Chapter 23

Titanium Dioxide Nanotube Arrays for Biomedical Implant Materials and Nanomedicine Applications

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http://dx.doi.org/10.5772/intechopen.73060

Abstract

Nanotechnology has become a research hotspot to explore functional nanodevices and design materials compatible with nanoscale topography. Recently, titanium dioxide nanotube arrays (TNA) have garnered considerable interest as biomedical implant materials and nanomedicine applications (such as nanotherapeutics, nanodiagnostics and nanobiosensors). In bio-implants studies, the properties of TNA nanostructures could modulate diverse cellular processes, such as cell adhesion, migration, proliferation, and differentiation. Furthermore, this unique structure of TNA provides larger surface area and energy to regulate positive cellular interactions toward the mechanosensitivity activities. As for an advanced medical application, the TNA—biomolecular interactions knowledge are critical for further characterization of nanomaterial particularly in nanotherapeutic manipulation. Knowledge of these aspects will create opportunities for better understanding which may help researchers to develop better nanomaterial products to be used in medicine and health-line services.

Keywords: titanium dioxide nanotube arrays, titania, titanium dioxides nanomaterial, biomaterial, nanomedicine, nanotherapeutic manipulation

1. Nano-properties of titanium dioxide nanotube arrays

Titanium dioxide (TiO_2) nanotube arrays are also referred to as titania nanotube arrays (TNA). Nanotubes layered by anodization in particular, have garnered considerable interest in the enhancement of orthopedic procedures due to their inherent high quality and cost-effectiveness [1, 2]. The anodization process produces continuous and vertically aligned TiO_2 nanotubes structure in an array form on the titanium (Ti) alloy surface as shown in **Figure 1**.

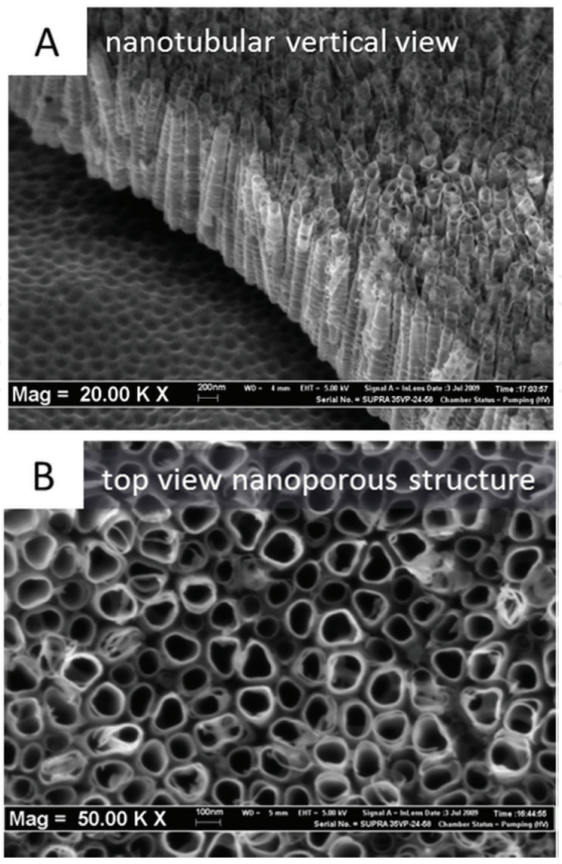

Figure 1. TNA nanomatrix observation by field emission scanning electron microscopy. (A) The surface modification by anodization produced nanotubular structure of TiO_2 layer (TNA) in vertical view and (B) nanoporous structure from top view; the formation of well-aligned nanotubular structure (nanotubes). The nanotubes were linked to each other and ripple marks occurred at the sidewalls.

Several researchers have investigated a range of parameters associated with the physical and element properties of TNA. The physical parameters involve different crystal structures, nanotubes diameter and length, as well as surface roughness. The element contents are the core compositions of TNA. The effect of different parameters could solely or communally modulate diverse cellular responses of the cells adhesion, migration, proliferation and differentiation [3, 4].

Interaction of these parameters may also result in the wettability factors of cellular interaction and biocompatibility [5]. Hence, these parameters need to be optimized before performing a detailed study of the material. This might also help in gaining an understanding of the cell-nanostructure interactions and designing novel regenerative biomaterials that could favorably modulate cellular responses to enhance the tissue regeneration [6–8].

