REVIEW PAPER

RBC Hitchhiking a vascular delivery approach in HIV/AIDS: A Critical Review

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ABSTRACT
The study gave a clear concept about the deadly disease named AIDS and currently, no cure can be found to prevent the adverse effect of this disease. AIDS mainly occurs after the attack of the Human immunodeficiency virus. The current study has demonstrated that RBC hitching can be considered as one of the most accepted models of treatment for AIDS. RBCs can be easily available and it has the best circulatory capacity among all RBCs, has the capability to bind with multiple substrates and also travel to every part of the host's tissue. In addition, Macrophages cannot treat RBC as foreign material; hence it will successfully reduce the chances of phagocytosis. RBC can be considered one of the best carriers for delivering drugs and also strengthening the immune response against HIV. However, in some cases, the immune cells of the host body cannot determine its own RBC. Therefore, encapsulation is required before transferring antiretroviral drugs in the body of the host's cells. The particular hitchhiking therapy showed less risk of failure and the dosage of drugs can be further modified in this case. Patients affected by HIV have been showing a noticeable response against the virus after successfully implementing drugs within their bodies.

Keywords: RBC, Macrophages, Nanotechnologies, immune response, AIDS, RBC hitchhiking, CD8+, APC, DNA, HIV

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INTRODUCTION

HIV or AIDS is one of the life threatening diseases for individuals of the entire world. The term AIDS mainly stands for "Acquired Immunodeficiency Syndrome" and it can be observed that there are no particular drugs present to treat this disease. AIDS mainly occurs by the attack of the Human Immunodeficiency Virus" [43]. The study is going to shed light on one of the most effective treatment approaches known as RBC Hitchhiking and Nanotechnologies to mitigate the severe effect of AIDS. Nanotechnology can be known as one of the emerging approaches or treatment techniques for developing the resistance of human beings against the deadly virus named HIV [44]. On the other hand, RBC hitchhiking can be considered as another process of transporting theragnostic agent to the red blood cells and it can improve the quality of blood after strengthening the working capacity of RBC particles. The study will further deal with the future effectiveness of RBC hitchhiking and nanotechnologies for the prevention of AIDS

Background of the research

The disease HIV mainly occurs due to the attack of the Immunodeficiency Virus and it directly attacks the immune system of the Human body. In the 21st century, AIDS is one of the major concerns for the entire world and there are no proper treatments available that can totally cure the impact of the HIV virus from the body. By the year 1981, the disease AIDS was first reported with the symptoms of Pneumonia[45]. However, the origin of the disease is still a mystery for individuals from all over the world. Other scientists from different regions stated that HIV 1 and HIV 2 belong to a non-human source. However, the further contamination process in the human body is still not known to all. The global rate of HIV contamination depicts that there are more than 2.9 Million people who have been suffering from the disease[1]. It can be observed that some scientists have named the HIV contamination as a pandemic. By the year 2016, there were near about 1.8 million emerging cases of HIV. The major risk of the disease is HIV attacking the immune system of the human's body and destroying the working capacity against any external sources such as viruses, toxins and bacteria. As a result, by the year 2016, a total of 1 million people died due to the disease called AIDS.

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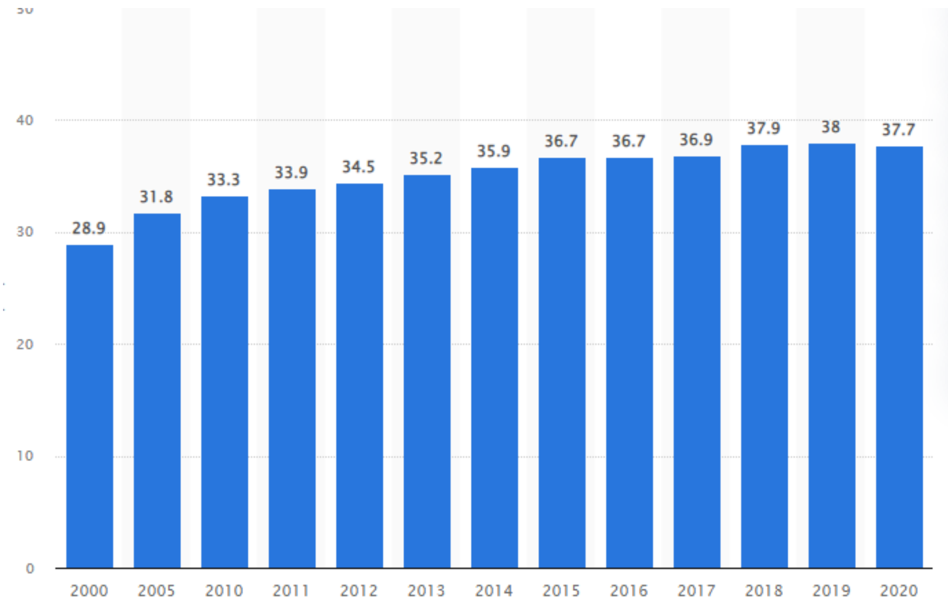

Figure 1: Global HIV contamination rate[1]

The study also demonstrates that HIV can be considered as "a sexually transmitted infection" and the disease is also spread by contact with the previously used infected needles of the carrier. During birth, the virus can also be transmitted to the baby's body from the mother's body. Individuals affected by the HIV virus may show different types of symptoms depending on their body's resistance power[46]. In maximum cases, individuals may have symptoms such as Flu, after 3 to 4 days of the infection. Apart from that some best possible signs of the disease are weight loss, muscle pain, Headache, Fever and Rash[2]. There are mainly three stages of HIV that can be observed, stage 1 is known as “Active HIV infection” , “stage 2 is known as “Chronic HIV infection” and stage 3 is the "Acquired immunodeficiency syndrome". During the initial phase of, it can be observed the presence of HIV in the white blood cells of the infected person's body. In the stage 2 phase, the HIV virus generally remains asymptomatic and continues the reproduction phase inside the patient's body. The last phase of contamination (AIDS) is the most life-threatening and the immune system of the host's body becomes totally inactive.

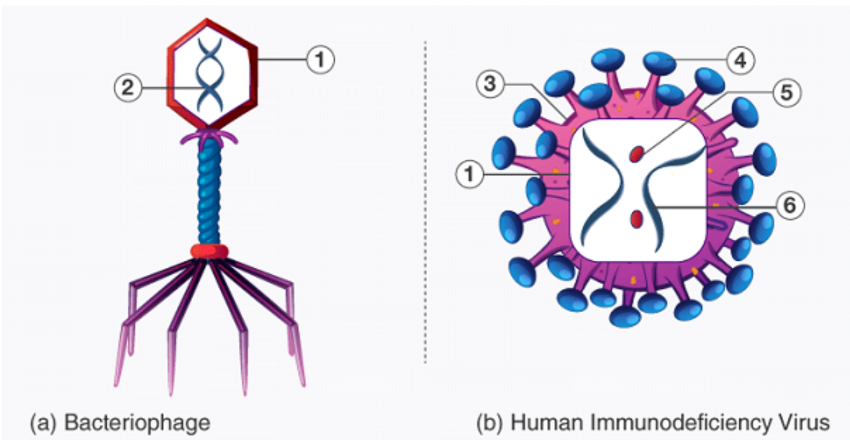

Figure 2: Structure of HIV[2]

Aim and Objectives

The objectives of the study are as follows,

- To evaluate the influence of nanotechnologies in treating AIDS.
- To understand the role of RBC as a carrier of drug delivery systems in the human body.
- To measure the process of RBC hitchhiking transfer into the vascular cells.
- To find out the role of nanotechnology to improve the vaccine delivery system to prevent AIDS.

Significance of the study

The study has a great significance to find out the severe effect of HIV on the immune system of the individual’s body. The particular research also helps to know the most accepted treatment therapies to reduce the effect of AIDS. In that case, nanotechnologies can be known as the antiretroviral therapy that showed a tremendous response against HIV [3]. The therapy takes a long time to reduce the effect of HIV, however, it has enormous potential in the prevention of the disease. The study is important because it will provide a brief concept about another treatment procedure named RBC hitchhiking.

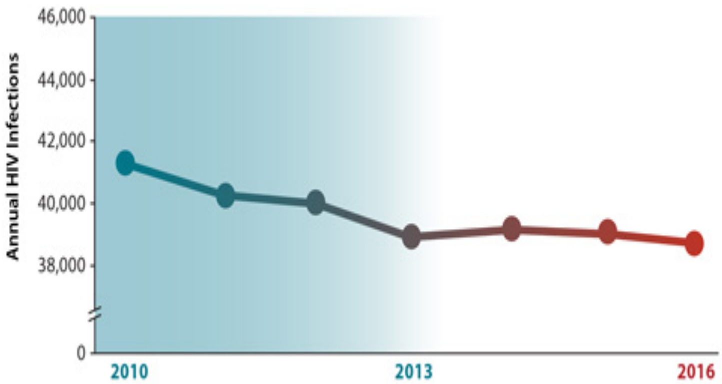

Figure 3: HIV prevention rate[3]

Literature review

Lifecycle of HIV

After entering the body, HIV generally targets attacking blood cells of the body and keeps attaching to it. In this context, it can be observed that the initial target for HIV is the T lymphocytes because those T lymphocyte cells are highly active and also coordinate with the other system of the body to build an immune system. The main component of T lymphocytes is the presence of receptors known as CD4. The receptors generally permit those receptors to attach and bind with the lymphocyte cells and in this way CD4+ complex system is formed by HIV[4]. One of the important characteristics of HIV is , it can store information such as RNA. After attaching to the receptors of T lymphocytes, the virus is generally responsible to release an essential enzyme called reverse transcriptase. In this way, HIV can successfully produce a copy of the Host's DNA and in this phase, the virus can easily mature because of the activity of the reverse transcriptase enzyme. In this phase of transmission, the formation of a huge amount of HIV inside the host's body can be observed due to the conversion of the virus's RNA into DNA material[47]. Mutation is the most accurate reason for the uncontrollable growth of the HIV inside the body of the patient and by that time HIV enhances their capacity to resist antiretroviral drugs. After that, the newly formed DNA copy of the virus can successfully infect the lymphocytes of the individual's immune system.

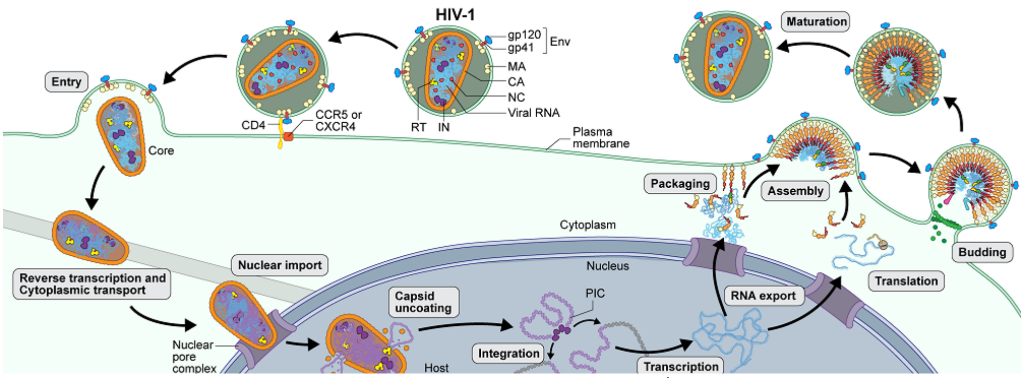

Figure 4: Life Cycle of HIV[4]

The activities of lymphocytes trigger the rapid growth of HIV through the replication process. On this note, it can be stated that every lymphocyte is capable of producing thousands of HIV and then the lymphocyte cells become destroyed through apoptosis. After a few days, the virus successfully contaminates every lymphocyte and after a few weeks, the blood and genital part of the infected person contains numerous HIV[5]. After the successful destruction of lymphocytes, the virus targets the other parts of the immune system. As a result, the body of individuals becomes weaker and it is not possible for the immune system to eliminate the virus from the infected person's body. The counting of the presence of CD4+ helps to understand the current phase of the infectious person's body. In that case, the maximum healthy individual contains 500 to 1000 CD4+ in the blood (Per microliter) [38]. A huge reduction of CD4+ can be observed after being infected with the HIV virus.

Issues in the current treatment strategy of HIV

After the discovery of the most life-threatening disease HIV, the effective vaccination system is still unknown for scientists all over the world. Issues can be seen in the trial and error process of drugs and the rapid failure of the process is the main cause to put more effort into proceeding with more clinical trials. The fundamental issues have been occurring in producing a vaccine for AIDS because the virus shows diversity in immune response and also in the sequencing process. The ineffectiveness of the method can be observed in the case of neutralising the effect of antibodies attached to CD4+ T cells [6]. Therefore, it is required to penetrate in the APC system to produce the response from T cell receptors. In this phase, complicated peptide molecules are generally processed and concentrated in MHC molecules and then it will be able to be introduced in front of CD8+ T cells. The trial and error phase depicts that, the fundamental challenges occur during the transportation of exogenous drug delivery. The drug is required to be capable of activating CD8+ cytotoxic T cells with the help of Cross presentation of the MHC class 1 process[38]. Hence, the emerging need of "cyto toxic delivery" of antigens with the help of cross presentation can be considered as one of the identical hurdles for manufacturing intracellular vaccines for HIV affected patients.

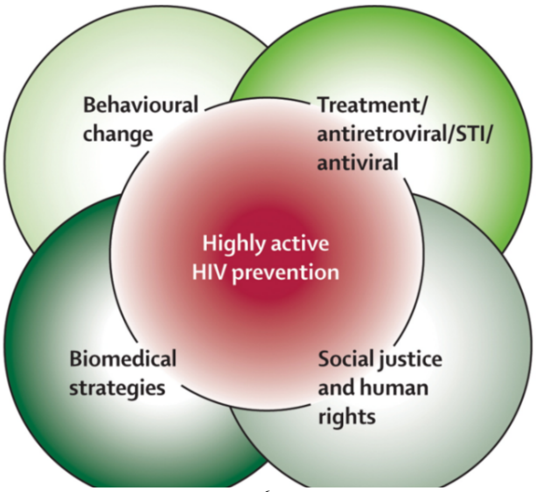

Figure 5: HIV prevention[6]

Recently, another technique has been used to treat AIDS and that is the HAART treatment method. In this process, total of 3 drugs is generally provided to the patients. Due to the poor compliance of patients, the HAART treatment process has been experiencing lots of challenges. Patients suffering from HIV should take daily medicines for curing the disease AIDS and sometimes patients forget to consume medicines[7]. The interruption of the medication process can lead to the chances of reinfection of HIV. Hence the formation of resistance of drugs is a diverse process due to the presence of various genes in HIV1. The virus is also capable of rapid mutation and sometimes failure can be seen in this process. The problem should be addressed through the individual drug testing method and it is also noticed that resistance testing pays an important role in evaluating the best combination for every patient. In contrast, side effects due to the rapid usage of medicines can be considered as another concern for the trial and error process[49]. After using various types of medicines, some patients may gradually form heart disease, cancer, early aging, diabetes and liver issues.

