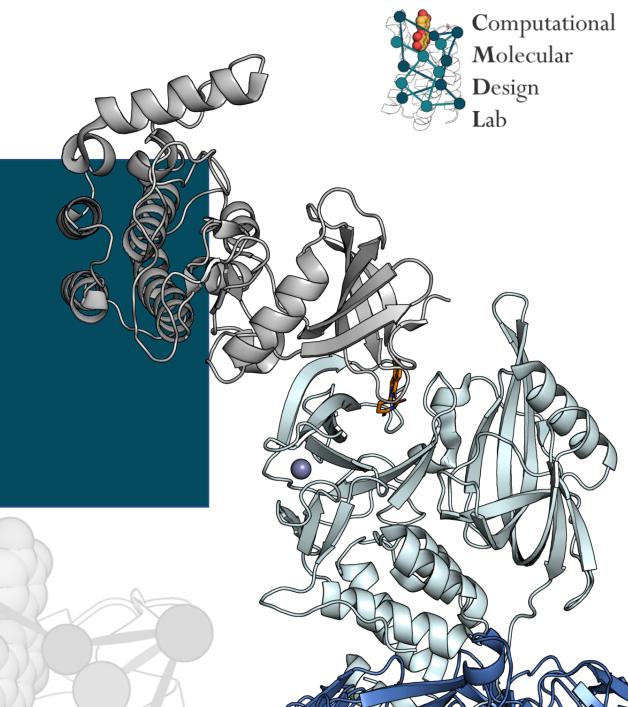


Computer Aided Drug Design for emerging therapeutic modalities

> Jordi Juarez-Jimenez, PhD Facultat de Farmàcia I Ciències de l'Alimentació November 2023





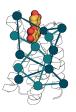




What is Computer Aided Drug Design?



## A needle in a haystack?



### Drug Discovery feels like...





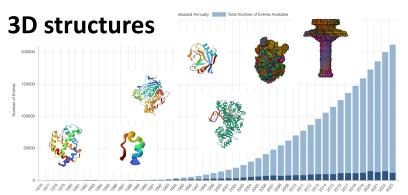
# Harnessing the power of computers to design novel bioactive molecules



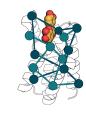




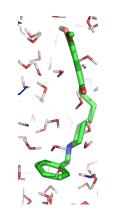




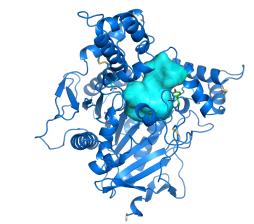
## A physicochemical description of the drug-target interaction



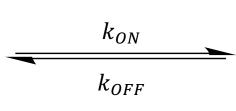




### **AChE**

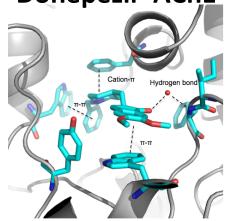


#### ∙ne ≪



$$K_a = \frac{[LR]}{[L][R]} = \frac{k_{ON}}{k_{OFF}}$$

### Donepezil- AChE



## Equilibrium

<u>(Thermodynamics)</u>

$$\Delta G_{bin} = -RT \ln K_a$$

## Out of equilibrium (Kinetics)

$$k = \frac{\kappa k_B T}{h} e^{-\frac{\Delta G^{\neq}}{RT}}$$



Only the complexity of the associated equations prevents the mathematical treatment of large part of physics and the whole chemistry.

