REVIEW

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Senolytic effects of first and second generation BCL-xL/BCL-2 dual degraders

E.S. Berezhnaya, A.V. Savustyanenko

Rostov State Medical University,
29 Nakhichevansky Ln., Rostov-on-Don, Russia, 344022

E-mail: bereznoy7@yandex.ru

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The aim. To conduct a literature review of current data on the senolytic effects of dual BCL-xL/BCL-2 degraders, including available molecules, their mechanism of action, efficacy, and safety.

Materials and Methods. Literature search was performed in PubMed, Science Direct, and SciELO databases using the keywords: “senolytics”, “BCL-xL/BCL-2 dual degraders”, “proteolysis targeting chimeras”, “753b”, “WH244”. In the eLIBRARY.ru database were used the next keywords: «сенолитики», «двойные деградаторы BCL-xL/BCL-2», «протеолиз-направленные химеры», «753b», «WH244».

Results. The accumulation of a small number of senescent cells in the body, due to their release of the senescence-associated secretory phenotype (SASP), contributes to the elimination of old and damaged cells. However, when the number of senescent cells becomes large, SASP triggers a chronic inflammatory process that accelerates aging and leads to the development of age-related diseases such as cancer, diabetes mellitus, atherosclerosis, etc. Therefore, there is a need to develop senolytics — drugs aimed to eliminate senescent cells. One possible way to achieve this is through the pharmacological induction of apoptosis. According to literature data, a chimeric molecule, 753b, was created using PROTACs technology. One end of it binds to an E3 ligase, the other to anti-apoptotic proteins (BCL-xL or BCL-2). As a result, all these molecules are brought together in space, forming a ternary complex. Due to proximity, the E3 ligase attaches ubiquitin molecules to the anti-apoptotic proteins, after which the proteasome destroys them. When BCL-xL and BCL-2 are degraded, apoptosis of senescent cells occurs. The molecule 753b is classified as a first-generation dual BCL-xL/BCL-2 degrader. Its anti-senescence and anti-tumor efficacy has been demonstrated in preclinical studies without the development of significant thrombocytopenia. Based on molecule 753b, a more potent analog was developed through two modifications — molecule WH244, which is classified as a second-generation dual BCL-xL/BCL-2 degrader.

Conclusion. Considering the data on efficacy and safety presented in the literature sources, further comprehensive research on molecules 753b, WH244, and/or their derivatives is required, including in clinical studies.

Keywords: senolytics; proteolysis targeting chimeras; BCL-xL/BCL-2 dual degraders; 753b; WH244

Abbreviations: SASP — senescence-associated secretory phenotype; SMIs — small molecule inhibitors; FDA — US Food and Drug Administration; PROTACs — Proteolysis Targeting Chimeras; UPS — ubiquitin-proteasome system; POI — protein of interest; VHL — von Hippel-Lindau protein; Ub — ubiquitin; SCLC — small cell lung cancer; MAFLD — metabolically associated fatty liver disease; MASH — metabolically associated steatohepatitis; AML — acute myeloid leukemia.

Сенолитические эффекты первого и второго поколения двойных деградаторов BCL-xL/BCL-2

Е.С. Бережная, А.В. Савустьяненко

Федеральное государственное бюджетное образовательное учреждение высшего образования
«Ростовский государственный медицинский университет»
Министерства здравоохранения Российской Федерации,
Россия, 344022, г. Ростов-на-Дону, пер. Нахичеванский, д. 29

E-mail: bereznoy7@yandex.ru

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Цель. Провести литературный обзор современных данных о сенолитических эффектах двойных деградаторов BCL-xL/BCL-2, включая доступные молекулы, механизм их действия, эффективность и безопасность.

Материалы и методы. Поиск литературы выполнен в базах PubMed, Science Direct, SciELO по ключевым словам: «senolytics», «BCL-xL/BCL-2 dual degraders», «proteolysis targeting chimeras», «753b», «WH244». В базе eLIBRARY.ru использовали следующие ключевые запросы: «сенолитики», «двойные деградаторы BCL-xL/BCL-2», «протеолиз-направленные химеры», «753b», «WH244».