Influence of nanotechnologies in treating AIDS

The rapid utilisation of nano technologies may trigger chances for introducing a revolutionising treatment method for multiple life-threatening diseases such as cancer. In this context, it can be observed that , patients from all over the world who have been suffering from Cancer, got the best benefits from the nanotechnology treatment. The FDA also approved lots of clinical trials for cancer patients. One of the identical characteristics of nanotechnology is the improved water solubility capacity. After taking assistance of nanotechnology, it must be possible to transfer poorly soluble medicine into the tissue or cells of the patient's body. In recent years, nanotechnologies have been using in different fields of medicine and also show the same effectiveness[8]. It is the therapeutic process by which a totally controlled release delivery system can be formed. The major aim of using technology for treating HIV is to enhance the adherence capacity of the drugs. Such delivery systems of drugs can easily release some hydrophobic and hydrophilic properties in the small size cells and tissues of the body. Therefore, the therapeutic delivery system of drugs mostly aimed to attach with the CD4+ T cells and the macrophages of the infected person’s body. In this way, the immune system can carry the drugs to the brain and every corner of the body for higher effectiveness [50]. In this way, drugs can be easily discharged into the patient's body after analysing the effectiveness. Therefore, the strategy can be beneficial for controlling HIV after the successful implementation of an antiretroviral drug delivery system.

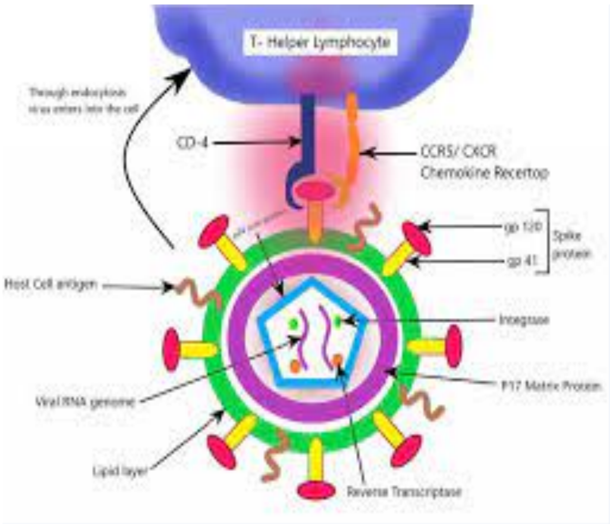

Figure 6: Drug Delivery system[8]

Macrophages are the main target for this therapy because macrophages are the key reservoir cells of the virus. On the other hand, it can be observed that HAART is the most recent way of treatment for the disease of AIDS. In this phase, there are a total of three doses of medicines that should be provided to the patient. However, the effectiveness of the treatment cannot be recorded properly due to the rapid failure. Multiple clinical trial and error procedures have been conducted to find out the most appropriate strategies to treat AIDS [9]. Due to the small size of the drugs in nanotechnology, the reaction of those drugs is also different from other conventional drugs. Some other advantages of nano technologies are proper control on the system of drug degradation, smooth delivery of transferring biological molecules such as peptides and proteins.

Role of RBC as a carrier of drug delivery system

RBC plays an essential role as a carrier of drugs in the whole therapeutic system because RBC can be easily available. The structure of the RBC cell can be considered as one of the simplest and the diameter of RBC is 6-7um. Red Blood Cells are generally homogeneous in nature and an average 10_{13} Number of RBC cells are present in average per microliter of blood[10]. One of the major characteristics of RBC is, it can flow rapidly through the vascular tissues. The Red Blood Cells are usually responsible to deliver carbon dye oxide and oxygen in the blood of human beings. In previous years, the RBCs are chosen for conducting the drug delivery system due to the high efficiency of RBC. Most of the drugs diffuse in the tissues of an individual's body via NCs transfer method. On the other hand, it can be observed that RBC does not have the property to extravasate apart from the "reticuloendothelial system"[52]. The RES system generally contains liver, bone marrow and spleen, hence the small or micro sized particles can easily move through the immune cells.

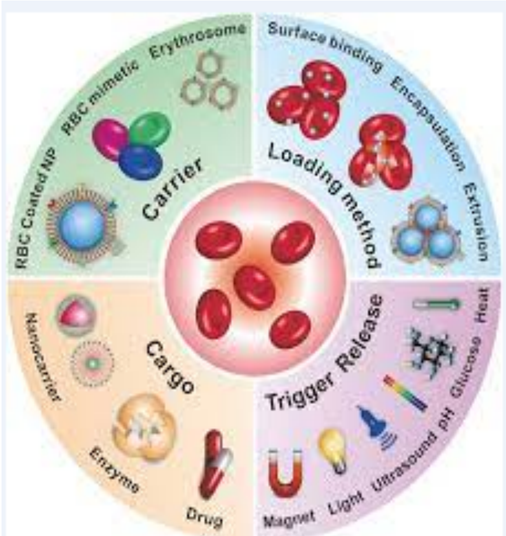

Figure 7: RBC and Drug delivery[10]

The elimination of external substances generally occurs by the RBC, white blood CELLS and NCs. The RES is naturally phagocytic in nature and also removes damaged RBC and other microorganisms. In addition, the hydrodynamic force of the Red Blood Cells enables reach at the centre of the vascular lumen and RBC can decrease the adhesion capacity of the negatively charged glycocalyx[53]. Multiple approaches have been generated at the time of conducting the encapsulation process of drugs. In a clinical perspective, the RBC-based Drug delivery research has entered depending on isolating RBCs through the drug loading process. In this process, a diverse range of drugs needs to be loaded into the isolated RBCs through a reversible osmotic swelling process[11]. The process mainly fosters the advantages of drug application by roaming into the bloodstream for a long time. After loading drugs in the RBC, those drugs may gradually mix with the plasma of the patient's body through the concentration method. The process can introduce new types of blood pool agents which can extravasate in a short time. Hence, after the application of the process, the oxygen carbon dioxide transfer within the organisms can be controlled by RBCs through circulation and the separation of Cargo from the patient’s body. There are different types of Cargo components present in the system such as enzymes, antigens, agents and probes.

Process of RBC hitchhiking

The particular study depicts that multiple testing by the other scientists has been done to achieve the isolation of RBC. Then injection was applied to the testing materials such as rats by the other scientist to find out the effectiveness of RBC to carry nanoparticles in the different parts of the body. After the testing, those scientists found that free nanoparticles were easily removed, whereas RBC bound nanoparticles were present there in the same manner. In that case, small substances do not have the capability to bind with RBC strongly and larger particles are showing a strong adhesion with RBC[12]. The chemistry of nanoparticles can be further evaluated after observing the results of In vitro testing by the other scientist. A viscometer can be considered as one of the important equipment that has been used in the Vitro process to measure the detachment rates. In this process, a scanning also needs to be done with the help of electron micrographs and that clearly indicates the formation of Dimples by the activities of nanoparticles[54]. It may trigger the increase of adhesion capacity of nanoparticles that help to build contact with RBC. After the RBC hitchhiking the nanoparticles remain in the system for a long time, however a sudden clearance of those substances leads to the formation of questions reading the effectiveness of the hitchhiking process[13]. After the total elimination of nanoparticles from the bloodstream, those attached RBCs are still present in the blood of the patient. In this context, it can be observed that, RBC hitchhiking can form the coating system for nanoparticles, henceforth phagocytic cells cannot engulf directly to these nanoparticles.

