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T-cell Membrane-Functionalized Nanosystems for Viral Infectious Diseases

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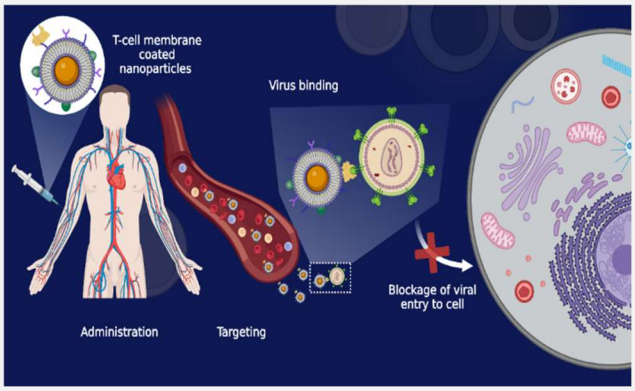
ABSTRACT



Being a universal obstacle, HIV requires a vaccine or potential cure. As a matter of fact, the invention of an efficacious vaccine or therapeutic cure for human immunodeficiency (HIV) is of paramount importance, which can provide potent and wide-ranging neutralization against viral infections. Although the genetic variation of this virus can hamper efforts, advanced technologies such as coating technology by cell membrane can mitigate the situation. To shed light on this matter, T-cell-membrane-coated nanoparticles are considerable. These nanoparticles have antigens that are naturally on the T cell surface and are fundamental for HIV binding, for instance, CD4 receptor and CCR5 or CXCR4 coreceptors. Not only HIV can be successfully neutralized by TNPs, but also, they can precisely bind to the intended targets of infected cells. Consequently, there would be a fall in the number of released HIV-1 particles through an autophagy-dependent mechanism with no drug being used off-target or cytotoxic effects on observer cells. In this review, we highlight the emerging role of T-cell-membrane-coated nanoparticles in the treatment of viral infectious diseases.

Keywords: AIDS, HIV, nanoparticles, cell membrane

1. Introduction

Nanoparticles (NPs) have been broadly explored in a variety of biomedical applications. Regardless of their advantages, the successful clinical translation of nanomaterials is still a dream [1-4]. The major challenges that explain the disparity between scientific and clinical findings are the reticuloendothelial system which recognizes NPs as a foreign substance and removes them [5, 6]. Besides, the complex circulatory environment that contains immune cells and high level of proteins further promote the clearance of NPs [7-12]. For decades, the surface decoration of NPs with polyethylene glycol (PEG) commonly known as PEGylation has been an important approach to extending the circulation time of NPs. However, recent studies reported the production of antibodies against PEG which has forced the drug delivery community to find an alternative biomimetic approach for stealing NPs . Therefore, researchers have explored a novel and potential method for camouflaging NPs via coating them with plasma membranes isolated from living cells[5, 13, 14]. This is an advanced approach for the fabrication of multifunctional NPs that can efficiently interact with biological systems, without being recognized and cleared as antigens by the reticuloendothelial system (RES) and MPS [15-17].

These cell membrane-coated NPs are core-shell structures that combine the advantages of both the intrinsic abilities of the natural cell membrane and the physicochemical characteristics of synthetic NPs [18]. In the game of hide-and-seek, these bioinspired NPs can deceive the host defense system and provide a prolonged circulation time [19, 20], and can actively target the cargo to the desired site [21]. The resulting nanostructure contains NPs core carrying a therapeutic agent to the target site and a cell membrane shell obtained from different cells [22]. The cell membranes

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can be isolated from different source cells including red blood cells (RBCs) [23-25], white blood cells (WBCs) [26], stem cells [27], and platelets [28]. Leukocytes or WBCs are an essential part of the host defense system which play leading roles in the inflammatory processes and exclusion of local infections in different diseases. Leukocytes exist in several forms such as lymphocytes, monocytes, eosinophils, basophils, and neutrophils which can be distinguished by their morphological and physiological characteristics [29].

