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Abstracts Paul-Martini-Workshop
Targeted Protein Degradation
April 16th, 2026, Berlin

Prof. Dr. Brenda Schulman | *Department of Molecular Machines and Signaling, Max Planck Institute of Biochemistry, München, Germany*

Structural Mechanism of E3 ligases

The ubiquitin system is governed by the transient assembly of conformationally dynamic complexes. The molecular machines catalyzing ubiquitylation form and function in response to stimuli ranging from endogenous signals to degrader drugs. We employ an integrated multidisciplinary approach to investigate crosstalk between cellular perturbations and the ubiquitin system—from discovering cellular pathways to uncovering the underlying biochemical and high-resolution structural mechanisms. In this talk, I will present our latest findings on the visualization of dynamic assemblies involved in ubiquitin-mediated regulation.

Prof. Dr. Sonja Lorenz | *Max-Planck-Institut für Multidisziplinäre Naturwissenschaften, Göttingen, Germany*

Understanding and manipulating ubiquitin ligase specificity

The ubiquitin system is a central regulator of protein functions in eukaryotes, governing myriad cellular pathways. Driven by an enzymatic cascade, including over 600 ubiquitin ligases (= E3 enzymes), ubiquitination dynamically modifies over 50.000 sites in the human proteome. Deregulation of this fine-tuned system is tightly linked to human diseases, making ubiquitination enzymes prime targets for therapeutic manipulations. While immunomodulatory drugs (IMiDs) and recent advances with proteolysis-targeting chimeras (PROTACs) and molecular glues have illustrated the value of harnessing ubiquitin ligase activities for therapeutic benefit, current clinical strategies target only a handful of RING-type ubiquitin ligases. In the same vein, the development of ubiquitin ligase inhibitors has been challenging, as these enzymes typically lack small-molecule binding pockets at their active sites, and our understanding of regulation mechanisms that may be exploited for allosteric inhibition is still limited. Two lines of basic, mechanistic discoveries by my research group have opened innovative opportunities to overcome these limitations: (i) We uncovered a druggable allosteric regulation mode in an infection-associated E3 from human-pathogenic Leishmania parasites, the causative agents of a major neglected tropical disease. (ii) We found that exogenous drug-like small molecules can serve as substrates of ubiquitin ligases in human cells. In my talk, I will provide an overview of these ongoing projects and their translational perspectives.

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Prof. Dr. Nicolas Thomä | *École Polytechnique Fédérale de Lausanne, Switzerland*

Examples of successful molecular glue development (e.g. estrogen receptor)

The Thomä lab focusses on the structure and function of macromolecular machines at the interface of chromatin biology and ubiquitin biology. Recent work from the lab demonstrated how transcription factors operate in the context of chromatin, and how endogenous and synthetic small molecules drive the degradation of transcription factors and other cellular proteins by leveraging the ubiquitin proteasome system. The latest results on molecular glues and other targeted degradation approaches for transcription factors will be presented.

Prof. Dr. Ivan *Đikić* | *Johann Wolfgang-Goethe-Universität Frankfurt am Main, Germany*

Proximity inducing modalities in antimicrobial therapeutics

Dr. Lianne Wieske | *University of Dundee, UK*

PROTAC and Molecular Glue degrader design and mechanism

Validation of ternary complex formation between the protein of interest (POI) and the E3 ligase is a key step in the development of molecular degraders, such as Proteolysis Targeting Chimeras (PROTACs) and molecular glues.[1] Native mass spectrometry (nMS) offers a robust method for simultaneous observation of all equilibrium species, allowing for rapid assessment of ternary complex formation. We show that nMS can be used to characterise binary, ternary and higher order complex formation of $CRL2^{VHL}$, using two different proteins of interest.[2]

The linker of a PROTAC is key for productive complex formation, where linker length and flexibility are the most important variables.[3-7] PROTACs require a minimum linker length to be effective, as short linkers can prevent productive complex formation. In contrast, there appears to be no hard upper limit at which the linker length becomes too long to successfully induce proximity.[8] Although incorporation of longer linkers generally lead to effective degraders, they can cause problems with solubility and oral absorption.[5, 8, 9] We have explored the introduction of a ferrocene moiety to enhance molecular chameleonicity, aiding oral bioavailability.[7] Extensive NMR studies have been used to obtain conformational information of several ferrocene containing PROTACs (FerroTACs) in solution.

