Cerium doped ZIF nanoparticles and hydroxyapatite co-deposited coating on titanium dioxide nanotubes array exhibiting biocompatibility and antibacterial property

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Abstract
Cerium has been used as an implanted alloy additive for many years for it can enhance the mechanical properties of the alloy and restrain the corrosion of the implant. