Review

Targets For CAR Therapy In Multiple Myeloma

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Abstract: Multiple myeloma (MM, plasma cell myeloma) is a heterogenous B-cell malignant tumor, which typically exhibits high recurrence rate, resistance to drugs and molecular diversity of tumor subclones. Given limited efficacy of standard therapy options, cellular immunotherapy featuring chimeric antigen receptor (CAR) has proven tangible potential in treatment for relapsed and refractory forms of MM. Rational choice of a tumor target, which shows high selectivity, stable expression and biological significance, is a key to successful implementation of CAR therapy. This review has summarized and analyzed data from literature on biological properties, features of expression, and clinical development stages of CAR cell products for MM treatment, which target BCMA, GPRC5D, FcRH5, SLAMF7, CD38, CD138, TACI, APRIL, CD19, TNFR2, CD44v6, CD70, NKG2D ligands, etc. Special focus is on strategic approaches to overcoming antigenic escape, such as multi-specific CAR constructs, logical activation sequences and controlled safety systems. The analysis underscores the need for integrating molecular selection of targets with cutting-edge bioengineering solutions as a key trend for raising efficacy, stability and safety of cellular therapy in case of MM.

Keywords: multiple myeloma; CAR-T; CAR-NK; tumor targets; immunotherapy; cellular therapy; antigen escape; multi-specific CAR; logical activation; safety of therapy

1. Introduction

Multiple myeloma (MM) is the second most widespread blood cancer disease, which exhibits pronounced molecular heterogeneity, aggressive clinical progression and high risk of drug resistance occurrence [1,2].

Contemporary MM treatment regimens include the use of target drugs, primarily proteasome inhibitors, which have proven their high efficacy across different stages of the disease [3–5]. Nevertheless, clinical application of such agents is limited by development of drug resistance, including cross-resistance to other antitumor agents [6].

Utilization of immunotherapy with monoclonal antibodies, such as daratumumab and elotuzumab that are embedded in contemporary MM treatment standards and have become an integral part of combined therapy regimens, has evolved into an extra therapeutic area [7]. When combined with other drugs, this contributes to higher efficacy and partial overcoming of resistance, although fails to solve the problem, i.e. completely eradicate the disease [8].

CAR (Chimeric Antigen Receptors)-based cellular therapy stands out as a breakthrough and promising approach to treatment of relapsed and refractory MM. CAR T-cell therapy has shown high frequency of therapeutic responses in patients that have used up the opportunities offered by standard treatment methods, which corroborates tangible potential of the technology [9,10].

The B-cell maturation antigen (BCMA), which is expressed essentially on the surface of malignant plasma cells, appears as the best-known target for CAR therapy in case of MM. However, long-term efficacy of BCMA-targeted therapy is limited with development of antigen-negative

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relapses and depletion of effector T-cells, which emphasizes the need for putting in place improved strategies and novel approaches to CAR creation [11,12].

2. Structural Organization and Biological Fundamentals of CAR Cell Products in Immunotherapy of Blood Cancer Diseases

CAR cell product-based immunotherapy holds a key position among contemporary strategies for treatment of blood cancer diseases such as MM due to its high specificity, capability for targeted destruction of tumor cells and efficacy in patients with resistant forms of disease [13–15]. Central to this therapy are the chimeric antigen receptors (CARs), artificially constructed molecules that instill in T-cells the capability for antigen-specific recognition, activation and proliferation regardless of the major histocompatibility complex (MHC) molecules [16]. This mechanism is pivotal in tumor evolution and immune escape, since malignant cells oftentimes lose expression of MHC molecules, thereby avoiding being recognized with traditional T-cell receptors [17].

CAR construct incorporates three functional segments: an extracellular antigen-binding domain, a transmembrane domain, and intracellular signaling domains [18]. As a rule, the extracellular domain is a single-chain variable fragment of scFv antibody with high specificity for tumor antigens [19]. The transmembrane domain acts as an anchor and fixes CAR on the T-cell surface, facilitating its stable expression and origination of multimeric complexes [20]. Intracellular signaling domains ensure activation of a T-cell in response to interaction with the target, determining the range of its functional activity, including proliferation, secretion of cytokines and cytotoxicity [21].

Two types of cellular products are used in contemporary cancer immunotherapy – CAR T- and CAR NK-cells, which differ by their cellular origin, and by constructional features of chimeric receptors [22–24].

The construct of CAR T-cells uses CD3ζ – a component of the T-cell receptor (TCR) signaling pathway, which ensures imitation of the physiological activation of T-lymphocytes as the intracellular signaling domain [25]. Co-stimulating domains CD28 and/or 4-1BB (CD137) are included into the CAR construct to enhance the antigen-specific response. CD28 ensures powerful primary activation of T-cells and facilitates their quick expansion; in its turn, 4-1BB maintains long-term survival, resistance to depletion, and promotes formation of memory T-cells [16,26].

Constructs of CAR NK-cells include signaling modules that are inherent for an innate immune system link – DAP10 (DNAX-activating protein 10) and DAP12 (DNAX-activating protein 12), as well as the co-stimulating receptor 2B4 (CD244). These elements initiate endogenous signaling cascades that are specific for activation of NK-cells, thus ensuring effective cytotoxic activity and secretion of pro-inflammatory cytokines [27,28]. Unlike CAR T-cells, CAR-NK have more controllable activation profile, which mitigates the risk origination of hyperactivation and cytokine storm, thereby preserving pronounced antitumor efficacy.

In most of CAR products, both CAR T- and CAR NK-cells, a single-chain variable fragment of scFv antibody is used as an extracellular antigen-binding domain [29]. However, some constructs of CAR NK-cells use innate immunity receptors, for instance NKG2D (Natural Killer Group 2D) and DNAM-1 (DNAX Accessory Molecule-1), as an extracellular domain. NKG2D recognizes stress-associated molecules MICA and MICB (MHC class I polypeptide-related sequence A/B), expressed by tumor cells. Expression level of these proteins on tumor cells is higher than in untransformed ones, which makes them selective targets [30].

Tumor antigen primary recognition process with a chimeric receptor (CAR) starts by interaction of the extracellular domain scFv with a specific epitope of a ligand molecule on the tumor cell surface [31]. The structural and chemical complementarity of scFv to the target epitope ensures high binding specificity, enabling to effectively distinguish tumor cells and minimize damage to healthy cells. The following act as the key features in this interaction: affinity, i.e. binding strength of one scFv with the epitope; avidity, i.e. the aggregate strength of multiple interactions between CAR and antigens; uniqueness of paratope, i,e. individual properties of antigen-binding center scFv. Combined, these

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parameters play a crucial role in functional outcome of interaction between the effector and tumor cells, determining the strength, duration and efficacy of immune response [32].