## We use approximate models to describe reality all the time...







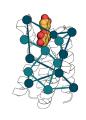


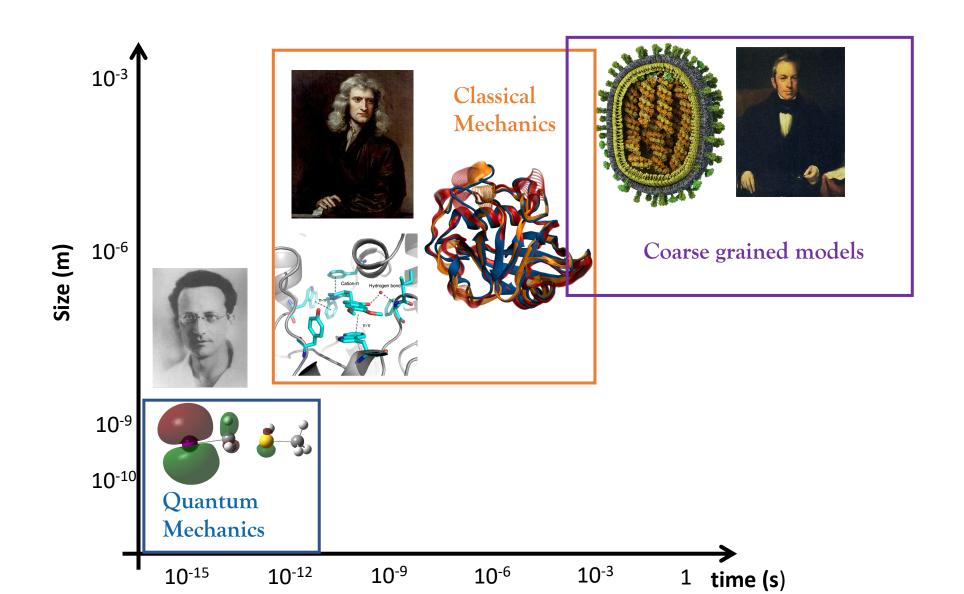






# Size and time scale delineate the applicability of computational models

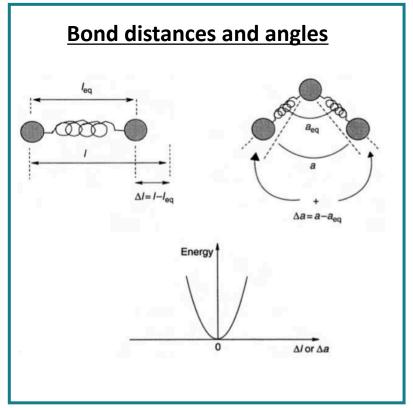


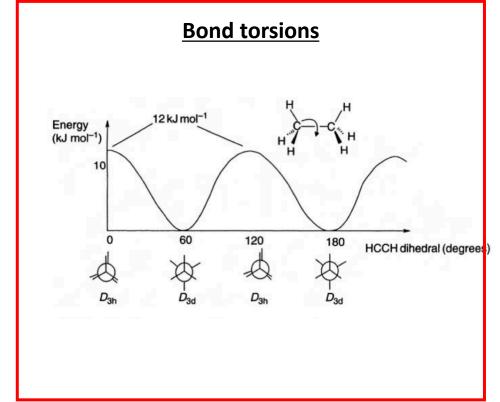


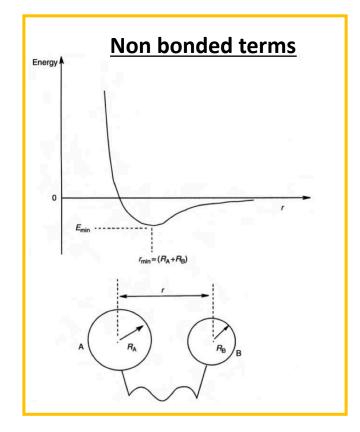
## Classical Forcefields: describing molecules using Newtonian physics



$$E = \sum_{bonds} E_{stretch} + \sum_{angles} E_{bend} + \sum_{dihedrals} E_{torsion} + \sum_{pairs} E_{nonbond}$$

