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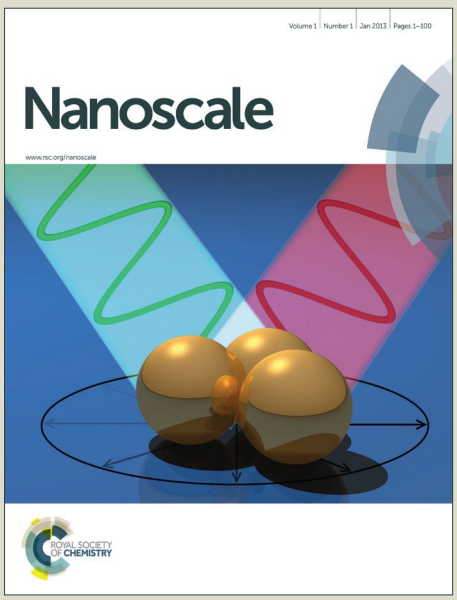

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Cite this: DOI: 10.1039/c0xx00000x

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Featured Article

Smart nanoparticles as targeting platforms for HIV infections

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

While Human Immunodeficiency Virus (HIV) infections are reducing in incidence with the advent of Highly Active Anti-retroviral Therapy (HAART), there remain a number of challenges including existence of reservoirs, drug resistance and anatomical barriers to antiretroviral therapy. To overcome these, smart nanoparticles with stimuli responsive release are proposed for delivery of anti-retroviral agents. The paper highlights the strategic similarities between the design of smart antiretroviral nanocarriers and those optimized for cancer chemotherapy. This includes the development of nanoparticles capable of passive and active targeting as well as those that are responsive to various internal and external triggers. For antiretroviral therapy, the relevant triggers for stimuli responsive release of drugs include semen, enzymes, endosomal escape, temperature and magnetic field. Deriving from the experience of cancer chemotherapy, additional potential triggers are light and ultrasound which remain hitherto unexplored in HIV therapy. In addition, the role of nanomicrobicides (nanogels), and virus mimetic nanoparticles are discussed from the point of view of prevention of HIV transmission. The challenges associated with translation of smart nanoparticles for HIV infections to realize the Millennium Development Goal of combating HIV infections is discussed.

Background

According to the World Health Organization, globally, 35 million (33.2 million–37.2 million) people were living with Human Immunodeficiency Virus (HIV) at the end of 2013.[1] 1.5 million people died of Acquired Immunodeficiency Syndrome (AIDS)-related illnesses worldwide in 2013.[1] However, in spite of the obvious despair that shadows these numbers, there have been significant reductions in the incidence of HIV infection. The number of adults and children who developed HIV infection in 2013 was 2.1 million (1.9 – 2.4 million) which plummeted from 2.5 million (2.3 – 2.7 million) in 2009.[2] These trends bear testimony to the tremendous strides made in achieving the objectives set by the Millennium Development Goals towards combating HIV/ AIDS and the 2011 Political Declaration on HIV and AIDS, both of which have the year 2015 as an important milestone year in halting and reversing the spread of HIV.[2, 3] In addition to the policy decisions and the immense planning that went into these programs worldwide, these achievements were possible due to the implementation and the reach of Anti-retroviral therapy (ART).[2, 4]

In fact, ART has been responsible in reducing the number of people acquiring HIV infection globally by 20% between 2001 and 2011.[4] Even in countries with a very high burden of HIV infection, ART has led to a decline in AIDS-related mortality rates.[4] The use of ART has been expanded to include the use of more potent regimens with multiple drugs from different classes termed as Highly Active Anti-retroviral Therapy (HAART) or Combination antiretroviral therapy (cART).[5] In the decade spanning from 2002-2012, scaling up of ART on a global scale has saved 4.2 million lives in low- and middle-income countries.[4] However, there still exist major challenges in the fight against HIV infections as the present day treatment is limited by the emergence of drug-resistance, toxicity, poor access to reservoirs, limited role in prevention and a limited ability to cross physical barriers like the blood brain barrier.[6]This has led to innovations in the treatment of HIV infections leveraging platforms developed using nanotechnology.

Nanomedicine has found applications in the diagnosis and treatment of several diseases with a major emphasis on cancers. Nanoparticles have the potential to address the draw-backs and limitations associated with the treatment of HIV infections. 'The present article features various nanotechnology platforms and strategies that can improve the efficiency of current antiretroviral therapy and address the challenges of viral reservoirs and drug resistance, the issues in their clinical translation and putting the future in perspective with the advent of these technologies.

Challenges of HIV infections

The etiologic agent of AIDS is HIV which is a human retrovirus belonging to the family Retroviridae and the subfamily of lentiviruses.[5] HIV is roughly spherical with 120 nm diameter and is composed of two-copies of positive single-stranded RNA, with approximately 10,000 nucleotides long genome.[5] This is converted to DNA by virally encoded reverse transcriptase.[5] The present day treatment of choice for HIV/AIDS referred to as HAART or cART[5] has proved to be quite successful and recorded

marked declines in the incidence of most common AIDS-defining conditions like recurrent bacterial pneumonia, tuberculosis, and pneumonia due to the unicellular yeast-like fungus *Pneumocystis jiroveci*.[5] What lies at the heart of HAART is the use of combination of drugs from different classes that are characterized by different mechanisms of actions.

The major classes of these antiretroviral agents include Nucleoside/Nucleotide reverse transcriptase inhibitors (NRTIs); Nonnucleoside reverse transcriptase inhibitors (NNRTIs); Protease inhibitors (PIs); Fusion inhibitors, Entry inhibitors and Integrase inhibitors.[5]

It is the cocktail of these drugs that are used for the treatment of patients with HIV/AIDS as a part of HAART.[5] However, in the post-HAART era, there are a number of challenges faced in the treatment of HIV infections. One of them is the fact that HAART is not devoid of side effects ranging from nausea, headache and diarrhea to more serious ones like peripheral neuropathy, pancreatitis and mitochondrial damage (in NRTIs) that can lead to liver conditions like hepatic steatosis and lactic acidosis.[5, 6] This is coupled by the fact that the daily dosing specimen is cumbersome and leads to reduced compliance by the patients.[6] These issues with drug therapy in HAART highlights a pressing need for innovations in delivery systems for HIV therapy. Presence of anatomical barriers like the blood brain barrier and the blood-placental barrier limits bioavailability to critical areas like the central nervous system and the growing fetus in an infected mother. Also, HIV resides in "sanctuaries" in the form of anatomical and intracellular reservoirs which result in latent HIV infection in spite of aggressive chemotherapy. Besides these, HIV is no exception to the increase in drug resistance as seen in chemotherapy for other diseases. These challenges are outlined in Fig. 1.

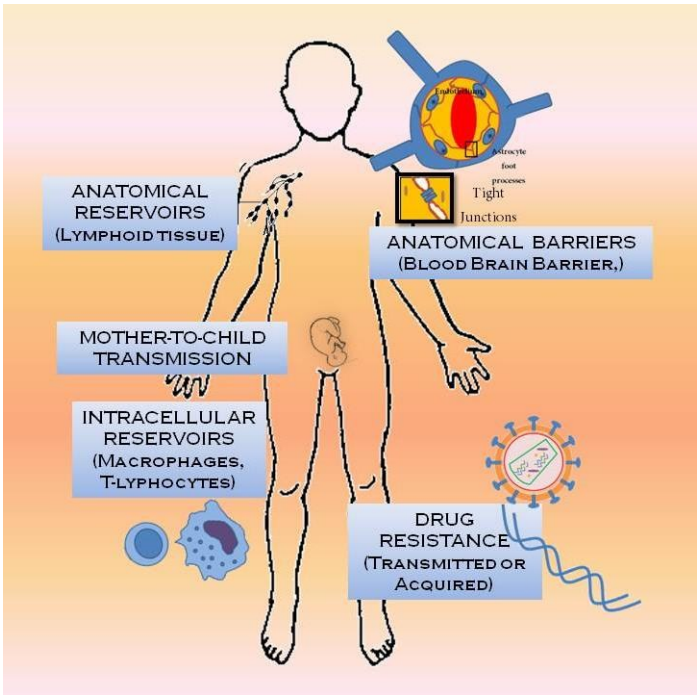

Fig. 1: Barriers in treatment of HIV infections

Reservoirs

HIV is known for its long period of latency. This is achieved to a certain extent by the formation of reservoirs or sanctuaries. Reservoirs exist in two distinct forms- intracellular reservoirs and anatomical reservoirs.[7] The challenge that HAART faces is that these areas are difficult to access by the conventional anti-retroviral agents as well as by the body's immune system.[7-9] This leads to latency of the viruses even after HAART and later can lead to the relapse of HIV infection.[7]

