Nico Thomä

Originally from **Germany**

Undergrad:
Biochemistry University of Cambridge (UK)

PhD Cambridge

Postdoc: Max Plank Institute (MPI)
Molecular Physiology (Germany)

Postdoc: Memorial Sloan
Kettering Cancer Center,
MSKCC (New York)

EPFL 2024

Groupleader:
Friedrich Miescher Institute (FMI), Basel (2006)

Vision and Rules

- Vision for the course:
  - Expose you to the **cutting edge** of Trends in Chemical Biology
  - Presented by **experts** in the field
  - Get an **overview** of the field/techniques in the **lectures**
  - Then take a **deep-Dive** into a paper (the week after)
- Ask questions (please !)
- Take notes & read some of the papers covered
- Attend lectures (please !)
- Attend exercises (please, please !)

Overview general

- Lecture **material** (slides, paper references) on Moodle
- Organization of **exercises**: 2 TAs (David & Alessandro)
- **Exam**: 2 pager & 10 min presentations + questions

Trends in Chemical Biology – Plan of a typical week

Wednesday → Thursday → Wednesday

Lecture (2h)
Experts in the Field

- **30 min** recap of lecture (Q&A)
- 1 paper: presented by 2 of you
- Everybody is expected to be ready to answer questions

Syllabus

		Speakers	Lectures titles
February 2025	Thu 20	Nicolas Thomä	Molecular Glues
	Thu 27	Nicolas Thomä	Proximity Inducers
March 2025	Thu 6	Markus Enzelberger	Biologics
	Thu 13	Roger Clerc	Incretins- end of diabesity?
	Thu 20	Alessio Ciulli	PROTACs
	Thu 27	Sebastian Essig	Covalent Chemistry
April 2025	Thu 3	Bruno Correia	Chemical Probes
	Thu 10	Giorgio Ottaviani	Pharmacology of Drugs
	Thu 17	Zuzanna Kozicka	Functional Genomics Screens
May 2025	Thu 1	Luca Naef	Computational approaches for Small Molecules
	Thu 8	Gerardo Turcatti	High Throughput Screening
	Thu 15	Colby Sandate	Structural Biology and Drug Discovery
	Thu 22	Bruno Correia	Protein Design

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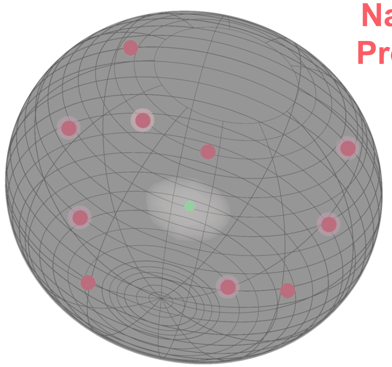
Bruno Correia

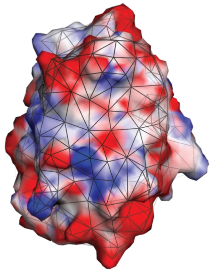
Protein Universe



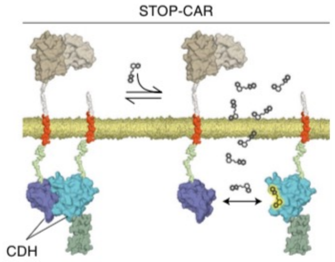
Can we expand the space of functional proteins through computational design?

Structure-Based Protein Design

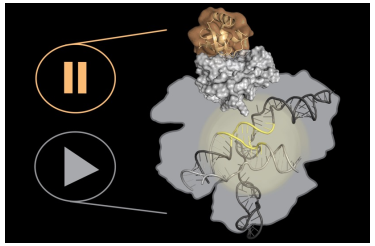
Protein surface fingerprints



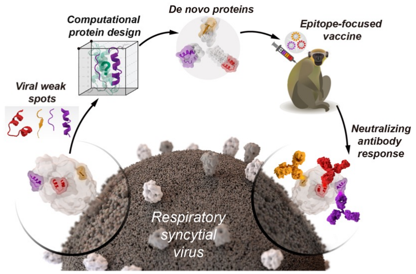
T-cell engineering



Genome editing



Vaccine design



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Markus Enzelberger

BACKGROUND

Markus is a partner located in Basel where he plays a central role in the launch of future newcos from Versant's Ridgeline Discovery Engine.

He is a seasoned executive with deep domain knowledge of drug discovery and development, especially in the protein field. Markus most recently was CSO and a member of the management board of MorphoSys. He joined the company in 2002 and is recognized as an authority in the field of protein engineering.

HISTORY

Markus holds a Ph.D. from the Technical University of Stuttgart, Germany.

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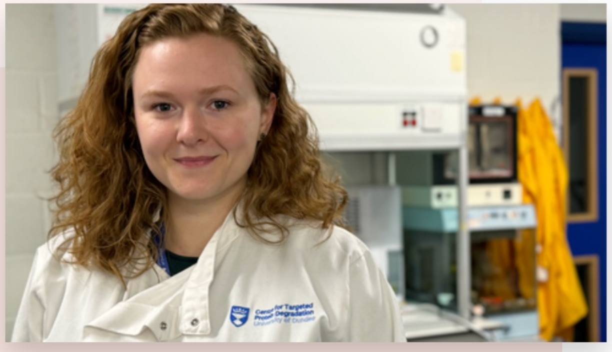
Alessio Ciulli & Charlotte Crowe

Press release

Researchers reveal new levels of detail in targeted protein degradation

Dundee researchers have revealed in the greatest detail yet the workings of molecules called 'protein degraders' which can be deployed to combat what have previously been regarded as 'undruggable' diseases, including cancers and neurodegenerative diseases

Published on 11 October 2024



University of Dundee

Home / People

Professor Alessio Ciulli

FRSE FRSC

Professor

Centre for Targeted Protein Degradation, School of Life Sciences

Director of the Centre for Targeted Protein Degradation

Centre for Targeted Protein Degradation, School of Life Sciences

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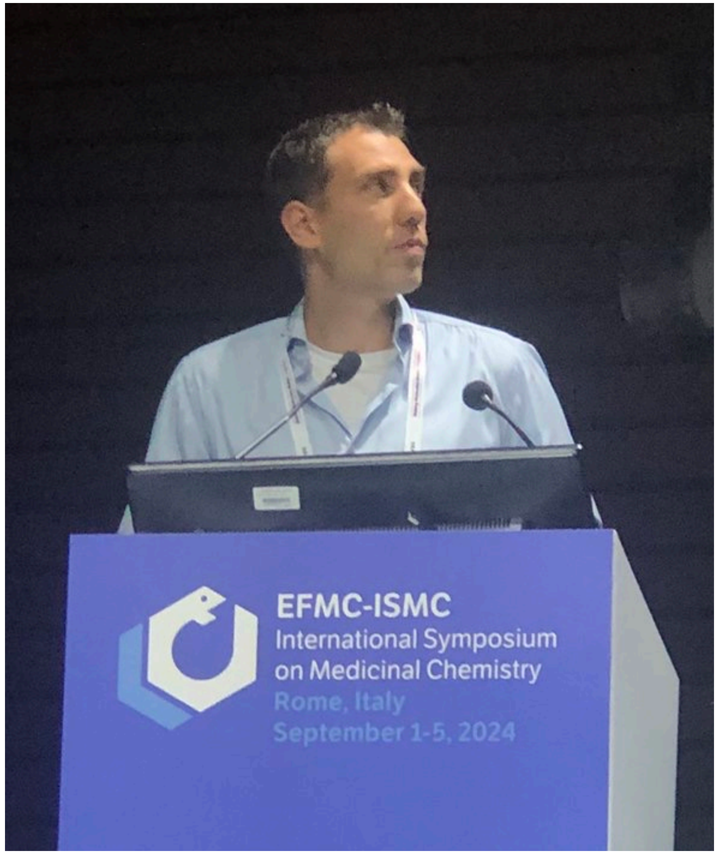
Sebastian Essig



Experience

Bayer
Full-time · 8 yrs 10 mos

Director & Group Leader Chemical Biology (Life Science Technology Department)
Dec 2021 - Present · 3 yrs 3 mos
Wuppertal, Nordrhein-Westfalen, Deutschland

// Chemoproteomics and High-Throughput Proteomics
// Covalent Chemistry and Library Setup... ...see more

Head of Laboratory Medicinal Chemistry
May 2016 - Dec 2022 · 6 yrs 8 mos
Elberfeld (Wuppertal) · On-site

// Project Leader of Lead Optimization Projects
// Bayer Science Fellow... ...see more

Visiting Scientist
Broad Institute of MIT and Harvard
Jun 2019 - Sep 2019 · 4 mos
Großraum Boston und Umgebung

Exploration & Initiation of Research Collaborations with focus on Chemical Biology, New Modalities & Drug Delivery

Postdoctoral Fellow
MRC Laboratory of Molecular Biology (LMB)
Oct 2013 - Mar 2016 · 2 yrs 6 mos
Cambridge, Großbritannien

// Modulation and Optical Control of Protein Functions by Genetically directed Bioorthogonal Ligand Tethering (BOLT)... ...see more

Colby Sandate

Colby Sandate · 1st

Postdoctoral Researcher at Friedrich Miescher Institute for Biomedical Research

Basel Metropolitan Area · Contact info

362 connections

Dirk Schübeler, Alexandra Bendel, and 39 other mutual connections

Message More

Friedrich Miescher Institute for Biomedical Research

The Scripps Research Institute

EPFL

Giorgio Ottaviani

BACKGROUND

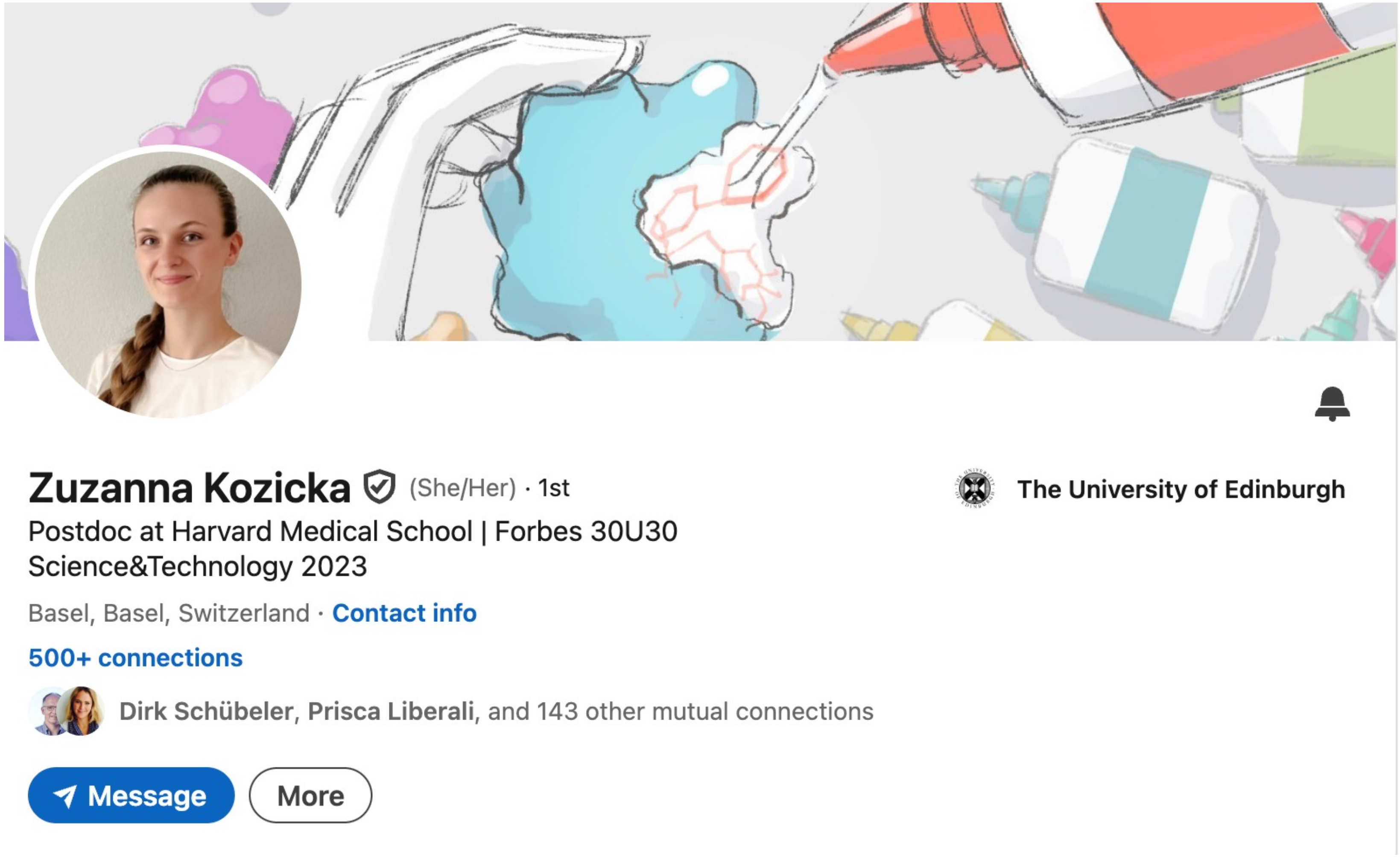
Giorgio is an Operating Partner at Versant and SVP of Preclinical Development at the firm's Ridgeline Discovery Engine. He is a drug development expert with proven successful scientific and global leadership track records.

HISTORY

Giorgio joined Ridgeline in 2018 from Roche where he served as Global Head of DMPK-PD Project Leaders and as Site Head of Non-Clinical Safety in Shanghai. Prior to Roche Giorgio worked at Novartis, Merck-Serono, and in the biotech industry. Giorgio brings to Ridgeline broad development expertise across therapeutic areas and modalities as well as a proven ability to lead multi-disciplinary cross-cultural teams.

Giorgio earned a Ph.D. in Pharmaceutical Chemistry from the University of Geneva (Switzerland) and is a certified toxicologist from the American Board of Toxicology (DABT).

Zuzanna Kozicka



SWISS NETWORK
IN CHEMICAL BIOLOGY

HOME ABOUT RESEARCH EDUCATION INDUSTRY NEWS & EVENTS CONTACT

SNE CHEMICAL BIOLOGY / GERARDO TURCATTI

Gerardo Turcatti

BSF ACCESS, EPFL

- Adjunct Professor

About Gerardo Turcatti

Gerardo Turcatti directs the Biomolecular Screening Facility, a multidisciplinary laboratory created in 2006 at the EPFL, to perform medium and high throughput screening in life sciences-related projects at the EPF. The facility has the necessary infrastructure, multidisciplinary expertise and flexibility to perform large screening programs using small interfering RNAs (siRNAs) and chemical collections in the areas of chemical biology, systems biology and drug discovery. The Academic Chemical Screening platform of Switzerland (ACCESS-BSF) provides the scientific community with chemical diversity, screening facilities and know-how in chemical genetic. Additionally, ACCESS-BSF pursues applied research axes that are driven by innovation in thematic areas related to preclinical drug discovery and discovery of bioactive probes.

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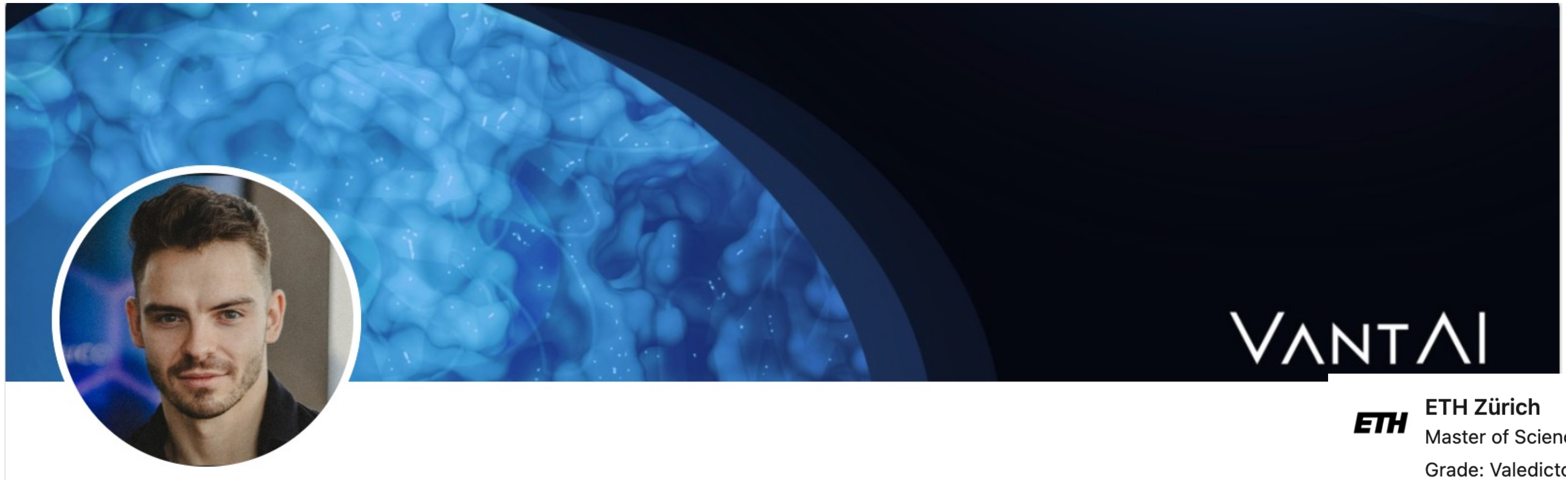
Luca Naef



Luca Naef · 2nd

Co-Founder & CTO at VantAI - We're hiring

New York, New York, United States · **Contact info**

500+ connections

Mikolaj Slabicki, **Hany Ibrahim**, and 40 other mutual connections

VantAI

ETH Zürich

ETH Zürich
Master of Science - MSc
Grade: Valedictorian

Elgar Fleisch Lab, Deep Learning for context aware computing

Stanford University School of Engineering
Bachelor of Science (Exchange) - BS

Fuller Lab

Developed and built a computer-controlled magnetic micromanipulator as stress-controlled rheometer for living cell monolayers in use for enhanced characterization of biomaterials, drug efficacy screening and stem cell research. Patent pending (US62/906914)

Hardware and Software stack

ETH Zürich
Bachelor of Science (BSc)

Top 3%
Focus Molecular Biology

UNSW
Bachelor of Science (Visiting) - BS, Molecular Biology
Grade: 6.0/6.0

Tokyo Institute of Technology
Master of Science (Visiting) - MS

Roger G. Clerc

roger.clerc@epfl.ch

Edit profile

Lecturer, EDBB - Teaching

EPFL AVP-PGE EDBB-ENS
AAB 0 19 (Bâtiment AAB)
Station 19
1015 Lausanne

Office: AAB 0 19
EPFL > VPA-AVP-DLE > AVP-DLE-EDOC > EDBB-ENS

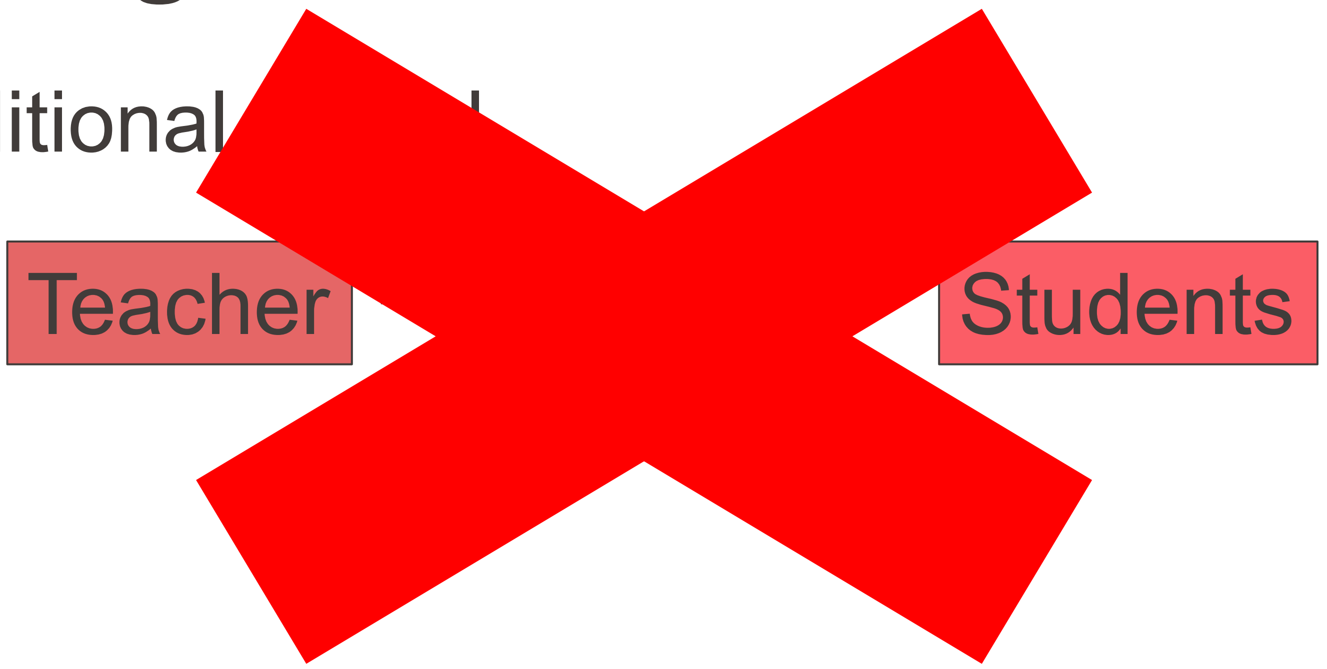
Guest, Doctoral program in biotechnology and biomedical engineering

vCard

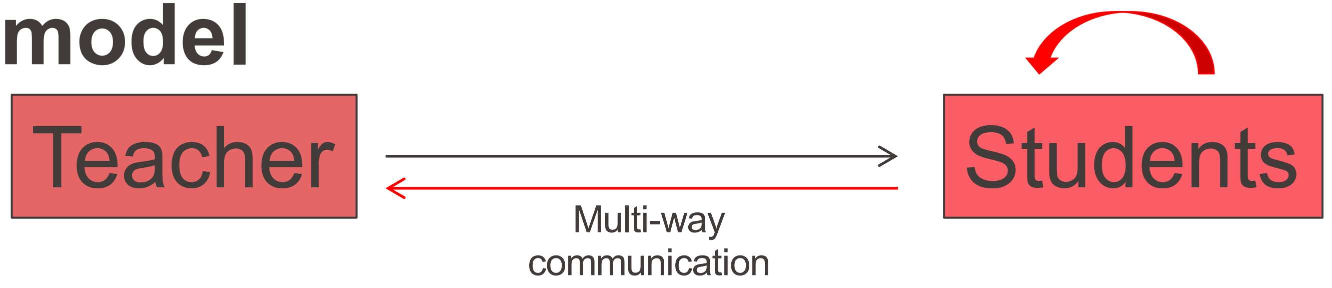
Administrative data

Teaching Model

Traditional



Our model



- Participation in the classroom
- Questions
- In person discussions
- Opportunities to meet the speaker

The challenges

What is “hard” to drug:
Transcription factors (unstructured)
Membrane proteins (agonists/antagonists)
Structural proteins without active site

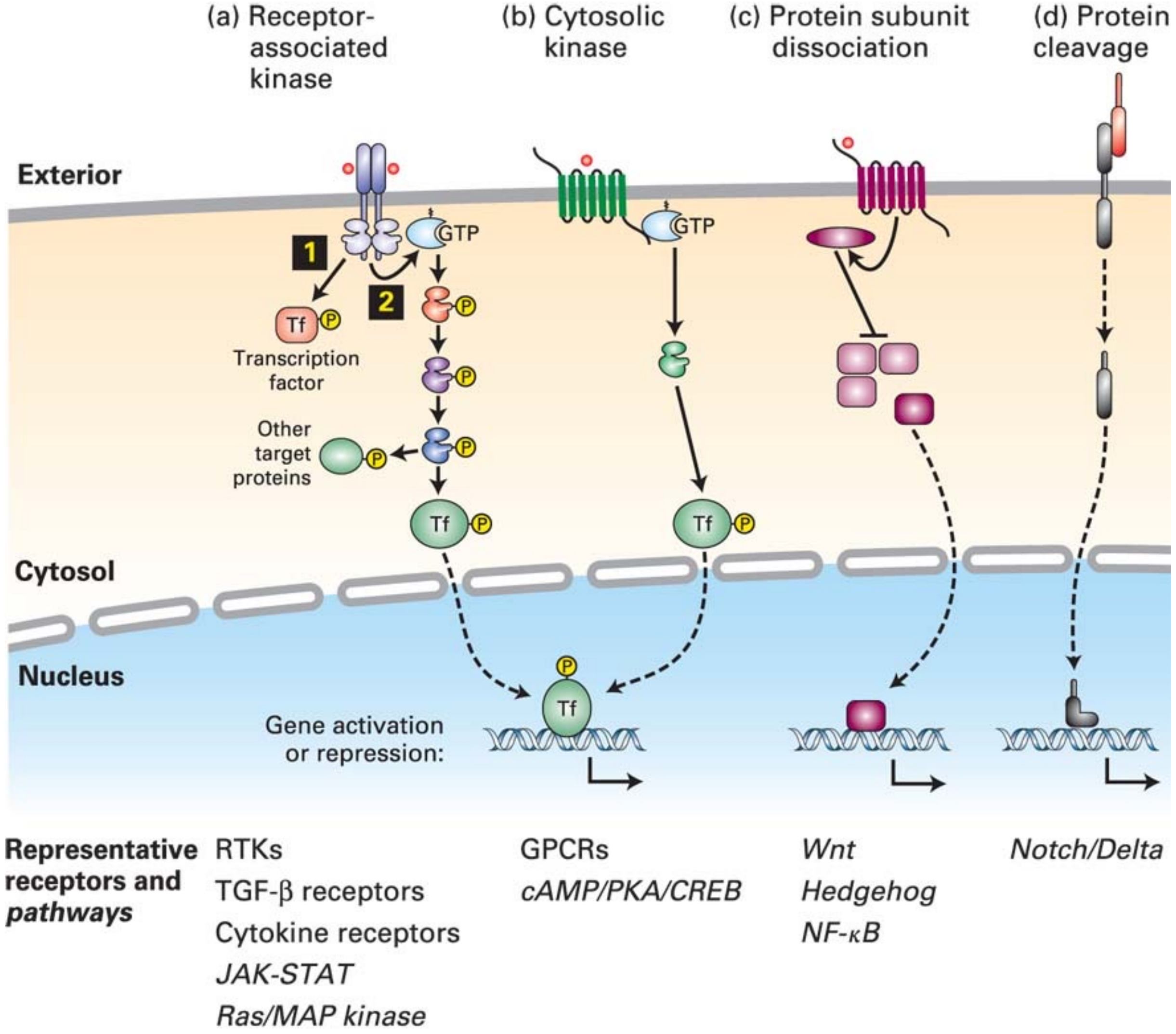


Figure 16.01
Molecular Cell Biology, eighth edition
© 2016 W.H. Freeman and Company

