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Conference Report

DMCCB Basel Symposium 2022: Intrinsically Disordered Proteins as Drug Targets

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Introduction and Overview

On the 31st of January 2022, the Swiss Chemical Society (SCS) Division of Medicinal Chemistry and Chemical Biology (DMCCB) organized the DMCCB Basel Symposium 2022, 'Intrinsically Disordered Proteins as Drug Targets'. The DMCCB Symposia are hosted annually, with each year's topic voted by the members of the DMCCB.

Intrinsically Disordered Proteins (IDPs) are highly flexible molecules that often serve as messengers of signals for regulation of cell function and growth.[1] These proteins typically contain more polar and charged amino acids than folded proteins, leading to a more solvated and flexible ('disordered') structure (Fig. 1).[1] Because of this, IDPs are able to adopt dynamic 3-dimensional structures based on their environment, protein-protein interactions (PPIs), and posttranslational modifications (PTMs), enabling exquisite control of IDP function and stability.[1–5] Changes to the delicate balance of IDPs can result in dysregulated cell growth, the formation of protein aggregates, or the disruption of other crucial biological functions leading to disease development.[1,2] Therefore, IDPs are highly valuable drug targets for the treatment of illnesses such as cancer and neurodegenerative diseases.[6–9] However, IDPs are notoriously difficult to target due to their lack of defined binding pockets and structural motifs.[6,7] The DMCCB Basel symposium 2022 addressed these challenges and reinforced the connections between chemical biology, computational chemistry, and drug discovery in the context of IDPs as drug targets.

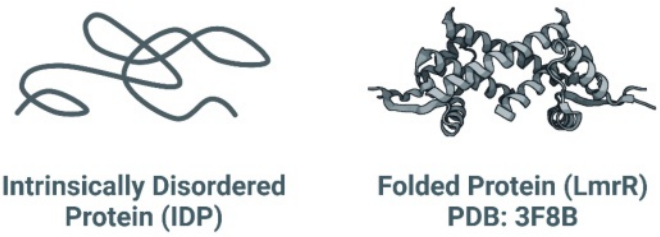


Fig. 1. Graphical representation of an Intrinsically Disordered Protein (IDP) compared to a typical folded protein. Here, LmrR is used as an example of a folded protein (PDB: 3F8B).[10] Figure created with BioRender.com.

The symposium was successfully held online through Zoom, featuring speakers and attendees from across Switzerland, wider Europe, the United States, and India. It was aimed at students in chemistry, pharmacy, biology, and at the medicinal chemistry and chemical biology community at large by including presentations from scientists based in pharmaceutical and biotech industries, as well as academia. Overall, there were 110 registered participants, with an even distribution of attendees from academia and industry, and roughly 75% of all participants were SCS members. Approximately 35% of attendees were female. In order of the conference program, invited speakers were:

- Prof. Birgit Strodel (Forshungzentrum Jülich, DE)
- Prof. Ben Schuler (University of Zurich, CH)
- Prof. Hilal Lashuel (EPFL, CH)
- Prof. Sarah Slavoff (Yale University, US)
- Prof. Daniel Nomura (UC Berkeley, US)
- Dr. Virginia Burger (New Equilibrium Biosciences, Cambridge, US).

Conference Proceedings

Prof. Dr. Jean-Louis Reymond opened the symposium by introducing the DMCCB, Swiss Chemical Society, CHIMIA, and provided a brief overview of IDPs, their importance, and current challenges in understanding and characterizing IDPs.

The first invited speaker, ***Prof. Birgit Strodel*** (Jülich), gave her presentation entitled 'Molecular simulations of IDPs: from exploring their structures to understanding their aggregation leading to diseases'. With a focus on amyloid-β peptide (Aβ), an aggregate-forming peptide implicated in Alzheimer's disease, Prof. Strodel described the use of energy landscapes and molecular dynamic simulations to study Aβ and its aggregation.[11] Through this, Aβ was found to exhibit differential folding at hydrophobic or hydrophilic surfaces, with homodimerization of Aβ occurring in both instances.[12] Understanding the folding and aggregation of Aβ is key to the development of Aβ-targeted drugs for Alzheimer's disease.

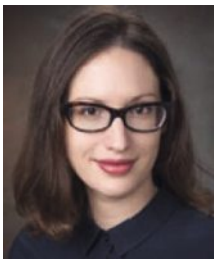
Prof. Ben Schuler (UZH) then presented work from his research group entitled 'Probing the dynamics and interaction mechanisms of intrinsically disordered proteins from single-molecule spectroscopy'. Prof. Schuler described the use of single-molecule FRET (Förster Resonance Energy Transfer) to measure inter- and intra-molecular dynamics of the IDP prothymosin-α (ProTα) and study its interactions with histone H1.[13] In contrast to the common assumption that IDPs typically exhibit low binding affinity with their interactor proteins, ProTα and H1 were found to form a highly disordered complex with picomolar affinity through polyelectrolyte interactions.[13,14] The formation of such disordered complexes can have important functional consequences: H1 binds to nucleosomes with femtomolar affinity, but ProTα can invade the H1-nucleosome complex and accelerate H1 dissociation.[15]

After a lunch break, the conference continued with nine short presentations from students and academics, namely:

- Aline Carrel (University of Bern, CH)
- Dr. Basilius Sauter (University of Basel, CH)
- Xingguang (Geo) Cai (University of Bern, CH)
- Dr. Chiara Borsari (University of Basel, CH)

- Prof. Jonathan Hall (ETH Zurich, CH)
- Prof. Michael Assfalg (University of Verona, Italy)
- Dilmehak Kaur (Indian Institute of Technology, India)
- Jinming Wu (Paul Scherrer Institute, CH)
- Dr. Ivan Urosev (University of Basel/ETH Zurich, CH).