The Ti surface readily reacts with oxygen upon contact and results in three titanium oxide crystalline phases such as rutile, brookite and anatase. These phases may also be responsible for the material biological properties [9]. Anatase phase is metastable and exhibit stronger interactions between metal and support, which would be advantageous for medical application [10]. Anatase phase shows better absorption properties of hydroxyl-OH- and phosphate-PO_4^{3+} than rutile titania in simulated body fluid which could favor bonelike apatite component to be

deposited [9]. The deposition of bone-like apatite component is crucial in mediating a positive osseointegration, the interaction of implant surface with surrounding bone tissues [11, 12].

Therefore, anatase crystal phase TNA has become a major interest in medical research. A study by Yu et al. [13] reported that anatase TNA could yield an optimal biological response for cell adhesion, spreading, proliferation and differentiation. TNA with 100 nm diameter have been suggested to provide similar characteristic as the natural bone topography comprising nanophase hydroxyapatite (100 nm size regime) in the collagen matrix [14, 15].

2. Potential application of TNA in biomedical implants

Biomaterials are the core needs in diverse medical areas such as for the orthopedic, dental, cardiovascular, and craniofacial implants [59–64]. In the past, Ti or Ti alloys were commonly used as biomaterial implants [16]. Besides having great mechanical properties and excellent corrosion resistance, titanium possesses a good biocompatibility, which related to the behavior and function of nontoxic materials in living systems [17, 18].

This metal surface is known to be cytocompatible, which refers to the ability to bind with biomolecules and supported cellular attachment (adhesion), growth and proliferation [11, 19–22]. Conventionally, Ti alloys have a thin layer of titania also known as titanium oxide (TiO_2) on the surface. This naturally occurring oxide of titanium (Ti^{4+}) resulted from the reduction–oxidation action of surrounding oxygen (O_2^{4-}) and water (H_2O) [23]. This oxidized layer of Ti is known to be bioactive which makes it possible to establish direct contact with bone cells and promote the formation of apatite (major component of bone tissue) [24].

To meet the expectation of successful biomedical implants, there is a critical need in reducing the post-operation healing time and safe placement of implants have become a major concern. This is because the human body has minimum time to react to osseointegration before the body starts rejecting the implants. The currently available implants possess these limitations. For instance, at the early stage of implantation of Ti implant materials into human body, the material surface cannot bind directly to living bone due to biologically inert metallic surface properties [25]. Hence, the healing period takes a longer time and sometimes the surface gets encapsulated over the time [26]. This attributes to poor osseointegration, leading to aseptic loosening of the implant, development of fibrous tissue (at interface of implant-bone), micromotion (at interface of bone implant) and/or wear debris formation (wear particles of bone implant interface) and further delamination (or fracture) between bone and implant material [26, 27].

The surface of implant materials plays a vital role in controlling osseointegration to decrease healing time; in this regard, scholars aim to improve or alter the biocompatibility of Ti implant surface for long-term clinical use [16]. Current studies focus on the potential of titania with a three-dimensional (3-D) microporous or nanoporous structure to enhance the formability of apatite (bone component) and the adherence speed of osteoblastic cells compared with that of a dense titania layer [28–30]. The nanometric scaled surface modification has shown to be critical for the tissue acceptance and cell survival.

Notably, the proposed TNA structure has adaptive features which are required to successfully improve cell interaction with the implant materials. The continuous and vertically aligned TNA topography demonstrates extremely larger surface area than the flat titanium surface and has been assumed to overcome current clinical implants limitations [31]. Moreover, this improved bioactive layer of inward growth TiO_2 nanotubes on Ti provides good adherence of the nanotube layer to the titanium metal which eventually rectifies the problems of existing ceramic coatings arising from weak interfacial bonding [28]. Besides that, TNA topography may provide similar characteristic as a natural bone topography (pore size/diameter ~ 60–100 nm) that might improve the interference of bone cells response [15].

