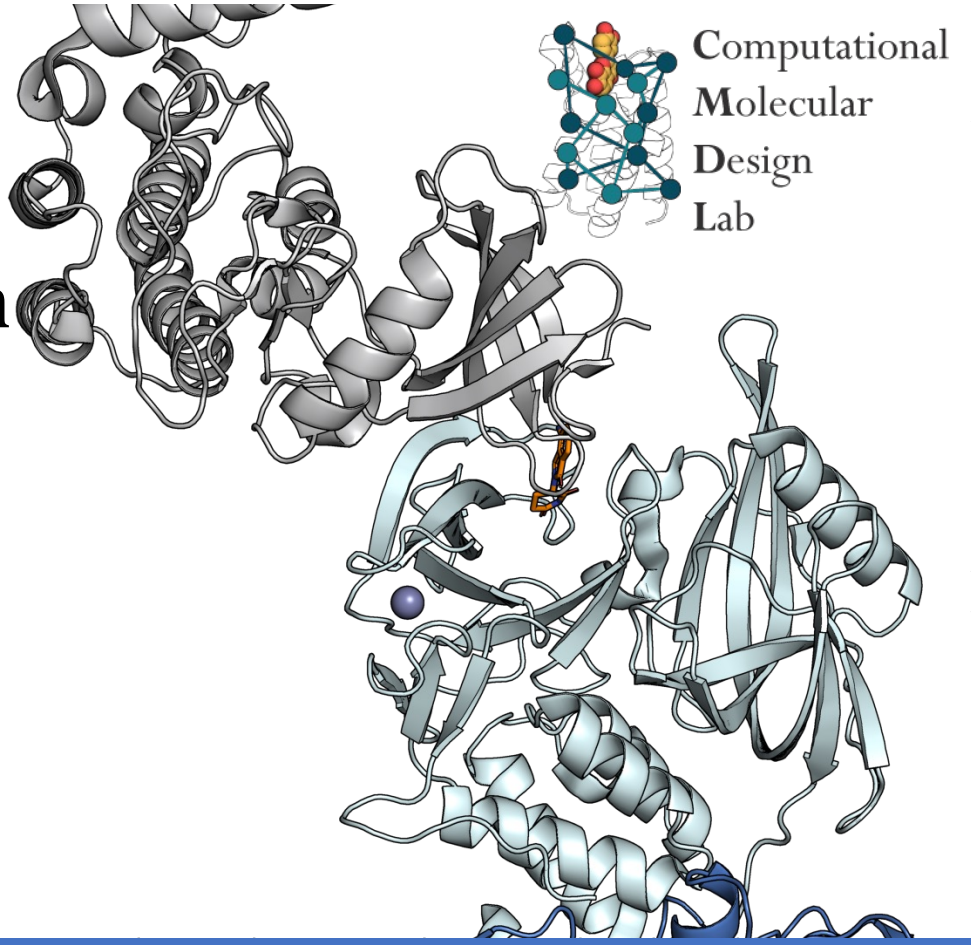
Understanding cooperative effects in PROTAC-Mediated Ternary Complexes for Protein Degradation



Computational Molecular Design Lab

UNIVERSITAT DE BARCELONA

Jordi Juarez-Jimenez, PhD

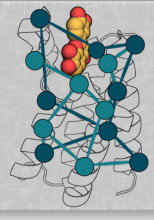
16th RES User Conference

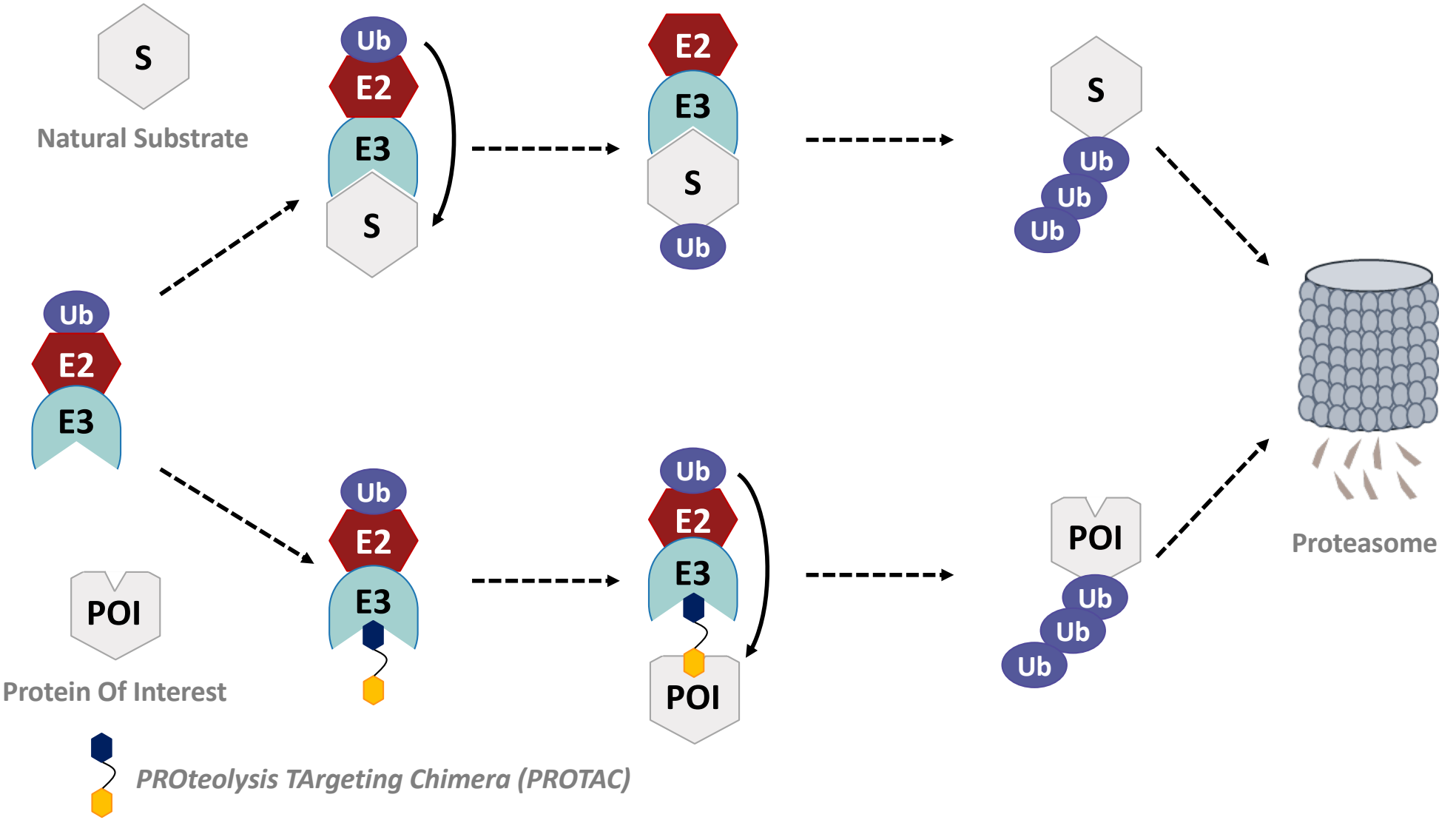
14th September 2022

Institut de Química Teòrica i Computacional
UNIVERSITAT DE BARCELONA

EXCELENCIA MARÍA DE MAEZTU

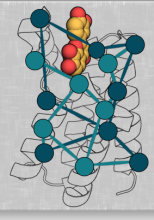
PROTAC: bifunctional molecules for Targeted Protein Degradation





Adapted from Martinez-Cartró, M. *Thesis Disertation* **2021**.

There are several possibilities to innovate in the design of protein degraders…



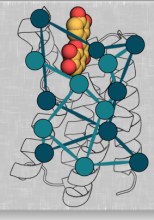
Therapeutical advantages of protein degradation over protein modulation

There are **great expectations** on 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**.

… but protein degradation remains a mostly empirical field



IN THE PIPELINE

Derek Lowe's commentary on drug discovery and the pharma industry. An editorially independent blog from the publishers of *Science Translational Medicine*. All content is Derek's own, and he does not in any way speak for his employer.

By Derek Lowe

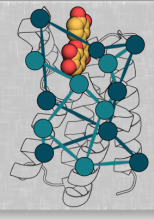
CHEMICAL BIOLOGY

Linked-Up Molecules Through the Years

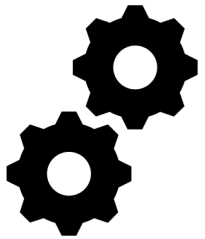
By Derek Lowe | 14 November, 2019

"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."

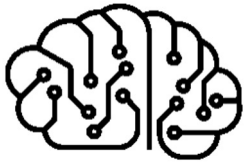
How CADD can contribute to the future of TPD



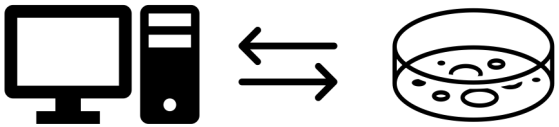
Identification new TPD efectors and new degradable targets.



Understanding the physichochemical phenomena underlying TPD.

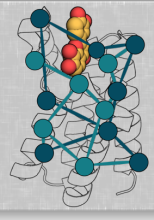


Generation of predictive and reliable models of cooperative effects and degradation.

