

Hematopoietic Progenitor Kinase 1 Inhibitors

Zhe Yuan^{1*}, Zhidan Pan²

¹ China Pharmaceutical University, Nanjing, China

² Shenzhen College of International Education, Shenzhen, China

* Corresponding Author Email: 1811581126@mail.sit.edu.cn

Abstract. Cancer, a general name for wide range of diseases that have the ability to make an impact on any parts of the human body and has been a fatal health issue that affects people around the world. Hematopoietic Progenitor Kinase 1 (HPK1), one member from the MAP4K family, is a kind of serine/threonine kinase. Destruction of HPK1 kinase raises the secretion of cytokine and T cell signaling, having positive impact on clearance of virus, and inhibition of tumor growth. Thus, HPK1 has been seen as a promising target that can be used in drug development for immunotherapy of tumors. HPK1 has a pivotal role of inhibition on the signaling pathway of the T-cell receptor, it also inhibits the proliferation and differentiation of B cells, DC cells, and NK cells. In this paper, we aimed to supply a detailed overview of research including the introduction of HPK1, research process on HPK1 inhibitors and different methods of developing new kinase inhibitors.

Keywords: HPK1 inhibitors; tumor immunotherapy; SAR.

1. Introduction

1.1. Cancer and immune oncology

In recent years, the prevalence and mortality rate of cancer have been increasing gradually. Compared with non-solid tumors, solid tumors like lung cancer and breast cancer are the main causes of death in cancer patients [1]. Tumor immunotherapy has become an emerging therapy in addition to the traditional three major methods of surgery, radiotherapy and chemotherapy. There are mainly four types of tumor immunotherapy: immune checkpoint inhibitors, cellular immunotherapy, tumor vaccines and non-specific immunomodulators. In the physiological state, immune cells specifically recognize cancer cell surface antigens, thereby inhibiting tumorigenesis and maintaining cellular homeostasis. There are three stages of elimination, balance and escape in the interaction between cancer cells and human immune cells. It eventually leads to a decrease in tumor cell surface antigens and escape immune responses, leading to the development of tumors [2]. After many clinical practices, immunotherapy has demonstrated its good application prospects in a variety of tumor treatments and even metastatic tumor treatment. Immunotherapy can improve the treatment effect, prolong the survival time, improve the living conditions of tumor patients, improve the quality of life, and is expected to achieve the goal of long-term tumor survival or complete cure of tumors [3].

1.2. Immune checkpoint inhibitors and HPK1 inhibitors

Among the current tumor immunotherapies, immune checkpoint inhibitor therapies have attracted much attention, such as PD-1/PD-L1 antibodies have been broadly used. However, antibody drugs have drawbacks. Immune checkpoint inhibitors are not suitable for all patients. The higher the patient's mutational load, the better the response to treatment. Many patients exhibit primary or acquired resistance to antibody drugs [4][5]. Antibody drugs also have pharmacokinetic shortcomings such as poor tumor tissue permeability and long half-life, and injection administration is inconvenient. In addition, antibodies act only on regulators existing on the surface of T cells [6]. Immune checkpoint inhibitor for patients has limited efficacy.

Small molecule inhibitors of tumor immunotherapy are being developed in large quantities. It has good pharmacokinetic parameters, including better tumor tissue permeability, half-life, can also be used orally, and has the advantage of controllable adverse immune reactions. Some small molecule

inhibitors also have the effect of improving the tumor immune microenvironment. These small molecule inhibitors can overcome the limitations of immune checkpoint inhibitors. It can be used alone or in combination with antibody drugs to exert immune synergy [7].

As a target of small molecule inhibitors in tumor immunology, HPK1, with the full name of hematopoietic progenitor kinase 1, has been confirmed as one of the negative regulators of T cell and B cell activation. It can promote T cell proliferation and upregulate expression of related cytokines by inhibiting HPK1. It has been reported that the combination of PD-1 antibody and HPK1 inhibitor can further enhance the antitumor activity of PD-1 antibody [8]. Therefore, the design of small molecule immunologic drugs for HPK1 targets has great development potential and application value.