CAR T-cells are predominantly produced from autologous or allogeneic (donor) T-lymphocytes, which undergo successive release, activation, gene modification (transduction) and expansion stages prior to infusion into a patient. In CAR NK therapy the range of sources for obtaining the cell material are sizably wider. Adult peripheral blood, umbilical cord blood, NK-92 cell line, induced pluripotent stem cells (iPSC) capable of differentiation into NK-cells can be used to obtain NK-cells. Variety of sources paves a way towards development of personalized and standardized CAR NK products, such as ready-to-use off-the-shelf medications, which drastically expands the clinical opportunities and enhances the scalability of the therapy [28, 33-35].

Despite the high clinical efficacy in treatment for blood cancer diseases, CAR T-cell therapy is oftentimes accompanied by development of grave side effects – the cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) [36,37].

Unlike CAR T, CAR NK-cells show more favorable safety profile, stipulated by more balanced natural mechanisms for regulating cytotoxic activity of NK-cells and their reduced capability for uncontrollable production of pro-inflammatory cytokines [27,30,38].

The state-of-the-art condition of CAR cell therapy is characterized by rapid growth and high clinical efficacy, which is facilitated by solid achievements in genetic engineering of chimeric antigen receptors. Most sweeping innovations are related to the structural optimization of CAR T- and CAR NK-cells, to the choice of most suitable antigen targets, and to improving the safety profile of therapy, while preserving the stable antitumor activity. Nonetheless, despite the successes, selectivity and stability of CAR interaction with tumor targets still make the key restrictive factor, as it determines both the immediate clinical effect and its duration.

To that effect, further evolution of this field is impossible without comprehensive engineering and molecular solutions with a view to overcome the immune escape mechanisms, boosting the affinity of interaction and functional resistance of CAR cells.

Optimizing the "CAR – tumor target" axis is evolving as the pivotal area for prospective research, with potential to substantially boost the efficacy and reliability of cellular immunotherapy.

Bioengineering Platforms and State-of-the-Art Strategies for Multi-Specific CAR Therapy in Cancer Immunotherapy

Development of poly-specific constructs, which can enable a single population of T-cells to simultaneously recognize several key tumor antigens, has emerged as a priority area in the contemporary cell engineering in the field of CAR therapy [39–41]. Such a strategy notably mitigates the risk of antigen escape, i.e. one of the basic mechanisms for tumor resistance to immunotherapy [42,43]. Moreover, poly-specific CAR platforms unveil new clinical prospects, including the potential for implementing the concept of personalized and adaptive cellular therapy that targets the molecular profile of tumor in a specific patient [44].

Modern biotechnology strategies of obtaining biospecificity in CAR therapy pursue creation of constructs that can recognize a bunch of tumor targets at once. Development of tandem CARs (TanCARs) with two and more successively located scFv domains is one of such approaches. Such extracellular domain architecture enables to simultaneously recognize various tumor antigens, to improve the receptor-to-ligand bond strength, accuracy, and stability of therapeutic response. An alternative is the ligand-based CARs, which rely on the use of natural ligands in extracellular domains of the receptor. An example is APRIL-CAR, which uses APRIL (A Proliferation-Inducing Ligand) ligand, capable of binding with several receptors expressed on tumor cells – namely, BCMA and TACI (Transmembrane Activator and CAML Interactor). Such an approach enables to expand the range of tumor targets recognition via multi-ligand interaction, while preserving the physiological specificity [45].

Development of bicistronic vectors that code various CARs facilitates expression of two robust receptors in one cell, which promotes more effective targeting of tumor cells with heterogenous

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profile of antigen expression [46]. An alternative approach, i.e. co-transduction, in which one T-cell is modified for expression of two or more CARs, ensures expanded antigen coverage of targets and may boost the efficacy of therapy in tumors with combined expression of antigens [47,48].

CAR constructs with logical activation elements, such as AND, NOT and OR gates, have been developed in recent years to enhance selectivity and mitigate the risk of off-tumor toxicity. The AND gate concept is that CAR T-cell activation only occurs in simultaneous recognition of two tumor antigens: one receptor initiates the activation signal, while the other implements co-stimulation [49]. NOT gates, implemented with the aid of inhibiting CARs (iCARs), function under the principle of suppressing effector activity of a T-cell during interaction with antigens expressing on healthy cells, and thereby ensure an extra safety control level. DiCAR constructs are made of several signaling domains and reliably inhibit the uncontrollable activity of effector cells [50–52].

Overcoming the immunosuppressive tumor microenvironment (TME) is a key problem for preserving the functional activity of CAR T-cells in vivo [53]. For this purpose, armored CAR T-cells of the third and subsequent generations are being developed; these have the capability to express pro-inflammatory cytokines IL-12, IL-15 and IL-18 that augment the antitumor immune response. Such cells can additionally be modified for expression of the dominant-negative transforming growth factor beta receptor II (TGF-βRII). TGF-βRII, expressed in CAR T-cells, block suppressive impact of TGF-β on T-lymphocytes [55–57].

The next stage in development of cellular therapy technologies is creation of a fourth-generation CAR – the TRUCK platform (T-cells redirected for universal cytokine killing), which ensures local secretion of pro-inflammatory cytokines in response to CAR binding with the tumor antigen [58,59]. This approach promotes augmentation of the antitumor immune response and precludes formation of immunosuppressive TME [60–62].

Fifth-generation CAR T-cells are additionally provided with intracellular domains that can activate signaling pathways associated with pro-inflammatory cytokines. These are elements of the JAK-STAT (Janus kinase – signal transducer and activator of transcription) signaling cascade, which ensures stable and autonomous cell activation even under unfavorable conditions [63].

Various molecular safety ‘switches’ that enable to control activity of modified T-cells are integrated into the CAR construct to enhance safety and controllability of the cellular therapy [64]. For instance, there have been created hypoxically inducible CARs activated solely under reduced oxygen content, typical for the tumor tissue. This approach ensures localized activation of CAR T-cells and mitigates the risk of damage to normal tissues [65,66].

Relapses of the malignant process remain frequent even after the minimal residual disease (MRD) state is achieved. As a rule, their occurrence is related to immune escape mechanisms due to the loss of target antigen expression by tumor cells and trogocytosis – the process in which the antigen is transferred to the CAR T-cell membrane and becomes unreachable for further recognition [67,68]. Multi-antigen CAR constructs capable of simultaneously recognizing several tumor targets, which drastically mitigates the risk of relapse occurrence and increases the stable effect of therapy, are being developed to overcome such restrictions [69,70].

The protocols based on combined or successful infusions of CAR products with varying antigen specificity attain extra clinical significance [71]. The use of similar treatment regimens is particularly promising in patients with refractory and relapsing forms of lymphomas, in whom successful therapy targeted at an expanded range of antigens promotes an increased frequency of remissions [72]. This novel therapeutic approach reduces the likelihood of relapse by eliminating the tumor clones with varying antigen expression, thereby minimizing the likelihood of immune escape [73,74].

