Chapter 7
Discussion on Advanced Targeted Nanomedical Application Scenarios for Treatment of Some Chronic Diseases

7.1 Introduction

In this chapter, classical discussions on the possible application of the ATN solution to the treatment of some chronic diseases are provided. The diseases discussed include cancer, Alzheimer's disease, acquired immunodeficiency syndrome (AIDS) and cardiovascular diseases. For each disease, discussion trails the pathophysiology and pathways of its occurrence. How the abnormalities in cell death regulation (apoptosis) significantly mediate the occurrence of some of these diseases is highlighted. Indeed, the inappropriate response of a cell to undergo apoptosis is a factor in many human conditions including cancer, AIDS, ischemia and neurodegenerative diseases [1]. The exposure in this chapter, like the rest of this work, is structured in a way that makes it accessible to readers with little or no background in medical science. Exemplary suggestions for defining possible ATN solutions to the various medical challenges mentioned above are given.

7.2 ATN Application to Cancer Treatment

7.2.1 Cancer Pathophysiology and Pathways

Cancer refers to a group of diseases that result from the uncontrolled growth of abnormal cells anywhere in a body (for example, breast, colon, lung and skin). A key driver of cancer is the impairment of a vital cellular function called apoptosis or programmed cell death. Apoptosis is generally crucial for processes such as proper embryonic development, regular cell turnover and accurate functioning of the immune system [2]. Hence, in response to damage to a cell's DNA and other cellular

U. Chude-Okonkwo et al., *Advanced Targeted Nanomedicine*, Nanomedicine and Nanotoxicology, https://doi.org/10.1007/978-3-030-11003-1_7

stresses, a normal cell will usually try to repair the damage [3]. But when the repair fails or if the damage (like the error in the DNA) or stress is great, the cell will initiate apoptosis.

Apoptosis is generally characterised by distinct morphological characteristics and energy-dependent biochemical mechanisms that result in the self-annihilation of the associated cells. It can occur through two pathways, namely the mitochondrial/intrinsic pathway [4] and the death receptor/extrinsic pathways [5]. The mitochondrial pathway is often initiated by intracellular stresses, while the death receptor pathway is initiated by the recruitment of cell surface receptors with specific ligands.

The mitochondrial pathway is tightly regulated by a group of structurally related proteins called the BCL-2 family [6]. These proteins are of two types, pro-apoptotic and anti-apoptotic, which regulate the permeability of the mitochondrial membrane. Under the influence of stress stimuli, such as the deprivation of growth factor, DNA damage, heat shock and genomic instability, the pro-apoptotic BCL-2 proteins alter the outer mitochondrial membrane by forming mitochondrial apoptosis-induced channels/pores in it [7]. These membrane channels allow the release of *cytochrome c* and other cytotoxic proteins into the cytosol. The *cytochrome c* interacts with the cytosolic adapter protein *Apaf-1* to activate a group of cysteine aspartic acid-specific proteases known as caspases, whose activation is central to apoptosis [8]. Several proteins are degraded by the caspases culminating in eventual cell death.

The extrinsic pathway is activated through diverse external signals from other cells in the body. For this pathway to be activated, the extrinsic signal may come from other cells such as the T lymphocytes [9]. The death ligands, often referred to as the FAS (also called *Apo-1* or *CD95*) ligands, bind to the death (FAS) receptors causing the oligomerisation of the receptors. This ligand–receptor complex initiates the clustering of adaptor proteins called FAS-associated death domain (FADD). The FADD protein then binds to a protein interaction domain termed death-effector domain (DED). The DED binds to a homologous motif in Procaspase-8. Upon recruitment by DED motif, Procaspase-8 oligomerisation drives its activation through self-cleavage. Active Caspase-8 then activates downstream Caspase-3, thereby committing the cell to apoptosis [10]. Just like in the case of the intrinsic pathway, several proteins including DNA fragmentation factor inhibitor are then degraded by the caspases culminating in eventual cell death.

In contrast to normal cells, cancer cells are generally less sensitive to similar stresses and tend to avoid apoptosis. The inappropriate response of a cell to undergo apoptosis is a factor in oncogenesis (cancer development) as well as other human conditions. Both the mitochondrial and the extrinsic apoptotic pathways are evaded by cancerous cells. The intrinsic pathway may be more sensitive in cancer formation than the extrinsic pathway, as many of the cellular stresses encountered by cancer cells are activators of this pathway [11]. In the mitochondrial pathway, a very common cause of oncogenesis is mutation of the p53 protein. The p53 protein is a nuclear transcription factor with a pro-apoptotic function for the regulation of the cell cycle. It is believed that the mutation of this gene alters its ability to regulate cell apoptosis, the checkpoints in the cell cycle, DNA repair, senescence and genomic integrity [12]. Hence, any mutation that causes p53 to lose any of its function will let the cell grow

indefinitely without control. Another important factor is the balance between the pro-apoptotic and anti-apoptotic members of BCL-2 proteins. Many cancers are able to evade apoptosis through the downregulation of pro-apoptotic proteins, or an increase in BCL-2 expression, thereby dysregulating the BCL-2 family members. Specifically, in cancer cells, a mutation of the BCL-2 gene that results in increased expression will suppress the normal function of the pro-apoptotic proteins. Conversely, if a mutation on the pro-apoptotic genes causes a downregulation of expression, the cell will also lose its ability to regulate apoptosis, again causing oncogenesis [12].

