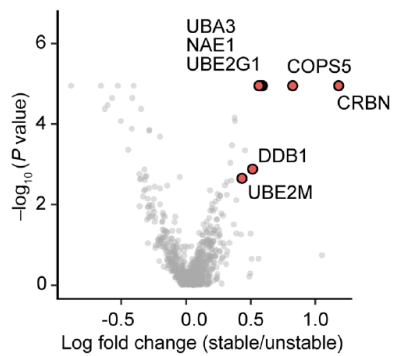


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Sievers, Petzold et al., *Science* 2018

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Genetic screens for resistance/degradation

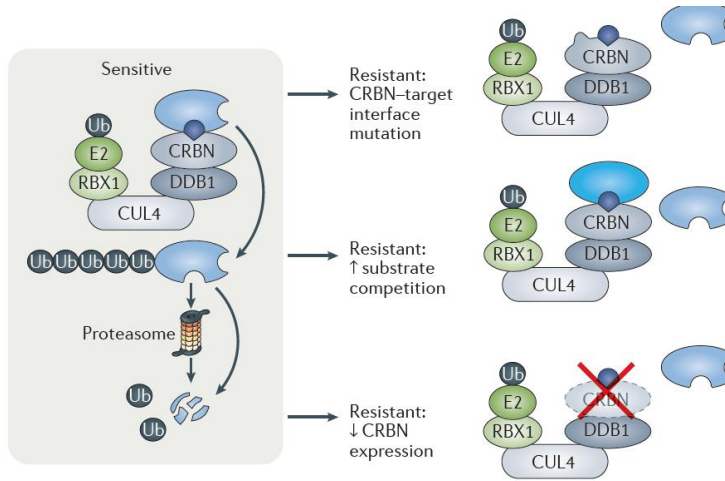


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Sellar, Sperling, et al., *JCI* 2022

34

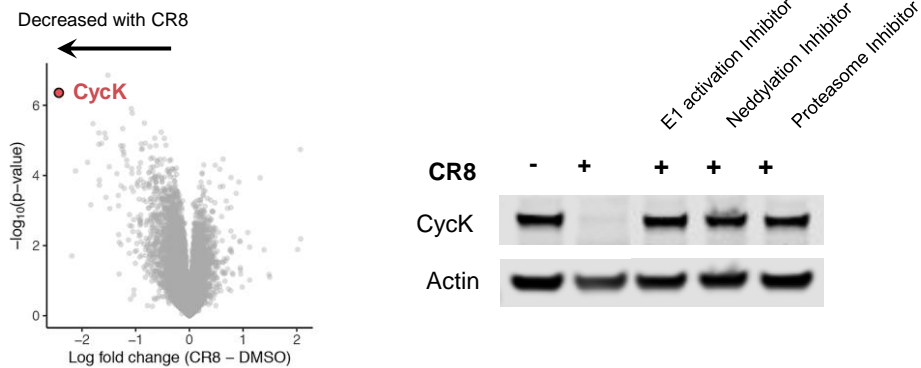
Mechanisms of resistance to lenalidomide



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CR8 induces degradation of Cyclin K (CycK)

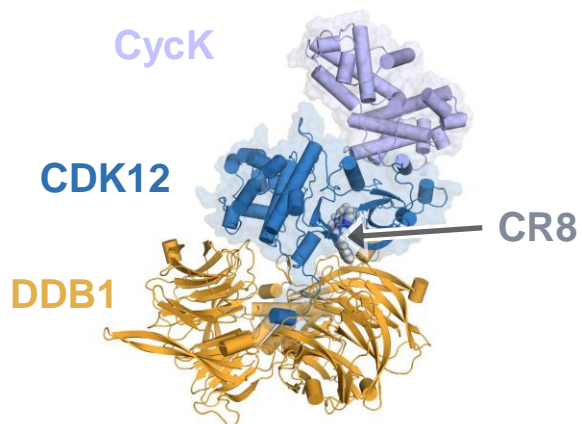


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Slabicki *et al.*, *Nature*, 2020

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CR8 is a molecular glue for DDB1 - CDK12