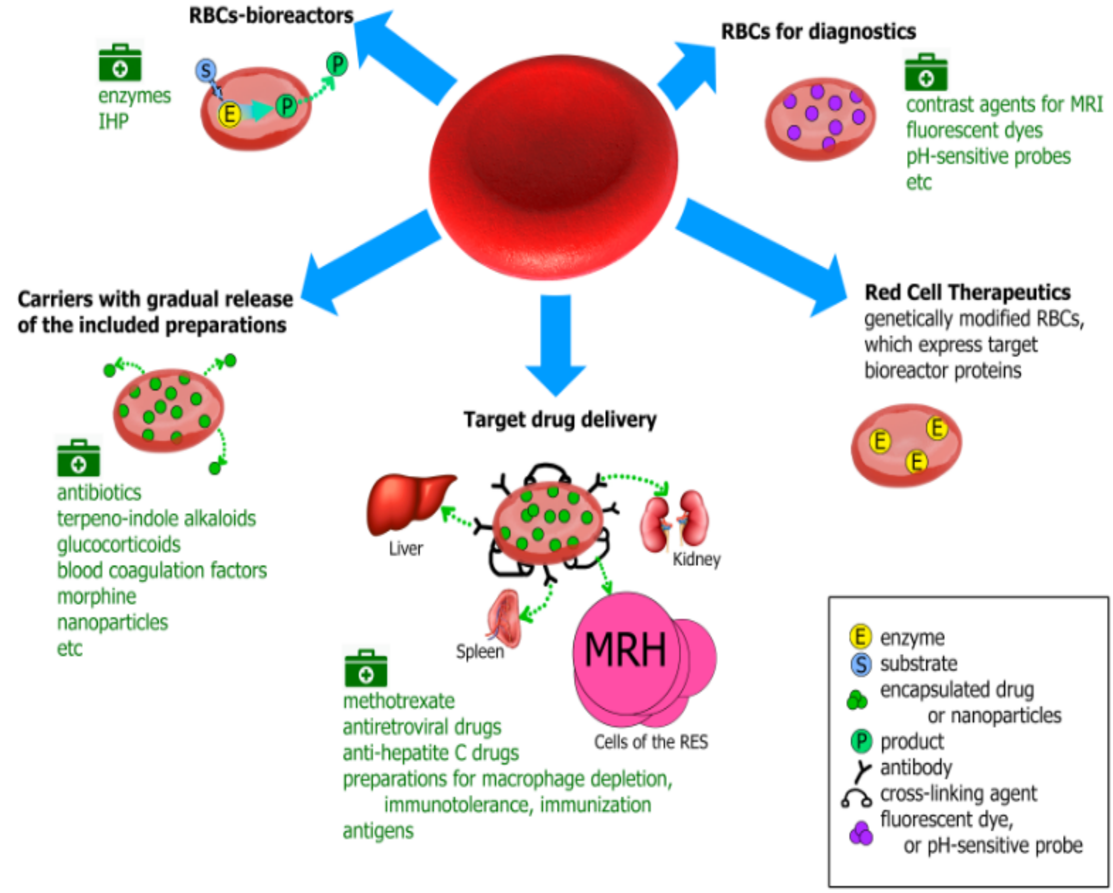

Figure 8: Process of RBC Hitchhiking[13]

The process of RBC hitchhiking builds a protection system for nanoparticles , so RES macrophages cannot remove particles from the surface of RBC. The previously mentioned mechanical forces are the main reason for the clearance of nanoparticles from the surface of RBC. The recent study helps to evaluate that the adhesion capacity of nanoparticles with RBC is mainly responsible for conducting the hitchhiking process[14]. The entire mechanism is regulated by two factors such as electrostatic interaction and also the hydrophobic interaction. In order to measure the detachment of RBC hitchhiking nanoparticles, a simple kinetic model can be beneficial for the evolution process. The tightly adhered nanoparticles have the tendency to work with greater amplitude and in that case alternation of biodistribution can be observed.

Role of nanotechnology to improve the vaccine delivery

The concept of using nanoparticles for the vaccination process has emerged after analysing the effectiveness of the system. In the previous years, a well organised controlled release system has been introduced for other multiple drugs. Delivering drugs through nanotechnology can enable the release of a huge number of antigens to generate long term immune responses. On the other hand, it can be noticed that nanoparticles are mostly responsible for the formation of antigen encapsulation structures to protect the antigens from other body fluids[15]. Nanoparticles primarily target the binding sites of APCs and it also binds with DCs to generate a strong immune response. It is the fundamental opportunity for the nanoparticles to deliver antigens inside the patient’s body. In recent years, progress can be observed in the part of designing nanoparticles for the effective delivery of drugs. In the case of direct presentation, the utilisation of nanotechnology helps antigens to attach to the surface and after the attachment, the immune response from B cells can be observed immediately. For establishing an active immune response for the prevention of the disease AIDS, it is necessary to build coordination between cellular and humoral responses[55]. The modern designs of nanoparticles have the capacity to act on both systems of antigens such as encapsulated DCs and also in the B Cells. However, continuous progress can be observed in the development of vaccines with the help of nanoparticles to treat AIDS.

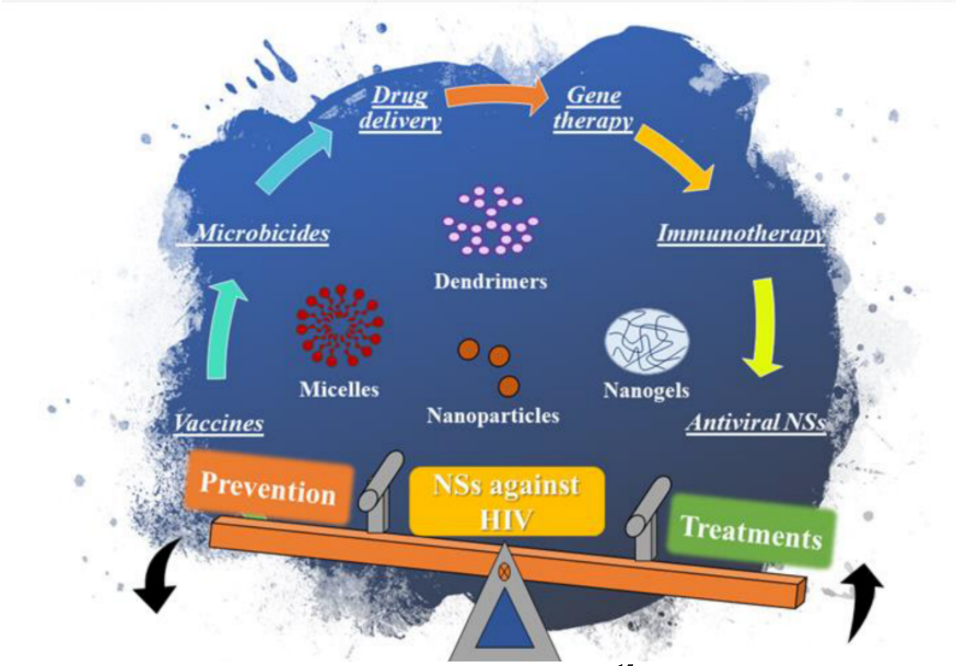

Figure 9: Nanotechnology[15]

The further investigation process illustrates that multiple lipid based systems can be beneficial for conducting the drug delivery for the patients. In this context, it can be observed that nanoparticles are mainly made up of "gamma glutamic acid" and a quantity of 120 gp protein can enhance the immunity of the targeted cells. The further application of these nanoparticles can induce a quick response from CD8+ cells[16] . In the other trial process, the rapid immunisation can be observed in the presence of gamma hPGA. In this way, nanoparticles are activating the specific antigens of CD8+T cells and conduct the encapsulation process. The presence of nanoparticles can generate more p24 serums as the form of antibodies and it can be denoted as a potent immunomodulator. The study clearly portrays that the efforts in the medicine trial process made huge progress in the vaccination system for AIDS. The future progress in this approach can be observed, after correcting some parameters such as ligand binding, targeting ligand, encapsulation, and surface density[56]. The betterment of the encapsulation process can lead to the formation of a well-designed vaccine delivery system for AIDS.