7.2.2 Exemplary Perspective of ATN Approach to Cancer Treatment

The discussion so far indicates that cancer cells result from a combination of factors that may have altered the cells' integrity, mechanism and structure in many different and probably random ways. Indeed, cancer cells express colossal individuality and heterogeneity, each with its own unique characteristics and highly variable and unpredictable responses. Consequently, there are no unique and uniform drugs for the treatment of cancer. Moreover, cancer cells are known to have the capability of adapting to new targeted therapies and developing drug resistance [13, 14]. Hence, a broad spectrum of therapeutic approaches may be required for cancer treatment. There are various contemporary approaches to the treatment of cancer. The particular approach or set of approaches employed will depend on the type/stage of cancer and other personalised physiological and molecular information relating to the patient. Examples of cancer treatment modalities include surgery, chemotherapy, radiation therapy, immunotherapy and hormone therapy.

7.2.3 Contemporary Modalities for Cancer Treatment

Surgery modality involves the removal of the cancer cells and probably, the surrounding tissues and lymph nodes. This approach is most effective when the cancer is still localised within its original site, which must also be accessible. There may be the rare possibility that the surgery might aid in the spread of cancer.

Chemotherapy modality [15] is a popular approach to cancer treatment, where specialised drugs such as *doxorubicin*, *methotrexate* and *cisplatin* are injected into the body to kill cancer cells. It is a systemic treatment, meaning that the drugs flow through the bloodstream to nearly every part of the body. Unlike surgery, which targets a specific location, chemotherapy targets all body locations that are accessible to blood flow. Chemotherapy primarily works by acting in many inhibitive ways to disrupt the division of cancer cells. It is good at killing cells that are dividing rapidly like the cancer cells and other cells in the body. As a result, the unintended damaging

of other healthy cells in the body gives rise to side effects such as loss of hair, poor appetite, nausea and vomiting, diarrhoea or mouth and lip sores [16].

Like the surgery modality, the radiation modality [17] targets cancers localised in the body. Radiation uses a directed high dose of X-ray beam to destroy cancer cells by inflicting overwhelming damage to their DNA, which causes the cells to stop dividing and die. The side effects of radiation are usually mild and depend on the amount of radiation given (the dose), the part of the body that is treated and the individual patient's response [18].

Immunotherapy modality [19] aids the body's natural ability to fight diseases to destroy cancer cells. Monoclonal antibodies, interferon, interleukin-2 and colony-stimulating factors are some types of biological therapies. The side effects caused by biological therapy vary with the specific mode of treatment. In general, these treatments tend to cause flu-like symptoms, such as fever, chills, muscle aches, loss of appetite, weakness, nausea, vomiting, diarrhoea and swelling [20].

In the use of hormone therapy [21] to treat cancer, certain cancers that depend on hormones for their growth are targeted. Oncogenesis associated with certain categories of cancer such as breast and prostate cancers depend on hormones to develop. This therapy may involve the removal of certain organs that produce some of the hormones that promote cancerous growth or using drugs to stop the secretion of such hormones. Some of the side effects include fluid retention, tiredness, weight gain, vomiting, nausea and loss of appetite [22]. Other effects include the loss of the functionalities associated with the affected hormones.

7.2.4 Hallmarks of Cancer Diseases

In [23], the hallmarks of cancer are illustrated (see Fig. 7.1). These include biological capabilities such as evading apoptosis, evading destruction by the immune system, evading cell growth suppressors, programming energy metabolising, promoting angiogenesis, facilitating endless replicative potential, sustaining proliferative signalling and triggering metastasis. These capabilities are underlined by genome instability, mutations and tumour-promoting inflammation. An understanding of these hallmarks is crucial to providing a solid foundation for understanding the biology of cancer and projecting novel and effective therapeutic approaches to the disease.

7.2.5 Possible Directions of ATN Solution to Cancer Treatment

While there have been many solutions and treatments proposed and applied to cancer treatment, the disease has remained elusive to any permanent and unified treatment. This is basically as a result of the complexity and heterogeneity of cancer biology