2. Structure and biological function of HPK1

HPK1 (MAP4K1) is a Ste20-like silk acid/threonine kinase that belongs to the MAP4K family. There are 5 other kinds of kinases in the family, GCK (MAP4K2), GLK (MAP4K3), HGK (MAP4K4), KHS (MAP4K5), and MINK (MAP4K6). The kinase structure of MAP4Ks is highly similar, consisting of an N-kinase domain, an intermediate proline-rich domain, and a citron homologous domain at the carboxyl end [9].

2.1. The Structure of HPK1

The structure of HPK1 is shown in figure 2.1.1 below. Four proline-rich motifs are present in HPK1, which are PR1, PR2, PR3 and PR4. Typical type II binding sites are present in PR1, PR2, and PR4, which bind to regulatory proteins containing SH3 regions to produce different regulatory effects. The carboxyl terminal is related to intramolecular interactions and plays a regulatory role. In addition, HPK1 contains 13 tyrosine residues as potential phosphorylation sites. Most of the residues can be phosphorylated with 70 kDa ZAP70 and bind to proteins containing SH2 regions [10].

The activated HPK1 has a classical kinase bilobar structure, the hinge region (hinge) is in Glu92~Gly97, and N-lobe and C-lobe are in Asp2~Met91 and Ser98~Asn293, respectively. ATP is combined with the interface among them. The purine base of AMPPNP binds with the hinge residues Glu92 and Cys94 via a root hydrogen bond; The ribose moiety binds with ASP101 and Ala141 respectively via hydrogen bonds [11].

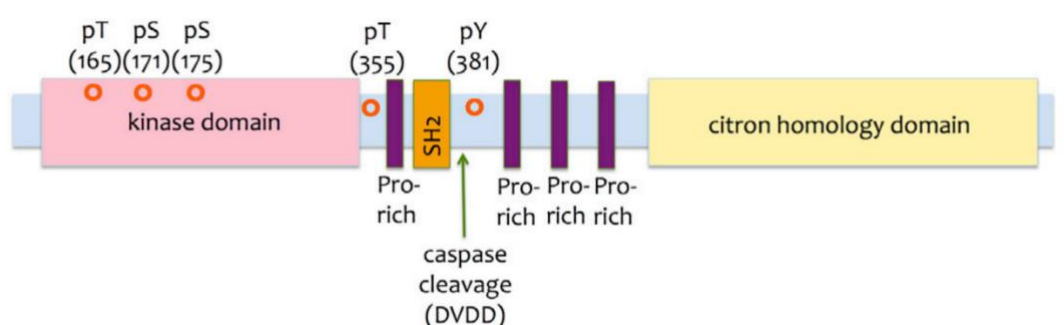


Fig. 1 HPK1 (full-length) protein domain [12]

(Pink: kinase domain, Purple: 4 proline-rich motifs, Orange: SH2 Yellow: citron homology domain)



Fig. 2 HPK1 co-crystal structure [12]

(Blue and purple region each represents a HPK1 protein)

2.2. Negative regulatory function on T cell of HPK1

The function of T cell is significantly negatively regulated by HPK1. As shown in Figure 2.3.2, after TCR forms a complex with CD3, HPK1 is recruited to be linked to LAT. Tyr381 on HPK1 is phosphorylated by ZAP-70, activated HPK1 phosphorylates Ser376 of SLP-76. The binding site of scaffold protein 14-3-3 is generated on SLP-76. Then the interaction between SLP-76 and 14-3-3 is recruited to ubiquitin ligase, destroying the stability of SLP-76/LAT complexes. Thus inhibits the intensity and timing of TCR signaling and blocks T cell activation and proliferation [10].