MATERIALS AND METHODS

Secondary data collection and analysis

The process of secondary data collection can be considered as one of the important ways to gather previously done research data. In order to obtain more knowledge or information regarding Nanotechnologies and RBC hitchhiking process, secondary data has been collected from some authentic journals. Moreover, journals were selected from the google scholar to avoid any kind of wrong information for this study. Anyone can get a huge amount of information on the internet and that data is free to access. Multiple researchers have published their works regarding these two therapeutic approaches and its connection with treating HIV[18]. The present study successfully took the assistance of this scholarly information to make the research content more authentic. After collecting secondary data, those information were properly analysed.

Method for nanotechnology

The current study has been done on the basis of the polymeric system, hence the drug rilpivirin (TMC278) has been used for the study by the other scientists. The drug TMC278 has the capability to stabilise the impact of TPGS1000 and Poloxamer 338[57]. The success rate of these experiments is not still confirmed, hence others decided to utilised both of these drugs on dogs and mice. After the application of those drugs, it can be observed that nanosuspension resulted at least three months in the case of dogs and only three weeks in the case of mice. Previously multiple studies have been done on the basis of nanosuspension and the stabilization has to be achieved with the help of a surfactant system made up of Lipoid E80[19]. In the case of the experiment process, macrophages were targeted and nanosuspension agents were loaded by the other scientist. After a successful injecting process, it can be observed that those drugs deliberately spread into the spleen, liver, and lungs of the experiment animal's body. As a result, experimented animals rats have gradually formed brain infections because of a sudden antiviral activity inside the brain. It will trigger the blood level up and the reaction of drugs is also seen within 14 days of successful injection of nanoparticles.

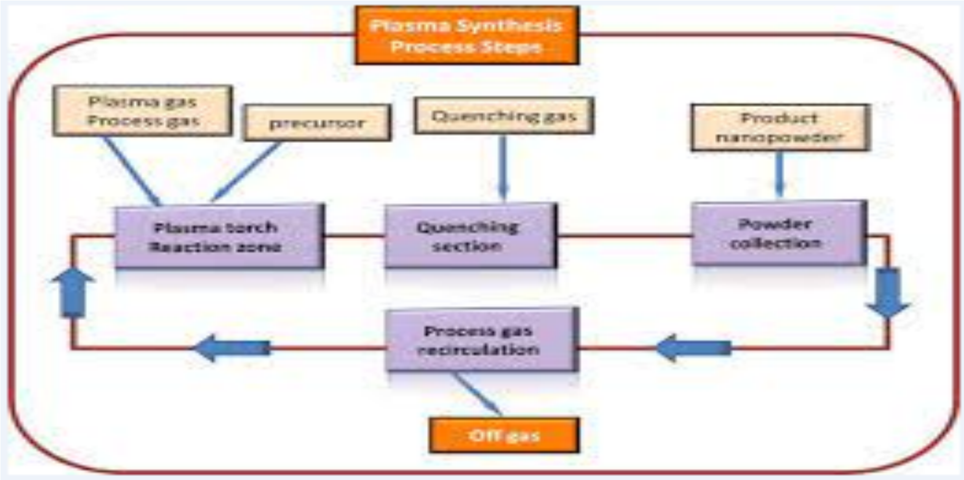

Figure 10: Process of Nanotechnology[19]

The previously done nanotechnological experiments have successfully proven that the level of drugs stay within the brain at least for 14 days. Hence the half-life of the dosage of indinavir was evaluated properly after the experiment. In this way, the further utilisation of drugs after targeting macrophages will provide a positive result and it can be further utilised in the case of in vivo process[20]. The drugs can be delivered to the brains of targeted animals with the help of nanotechnologies. On the other hand, another strategy has been used in nanotechnologies and it can be denoted as an antiretroviral drug delivery system. Macrophages can be considered as the fundamental reservoir cells of HIV and macrophages also have multiple receptors such as mannose, formyl peptide and galactose. These receptors can be used further for "receptor mediated internalisation" process and another drug named Stavudine also utilised for the research purpose by other researchers. After that encapsulation process was conducted with the help of various liposomes. The further conjugation process with galactose and mannose will lead to an enhanced rate of cellular intake. The drug Stavudine can be considered as a water soluble drug with a reduced half-life of serum[21]. In the case of enhanced uptake of drugs in the cells can act deliberately on the tissues of the experimental animals. It can be observed that liposomes are the key factor that can easily bind with drugs and depicts effectiveness. On the other hand, another drug Zidovudine was also applied to the experiment Animals and it can be noticed that the particular drug is almost insoluble in water and its half-life is 1 hour. The encapsulation of the drug was conducted properly before usage and it enhanced the localization process in the spleen and lymph nodes[58]. The finding of such experiments demonstrates that lots of nucleoside drugs also have a decreased number of serum half-lives. The dosage of these drugs such as zidovudine has the capability to stay 1 hour in the plasma. Hence, the nanotechnology experiments have targeted to enhance the half-life of these drugs for a better encapsulation process.

Figure 11: Nanotechnology for HIV treatment[21]

In contrast, the experiments in the human body were also conducted after utilisation of "mannose targeted poly dendrimer" and successfully delivered the drug known as efavirenz. In the case of experiments within the human body, those other scientists also selected macrophages in a different area of in vivo experiments[22]. The nanocarrier becomes folded in 12 , that enhances the uptake of drugs in comparison with the free drug. Another drug named lamivudine also utilised in the similar experiments in the case of in vivo process. After using the drug, it can be observed that the immune system of humans shows the higher rate of "anti-HIV activities". In addition, the other experiments were done after using "tetra peptide tuftsin" and were properly conjugated with the similar types of dendrimer to build a proper target mechanism for macrophage bound with efavirenz[23]. Hence the new experiment approaches have the capacity to promote a new framework for HIV reservoirs and in this approach the nanocarrier drugs were completely bound to peptide PEG and fMLF. The observation from the experiments demonstrates that fMLF targeted nanocarriers increase the drug intake in the different parts of the body such as kidney, spleen and Liver.

Method for RBC Hitchhiking

The RBC hitchhiking process incorporates NC cells and the effectiveness of both of the cells in case of drug delivery can be considered as one of the most significant approaches. At the initial phase, NCs cells were successfully loaded into the RBC and the water solubility of Red blood cells was properly checked after dipping it into a hypotonic solution for a long time[59]. RBC cells have numerous pores on the surface and those pores are mainly responsible for inducing the membrane of RBC to experience swelling . Due to the rapid osmotic swelling the size of RBC was enhanced up to 50 nm. In that case , larger components are mainly responsible for damaging RBC. On the other hand, it can be observed that , the binding activity between RBC and NCs is more stable and less traumatic in nature[67]. The further RBC hitchhiking method shows a better and positive result on treating HIV. In addition , other researchers have been showing interest in loading nanoparticles on the RBC carriers. Some of the approaches that facilitate the process of drug delivery are, magnetic resonance, imaging probes, isotopes and "ultrasound based drug delivery approaches" [24]. A recent success can be achieved in the drug delivery system after using RBC for the method. At the initial phase , the collaboration between NCs and RBC were combined to form a hybrid named DDS. primarily, the coating system of RBC needs to be accomplished with "Polyethylene Glycol"(PEG) and after the coupling process with RBC those drugs can circulate in the blood for a long time.