In spite of remarkable progress in engineering of CAR constructs, rational choice of a tumor target remains key to clinical efficacy. This problem becomes particularly relevant in pronounced molecular and phenotypic heterogeneity that is inherent for MM. In such cases, stability of antigen expression on tumor cells, and their absence on normal tissues has a direct impact on both efficacy and safety of the therapy.

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3. Tumor Targets in CAR Therapy for Multiple Myeloma

Rational choice of a tumor target is among the crucial stages in development and clinical implementation of CAR cell therapy. It pursues the maximal therapeutic effect, while simultaneously mitigating the risk of unwanted immunological complications, such as systemic toxicity and autoimmune reactions [75].

Presence of a tumor antigen which is capable of ensuring highly specific and reproducible recognition of pathological cells with minimal or absent expression in healthy tissues is key to successful application of CAR therapy. This approach is critical to prevent development of on-target, off-tumor toxicity – a hazardous phenomenon, in which CAR cells attack body normal cells that express low level of target antigen. This phenomenon remains one of the main restrictions for application of immunotherapy in case of malignant neoplasms, including MM.

MM is characterized by pronounced molecular and phenotypic heterogeneity, which suggests availability of multiple subclonal populations of tumor cells that differ by the level and range of surface antigen expression. This factor substantially complicates the choice of the single universal therapeutic target, which can ensure effective and selective impact [76,77].

When choosing an optimal antigen in the contemporary stage of CAR cell technology development, apart from its selectivity and expression level also account for a bunch of other critical parameters, including biological role of antigen in tumor pathogenesis and progression, expression stability in all subpopulations of myeloma cells, a link to development of drug resistance, and the likelihood of cross-reactivity with normal tissues [78]. Moreover, translational potential of a chosen target should also be analyzed for scalability of manufacturing processes and clinical applicability, including the standardization and commercialization capability [79,80].

Comprehensive examination of tumor target features, including analysis of their biological function, expression level and stability on myeloma cells, and evaluation of biological significance, clinical potential and possible application restrictions as part of the CAR cell therapy, is a field in development of more effective and safer MM treatment strategies [81,82]. Particularly noteworthy in this connection is reviewing of most promising targets in case of MM, with high utilization potential in the construct of CAR receptors (Table 1).

Table 1. Parameters of tumor targets for CAR therapy.

Target	Expression	Expression in normal tissues	Risk of off-tumor toxicity	Development stage
BCMA	High, stable	Plasma cells	Low	Registration (ide-cel, cilta-cel)
GPRC5D	High	Squamous epithelium	Low	Phase I/II
FcRH5	Moderately high	Few	Low	Phase I/II
SLAMF7	Moderate	NK, DC, T-cells	Average	Phase I
CD38	High	Immune and epith. cells	Average	Phase I
CD138	High	Epithelium	Average	Phase I
TACI	Variable	B-cells	Low	Preclinical
APRIL	No data available	No data available	No data available	Preclinical
CD19	Residual (subclones)	B-cells	Average	Preclinical/Phase I
TNFR2	Moderate	Tregs, stroma	Average/high	Preclinical
CD44v6	Variable	Keratinocytes	High	Preclinical
CD70	Moderate	Activ. immune cells	Average	Phase I
NKG2D ligands	Heterogenous	Minimal	Low	Phase I
CD56	70% of cases	NK-cells	Average	Preclinical

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Integrin β7	Prevalently	Minimal	Low	Preclinical
CD123	Low	Plasm. DC	Average	Preclinical
Lewis-Y	≈50%	Low	Average	Phase I

3.1. B-Cell Maturation Antigen (BCMA)

BCMA, also known as TNFRSF17 (Tumor Necrosis Factor Receptor Superfamily Member 17), is a single-chain transmembrane protein that belongs to the tumor necrosis factor receptor superfamily (TNFRSF). Its construct includes extracellular cysteine-rich domain (CRD), a transmembrane segment, and a short cytoplasmic domain [83,84]. These features of construct stipulate for BCMA high selectivity as a therapeutic target for CAR cell therapy of MM, since the extracellular CRD ensures stable and specific binding with the scFv fragment of CAR receptor [85,86]. Standing as an extra benefit is absence of tangible homology of the BCMA's extracellular area with other receptors, which mitigates the risk of cross-reactivity and on-target, off-tumor toxicity [86–88].

BCMA is expressed stably and with high density on the surface of malignant plasma cells, whereby is virtually absent in other tissues, save for normal plasma cells [89]. This makes BCMA an attractive target not only for CAR cell therapy, but also for other immunotherapy strategies.

On the molecular level, BCMA is engaged in survival regulation of plasma cells. The interaction with APRIL or BAFF (B-cell Activating Factor) ligand activates NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells), PI3K/AKT (phosphatidylinositol-3-kinase/protein kinase B) and MAPK/ERK (mitogen-activated protein kinase/extracellular signal-regulated kinase) signaling cascades, which promote growth, survival and resistance of myeloma cells to apoptosis [89,90].

Clinical data corroborate that BCMA high expression level correlates with intensity of antitumor response, the likelihood of achieving complete remission, and with the duration of relapse-free and overall survival [84,91].

Clinical trials, including KarMMa (for idecabtagene vicleucel, ide-cel) and CARTITUDE-1 (for ciltacabtagene autoleucel, cilta-cel), have shown high efficacy of BCMA-specific CAR T-cells in patients with relapsing and refractory MM [92,93]. Idecabtagene vicleucel (ide-cel, Abecma) is the first registered BCMA-specific CAR-T product. The KarMMa trial reached the objective response rate (ORR) of 73%, complete remission (CR) in 33% of patients, the median overall survival was 19.4 months, and survival without progression – 8.8 months. Side effects included CRS in 84% of patients (grade > 3 in 5%) and ICANS in 18% (grade > 3 in 3%) [91].

Ciltacabtagene autoleucel (cilta-cel, Carvykti) is the second-generation product that contains two scFv domains that recognize various BCMA epitopes, which ensures high avidity and efficacy [94,95]. CARTITUDE-1 trial reached ORR of 97%, and strict complete remission observed in 67% of patients, whereas the median response duration exceeded 24 months. CRS emerged in 95% of patients (grade ≥3 in 5%), ICANS in 21% of them, mainly low or average severity.

Despite the impressive clinical results, long-term efficacy of BCMA-specific CAR-T therapy remains limited. Development of antigen-negative relapses, resulting from selective elimination of BCMA-positive cells and the subsequent survival of clones that lost expression of this antigen, is a key factor that precludes its stability. [96]. Occurrence of the disease relapses is linked to existence of the soluble BCMA form (sBCMA), which circulates in the blood and competes with the membrane bound BCMA for CAR receptor, thereby decreasing the efficacy of therapy and potentiating its immune escape [97,98].