Результаты. Накопление в организме небольшого количества стареющих (сенесцентных) клеток благодаря высвобождению ими сенесцентно-ассоциированного секреторного фенотипа (SASP) способствует уничтожению старых и повреждённых клеток. Однако, когда сенесцентных клеток становится много, SASP запускает хронический воспалительный процесс, который ускоряет старение и ведет к развитию возраст-связанных заболеваний, таких как рак, сахарный диабет, атеросклероз и пр. Следовательно, возникает необходимость в разработке сенолитиков — лекарственных препаратов, направленных на уничтожение сенесцентных клеток. Один из возможных путей достижения этого сводится к фармакологической индукции апоптоза. По данным литературы с помощью технологии PROTACs была создана химерная молекула 753b. Один ее конец связывается с Е3-лигазой, другой с антиапоптотическими белками (BCL-xL или BCL-2). В результате все эти молекулы сближаются в пространстве, формируя тройной комплекс. Благодаря близости Е3-лигаза присоединяет молекулы убиквитина к антиапоптотическим белкам, после чего протеосома их разрушает. Когда BCL-xL и BCL-2 разрушены, происходит апоптоз сенесцентных клеток. Молекулу 753b относят к первому поколению двойных деградаторов BCL-xL/BCL-2. В доклинических исследованиях была продемонстрирована ее антисенесцентная и противоопухолевая эффективность, без развития выраженной тромбоцитопении. На базе молекулы 753b за счёт двух модификаций был разработан ее более сильный аналог — молекула WH244, которую относят ко второму поколению двойных деградаторов BCL-xL/BCL-2.

Заключение. Учитывая представленные в литературных источниках данные по эффективности и безопасности, требуется дальнейшее всестороннее исследование молекул 753b, WH244 и/или их производных, в том числе и в клинических исследованиях.

Ключевые слова: сенолитики; протеолиз-направленные химеры; двойные деградаторы BCL-xL/BCL-2; 753b; WH244

Список сокращений: SASP — сенесцентно-ассоциированный секреторный фенотип; SMIs — маломолекулярные ингибиторы; FDA — Управление по контролю за качеством пищевых продуктов и лекарственных средств США; PROTACs — протеолиз-направленные химеры; UPS — убиквитин-протеосомная система; POI — целевой белок; pVHL — белок фон Хиппеля-Линдау; Ub — убиквитин; SCLC — мелкоклеточный рак лёгкого; МАЖБП — метаболически ассоциированная жировая болезнь печени; МАСГ — метаболически ассоциированный стеатогепатит; ОМЛ — острый миелоидный лейкоз.

INTRODUCTION

The term “cellular senescence” was proposed by L. Hayflick and P.S. Moorhead based on the observation that normal cells have limited proliferative capacity—after a long period of cultivation, they exit the cell cycle and enter a state of stable growth arrest [1, 2]. This type of senescence was named “replicative senescence” and is associated with telomere shortening and/or dysfunction [3, 4].

Later, the phenomenon of “premature cellular senescence,” not related to telomere shortening, was discovered. Its development is caused by the influence of various endogenous and exogenous stressors on the cell, such as inadequate cell culture conditions, oncogenic factors, genotoxic factors, chemotherapy, radiotherapy, etc. [5–8].

The transient accumulation of a limited number of senescent cells in the body, by any of the above-mentioned methods, has a positive physiological significance. The biologically active substances they produce—the so-called senescence-associated secretory phenotype (SASP)—attract immune system cells, which destroy old and damaged cells, and stimulate the proliferation and differentiation of stem cells and progenitor cells, allowing for the replenishment of cell populations in damaged tissues. In particular, this is one of the important mechanisms in the fight against carcinogenesis [9].

However, the prolonged accumulation of a large number of senescent cells leads to the opposite effect. The SASP released by them triggers a chronic inflammatory process [10, 11], which accelerates aging

and leads to the development of age-related diseases such as cancer, diabetes mellitus, atherosclerosis, and others [12–14].