References:

1. Scott J. Hughes and A. Ciulli, Essays Biochem., 2017, 61, 505-516.
2. L. M. Sternicki, C. Crowe, L. H. E. Wieske, A. Ciulli and S. A. Poulsen, bioRxiv, 2026, DOI: 10.64898/2025.12.04.692288.
3. Y. Esubalew Abeje, L. H. E. Wieske, V. Poongavanam, S. Maassen, Y. Atilaw, P. Cromm, L. Lehmann, M. Erdelyi, D. Meibom and J. Kihlberg, J. Med. Chem., 2025, 68, 638-657.
4. H. Lan, O. Hsia, M. A. Nakasone, A. Wijaya, A. Ciulli, C. Butts and V. Aggarwal, ChemRxiv, 2024, DOI: 10.26434/chemrxiv-2024-5dbnb.
5. V. Poongavanam, Y. Atilaw, S. Siegel, A. Giese, L. Lehmann, D. Meibom, M. Erdelyi and J. Kihlberg, J. Med. Chem., 2022, 65, 13029-13040.
6. V. Poongavanam, S. Peintner, Y. Abeje, F. Kölling, D. Meibom, M. Erdelyi and J. Kihlberg, ACS Med. Chem. Lett., 2025, 16, 681-687.
7. A. Salerno, L. H. E. Wieske, C. J. Diehl and A. Ciulli, J. Am. Chem. Soc., 2025, 147, 13328-13344.
8. R. I. Troup, C. Fallan and M. G. J. Baud, Explor. Target Antitumor. Ther., 2020, 1, 273-312.
9. T. A. Bemis, J. J. La Clair and M. D. Burkart, J. Med. Chem., 2021, 64, 8042-8052.

Prof. Dr. Elmar Wolf | *Biochemical Institute, Christian-Albrechts-Universität zu Kiel, Germany* | *Institute of Experimental Medicine, Universitätsklinikum Schleswig-Holstein, Kiel*

PROTAC degraders - Targets

Transcription factors of the MYC family are among the most frequently amplified oncogenes in human tumors, and established cancers remain dependent on their elevated expression. However, MYC proteins lack intrinsic enzymatic activity and are largely intrinsically disordered, which has hindered their direct pharmacological targeting.

Instead of targeting MYC directly, we aim to degrade its binding partners using bivalent degrader molecules known as PROTACs (proteolysis-targeting chimeras). Our most advanced PROTAC development program focuses on the MYC-interacting mitotic kinase AURORA-A and has led to three key observations 1-5. First, we found that formation of the degrader complex is stabilized by cooperative binding between AURORA-A and the E3 ligase CEREBLON. Second, degrader-mediated depletion of AURORA-A induces an S-phase defect, which contrasts with the cell cycle effects observed upon kinase inhibition, thereby highlighting an important non-catalytic role of AURORA-A during DNA replication. Third, AURORA-A degradation triggers widespread apoptosis in cancer cell lines.

Together, these findings establish targeted AURORA-A degradation as a promising strategy for therapeutic intervention and provide a versatile starting point for the development of novel anticancer agents.

References:

1. O'Hanlon, J.A., Gutsche, K., Muller, J.E., Ranjan Prusty, N., Mirza, A., Roumeliotis, T.I., Yang, H., Stubbs, M., Hallett, S.T., Eing, L., et al. (2026). Unhooking the Hook: Optimization of the Aurora A Targeting PROTAC JB170 to CCT400028, an In Vitro Degrader Chemical Probe. J Med Chem *69*, 1552–1567. 10.1021/acs.jmedchem.5c03024.

2. Sflakidou, E., Adhikari, B., Siokatas, C., Wolf, E., and Sarli, V. (2024). Development of 2-Aminoadenine-Based Proteolysis-Targeting Chimeras (PROTACs) as Novel Potent Degraders of Monopolar Spindle 1 and Aurora Kinases. ACS Pharmacol Transl Sci *7*, 3488–3501. 10.1021/acsptsci.4c00405.
3. Bozilovic, J., Eing, L., Berger, B.T., Adhikari, B., Weckesser, J., Berner, N.B., Wilhelm, S., Kuster, B., Wolf, E., and Knapp, S. (2022). Novel, highly potent PROTACs targeting AURORA-A kinase. Current Research in Chemical Biology *2*.
4. Adhikari, B., Bozilovic, J., Diebold, M., Schwarz, J.D., Hofstetter, J., Schroder, M., Wanior, M., Narain, A., Vogt, M., Dudvarski Stankovic, N., et al. (2020). PROTAC-mediated degradation reveals a non-catalytic function of AURORA-A kinase. Nature chemical biology *16*, 1179–1188. 10.1038/s41589-020-00652-y.
5. Mitrovic, M., Greco, F.A., Garcia, Y.C., Lucic, A., Hoffmann, L., Chander, R., Schonfeld, J., Liebisch, N., Sivashanmugam, S.A., Schwalm, M.P., et al. (2026). Click. Screen. Degrade. A Miniaturized D2B Workflow for Rapid PROTAC Discovery. J Med Chem 69, 2599–2624. 10.1021/acs.jmedchem.5c02543.

