Review Article
AMERICAN JOURNAL OF PHARMACY AND HEALTH RESEARCH
www.ajphr.com
2017, Volume 5, Issue 5
ISSN: 2321–3647(online)

A Review On Application of HIV Inhibition Using Carbon Nanotubes

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ABSTRACT

Successful treatment and Control of HIV/AIDS is one of the biggest challenge of 21st century. The situation demands development of effective prevention strategies to control the pandemic of AIDS. Due to availability of an effective HIV vaccine, antiretroviral drug and nucleic acid therapeutics like siRNA have been explored for HIV prophylaxis. Nanomedicine, the structure is similar to biological structures and useful for in-vitro and in-vivo researches. Carbon nanotubes were discovered in 1991 by Sumio lijima of NEC. Nanuotube electronic devices provide highly specific electronic sensors for detecting clinically important bimolecules like antibodies associated with human autoimmune disease and targeted delivery of drugs.

Keywords: AIDS, Nanotube, Carbon nanotube, Graphene tubes.

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Received 08 January 2017, Accepted 21January 2017

Please cite this article as: Mohanavelu N *et al.*, Niosomes: An Exploration of A Novel Research Platform In Drug Delivery. American Journal of Pharmacy & Health Research 2017.

INTRODUCTION

AIDS- Acquired Immune Deficiency Syndrome

Immune deficiency Virus is a disease that attacks the human immune system. HIV uses human T-Cells and CD4 cells to reproduce, which eventually destroys those cells and destroys the immune system. HIV is suppressed in the body using antiretroviral drugs, or ARVs. Highly active antiretroviral therapy (HAART) that combines multiple antiretroviral drugs may be implemented for treatment. Thirty antiretroviral drugs are approved by the U.S. Food Drug Administration for use in treating HIV infection. These do not eliminate HIV from the body, but instead suppress the virus and make it possible for those infected with HIV to live longer lives. The virus can be suppressed for decades using therapies. Five classes of HIV drugs are on the market, each of which attacks the virus at different points in its evolution. Some drugs work by blocking a step in virus reproduction, while others prevent the virus from copying its own DNA or from entering the cells.[1]

Antiretroviral drug used in HIV are Stavudine (D4T), delavirdine (DLV), saquinavir (SQV), Ampenavir, Dapivirine, Ritonavir, Indinavir, ritonavir, atazanavir, and efavirenz, D4T, DLV, SQV, D4T-nucleoside reverse transcriptase inhibitor, Ritonavir, Lopinavir and Efavirenz, Rilpivirine, Stavudine.[2]

Anti-retroviral therapy is associated with numerous complications that are influenced by intake of other drugs by the patient, and other underlying conditions in the patient such as hepatitis and tuberculosis. The common adverse effects of ART include: Bleeding events,

Loss of bone density, Bone marrow suppression, increased risk of heart attacks, Gallstones, Insulin resistance and diabetes mellitus, Altered lipid metabolism (dyslipidemia), Nausea and vomiting, fatty change in liver, Hyper sensitivity reactions, Lactic acidosis, Altered body fat distribution, Myopathy (muscle involvement), Peripheral neuropathy, Renal stones, Stevens – Johnson syndrome. Toxicities are managed by modifying dosage or switching over to an alternative drug or regimen. The patient's viral load needs to be monitored at regular intervals to ensure continued viral suppression. In spite of such interventions, the drug compliance may be poor in some patients.[3]

Limitations

The overall benefits of viral suppression and improved immune function as a result effective antiretroviral therapy (ART) far outweigh the risks associated with the adverse effects of some antiretroviral (ARV) drugs. Fortunately, newer ARV regimens are associated with fewer serious

and intolerable adverse effects that regimens used in the past. Generally, less than 10% of ART – native patients enrolled in randomized trials have treatment- limiting adverse events. The clinician must consider potential adverse effects when selecting an ARV regimen, as well as the individual patient's comorbidities, concomitant medications, and prior history of drug intolerances.

In Gene therapy technique, delivery of siRNA to specific cells and tissues has been the major challenge in realizing the potentials of RNAi. Nanotechnology provide a platform to solve this problem by providing a non-viral alternative for effective and safe delivery. The first non-targeted delivery of siRNA in humans through self-assembling ,cyclodextrin polymers-based nano particles for cancer treatment have recently entered Phase I clinical trial. [4]