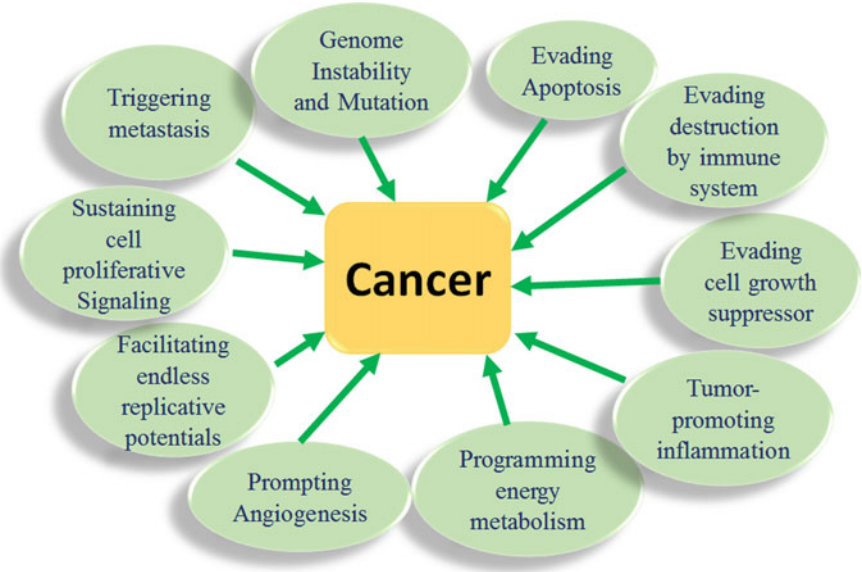

Fig. 7.1 Therapeutic targeting of the hallmarks of cancer

as well as the incomplete understanding and unpredictability of the disease. The nature of cancer, summarised in the hallmarks depicted in Fig. 7.1, is rooted in fundamentally entangled molecular mechanisms of cell operation, which equip it with very resilient capabilities and incredible survival strategies. Therefore, there is the need to explore more options in the frontier of the war against cancer. For the fact that cancer manifest as a result of fundamental mechanisms of cell operation, a multi-facet approach to cancer research and treatment is a promising option. Such effort that would unite ideas and experts from a broad cross section of related and unrelated fields could help in tackling this difficult health challenge and enable the development of a permanent cure.

One such option is rooted in the principle of nanomedicine and ATN in particular, which are purely interdisciplinary medical solutions. Indeed, modalities such as chemotherapy, radiation therapy, immunotherapy, hormone therapy and even surgery, can be offered on the platform of the ATN solution in a more effective way. This can be achieved by using various techniques/principles from the nanomedical arsenal such as targeted drug/agent delivery, nanorobotics, molecular communication, systems biology and other ATN subsystems and concepts.

The ATN solution promises to treat the cancer problem as a communication problem with a communication engineering solution. In this sense, cancer is considered in part as a breakdown of intercellular regulation for which systems biology ideas and tools built upon the principles of communication engineering can be employed

to acquire an in-depth, unified understanding of the cancer phenomena and characteristics. This will promote the discovery of new drugs and approaches for the development of vaccines. The ATN tool of targeted drug delivery can help to improve drug therapeutic index by ensuring efficacious bioavailability of cancer therapeutic nanoparticles at the targeted sites at reduced toxicity. In vivo real-time molecular sensing can be used to achieve more sensitive and early cancer diagnosis. Particulate imaging agents can be employed to achieve deep tissue visualisation of cancer cells and the therapeutic process. The ATN solution can also address the heterogeneity challenge in cancer occurrence by employing a personalised approach to treatment. For instance, it is known that if the human epidermal growth factor receptor 2 (Her2) is present in breast cancer cells, certain cancer drugs that specifically target this growth factor receptor can be used to kill those cancer cells. However, if Her2 is not present, then such drugs will be ineffective [24]. Moreover, with the real-time monitoring of the therapeutic process, challenges such as drug resistance and behavioural change in the disease pathology can be observed and addressed.

7.3 ATN Application to Alzheimer's Disease

7.3.1 Alzheimer Disease Pathophysiology and Pathways

Alzheimer's disease is an irreversible neurodegenerative disorder with a long preclinical progressive course, and is the leading cause of dementia, which is prevalent among senior citizens. It is presently incurable and marked by reasoning and interactive impairment that considerably interfere with social and occupational capability of the patient. It affects over 35 million people worldwide, and one in nine over the age of 69 [25].

The brain is basically composed of neurons, which are interconnected to form a vast network of neuro-signalling highways and tracks. Each neuron is connected to another through the synapse, which enables the transmission of information from one neuron to another as the signal propagates through the neuronal network. First described in 1906 by Dr. Alois Alzheimer when he was performing a histopathological examination for one of his patients, Alzheimer's disease is pathologically characterised by the formation of two lesions, namely the extracellular senile plaques and intracellular neurofibrillary tangles [26, 27] depicted in Figs. 7.2 and 7.3. The formation of these lesions starts long before the symptoms of the disease begin to manifest. The senile plaque is composed of the beta-amyloidal protein [26], while the neurofibrillary tangles are composed of modified tau proteins [27]. The formation of the plaques and tangles alters/disrupts neuron-to-neuron signalling, which impairs brain function.