Based on their positive physiological role, researchers initially made efforts to artificially induce cellular senescence [15]. When the negative effects of an excess of senescent cells became clear, attention shifted to finding ways to reduce their number and/or activity [16]. To date, four groups of such agents with the aforementioned effect are known [17–19]:

- senolytics (destroy senescent cells);
- senomorphs (suppress SASP release);
- senoblockers (block the transition of normal cells into a senescent state);
- senoreversers (enhance the exit of senescent cells from this state).

Until relatively recently, it was unclear whether senescent cells were causally involved in age-related dysfunction and whether their elimination would have a positive effect. However, it was demonstrated that genetic ablation of p16Ink4a-positive senescent cells using INK-ATTAC, which functions as a suicide transgene, along with the administration of the recombinant dimerization protein AP20187, prolonged the lifespan of mice and delayed the onset of many age-related diseases and disorders in mice with accelerated and normal aging. These data confirm the expediency and effectiveness of the first group of drugs mentioned above—senolytics [9, 20, 21]. The other groups were not the focus of our article.

Since the action of senolytics is directed at senescent cells, it is important to note a number of characteristics that distinguish them from normal cells. In particular, they have an increased size and irregular shape, altered cell membrane composition, increased content of mitochondria and lysosomes, structural remodeling and destabilization of the nuclear membrane, their cell cycle is usually arrested in the G1 phase, they lack apoptosis, etc. [15]. Pharmacological induction of apoptosis is one of the important pathways for eliminating an excess number of senescent cells by senolytic agents [22–25].

Thus, considering the scientific and practical significance of the topic, we have dedicated this review to senolytics that induce apoptosis of senescent cells by influencing BCL-xL and BCL-2 molecules. In this context, we have focused primarily on those that achieve this by degrading BCL-xL and BCL-2.

THE AIM. To conduct a literature review of current data on the senolytic effects of BCL-xL/BCL-2 dual degraders, including available molecules, their mechanism of action, efficacy, and safety.

MATERIALS AND METHODS

Literature search was performed in the PubMed, Science Direct, and SciELO databases using the keywords: “senolytics”, “BCL-xL/BCL-2 dual degraders”, “proteolysis targeting chimeras”, “753b”, “WH244”. In the eLIBRARY.ru database (in Russian), the following search queries were used: «сенолитики», «двойные деградаторы BCL-xL/BCL-2», «протеолиз-направленные химеры», «753b», «WH244». None of the molecules belonging to the class of BCL-xL/BCL-2 dual degraders have been included in clinical studies. Consequently, this review is based on preclinical studies of these molecules. Original articles in full text or abstract form were considered, excluding conference materials, short communications, etc.

During the search in the PubMed database with all keywords, 24 studies were found. Of these, 18 were excluded because the molecule of interest, 753b, belonging to the first generation of BCL-xL/BCL-2 dual degraders, has the same spelling as the V-79-753B cell line, which represents Chinese hamster lung fibroblasts and is used in radiation biology and toxicology to study DNA damage, repair, and mutation. Furthermore, one study was a preprint that had not undergone peer review in a scientific journal. The final version of this article (after peer review) was present separately in the search results and was considered by us. Thus, 5 articles from the PubMed database were included in this review.

A similar search in the Science Direct database using all keywords revealed 60 studies. Following the approach described above, 59 studies were excluded as not matching the specified objective. Only one work was included in this review, but it was among the 5 articles found in the PubMed database.

No publications were found in the eLIBRARY.ru and SciELO databases using the keywords.

Consequently, a total of 5 preclinical studies were found across all databases, which were ultimately included in this review. The small number of articles is related to the novelty of the molecules being studied

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and, in general, this scientific direction—all works were performed between 2021 and 2025.

The chemical formulas of molecules 753b and WH244 are borrowed from reference [26]. To facilitate the reader's comprehension, the following designations are made on them: ligand binding to VHL (E3 ligase); intermediate linker; ligand binding to BCL-xL/BCL-2. Red arrows in the WH244 molecule indicate the 1,4-dimethylpiperazine fragment and the site where a bridging carbon atom is added to the morpholine group. A detailed explanation is provided in the text.