To mitigate the risk of therapeutic inefficacy caused by antigen escape, poly-specific CAR products are being developed, simultaneously targeting the BCMA and extra tumor antigens, such as GPRC5D, FcRH5, and others. Similar platforms expand the range of target antigens and boost stability of clinical effect due to more effective targeting the tumor cell heterogenous clones [88,99]. Development of high-affinity scFv domains is in the pipeline. These can selectively recognize solely the membrane bound form of BCMA (mBCMA), excluding interaction with its soluble form (sBCMA). This increases specificity and efficacy of CAR cell activation [86,98].

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Embedded in the clinical practice have been combined therapeutic strategies that stipulate for co-application of BCMA-targeted CAR T-cells with immune checkpoint inhibitors, such as PD-1, and with γ-secretase inhibitors. The latter promote a decrease in the level of soluble BCMA (sBCMA) and higher expression of the membrane BCMA (mBCMA) on the surface of tumor cells, thereby boosting the efficacy of CAR T therapy [100,101].

Another novel field of development is creation of armored CAR cells, which are stable in immunosuppressive TME and capable of secreting pro-inflammatory cytokines, which enhances their proliferation and functional activity [102,103].

Along with autologous platforms, also progressing has been the field of creating allogenous off-the-shelf CAR T- or CAR NK-cells, which target BCMA and are produced from iPSC or from donor material. These technologies enable to standardize the production, increase the affordability of therapy and reduce its cost, at the same time ensuring controllable engineering modification to prevent allogenous immune reactions [103,104].

Hence, BCMA is worthily acting as the centerpiece among cellular therapy targets in MM, due to a fusion of high specificity, stable expression and notable functional role in the disease pathogenesis. The variety of approaches to modification of BCMA-targeted platforms corroborate its strategic significance in existing the promising therapeutic strategies.

3.2. G Protein-Coupled Receptor Class C Group 5 Member D (GPRC5D)

GPRC5D is a transmembrane protein falling within the superfamily of G protein-coupled receptors (GPCR). It possesses a compact extracellular N-end domain, which makes it an easy target for coupling with scFv contained in CAR receptors [99,105]. GPRC5D high expression stability in myeloma cells and its accessibility on the tumor surface facilitate quick and effective interaction with CAR cells, ensuring reliable activation of the effector response [106,107].

GPRC5D expression outside the tumor tissue is restricted and mostly displayed turns up in stratified flat squamous epithelium, which mitigates the risk of on-target, off-tumor toxicity development. [107,108].

The clinical and preclinical trials corroborate the favorable safety profile of GPRC5D-specific CAR products. Dermal toxicity related to GPRC5D expression in the epithelium is primarily registered in the mild and reversible form [109]. CRS is observed in 75-80% of patients, mainly I–II severity grade, and is well controlled [110,111]. ICANS is registered in less than 10% of patients and primarily flows in the mild form [112,113]. Hence, the toxicity profile of GPRC5D-targeted CAR products is deemed more favorable than in some BCMA-specific CAR systems [114].

For the first time, clinical efficacy was confirmed in OriCAR-017 (phase 1, POLARIS) and CARTITUDE-2 trials, where the patients with relapsing or refractory MM, who had earlier received BCMA-targeted therapy, reached the overall response rate (ORR) of 70-90% [111,112].

Prevention of antigen escape is still a key problem in treatment for MM characterized by high heterogeneity. Bispecific CAR products have been developed in this connection that are simultaneously targeting GPRC5D and BCMA, both in CAR-T and in CAR-NK format. Similar platforms display improved clinical outcomes and resistance to incidence of relapses [115,116]. Moreover, poly-specific constructs with inclusion of IL-15 (armored CAR) and allogenous off-the-shelf CAR NK-products have been actively promoted, which ensures additional affordability of the therapy, cost reduction and potential for wide clinical application [117,118].

Hence, GPRC5D holds a prominent place among promising targets for cellular therapy of multiple myeloma, namely in patients with resistivity or relapsing after BCMA-specific therapy. The ongoing development of GPRC5D-targeted bispecific and allogenous platforms opens up new opportunities for effective and safe treatment for this patient group.

3.3. Fc Receptor-Homolog 5 (FcRH5, CD307)

FcRH5 is a transmembrane glycoprotein, falling with the family of FcR-like receptors. It is mostly expressed on mature B-cells, plasma cells and malignant transformed cells in MM [101,119]. FcRH5

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restricted expression in normal conditions and its high abundance on tumor plasma cells substantiate for its potential as a cellular therapy target, particularly in patients with relapsing or refractory course of disease [120].

Extracellular segment of FcRH5 includes nine Ig-like domains, which represents a lengthy structure with multiple potential epitopes for coupling with CAR receptors. Such an architecture promotes high specificity and mitigates the risk of cross-reactivity [120]. Transmembrane domain of FcRH5 ensures solid fixation in the membrane and maintains stable expression on the surface of tumor cells – a critical condition for stable effect of CAR therapy.

FcRH5 expression has been discovered in all subclones of myeloma cells, including those that originate after loss of BCMA expression or resistance to BCMA-specific therapy [121]. This enables to use FcRH5 as a target for second-line therapy and as a component for poly- and bispecific platforms [122]. A series of preclinical trials has indicated that FcRH5-specific CAR T-cells possess high cytotoxicity in in vitro and in vivo models, which results in complete eradication of tumor cells without substantial toxic effects [101,120].

Also, FcRH5-targeted CAR-NK platforms have been actively developed, and in preclinical models they demonstrate high specificity, low alloreactivity risk and a potential for large-scale off-the-shelf production [123]. The clinical trials of FcRH5-specific CAR-T and FcRH5-targeted bispecific antibodies show predictable and controllable toxicity profile. The major side effects include CRS and ICANS, generally reversible and of moderate severity [124,125].

Dur to its high expression and antigen stability, FcRH5 has been increasingly oftener included into the poly- and bispecific CAR platforms (for instance, FcRH5+BCMA, FcRH5+GPRC5D), which is particularly promising for combating antigen escape in case of tumor heterogeneity [126,127].

As indicated by preclinical trials, inclusion of co-stimulating domains 4-1BB (CD137) or ICOS (Inducible T-cell COStimulator) into FcRH5-targeted CAR constructs substantially improves proliferative activity, persistence and functional stability of effector cells in vivo. This ensures steady and prolonged clinical effect, which is particularly crucial in refractory forms of MM [128–131].

In phase I–II clinical trials FcRH5-specific CAR T-cells and bispecific antibodies have demonstrated high overall response rate even in patients who had earlier been resistant to BCMA-targeted drugs [121]. Mostly moderate side effects have been revealed, which confirms the favorable profile of manageable toxicity.