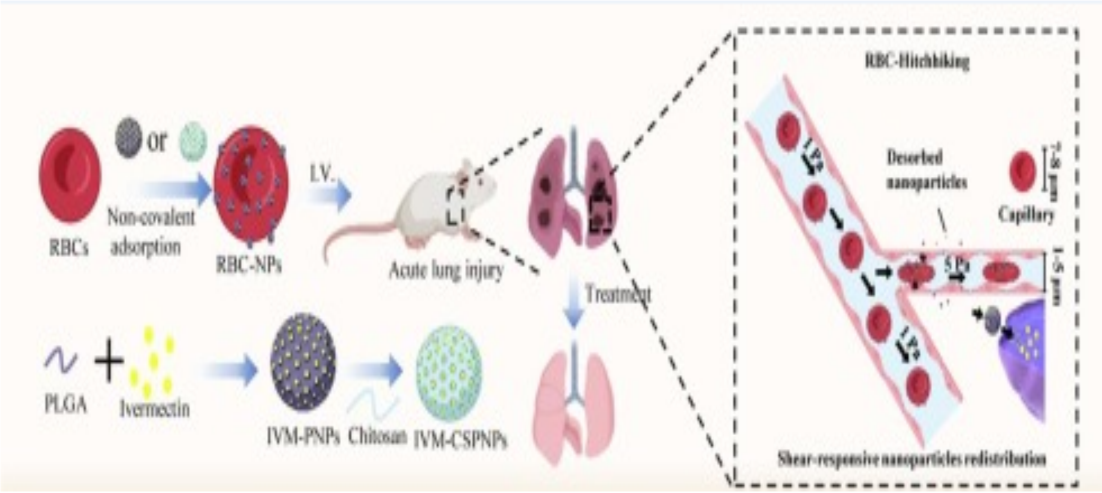

Figure 12: RBC Hitchhiking[24]

In contrast, it can be stated that the RBC hitchhiking process has the capability to alter the main characteristics of nanoparticles and is also responsible to enhance the half-life of the circulation process. The excessive intake of drugs by the lungs can be observed after the RBC hitchhiking process. The improved potentiality is one of the major characteristics of RBC and the entire system brought marvelous changes in the pharmacokinetics[25]. In the primary phase, RBC particles were isolated before starting the loading process. It can be considered one of the most novel approaches which includes the osmotic swelling of the RBC. The experimental approaches helps individuals to understand that penetration of peptides are necessary to transfer therapeutic agents into the carrier RBC. In the next phase, RBC becomes fused with drug loaded liposomes[60]. The process of drug encapsulation has been conducted by the other scientists through ex vitro or in vitro method. Osmotic swelling process plays an important role in the loading of RBC with selected drugs.

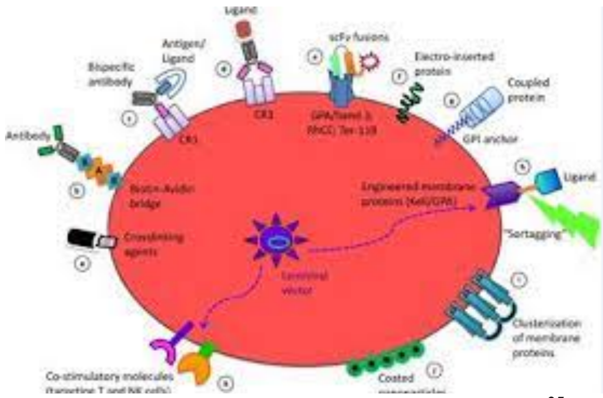

Figure 13: Red blood cell membrane process[25]

After washing RBCs, they are poured into the hypotonic solutions with fully loaded drugs. Washing is an essential step and it can enhance the capacity of RBC to load multiple drugs and then semi-automatic equipment can be used to proceed with the loading method. After conducting a proper washing, then RBCs can be infused in the patient's intravascular system. All these are subjected to RBC based clinical trials which have been showing a better result in the drug delivery system[26]. The RBC based hitchhiking process usually includes two distinct methods. The primary method is the encapsulation process into the RBC with the help of enzyme activities that will break into small substrates within the blood. These substrates are mainly responsible for detecting the toxic substances present in the blood. Further experiments illustrate that Encapsulated RBC can show the effectiveness and roam within the blood for a long time. Moreover, an encapsulated RBC can stay in the blood plasma, otherwise it may be engulfed by the macrophages.

DISCUSSION

From the above mentioned study it can be discussed that RBC hitchhiking is one of the novel approaches for the drug delivery system to treat AIDS. In recent years , RBC hitchhiking can be used as a nanocarrier technique to build a strong resistance system against HIV. Before starting the process, it is required to accomplish the surface loading of RBCs through the chemical conjugation method[66]. Further isolation can be possible after isolating RBCs in Ex vivo process. Newer technologies have achieved a significant growth in genetic engineering, by which artificial sequences can be created and exposed. As a result, the conjugation can be possible at the specific reaction sites[27]. In addition, nanocarriers should be observed by the RBC present in the circulatory system and it may trigger the formation if RBC hitchhiking. RBC is generally capable of carrying the agents which have already bound with the surface and then those agents need to be infused in the intravascular system.

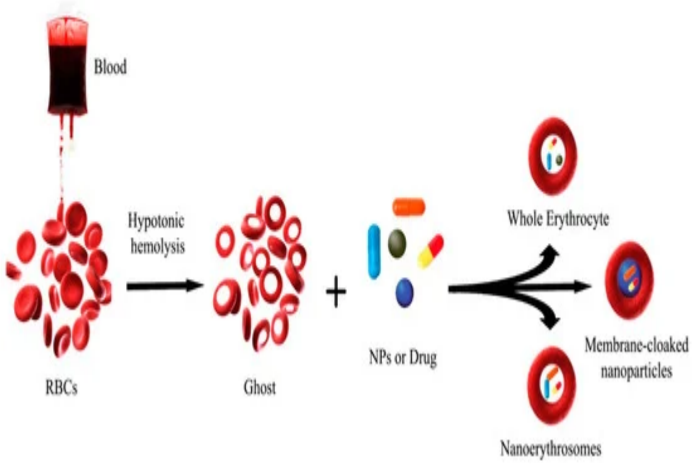

Figure 14: Encapsulation of RBC[27]

In other processes of drug delivery, conjugation can be noticed between carriers and drugs , sometimes both of them react with antibodies , ligands or peptides to bind with the surface of RBC. in this new and innovative approach , drugs should be selected properly and processed with specific protocols. Initially, surface loading processes need to be related with ex vivo protocols of RBC loading and in this phase RBC act as donor[2]. This particular process is destructive and also harms RBCs and loading should be hampered if proceed with this approach. The second step is a simple injection put into the intravascular membrane of the HIV patients. As a result, RBC immediately targets the nanoparticles and binding procedures start instantly in the circulatory system of the patient's body. Therefore, the drug delivery system based on the process of surface loading is an effective approach and the redistribution of particles or agents can be possible[29]. The process enhances the activities of the phagocytic cells and the activities of phagocytic cells also include the area of vascular endothelium and hepatic sinuses. These RBCs bound with drugs can successfully regulate body fluids , inflammation and also capture the external pathological agents.

