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FULL PAPER

EFMC – Trends in Medicinal Chemistry and Chemical Biology

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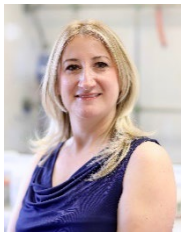
After a training in chemistry at the University of Pisa, Italy, Dr **Paola B. Arimondo** obtained a PhD in biophysics at the MNHN, Paris, and a PhD in chemistry at the Scuola Normale Superiore of Pisa. She heads the Epigenetic Biological Chemistry Unit in the Department of Structural Biology and Chemistry of the Pasteur Institute, and the CNRS-Institute Pasteur UMR 3523 Chem4Life in Paris, France. Her research focuses on epigenetic regulation and its targeting with chemical molecules. She previously directed the Epigenetic Targeting of Cancer (ETaC) unit, a joint public-private laboratory between the CNRS and Pierre Fabre Laboratories, in Toulouse, France.



Dr Maria Duca studied at the Faculty of Pharmacy, of the University of Bologna, Italy, she obtained her PhD in Molecular Biochemistry from the National Natural History Museum, Paris, France and pursued her research activities with a post-doctoral training in Sydney Hecht's lab (Department of Chemistry, University of Virginia, USA). Currently, she works as a CNRS Research Director at Université Côte d'Azur where she leads a team entitled Targeting of Nucleic Acids. Her research activities focus on the targeting of non-coding RNAs using synthetic small molecules for anticancer, antiviral, and antimicrobial applications.

Dr Sebastian Essig studied chemistry and biology at the University of Heidelberg, Germany and obtained his PhD in organic chemistry in 2013. Subsequently, he joined the group of Prof. Jason Chin at the MRC Laboratory of Molecular Biology in Cambridge, U.K., where he completed his postdoctoral training in chemical biology and synthetic biology. In 2016 he started at Bayer AG as a medicinal chemist where he was involved in different drug discovery programs. He is currently Director for Chemical Biology in Bayer's Life Science Technology Department focusing on chemoproteomics methods, covalent chemistry, novel target discovery and deconvolution strategies.

Dr Uwe Grether received his Diploma degree in chemistry at the University of Karlsruhe, Germany, where he subsequently earned his Ph.D. in organic chemistry with Professor Herbert Waldmann in 2000. After that, he joined Professor James D. White's group at Oregon State University for his postdoctoral research. In 2001, Dr Grether started at the Pharma Research and Early Development unit of F. Hoffmann-La Roche Ltd. in Basel, Switzerland. His research interests include medicinal chemistry, late-stage functionalization and chemical biology focusing on holistic approaches toward a clinical end-goal.

Dr Arne C. Rufer received his doctoral degree in biochemistry from the University of Cologne. He solved the crystal structure of the diabetes target carnitine palmitoyltransferase in close collaboration with F. Hoffmann-La Roche Ltd. During his postdoc at the Max-Planck-Institute for Medical Research, he used biophysical methods to characterize binding modes of adaptor proteins. After returning to F. Hoffmann-La Roche Ltd, he continued to link biochemical and biophysical approaches for target assessment, lead identification, and lead optimization in various roles. He founded a Mechanistic Enzymology group and is now Senior Principal Scientist and Section Head in the Lead Discovery department.

Prof. Gianluca Sbardella is Professor in Medicinal Chemistry and Chemical Biology at the University of Salerno (Italy) since 2016. He received his PhD (1997) from the University of Rome "La Sapienza". After his postdoctoral training, he was a research associate at the University of Siena then joined the University of Salerno. In 2004 he was a visiting professor in Michael E. Jung's group at UCLA. His research focuses on epigenetic drug discovery spanning synthetic strategies, medicinal chemistry, chemical biology, and biophysical techniques. He is a Past President of the Medicinal Chemistry Division of the Italian Chemical Society and Secretary of the EFMC EC.

Dr Ullrich Schopfer is the Head of the Chemical Biology & Therapeutics platform at the Novartis Institutes for BioMedical Research in Basel, Switzerland. He leads matrixed teams with expertise in biochemical and cell-based assays, structural biology, biophysics and cheminformatics involved in discovery projects across oncology, respiratory and musculoskeletal diseases. He obtained his PhD in organic chemistry in 1997 with Prof. R. W. Hoffmann at the Philipp University in Marburg, and was a postdoctoral fellow with Prof. R. Noyori at Nagoya University before joining in Novartis in 1998.

Dr Antoni Torrens obtained his PhD in pharmacy at the University of Barcelona. He joined ESTEVE Pharmaceuticals in 1989, where he was Director of Discovery Chemistry. He directly contributed to the discovery and development of several drug candidates for infection, pain, and CNS diseases. He is currently working for Welab Barcelona and for ABAC Therapeutics. He is Treasurer of EFMC and Past-President of the Spanish Medicinal Chemistry Society.

Prof. Mario van der Stelt is the chair of Molecular Physiology at Leiden University and principal investigator at Oncode Institute. By developing and integrating innovative chemical biology tools and concepts in medicinal chemistry, he aims to efficiently identify clinical candidates for cancer and brain disorders. He draws from his experience as a project leader at Merck Research Laboratories (former Organon NV, the Netherlands), where he led drug discovery programs in various therapeutic areas. At Leiden University, he develops chemical probes for use

in activity-based proteomic and chemical genetic strategies to determine on- and off-target profiles for compounds in biological systems.

Former student of the Ecole Normale Supérieure in Paris, **Dr Boris Vauzeilles** prepared his PhD with Prof. Pierre Sinaÿ, before joining Prof. Julius Rebek, Jr. for a post-doctoral experience. He then returned to France as a CNRS researcher. In 2015 he initiated the *Department of Chemical Biology* at the Institut de Chimie des Substances Naturelles in Gif-sur-Yvette (ICSN). He is also the co-founder of a startup company. His research is mainly focused on the use of synthetic chemistry to develop molecular tools designed to probe biological processes. Since early 2020, he is the Director of ICSN.

Dr Olalla Vázquez is an Associate Professor in chemical biology at the University of Marburg since 2021. She received her PhD (2010) from the University of Santiago de Compostela with Prof. Jose Luis Mascareñas and Prof. Eugenio Vázquez. Afterwards, she joined Seitz's lab as Marie Curie postdoctoral fellow at Humboldt University. In 2014 she was appointed as an Assistant Professor at the University of Marburg to manage the new chemical biology division. Since then, she pursues the complete understanding of biology at molecular level to control it on demand using optochemical tools, epigenetic chemical probes and biomolecules.

Dr Andrew Zhang is the Director and Head of Chemical Biology at AstraZeneca. His group uses a combination of chemistry and proteomics to uncover the mechanisms of hits, leads, and candidate drugs to understand their target(s), drivers of efficacy, and potential safety concerns. Andrew was trained at the interface of chemistry and molecular and cell biology at the University of California, Berkeley. After a PhD with Prof. David Spiegel at Yale University around small molecule immunomodulators he did a postdoctoral appointment at the Ontario Institute for Cancer Research (Toronto, Canada). Recently, he obtained a MBA from the University of Pennsylvania Wharton Executive MBA program.

Abstract: Ground-breaking research in disease biology and continuous efforts in method development have uncovered a range of potential new drug targets. Increasingly, the drug discovery process is informed by technologies involving chemical probes as tools. Applications for chemical probes comprise target identification and assessment, as well as the qualification of small molecules as chemical starting points and drug candidates. Progress in probe chemistry has opened the way to novel assay formats and pharmaceutical compound classes. The European Federation of Medicinal Chemistry and Chemical Biology (EFMC) has launched the Chemical Biology Initiative to advance science in the field of medicinal chemistry and chemical biology, while representing all members of this extended scientific community. This review provides an overview of the many important developments in the field of chemical biology that have happened at the lively interface of academic and industrial research.