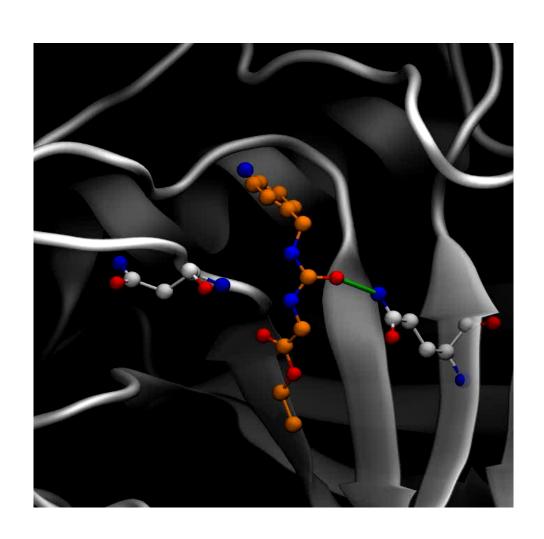


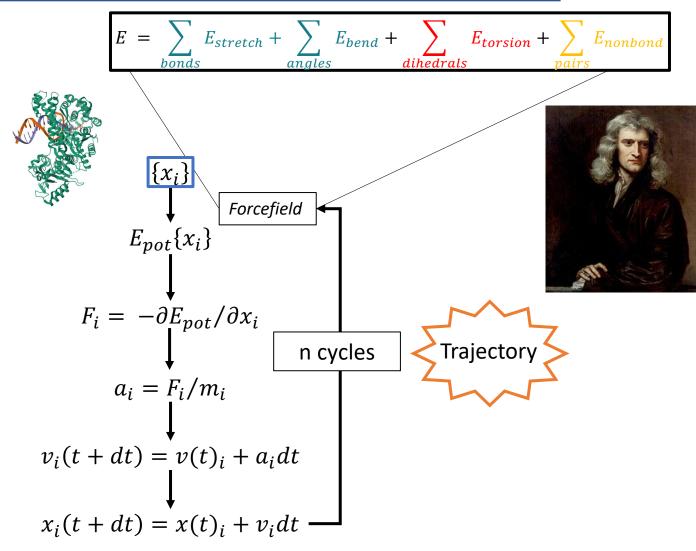




### Molecular Dynamics of protein-ligand interaction





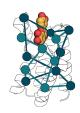


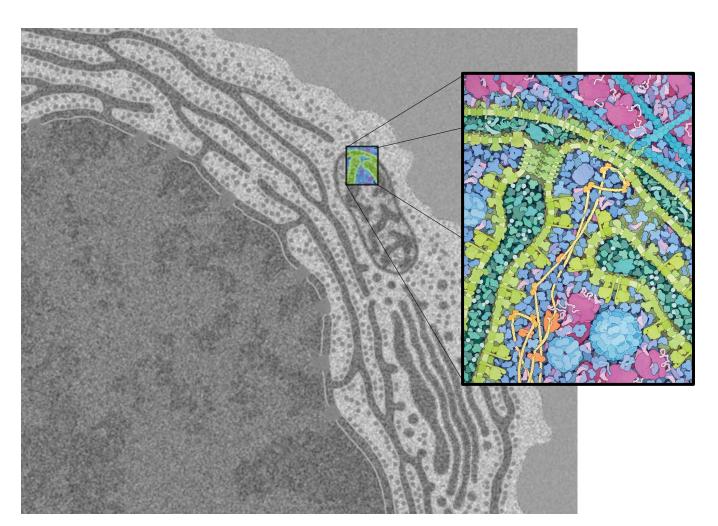
П

 $\label{eq:continuous} Understanding \ the \ drug-dependent$   $\ degradation \ of \ the \ CRBN \ neosubstrate \ CK1\alpha$ 



### Could we stabilize any transient protein-protein contact and control cell behaviour?





Invisible PPI complexes





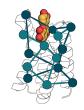






Adapted from Goodsell, D. S. Biochem Mol Biol Edu 2010.

## Could we stabilize any transient protein-protein contact and control cell behaviour?



### Nature does it often...

Ciclosporine A (Isolated from *T. inflatum*)

Paclitaxel (Isolated from *T. brevifolia*)

Sirolimus (Isolated from *S. hygroscopicus*)

Thalidomide

Lenalidomide

Pomalidomide

...and we did it too, we were just not aware of it

# A completely unexpected mechanism of action with daunting consequences.





#### may depend on the safety of 'Distaval'

Consider the physical contained a conversational barbilitants. Var any byas, the harbitimates contained a conversational barbilitants. Var any byas, the harbitimates calaim as mounting tool cold with a both highly effective.

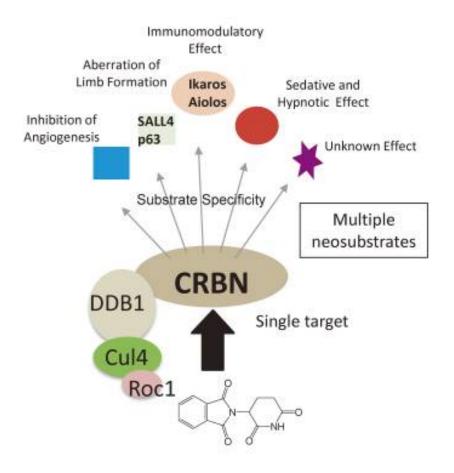
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As a hypoxide at beddiner;
ADULTS 16 ong, to 200 mg,
INFANTS AND CHELLDREN:
20 mg, to 100 mg.
As a daytime sedative;
As a daytime sedative;
AND CHELLDREN: Up to 25mg,
AND CHELLDREN: Up to 25mg,
AND CHELLDREN: Up to 25mg
COOFficie to 25mg, two or trumedable
Distants' Tyruc (300 mg, tableta).
Basic cost to N.R.R. of 12 tablets for
Cinpensing pack of one branded—1: o



#### Reproduced from Museums Victoria Collection

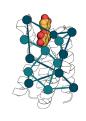


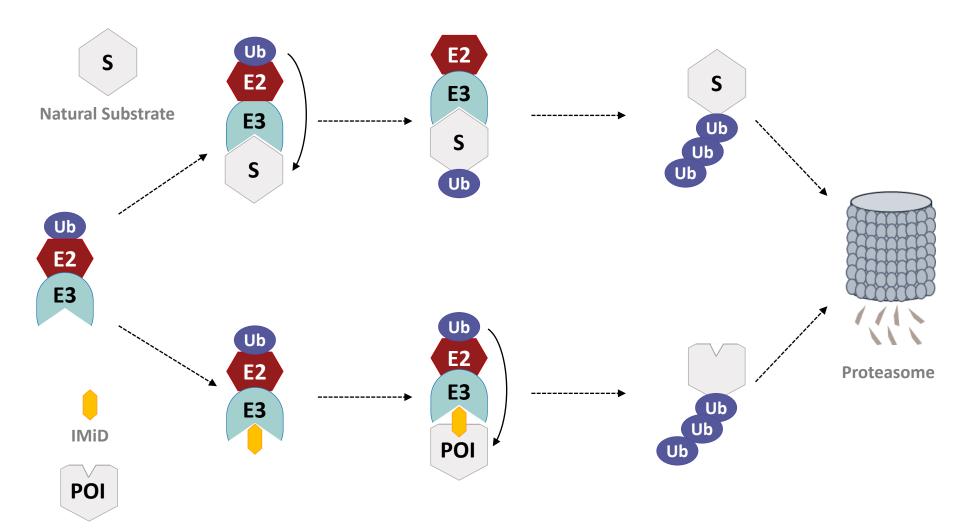


#### Thalidomide

Ito, et.al. Proc. Jpn. Acad. Ser. B Phys. Biol. Sci. 2020.