Nanomedicine

Nanomedicine is the application of the nanotechnology, which ranges from application of nanomaterials to nanoelectronic biosensors medicinally. The functionality can be attain to nanomedicine by interaction with the biomolecule. As most of nanomaterial structure is similar to the biological structures these can be widely useful for in vitro and in vivo researches. With of invention, its widely using in the development of diagnostic devices, analytical tools, drug delivery vehicles and physical therapy applications. Nanotechnology involves the manipulation of matter at the level of atoms, molecular fragments. According to definition, Nanotechnology is the manipulation of matter with at least one dimension sixed from 1 to 100 nanometers. Nanotechnology may be employed to generate many new materials and devices with a host of applications, including the field of medicine (nanomedicine). The use of nanotechnology as an approach for delivery of drugs is revolutionizing medical treatment in several fields of medicine. Cancer chemotherapy has seen the biggest impact so far, with significant advances in the last few decades.[2]Using nanotechnology, it has become possible to achieve improved delivery of poorly water-soluble drugs, targeted delivery of drugs to specific cells or tissues and intracellular delivery of macromolecules.[5]

Nanotechnology- based platforms for systemic delivery of antiretroviral drugs could have similar advantages. Controlled-release delivery systems can enhance their half-lives, keeping them in circulation at therapeutic concentrations for longer periods of time. This could have major implications in improving adherence to the drugs. Nanoscale delivery systems also enhance and modulate the distribution of hydrophobic and hydrophilic drugs into and within different tissues due to their small size. This particular feature of nanoscale delivery systems appears to hold the most promise for their use in clinical treatment and prevention of HIV. Specifically, targeted

delivery of antiretroviral drugs to $CD4^{+}$T cells and macrophages as well as delivery to the brain and other organ systems could ensure that drugs reach latent reservoirs.[6] Moreover, by controlling the release profiles of the delivery systems, drugs could be released over a longer time and at higher effective doses to the specific targets.

Macrophages, the major HIV reservoir cells, have various receptors on their surface such as formal peptide, mannose, galactose and Fc receptors, which could be utilized for receptor-mediated internalization. The drug stavudine was encapsulated using various liposomes (120-200nm) conjugated with mannose and glactose, resulting in increased cellular uptake compared with free drug or plain liposomes, and generating significant level of the drug in liver, spleen and lungs. Stavudine is a water-soluble drug with a very short serum half-life (1h). Hence, the increased cellular uptake and sustained release in the tissues afforded by targeted liposomes is a major improvement compared with free drug zidovudine, with half-life of 1h and low solubility, was also encapsulated in a mannose-targeted liposome made from stearylamine, showing increased localization in lymph node and spleen. An important factor to consider here is that although most of the nucleoside drugs such as stavudine and zidovudine have short serum half-lives, the clinically relevant half-life is that of the intracellular triphosphate form of the drug.

Types of Nanomaterials

Types of Nanomaterial used in HIV therapeutics	Advantages	Limitations
• Liposome	• Quick clearance from the circulation and allows delivery of antiretrovirals using macrophages with greater entrapment efficiency and a longer half-life in circulation • Ideal for transdermal delivery	• Hydrophilic drug loading capacity is low due to very low volume of core, there by limiting their long term use • Physical and biological stability of the antiretroviral drug is less
• Dendrimers	• Properties of the dendrimer depends on the multivalent surface • The precise physicochemical properties of the dendrimer can be controlled by controlling the core groups, the extent of branching and the nature of the functional groups on the surface	• Low therapeutic index and cytotoxicity

• Synthetic polymeric nanoparticle like-polylactides, polyglycolides, polyanhydrides, polyorthoesters, polycyanoacrylates, polycaprolactone	• Precise chemical composition • Highly predictable physical properties such as controlled rate of disassociation, permeability, degradation, erosion and targeting capability • Nontoxic and free from leachable impurities	• Biodegradable
• Inorganic nanoparticles-Iron oxide, Quantum dots and rods Gold particles, Organically modified silica particles	• Posses outstanding optical, catalytic, electronic and magnetic properties • Uniquecharacteristic properties such as nanometer dimensions, tunable imaging properties and multi functionality	• Immunogenic • Toxicity issues
• Natural polymers prepared from biologically active agents on encapsulated within natural polymers such as-Cellulose, gelatin, chitosan, pullulan, alginate, gliadin	• Mildly biodegradable and immunogenic nanoparticles	• Very widely varied in physical and chemical composition • Biodegradable
• Micelles	• Slower rate of dissociation ,allowing retention of loaded drugs for a longer period of time and eventually achieving higher accumulation of a drug at the target site	• Drug absorption and activity depends on the release from micelle • Surfactants irritate mucous membrane

Nanotechnology can impact HIV therapy at several levels. (1) Nanoparticles by themselves have therapeutic effects since they can penetrate and neutralize the virus, by structural interference with viral assembly and thereby inhibit viral replivation. (2) Nanotechnology allows improved delivery platforms for systemic delivery of antiretroviral drugs, by allowing controlled release of antiretroviral drugs in circulation, thereby enhancing their half-lives and effectiveness, all of which can have a major implication in improving adherence to drugs in HIV infected patients. (3) Gene immunotherapy can be significantly improved using various nanomaterials. Nanotechnology-based vaccines have the ability to target specific immune cells, eliciting a controlled and sustained HIV-1 specific antibody and cellular immune response.