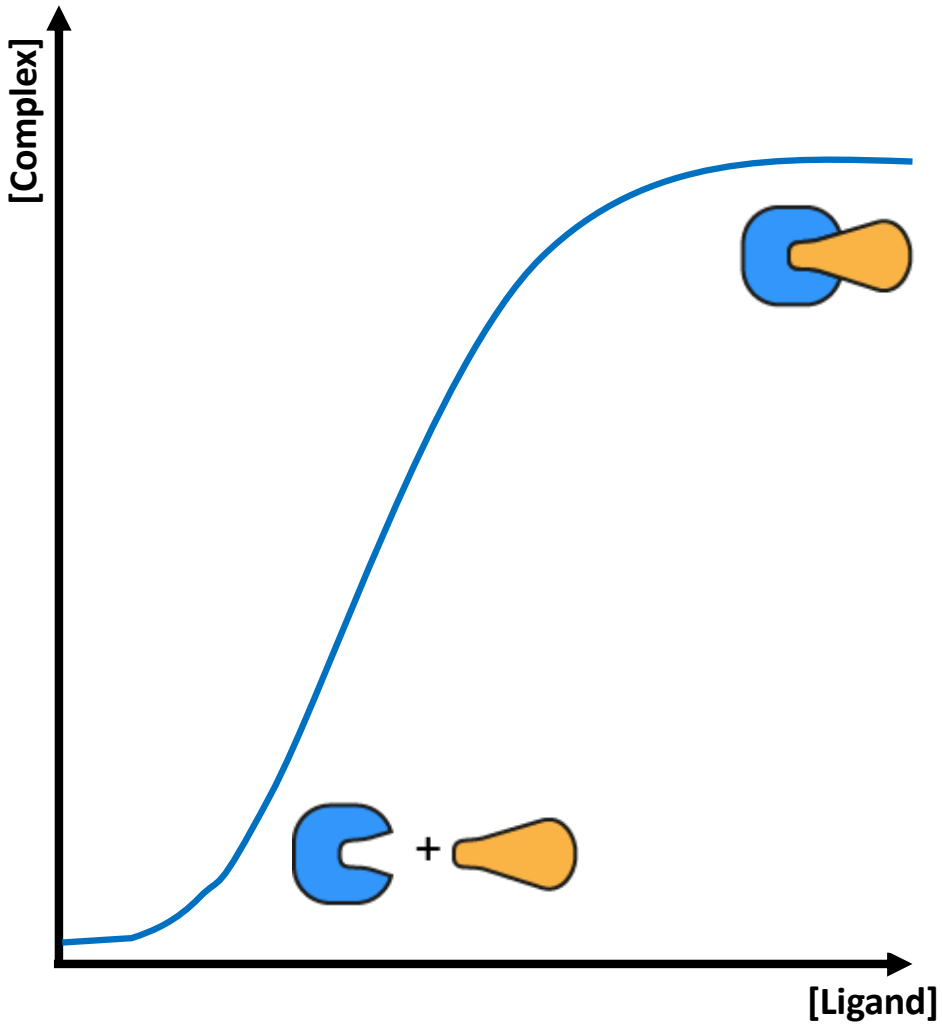


Development of integrated computational-experimental workflows.

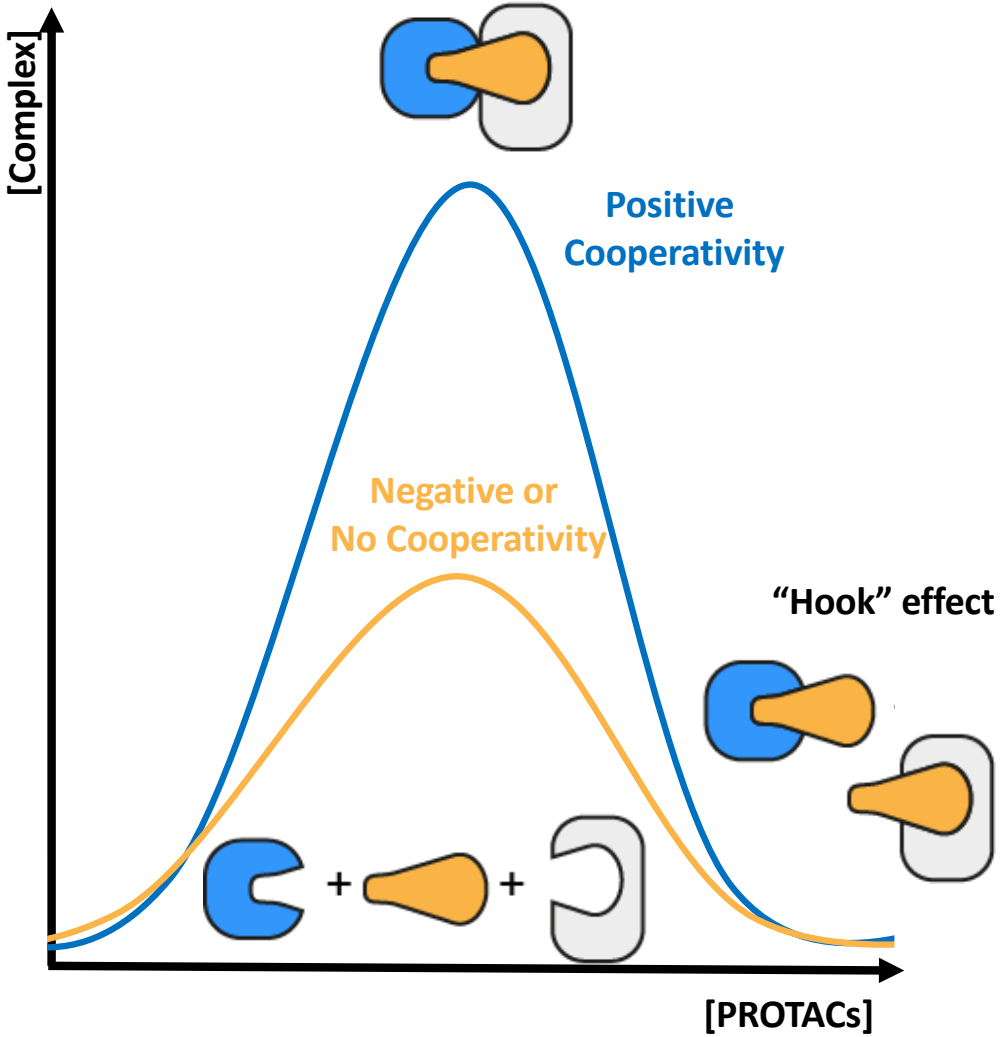
Design of PROTACs requires considering three-body complexes



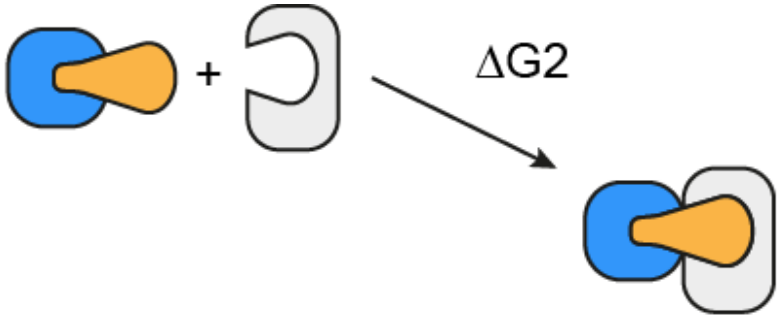
Two-body complex



Three-body complex



Cooperativity: when the total is not the sum of its parts



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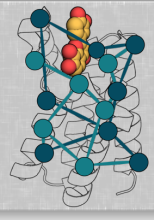
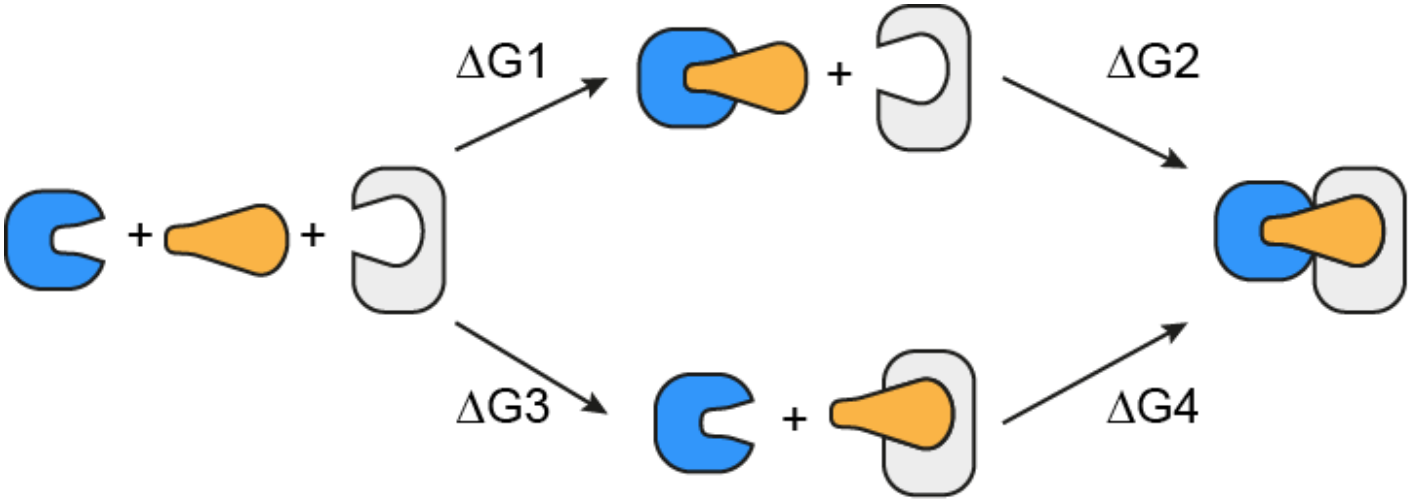




If no cooperativity:

$\Delta G1 = \Delta G4$

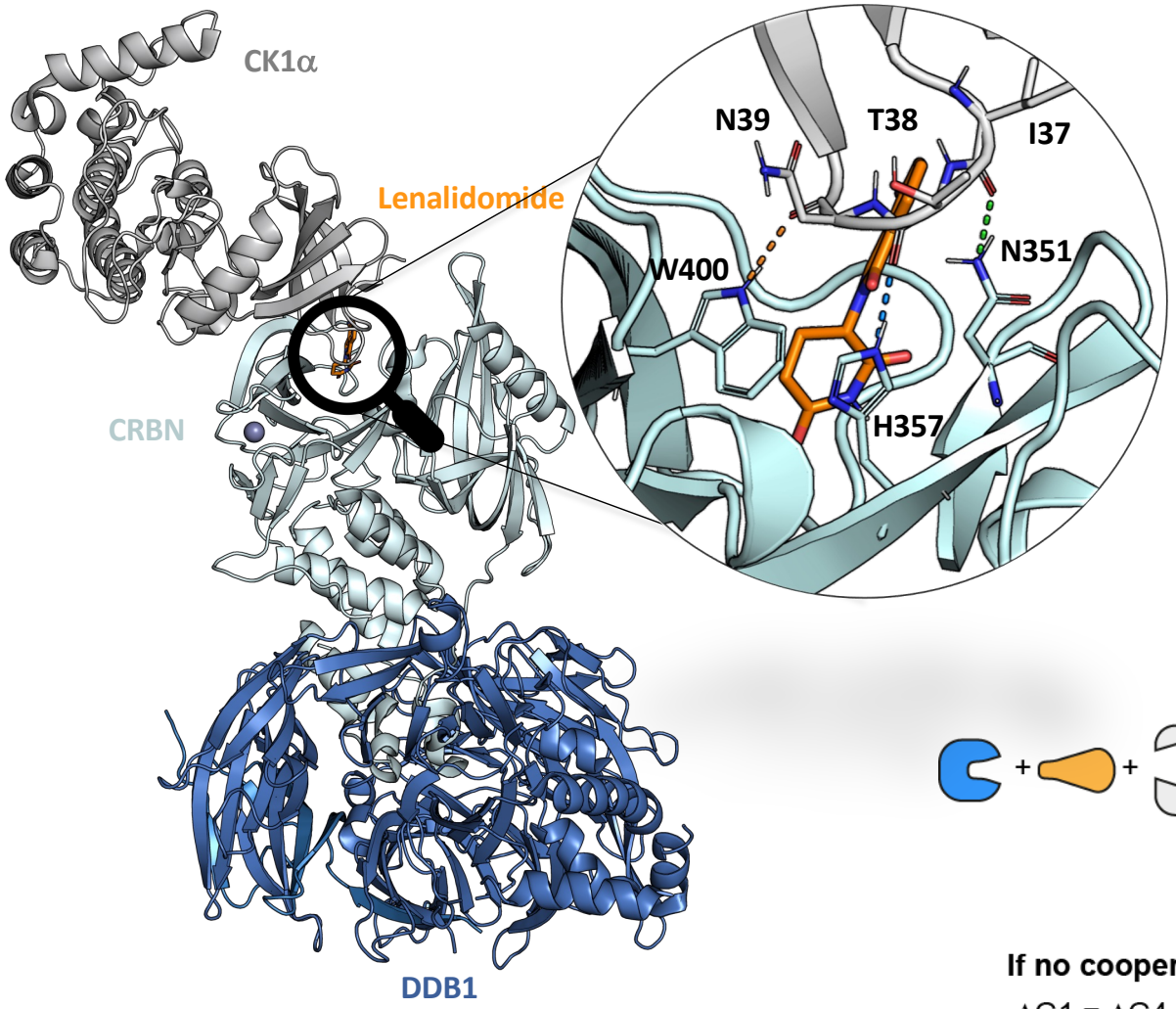
$\Delta G2 = \Delta G3$

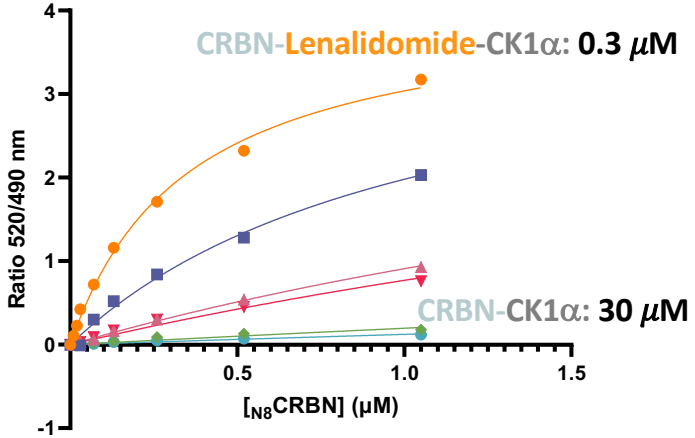
If cooperativity:

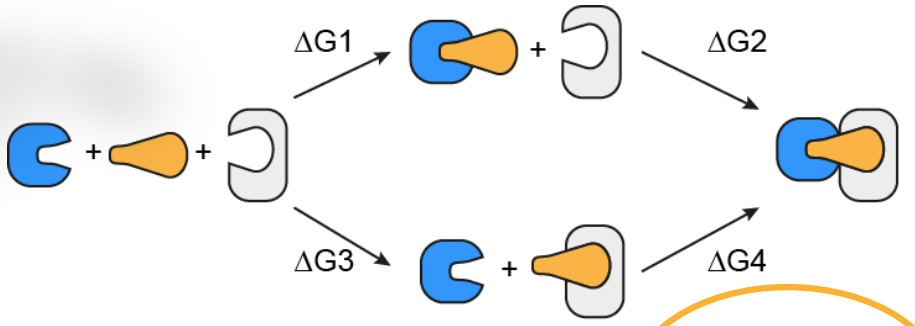
$\Delta G1 \neq \Delta G4$

$\Delta G2 \neq \Delta G3$

The Cereblon-Lenalidomide-CK1α interaction







If no cooperativity:

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If cooperativity:

$\Delta G1 \neq \Delta G4$

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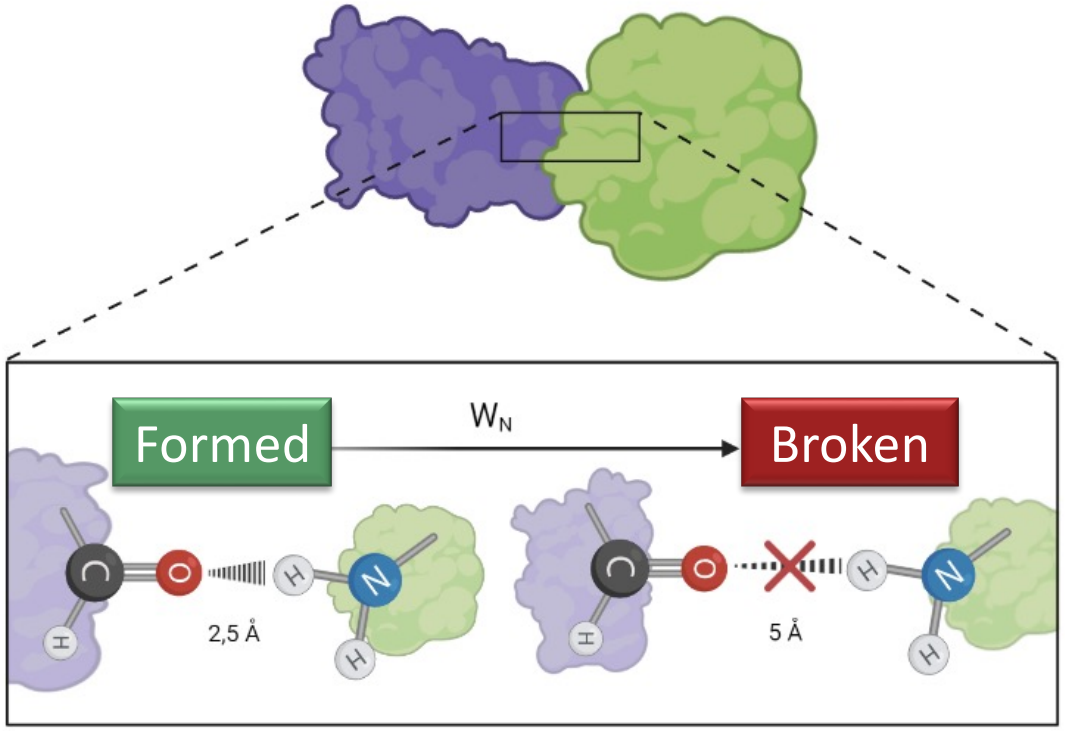
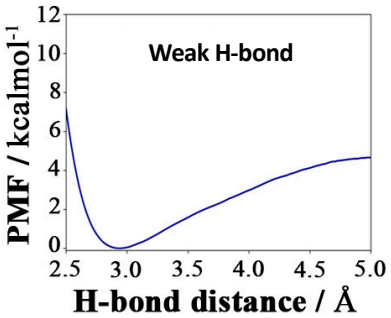
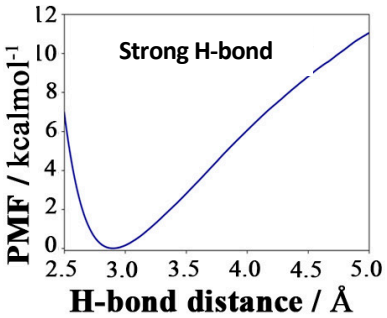
Adapted from Petzold, et. al. *Nature* **2016**.

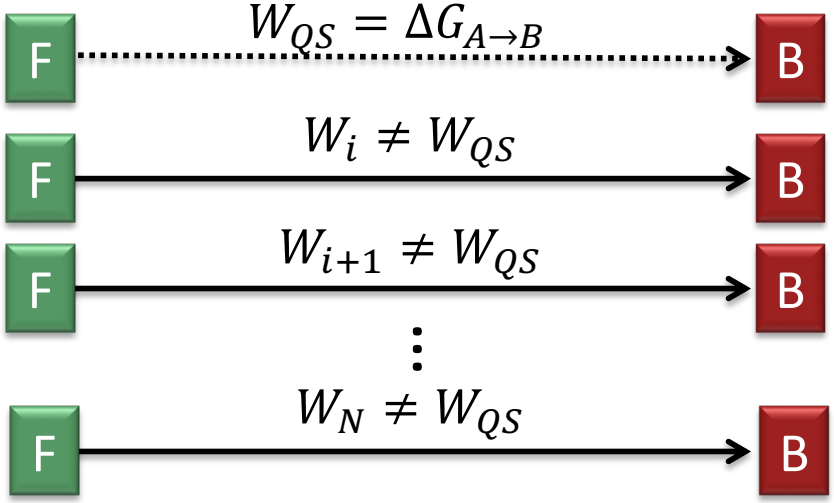
Methodological approach

Steered Molecular Dynamics









$$\langle W_{A\to B}\rangle = W_{QS} + W_{Dis} > \Delta G_{A\to B}$$

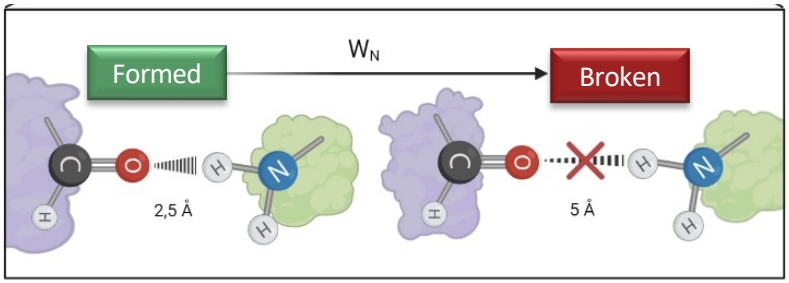
Jarzynski's equality:

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

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

Xiong et. al. *Theo. Chem. Acc.* **2006**

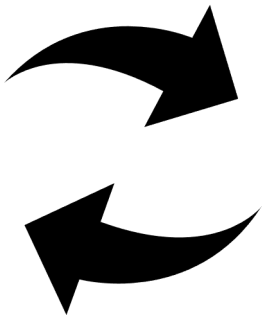
HPC servers are essential for the implementation of the approach



Required wallclock time (Local resources):

ca. 6h x SMD
x 3 H-bonds
x 100 SMD
x 6 systems

ca. 450 days!