Since molecules 753b and WH244 are created using PROTACs technology, the advantages of this technology are listed in this review based on additional literature sources.

RESULTS AND DISCUSSION

First generation of BCL-xL/BCL-2 dual degraders

History of the creation of molecule 753b

Members of the BCL-2 family of proteins are key regulators of cellular apoptosis and include both anti-apoptotic (BCL-2, BCL-xL, MCL-1, etc.) and pro-apoptotic (BAD, BIM, PUMA, BAK, BAX, etc.) proteins. In cancer cells, their balance is shifted towards anti-apoptotic proteins, which contributes to tumor initiation, progression, and the development of drug resistance [26]. Initially, so-called small molecule inhibitors (SMIs) that can directly inhibit the function of anti-apoptotic proteins came into researchers' focus. Among them, venetoclax (ABT199) can selectively inhibit BCL-2 and is the only anti-tumor drug targeting BCL-2 family members that has been approved by the FDA (US Food and Drug Administration). It is also approved for use in the Russian Federation[1]. In general, it is used to treat hematological malignancies whose survival depends more on BCL-2. However, venetoclax is poorly effective in treating solid tumors, whose survival depends more on BCL-xL [26–29].

An effect on both hematological and solid tumors was observed with navitoclax (ABT263), a non-selective small molecule inhibitor that preceded venetoclax and directly inhibited BCL-2 and BCL-xL. However, during its trials, a serious side effect was discovered—thrombocytopenia, as BCL-xL proved important for the survival of circulating platelets. Due to this side effect, navitoclax was not introduced for clinical practice [26, 30].

Researchers then changed their strategy and, instead of small molecule inhibitors (SMIs), began using proteolysis-targeting chimeras (PROTACs), which do not inhibit but rather degrade proteins. Accordingly, the molecule DT2216 was created based on navitoclax (ABT263). However, researchers were again met with an unpleasant surprise: although DT2216 bound to both BCL-2 and BCL-xL *in vitro* in a cell-free system, it degraded only BCL-xL, but not BCL-2, within cells. One problem was solved—due to the specific characteristics of PROTAC technology, thrombocytopenia did not develop. However, the much-needed simultaneous effect on both anti-apoptotic proteins (BCL-xL and BCL-2) was lost [26].

Further refinement of the DT2216 molecule, while maintaining the same PROTAC technology, led to the creation of a new molecule represented by two mixed stereoisomers, 753a and 753b. After their separation, the S-enantiomer (753a) only partially degraded BCL-xL and did not degrade BCL-2, whereas the R-enantiomer (753b) effectively degraded both BCL-xL and BCL-2 [31].

Thus, the molecule 753b became the first representative of the BCL-xL/BCL-2 dual degrader class. Due to the specific characteristics of PROTAC technology, its application does not lead to the development of thrombocytopenia.

Mechanism of action of molecule 753b

The functioning of the ubiquitin-proteasome system (UPS) is the primary intracellular non-lysosomal mechanism responsible for protein homeostasis, as it degrades old and damaged proteins, misfolded proteins, and regulatory proteins that have reached the end of their lifespan. During the enzymatic cascade, a ubiquitin-activating enzyme (E1) activates ubiquitin, a ubiquitin-conjugating enzyme (E2) captures and transfers ubiquitin, and a ubiquitin ligase (E3) attaches ubiquitin to the target protein. Subsequently, the proteasome degrades it [32–35].

PROTAC technology involves the creation of heterobifunctional molecules composed of two

[1] Venetoclax. LP-No. (004567)-(RG-RU). The State Register of Medicines of Russian Federation. Available from: https://grls.minzdrav.gov.ru/Grls_View_ v2.aspx?routingGuid=719240d6-b494-446a-b1a6-28c1faa3adba. Russian

ligands connected by an intermediate linker [36–38]. One ligand is specific for binding to an E3 ligase, and the other ligand is specific for binding to the protein of interest (POI). A typical representation of such a molecule is shown in Figure 1 [39–41].