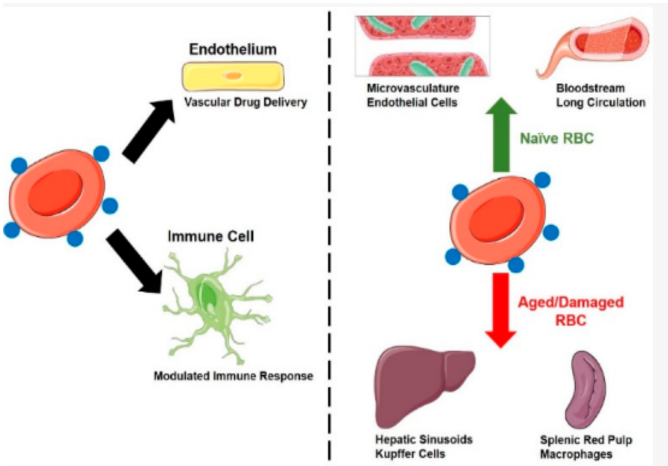

Figure 15: Surface loading before RBC Hitchhiking[28]

On the other hand, the developed drug delivery method based on RBC can be further altered and the affinity of drugs on multiple therapeutic sites can be further modified. In the other experiments RBCs can be further bound with antibodies and study can be conducted through in vitro and in vivo process. In case of forming a strong immunity against HIV, it is required to test the activity of leukocytes[30]. Hence, RBC was also used in targeting diverse cells such as endothelial cells, leukocytes and smooth muscle cells. The persuasion for RBC loading process has been conducted for both anti-inflammatory and antithrombotic agents. The presence of fibrinolytic agents can be considered as a threat factor for the experimental animals and it may lead to the formation of stroke, hypoxia, or trauma in the brain.

The encapsulation process for RBC may lead to the surface loading process that can modulate immediate response for the host immune system against some external particles such as HIV. During the phase of loading drugs into RBC, it can successfully detach cargoes from the surface of the body. Therefore coupling with the surface area of large RBC can hinder the ability of drugs during the interaction with receptors[31]. Additionally, drugs attached with RBC are generally impacted by RBC glycocalyx. The loading method of drugs with RBC can deliberately modify the pharmacological profile. RBC are naturally featured with some innovative engineering methods in which it can reduce immunogenicity. The term immunogenicity can be further explained as a process to camouflage the properties of allogenic erythrocytes and form RBC for the universal usage purposes. In this process polymer coagulation is one of the necessary approaches to accomplish the conjugation process with RBC surface[42]. There are different types of polymer that can be seen in this process such as "polyethylene glycol" (PEG) and "hyperbranched polyglycerol". For detecting antigens the RBC and PEG become combined after the utilisation of "glycophorin A epitopes" .

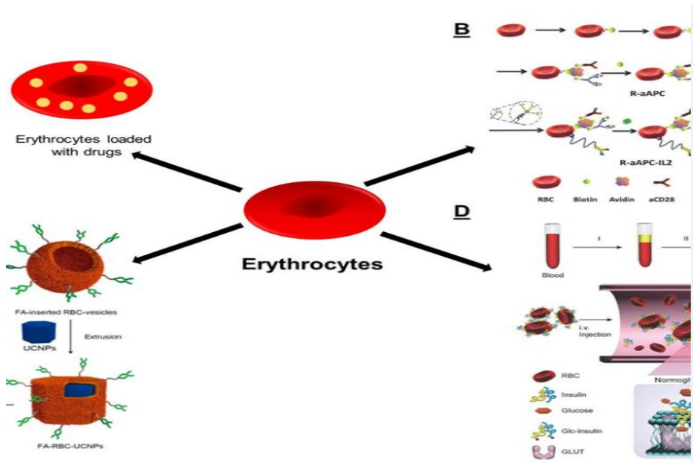

Figure 16: RBC loading process[31]

RBC demonstrates an unique feature from the overview of engineering and it can be observed that RBC at their mature phase permits the attachment process of immunomodulatory drugs. These drugs can rapidly switch in various phenotypes without changing the physiological functions. Cell based therapies can be introduced based on such characteristics of RBC, and macrophages are mainly responsible for showing switching phenotypes due to the progression of the disease[32]. Additionally, RBC can reach to every part of the body and even within the tissue, henceforth a tissue based therapy can be evaluated after optimising the parameters of the injection process. Different types of biochemical properties can be observed within the structure of RBC and these factors allow RBC to conduct the squeezing method in the blood vessels. In this way, RBC can set its targets in capillary bed and vascular endothelia. The presence of immune characteristics within RBC introduces an opportunity to form coupling and then it leads to the physical absorption of some complex particles such as bacteria or virus. After detecting the presence of antigens, RBC immediately transfers to those antigens inside the spleen[33]. In this way, immunological intervention can be possible against the life threatening virus HIV. One of the identical approaches is the rapid absorption of nanocarriers in the surface of RBC, which is specifically known as the RBC hitchhiking process. In this case, a formation of non-covalent bonding can be further noticed between the membrane of RBC and nanocarriers. Some of those best possible interactions are hydrophobic or electrostatic interaction. The above mentioned interactions helps to conduct successful binding with different types of nanocarriers such as natural and synthetic substances[65]. Additionally, the RBC hitchhiking process can enhance the circulation time after successfully decreasing the number of nanocarriers from the "reticuloendothelial system.

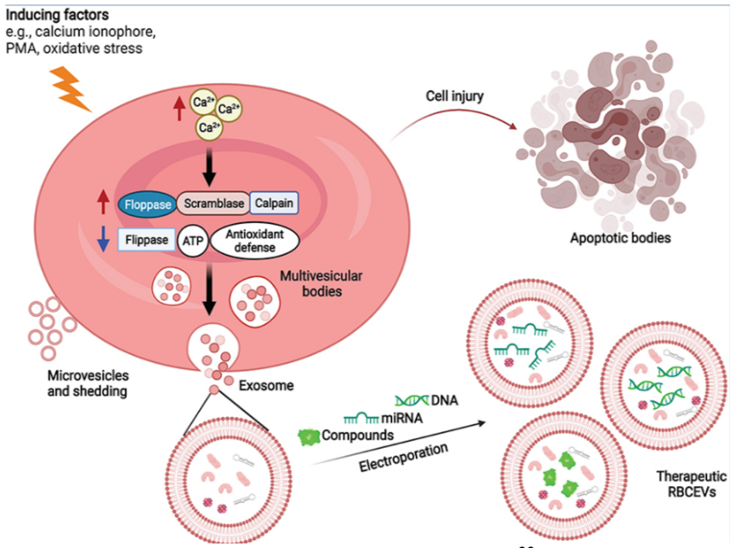

Figure 17: Activities of RBC[33]

After observing the effect of drugs in the extra vascular system, it can be stated that drugs need to overcome multiple constraints to enter in the circulation process. After entering into the circulatory system, drugs can easily move in the tissues through blood. This process can be known as distribution Some drawbacks of the distribution process include diffusion, active transport, binding of cells and vascular permeability[34]. If the perfusion capacity of the tissue is high then blood flow should be smooth in the circulatory system. In order to form proper drugs for any disease , it is required to understand different characteristics of drugs. For instance, it can be stated that the RBC hitchhiking method can target the nanocarriers which belong to the chemotherapeutic drug family and the RBC hitchhiking method can improve "the anti-tumor efficacy".

