Targeted protein degradation

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Proximity-inducing pharmacology

Controlled interactions between macromolecules are fundamental regulatory layers. Hijacking these circuits via proximity-inducing small molecules offers many therapeutic opportunities. The organizers, Georg Winter and Cristina Mayor-Ruiz, report on the latest trends in this emerging field discussed at the 39th IRB-BioMed Conference in Barcelona.

Fig. 1 | Attendees at the 39th IRB-BioMed Conference,"Proximity-inducing pharmacology: targeted protein degradation and beyond," held in Barcelona on 22–25 May 2023. Sponsored by the BBVA Foundation. Copyright IRB Barcelona.

The interest in proximity-inducing pharmacology has experienced a resurgence that was arguably motivated by the current progress in the field of targeted protein degradation (TPD). TPD depends on small molecules that induce proximity between a protein of interest (POI) and an effector of the cellular degradation machinery, often an E3 ubiquitin ligase, thus causing degradation of the POI. The 39th IRB (Institute for Research in Biomedicine)-BioMed Conference, "Proximity-inducing pharmacology: Targeted protein degradation and beyond," was held on 22–25 May 2023 in Barcelona (https://www.irbbarcelona.org/en/events/proximity-inducing-pharmacology-targeted-protein-degradation-and-beyond). This meeting was free of registration fees for attendants and sought to provide an interdisciplinary forum for researchers interested in the chemical modulation of biomolecules' fates by means of induced interactions. Scientists in many areas of drug discovery used this opportunity to engage in insightful discussions, exploring both the prospects and challenges within this captivating field. This report summarizes the successful event, outlining the key topics, emerging trends and research questions.

On the first day of the conference, a significant point of emphasis was placed on small-molecule 'degraders', which are compounds that induce degradation of a POI usually by inducing proximity to an E3 ubiquitin ligase, causing POI ubiquitination and proteasomal degradation. Protein degraders are commonly classified as either proteolysis-targeting chimeras (PROTACs) or molecular glue degraders (MGDs). PROTACs are 'bivalent' and feature a dedicated ligand for the POI and a dedicated E3 binder, connected by a linker. MGDs, in contrast, are 'monovalent' and connect POI and E3 in a highly cooperative manner, typically by binding only one of them in isolation. Data presented at the conference highlighted some of the known advantages of degraders, such as greater selectivity, over conventional small-molecule antagonists, as exemplified by selective degraders for the cancer-relevant targets CBP (Danette Daniels, Foghorn Therapeutics, USA) or SMARCA2 (William Farnaby, University of Dundee, UK)[1]. Another active line of research in the PROTAC field on display was the effort to unlock novel E3 ligases for PROTAC-mediated degradation (such as SIAH1 and SIAH2). Further research will be required to understand whether chemical control over new ligases will allow the degradation of additional proteins, whether they enable tissue- or context-specific degradation strategies and whether they can address anticipated resistance mechanisms in the clinic.

Compared with PROTACs, design principles for MGDs are less straightforward. Hence, rational approaches to developing MGDs are urgently needed. To this goal, efforts to prospectively design MGDs that rely on computational and experimental approaches, such as virtual mapping of interaction energies or deep mutational scanning, were presented. We expect that it will become increasingly feasible to nominate matching POI–E3 pairs with complementary protein surface topologies for ensuing MGD discovery. This process will be further empowered by mechanistic investigation of serendipitously identified degraders, via functional genomics and structural investigation. This was exemplified by efforts to characterize the mechanism of action of the ligand-induced degradation of nuclear hormone receptors, highlighting the role of the quality control ligase UBR5 (Nicolas Thomä, Friedrich Miescher Institute for Biomedical Research (FMI), Switzerland)[2]. Finally, the clear demarcation between PROTACs and MGDs that was initially perceived might need to be reconsidered. With an increasing mechanistic understanding, we are starting to appreciate that bivalent ligands can display a very glue-like behavior, thus arguing that the dogmatic differentiation between PROTACs and glues might not always apply. This point was most apparent with regard to the mechanistic dissection of a novel BRD4 degrader, which revealed a unique mechanism of action. This degrader functions as a bivalent intramolecular glue that engages both bromodomains of BRD4 in cis, which stabilizes an intrinsic affinity between BRD4 and the E3

ligase DCAF16, causing BRD4 ubiquitination and degradation (Angus Cowan, University of Dundee, UK)[3].