Accordingly, after administration into the body, PROTACs, through their ligands, bind to the E3 ligase and the target protein, forming a ternary complex that spatially brings them close together (see Fig. 1). Under these conditions, the E3 ligase attaches multiple ubiquitin molecules to the target protein, a process called polyubiquitination (pink color in Figure 1), after which the proteasome degrades it [36].

As noted above, molecule 753b was created using PROTAC technology. One of its ligands is designed to bind to an E3 ligase, and the other to the target protein, which is BCL-xL or BCL-2. As a result, the proteasome degrades both anti-apoptotic proteins, which is why 753b is classified as a BCL-xL/BCL-2 dual degrader [31].

It is important to clarify that the ligand of 753b that binds to the E3 ligase specifically binds to the VHL (von Hippel-Lindau) protein, which is part of the E3 ubiquitin ligase complex along with other proteins. The VHL protein is practically absent in platelets, which is why 753b does not degrade BCL-xL in them and, consequently, cannot cause significant thrombocytopenia [41, 42].

The chemical structure of molecule 753b and the arrangement of its ligands are presented in Figure 1.

Results of preclinical studies of molecule 753b

A review of electronic databases revealed 3 preclinical studies of molecule 753b.

S. Khan et al. [43] evaluated the anti-tumor effects of 753b on BCL-xL/BCL-2 co-dependent SCLC cell lines and H146 xenograft models. (In both cases, this refers to small cell lung cancer, but experiments with SCLC were performed *in vitro*, while H146 was injected subcutaneously into mice with subsequent tumor growth; co-dependence means that the survival of SCLC cells is ensured by inhibiting apoptosis by both BCL-xL and BCL-2 molecules simultaneously). The study found that 753b degraded BCL-xL and BCL-2 in both SCLC cells and H146 cells. Importantly, 753b proved to be a more potent molecule than DT2216, navitoclax, or the DT2216+venetoclax combination in reducing the viability of BCL-xL/BCL-2 co-dependent SCLC cell lines in cell culture *in vitro*. Weekly administration of 5 mg/kg 753b led to a significant delay in tumor growth in H146 xenograft models *in vivo* ($p < 0.0001$), similar to the DT2216+venetoclax combination. Additionally, administration of 5 mg/kg 753b every 4 days caused tumor regression. At this dose, 753b was well-tolerated in mice, without the development of severe thrombocytopenia (observed with navitoclax) and without changes in mouse weight. The obtained results indicate that 753b, a BCL-xL/BCL-2 dual degrader, may be an effective and safe therapeutic agent in SCLC patients. This fact requires confirmation in future clinical studies.

In their work, Y. Yang et al. [44] evaluated the anti-senescence and anti-tumor effects of 753b. It was found that administration of this agent selectively reduced the number of senescent cells in the livers of old mice and STAM mice, partly due to their sequestration in the liver. (STAM™ mice are a commercial model for pharmacological evaluation of drugs for liver fat damage and associated tumor growth). Moreover, 753b effectively ($p < 0.05$) reduced the progression of metabolic-associated fatty liver disease (MAFLD) and the development of hepatocellular carcinoma in STAM mice, even after the mice developed significant metabolic-associated steatohepatitis (MASH) and liver fibrosis. The obtained data suggest that 753b could become a potential therapeutic agent for MAFLD, helping to reduce the incidence of MASH-induced hepatocellular carcinomas.

In the work by Y. Jia et al. [42], the anti-senescence and anti-tumor effects of 753b were evaluated. It was found that administration of this molecule significantly ($p < 0.05$) reduced cell viability and induced dose-dependent degradation of BCL-xL and BCL-2 in a subpopulation of hematopoietic cell lines, primary samples of acute myeloid leukemia (AML) *in vitro*, and patient-derived AML xenograft models *in vivo*. In the latter case, the authors noted the absence of thrombocytopenia. Additionally, the senolytic activity of 753b was demonstrated, enhancing the efficacy of chemotherapy by reducing the severity of chemotherapy-induced cellular senescence ($p < 0.01$). The obtained results provide preclinical justification for the use of 753b in AML therapy. They also suggest that administering 753b in combination with chemotherapy may provide an additional therapeutic effect by combating chemoresistance caused by cellular senescence.