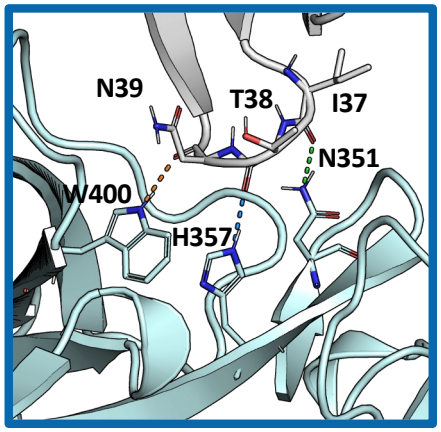
RED ESPAÑOLA DE SUPERCOMPUTACIÓN

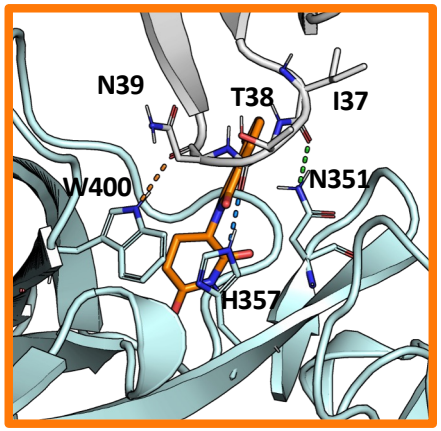
Real wallclock time (MareNostrum4 Power9):

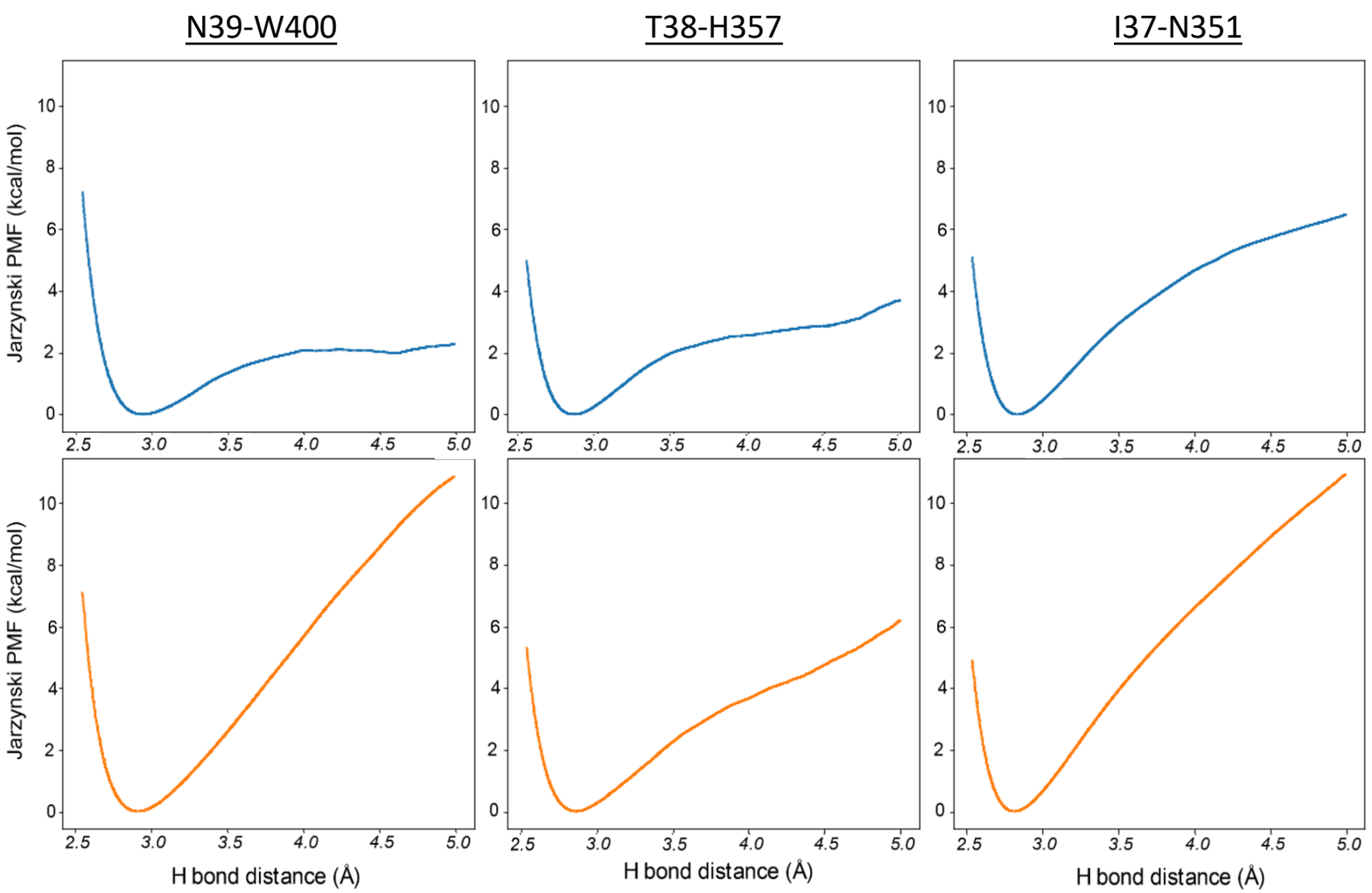
ca. 10 days

MareNostrum Picture: Vikipedia (author: Martidaniel)

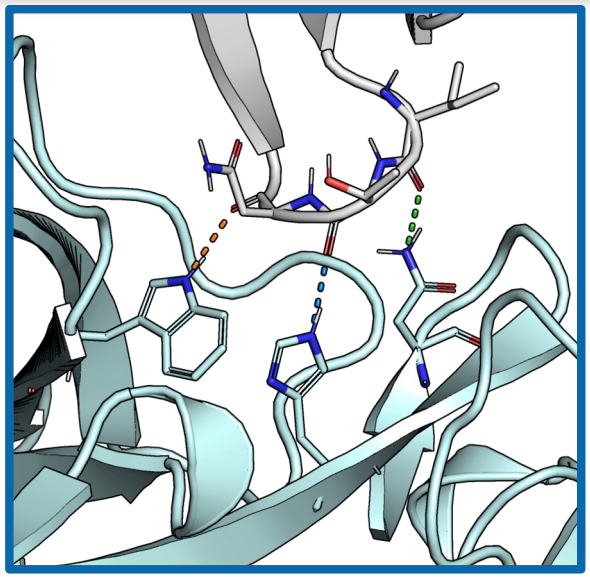
Lenalidomide strengthens the three key H-bonds

