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Dendrimers in Anti-HIV Therapy

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1. Introduction

Human immunodeficiency virus (HIV), a retrovirus that was clinically detected in 1980 and demonstrated to be the causative agent of acquired immunodeficiency syndrome (AIDS), had resulted in over 25 million deaths by 2005. Currently, more than 33 million people are HIV-positive, and approximately 2.6 million people were newly infected and 1.8 million died of AIDS-related disorders in 2009. Antiretroviral therapy (ART), available from the mid-1990s, greatly improves the quality of life for HIV-infected persons and reduces mortality. However, there are several limitations to obtaining recovery from HIV infection including drug resistance, high rate of viral mutations, limited number of targets, low bioavailability of some compounds, presence of viral reservoirs and severe side-effects. The inability of standard highly active anti-retroviral therapy (HAART) drugs to penetrate some cells ensures that virus replication continues, although the common viral load can be reduced to undetectable levels [Finzi, 1997]. In addition, owing to the high cost and complexity of current HIV therapies, fewer than 5% of HIV infected patients worldwide receive antiretroviral treatment, and in underdeveloped countries access to such drugs is severely restricted. Therefore, development of preventive and therapeutic vaccines represents a tremendous challenge to AIDS researchers. In Europe the elaboration of new therapies is one of the main goals and several studies have concerned nanotechnology, with gene therapy being proposed as a good alternative that can efficiently inhibit gene expression in a sequence-specific manner. Dendrimers, a new class of polymeric molecules, are potential candidates for developing preventive antiretroviral vaccines where the delivery vehicles have low level cytotoxicity and targeted action. The aim of this chapter is to summarize studies concerning dendrimers and their application as therapy against HIV-1.

2. HIV-1 pandemic. Fail of HAART. The necessity of a new therapy approach

Conventional antiretroviral therapy consists of a combination of antiviral drugs to decrease the mortality of HIV-1 infected patients [Palella et al., 1998], with the mixture of drugs interfering with various stages of the virus life cycle at one time. Therefore, antiretroviral therapies (ART) are targeted to block key steps of the viral replication cycle: binding and fusing to the target host CD4 T-cell, reverse transcription of the viral RNA, and integration

of viral DNA into host DNA. For a better understanding of novel approaches such as dendrimer based therapies, a brief description of the viral life cycle is required.

The first step in the viral life cycle is attachment, fusion of the viral envelope and consequent entry into an immune cell. CD4 receptors bind the viral surface protein gp120, enabling further interaction with co-receptor proteins, predominantly CCR5 and CXCR4 [Eckert et al., 2001]. After CD4-virus binding, conformational changes in gp120 initiate fusion of the two membranes by reorientation of the transmembrane protein gp41. This step is a target for preventive therapy and drugs, and several HIV entry inhibitors are the subject of clinical trials. Among them, Enfuvirtide, Sifurvitide (blocks the surface envelope glycoprotein 41 of HIV-1, already approved) [Lalezari et al., 2003], Aplaviroc, Vicriviroc and Maraviroc are host co-receptor CCR5 antagonists [Liu et al., 1996; Dean et al., 1996], AMD11070 (CXCR4 antagonist, in phase II clinical trials) [De Clercq, 2003; Hendrix et al. 2004] and other associated entry and fusion drugs are being developed and await approval [Esté & Telenti, 2007].

Viral reverse transcriptase copies the single-stranded RNA into double-stranded DNA. RT inhibitors are divided into two fundamentally different groups: nucleosides (NRTI) and non-nucleosides (NNRTI); AZV was approved six years after the discovery of HIV-1. The NTRIs represent nucleosides, mimic natural ones and are capable of competing with them. Activity, effectiveness and toxicity are highly dependent on the design of the NTRI. NNRTIS were developed to fight the virus selectively. Being approved, RTs reduce the viral load effectively, but toxicity, pharmacokinetics, drug clearance, dosing, cost and drug adherence are limiting factors, and multiple resistance remains the main obstacle [Basavapathruni & Anderson, 2007]. Delivering RTs using non-toxic vehicles can greatly improve the clinical effect.