Prof. Dr. Stefan Pfister | *Hopp-Kindertumorzentrum, Heidelberg, Germany*

PROTECT – Harnessing PROTEin Degradation for Advanced Childhood Tumours

Background:
Cancer remains the leading cause of disease-related death in children in industrialized countries. Although treatments have improved, almost all therapies used in children are adapted from adult cancer drugs. These do not always address the unique biological features of pediatric tumors. Unlike adult cancers, pediatric tumors often have a low number of mutations but frequently contain fusion oncogenes, often involving transcription factors. Because of this, many important targets are considered "undruggable," meaning they cannot be easily addressed with traditional drugs. Therefore, there is a strong need for new, more precise treatment approaches designed specifically for children to improve outcomes and lower toxicity.

Methods and Approach:
The PROTECT consortium, funded as a Cancer Grand Challenge project (https://www.cancergrandchallenges.org/protect) brings together transatlantic experts from different fields to develop new targeted therapies for pediatric solid tumors. The project focuses on two main strategies.

First, it uses advanced technologies for targeted protein degradation, such as PROTACs and molecular glues. These approaches do not just block harmful proteins but actively destroy them, opening new possibilities for targets that were previously difficult to target.

Second, PROTECT develops innovative cellular therapies, including CAR T-cells with controllable ("switchable") functions utilizing the same principle of protein degradation. These engineered immune cells can be regulated during treatment to improve safety and effectiveness by preventing rapid exhaustion.

A structured prioritization process with clear milestones and Go/No-Go criteria ensures that only the most promising targets and drug candidates are advanced. The project pipeline covers both early drug discovery and preclinical development.

Results:
In terms of pediatric-specific targets, PROTECT largely focuses on two main classes:

- Synthetic lethal pairs of paralogues (i.e., pairs of functionally and structurally highly similar proteins) such as **VRK1** and VRK2 as well as **NXT1** and NXT2 which were shown in dependency mapping projects to comprise exquisite vulnerabilities in cancers in which the paralogue is silenced. To this end, **VRK1** was validated as a key target based on its synthetic lethal interaction with VRK2 in tumors of neuronal origin. First covalent inhibitors show high potency, selectivity, and strong binding to the target.
- The second class of targets is comprised of pediatric-specific fusion oncogenes such as **SSX-SS18** (main driver in synovial sarcoma) and **ZFTA-RELA** (main driver in ependymoma). For both of these, initial screens have identified first hits, which are now being optimized.

In addition, a novel CAR T-cell approach with an "OFF-switch" mechanism was developed. This system allows temporary control of CAR T-activity through drugs, also utilizing protein degradation, leading to improved long-term function and reduced exhaustion of these therapeutic T cells.

Conclusion:
PROTECT shows that interdisciplinary collaboration and combining modern drug development technologies with advanced immunotherapy can create new treatment options for previously untreatable targets in pediatric tumors. The results so far provide a strong foundation for further development toward clinical trials and highlight the feasibility and potential of mechanism-of-action driven treatment approaches even in rare indications such as pediatric oncology.

Dr. Johanna Huchting | *Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Discovery Research ScreeningPort, Hamburg, Germany*

Assays and workflows for molecular degrader discovery

Most traditional drugs work by directly changing the activity of a specific protein. Instead, proximity-inducing drugs ("proxidrugs") reshape how proteins interact with one another. A key example is targeted protein degradation, where a drug brings an unwanted protein to the cell's own disposal system, leading to its removal. To fully realize the potential of proxidrugs and overcome some of the shortcomings of traditional drugs, we need tailored discovery methods that can reliably find the right compounds and carefully evaluate their effects.

