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A Novel Approach in Cancer Immunotherapy: CAR T-CELL Therapy

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Abstract

Chimeric Antigen Receptor (CAR) T-cell therapy is a progressive invention in cancer immunotherapy. In recent years, the emergence of CAR T therapies in clinical practice has led to a new advancement in the treatment of patients diagnosed with solid tumours and haematological malignancies. The most serious negative impacts of CAR T-cell therapy include cytokine release syndrome, which may affect antitumor efficacy. This is said to be an innovation in immunotherapy, targeted against tumour-associated antigens. Among the numerous methods to treat cancer, one method is CAR T-cell therapy, which treats cancer in association with the immune system. In this review, epidemiology and aetiology of cancer were discussed briefly, along with properties of cancer cells, cancer immunotherapy and chimeric antigen receptor design.

Major Findings: CAR T-cell therapy has emerged as a promising and innovative strategy in cancer immunotherapy, utilizing genetically engineered T-cells to specifically recognize and eliminate tumor-associated antigens. In the present review, targeted therapies, particularly those directed against CD19, have demonstrated significant clinical success in hematological malignancies such as leukemia and lymphoma. However, challenges such as cytokine release syndrome, neurological toxicities, and limited effectiveness in solid tumors continue to restrict its widespread clinical application. Targets and current challenges of CAR T-cell therapy were discussed in this review.

Keywords: Cell-transfer-based Immunotherapy, Chimeric Antigen Receptor, Cytokine Release Syndrome

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1. Introduction

Cancer is one of the most devastating and prevalent medical conditions in the world, related to the condition of uncontrollable cell growth leading to the formation of a cluster or clump of cells at a particular site in the body, indicating a carcinogenic condition[1]. These carcinomas can be of benign or malignant types, of which the latter has the property of spreading throughout the body; if not treated, it may be fatal[2].

The fatal nature of a benign tumour can be determined based on the site of its origin. Both tumour types can be distinguished by their capacity for de-differentiation and invasiveness. The terms cancer, malignant neoplasm, and malignant tumour are regarded as synonyms. Most cancers are precipitated as a result of genetic changes. All the tumours are solid in nature, except in the case of leukemia[1].

"ALL THE BENIGN TUMORS ARE NOT FATAL, BUT ALL THE MALIGNANT TUMORS ARE FATAL."

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2. Epidemiology

It deals with the distribution and control of diseases and health-related factors among the population. Cancer, a hazardous disease, is one of the major reasons for the vast rate of mortality. It is seen in one out of three people during their lifetime. In 2001, nearly 270,000 cases were reported in the UK, leading to a high death rate[3]. Among them, lung cancer, breast cancer and prostate cancer are the most prominent types. Cancer incidence is rapidly increasing in developing countries as well as in developed nations due to lifestyle factors, lack of exercise, modern habits, and junk foods[4].

According to the ICMR report, cancer is one of the most frequently seen cases and a highly affecting disease in India. Globally, cancer was responsible for death of 599,601 people in 2019. Every day, 1300 cancer-associated deaths are recorded; these statistics are truly alarming[5].

In 2021, 26.7 million people were affected, and in the northern region, 2,048 patients per 1,000,000 were affected by cancer. In the northeast, 2,177 individuals per 1,000,000 were affected. It was mostly seen in men than in women[6] as stated in Figure 1. In earlier days, people were more effected to cancer due to alcohol consumption and cigar smoking, but now, it is due to obesity, radiation from mobiles and mobile towers, vegetables cultivated by using chemicals (Potash), food adulteration and artificial colours used in the food[7].

3. Cancer Immunotherapy-Adoptive Cell Therapy

Immunotherapy, commonly called biological therapy, is regarded as the fifth pillar in cancer treatment. It works on the principle of identifying and eliminating the cancer cells. This work is done by the T-cells[8]. They work by potentiating immune cells by relieving their suppression or by directly activating them to perform their immune functions more effectively.

Initially, in the 1900s, people affected with cancer were injected with Tumour Necrosis Factor (TNF) as a cancer immunotherapy. As some toxicities were precipitated, like fever, rigors and pulmonary oedema, its use in cancer treatment was limited[9].