In the afternoon session, ***Prof. Hilal Lashuel*** (EPFL) presented 'Posttranslational modifications (PTMs) in Parkinson's disease and synucleinopathies: from mechanisms to novel targets and therapeutic opportunities'. Prof. Lashuel stated that "targeting PTMs represents a viable strategy to treat neurodegenerative diseases" and described the occurrence of specific disease-related PTM-patterns on α-synuclein that could serve as a potential diagnostic tool. In particular, the PTMs of phosphorylation and glycosylation were studied. Each individual PTM – and combinations thereof – was found to influence aggregation, stability, and/or degradation of α-synuclein.[16,17] Through characterization of PTMs and PTM crosstalk, these phenomena could be used to diagnose or treat illnesses such as Parkinson's disease.[18]



Prof. Sarah Slavoff (Yale, US) presented her talk 'Dark matter of the human genome' describing work into the discovery of new small-open reading frames (smORFs) and identification of the peptides/microproteins encoded therein.[19] A large majority of smORFs and microproteins are predicted to be intrinsically disordered, and some are known to be important cellular components for biological function. Prof. Slavoff discussed the significance of PTMs for controlling the stability and function of the intrinsically disordered microprotein, NBDY, which is involved in RNA decay and liquid-liquid phase separation.[20] Phosphorylation of NBDY was found to be a key determinant of phase separation of RNA liquid droplets, thereby influencing RNA decay and cell proliferation.[20,21]

The final session of the symposium began with ***Prof. Daniel Nomura*** (UC Berkely, US), who gave his talk 'Reimagining Druggability using Chemoproteomic Approaches', which addressed the challenges in targeting IDPs due to their lack of defined structural motifs and binding pockets.[22] Prof. Nomura described the development of covalent inhibitors targeting an intrinsically reactive cysteine in the oncogenic IDP, c-Myc, presenting a highly promising approach to "drug the undruggable".[23] Following this, Prof. Nomura presented the development of covalent ligands for PROTAC (proteolysis-targeting chimera) for protein degradation, as well as DUBTACs (deubiquitinase-targeting chimeras)[24] for protein stabilization, using chemoproteomics for screening of covalent ligands to target specific proteins for PROTAC or DUBTAC action.[25]

Dr. Virginia Burger and ***Dr. Kara Herlihy*** then gave a short presentation about New Equilibrium Biosciences, a start-up company utilizing machine learning to uncover hidden druggable sites and conformations of IDPs.[26] Their software models the molecular dynamics of IDPs and integrates experimental data to identify potential binding pockets/modes in IDP drug targets. After their presentation, Dr. Burger and Dr. Herlihy then engaged the audience in a follow up discussion about experimental methods for measuring IDP kinetics, and what the next "undruggable" targets might be, after IDPs.

To conclude the symposium, the winners of the Best Oral Communication awards from the short oral presentation session were announced. First place was awarded to *Dr.* ***Ivan Urosev*** (UniBas/ETHZ) for his presentation 'Phase separation of intrinsically disordered protein polymers mechanically stiffens fibrin clots'. Runner-up was awarded to ***Jinming Wu*** (Paul Scherrer Institute) for her presentation 'Cryo-electron microscopy imagining of Alzheimer's amyloid-β 42 oligomers displayed on a functionally and structurally relevant scaffold'. The prizes for these awards were kindly donated by *Helvetica Chimica Acta*. Congratulations to Ivan and Jinming for their excellent presentations, and to all participants of the short communications session for the exceptional quality overall.

Dr. Ivan Urosev (left), winner of the Presentation Award, and runner-up Jinming Wu (right).

Summary and Outlook

The DMCCB Basel Symposium 2022, 'Intrinsically Disordered Proteins as Drug Targets', provided a great opportunity for scientists across a range of fields to discuss the recent advancements and remaining challenges towards understanding IDPs. Each presentation was met with engaging questions from the audience, leading to further in-depth discussions.

A recurring sub-theme of this symposium was the role of PTMs in the structure, function, and stability of IDPs. The importance of PTMs and PTM-crosstalk were highlighted in examples of PTM-mediated regulation of IDPs in healthy cells (PTMs of NBDY, presented by Prof. Dr. Sarah Slavoff), and in examples of disease-related PTMs involved in dysregulation and aggregation of IDPs (PTMs of α-synuclein, presented by Prof. Hilal Lashuel). Future research into identifying key PTMs, incorporating these PTMs into computational models of IDPs, and targeting disease-related PTMs are expected to greatly advance our understanding of IDPs and expedite IDP-targeted drug development.

Key challenges addressed during the symposium centered around the difficulties in obtaining IDPs for biochemical studies, computational modelling of IDPs, and observing IDPs *in vivo*. As IDPs behave very differently to folded proteins, standard biochemical (*e.g.* recombinant expression) and molecular dynamics simulations developed for folded proteins are often not transferable to IDPs. Furthermore, as IDPs are heavily influenced by their surrounding environments, obtaining *in vivo* data of IDP dynamics is crucial to truly understand the functions and interactions of IDPs in living systems and to guide drug development. Interdisciplinary approaches to develop new *in vivo*, *in vitro*, and *in silico* methods specific to IDPs will accelerate the design and discovery of IDP-targeting drugs.

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