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The 17th EFMC Short Course on Medicinal Chemistry on Small Molecule Protein Degraders

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The 17th EFMC Short Course on Medicinal Chemistry took place April 23–26, 2023 in Oegstgeest, near Leiden in the Netherlands. It covered for the first time the exciting topic of Targeted Protein Degradation (full title: *Small Molecule Protein Degraders: A New Opportunity for Drug Design and Development*). The course was oversubscribed, with 35 attendees and 6 instructors mainly from Europe but also from the US and South Africa, and representing both industry and academia. This report summarizes the successful event, key lectures given and topics discussed.

Introduction

The EFMC Short Courses are an initiative of the European Federation for Medicinal chemistry and Chemical biology (EFMC), established as a service to the community of medicinal chemists and chemical biologists. Medicinal Chemistry is of vital importance to the discovery and development of medicines. Modern medicines' discovery is interdisciplinary by nature, and it is therefore important for drug discovery scientists to gain knowledge in the various relevant scientific areas.

The Short Course series started in 2009, and since then, coronavirus crisis excluded, courses have been organized on an annual basis around April/May at the Castle Oud Poelgeest, Oegstgeest, near Leiden in The Netherlands, a venue conveniently located in the midst of a beautiful natural park. The Short Courses are a key element of the EFMC's mission to promote the training of medicinal chemists and are especially intended for young scientists from academia and industry. A key characteristic of the course is the limited number of participants, set to 35, to allow for in depth discussions between attendees and speakers. Another attractive feature of the EFMC Short Courses is the relatively low participation fee lowering the barrier of participation. It is possible to do so as the speakers do not require an honorarium. The general concept of the course is to provide a deep-dive course on one specific topic in the wider field of medicinal chemistry and chemical biology, with presentations given by senior scientists from industry and academia. It is a three-day course split into sets of three-hour lectures from each instructor including interactive training modules. The social get-together on the Sunday evening sets the scene for an intimate and interactive atmosphere amongst all participants allowing for networking as one additional goal of the workshop.

Every year a theme is selected by the EFMC Short Course Committee, currently chaired by Laura Heitman, and the EFMC executive board. Over the years, a broad range of topics have been addressed, such as Molecular Recognition, Engineering of Biopharmaceuticals, Small-Molecule Modulation of Protein-Protein Interactions, Modulation of Enzymes, Drug-Target Interactions, Peptide Therapeutics, Fragment-based Drug Discovery and more recently G-protein coupled receptors (GPCR) Drug Discovery. Protein degradation was selected as the theme for the 17th Course which was held in April 2023, introducing the topic for the first time. In the last ten years there have been significant developments in the field of designing small molecule protein degraders both as chemical tools and clinical candidates. With the course, we aimed to introduce protein degraders, and provide opportunities for in depth discussions on the key aspects of degrader design and development for medicinal chemists and beyond. Herein we give an overview of the key lectures and topics covered during the course.

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Presentations

1. Monday morning. Introduction to Small Molecule Degraders: PROTACS and Molecular Glues. Alessio Ciulli & Suzanne O'Connor

The conference opened with introductions around the room. This year we had participants and speakers from 16 different countries with approximately equal representation from academia and industry. Many had hands on experience in the field of targeted protein degradation (TPD) either at PhD or post-doctoral level. Others had extensive experience in optimisation of more classical small molecule inhibitors and were looking to bring up-to-date expertise in protein degraders back to their groups.

The introductory lectures were given by Prof. Alessio Ciulli and Dr Suzanne O'Connor (Centre for Targeted Protein Degradation (CeTPD), University of Dundee, UK). In their talks, they introduced the history and concept of small molecule degraders.[1] Protein degraders are most often described as either proteolysis-targeting chimeras (PROTACs) or molecular glues, depending on whether they are "bivalent" i.e. composed of two ligands joined by a linker, or "monovalent" i.e. typically lacking a linker and second binding ligand. The lecturers gave a high-level overview of the field, including the discovery of small-molecule ligands for the von Hippel-Lindau (VHL) and cereblon (CRBN) that are the two most widely used E3 ligases to develop degraders to date, both academically and therapeutically.[2] They discussed the steps involved in the mechanism of action of protein degraders (Figure 1), with examples drawn from studies with the PROTAC degrader MZ1, that has been well-characterized and widely used in the field since it was first reported.[3]