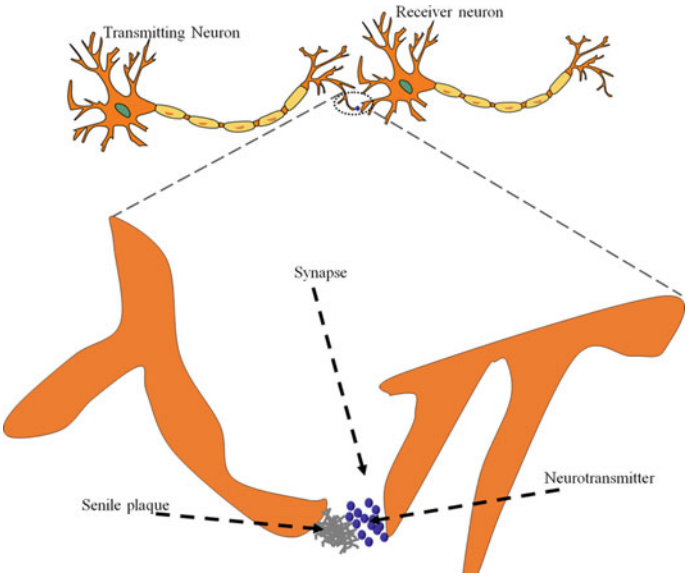

Fig. 7.2 Formation of extracellular senile plaques

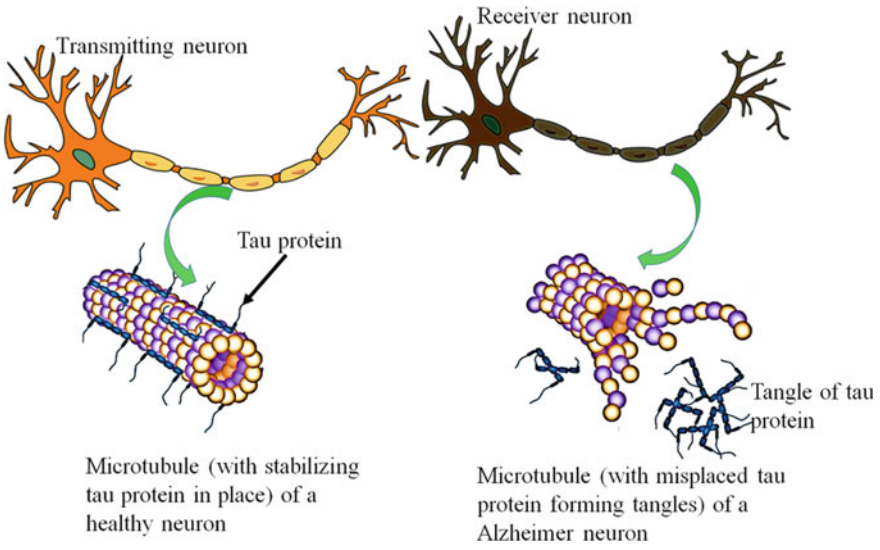

Fig. 7.3 Formation of intracellular neurofibrillary tangles

To address the Alzheimer's disease challenge, advances in the field of pathogenesis have inspired researchers to investigate and develop pharmacological therapeutics aligned towards the pathophysiological events of the disease. However, the complete understanding of the factors, mechanism, sequence of events and phenomena that result in the formation of the plaques and tangles (pathogenic process) is still elusive. Hence, contemporary treatment approaches have minimal impact on the disease. These current therapeutics only slow down disease progression and offer symptomatic relief.

7.3.2 Exemplary ATN Solution Perspective to Alzheimer's Disease Treatment

Despite the large amount of scientific research and invested financial resources, prevention strategies and effective therapy for Alzheimer's disease are yet to be achieved, which is basically due to the fact that the disease is still not well understood. The fundamentally accepted hallmarks of Alzheimer's disease pathology are the build-up of amyloid plaques, the formation of neurofibrillary tangles and eventual neuronal degeneration. However, numerous questions are yet to be answered. For instance, what is the exact sequence of the molecular mechanisms that lead to the formation of the senile plaques and the tangles? Which of the phenomena occur to trigger the occurrence of the other? What is the role of genetic (family history) and environmental risk factors (such as injury and climate) in the occurrence of the disease? And, how can the disease be accurately diagnosed much earlier?

As is always suggested, and rightly so, for many life challenges that have no known solution, the diagnostic and therapeutic challenges of the Alzheimer's disease require interdisciplinary research efforts. Again, nanomedicine certainly bears promising new approaches for addressing the Alzheimer's disease challenges [28, 29]. Nanomedicine tools such as the use of nanosystems with highly precise and sensitive capabilities for early diagnosis, and nanovectors for precise and effective delivery of diagnostic/therapeutic/monitoring agents, can provide more effective ways of addressing the disease challenges. For instance, like for any disease but especially in the case of the Alzheimer's, early diagnosis is vital for effective treatment and the prevention of further neurodegeneration. Since, the degeneration starts long before symptoms appear, early detection is possible when the right tools are available. The currently used diagnostic tools, such as clinical assessments, neuroimaging, neuropsychological testing and the detection of cerebrospinal fluid biomarkers [3], cannot be used to achieve early detection. Nanosystems with high-molecular level sensitivity that are delivered directly into the brain tissues bear great potential in achieving early detection of disease pathology [30]. Also, the delivery of drugs/agents to the defective neurons requires that the drugs/agents be able to cross the blood–brain barrier (BBB) and reach pharmacologically relevant levels. Nanosystems with specialised surface chemistry can handle such task [31, 32].