In addition to the PROTAC and MGD strategies based on the ubiquitin–proteasome system, the conference revealed a strong interest in expanding the TPD field toward other cellular degradation systems. On the one hand, this will further increase the reach of this modality to extracellular or membrane proteins as well, as exemplified by lysosomal targeting chimeras, or LYTACs (Green Ahn, Stanford University, USA)[4]. On the other hand, this will enable TPD in, for instance, bacteria, where prototypical 'BacPROTACs' can eliminate target proteins by hijacking the Clp protease system, thus providing an exciting avenue for the design of a completely new type of antibiotics (Francesca Morreale, The Crick Institute, UK; David Hoi, Research Institute of Molecular Pathology (IMP), Austria)[5,6].

The remarkable advances in TPD have fueled great interest in other proximity-inducing concepts that can endow proteins and transcripts with new functions. What was once a mere curiosity in the realm of chemistry has now grown into a remarkable collection of inducers of proximity that goes beyond protein degradation. This was the focus of the second day of the conference. Leaders in this area discussed how harnessing the power of selective biomolecule interactions and enzymatic control could modulate important biological processes. In brief, the innovations beyond TPD revolved around two key areas: (i) protein post-translational editing and (ii) non-post-translational models of induced proximity. Several examples showcased the versatility of drug-induced proximity to enzymes such as deubiquitinases, kinases, phosphatases or acetyltransferases for manipulating post-translational modifications on a POI. From these talks, a key theme was noted: there is a firm dedication in the field to expanding this area of proximity-inducing modalities. How often will the targeted addition or removal of a post-translational modification affect the function or localization of a POI? How straightforward will it be to control selectivity, and which parameters will drive potency? These and related questions emerged from the research presented.

Presentations related to non-post-translational concepts of induced proximity started with discussion of the mechanism of action of monovalent small molecules that can orchestrate non-enzymatic protein–protein interactions and lead to the selective elimination of cancer cells with high levels of one of such proteins, as illustrated by the 'velcrin' molecules (Heidi Greulich, Broad Institute, USA). Bivalent molecules also had an important place in this part of the conference, as exemplified by an inspiring talk by Craig Crews (Yale University, USA) outlining recent efforts in inducing proximity between an essential pan-expressed protein and another protein that is selectively expressed in cancer tissue (RIPTACs)[7]. This and similar strategies are emerging as new means to exploit cancer vulnerabilities. Finally, the talks showcased how current efforts in the field extend beyond the confines of protein interactions and post-translational modifications, now encompassing the domain of nucleic acids as well. Along these lines, Matthew Disney (Scripps Research Institute, USA) shared an impressive elucidation of the fundamental principles that govern the recognition of RNA structures by small molecules to enable the design of RIBOTACs, bivalent molecules that trigger targeted degradation of RNAs via RNase recruitment[8].

Overall, the key lessons of the second day of the conference underscored that, as in the early days of degraders, open questions remain: How target-generalizable are the new modalities? Is the endogenous function of hijacked enzymes perturbed? Can we move from chemical tools to clinical compounds? In the years ahead, the collective results will provide further profiling and comprehension of these next-generation proximity modulators. We anticipate that these efforts will not only generate even greater interest but also demonstrate the immense potential inherent in this class of drugs.

The last day of the conference was dedicated to discussing how computational approaches may expedite drug-discovery progress in the field of proximity-inducing pharmacology. Computational models have now started to harness experimental data with the aim of identifying and helping to rationally design new modulators of proximity, with most talks in the session focusing on degraders. The current challenge remains the accurate in silico prediction and analysis of ternary complex formation. In brief, current trends in the computational prioritization of E3–target pairs for glue discovery and approaches for PROTAC linker modeling were discussed. The importance of systems biology for drug development, and the application of artificial intelligence in ligand identification, were also recurrent themes. As a nice closing lecture, Natalia Szulc (International Institute of Molecular and Cell Biology, Poland) guided the audience through the portal DEGRONOPEDIA, which allows proteome-wide inspection of degrons, the minimal elements within proteins that are sufficient for endogenous E3 binding[9]. Similar repositories could help rationalize future drug-discovery efforts. Overall, the computational work presented emphasized the need for a dynamic 'dialogue' between the data gathered in the field, especially through biophysics approaches, and structural elucidations. This integration is paramount to advancing the rationalization of computational degrader design.

In conclusion, as our understanding of drug-induced interactions continues to grow and as the application of this strategy in disease expands, we can anticipate a plethora of further advances. With an impressive lineup consisting of 20 invited speakers, 15 short talks and 40 poster presentations, this conference became a forum to discuss and map out future challenges and opportunities, and left an indelible mark on all those who attended (Fig. 1). As organizers, we want to express our sincere gratitude to all the colleagues who attended and whose vivid participation and engagement made this conference truly exceptional.

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Competing interests

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