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ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iedc20

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To cite this article: Esra Balıkçı, Anne-Sophie M. C. Marques, Jesper S. Hansen & Kilian V. M. Huber (2023) Open resources for chemical probes and their implications for future drug discovery, Expert Opinion on Drug Discovery, 18:5, 505-513, DOI: 10.1080/17460441.2023.2199979

To link to this article: https://doi.org/10.1080/17460441.2023.2199979

Published online: 16 Apr 2023.

EXPERT OPINION ON DRUG DISCOVERY
2023, VOL. 18, NO. 5, 505–513
https://doi.org/10.1080/17460441.2023.2199979

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REVIEW

Open resources for chemical probes and their implications for future drug discovery

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ABSTRACT

Introduction: The rational development of new therapeutics requires a thorough understanding of how aberrant signalling affects cellular homeostasis and causes human disease. Chemical probes are tool compounds with well-defined mechanism-of-action enabling modulation of, for example, domain-specific protein properties in a temporal manner, thereby complementing other target validation methods such as genetic gain- and loss-of-function approaches.

Areas covered: In this review, the authors summarize recent advances in chemical probe development for emerging target classes such as solute carriers and ubiquitin-related targets and highlight open resources to inform and facilitate chemical probe discovery as well as tool compound selection for target validation and phenotypic screening.

Expert opinion: Chemical probes are powerful tools for drug discovery that have led to fundamental insights into biological processes and have paved the way for the development of first-in-class drugs. Open resources can inform on various aspects of chemical probe development and provide access to data and recommendations on use of chemical probes to catalyse collaborative science and help accelerate drug target identification and validation.

ARTICLE HISTORY
Received 20 January 2023
Accepted 3 April 2023

KEYWORDS
Chemical probes; drug discovery; open science; solute carriers; ubiquitination; targeted protein degradation

1. Introduction

Although small molecule drugs are sometimes referred to as targeted therapeutics, data suggest that many, if not most, Food and Drug Administration (FDA)-approved pharmaceuticals interact with several proteins inside cells [1]. Therefore, their use as tools to dissect biological pathways is confined, for example, by the innate promiscuity of co-factor mimetic compounds. Highly selective chemical probes are therefore important complementary tools to unravel the biology of less well-characterized or even unexplored proteins and emerging target classes. Chemical probes should, ideally, selectively modulate the activity of a specific protein or its respective biological function(s) in a manner that is preferably reversible and temporal [2,3]. Strict quality criteria defining potency, selectivity, and cell permeability are needed in order to effectively accomplish this goal across the druggable genome and to boost robustness in preclinical target validation (Figure 1, reviewed in detail in refs [4–6]). Importantly, chemical probes may act as inhibitors or activators that modulate protein activities, degraders leading to a chemical knockdown of a protein of interest or molecular glues, for example, that stabilize protein–protein interactions. As a result, several tool compounds may be needed to survey different functions of a given protein. Multiple distinct chemotypes and control compounds should be established for a given target to further increase confidence in the interpretation of observed phenotypes [7]. It is important to keep in mind that although chemical probes aim to accelerate drug development, their primary goal is to investigate a particular function of a given target, which in many instances may not result in a desirable phenotype [8]. Over the past two decades, the value of chemical probes has become increasingly recognized fueled by the discovery of tool compounds such as JQ1 [9] and I-BET [10] that have helped pave the way into an expanding universe of human bromodomain research. These compounds have provided new insights into transcription and chromatin regulation and how these processes are linked to the disease development. Particular areas of recent interest for chemical probe development are solute carriers and ubiquitin biology related targets, which will be discussed in more detail later.