Once synthesized, the viral DNA is incorporated into a pre-integration complex to be transported to the nucleus. Viral proteins facilitate transportation and integration of the DNA chain into the host genome. At the late phase, mRNAs are produced and move out of nucleus to undergo translation and protein synthesis. After viral particle budding, viral DNA leaves the cell via exocytosis.

The genome of HIV is encoded by single-stranded RNA [Turner & Summers, 1999].

However, HAART prevents HIV-1 infected patients from making a complete recovery [Sekaly, 2008], and this therapy is associated with dangerous side-effects including mitochondrial toxicity and myopathy [Scruggs & Dirks Naylor, 2008], lipodystrophy [Mallewa et al., 2008] associated with insulin resistance and lipid abnormalities [Mallon, 2007], and induced liver injury [Inductivo-Yu & Bonacini, 2008]. Therefore, new approaches to treating HIV-positive individuals are required that are selective and impact only infected cells, or have no effects on healthy cells. Treatment systems that can cross the blood-brain barrier would be advantageous, and gene therapy [Strayer et al., 2008] or delivery using nanostructures could be realistic alternatives.

3. Gene therapy: mechanism of RNA interference

Gene therapy is a technique for replacing mutant genes in cells and tissues, and has been utilized for disorders such as Alzheimer's disease and Parkinson's syndrome [Kelly, 2007]. The ability to repair genes within a cell is a new potential approach for treatment of cells and tissues that possess abnormal gene patterns. Gene therapy is based on two conceptually

different approaches. The first, called up-regulation, suggests delivery of nucleic acids or corresponding constructs for expression of the gene of interest under the control of an appropriate promoter, resulting in increased target activity, i.e. in production of a protein playing the role of a drug. The other approach concerns the delivery of oligomeric genetic materials such as antisense oligodeoxynucleotides or siRNA (short interfering RNA) that cause a decrease in the target activity, resulting in inhibition of harmful mRNA expression and/or synthesis of harmful proteins. Referred to as down-regulation or gene silencing, this approach became key to the development of anti-cancer and anti-HIV vaccines.

RNA interference (RNAi) was first used in plants as a tool for changing the color of petunias [Napoli et al. 1990; Sen & Blau, 2006]. RNAi as a gene silencing tool has wide therapeutic applications and can be utilized in animal cells [Guo & Kemphues, 1995]. Three mechanisms can be applied within a cell, depending on the type of effector molecules: antisense single-stranded oligonucleotides (ODN), double-stranded antisense small interfering RNA (siRNA) and ribozymes.

RNA interference is based on the ability of ODN, siRNA and ribozymes to stimulate specific degradation of an mRNA target with a sequence complementary to one or two strands of ODN, siRNA and ribozymes. When long double-stranded RNA enters a cell, it undergoes cleavage by endonucleases, resulting in short 19-21 bp double-stranded fragments with two protruding nucleotides at the 3'-ends of the strands. These short duplexes, called siRNA, form within a complex with protein catalytic structures causing directed degradation of complementary target mRNA. RNA interference is used to regulate gene expression and as a method for investigating functional genomics in eukaryotes. As for other nucleic acids, one of the main limitations of RNA interference for gene therapy concerns delivery of ODN or siRNA into cells.

4. Barriers and vectors for delivering nucleic acids

To explain the necessity for nucleic acid delivery systems, the barriers to nucleic acid delivery within organisms need to be discussed. Normally, introduction of free nucleic acid is accompanied by its enzymic degradation in the organism. Furthermore, RNAi effectors are unable to cross biological membranes readily owing to their strong negative charge, inducing poor cellular uptake. Therefore, delivery agents should maintain the biological activity of drugs and promote cell penetrating activities so that the process of RNAi is efficient; this necessitates the existence of vectors for nucleic acid packing and transport. Vectors aid nucleic acid delivery to zones necessary for its localization and provide efficient intracellular transport, predominantly to the nucleus. Viral vectors are efficient but shortcomings include high immunogenicity and carcinogenicity in vivo [Mulligan, 1993; Briand & Kahn, 1993]. Compared to viral systems, synthetic (non-viral) systems are characterized by lower efficiency but higher flexibility and safety [Eliyahu et al., 2005]. Normally, packing of nucleic acids is provided by electrostatic interaction of the anionic phosphate groups with positive charges on the synthetic vector, resulting in complex formation.