Introduction

The European Federation for Medicinal chemistry and Chemical biology (EFMC) covers a constantly evolving scientific continuum.[1] Historically, the practice of medicinal chemistry has focused on drug candidate optimisation. Despite many spectacular successes, unresolved challenges led to an expansion of activities towards chemical probe development and chemical biology,[2] a discipline which is rapidly growing and contributing to target identification, mechanistic studies, as well as to the development of imaging and diagnostic tools[3]. Computational chemistry has also been part of this adventure for decades, and after a period focused mostly on data compilation and later, modelling, it now ventures into machine learning (ML) and artificial intelligence (AI) applications, as exemplified by the development of e.g., recommender programs and generative chemistry.[4] EFMC is constantly adapting its scope and supporting these trends, i.e., it has expanded to include chemical biology[5] and reinforced its support of computational chemistry through the recently launched EFMC^2 initiative (EFMC + Computational chemistry).[6] The latter aims to strengthen the digital community, connect industry and academia, and reinforce best practices in computational chemistry applied to drug discovery.

Recent developments in chemical biology

Chemical biology plays a fundamental role in studying biological mechanisms in cells, tissues and organisms and can contribute to the discovery and validation of new therapeutic targets. As its techniques evolve and become more reliable, its influence keeps increasing. Chemical biologists generate and exploit chemical compounds and tools with which they answer questions on cell biology and intracellular pathways, including on their *in vivo* relevance. These efforts support the overall drug discovery process by facilitating the selection and early validation of therapeutic targets. While medicinal chemists long had to rely on poorly translatable disease models, an improved molecular understanding of disease using more specific preclinical tools allows the drug discovery process to better address the causes of disease rather than merely treating their symptoms. These advances are obviously the fruits of pharmacological and molecular studies, but also structural biology, genomics, transcriptomics, proteomics, and metabolomics. They are enabled by novel and specific biological tools, or by dedicated chemical compounds generated by synthetic organic chemists.

The various -omics studies have gifted us a great wealth of actionable information on disease aetiology and treatment, but these only bear fruit through the unique contributions of data scientists and bioinformaticians. The modern medicinal chemists and chemical biologists thus need to have some proficiency in handling and understanding large datasets: the ability to speak and interact with data scientists and programmers is a skill set of growing importance, and a trend expected to further gain in importance. This is not really a concern for medicinal chemists, who have always shown a pragmatic attitude whenever a new technique demonstrated the possibility of helping their purpose of better understanding biology and more effectively treating diseases. Structural biology provides critical information for molecular optimisation programs and is a prime example demonstrating the ability of chemical biologists and medicinal chemists to quickly integrate useful aspects of adjacent technologies into their own workflows. Beginning with NMR and

X-ray structure, and over the last few years with the development of cryogenic electron microscopy (cryo-EM),[7] as well as AI-based structural prediction tools,[8] cutting edge developments in structural biology have become part of the thinking process of drug and molecular probe developers.

Advanced studies on patient-derived cells and organoids, together with genomic and epigenetic insights, allow an entry into the development of personalized medicine. This represents an important step forward in providing adequate, customized treatment for diseases where patient heterogeneity plays a critical role. Chemical biology contributes new diagnostic tools via the development of smart molecular probes, and is an enabler of personalized medicine, including easily implementable companion diagnostics. Molecular probes support and impact all phases of drug discovery programs, starting with target identification and validation, as well as assay development.[9] They open the way to lead generation, and potentially support preclinical studies and human trials with biomarkers and target engagement tools.[10] Figure 1 illustrates the general ideal of fundamental studies and methodologies needed during drug discovery processes (roots) and the actual aims that can be reached from the easiest ones (low-hanging fruits) to the most difficult but maybe more rewarding opportunities (high-hanging fruits).

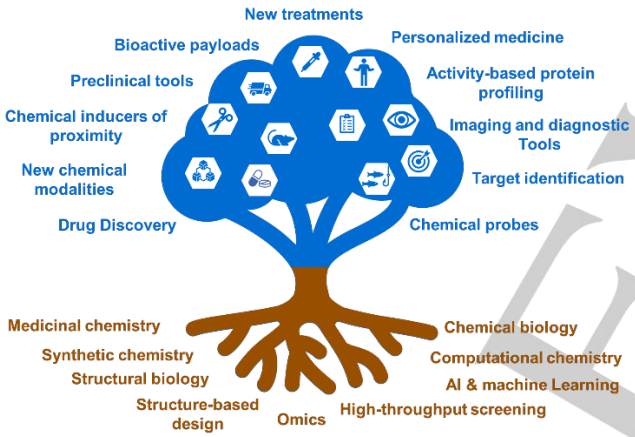


Figure 1. The tree of drug discovery: rooted in scientific disciplines and blooming opportunities. A diversity of low-hanging fruits can be harvested, but they depend on the branch one relies on, and many fruits are not so easy to reach.

Chemical biology concepts and tools go far beyond small molecule probes,[11] which are mainly generated by high-throughput screening and medicinal chemistry efforts. Sophisticated chemical biology tools can sometimes bear a range of non-drug-like functionalities, such as click chemistry groups,[12] photocages and photoswitches,[13] covalently reactive groups (e.g., warheads which can irreversibly bind to amino acids),[14] protein-tags (e.g., SNAP- and HaloTags),[15] chemical labels, dyes[16] and many more (Figure 2). Combining these functionally modified probes with modern omics, imaging, biophysical and molecular biology approaches is leading to completely novel research directions and breakthrough innovations in the drug discovery field. These strategies have a huge impact on the way researchers identify, understand, and modulate the biology of disease relevant targets, which is leading to a significant expansion of the druggable space. For instance, the FDA approval of Sotorasib, the first inhibitor of KRAS G12C, for a target which was considered undruggable for decades,[17] was made possible by the discovery of a novel allosteric switch II pocket based on a reactive disulphide tethering approach that combines covalent targeting and protein mass spectrometry (MS).[18]

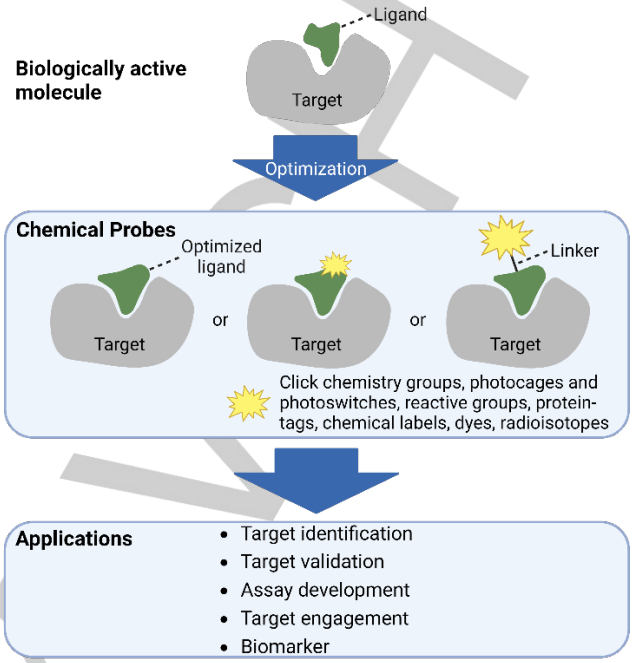


Figure 2. Examples of applications of chemical probes. Biologically active molecules are optimized toward tailor-made chemical probes using iterative chemical enhancement cycles. Classic chemical probes concentrate on interrogating target pharmacology questions. Labelled chemical probes contain one or more reporter units or handles for a subsequent further modification and allow the characterization of ligand-target interactions. Optionally, the target recognition element and reporter unit can be interconnected via a linker. Chemical probes address fundamental questions impact all stages of drug discovery programs starting from target identification and validation up to applications as target engagement biomarkers in clinical studies. Figure 2 was created with BioRender.com.

