

Research Progress on USP14-Mediated Protein Homeostasis Regulation in the Tumorigenesis, Progression and Drug Resistance of Multiple Myeloma

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Abstract: Multiple myeloma (MM) is a plasma cell malignancy highly dependent on the protein homeostasis network. MM cells, due to their continuous synthesis and secretion of large amounts of immunoglobulins, have a high dependence on protein folding, transport, and degradation processes; thus, protein homeostasis imbalance not only participates in the occurrence and development of MM but is also closely related to the response to proteasome inhibitor therapy and the formation of drug resistance. USP14 is a proteasome-associated deubiquitinase located on the 26S proteasome, which can participate in the maintenance of intracellular protein homeostasis by regulating the deubiquitination of substrate proteins, the removal of ubiquitin chains, and proteasome function. Recent studies have shown that USP14 plays an important role in the regulation of tumor-related protein homeostasis; in MM, the latest research further suggests that USP14 can participate in tumor progression and ferroptosis resistance by mediating the deubiquitination of SLC7A11. This article reviews the research progress of USP14-mediated protein homeostasis regulation in the occurrence, development, and drug resistance of MM based on the structural and functional characteristics of USP14, and summarizes the potential therapeutic value of targeting USP14, with the aim of providing a reference for related mechanism research and the exploration of targeted intervention strategies.

Keywords: Multiple myeloma; USP14; Protein homeostasis; Deubiquitination; Drug resistance; Ferroptosis

1. Introduction

As a common hematologic malignancy, multiple myeloma (MM) relies heavily on proteostasis due to the massive immunoglobulin synthesis in malignant plasma cells. Proteostatic imbalance is closely associated with disease progression and drug resistance, while first-line agents such as proteasome inhibitors still fail to overcome relapse and resistance^[1].

The ubiquitin–proteasome system (UPS) serves as the core pathway for maintaining proteostasis. USP14, a deubiquitinating enzyme localized to the 26S proteasome, is regulated by conformational changes and post-translational modifications^[2] and exerts dual regulatory effects on the proteasome. It is widely involved in cell cycle progression, stress adaptation, apoptosis, and other biological processes, playing a key role in tumorigenesis, progression, and drug resistance.

Studies have shown that USP14 is essential for the survival of MM cells. Its upregulation is linked to cell adhesion-mediated drug resistance^[3], and it can modulate ferroptosis and tumor progression by regulating the deubiquitination of SLC7A11 via HSPA9^[4]. Inhibition of USP14 leads to the accumulation of ubiquitinated proteins, triggers endoplasmic reticulum stress, and induces apoptosis^[5].

As both a stress buffer and a survival regulator, USP14 provides an important basis for further exploring the mechanisms of drug resistance in MM and developing targeted therapeutic strategies.

2. USP14-Mediated Proteostasis Regulation and Drug Resistance in Multiple Myeloma

2.1 USP14 and Proteasome Inhibitor Resistance

Proteasome inhibitors are important foundational drugs for the treatment of multiple myeloma, but the emergence of primary or secondary resistance remains a key cause of disease relapse and treatment failure. Recent studies have shown that proteasome inhibitor resistance is not only caused by single-target alterations but is closely related to multiple mechanisms, including proteostasis load adaptation, unfolded protein response, heat shock response, autophagy, and redox homeostasis remodeling^[1,6,7]. As a proteasome-associated deubiquitinating enzyme, USP14 is located at a critical node of the proteostasis regulatory network, so its role in proteasome inhibitor resistance in multiple myeloma has gradually attracted attention.

From functional evidence, the deubiquitinating enzyme inhibitor b-AP15 targeting USP14/UCHL5 induces the accumulation of high-molecular-weight ubiquitin conjugates, activates stress damage, and enhances apoptosis in multiple myeloma cells, while overcoming bortezomib resistance to a certain extent^[5]. Subsequent studies on VLX1570 further demonstrated that interfering with proteasome-associated deubiquitinating activity significantly reduces myeloma cell survival and shows certain anti-tumor activity in clinical exploration of relapsed/refractory multiple myeloma^[8]. These results suggest that USP14-related deubiquitination regulation may be involved in the adaptation of multiple myeloma cells to proteasome inhibitor pressure.