Nucleic acid complexes with liposomes and various cationic linear polymers are the most widely used non-viral vectors. Complexes with liposomes are called lipoplexes, and those with linear polymers are called polyplexes. However, the development of nanotechnology led to the appearance of new nanocomposites for gene delivery – dendrimers [Eliyahu et al., 2005].

5. Dendrimers as new class of nanoparticles for drug and gene delivery

The application of nanotechnology in biology and medicine induced the appearance of new devices, supramolecular systems, structures, complexes and composites. Dendrimers (from the Greek "dendron" – tree and "meros" – branch) are excellent examples of nanotechnological composites [Newkome et al., 1986; Tomalia, 1995; Fischer & Vogtle, 1999]. They are globular in shape, with a topological structure formed by monomeric subunit branches diverging to the sides from the central nucleus (Fig. 1). Properties of synthesized macromolecules can be precisely assigned in advance by choosing appropriate monomers and functional groups [Newkome et al., 1986; Tomalia, 1995; Fischer & Vogtle, 1999; Bosman et al., 1999]. The following features can be distinguished in dendrimers: (i) multivalent surface containing numerous potentially active sites; (ii) envelopes surrounding the nucleus; (iii) the nucleus with attached dendrons.

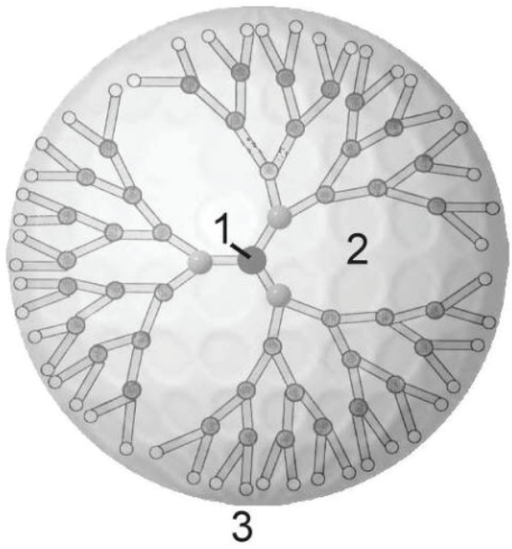

Fig. 1. Dendrimer structure. 1) Nucleus, 2) Internal cavities, 3) Surface groups.

Two main strategies have been used during dendrimer synthesis: a divergent method, in which dendron growth begins from the nucleus, and a convergent method in which already finished dendrimer branches join the nucleus. According to the divergent method proposed by the Tomalia and Vogtle groups [Tomalia, 1995; Fischer & Vogtle, 1999], dendrimer synthesis includes association of monomeric modules in a radial structure, from one branch to another, following definite rules. In particular, the dendrimer increases in size from one layer to another (from one generation to the next). According to the convergent method proposed by Hawker and Frechet [Hawker & Frechet, 1990], branches join the nucleus at the final stage of the process and form the dendrimer, and are grown first in the course of dendrimer synthesis.

An interesting property of dendrimers is the dependence of their solution viscosity on molecular mass, which differs from that for linear polymers [Frechet, 1994]. Solution viscosity for linear polymers is described by the exponential function $\eta \sim C^N$, where C is polymer concentration and N is the exponential parameter ($1 < N < 10$), but the viscosity of dendrimer solutions is described by the linear function $\eta = \eta_0(1 + k\varphi)$, where k is a constant