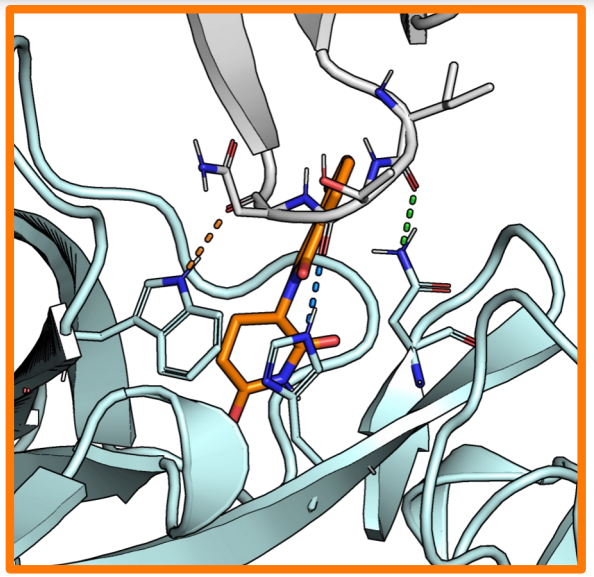


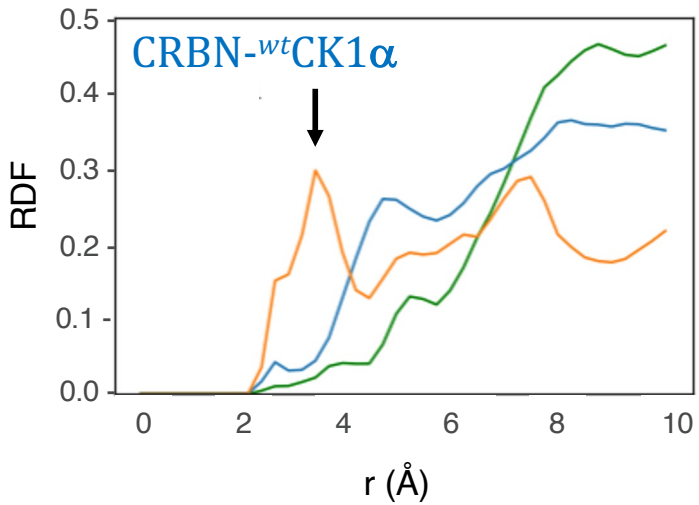




H-bonds in the ternary complex are highly shielded from incoming water molecules



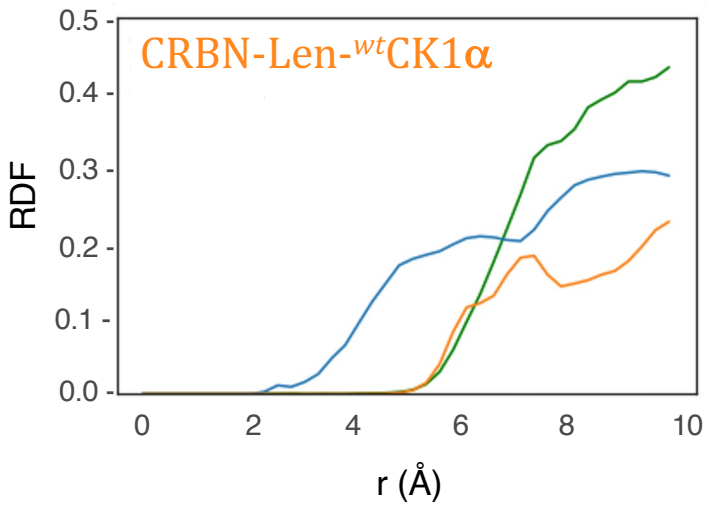




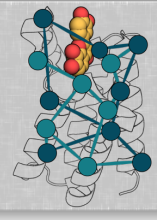
N39-W400

T38-H357

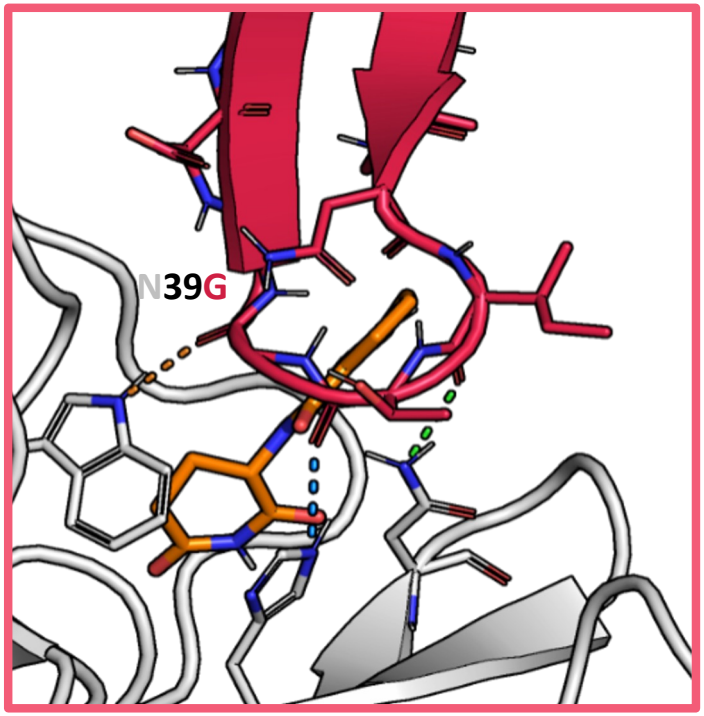
I37-N351

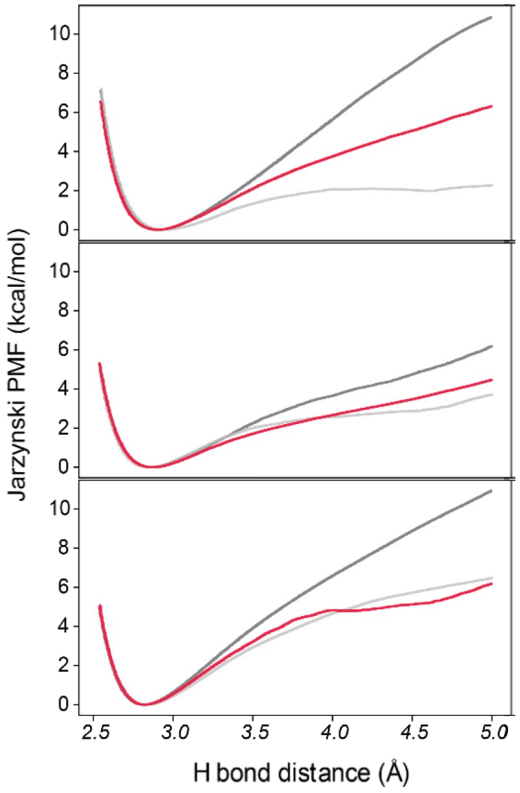


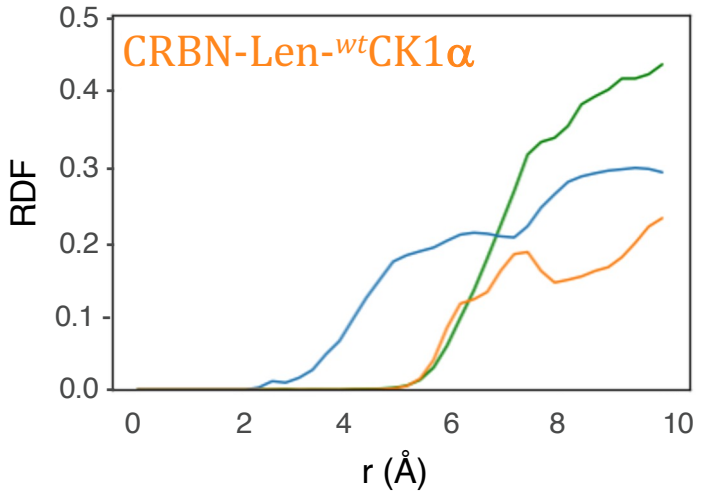
CRBN-Len-^{N39G}CK1α has weaker H-bonds and reduced hydrophobic shielding