A unique and unifying feature of the mode of action of small molecules degraders is the formation of a ternary complex between the degrader, the target protein, and the E3 ligase.[4] This step is important, because it is the recruitment of the target protein in proximity to the E3 ligase that leads to the target being ubiquitinated and ultimately degraded by the proteasome and eliminated from inside the cell. Other key concepts of TPD were outlined, such as how we should assess improvements in protein degradation and the time dependency of these measurements, the hook effect, cooperativity (alpha) and selectivity of protein degradation, which is ultimately assessed using unbiased global proteomics via mass spectrometry.[5] The opening lectures were interspersed with discussion elements including what we should consider before embarking on a PROTAC programme when small molecule inhibition is not successful as well as understanding why we often don't see fast and complete degradation until the PROTACs have been extensively optimised. This allowed for informed and in-depth discussions in later sessions.

2. Monday afternoon. The Ternary Complex E3-Degrader Target: Biophysical Binding Assays and Structures. Chun-Wa Chung

The day continued with lectures from Chun-wa Chung (GSK, UK) on structural and biophysical methods to study protein-ligand and protein-protein interactions, with a major focus on the ternary complex formed by degrader molecules, the E3 ligase and the target protein.

The journey of PROTACs (Figure 1) often starts with the identification of binders to the target of interest. Recent methodologies that do this in a site-agnostic manner include DNA encoded libraries and affinity selection mass spectrometry.[6] Following binder identification, binary and ternary complex affinities, kinetics and cooperativity can be quantified by methods such as surface plasmon resonance (SPR).[7] The emerging single molecule methods of mass photometry and native mass spectrometry are useful tools to understand the distribution of species formed by PROTACs, helping address questions such as degradation selectivity and the stoichiometry and composition of complexes.[8] Hydrogen-deuterium exchange mass spectrometry can be used to provide

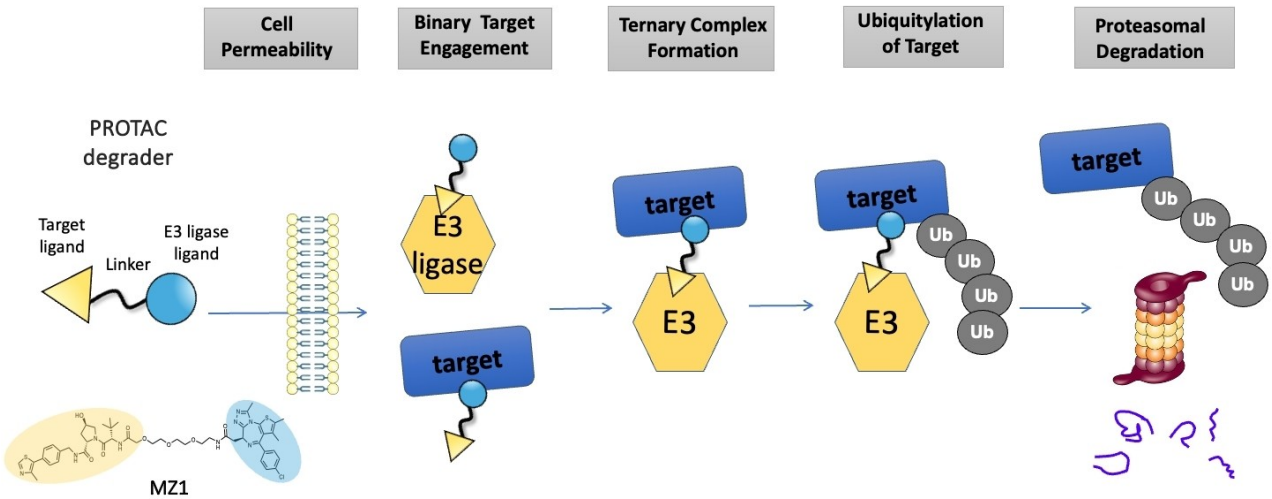

Figure 1. The journey of a PROTAC degrader, outlining the steps involved in the mode of action.