and φ is the disperse phase volume fraction. Therefore, on increasing dendrimer generation (molecular mass), at a certain point the viscosity in solution begins to decrease. This effect is the result of globular dimensions of high dendrimer generations [Matthews et al., 1998].
With regard to modifications, over 100 types of dendrimers have been synthesized, although there are five common families.
Polyamide amine (PAMAM) dendrimers [Tomalia, 1995] are based on the ethylenediamine nucleus, and their branches are designed from methyl acrylate and ethylenediamine. Half generations of PAMAM dendrimers have surface carboxyls, while complete generations have surface amino groups. At present, there is an abundant choice of PAMAM dendrimers with various types of surface groups. Polypropyleneimine (PPI) dendrimers [Matthews et al., 1998] are based on the butylenediamine nucleus and polypropyleneimine monomers. Besides PPI, another popular abbreviation of these dendrimers is DAB (diaminobutyl), based on the name of the nucleus, and these are commercially available. Phosphorus dendrimers were synthesized by the Majoral and Caminade group [Majoral et al., 2002]. Phosphorus atoms are present in the nucleus and branches of these dendrimers. Carbosilane dendrimers are based on a silicon nucleus and have ammonium or amino groups at the periphery [Ortega et al., 2006]. Polylysine dendrimers are based on the amino acid lysine and have polylysine branches and surface groups [Vlasov, 2006], and these are commercially available.
The architecture and properties of dendrimers depends on the generation. Low generations of dendrimers have an open, flattened and asymmetric shape, but as the generation increases the structure becomes globular and densely packed at the periphery. Inside dendrimers there are empty cavities where small therapeutic molecules can be entrapped and safely transported to targets. Another important feature of dendrimers is monodispersity. The classical polymerization process is usually random and produces molecules of different sizes, whereas the size and molecular mass of dendrimers can be specifically controlled during synthesis.
Dendrimers possess many functional end groups, which are responsible for high solubility and reactivity. Long chain molecules with many reaction sites interact with dendrimers by wrapping around them, as normally happens for single- or double-stranded nucleic acids. These properties make dendrimers suitable for targeting, microarray systems, and catalysis and drug delivery systems [Matthews et al., 1998].

6. Dendrimers themselves as anti-HIV therapeutic agents

Dendrimers are anti-HIV therapeutic agents. PAMAM polyanionic phenyldicarboxylic acid (BRI6195) and naphthyldisulfonic acid (BRI2923) terminated dendrimers were synthesized as inhibitors of the viral replication cycle in different strains of HIV-1 and in various cell lines including those that display reverse transcription resistance. Suppression provided by such macromolecules is based on the interaction with the envelope protein gp120, which prevents the first steps of cell infection, i.e. binding to host-cells. Owing to the different cell penetration rates of BRI6195 and BRI2923 compounds, the latter was demonstrated to exhibit another antiviral activity during reverse transcription and integration steps. Unfortunately, it has been found that some gp120 mutations display inconsistency, preventing the described PAMAM dendrimers from completely and successfully curing patients after treating cells [Witvrouw, 2000].

A new class of polycationic molecules called "VIOLOGEN" was synthesized and investigated by Asaftei and De Clercq as candidate antiviral drugs [Asaftei & De Clercq, 2010]. They represented dendrimers with bipyridiniumhexafluorophosphate end groups consisting of viologen units, synthesized with a phenyl- or benzyl-type core, carrying between one and 90 charges per molecule. Inhibition of HIV-1 replication of some constituents in MT-4 cells were demonstrated at EC50=0.26±0.08 μM, SI=75.7. Investigation of the activity of compounds on peripheral blood mononuclear cells (PBMC) demonstrated their inability to interfere with the viral life cycle, showing that the mechanism of HIV-1 inhibition concerned dendrimers and heparin sulfate interaction. Therefore, it was concluded that viologen compounds block the electrostatic interaction of cell surfaces and viral particles. Polycationic dendrimers were tested in two steric architectures: spheroidal and comb-branched. This demonstrated that spherical branched organization is an advanced property of dendrimeric molecules. Spherical forms of "VIOLOGEN" bound to the viral envelope better than comb-branched dendrimers, indicating increased efficacy against the virus. Moreover, the intensity of viral activity correlated with surface charges, i.e. a lack of charges reduced attempts to stop HIV-1 replication in cells [Asaftei & De Clercq, 2010].