Indeed, MS plays an important role in chemical biology and chemoproteomics methods have been largely implemented.[19] Tandem mass tag multiplexing for quantification and identification of biological macromolecules by MS can be applied to proteins, peptides, and nucleic acids, and allows a significant improvement of the throughput of MS-based approaches. This and other technological improvements such as data-independent acquisition (DIA) allow the further expansion of the chemoproteomics toolbox and its application to drug discovery.[20] The development of thermal proteome profiling techniques such as Cellular Thermal Shift Assays (CETSA-MS)[21] or Limited Proteolysis-coupled mass spectrometry (LiP-MS)[22] allow a label-free detection of small molecule on-target and off-target interactions in a native cellular environment, enabling advanced target engagement and binding site analysis studies. The chemoproteomics-based toolbox to study the interactome of proteins, protein complexes and small molecules is complemented by proximity labelling approaches such as APEX, BioID and TurboID.[23] Here, the protein interaction network is labeled by tagging proteins of interest with peroxidases or biotin ligase subunits and group transfer of biotinylated probes to their native interaction partners. Recently, an intense application of this toolbox allowed to determine the complete protein interactome of an entire cell,[24] and one of the latest combinations of photoaffinity labelling, photo-catalysis, antibody engineering, and proximity ligation, allowed the micromapping of cell surface interactomes.[25]

Affinity- or activity-based protein profiling (ABPP)[26] is another chemical biology technique with a strong impact. It can determine target protein engagement and off-target activities of molecules in their cellular environment, bringing added value in optimising the target (and off-target) engagement profile of drug candidates. The strategy is based on the use of a chemical probe consisting of a ligand bound to a clickable moiety (e.g., an alkyne) in addition to a crosslinking element (Figure 3). Cells or extracts are treated with the probe, irradiated to crosslink the ligand's protein targets, and proteins are extracted. After coupling to biotin (e.g.; Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC) click chemistry), the targeted proteins are purified by affinity and analysed by mass spectrometry. ABPP provides information on the required concentration of a ligand to obtain full target engagement, while minimizing the risk for unwanted off-target interactions by preventing overexposure.[26a]

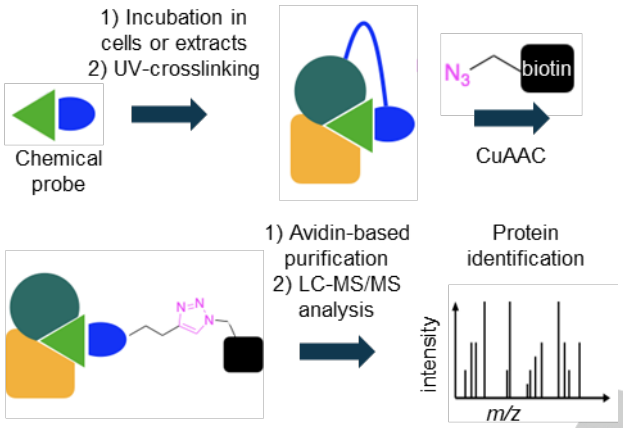


Figure 3. Example of a ABPP strategy to identify the protein targets of a chemical inhibitor/ligand (green triangle) by in cell crosslinking, affinity pull-down after click chemistry and mass spectrometry analysis.

The prerequisite of a successful ABPP approach is the availability of a chemical probe that undergoes irreversible covalent bond formation to a druggable site upon binding to a target or to several members of a target class. Probe binding selectivity can then be determined in competition against candidate drug molecules. This approach can also be used for the systematic deconvolution of target engagement following phenotypic screens (Figure 4). ABPP has emerged as a powerful technology for mapping interactions between small molecules and proteins on a proteome-wide scale in living systems and makes use of mechanism-based chemical probes that react with the catalytic nucleophile of enzymes in their native biological environment, such as cells, organoids, tissues, and patient material.[26b] In addition, ABPP approaches are frequently used as powerful lead finding strategies following phenotypic screens. The experimental evaluation of drug-target interactions may be guided by computational methods to analyse and predict polypharmacological properties.[27-29]. They allow the discovery of novel drug-target combinations, leading to novel chemical probes and novel druggable pockets for targets that could not be drugged yet.[30] From a chemical probe perspective, covalent warheads reacting with either cysteine or lysine residues[31] can be used in ABPP, as well as photoaffinity labelling (PAL) groups.[32]

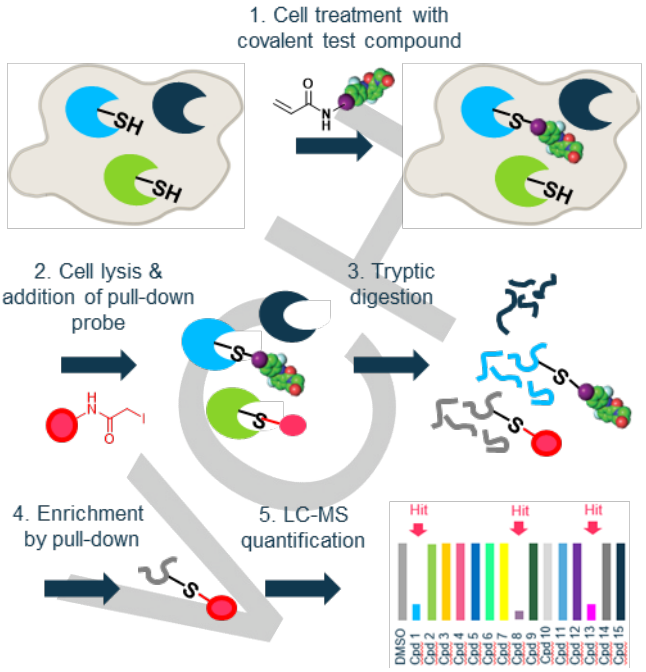


Figure 4. Illustration of a covalent cysteome-wide ABPP approach allowing the discovery of various ligand-protein interactions. Best current setup: >14000 cysteines, >8000 proteins, <20 min/compound/instrument when pooling 16 samples by tandem mass tag (TMT) labeling.