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information about binding sites, protein dynamics and conformation, and guide docking models of binary and ternary complexes.[9] The biophysics session included discussions on the significance of cooperativity changes during chemical optimisation and the interpretation of differences in measured cooperativity values generated by different techniques as they relate to degradation. X-ray crystallography and cryo-electron microscopy (cryo-EM) provide higher resolution structural understanding of ternary complexes. Structural insights rationalising the cooperativity and selectivity profile of PROTACs and molecular glues have emerged, and the field of structure based PROTAC design is developing.[4b,10] The elegant cryo-EM work of Watson et al. that demonstrates how molecular glue degraders affect the closed/open conformational equilibrium of the E3 ligase CRBN provides a sobering reminder of the complexity of the molecular drivers of degradation and the influence of conformational dynamics on multiple steps in the ubiquitination cascade.[11] The choice of structural technique was discussed in the context of the practicality, accessibility, information content and ability to guide iterative PROTAC optimisation. The opportunities and challenges of using ternary complexes to guide rational degrader design were a further discussion point.

Following the afternoon lectures, the group was taken on a one-hour walking tour through the beautiful city of Leiden, followed by dinner in a city restaurant. The walking tour provided a relaxed atmosphere and another moment for interaction between participants and lecturers, while seeing several highlights in the 17th century city centre of Leiden. For example, we saw where Rembrandt grew up as a young painter and received his first painting lessons and training. Moreover, we observed the great historical connection that Leiden has with its university (founded in 1575).

3. Tuesday morning. Clinical Aspects of Small Molecule Protein Degraders. Ingo Hartung

Ingo Hartung (Merck KGaA, Germany) kicked off the second day of lectures with an overview of small molecule protein degraders in clinical studies. To date >25 bivalent PROTACs and >10 monovalent molecular glues are in clinical trials (Tables 1,2), highlighting the rapid progression of this therapeutic modality.[12]

Molecular glue degraders of disease-causing proteins are a clinically validated drug modality with lenalidomide, a degrader of B cell transcription factors, being the world's best-selling small molecule oncology drug. However, lenalidomide-like immunomodulatory drugs ("IMiDs") degrade many transcription factors in parallel and are burdened by safety concerns, most concerningly teratogenicity which has been linked to degradation of SALL4.[2b] Sequence differences between human and rodent cereblon (CRBN), the E3 ligase hijacked by IMiDs, complicate preclinical safety assessment. The clinical landscape of molecular glue degraders (Table 1) is dominated by IMiD derivatives with tuned degradation profiles, like Novartis' IKZF2 degrader DKY709 and Monte Rosa's GSPT1 degrader MRT-2359, both recently advanced into Phase1 testing. The only other E3 ligase for which molecular glue degraders are in clinical testing is DCAF15 (indisulam derivatives). Rational approaches for the de novo identification of glue degraders are heavily pursued in academic and industrial settings.[13] The field of molecular glue

Table 1. Monovalent molecular glue degrader drugs in clinical trials, as of June 2023. Source: Beacon database (https://beacon-intelligence.com/). Abbreviations: NSCLC, Non-small Cell Lung Cancer; TNBC, triple-negative breast cancer; CRC, colorectal cancer; AML, acute myeloid leukemia; DLBCL, Diffuse-Large B-Cell Lymphoma.