- Later, in 1922, the FDA (Food and Drug Administration) approved the use of Interleukin-2 (IL-2) for renal cancer and in 1998 for treating metastatic melanoma. Due to its greater adverse effects compared to its benefits, the use of interleukin-2 was limited[9] as stated in Table 1.
- Bacillus Calmette-Guerin (BCG) was the first vaccine licensed by the FDA to treat superficial bladder cancer in 1990. Similarly, in 2010, the Sipuleucel-T vaccine was approved to extend the life of patients suffering from prostate cancer[10] stated in Table 1.

3.1 CAR T-Cell Therapy

It is an innovation in immune cell therapy for cancer. This is a result of 8 years of prolonged research and is likely to be available in India from 2023. At present, patients have to travel abroad for this treatment, which would cost up to 3-4 crores[11].

3.2 Chimeric Antigen Receptor Design

The chimeric antigen receptor consists of 4 domains joined in sequence, specifically,

- Targeting moiety
- A hinge region

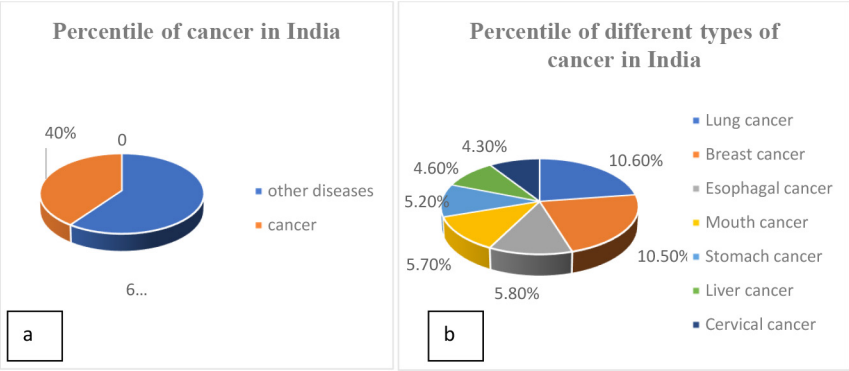


Figure 1. **(a)** Prevalence of cancer, **(b)** Prevalence of different types of cancers in India.

- A transmembrane element
- A signalling Endo-domain[21]

3.2.1 Targeting Moiety

The antigen-recognising site is present in the ectoderm of the receptor. The antigen-recognising region is a single-chain variable fragment (ScFV), which is a fusion protein, often known as a chimeric protein[22]. ScFV comprises a set of light and heavy immunoglobulin chains paired by short linker peptides. It consists of hydrophilic residues like serine-glycine for flexibility and glutamate-lysine for solubility. The other antigen-recognition domains include TNF receptors, cytokines, and growth factors[23].

3.2.2 Hinge Region

The hinge or spacer domain is the extracellular segment that extends the binding units across the transmembrane domain. The hinge functions enable flexibility to overcome limitations and contribute to the length required for the antigen-binding domain to reach the targeted epitope[24]. The chosen hinge primarily seems to affect CAR functionality since variations in the hinge region's length and content can have an impact on signalling, CAR expression, flexibility, epitope recognition, and activation output strength. Furthermore, it has been hypothesised that the spacer length serves a crucial role in ensuring that there is enough intercellular distance for the development of immunological synapses[25]. The hinge sections that are utilised most often are derived from amino acid sequences found in CD8, CD28, IgG1, or IgG4. However, because IgG-derived cells can interact with FcϒR receptors, they can promote CAR-T cell depletion and consequently lower persistence *in vivo*. By choosing a different hinge region or by doing additional engineering based on structural or functional concerns, these impacts can be avoided[14].

3.2.3 Transmembrane Element

The hydrophobic α-helix that traverses the membrane is called the transmembrane domain. For receptors to remain stable, the transmembrane domain is essential. The majority of transmembrane domains are obtained from natural proteins such as CD4, CD28, and CB3 zeta. The most stable domain at the moment is the CD28 transmembrane domain[15].