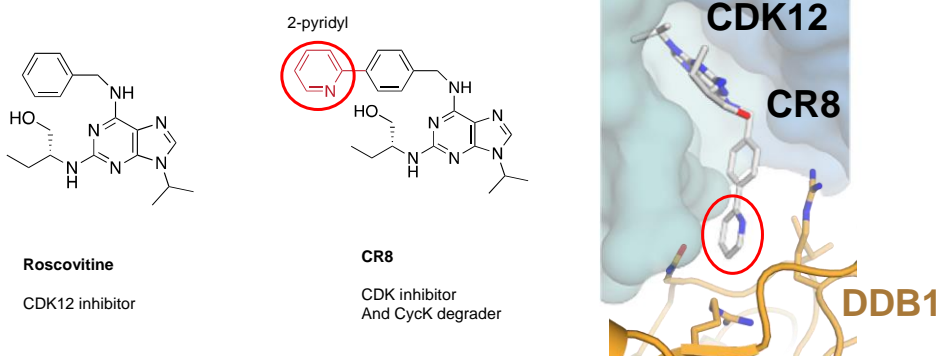


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Slabicki *et al.*, *Nature*, 2020

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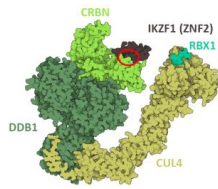
From inhibitor to degrader



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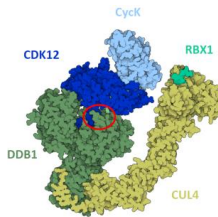
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Summary: molecular glue degraders



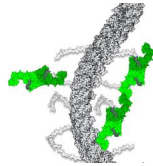
- Thalidomide derivatives act as molecular glues, inducing ubiquitination and degradation of substrates by the CRL4^{CRBN} ubiquitin ligase

- Different thalidomide derivatives target distinct substrates for degradation
- Mouse-human differences determine drug activity



- CR8 acts as a molecular glue between DDB1 and CDK12

- Induces degradation of Cyclin K



- BI-3802 induces polymerization and subsequent degradation of BCL6

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Acknowledgements

Dana-Farber

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Expansion of the Druggable Genome Through Rational Molecular Glue Discovery

Disclosures: Former employee, equity holder at Celgene and BMS. Current employee, equity holder at Neomorph.

ACS / CAS Webinar on Molecular Glues

Phil Chamberlain, DPhil.
Co-Founder, President and CEO
October 5th, 2022

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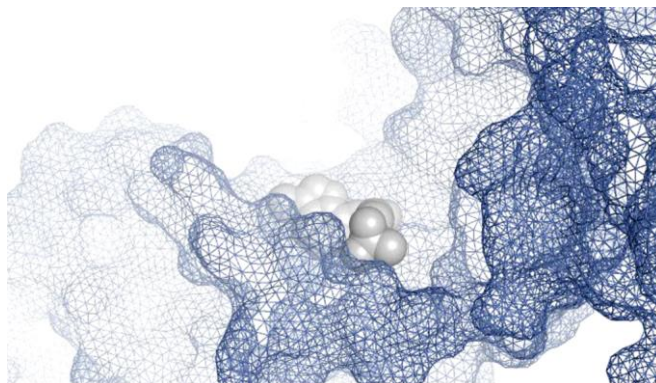


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Molecular Glues Confer Neomorphic Functions to the Cellular Machinery

Merriam-Webster definition of Neomorph:

1: a **structure that is not derived from a similar structure** in an ancestor. 2 : a mutant gene **having a function distinct** from that of any nonmutant gene of the same locus.



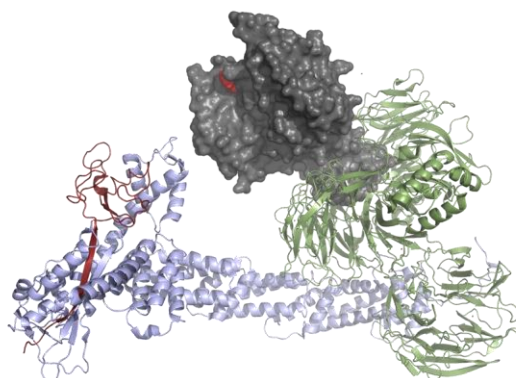
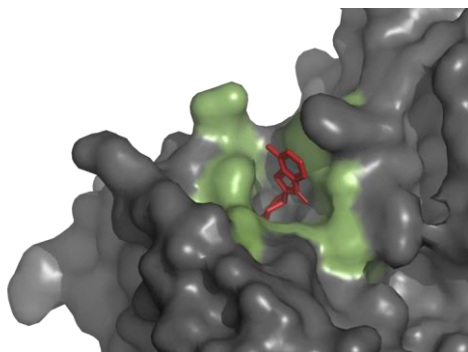
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Philip Chamberlain: ACS Molecular Glues: October 5th 2022