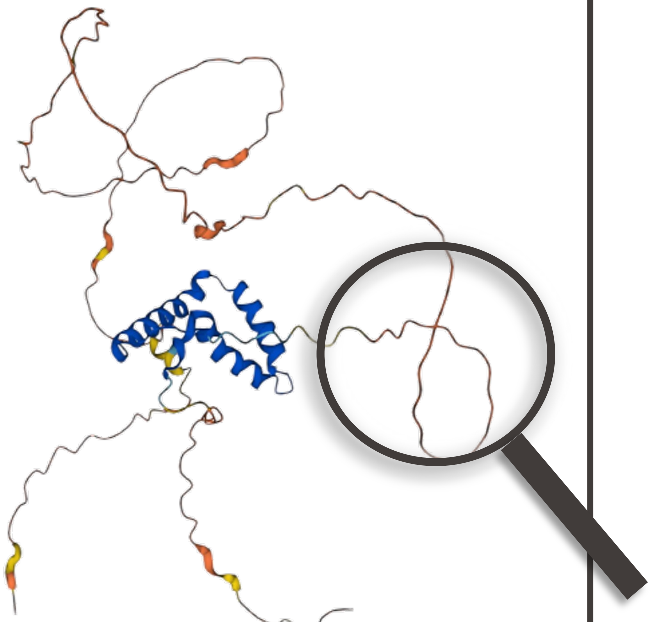
Nicolas Thomä

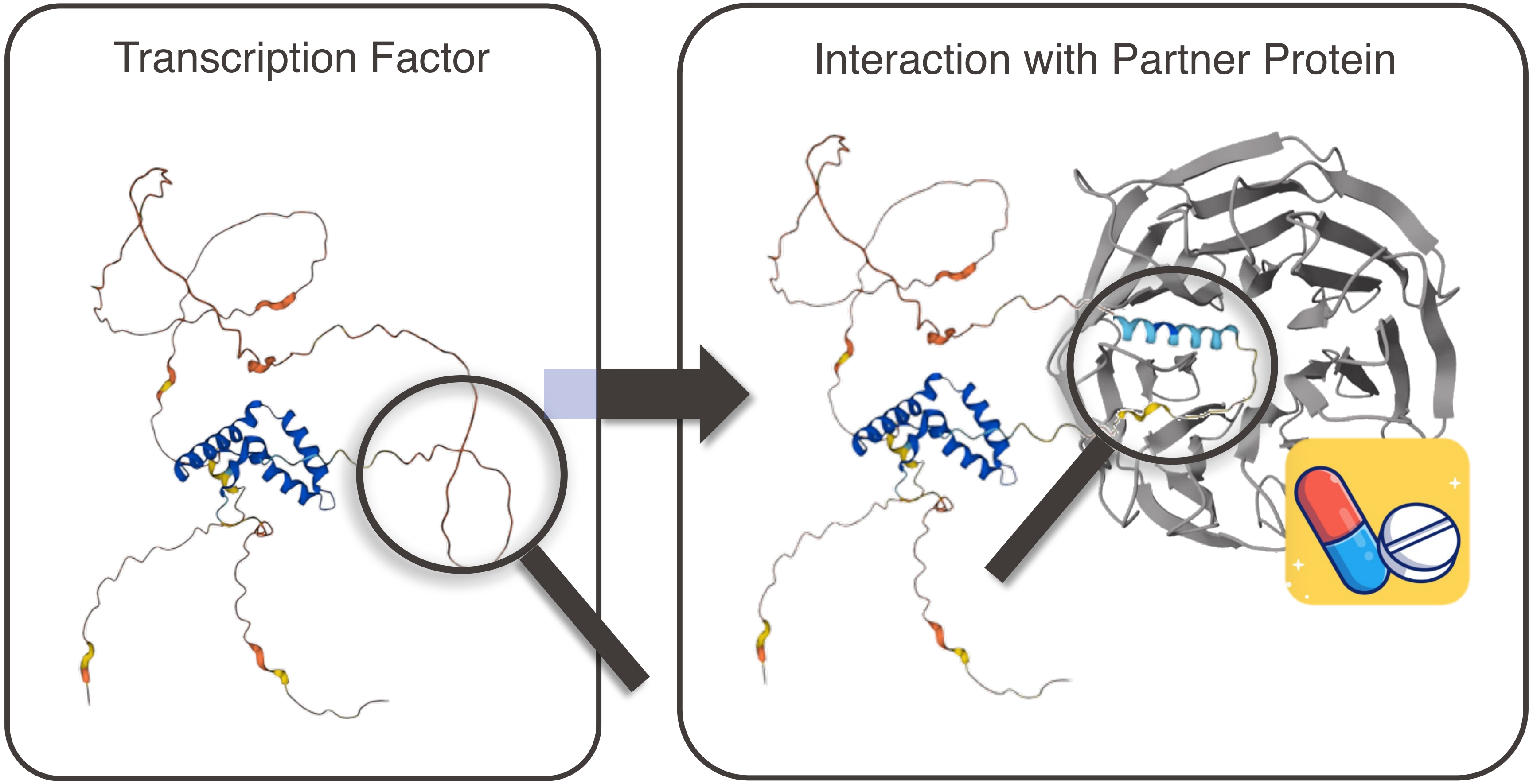
06.03.25

MOLECULAR GLUES

IF IT IS BROKE - GLUE IT

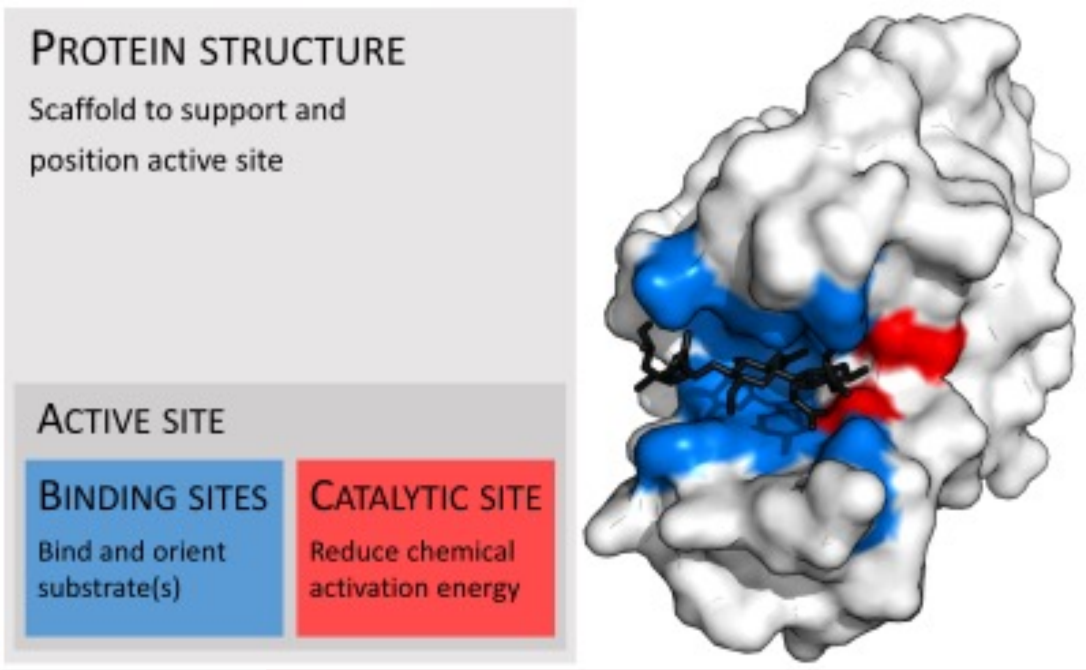
Transcription Factor



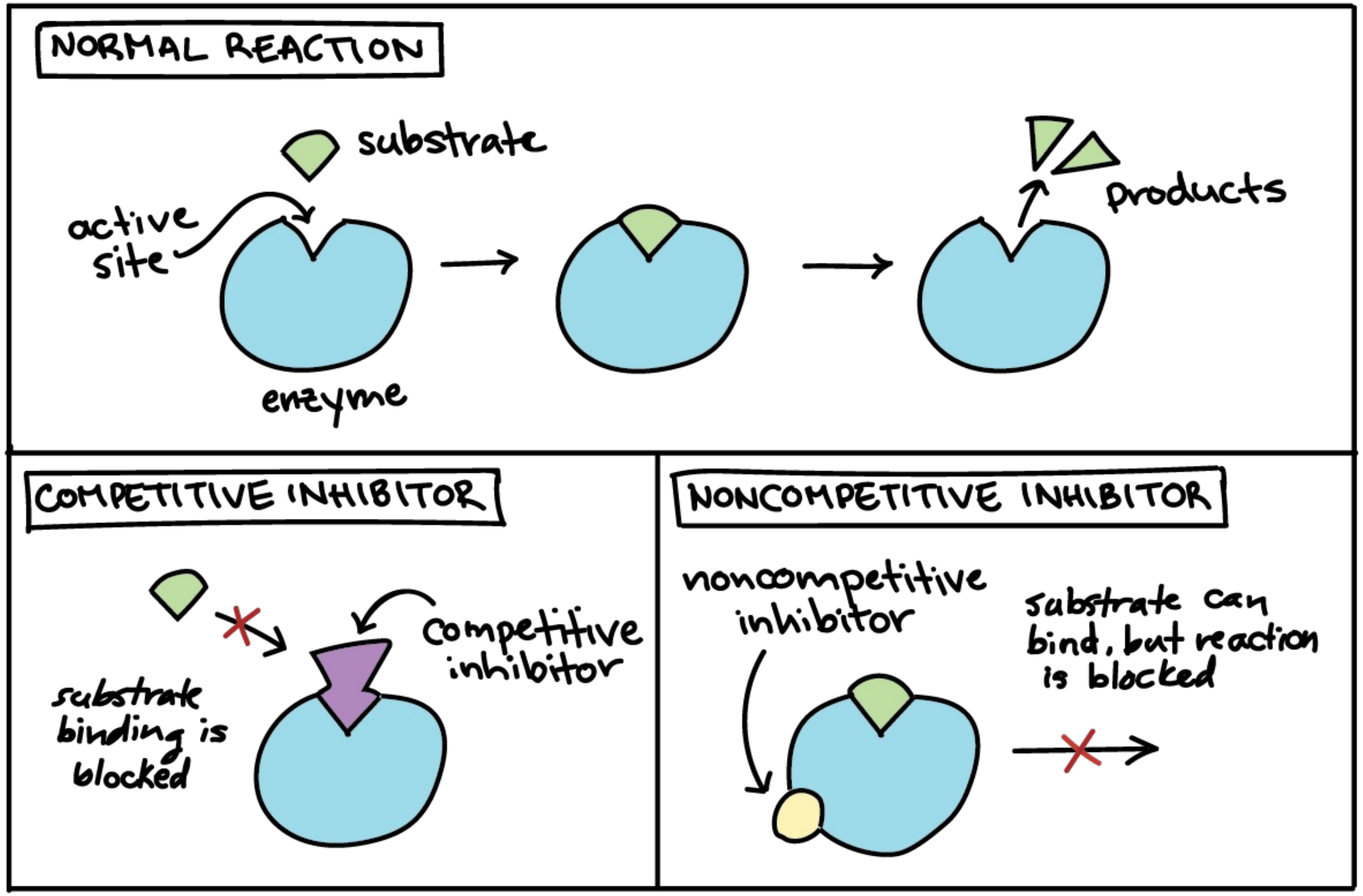

Transcription Factor
Interaction with Partner Protein

Emil Fischer

"Only with a similar geometrical structure can molecules approach each other closely, and thus initiate a chemical reaction. To use a picture, I should say that the enzyme and substrate must fit each other like a **lock and key**."



Drugging the Active site

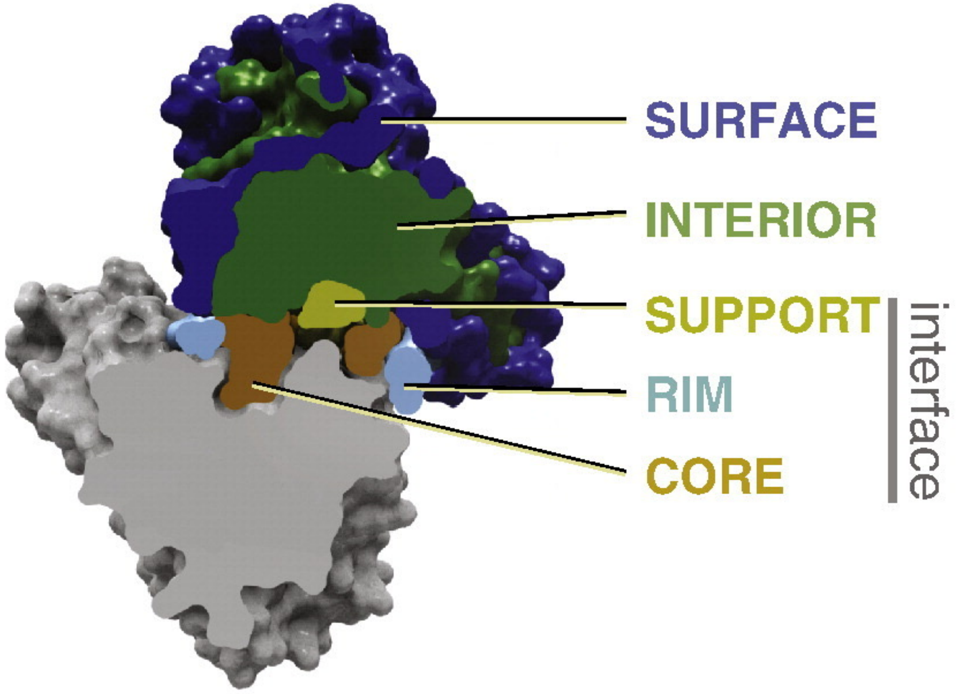


Link

Active Sites are "Easy" to Drug

but here is the Problem

Cross-section of a protein complex



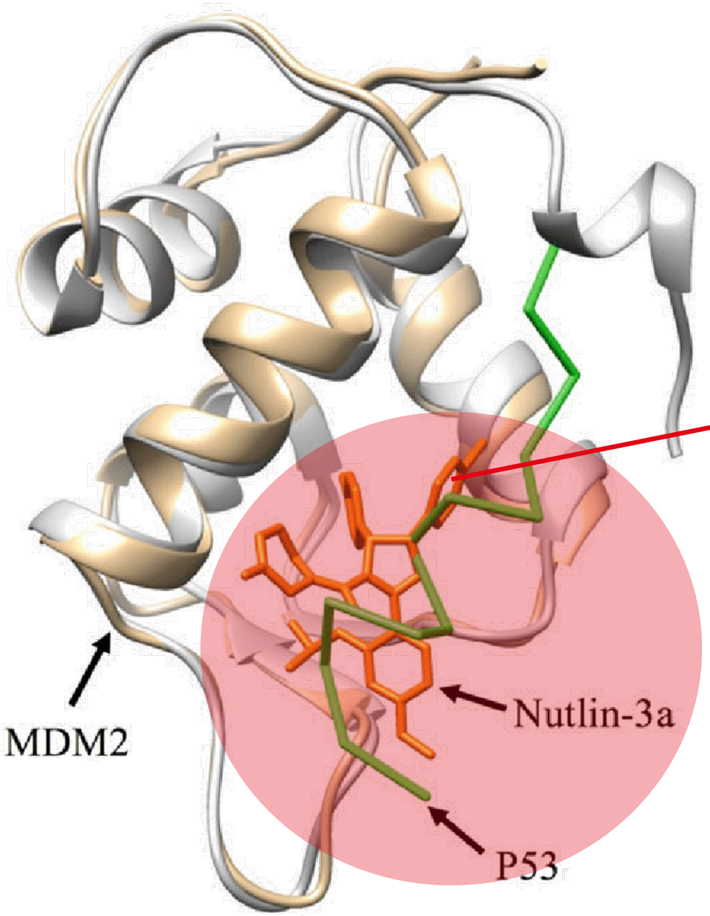
Levy, J Mol Biol 2010

Protein-Protein interfaces are large (> 200-300 Å^2)

Compounds can only cover a fraction of this.

Very few success cases

here is one: p53/MDM2

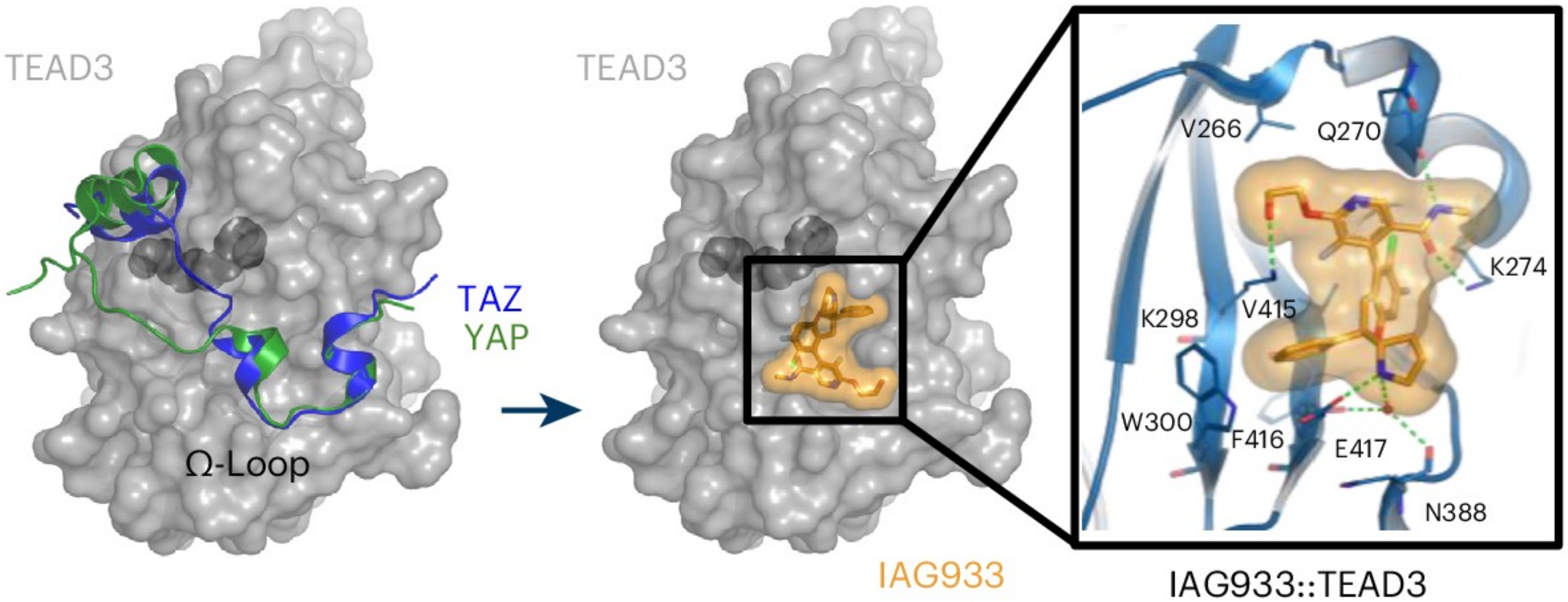


COMPOUND occupies the binding site for **p53**

Very few success cases

… And one more: YAP/TEAD/IAG933

The drug mimics interactions of TAZ/YAP and blocks the binding site

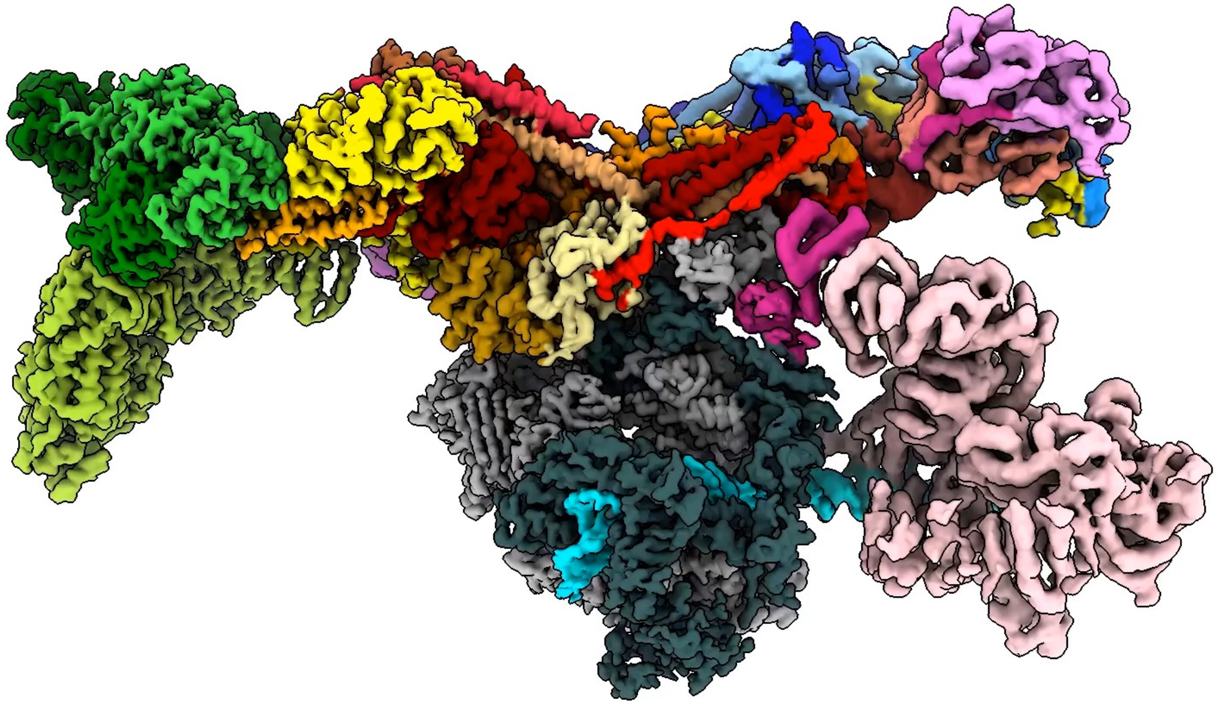


Chapeau *et al.*, Nat Cancer 2024

… simple, peptidic, binding sites can (sometimes) be blocked by compounds, but …

Protein-Protein interfaces

are large and involving more than a Peptide



cPIC: RNA Pol II GTFs DNA
TFIIH: cTFIIH Mat1 cyclin-H CDK7
MedHead: Med6 Med8 Med11 Med17 Med18 Med20 Med22 Med27 Med28 Med29 Med30
MedMiddle: Med1 Med4 Med7 Med9 Med10 Med19 Med21 Med26 Med31
MedTail: Med15 Med16 Med23 Med24 Med25 Scaffold: Med14

The reductionist trap of 1990' X-ray crystallography:

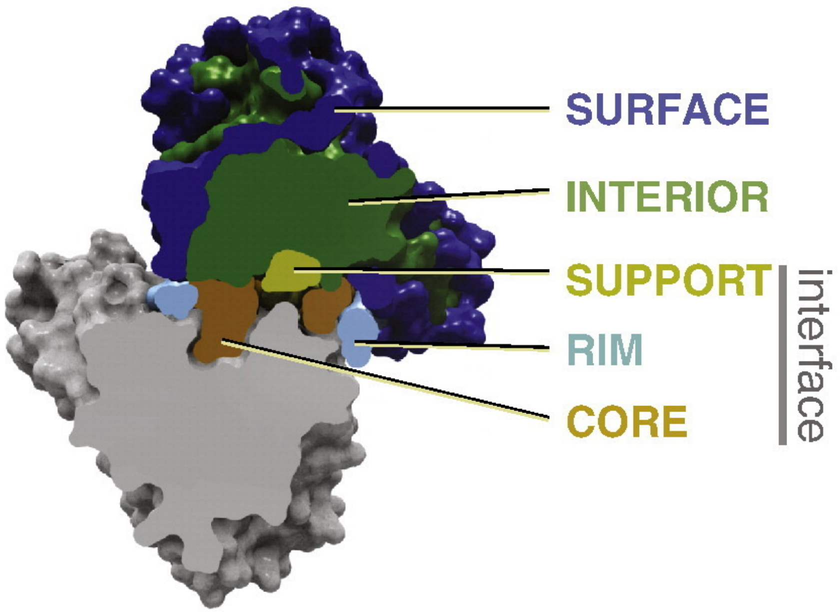
Now with cryo-EM:
the binding sites of the full length proteins are much, much bigger than a peptide!

Shown here –
human Mediator

Chen, Yin, Li, Wu, Qi, Wang, Liu *et al.*, Science 2021

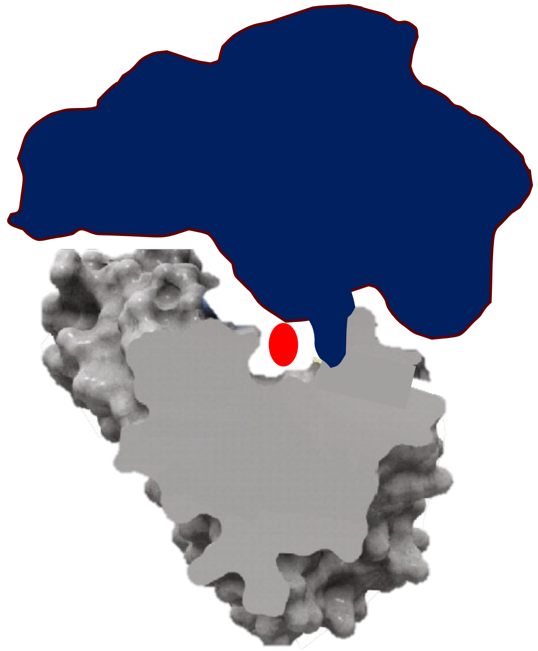
Why is it hard to drug PPIs?

Cross-section of a protein complex

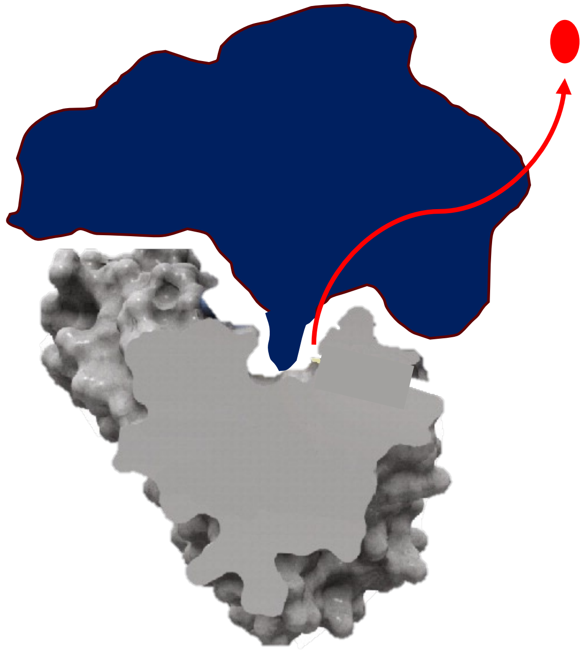


Levy, J Mol Biol 2010

PROTEINS ARE PLASTIC AND ACCOMMODATE THE INHIBITOR

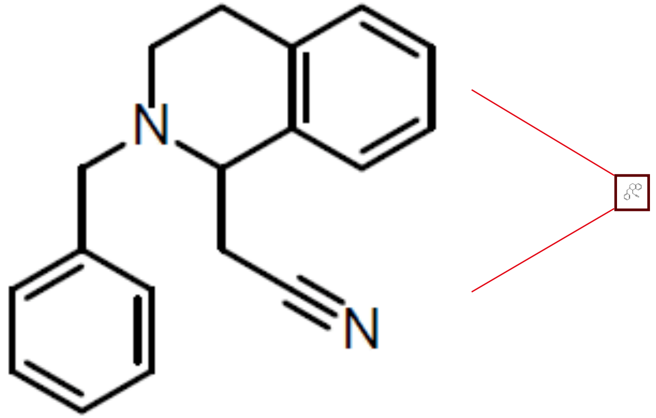


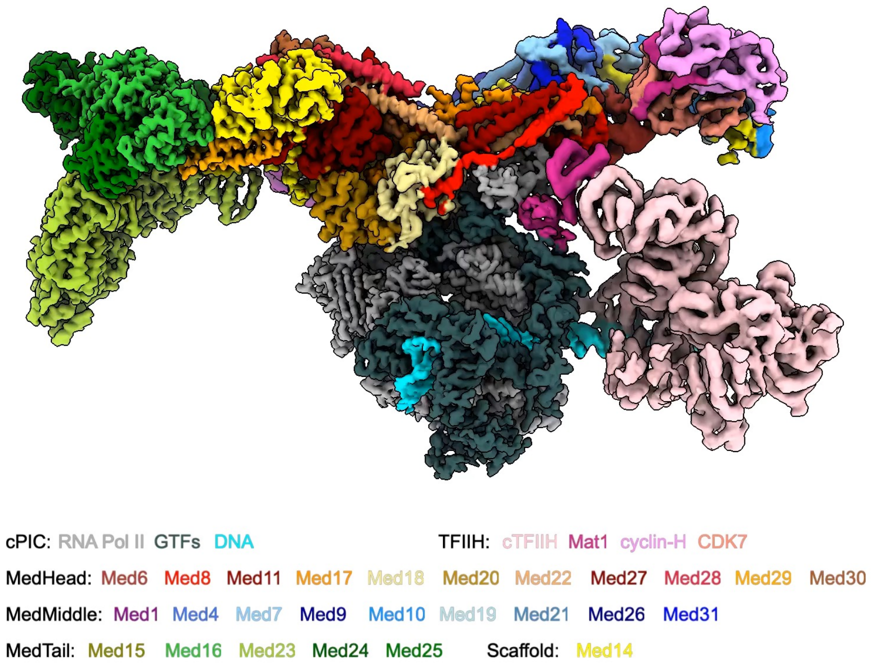
THE INHIBITOR CAN NOT COMPETE WITH THE PROTEIN FOR BINDING

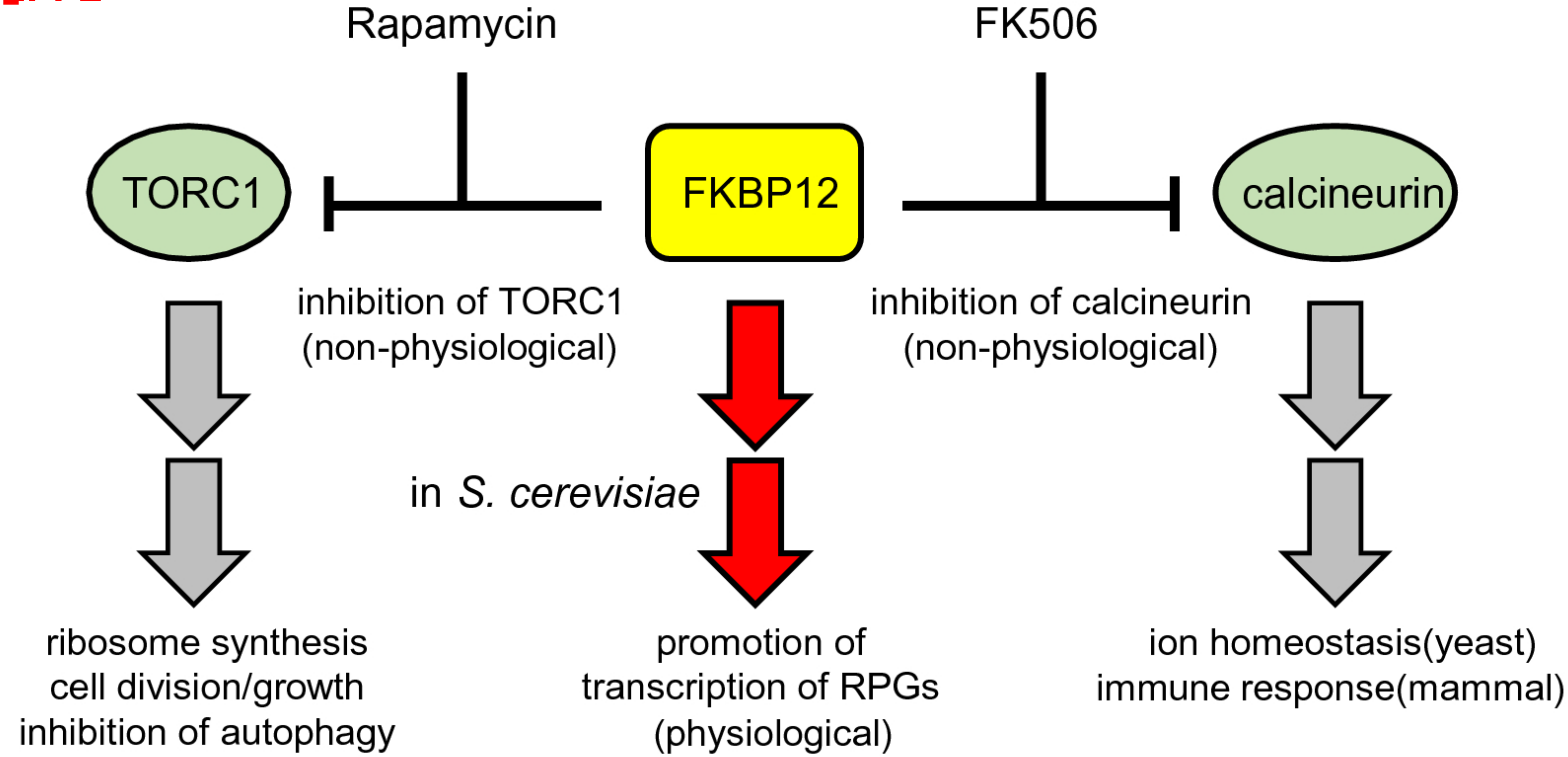


Why is it hard to drug PPIs?

- Large Interface for protein-protein interactions
- Tiny compound cannot counteract the proteins



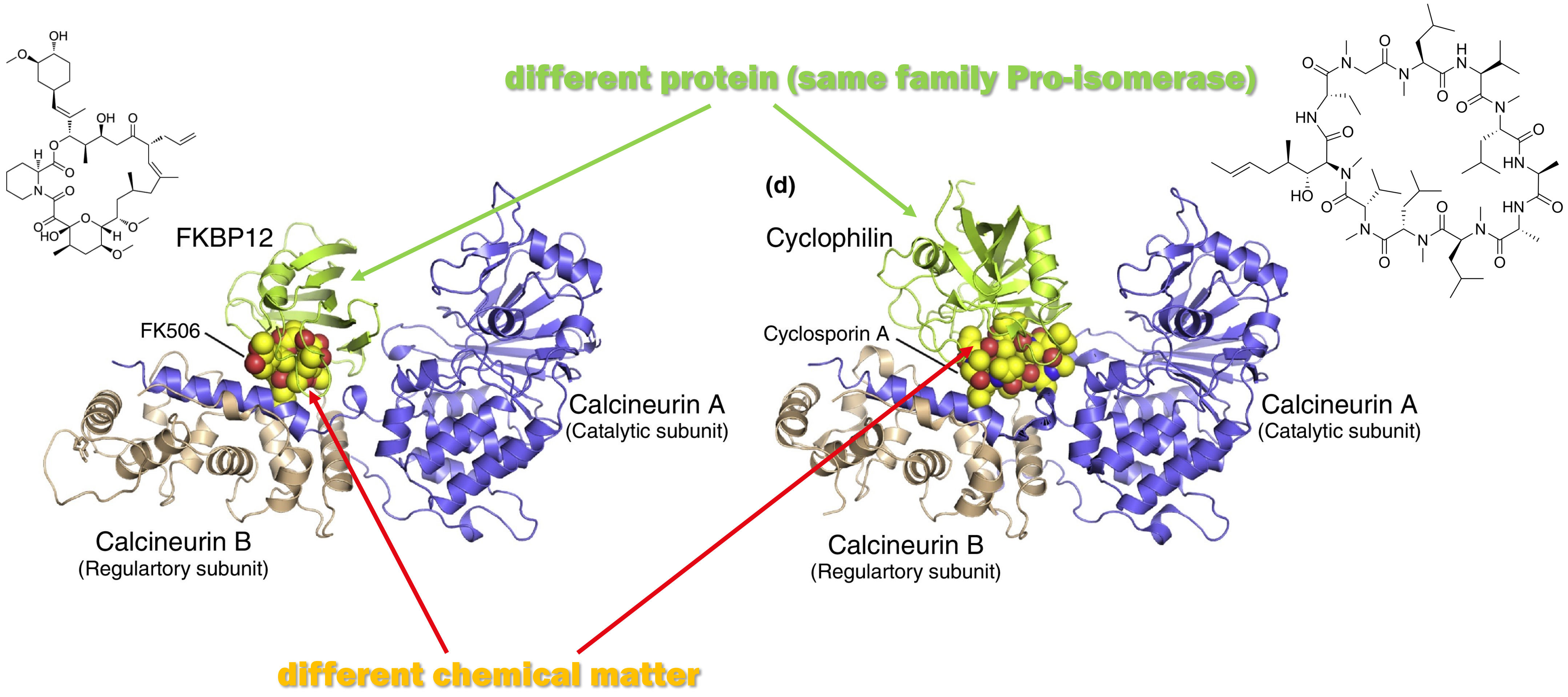


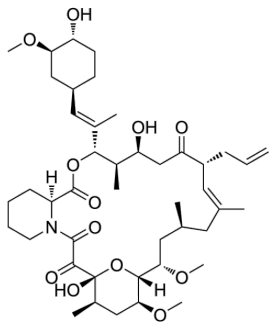


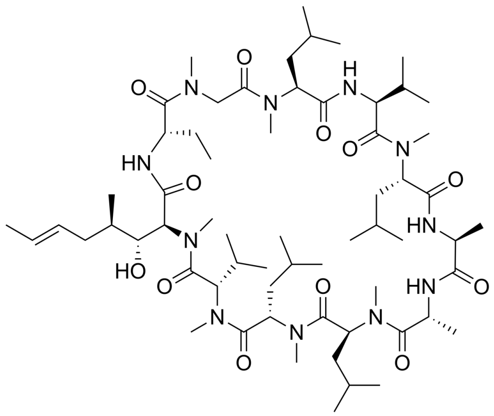
https://link.springer.com/article/10.1007/s00294-020-01142-3/figures/3

THE MOTHER OF ALL GLUES

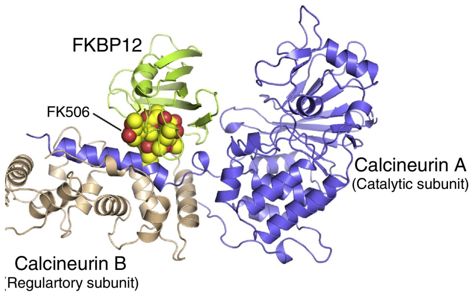
FROM MOTHER-NATURE (NATURAL PRODUCT)