Thus, FcRH5 has been viewed as a most promising and clinically meaningful targets in the arsenal of cellular therapy for multiple myeloma. Its application as a target for new generations of CAR products enables to expand the range of therapy, enhance resistance to relapsing, and provide for treatment of patients who do not respond to BCMA-targeted strategies.

3.4. CD38 as a Therapeutic Target for Cellular Immunotherapy

CD38 is a type II transmembrane glycoprotein with a wide array of biological functions. It is engaged in intercellular adhesion and acts as a component in cellular signaling systems [132]. Owing to its enzymatic activity, CD38 is engaged in regulation of metabolism, energy metabolism, the innate and adaptive immune response [84,133].

Molecular structure of CD38 includes a short cytoplasmic N-end fragment, a transmembrane domain, and a lengthy extracellular segment, which is responsible for catalysis of enzymatic reactions and interaction with the extracellular matrix components [134].

CD38 has high and stable expression on the surface of myeloma plasma cells in all the disease stages, which makes it an attractive target for targeted therapy [135,136]. This marker is also expressed in a number of immune system normal cells (activated T- *и* B-lymphocytes, NK-cells, monocytes), and in epithelial cells (for instance, type II alveolocytes) and lymphoid organs, which boosts the risk for incidence of on-target, off-tumor toxicity.

CAR constructs that are able to recognize cells with high expression of CD38 typical for myeloma have been developed with a view to increase selectivity and decrease toxicity [66,137]. Likewise developed have been the constructs with controllable inactivation of CAR-cells (safety switches) – for

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instance, inducible apoptotic cascades (iCasp9) or pharmacologically controlled suppression of CAR signaling [138,139].

A row of preclinical trials have displays high cytotoxic activity of Cd38-specific CAR T-cells both for in vitro, and in vivo models [139]. Results of phase I clinical trial (for example, NCT03473496) have confirmed relative safety and efficacy of Cd38-specific CAR T-cells in patients with relapsing and refractory multiple myeloma [140,141].

Creation of bispecific CAR constructs, which can simultaneously recognize CD38 and BCMA, is a promising field. Similar platforms show synergistic effect, boosting efficacy and decreasing the likelihood of resistance occurrence [84,142,143].

Altogether, the further optimization of CAR receptors towards higher efficacy and safety, adoption of poly-specific approaches unveil new opportunities for expanding the therapeutic window and clinical applicability of Cd38-specific products in multiple myeloma.

3.5. Signaling Lymphocytic Activation Molecule Family 7 (SLAMF7)

SLAMF7/CD319 is a transmembrane glycoprotein from the family of SLAM receptors, playing a crucial role in coordination of the innate and adaptive immune response [144]. Expression of SLAMF7 has been mainly observed on plasma cells, NK-cells, dendritic cells, and individual subpopulations of T-lymphocytes, while nearly absent on hematopoietic stem cells, which makes the molecule an attractive target for cellular immunotherapy [145].

The SLAMF7 construct includes two extracellular immunoglobulin-like domains - a distal V domain and a proximal C2 domain, both engaged in intermolecular interactions and recognition by effector cells [146,147]. As indicated by preclinical trials, both domains may serve as independent epitopes for creation of CAR constructs with varying functional profile. However, high expression of SLAMF7 on NK-cells creates an autocytotoxicity risk from SLAMF7-targeted CAR T-cells, which may weaken the natural immune surveillance and increase the likelihood of infectious complications [148–150].

To minimize the risk, various modifications of both CAR-T and CAR-NK platforms have been implemented using genome editing technologies and introduction of inhibiting signaling domains that enable to preserve the antitumor activity [151].

Efficacy and high specificity of SLAMF7-specific CAR T-cells has been corroborated by both preclinical models and in early phases of clinical trials. In phase I trial (NCT03710421) the overall response rate (ORR) exceeded 50%, including cases of complete and strict complete remission. CRS was mainly observed in mild or moderate form, without multiple episodes of heavy neurotoxicity [140,152,153].

Alongside CAR-T, actively developed have been SLAMF7-targeted CAR NK-cells, which represent a promising platform due to reduced toxicity and the capability of delivering off-the-shelf products.

Hence, SLAMF7 glycoprotein is a highly specific, biologically substantiated and clinically proven target for cellular therapy in multiple myeloma. SLAMF7 inclusion into poly-specific CAR constructs, which can simultaneously recognize several antigens, may drastically boost the antitumor efficacy and mitigate the risk of antigen escape.

3.6. CD138 (Syndecan-1) as a Therapeutic Target for Cellular Immunotherapy

CD138 (syndecan-1) is a transmembrane heparan sulfate proteoglycan falling within the syndecan family. It plays a key role in regulation of cellular adhesion, migration, transferring signals inside the cell in coupling with growth factors, morphogens, chemokines, enzymes, and extracellular matrix components [154].

The extracellular domain of CD138 contains heparan and chondroitin sulfate chains, which ensure interaction with extracellular matrix components. The transmembrane component fixes a molecule in the membrane, whereas a highly restricted short cytoplasmic section is engaged in signal transfer via the cytoskeleton. Such structure enables engagement of CD138 in a wide range of

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physiological and pathological processes, including tumor growth and invasion. High accessibility of the extracellular section makes CD138 an easy target for coupling with CAR receptors and the following activation of T-cell effector functions [144].

CD138 is distinct for its stable and intense expression on MM cells [155,156]. Normally, protein is expressed on mature plasma and epithelial cells, which is used in diagnostics, whereas its expression on hematopoietic stem cells is minimal, which mitigates the risk of damage to the hematological system regenerative pool [157,158]. However, CD138 presence on the epithelium of various organs may stimulate the growth of off-target toxicity when using CD138-specific CAR T-cells.

Engineering strategies are being adopted to minimize such effects: lower affinity CAR receptors are used, which are capable to differentiate the tumor and normal cells by antigen expression level [137], as well as systems for controllable shutdown of CAR cells (safety switches) in development of undesired toxicity.

Preclinical trials have indicated high cytotoxicity Cd138-targeted CAR T-cells, both in vitro and in vivo [155]. Clinical data, including phase I testing (NCT03778346), have confirmed the acceptable safety profile: As a rule, CRS was mild, neurotoxicity was rare, and response level varied from partial to complete and strict complete remissions [158]. Moderate persistence of CAR cells was observed, which emphasizes the need for optimization of their viability and functional robustness [156].

Thus, CD138 remains a meaningful target for cellular therapy in multiple myeloma. Despite potential restrictions, further evolution of CAR engineering and streamlining of effector cell activation control open up the prospects for enhancing the efficacy and clinical applicability of CD138-specific approaches.