Beyond ABPP, photoaffinity-based labelling methods for off-target, binding site and target-based lead discovery are increasingly applied and constantly improved.[33] Introduction of photocaging and photoswitching groups in drug-like scaffolds allow a spatio-temporal control of target-ligand interactions for biological studies.[34] Combinations with protein engineering or synthetic biology approaches such as genetic code expansion[35] are promising tools to gain deeper biological insights in various target classes.[36] Target validation of entire protein families can be significantly facilitated by enhancing the optimization of small molecule probes with genetic engineering techniques (chemical genetics).[37] In these cases, a modified inhibitor or cofactor which does not fit well in the wild type binding pocket (bump) can be adjusted to a mutated binding pocket (hole) in the protein of interest.[38] "Bump and hole" approaches were successfully used to study the functional relevance of a domain or an entire protein in various target families, without requiring an extensive drug discovery project to provide chemical probes for every family member. Furthermore, chemical genetics approaches were applied to explain why chemical and genetic knock-out studies do not always predict the results of clinical trials.[39]

Deep biological insights can also be gained by chemotranscriptomics, leading to the discovery of novel modes of actions when small molecular probes or drugs are combined with transcriptome-wide RNA sequencing technologies. For instance, the L1000 approach[40] initially allowed for a robust quantification of several hundred transcripts. The throughput and robustness of the sequencing technology was subsequently improved to several thousand transcripts (DRUG-seq)[41] and in the meantime reaches, by multiplexing, up to single cell resolution (e.g., SciPlex).[42]

In addition to protein engineering-based tagging and labelling strategies, chemical labelling probes for live cell imaging have become increasingly important for phenotypic drug discovery, high-content imaging and target localization studies.[43] The simultaneous use of several dyes and labelling strategies in "cell

painting" approaches, with integrated data analysis by machine learning algorithms, have the potential to significantly accelerate future phenotypic drug and target discovery approaches.[44]

The 2021 Nobel Prize in Physiology or Medicine recognized the power of smart molecular probes in deciphering biological processes.[45] The design, synthesis, and validation of such species-specific or activity-specific chemical probes for *in vivo* applications remains a major field of development. Such tools can be used for imaging of specific pathologic events such as inflammation, infection or cancer, and their design can often be extrapolated for the elaboration of pro-drug or even theranostic strategies.

The advent of **bioorthogonal chemistry**[46], recognized by the 2022 Nobel Prize in Chemistry, has led to many developments in cellular chemical biology. Beyond diagnosis and identification of live pathogens,[47] transferring these technologies in live animals[48] remains a challenge that now seems reachable.[49] Recent developments include the use of biorthogonal click chemistry to control the bioactivity and bioavailability of a drug such as warfarin,[50] of the implementation of click and release strategies to control the timing of drug release from a bioconjugate[51] or from targeted micelles.[52] Although many applications remain at a relatively fundamental proof of concept level, it should be noted that this rapidly expanding field has now reached clinical trials with the Click Activated Protodrugs Against Cancer (CAPAC) platform.[53]

While chemical probes are indispensable to study cell biology and target engagement in preclinical models, a similar purpose is fulfilled in the clinic by **radiolabelled imaging agents**. In fact, PET (positron emission tomography) and SPECT (single photon emission computer tomography) imaging agents are used both for drug candidate selection and for facilitating their clinical development. One main area of application is clinical therapeutic dose selection, which is always challenging when no predictive animal model or validated clinical biomarker is available, especially for targets in the central nervous system or organs that cannot be sampled easily. For these drugs, imaging agents are the only way to quantify target engagement in patients and predict a clinical dose that will achieve efficacy with minimal unwanted effects.[54] Another important use is disease quantification, which enables the stratification of patients at the molecular level, disease staging, and the monitoring of disease progression.[55] Imaging agents directed towards disease-associated pathways prove particularly useful in this respect, as illustrated by e.g. amyloid imaging agents in Alzheimer's disease.[56]

The optimisation of chemical probes is a prime example of cross-discipline collaboration between medicinal chemists and chemical biologists. It follows specific rules,[9] and this is also true for radiolabelled imaging agents.[57] Many imaging agents are based on small molecules radiolabelled with short-lived positron emitters, e.g., ^{18}F or ^{11}C for PET or ^{123}I for SPECT. Peptides, macrocycles, and antibodies can also be used e.g., in combination with ^{68}Ga or longer-lived isotopes such as ^{111}In or ^{99m}Tc.[58] Together, they cover a range of properties, making it possible to address a variety of questions in the clinical setting, and providing clinicians with translational information that would be impossible to acquire otherwise.

Trends in new chemical modalities

The last few years have seen a rapidly expanding range of chemical modalities being explored for their potential to modulate cellular pathways in novel ways, among others including the concept of modulating target expression, rather than target function.[59] Medicinal chemists and chemical biologists have frequently joined efforts to broaden the range of therapeutic principles they optimized, aiming to exploit increasingly diverse drug targets.[60] They have explored previously intractable therapeutic concepts by adding poly-functional modalities, peptides, proteins, macrocycles, and nucleotide-based therapeutics to their low-molecular weight (LMW) armamentarium. Among others, the field of chemical inducers of proximity (Figure 5) unifies and brings out the best contributions of chemical biology and medicinal chemistry. Over the last three decades, multiple examples of synthetic constructs addressing new biology principles have been published,[61,62] including methods to redirect the immune response, for instance through bifunctional molecules[63] and CAR-T cell modulation.[64]

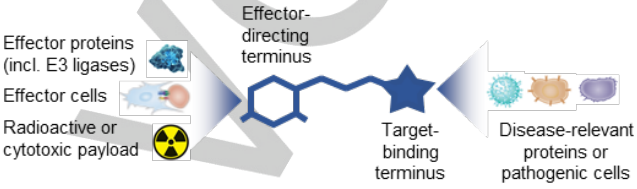


Figure 5. Chemical inducers of proximity are bifunctional molecules combining effector- and target-binding moieties, and are able to bring a therapeutic effector in the immediate vicinity of a disease-related protein or pathogenic cell.

What can be achieved in this vast domain, and how chemical biology and medicinal chemistry can work in synergy, is exemplified by the **PROteolysis TArgeting Chimeras**, PROTACs.[65] The concept originated in the late 1990s and the first PROTACs was reported by Craig Crews in 2001, with the degradation of methionine aminopeptidase 2 by the E3 ligase SCF.[66] This showed that the ubiquitin proteasomal system could be hijacked to increase the degradation of disease-causing proteins, something that is only possible through the use of a synthetic construct bringing together a protein of interest and an E3 ligase. The discovery of cereblon as the target of thalidomide[67] and the identification of SALL4 degradation as the driver of the teratogenic effects of the IMiD drugs[68] are among the most impactful findings in the past few decades. This discovery accelerated the development of PROTACs from a concept for probing biology to a new therapeutic modality,[69,70] where thalidomide has transformed from a failed drug to a critical component of potential life-saving medicines.

Bifunctional molecules such as PROTACs can have vastly different physicochemical properties compared to small molecules,[71] and traditional optimisation principles such as the rule of 5 cannot be used.[72] One challenge facing the design of bifunctional molecules for therapeutic use is the need to account for ternary instead of binary complex equilibria. In particular, the aspect of auto-inhibition at high concentrations of the bifunctional construct can result in a decrease in efficacy.[73] As a consequence, in addition to parameters such as on and off rates, E3 and target levels and turnover rates become critically important for mechanistic models.[74] A consequence of the formation of ternary complexes is that the degradation selectivity profile of these drugs may diverge from their binding selectivity profile.[75]

Recent advances in chemical biology and an increased understanding of the profile requirement of these constructs can guide their optimisation. This has vastly expanded the possibilities

of proximity induction beyond PROTACs and proteasomal driven degradation. Indeed, efforts are under way to harness different parts of the cellular machinery, such as the lysosomal pathways,[76] as well as autophagy-mediated mechanisms[77] for degradation. Further variations of the concept, with e.g., antibody based PROTACs (AbTACs)[78] or small molecules targeting RNA (RIBOTACs)[79] present additional opportunities to expand the range of druggable targets.[80] The concept of chemically induced proximity is also increasingly used to recruit and exploit enzymatic activities other than ubiquitination. Examples include post-translational modifications such as targeted phosphorylation,[81] dephosphorylation,[82] acetylation (AceTAGs).[83] More recently, deubiquitinases (DUBs) have emerged as a potential target class. Modulating DUBs can offer a distinct strategy to regulate proteins that are important for preventing serious diseases, like tumor suppressors.[84] A considerable amount of effort has been placed in understanding the mechanism of DUBs and in particular their substrate selectivity[85]. Recent work out of the Nomura group have identified a class of compounds coined DUBs targeting chimera (DUBTACs) that redirect DUBs to target proteins and in an opposite mechanism to PROTACs, modulate deubiquitination and in turn the stability of these proteins.[86] Notably, when identifying ligands for DUBTACs, compounds that directly modulate the function of DUBs may not be the choice candidates; rather, the Nomura group applied their chemoproteomics platform to identify covalent, allosteric warheads to harness the DUB OTUB1 to deubiquitinate and stabilize the tumor suppressor kinase WEE1. Taken together, modular approaches that link targeting moieties with elements providing functional activity are also driving advances in complex biologics: Cellular targeting of bioactive payloads to specific cell types, by binding to cell-specific surface proteins, is a rapidly developing field and underpins the selectivity of several emerging new modalities.[87]