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Lessons from Thalidomide Analogs as Prototype Glues

- Thalidomide analogues are molecular glues that create a hotspot for protein-protein interactions on the surface of the CRL4^{CRBN} E3 ubiquitin ligase



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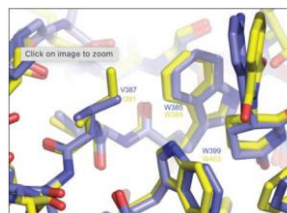
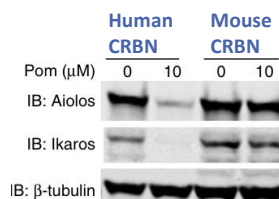
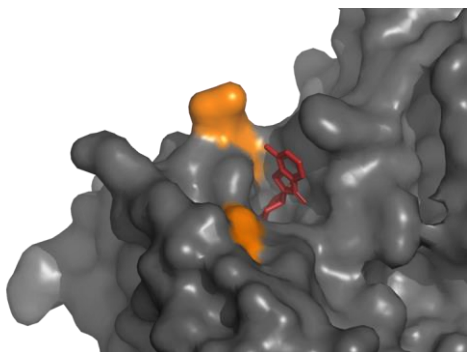
Chamberlain et al. NSMB 2014
Fischer et al. Nature 2014

Philip Chamberlain: ACS Molecular Glues: October 5th 2022

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Lessons from Thalidomide Analogs as Prototype Glues

- Two polymorphisms on the cereblon surface explain species resistance to Ikaros
 - Impaired protein-protein interactions at the hotspot



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Philip Chamberlain: ACS Molecular Glues: October 5th 2022

Chamberlain et al. NSMB 2014

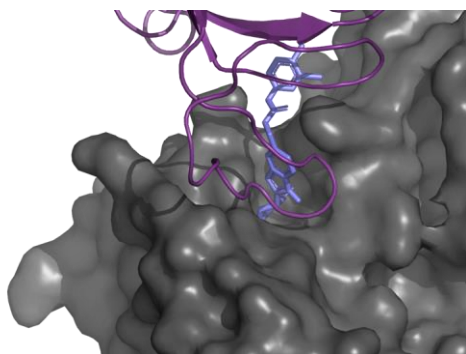
Kronke et al. Nature 2015

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Lessons from Thalidomide Analogs as Prototype Glues



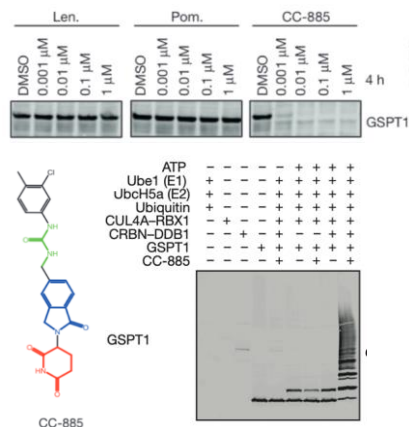
- GSPT1 is recruited via a glycine containing beta-turn to surface of cereblon by CC-885
- Common essential protein with a key role in protein translation
- **Key demonstration that new proteins could be recruited to cereblon and degraded**



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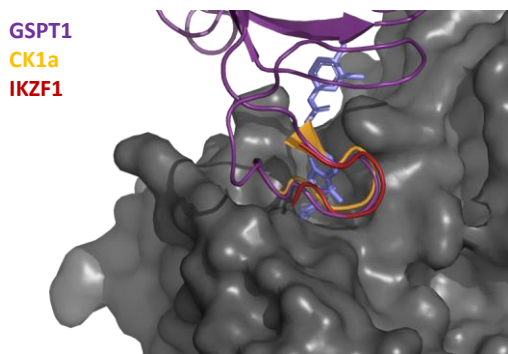
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Matyskiela, Lu, Ito et al. Nature 2016