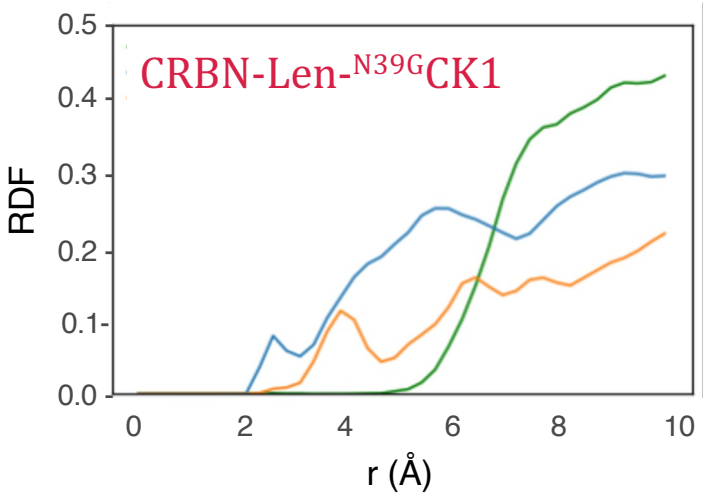


N39-W400 T38-H357 I37-N351

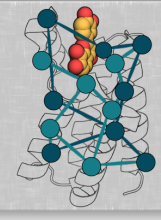


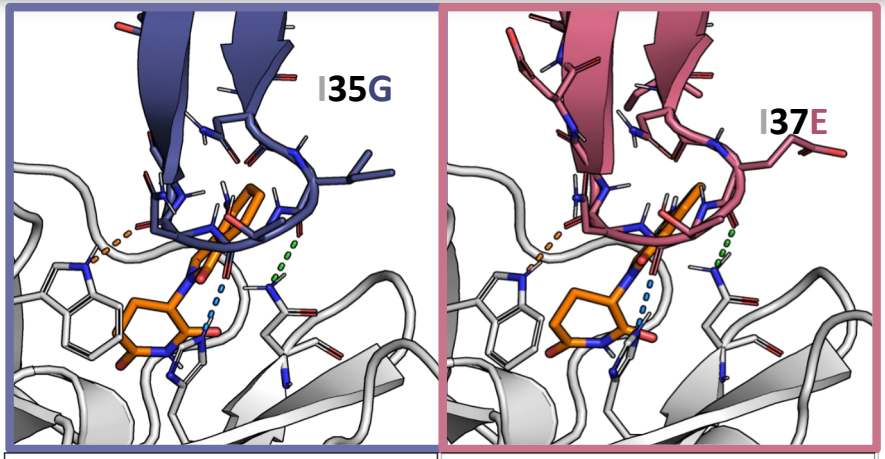


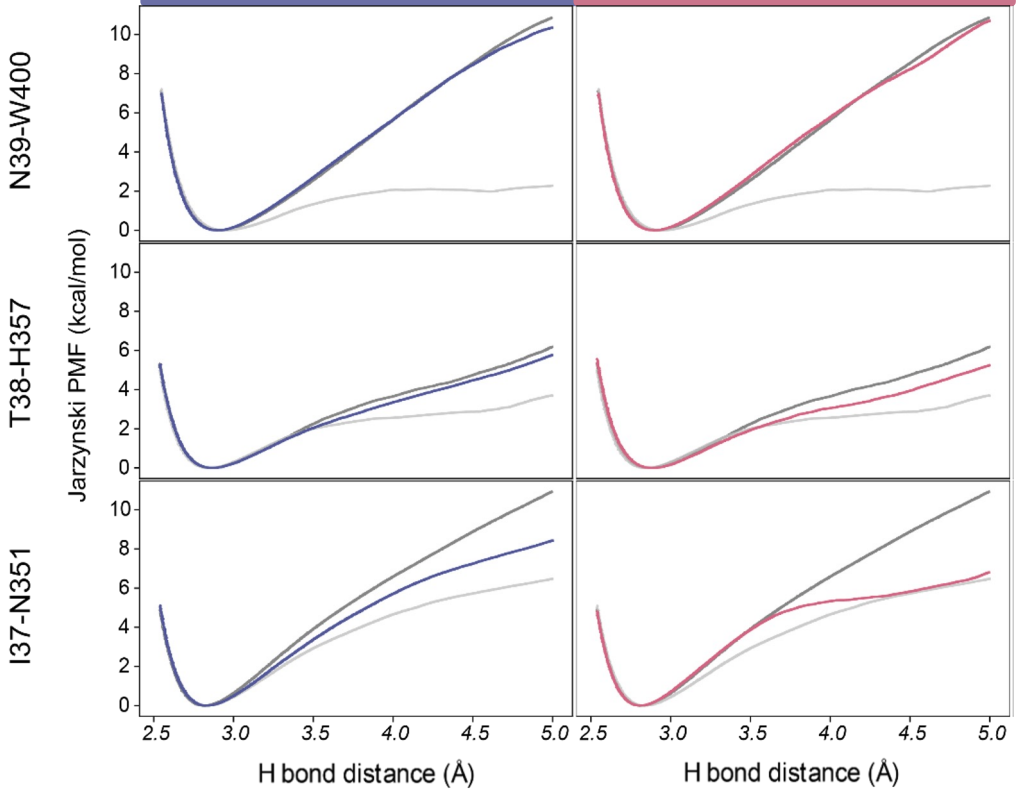


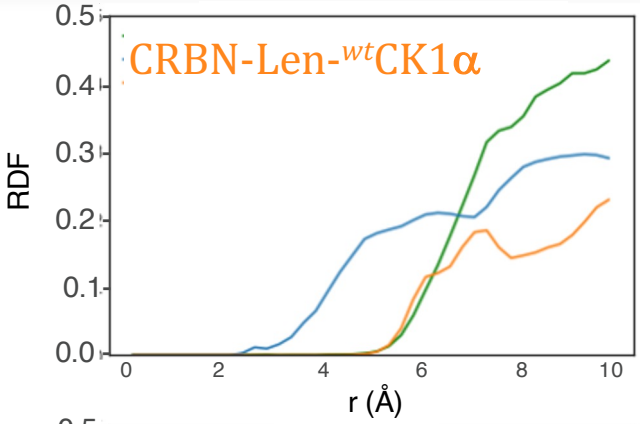


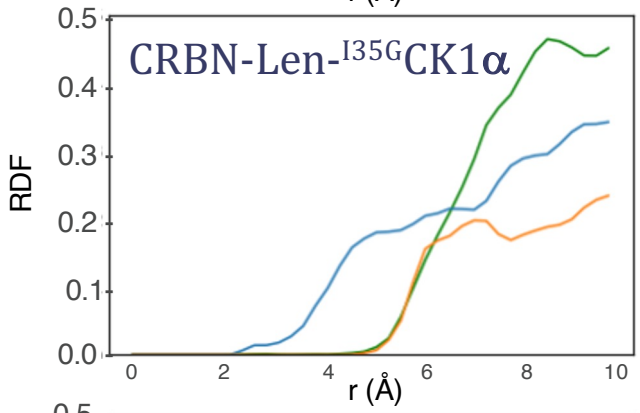
^{I35G}CK1α and ^{I37E}CK1α display less dependence between H-bond strength and shielding

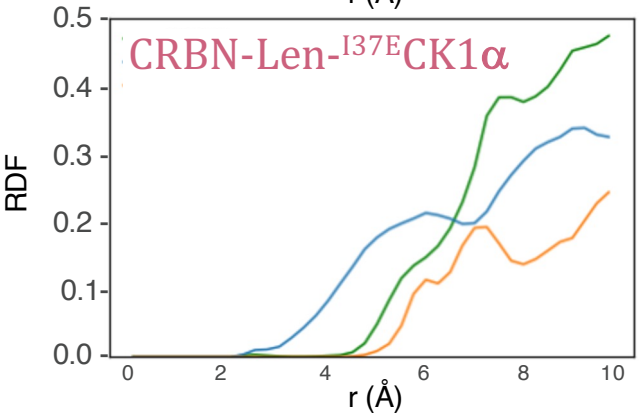




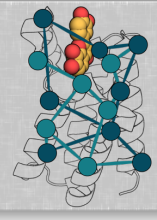




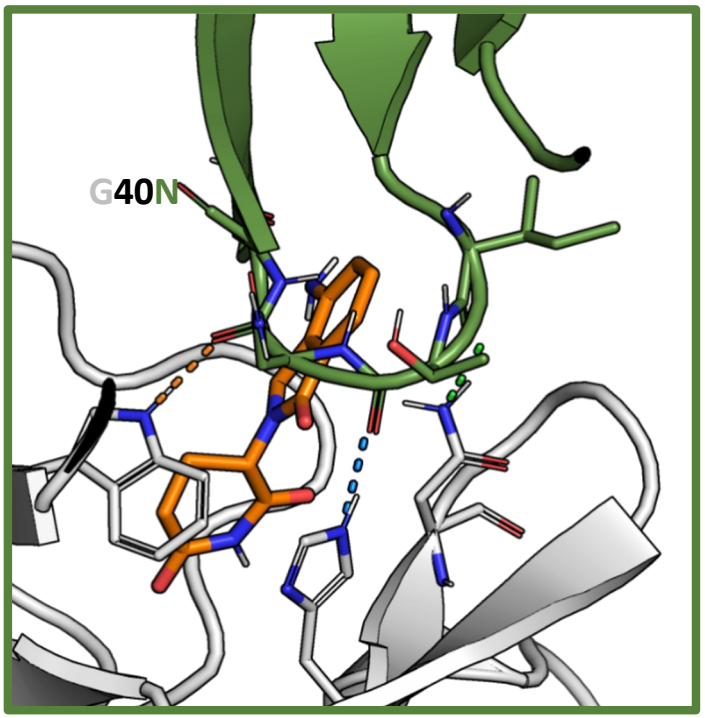


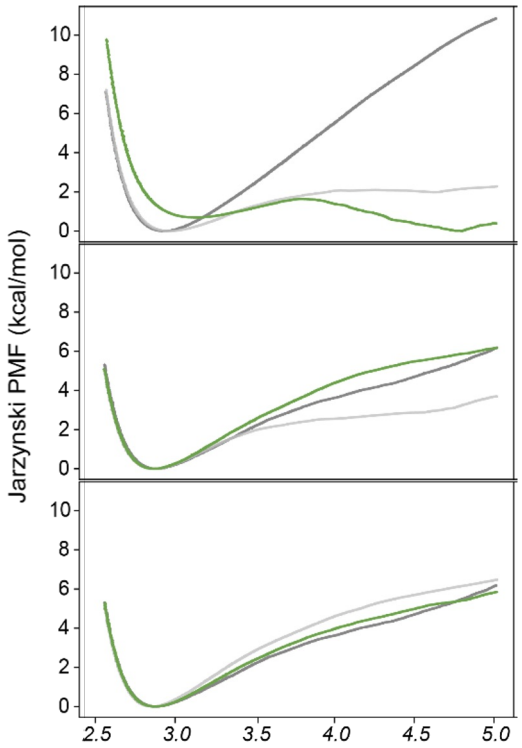


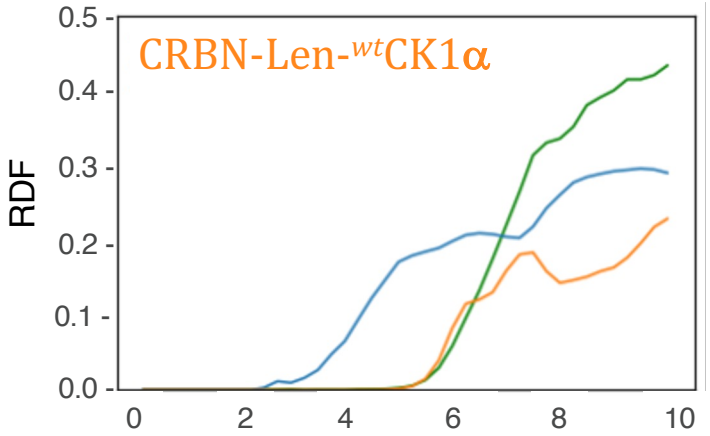
CRBN-Len-^{G40N}CK1α has the weakest set of H-bonds but the highest hydrophobic shielding