Another promising approach that leverages chemically induced proximity[88] in cells is represented by **molecular glues**. Originated in 1991 and reported in a publication the following year by Stuart L. Schreiber,[89] the term "molecular glues" refers to small molecules that mediate the interaction between two proteins that do not normally interact. The immunosuppressants cyclosporin A (CsA) binding to the cyclophilin-calcineurin interface, FK506 and rapamycin binding the FK binding protein (FKBP)-calcineurin interface were early examples of molecular glues. Most recent examples induce a novel interaction between a substrate receptor of an E3 ubiquitin ligase and a target protein, leading to its proteolysis (molecular glue degraders).[90] Therefore, just like PROTACs, these molecules are binding to a naturally occurring PPI interface, with contacts optimized for both the substrate and ligase within the same small molecular entity.[91] Thalidomide and its derivatives pomalidomide and lenalidomide are early clinically approved drugs for the treatment of multiple myeloma and other hematologic malignancies. They are degrading two transcription factors, Ikaros (IKZF1) and Aiolos (IKZF3), by recruiting them to the $CRL4^{CRBN}$ complex but are also degrading various other proteins.[92] Several more recent preclinical and clinical drug candidates are rationally designed based on the Immunomodulatory imide drugs (IMiDs) scaffold and are binding to the cereblon (CRBN) E3 ligase complex. CC-92480 (mezigdomide) and CC-99282 (golcadomide) are targeted against IKZF1 and IKZF3, CC-885 and CC-9009 against GSPT1. CC-122 (avadomide) and CC-220 (iberdomide) are binding to IKZF1/3 and ZFP91/98. Apart from these rationally designed glue degraders several molecules such as indisulam degrading RBM39, BI-3802 degrading BCL6, NRX-252114 degrading mutant β-catenin were discovered by HTS screens, phenotypic screens, larger chemoproteomics based mode of action studies, or other serendipity-driven approaches.[93]

Concepts directed towards a more rational discovery of molecular glues and glue degraders are getting increasingly important. A functional genomics screen with five drugs binding to substrate receptors of the of cullin RING ligases (CRLs) led to the discovery of the E2 ligase UBE2M as key resistance regulator of CRL mediated degradation. CRISPR-Cas9-induced mutation of UBE2M and comparison of rescue phenotypes in hyponeddylated versus neddylated cell lines was used for one of the first scalable rational glue degrader screens.[94] This assay setup shows in an exemplary fashion how combined approaches based on a broad chemical biology toolbox can lead to novel and challenging assay designs.

With the recent marketing authorization of Lutathera® ([^{177}Lu]Lu-oxodotreotide)[95] and Pluvicto® ([^{177}Lu]-vipivotide tetraxetan),[96] **radioligand therapies** (RLT) are emerging as a safe and effective therapeutic approach for several types of cancers.[97] In RLT, cytotoxic doses of radiation are delivered to cancer cells by conjugating α- or β-emitting radionuclides to targeting ligands that preferentially bind to cancer cells or the surrounding stroma. The ability to develop companion imaging agents by simply changing the radionuclide to ^{68}Ga and enable the non-invasive visualization of the therapeutic agent biodistribution is a major advantage of this approach. As illustrated in Figure 6, RLTs consist of a chelator (in this example, DOTA), whose role is to tightly bind the therapeutic or imaging radioisotope, and of a target-binding motif. Both elements are connected by a linker, which influences the overall pharmacokinetics of the construct and is important in its optimisation.[98]

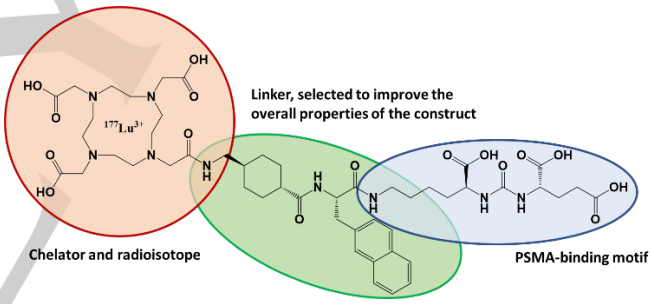


Figure 6. Structure of Pluvicto®, illustrating the modulatory construction of RLTs.

Peptides and peptidic macrocycles are not new to drug discovery, but their optimisation remains an area of intense research. They complement the drug-like space covered by low molecular weight (LMW) drug candidates, with structures that can achieve larger levels of complexity, and are often better suited to inhibit e.g., protein-protein interactions. Despite physicochemical properties diverging from those required for drug-likeness in LMW compounds, and a more frequent need for formulation to control oral absorption,[99] macrocycles can achieve surprisingly good oral bioavailability and organ distribution. This is illustrated by e.g., PAANIB-1, a PAAN/MIF nuclease inhibitor, which despite a MW of 1169 Da and high lipophilicity, showed *in vivo* efficacy against α-synuclein and MPTP-induced degeneration of dopaminergic neurons after reaching around 3 μM concentration in the mouse brain after 10 mg/kg oral administration.[100] Recent developments in understanding how to take advantage of the high affinity and potency of peptides while optimizing their drug-like properties has enhanced their attractiveness for therapeutic uses. Progress in screening techniques, side-chain modifications[101] and cyclization strategies[102] have helped address stability and permeability limitations, by fixing the secondary structure of peptides in specific conformations. Reliably and efficiently optimizing peptides into drugs remains challenging, in part due to a lack of *in silico* models

able to predict their flexibility, chameleonic behaviour[103] and cell permeability. Most drug candidates in this category are linear or macrocyclic peptides, while branched peptides remain largely unexploited. A recent success in this area is the rationally designed macrocyclic MK-0616,[104] an orally bioavailable PCSK9 inhibitor in clinical development.

The identification of disease-causing genetic alterations represents a tremendous opportunity in personalized medicine, opening the possibility to precisely treat genetically diseases. In recent years, oligonucleotide therapeutics, which include antisense oligonucleotides (ASOs), locked nucleic acids (LNA), small interfering RNA (siRNAs), microRNA (miRNAs), aptamers, and DNAzymes[105] have emerged as very promising drug modalities. This therapeutic principle has become reality with 15 compounds approved by the FDA or EMA for the treatment of multiple indications, including several rare diseases. Furthermore, the progress made in other indications and the fact that over 100 compounds are presently undergoing clinical trials make this modality a very attractive therapeutic alternative. A successful example is eteplirsen, marketed in the USA in 2016 by Sarepta Therapeutics[106]. Eteplirsen was approved by the FDA in 2016 for Duchenne muscular dystrophy. It is a third generation ASO, a phosphorodiamidate-morpholino oligomer (PMO) targeting RNA, however with a limited efficacy in patients.