Lessons from Thalidomide Analogs as Prototype Glues

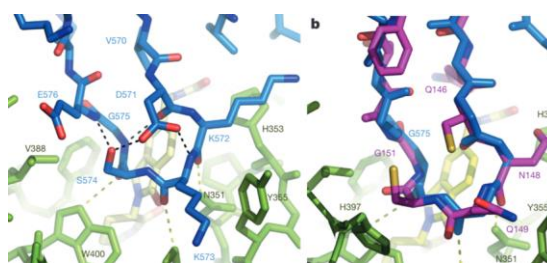
- First generation neosubstrates all recruited via homologous backbone-mediated interactions
- Highly abundant structural degnon defined, **prospective neosubstrate searching enabled**



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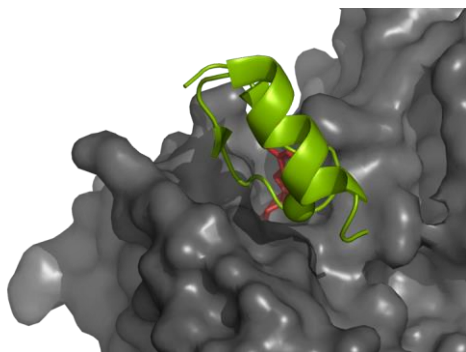


position. Therefore, the degnon is not the linear peptide sequence, but rather the geometric arrangement of three backbone hydrogen bond acceptors at the apex of a turn (positions i , $i+1$, and $i+2$), with a glycine residue at a key position ($i+3$).

Matyskiela, Lu, Ito et al. Nature 2016

Lessons from Thalidomide Analogs as Prototype Glues

- Prospective surveys identified SALL4 as the major driver of teratogenicity
- Structure of SALL4 complex reveals sequence and conformational changes that reveal paths to **rational design for selectivity and the discovery of safer cereblon modulators**

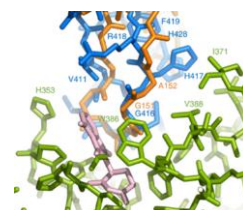
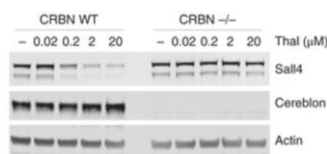


ORIGINAL ARTICLE

Mutations at the *SALL4* locus on chromosome 20 result in a range of clinically overlapping phenotypes, including Okihiro syndrome, Holt-Oram syndrome, acro-renal-ocular syndrome, and patients previously reported to represent thalidomide embryopathy

J Kohlhase, L Schubert, M Liebers, A Rauch, K Becker, S N Mohammed, R Newbury-Ecob, W Reardon

J Med Genet 2003;40:473-478



Matyskiela et al. NCB 2018
Donovan et al. eLife 2018
Mayskiela et al. NSMB 2020

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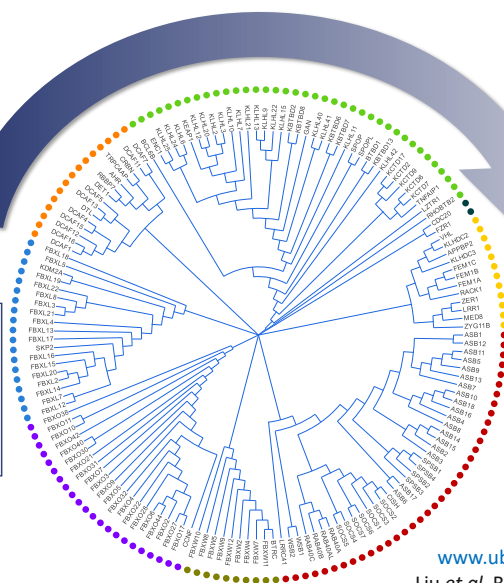
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Advancing from Proven Systems to Novel Glue Mechanisms

Literature Systems

- Highly actionable near-term opportunities in an increasingly crowded space



Next Generation Mechanisms

- 100s of additional ligases with potential for new activity
- Potential for expansion of druggable genome
- Differentiated pharmacology