Intracellular Reservoirs

The intracellular reservoirs are the resting CD4+ T-lymphocytes and the macrophages.[5, 7] The CD4+ T-cells are responsible for "post-integration latency" where the HIV provirus stably integrates into the cellular genome but remains latent until an activation signal ultimately results in an infection.[5] On the other hand, cells of the monocyte lineage exhibit low cytopathic effects by HIV in spite of the fact that HIV replicate extensively in these cells. Hence, like the CD4+ T-cells, monocyte-lineage cells like tissue macrophages act as reservoirs of HIV infection.[5] Other similar reservoirs include follicular dendritic cells.[9] Recently, a widely debated "shock and kill" approach has been suggested by Archin *et al.* using the histone deacetylase inhibitor, vorinostat (suberoylanilide hydroxamic acid, SAHA) to increase HIV RNA synthesis, the infected cells would then be killed either by the virus itself or by the patient's immune system.[10, 11] This has been proposed to be supplemented by an intensified HAART to protect the uninfected cells from the infection.[10, 11] The debates surrounding the provocative treatment-based study include ethical concerns, increased cost and need for leukapheresis, limited subset of population responding to vorinostat and drug

toxicities.[11] This calls for better technologies that are safer, affordable and accessible.[11]

Anatomical Reservoirs

HIV latency is also due to anatomical reservoirs comprising of secondary lymphoid tissue, testes, liver, kidney, lungs, the gut and the brain.[6, 9] These areas are again difficult for anti-retroviral agents to enter.[6] Besides, the abundance of viruses in the lymphoid tissue allows easy access for the virus to the susceptible cells leading to persistence of infection.[12]

Drug Resistance

Even during antiretroviral drug therapy, there is a possibility of replication of HIV. This is referred to as HIV Drug Resistance (HIVDR).[13] HIVDR is categorized into the following: a. *transmitted resistance*, when there is transmission of a drug-resistant virus in a previously uninfected individual;[13] and b. *acquired resistance*, in patients receiving ART where a Darwinian model of continuous selection is followed to tide over the pressure of drugs, allowing the survival as well as replication of only those viruses which are able to alter themselves.[13, 14]

Reverse transcription in HIV is error prone with an average introduction of one mutation for each viral genome transcribed.[14] Also, HIV has a replication rate of the order of 10^{10} virons per day which lead to a large number of mutations.[14] The resultant viral quasi-species with one or more mutations are diverse as compared to the wild type HIV.[14] Resistance to ART and subsequent rapid replication is the resultant of these numerous mutations that take place in the quasi species in the presence of pressure of drugs.[14] These mutations can be in the form of base substitutions, duplications, insertions and even recombinations.[14]

The resistance to HIV infections can be detected either by *genotypic testing* which is essential for prediction of resistance or by *phenotypic testing* which measures the actual susceptibility of the patient to specific drugs using recombinant or using viral cultures from patients.[14] The recent data show that between 10 and 17% of ART-naive individuals in Europe, the United States, Japan and Australia have drug resistance to at least one antiretroviral drug while the acquired drug resistance is much higher at around 80% for at least a single drug.[13]

The development of resistance is an important challenge in the treatment of HIV as it results in failure of treatment, use of costlier second- and third- line treatments and spread of drug resistant HIV.[13] This warrants for novel strategies that can tackle drug resistance and help in the better treatment of the infection.

Anatomical Barriers: Development of "drug sanctuaries"

Blood-tissue barriers form important anatomical barriers that help limiting the penetration of toxic and infectious agents into these vital organs.[15] With respect to the management of HIV infections, these barriers limit the anti-retroviral drug penetration.[15] It results in the development of partial "drug sanctuaries" in the central nervous system, the retina, and the testes which possess such anatomical barriers.[15] Another important area where the "drug sanctuaries" are developed is the placenta which is otherwise a barrier between the fetal and maternal circulations but also prevents the entry of drugs into the fetal circulation.[16] This barrier has serious implications in the maternal to child transmission of HIV.[16] Blood-tissue barriers form important anatomical barriers that help limiting the penetration of toxic and infectious agents into these vital organs. In other cases, barriers in drug delivery may lead to reduced absorption of other drugs due to conditions like malabsorption, thus limiting the bioavailability of lipid soluble drugs.

Blood Brain Barrier (BBB)

The CNS, a critical anatomical reservoir, is mainly sheltered by the blood-brain barrier (BBB) which can cause considerable hindrance in drug penetration to CNS. Blood-brain barrier is comprised mainly of the tight junctions between endothelial cells of brain capillaries and the astrocytes with their vascular processes that surround most of the outer surface of these capillaries. Before molecules in the blood can enter neurons in the CNS, they may have to pass through both the endothelial cells and the astrocytes.[17] Paracellular movement of molecules between epithelial cells when restricted, the molecules take the transcellular route and pass through the epithelial cells. Molecules that can successfully achieve this include nonpolar molecules (oxygen and carbon dioxide), organic molecules (alcohol and barbiturates) that pass through phospholipid components of the plasma membranes of the capillary endothelial cells while ions and polar molecules require ion channels and carrier proteins in the plasma membrane. [17, 18] This selectivity of the brain through the blood brain barrier is of great importance in warding off infections to the brain. The main work of BBB is to isolate the brain from the circulating blood and that of blood-CSF barriers is to control the molecules and cells passage in to the CSF.[19]

Placental barriers: implications in Prevention of Mother-to-child transmission (PMTCT)

The placenta allows the exchange of gases, nutrients and waste between the fetal and the maternal compartments while preventing the exchange of drugs and xenobiotics.[16] One of the goals of present day efforts against HIV is to eliminate new infections among children by 2015 and keep their mothers alive.[3, 4] This is the key component of the "prevention of maternal-to-child transmission" of HIV from an HIV-positive mother to her child during pregnancy, labor, delivery or breastfeeding. This is achieved by anti-retroviral treatment to the nursing mothers to reduce the viral load in her blood and genital secretions. A rather novel approach is to use drugs which can cross the placenta to reach the amniotic fluid and the fetal circulation to provide early protection to the fetus.[16] This however, has limitations and only few drugs are able to do the same. Notable among these are raltegravir and nevirapine using the passive as well as active transport across the placenta.[16] This critically blocks many anti-retroviral agents to cross the placenta and help in PMTCT. However, many more strategies to increase the efficiency of drugs that prevent mother to child transmission are desirable.

Strategies for designing nanoparticles for HIV

Nanocarriers are of organic or inorganic origins including but not limited to lipids, protein, polymers, dendrimers, carbon nanotubes

and inorganic materials like gold and silica.[8, 20] Nevertheless, they need careful fabrication for them to act as aids in the therapeutics of diseases like cancer and HIV/AIDS.[20] Nanocarriers carry these in the form of payloads which are encapsulated, complexed or chemically conjugated with them.[8, 20]

Criteria to be fulfilled for nanoparticle platforms in HIV infections

The rapidity of replication of HIV depends on the drug resistance conferred by mutations in the HIV, the prevalence of the resultant quasi-viruses in the patient and finally on the level of drug reaching the site of HIV and its reservoirs.[14] The design of the nanoparticles for addressing the challenges of treating HIV infections require the alteration of the bioavailability and pharmacokinetics of the drugs allowing increased accumulation and targeting in the reservoir sites while overcoming drug resistance by bypassing the effects of cellular efflux pumps. Further, there is a need for needle-free, technologies for long term delivery of drugs which are stigma-free in order to ensure increased compliance. Smart nanoparticle platforms are being developed with these characters to provide advantage over conventional chemotherapy.