Furthermore, the unique structure of TNA exhibit surface area that is three times higher than that of flat titanium, creating additional spaces for cell interaction particularly at the cell extracellular matrix level; this structure may also address the limitations of existing clinical implants [14, 21, 32, 33]. Moreover, the improved bioactive layer of the oxide nanotube structures on Ti allows the nanotube layer to adhere to the titanium metal (metastable), leading to stronger interfacial bonding that that of existing ceramic coatings [34]. These nanostructure properties can increase the surface energy and improve interactions with various proteins (such as vitronectin and fibronectin), resulting in enhanced specific cell adhesion and osseointegration [13, 35–38]. Yu et al. [13] reported that anatase TNA elicits optimal biological responses for cell adhesion, spreading, proliferation, and differentiation. Furthermore, the surfaces of these nanostructures can effectively reduce inflammatory responses compared with surfaces of conventional implants [39–41]. Therefore, the proposed TNA structure possesses adaptive features that can successfully improve cell interaction with the implant materials and may potentially enhance osseointegration [42–44].

2.1. Examples of biomedical implants

An orthopedic implant is a medical device built from metallic alloys such as Ti which is used to replace a missing joint or bone or to support a damaged bone. It may consist of a single type or comprise modular parts of biomaterial. For example, bone plates and bone screws used in spinal fusion surgery and fixation of fractured bone part. Meanwhile, the hip and knee replacements are medically termed as artificial joints or prostheses used to treat various type of arthritis affecting these joints, which are common health complaints in elderly patients. Besides, the bone implants are also used to treat the bone damaged from accident or cancer or musculoskeletal diseases [30].

Dental implant is an artificial tooth root made of Ti used to place into the jaw and hold a dental prosthesis as replacement for tooth or bridge. This technique was invented in 1952 by a Swedish orthopedic surgeon named Per-Ingvar Brånemark [45]. The implant is considered the standard in replacement of missing teeth due to periodontal diseases, injuries, or some other reasons [46]. Dental implants are divided into three types, namely, the osseointegrated, mini-implant for orthodontic anchorage, and zygomatic [47]. Besides, another important implant used in dental application is the titanium mesh membrane. This barrier implant membrane surface provides great mechanical properties for Guided Bone Regeneration (GBR) treatment to assist the new bone formation [48].

Cardiovascular implants use Ti metals for the replacement of heart valves (pacemaker cases and defibrillators), endovascular stents, and stent-graft combinations. These implants help to overcome cardiovascular diseases which physically damage the heart, resulting in loss of cardiac function. The types of implants are classified as temporary internal, temporary external and permanent internal devices. One of the demands is stents which include the bare metal stents, drug-eluting stent, and bioabsorbable stents [49]. Craniofacial implants are important in the application of craniofacial prostheses or also known as an epistheses. Epistheses may be used to repair or improve absence of facial structures due to malformation present at birth, operations that involve treatment for cancer, or trauma. The osseointegrated titanium implant is one of the common types of implants used in epistheses [45].

Further development and improvement on the implant is required for complete compatibility with the area of implantation, for shorter surgical duration and improved cosmesis [30, 50].

3. Potential application of TNA in nanomedicine

The application of nanotechnology in medicine has led to a new concept termed as nanomedicine. Nanosized materials exhibit extraordinary functional characteristics due to their unique dimension properties. This nanomaterial technology could lead to advances in medical therapies various diseases, especially cancers. TNA might improve efficiency of an existing therapies and diagnostic methods. In addition, this it could also reduce the total medical care expenses. The further prospect of TNA will be discussed in this section especially for nanotherapeutics, nanodiagnostics, and nanobiosensors applications [42].

3.1. Nanotherapeutics: Nanomedicine in therapy

3.1.1. Nanodrug delivery agents

New nanoengineering approaches allow target drug delivery, improve drug solubility, increase therapeutic index, extend drug half-life, and decrease drug immunogenicity. Nanotherapeutics enables the delivery of drugs to specific cells by using nanostructured materials [51]. This property overcomes the limitations of systemic drug administration and may potentially revolutionize treatment of numerous diseases [52].

3.1.2. Nanomatrix therapeutic induction

The inner volume of TiO_2 nanotubes can be also filled with chemicals and biomolecules, such as enzymes or proteins. Subsequently, TNA could be applied into new drug-releasing implants for emerging therapies for localized drug delivery [53, 54]. Whereby, the TNA topology can be coated with inflammation-reducing drugs, such as dexamethasone, by using simple physical adsorption or deposition of the drug by magnetic stimuli-responsive drug delivery system as described in **Figure 2**. This technology may act together radiation therapy and even stem cell transplant for an intensification therapy which also known as consolidation or postremission therapy.