Limitations

There has been tremendous development over the last decade with respect to the types of nanomaterials available for biomedical applications; an enormous range of shapes, sizes, surface

modifications and functional modality options have been developed, but the main issue of their interaction in biological systems remains to be resolved. Although, some degree of success is observed in vitro studies, many studies have not moved beyond the preclinical stage due to challenges that include unwarranted interactions with plasma proteins in systemic circulation, inability to overcome biological barriers, nonspecific distribution in the body, and aggregation and accumulation within specific organs such as kidney resulting in toxicity. Thus toxicity of nanomaterials, stability in physiological conditions and a lack of adequate reliable and affordable HIV/AIDS animal models for in-vivo studies, during these nanoparticles are some of the key obstacles in HIV-1 nanotherapeutics. In spite of these limitations, nanotechnology holds great potential for impact in the field of HIV treatment and prevention. Multidisciplinary research across disciplines of biology, medicine, chemistry, pharmaceutical sciences, and bioengineering will revolutionize the field of nanomedicine in the near future.[2]

Carbon nanotubes & graphene

Carbon nanotubes are allotropes of carbon with a cylindrical long hollow structures and have mechanical, electrical, thermal, optical and chemical properties and these nanotubes are constructed with length to diameter ratio of 132,000,000:1. Single walled carbon nanotubes are being used as a platform for investigating surface-protein and protein-protien binding and also to develop highly specific electronic biomolecule detectors. The scheme combined with the sensitivity of nanotube electronic devices provides highly specific electronic sensors for detecting clinically important biomolecules like antibodies associated with human autoimmune disease.

Graphene, a two-dimensional, thin and single-layered sheet of sp^2 hybridized carbon atoms, hexagonal lattice in which one atom forms each vertex has attracted much attention from researchers due to its interesting mechanical, optical, thermal, electrochemical and electronic properties. These exceptional properties have opened up new opportunities for the application of this nanomaterial in the future devices and systems.[7]Graphene and its derivatives have shown outstanding potentials in many fields such as nanoelectonics, engineering nanocomposite materials energy storage, field effect transistor (FET), organic light emission diodes (OLED), sensors, catalysis and biomedical application (biosencor, biodevices, drug and gene delivery, cancer therapy etc). Classification of carbon nanotubes

- Single –walled
- Multi-walled

- Double-walled
- Torus
- Fullerence
- Nanobud
- Functionalized CNTs[8]

Characterisation and properties of CNTs

- RAMAN spectroscopy suitable for the quick and reliable screening of the presence of SWCNT
- Transmission electron microscopy allowing for the assessment of detailed structures
- CNTs have very interesting physicochemical properties such as ordered structure with high ratio, ultra light weight, high mechanical strength, high electrical conductivity, high thermal conductivity, metallic or semi metallic behavior and high surface area.
- Extraordinary electronical conductivity, heat conductivity, and mechanical properties.
- The carbon nanotubes are expected to have high stiffness and axial strength as a result of the carbon-carbon sp^2 bonding.
- Nanotubes offer a natural template for exploring the effects of reduced dimensionality towards fabricating the best thermoelectric material.

Carbon nanotubes have the right combination of properties- nanometersize diameter, structural integrity, high electrical conductivity, and chemical stability- that make good electron emitters. Electron field emission from carbon nanotubes was first demonstrated in 1995, and has since been studied intensively on various carbon nanotube materials.

Electronic properties

Graphene has very high electrical conductivity as it is a zerogap semi-conductor, because its conduction and valance bands meet at the Dirac points. In grapheme, each Carbon atom is bonded with three other atoms due to sp^2-hybridization. This leaves one electron in the third dimension freely available for electronic conduction. Electronic mobility of Graphene is very high even at room temperature. It has been experimentally proven that its electron mobility is nearly independent of temperature.

Mechanical Properties

According to Changgu Lee, Graphene is the strongest material ever tested, with a tensile strength of 130 GPa and a Young's Modulus (defines stiffness) of 1 TPa . Apart from this, Graphene is unbelievably light, weighing about only 0.77 mg/m^2.

Optical properties

Due to Graphene's properties of wavelength-insensitive ultrafast saturable absorption, full band mode locking has been achieved.