2. Open resources for chemical probe development

Chemical probe development involves several steps such as target identification and assay development analogous to classic target-based drug discovery projects. It is crucial to conduct a careful and thorough review of the target biology literature as well as any relevant chemical matter that may be available. Target tractability, protein biochemistry (such as whether the protein can be generated recombinantly),

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Article highlights

- Chemical probes are powerful tools to elucidate biology and uncover new therapeutic paradigms
- Chemical probes can also provide starting points for assay development and help open up new target classes with economic impact
- Stringent selectivity and potency criteria are essential for target validation using chemical probes
- Technological advances and innovative chemical biology approaches have helped to improve and accelerate chemical probe design
- Open resources and open science initiatives for chemical probe development ensure high quality standards are maintained and facilitate timely dissemination of reagents and results
- Freely accessible chemical probes can be a catalyst for crowdsourcing science to unlock the full potential of the human druggable genome

functional or biophysical assays, the existence of small molecule inhibitors, and other factors (peptides, antibodies, complex binding partners) are also assessed in this process. In order to address these points, there are several public databases that can help navigate the literature and associated data. Once a target has been identified, the chemical probe development process revolves mainly around iterative rounds of screening and medicinal chemistry (Figure 2).

Databases such as UniProt [11], OMIM [12], OpenTargets, and canSAR [13], which collect information on gene, structure, function, and disease association, offer succinct summaries on individual targets and link out to other relevant data repositories (Table 1). Such portals are a convenient means to browse large scale omics datasets, such as DepMap, which provides insights into gene essentiality and co-dependencies based on genome-wide CRISPR screens [15]. Proteomics data available from CCLE, NCI, and proteomicsDB [22] can inform on expression levels and effect of genetic and/or chemical perturbations [55]. Although more focused in its approach, CMap provides access to gene expression signatures following perturbations with small molecules, gene knockdown, or overexpression [16]. For details on protein complex partners which may be relevant for a given target function or help identify essential co-factors and chaperones, protein–protein interaction (PPI) databases such as BioGRID [29], IntAct [30], Pathway Commons PPIDs [31], and NURSA [32] accumulate data from hundreds of comprehensive studies ranging from affinity purification coupled to mass spectrometry (AP-MS) or Western blotting to co-purification/reconstitution of recombinant proteins. There are also a variety of target-class focused databases, such as UbiHub, which provides information on E3 ligases and other UPS proteins, including availability of protein 3D structures and ligands [17]. The DUB Portal surveys multi-omics data focusing on deubiquitinating enzymes (DUBs) with regard to their function, substrates, and known interaction partners [18].

The footprint of artificial intelligence (AI) is also consistently increasing across all areas relevant to medical research (Figure 3), including the search and design of small molecules [57,58]. One of the first examples of hit identification using a combination of different AI-based software and platforms is the discovery of ISM042-2-001, a potent CDK20 inhibitor [58]. In this instance, a combination of protein structure prediction using AlphaFold [26,59] with PandaOmics [60], a biocomputational platform and Chemistry42 [61], an AI-tool for accelerating small-molecule drug design, enabled the generation and testing of small-molecule binders for CDK20 within 30 days.

Availability of chemical matter for a given target or pathway can greatly facilitate the probe development process. In this context, the Chemical Probes Portal provides a star-based expert assessment of available tool compounds [36]. Other initiatives such as ChEMBL [37,38], SGC [51], ProbeMiner [39], Probes & Drugs [40], opnMe [41], Probe Reports from the NIH Molecular Libraries Program (MLP), Gray Lab, etc. (see Table 1), are high quality chemistry resources offering general or focused sets of small molecules with adequate properties for cellular studies. DrugBank [42–45] and DrugCentral [46] collate drug data including mechanisms and targets while BindingDB [28] informs on reported biophysical binding affinities. The Cancer Therapeutics Response Portal (CTRP) from the Broad Institute [19–21] is another web-based resource which harbors a variety of datasets related to compounds such as their association with cancer genetics and cell lineage features.