3.1.3. Nano-immunomodulatory agents

Nanomaterial technology allows the development of new immunomodulatory agents, which are either immunologically active components or immunosuppressive agents. This nanostructured material could effectively surpass vaccination, adjuvants, and other immunomodulatory drug treatments. Besides, this unique surface structure could act together with an immunosuppressive agent to therapeutically prevent damage to immune response toward unsuccessful transplant in allergic or even localized autoimmune reaction. Hence, this technology could improve the clinical outcomes of treatments for a range of infectious and noninfectious diseases [55].

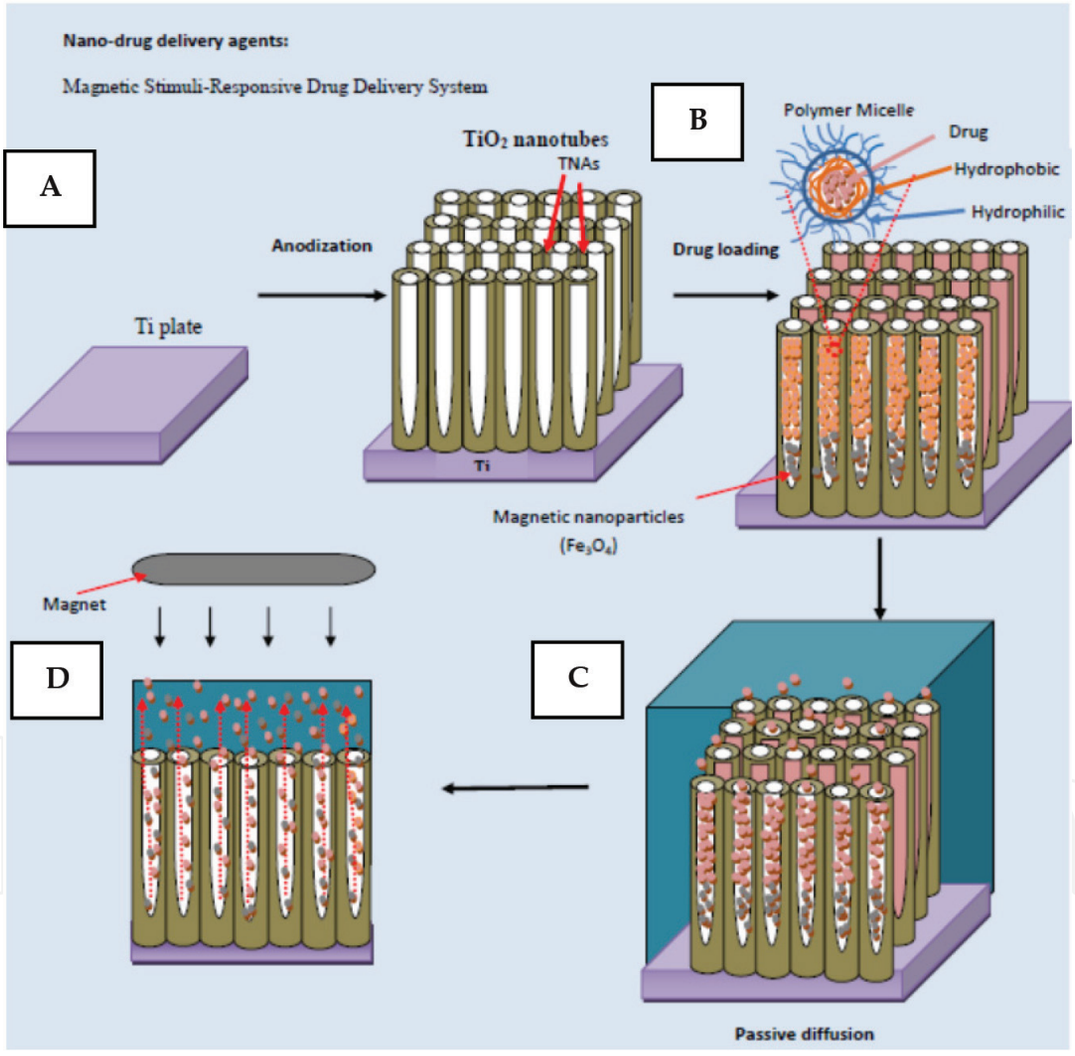

Figure 2. TNA nanomatrix as therapeutics system. (A) The system composes TNA structures created on a Ti surface, (B) loaded with drug-encapsulated polymer micelles at the top acting as drug-carriers and magnet nanoparticles (MNs) at the bottom of the nanotubes. A magnetic stimulated release of drug-carriers was achieved by activating magnetic nanoparticles loaded at the bottom of the nanotubes. (C) The drug may move from a region of high concentration to one of lower concentration via passive diffusion activity. (D) The stimuli-release concept is based on applying a magnetic field to induce the movement of magnetic particles from the bottom and force the release polymer micelles out from the TNA.