In this review, we highlight the virus infectious diseases, particularly the Human immunodeficiency virus (HIV), and its mechanism of action. In addition, the characteristics and role of T-cell coated nanoparticles besides their applications for viral infectious disease are discussed. Finally, the current limitations and the perspectives on the application of these systems are reviewed.

2. Viral infectious diseases

In comparison to bare NPs, those covered with a membrane might more effectively distribute their payload, support phototherapy, and mediate immunoregulation. The membrane surface proteins may bring additional options to increase the range of their applicability. Human immunodeficiency virus (HIV) type-1 infection is still fatal despite recent developments in treatment [30]. HIV remains in residual cells regardless of the combination of antiretroviral therapy's effectiveness in maintaining the plasma virus under control at an extremely low level [31]. Viral elimination is significantly hampered by residual viruses that evade the therapy and continue to keep active viral replication in dormant cells [32, 33].

The current antiviral regimen must be taken forever. Viral reactivation happens quickly within days or weeks of therapy withdrawal The effectiveness of traditional pharmacological therapy is further hampered by side effects and the development of antimicrobial resistance [34]. Generally neutralizing antibodies that target the circulation of HIV virions' glycoproteins on the HIV surface have received a great deal of attention as a solution to these problems [35, 36]. Nevertheless, because the level of immunity these antibodies produce is still low, neutralizing cell-free viruses is inadequate, and the effectiveness of the therapy is still insufficient [37].

As precautionary action against HIV infection, much effort has been made to create safe and efficacious vaccinations [38]. However, no HIV envelope (Env) immunogen which may induce (antibodies with broadly neutralizing activity) has been discovered thus far [39]. There is a vital need for novel treatments against HIV infection. Therapeutic nanoparticles designed to enhance the prevention and treatment of HIV infection have recently been created [40, 41]. To increase the tolerance, systemic half-life, and effectiveness of antiviral medications, for instance, nanoparticles have been employed as delivery systems [42].

Additionally, it has been observed that certain nanoparticles can directly obstruct viral assembling processes and hinder viral replication through pathways such as multivalent expression of small molecules and direct blocking [43]. Short interfering RNAs (siRNAs) can now be delivered nonviral to a class of cells (such as CD4+ lymphocytes, macrophages, and dendritic cells) and HIV viruses to the mute expression of genes [44]. By improving immunological targeting and combining the expression of the antigen and the adjuvant, nanoparticle-based vaccine techniques also have a significant potential for regulating host immune responses, that collectively improve safety and anti-HIV immunity [40]. Cell-membrane-coated nanoparticles have just come to light as a novel biomimetic system to treat a variety of human ailments [45].

These nanoparticles can resemble donor cells for biological properties since they are created by wrapping fabricated cores with the natural cellular membrane. Cell-membrane-cloaked nanoparticles can be used to deceive sensitive cells into allowing pathogens to be neutralized. Particularly, nanoparticles covered in a red blood cell membrane (RBC-NPs) have shown a strong ability to neutralize pathogenic autoantibodies, neurotoxins, and bacterial pore-forming toxins [46]. Similarly to this, endotoxins and inflammatory cytokines may be neutralized by nanoparticles wrapped with a macrophage membrane [47].

After the initial development, nanoparticles covered with membranes from numerous cell types, including cancerous cells, thrombocytes, leukocytes, stem cells, and bacteria, have been successfully manufactured. These nanoparticles offer a wide range of therapeutic opportunities due to their cell-mimicking characteristics and complex biointerfacing

[48]. Thus, cell-membrane-coated nanoparticles with a distinctive capacity for biomimicry led to invent this technology for prospective HIV treatment (**Figure 1**).