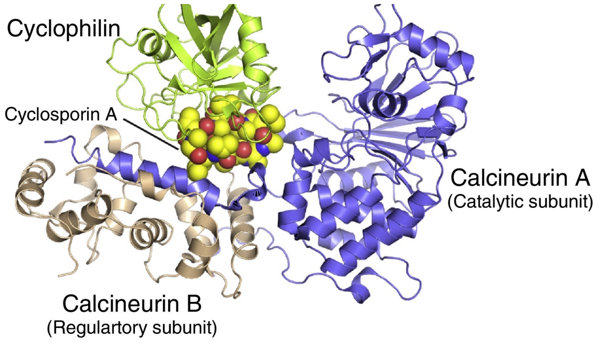






- Different chemical matter
- One shared protein

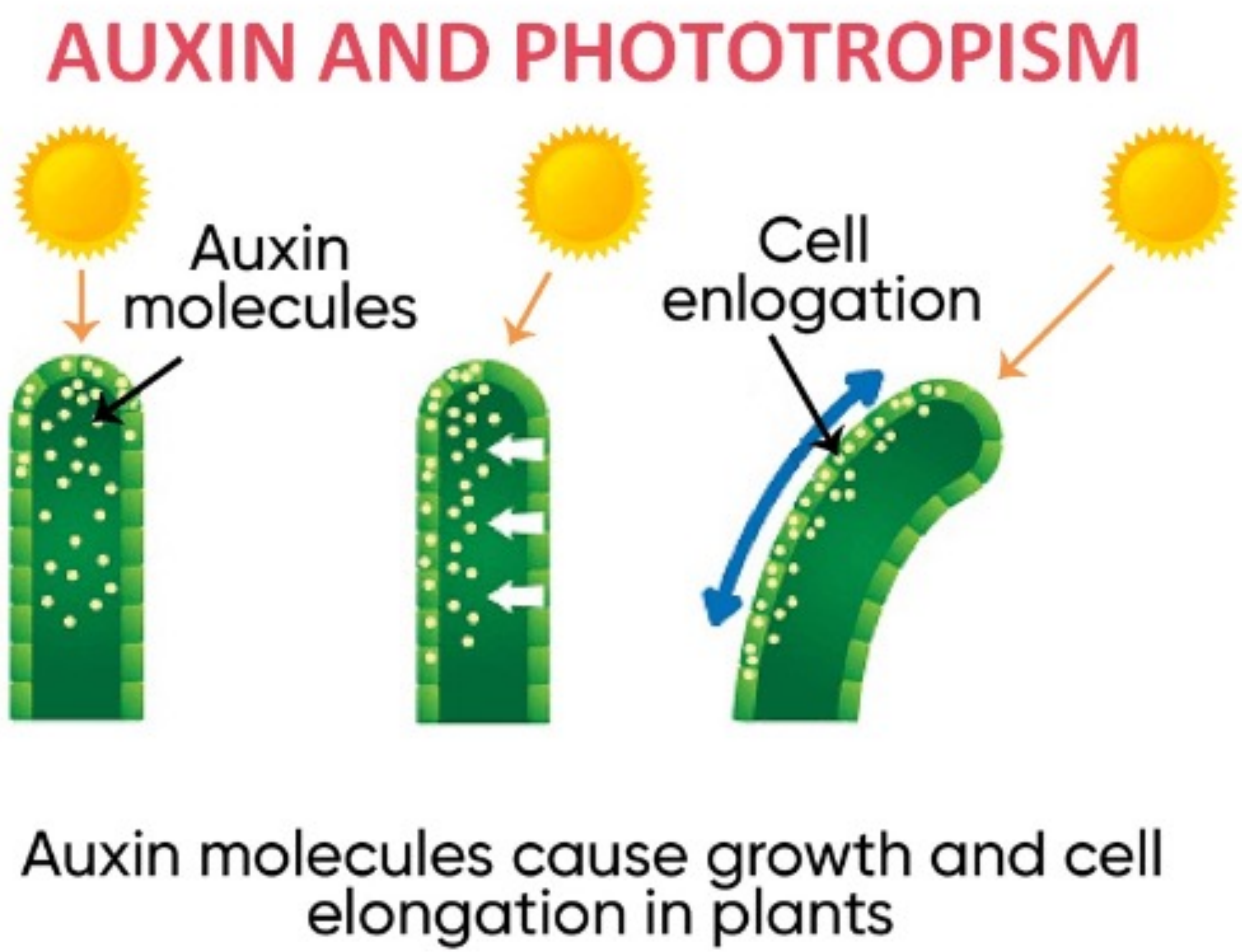




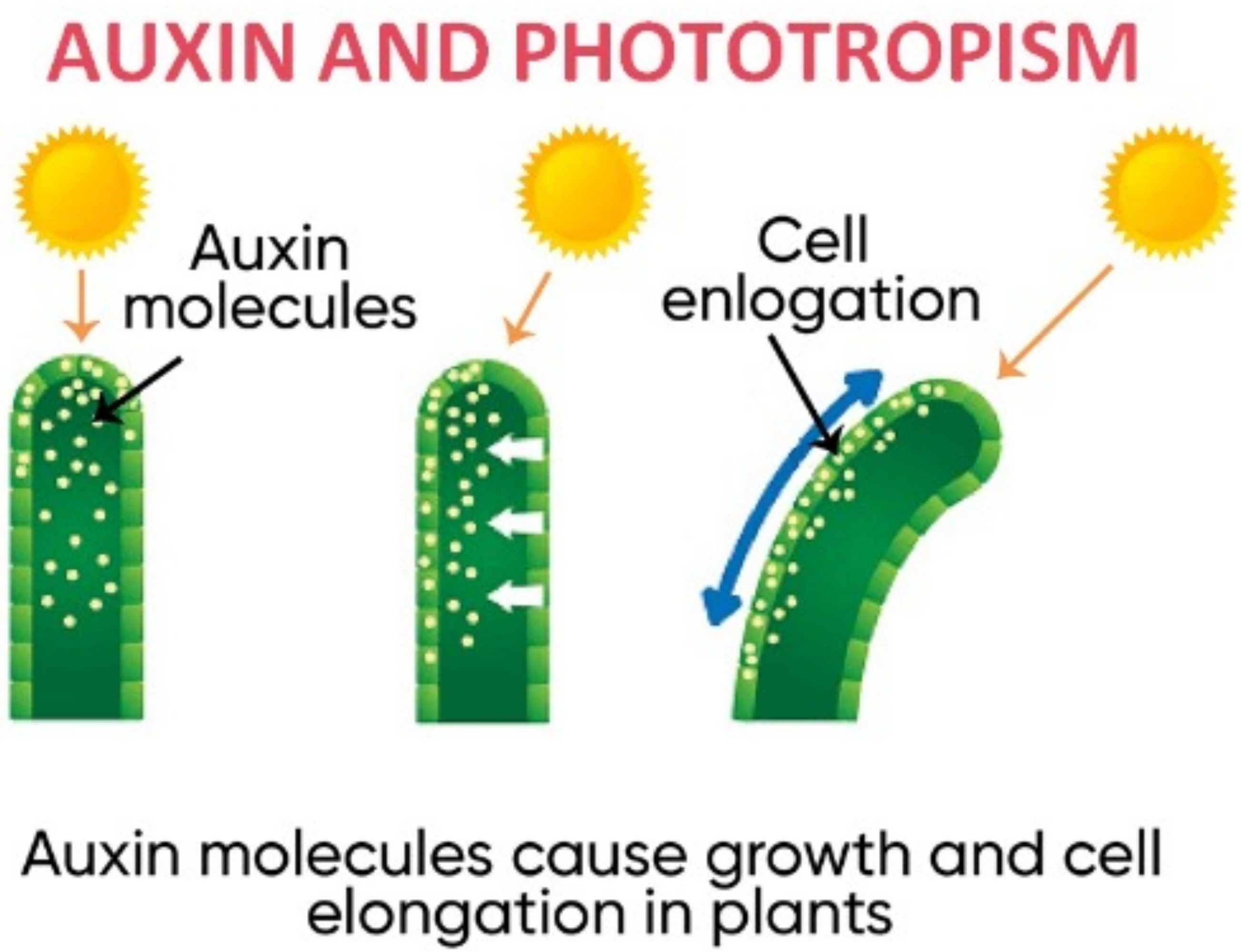
- Different effectors

HOW CAN THIS BE … ?

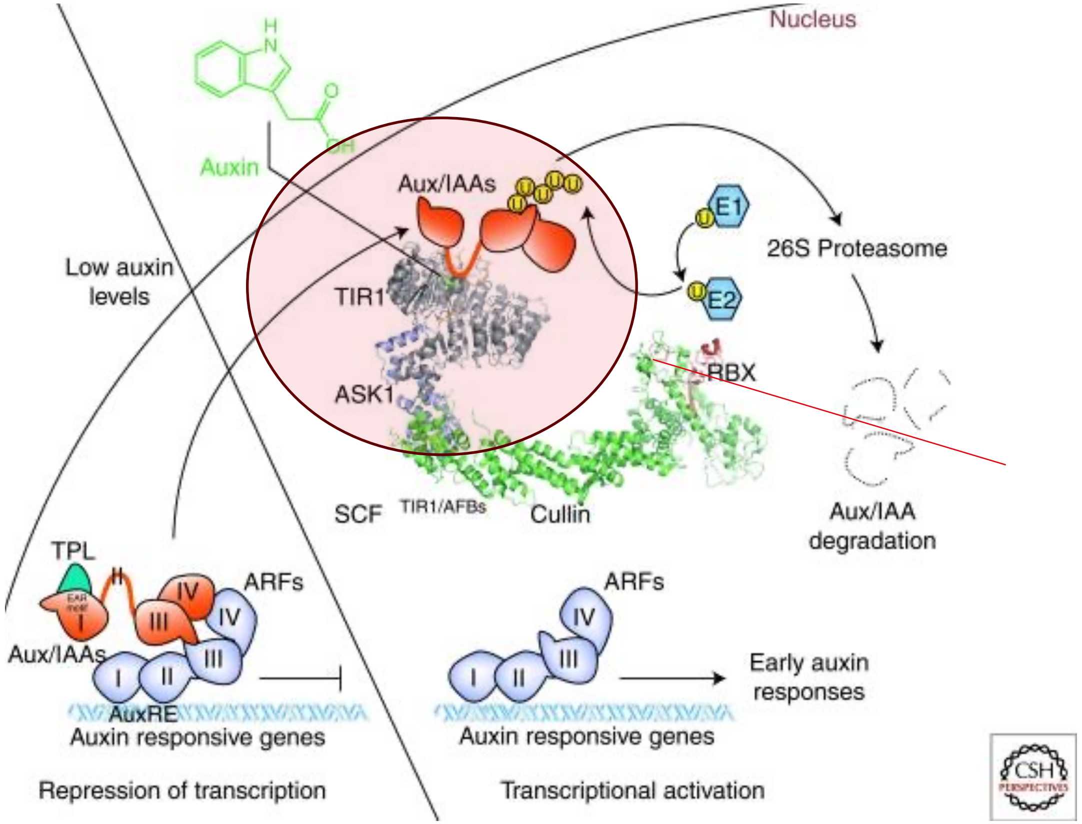
AUXIN: A MOLECULAR GLUE DEGRADER



AUXIN: A MOLECULAR GLUE DEGRADER

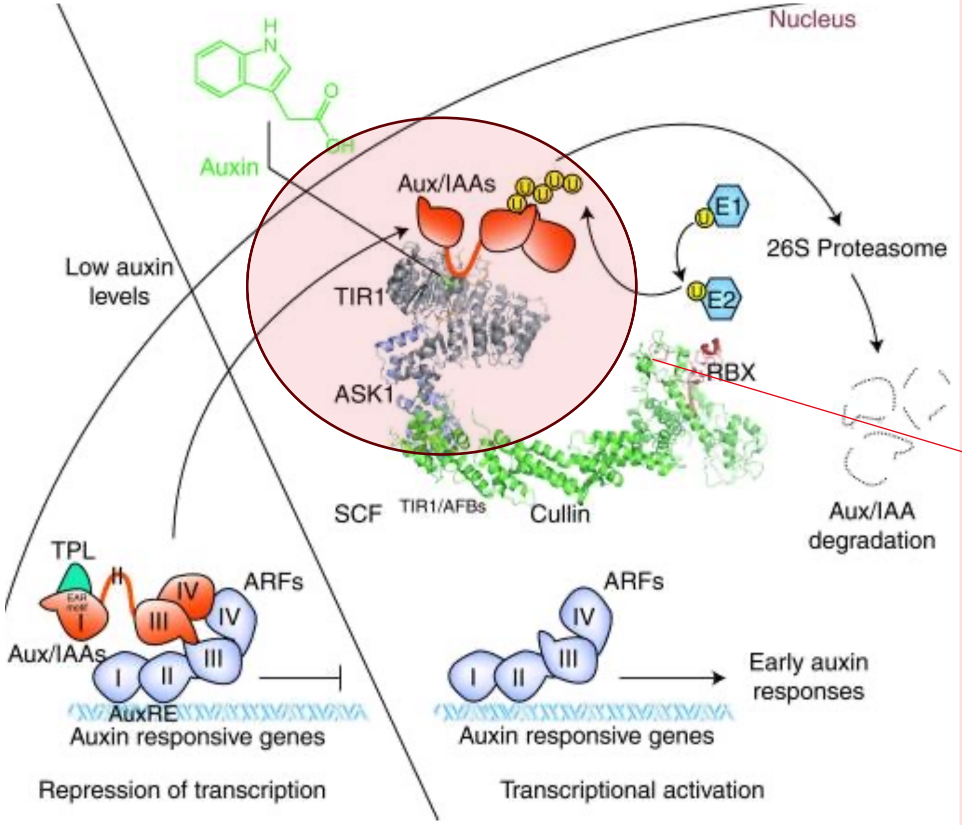


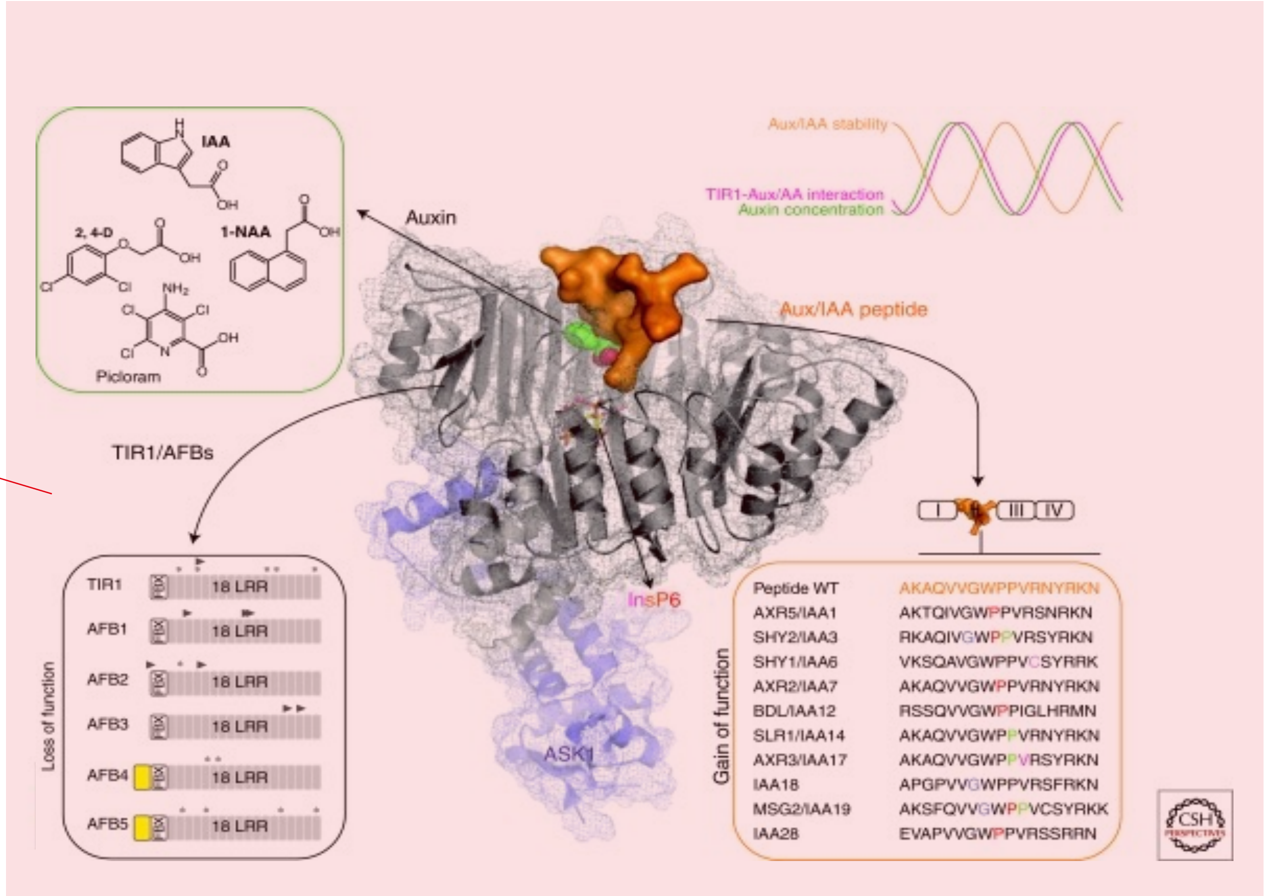
MOLECULAR GLUE DEGRADERS



Calderon-Villalobos, 2010

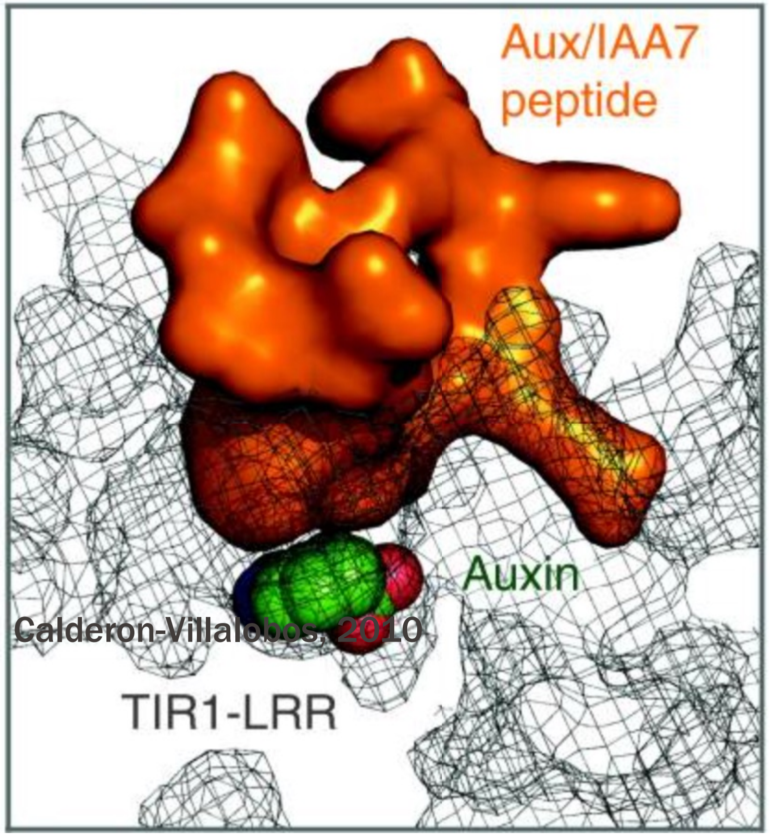
MOLECULAR GLUE DEGRADERS





Calderon-Villalobos, 2010

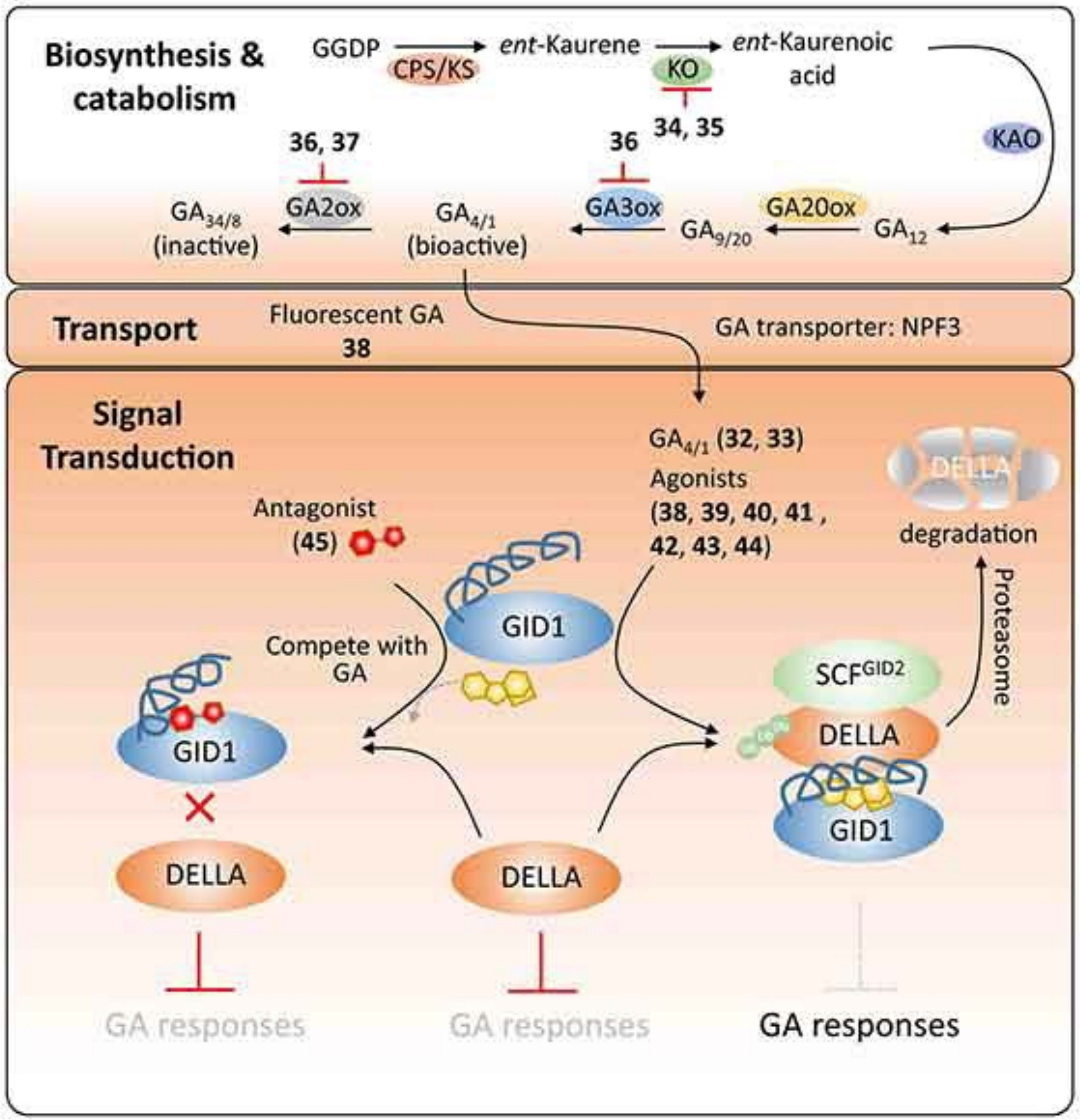
MOLECULAR GLUE DEGRADERS



Calderon-Villalobos, 2010

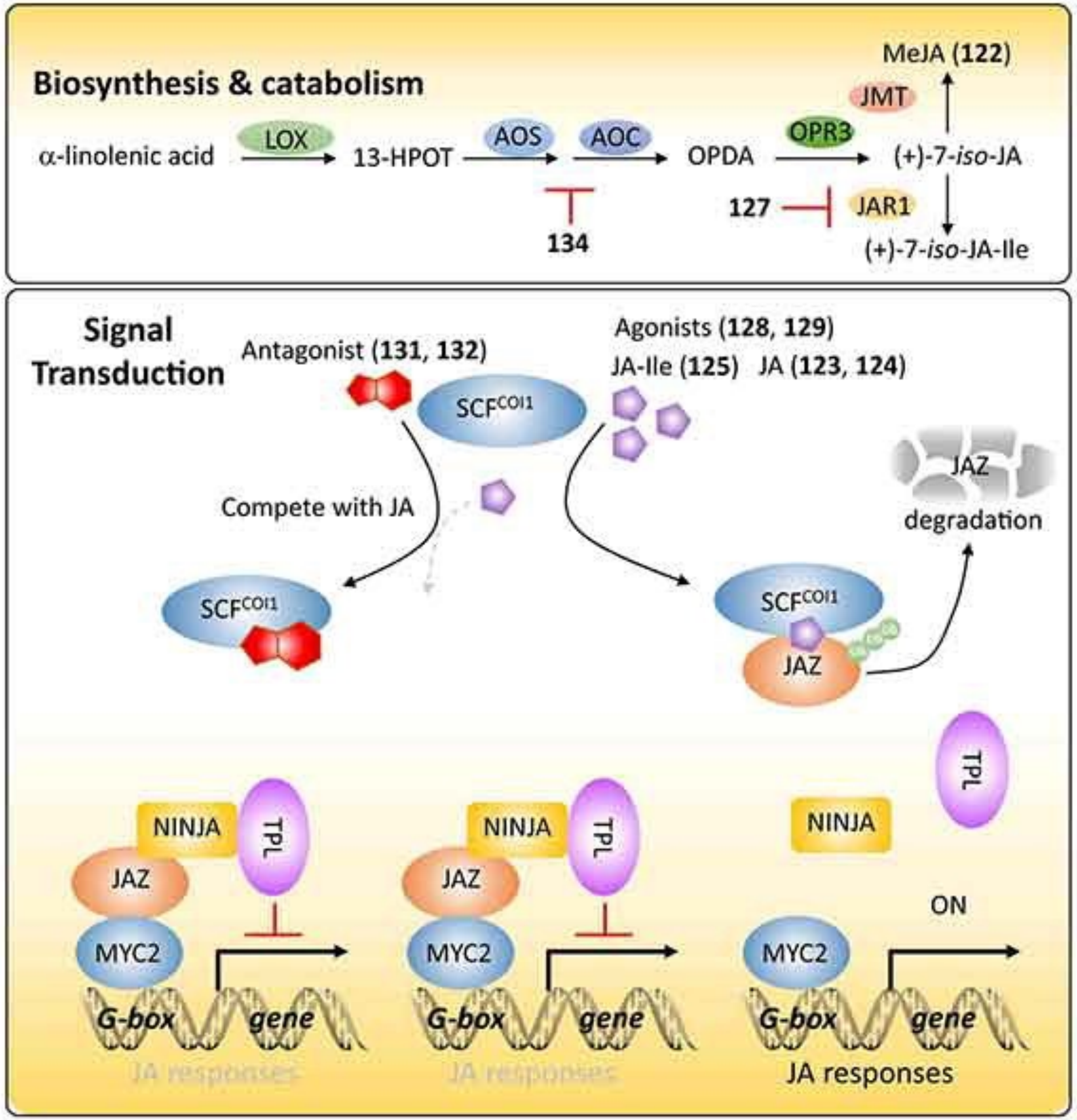
Stringolactone
Gibberellic Acid
Salicylic Acid
Auxin
Jasmonate
Ethylene

Gibberelin

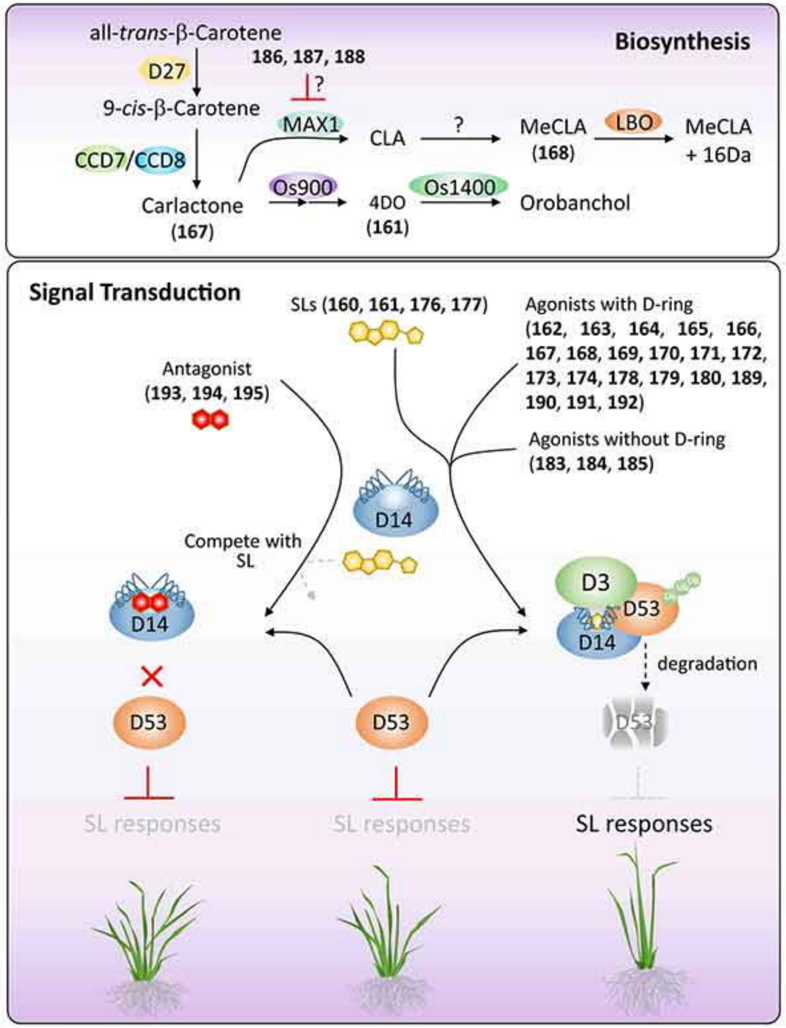


https://www.tandfonline.com/doi/full/10.1080/09168451.2018.1462693#d1e420

Jasmonate

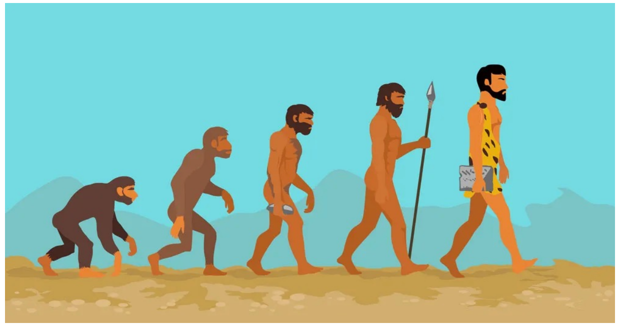

Biosynthesis & catabolism
α-linolenic acid
LOX
13-HPOT
AOS
AOC
OPDA
OPR3
(+)-7-iso-JA
JMT
MeJA (122)
JAR1
(+)-7-iso-JA-Ile
127
134
Signal Transduction
Antagonist (131, 132)
Agonists (128, 129)
JA-Ile (125) JA (123, 124)
SCFCOI1
Compete with JA
SCFCOI1
SCFCOI1
JAZ
JAZ degradation
NINJA
TPL
JAZ
MYC2
G-box
gene
JA responses
NINJA
TPL
JAZ
MYC2
G-box
gene
JA responses
TPL
NINJA
ON
MYC2
G-box
gene
JA responses

Stringolactone



Lots of small molecules,
That degrade proteins in plants!
The proteins degraded are largely
Transcription factors ?!

What about



Stringolactone

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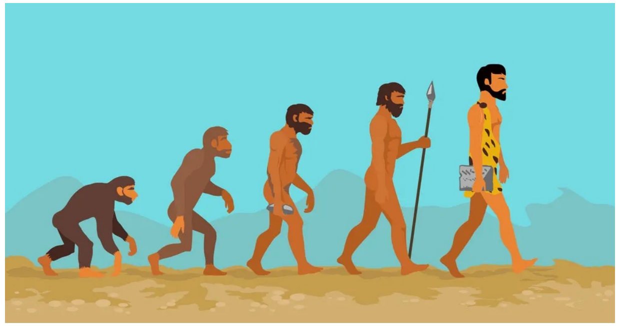

Birth defect crisis [edit]

The total number of embryos affected by the use of thalidomide during pregnancy is estimated at more than 10,000, and potentially up to 20,000; of these, approximately 40 percent died at or shortly after the time of birth.[3][9][10] Those who survived had limb, eye, urinary tract, and heart defects.[6] Its initial entry into the U.S. market was prevented by Frances Oldham Kelsey at the U.S. Food and Drug Administration (FDA).[4] The birth defects of thalidomide led to the development of greater drug regulation and monitoring in many countries.[4][6]

The severity and location of the deformities depended on how many days into the pregnancy the mother was before beginning treatment; thalidomide taken on the 20th day of pregnancy caused central brain damage, day 21 would damage the eyes, day 22 the ears and face, day 24 the arms, and leg damage would occur if taken up to day 28. Thalidomide did not damage the fetus if taken after 42 days' gestation.[11][12]

EPFL

Identification of a Primary Target of Thalidomide Teratogenicity

Takumi Ito,[1]* Hideki Ando,[2]* Takayuki Suzuki,[3,4] Toshihiko Ogura,[3] Kentaro Hotta,[2] Yoshimasa Imamura,[5] Yuki Yamaguchi,[2] Hiroshi Handa[1,2]†

Half a century ago, thalidomide was widely prescribed to pregnant women as a sedative but was found to be teratogenic, causing multiple birth defects. Today, thalidomide is still used in the treatment of leprosy and multiple myeloma, although how it causes limb malformation and other developmental defects is unknown. Here, we identified cereblon (CRBN) as a thalidomide-binding protein. CRBN forms an E3 ubiquitin ligase complex with damaged DNA binding protein 1 (DDB1) and Cul4A that is important for limb outgrowth and expression of the fibroblast growth factor Fgf8 in zebrafish and chicks. Thalidomide initiates its teratogenic effects by binding to CRBN and inhibiting the associated ubiquitin ligase activity. This study reveals a basis for thalidomide teratogenicity and may contribute to the development of new thalidomide derivatives without teratogenic activity.