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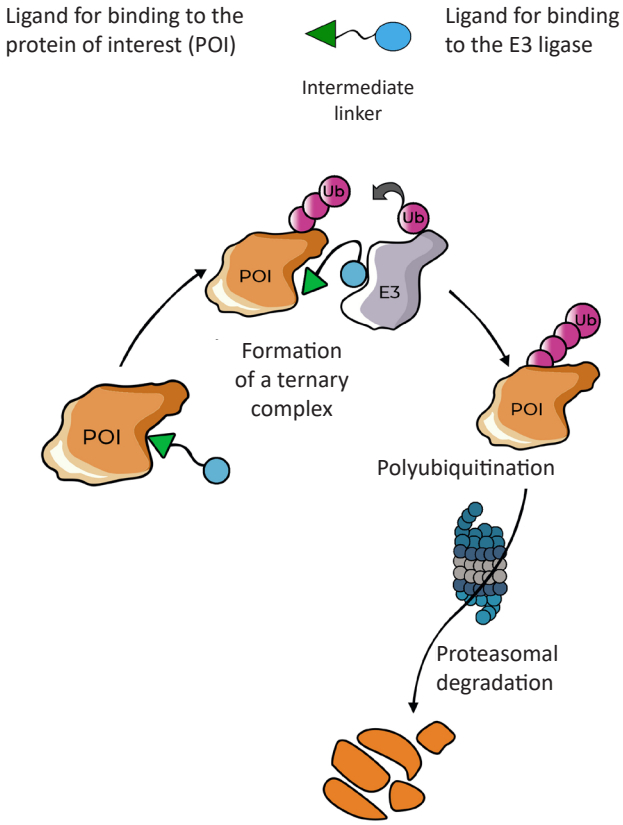

Figure 1 — Structure of PROTAC molecules (top) and their mechanism of action (bottom).
Note: POI — protein of interest, E3—E3 ligase, Ub — ubiquitin (pink color), PROTACs — proteolysis-targeting chimeras.
Figure adapted from source [36] under the Creative Commons Attribution (CC BY 4.0) license.

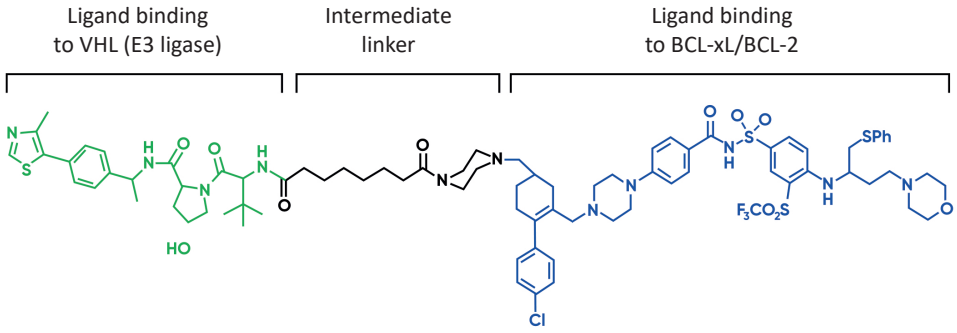

Figure 2 — Structure of molecule 753b.

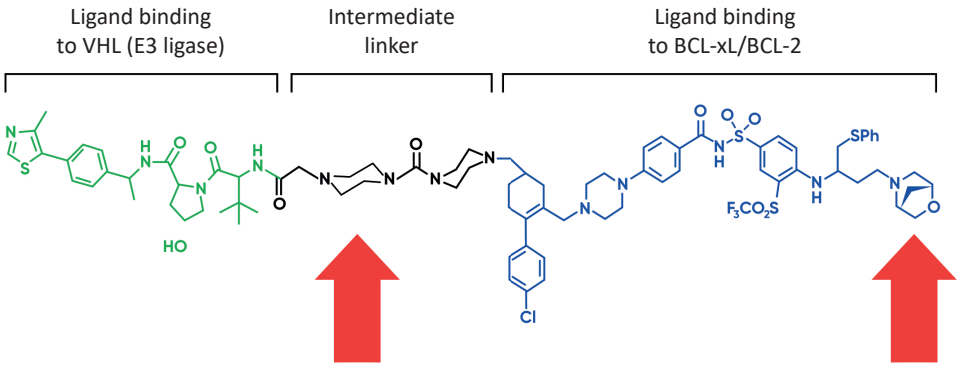

Figure 3 — Structure of molecule WH244.