4. Signalling Endodomain

In the endo-domain of the CAR, the intracellular T-cell signalling domain is present. After antigen recognition, the receptor clusters and transmits activation signals to the cell. The most often employed domain is CD3 zeta,

Table 1. List of FDA-approved CAR T-cell therapies

Generic name	Brand name	Target antigen	Treatment targeted	Treatment population
Tisagenlecleucel[12]	Kymriah	CD19	B cell ACUTE Lymphoblastic Leukaemia (ALL) B-cell Non-Hodgkin Lymphoma (NHL)	Adults and young children with relapsed or refractory B-cell NHL
Axicabtageneciloleucel[13]	Yescarta	CD19	B-cell non-Hodgkin lymphoma and follicular lymphoma	Adults with relapsed or refractory B-cell NHL and refractory follicular lymphoma
Brexucabtageneautoleucel[14]	Tecartus	CD19	Mantle Cell Lymphoma (MCL) and B-cell Acute Lymphoblastic Leukaemia (ALL)	Adults with relapsed or refractory MCL and B-cell ALL
Ciltacabtageneautoleucel[15]	Carvykti	BCMA	Multiple myeloma	Adults with refractory or relapsed myeloma
Idecabtagenevicleucel[16]	Abecma	BCMA	Multiple myeloma	Adults with relapsed or refractory myeloma
Lisocabtagenemaraleucel[17]	Breyanzi	CD19	B-cell non-Hodgkin Lymphoma (NHL)	Young population with refractory or relapsed B-cell NHL[18-20]

which has three components and, following the binding of the antigen, generates co-stimulatory molecules that activate T cells. This process has been carried out for four generations. Co-stimulatory molecules, namely, CD28 4-1bcd, have been incorporated into CAR cells for further enhancement of therapeutic effect[16].

The only activation signalling domain present in first-generation CARs is the CD3 zeta signalling domain; however, its capacity to expand tumour efficacy is inadequate. Consequently, second-generation CAR T cells have demonstrated strong MT tumour effectiveness *in vivo* for B-cell malignancies. These cells feature co-stimulatory signalling domains that increase the signal function with CD28 or 4-1BB signalling domains. CAR cells that use Eco's co-stimulatory domain have a longer survival time than those that use CD28[17]. To increase the anti-tumour efficacy, a co-stimulatory domain (4-1BB) is added in the third generation. In the fourth generation of CARs, cytokine genes are headed and these CAR-T cells are modified with cytokine genes to have tumour efficacy. In contrast, receptor R2DS2 and maximum acting protein are used to replace CD3C and co-stimulatory molecules to enhance the proliferation and function of CART-cells which can destroy solid tumours efficiently. According to these, cells can help cure autoimmune disorders and viral infections[21].

4.1 Construction of CAR T-Cells

There are several steps to construct CAR T-cells. Initially target tumour antigen needs to be chosen from the collected apheresis for affinity screening to identify the optimised antibody and obtain the gene sequence of the selected antibody. Then, according to the design of CAR construction, CAR genes are synthesised and packaged into viral vectors[22]. Further, these CAR genes are delivered through lentiviral transfection culture, the transgenic T-cells and the selected T-cells with CAR expression. Lastly, prior to clinical trials, these newly created CAR T-cells are evaluated for their quality, for the ability of proliferation of CAR receptors and expression of cytotoxicity, cytokine release and anti- tumor function in both *in-vivo* and *in vitro*[23].

4.2 Targets of CAR T-cell Therapy

Chimeric antigen receptor therapy is used to avoid damage to healthy tissues; therefore, tumour cells must be the only targets. To date, numerous tumour-associated antigens have been targeted in an attempt to achieve the best possible therapeutic outcome. Finding the perfect biomarker to serve as an antitumor target is challenging because these biomarkers are infrequently expressed on healthy cells and are highly expressed on the surface of tumour cells[26,27]. Typically, the selected biomarkers reveal high expression level discrimination between tumour and healthy cells. For this reason, we need to closely monitor the off-target tumour cytotoxicity of CAR T-cell therapy[28-31]. The cluster of CD19 is regarded as a star biomarker in CAR T-cell therapy. Besides CD19, other biomarkers of targeting numerous types of tumour cells are used as CAR T targets in clinical trials[32,33]. The immunoglobulin (IG) superfamily 95-kDa transmembrane glycoprotein is recognised as the CD19 antigen. CD19 is recognised as a transmembrane domain of type-1[34,35].