Mechanistically, recent literature proposes that multiple myeloma cells can reduce drug sensitivity under proteasome inhibitor treatment by redistributing proteostasis load, enhancing stress buffering capacity, and remodeling protein degradation-related pathways^[6,7]. As an important regulator of proteasomal substrate processing and ubiquitin chain editing, USP14 can theoretically indirectly support the formation of drug resistance phenotypes by affecting abnormal protein clearance efficiency, alleviating proteotoxic stress, and maintaining the stability of key survival-related substrates. Although direct mechanistic evidence for USP14 alone mediating proteasome inhibitor resistance in multiple myeloma is still relatively limited, existing studies have indicated its non-negligible biological significance in this process.

Overall, the relationship between USP14 and proteasome inhibitor resistance in multiple myeloma has initially emerged: on the one hand, USP14-mediated deubiquitination regulation helps myeloma cells buffer drug-induced proteotoxic stress; on the other hand, targeting USP14-related activity can restore drug sensitivity in drug-resistant cells to a certain extent^[1,5-9]. Thus, USP14 may be an important regulatory node connecting proteostasis adaptation and proteasome inhibitor resistance.

2.2 USP14 and Cell Adhesion-Mediated Drug Resistance (CAM-DR)

Cell adhesion-mediated drug resistance (CAM-DR) is one of the important drug resistance mechanisms in multiple myeloma. After adhering to bone marrow stromal cells or extracellular matrix, multiple myeloma cells gain additional survival advantages and reduce sensitivity to chemotherapeutic drugs and some targeted drugs. Existing studies have shown that USP14 is closely related to the formation of CAM-DR in multiple myeloma cells, with its expression upregulated in adhesion models and downregulated in apoptosis models, suggesting that USP14 may participate in the regulation of microenvironment-dependent survival phenotypes^[3].

Xu et al. found that changes in USP14 expression affect the adhesion ability, apoptosis level, and drug response of multiple myeloma cells; further mechanistic analysis indicated that the process by which USP14 participates in CAM-DR may be related to aberrant regulation of the Bcl-xL anti-apoptotic pathway and Wnt signaling^[3]. This demonstrates that the role of USP14 in multiple myeloma is not limited to proteasomal substrate deubiquitination itself but may also enhance tumor cell tolerance to therapeutic pressure by linking cell adhesion, anti-apoptotic signaling, and proteostasis adaptation.

From a proteostasis perspective, the microenvironmental protection provided by CAM-DR is not an isolated event but is coupled with the ability of multiple myeloma cells to adapt to stress and proteotoxic load^[3]. Recent studies on proteostasis and drug resistance in multiple myeloma suggest that tumor cells can maintain survival by remodeling unfolded protein response, heat shock response, autophagy, and other stress buffering mechanisms; as a proteasome-associated deubiquitinating enzyme, USP14 is located at a critical node of this adaptive network, so its involvement in CAM-DR is theoretically reasonable^[1,3,10].

Overall, existing evidence suggests that USP14 may participate in the formation and maintenance of CAM-DR by promoting adhesion-related survival signals and enhancing microenvironmental protective effects in multiple myeloma^[3]. However, the direct substrates and complete molecular mechanisms corresponding to USP14 in microenvironmental drug resistance of multiple myeloma remain to be further elucidated.

2.3 USP14 and Ferroptosis Resistance

Ferroptosis is a form of cell death characterized by iron-dependent accumulation of lipid peroxidation, which has been recognized in recent years as closely related to the pathogenesis, progression, and therapeutic response of multiple myeloma^[11]. Due to the persistent hypermetabolic and stressful state of multiple myeloma cells, they are highly dependent on the regulation of redox homeostasis and lipid peroxidation damage, so aberrant expression of ferroptosis-related molecules can provide additional survival advantages for tumor cells^[11].

Recent studies have directly incorporated USP14 into the ferroptosis regulatory network of multiple myeloma. Shen et al. found that HSPA9 enhances the deubiquitination of SLC7A11 by USP14, thereby improving SLC7A11 protein stability, strengthening the ability of multiple myeloma cells to clear lipid peroxidation damage, ultimately promoting tumor progression and enhancing ferroptosis resistance^[4]. This suggests that USP14 not only participates in general proteostasis maintenance in multiple myeloma but also directly links deubiquitination regulation to cell death remodeling by stabilizing specific key substrates.