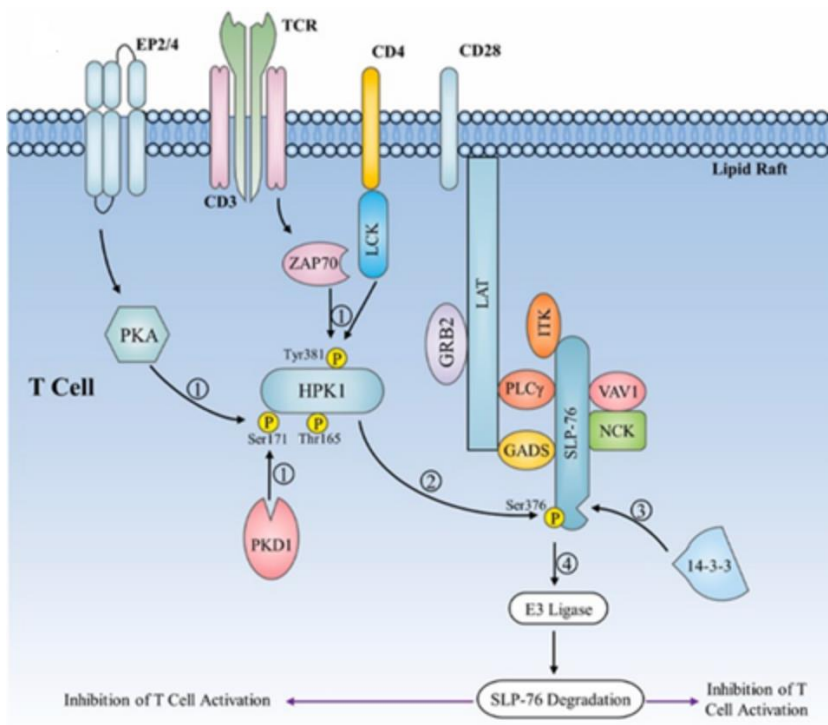


Fig. 3 Regulatory role of HPK1 in inhibition of T cell activation [10]

3. Progress of Research on HPK1 small molecule inhibitors

As a promising tumor immunotherapy target, HPK1 has developed many small molecule inhibitors of different maternal nuclear types. Due to the high homology of kinase sequences within the MAP1K family and the different regulatory pathways of different kinases in the family [13], side effects are prone to occur if the compound is not selective well. Therefore, the main design challenge is to balance the selectivity and activity of inhibitors. Most studies have designed compounds for the HPK1's highly conserved ATP-binding region. Simulated binding images of HPK1 inhibitors to HPK1 kinase domains show that the binding pattern of HPK1 kinase domains conforms to the "solvent exposed region-hinge binder -P-loop interactor". HPK1 inhibitors interact with amino acid residues Glu92 and Cys94 in the hinge region, Asp155 in hydrophobic pockets and Asp101 in the solvent region. These amino acid residue sites are essential for increasing compound activity and enhancing selectivity. Most research institutions and research groups design compounds through high-throughput screening and receptor-based structural design (SBDD). And most of them assume that the receptor domain is the binding pattern described above, which results in poor selectivity for most compounds. Therefore, in order to further obtain good selectivity and activity, the institute will further optimize the compound structure. To compensate for the lack of inhibitors targeting the ATP-binding domain, some institutions have turned to the development of allosteric inhibitors; Or use PROTAC technique to develop PROTAC drugs for better therapeutic outcomes.

3.1. Development of HPK1 inhibitors in clinical trials

According to statistics, there are more than 20 kinds of HPK1 inhibitors currently under research, which are basically in the preclinical and drug discovery stage, because there are many difficulties met in the research and develop process of small molecule inhibitors of HPK1, especially the similarity of the structure of MAP4K family members is very high, and its kinase domain has a high degree of sequence homology with HPK1, and it is difficult to find a balance between selectivity and potency. In addition, it is necessary to continuously improve the cell activity, physicochemical properties, pharmacokinetic properties, etc. of optimized compounds to obtain a class of HPK1 small molecule inhibitors with better effect [14]. Therefore, only 6 drugs have entered the clinical stage. Only one of their structures has been disclosed.

The first inhibitor is CFI-402411 developed by Treadwell Therapeutics, which is highly effective. Current research shows that it can initiate immunity, mainly by weakening the inhibition of T cell receptors (TCRs), disrupting the expression of abnormal cell factors, altering the tumor immunosuppressive environment through regulatory T cells or Tregs, and having a powerful anti-leukemia effect in several mouse models. Advanced solid cancer patients can utilize CFI-40241 both alone and in conjunction with pembrolizumab injection [15].

The second is NDI-101150, an oral small molecule inhibitor. It was developed by Nimbus and is a therapy for solid tumors. Preclinical research proved that NDI-101150 has strong cellular potency and has $> 100 \times$ selectivity for all MAP4K family members [16].

The third is the HPK1 small molecule inhibitor PRJ1-3024 developed by Zhuhai Yufan Biotechnology Company, and PRJ1-3024 capsules entered clinical trials in the United States and China in November 2021 and February 2022 respectively, mainly used for immunotherapy of pancreatic cancer, colorectal cancer, liver cancer and other malignant tumors [17].