# TPD: Hijacking the Ubiquitin-Proteasome system to degrade harmful proteins





**Protein Of Interest** 

# Computer-Aided Drug Design (CADD) can be instrumental to the future of TPD





**Therapeutical advantages** of protein degradation over protein modulation.



**Great expectations** about the number and type of targets that can be engaged.



Opportunity to repurpose compound libraries with limited affinity or with sub-optimal phenotypic effects.



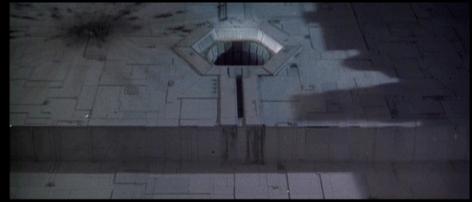
Early development stage grants great scope for securing **novel intellectual property**.





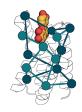


## Trust the Force...



Protein Degradation

# The need for rational approaches to TPD has been highlighted for years





#### IN THE PIPELINE

Derek Lowe's commentary on drug discovery and the pharma industry. An editorially independent blog, all content is Derek's own, and he does not in any way speak for his employer.

IN THE PIPELINE CHEMICAL BIOLOGY

### **Linked-Up Molecules Through the Years**

14 NOV 2019 · BY DEREK LOWE · 5 MIN READ · COMMENTS

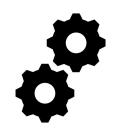
"TPD remains a rather. . .empirical. . .field for now, which in practice means that you'd better try this and try that and try that other thing over there, what the heck. It would make everyone feel better if that weren't the case, and everyone would be far more efficient steely-eyed protein degradation masters sitting in mission control and pointing out targets, but that is a vision for the future."

## Computer-Aided Drug Design (CADD) can be instrumental to the future of TPD





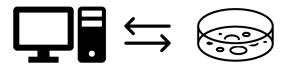
Identification of new TPD efectors and new degradable targets.



Understanding the physichochemical phenomena underlying TPD.



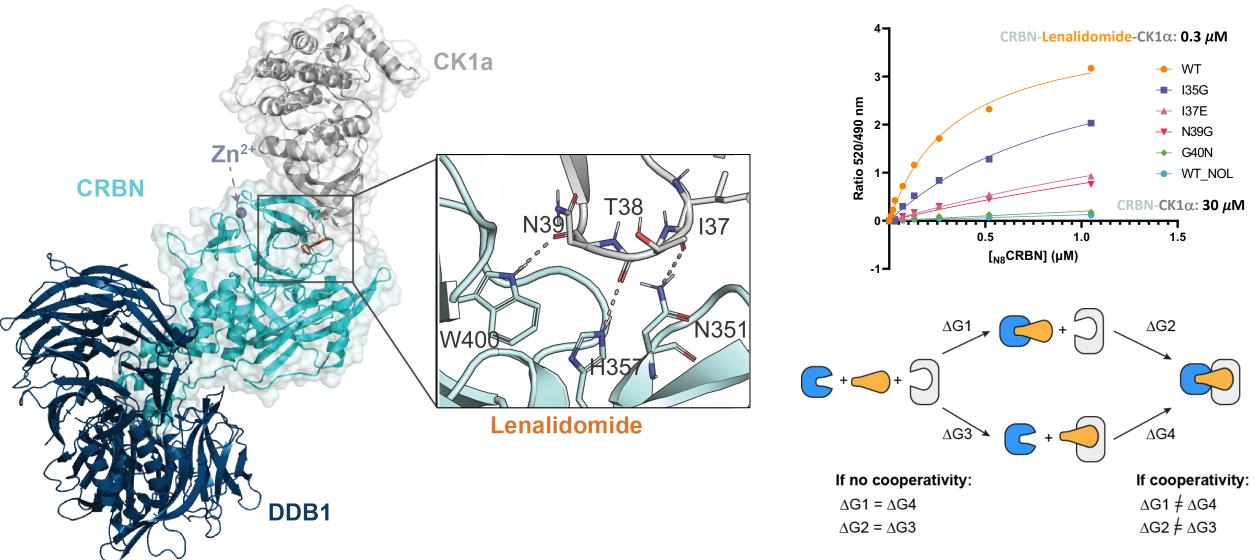
Generation of predictive and reliable models of degradation.