3.1.4. Nano-antibacterial agents

Bacterial infection of in-dwelling medical devices could be controlled by the technology of TNA nanomatrix surface coated with infection-reducing drugs, such as penicillin and streptomycin (**Figure 3**). Traditional antibiotic treatment is limited in solving the bacterial infection problem. Kulkarni et al. [58] discovered that the use of nanotubes with large diameter (30–100 nm) might reduce the growth of bacteria, such as *Staphylococcus aureus* and *Staphylococcus epidermidis*, compared with the smaller size of nanotube (20 nm).

3.1.5. Nano-blood-contacting agents

Adsorption of blood proteins is the immediate primary outcome observed at the implant–liquid interface [55]. TNA able to increase the formation of fibrin network by transforming

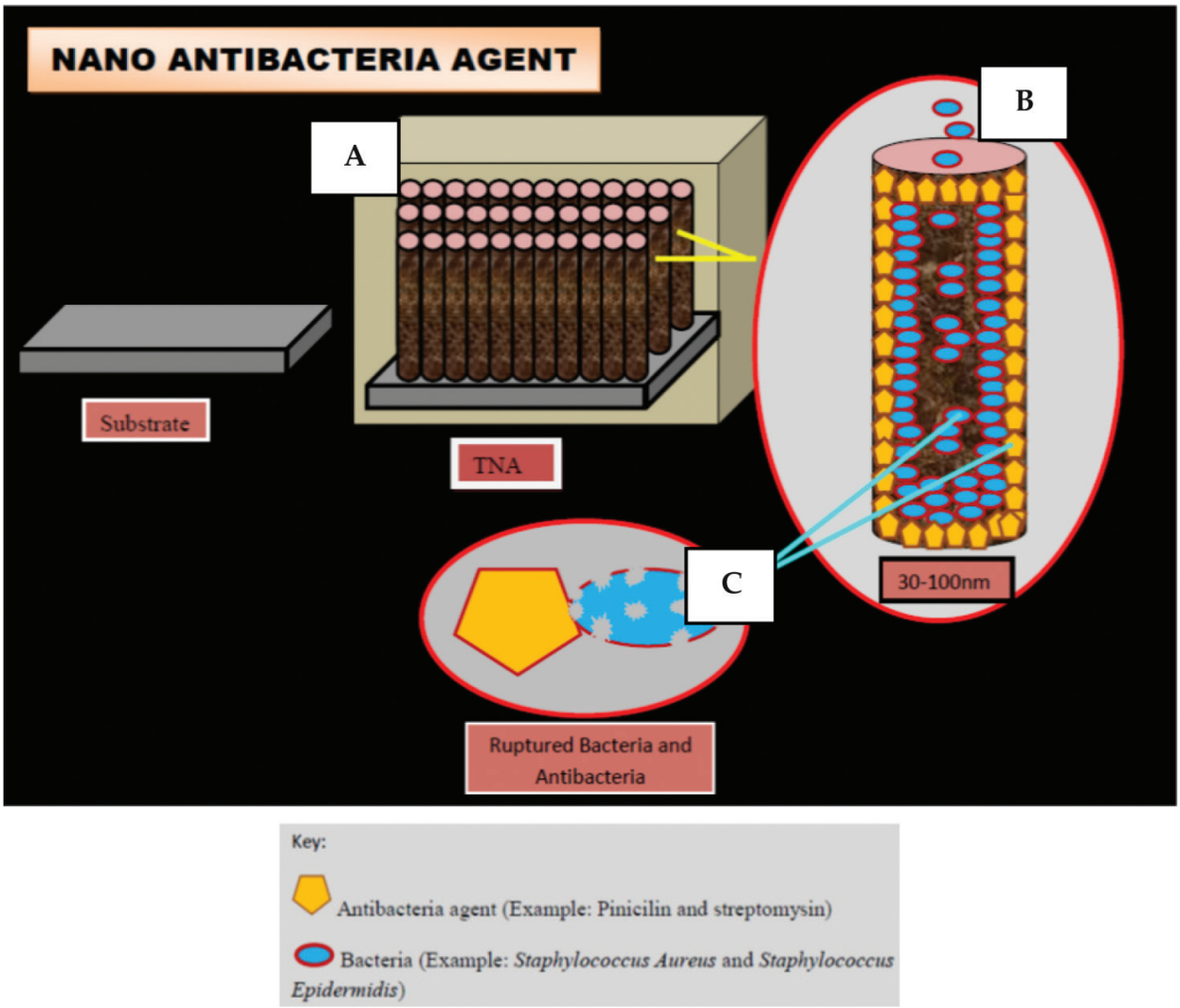

Figure 3. TNA as nano-antibacterial agent. (A) The TNA could be aligned on any medical device surface (substrate) and may act as antimicrobial chemotherapy agent. (B) The bactericidal antibiotics such as *Penicillin a*nd *Streptomycin* can be coated at TNA cylindrical inner surface. (C) This antibacterial surface will inhibit and avoid bacteria grow, thus may reduce the bacteria infection risk from the system.

fibrinogen to fibrin and reduce clotting time also forming dense fibrin network (**Figure 4**). Moreover, TNA elicited low monocyte activation and cytokine secretion. The adsorption of biomaterial and blood able to evaluate by using a micro-BCA assay and X-ray photoelectron spectroscopy (XPS) [56].