Drug	Target	E3 ligase	Disease	Company	Phase
Thalidomide	IKZF1/3, ZNFs	CRBN	Lymphoma, Multiple Myeloma, others	Cellgene/BMS	approved
Lenalidomide	IKZF1/3, CK1a, ZNFs	CRBN	Myelodysplastic Syndrome, Lymphoma, Multiple Myeloma, others	Cellgene/BMS	approved
Pomalidomide	IKZF1/3, ZNFs	CRBN	Lymphoma, Multiple Myeloma, others	Cellgene/BMS	approved
Iberdomide (CC-220)	IKZF1/3, ZNFs	CRBN	Lymphoma, Multiple Myeloma	Cellgene/BMS	Phase 2
Avadomide (CC-122)	IKZF1/3, ZNFs	CRBN	Lymphoma, Melanoma	Cellgene/BMS	Phase 2
Tasisulam (LY573636)	RBM39	DCAF15	Melanoma, NSCLC, Sarcoma, other solid tumours	Eli-Lilly	Phase 3
Indisulam (E7070)	RBM39	DCAF15	CRC, Leukemia, Melanoma, other solid tumours	Eisai	Phase 1
E7820	RBM39	DCAF15	AML, Colorectal, Lymphoma, other solid tumours	Eisai	Phase 1
DKY709	IKZF2, SALL4	CRBN	Colorectal, Melanoma, NSCLC, Nasopharyngeal, TNBC	Novartis	Phase 1
CC-90009	GSPT1	CRBN	AML, Myelodysplastic Syndromes	Cellgene/BMS	Phase 1
Mezigdomide (CC-92480)	IKZF1/3	CRBN	Multiple Myeloma	Cellgene/BMS	Phase 1
CC-99282	IKZF1/3	CRBN	Lymphoma	Cellgene/BMS	Phase 1
CFT7455	IKZF1/3	CRBN	Lymphoma, Multiple Myeloma	C4 Therapeutics	Phase 1
MRT2359	GSPT1	CRBN	DLBCL, NSCLC, MYC Amplified Solid Tumours	Monte Rosa Therapeutics	Phase 1

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degraders will likely see significant innovation within the next 5 years.

Although it was only in 2019 that a patient was treated for the first time with a bifunctional degrader, more than 25 PROTACs are now in clinical studies (Table 2).[14] The most advanced clinical PROTACs target the Androgen Receptor (AR), Estrogen Receptor (ER), and Bruton's Tyrosine Kinase (BTK) resulting from a strategic decision to validate a novel drug modality rather with clinically well understood biological targets. First PROTACs against previously undrugged targets are now also in Phase1 testing (e.g. KRasG12D, BRD9, SMARCA2). However, there is some concern in the field that not enough efforts are directed against such difficult-to-drug targets and that overreliance on oral dosing may further limit the currently pursued target space. With Arvinas' PROTACs ARV-471 and ARV-110 having shown target degradation in patients, the PROTAC mode-of-action can be considered clinically validated. Reaching sufficient exposure in humans after oral dosing with such beyond rule-of-5 molecules has thus been proven to be achievable. Public domain information about developability risks of PROTACs are still limited. Establishing scalable synthetic routes requires over-average investments for such large molecules. Chemical instability of IMiDs and difficulties in generating crystalline material can add further complexity.

Small molecule protein degraders have great potential for cell biology studies as they complement genetic tools to knock-down proteins of interest. While not discussed in the lecture, the participants of the short course were provided with reading material outlining a framework for quality criteria for small molecule degraders for such cell biology studies.[15]

4. Tuesday afternoon. Medicinal Chemistry Optimisation of Small Molecule Degraders. Andrea Testa

After lunch Andrea Testa (Amphista Therapeutics, UK) opened the session discussing the aspects that guide target selection for a TPD drug discovery program: rationale for degradation versus inhibition, target tractability/ligandability, level of clinical validation or connection with human disease but also patient

Table 2. PROTAC degrader drugs in clinical trials, as of June 2023. Source: Beacon database (https://beacon-intelligence.com/).