Development of integrated computational-experimental workflows.

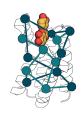
## Lenalidomide does not generate a new interaction interface between Cereblon and $\text{CK}1\alpha$

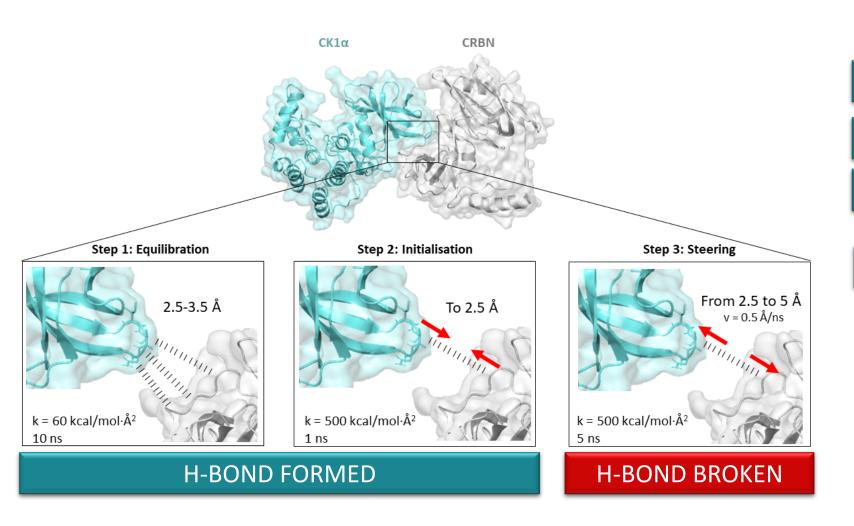


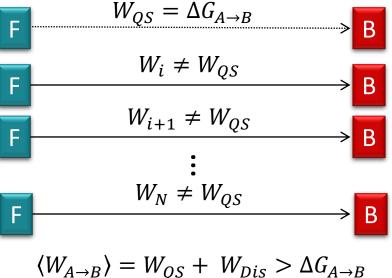


Petzold, et. al. Nature. 2016.

# Steered Molecular Dynamics provides a fast way to explore the strenght of polar interactions





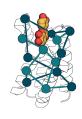


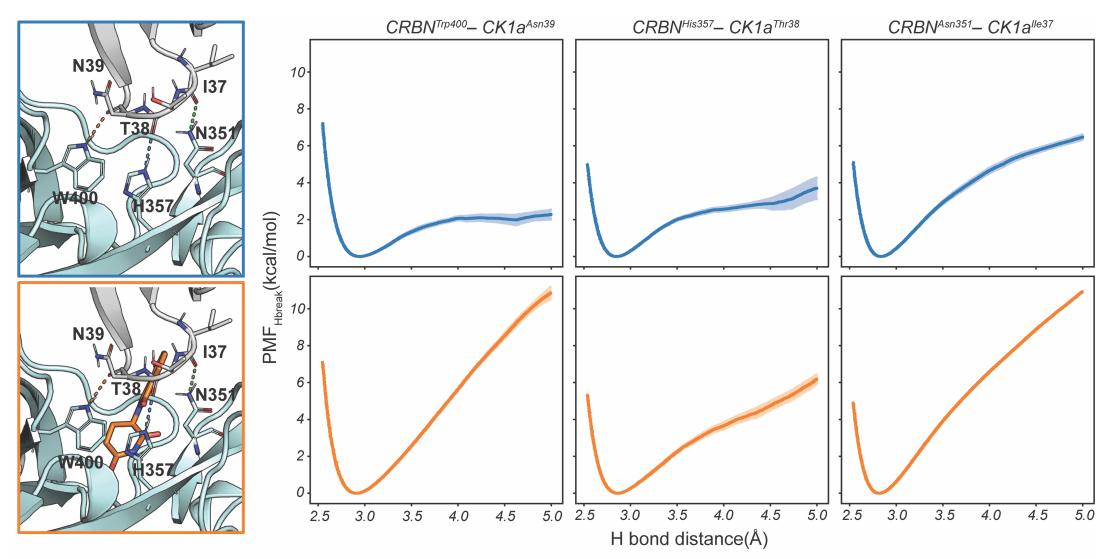
Jarzynski's equality:

$$e^{-\Delta G/k_BT} = \langle e^{-W_i/k_BT} \rangle$$

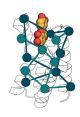
$$\Delta G_{A \to B} = -k_B T \ln \sum_{i=1}^{N} \frac{e^{-W_i/k_B T}}{N}$$