Strategies to facilitate intracellular uptake and transport at reservoir sites

The CD4+ T cells and macrophages are intracellular reservoirs for HIV-1, which are preferred locations of the virus. In an attempt to develop a safe and potent alternative for the presently available treatment options, it is necessary to target these reservoirs that prevent the entry of ART. To achieve this, nanoparticles must be targeted to activate primary human CD4+ T lymphocytes, macrophages, and other intracellular reservoirs. CD4 is one of the most common examples of targeting used in targeting of intracellular reservoirs. Endsley and Ho used CD4 targeted lipid nanoparticles for selective binding to CD4+ cells and efficient transport of indinavir to these cells. Thus, strategies can be made to reach the reservoirs and better deal with HIV infections and relapses arising out of conventional therapy.[21]

Macrophages are also attracting more attention in recent years as targeted cells.[22] One such formulation demonstrated by Kovochich *et al.* in a humanized mouse model, involved the use of a nanoparticle loaded with bryostatin-2 (protein kinase C activator) and nelfinavir (protease inhibitor).[23] These particles were capable of activating the latent viruses and inhibiting the viral spread.[23] Amongst many non-viral receptors which are expressed on macrophages (which can be served as a target site for drug delivery), the formyl peptide receptor (fMLF as the targeting agent), mannose receptor (mannose as the targeting agent), and Fc receptor (Fc as the targeting agent) are few of the promising receptors that can be used for targeting.[24] Wan *et al.*, have investigated the peritoneal macrophage uptake, pharmacokinetics and biodistribution of macrophage targeted PEG-fMLF nanocarriers for improving HIV drug delivery.[25] The results reveal enhanced accumulation of the PEG nanocarriers with several copies of fMLF in peritoneal macrophages and macrophages residing in other tissues (e.g. liver, kidneys and spleen). This targeting ability, combined with the prolonged plasma residence of 20 kDa PEG, makes the acetyl-C-[AAK(PEG5K-fMLF)]4-amide a promising nanocarrier for improving macrophage targeting *in vivo*.[25] There is a need to develop nanoparticles which can specifically be taken up by macrophages and after phagocytosis release the drug intracellularly. Similarly, the intracellular uptake of nanoparticles containing lopinavir, ritonavir and efavirenz were studied by Destache *et al.* After incubating these nanoparticles as well as free drugs with polymorphonuclear cells (PBMCs), it was observed that the free drug intracellular concentration of all three drugs was maximum at 8.0 hours.[26] The peak concentration with nanoparticles was observed at 96 hours for lopinavir and ritonavir and 24 hours for efavirenz. This intensification of intracellular uptake of nanoparticle is due to engulfment of the particles by macrophages, which is strategic, as HIV-1 survives on host DNA replication.[26] With such strategies increased drug concentration and residence time of the drug in target cells can be achieved which eventually results in more efficient reduction in viral loads.

Targeting anatomical reservoirs: targeting the lymphatic system

Exploitation of nanoparticles for targeting the lymphatic system including lymph nodes, the liver and spleen, may provide an effective substitute for existing antiretroviral treatments. For example, stavudine entrapped lipid nanoparticles may be utilized for effective and targeted delivery to cellular and anatomical HIV reservoirs. A study by Shegokar and Singh demonstrates the efficiency of these nanoparticles for prolonged residence in splenic tissues.[27] In another strategy, pH dependent nanoparticles of indinavir were investigated in macaques. Lipid–indinavir nanoparticles were capable of encapsulation of an aqueous marker calcein and anti-HIV drug ^{3}H-phosphonylmethoxypropyl-adenine (PMPA) having 35–120 nm diameters and pH-dependent release. The targeting effect of the formulation was mainly due to the smaller particle size, as the smaller nanoparticles were trapped in the lymph nodes easily during circulation through lymphatic system.[28]

Transport across anatomical barriers and addressing drug resistance

Numerous antiretroviral drugs have inhibited drug distribution in brain due to the natural barriers, in particular the blood–brain barriers. To regulate and inhibit viral infection, appropriate drug concentrations need to be achieved in these inaccessible areas like the central nervous system (CNS). Nanotechnology allows the design of nanoparticle strategies that can cross the BBB to increase the reach of antiretroviral drugs in the brain. Atazanavir concentration was significantly improved in human brain microvessel endothelial cell line (hCMEC/D3) after encapsulating within solid lipid nanoparticles. [29]. In addition to this, nanomaterials in targeted delivery of antiretroviral drugs can bypass efflux pumps responsible for drug resistance. In order to enhance these characters in the antiretroviral drug delivery to CNS, several nanoparticle-mediated alternatives have been proposed. Recently, Kuo and Lee studied methylmethacrylate-sulfopropylmethacrylate nanoparticles with attached RMP-7, a bradykinin type II (B2) receptor agonist, for targeting delivery of stavudine, delavirdine and saquinavir drugs across the BBB.[30] They have calculated the permeability coefficient of these drugs

in co-culture models of human brain-microvascular endothelial cells and human astrocytes. The permeability of the nanoencapsulated drugs across the BBB improved by endocytosis of RMP-7/MMA–SPM NPs and tight junction mediation.[30] Mahajan *et al.* in 2010 have integrated saquinavir within transferrin (Tf)-conjugated quantum rods (QRs).[31] The QR-Tf-Saquinavir nanoparticles crossed the BBB and inhibited HIV-1 replication considerably in infected peripheral blood mononuclear cells (PBMCs), confirming their anti-HIV-1 potential in brain. The results of this study provide the novel platform for development of QR based nanoparticle drugs with conjugated anti-retrovirals, which can effectively cross the BBB along with efficient targeted delivery in CNS.[31] Also, the placenta is an important barrier to drug delivery with the membrane pore size being 10 nm^3. However, the passage of HIV itself (~100 nm^3) has lead scientists to believe the presence of placental inflammations that may result in increasing pore sizes.[32] Nanoparticles can be developed leveraging these increased pore sizes to increase drug levels in the fetal circulation and helping in PMTCT. The development of such technologies can help us achieve the goal set by the Global Plan towards the elimination of new infections among children by 2015 and keeping their mothers alive by prevention of new HIV infections among women of reproductive age.[33]

This underscores the fact that nanoparticles impart spatial and temporal control over the delivery of drugs to the rather inaccessible areas of the body.

Tackling mucosal reservoirs

For addressing mucosal reservoirs, antiretroviral drugs need to form effective drug depots at mucosal sites. The drug must pass through the mucus layer which is few hundred microns thick so that to avoid clearance and to reach to the underlying epithelium. Mucoadhesive and mucus penetrating nanoparticles can warrant the prolonged retention and enhanced absorption of inadequately absorbable drugs. The mucoadhesive NPs can be synthesized by using polymers, like chitosan, pectins, poloxamers, and their derivatives. For example, Meng *et al.* synthesized chitosan nanoparticles loaded with tenofovir, to maximize microbicide mucoadhesion. They have confirmed the mucoadhesive property of the NPs on vaginal epithelial cells.[34]

Development of nanoparticles using materials with intrinsic anti-retroviral activity

The essential similarity between all the strategies employed is the fact that they can be used for the delivery of drugs. In addition to these, the materials used for the development of these particles can themselves be modified for anti-retroviral activity.[6] The most promising examples in this category include fullerenes, carbon nanotubes, dendrimers and silver nanoparticles. In a slight variation, gold nanoparticles can improve antiviral effects of other molecules.[6] As an example, fullerene derivative complexes like C_{60} molecules can fit into the hydrophobic clefts of the human immunodeficiency virus (HIV)-1 protease.[35] Further research has led to the substantiation of the efficacy of fullerene derivatives and bioconjugates in the inhibition of the protease and intrinsic retroviral activity.[35] Carbon nanotubes have potential as allosteric inhibitors to HIV-1 integrase.[36] Another pertinent example is that of silver nanoparticles which preferentially bind to HIV-1 gp120 subunit of the viral envelope glycoprotein and inhibit the infectivity of the virus *in vitro*. However, most of these studies have been developed until the *in vitro* stage. Further development in these lines can lead to a multi-pronged approach in the treatment of HIV/AIDS.