The scientific group led by Prof. Majoral [Pérez-Anes et al., 2010] is developing multivalent catanionic galactosylceramide (GalCer) dendritic analogs with antiviral activity (inhibition of HIV-1 entry into the host-cell), based on treating epithelial cells with a lack of CD4 receptors. The HIV virus targets immune cells via a specific interaction between gp120 and the amino-terminal immunoglobulin domain of CD4 [Ho et al., 1995]. Therefore, it was supposed that the presence of this receptor was the determining factor for cells to absorb small viral particles. However, the human immunodeficiency type 1 virus was subsequently found to bind to CD4 (-) cells. Widely expressed at cell surfaces, glycosphingolipid GalCer plays the role of an alternative receptor for gp120 [Yahi et al., 1994], explaining why success of infection depends on GalCer/gp120 interaction in cells with a blocked or absent CD4 (+)-mediated pathway. The first attempt to use this concept was in 2000, when multivalent polysulfated PPI glycodendrimers were tested as binding antagonists of the virus. Results indicated similar inhibitory and cytotoxicity properties as dextran sulfate [Kensinger et al., 2004]. More recent in vitro studies have demonstrated that HIV-1 inhibitory properties of compounds, based on phosphonic acid terminated dendrimers and N-hexadecylamino lactitol moieties, make them promising anti-HIV drug candidates. However, their low therapeutic indices in cellular studies required scientists to modify the stability of assemblies in vitro.

Another attempt to uncover novel antiviral dendrimers resulted in scientists using the disaccharide cellobiose as a terminal layer of polylysine dendrimers generation 3. Further sulfation of the terminating groups allowed them to interact with the viral surface electrostatically, particularly with the positively charged envelope glycoprotein gp120. Polylysine dendrimers exhibited antiviral activity as high as that of approved drugs, maintaining low level cytotoxicity and revealing additional anticoagulant properties. Very low level anti-HIV-1 activity and anticoagulant activities responsible for uncontrolled bleeding are substantial shortcomings of this method [Han et al., 2010].

The so-called "Trojan horse", in vitro studies of HIV treatments with low cytotoxicity, is the new concept in HIV research. Such an approach has demonstrated that a polylysine dendrimer-based container is the optimal choice for initiating cytotoxic mechanisms

comprising proteins penetrating cells to inhibit the chymotrypsin-like activity of proteasomes. The "Trojan horse" includes small cytotoxic molecules as functioning agents conjugated with a "steric cap", and a relatively big carrier to avoid immediate entry into the catalytic hollow of proteasomes. The effect is thought to be activated by viral proteases via cleavage of the linkage between the agent and nanoparticle, although further investigations are required to validate this type of approach [Buckley et al., 2011].

At present there is only one product based on dendrimers on the market. The product, VivaGel®, is produced by Starpharma and protects again sexually transmitted diseases and human immunodeficiency virus (HIV). It is a vaginal microbicide gel under development for the prevention of sexually transmitted infections (STIs) including genital herpes and HIV infection. The VivaGel® product concept is designed to offer a safe, convenient and affordable means for women to protect themselves from infection with genital herpes and HIV during sex. Surveys demonstrate that there is substantial demand in North America and Europe for such a product, with an estimated billion dollar market for STI prevention products in the developed world.

7. Potential revolution in gene delivery: dendrimers as gene carriers in anti-HIV therapy

No dendrimer-based delivery systems are approved or the subject of clinical trials for HIV-1 treatment as an application of gene therapy. Nevertheless, numerous studies are currently underway to develop vectors based on dendrimeric polymers for improved delivery of approved drugs and nucleic acids, as this is a promising approach that can potentially overcome all known safety issues. There are several reviews concerning the application of nanotechnology [Neves et al., 2010; Mallipeddi & Rohan, 2010; Sharma & Garg, 2010], but none provides total and complete descriptions of associated problems. This sub-section has, as far as possible, attempted to summarize all attempts to elaborate effective nucleic acid carriers by applying various types of dendrimers, generations and with different modifications.