It exerts a vital part in determining the intrinsic B-cell signalling threshold by regulating both the dependent and independent signalling of B-cell receptors[36]. It has significance in both the formation of antigen-independent B cells and the activation of B cells initiated by the immunoglobulin. For the body to develop the best possible immune response against B-cells, CD19 is essential[37]. CD19 forms a signal transduction complex with CD21, CD81, and CD225. Most B-cell-derived malignancies display CD19 expression[38]. A significant function of CD19 is reported in clinical oncology. Despite its considerable success, CD19 targeted CARS has been used to treat B-cell malignancies, with a response rate of 70–90% in both acute and chronic leukaemias[12,39]. In 1980, CD20 was discovered, which contains the first B-cell marker. It is a portion of the membrane that is not glycoside and has two extracellular loops. Every B-cell surface generates CD20, which steadily rises in concentration until maturity. It is thought to modulate calcium release from the BCR and function as a calcium channel in the cell membrane[38,40].

It was further determined that the malignant B-cells express it on their surface. Tumour necrosis factor, or antigen BCM, is a receptor superfamily 17, which is mostly expressed on terminally differentiated B-cells. When it binds to its ligand, the B-cell activator of the TNF family is activated, which leads to its proliferation[41,42].

4.3 CAR T Targets of Solid Tumours

Multiple studies have looked at engineering cells to circumvent the ways by which tumours might

restrict T-cell activity. CAR T-cells have proven to be therapeutically effective in orthotopic or metastatic xenograft mouse models, as well as *in vitro*. Research has indicated that CAR T-cells expressing CXCR2 chemokine receptors can effectively target IL-8. However, these chemokine receptors exhibit effective antitumor activity against pancreatic cancers that express αvβ6[43,44]. It is interesting to note that 4-1BB co-stimulation may minimise PD-1 expression in the T-cells that are produced, thereby demonstrating stronger antitumor efficacy against tumour cells that express PD-L1. Preclinical research and clinical trials have examined numerous antigen targets, notably CD24, MUC-I, PSCA, mesothelin, and FAP, for pancreatic cancer CAR T-cell treatment[45,46].

Triple-Negative Breast Cancer (TNBC) tumour cells can be effectively killed by CAR T-cells in a very precise way. CARs containing both CD3 zeta and CD28 signalling domains are specifically present in MUC28z CAR T-cells, which enhances the synthesis of granzyme B, IFN-B, and other cytokines and chemokines produced by Th1 cells. Furthermore, MUC28z CAR T-cell signalling eliminates TNBC cell proliferation with a single dose[47]. In TNBC tumour models, 4-1BB or CD27 co-stimulation boosted NKG2D CAR T-cells implicated in antitumor action, according to another study[48,49]. Through HER family receptors, CAR T-cells assist HRG1β in effectively preventing the proliferation of breast cancer cells. Mesohaline is another biomarker that has purportedly shown potential in immunotherapy for breast cancer, and this has been identified by specific CAR T-cells[50,51].

4.4 Thyroid Cancer

This CAR T-cell's preclinical efficacy is related to its specificity for intercellular adhesion molecule-1 (ICAM-1). Patients with thyroid cancer have a greater percentage of soluble ICAM-1 present in their serum, which may neutralise peripheral anti-ICAM-1 CAR-T cells before they recognise ICAM-1 positive tumour cells[34], (Support *et al.* 2022). Given that medullary thyroid cancers (MTCs) frequently contain carcinoembryonic antigen (CEA) and the GDNF family receptor α4, MTCs may be a good candidate for CAR T-cell therapies. Indeed, preclinical research is simultaneously being done on CAR T-cell techniques specific to GFRA 4 [52,53].

4.5 Brain Cancer

Multiple research studies employing CAR- T cells for glioblastoma (GBM) have been performed and are ongoing. Ten patients with recurrent GBM participated in the first human clinical trial, which analysed the impact of intravenous injection of EGFRvIII CAR-T cells[54,55] showed in Table 2.