Several target-focused chemical probe programs have emerged over the years. Many of these comprise international consortia involving both academic as well as industry partners. In Europe, the EU's Innovative Medicines Initiative (IMI) has spearheaded open-access efforts to help achieve step-changes in chemical probe discovery in new areas. For example, EUbOPEN aims to develop and establish new technologies and methods to accelerate hit identification and chemical probe discovery to provide an expanded set of chemical probes for phenotypic screening [62]. RESOLUTE, another IMI-funded consortium, is focusing on establishing an open resource for studying solute carrier (SLC) transporters to explore SLC biology and their potential as drug targets [53]. The reagents provided include codon-optimized plasmids for protein expression as well as SLC-overexpression and knock-out cell lines. Data comprising information on functional assays and binders, such as nanobodies and antibodies, as well as transcriptomics, proteomics, and metabolomics data, are captured via an online portal. These efforts are complemented by initiatives such as EU-OPENSCREEN, a European Research Infrastructure Consortium (ERIC) centered on open access high-throughput screening platforms as well as medicinal chemistry technologies [63]. Chemical probe discovery has also greatly benefitted from structural biology consortia such as the Structural Genomics Consortium (SGC), RIKEN, and Protein Structure Initiative (PSI) [52]. On top of technical improvements enabled by these collaborations, such as high-throughput X-ray crystallography workflows, which have dramatically increased the number of available structures in the Protein Data Bank (PDB) [24,25], many initiatives have also recognized the importance of making outputs available in an unrestricted, open access manner to facilitate partnerships, maximize efficiency, and avoid duplication of effort.

3. Chemical probe development for SLCs and the ubiquitin-proteasome system (UPS)

The integral membrane protein family of SLC and the UPS represent two areas of emerging medical interest. Using these two areas as examples, we will explore methodologies