The ability of **oligonucleotide therapeutics** to exploit targets previously considered undruggable makes them ideally suited for cancer treatment. Oligonucleotide therapies for oncology exploit their high-affinity specific binding to targets aberrantly spliced, or to abnormally expressed genes driving cancer progression.[107] There is no oligonucleotide marketed for cancer yet, but ongoing clinical studies are promising. Very interestingly, their application to tackle antimicrobial resistance (AMR) has recently emerged. AMR has become a major issue in public health and an economical burden worldwide. Recent progress in this research area is aimed to produce antisense compounds that silence or reduce expression of antibiotic resistance genes. These compounds could then be administered as adjuvants to the antibiotic, reducing resistance levels, which would be especially useful in resistance involving third generation cephalosporins. Lipid oligonucleotides (LONs) were shown to be efficient in decreasing the Minimum Inhibitory Concentration (MIC) of resistant bacteria to ceftriaxone.[108] However, some issues have yet to be addressed, and the main challenge is to deliver these molecules inside cells, particularly for extrahepatic tissues. Several strategies are explored by oligonucleotide-based drug platforms focusing on chemical modification, bioconjugation, and the use of nanocarriers[109] to improve delivery. Additional chemical modifications are aimed to improve binding affinity, resistance to nucleases, and pharmacokinetic profiles.[110] In parallel, studies devoted to overcoming the cell endosomal barriers are evolving very rapidly and will eventually allow oligonucleotide therapeutics to join the therapeutic armamentarium.

Overall, these new modalities represent a very promising complement to LMW drugs, but they come with their own challenges. Their development is mostly justified when the latter are unsuitable or cannot provide the desired therapeutic effect. Ultimately, the selection of the proper modality, which depends on the therapeutic target and defines the achievable product profile, is critical for a successful drug discovery program.

Covalent inhibitors are also attracting strong interest in drug discovery and represent a significant proportion of the drug candidates that reach clinical use.[111] Concerns about their potential lack of selectivity and off-target toxicity was often voiced in the past, but their overall profiles are often amazingly advantageous and allow access to targets otherwise considered difficult to drug.[112] Several factors are important in their optimisation, such as an understanding of the natural turnover of the target protein, as well as a careful optimisation of the warhead reactivity to enhance selectivity. Beyond their development as drug candidates, they have been used as probes to decipher or modulate biological processes,[113] to develop high throughput screening strategies,[114] for the specific labelling of proteins,[115] or as warheads in the design of new modalities,[116] helping expand the modern drug discovery toolbox. As such, although covalency is neither a new concept nor a panacea, it is a frequently used principle for the discovery of covalent probes for chemical biology, as well as of clinically successful drugs. However, the combination of covalent chemistry such as incorporation of Cysteine Reactive Groups (CRGs) into fragments and lead-like molecules with MS based or ABPP approaches recently revolutionized the discovery of covalent lead structures and molecular targets which can be addressed by a covalent approach.[117] Further progress in the field will be achieved by fine tuning or discovery of chemically novel warhead motifs. The current toolbox is mainly targeting cysteine and lysine residues.[118] When possible, selective targeting of other amino acid residues will have a huge impact on both the usage of covalent approaches in drug discovery programs and the design of novel Chemoproteomics assays, expanding the search for novel targets and druggable matter.

Trends in new target classes

There are still many opportunities for therapeutic discovery in historically important drug target classes such as kinases or GPCRs. Beyond this, some important protein classes have hardly been explored, and they undoubtedly represent promising options for new developments. A few examples are discussed below.

Phosphatases: In contrast to kinases, of which 518 have been identified in the human genome[119] and which have led to over 75 FDA-approved kinase inhibitors, the 189 human phosphatases[120] have been much less studied.[121] No drug acting on these enzymes has been brought to the market so far, with the exception of tacrolimus and cyclosporin, which bind to FKBP and cyclophilin respectively, indirectly inhibiting the serine/threonine phosphatase calcineurin. Phosphatases have a large potential for anticancer activity, with a variety of targets described in the literature, but carry a reputation for undruggability. Indeed, the phosphorylated substate of these enzymes is highly charged: inhibitors fitting in the catalytic pocket are very polar, making it difficult to find drug candidates with adequate pharmacokinetic properties. A comparable challenge was previously seen in the field of glutamate receptors and solved to a large extent by developing drugs targeted to allosteric binding sites.[122] Accordingly, the recent identification of allosteric inhibitors for SHP2[123] may show the way toward target-oriented medicinal chemistry on phosphatases. Various types of non-allosteric SHP2 inhibitors are being investigated, including orthosteric inhibitors, heterobifunctional degraders and intramolecular molecular glues that lock SHP in an inactive conformation.[124] The compound BBP-398 is an example of a novel type of intramolecular glue and its clinical evaluation is underway.[125] In addition to the well-known phospho-tyrosine and phospho-serine/threonine phosphatases the human genome also encodes for phospho-histidine and phospho-lipid phosphatases, and inhibitors of both of these phosphatase families are being explored.[126 Thus, phosphatases once considered difficult to study and modulate[127] are coming back into focus as a target class with recognized therapeutic potential.[128]

Solute Liquid Carriers (SLCs) belong to a class of cell-membrane associated proteins that controls molecular and ionic transport. This large family of transporters counts 446 members, facilitating the transport of solutes across cell membranes. Many of them are associated with specific diseases,[129] but a paucity of relevant chemical probes and biological assays has so far limited their study. To tackle this issue, the RESOLUTE consortium, started in 2018, aims to encourage research on SLCs by providing biological tools, assays, and functional information. It has already delivered solid results, and these have been made openly accessible.[130] As progress is made and new tools become available, it is expected that targets for treating diverse conditions including cancer,[129b] neurological,[129c] or metabolic diseases will be identified,[129d] establishing SLCs as a novel target class for medical research.

Similarly, and despite two decades of research, drugs acting through the family of eukaryotic conserved regulatory proteins **14-3-3** have barely been explored.[131] 14-3-3 proteins bind to several hundred intracellular molecular partners, with potential for treating multiple diseases, again including cancer, neurodegenerative or metabolic disorders. While still far from optimal, some small molecules acting as glues for stabilizing interactions with 14-3-3 regulatory proteins, or small molecules modulating their action have been found,[132] giving hope that therapies based on this approach might one day be developed.

The area of **gene modulation by small molecules** is in rapid expansion, as illustrated by RNA-targeting agents including small interfering RNAs (siRNA), antisense oligonucleotides (ASOs), and low molecular weight gene-splicing modifiers such as Risdiplam and Branaplam.[133,134] There are many targets that await more thorough exploration including transcription factors[135] or drugs targeting coding and non-coding RNAs.[136] These will widen the landscape of current medicinal chemistry, and open the way for the treatment of currently incurable diseases. The current SARS-CoV-2 pandemic and associated mRNA vaccines illustrate that many of the pharmacological and delivery hurdles of new modalities can be overcome, even though specific solutions might need to be found for each modality and application. Indeed, the exploration of novel chemical space comes with its own challenges: each modality has specific advantages and intrinsic weaknesses, which may include challenging bioanalytics, complex pharmacokinetics, and limited delivery options, making clinical development and dose selection difficult. They may also be structurally complex, more costly to synthesize and harder to formulate than low molecular-weight drugs.

New trends in drug discovery

Digitalization rapidly increases the capacity of medicinal chemists to tackle complex optimisation projects, supporting all aspects of design, synthesis, testing, and evaluation. Digital tools provide searchable aggregated data, can predict some compound properties, and make recommendations to medicinal chemists. Augmented drug design enabled by the combination of human and machine intelligence generate insights that can accelerate drug discovery. The building of integrated platforms driven by artificial intelligence and combining structural, biological, synthetic, and analytical data is progressing, providing a first taste of the tools that might become available to future drug discovery chemists.