HAART antiviral therapy has critical side effects and does not provide complete recovery from infection. Furthermore, some medical components often included in drug cocktails for antiviral chemotherapy (for example NRTIs) cause intensified neuropathological disorders [Cherry et al., 2003] that can lead to nervous system degradation. Targeting familiar drug molecules directly to infected cells would improve their safety.

Dendrimer-based carriers were developed to support, rationalize and improve drug efficiency, avoiding consequences observed for pure drugs that were administered without special carriers. Polymolecular compounds were proposed as a delivery system. Nanogel particles consisting of PEG- (polyethylene glycol) and Pluronic-PEI- (polyethylenimine) biodegradable networks, i.e. star PEG-g-PEI and PAMAM-PEI-g-PEG, were synthesized and investigated in terms of drug delivery analysis. Recent studies have shown that the phosphorylate-modified nucleoside analogs zidovudine (AZT) and didanosine (ddI) coupled with nanogels were effective in terms of cellular uptake and had increased and upgraded target selectivity. Moreover, the process of mtDNA depletion, responsible for neuropathy reinforcing, was reduced threefold by administering NRTIs with nanocarriers rather than using a pure NRTI injection [Vinogradov et al., 2010]. Such vectors were demonstrated to be a promising tool for reaching viral reservoirs in the central nervous system (CNS) and were capable of crossing the blood-brain barrier [McGee et al., 2006].

When cells infected with HIV-1 can be killed in a targeted manner, mature non-proliferating active macrophages in the organism can reproduce viral particles, and this is one reason for the failure of existing therapies. Development of non-toxic targeting nanocarriers could be vital in overcoming this problem.

Modified PPI dendrimers have been used for the aim of targeted delivery into cells involved in highly conserved retention, and mannosylated PPI dendrimers possess double the effect in terms of viral attack, improving biological properties of drugs and displaying antiviral activity themselves owing to specific binding and their penetrating ability via cell receptors [Dutta & Jain, 2007]. As demonstrated for complexes of coupled tuftsin and zidovudine, antiretroviral activity of each separate compound was not enough for them to be considered anti-HIV agents in isolation, but when conjugated they represent a good method and are likely to enter phase I clinical trials [Fridkin et al., 2005]. Modifying dendrimers with tuftsin revealed them as the most biocompatible carriers, demonstrating striking results in studies concerning infected macrophages [Dutta et al., 2007]. Tuftsin is a tetrapeptide (Thr-Lys-Pro-Arg) related to macrophage activation, and it binds specifically to macrophages, monocytes and polymorphonuclear leukocytes. Its covalent conjugation with 5 generation PPI dendrimers increases entrapment (49.3%) of Efavirenz into the internal cavities of the transmitting agent, compared with 37.5% entrapment efficiency for unmodified dendrimers. Such vehicles significantly prolong release of the non-nucleoside reverse transcriptase inhibitor Efavirenz through controlled drug administration. This delivery system also provides 34-fold increased cellular uptake and more than 7-fold augmented anti-HIV activity compared with pure drugs without carriers [Dutta et al., 2008].

PPI dendrimers are characterized as good binding agents for antisense oligodeoxynucleotides, resulting in compact complexes with close to neutral charge. Amino-terminated dendrimers of second, third and fourth generations can produce dendriplexes suitable for cell transfection and to release cargos in a time-dependent manner [Pedziwiatr-Werbicka et al., 2011]. Only first stage results have been published so far, but this should not minimize the importance and potential of such an approach.

The most studied PAMAM dendrimers have the potential to inhibit viral replication by blocking interaction of the Tat peptide and transacting responsive element (TAR) RNA. This process is essential for the production of full-length viral transcripts and proliferation of the virus. Establishment of new drugs that disrupt this binding within cells is a new concept for anti-HIV-1 therapeutics. [Zhao et al., 2004].