4.6 CAR T Targets of Haematological Malignancies

Hematologic malignancies, frequently referred to as blood cancers, represented 10% of all cancer cases in the United States in 2019 and are triggered by an unregulated proliferation of aberrant blood cells[58,59]. Although clinical trials with solid tumours provided initial insight into the efficacy of CAR T-cell therapy, the treatment of hematologic malignancies has shown immense potential with this approach in recent years[60,61]. While certain CAR-T cells continue to exhibit a memory phenotype and respond more quickly, overall, the response time for CAR T-cell therapy is shorter than that of other therapeutic approaches, such as immune checkpoint inhibition and tumour vaccines[3,62]. The FDA has approved three novel medications for the treatment of acute lymphoblastic leukaemia and refractory diffuse large B-cell lymphoma (DLBCL) as a result of these efforts[22,63].

4.7 Hodgkin Lymphoma

CAR T-Cell therapy targeting CD30 has demonstrated a long-lasting antitumor response in mouse models of Hodgkin lymphoma and Hodgkin lymphoma cell lines[64,65]. In Hodgkin lymphoma mouse models, anti-CD30 CAR-T cells migrate toward tumours more

Table 2. Different targets of CAR T-cell therapy

Target	CAR structure	Malignacy
HER2 MUC1[56]	CD3 zeta and CD28	Breast cancer
EGFRvIII	3Dzeta and 41BB	Glioma
FAP	CD3 zeta and CD28	Lung cancer
Mesothelin CD19	CD3 zeta and 41BB	Pancreatic cancer
FR [57]	CD3 zeta and CD27	Ovarian cancer and breast cancer

readily when CCR4 expression is stimulated. Antitumor responses have been seen in phase-1 clinical trials with or without precondition chemotherapy[8,66].

4.8 Non-Hodgkin Lymphoma (NHL)

Non-Hodgkin lymphoma accounts for about 4% of all cancer cases in the United States. B-cell lymphoma (BCL) and T-cell lymphoma (TCL) are two subtypes of non-Hodgkin lymphoma[67,68]. While some TCLs show the CD30 marker, the majority of BCL cells display the B-cell differentiation markers CD19 and CD20[69].

4.9 B-Cell Lymphoma (BCL)

Preclinical models are being used to assess the anticancer potential of three appealing targets: immunoglobulin kappa light chain, which is present on MCL, DLBCL, and NHLS; CD23, which is present on CLL cells; and ROR1, which is present on CLL and MCL [70]. According to many researchers, CD22 is another strong target antigen expressed in B-ALL and other B-cell lymphomas.

In an effort to decrease side effects and increase therapeutic selectivity towards tumour cells, recent efforts in CAR T-cell research have focused on identifying novel B-cell surface indicators[71,72]. Preclinical models are being used to assess the anticancer potential of three appealing targets: immunoglobulin kappa light chain, which is present on MCL, DLBCL, and NHLS; CD23, which is present on CLL cells; and ROR1, which is present on CLL and MCL[73-76].

In an effort to decrease side effects and increase therapeutic selectivity towards tumour cells, recent efforts in CAR T-cell research have focused on identifying novel B-cell surface indicators[17]. Three alluring targets, including

Table 3. List of T-cells used in cancer treatment

Target	CAR structure	Malignancy
CD19	CD3 zeta and CD28, CD3 zeta and 41BB	Lymphoma and leukemia
CD22	CD3 zeta and CD28,	Follicular lymphoma, ALL, DLBCL
CD20	CD3 zeta, CD3 zeta and 41BB	CD20-positive malignancies
CD19 CD20	CD3 zeta and 41BB	Leukaemia and lymphoma
ROR1	CD3 zeta and 41BB	CLL and SLL
CD19 PSMA	CD3 zeta and CD28 PD1 or CTLA4	Leukemia

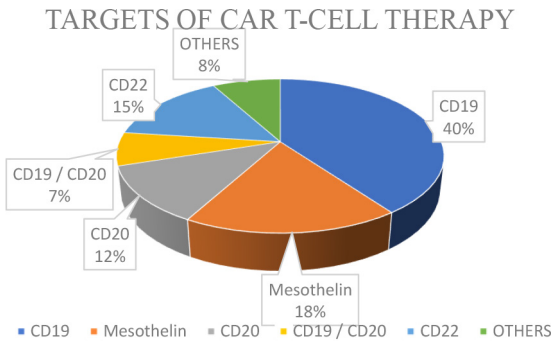


Figure 2. Figure showing different types of CART cells used for various cancer treatments.