EPFL

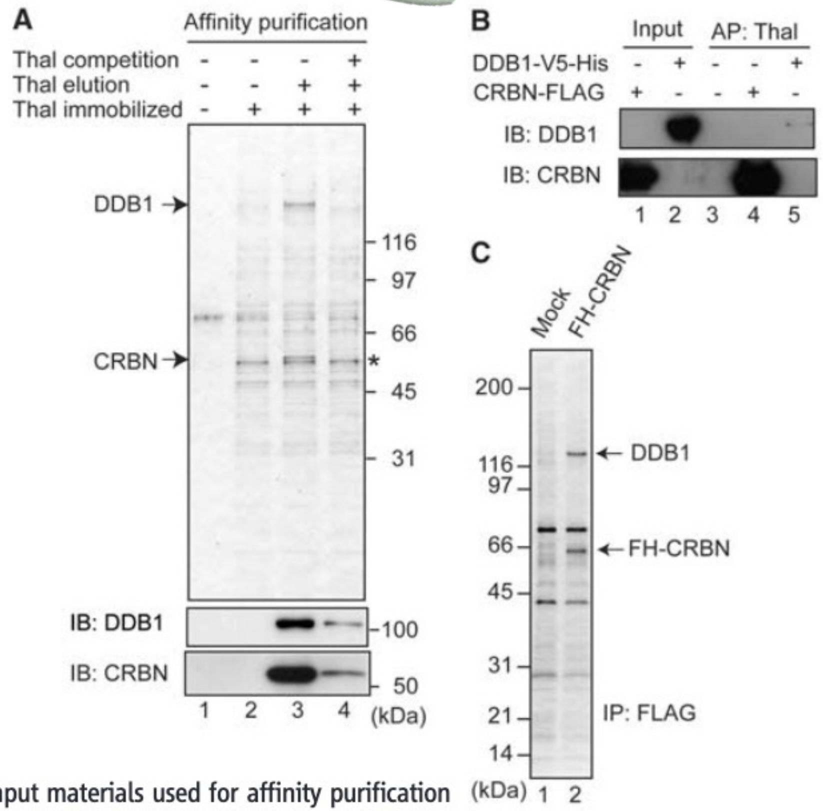

Fig. 1. Thalidomide binds to CRBN and DDB1. **(A)** Thalidomide (Thal)-binding proteins were purified from HeLa cell extracts by using thalidomide-immobilized (+) or control (–) beads. Where indicated, bound proteins were eluted with free thalidomide. As indicated, 0.3 mM thalidomide was added to extracts before incubation with the beads. Eluted proteins were analyzed by silver staining (top) or immunoblotting (IB) (bottom). Asterisk indicates nonspecific signal. **(B)** Purified recombinant CRBN-FLAG and DDB1-V5-His were, respectively, incubated with thalidomide beads. Input materials used for affinity purification (AP) and bound materials were immunoblotted. **(C)** FH-CRBN was immunoprecipitated (IP) from 293T cells stably expressing FH-CRBN or from control cells, followed by SDS gel electrophoresis and silver staining.

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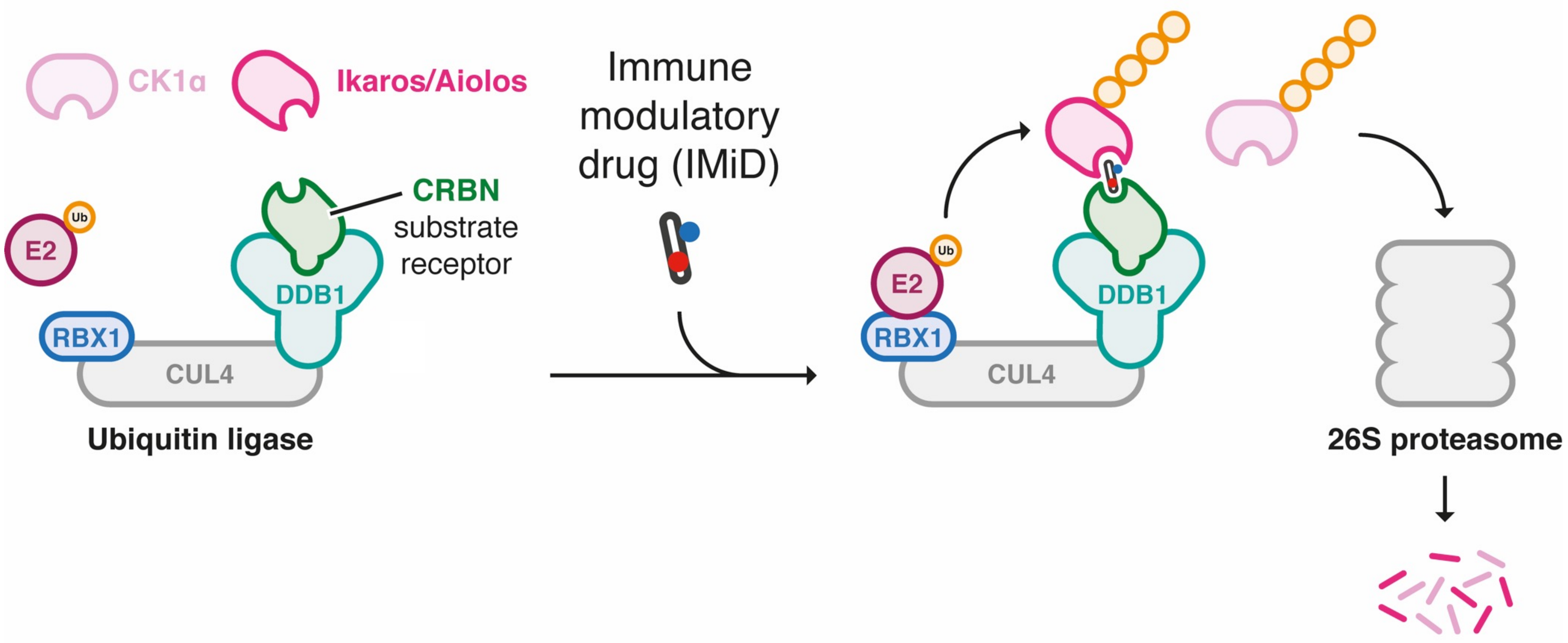
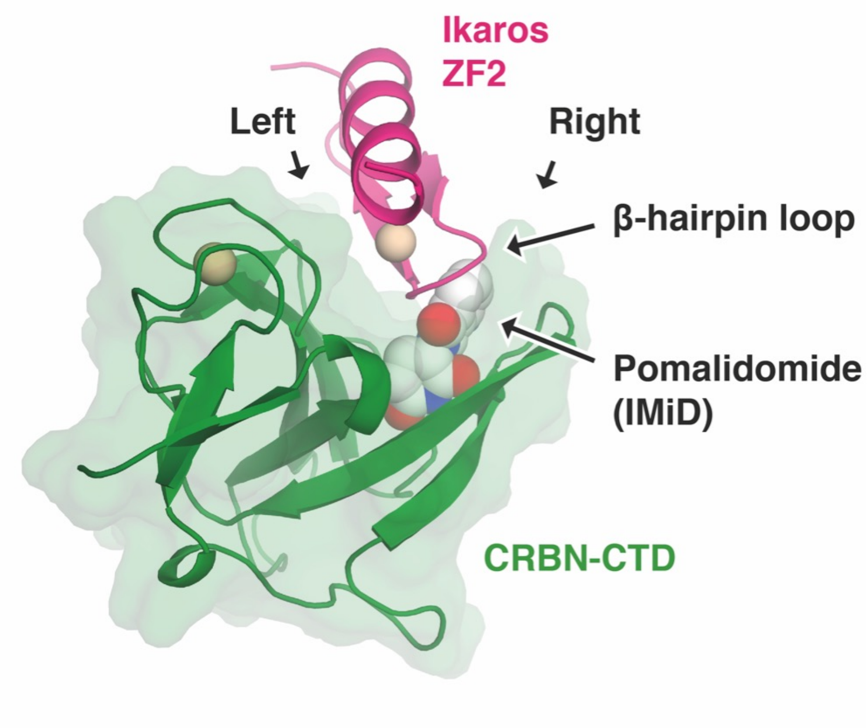
A MOLECULAR GLUE DEGRADER DRUG

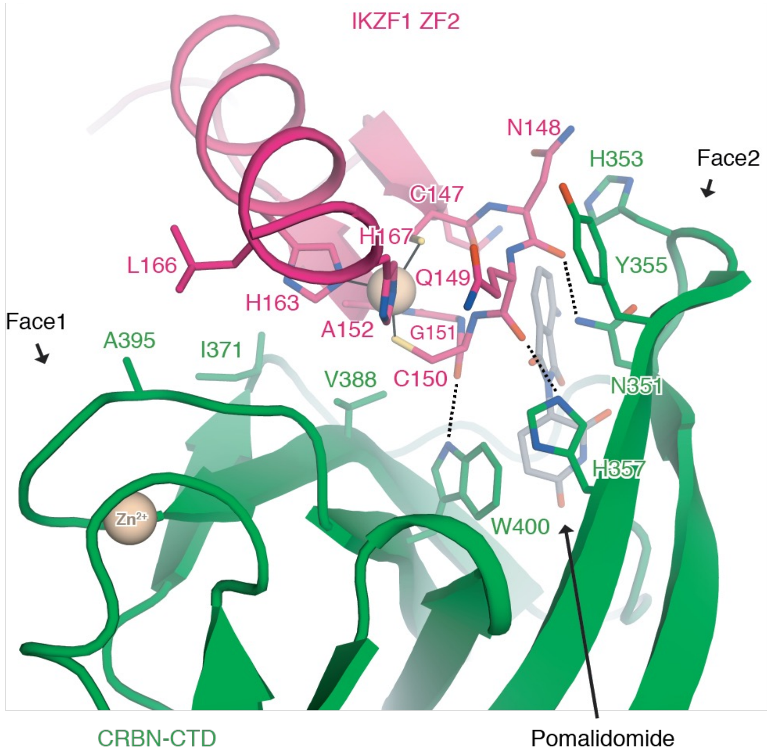
[THAT WAS ALREADY FDA APPROVED]



IMiD DRUGs

IN MULTIPLE MYELOMA





DEGRADING THE IKAROS (TF) ZINC-FINGER

ARTICLE

doi:10.1038/nature14610

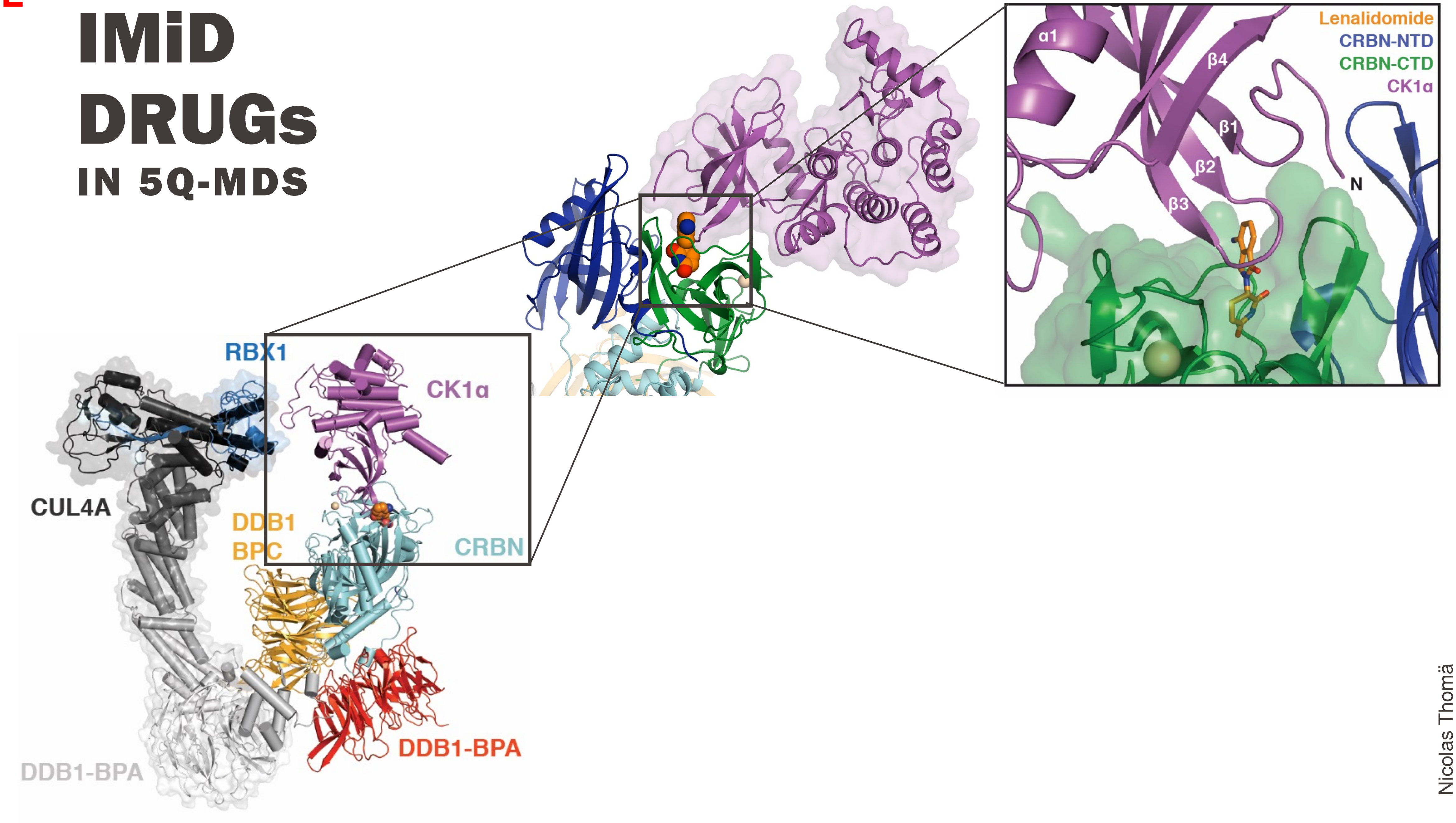
Lenalidomide induces ubiquitination and degradation of CK1α in del(5q) MDS

Jan Krönke[1,2,3]*, Emma C. Fink[1,3]*, Paul W. Hollenbach[4], Kyle J. MacBeth[4], Slater N. Hurst[1], Namrata D. Udeshi[3], Philip P. Chamberlain[4], D. R. Mani[3], Hon Wah Man[4], Anita K. Gandhi[4], Tanya Svinkina[3], Rebekka K. Schneider[1], Marie McConkey[1], Marcus Järås[1], Elizabeth Griffiths[5], Meir Wetzler[5], Lars Bullinger[2], Brian E. Cathers[4], Steven A. Carr[3], Rajesh Chopra[4] & Benjamin L. Ebert[1,3]

Lenalidomide is a highly effective treatment for myelodysplastic syndrome (MDS) with deletion of chromosome 5q (del(5q)). Here, we demonstrate that lenalidomide induces the ubiquitination of casein kinase 1A1 (CK1α) by the E3 ubiquitin ligase CUL4–RBX1–DDB1–CRBN (known as $CRL4^{CRBN}$), resulting in CK1α degradation. CK1α is encoded by a gene within the common deleted region for del(5q) MDS and haploinsufficient expression sensitizes cells to lenalidomide therapy, providing a mechanistic basis for the therapeutic window of lenalidomide in del(5q) MDS. We found that mouse cells are resistant to lenalidomide but that changing a single amino acid in mouse Crbn to the corresponding human residue enables lenalidomide-dependent degradation of CK1α. We further demonstrate that minor side chain modifications in thalidomide and a novel analogue, CC-122, can modulate the spectrum of substrates targeted by $CRL4^{CRBN}$. These findings have implications for the clinical activity of lenalidomide and related compounds, and demonstrate the therapeutic potential of novel modulators of E3 ubiquitin ligases.

IMiD DRUGs

IN 5Q-MDS



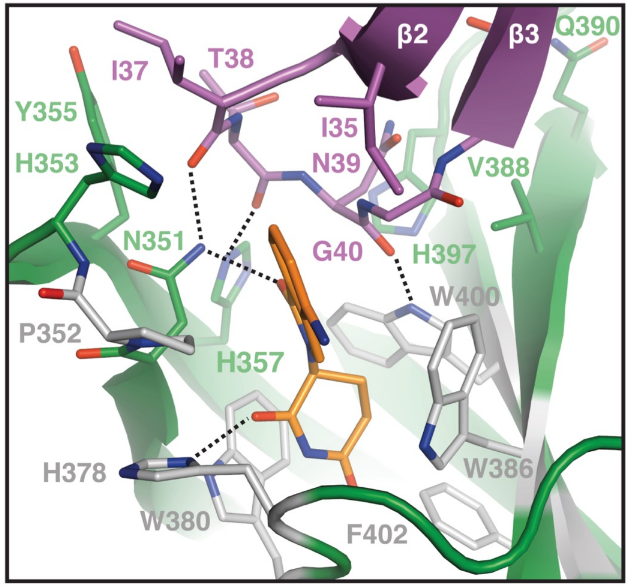
THE G-LOOP

CK1α

KINASE

Ikaros

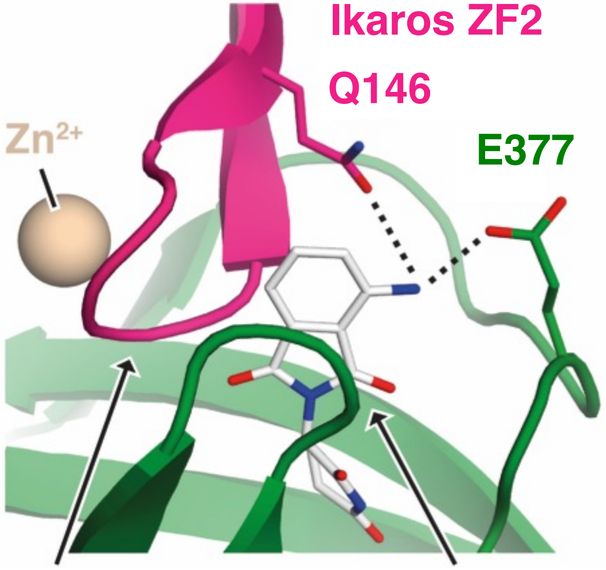
ZINC-FINGER



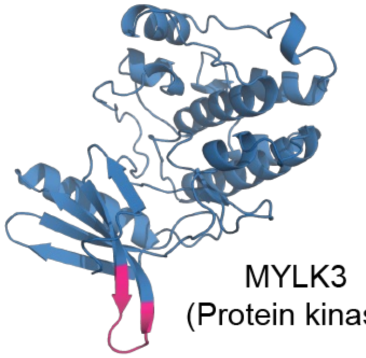
Ikaros P F Q C N Q C G A S F
CK1α L A I N I T N G E E V

β-hairpin

Ikaros ZF2

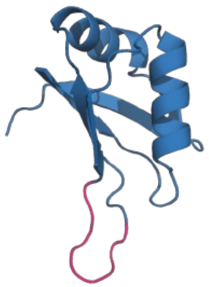


OVER 10% OF HUMAN PROTEINS HAVE A G-LOOP



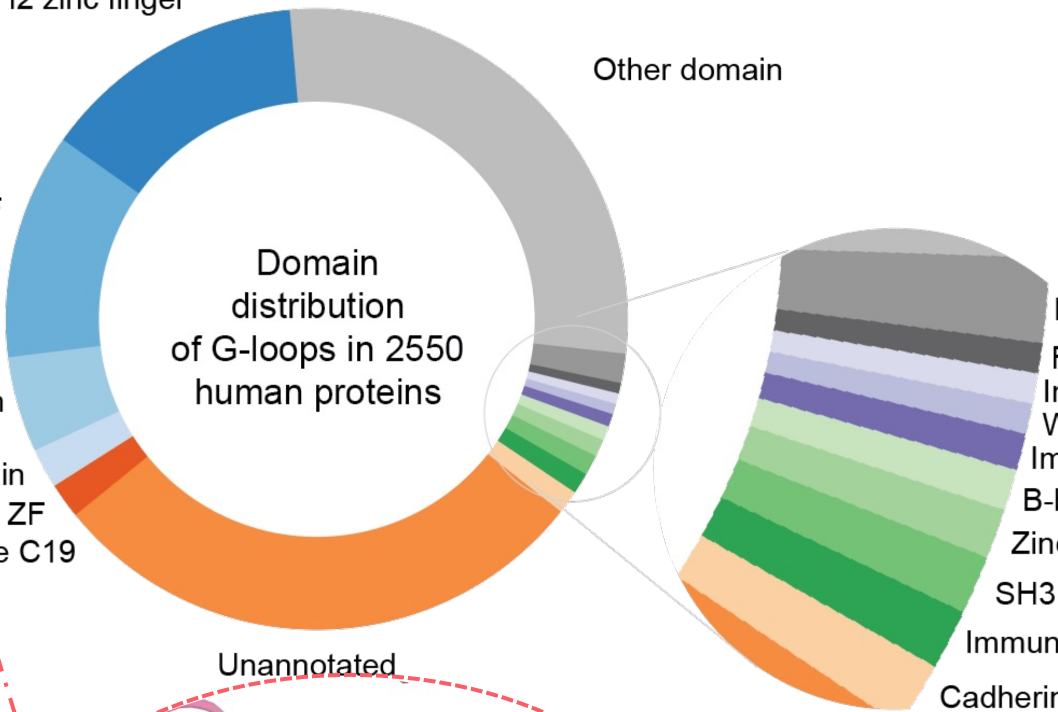
MYLK3
(Protein kinase)

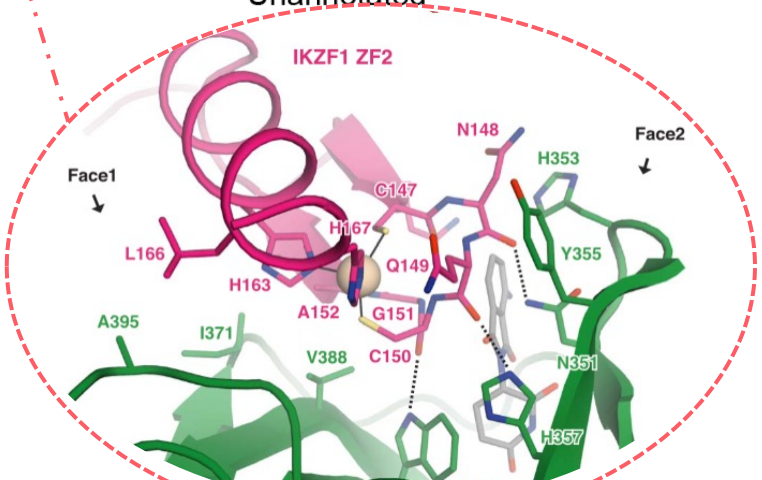
USP3
(Peptidase C19)



CPSF7
(Rna-recognition)

CRIP2
(LIM-type ZF)



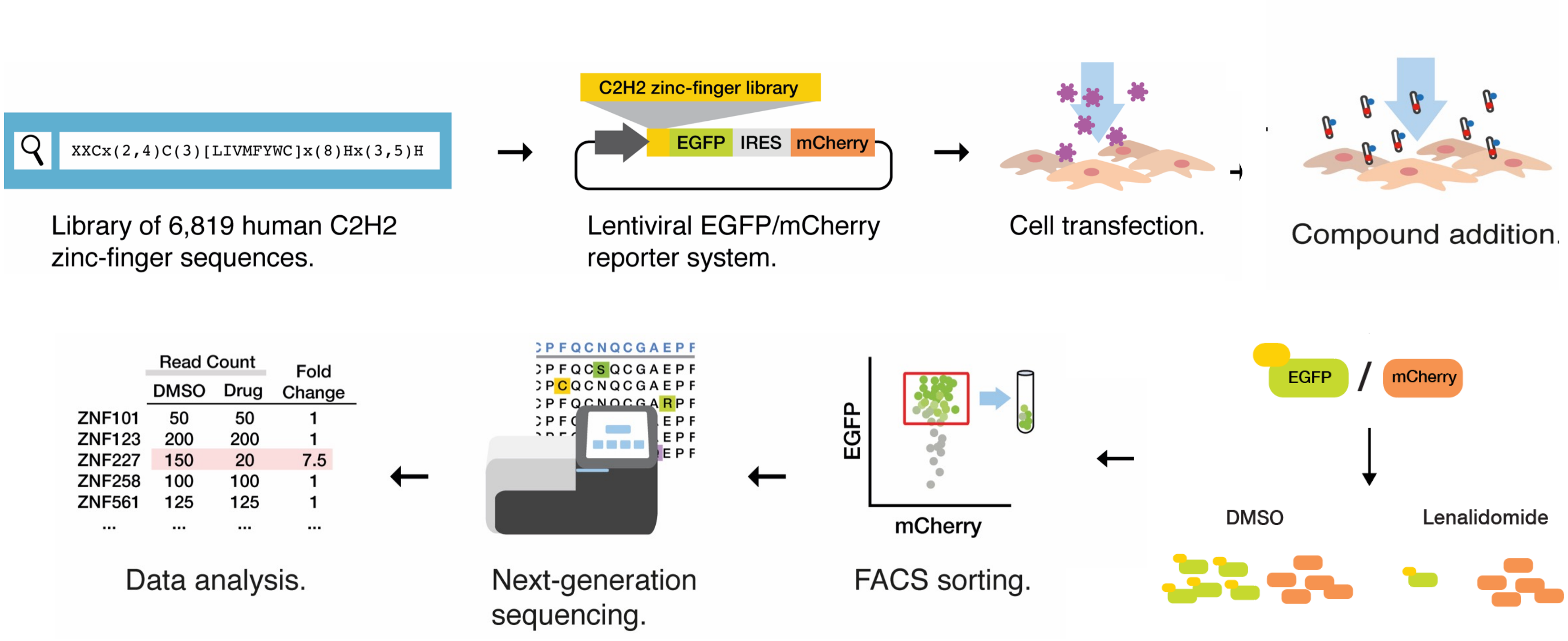


HGFAC
(EGF-like)

ARGHEF19
(SH3 domain)

HOW TO FIND PROTEINS DEGRADED BY IMiDs

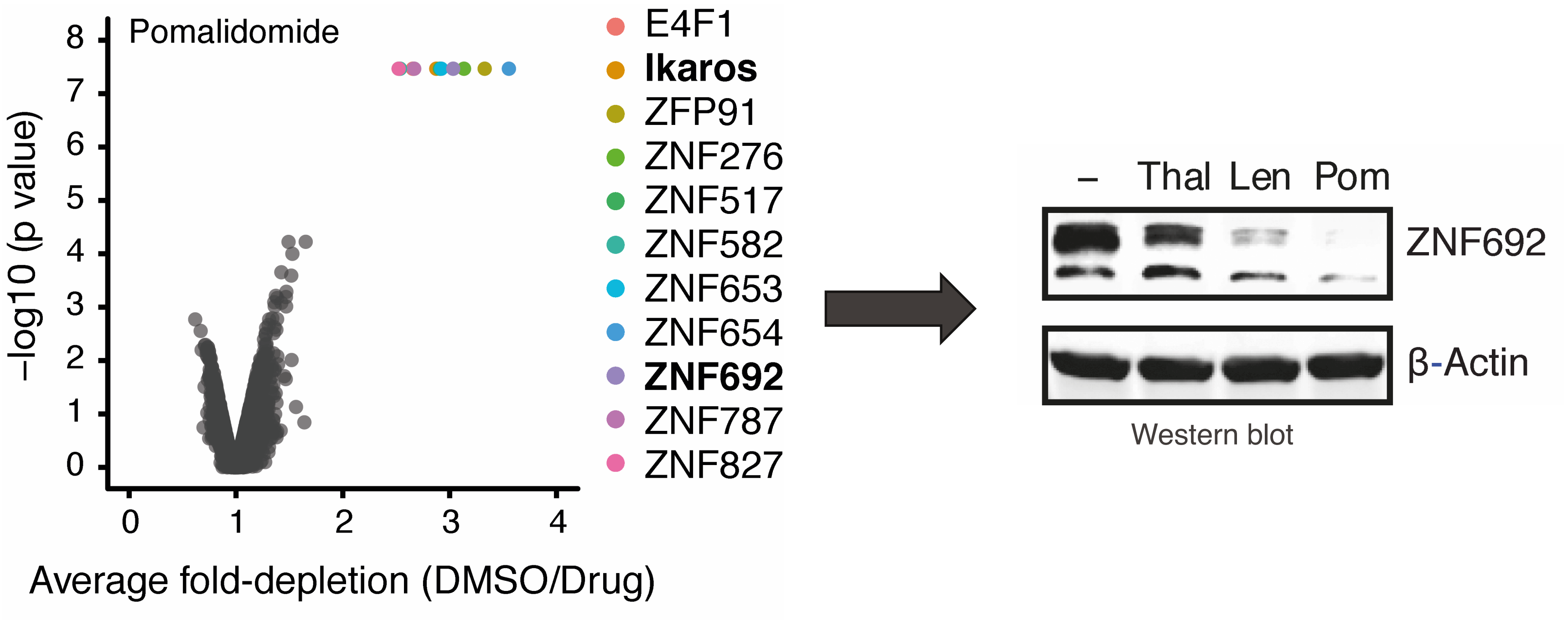
FUNCTIONAL GENOMICS MAGIC!



	Read Count DMSO	Read Count Drug	Fold Change
ZNF101	50	50	1
ZNF123	200	200	1
ZNF227	150	20	7.5
ZNF258	100	100	1
ZNF561	125	125	1
...	...	...	...

HOW TO FIND PROTEINS DEGRADED BY IMiDs

FUNCTIONAL GENOMICS MAGIC!



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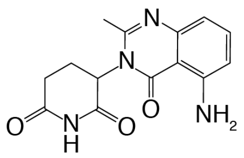
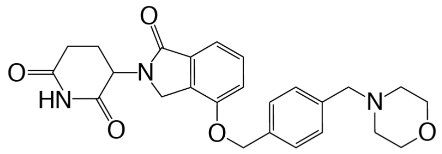
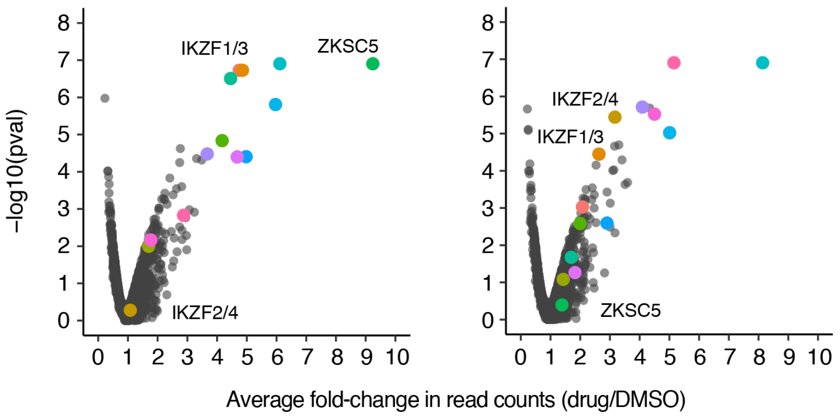
COMPOUND MODIFICATIONS TUNE ZF SPECIFICITY



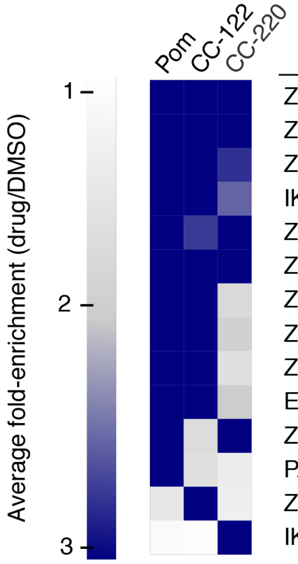
CC-122



CC-220



Gene	Amnio acids
E4F1	220-242
IKZF1/3	145-167 / 146-168
IKZF2/4	**140-162 / 187-209**
PATZ1	383-405
ZFP91	400-422
ZKSC5	**430-452**
ZN276	524-546
ZN517	452-474
ZN582	395-417
ZN653	556-578
ZN654	25-47
ZN692	417-439
ZN787	178-200
ZN827	374-396

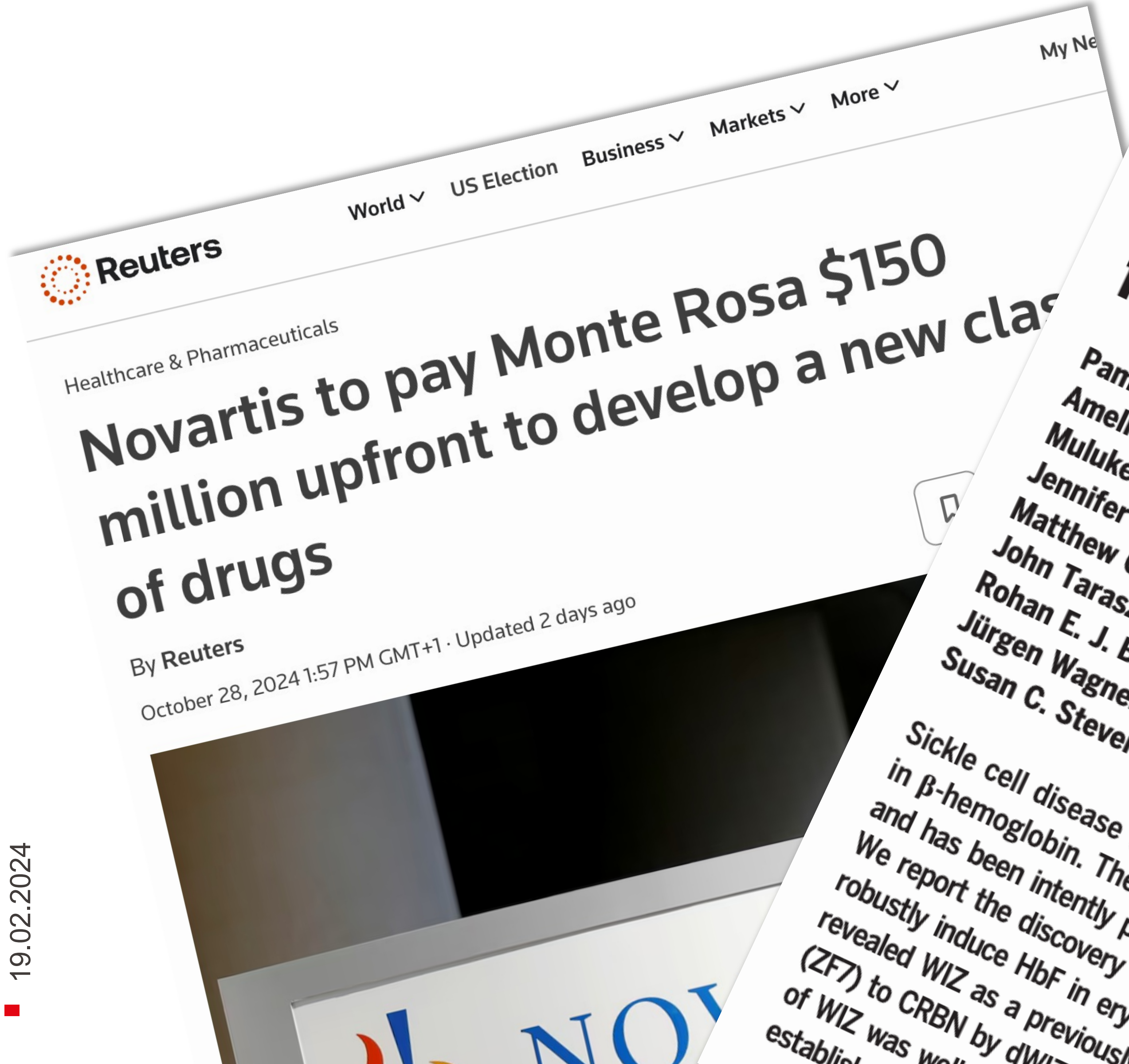


Gene	Amino Acids
ZNF517	452-474
ZNF582	95-417
ZNF653	556-578
IKZF1/3	145-167 / 146-168
ZNF827	374-396
ZNF654	25-47
ZNF692	417-439
ZFP91	400-422
ZNF276	524-546
E4F1	220-242
ZNF787	178-200
PATZ1	383-405
ZKSC5	430-452
IKZF2/4	140-162 / 187-209

Why was it so hard to find the Thalidomide Target?