The fourth is BGB-15025 developed by BeiGene, and the research data shows that BGB-15025 shows obvious impact on both in vivo and vitro; It not only increases the formation of IL2, but also enhances the inhibition of SLP76 phosphorylation, and has a positive dosage response [18].

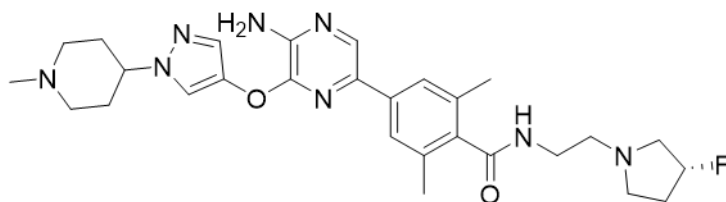


Fig. 4 Structure of BGB-15025 [18]

The fifth is PF-07265028, developed by Pfizer Inc, and the indications under study are gastroesophageal junction cancer, non-small cell lung cancer and solid tumors [19].

The sixth is RGT-264 phosphate tablets developed by Ruige Pharmaceutical, which is a kind of highly active and selective HPK1 inhibitor. It has significant selectivity for a variety of susceptible immune kinases. RGT-264 phosphate tablet pharmacokinetics, preliminary effectiveness, and safety in patients who suffer from advanced solid tumors are currently being assessed [20].

Table 1. Process of clinical research of HPK1 small-molecule inhibitor

Drug	Research Phase	Clinical indications	R&D units
CFI-402411	Clinical Phase II	NSCLC, small-cell lung cancer, melanoma, Merkel cell carcinoma, hepatocellular cancer, breast cancer, gastric cancer	Treadwell Therapeutics
NDI-101150	Clinical Phase II	Solid tumor	Nimbus Therapeutics LLC
PRJ1-3024	Clinical Phase II/I	Solid tumor	Zhuhai Yufan Biotechnologies Co.Ltd
BGB-15025	Clinical Phase I	Advanced solid tumors	Beigene Shenzhou Biology Science and Technology Company
PF-07265028	Clinical Phase I	Solid tumors	Pfizer Inc
RGT-264	Clinical Phase I	Advanced solid tumors	Regor Therapeutics Group

3.2. Existing drug modification

Modifying the existing drug can be an efficient way to develop new therapies. Following part will focus on modification of existing drugs, and HPK1 inhibitors designed by remodeling the Dovitinib. In 2016, University Health Network (UHN) had announced the first patent describing the HPK1 inhibitor [21]. In a kinase IC₅₀ test, Dovitinib demonstrated good HPK1 inhibitory activity. UHN refers structurally to Dovitinib in HPK1 inhibitor. They maintained the mother nucleus of Dovitinib and changed the substituents of Dovitinib to get a range of different alike thienopyridinone compounds. Researchers obtained compounds A1 and A2 with good inhibitory activity, but A1 and A2 are not highly selective.