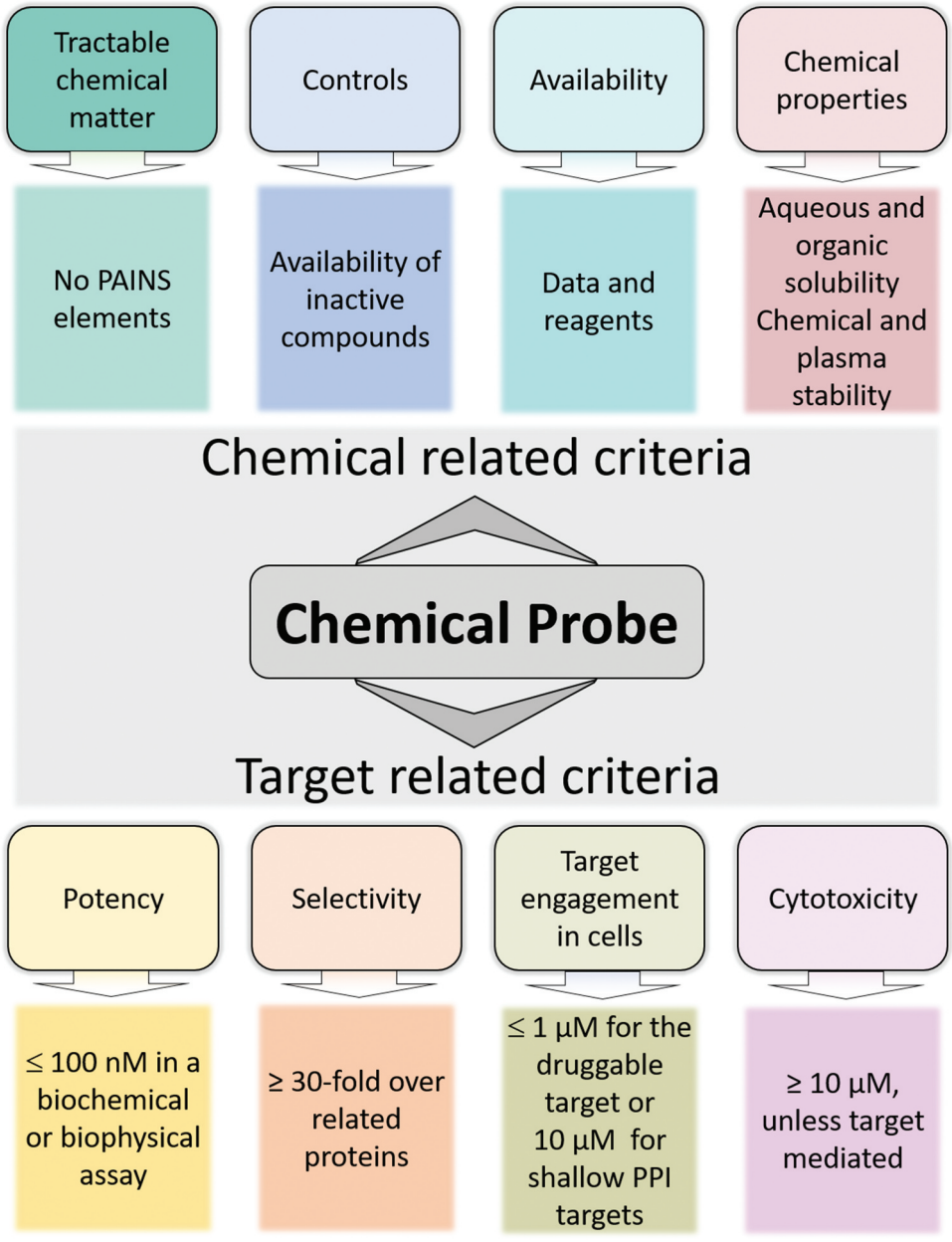

Figure 1. Considerations for evaluating chemical probes.

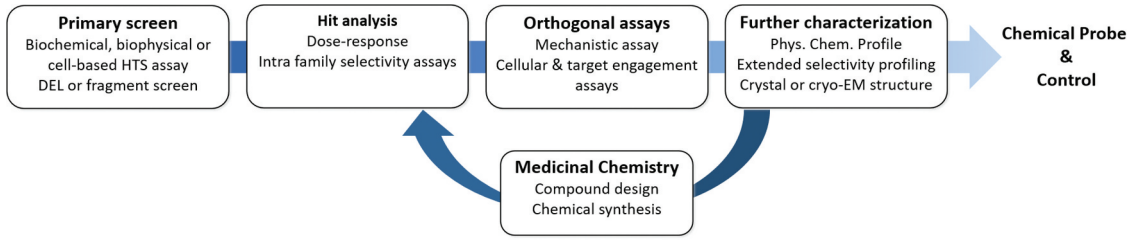

Figure 2. Core activities of chemical probe development.

Table 1. A selection of open resources for chemical probe development.