Drug	Target	Disease	Company
Bavdegalutamide (ARV-110)	AR	Prostate Cancer	Arvinas
ARV-766	AR	Prostate Cancer	Arvinas
AC176	AR	Prostate Cancer	Accutar Bio
GT20029	AR	Acne, Acne Vulgaris, Androgenic alopecia,	Suzhou Kintor Pharmaceutical Inc.
HP518	AR	Prostate Cancer	Hinova
CC-94676 (AR-LDD)	AR	Adenocarcinoma of the Prostate, Castration Resistant Prostate Cancer, etc.	Bristol-Myers Squib
NX-2127	BTK	B-Cell Malignancies	Nurix
NX-5948	BTK	B-Cell Malignancies	Nurix
BGB-16673	BTK	B-Cell Malignancies; Lymphoma	BeiGene
HSK29116	BTK	B-Cell Malignancies; Lymphoma	Haisco Pharmaceutical
ABBV-101	BTK	ALK Positive Anaplastic Large Cell Lymphoma,	Abbvie
CG001419	TRK	Advanced Solid Tumors, etc.	Cullgen Inc.
CG428	TRK	Alopecia, Breast Cancer, Colorectal Carcinoma, etc.	Cullgen Inc.
ARV-471	ER	Breast Cancer	Arvinas
AC0682	ER	Breast Cancer	Accutar Bio
FHD-609	BRD9	Synovial Sarcoma	Foghorn Therapeutics
CFT8634	BRD9	Advanced Cancers, Chordoma, etc.	C4 Therapeutics
KT-413	IRAK4	B-Cell Malignancies; Lymphoma	Kymera Therapeutics
KT-474	IRAK4	Eczema; Hidradenitis Suppurativa; etc.	Kymera Therapeutics
KT-253	MDM2	Acute Myeloid Leukemia	Biognosys, Kymera Therapeutics
CFT1946	BRAF (V600X)	Anaplastic Thyroid Cancer, BRAF Mutant Cancers, etc.	C4 Therapeutics
ASP-3082	KRAS G12D	Lung and other cancer	Astellas
PRT3789	SMARCA2/4	Advanced Solid Tumors, etc.	Prelude Therapeutics
DT2216	Bcl-xL	Hematological Malignancies; etc.	Dialectic Therapeutics
HSK40118	EGFR	Advanced EGFR Mutated Non-small Cell Lung Cancer, etc.	Haisco pharmaceutical
KT-333	STAT3	Solid Tumours; Lymphoma	Kymera Therapeutics

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population, time and cost to recruit patients for clinical studies, competitive landscape and opportunities for population expansion post-approval. This was followed by a deep dive into concepts and approaches to identify and optimize protein degraders, ranging from screening approaches and tactics to design principles and strategies, and lessons learnt from his own experiences in academia and industry. Regarding the hit identification process, considerations were made on how to design a fit for purpose screening library: from the quality (potency, selectivity and molecular properties) of the target and E3 ligase ligands, to linker selection and chemical strategies to assemble libraries in a high throughput manner.

Moving onto medicinal chemistry optimisation of degraders, the potential of structure-based PROTAC design[10a] and "end to end" degradation assays (measure of in cell target engagement, cooperativity, rate of ubiquitination)[16] in guiding medicinal chemistry efforts were discussed. Challenges related to the collection of reliable in vitro distribution, metabolism, and pharmacokinetics (DMPK) data to build effective in vitro-in vivo correlation for compounds beyond the rule of 5 and potential "tips and tricks" were shared and discussed with the audience.[17] The significance of the free drug hypothesis, kinetics of degradation and protein resynthesis as drivers of the pharmacodynamic effects of protein degraders,[18] as well as some interesting examples of pharmacokinetics-pharmacodynamics (PK-PD) disconnection were presented,[10d,19] together with some important safety considerations (mainly related to selectivity, transporters/CYP/hERG interactions) related to protein degraders approaching the clinic. Finally, the session touched on the learnings that were made on designing orally bioavailable degraders, using an example dataset collected by Amphista and some specific examples from advanced clinical candidates.

Following the afternoon lectures, the group enjoyed some free time, before dinner at the hotel followed by a get-together at the Castle.

5. Wednesday morning. Importance of Cellular Degradation Kinetics and Mechanisms for Development of Potent Therapeutic Degraders. Danette Daniels

In the final session of the course, Danette L. Daniels (Foghorn Therapeutics, US) switched gears with an in-depth look into the diverse dynamics and cellular mechanisms of degraders, and the approaches to study these.[20] She also discussed the various ways in which degradation can be leveraged to overcome challenges presented by other therapeutic modalities and finished the course with forward-looking slides on the broader field of induced proximity.