SLC7A11 is a key component of system Xc⁻ and plays a central role in cystine uptake, glutathione synthesis, and antioxidant defense. USP14-mediated deubiquitination and stabilization of SLC7A11 help maintain redox homeostasis, alleviate lipid peroxidation stress, and reduce cellular sensitivity to ferroptosis induction in multiple myeloma^[11]. Therefore, from a proteostasis perspective, the promotion of ferroptosis resistance by USP14 is not an isolated event but an important component of adaptive survival in multiple myeloma cells through the regulation of key protein stability.

Overall, existing evidence supports that USP14 participates in the formation of ferroptosis resistance in multiple myeloma, with its mechanism mainly reflected in the deubiquitination regulation of SLC7A11 stability^[4]. This finding not only expands the understanding of USP14 function in multiple myeloma but also indicates that it may be a key molecular node connecting proteostasis maintenance, redox adaptation, and therapeutic resistance.

2.4 The Role of USP14 in the Drug Resistance-Related Proteostasis Adaptation Network of Multiple Myeloma

In addition to proteasome inhibitor resistance, CAM-DR, and ferroptosis resistance, therapeutic resistance in multiple myeloma is also closely related to a broader proteostasis adaptation network. Recent studies suggest that under sustained therapeutic pressure, multiple myeloma cells can buffer abnormal protein accumulation and cytotoxic damage by re-regulating unfolded protein response, heat shock response, redox homeostasis, autophagy, and proteasomal "rebound" response, thereby maintaining survival and promoting drug resistance^[1,7,12]. In this context, although USP14 lacks direct evidence covering all drug resistance types, its molecular position determines its potential involvement in multiple proteostasis adaptation processes.

Mechanistically, USP14 affects abnormal protein clearance and proteotoxic stress buffering by regulating the editing of ubiquitin chains on proteasome-bound substrates and substrate processing efficiency on the one hand; on the other hand, it links proteostasis regulation to cell survival, oxidative stress adaptation, and cell death remodeling by stabilizing specific key substrates. Previous studies have shown that USP14 participates in ferroptosis resistance by stabilizing SLC7A11 and is associated with adhesion, anti-apoptosis, and aberrant Wnt signaling in microenvironment-related drug resistance models of multiple myeloma, suggesting that its role is not limited to a single drug resistance mode but is embedded in a cross-pathway proteostasis adaptation network^[3,4].

In addition, recent reviews on the drug resistance mechanisms of multiple myeloma point out that in addition to classical proteasome inhibitor resistance, immunomodulatory drug resistance, stress-induced transcriptional program remodeling, and tumor microenvironment-dependent escape are also related to enhanced proteostasis maintenance and stress buffering capacity^[7]. Therefore, from a review perspective, USP14-mediated deubiquitination regulation is more appropriately understood as a regulatory node in

the adaptive survival network of multiple myeloma cells: it can reduce therapy-induced proteotoxic stress by maintaining protein degradation balance and may enhance cellular tolerance to stress and drug intervention by affecting the stability of specific substrates.

Overall, existing evidence supports understanding USP14 within the drug resistance-related proteostasis network of multiple myeloma. Although the direct substrates and precise mechanisms corresponding to its role in different drug resistance types are not yet fully clear, research on USP14 helps to understand the therapeutic resistance of multiple myeloma from a more holistic proteostasis perspective and provides a basis for exploring subsequent targeted intervention strategies.

3. Therapeutic Strategies Targeting USP14 to Intervene in Proteostasis

3.1 Research Progress of USP14-Related Inhibitors

In recent years, small-molecule inhibitors targeting deubiquitinating enzymes have gradually become an important direction in anti-tumor drug development, among which USP14 has attracted attention due to its dual functions of proteasome-associated deubiquitinating activity and proteostasis regulation^[13,14]. Based on existing studies, USP14-related inhibition strategies can be roughly divided into two categories: one is 19S proteasome-associated DUB inhibitors represented by VLX1570, which mainly target USP14 and UCHL5; the other is small-molecule inhibitors relatively specific to USP14 represented by IU1 and its derivatives^[2,13,15].

In multiple myeloma (MM), VLX1570 is a representative USP14-related compound in the past decade. Relevant studies have shown that VLX1570 induces the accumulation of high-molecular-weight ubiquitin conjugates, enhances proteotoxic stress, and promotes apoptosis in multiple myeloma cells, thereby inhibiting tumor cell growth^[8]. Subsequent Phase I studies further showed that VLX1570 was once used in clinical exploration for patients with relapsed/refractory multiple myeloma^[8]. However, the effect of such drugs is not strictly limited to a single USP14 target; more precisely, they belong to inhibition strategies targeting 19S proteasome-associated deubiquitinating activity^[2,8].