3.7. CD19 as a Therapeutic Target for Cellular Immunotherapy

CD19 is a transmembrane glycoprotein from the immunoglobulin superfamily and is expressed primarily on the membrane of mature and immature B-lymphocytes [159]. It plays a key role in activation, proliferation and survival of B-cells, functioning as a co-receptor in composition of the B-cell receptor (BCR) signaling complex, which makes it a critical element for immune response regulation [160,161].

Despite the fact that MM is falling within the tumors of plasma cells, some surveys describe subpopulations of myeloma cells with residual expression of CD19, the presence of which is associated with an unfavorable forecast, relapses and resistance to therapy [162–164]. This justifies the interest for CD19 as an extra therapeutic target within the scope of multi-target approaches.

The antigen escape phenomenon remains one of the main problems. It is related to mutations, expression disorder, alternative splicing of mRNA or disorder in formation of disulfide bridges, which results in loss of CD19 expression [165,166]. Nonetheless, in preclinical trials CD19-specific CAR T-cells have demonstrated pronounced activity versus CD19-positive subclones of myeloma cells, both in monospecific format, and as parts of tandem constructs jointly with anti-BCMA CAR [167,168]. Moreover, such cell products have revealed selectivity versus the tumor cells with minimal impact on normal subpopulations of immune cells [2].

Dual- (CD19 and BCMA) and poly-specific targeting platforms have been actively developed in recent years, which enables to effectively overcome the intraclonal heterogeneity, prevent antigen escape and minimize the MRD growth rate [169–172]. Likewise emerging have been the strategies that provide for successive or combined injection of CD19- and BCMA-specific CAR products, especially to patients after deep tumor reduction in BCMA-targeted therapy, where resistant CD19-positive clones survive [173–175].

Based on the accumulated preclinical and clinical data, CD19 has been viewed as a promising target for application in multi-target cellular immunotherapy in MM patients, notably in the occurrence of relapses and resistance to BCMA-targeted treatment [131].

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3.8. Tumor Necrosis Factor Receptor 2 (TNFR2, TNFRSF1B)

TNFR2 is a transmembrane protein of the TNF receptor family. Unlike TNFR1, its expression is restricted within a few cell types, such as regulatory T-cells (Tregs), myeloid-derived suppressor cells, endothelium, tumor cells with diverse histogenesis, including MM cells, and microenvironment cells [176,177]. Such selective expression underpins the key role of TNFR2 in formation of immunosuppressive microenvironment and maintaining the functional activity of Tregs, which makes a contribution into tumor resistance to immune surveillance [178].

TNFR2 construct includes four extracellular cysteine-rich domains (CRDs), a transmembrane section, and an intracellular domain, and lacks a death domain, which differs it from TNFR1. This enables to activate alternative signaling cascades, including NF-κB and PI3K/AKT, which contribute to survival, proliferation and immunoregulation [179]. The presence of several CRD domains makes TNFR2 a promising target for high-affinity CAR constructs.

TNFR2-specific CAR T-cells demonstrate ability to suppress the growth of TNFR2-positive tumors via remodeling of tumor microenvironment and suppression of Tregs [180,181]. Moreover, developed have been bispecific CAR platforms that simultaneously recognize TNFR2 and other antigens, such as BCMA or GPRC5D, which boosts selectivity and mitigates the risk of antigen escape [182].

Creation of armored CAR products with resistance to immunosuppressive factors are aimed at enhanced functional stability of cells and proliferative potential in unfavorable tumor environment [183]. The promising outlook of such an approach is confirmed by results from early phase clinical trials, which evaluate the safety of TNFR2-CAR-T in patients with relapsing tumors, including in MM [184]. Moreover, TNFR2-specific CAR NK-cells, capable of effectively infiltrating the tumor and destroying the TNFR2-positive cells by secretion of interferon-γ and granzymes, are undergoing active development [177,181].

Despite predominantly tumor-associated expression, TNFR2 is represented on the surface membrane of Tregs and is engaged in regulation of their activity. This fact requires careful attitude - excessive suppression of the subpopulation may lead to occurrence of autoimmune diseases. Therefore, we see the use of platforms with regulated activation and safety switch systems that ensure controllable action of CAR cells [183].

In general, TNFR2 is a promising cellular immunotherapy target, which is focused on overcoming immunosuppression, enhancing the antitumor response and expanding the opportunities for personalized treatment of resistant multiple myeloma forms.

3.9. CD44v6 as a Target for Cellular Therapy of Multiple Myeloma

CD44v6 is a variant isoform of CD44 transmembrane glycoprotein, derived in alternative splicing with inclusion of v6 exon into the molecule's extracellular domain [185]. This modification drastically alters spatial structure of the extracellular section, enhancing its interaction with hyaluronic acid, metalloproteases, and with VEGF (Vascular Endothelial Growth Factor) and HGF (Hepatocyte Growth Factor) growth factors, which promotes invasiveness and survival of tumor cells [186,187].

CD44v6 overexpression is typical for aggressive MM forms and is associated with disease progression. CD44v6 expression is observed in 17% of patients in early MM stages and reaches 43% in case of plasma cell leukemia [188], whereby it is often linked with 13q14 deletion – an unfavorable prognostic marker [189].

CD44v6 is deemed as a promising target for immunotherapy owing to restricted expression in normal tissues and high abundance on tumor cells. However, its presence on keratinocytes and epithelium of mucous membranes creates the risk for occurrence of on-target, off-tumor toxicity, which requires to develop safe engineering solutions [190].

This is the purpose for applying low-affinity CAR constructs, capable of differentiating cells with high and low Cd44v6 expression, as well as safety switch systems for urgent inhibition of effector cells if complications develop [191]. Particularly interesting are CAR-NK platforms, which

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demonstrate innate antitumor activity and reduced rate of CRS incidence as compared with CAR-T [24,192].

Preclinical trials have confirmed high efficacy of both CD44v6-CAR-T, and CAR NK-cells versus CD44v6-positive tumors, without pronounced damage to normal tissues [193,194]. The first clinical trials (phases I/IIa) of CD44v6-targeted CAR products in patients with refractory hematological solid tumors, including MM, have demonstrated controllable safety profile and preliminary efficacy [195,196]. CD44v6 as a target is made a part of poly- and bispecific CAR platforms, intended to overcome antigen escape and intratumoral heterogeneity [197].

Hence, CD44v6 is a prominent target for cellular therapy of multiple myeloma, with high therapeutic potential, provided meticulous engineering optimization of safety.

3.10. CD70 as a Therapeutic Target for Cellular Immunotherapy

CD70 is a transmembrane protein from TNF receptor family. It is expressed primarily on activated B- and T-lymphocytes, dendritic cells, and on a series of malignant transformed cells, including plasma cells in MM [198].