3.2. Nanodiagnostics

Nanobiotechnology and molecular diagnosis are emerging concepts in nanodiagnostics for development of personalized medicine or cancer therapy. With the advances in nanotechnology, biomarkers can be refined using nanomaterials, which provide high volume/surface ratio and multifunctionality. Diagnostic information is obtained based on pharmacogenetics, pharmacogenomics, pharmacoproteomics, and environmental factors influencing responses to therapy. This approach provides effective and progressive personalized treatment, which is tailored directly from the genetic makeup of an individual, thereby preventing unwanted side-effects [57].

3.3. Nano-biosensors

Biosensors are analytical devices used to detect biological analytes, such as biomolecules (protein, lipid, DNA, and RNA), and biological cells (blood cell, virus, and microorganism). These devices present wide applications, including for detection of infectious organisms and

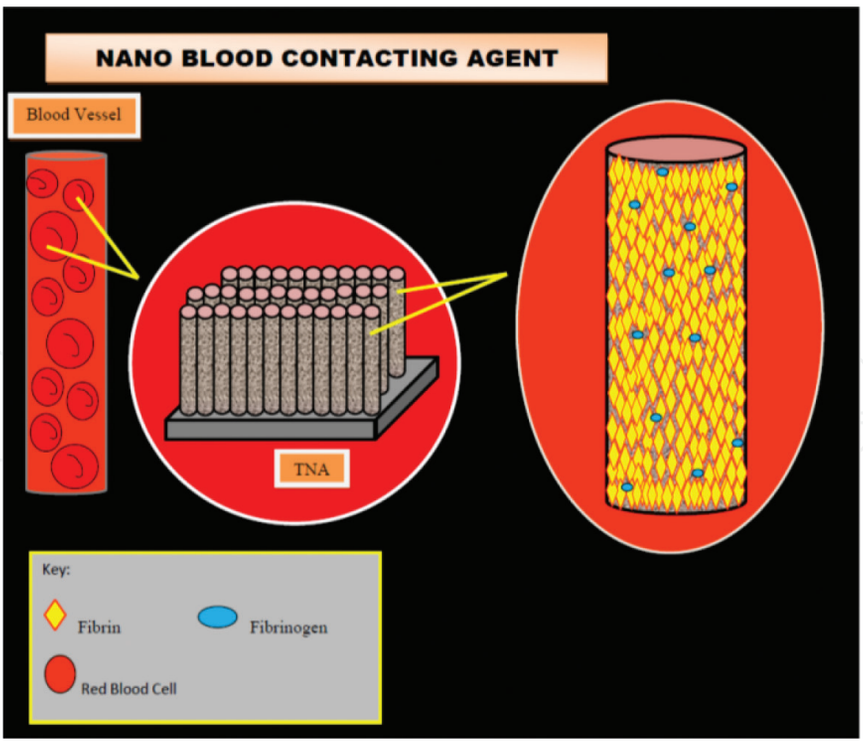

Figure 4. TNA as nano-blood-contacting agent. The TNA topology could enhance increase the protein adsorption of blood serum, adhesion and activation of platelets (fibrin and fibrinogen) and kinetics of whole blood coagulation. Thus, the TNA surface may provide interconnecting between the biological substances for providential blood-related implants.