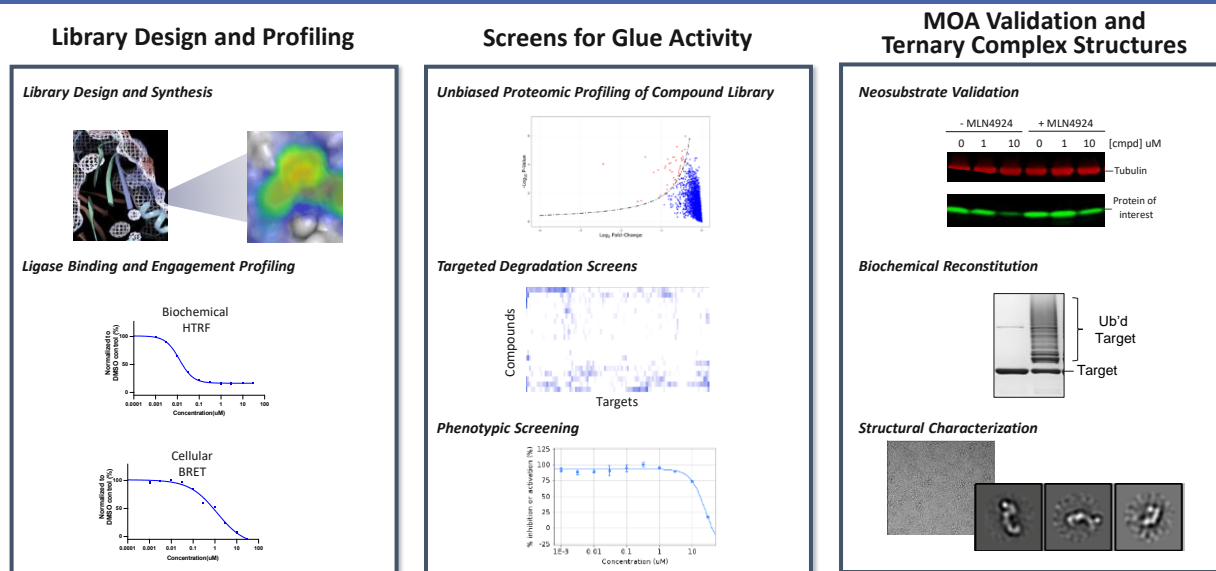
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www.ubihub.thesgc.org
Liu et al. Bioinformatics 2019

Example of Novel Glue Discovery for a Next-Generation Ligase System

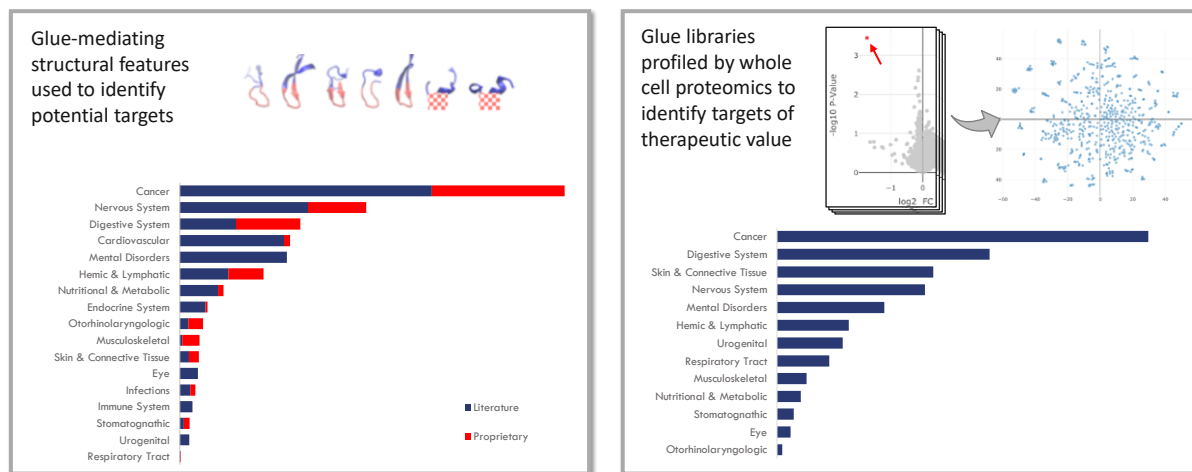


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Molecular Glues Offer Potential for Massive Expansion of the Druggable Genome

Abundance of glue target proteins identified from both degron surveys and proteomic profiling



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- Former colleagues from at **Celgene and BMS**, as well as former academic collaborators (Ben Ebert, Hiroshi Handa, Gabe Lander)
- Colleagues at Neomorph
- Collaborators at the Center for Protein Degradation



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in the questions window!



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Co-produced with ACS on Campus and ACS Publications



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