Title
Introduction to the themed collection on Covalent Drug Discovery

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Introduction to the themed collection on Covalent Drug Discovery

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Covalent drugs and chemical probes are powerful tools for therapeutic research, which offer distinct pharmacological advantages compared to reversible binding small molecule ligands. Increased potency and duration of effect are ubiquitous features of irreversible or reversible covalent protein engagement. The resulting favorable pharmacokinetic–pharmacodynamic (PKPD) profiles afford enhanced target engagement and improved "druggability", particularly for targets with long resynthesis rates. Covalent compounds are also distinguished by high selectivity, even across highly homologous family members' sites (*e.g.* kinases), as the absence of the labeled amino acid in otherwise related binding sites acts as a stringent filter that eliminates off-target binding. The relative ease of accessing resistant proteins and cell lines through a simple mutation of the targeted amino acid (*e.g.* Cys → Ala/Ser) streamlines target validation and mode-of-action studies. Finally, by covalently engaging the target, and possibly its off-targets, an irreversible probe facilitates the development of occupancy biomarkers that also aid in validation and selectivity determination, which are essential to develop translational pharmacological information and, consequently, high-quality clinical candidates. For example, mass spectrometry methods and the use of clickable covalent probes can be used to quantify target coverage by the drug candidate *in vivo*, which builds a correlation between occupancy and pharmacological effects that helps refine dose projections for phase II clinical trials. For these reasons, covalent drug discovery has become an essential component of modern drug discovery pipelines, and advances in medicinal chemistry and chemical biology underpin this progress.

Most covalent approaches target cysteine, which is distinguished by its nucleophilic thiol or thiolate side chain. With low off-target reactivity, acrylamides have become the go-to electrophilic warhead in covalent drug design. As a result, there are currently 34 cysteine-targeting unsubstituted acrylamide drugs and drug candidates in development. Initially, a major concern regarding covalent drug development was the potential for cross-reaction with proteins and DNA, resulting in adverse events such as immunoreactivity and genotoxicity. This has been addressed through the amelioration of intrinsic reactivity whilst enhancing equilibrium binding interactions with the target, and optimization of PKPD such that circulating drug levels are minimized. This increased understanding of the risks of covalent drugs, and how to mitigate them, has helped the field's recent resurgence.

Significant advances have been made in covalent drug discovery, yet many opportunities remain to be fully explored or exploited. The following examples highlight some areas that merit further study:

- diversify cysteine-targeting electrophiles beyond acrylamides to engage recalcitrant cysteines and to expand the druggable cysteinome;
- the scarcity of cysteine in protein binding sites necessitates the advancement of new electrophiles that target alternative side chains. Such warheads need further research to optimize the metabolism and toxicological profiles. In cancer, it will be interesting to understand the rate of emergence of resistance compared to cysteine-targeting drugs;
- the orthogonality of nucleophilic drugs that engage protein electrophiles provides intriguing possibilities – more work is needed to understand the breadth of these opportunities;
- improvements in functionalized clickable covalent chemical probes, and mass spectrometry techniques, are needed to effectively map the entire

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ligandable reactive proteome, and integrating this information with computational biology will significantly influence therapeutic target selection;

- covalent small molecules targeting RNA will likely enhance the potency and selectivity of current reversible inhibitors;
- site-specific ligand-mediated chemical mutagenesis of proteins in cells, such as the conversion of cysteine or serine to dehydroalanine, will engender target proteins with neofunctionality;
- therapeutic proteins bearing reactive warheads that crosslink to their partners in, and between, cells demonstrate opportunities to move beyond small molecule drug discovery.

This themed collection highlights state-of-the-art advancements in covalent drug discovery. The articles, reviews, and opinion pieces exemplify and discuss the challenges and opportunities for this continually evolving area of medicinal chemistry. These works demonstrate the diverse impact of covalent drug discovery, and they emphasize the influence this field has had on other areas of therapeutic research, including targeted protein degradation, protein–protein interaction inhibition, fragment-based approaches, allosteric inhibition, and chemoproteomics. As shown by the broad scope of the articles in this collection and as precedented by past and current successes, the field of covalent drug discovery will no doubt continue to grow, and there remain many untapped opportunities for further innovation.

Conflicts of interest

L. H. J. serves on the scientific advisory boards for, and holds equity in, Interline Therapeutics and Rapafusyn Pharmaceuticals, consults for Umbra Therapeutics, Ananke Therapeutics and Matchpoint Therapeutics, and holds equity in Jnana Therapeutics. The Center for Protein Degradation at DFCI receives research funding from Deerfield. K. M. B. and Z. P. have no conflicts to declare.