CD23 (found on CLL cells), ROR1 (present on CLL and MCL) and immunoglobulin kappa light chain (present on MCL, DLBCL and NHLS), are being evaluated for their anticancer activity in preclinical models. Another strong target antigen expressed in B-cell lymphomas, including B-ALL, is CD22[77,78].

4.10 T-Cell Lymphoma (TCL)

Allogenic HCT is the exclusive therapy option for TCL at this time. The creation of CAR T-cell therapy has the potential to be revolutionary, but only if antigen markers unique to malignant T-cells are found[79,80] as in Figure 2, Table 3.

5. Limitations of CAR T-Cell Therapy

5.1 Cytokine Release Syndrome (CRS)

Rapid and widespread cytokine release into the bloodstream during CRS might result in dangerously elevated fevers. The symptoms of CRS can vary from minor flu-like symptoms to more severe ones, such as fever, chills, headaches, and nausea[81,82].

5.2 Neurologic Toxicities

Some of the symptoms associated with neurologic toxicities include language difficulties, disorientation, involuntary muscle twitching, hallucinations, unresponsiveness, and seizures[83].

5.3 Tumour Lysis Syndrome

A class of metabolic complications that might arise from the disintegration of dying tumour cells; these typically happen when harmful cancer treatments begin[84].

5.4 Anaphylaxis (Possibly Life-Threatening Allergic Response)[85,86]

Symptoms associated with anaphylaxis include facial swelling, low blood pressure, and respiratory distress.

Hard to achieve long-term activity.

Hard to industrialise and mass-produce.

On-target, off-tumour-toxicity.

Represent significant potential for healing hematological cancers like leukaemia, but they are less successful in treating solid tumours.

Cerebral oedema[87].

6. Advantages of CAR-T Cell Therapy

- Chimeric antigen receptors have HLA-unrestricted action in contrast to T-Cell Receptors (TCRs).
- Detecting and targeting non-protein antigens such as glycolipids, polysaccharides, and glycoproteins.
- Enhanced tumour antigen affinity toward long-term recognition and better probability of T-cell activation[88].
- Possesses a comparatively simpler construction than the TCR complex.
- Targeting tumour cell surface antigen can help overcome certain obstacles to tumour immune escape, such as minimising endogenous antigen expression and MHC[89].
- Since CAR T-cell treatment is a "living drug," its advantages may persist for several years.
- The primary advantage of CAR - cell therapy is its potential for curative treatment for individuals whose benign tumours have not responded to other types of treatment[9,90].

7. Risk Factors

7.1 Treatment Not Working

Very few treatments work 100% of the time. It is possible that CAR-T cell therapy won't kill all the cancer cells. And because it is often used as a last resort, may not have other options if CAR T therapy doesn't work[91,92].

7.2 Lack of Data

The first CAR T-cell therapy was approved in 2017, which means there is still limited data on the long-term effects of the treatment, including its overall effectiveness[93,94].

8. Conclusion

Over the next couple of years, CAR T-cells—the best example of T-cell genetic engineering—should develop into a common cancer treatment for B-cell malignancies, providing us with emerging possibilities. However, the recurrence of tumour antigen escape due to the selective immunological pressure exerted by CAR T-cells exposes a limitation of this innovative approach[95,96]. Furthermore, the use of solid tumours with lower efficacy and on-target/off-target toxicity has not produced a similar surprise, indicating that improving the reliability and efficiency of CAR-T cells has to be taken into consideration as a first step in the development of innovative CAR designs[41,97]. These cells are altering the way that cancer therapy is explained. Recently, the FDA has approved CD19 CAR T-cells for the treatment of various cancers. There is a significant therapeutic effect of engineered CAR T-cells when compared to antibody-based treatment and other targeted inhibitors. CAR T-cells will soon become off-the-shelf and likely heal the treatment of human cancers[98,99].

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10. Data Availability Statement

Data available on request due to privacy/ethical restrictions.

11. Conflicts of Interest

The authors declare no conflict of interest

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All authors have read and agreed to the published version of the manuscript.

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