Category	Databases	Context & URL	Refs
Gene & Phenotype	OMIM	Human genes and genetic phenotypes; https://www.omim.org/	[12]
	OpenTargets	Human genetics and genomics data; https://www.opentargets.org/	[14]
	canSAR	Cancer drug target predictions; https://cansar.ai/	[13]
	DepMap	Gene dependencies in human cancer cell lines; https://depmap.org/portal/	[15]
	CMap	Cellular signatures with genetic or small-molecule perturbation; https://maayanlab.cloud/Harmonizome/dataset/CMAP+Signatures+of+Differentially+Expressed+Genes+for+Small+Molecules	[16]
	UbiHub	Ubiquitination target prioritization and drug design; https://ubihub.thesgc.org/static/UbiHub.html	[17]
	DUB Portal	DUB function in oncology; https://labsyspharm.github.io/dubportal/	[18]
	CTRP	Cancer cell lines and sensitivity to small-molecules; https://portals.broadinstitute.org/ctrp.v2.1/	[19–21]
Protein	UniProt	Protein sequence and functional information; https://www.uniprot.org/	[11]
	ProteomicsDB	Multi-omics and multi-organism resource; https://www.proteomicsdb.org/	[22]
	Human Protein Atlas	Human proteins in cells, tissues and organs; https://www.proteinatlas.org/	[23]
	Protein Data Bank	X-ray or cryo-EM protein structures; https://www.rcsb.org/	[24,25]
	AlphaFold	AI-based 3D protein structure predictions; https://alphafold.ebi.ac.uk/	[26,27]
	BindingDB	Binding affinities of proteins with drug-like ligands; https://www.bindingdb.org/rwd/bind/index.jsp	[28]
	BioGRID	Protein-protein, genetic and chemical interactions, and post-translational modifications; https://thebiogrid.org/	[29]
	IntAct	System and analysis tools for molecular interaction data; https://www.ebi.ac.uk/intact/home	[30]
	Pathway Commons	Pathway data from multiple organisms; https://www.pathwaycommons.org/	[31]
	NURSA	Protein complexes datasets; https://maayanlab.cloud/Harmonizome/dataset/NURSA+Protein+Complexes	[32]
	FragMax,	Crystallographic fragment screening; https://www.maxiv.lu.se/beamlines-accelerators/science-initiatives/fragmax-biomax-fragment-screening-platform/	[33]
	XChem	Crystallographic fragment screening; https://www.diamond.ac.uk/Instruments/Mx/Fragment-Screening.html	[34]
	CRIMS-HTX lab	Crystallographic fragment screening; https://htxlab.embl.fr/#/	[35]
Chemical	Chemical Probes Portal	Chemical probes and chemical tool compounds; https://www.chemicalprobes.org/	[36]
	ChEMBL	Drug-like molecules; https://www.ebi.ac.uk/chembl/	[37,38]
	ProbeMiner	Chemical Probes; https://probeminer.icr.ac.uk/#/	[39]
	Probes & Drugs	Bioactive compound libraries; https://www.probes-drugs.org/home/	[40]
	opnMe	Open-access Boehringer Ingelheim molecule library; https://www.opnme.com/	[41]
	DrugBank	Information on drugs and drug targets; https://go.drugbank.com/	[42–45]
	DrugCentral	Information on drugs; https://drugcentral.org/	[46]
	Gray Lab	First-in-class chemical probes; https://graylab.stanford.edu/probe-resources/	
	PROTAC-DB	Structural information and experimental data of PROTACs; http://cadd.zju.edu.cn/protacdb/about	[47]
	PROTACpedia	Manually curated data on PROTACS; https://protacpedia.weizmann.ac.il/ptcb/main	
	DELopen	DNA-encoded compound libraries; https://hits.wuxiapptec.com/delopen	[48–50]
Consortia	SGC	Genomics and structural biology; https://www.thesgc.org/	[51]
	RIKEN	Structural biology; https://www.riken.jp/en/	
	PSI	Structural biology; https://web.archive.org/web/20090113222901/http://www.nigms.nih.gov/News/Reports/PSIAssessmentPanel2007.htm	[52]
	RESOLUTE	SLC biology; https://re-solute.eu/	[53]
	EUbOPEN	Chemogenomics, tools for probe development and chemical probes; https://www.eubopen.org/	
	EU-OPENSCREEN	High-throughput screening and medicinal chemistry; https://www.eu-openscreen.eu/	
	NIH Molecular Libraries Program	Small-molecule chemical probes; https://www.ncbi.nlm.nih.gov/books/NBK47352/	[8,54]

for assay development, screening, hit finding, including new modalities, as well as relevant technical and target-specific obstacles and considerations, in the sections that follow.

3.1. SLCs

SLCs comprise the largest family of transporters in the human genome with more than 450 members, currently divided into 66 different families based on either sequence, fold, or functional similarity [64]. These proteins are integral membrane proteins residing in cellular membranes with more than half localized to the plasma membrane [65]. SLCs transport a wide range of small molecules, including metabolites, nutrients, amino acids, hormones, metal ions, as well as small molecule drugs across cell membranes [65]. The spectrum of on average≥100 different types of SLCs produced by a given cell defines the intracellular composition of solutes such as metabolites and drugs [66]. Not surprisingly, many SLCs have been implicated in common diseases such as cancer, diabetes, heart disease, Alzheimer's, and neuropsychiatric disorders. Hence, SLCs are emerging as a superfamily of highly disease-relevant and pharmacologically tractable proteins. The importance of SLCs as pharmacological targets is demonstrated by the fact that the most successful therapy for depression includes blocking serotonin reuptake with fluoxetine (Prozac), which works as an antagonist of the serotonin transporter SLC6A4 [67].