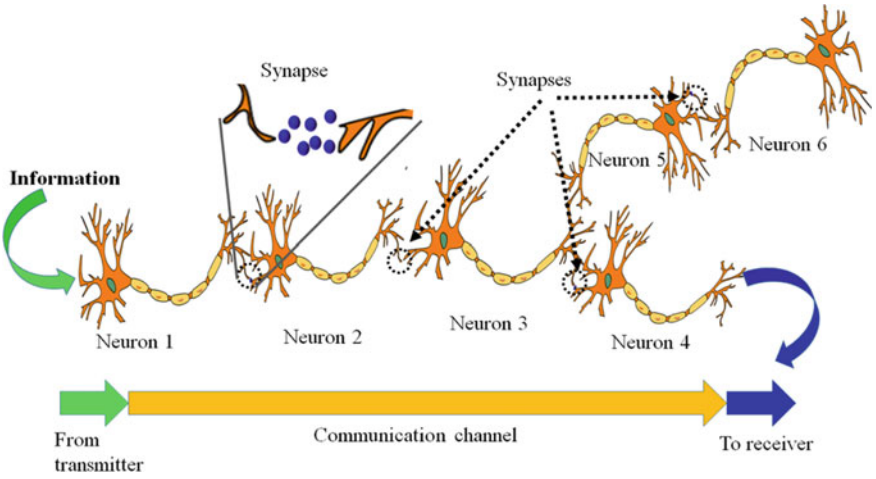

Fig. 7.4 Simple neuronal circuit

However, any curative measure for the disease requires complete understanding of its molecular mechanism. One of the approaches to achieving this understanding is to model and analyse the entire neuronal signal propagation from the perspective of communication engineering. Indeed, all neurological disorders are due to disruption of the communication channel between one neuron and another, such as in the circuit depicted in Fig. 7.4. Molecular communication, which is part of the fabric of the ATN solution, can enable the systems biology theoretic modelling and promote a deeper understanding of the Alzheimer's disease in a new way. This approach will also provide the capability to analyse pathological conditions on an individual basis in order to personalise treatment. Moreover, molecular communication engineering can provide specialised nanosystems in the form of synthetic neurons to replace degenerated neurons or reconfigure damaged signalling pathways to re-establish communication, thereby delivering neuro-regeneration and neuro-protection capabilities in the disease treatment.

Further, the integration of ATN tools such as body area networks and off-body networks will provide extended capability for more efficient real-time monitoring and control of the treatment process.

7.4 ATN Application to HIV Treatment

7.4.1 HIV Pathophysiology and Pathways

The human immunodeficiency virus (HIV) is a virus that attacks the immune system, thereby causing the disease called acquired immunodeficiency syndrome (AIDS). The virus acts by attacking the immune cells, thereby preventing them from fighting

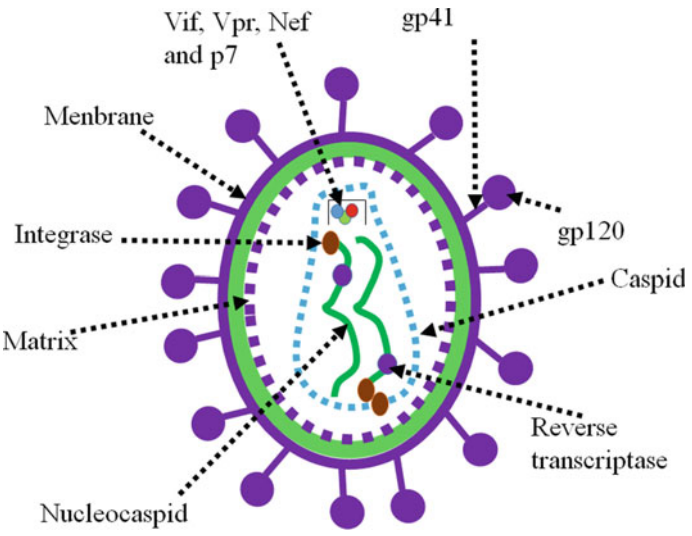

Fig. 7.5 Schematic of the HIV lentivirus

other infections that may arise in the body, which will ultimately kill the patient. The immune system protects the body by identifying invading antigens on pathogens such as bacteria and viruses and attacking them. The interaction between the immune cells/antibodies and the antigens on the pathogens induces a state of sensitivity and immune responsiveness, which ultimately destroys the antigen, allowing the body to be free of infections.

The immune system basically consists of systems such as the blood, lymph nodes/lymphatic vessels, adenoids, spleen, bone marrow, tonsils, thymus gland and appendix [33]. These components are vital in the production and development of lymphocytes, namely T lymphocytes (or T cells) or white blood cells and B lymphocytes (or B cells). The T lymphocytes basically regulate the immune system and kill cells that bear specific target antigens. On the other hand, the B lymphocytes provide antibody immunity and can recognise specific antigen targets and secrete specific antibodies, which are highly specialised serum protein molecules. These antibodies then coat antigens, thereby making the antigens more vulnerable to phagocytosis, or trigger a complement system that informs an inflammatory response.

The specific attack on the T lymphocytes (T helper cells) by the HIV destroys these cells, and the resultant replication of the virus weakens the immune system in general, leaving the body vulnerable to infections. The schematic of the HIV lentivirus, which is about 100 nm in diameter, is shown in Fig. 7.5. It consists of a cylindrical centre enclosed by a sphere-shaped lipid bilayer envelope. On the surface membrane are two viral glycoproteins, gp120 and gp41, which play an important role in the virus attack mechanism. To enter and attack the cell, the gp120 and gp41 mediate the recognition of the surface receptors (CD4 and CCR5) specifically expressed on the

