Journal of
Nanomedicine & Nanotechnology

DOI: 10.4172/2157-7439.1000e107

Editorial Open Access

Anodized Nanotubular TiO_2 Structures Significantly Improve Titanium Implant Materials *In Vitro* and *In Vivo*

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Biomedical applications of nanotechnology, the science that deals with materials with dimensions on the scale of one billionth of a meter (10^{-9} m=1 nm), are a growing international trend offering the opportunity to control material properties including improving electrical conductivity, optical properties, catalysis, mechanical strength and biological activity. Simultaneously, nanotechnology offers the ability to create biologically inspired surface properties including roughness, wettability, and topography to promote better cell functions [1-4]. Anodization of titanium (Ti) is one such technology that can be used to inexpensively create uniform TiO_2 nanotubes on a Ti surface (conventional and nanotubular Ti surfaces are shown in Figure 1). Because of the ease of fabrication and improved biocompatibility properties, applications of Ti anodization are increasing and now include controlling stem cell-implant interactions [5,6], increasing bone growth [7-10], decreasing bacterial functions [11-13], improving bladder and stent urothelialization [11,14], improving skin growth [15,16], and reducing inflammation [7,16]. Thus, anodizing Ti to possess nanotubes is a promising technology for creating well-ordered nanotopographies on implant surfaces to improve a wide range of cellular responses.

Moreover, a simple modification of the fabrication procedures, such as variations in anodization voltage and the use of heat treatment, can control Ti surface properties and subsequent biological responses. Many studies have shown that using anodization to create nanotubes on a Ti surface shows great promise *in vitro* by tailoring specific surface properties such as nanotube diameter, surface chemistry, and TiO_2 crystallinity [5,6,12,13]. For example, heat treatment is one of the most widely used post-fabrication procedures which increases crystallinity of as-produced amorphous TiO_2 nanotubes and removes surface fluorine to improve cell responses and decrease bacterial functions [5,6,12,13].

Equally as important, *in vivo* studies have been conducted showing continued promise for anodizing nanotubular Ti for various orthopedic applications to increase bone growth, decrease inflammation, and improve skin growth [7,9,10]. In one study by Puckett [7], an Intraosseous Transcutaneous Amputee Prosthesis (or ITAP) rat femur amputation model was used. With this innovative testing methodology, various parameters of bone growth, skin growth, and inflammation were investigated on anodized nanotubular Ti simultaneously *in vivo*. The qualitative evaluations of skin formation indicated a more favorable interaction with nanorough and nanotubular Ti, with less inflammation than conventional Ti. There were also no signs of infection using the anodized nanotubular Ti while conventional Ti showed significant signs of infection (puss formation, inflammed tissue, etc.) after all time points of the study. While moving forward, anodized Ti also needs to be further tested under a wide variety of *in vivo* implant conditions, such as for improved bladder and vascular stent endothelialization.

Most importantly, there is still a need for medical devices that employ anodized nanotubular Ti technologies for human use. One of the future directions for anodized nanotubular Ti is to examine proper sterilization techniques. With an intended use as an implant material, one needs to be certain that the TiO_2 nanotubes can be easily and efficiently sterilized for the clinical setting. This is currently under investigation by our laboratory, where the effect of different sterilization techniques including Ultraviolet (UV) light, autoclaving and ethanol treatment, has been shown to alter key surface properties of both anodized nantubular Ti and conventional Ti substrates affecting their cytocompability properties.

Another topic that has not undergone thorough investigation is the consequence of the wear debris generated from the nanotube structures. First and foremost, it would be important to examine whether the anodized TiO_2 nanotubes are easily removed and if they create wear debris. A careful investigation of how the body deals with this wear debris is crucial for the future use of anodized nanotubular Ti as a potential implant material. However, as this article described, there are a great number of promising medical applications for anodized nanotubular Ti whose investigation has only just begun. By simply manipulating crystallinity of the TiO_2 nanotubes and changing nanotubular dimensions, a variety of cell responses ranging from controlling mesenchymal stem cell differentiation to decreasing bacteria growth and inflammation can be realized. With this in mind,

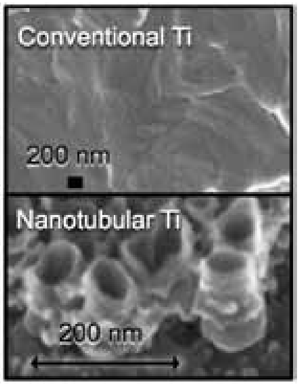

Figure 1: Conventional Ti implants (top) can be modified through an anodization process to create nanotubular Ti (bottom) which can improve cell responses, decrease inflammation, and decrease bacteria functions [15].

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Received April 17, 2012; **Accepted** April 19, 2012; **Published** April 22, 2012

Citation: Kummer KM, Taylor EN, Webster TJ (2012) Anodized Nanotubular TiO_2 Structures Significantly Improve Titanium Implant Materials *In Vitro* and *In Vivo*. J Nanomed Nanotechol 3:e107. doi:10.4172/2157-7439.1000e107

anodized nanotubular Ti shows great promise as a more bioactive substrate compared to conventional Ti in the next generation of improved biomaterials.

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