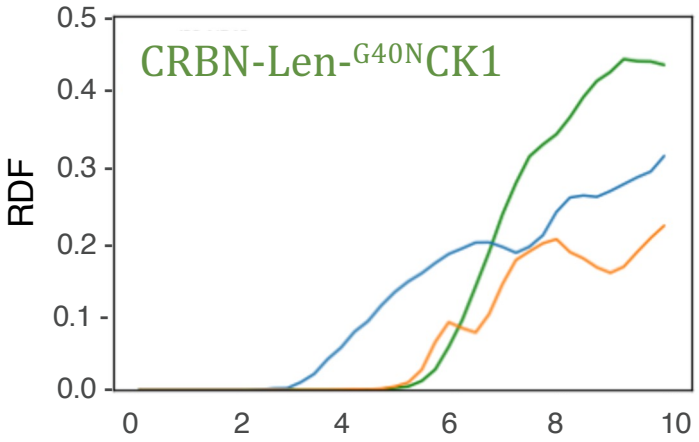


N39-W400 T38-H357 I37-N351

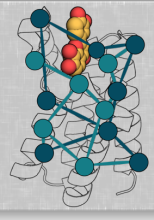


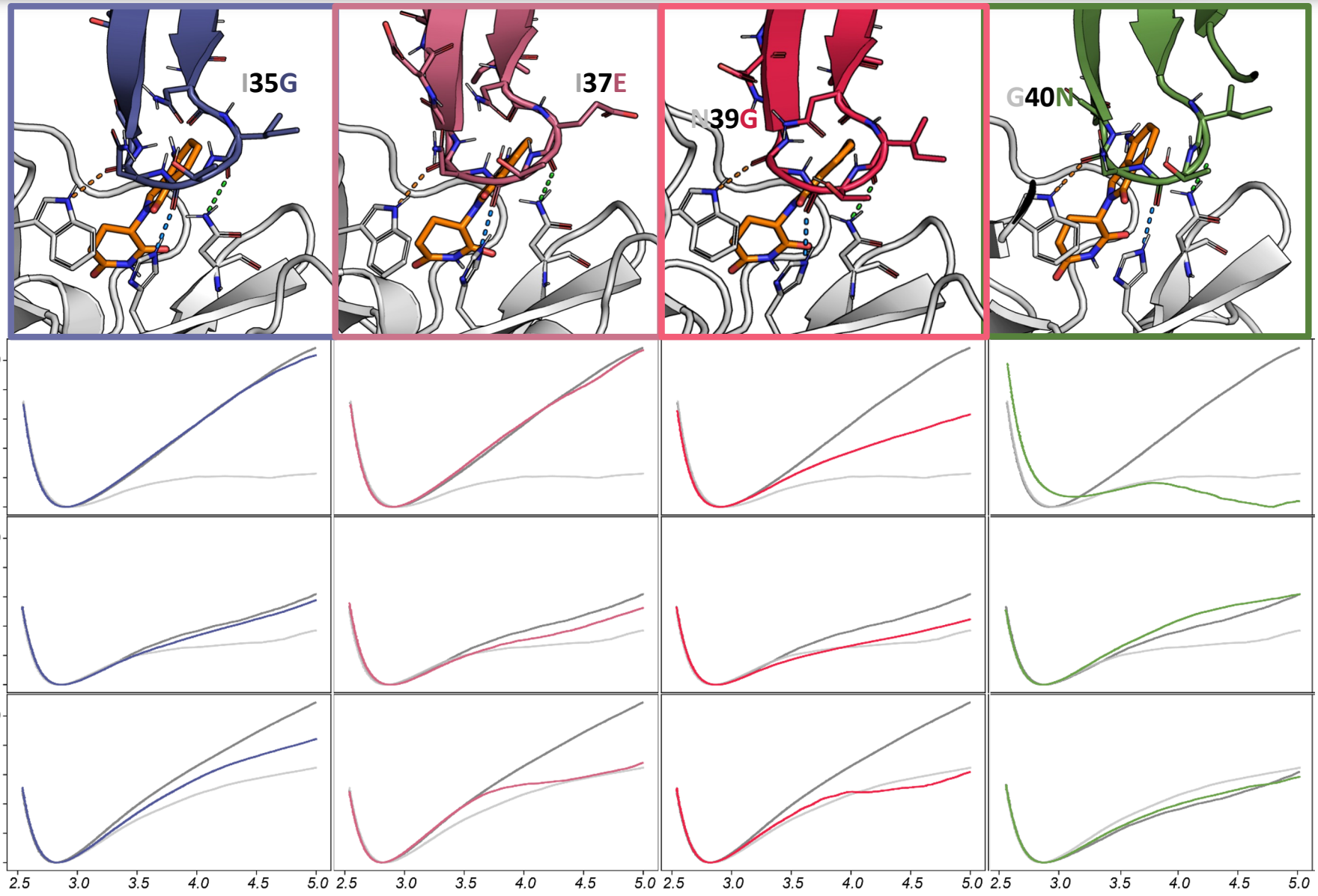




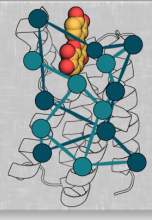


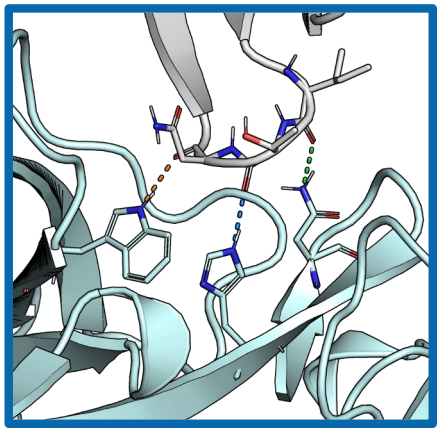
Mutations in CK1 affect the strength of H-bonds even in the presence of lenalidomide

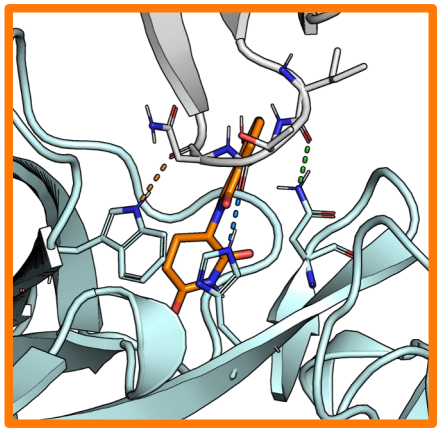




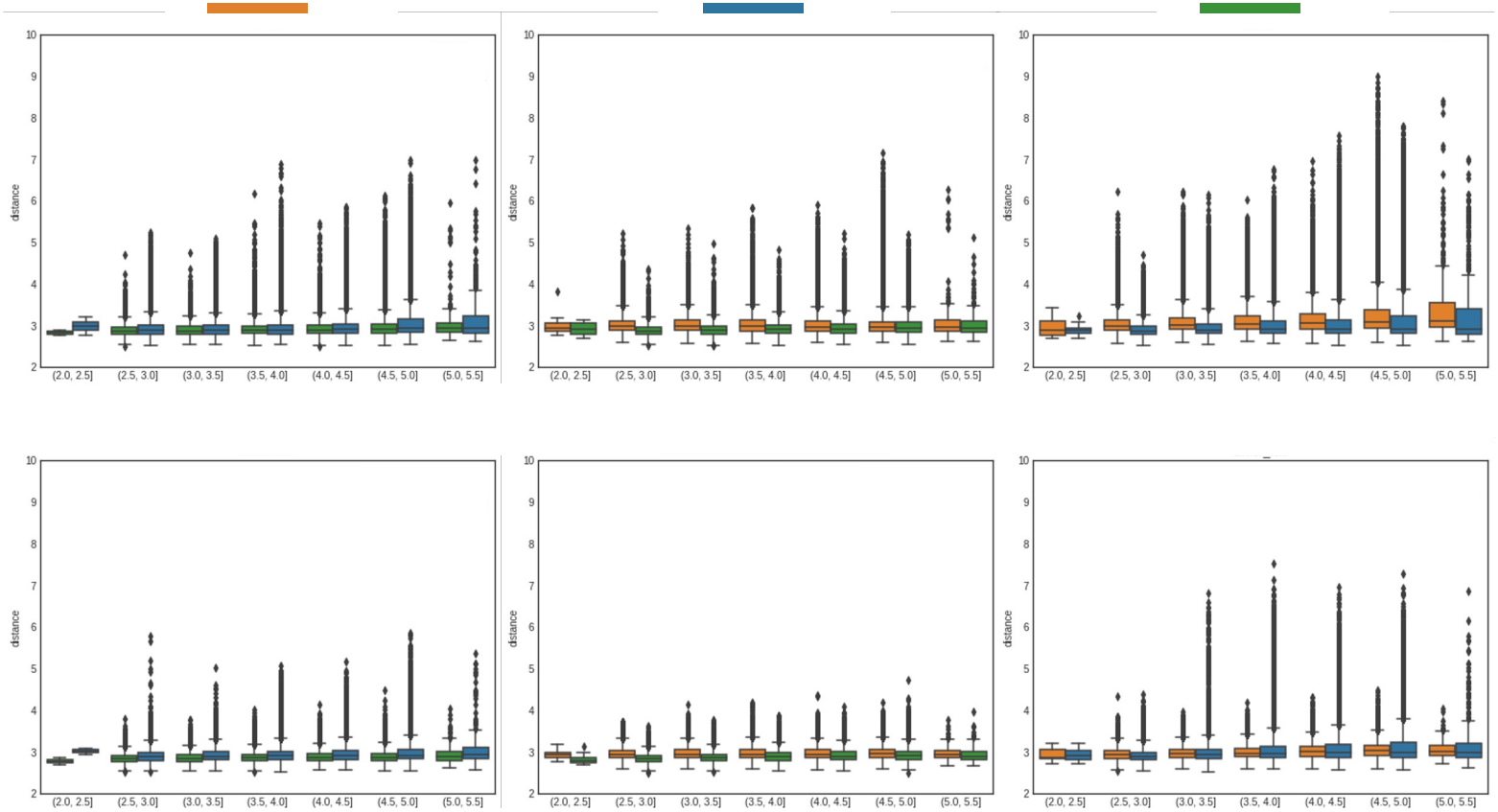
Breakage of the three H-bonds shows little interdependence