Unique molecular characteristics of CD70 stipulate for its high selectivity as a target for cellular therapy. Namely, CAR constructs that are based on CD70 interaction with its natural ligand CD27 demonstrate high rates of expansion and persistence of effector cells in vivo, which is required to maintain the steady antitumor effect [199].

Preclinical trials have confirmed high cytotoxic activity of CD70-specific CAR T-cells in respect of the myeloma cells, whereby noted has been low toxicity in respect of normal tissues, including hematopoietic stem cells, thanks to minimal CD70 expression of extratumor or activated immune cells [200,202]. Further optimization of CAR receptor construct via molecular modeling of CD70-CD27 interaction has enabled to enhance proliferation, survival and specificity in action of modified T-cells.

Allogenous CD70-specific CAR-T products, constructed using CRISPR/Cas9 technology, have been actively developed in recent years. They pass clinical evaluation in patients with refractory MM forms and solid tumors (CTX131, NCT04554425 trials), demonstrating the acceptable safety profile in early phases [202,203].

Development of CD70-targeted CAR NK-cells has been underway. Preclinical trials have demonstrated their high specificity and efficacy. The first clinical data corroborate potential of this approach for MM therapy, especially in case of CD19-negative forms of the disease [204–206].

Particularly interesting have been dual-targeting strategies, which are simultaneously aimed at CD70 and BCMA, and aid to overcome the clonal heterogeneity and minimize the risk of antigen escape [207].

Hence, CD70 is a highly specific and biologically substantiated target for cellular therapy in multiple myeloma. Integration of CD70-targeted CAR-T and CAR-NK platforms, including bispecific constructs, opens up prospects for increasing therapeutic efficacy, deepening and prolonging remission in patients with relapsing and refractory MM forms.

3.11. Transmembrane Activator and CAML Interactor (TACI, TNFRSF13B)

TACI is a transmembrane receptor from the tumor necrosis factor (TNF) receptor superfamily and plays a key role for regulation of plasma cells survival, differentiation, and homeostasis. In physiological conditions, TACI expression is primarily observed on activated B-lymphocytes and plasma cells, where it performs immunoregulatory functions via interaction with BAFF (B-cell Activating Factor) and APRIL (A Proliferation-Inducing Ligand) ligands [208]. Binding of these ligands with TACI activates the intracellular signaling cascades that regulate production of antibodies, maintaining the survival of long-lived plasma cells, and B-cell homeostasis.

TACI is often co-expressed with BCMA on the surface of malignant plasma cells in MM. As indicated by the trials, the co-expression of these molecules is observed in most of the myeloma clones, whereby TACI expression may be higher and more stable in later stages of the disease [131;

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121]. These features acquire special significance against the background of a renowned escape mechanisms via the BCMA loss, since it makes TACI an attractive standby therapeutic target [209].

Surveys on TACI-specific CAR T-cells confirm their high efficacy versus TACI-positive MM cells in in vitro and in vivo systems [210]. These cells demonstrate quick expansion, steady persistence, pronounced tumor eradication, and a possibility for disease control during heterogenous expression of targets [211]. Given that, toxicity for untransformed cells is revealed on the minimal level.

This is the reason for active adoption of bispecific CAR constructs that simultaneously target and BCMA and TACI [209,212]. Such an approach minimizes the risk of relapse caused by antigen escape and ensures a wide coverage of tumor subclones. State-of-the-art developments include creation of fully humane CAR constructs and armored CAR T-cells with enhanced signaling activity, which are capable of overcoming immunosuppressive impact of tumor environment.

Hence, TACI inclusion as a target for CAR-T therapy in MM is a promising field, corroborated by molecular logic and clinical relevance. The combined targeting of BCMA and TACI opens up opportunities for enhancing the depth and duration of remissions, namely in patients with high relapse risk and heterogenous antigen expression.

3.12. A Proliferation-Inducing Ligand (APRIL)

APRIL is a part of the TNF family, appears as a natural ligand for BCMA and TACI receptors [213]. The interaction of APRIL with these receptors is fundamental for maintaining the viability, differentiation and homeostasis of plasma cells, which is critical for their long-term functioning [214].

Since APRIL shows high affinity to BCMA and TACI receptors, there have been developed CAR constructs, in which the modified APRIL is used as an antigen binding domain. This architecture is beneficial for capability of simultaneously targeting two targets with no need to apply complex, in terms of engineering, bispecific antibodies. This simplifies the structure of CAR platforms and increases their versatility and flexibility [215].

As indicated by preclinical trials, APRIL-CAR T-cells effectively destroy tumor clones that express BCMA, TACI or both the markers, which ensures a wider coverage of the tumor heterogeneity [216]. Such dual targeting mitigates the risk of antigen escape - a key restriction for conventional CAR-T platforms - and helps achieve the deep and steady remission [217].

Additional optimization for spatial configuration of the APRIL domain in CAR construct, as well as enhancing signaling modules (for instance, inclusion of co-stimulating CD28 or 4-1BB domains) have enabled a substantial increase in persistence and functional activity of effector cells, especially in immunosuppressive microenvironment, typical for MM [218].

Hence, APRIL-targeted CAR platforms form one more promising field for cellular therapy of multiple myeloma, ensuring expansion of the range, decrease of the relapse likelihood and enhancement of the overall treatment efficacy.

3.13. NKG2D ligands (NKG2DL) as a Target for Cellular Therapy of Multiple Myeloma

NKG2D ligands are stressed-induced molecules, which include MICA, MICB and ULBP protein family (UL16-binding proteins) [219]. These molecules are expressed on the surface of cells in response to stresses, such as DNA damage, hypoxia, viral infection, tumor transformation [220]. With expression in normal tissues the level of NKG2D ligands remains very low. Such selectivity makes the molecules promising targets for immunotherapy of multiple myeloma (MM).

NKG2D receptor is expressed on NK-cells, γδ-T cells and $CD8^+$ cytotoxic T-lymphocytes, enabling the interaction between innate and adaptive immunity [221]. Binding of NKG2D ligands on the surface of tumor cells with receptor on effector immune cells triggers a powerful immune activation and destruction of tumor cells even in case of phenotypic heterogeneity of tumor [222]. This mechanism helps overcome the antigen escape, attack various tumor clones and maintain steady immune control.

NKG2D-based deriving of CAR receptors enables to activate the innate immune recognition mechanisms. The constructs that utilize the full NKG2D receptor ensure a wide range of action versus

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phenotypically heterogenous myeloma cells [219; 220]. In early phase clinical trials, the efficacy of NKG2D-CAR T-cells has been demonstrated in patients with acute myeloid leukemia, myelodysplastic syndrome and relapsing/refractory MM. The application of full NKG2D receptor-based autologous CAR T-cells with the CD3ζ signaling domain has indicated good tolerability and clinical activity signs.