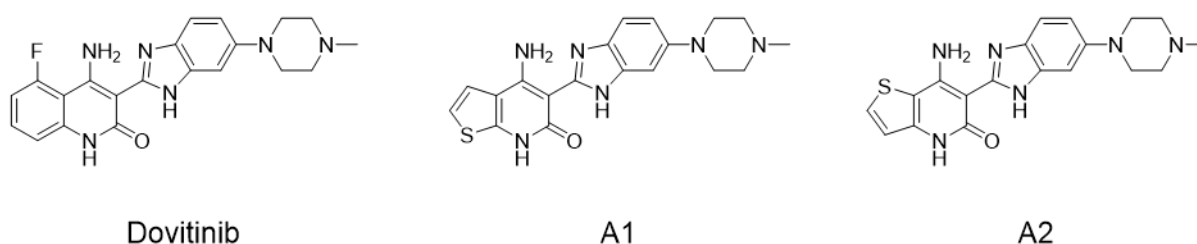


Fig. 5 Structure of Dovitinib, A1 and A2

3.3. High throughput and SBDD

Quinazoline series are typical series of HPK1 small molecule inhibitors. Researchers first identified the quinazoline series as HPK1 inhibitors by means of high-throughput screen. B1 shows weak enzymatic potency (HPK1 IC₅₀ = 580 nM). Optimization was first centered on enhancing HPK1's enzymatic potency. Researchers developed a collection of substructures to research the structure-activity relationships (SAR) near R1. Among those compounds, pyrazole analog compound B2 reached picomolar enzymatic potency (HPK1 IC₅₀ = 1.0 nM) and was the only active compound in the functional primary T cell IL-2 assay (EC₅₀ = 170 nM). Additionally, it demonstrated positive ADME, physicochemical characteristics, including high penetration in the Caco2 test, adequate intrinsic clearance in the mouse hepatocyte test, and high solubility. When it was taken by mouse, the oral bioavailability reached 80% in a single dose. B2 was further tested to identify its kinase selectivity. But B2 hit around 25% of the tested 397 kinases with a percent inhibition > 90% at 1 μM. Researchers then started optimization for greater pSLP76 cellular potency and kinase selectivity. The co-crystal structure of B2 coupled to the ATP binding region was disclosed to support this optimization. The aminopyrimidine attaches to Cys94 at two sites for B2 to bind to the hinge binder. Further, B2 exhibits key interaction with Lys46 utilizing the pyrazole moiety. Researchers tried to investigate more of the area around R1, therefore, further pyrazole substructures were carried out for R1. All tested compounds with modified R1 displayed strong T cell toxicity. Later, researchers selected compound C1 as tool compound and disclosed its co-crystal structure. C1 was reported to have HPK1 IC₅₀ of 0.018 nM and better induce T cells to produce more IL-2. And it had pSLP76 IC₅₀ of 10 nM. It had IL-2 EC₅₀ = 12 nM, even with low cytotoxicity. Although C1 had extraordinary intrinsic clearance during the mouse hepatocyte assay and low permeability in Caco2 assay. In comparison to the B2 co-crystal, 1c has a crucial hydrogen bond interaction with Lys46 and a hinge binding to Cys94. It's believed that HPK1 is highly flexible. So, researchers introduced a different structure replacing the pyrazole and a dihydroisobenzofuran like 1c in place of the other side in B2. The promoted compound – B3 had both higher enzymatic and cell potency, high IL-2 activity and low cytotoxicity. And it's tested to be of better kinase selectivity. But B3 showed good permeability and intrinsic clearance in mouse hepatocyte test. The next step, researchers focused on its lipophilicity and suboptimal clearance. Then a series of compounds with different R2 were designed. B4 and B5 showed digital nM potency in activity tests with IL-2 secretion promotion and lower logD. B4 and B5 were short of good oral exposure. The balance of potency, ADME and physchem characteristics is very difficult to adjust because of the divergence between clearance in vitro and in vivo as well as the gap between lipophilicity and metabolic stability [22].