Application of CNTs

The advancement of new-found nanomaterials provides a fascinating opportunity for development in different fields because of their structures, components and properties. In comparison with its precursor, carbon nanotube (CNT), grapheme exhibits some merits like low cost, two external surfaces, facile fabrication and modification and absence of toxic metal particle.[9] The variety of these is vast, and the commercialization timelines involved vary from now to ten years from now or more. Some of the potential markets are enoromous which will leave us the taste of the possibilities.

MWNTs can offer the same improvements in strength to a polymer composite without the blackening and often with a smaller amount of added material (Called the filler). The greater aspect ratio (i.e. length compared to diameter) of the newer material can make plastics conducting with a smaller filler load, one significant application being electrostatic painting of composites in products such as car parts. Additionally, the surface of the composite is smoother, which benefits more refined structures such as platens for computer disk drives. The inverse progression is seen in terms of ease of manufacturing – the more perfect, and thus more structurally valuable, the material, the harder it is to produce in quantity at a good price. The improvements seen in the strength -to - weight ratios of composite materials could soar, impacting a wide variety of industries from sports equipment to furniture, from the construction industry to kitchenware, and from automobiles to airplanes and spacecraft (the aerospace industry is probably the one that stands to reap the greatest rewards). In fact a carbon nanotube composite has recently been reported that is six times stronger than conventional carbon fiber composites.

The Bio-medical application to nanotechnology provides a valuable route for further miniaturization and improvement of performance of artificial devices. The synergetic future of nano graphene and biotechnology holds great promise for its applications in the fields like gene and drug delivery, Tissue engineering and cancer therapy.

Carbon nanotubes in HIV

Recent breakouts of SARS, avian flu and swine flu have indicated that infectious disease has become a critical public health issue with global concerns. Some infectious diseases, such as AIDS, have turned out to be deadly, and no effective therapies have been available to date. The

medicinal application of nanotechnology has shed light on the quick diagnosis and effective therapy of infectious diseases. According to Kang et al, pristine SWCNTs exhibited an antimicrobial effect in a size-dependent manner, indicating that they might be useful as building blocks for antimicrobial therapeutics. Organic modification on the surface of CNTs can generate sites for the attachment of bioactive molecules, the secondary structure of which can be preserved and hence elicit specific anti-epitope antibodies. The antibody recognition to the conjugates was facilitated by this coupling. CNTs can also play a part in viral diseases therapy by providing high- sensitive detecting devices. For example, a coordinated bio- sensor made of Au nanoparticles answers SWCNTs has been studied for detecting the nanomolar scale of HIV-1 PR, an aspartic protease responsible for virion assembly and maturation. The realization of sensitive detection of this protease was promising to expedite development of effective HIV-1 PR inhibitors. Another example in viral disease diagnosis is the electrical detection of hepatitis C virus RNa. A large surface-to-volume ratio and unique electronic properties made CNTs a welcome component for fabricating high-sensitive biodetectors, which were crucially needed in the diagnosis of viral diseases and the development of new anti-viral drugs. It was predictable, therefore that CNTs might contribute considerably to the treatment of infectious diseases in the future.

A fusion protein, with a peptide transduction domain and a double stranded RNA-binding domain was used to encapsulate and deliver siRNA to T-cells in-vivo. CD4-CD8-specific siRNA delivery caused RNAi responses with no adverse effects such as cytotoxicity or immune-stimulation. Similarly a protamine-antibody fusion protein based siRNA delivery demonstrated that siRNA knockdown of the gag gene can inhibit HIV replication in primary T-cells.[10]

An effective vaccine must induce a potent immune response, either at cellular level, stimulating cytotoxic T cells which target and destroy infected cells or at humoral level, through stimulation of the production of neutralizing antibodies which promote sonization and consequent pathogen clearance. Vaccines against some pathogens, like HIV or Malaria, due to their complexity, would require both responses to be fully efficient in preventing infection and eliminating circulating pathogens. Innate immune responses are also important in vaccination, since they play a crucial role in antigen presentation and immune cells recruitment to infection sites.

CONCLUSION

Nanotechnology can impact the treatment and prevention of HIV/AIDS with various innovative approaches, Treatment options may be improved using nanotechnology platforms for delivery of

antiretroviral drugs. Controlled and sustained release of the drugs could improve patient adherence to drug regimens, increasing treatment effectiveness. Targeted nanoparticles utilizing ligands such as mannose, galactose, tuftsin and fMLE peptides have been used to target macrophages, major HIV viral reservoirs. Newer treatment approaches, such as gene therapy and immunotherapy, can be enhanced with nanotechnology. Overall, these are exciting times for nanotechnology research and the pace of scientific discovery is beginning to gain momentum. It is widely accepted that with continued support, medicine and the field of HIV/AIDS will be important beneficiaries of nanotechnology for years to come.

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