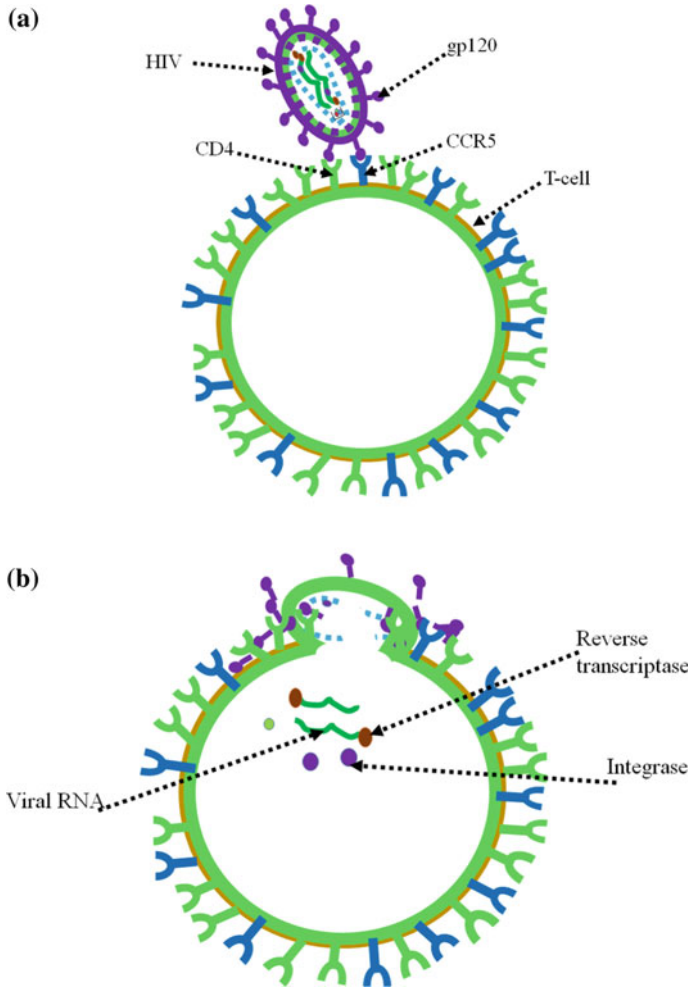

Fig. 7.6 Schematic of the HIV invasion of the T cell: **a** The virus approaches the T cell and binds to its CD4 and CCR5 receptors. **b** The bond enables it to fuse to the membrane of the T cell and empty its genetic material into the T cell's cytoplasm

surface of the T cell of the host [34]. This enables the virus to attach itself to the receptors, fuse to the cell membrane, and empty its genetic material into the host cell to invade it, as illustrated in Fig. 7.6. The viral capsid encloses two single-stranded copies of the viral RNA, as well as multiple proteins and enzymes necessary for HIV replication and maturation, which include reverse transcriptase and integrase. Various accessory regulatory proteins such as the viral infectivity factor (Vif), viral protein *R* (vpr), negative regulatory factor (Nef) and the viral structural proteins like the nucleocapsid protein p7, are important in the viral replication and for increasing

HIVs contagion rate. Once the viral RNA, the accessory regulatory proteins and the structural proteins are emptied inside the host T cell, the cell's machinery can replicate the virus using these viral materials, and go on to infect more T cells.

7.4.2 Exemplary ATN Solution Perspective on HIV Treatment

HIV infection has become one of the most devastating diseases in the contemporary world and has remained largely incurable despite the enormous scientific and financial resources having been dedicated to finding a cure. The hallmark of HIV infection is characterised by progressively profound immunodeficiency, a long clinical latency period and opportunistic infections [35–37]. Typically, the replication of the virus within the T lymphocytes that express CD4 cells results in the qualitative and quantitative depletion of the CD4 cell counts, a phenomenon on which contemporary diagnostic steps depend [38].

From the time the virus was identified as the cause of the disease until now, enormous research efforts have been intensely channelled into finding prevention and curative strategies for the disease. The contemporary efforts have resulted in the development of highly active antiretroviral therapy, which involves a combination of antiretroviral drugs. These drugs have been able to act on the disease in a way that aids in extending the lifespan of the HIV-infected patient. The goal of the contemporary treatment is to prevent the immune system from deteriorating to the point that opportunistic infections become more likely. The challenges with this therapeutic approach are schematically illustrated in Fig. 7.7.

Ideally, contemporary HIV disease therapy works by inhibiting the various viral enzymes critical to the replication of the virus. These enzymes are primarily the reverse transcriptase, integrase and protease. With this approach, the virus may likely remain in the body, but will be unable to replicate as one or more of the phases of its replication cycle are inhibited by the antiretroviral drugs. However, inappropriate dose and poor bioavailability of the therapeutic molecules will definitely impact on the antiretroviral drugs' effectiveness. With the right dose and bioavailability, the replication process is suppressed as long as the patient continues to take the drugs diligently. Excess dose results in side effects, which may include fatigue, diarrhoea, insomnia, rashes and numbness. However, subtherapeutic dose (which may be as a result of non-adherence to daily dosage recommendations) and poor bioavailability result in the cellular and anatomical regions across the body, often termed sanctuary sites, where the virus can continue to replicate in sub-therapeutic drug concentrations [39]. Moreover, the current therapy does not eliminate the viruses from the body; hence, it is employed to simply extend the lifespan of the patient. For patients whose immune systems are greatly weakened, the current approach may not offer the desired immune reconstitution. Therefore, there is a global quest for the development of effective permanent therapy as well as the possibility of vaccines.