Thus, the preclinical studies presented have confirmed the anti-senescence and anti-tumor effects of 753b, without the development of significant thrombocytopenia. Consequently, molecule 753b and/or its derivatives are good candidates for future clinical studies.

Second-generation BCL-xL/BCL-2 dual degraders

The researchers who developed molecule 753b studied the crystal structure of the ternary complexes VHL (E3 ligase)/753b/BCL-xL and VHL (E3 ligase)/753b/BCL-2. This allowed for several useful modifications and the synthesis of a new molecule, WH244 (Fig. 3) [26].

Specifically, in the intermediate linker, the 6-carbon alkyl chain (753b) was replaced with a 1,4-dimethylpiperazine fragment (WH244), and in the ligand that binds to BCL-xL or BCL-2, a bridging carbon atom was added to the morpholine group (753b) (WH244). This group is the last in the ligand and directly binds to BCL-xL or BCL-2.

The introduction of the aforementioned 1,4-dimethylpiperazine fragment into the intermediate linker of WH244 provided the following advantages:

- Increased rigidity of the intermediate linker (unlike the flexible 6-carbon alkyl chain), which is important for maintaining the overall structure of the ternary complex;
- Improved electrostatic interaction between the ionizable amino group of 1,4-dimethylpiperazine and BCL-2, which is important for maintaining the ternary complex.

The introduction of a bridging carbon atom into the morpholine group of WH244 resulted in stronger binding of the corresponding ligand to BCL-xL/BCL-2, which is important for maintaining the ternary complex.

Maintaining an optimal ternary complex structure promotes closer proximity between the E3 ligase and BCL-xL/BCL-2, thereby stimulating their degradation.

Based on the results of cellular experiments [26], WH244 induced greater death of Jurkat cancer cells (co-dependent on BCL-xL/BCL-2) compared to small molecule inhibitors (SMIs), DT2216, and 753b. The HiBiT degradation assay in live cells also confirmed superior performance of WH244 compared to 753b.

Advantages of PROTAC technology

Since both molecules discussed (753b, WH244) are created using PROTAC technology, it is worth noting the advantages of this technology.

Traditional small molecule inhibitors (SMIs) demonstrate so-called "occupancy-driven pharmacology": they bind to proteins and directly inhibit their activity. This requires the constant presence of SMIs at a sufficient concentration [45–47]. PROTACs operate on the principle of "event-driven pharmacology": the drugs initiate a cellular event, such as protein degradation, which leads to a decrease in the target protein concentration. These effects last for some time even after drug withdrawal, as cells require time for protein resynthesis [48, 49].

PROTACs act substoichiometrically—one molecule can degrade many molecules of the target protein (after degrading one molecule of the target protein, PROTACs are released to bind and degrade another molecule of the target protein, and so on) [50–52]. For this reason, the concentration of PROTACs should be lower compared to the concentration of SMIs to achieve a therapeutic effect [53, 54].

PROTACs can selectively degrade target proteins in a tissue/cell-specific manner [26, 55].

Target proteins can mutate, leading to the development of drug resistance. However, PROTACs degrade the protein regardless of mutations, thus overcoming drug resistance [56, 57].

Proteins that lack catalytic activity and/or have catalytically independent functions are considered "difficult-to-target" due to the absence of active sites for binding. However, PROTACs degrade the entire protein and do not require such binding sites, consequently reaching these very "difficult-to-target" proteins [61–63].

Thus, the presented literature data indicate a number of advantages of PROTAC technology, which justifies the development of new drug candidates.