Carbosilane dendrimers containing ammonium or amine groups at their periphery are nanocarriers that are appropriate vectors for successful gene therapy against HIV-1. They are water-soluble and polycationic, and effectively bind small nucleic acid chains. After complete dendriplex formation, antiviral oligodeoxynucleotides (ODN) were immune to the actions of their binding proteins [Shcharbin et al., 2007; Chonco et al., 2007], and the inhibitory effect of viral replication in cells in the presence of human plasma was increased by 25-30%, similar to that for naked ODNs. In order to conserve the biological ability of siRNA to have a role in the RNA interference process inside infected lymphocytes, second generation amino-terminated carbosilane dendrimers (2G-NN8 and 2G-NN16) were tested, resulting in formation of strong complexes with siRNAs (siP24, siNEF and siGAG1 [Shcharbin et al., 2011]. These are antisense to HIV regions responsible for p24, nef and gag protein expression, respectively, with diameters between 300 and 370nm, protection against RNase digestion, low cytotoxicity at therapeutic concentrations (sufficient to 40% HIV

inhibition), and comparatively good ability to inhibit viral replication in peripheral blood mononuclear cells and human leukemia T lymphocytes. Gradual hydrolysis of the interior carbon-silicon bonds leads to time delayed cargo liberation (4-24 hours), which would be important for treatment as the necessary amounts of siRNA and ODNs would be decreased and the effect is believed to be longer [Weber et al., 2008]. 2G-NN16 dendrimers coupled with antiviral siRNA have been demonstrated to cross the blood-brain barrier (BBB) in an in vitro model, making the possibility of conducting gene therapy using dendrimer-based delivery in human astrocytes and to fight viruses within CNS cells a more realistic option. Transfection with infected and non-infected human astrocytoma cells did not result in significant cytotoxicity when treated with up to 24μM/ml dendriplexes, while sequence-specific down-regulation of the housekeeping gene GAPDH was observed, indicating the ability of siRNA to exert its biological function. At the same time, inhibition of X4-HIV NL4-3 and R5-HIV strains of HIV-1 by dendriplexes was 80% as effective as treating cells with naked siRNA. In spite of numerous positive results for carbosilane dendrimers as a delivery system in in vitro studies, this approach is still at the pre-clinical experimental stage. Theoretically, dendriplexes did not have sufficiently small-scale diameters to penetrate deeply into brain issues, but in practice transcytosis though the blood-brain barrier was demonstrated. Furthermore, structural and functional alterations of BBB occur during HIV infection [Jiménez et al., 2010]. Injection of pure dendrimers causes a high rate of cell death due to electrostatic interactions of polycationic surface groups and negatively charged cell membranes, although this has no effect on pivotal properties of dendritic cells (mature and immature) in terms of linking adaptive and innate immunities [Pion et al., 2010].

8. Conclusion

Dendrimers are nanomaterials with great potential to be anti-HIV therapies of the future. However, despite potential applications, at present there is only one product based on dendrimers available on the market. This product, VivaGel® (Starpharma, Australia), protects against sexually transmitted diseases and human immunodeficiency virus. Systematic studies concerning dendrimers are required for the development of new dendrimer-based antiretroviral drugs.

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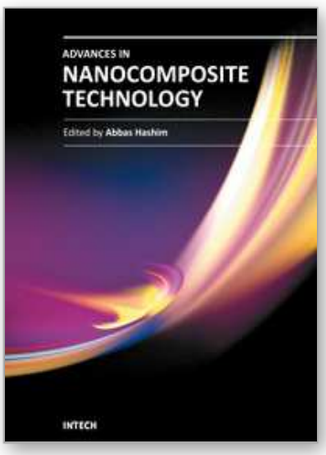

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The book â€œAdvances in Nanocomposite Technologyâ€ contains 16 chapters divided in three sections. Section one, â€œElectronic Applicationsâ€, deals with the preparation and characterization of nanocomposite materials for electronic applications and studies. In section two, â€œMaterial Nanocompositesâ€, the advanced research of polymer nanocomposite material and polymer-clay, ceramic, silicate glass-based nanocomposite and the functionality of graphene nanocomposites is presented. The â€œHuman and Bioapplicationsâ€ section is describing how nanostructures are synthesized and draw attention on wide variety of nanostructures available for biological research and treatment applications. We believe that this book offers broad examples of existing developments in nanocomposite technology research and an excellent introduction to nanoelectronics, nanomaterial applications and bionanocomposites.

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