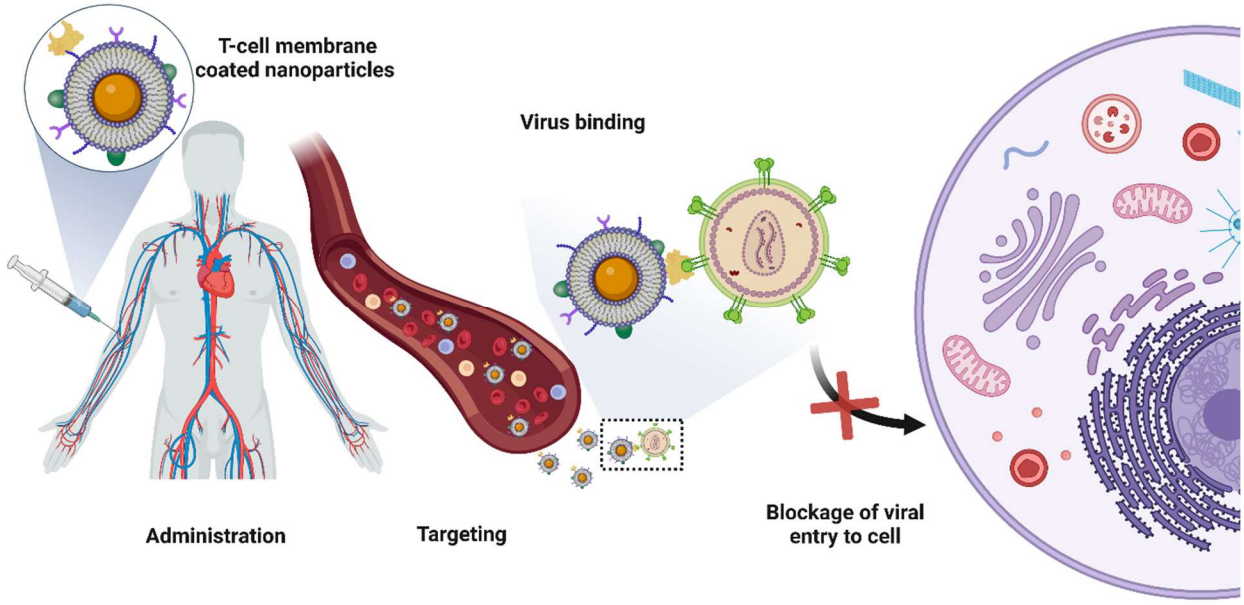

Figure 1. Schematic illustration of the application of the T-cell membrane coated nanoparticles for viral infectious diseases treatment.

The study team of Wei et al. [49] was prompted by recent developments in cell-membrane coating technology and gathered and wrapped CD4+ T cell plasma membranes over polymer cores (**Figure 2**). The accompanying CD4 receptor and CCR5 or CXCR4 coreceptors, as well as other T cell surface antigens necessary for HIV attachment, were inherited by the T cell membrane-coated nanoparticles referred to as TPNs. By distracting the viruses from their designated host targets, the TNPs destroy HIV by serving as a camouflage for the viral attack. Instead of directly reducing the viral replication mechanism, this decoy method mimics host cell activities for viral inactivation, which can overcome HIV genetic diversity [49]. In this study, it was shown that TNPs specifically bind with gp120, a crucial HIV surface glycoprotein, and prevent gp120-induced CD4+ T cell death. TNPs also efficiently counteract the viral infection of human monocyte-derived macrophages and peripheral mononuclear blood cells when introduced to HIV. TNPs have a significant opportunity as a new HIV infection treatment since they take advantage of natural T-cell capabilities [49].