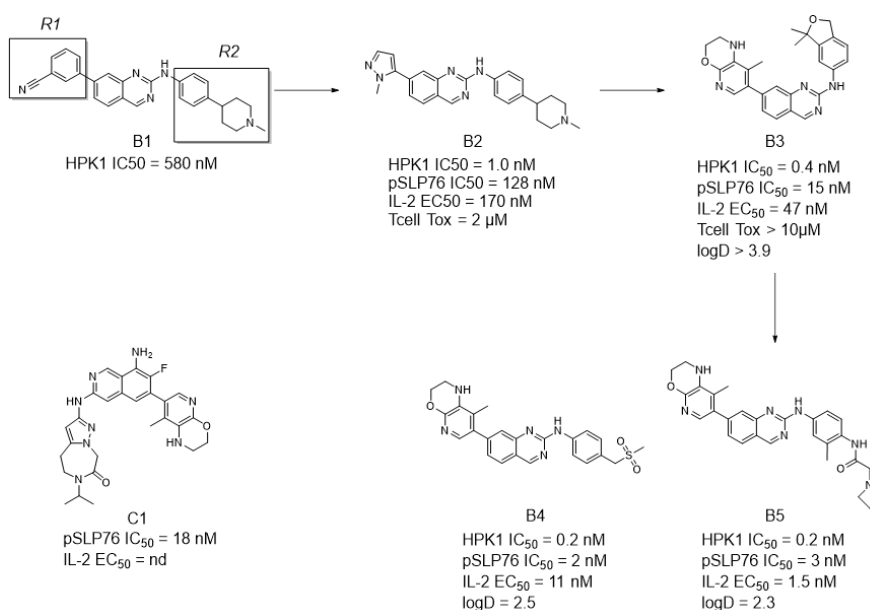


Fig. 6 Optimization of quinazoline HPK1 inhibitors

3.4. Allosteric inhibitors

As the previous parts of the paper had mentioned, there are different types of kinase inhibitors. Among all the kinase inhibitors, most of them usually belong to type I or type II, and both types are orthostatic. The difference between them is the place they are targeting. Type I inhibitors aimed at the site of ATP-binding of the activated kinase, while type II inhibitors aimed the inactivated ones. However, although the kinase inhibitors developed mainly belong to type I or type II, the unsatisfying selectivity and subsequent side effects are still concerned.

The following type of inhibitors, allosteric inhibitors, have the ability to improve the situation. Allosteric inhibitors belong to the non-ATP competition class of kinase inhibitors, including type III and type IV inhibitors. Instead of directly affecting the ATP-binding site, type III inhibitors affect the surrounding domain of the ATP-binding site. After binding, it will change the position of α -helix, and form inactive conformation of the enzyme. Not affecting the binding site of ATP straightforwardly either, the type IV inhibitors affect the distant area from the ATP-binding site. Different from type I or type II compounds, these kinds of inhibitors have better selectivity and can be used to decrease drug resistance by overriding the ATP binding site mutation [23]. Compared to other inhibitors, allosteric inhibitors have more precise regulation and less side effects. All these advantages are due to the most common allosteric regulation used in allosteric inhibitors: negative feedback regulation, the activity of certain enzymes at the front end of the pathway is inhibited through the end product of a metabolic pathway [24].

An allosteric inhibitor of HPK1 was discovered in 2021 by Weixue Wang, et al. D1 is an inactive conformation-selective triazolopyrimidinone HPK1 inhibitor. D1 binds more effectively with unphosphorylated HPK1 >24-fold than with active HPK1. Since it is an allosteric inhibitor, it is non-ATP competitive and has high selectivity [25].

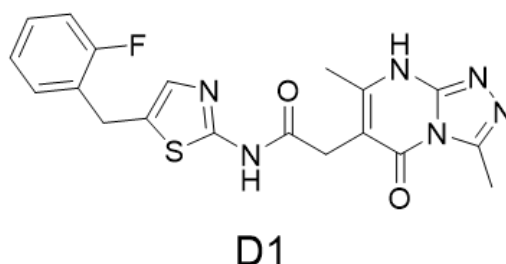


Fig. 7 Structure of D1 [25]

3.5. HPK1 inhibitors of PROTAC technology

Proteolysis targeting chimeric (PROTAC), being presented as a promising method for discovery of drug and tool development in field of science, is a useful tool that can degrade targeted protein, and this can impact tumor growth by ubiquitinate the target proteins through the ubiquitin-proteasome system (UPS) [26]. The PROTACs molecules have two heads, one bind target protein, while another recruits an E3 ubiquitin ligase [27]. Compared with traditional inhibitors, PROTACs molecules have a variety of advantages due to PROTACs molecules particularity. Compared with most of the kinase inhibitors, PROTACs molecules have special mechanism to bind the target protein as mentioned before, they degrade the protein instead of binding the site. Thus, using PROTACs molecules can target the undruggable target, and can decrease the drug resistance [28].

From the previous research and experiment the researchers found out that degradation of a target protein has significant advantages than the original inhibition method [29]. They then involved PROTAC to develop new molecules. First, it was a heterobifunctional small molecule: E2, developed from a HPK1 inhibitor E1, and it promoted ubiquitination and degradation of HPK1 [29].

E3' was built by linking E1 to the Cereblon (CRBN) ligand thalidomide [30]. In vivo experiment, E3' has shown remarkable effect on tumor growth inhibition than E1 and the control group of ddH₂O in mice with subcutaneous 4T-1 tumors. The researchers then want to determine whether using E3' for a step of treatment will be able to significantly improve the efficiency of antitumor of the CAR-T

cells by using ex vivo experiment. The results show that degradation of HPK1 by E3' had stepped up the in vivo antitumor efficiency of BCMA CAR-T cell therapy [29].