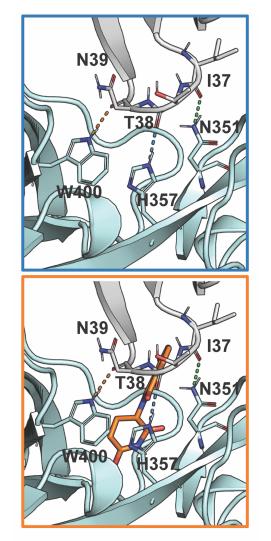
# The presence of Lenalidomide strengthens three key H-bonds at the Cereblon-CK1lpha interface

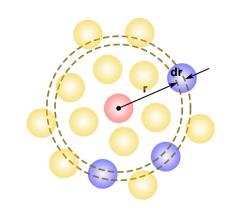


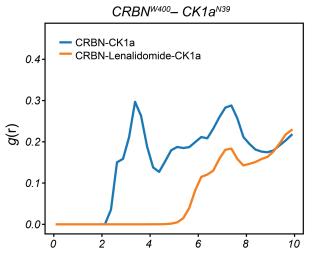


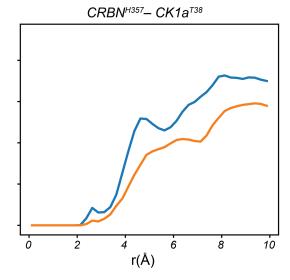
## Lenalidomide reduces the value of radial distribution function of water molecules around the H-bonds