molecular detection of biomarkers for disease diagnosis. Biosensors consist of physicochemical transducers (electrochemical, mass, optical, and thermal) and biological analytes as a molecular recognition system. The sensitivity of biosensors depends on the properties of the transducers and the bio-recognition element. Nanostructured transducers with TNA could be used as diagnostic tools with increased sensitivity, specificity, and reliability for medical applications [42].

4. Molecular cross-talks between TNA and molecular stability

The nanometric scaled topography of biomedical products plays a decisive role in the surrounding tissue acceptance, cellular stability and cell survival [59–64]. It is important to understand nanomaterials-molecular interactions at different cellular mechanisms in order to predict the safety of nanomaterials application and their long-term effects. The study of molecular signaling pathways could help to explain the cell fate activity when it interacts with this nanomaterial. A study by Arcelli et al. [9] has found that Ti with various surface textures on osteoblast cells is able to regulate the expression of genes that are linked to osteoblast differentiation and bone regeneration such as TIMP1, PTN, and RUNX1 whether directly or indirectly. The indirect mechanism has been found through cell communication (PLCG2 and EPHA7), cellular proliferation, differentiation (MSX1), cycle regulation (RASSF2 and WDR26) and cell adhesion (TNC, TNXB, ZFHX1B and TRPM7).

Furthermore, material surface textures interaction may trigger various cellular mechanisms such as tissue remodeling (reorganization or restoration of existing tissues), organization of extracellular matrix and protein development, arrangement and disassembly activities (biogenesis), bone remodeling (bone matrix, reabsorption minerals and bone development), morphogenesis of anatomical structure and macromolecule complex assembly of biological process. Most of material surface textures such as nanorough/nanomaterials interactions are predicted from functional analysis using bioinformatics software such as gene ontology (GO) analysis [64]. However, precise laboratory work needs to be done in accordance with these mechanisms and the knowledge of designing safe nano-biomedical products from molecular genetic aspects.

The nanomaterial technology could lead to advances in medical therapies for a variety of diseases, especially cancer. Indeed, nanotechnology may have a great impact in medicine and healthline. However, little is known about the impact of nanotechnology on human health and also on the environment especially in terms of new mechanisms associated with nanotoxicology [4, 65]. Nanomaterial toxicological profile requires the analysis of different endpoints and cellular mechanisms. Numerous studies have indicated that some nanoparticles reveal traces of toxicity in biological systems [66]. This has led to an interest in the area of nanotoxicology, which examines the possible toxicity of nanomaterial products for advanced medical applications. These research issues have underlined the need for toxicogenomic studies which govern the examination of toxicology, genomics, proteomics and metabolomics of human cells interaction with targeted nanomaterial product. The need of molecular biology study on nanomaterial product is important in the development of specific strategies treatment especially in nanotherapeutic manipulation.

5. Conclusion

Nanotechnology in biomedical field focuses on improving the existing therapies and diagnostic methods. The aim of developments in this area is to improve the available practice efficiency and reusability, thus saving the total medical cost. Presently, TNA nanostructure provides a promising approach for the advanced biomedical implant and nanomedicine applications. Furthermore, TNA opens up the possible tie-up in nanotherapeutics, nanodiagnostics and nano-biosensors. Further research must be conducted to explore nanomaterial-biomolecular interactions in order to develop novel or improved biomaterials products for medicine and health-line services.

Acknowledgements

This book chapter began from a doctoral thesis submitted to Universiti Sains Malaysia in year 2016 by Rabiatul Basria S.M.N. Mydin. The authors would like to thank Universiti Sains Malaysia USM-Short Term Research Grant (304/CIPPT/6315073) for sponsoring this work. The authors gratefully acknowledge the internship students contributions from Sultan Idris Education University: Najihah Azizan, Siti Nur Syahirah Zahari and Farah Syahira Mohamad Zamir in refining all the schematic diagram presented in this book chapter.

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