However, the function of many SLCs is still unknown, and there are few medicines that target these transporters [68,69]. The difficulty in developing routine medium- and high-throughput assays has hampered both basic SLC biology and the development of selective small molecule inhibitors and activators to further investigate their roles in cells and inform drug design. Whereas, it is common practice for soluble proteins to compare assays using purified proteins with effects in orthogonal cell-based assays, in case of membrane proteins, and SLCs in particular, there are substantial challenges due to a lack of available methods for studying transport with

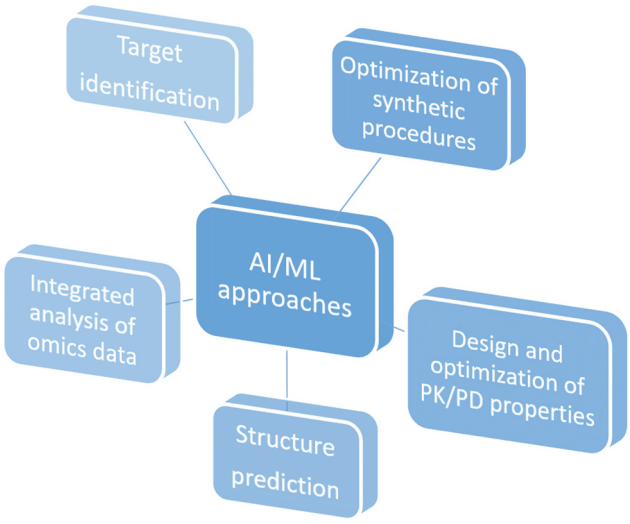

Figure 3. Applications for artificial intelligence (AI) and machine learning (ML) approaches in chemical probe development. (Reviewed in detail in ref [56]).

purified proteins. This is largely owed to the fact that SLCs have partially hydrophobic surfaces due to their localization in cellular lipid membranes. Extraction, purification, and reconstitution of SLCs into artificial membranes are often inefficient and low-yielding processes which significantly impairs the ability to obtain relevant amounts of active SLC proteins. Consequently, most high-throughput studies with membrane transporters rely on cell-based systems which have been proven efficient for GPCRs and ion channels. However, in case of transporters such approaches are complicated by the fact that most cell types usually have a large repertoire of different, sometimes redundant transporters that may transport the same substrate. As a result, interpretation of cell-based assay data is frequently difficult, and orthogonal protein-based assays are therefore critical for SLC probe development. Compounds that target the substrate site to lock the SLC structure in a conformation that blocks solute transport represent the traditional approach in the area of chemical probe development, yet to realize the full potential of this significant human protein family, new strategies are required.

3.2. UPS

Ubiquitination is the second most observed posttranslational modification in human proteins [70]. This process involves the cooperative activity of E1, E2, and E3 enzymes to tag protein substrates with ubiquitin chains to induce their proteasomal degradation. Components of the ubiquitin system are attractive therapeutic targets since aberrations in this process have been associated with many diseases such as cancer and neurodegeneration [71,72]. Several UPS-targeting small molecules have been approved or are undergoing clinical trials (see literature for relevant reviews, such as [73]). The best characterized E3 ligase modulators include thalidomide and its derivatives lenalidomide and pomalidomide, also called immunomodulatory drugs (ImiDs), which are approved for the treatment of multiple myeloma. These compounds enable surface remodeling of the E3 ligase substrate receptor cereblon (CRBN), altering its affinity for preferred substrates. Subsequent modifications to these so-called molecular glues yielded compounds with greater selectivity and a broader range of compatible substrates [74–76]. Aside from their therapeutic value, these drugs have paved the way for the emerging area of targeted protein degradation (TPD), highlighting the vast potential of proximity-induced pharmacology [77–79].

4. New tools and approaches to support chemical probe development

Successful probe development relies on robust and informative assays to enable screening and assessing selectivity and cellular target engagement. Here, we discuss a selection of recent advancements in tools and approaches to interrogate SLC and UPS biology, serving as non-exhaustive examples of how novel strategies can be employed to develop chemical probes for new and emerging target classes.