In addition to the above inhibitors, IU1 and its derivatives represent another inhibition strategy relatively specific to USP14. Studies have suggested that IU1 inhibits USP14 deubiquitinating activity by acting on sites near the USP14 catalytic domain, providing a basis for the subsequent development of more selective USP14 inhibitors^[2,13,15]. However, for multiple myeloma, VLX1570 is still the main compound with relatively direct experimental and clinical relevance, while IU1 analogs are mostly in the stage of mechanistic research and early drug optimization.

Overall, current research on USP14-related inhibitors has shown certain anti-myeloma potential, with the core significance of breaking the adaptive maintenance of proteostasis in tumor cells by interfering with proteasome-associated deubiquitinating activity. However, from a drug development perspective, existing representative molecules still suffer from insufficient selectivity, off-target effects, and limited safety evaluation. Therefore, how to obtain more specific and clinically translatable USP14-targeted compounds remains the focus of future research.

3.2 Potential Value of Targeting USP14 to Regulate Proteostasis in Multiple Myeloma

From the biological characteristics of multiple myeloma, targeting USP14 has a clear theoretical basis. Multiple myeloma cells are in a state of long-term high protein synthesis, high secretion, and continuous stress, with a high dependence on the proteostasis network; as a regulator of proteasome-associated deubiquitination, USP14 has functions including substrate ubiquitin chain editing, proteasomal function regulation, and maintenance of key substrate stability, making it a promising target for intervening in proteostasis adaptation in multiple myeloma^[1,4,14].

First, targeting USP14 helps break the dependence of multiple myeloma cells on abnormal protein clearance and proteotoxic stress buffering. Existing studies have shown that interfering with proteasome-associated deubiquitinating activity leads to the accumulation of high-molecular-weight ubiquitin conjugates, enhances endoplasmic reticulum stress, and induces tumor cell death, suggesting that USP14-related inhibition strategies may weaken the survival advantage of multiple myeloma cells by disrupting proteostasis maintenance^[12]. Compared with simply inhibiting proteasomal catalytic activity, targeting the 19S regulatory level represented by USP14 can theoretically affect protein degradation from the perspective of substrate processing and ubiquitin chain editing, providing a different intervention entry point for proteostasis regulation from traditional proteasome inhibitors^[2].

Second, USP14 may have potential value in overcoming certain types of drug resistance. Previous studies have indicated that USP14-related deubiquitinating activity is associated with proteasome inhibitor resistance, CAM-DR, and ferroptosis resistance; among them, the finding that USP14 participates in ferroptosis resistance in multiple myeloma by stabilizing SLC7A11 further demonstrates that its intervention value is not only reflected in general protein degradation regulation but also may reshape cell death sensitivity by affecting the stability of specific key substrates^[3,4,11]. Therefore, targeting USP14 may provide a new approach to improving the therapeutic sensitivity of drug-resistant multiple myeloma cells.

In addition, from the perspective of combination therapy, USP14-targeted strategies have certain expansion space. Since the formation of multiple myeloma drug resistance usually involves multiple processes such as proteostasis remodeling, enhanced stress buffering, and microenvironmental protection, combining USP14-targeted intervention with proteasome inhibitors, ferroptosis-inducing strategies, or other stress-related therapies may theoretically produce complementary effects^[7,11,12]. However, such combination applications in multiple myeloma are still mainly at the stage of theoretical deduction and preliminary research, and their specific applicable scenarios and efficacy require more experimental evidence.

Overall, as a key molecule connecting proteasome-associated deubiquitination regulation, maintenance of key substrate stability, and cellular stress adaptation, USP14 has certain potential therapeutic value in multiple myeloma. However, this value is currently mainly based on cellular and preclinical research, and how to translate it into more selective and operable therapeutic strategies remains to be further explored.