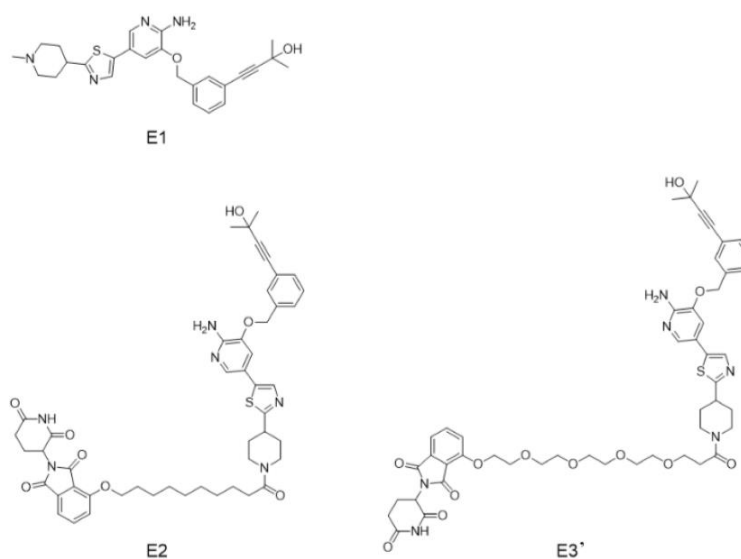


Fig.8 Structure of E1, E2, E3' [29]

4. Conclusion

From the time when HPK1 was discovered to be a promising target of tumor therapy, the research and development of HPK1 inhibitors have become an important field. By analyzing different methods used to develop HPK1 inhibitors, it is shown that some inhibitors made by specific technologies work more efficiently. Though most of the inhibitors are now type I and II, it is still difficult to develop HPK1 small molecule inhibitors from the ATP-binding site. For type I and type II inhibitors, maintenance of selectivity is still a challenge, and drug resistance is also a concern. However, the development of new technologies is improving the situation. To develop more efficient inhibitors by improving the properties of all aspects, it is necessary to have a clearer eutectic structure as a guide, or adopt different development ideas, for example, using allosteric inhibitors, PROTAC or other technologies.

Authors Contribution

All the authors contributed equally, and their names were listed in alphabetical order.

References

- [1] Bray, Freddie, et al. "Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries." *CA: a cancer journal for clinicians* 68.6 (2018): 394-424.
- [2] Kim, Ryungsa. "Cancer immunoediting: from immune surveillance to immune escape." *Cancer Immunotherapy* (2007): 9-27.
- [3] Pan, Yang, et al. "RNA dysregulation: an expanding source of cancer immunotherapy targets." *Trends in pharmacological sciences* 42.4 (2021): 268-282.
- [4] Restifo, Nicholas P., Mark J. Smyth, and Alexandra Snyder. "Acquired resistance to immunotherapy and future challenges." *Nature Reviews Cancer* 16.2 (2016): 121-126.
- [5] Sharma, Padmanee, et al. "Primary, adaptive, and acquired resistance to cancer immunotherapy." *Cell* 168.4 (2017): 707-723.