4.1. Natural binders

Camelid nanobody binders can contribute to the deorphanisation of targets such as SLCs by providing complementary tools for modulating transporter function and facilitating structural biology experiments. Inhibitory nanobodies have been described for the vesicular glutamate transporter-1, SLC17A7 [80], and recently, structural information of nanobodies binding to two peptide transporters provided new insights into peptide and prodrug recognition by SLC15A1 and SLC15A2 [81]. Nanobodies have been suggested to have considerable potential in the development of future medicines [82], including structure-guided small molecule drug discovery [83]. An exciting example is the recently identified protein complex consisting of SLC6A19 and angiotensin-converting enzyme 2 (ACE2) that is recognized by the Spike glycoprotein on virus particle surfaces and is likely to enhance the entry of some coronaviruses, such as SARS-CoV-2, into cells [84]. Studies have shown that neutralizing antibodies can prevent virus infection *in vitro* by blocking Spike protein recognition sites on cell surfaces [85]. It will be interesting to see how these data will affect the development of small-molecule binders that may be able to prevent COVID-19 infections in humans in the future.

4.2. Fragment and DNA-encoded library screening

Most high-throughput screening (HTS) campaigns are designed to survey compounds with a minimum size of 250 Da that have the ability to bind to a protein via hydrogen bonding or hydrophobic interaction networks. Fragment-based drug discovery (FBDD) aims to extend screening to include compounds with low molecular weight and complexity. Conceptually, this approach enables decreasing the chemical space whilst maximizing promiscuity to address a broad range of targets. The reduced complexity of fragments increases the possible number of binding sites, resulting in higher hit rates. Selected fragments can then be further optimized using fragment-merging or other classic structure-based design methods.

As fragment hits tend to have low affinity and potency, various biophysical methods have been evaluated for primary screening efforts. Early initiatives, for example, used nuclear magnetic resonance (NMR) to explore structure–activity relationships (SAR) [86]. Later, technological advances allowed for high-throughput X-ray crystallography to be used for studying fragment–protein interactions. This method is based on soaking of fragment libraries into preformed crystals. Current methodologies allow for the screening of fragment libraries of up to a thousand molecules each week on average. Along with advancements in beam sources, detectors, and software analysis, collaborative efforts have resulted in the establishment of such screening systems, such as the CRIMS-HTX lab, FragMax, and XChem, at a number of synchrotrons [33–35,87,88]. Recently, crystallographic fragment screening provided several tractable starting points for the main protease M^{Pro} of SARS-CoV-2, demonstrating the power and versatility of this approach [89]. Similarly, another study on the SARS-CoV-2 NSP13 helicase identified fragments hits for the development of selective probes [90]. As demonstrated in these studies, one of the most exciting aspects of crystallographic fragment screening is the possibility of uncovering ligands for novel binding pockets or allosteric sites. DNA-encoded library (DEL) screening has also gained a lot of attraction over the last couple of years, thanks to its ability to sample billions of compounds in a rapid and cost-effective way [48–50]. Recent offerings such as DELopen provide academic researchers with access to established DEL libraries and enable performing screens in-house.

4.3. PROTACs

PROTACs are heterobifunctional molecules that may bind a protein of interest (POI) and an E3 ubiquitin ligase at the same time resulting in the formation of a ternary complex [91–94]. When both the POI and E3 are in close proximity, the target protein is ubiquitinated by the E3 ligase and subsequently recruited to the proteasome for degradation. Beyond their therapeutic potential, PROTACs represent highly valuable and versatile chemical biology tools for target validation [95]. They work in a fundamentally different way than traditional inhibitors or antibodies and can be thought of as a chemical alternative to gene knockdown, for example, using siRNA. PROTAC-mediated target degradation can help answer hitherto technically inapproachable complex biological questions. Analogous to classical chemical probes, degraders need to be thoroughly characterized, which necessitates an understanding of their proteome-wide effects as well as the pharmacology innate to the respective target and E3 ligase.

The PROTAC-DB and PROTACpedia databases collate various pieces of information on heterobifunctional degraders such as target class, chemical structure, and degradation capacity [47]. Recently, the first-in-class SLC degrader d9A–2 has been reported [96]. This PROTAC employs an optimized SLC9 ligand and a CRBN-recruiting warhead connected via a PEG linker allowing for efficient SLC9A1 degradation as demonstrated in two cell lines resulting in perturbation of cellular pH homeostasis as expected for the SLC9 family. Interestingly, d9A–2 also affected other SLCs on the cell surface and, to a lesser extent, other SLC family members at intracellular membrane sites [96]. The fact that SLCs can be targeted for degradation with no or limited knowledge of substrate specificity makes this an attractive strategy for future SLC probe development.