- There are so many
- They are transcription factors … so they have secondary effects

MORE CRBN TARGETS TO COME !


Reuters

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Healthcare & Pharmaceuticals

Novartis to pay Monte Rosa $150 million upfront to develop a new clas of drugs

By Reuters

October 28, 2024 1:57 PM GMT+1 · Updated 2 days ago


RESEARCH

DRUG DEVELOPMENT

A molecular glue degrader of the WIZ transc factor for fetal hemoglobin induction

Pamela Y. Ting[1]*, Sneha Borikar[1], John Ryan Kerrigan[1], Noel M. Thomsen[1], Eamon Aghania Amelia E. Hinman[1], Alejandro Reyes[2], Nicolas Pizzato[2], Barna D. Fodor[2], Fabian Wu[2], Muluken S. Belew[1]†, Xiaohong Mao[1], Jian Wang[1], Shripad Chitnis[1], Wei Niu[1]‡, Amanda Hachey Jennifer S. Cobb[1], Nikolas A. Savage[1], Ashley Burke[1], Joshiawa Paulk[1], Dustin Dovala[3], James L Matthew C. Clifton[3], Elizabeth Ornelas[3], Xiaolei Ma[3]§, Nathaniel F. Ware[1], Carina C. Sanchez[1], John Taraszka[1], Remi Terranova[2], Judith Knehr[2], Marc Altorfer[2], S. Whitney Barnes[4], Rohan E. J. Beckwith[1]¶, Jonathan M. Solomon[1], Natalie A. Dales[1]#, Andrew W. Patters Jürgen Wagner[2], Tewis Bouwmeester[2], Glenn Dranoff[1]**, Susan C. Stevenson[1], James E. Bradner[1]*††

Sickle cell disease (SCD) is a prevalent, life-threatening cond in β-hemoglobin. Therapeutic induction of fetal hemog and has been intently pursued. However, safe and We report the discovery of dWIZ-1 and dWI robustly induce HbF in erythroblasts revealed WIZ as a previously (ZF7) to CRBN by dWI of WIZ was we establis

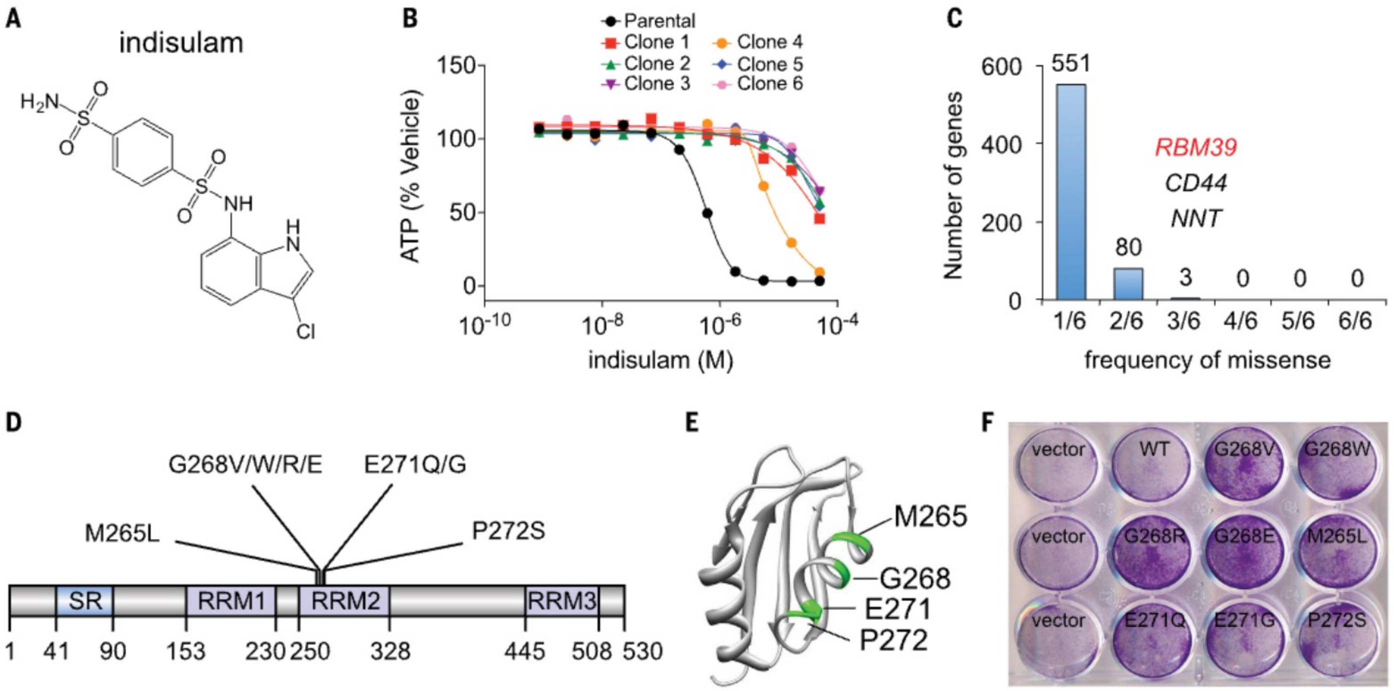
THALIDOMIDE:
POSSIBLY NOT A UNICORN?!

Nicolas Thomä

CANCER THERAPY

Anticancer sulfonamides target splicing by inducing RBM39 degradation via recruitment to DCAF15

Ting Han,[1] Maria Goralski,[2*] Nicholas Gaskill,[2*] Emanuela Capota,[2] Jiwoong Kim,[3,4] Tabitha C. Ting,[5] Yang Xie,[3,4] Noelle S. Williams,[1,4] Deepak Nijhawan[1,2,4]†



Anticancer sulfonamides target splicing by inducing RBM39 degradation via recruitment to DCAF15

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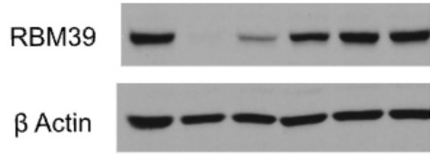
	HCT116 parental					
indisulam	-	+	+	+	+	+
MLN4924 (nM)	-	-	10	30	100	300



CANCER THERAPY

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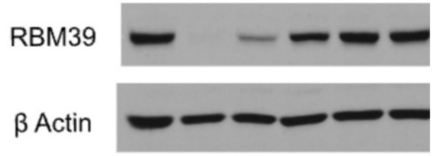
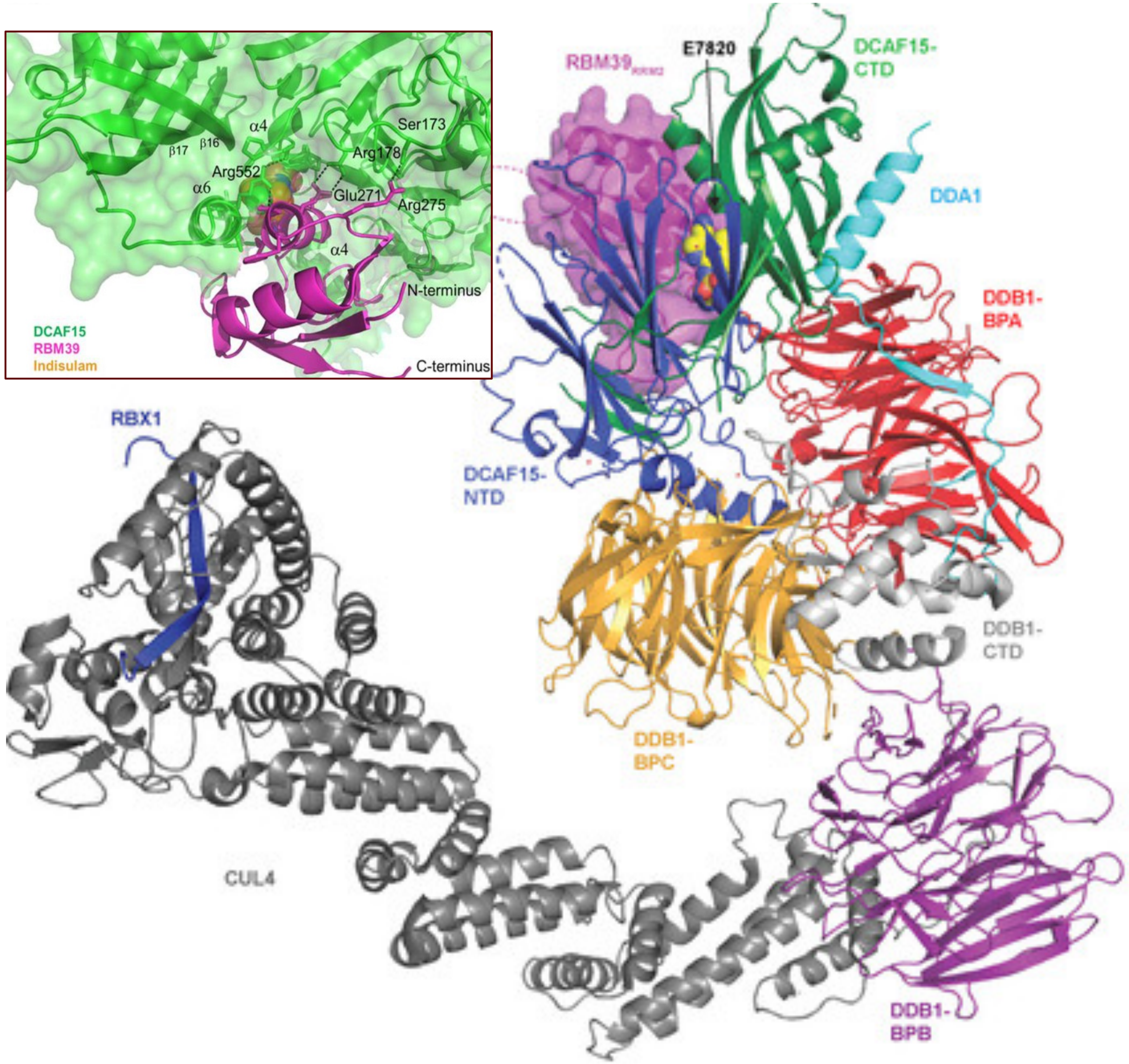


RBM39-3xFLAG IP peptide counts

indisulam	-	+
RBM39	267	259
CUL4A	1	11
CUL4B	0	16
DDB1	5	52
DDA1	0	4
DCAF15	0	11

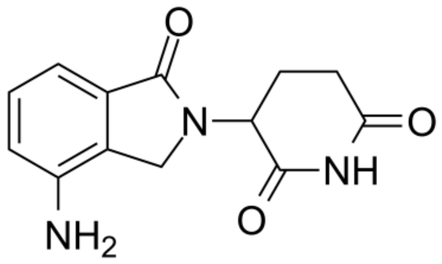
INDISULAM

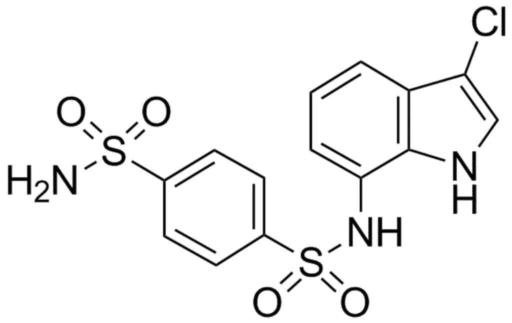
(ANOTHER  !!!)

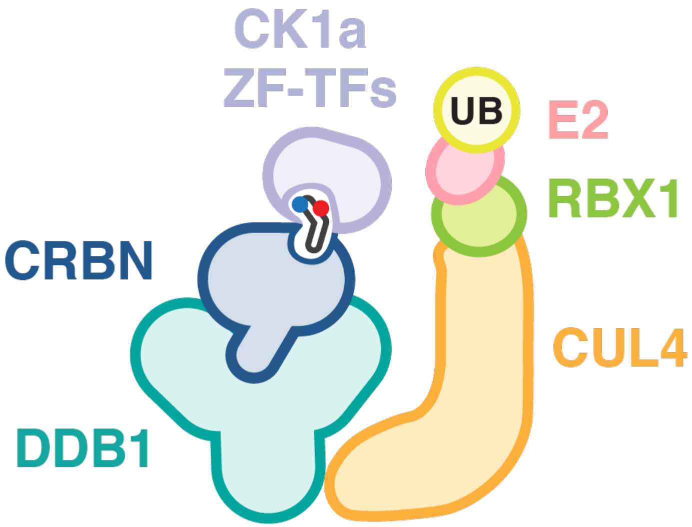


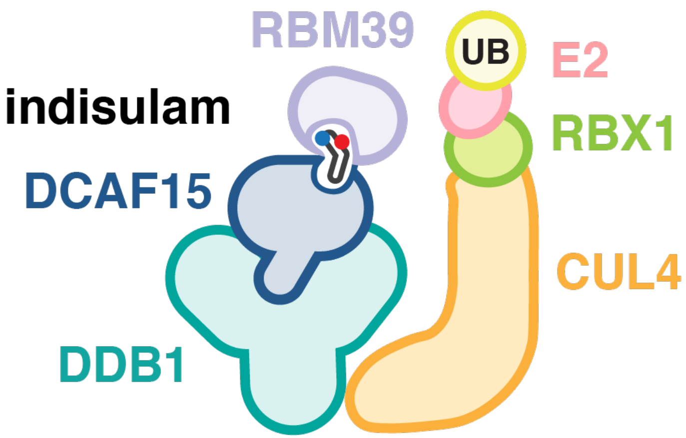
TWO MOLECULAR GLUE DEGRADERS

[same principle]

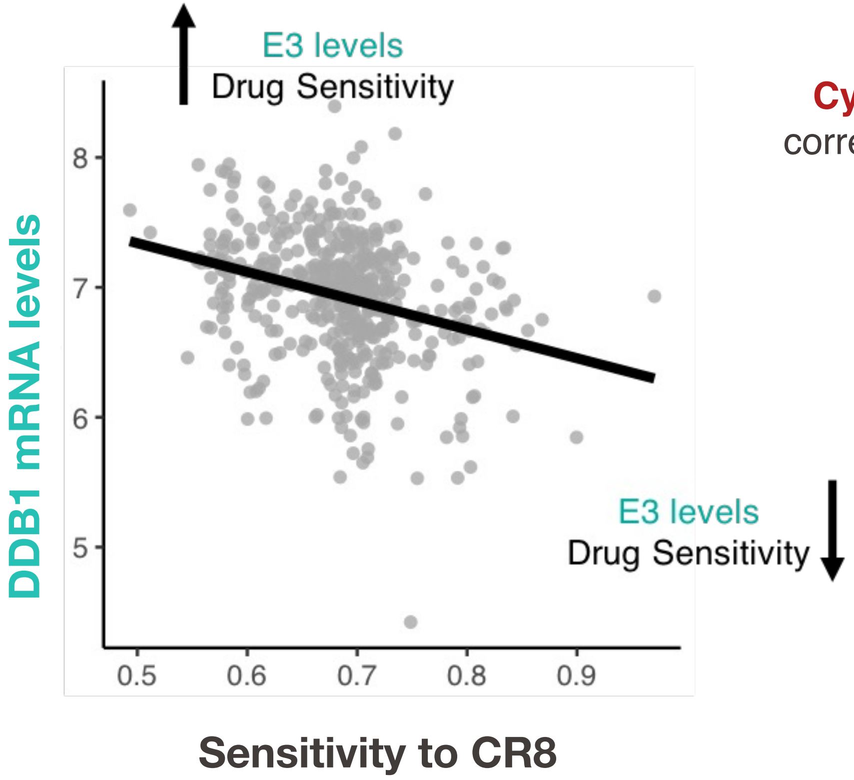




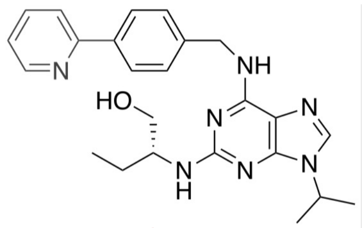




BIOINFORMATIC SCREEN TO IDENTIFY NOVEL DEGRADERS

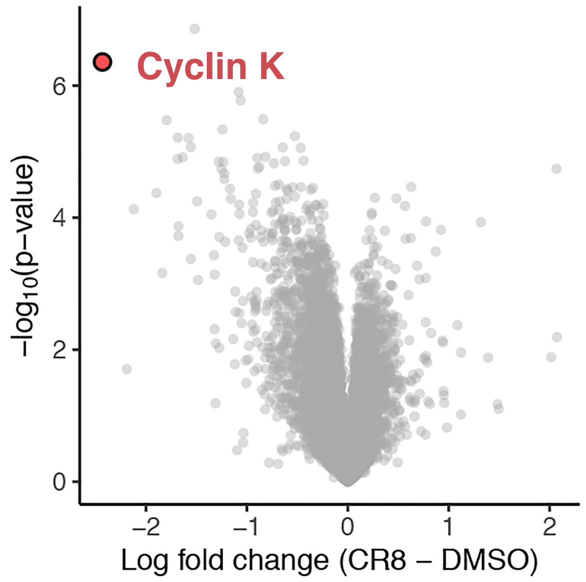


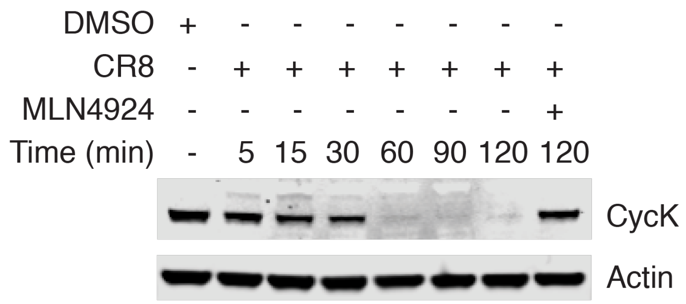
Cytotoxicity of a kinase inhibitor CR8 correlates with **expression levels of DDB1**

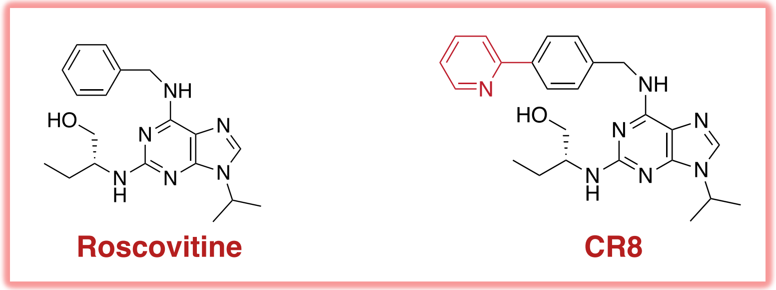


CR8

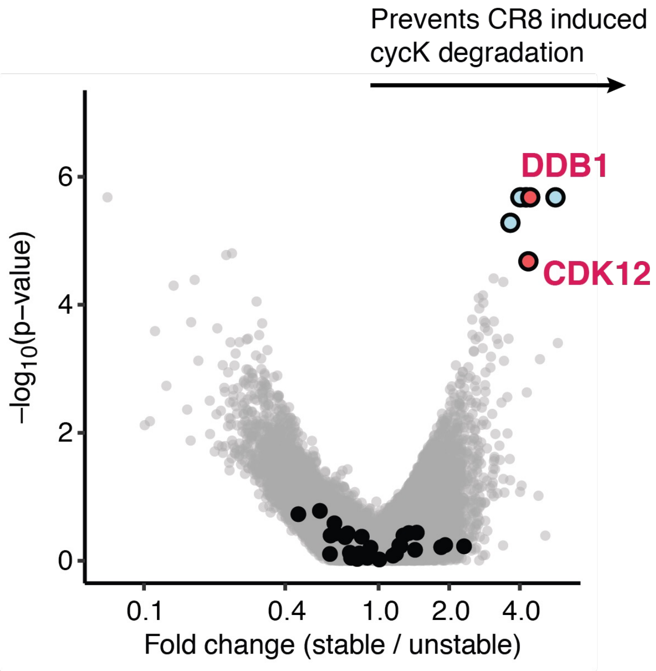
CR8 PROMOTES PROTEASOMAL DEGRADATION OF CYCLIN K

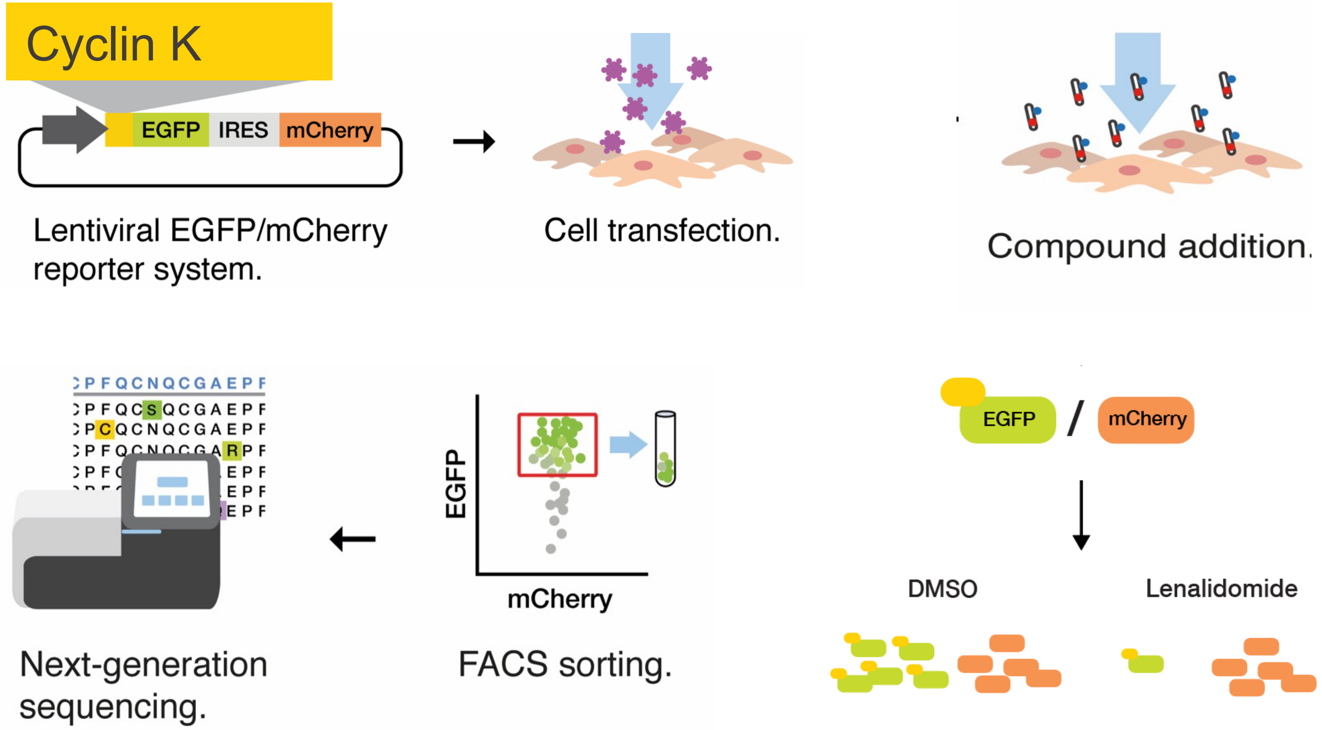






CYCLIN K DEGRADATION: WHO IS REQUIRED?





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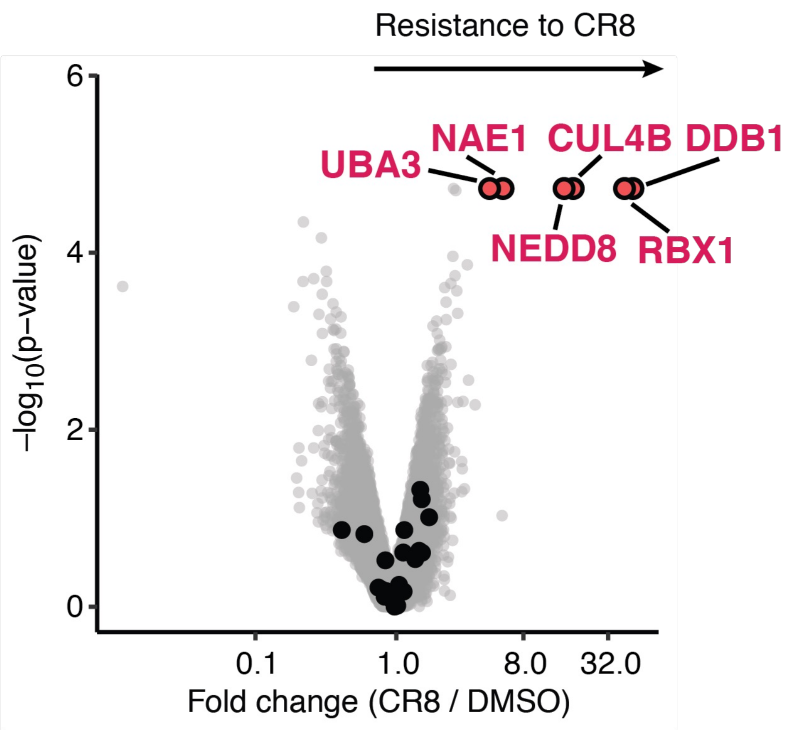
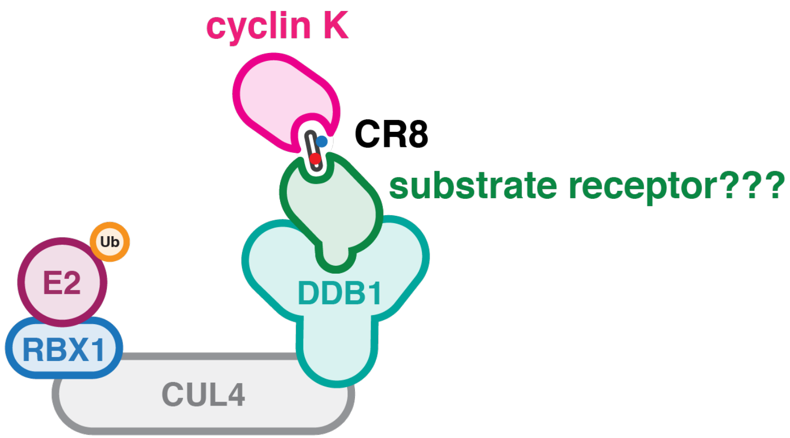
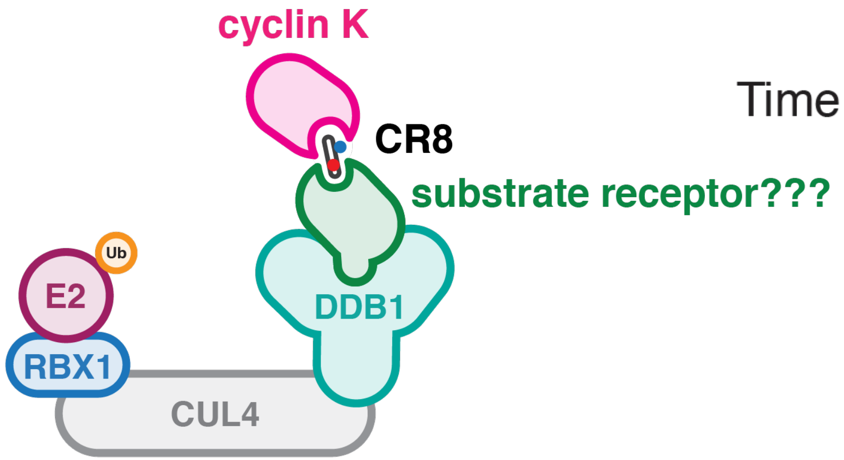
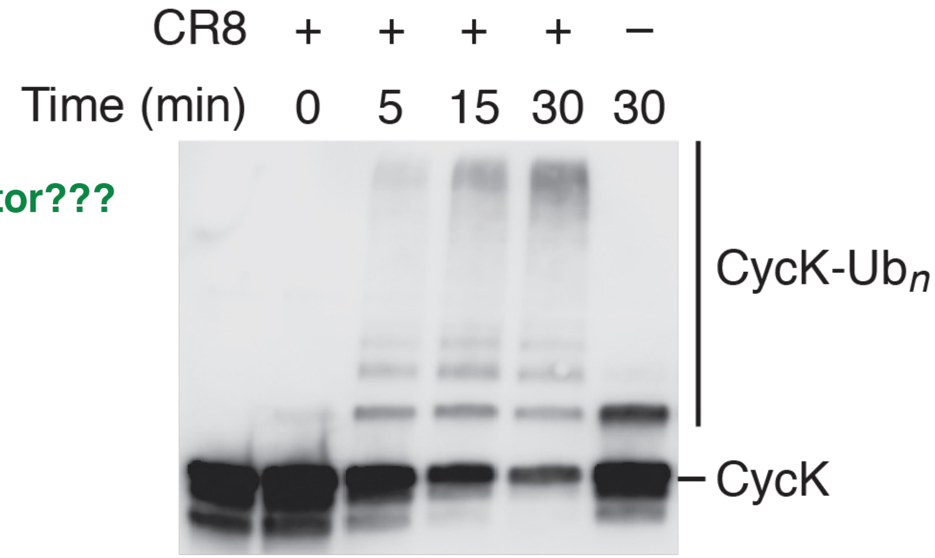
CYCLIN K DEGRADATION REQUIRES CDK12 + CUL4, DDB1



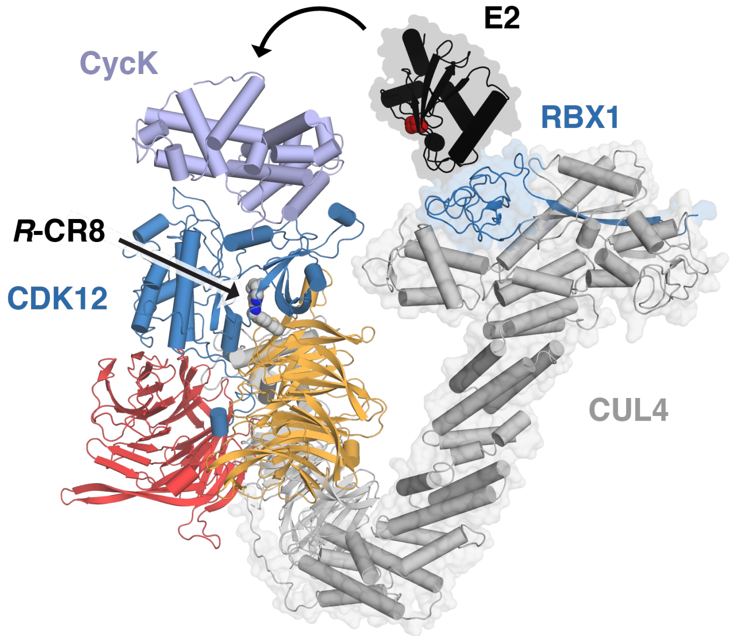


CYCLIN K DEGRADATION REQUIRES NO SUBSTRATE RECEPTOR !?