Review Limitations

This review, dedicated to the senolytic effects of first and second-generation dual BCL-xL/BCL-2 degraders, was conducted in the form of a simple descriptive review. At the same time, in recent decades, systematic reviews and meta-analyses, originally developed for clinical research, are increasingly being used to analyze preclinical experimental data. This allows for the generalization of results, identification of knowledge gaps, and improvement of the translation of laboratory data to the human body. We could not utilize these more complex assessment methods due to the small number of initial (primary) studies.

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One limitation is related to the study selection methodology. Typically, several authors independently search for publications in databases. After that, they compare and combine the search results, and discuss controversial articles. In our review, we considered it sufficient for one author to perform the search work, given the novelty of the topic and the associated small number of works.

In each of the publications dedicated to molecules 753b and WH244, approximately 10–20 researchers from different scientific centers participated. Some researchers changed, while others were represented by the same individuals. This suggests that, to some extent, all articles were written by the same team of authors, which may introduce an error into the presented data.

The WH244 molecule is a new development and currently the sole representative of the second generation of dual BCL-xL/BCL-2 degraders. Only one pilot study was dedicated to it, which is insufficient to draw definitive conclusions about its efficacy.

CONCLUSION

The development of molecules 753b and WH244 marks an important stage not only in oncology but also in the fight against aging, owing to their pronounced senolytic effect. The main problem with earlier drugs, such as navitoclax, was the development of severe thrombocytopenia. Since platelets critically depend on the BCL-xL protein, its direct inhibition led to their mass death. Due to this side effect, navitoclax was never approved for clinical use.

Dual degraders (PROTACs) work differently. Instead of simply inhibiting the active center of the protein, molecules 753b and WH244 bind BCL-xL and BCL-2 for subsequent destruction by the cellular disposal system. The key to safety here lies in tissue specificity. Preclinical data show that degradation mechanisms in platelets hardly occur. This creates a wide therapeutic window: a powerful senolytic effect—clearing the body of defective cells—is achieved without a critical drop in platelet levels.

The transition from the first generation of degraders (753b) to the second (WH244) has further increased affinity to targets and improved pharmacokinetics. WH244 demonstrates deeper protein degradation at lower concentrations, making it a promising candidate for the therapy of age-dependent pathology and systemic tissue rejuvenation resistant to standard geroprotectors.

Moreover, the innovative architecture of molecules 753b and WH244 allows for more effective overcoming of pathological cell survival mechanisms. Unlike traditional small molecule inhibitors, which can be displaced by increased concentrations of anti-apoptotic proteins, degraders operate on a catalytic principle: one drug molecule can sequentially destroy multiple target proteins. This ensures a prolonged senolytic effect even after the drug concentration in blood plasma decreases.

Collectively, all of the above transforms BCL-xL/BCL-2 degraders into a powerful tool in biogerontology, capable of fundamentally changing the approach to treating chronic diseases and extending active longevity. Their expected synergy with other regenerative medicine methods should be noted separately.

Thus, the advantages of PROTAC technology are evident, and the new molecules mentioned in this review (753b and WH244), as well as their future derivatives, require further comprehensive study, including clinical trials. Particular attention should be paid to optimizing pharmacokinetic properties and assessing long-term safety. A deep understanding of the mechanisms of selective target protein degradation will expand the therapeutic arsenal, opening unique opportunities for the targeted treatment of complex pathologies that were previously considered practically incurable.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

Elizaveta S. Berezhnaya — conceptualization, visualization, writing—original draft, writing—review & editing; Andrey V. Savustyanenko — formal analysis, visualization, writing—original draftю All authors confirm that their authorship meets the international ICMJE criteria (all authors made a significant contribution to the development of the concept and preparation of the article, read and approved the final version before publication).

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AUTHORS

Elizaveta S. Berezhnaya — Doctor of Sciences (Pharmacy), Assistant Professor, Head of the Department of Pharmacology and Clinical Pharmacology, Rostov State Medical University. ORCID ID: 0000-0003-2458-922X. E-mail: bereznoy7@yandex.ru

Andrey V. Savustyanenko — Candidate of Sciences (Medicine), Assistant Professor of the Department of Pharmacology and Clinical Pharmacology, Rostov State Medical University. ORCID ID: 0009-0008-9332-6179. E-mail: savustyanenko@yandex.ru