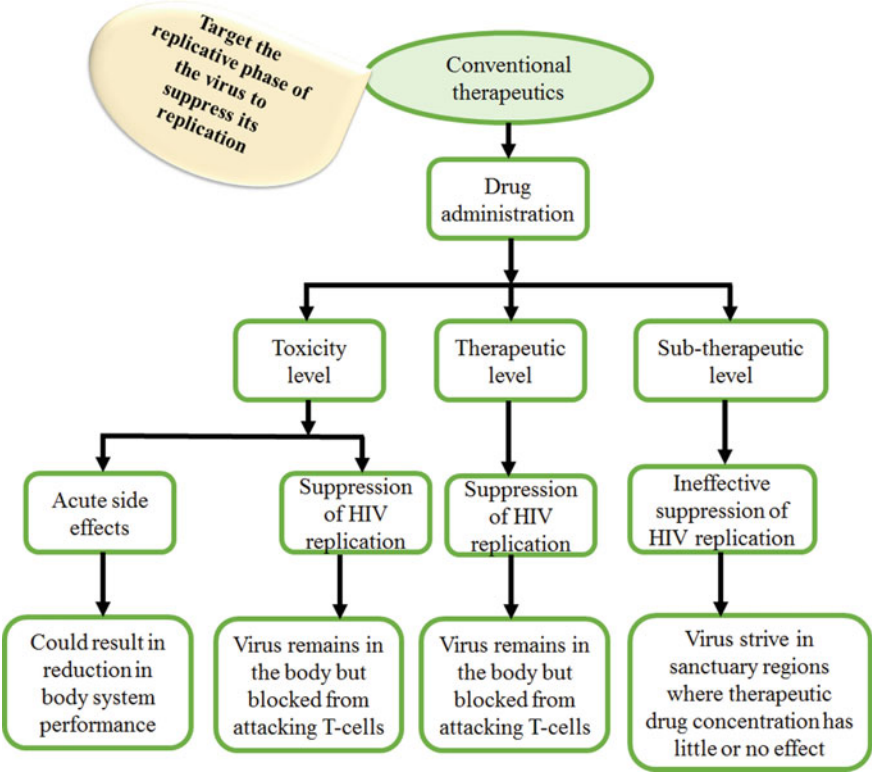

Fig. 7.7 Schematic illustration of the challenges associated with the contemporary therapeutic approach to HIV

It is also important to note that the characterisation of the many incurable diseases is centred on the uniqueness of detailed molecular profiling of the patient. This characterisation is distinctive for each HIV patient. For instance, it is expected that the ability of the virus to mutate over the course of administration may vary in different patients at different times [40]. Hence, the effectiveness of a set of antiretroviral drugs is dependent on finding the right treatment for the right patient at the right time. and it is based on detailed molecular profiling of the patient.

Again, nanomedicine, which sits on the ATN platform, promises to offer unique, interesting, novel and effective approaches to addressing the HIV challenge [41–43], as depicted in Fig. 7.8. For instance, molecular-level communication mapping, nanomedicine tools such as targeted drug delivery (to enhance bioavailability), high-precision and sensitive nanosystem and gene editing, networking capability among sets of nanosystems and robotics capabilities can provide more effective ways of tackling the HIV menace. A nanomedical approach has the potential to provide complete eradication of the virus, resulting in a cure. This can be achieved by molecular communications, nanoscale-level modelling and analysis of the disease with a view