The presentation will include a set of experimental and computational tools we use to discover and evaluate these drugs at Fraunhofer ITMP. Our laboratory screening relies on

highly automated experiments in small-volume formats, allowing large numbers of compounds to be tested efficiently. We use several complementary measurement techniques, including antibody-based assays and advanced cell imaging, to directly measure protein levels and localization, and to observe changes in cell morphology. To support potential applications in diseases of the central nervous system we implement a human induced pluripotent stem-cell-based model of the blood–brain barrier that assesses whether these molecules can reach the brain. Further, we develop informatic tools and machine learning models to enable efficient knowledge exploration, property prediction, and interpretation of complex experimental data.

Prof. Dr. Stefan Knapp | *Institute for Pharmaceutical Chemistry | Structural Genomics Consortium, Buchmann Institute for Life Sciences, Johann Wolfgang Goethe-University Frankfurt am Main, Germany*

Proximity Pharmacology

The concept of small-molecule-induced proximity has opened up a new area of drug development. The first generation of proximity-inducing drugs focused on developing degraders, such as molecular glues and PROTACs. However, proximity inducers may have a much wider scope than just degrader development. Because of time-consuming multistep synthesis and evaluation cycles, the discovery of new bifunctional molecules will require a rethink of the small molecule discovery process. In this short talk, I will present new screening technologies for ligand discovery, as well as direct-to-biology approaches to make synthesis and testing cycles more efficient for discovering bifunctional molecules.

Dr. Raymond Deshaies | *Division of Biology and Biological Engineering, California Institute of Technology, Pasadena CA, USA*

Reflections on the discovery of proteolysis-targeting chimeric molecules (Protacs)

Protein degradation by the ubiquitin-proteasome system (UPS) is the major mechanism for clearance of proteins in the cytosol and nucleus. The UPS has the remarkable property that it can degrade every protein encoded in the genome (as evidenced by its broad role in quality control of newly-translated proteins), while also targeting specific proteins in a manner that is both highly selective and tightly regulated. This arises in large part because the human genome encodes 672 high-confidence ubiquitin ligase/E3 enzymes that specify substrate selection. These properties render the UPS ripe for exploitation as a mechanism to pharmacologically manipulate cell physiology.

Indeed, this has not escaped the attention of viruses. There are numerous examples of tiny virally-encoded proteins that serve as adaptors to link a cellular protein that would restrict

viral propagation to an ubiquitin ligase that mediates ubiquitination and subsequent degradation of the viral protein. Collectively, these observations inspired Craig Crews and me to devise heterobifunctional proteolysis-targeting chimeric molecules (Protacs) that simultaneously bind an ubiquitin ligase (either SCFb-TrCP or CRL2VHL) and a specific cellular target protein, resulting in ubiquitination and degradation of the target protein. Major contributions by multiple labs over the ensuing 25 years have led to emergence of the 'TPD' (Targeted Protein Degradation) field and more generally in the development of an array of different 'TAC' (Targeting Chimeras) platforms that modulate target pharmacology via induced proximity with a variety of different effector mechanisms.

Prof. Dr. Maike Windbergs | *Institute of Pharmaceutical Technology, Johann Wolfgang-Goethe-Universität Frankfurt am Main, Germany*

From discovery to clinics: Enabling bioavailability of PROTACS by biorelevant permeation testing and nanocarriers

Proximity-inducing molecules hold significant promise as next-generation therapeutics for diseases that currently lack effective treatments. However, their translation into clinical applications remains challenging, as many of these compounds exhibit low bioavailability due to their high molecular weight and poor aqueous solubility. Conventional preclinical permeability assays often fail to accurately predict intestinal absorption, thereby limiting effective candidate selection and structural optimization.

This presentation introduces advanced, modified permeation assays based on three-dimensional human intestinal tissue models combined with artificial intestinal media that mimic endogenous solubilization and absorption processes in the gastrointestinal tract.

In addition, effective delivery of proximity inducers to their intracellular targets requires suitable carrier systems. To date, most in vivo studies have relied on parenteral administration, with oral delivery remaining a key yet unresolved objective. Given that oral administration is the preferred therapeutic route, improving oral bioavailability is of central importance.

This work further presents targeted nanoparticle-based delivery strategies designed to enhance intestinal permeation while maintaining intracellular activity. Encapsulation within nanoparticles enabled successful transport across the epithelial barrier, whereas the free compound was unable to permeate the membrane. Moreover, efficient intracellular release and subsequent ternary complex formation were successfully demonstrated.