Development of improved constructs has been underway, which include co-stimulating modules, such as DAP10 and DAP12. This is aimed at enhancement of metabolic activity, resistance to depletion and prolonged persistence of CAR cells in the immunosuppressive tumor microenvironment [2; 102].

This way, the system of NKG2D-NKG2D ligands is a versatile and selective target for MM cellular therapy. It has been particularly relevant in pronounced tumor heterogeneity and augmentation of therapeutic resistance, ensuring a potential for development of steady and effective treatment strategies.

3.14. Alternative Targets for CAR Cell Therapy in Multiple Myeloma

Further to the best known targets for CAR therapy in MM, undergoing preclinical trials have been cellular products that target alternative molecules, possessing therapeutic potential [121]. These include CD56, an activated form of integrin β7 [223], CD123, and tumor-associated antigen Lewis-Y [224]. The choice of these targets is due to restricted expression in normal tissues and engagement in the MM pathogenesis, which makes them attractive for development of selective CAR-cell constructs [225,226].

CD56, the neural cell adhesion molecule (NCAM), is expressed in more than 70% of MM patients and plays a crucial role in migration and adhesion of tumor cells in the bone marrow [227,228]. Absence of CD56 expression is associated with more aggressive course of multiple myeloma and a trend for increasing the quantity of plasma cells in the peripheral blood. [229]. In normal tissues CD56 expression is primarily restricted with NK-cells, which required a comprehensive safety evaluation in the development of CD56-specific CAR cells. Nevertheless, preclinical data have shown tangible antitumor activity of CAR T-cells, targeted against this antigen [157].

Integrin β7, especially in its activated form, has been viewed as a promising therapeutic target, since it is primarily expressed on MM cells [230]. The use of MMG49 monoclonal antibody, which selectively recognizes the activated form of integrin β7, has enabled to engineer CAR constructs with high antigen specificity and mitigated risk of off-tumor toxicity [230]. Preclinical trials have demonstrated the capability of such CAR cells to selectively lyse the multiple myeloma cells, while not affecting the healthy hematopoietic cells [114].

CD123 (α-subunit of interleukin-3 receptor) is an antigen which is expressed on tumor stem cells and plasmacytoid dendritic cells, engaged in formation of the immunosuppressive microenvironment in multiple myeloma [231,232]. Despite being actively investigated as a therapeutic target in acute myeloid leukemia, CD123 potential in therapy for multiple myeloma remains understudied [233,234]. Restricted CD123 expression in normal tissues opens up the prospects for its use in immunotherapy, but additional surveys are needed in view of possible hematological toxicity.

Lewis-Y is a tumor-associated carbohydrate antigen, expressed on the surface of cells in various malignant neoplasms, including MM [235]. In preclinical trials Lewis-Y-specific CAR T-cells have demonstrated pronounced antitumor activity [235,236]. A phase I clinical trial has shown cases of temporary remission and disease stabilization for the period up to 23 months [237]. Moreover, infiltration and prolonged persistence of CAR T-cells (up to 10 months) has been confirmed, which is deemed a crucial factor for efficacy of the therapy [224].

Despite the encouraging preclinical and limited clinical results, the scope of data accumulated on alternative targets yields drastically to BCMA-targeted strategies. The matters of toxicity, antigen escape and therapeutic response stability have remained unsolved [121]. In this connection, very relevant has been development of multi-antigen CAR constructs, engineering platforms with

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controllable activation of effector cells (for instance, systems like AND gate), and adoption of safety systems for quick and controllable suppression of cytotoxic activity should any undesired effects occur [2,238,239].

Hence, CD56, integrin β7, CD123 and Lewis-Y appear as biologically substantiated targets for further development of CAR cellular therapy for multiple myeloma. Their integration in the clinical practice will require additional surveys with a focus on safety, specificity and long-term efficacy of therapeutic response [114].

4. Conclusions

MM is among the most challenging and heterogenous liquid tumors characterized by high relapse incidence and formation of multiple drug resistance mechanisms. Despite the achievements of target and antibody therapy, no radical recovery from the disease has been obtained so far, which necessitates introduction of game-changing therapeutic approaches.

CAR cell therapy, which relies on application of genetically modified effector cells, is a most breakthrough area in treatment for relapsing and refractory forms of MM. Its efficacy is defined by multiple factors, rational choice of tumor target being the key one. The presented review has analyzed data on biological properties, level and stability of expression, selectivity, and clinical development stages of target molecules, such as BCMA, GPRC5D, FcRH5, SLAMF7, CD38, CD138, TACI, APRIL, CD19, CD44v6, TNFR2, CD70, NKG2D ligands, etc.

BCMA is the most verified and clinically proven target for CAR cell therapy in MM. High density of BCMA expression on malignant plasma cells, its minimal occurrence in normal tissues and proven efficacy in KarMMa and CARTITUDE-1 clinical trials have ensured adoption of BCMA-specific CAR-T products (ide-cel and cilta-cel) in clinical practice. However, despite the high frequency of therapeutic response, the use of this target shows some restrictions, including development of antigen-negative relapses and presence of the soluble BCMA form (sBCMA), which decreases the efficacy of cellular therapy.

The most promising targets in the advanced stage of clinical development include GPRC5D and FcRH5, which demonstrate high specificity to myeloma cells, the favorable safety profile and efficacy in patients who had earlier received BCMA-specific therapy. Development of bispecific CAR products, which simultaneously target BCMA and GPRC5D/FcRH5, has shown encouraging results in overcoming antigen escape and increasing stability of clinical response.

Second-line targets, such as SLAMF7, CD38, CD138, TACI and APRIL, possess biological validity, high expression on myeloma cells and proven therapeutic potential in preclinical and early clinical trials. These are being actively integrated into multi-specific CAR platforms that pursue expanded coverage of tumor subclones in MM.

Meanwhile, the use of some targets requires particular care, due to the risk of on-target, off-tumor toxicity or involvement in regulation of immune homeostasis. These include CD44v6, TNFR2, CD70 and CD19, which also express on normal epithelial or immune cells. CAR logical activation strategies (AND/NOT gates), low-affinity receptors and controllable inactivation systems (safety switches) are used to increase therapeutic effect selectivity and controllability in respect of these targets.

Eventually, alternative targets, such as CD56, activated form of integrin β7, CD123 and Lewis-Y, are primarily in the preclinical validation stage. Their restricted expression in normal tissues, engagement in MM pathogenesis and antitumor activity displayed in vitro and in vivo make those stand as potential candidates for further research and inclusion into the multi-target constructs.

Hence, the choice of a tumor target in multiple myeloma is determined by a set of parameters, including expression stability and level, selectivity, biological significance, and potential for antigen escape. Optimization of antigen targeting via multi-specific CAR constructs, logically programmed platforms and controllable safety mechanisms is a key field in development of more effective, steady and safe forms of cellular therapy in MM.

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