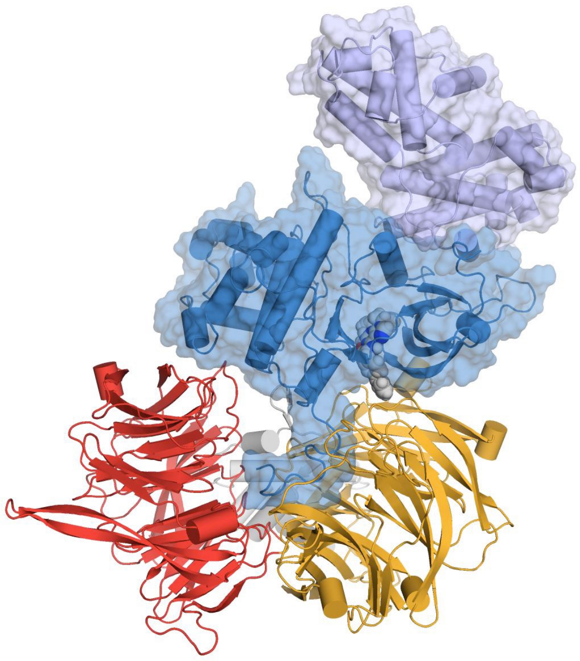


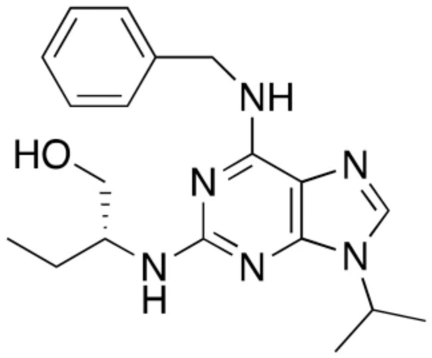


THE KINASE IS THE RECEPTOR!!!!?

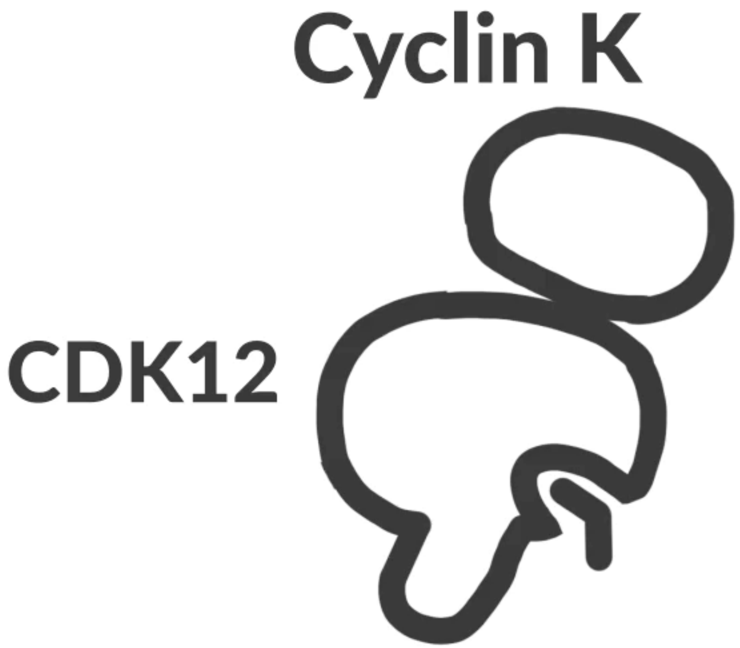


CUL4-RBX1-DDB1 bound to CR8-CDK12-cycK



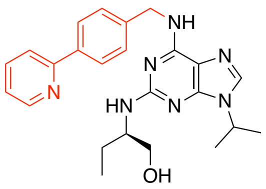


Roscovitine

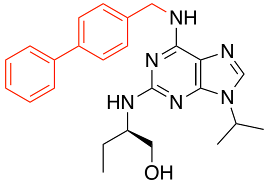



GLUE

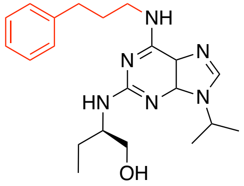
MANY WAYS TO GLUE



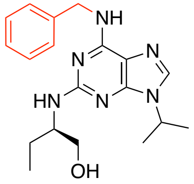
CR8



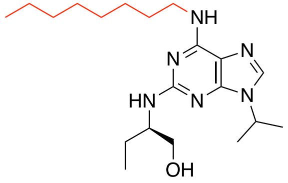
DS16



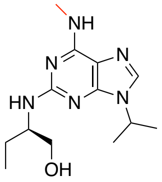
DS11



Roscovitine

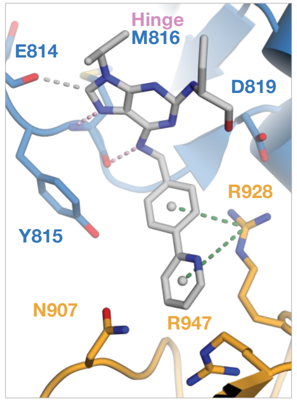


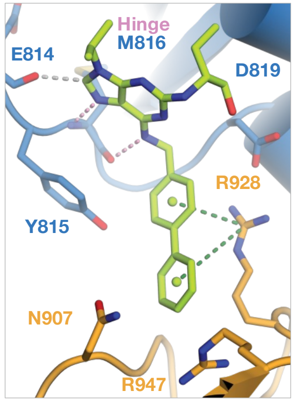
DS06

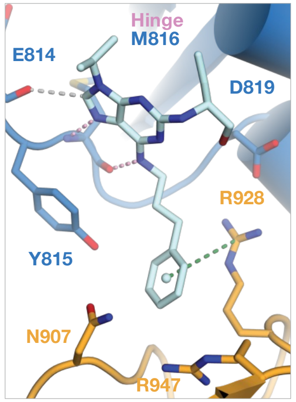


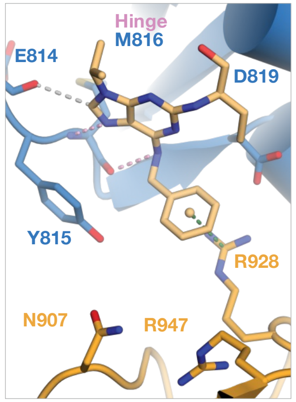
DS23

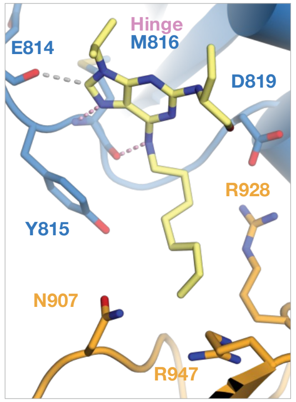
CDK12











no crystallizable complex

DDB1

	CR8	DS16	DS11	Roscovitine	DS06	DS23
TR-FRET EC $_{50}$ [nM]	16 ± 1	17 ± 1	57 ± 3	703 ± 144	1162 ± 115	n.d.

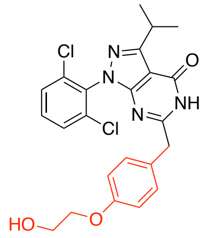
EPFL

MANY MORE WAYS TO GLUE

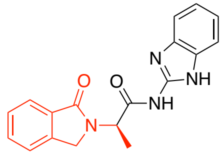
WITH MUCH DIFFERENT CHEMISTRY

polar gluing moiety

much smaller compound

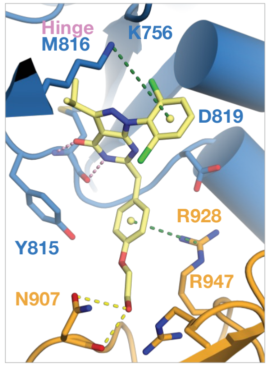


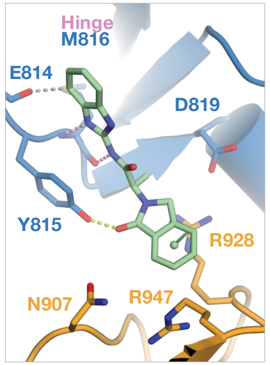
21195



919278

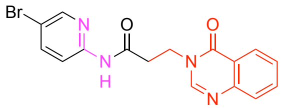
CDK12



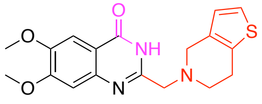


DDB1

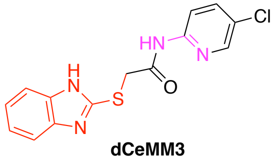
TR-FRET EC_{50} [nM]	12 ± 1	38 ± 2



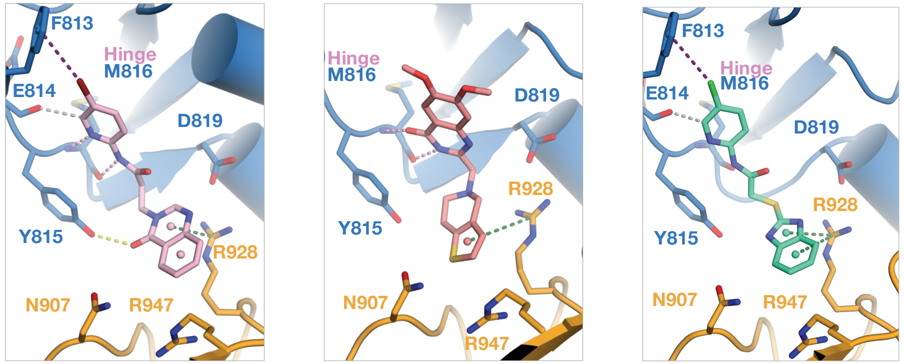
Z7



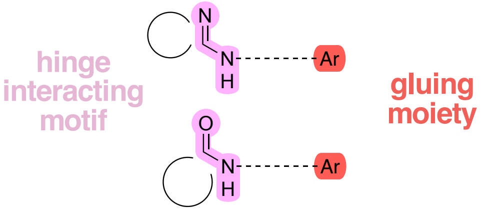
Z12

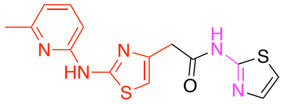


dCeMM3

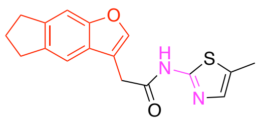


and many more with the same **fingerprint**:





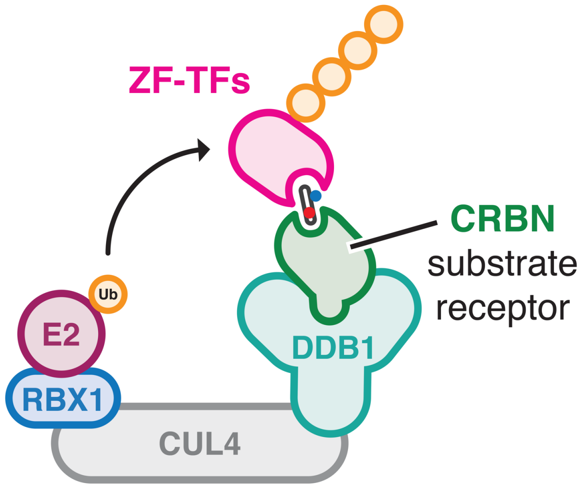
HQ461



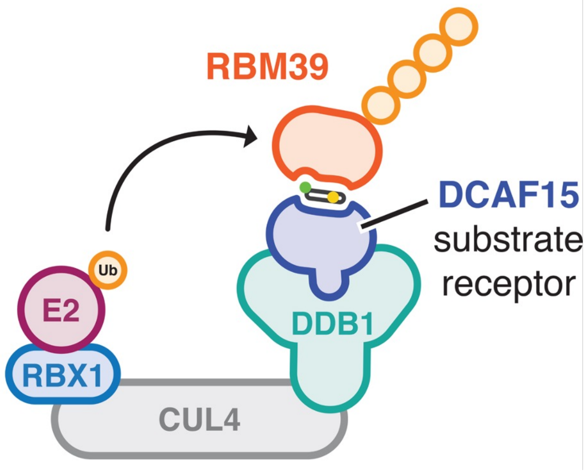
NCT02

HQ461: Lv et al., eLife (2020); **NCT02**: Dieter et al., Cell Reports (2021); **dCeMM3**: Mayor-Ruiz et al., Nature Chem Biol (2020); **Z7 and Z12**: Winter lab (*unpublished*)

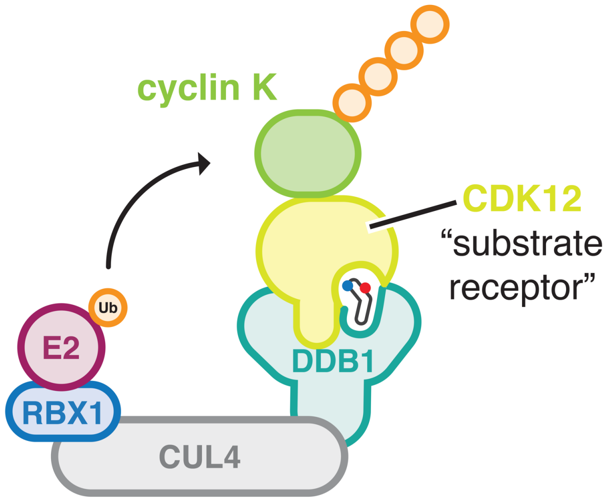
GLUE DEGRADERS (2020 EDITION!)



Ito *et al.* (2010), Lu *et al.* (2014), Kronke *et al.* (2014), Gandhi *et al.* (2014), Petzold *et al.* (2016), Sievers *et al.* (2018)



Owa *et al.* (1999), Han *et al.* (2017), Uehara *et al.* (2017), Du *et al.* (2019), Bussiere *et al.* (2019), Faust *et al.* (2020)

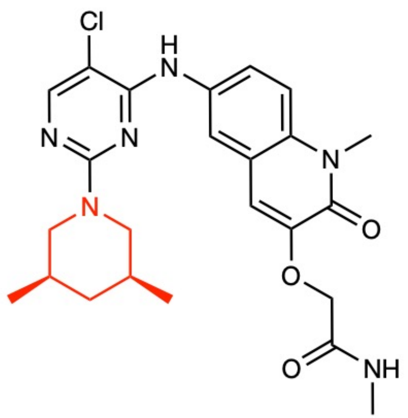


Slabicki, Kozicka, Petzold *et al.*, 2020

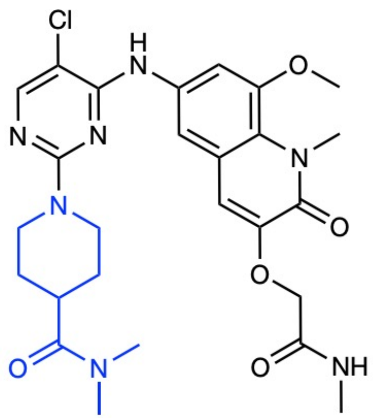
POLYMERISATION GLUES

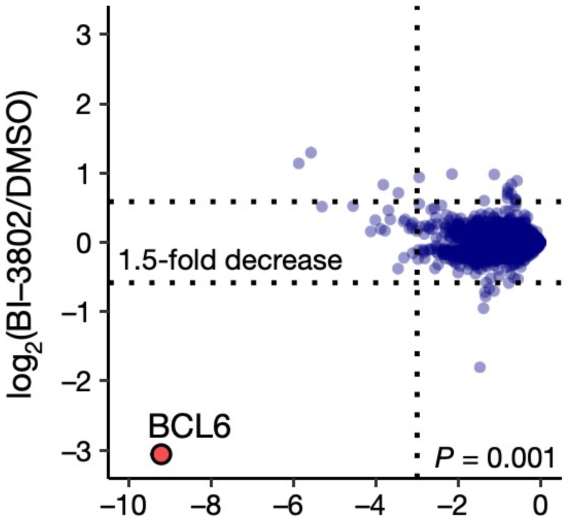
BCL6

BI-3802



BI-3812



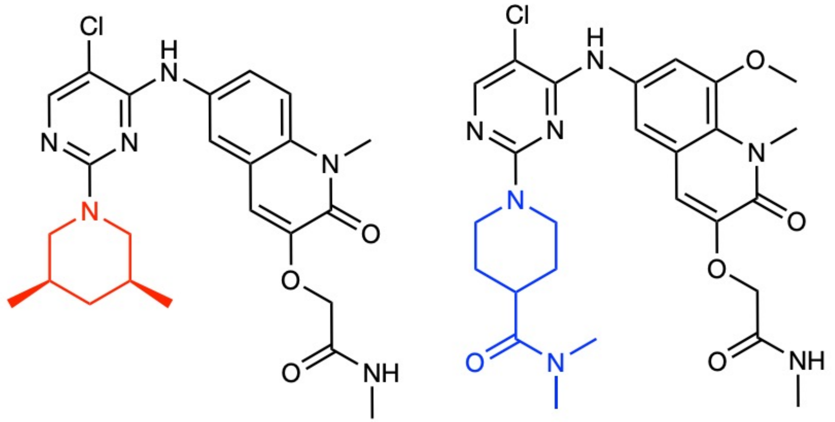


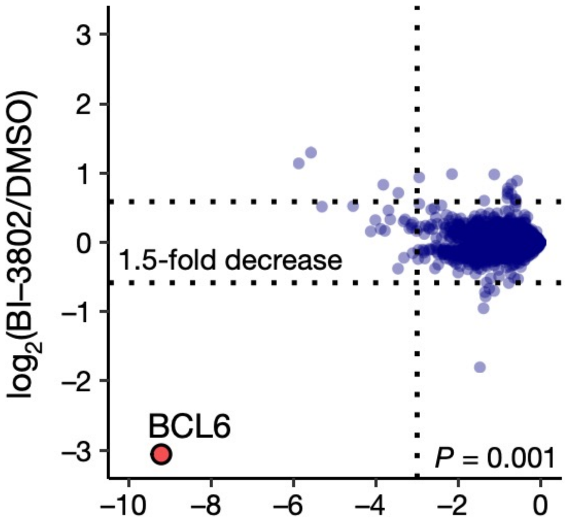
Słabicki, Yoon, Koeppel et al. (2020)

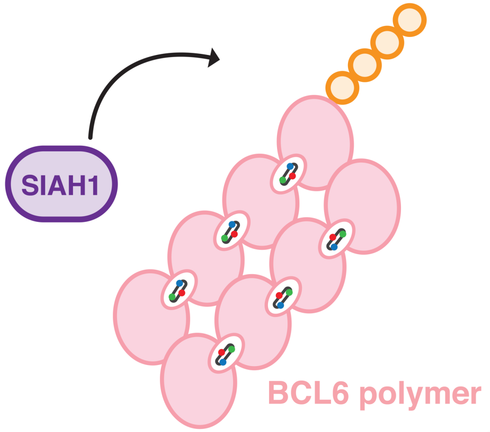
POLYMERISATION GLUES

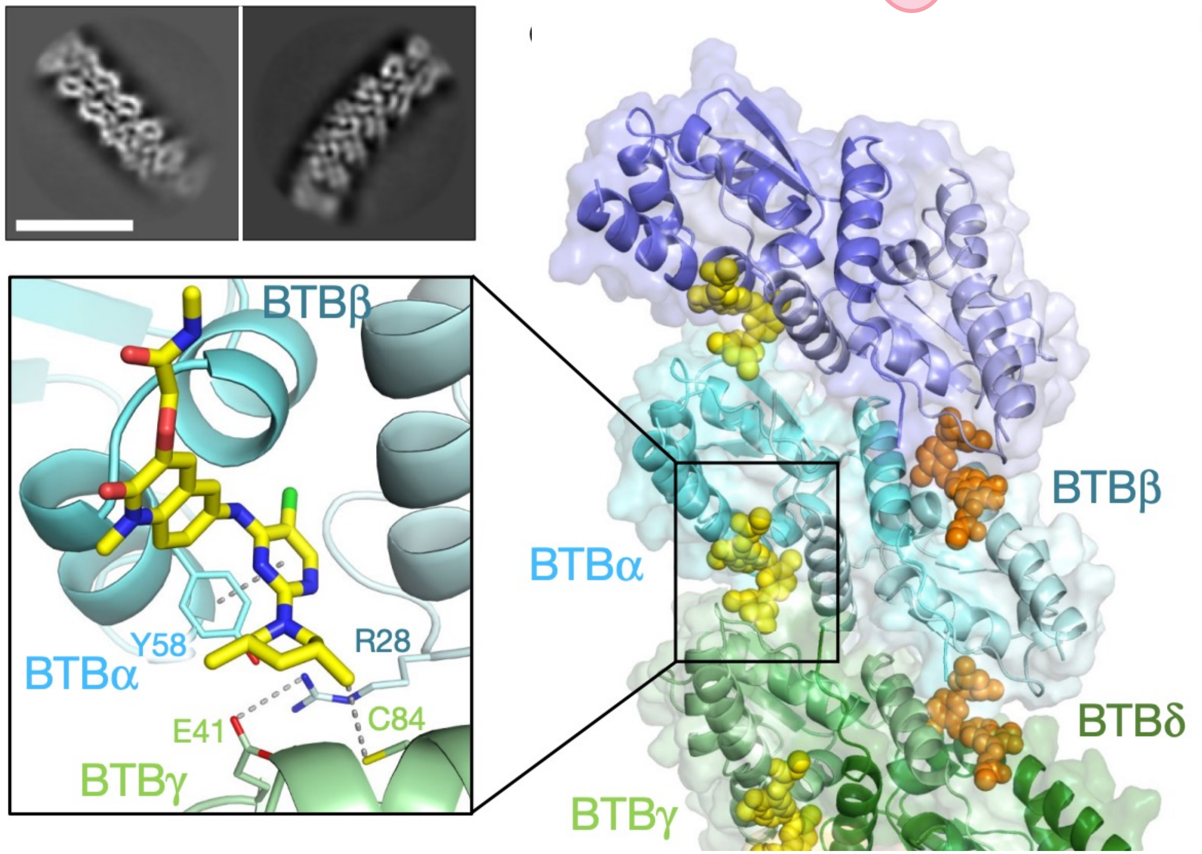
BCL6

BI-3802 BI-3812





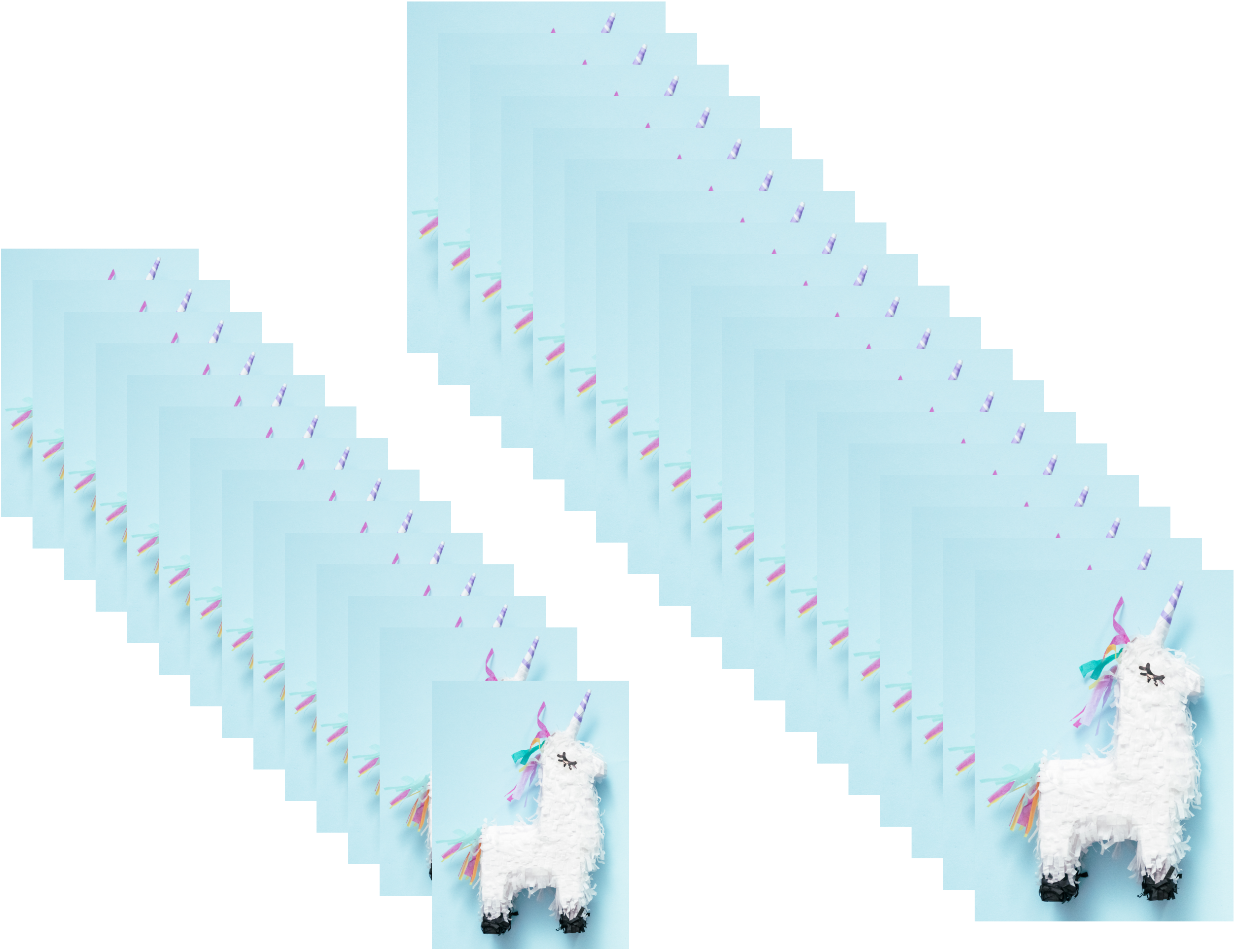




Słabicki, Yoon, Koeppel et al. (2020)

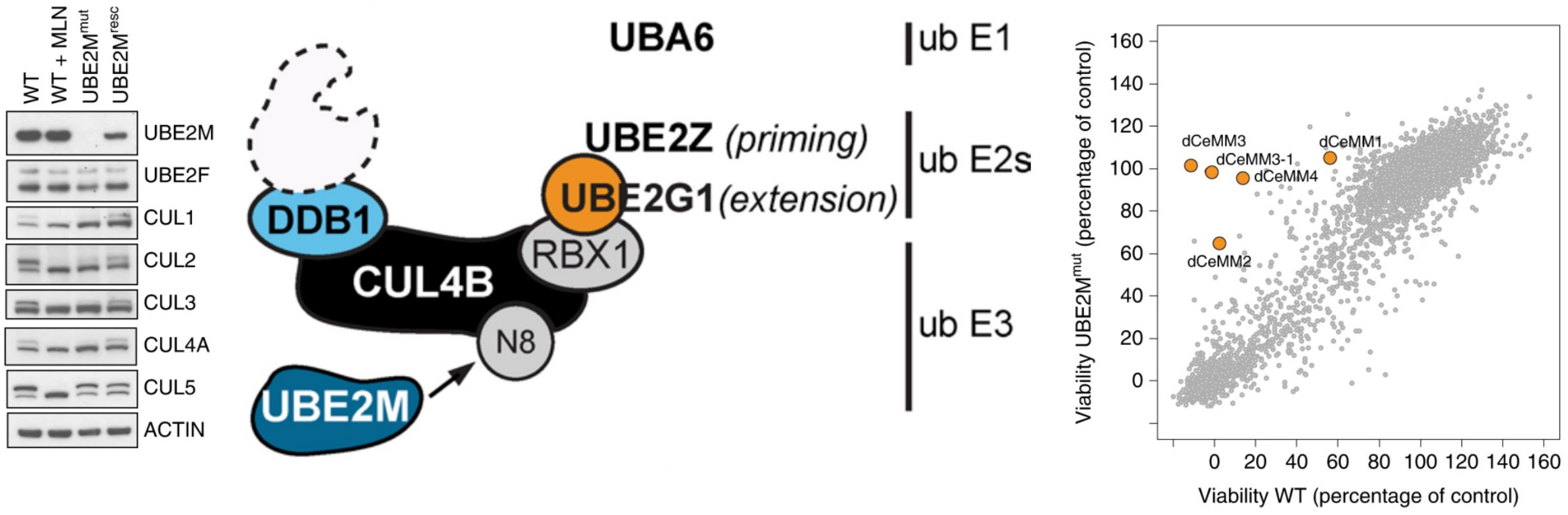
Nicolas Thomä

MANY MORE UNICORNS BUT HOW TO FIND THEM?