- [6] Dhanak, Dashyant, et al. "Small-molecule targets in immuno-oncology." *Cell chemical biology* 24.9 (2017): 1148-1160.
- [7] Cheng, Binbin, et al. "Recent advances in small molecule-based cancer immunotherapy." *European Journal of Medicinal Chemistry* 157 (2018): 582-598.
- [8] Hernandez, Sairy, et al. "The kinase activity of hematopoietic progenitor kinase 1 is essential for the regulation of T cell function." *Cell reports* 25.1 (2018): 80-94.
- [9] Chuang, Huai-Chia, Xiaohong Wang, and Tse-Hua Tan. "MAP4K family kinases in immunity and inflammation." *Advances in immunology* 129 (2016): 277-314.
- [10] Zhu, Qiangsheng, et al. "Hematopoietic progenitor kinase 1 in tumor immunology: a medicinal chemistry perspective." *Journal of Medicinal Chemistry* 65.12 (2022): 8065-8090.
- [11] Wu, Ping, et al. "Hematopoietic progenitor kinase-1 structure in a domain-swapped dimer." *Structure* 27.1 (2019): 125-133.
- [12] Lau, Wai L., et al. "Using yeast surface display to engineer a soluble and crystallizable construct of hematopoietic progenitor kinase 1 (HPK1)." *Acta Crystallographica Section F: Structural Biology Communications* 77.1 (2021): 22-28.
- [13] Chuang, Huai-Chia, and Tse-Hua Tan. "MAP4K family kinases and DUSP family phosphatases in T-cell signaling and systemic lupus erythematosus." *Cells* 8.11 (2019): 1433.
- [14] Delpire, Eric. "The mammalian family of sterile 20p-like protein kinases." *Pflügers Archiv-European Journal of Physiology* 458 (2009): 953-967.
- [15] "Safety and Efficacy Study of CFI-402411 in Subjects with Advanced Solid Malignancies - Full Text View - ClinicalTrials.gov." Clinicaltrials.gov, classic.clinicaltrials.gov/ct2/show/NCT04521413. Accessed 30 Sept. 2023.
- [16] Study of NDI 1150-101 in Patients with Solid Tumors. <https://clinicaltrials.gov/ct2/show/NCT05128487?cond=HPK1&draw=1&rank=10> (accessed September 24, 2023).
- [17] A Phase I/II Study to Evaluate the Safety, Pharmacokinetics and Efficacy of PRJ1-3024 in Subjects with Advanced Solid Tumors. <https://clinicaltrials.gov/ct2/show/NCT05315167?cond=HPK1&draw=1&rank=7> (accessed September 24, 2023)
- [18] BGB-15025 Alone and in Combination with Anti-PD-1 Monoclonal Antibody Tislelizumab in Participants with Advanced Solid Tumors. <https://clinicaltrials.gov/ct2/show/NCT04649385> (accessed September 24, 2023)
- [19] PF-07265028 As Single Agent and In Combination with Sasanlimab in Advanced or Metastatic Solid Tumors. <https://www.clinicaltrials.gov/ct2/show/NCT05233436?cond=HPK1&draw=2&rank=5> (accessed September 24, 2023)
- [20] A Phase I Study of RGT-264 in Subjects with Advanced Solid Tumors. <https://www.clinicaltrials.gov/ct2/show/NCT05764915?term=HPK1&cond=HPK1&draw=2&rank=5> (accessed September 24, 2023)
- [21] UNIVERSITY HEALTH NETWORK. Compiler: WO2016205942A1[P]. 2016-12-29.
- [22] Toure, Momar, et al. "Discovery of quinazoline HPK1 inhibitors with high cellular potency." *Bioorganic & Medicinal Chemistry* 92 (2023): 117423.
- [23] Wang, Beilei, et al. "An overview of kinase downregulators and recent advances in discovery approaches." *Signal Transduction and Targeted Therapy* 6.1 (2021): 423.
- [24] "What is allosteric inhibitor?". [www.globecancer.com http://www.globecancer.com/azzx/show.php?itemid=14419#:~:text=%E5%88%AB%E6%9E%84%E6%8A%91%E5%88%B6%E5%89%82%E5%8F%88%E5%8F%AB%E5%8F%98](http://www.globecancer.com/azzx/show.php?itemid=14419#:~:text=%E5%88%AB%E6%9E%84%E6%8A%91%E5%88%B6%E5%89%82%E5%8F%88%E5%8F%AB%E5%8F%98) [Accessed 23 Sep. 2023].
- [25] Wang, Weixue, et al. "Discovery of an allosteric, inactive conformation-selective inhibitor of full-length HPK1 utilizing a kinase cascade assay." *Biochemistry* 60.41 (2021): 3114-3124..
- [26] Qi, Si-Min, et al. "PROTAC: an effective targeted protein degradation strategy for cancer therapy." *Frontiers in Pharmacology* 12 (2021): 692574.

- [27] " PROTACs and Molecular Glues. ". www.astrazeneca.com <https://www.astrazeneca.com/r-d/next-generation-therapeutics/protacs.html>.
- [28] " PROTAC Technology: tool for new therapies development. " <https://www.drugtimes.cn/2021/08/28/xinyaoyanfaliqiprotacjishuzuiquanjiedu/>
- [29] Si, Jingwen, et al. "Hematopoietic progenitor kinase1 (HPK1) mediates T cell dysfunction and is a druggable target for T cell-based immunotherapies." *Cancer Cell* 38.4 (2020): 551-566.
- [30] Dale, Brandon, et al. "Advancing targeted protein degradation for cancer therapy." *Nature Reviews Cancer* 21.10 (2021): 638-654.