For instance, synthesis-prediction tools trained on reaction databases are now developing rapidly.[137] While still in need of refinement, they provide useful digests of known reaction conditions, and generate synthetic pathways as helpful suggestions to medicinal chemists. These predictions can be combined with automatized synthesis and purification systems, enabling the design of robotic units that can operate simple optimisation processes semi-independently. New technologies automatizing synthetic reactions are already available,[138] which may play an important role in standardizing reaction conditions and facilitating automatization. Ultimately, computers might be used to guide robotic synthesis systems – but much work remains to be done before they become universally applicable. They have been trained on limited data sets, with a strong bias for a few high-yielding reaction conditions (e.g., amide formation, Pd-catalysed arylations and protections or deprotections), which are plentiful in the literature. Another limitation to the development of such applications is that much work remains to be done to improve the quality of the data they rely on. Further efforts in terms of data validation, standardization, scope, and relevance are required to improve the applicability of these tools. These challenges will eventually be overcome, allowing the full exploitation of artificial intelligence (AI) principles for synthesis prediction.

Nevertheless, ML and AI will have difficulties replacing the experience and intuition of medicinal chemists, despite attempts at capturing them using deep neural networks.[139] Indeed, variations in biological assay results and set-up, their interpretation as well as inconsistencies in data capture and annotation make it very difficult for AI to “understand” and process this information.[140] High-quality ML-based models require several thousand data points, and this limits their domain of application to relatively simple questions, such as the prediction of physicochemical properties, e.g., solubility or permeability. Such tools are valuable to support optimisation programs but are still very far from addressing the level of complexity encountered in full medicinal chemistry programs. It is foreseeable that the gap between the standardization level required by AI approaches and constantly evolving, creative scientific endeavours will never be filled. This will limit the application of ML and AI to the analysis and interpretation of large data sets, in relatively well-established areas. The intuition of a medicinal chemist remains unique. It is based on personal experience and integrates a huge diversity of information. Human brains can ponder the contribution of specific data points dynamically, depending on their relevance and experimental precision. Studying the intuition guiding medicinal chemists might help AI make better choices, but it will not be easy to model the process by which scientists deal with hypothesis-building, thought association, and the flexible inclusion of data based on personal experience.

Accordingly, one of the most spectacular successes of deep learning is the **sequence-based prediction of protein structures**. Using 50 years of high-quality protein structure data accumulated in the Protein Data Bank (PDB), the AlphaFold2[8] algorithms can predict two third of protein structures, with an accuracy equivalent to experimental data. Even though the method comes with limitations, such as the inability to provide information about disordered domains, a consequence of its exclusive training on folded proteins, it clearly demonstrates the potential of machine learning to address complex issues relevant to drug discovery. If such approaches can be refined to include the non-amino acid components that influence protein structure (e.g., ions, post-translational modifications or cofactors), and extended to predict ligand binding, they will transform drug discovery. Similarly, another area of remarkable progress is **image analysis**, where deep learning has enabled the automatization of histological studies including cell identification and protein localization, based on very large collections of millions of images.[141]

Looking forward, the role of medicinal chemists and chemical biologists will remain critical for the exploration of the most novel therapeutic targets and modalities, as well as for the development of more creative approaches. A typical target category that will resist computer-based structural approaches is represented by intrinsically disordered proteins (IDPs), which are involved in sophisticated signalling and regulatory mechanisms. Their characterization is complex and they are particularly challenging drug targets, as exemplified by intrinsically disordered transcription factors.[142] Interestingly, nuclear magnetic resonance (NMR) is able to detect transient secondary structures,[143] and is often used in combination with other techniques such as single-molecule Förster resonance energy transfer (smFRET) and small-angle X-ray scattering (SAXS), or electron paramagnetic resonance (EPR) to provide ensemble-averaged structural information on IDPs.[144] So far, this approach remains limited to small fractions of the full protein sequence and the structures of IDPs remain hard to precisely quantify, limiting options for structure-based drug design. Nevertheless, the study of large molecular complexes including intrinsically disordered proteins (IDPs) by NMR has the potential to provide access to targets that were so far almost impossible to drug rationally. In combination with the prediction of protein folding, these studies will allow for unprecedented developments in integrative structural biology, opening the path to direct intervention on large, heterogeneous, and therapeutically relevant cellular components.

One can imagine a time when protein structure and ligand binding prediction methods will be linked to generative chemistry protocols. Associated with recommender programs selecting drug candidates synthesizable from commercially accessible building blocks, they will facilitate the exploration of new therapeutic principles. When this is achieved, machine learning will have revolutionized drug discovery, accelerating the optimisation of chemical probes and drug candidates, at least for targets where sufficient preliminary information is available. While this will be a valuable tool to facilitate the work of medicinal chemists, the final optimisation of drug candidates – the real challenge in drug discovery – will still rely on the skills and experience of seasoned medicinal chemists.

Polypharmacology. Target-based drug discovery generally builds on the one molecule, one target paradigm, in that a single selective molecule binds to one macromolecular target, affecting its function. While non-target related side effects are often due to the engagement of off-targets, it is increasingly appreciated that a given drug may act on multiple targets to elicit its effect. Interestingly, the shift from avoiding binding promiscuity in lead optimisation to dialling in selected additional target interactions is the foundation of polypharmacology,[27] which may enable more effective therapeutic options, as well as facilitate drug repurposing. Drugs optimized for activity on multiple targets can address several aspects of a disease, both causal and symptomatic, and therefore have the potential to be more effective than a specifically targeted molecule. In addition, such an approach allows engaging multiple therapeutic targets with the same time course, avoiding complex dosage regimens and unwanted pharmacokinetic effects such as drug-drug interactions (Figure 7). Classical selectivity panel screening against isoforms of an anticipated drug target and of off-targets associated with detrimental side effect remain important to guide medicinal chemistry. Nevertheless, new chemical biology principles expand this technical repertoire.

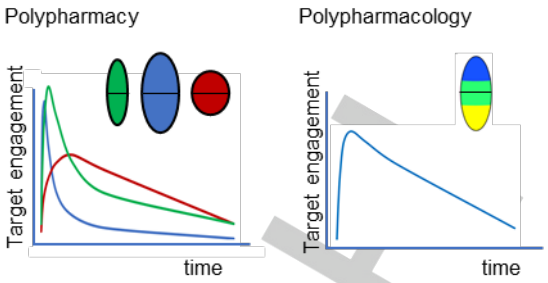


Figure 7. One advantage of using a drug optimized for activity on multiple targets (polypharmacology), versus using concomitant medications (polypharmacy), is the possibility to engage multiple therapeutic pathways with the same time course.