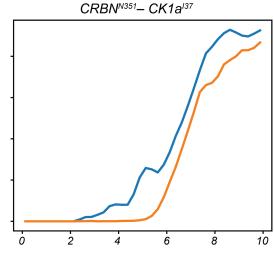






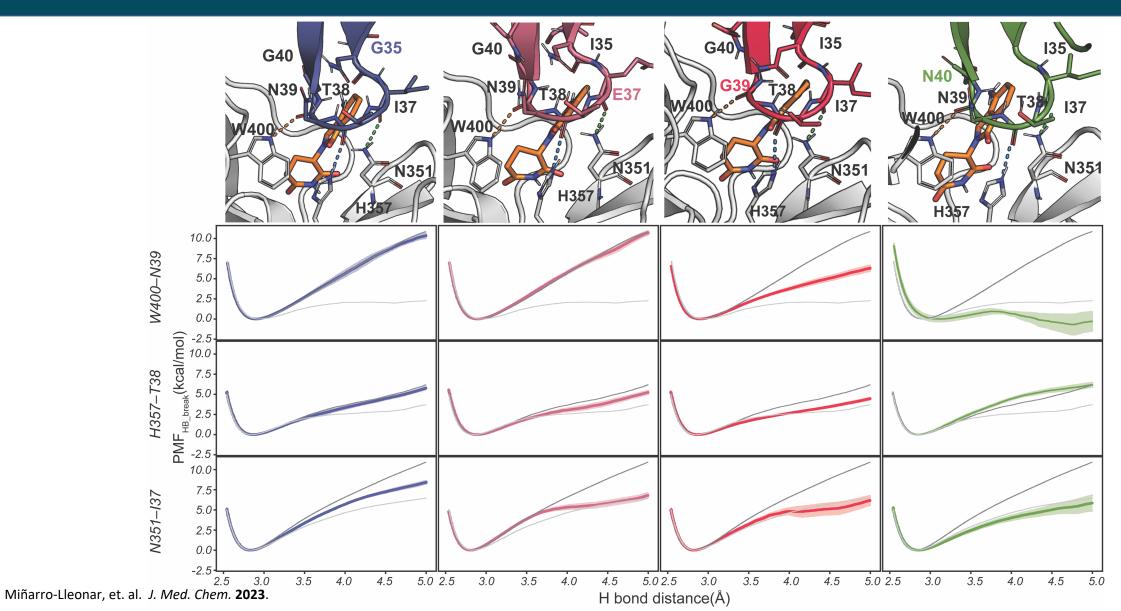




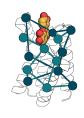


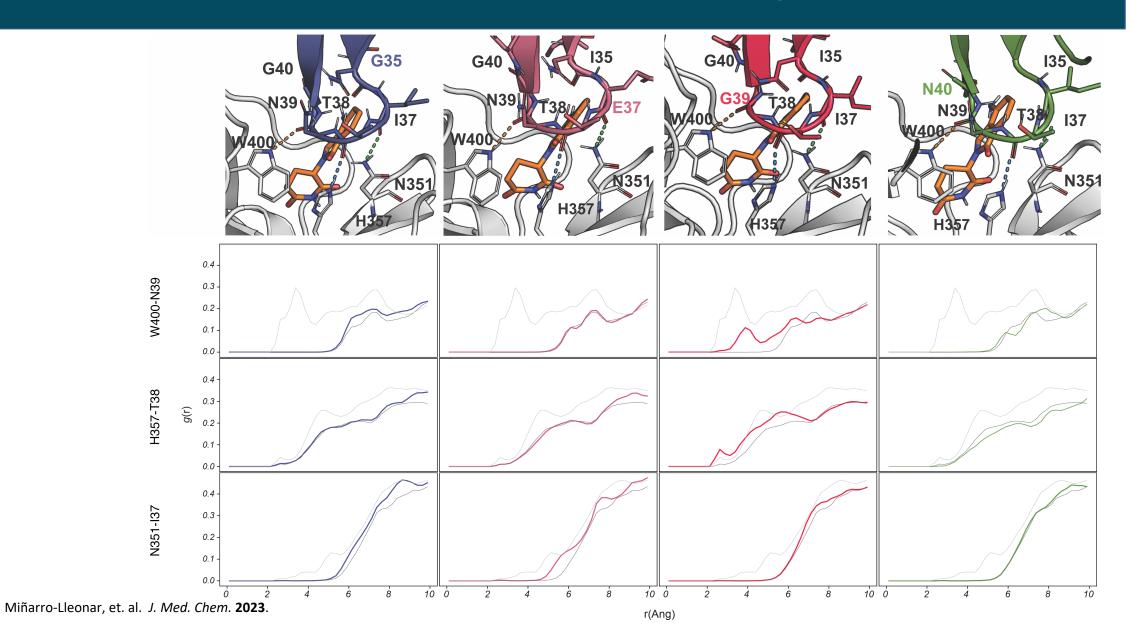
# Point mutations in CK1 $\alpha$ partially or completely reverse the effect of lenalidomide...





## ...but RDF pattern does not predict the strenght of the H-bond





Lenalidomide stabilizes proteinprotein complexes by turning labile intermolecular H-bonds into robust interactions.

Marina Miñarro-Lleonar, Andrea Bertran-Mostazo, Jorge Duro, Xavier Barril, Jordi Juárez-Jiménez









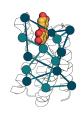
Institut de Química Teòrica i Computacional

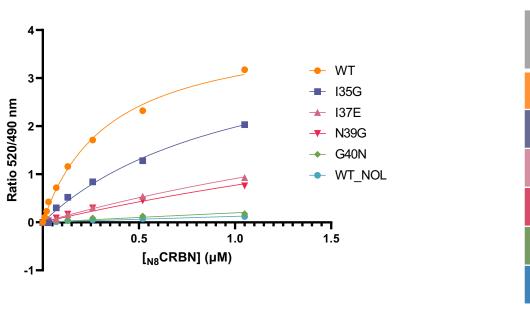


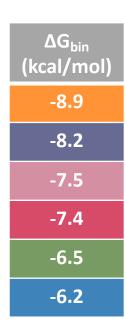


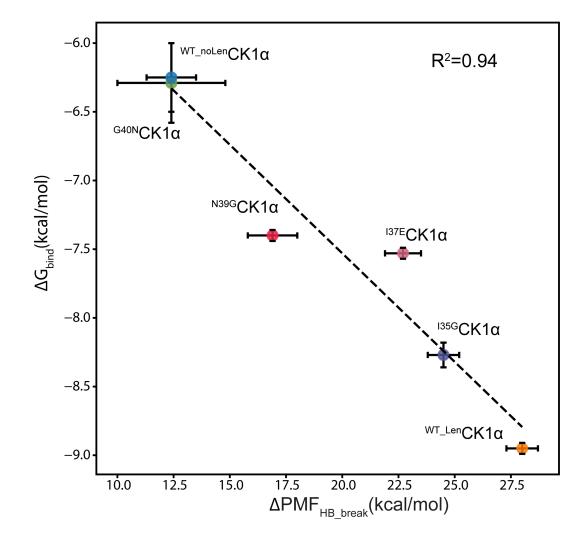


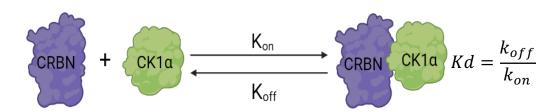
## Combined H-bond strength is a predictor of the CK1 $\alpha$ -CRBN stability