These strategies paved way for research in development of nanoparticles for delivery of anti-retroviral drugs. Many such particles were developed for various drug classes. Fig. 1 outlines some of the currently used nanoparticles for conventional antiretroviral drug delivery

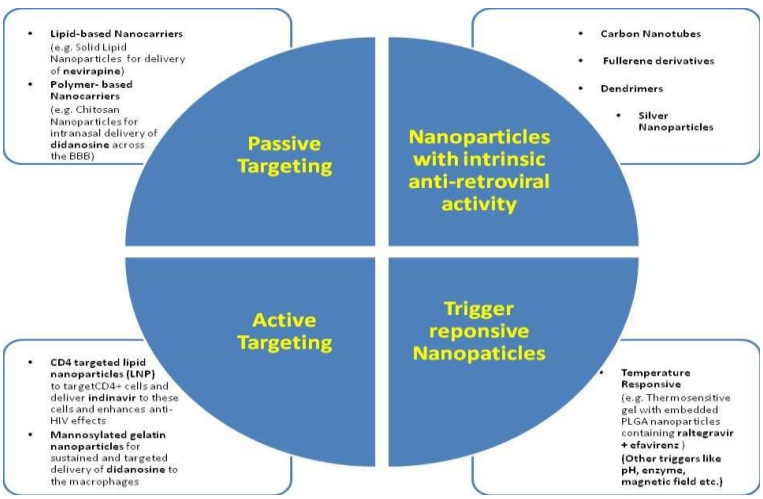

Fig 2. Strategies for the development of nanoparticles for drug delivery against HIV/AIDS

Smart Nanoparticles: Lessons from Cancer Therapy

The development of various smart nanoparticles is based on extensive experience with the development of smart nanoparticles for cancers. As with HIV/AIDS, one of the major issues in the drug delivery of cancers is the challenge of providing a time and space controlled drug delivery of the otherwise highly toxic

chemotherapeutic agents.[37] This gave rise to the concept of "targeted therapy". Targeted therapy is directed to selectively target drugs to its area of intended action while leaving the normal cells unharmed. This increases the bioavailability of the drug while reducing the associated toxicities. While discussing targeted therapy for each of these diseases, we would also need to differentiate the two. The major differences between nanotechnology strategies for addressing cancer and HIV/AIDS are outlined in Table 1.

Table 1. Distinction between the strategies employed for the design of smart nanoparticles in cancer and HIV infections

No.	Distinction	Cancer	HIV/AIDS
1.	**Challenges**	Delivery of drugs to the central necrotic zone of solid tumors, development of drug resistance, toxicity and side effects, delivery across barriers.	Delivery of drugs into the reservoirs, development of drug resistance, maternal to child transmission of HIV, toxicity, side effects, delivery across barriers.
2.	**Abnormalities leveraged for passive targeting in drug delivery**	Size dependant accumulation due to enhanced Permeability and Retention Effect through leaky cancerous capillaries	Intracellular reservoirs (macrophages) phagocytose drug containing nanoparticles in a sized dependant manner
3.	**Abnormalities leveraged for active targeting in drug delivery**	Receptors or surface molecules over-expressed in diseased organs, tissues, cells or subcellular domains. (HER2, transferrin receptors). Ligand-mediated targeting by attaching ligands specific to these receptors on nanoparticles.	Receptors on the surface of anatomical reservoirs of HIV e.g. lymphocytes (CD4 receptors) and macrophages (macrophage-mannose interaction)
4.	**Triggers leveraged in Drug Delivery**	Internal triggers like pH, temperature and enzymes. External triggers like ultrasound, light and temperature.	Internal triggers aiding endosomal escape, semen, enzymes and temperature. External triggers like temperature and magnetic field.

Keeping in mind the differences, the following are some of the key methods of achieving a targeted therapy in cancers and HIV/AIDS.

Passive Targeting

Passive targeting of nanocarriers uses the phenomenon of size-flow-filtration which makes drug delivery easy to tumors, the reticular endothelial system, and lymph nodes.[24] As an example, in cancers, the small sizes of the nanocarriers helps them to be targeted at specific sites through mechanisms like passive targeting through the Enhanced Permeation and Retention effect (EPR effect).[38] This mechanism relies on the abnormally large gap junctions in the endothelium of the blood vessels of the tumor cells which are formed as part of sustained angiogenesis in the tumors leading to enhanced permeability[39, 40] and -altered lymphatic drainage favoring retention[40]. To a certain extent, nanoparticle composition, shape and half-life also determine the success of this mode of targeting.[40]

Similarly, in HIV/AIDS, this passive targeting to lymph node is a key to a better delivery of drugs.[24] This is because they are important induction sites and HIV-1 replication site through T-cells. This is either achieved through the agency of macrophages by using nanocarriers attracting them like aged red blood cells[41], yeast ghost cells[42] and *in vitro* nanoparticles entrapped macrophages[43] or through the use of subcutaneous injection of drug loaded nanoparticles in an area close to the thoracic duct.[44] Subcutaneous injections reduces the need for surface targeting modifications and again are an example of size-flow-filtration based on nanoparticles of around 100 nm which easily enter lymphatics.[44] With smart nanoparticles, controlled-release of drug is possible which can lead to longer circulation times and enhanced half-lives of various anti-retroviral drugs. As an example, Dou *et al.* developed nanoparticles of indinavir loaded into carrier bone marrow-derived macrophages (BMMs).[43] Tissue and sera drug levels indicated sustained release of the drug for 2 weeks.[43 6] While free drugs (both hydrophobic and hydrophilic) have limited bioavailability in the different tissues of the body, the use of smart nanoscale delivery systems, due to their small size allows adequate distribution in different tissues especially the reservoirs that are otherwise inaccessible to free drugs.[6] Lipid-indinavir nanoparticles developed by Kinman *et al.*, for example, when given subcutaneously, were found to provide peripheral and visceral lymph nodes indinavir concentrations 250% to 2270% higher than plasma indinavir concentrations.[44] Compared to free drugs, passive targeting thus has implications in the ultimate bioavailability of drugs and can reach otherwise inaccessible areas of the body. It is one of the key elements in the targeted drug delivery for HIV/AIDS sans the cost and complexity involved in active targeting.