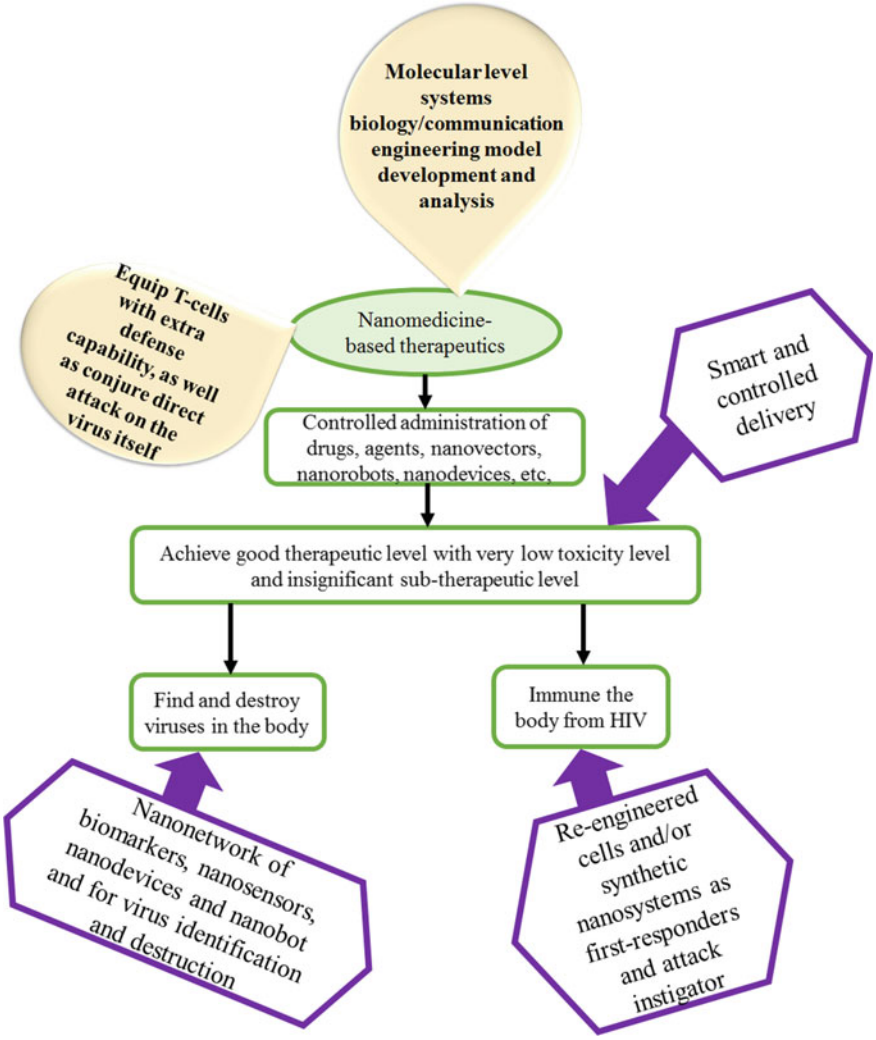

Fig. 7.8 Schematic illustration of the ATN approaches to HIV therapeutics

to obtaining a deeper understanding of the disease. Such exercises will facilitate the definition of accurate strategies for therapy and vaccination. For example, synthetic T cells or T cells extracted from HIV-positive patients with one or two of the receptors modified by gene editing or other related processes, can be used to fight the disease [44]. Moreover, by using ATN tools such as body area networks and IoBNT, real-time monitoring of therapeutic processes and remote control over the process can be achieved.

7.5 ATN Application to CVD Treatment

7.5.1 CVD Pathophysiology and Pathways

Cardiovascular diseases (CVD) such as heart failure, myocardial infarction, stroke and hypertension are among the most common causes of death in many countries of the world [45, 46]. As the name suggests, CVD encompasses all pathologies of the heart (cardiac) or circulatory system (vascular). The disease called atherosclerosis, which involves the building up of plaque resulting in the hardening and the narrowing of arteries, is generally implicated in CVD. The formation of plaque is driven by a low level of anti-oxidant enzymes such as glutathione peroxidase. A low level of this enzyme results in the oxidation of reactive oxygen species such as superoxide anion, hydrogen peroxide, lipid peroxides and peroxynitrite. Also, an increase in the production of *angiotensin II* (a hormone that regulates blood pressure and mediates tissue injury) and a reduction in glutathione peroxidase as results of cigarette smoking (which facilitates hypertension), result in high oxidation stress. The oxidation process eventually leads to enhanced inflammation and the eventual formation of plaque.

The plaque formed in the blood vessels may partially or completely occlude oxygen-rich blood from some cells. Partial occlusion results in poor blood circulation, which can have negative and consequential effects on the entire body. Depending on where the plaque is formed, symptoms of this condition may include fatigue, shortness of breath, feeling light-headed, loss of memory and unexplained headaches, cramps and numbness, loss of appetite, unexplained weight loss, colour swelling in the hands/feet/ankles and change in skin. Complete blocking of the blood vessel will reduce the oxygen and nutrient supply to the cells beyond the occlusion points, thereby triggering unintended apoptosis and inflammation in the cells. In the heart, *angina* will occur and possibly heart failure. In the brain, ischemic attack or stroke may result. When it is associated with the blood vessels leading to the arms and legs, peripheral artery diseases arise. If the occlusion is in the arteries leading to the kidneys, high blood pressure or kidney failure develop. In some scenarios, the plaque can burst, triggering a blood clot called an embolus, which can break off from the atherosclerotic plaque and travel in the bloodstream to lodge in a blood vessel [47]. The process can result in an embolic stroke [48].

7.5.2 Exemplary ATN Solution Perspective on CVD Treatment

The contemporary approaches to the treatment of CVD are basically either non-invasive or invasive [49, 50]. The non-invasive therapies include prescription medication and lifestyle alterations, while the invasive approach includes surgical therapy. These approaches act to inhibit enzymes and block receptors implicated in the disease [51, 52]. However, to maintain good health, many CVD patients are required

to be on medications for the rest of their lives, since no permanent cure is available. Consequently, the development of novel techniques for the early detection and treatment of CVD is crucial.

Nanomedicine in general, and ATN, in particular, may offer a novel approach and tools for monitoring, diagnosing, preventing, repairing damaged cells and ultimately treating the disease. ATN can offer the following advantages for CVD treatment.

i. Like most chronic diseases, the cause of CVD lies in altered biosignalling, which can be studied under the platform of molecular communication. Hence, ATN can offer deeper and more accurately personalised molecular-level modelling that is based on molecular communication concepts and tools. This may result in the discovery of novel therapeutic approach that may include gene therapies.
ii. Early diagnosis using nanoscale tools, devices and mechanisms is possible with ATN. Since autopsy studies show that atherosclerosis develops slowly over many years, nanoscopic tools such as high-precision and sensitive nanosystem can be used in the early detection of the onset of atherosclerosis.
iii. Targeted and smart delivery of CVD therapeutic molecules to any defective cell in the body where they are needed using nanosystem network is achievable.
iv. Synthesising new nanosystems by means of tissue engineering to replace defective valves, damaged heart muscle, clogged blood vessels, etc. can be realised. The ATN will also handle the transportation of the synthetically engineered biological systems to different locations in the body for therapeutic purposes. Nanoscale surgery may also replace contemporary surgical practice such as coronary artery bypass grafting and angioplasty.
v. Molecular imaging agents can be used to visualise and identify disease more specifically.
vi. By using ATN tools such as body area network and IoBNT, real-time monitoring of therapeutic processes and remote control over the process can be achieved. Devices such as biosignal sensors and implants can be used to monitor and correct some anomalies.

In the near future, it is considered that the nanomedicine approach will enable the establishment of accurate ‘personalised medicine’. It is also considered that gene therapies for cardiovascular applications will have potential usage in the field of cardiovascular applications in coming years.

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