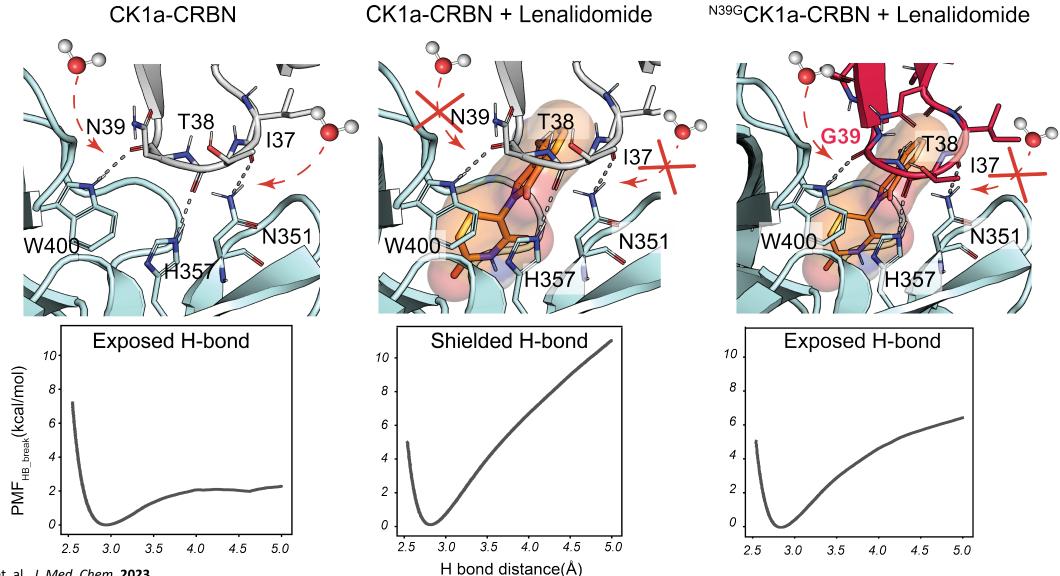






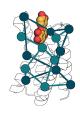
### Our lenalidomide-dependent stabilization mechanism hypothesis





Miñarro-Lleonar, et. al. J. Med. Chem. 2023.

## Our lenalidomide-dependent stabilization mechanism hypothesis





#### IN THE PIPELINE

Derek Lowe's commentary on drug discovery and the pharma industry. An editorially independent blog, all content is Derek's own, and he does not in any way speak for his employer.

IN THE PIPELINE BIOLOGICAL NEWS

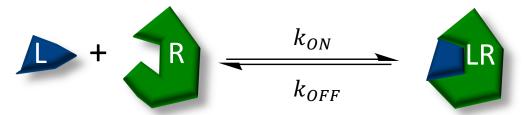
## **How Glues Do the Gluing**

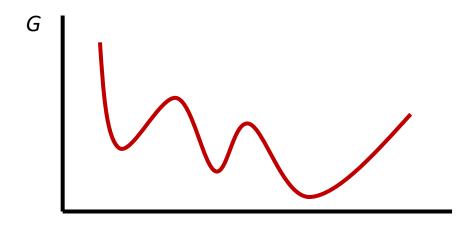
1 MAY 2023 · BY DEREK LOWE · 3 MIN READ · COMMENTS

### Final Remarks



Understanding biological mechanisms (including drug binding) often requires understanding of the underlying energetic landscape.

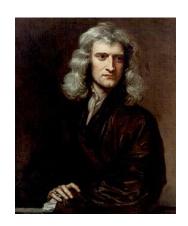




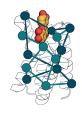
Energetic surfaces are defined by minima and maxima that relate to thermodynamic and kinetic properties, respectively.

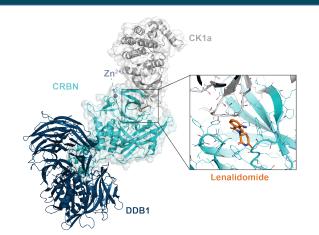
Methods based in classical dynamics are powerful tools to explore the energetic surfaces of protein-ligand binding

R



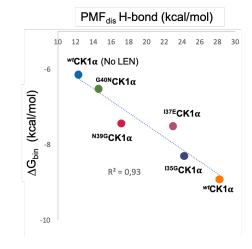
### Final Remarks

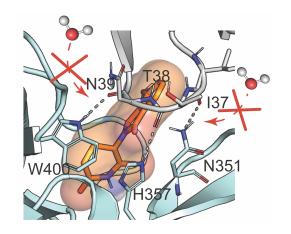




The affinity of Lenalidomide mediated CRBN-CK1 $\alpha$  complexes relies on the strength of three key H-bond interactions.

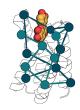
The strength of key H-bonds in protein-protein interactions can help to rank the stability of ternary complexes.





CRBN-CK1 $\alpha$  provides proof of concept of the importance of accounting for non-additive effects in the future development of molecular glues.

### Acknowledgements





### Computational Molecular Design







Marina Miñarro



Andrea Bertran



Jorge Duro



Institut de Química Teòrica i Computacional UNIVERSITAT DE BARCELONA





### **Funding**





This work was funded under the research project PID2020-115683GA-I00 financed by the Ministry of Science and Innovation and the National Research Agency MCIN/AEI/10.13039/501100011033.

### **Computational facilities**







Donat el caràcter i la finalitat exclusivament docent i eminentment il·lustrativa de les explicacions d'aquesta presentació, l'autor s'acull a l'article 32 de la Llei de Propietat Intel·lectual vigent respecte de l'ús parcial d'obres alienes com ara imatges, gràfics o altre material contingudes en les diferents diapositives





Computer Aided Drug Design for emerging therapeutic modalities

> Jordi Juarez-Jimenez, PhD Facultat de Farmàcia I Ciències de l'Alimentació November 2023