Active Targeting

Active targeting is much more specific and involves the conjugation of a tumor-specific ligand (like antibodies, peptides, cell surface ligands) to nanoparticles for their specific delivery of tumor sites. [40] Targets in tumors include tumor antigens, cell

surface receptors that are internalized.[40] It helps in a better delivery of nanoparticles to the tumor with a specific characteristic as compared to the other parts of the body. An example of active targeting in cancers is anti-HER2 targeting moieties on liposomal surfaces which markedly increase their uptake in HER2-expressing cancer cells.[45]

On adapting this strategy for HIV, active targeting involves nanoparticles designed to target specific receptors present on the surface of HIV, infected macrophages and T-lymphocytes. The receptors on the virus can be targeted to reduce their infectivity to the cells, a concept similar to the fusion inhibitors (viz. enfuvirtide which prevents HIV infection of the cells through inhibition of chemokine receptor 5 (CCR5)). Similarly, HIV gp120 receptors can be targeted using nanoparticles containing mannose or amphiphilic sulfate-ended ligands on their surface.[46, 47] This causes reduced entry of viruses into various cells like T-lymphocytes and dendritic cells because of the already inhibited gp120 which can no longer participate in cell entry. As an example, Gianvincenzo *et al.* used 2 nm gold nanoparticles modified with sulfated ligands to target gp120 antigens in the HIV envelope and inhibit them.[46] gp120 is involved in the adsorption/fusion process of the virus infection and the binding of these ligands reduced infection of T-lymphocytes.[46] In addition to this strategy, the precise targeting of host receptors helps in the increased bioavailability of the anti-retroviral drugs in the reservoirs or against HIV, thus reducing the side effects. In one experiment by Pollock *et al.* (2008), N-butyldeoxynojirimycin (NB-DNJ), an inhibitor of HIV gp120 folding, was encapsulated into soluble CD4 surface-modified liposomes to target PBMCs. Along with this; the pH-sensitive liposomes could withstand low pH so as to assist endosomal escape. The uptake was increased 5 fold in HIV-infected cells as compared to uninfected cells due to this targeting strategy.[48] It is possible to tailor approaches for actively targeted nanoparticles to various HIV infected sites.

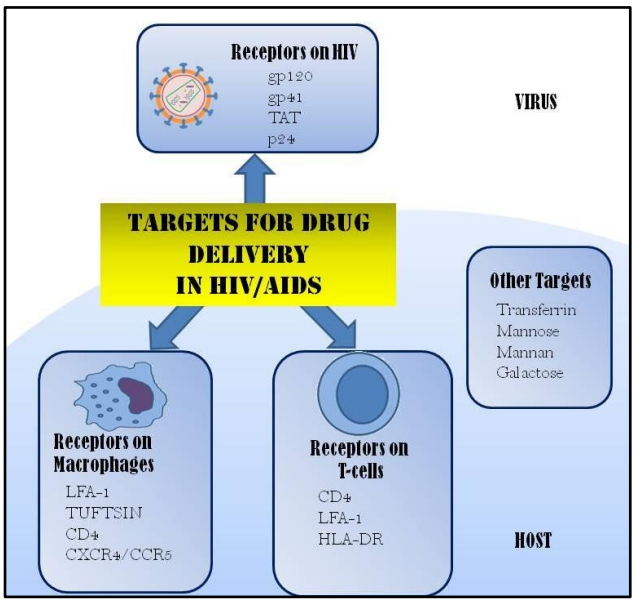

Fig. 3: Active targeting in drug delivery in HIV/AIDS

Trigger Responsive Carriers

As of the present day, the trigger-responsive nanoparticles have generated a lot of interest because of their ability to act as **"remote switches"** in cancer therapeutics.[38] In fact, it is the ability of these particles to turn on or off the therapeutic effects of the payload they carry based on the presence or absence of a stimulus/trigger that makes them highly specific to tumor cells.[38] Besides, this can be achieved at much lower costs that those associated with the biological targeting moieties which are also many a times not efficient enough as they are associated with only a small fraction of cancer cell types.[38]

The basis of operation of the trigger-responsive nanoparticles is the fact that the nanocarriers undergo large and abrupt modification of their structural compositions and conformations due to the presence or absence of various physical, chemical and biochemical stimuli thereby promoting the release of the active species to the specific biological environment.[20, 38] However, all this come with a basic necessity that the stimuli which evoke the response by the nanocarriers must be disease specific which would result further in the temporally and spatially precise release of the payloads at the desired sites, here the tumor sites.[20]

The stimuli evoking the responses may be the unique physicochemical properties of the cancers and thus serve as "internal triggers". e.g. pH, enzymes, temperature, redox potential etc.[20, 38] On the other hand, "external triggers" for the delivery of these particles those that do not depend on the properties of the cancers and need to be provide externally to evoke the response e.g. ultrasound, photothermal therapy (light), temperature (nanoheaters), magnetic fields etc.[20, 38] Some of these have been illustrated in the Figure 4.

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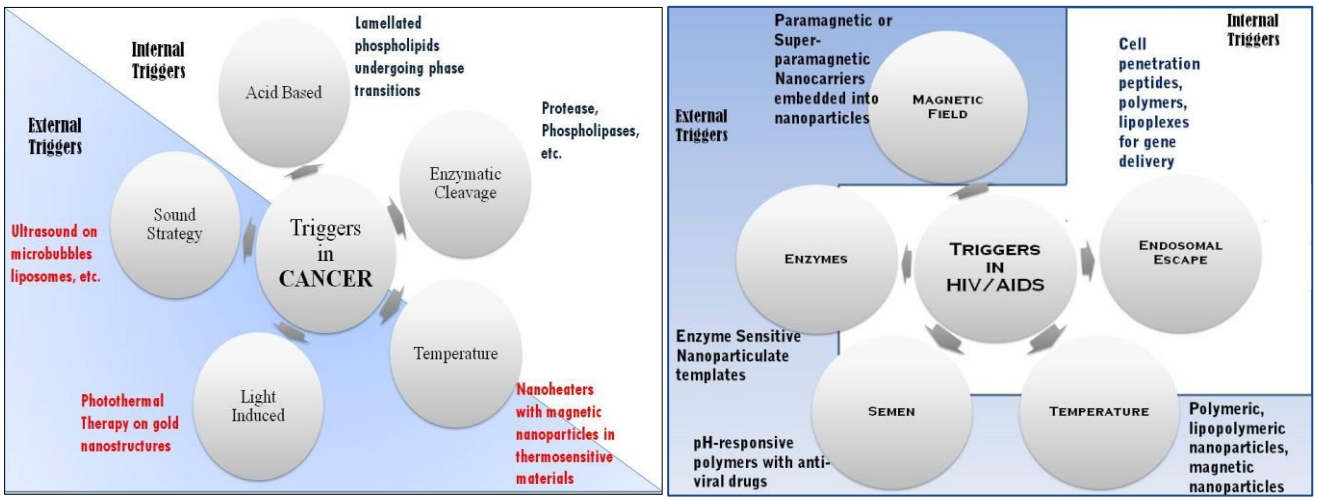

Fig. 4: Examples of various triggers for trigger responsive nanoparticles in Cancer (left) and HIV/AIDS (right)

Trigger Responsive nanoparticles in HIV treatment: "Smart nanoparticles"

Some of the similarities and differences in the strategies of trigger responsive nanoparticles for HIV infections as opposed to cancers are highlighted in Figure 3.

Semen triggered nanoparticles

It is established that unprotected sexual intercourse is a major route for the transmission of HIV-1 infection.[49, 50] Chemically, semen is a mixture of components like spermatozoa with carbohydrates, lipids, proteins and ions produced from testis, epididymis, prostate, seminal vesicles and accessory glands.[49, 51] Semen acts as a carrier for viruses through free virions, spermatozoa-associated virions and infected leukocytes.[49] Besides, it has been postulated that semen raises the vaginal pH for several hours after sexual contact resulting in an environment conducive for HIV-1 infection.[49]

The rationale behind the development of trigger responsive nanoparticles is to use this sudden and sustained change in pH for the time and space controlled delivery of therapeutic agents. The characteristic features of the nanoparticles developed thereof would be a high stability in acidic pH (< 4.5) of healthy vaginal fluid and instant disruption on contact with alkaline pH (7.4-8.4) of human semen, leading to release of encapsulated drugs. Hence, use of semen triggered drug delivery as a mode of pH triggered drug delivery has a potential to be used in the prevention of HIV infection right at the point of contact.