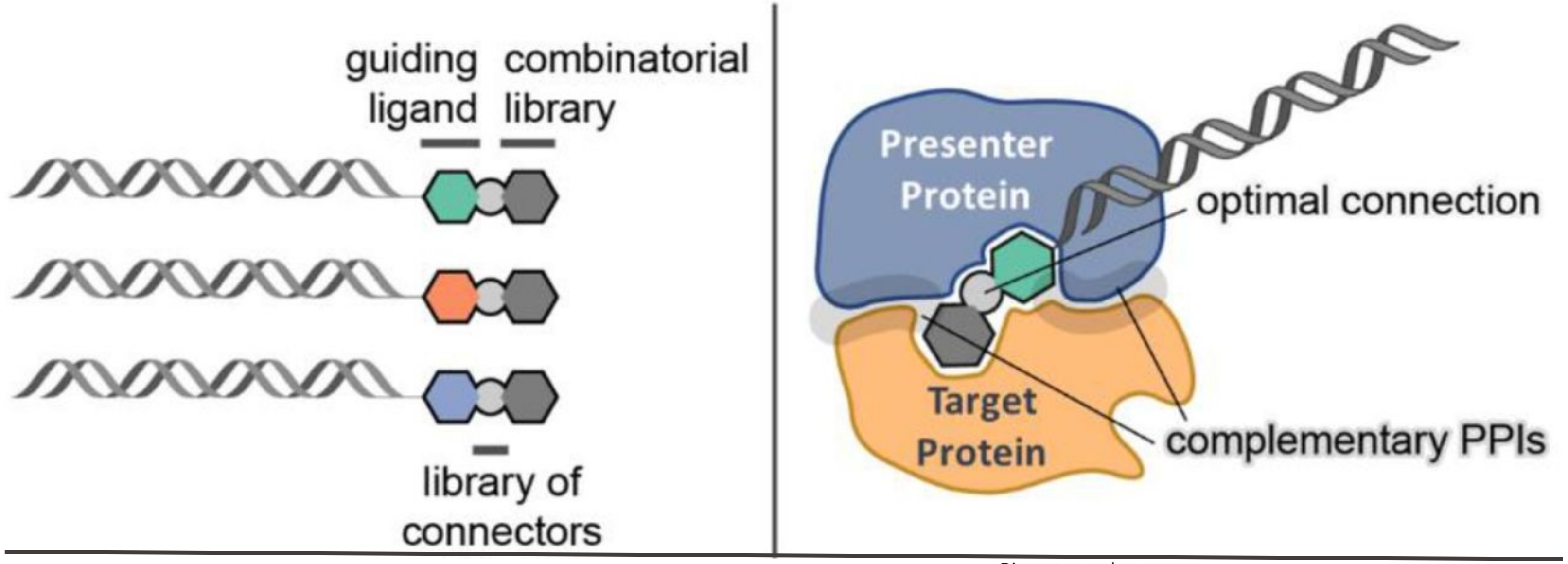
SCREEN FOR CULLIN-BASED MOLECULAR GLUES

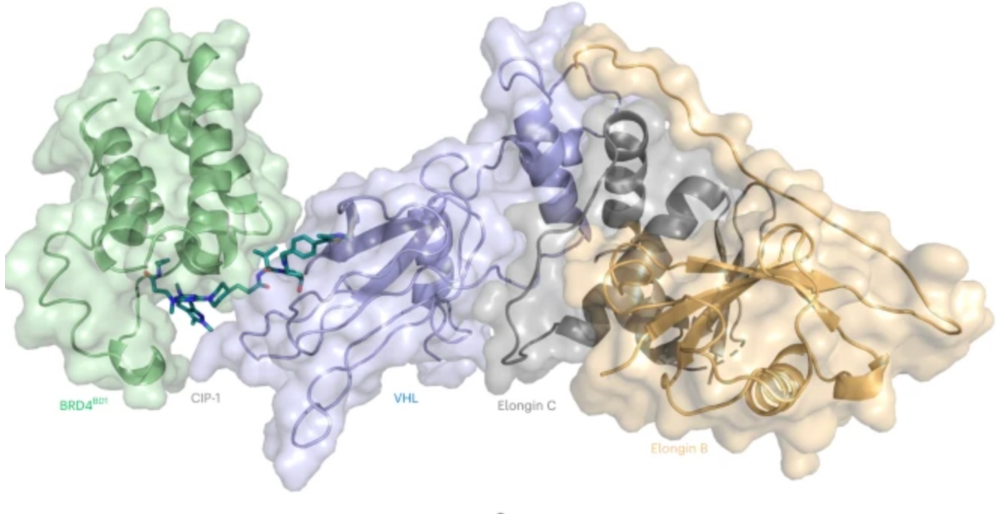
BY NEDDYLATION INHIBITION

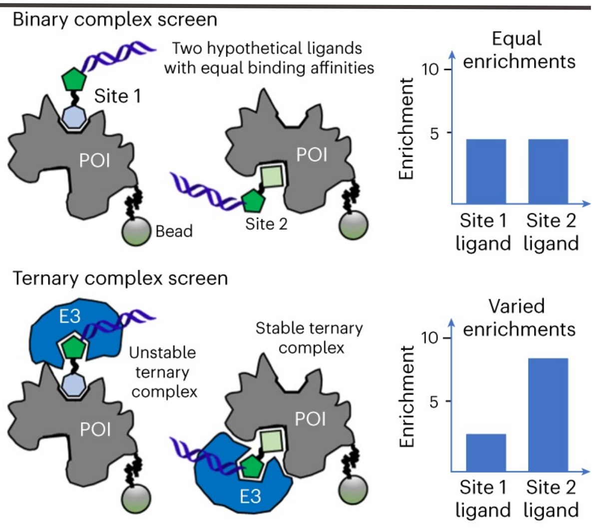


Major-Ruiz *et al.* (2020)

DEL SCREEN FOR GLUES



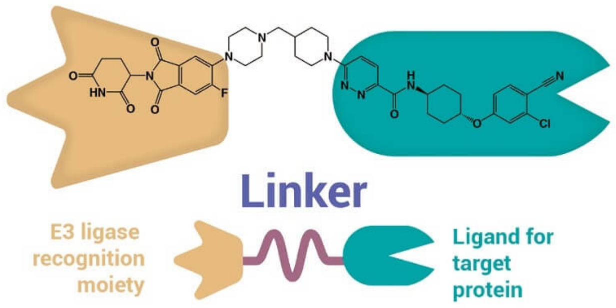


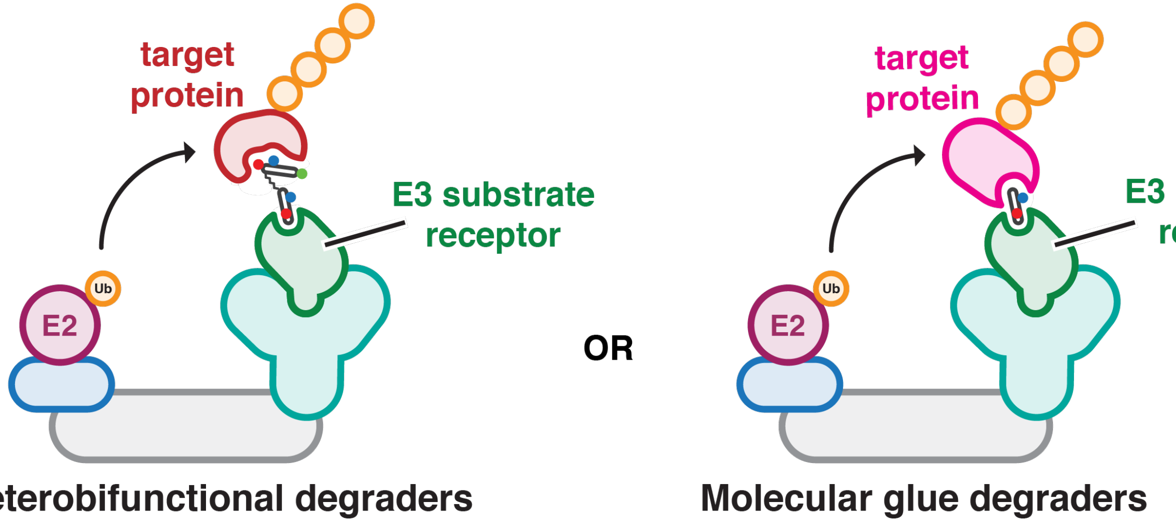


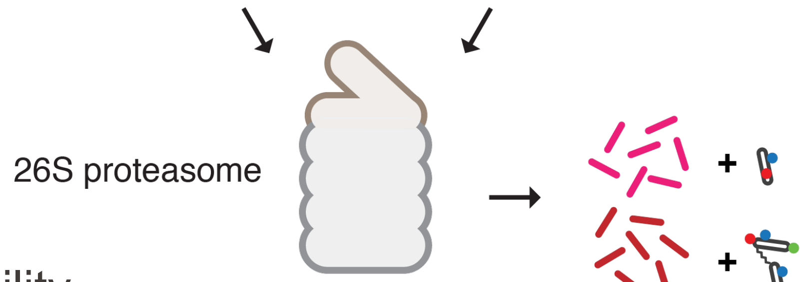
Mason *et al.* (2023)

PROTACs:

THE TWO EXTREMES OF THE TARGETED PROTEIN DEGRADATION CONTINUUM



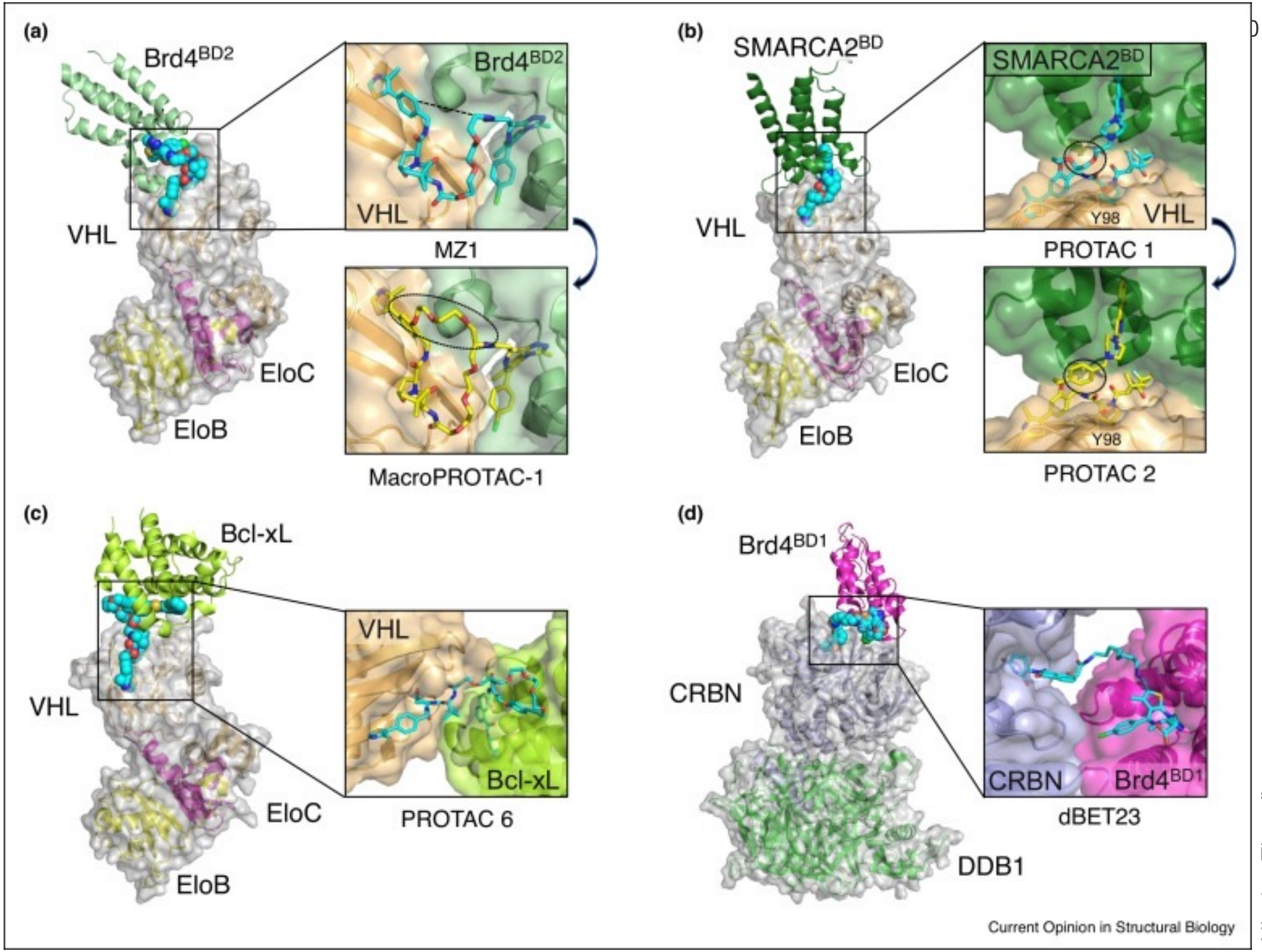




Rational design
Dependent on ligand availability
High(er) M_W

Serendipitous discovery
Less reliant on ligands/pockets
Small(er) and intrinsically more drug-like

PROTEIN-PROTEIN INTERACTION IN PROTACS

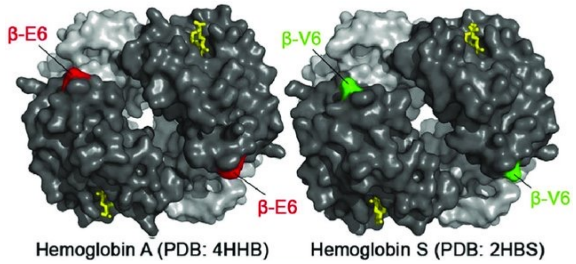


Ramachandran *et al.* (2020)

HOW CAN THIS BE … ?

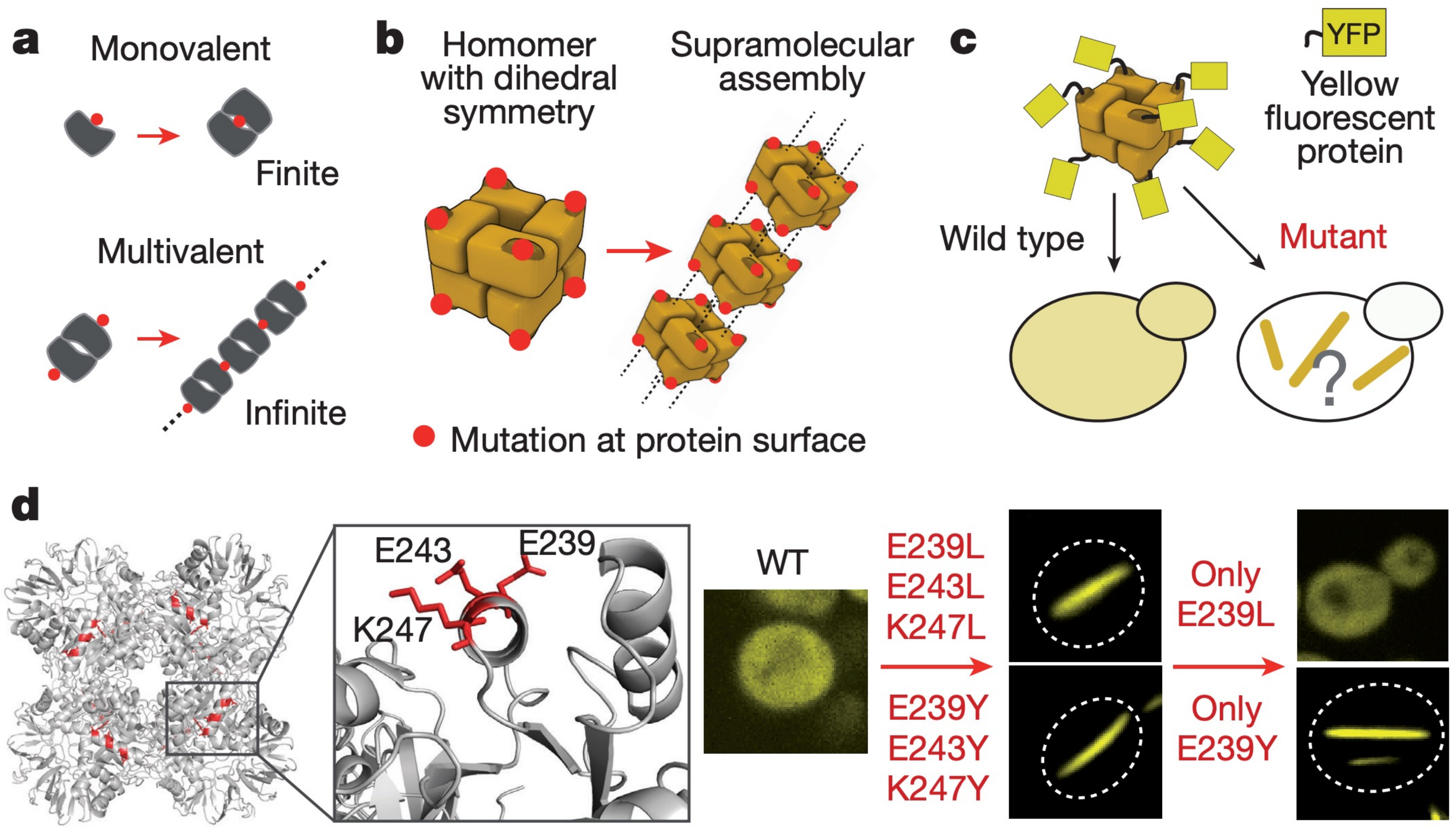
Proteins evolve on the edge of supramolecular self-assembly

Hector Garcia-Seisdedos[1], Charly Empereur-Mot[1]†, Nadav Elad[2] & Emmanuel D. Levy[1]

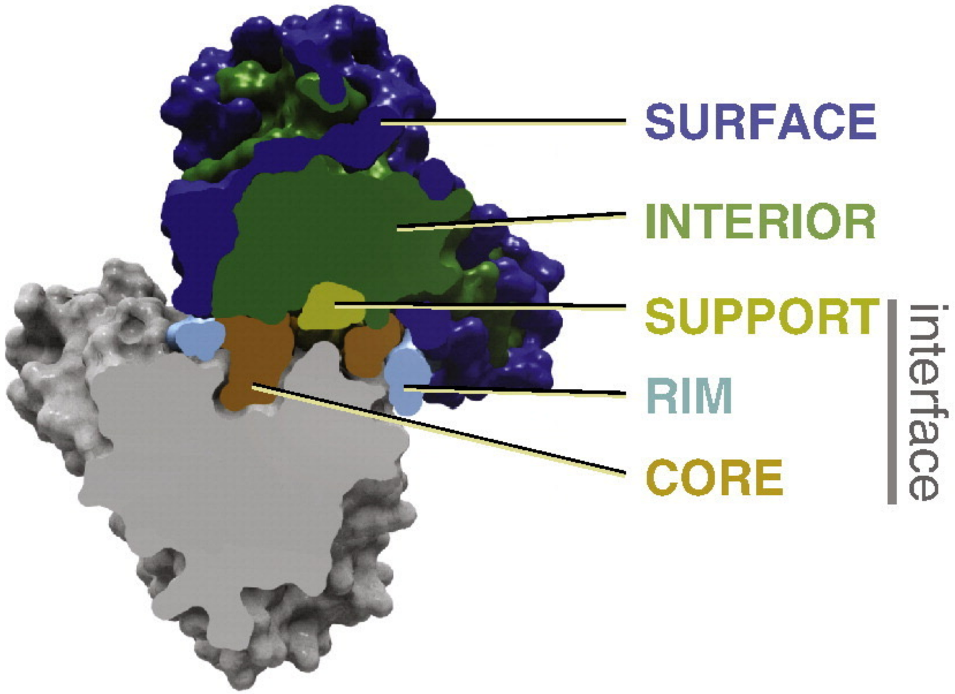


A single glutamate → valine change causes haemoglobin to form insoluble fibers

Adapted from Clark *et al.* (2012)



Cross-section of a protein complex



Amino acid composition analysis

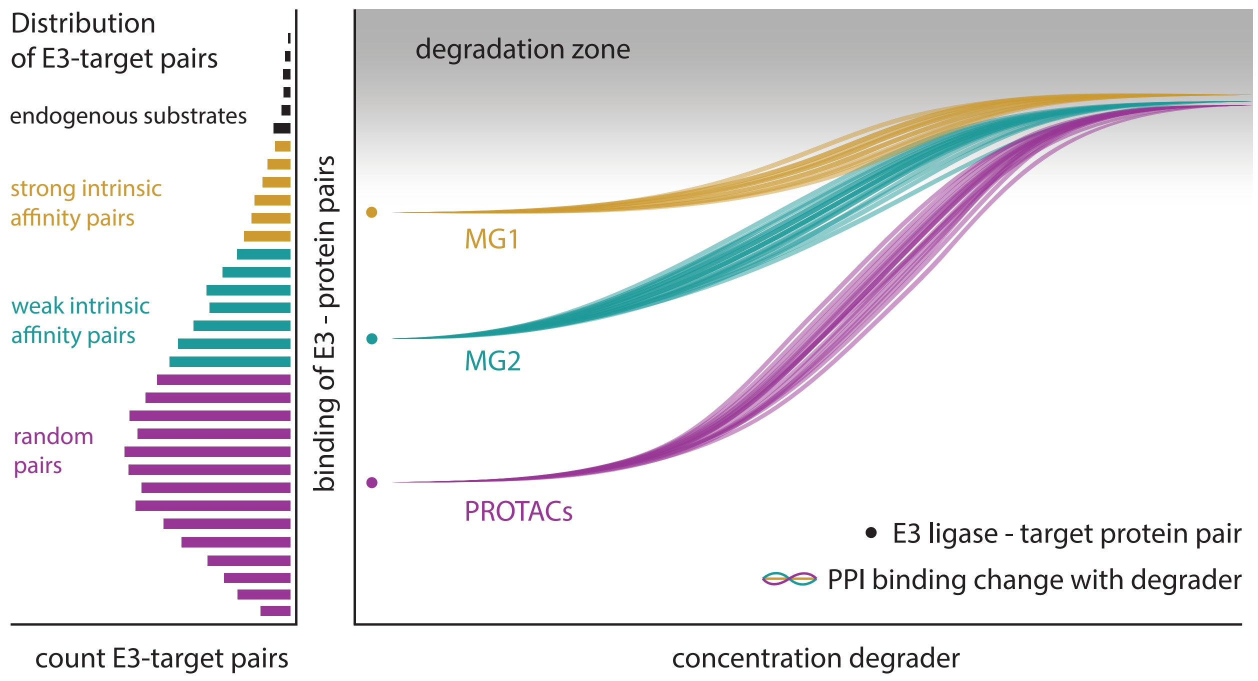
SURFACE ~ RIM

INTERIOR ~ SUPPORT

SURFACE ≁ CORE

Only 2 substitutions can shift an average surface patch of ten amino acids into an equivalently sized interface core

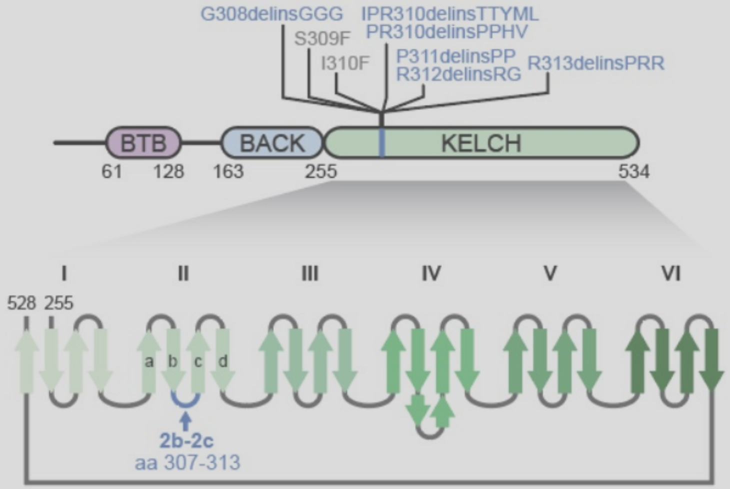
THERMO-DYNAMIC MODEL

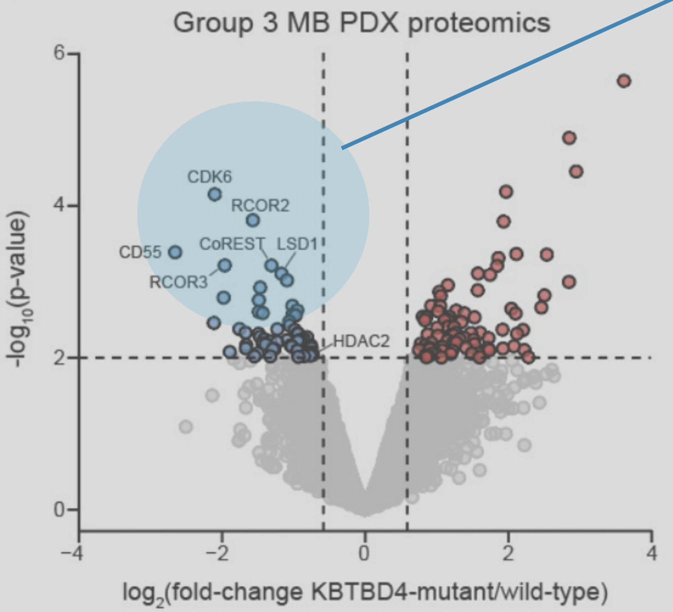


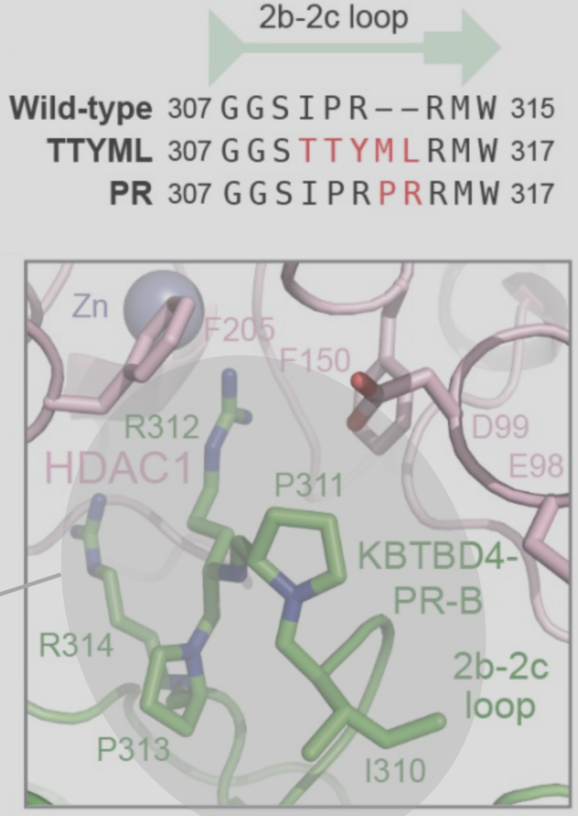
KBTBD4:

GAIN-OF-FUNCTION BY CANCER MUTATIONS

CANCER MUTATIONS TRIGGER COREST DEGRADATION





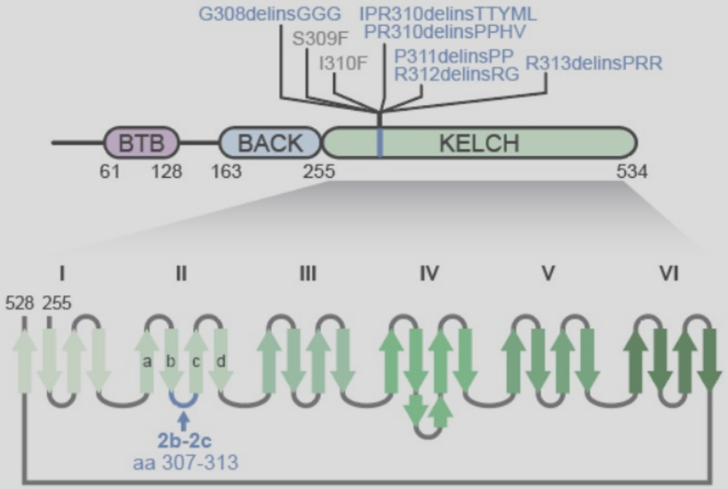


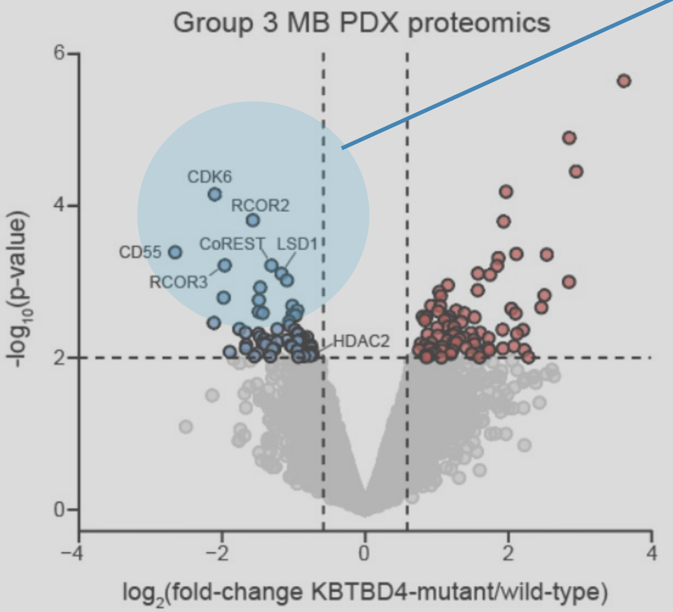
THE INSERTION MUTATION ON THE RECEPTOR IS SUFFICIENT TO BIND COREST SO TIGHT THAT IT IS DEGRADED

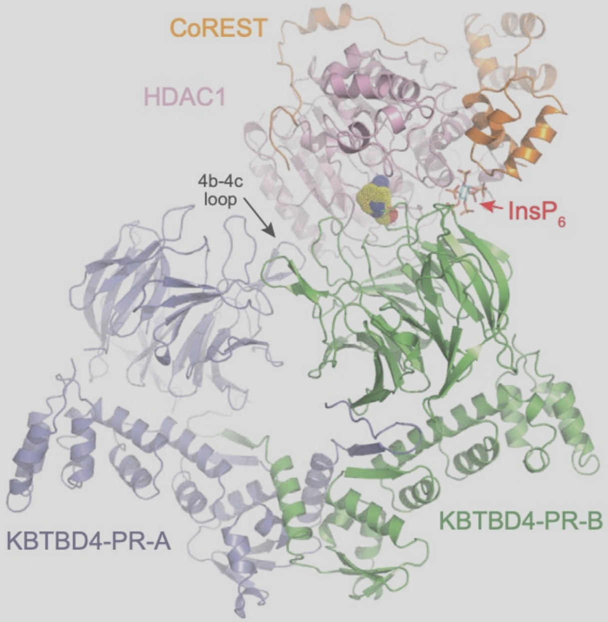
KBTBD4:

GAIN-OF-FUNCTION BY CANCER MUTATIONS

CANCER MUTATIONS TRIGGER COREST DEGRADATION





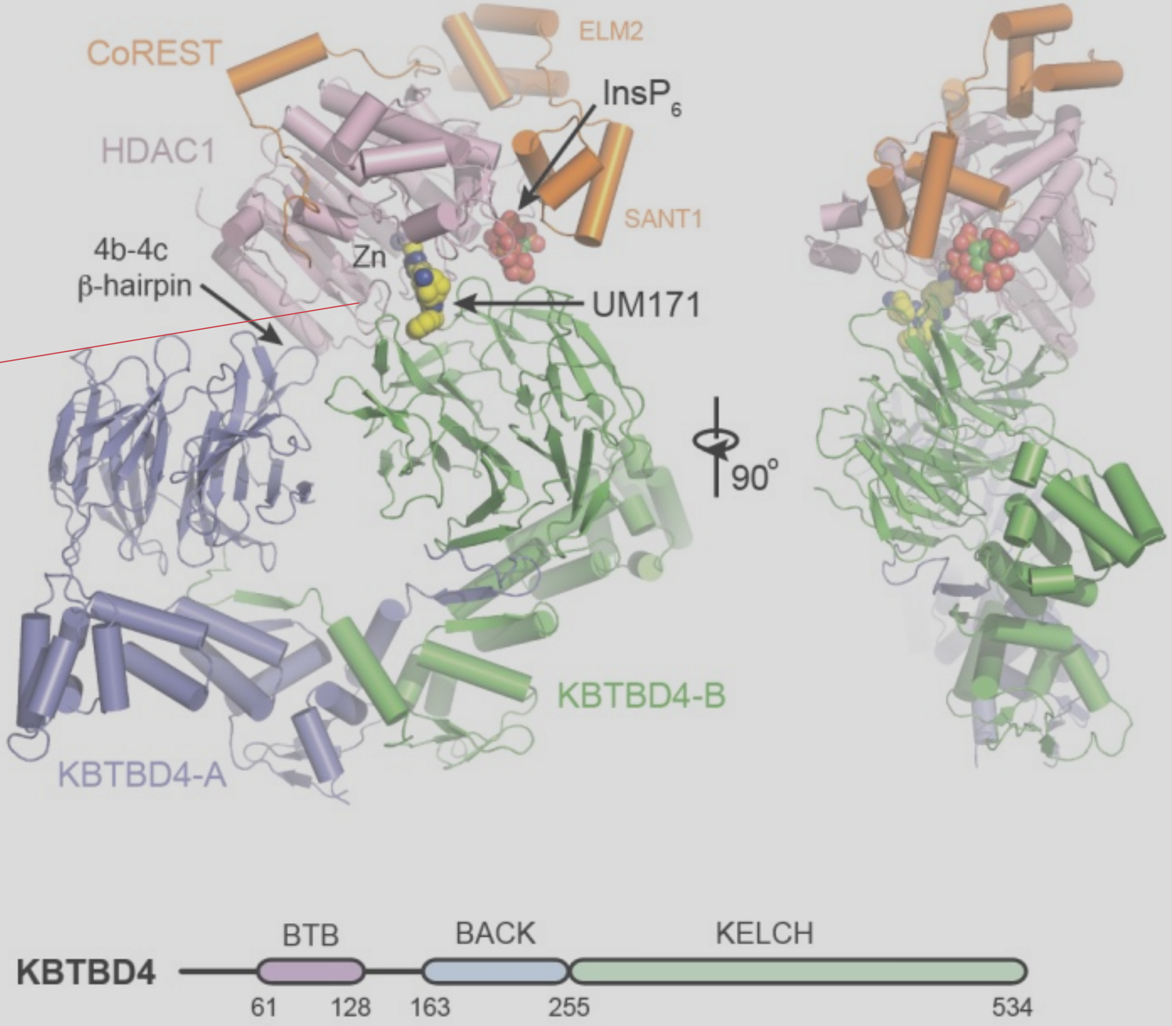


Xie, Zhang, Yeo, Lee *et al.*, bioRxiv 2024

KBTBD4:

