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Original Research Article

# Photoactivated titania-based nanomaterials for potential application as cardiovascular stent coatings



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ABSTRACT

Intravascular stenting of atherosclerotic coronary arteries is a life-saving, widely used procedure in interventional cardiology. Adverse clinical outcomes such as restenosis highlight the importance of meeting the excellent biocompatibility by cardiovascular implants. Many attempts have been made to improve the safety profile of implant surface. We for the first time developed the photoactive intravascular titania-based nanomaterials for the application as cardiovascular stent coating. Photoactive biomaterial deposited on the cardiovascular stent surface demonstrated promising features, making it an excellent substrate for endothelial cells growth and proliferation. The biocompatibility of these coatings has been compared with 316L stainless steel surfaces typically used in commercial coronary stents production. The results of the study proved that the innovative titania-based coatings have better biocompatibility characteristics than the 316L stainless steel and in regard of its antithrombotic potential provided protection against restenosis. Furthermore, the titania coating supported endothelial cells attachment and proliferation, and induced prolonged plasma recalcification time in comparison with stainless steel surface. Innovative photoactive titania coating can be an important factor to prevent the process of the restenosis in the place of implantation.

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## 1. Introduction

Atherosclerosis with its life threatening complications (i.e. myocardial infarction MI) remains a major clinical problem, not only in Europe and in the USA, but also in developing countries [1]. Intravascular interventions (PCI) with intravessel stenting are nowadays a golden standard in cardiology. Nevertheless, they still suffer from some major drawbacks. The problem of the restenosis is a real challenge at the cardiology, affects many patients and is posing great threats to their health, causes public and economic heavy costs. In-stent thrombosis and restenosis lead to repeated vessel occlusion and affects the long-term clinical outcomes of PCI. Both undesired processes are strongly reliant on endothelial coverage of stent struts. There are some possible strategies to diminish the risk of restenosis and thrombosis such as increasing endothelial cell specificity toward stent surface or to reduce intraplaque inflammation [2]. To address this problem we designed innovative photoactive titania-based nanomaterials for coronary stent coating to facilitate re-endothelialization of stent material thus increase the biocompatibility of intravessel implant.

Titanium dioxide has shown improved biocompatibility as material for medical implants [3] and its application as the cardiovascular stent coating is promising in cardiology [4,5].

Titania is known for its chemical stability, high resistance to acids or alkali and is one of the most studied semiconductors for photocatalytic reactions [6–8]. In recent years much emphasis was put on examining titanium dioxide ( $\text{TiO}_2$ ) characteristics in macro- and nanoscale. One of the  $\text{TiO}_2$  properties is its photoactivity as titanium dioxide is known as one of the most photocatalytic material with strong oxidizing properties and long-term stability [9–11]. These unique properties have shown potential in photodynamic killing of tumor cells in cancer treatment [12,13], but also against various pollutants and microorganisms [14]. The studies indicated that  $\text{TiO}_2$  photoactivation occurs if the energy of photons is equal or higher than the band gap of the material excited [15]. It has been shown that UV irradiation of titanium dioxide in solution generated free radicals such as  $\text{OH}^*$ ,  $\text{H}_2\text{O}_2$ ,  $\text{O}_2$  that are very reactive compounds oxidizing biological molecules [16]. Moreover,  $\text{TiO}_2$  is an ideal photocatalyst as biologically inert, corrosion resistant, photoactive under light exposure, non-toxic material that additionally, does not produce any hazardous waste [17,18]. In the study two types of titanium-based coatings on 316L stainless steel were analyzed for their physico-chemical and biological properties to improve the biocompatibility of the innovative photoactive surface preventing the process of the restenosis of the cardiovascular implant.

## 2. Materials and methods

### 2.1. Synthesis of titania-based coatings

Titania-based coatings were prepared by a sol-gel route [19,20]. Sols obtained in the study were prepared from tetraethyl orthotitanate (TEOT), tetraethyl orthosilicate (TEOS) and 96% ethyl alcohol ( $\text{C}_2\text{H}_5\text{OH}$ ). Two types of titania-based coatings

were prepared. In the first type (T13), a solution of TEOT/TEOS was prepared with a molar ratio of 1.6:1:20 for TEOT:TEOS: $\text{C}_2\text{H}_5\text{OH}$ . The second type coating (T15) has a molar ratio of 1:44 for TEOT: $\text{C}_2\text{H}_5\text{OH}$  and did not contain TEOS. Importantly, in both processes 36% hydrochloric acid was added to ensure the acidic hydrolysis at pH of 2. The mixture was stirred with a speed of 300 revolutions per minute (rpm) at room temperature. Stainless steel disks (316L-SLS) used for commercial production of coronary and peripheral vessels stents (Balton Sp. z o.o.) were used throughout the study as bare metal benchmarks and substrates for spin coating of titania-based coatings. Stainless steel disks were 10 mm in diameter and 0.5 mm in thickness. The thickness of the coatings was measured by using cross-sectional scanning electron microscopy (SEM). The thickness of the T13 coating was found to be ca. 300 nm and the T15 coating was ca. 500 nm.

### 2.2. In situ photoexcitation set-up

Although the titania nanomaterials exhibit the absorption in the range 300–450 nm with maximum of absorption for wavelength 365 nm, the semiconductor CW laser  $\lambda = 405$  nm (TopGaN, Poland) was chosen as an excitation source to avoid the possible phototoxicity of prepared coatings induced by UVA irradiation during the interaction with endothelial cells. We could not use harmful ultraviolet radiation, specifically the UVB (280–315 nm), because it kills cells by damaging their DNA [21]. Generally, the DNA damage can cause cell death unless it is either repaired or tolerated. A gene product, called P53, is one of the responsible parties for slowing the cell cycle and checking for damage. P53 has been described as “the guardian of the genome”, referring to its role in conserving stability by preventing genome mutation [22]. If the damage is fixable, P53 sends in the repair machinery. If the damage is too extensive, it directs the cell to apoptosis, or programmed cell death. Therefore, the UV radiation kills cells because of the accumulation of the DNA damage.

Laser light was guided through the optical fiber with a core diameter of 200  $\mu\text{m}$ . The fiber output was located at a distance of 5 mm from the disks so that the output power density on a plate was 0.49  $\text{mW}/\text{cm}^2$ . After 4 min exposure, the dose of the delivered light energy was calculated to be 117.6  $\text{mJ}/\text{cm}^2$ .

### 2.3. Kelvin Probe Microscopy – surface potential measurements

Surface potential (SP) of the stainless steel samples (316L) and two types of titania coatings (T13 and T15) deposited on stainless steel disks, was measured by means of Kelvin Probe Microscopy (Scanning Kelvin Probe Corrosion System (RHC020), KPTechnology, UK). KPM studies were performed with a 1 mm tip, in a controlled humidity chamber. SP of these samples was measured in situ before and after photoirradiation by CW laser ( $\lambda = 405$  nm). The mean values of surface potential (SP) calculated are presented graphically.

### 2.4. Field emission-scanning electron microscopy (FE-SEM)

SEM micrographs were recorded using a high-resolution Hitachi SU-70 instrument. All samples were coated with a

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