Zhang *et al.* leveraged this technology for drug release of tenofovir and tenofovir disoproxil fumarate. Nanoparticles of copolymers of poly(lactide-*co*-glycolide) and methacrylic acid were developed as drug delivery systems biocompatible to the vaginal physiology and with the potential for drug delivery on contact with semen.[52] Similarly, Huang *et al.* developed pH-responsive electrospun fibers of cellulose acetate phthalate (CAP) incorporated with anti-viral drugs like tenofovir disoproxil fumarate.[53] The essential advantage of this semen triggered pH-dependent release was that in addition to the drugs delivered, CAP has been reported to have intrinsic antimicrobial activity, which effectively neutralized HIV *in vitro*.[53] While the pH change associated with the presence of semen has been exploited as a trigger for release of drugs in the vagina after sexual intercourse, there are several compositional differences between the vaginal fluids and semen which may also lead to interesting strategies for trigger responsive antiretroviral drug delivery.

Enzyme triggered nanoparticles

Enzyme triggered drug delivery in HIV is also on the lines of semen-triggered delivery. Many enzymes in the semen like hyaluronidase and prostate specific antigen can act as triggers for the delivery of drugs on contact with semen.[54, 55] Recently, there has been development of such smart polymers especially as gene carriers which can release its payload on coming in contact with viral enzymes. One such example was put forth by Asai *et al.* who created polymer-cationic peptide conjugates incorporating a HIV protease cleavable sequence.[56] The cleavage of the polymer is selective and takes place only where the protease is active and results in delivery of the payload (e.g. DNA).[56] This is of great interest as a non-viral drug/gene delivery method for HIV-infected cells.

Endosomal escape as a trigger for gene therapy: DNA nanostructures

In addition to the tremendous developments in anti-retroviral therapy, gene therapy is increasingly attracting attention.[6] Gene

therapy includes the development of such technologies that can lead to successful transfection of a genetic material (viz. DNA, siRNA, RNA decoys, aptamers etc.) into the cell and thereby interfere HIV infection or replication.[6] However, in the transit of the genetic material from the drug delivery system to the nucleus of the target cell, a crucial check point is that of the endosomes which have acidic pH and degradative enzymes.[57] Nanotechnology approaches this check point through the development of such technologies that cause early endosomal escape of the genetic material from drug delivery vehicles before the genetic material is degraded in the endosomes.[57] A number of non-viral approaches like proton-sponge hypothesis, flip-flop mechanism, endosomal membrane fusion or destabilization mechanism, pore formation and photochemical internalization (PCI) have been attempted for the process.[57]

The proton-sponge hypothesis is based on the concept that the endosomes are acidic due to the presence of proton pumps in its membrane that pump in the protons from the cytosol into the endosomes. However, in case of cationic polymers that get entrapped in the endosomes, the polymers take up most of the protons and thus the acidification of endosomes is not adequately achieved. This stimulates higher entry of protons into the endosomes and consequently increased swelling due to osmotic pressure of the surrounding fluid leading to the endosomal rupture and hence, endosomal escape. This facilitates transfection of genetic material in the cells. Cationic polymers like polyethylenimine (PEI) are one such example for non-viral delivery of DNA/RNA.[58] This concept has been leveraged for the development of AIDS vaccines by Rodrigo Garzón *et al.* .[59] The authors developed a complex of PEI along with HIV envelope glycoprotein 120 (gp120) to elicit a strong immune response against the virus.[59] This was proposed to be an effective vaccination against AIDS both systemically and locally.[59] However, there are issues with cationic nanoparticles in having a high accumulation in the liver and lung, high cytotoxicity and a potential to cause splenomegaly and hemobilia.[60] Hence, there is a need to modify these particles for better biocompatibility.

The flip-flop mechanism is another concept that holds true in cases of cationic lipoplexes that contain a cationic phospholipid and an anionic phospholipid held together electrostatically.[57] This provides yet another mechanism for the escape of the genetic material from the endosomes. The cationic lipoplexes and the negatively charged lipids present in the endosomal membrane interact to allow the lateral diffusion of the endosomal anionic lipids into the lipoplexes resulting in neutralization of charge.[57] Consequently, the nucleic acids are no longer bound to the positively charged lipoplexes and are released to the cytoplasm allowing endosomal escape.[57] Zhou *et al.* showed that the role of dioleoylphosphatidylethanolamine (DOPE) as a helper lipid which uses the flip-flop mechanism for fusion between liposomes and the endosomal membrane allow endosomal escape of encapsulated genetic material [61] DOPE transforms from its lamellar to inverted hexagonal phase inside the endosome promoting fusion of lipid bilayers.[61]

Endosomal fusion or destabilization can also be achieved by cell-penetration peptides (CPPs). Broadly classified as cationic and/or amphipathic peptides, CPPs contain 10-30 residues of amino acids which carry cargo into the intracellular compartment keeping an intact plasma membrane.[57] These peptides have a special place in HIV treatment as they were first derived from TAT peptide from the transcription activating factor of human immunodeficiency virus 1 (HIV-l).[57]

Pore formation and photochemical internalization (PCI) using photosensitizers are other methods for the endosomal escape of genetic materials in the treatment of HIV/AIDS.[57]

The major mechanisms of endosomal escape are outlined in the Fig. 5.

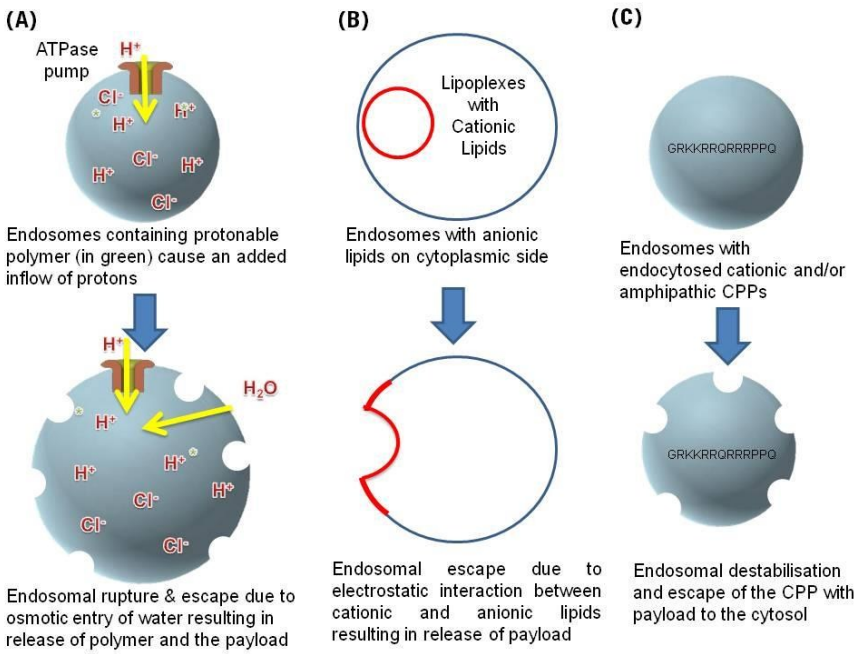

Fig. 5: Major Mechanisms of Endosomal escape: (A) Proton Pump Hypothesis, (B) Flip-flop mechanism and (C) Endosomal Fusion/ Destabilization

Cite this: DOI: 10.1039/c0xx00000x
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Featured Article