5. Expert opinion

Chemical probes have the potential to be transformative tools by opening up new target classes and establishing new therapeutic concepts. While they are best employed in conjunction with orthogonal target validation approaches, such as genome editing, the power and traction of chemical probes is unique as exemplified by the game changing impact of bromodomain and extraterminal domain (BET) inhibitors on chromatin chemical biology. Their versatility in exploring biological systems, as well as their general ease of use, have aided in the advancement of our fundamental understanding of biological systems and disease mechanisms. Chemical probes are invaluable assets for drug target validation, helping to accelerate drug discovery while reducing duplication of effort. Consequently, there is broad agreement that such tools and associated data should be freely available to researchers with no limits on use in order to fully realize their potential. However, the development of high quality reagents as well as curating and maintaining these resources represent a substantial logistical as well as financial challenge. With the development of new chemical modalities, such as protein degraders, the chemical probe toolbox continues to expand and new types of information such as multi-omics, cell painting, and single cell data need to be captured and linked to compounds and orthogonal assay results [97]. Preserving such data and making it accessible to the community will be key to help unlock the power of AI and machine-learning (ML) based approaches for medicine. Such methods are potentially powerful tools that can aid in many aspects of a drug discovery project. In particular, combining several AI platforms and software can significantly accelerate the discovery of new small molecule ligands for novel and complex targets. We expect such integrated platforms to evolve enabling improved predictions including modeling of protein dynamics or protein–ligand complexes structures.

Although open resources and databases for genomics, transcriptomics, proteomics, and chemical biology data are rapidly expanding, similar searchable databases for biochemical and biophysical assays, antibodies, and screening protocols that are not locked behind a paywall have so far received comparable little attention. A potential template for capturing such data could be the integration of target-enabling packages (TEPs, https://www.thesgc.org/tep) into existing repositories like OpenTargets. Validation data such as immunoprecipitation and CRISPR KO experiments for antibodies would be critical to include [98,99]. A similar case could be made for depositing information for nanobody binders, which are highly relevant for a number of target classes, including GPCRs [100–102], ion channels [103–105], E3 ligases [106], and phosphoinositide 3-kinases [107,108].

While we have attempted to showcase a representative subset of freely available databases and general strategies for chemical probe development, it is important to acknowledge that there are many more specialized databases and data repositories, including commercial ones such as CAS (https://www.cas.org/), which are

complementary to the ones listed here. As expected, results may vary substantially depending on the intended target audience and how primary data are extracted, processed, and scored from the literature. Expert-based reviews, of course, frequently disagree with algorithmic interpretations of data, and vice versa. Even though many websites offer APIs for convenient access to data and other features, a lack of such protocols hinders systematic evaluation of compounds and respective properties. Most vendors and chemical suppliers also provide structural information and brief summaries on biochemical and cellular properties of available chemical probes, but researchers may find it difficult to assess important parameters, such as selectivity in a comprehensive manner. To eliminate bias and avoid scaffold-inherent off-target effects, it is good practice to use multiple and structurally diverse chemical probes for a particular target. In general, small molecule chemical probes are currently targeting only a fraction of the druggable genome and many are not optimized for *in vivo* use in model organisms. It is also worth noting that technically, chemical probes may also comprise peptides and oligonucleotides, which are not covered in this review. As our understanding of biology continues to evolve, it will be exciting to see new chemical probes and probe modalities emerge for areas such as proximity-induced pharmacology, RNA, and phenomena like liquid–liquid phase separation.

Funding

This project received funding from the Innovative Medicines Initiative 2 Joint Undertaking (JU) under grant agreement No 875510. The JU receives support from the European Union's Horizon 2020 research and innovation program, the European Federation of Pharmaceutical Industries and Associations (EFPIA), the Ontario Institute for Cancer Research, the Royal Institution for the Advancement of Learning McGill University, the KTH Royal Institute of Technology (Kungliga Tekniska Hoegskolan) and Diamond Light Source Limited.

Declaration of interest

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.References

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