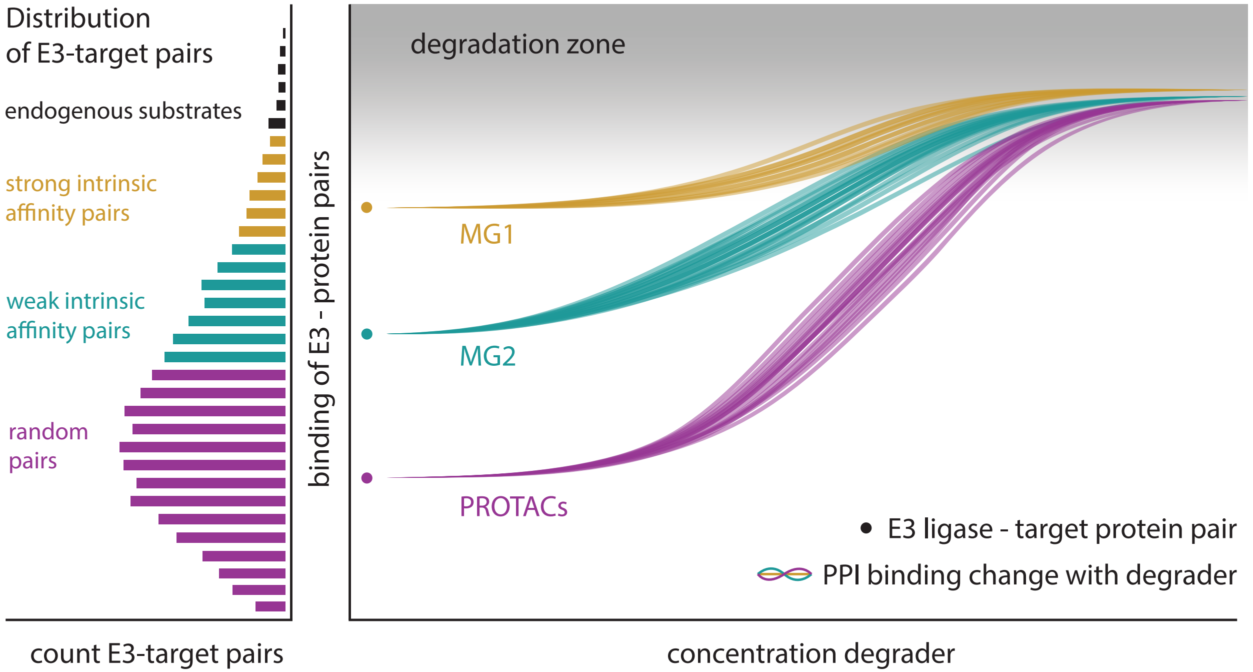
GAIN-OF-FUNCTION BY CANCER MUTATIONS

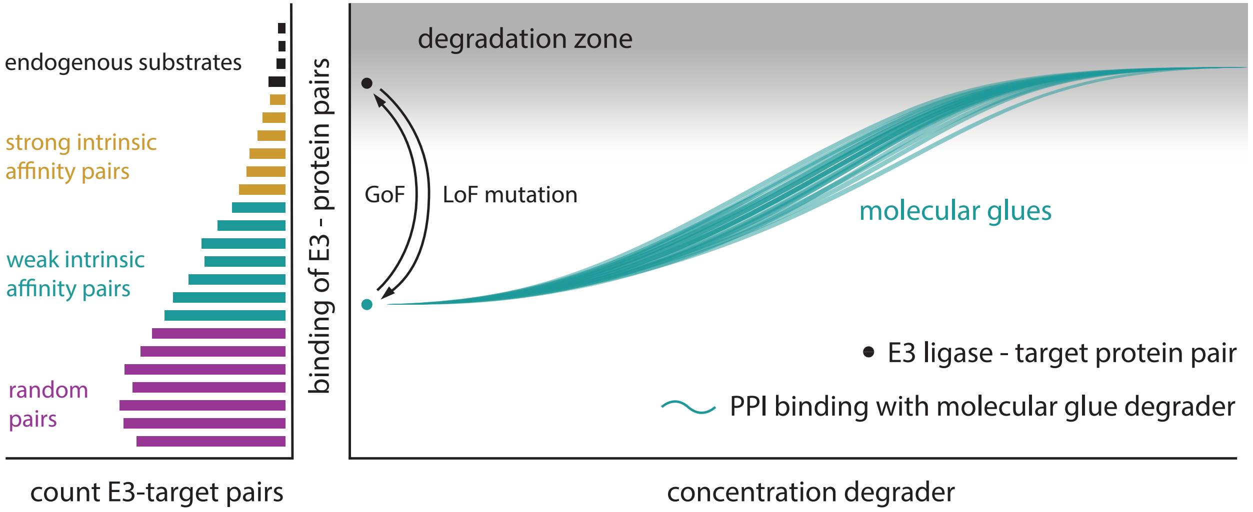
UM171 MOLECULAR GLUE DEGRADER FOR COREST



Xie, Zhang, Yeo, Lee *et al.*, bioRxiv 2024

THERMO-DYNAMIC MODEL



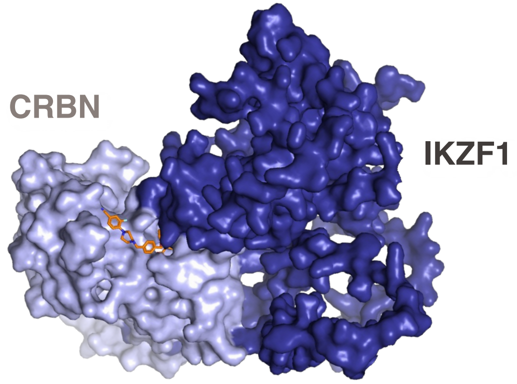


Nicolas Thomä

Bonus Round …. Endogenous “Glues”

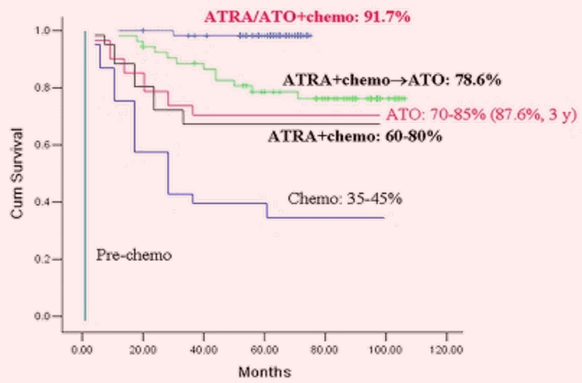
Drugging Transcription Factors: the success stories …

IKZF1 and IKZF3



Lenalidomide: Multiple **M**yeloma

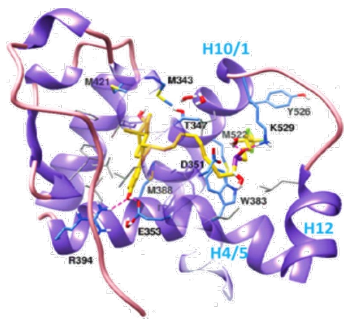
PML-RARA



All-(trans)-retinoic acid (ATRA) &

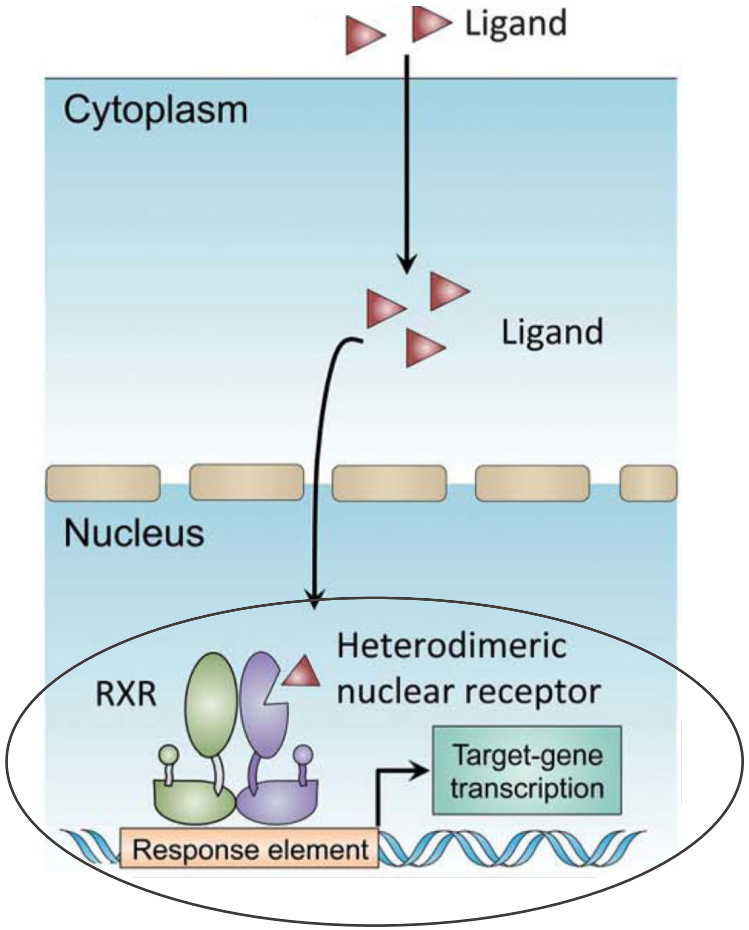
ATO: Acute **P**ro**m**yelocytic **L**eukemia (APML)

ERa



Fulvestrant: Breast Cancer

Nuclear Hormone Receptors (NR)



Adapted from Glass *et al.*, (2013) *Nat Rev Immunol*

- Transcription factors that directly bind DNA
- Humans have ~48 genes that encode NRs

Retinoic acid Receptor

Estrogen Receptor

Androgen Receptor

Progesterone Receptor

Glucoccorticoid Receptor

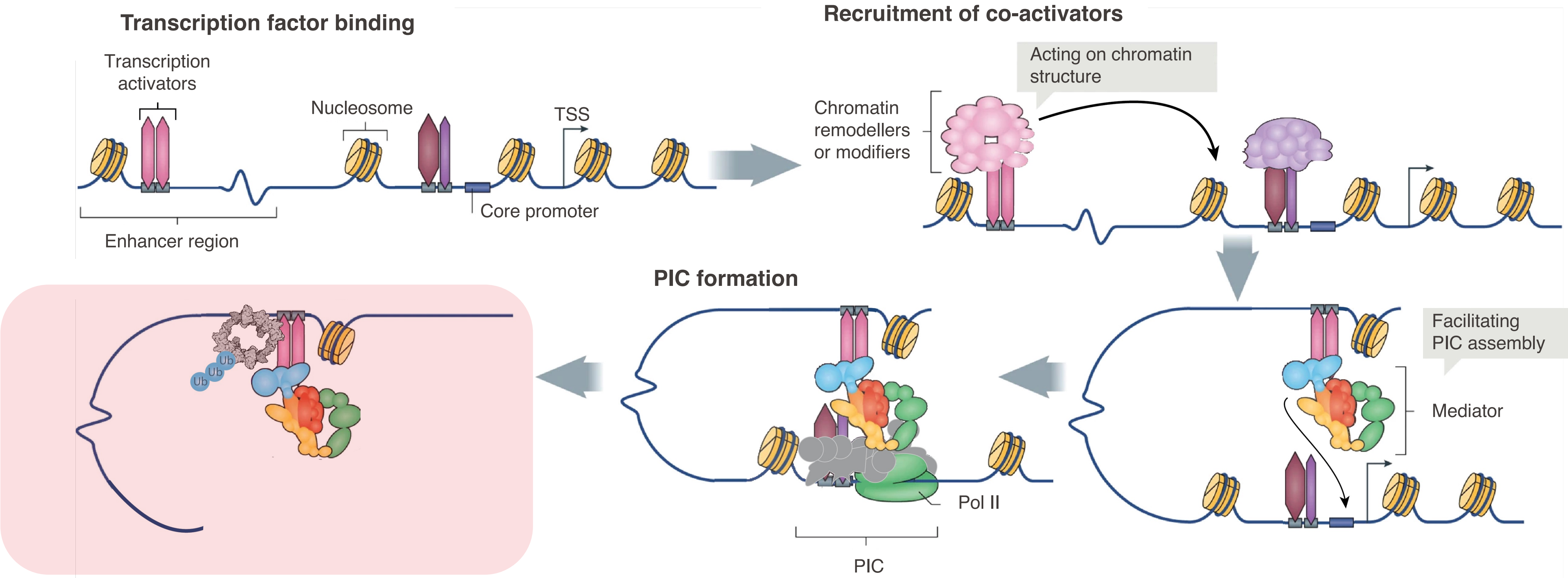
Thyroid hormone

Receptor

Vitamin D Receptor

Liver X Receptor

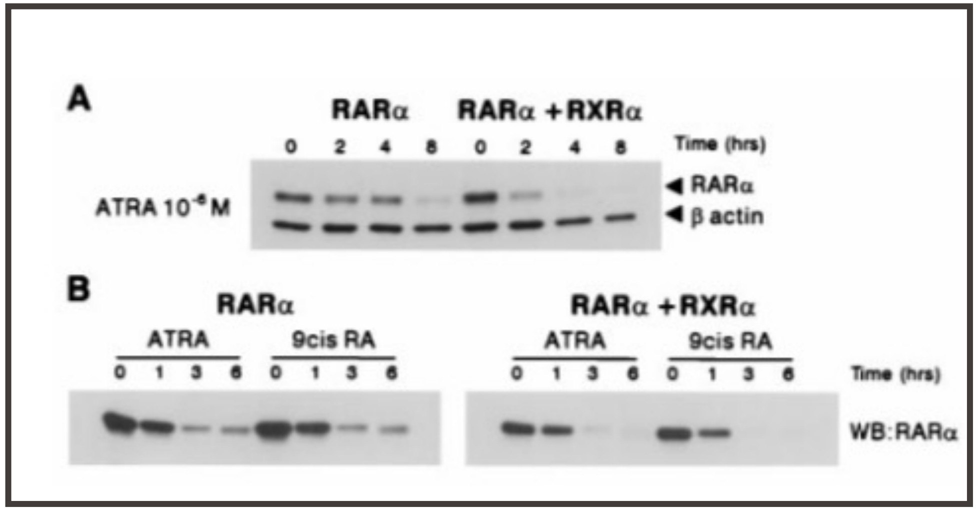
Nuclear hormone receptors:
Deposition, Transcription, Degradation



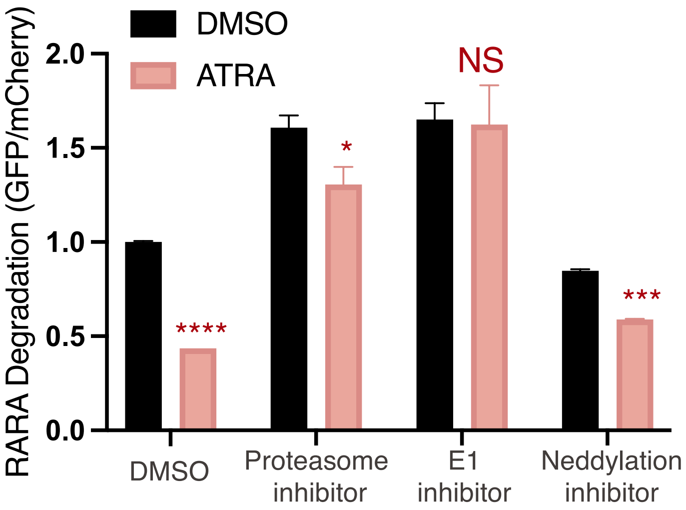
Soutourina (2018) *Nature Review Mol Cell Biol*

Agonist ligands induce Nuclear Hormone Receptor degradation

All-*trans* retinoic acid cures
Acute Promyelocytic Leukemia
via degradation of the oncoprotein
fusion PML-RARA



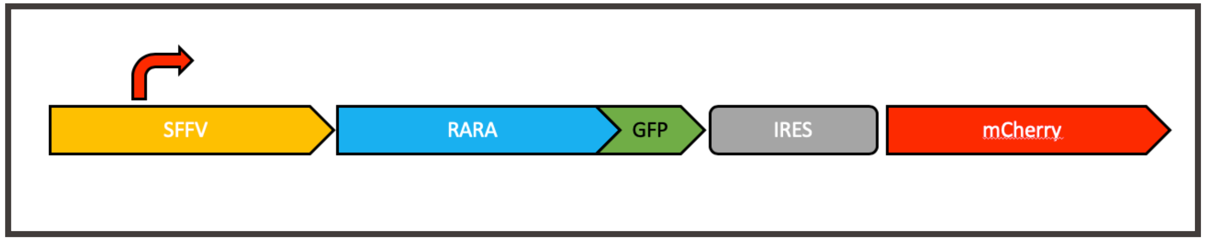
Zhu *et al.*, (1999) *PNAS*

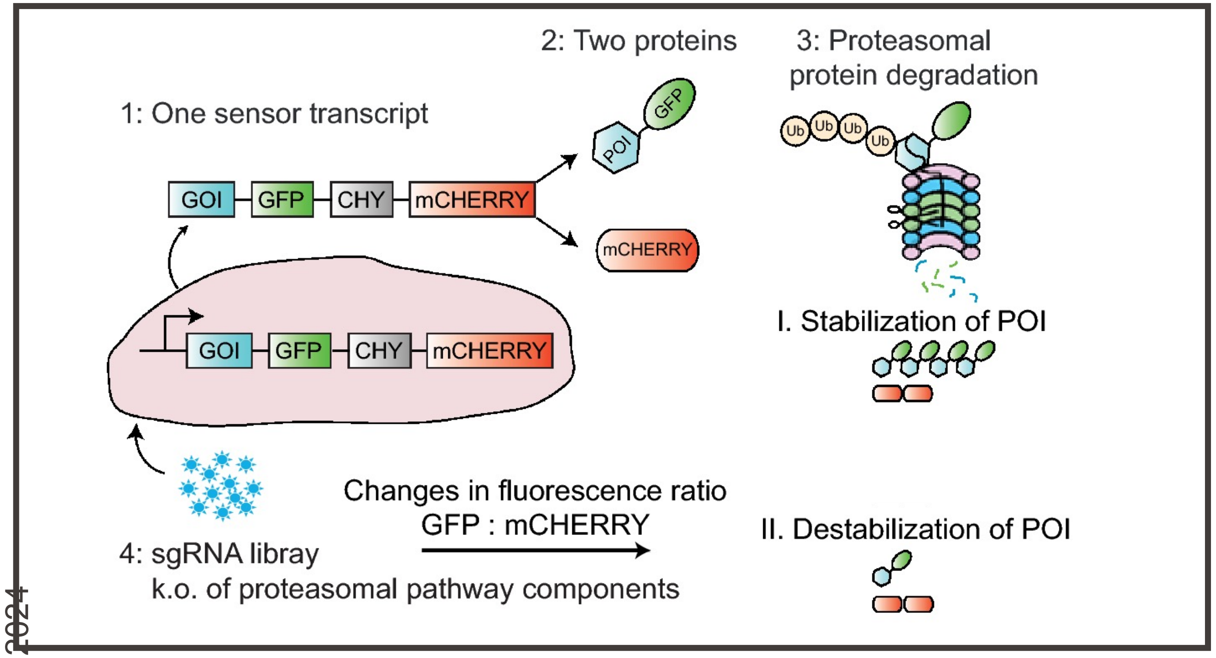


Jonathan Tsai

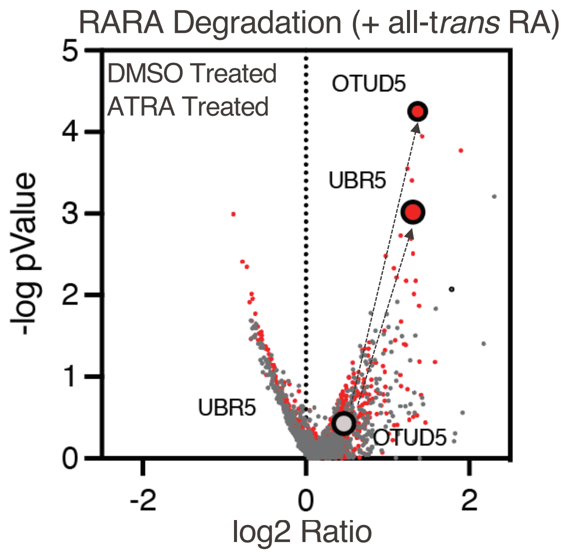
EPFL

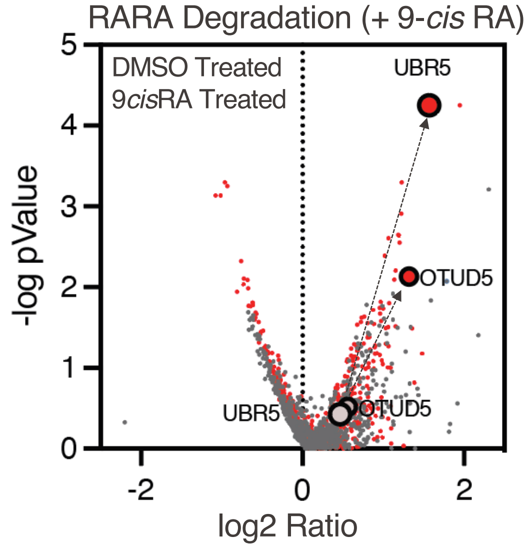
CRISPR-screen to identify E3-ligase responsible for RARA degradation





Adapted from Schukur *et al.*, (2020) *Sci Rep*



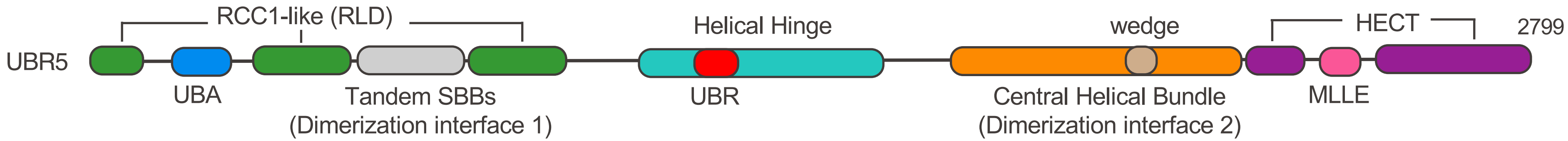


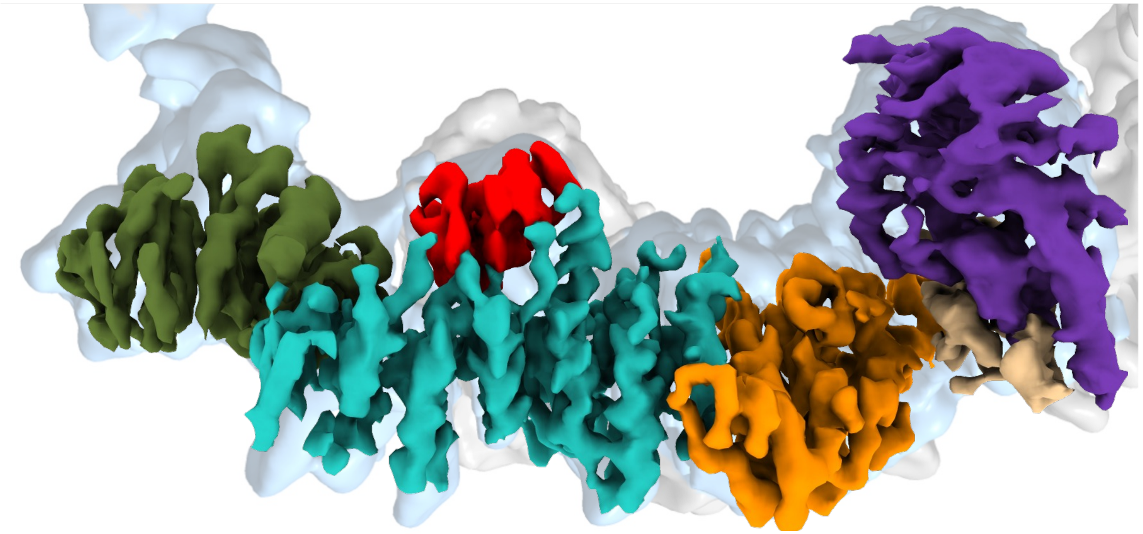
Yen-der Li

Mikołaj Słabicki

Jonathan Tsai

Structure of human UBR5

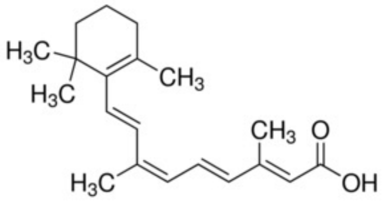




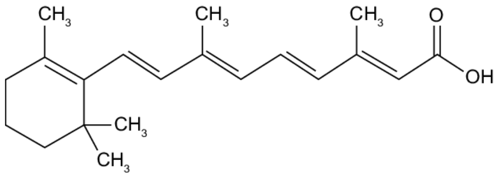
Jacob Aguirre

The RARA/RXRA agonist conformation is recognized by UBR5

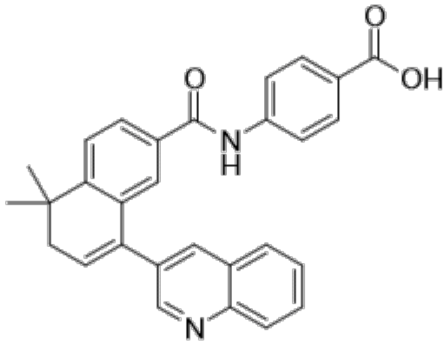
9-cis RA (agonist)



all-*trans* RA (agonist)



BMS-614 (antagonist)



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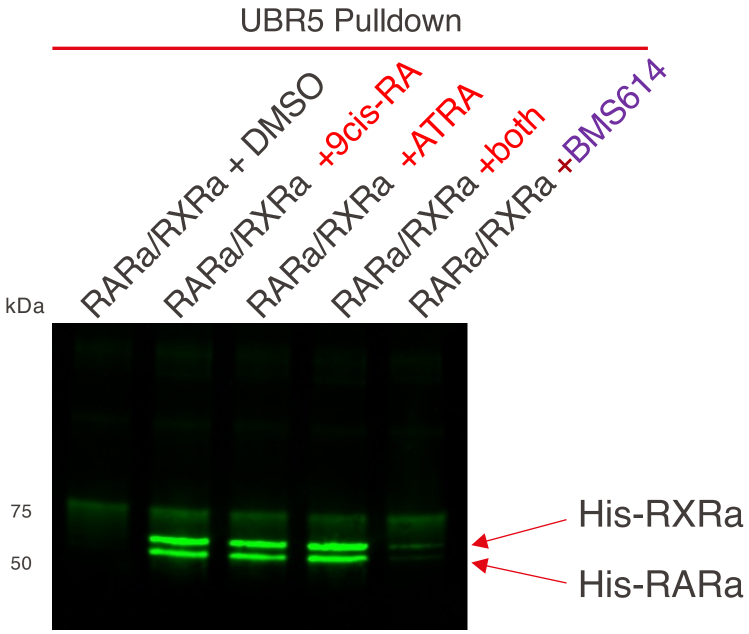
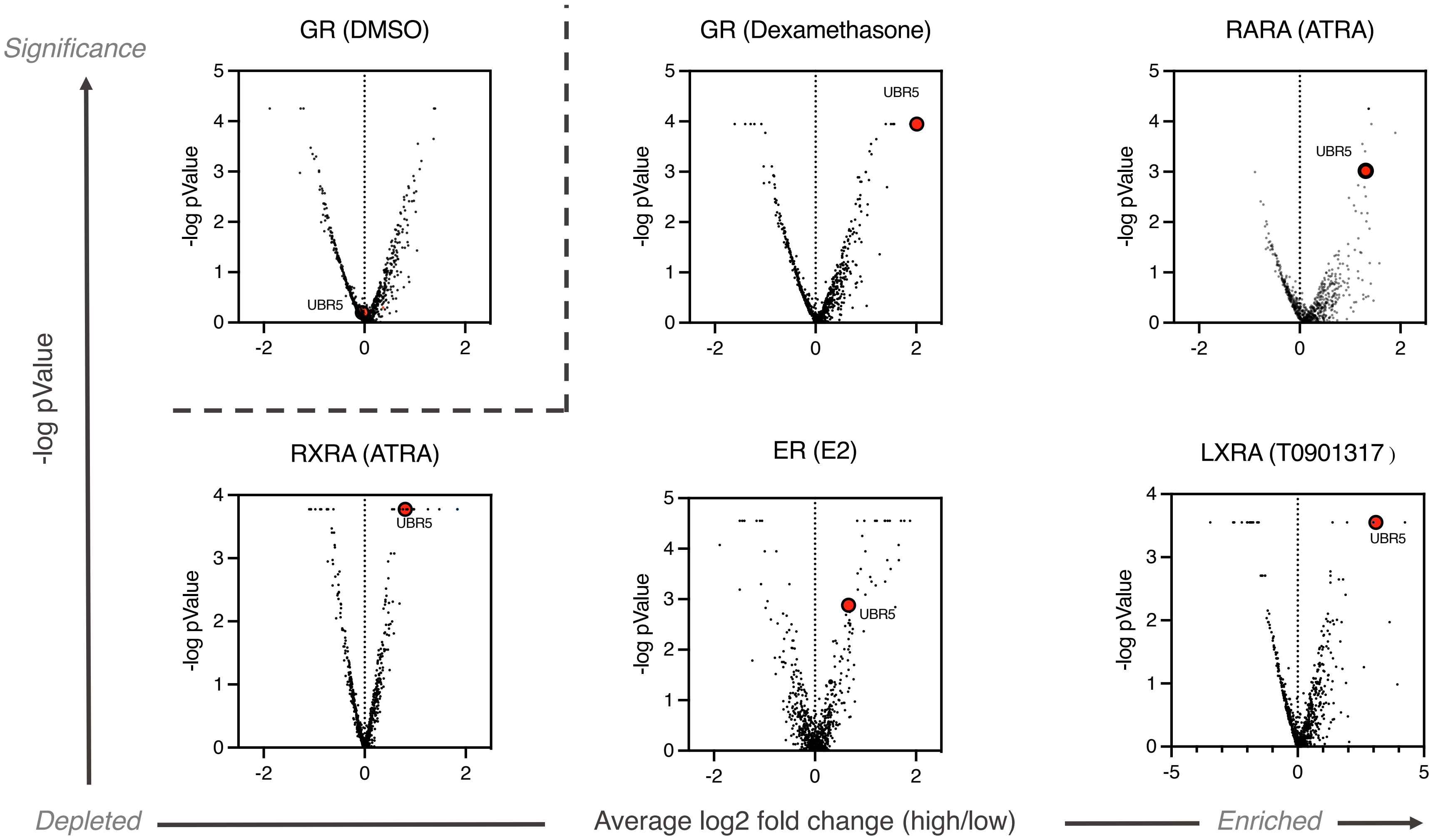


Anti-His

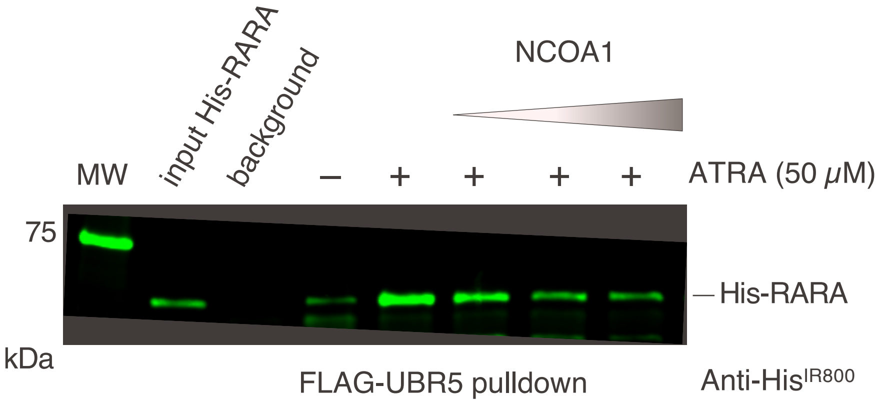
Tsai, Aguirre, *et al.*, (2023) *Mol Cell*

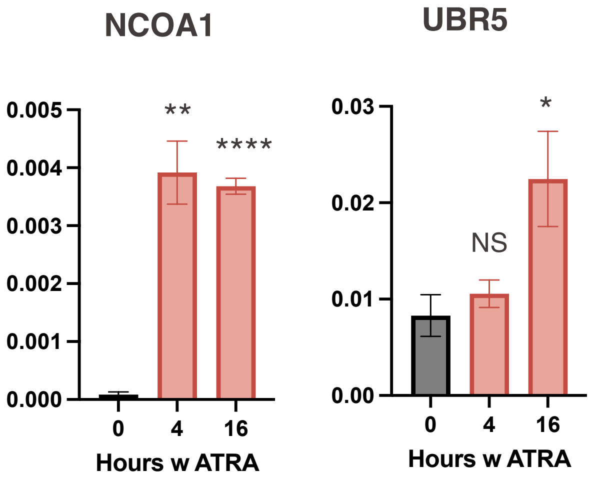
UBR5 governs degradation of multiple NRs
in response to agonists

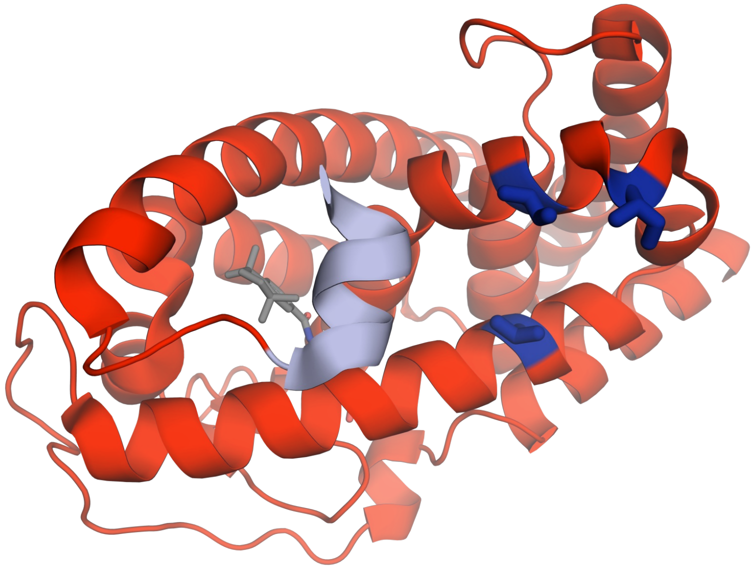


Tsai, Aguirre, *et al.*, (2023) *Mol Cell*

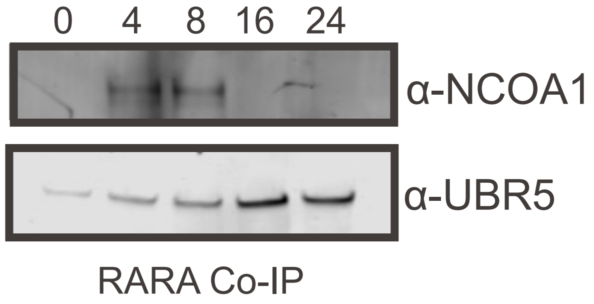
Co-repressors/co-activators and UBR5 bind NRs in a mutually exclusive manner







RARA (PDB: 3KMR)



Jacob Aguirre

Jonathan Tsai

The UBR5 negative feedback loop switches OFF NR signaling