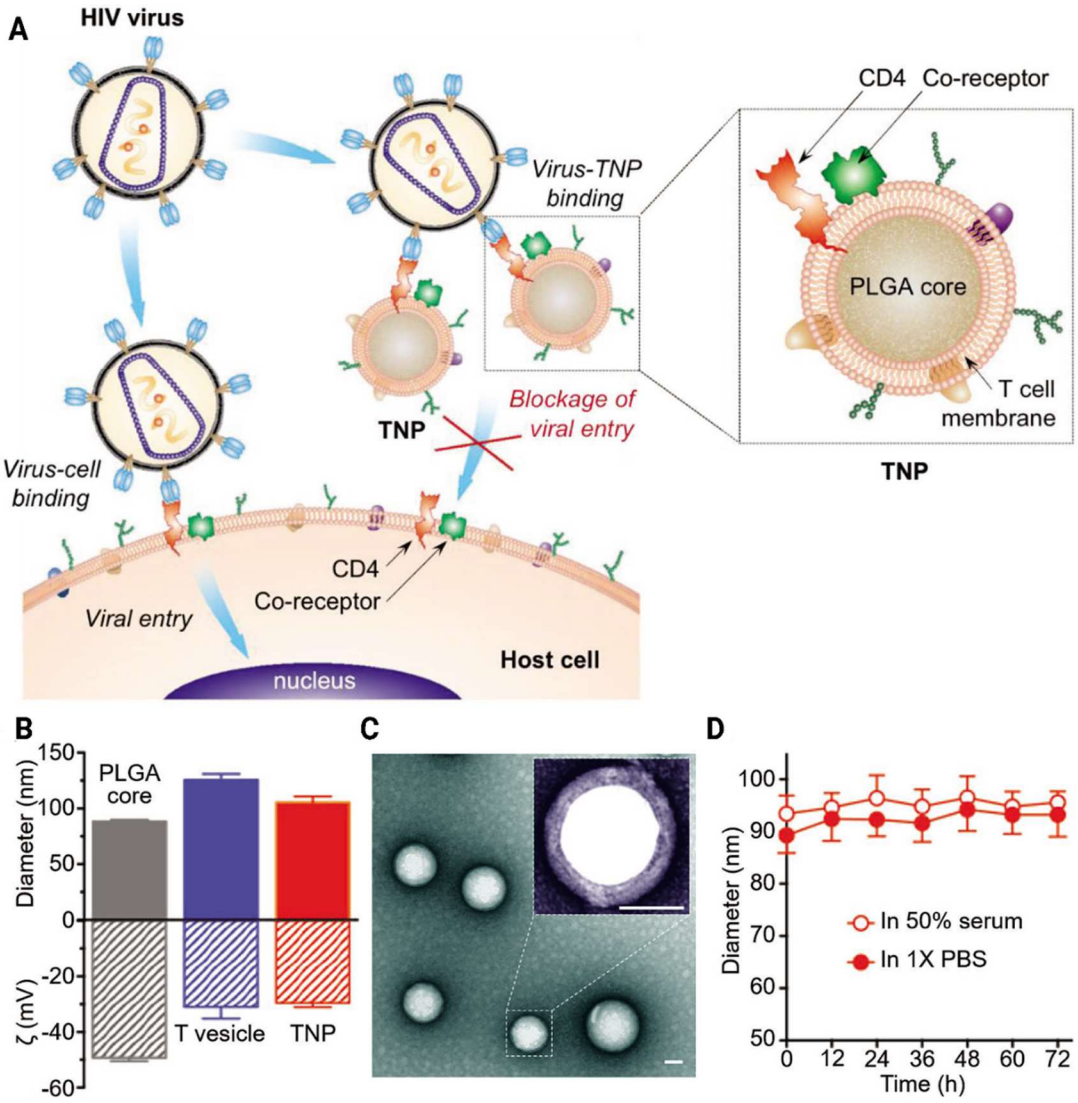

Figure 2. (**A**) Cartoon of TNPs designed for attenuating HIV infectivity. TNPs were constructed by wrapping polymeric cores with natural CD4+ T cell membranes, which contain key antigens including CD4 receptor and CCR5 or CXCR4 coreceptors for viral targeting. (**B**) Dynamic light scattering measurements of hydrodynamic size (diameter, nm) and surface zeta potential (ζ, mV) of PLGA cores, T-cell-membrane-derived vesicles (T vesicles), and TNPs. Error bars represent standard deviations (n = 3). (**C**) Transmission electron microscopy images of TNPs negatively stained with uranyl acetate. Scale bar = 50 nm. Inset: A zoomed-in view of a single TNP. Scale bare = 50 nm. (**D**) Stability of TNPs in 1× PBS or 50% fetal bovine serum, determined by monitoring particle size (diameter, nm), over a span of 72 h. TNPs: T-cell-membrane-coated nanoparticles. Reprinted from [49] with permission from Wiley.