Additionally, the study has aimed to improve the current antiretroviral therapy; hence it is required to evaluate some alternative methods to control HIV. Gene therapy can be considered another alternative to decrease the rate of replication of HIV. Some other nucleic acid substances such as RNA, ribosome, proteins and DNA can also be utilised in interfering the replication of virus[35]. All types of treatment procedures are just going through some trial and error stages, hence gene therapy also can be taken as another trial process of clinal therapy. The recent studies help individuals to evaluate that gene therapy is at the phase II and it depicts that the further transferring of genes is a safe and secure method for the HIV affected individuals. These efforts play an essential role to find alternative innovative approaches for the treatment of AIDS. During the gene therapy, the indicators showed that virus genes contain toxicity and that may lead to the formation of sudden mutagenesis in the cells of the HIV patient[36]. Some emerging limitations for the experiments have triggered the need for further investigation for the gene delivery by using nanotechnology platforms. The component RNAi contains a huge potential for the therapeutic effect against HIV[61].Gene silencing can be considered as another approach which can act on the double stranded RNA and also capable of destroying mRNA. In the process of gene therapy, the RNA can further set its target to other stages of the Virus life cycle. In order to arrest the site of replication if Virus genome, the gene therapy mainly targets CD4 genes. In the early phase of the treatment process, the delivery method of non-viral SiRNA in the body of HIV is one of the necessary approaches[37]. In this method encapsulation has been done with the help of a peptide and a RNA binding domain. In Vivo processes need to be accomplished properly to transfer siRNA within the T cells . In that case, CD8 and CD4 showed the response against the cytotoxicity created by the reaction of HIV.

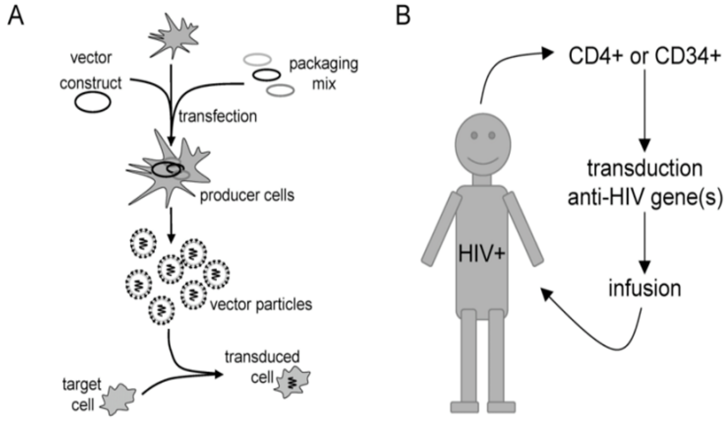

Figure 18: Gene therapy for HIV[36]

On the other hand, it can be observed that the fundamental role of HIV is to attack the immune system of individuals, so that the body cannot respond against the activity of Virus. Nanotechnologies also focused on some alternative therapies and it can be noticed that "immunotherapy" is one of them. The major aim of the immunotherapy process is to deliver immediate response against the virus genome and its effect in the host body[38]. The response of cytotoxic T cells can be easily observed in the body of the host cells, however the activities of B cells are absent in that case. Due to the long time presence and reaction of Virus in the patient's body CD4+ cells become inactive in nature. In this context, the fundamental impact of HIV can be measured with the losing cells of CD4+. These cells can be further known as T helper cells, which are usually utilised by the immune system for the support process [39]. The rapid loss of response by the immune system of the patient can cause the formation of immunosuppression. Immunotherapy can be known as a therapeutic method which incorporates the usage of immunomodulatory agents to build a strong response against a deadly disease such as HIV/AIDS. Cytokines play an important role in immunotherapy and it can be sent to the host body after detecting the presence of antigens. Some commonly used cytokines are IL2 and IL 15, hence the newly developed immunity required the presence of more antigen presenting cells or APC to induce the effect of CD4+ and CD8+ cells [40]. The commonly known APC is dendritic cells which are mainly responsible for developing antibodies against the Virus toxic substances. Maximum clinical trials for immunotherapy has been done in the Ex vivo DCs. In this way, new therapies of nanotechnology have successfully attracted the attention of other scientists from all over the world. Lots of opportunities can be detected by those researchers in the utilisation of target based nano technology for achieving immense immune response against HIV[41]. Despite all these nanotechnological therapies, it can be observed that RBC hitchhiking is one of the widely accepted therapies for delivering drugs in the patient's body. The particular drug delivery system does not require complexity and only an injection process needs to be followed to inject selected drugs within the HIV affected patient's body.

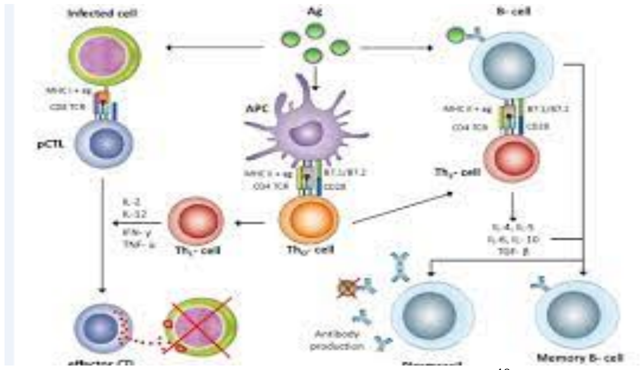

Figure 19: Immunotherapy for HIV[40]

CONCLUSION

From the above study it can be stated that AIDS is one of the life threatening and and there is no appropriate medication or curing therapy available to suppress the effect of HIV. In that case, modern studies have found that RBC hitchhiking is one of the novel approaches for drug delivery. RBC can easily reach into every tissue of the host's body. Hence binding nanoparticles with the surface of RBC can move freely in the body of an infected person without any chances of getting attacked by the macrophages [62]. The study depicts that the process of nanotechnology can prevent the disease HIV with the help of multiple approaches. In this way, treatments can be easily improved after using a proper nanotechnology platform for transmitting antiretroviral drugs. Patients suffering from HIV can easily generate an immune response and nanoparticles can successfully bind with those drugs. The experiment methods demonstrated that ligand binding is the major activity of nanoparticles and some of those ligands are galactose and mannose, fMLF and tuftsin. All these ligands generally target the macrophages present in the immune system and it can be observed that macrophages are the main reservoirs of the virus HIV [63]. In the future perspective, scientists from all over the world have targeted more than 2 or 3 drugs in the process of nanoparticle systems. The effectiveness of this method can be seen in nanotechnology therapy and the further research will cover the area of delivering both hydrophilic and hydrophobic drugs in the genes of the HIV patients. These experiments can successfully portray the versatility of the antiviral drugs. On the other hand, nanoparticles have the ability to reduce the rate of replication of HIV in the human body. Moreover, some other nanoparticles such as dendrimers and "inorganic nanoparticles" can also enhance the antiviral effects of different molecules to build a strong immunity against HIV.On the other hand, the study also helps individuals to understand that RBC hitchhiking is another innovative approach for strengthening the drug delivery system for the near future. Some fundamental characteristics of RBC are uniform, large, degradable, large circulation rate and an appropriate carrier. In comparison to NCs, RBC are more preferred to conduct the hitchhiking process. Hence, biomedical researchers have shown interest to combine two approaches to form an innovative drug delivery system [64]. After association of NCs with RBC, the combination showed an impactful outcome and it will foster the vascular counterparts. Cells such as RBC and Nc demonstrated an effectiveness in the hitchhiking process to develop immune cells. The highly active immune cells are then able to modify some other type of stem cells into progenitors. Additionally, RBC has specific features to activate leukocytes and platelets to deliver drugs to every corner of the body. Platelets can successfully transfer oxygen and carbon dioxide at the site of blood clotting. The cooperation between RBC and NC can be considered as one of the challenging factors because of diversity, and complexity. At the initial phase, the RBC hitchhiking method was conducted on mice and lots of questions formed regarding the RH purpose. In the case of multiple species, the size of capillaries and RBC's were mismatched. Lots of differences in the size of cells can be observed between the RBC size of humans and mice. In this way, a successful drug delivery system with the help of RBC hitchhiking was formed by the biomedical scientists to reduce the impact of HIV.

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