3.3 Current Problems and Challenges

Although targeting USP14 to intervene in proteostasis shows certain potential value in multiple myeloma, relevant research and translational application still face various problems at this stage. First, insufficient drug selectivity remains the most prominent limitation. VLX1570, the most closely related representative compound to multiple myeloma, mainly targets 19S proteasome-associated deubiquitinating activity and is not a strict USP14 single-target inhibitor. Therefore, it is necessary to further clarify how much of its anti-tumor effect comes from USP14 itself and how much from the co-intervention of other DUBs or related pathways^[2,8,15].

Second, the key substrate profile and specific action network of USP14 in multiple myeloma are not sufficiently clear. At present, relatively direct mechanistic evidence in multiple myeloma mainly focuses on USP14-mediated SLC7A11 deubiquitination promoting ferroptosis resistance and the association between proteasome-associated deubiquitinating activity and drug resistance phenotypes; however, the core substrates and upstream/downstream signaling networks corresponding to USP14 in different drug resistance types, microenvironmental backgrounds, and therapeutic stages lack systematic elucidation. This incomplete mechanistic understanding limits the precise design and indication definition of USP14-targeted strategies.

Third, clinical translation evidence is still limited. Current clinical exploration directly related to multiple myeloma mainly focuses on VLX1570, but its clinical research scale is small, and practical obstacles in safety and tolerability have emerged during drug development, indicating a significant gap between preclinical activity and clinical applicability^[8]. In addition, multiple myeloma itself has strong molecular heterogeneity and microenvironmental dependence; whether simply targeting a single proteostasis regulatory node can achieve stable efficacy in different patient subgroups remains to be further verified^[7].

Finally, the optimal mode of combination therapy strategies has not been determined. Theoretically, USP14-targeted intervention can complement proteasome inhibitors, ferroptosis-inducing strategies, and other stress-related therapies, but current evidence is still dominated by preliminary research and mechanistic speculation, lacking systematic verification in multiple myeloma models and clinical data. Therefore, future research still needs to advance in improving inhibitor selectivity, clarifying key substrates and action networks of USP14 in multiple myeloma, optimizing combination regimens, and strengthening safety evaluation.

4. Summary and Outlook

Multiple myeloma (MM) is the second most common hematologic malignancy worldwide. Its core

pathological feature is the clonal proliferation of malignant plasma cells in the bone marrow, accompanied by excessive secretion of large amounts of abnormal monoclonal immunoglobulins. Due to the sustained and robust immunoglobulin synthesis and secretion in MM cells, these cells are highly dependent on the proteostasis network that governs protein folding, trafficking, and degradation. Proteostatic imbalance not only serves as a key driver of malignant progression in MM but also is closely associated with therapeutic response and the development of drug resistance in patients^[1]. Although first-line targeted agents represented by proteasome inhibitors and immunomodulatory drugs have significantly improved survival outcomes in MM patients, drug resistance and disease relapse remain central challenges in clinical practice. Most patients eventually develop relapsed/refractory multiple myeloma, highlighting the urgent need to explore novel intervention targets from the perspective of proteostasis regulation^[1,7].

The ubiquitin–proteasome system (UPS) constitutes the core pathway maintaining intracellular proteostasis. As important components of the UPS, deubiquitinating enzymes (DUBs) participate in various biological processes including protein degradation, signal transduction, and stress adaptation by cleaving ubiquitin chains from substrate proteins or modifying ubiquitin signals^[6,13]. Among them, USP14 is a proteasome-associated deubiquitinating enzyme localized to the 26S proteasome. Its activity is regulated by proteasome binding status, conformational rearrangement, and post-translational modifications such as phosphorylation at Ser432, and it maintains the dynamic balance of proteostasis by modulating ubiquitin chain cleavage and substrate processing^[2,14].

Functionally, USP14 exerts dual regulatory effects on the proteasome: it can stabilize substrate proteins by trimming their ubiquitin chains or promote conformational activation of the proteasome, thereby participating in the fine-tuning of proteostasis. Meanwhile, USP14 is widely involved in cell cycle progression, stress adaptation, apoptosis, and mitochondrial homeostasis, playing a critical regulatory role in tumor development, progression, and therapeutic resistance^[14].

In MM, studies have confirmed that USP14-mediated deubiquitination is essential for the survival of MM cells. Its upregulation is related to cell adhesion-mediated drug resistance^[3]. Moreover, USP14 can enhance the deubiquitination of SLC7A11 through HSPA9, thereby regulating ferroptosis sensitivity and promoting tumor progression^[4]. Inhibition of USP14 activity leads to abnormal accumulation of high-molecular-weight ubiquitinated proteins, induces endoplasmic reticulum stress and proteotoxic damage, and ultimately triggers apoptosis in MM cells^[5,12].