As mentioned, It is extremely desirable to develop therapeutic approaches that effectively and broadly neutralize HIV-1 infection. In related work, the ability of membrane-coated $CD4^+$ T cell nanoparticles (TNP) to neutralize a variety of HIV-1 strains was examined [50]. With a mean 80% inhibitory concentration (IC80) of 819 g m-1, TNP demonstrated exceptional neutralizing scope and potency. They neutralized all 125 HIV-1 pseudotyped viruses tested, including recombinant forms and transmitted/founder viruses. While not affecting uninfected cells, TNP also specifically bonded to and stimulated autophagy in HIV-1-infected CD4+ T cells and macrophages. This TNP-mediated autophagy suppressed cell-associated HIV-1 and prevented viral release in phospholipase D1 in and dose-dependent manner. This effect was diminished by the genetic or pharmacological suppression of autophagy. In order

to reduce the HIV-1 pool, we can use TNP as therapeutic drug to neutralize cell-free HIV-1 and to attack HIV-1 gp120-displaying cells (**Figure 3**) [50].

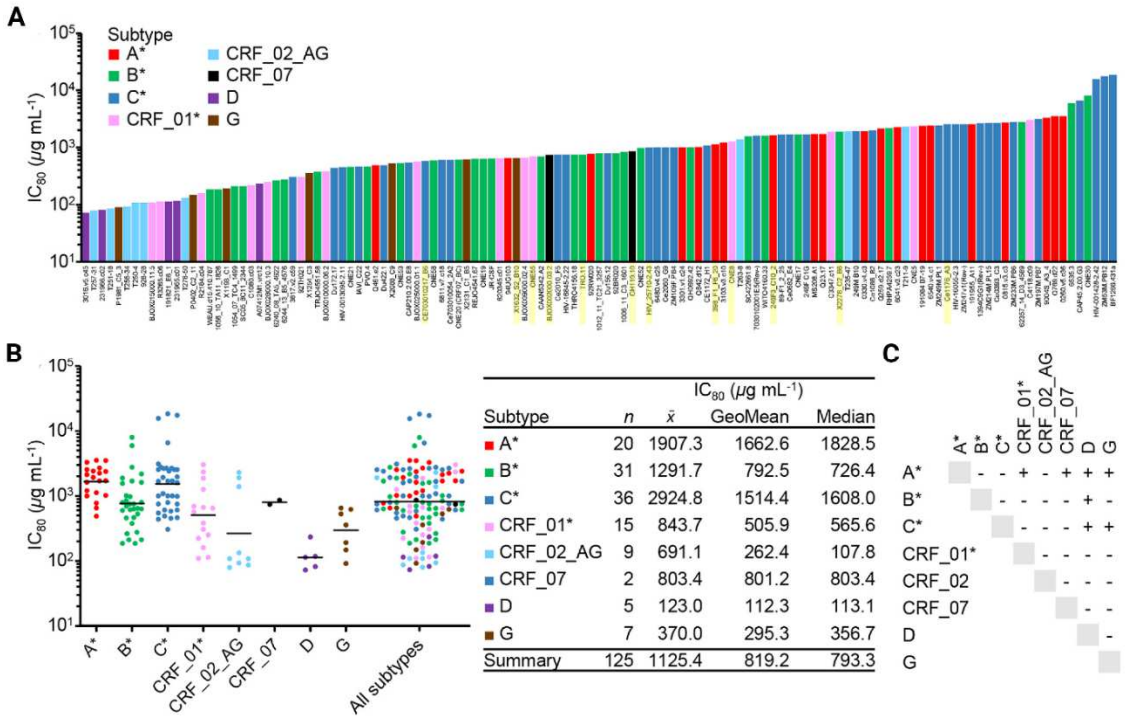

Figure 3. (**A**) Neutralization potency (IC80) of TNP toward various HIV Env-pseudoviruses (**B**) Neutralization potencies (IC80) for TNP toward the multisubtype pseudoviruses. Reproduced from [50] under CC BY 4.0 license open access.