In the first part of her lecture, she focused on cellular kinetic degradation profiles,[21] with an interactive session where members of the course tried to predict profiles based upon differential mechanistic characteristics of degraders.[20b] The discussion focused upon parameters beyond DC_{50} (concentration achieving 50% of total protein degradation) including rates, target resynthesis, native half-lives, concentration dependency, and hook effect.[20b] She shared lessons learnt from the development of cellular degrader technologies at Promega Corporation for the study of cellular ternary complex, ubiquitination, permeability, and residence time and demonstrated how these enabled understanding of mechanism of action of trivalent PROTACs.[22]

In the second part, the focus shifted towards development of therapeutic degraders, including the biological considerations and opportunities when starting new programs. She discussed differences and respective caveats between genetic CRISPR knockout and shRNA/siRNA. She then introduced the most used degron systems,[23] such as Auxin-inducible degron (AID),[24] HaloPROTACs,[25] dTAG,[26] and BromoTAG,[27] for studying the biology of target loss prior to having a tool compound. As for the opportunities, several examples were shown where initial pan-target inhibitors converted to PROTACs yielded selective family member degradation,[5] and molecular modelling of CRL complexes:PROTAC:target could help predict productive ubiquitination.[28] She finalized the session and course highlighting the next-generation modes of degraders which further expand the druggable target space to secreted proteins, membrane proteins, nucleic acids, and targets removed via pathways other than the ubiquitin-proteasome pathway.[29] Lastly, she showed how the broad concept of induced proximity is being applied to modulate protein function by impacting a large swath of post-translational modification beyond ubiquitination and how this is opening the door to new thinking.[30]

Conclusions

The 17th Course on Medicinal Chemistry was extremely well received, as evidenced by the overwhelming positive feedback from the conference participants. For example, the feedback survey immediately after the conference indicated that the course improved the participant's knowledge, as it covered many important aspects in the TPD field. The attendees also appreciated that it was interactive and had a limited number of participants to allow in depth discussion between the attendees and speakers. Moreover, they enjoyed the venue and social activity, which aided in creating a very informal atmosphere. Importantly, all participants in the survey indicated that they were looking forward to sharing their learnings and experiences with their colleagues and collaborators once back at work, and that they would recommend this meeting to their colleagues and friends, and the wider growing field of TPD. To this end, the EFMC has a "best practices" group which are releasing general documents on the best practice in different areas of medicinal chemistry and chemical biology, and further TPD teaching materials are expected to be released form this initiative soon (http://www.efmc.info/best-practices).

As this year's edition of the course was very successful, it was for the first time decided to record the presentations and make the replay accessible to interested researchers so that an even larger community could be reached. We are thankful to the speakers for accommodating this format, which will be

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considered for future editions of the Short Courses. The organizing committee is already considering for TPD to be chosen again as topic of the Course, perhaps in 2 or 3 years time. We are very keen to ensure that this course best serves and nurtures the growing community of early-career medicinal chemists and chemical biologists in TPD and related modalities, therefore do not hesitate to contact any of the corresponding authors with suggestions and comments.

Abbreviations

CRBN	Cereblon
cryo-EM	cryo-electron microscopy
DMPK	distribution, metabolism, and pharmacokinetics
IMiDs	immunomodulatory drugs
MoA	Mode of action
PROTACs	proteolysis-targeting chimeras
TPD	targeted protein degradation
VHL	von Hippel-Lindau
ZNFs	Zing-finger proteins

Conflict of Interests

The authors declare the following competing financial interest: The A.C. laboratory receives or has received sponsored research support from Almirall, Amgen, Amphista Therapeutics, Boehringer Ingelheim, Eisai Co., Merck KGaA, Nurix Therapeutics, Ono Pharmaceuticals, and Tocris-BioTechne. A.C. is a scientific founder, advisor, and shareholder of Amphista Therapeutics, a company that is developing targeted protein degradation therapeutic platforms. C.-W.C. is an employee of GSK. I.V.H. is an employee of Merck KGaA and a former employee of Bayer AG and stockholder in both. A.T. is an employee of Amphista Therapeutics. D.L.D. is an employee of Foghorn Therapeutics, and L.H. receives or has received sponsored research support from AstraZeneca, F. Hoffman-La Roche, Janssen, Promega and Vertex Pharmaceuticals. The other authors report no competing interest.

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