In summary, USP14 acts as both a stress buffering factor and a survival regulatory node in MM, providing an important theoretical basis for further dissecting the mechanisms of MM drug resistance and developing novel targeted intervention strategies.

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References

- [1] SEDLACEK J. Impact of proteostasis workload on sensitivity to proteasome inhibitors in multiple myeloma [J]. *Clinical and Experimental Medicine*, 2025, 25(1): 176.
- [2] DASH R, TRAN N N, LEE S B, et al. Structural Dynamics Analysis of USP14 Activation by AKT-Mediated Phosphorylation[J]. *Cells*, 2024, 13(11): 955.
- [3] XU X, LIU J, SHEN C, et al. The role of ubiquitin-specific protease 14 (USP 14) in cell adhesion-mediated drug resistance (CAM-DR) of multiple myeloma cells[J]. *European Journal of Haematology*, 2017, 98(1): 4-12.
- [4] SHEN N, XIA Y, SHEN X, et al. HSPA9 contributes to tumor progression and ferroptosis resistance by enhancing USP14-driven SLC7A11 deubiquitination in multiple myeloma[J]. *Cell Reports*, 2025, 44(5): 115720.
- [5] TIAN Z, D'ARCY P, WANG X, et al. A novel small molecule inhibitor of deubiquitylating enzyme USP14 and UCHL5 induces apoptosis in multiple myeloma and overcomes bortezomib resistance[J]. *Blood*, 2014, 123(5): 706-716.
- [6] LEZAMA R A, GUDIÑO GARCÍA A, LÓPEZ RAMÍREZ K, et al. Mechanism regulation of endoplasmic reticulum stress in multiple myeloma cells: modulation of the UPR, UPS, autophagy, HSPs, and potential therapeutic targets[J]. *Expert Review of Hematology*, 2026, 19(2): 143-156.
- [7] TEOH P J, KOH M Y, MITSIADES C, et al. Resistance to immunomodulatory drugs in multiple

- myeloma: the cereblon pathway and beyond*[J]. *Haematologica*, 2025, 110(5): 1074-1091.
- [8] ROWINSKY E K, PANER A, BERDEJA J G, et al. Phase 1 study of the protein deubiquitinase inhibitor VLX1570 in patients with relapsed and/or refractory multiple myeloma[J]. *Investigational New Drugs*, 2020, 38(5): 1448-1453.
- [9] FERGUSON I D, LIN Y H T, LAM C, et al. Allosteric HSP70 inhibitors perturb mitochondrial proteostasis and overcome proteasome inhibitor resistance in multiple myeloma[J]. *Cell Chemical Biology*, 2022, 29(8): 1288-1302.
- [10] VÁTSVEEN T K, GILIBERTO M, BJORNSDOTTIR V, et al. Targeting proteostasis in multiple myeloma through inhibition of LTK[J]. *Leukemia*, 2025, 39(9): 2237-2245.
- [11] SHI J, LU Y, WEI W, et al. Ferroptosis: a novel pharmacological mechanism against multiple myeloma[J]. *Frontiers in Pharmacology*, 2025, 16: 1606804.
- [12] YUAN S, SHE D, JIANG S, et al. Endoplasmic reticulum stress and therapeutic strategies in metabolic, neurodegenerative diseases and cancer[J]. *Molecular Medicine*, 2024, 30(1): 40.
- [13] XIAN Y, YE J, TANG Y, et al. Deubiquitinases as novel therapeutic targets for diseases[J]. *MedComm*, 2024, 5(12): e70036.
- [14] WANG F, NING S, YU B, et al. USP14: Structure, Function, and Target Inhibition[J]. *Frontiers in Pharmacology*, 2022, 12: 801328.
- [15] WARD J A, PINTO-FERNANDEZ A, CORNELISSEN L, et al. Re-Evaluating the Mechanism of Action of α,β -Unsaturated Carbonyl DUB Inhibitors b-AP15 and VLX1570: A Paradigmatic Example of Unspecific Protein Cross-linking with Michael Acceptor Motif-Containing Drugs[J]. *Journal of Medicinal Chemistry*, 2020, 63(7): 3756-3762.