3. Conclusion and outlook

Coated nanoparticles with cell membranes have proven to be viable nanoplatforms with excellent biocompatibility. Due to their distinctive biological characteristics, these biomimetic nanoparticles have gained considerable interest. To acquire the advantages, such as extending blood circulation, immune escape, and site-specific targeting, a top-down strategy is designed to develop T-cell membrane-based biomimetic nanosystems [51].

The immunological proteins on cell membranes are primarily responsible for the precise targeting potential of these biomimetic nanoparticles. Despite this advantage, immunological membranes make them susceptible to undesirable biological side effects, which restricts their potential use [52]. Additionally, there are concerns regarding immunogenicity problems related to major histocompatibility complex (MHC) molecules on membranes that require further research [53]. Therefore, it is crucial to transition from coating on the NPs to patient-derived cell membrane extraction for personal usage. Inserting nanodrugs into biomimetic T-cell membranes can resemble normal cells and improve the therapeutic efficacy of nanomedicines. Due to their excellent biocompatibility and specificity, the use of membranes made from immune cells particularly has revolutionized the field of targeted administration of drugs.

Despite the current advances in T-cell membrane-based biomimetic nanosystems for viral infection therapy, it is a long way to be applied in clinics. Firstly, the complex and inefficient process during the preparation of T-cell membrane-coated nanosystems has limited further usage. In addition, the certain mechanisms of the structural units and their specific functional proteins on the T-cell membrane need to be further confirmed. Furthermore, the immunogenicity and potential cytotoxicity still need to be further investigated before these biomimetic nanosystems are applied in clinics. Additionally, the current synthesis and formulation of these biomimetic nanosystems for viral infections therapy involve multiple steps that may introduce multiple processes of variability. Some important characteristics, such as purity and integrity, in particular, need further study and elucidation. Similarly, T-cell membrane coating methods have not yet been successfully developed for use in viral infection therapy (**Figure 4**).

These cell membranes need to be extensively developed in the future for viral infection treatment and other medical applications.

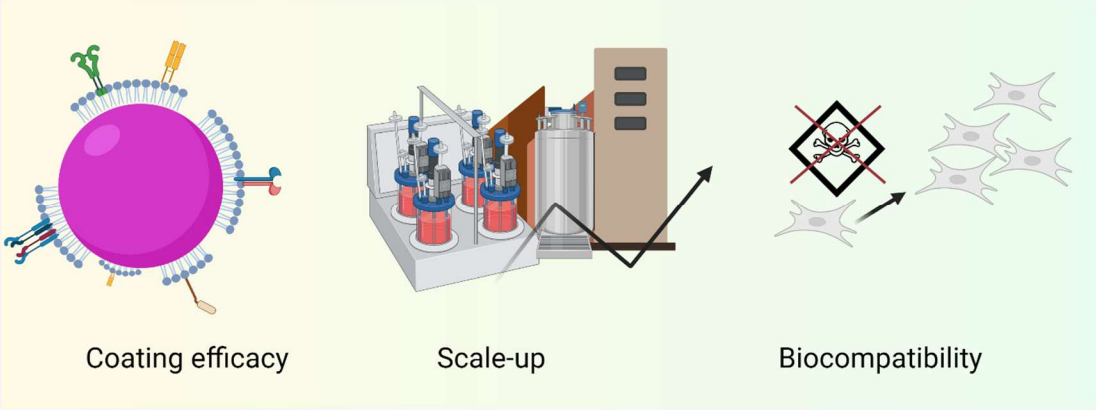

Figure 4. Schematic presentation on the challenge in T cell coated nanoparticles for clinical translation.

Authors' contributions

All authors contributed to drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

Declaration of competing interest

The authors declare no competing interest.

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