Alzheimer's Disease (AD) is a neurodegenerative disease with multifactorial causes and complex pathophysiology and pathobiochemistry. The use of chemical probes for positron emission tomography allows imaging of amyloid and tau deposits and are meanwhile recognized as an established tool for diagnosis and patient stratification in AD. There is however only very limited progress in the treatment of AD despite multiple clinical trials with drugs acting on various targets, including BACE inhibitors and antibodies against amyloid and Tau protein aggregates. The drugs in clinical use for treatment of AD are rivastigmine and other inhibitors of acetylcholine esterase (AChE). An unspecific and limited neuroprotective effect elicited by antioxidants in AD has been described for several natural and synthetic compounds, some of which were shown to be inhibitors of the established target acetylcholine esterase.[145,146] Hybrid molecules combining AChE inhibitor and antioxidant properties have also been investigated.[145,147] A proteomics approach based on ABPP may allow to delineate the molecular targets of small molecules with neuroprotective effects in AD, as exemplified using taxifolin derivatives, used as chemical probes to generate new target hypotheses for this compound class.[148]

Ganetespib and luminespib are drug candidates for the treatment of cancer. A recent study evaluated the kinase inhibition of these heat shock protein HSP90 inhibitors.[149] Experimental screening of their inhibitory potency against a kinase panel revealed distinct coverage of the orthosteric ATP-site binders, with ganetespib and luminespib respectively inhibiting 21 and 2 out of 382 kinases, and a retrospective analysis showed that the kinase polypharmacology of luminespib markedly evolved during the hit-to-lead drug discovery process. Combinations of HSP90 and kinase inhibitors are potential cancer treatment, and kinases lend themselves to ABPP due to the availability of potent, cell-permeable probes, which could facilitate repurposing strategies.[150] Approaches utilizing multi-targeted probes for investigating suitable target combinations to leverage poly-pharmacology, as well as probes directed against single targets for the determination of target engagement and therapeutic window have shown promising results for kinase targets.[151,152]

Crowdfunding efforts such as Target 2035, led by the Structural Genomics Consortium, might help provide tools for a broader approach to polypharmacology. It aims to identify and make chemical probes available for every protein in the human proteome.[153] While still an aspirational conceptual framework, such community efforts promise to greatly facilitate systematic pathway interrogation and validation of putative drug targets. Among many potential applications, the discovery and development of multi-targeted drugs is likely to benefit from tool compounds made available through this initiative.

Finally, **synthetic chemistry** remains critical in medicinal chemistry and chemical biology.[154] New approaches such as DNA-encoded libraries (DEL), non-natural peptides, antibody-drug conjugates, macrocycles, degraders, and nature-derived molecules heavily rely on new synthetic methodologies. This exploration of novel chemical spaces also generates intellectual property, a basic requirement for novel drug development. Innovative synthetic methods are particularly impactful when combined with automation and efficient analytical methods, allowing the rapid exploration of chemical derivatives around molecules of interest. While the fully automated exploration of structure-activity relationships will remain out of reach in the foreseeable future, computer-driven synthetic equipment with in-line analytics, coupled with *in vitro* assays and machine learning applications already show promise.[155] They prove increasingly able to address questions related to simple modifications of early drug candidates, and have the potential to take over the tedious and less innovative parts of the medicinal chemistry process, while decreasing experimental costs and turnaround time. These methods are currently limited by the ability of *in silico* methods to reliably select promising designs, as well as by synthetic limitations, which prevent the exploration of structurally related molecules requiring multi-step modifications. Some recent developments have nevertheless shown progress, including high-throughput experimentation to optimize the use of catalysts or reagents,[156] which helps extend the scope and applicability of chemical reactions towards innovative scaffolds. New synthetic methods also enable the use of unusual chemical groups to explore novel chemical space and improve physicochemical or pharmacokinetic properties of drug candidates.[157] Finally, novel biotransformation using genetically optimized enzymes[158] or catalytic C-H activation[159] for late-stage functionalization (LSF) shows much promise, providing access to synthetically difficult-to-reach, novel chemical space (Figure 8). Medicinal chemists increasingly take advantage of novel enzymatic systems, as their application to functionalize chemical scaffolds in positions that are unusual or difficult to reach provides direct access to unexplored chemical space. It also facilitates the stereoselective modification of drug candidates and the preparation of drug metabolites under eco-friendly conditions.

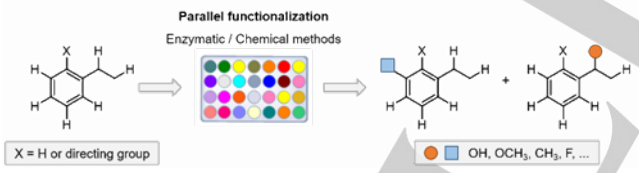


Figure 8. Directed as well as non-directed late-stage diversification methods can considerably accelerate access to new drug molecules. Figure reproduced under licence CC BY 4.0 from *CHIMIA*, **2022**, *76*, 258.

In combination with new chemical methodologies, LSF approaches offer significant potential for modern drug discovery in supporting diversity-oriented synthesis, allowing for the installation of transient handles such as boron or phosphorus containing groups[160] and the decoration of 3-dimensional building blocks with intrinsically high drug-likeness.[161] Combining LSF with recent advances in high-throughput experimentation (HTE), lab automation methods, design of experiment (DOE) software, machine learning and artificial intelligence might enable the generation of tools for predicting individual C–H bond manipulations in a prospective manner, allowing the efficient synthesis of structurally novel target molecule.[162]

In addition to synthetic approaches, a reflection on the limits and properties of the currently accessible chemical space is critical: Despite the screening of large compound libraries, it has been very difficult to find ligands for some target classes (e.g., transcription factors), while for other target classes (e.g., RNA modulators), structural diversity is very limited. These targets cannot easily be exploited with new modalities either. A broader exploration of the chemical space to enhance chemical libraries with structurally diverse molecules, including less-easy to synthesize, information-rich molecules, might allow addressing some of these issues.[163]

Conclusion

The science of drug discovery must be conducted with the highest possible quality to limit late-stage clinical failures, which happen during the costliest phase of the drug development process. It requires the application of best practices in developing and using chemical probes[9] to explore cellular pathways, in identifying and validating therapeutic targets, as well as for hits generation[164] and optimisation. In addition, it calls for a perfect understanding of the required drug profile, and the use of assays and disease models that allow a thorough appreciation of the *in vivo* properties and action of new molecules.
Beyond technical and operational challenges, and to reach the highest levels of quality in research, chemical biologists and medicinal chemists should further strengthen their community to optimally use synergies and resources. The science behind target identification, lead discovery and drug optimisation is defined by the nature of the target, the pursued mode of action and clinical requirements. Industry and academic laboratories usually operate with different goals, reward systems and timelines: industrial researchers aim to generate marketable drugs, and academics aim to advance science for the purpose of gaining knowledge and publishing. Nevertheless, they operate in a scientific continuum, and it is encouraging to see the growing number of public-private partnerships and consortia that aim at finding solutions for currently unmet medical needs.[130,153,165] Defining complementary objectives that honour each member's interests and available resources is the key to successful collaborations between industry and academic laboratories. Such collaborations have already delivered tangible outcome in the form of, e.g., well annotated chemical probe and chemical genomics compound libraries, enabling extended target identification and pathway interrogation activities to explore disease biology.[166] Overall, as we get better at exploiting chemical biology and medicinal chemistry synergies and linking potential therapeutic targets and human diseases, we will improve our ability to translate these findings into clinically useful drugs.

Keywords: medicinal chemistry • chemical biology • computational chemistry • trends • EFMC

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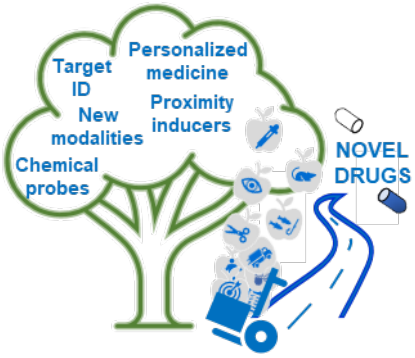

A wealth of opportunities: Novel tools for chemical biology including chemical inducers of proximity, designer probes or e.g., RNA-targeting agents enable innovative tactics for therapeutic approaches. This article explores recent developments combining the power of medicinal chemistry and chemical biology, highlighting their extraordinary potential to address sophisticated biological questions and manipulate complex biological pathways to develop novel therapies.

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