Temperature triggered nanoparticles

Temperature triggered drug delivery systems usually undergo a change in the solvent properties, hydration states, the hydrophilic-hydrophobic balance depending upon heating and thus resulting in a phase transition.[20, 62] The solvent properties change from a good solvent at temperatures below the Lower Critical Solution Temperature (LCST) to a poor solvent at temperatures above, leading to changes in morphology from an extended random coil to a collapsed chain.[62] In other words, these systems when heated above the LCST leads to dehydration and collapse due to increased hydrophobicity.[20] Polymers like hydrogels are 3-dimentional polymeric networks form semi solid state after dispersed in water. In case of thermosensitive polymers, the covalently linked hydrogel changes their degree of swelling due to the temperature. Unlike the conventional gels, thermosensitive gels are liquid below their LCST but become adhesive at higher temperatures. This phase alteration seen in hydrogels can be modified to keep the LCST close to 37ºC so that they are liquid during storage and can gel when introduced into the body. This response to temperature makes it possible to develop smart depot release systems for locoregional drug delivery at reservoir sites. [63] In 2012 Date *et al.*, have synthesized a thermosensitive vaginal gel containing raltegravir + efavirenz loaded nanoparticles for HIV treatment.[64] The thermosensitivity was confirmed by the transwell experiment in which the nanoparticles have successfully transferred from the thermosensitive gel and have been taken up rapidly by the HeLa cells.[64] In another such experiment, the thermoreversible tenofovir loaded PLGA nanoparticles were prepared for vaginal delivery. Poloxamer 407 and Pluronic® F-108 forms a gel matrix in temperature range between 28-30ºC and returns to its solution state when kept at 2-8ºC. To optimize the gelling temperature with vaginal temperature, different combinations of Poloxamer 407 and Pluronic® F-108 can be used. The sustained release behavior of tenofovir loaded PLGA nanoparticles are confirmed by *in vitro* release data in presence of the trigger.[65]

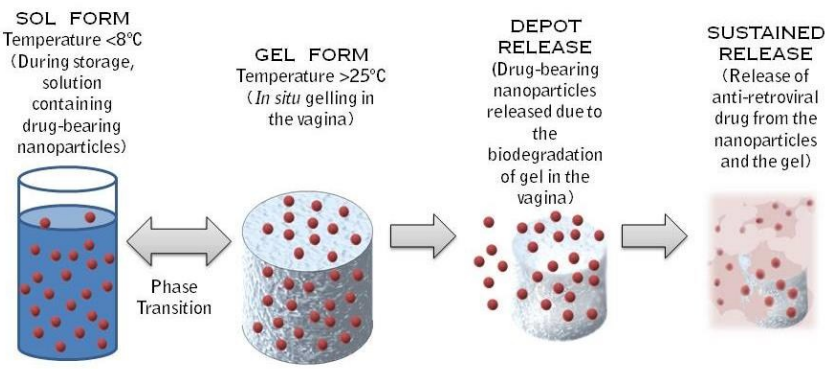

Fig. 6: Illustration of a temperature triggered drug delivery system for treatment of HIV.

Magnetic-field triggered nanoparticles:

Magnetic field hyperthermia employing magnetic fields with superparamagnetic iron oxide nanoparticles (SPIONs) are an interesting method to generate hyperthermia aiding in treatment of HIV/AIDS while simultaneously imaging them using Magnetic Resonance Imaging (MRI). This is partly due to the fact that HIV-specific cytotoxic T-lymphocytes are able to attack HIV-infected cells more efficiently at higher temperatures.[66] Experiments by Williams *et al.* using the SPIONs FeraSpin R helped in concluding that SPIONs can be easily taken up by cytotoxic T-cells but were not yet able to achieve temperatures necessary for affecting cell physiology to lead to cell death. Thus, thermotherapy with SPIONs has not yet been successful in HIV/AIDS. With better methods of uptake, these particles will be of great use in imaging and treatment of HIV including latent infections.[66]

Apart from hyperthermia, magnetic nanoparticles also serve as field-controlled drug transporters with the distinctive ability of triggered release after bypassing the blood–brain barrier. These nanocarriers generally involve paramagnetic or super-paramagnetic materials either embedded into polymeric nanoparticles.[20, 67] The mechanism involved in magnetic drug delivery system is transporting the magnetic nanoparticles loaded with drug to the specific site underneath the stimuli of external magnetic field. However the nanoparticles are magnetic only under the influence of an external magnetic field and remain inactive after removing the external magnetic field. To treat neurological manifestations of AIDS, Saiyed *et al.* evaluated the specific drug targeting to the brain using 3'-azido-3'-deoxythymidine-5'-triphosphate (AZTTP, Zidovudine triphosphate) bound with magnetic nanoparticles (MP-AZTTP) and encapsulated within liposomes. These MP-AZTTP liposomes were transported across the BBB in presence of an external magnetic field. The passage across the BBB is mediated either by direct delivery of MP-AZTTP loaded liposomes under the

influence of an external magnetic field resulting in an apparent permeability of magnetic AZTTP liposomes or by uptake of the nanocarriers by circulating monocytes/macrophages which can then pass through the BBB.[68]A threefold increase in drug permeation through the BBB was observed with this strategy.

Other unexplored triggers for antiretroviral therapy

In the treatment of cancers, a host of other triggers have been used like near infrared light and ultrasound.[20] The utility of ultrasound triggered drug delivery lies in the fact that the modality helps in the enhanced uptake of the drug through ultrasound contrast agents like microbubbles, liposomes etc.[37] This localization of the drug to the target tissue helps in reduction of dose and their subsequent adverse effects especially in those with a low therapeutic window.[37] It has been of great use in the delivery of a variety of therapeutic entities [37] viz. (a) low molecular weight drugs like doxorubicin and paclitaxel (b) large biomolecules like genetic drugs and proteins and, finally, (c) drugs encapsulated in nanoparticles. Besides, Mcdannold *et al.* (2012) showed that blood brain barrier can be disrupted temporarily by using microbubbles with ExAblate 4000 low-frequency Tc MRg focused ultrasound system (InSightec) without eliciting any histological or functional damage in rhesus macaques.[69] With respect to HIV infection, this trigger is yet unexplored with a tremendous potential to allow nanoparticles to cross the blood brain barrier and other anatomical barriers.

The light-responsive drug delivery system is attracting much attention in few recent years due to their non-invasive control. Recently a varied range of electromagnetic waves ultraviolet, visible or near-infrared (NIR) light have been recommended to attained on-demand drug release. There are different approaches available depend on single or multiple on-off drug release event activated by light triggered structural alteration of the nanocarriers.[70]

Ultrasound triggered and light responsive drug delivery bear testimony to the fact that there is a need for identification of better triggers, both internal and external, that can help the precise time- and space- controlled delivery of drugs. In fact, there is a growing trend for the use of "Multipronged approach" or the use of "Dual Responsive Nanocarriers" with the simultaneous deployment of two or more triggers (combination of internal and external ones) for the further improvement of the precision of drug delivery through the use of these nanoparticles.[20, 38] Soppimath *et al.* developed polymeric core-shell nanoparticles responsive to pH and temperature for intracellular drug delivery in tumors.[71] Such multiple strategies improve the precision and control of the triggered nanostructures and have been used extensively for anti-cancer drugs. Developing such a system for HIV/AIDS is an interesting area of enquiry.

Thus, while the concept of trigger responsive nanoparticles is widely prevalent in cancer therapeutics, it is a recently emerging one in the area of nanoparticle therapies for HIV infections.

Nanomicrobicides (Nanogels)

Prevention is as important in the management of HIV/AIDS as is the treatment. Nanotechnology has provided useful innovations to address the issue of prevention of transmission of HIV. The poster child for the use of nanotechnology in HIV infections is a potent nanomicrobicide gel called SPL7013 Gel (VivaGel®).[72, 73] It is a vaginal gel developed by Starpharma Pty Ltd (Melbourne, Australia) for prevention of bacterial vaginosis, which eventually found application in HIV prevention and is now in the Phase III of development.[72, 73] SPL7013 is the active component of this gel and is a dendrimer comprising of a divalent benzhydrylamine (BHA) core with radiating lysine branches of four generations and the outermost branches being capped with naphthalene disulfonic acid groups.[72, 73] Interactions resulting from negatively charged surface of a polyanion-based entry inhibitor and positively charged surface of HIV may prevent attachment and entry of the virus into healthy cells.[72, 73] Antiviral activity was observed against HIV-1starting immediately and continuing up to 3 hours after intravaginal administration of VivaGel.[72] This gel was well tolerated both among women and men.[72, 73] In another example, Jallouk *et al.* developed a HIV virucide with melittin nanoparticles targeting the sperm surface antigen, sperm adhesion molecule 1 (SPAM1).[74] Melittin was chosen for its fusogenic properties and electrostatic affinity for virions and has proved to be an inhibitor of HIV infectivity by physical disruption of the viral lipid envelope while being both therapeutic and safe.[74, 75] The nanoparticles potentially aggregated infective sperms resulting in a preventive anti-retroviral activity.[74] Studies performed in continuation to this strategy have proved that mellitin nanoparticles, unlike mellitin by itself, are non-toxic to sperms and vaginal epithelial cells and might therefore form the basis for a potent vaginal gel based virucide[74]. Such novel nanoparticles have strategies that would not be susceptible to HIV mutational resistance seen with standard therapies.