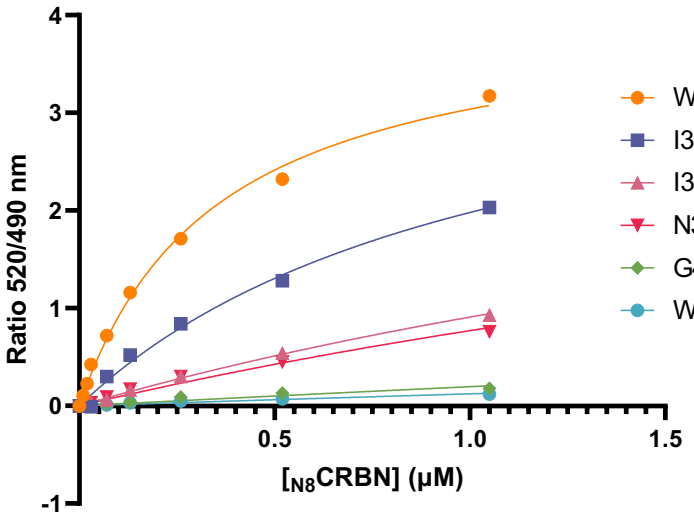




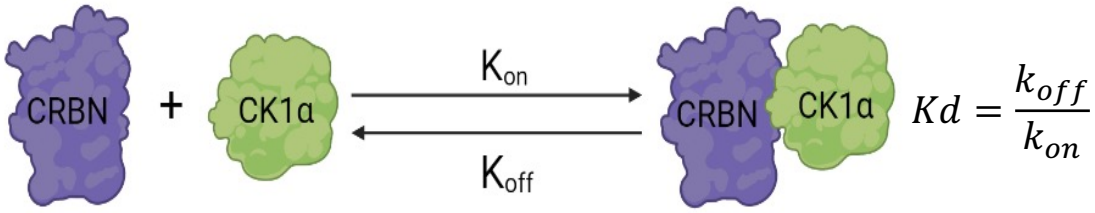
N39-W400 **T38-H357** **I37-N351**



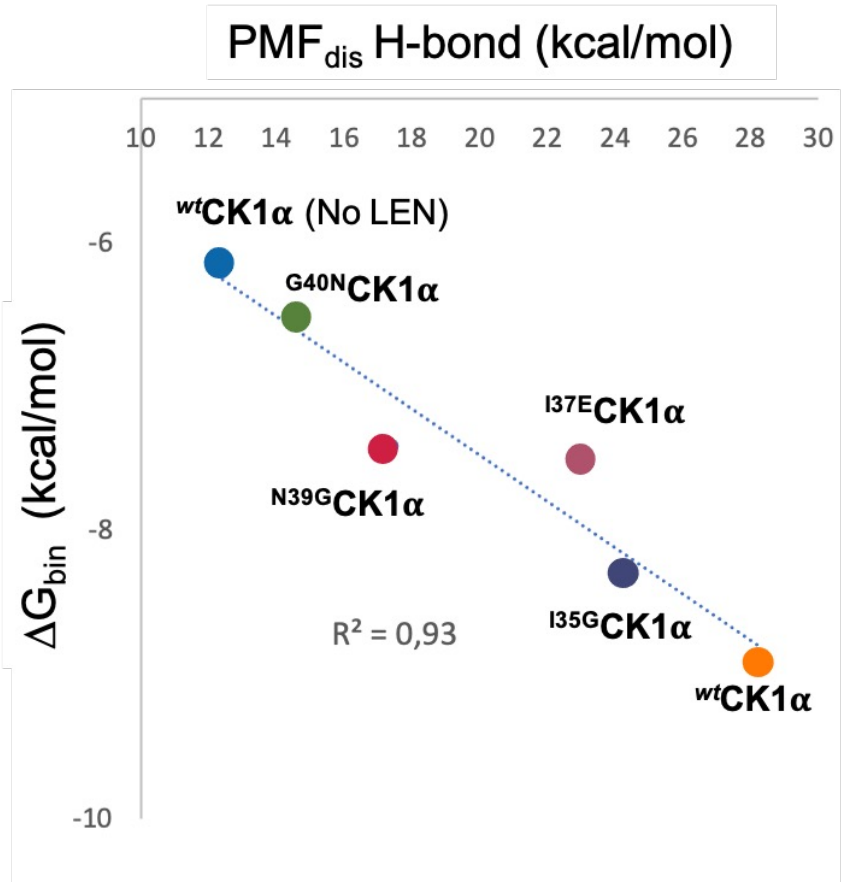
The additive PMF correlates with the affinity of the ternary complex



ΔG_{bin} (kcal/mol)
-8.9
-8.2
-7.5
-7.4
-6.5
-6.2

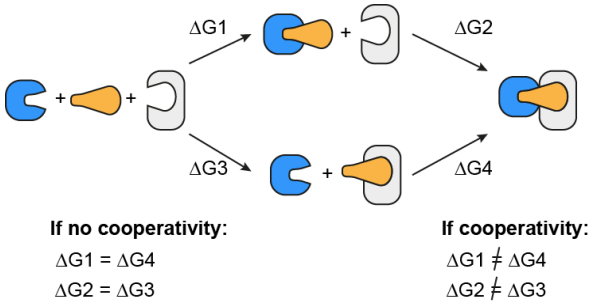


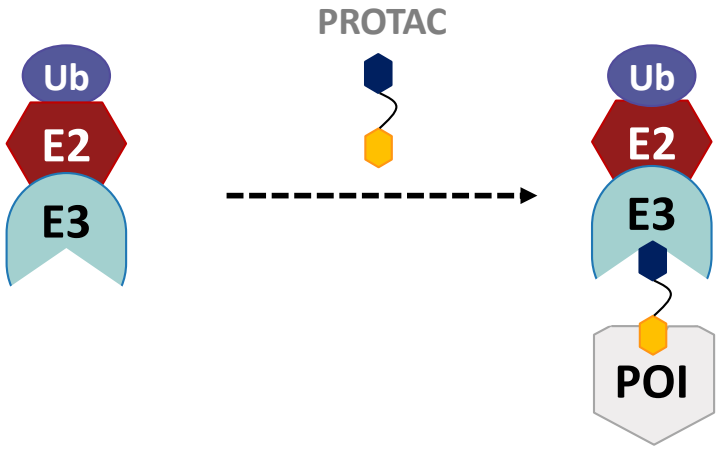
$$Kd = \frac{k_{off}}{k_{on}}$$



Conclusions

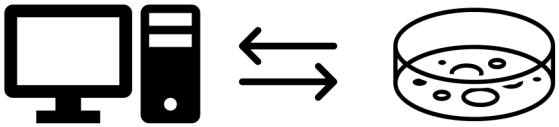
Understanding chemical cooperativity will help in the rational design of PROTACs.





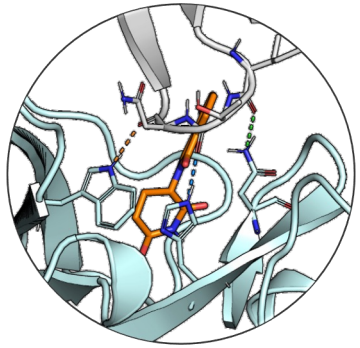
TPD based on PROTACs are an emerging and promising technology for the development of new therapeutics.

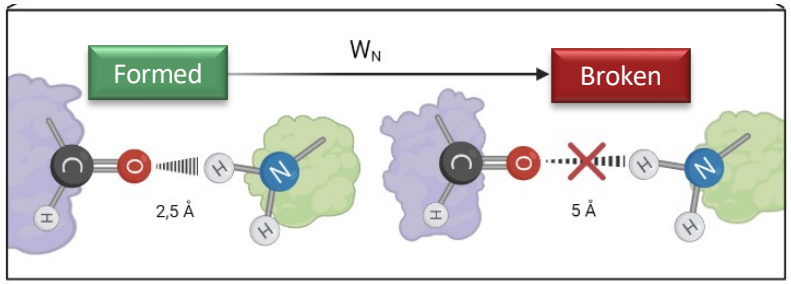
New approaches and workflows will be required for CADD to have an impact in the design of PROTACS.



Conclusions

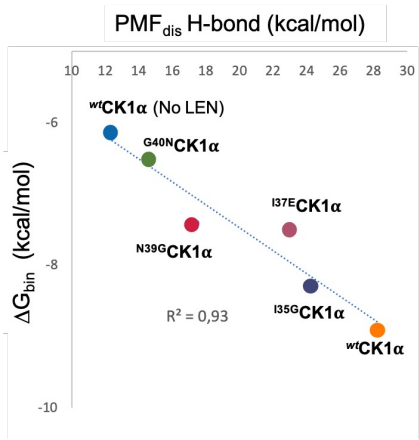
The affinity of Lenalidomide mediated CRBN-CK1α complexes relies on the strength of three key H-bond interactions.





Establishing the strength of key H-bonds in protein-protein interactions can rank the stability of ternary complexes involving similar partners.

CRBN-CK1α provides proof of concept for an easy-to-implement approach to assess non-additive effects that maybe extensible to other molecular systems in TPD and beyond.



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Computational facilities

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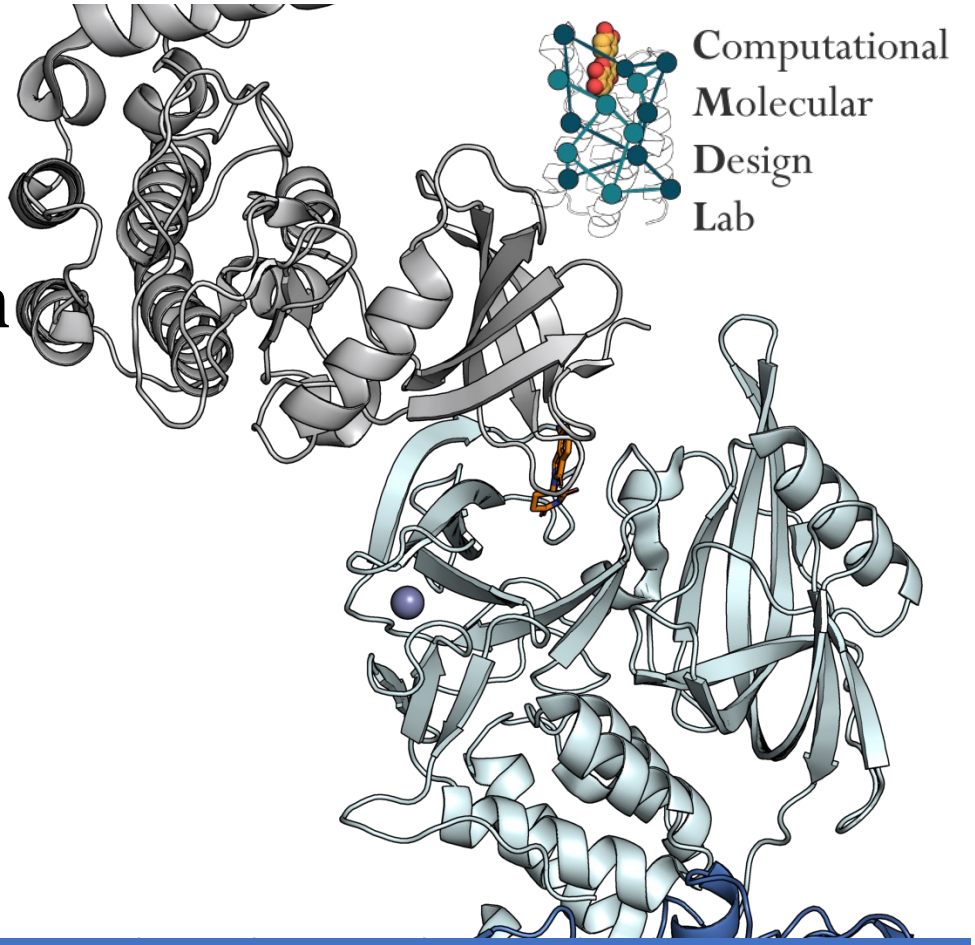
Understanding cooperative effects in PROTAC-Mediated Ternary Complexes for Protein Degradation



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Jordi Juarez-Jimenez, PhD

16th RES User Conference

14th September 2022

Institut de Química Teòrica i Computacional
UNIVERSITAT DE BARCELONA

EXCELENCIA MARÍA DE MAEZTU