Nanoparticle Vaccines

The synthesis of vaccine factually relies on Louis Pasteur's "isolate, inactivate, inject" hypothesis. Conventional vaccines include live attenuated microbes, killed microbes or components of microbes. Although the immunization with vaccine has a prime influence on regulating the infectious diseases, some vaccines do not offer a protection against disease. In addition, in spite of extensive research, some of the vaccines have been unsuccessful due to safety issues or absence of efficacy in human.[76]

The use of nanotechnology in the development of vaccines is increasing in recent years. The consideration has been focused on the use of nanoparticles as delivery vehicles for vaccines. The antigenic material undergoes fast degradation or deliberates a short-lived, limited immune response after injecting in to the circulatory system. This problem can be overcome by encapsulating the vaccine antigen within or on to the surface of the nanoparticles.[76] The development of DermaVir® (Genetic Immunity Kft, Budapest, Hungary and McLean, Virginia, USA), an experimental HIV/AIDS therapeutic vaccine is a leading example which is now in Phase III clinical trials. It is known to be composed of a polyethyleneimine nanoparticles encapsulating single plasmid DNA that expresses 15 HIV antigens thus mimicking the virus.[77] It is applied as a skin patch to the epidermis and has been found to act intracellularly to induce an adequate immune response against HIV.[77] Also, Phase I clinical

trials have been completed a nanovaccine (Tat Oyi) containing a 3-D epitope triggering neutralizing antibodies by targeting HIV-1 Tat protein.[78] The Tat protein is supposed to protect the HIV-1 infected cells from the cellular immune response. It was observed that macaques after immunization with Tat Oyi vaccine could neutralize the HIV and eradicate virus infected cells.[79] Currently, the vaccine is in Phase II clinical trials.[79] It has been shown to benefit the patients by reducing the incidence of autoimmune responses that were rather common with the presently developed vaccines.[78]

Virus mimetic Nanoparticles

Virus like particles (VLPs), are some of the earliest designed biomimetic nanoparticles, which are based on structural viral proteins. VLPs are composed of integral material for self-assembly, and mimic the morphology of the pathogen. However, VLPs differ from viruses being non-infective and non-replicating, as they have lack of infectious genetic material These key characteristics of VLPs are exploited in drug delivery area for targeted delivery.[80]

DermaVir® as explained earlier as a vaccine with antigens expressing through a nanoparticle is yet another example of a virus mimetic nanoparticle capable of producing multiple HIV antigens.[77] Similarly, Xu *et al.* have synthesized a nanoadjuvant of fullerenol, for use as a HIV-1 DNA vaccine.[81] It is morphologically similar to the virus and mechanically functions as a plasmid DNA carrier which activates the of host immune system. In this study the mice were intradermally immunized with the fullerenol-Env complex, which are engulfed by the dendritic cells (DCs) in the skin, activating the toll-like receptors (TLRs) present on the surface of DCs. The virus-like particles prevent the enzymatic degradation of the DNA antigen during this process. After the nanoparticles are engulfed by the DCs, the cells migrate from vaccination site to the lymph node. While reaching the target site, the DCs present the Env peptide-MHC complexes on their surface. The Env peptide-MHC complexes can be recognized by the newly formed T cells with receptors (TCRs) which in turn triggers the immune response.[81] With increasing knowledge in basic and clinical research, the development of virus mimetic particles for drug delivery is evolving allowing better biomimicry-based drug delivery systems.

Translational Challenges

In spite of the strides being made in the development of "smarter" nanoparticles, there has been limited translation of the nanoparticles developed in HIV/AIDS from labs to the clinics.[82] This has resulted in a very few clinical trials. The most important products that made way into clinical trials are DermaVir®, VivaGel® and certain nanovaccines like Tat Oyi which are known to be used as preventive measures for HIV/AIDS.[79, 83] However, nanoparticles developed for the treatment of HIV/AIDS have not yet seen the light of clinical medicine. Most of these products are in their preclinical stages and await significant experimental and clinical validation before their entry into the clinics.[84] However, the development of nanoparticles in cancer has led to a number of clinical trials against the complications of HIV/AIDS like Burkitt's lymphoma or Kaposi's sarcoma.[83]

In addition to this, acceleration of the translation of nanotechnology based platforms in HIV infections is warranted. The use of GRAS approved nanomaterials, high stability and safety of the nanoparticles, and the use of easily scalable manufacturing techniques can aid in the early translation of the innovative technologies.

Future Perspectives for Nanotechnology in the fight against HIV

In spite of the obvious roadblocks that remain in the translation of smart nanoparticles from the labs to the clinics, there is indeed great potential held by these in the management of HIV. As has been seen in cancer, these nanoparticles can greatly help in precise anti-retroviral drug delivery in HIV infections.

Use of passive or active targeting, use of triggers and preventive strategies enable nanoparticles to increase efficacy of antiretroviral therapy. Depots of nanoparticles within reservoirs can help address drug resistance more effectively than free drugs. While, many of the strategies require the presence of infection for targeting purposes, recent concepts like trigger-responsive drug delivery, active targeting to various non-viral targets and virus mimetic nanoparticles have proved to be beneficial in improving delivery of various therapeutic payloads to both infected cells as well as susceptible ones. They have proven useful in eliciting immune responses in case of vaccines. Besides they are also adept to cross anatomical barriers, target drug reservoirs and overcome drug resistance.

Concepts like "virological synapses" that explain cell-to-cell infection have emerged recently and nanoparticles targeting these pathways are being developed using the concepts of VLPs exploiting the process of infectivity of HIV. These include actively targeted self-assembled artificial virus nanoparticles (AVNs) which can target key cells of the immune system.[85] Targeting of nanoparticles may also be directed to these specific steps allowing us overcome a number of challenges in conventional anti-retroviral therapy like non-specificity and toxicity.

Among novel concepts, many triggers already in use in cancers are still to be explored to develop trigger responsive nanoparticles for HIV/AIDS. Smart trigger-responsive nanoparticles can help in the focused release of drugs at reservoir sites, cross anatomical barriers and reduce drug resistance.

Besides, a significant area is the prevention of maternal-to-child transmission that is in want of such safe technologies that can reduce the incidence of HIV infections in children by effectively crossing the placenta. Gold nanoparticles may be interesting candidates for this purpose but need further confirmation regarding their accumulation in the placenta, their safety and biocompatibility.[86]

Thus, smart nanoparticles play a role as stimuli responsive nanomedicine for reservoir specific drug delivery as well as act as potential agents by themselves for the treatment and prevention of HIV/AIDS.

Conclusions

In conclusion, nanocarriers can help in addressing various challenges surrounding HIV/AIDS. The development of smart nanoparticles responsive to various triggers and allowing time- and space- controlled delivery of therapeutic agents are an important platform for tackling drug reservoirs in HIV infection. Smart nanoparticles responsive to semen, enzymes, endosomal escape, temperature and magnetic field as well as concepts like nanomicrobicides and vaccines have the potential to augment existing antiretroviral therapies and help in achieving the Millennium Development Goal to combat this wide-spread disease.

Notes

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Acknowledgements: We are thankful to the Indian Council of Medical Research and National Institutes of Health, USA (NIH)- Intramural to India (I to I) Program for Prevention of Sexually Transmitted Diseases for the support.

† Electronic Supplementary Information (ESI): None

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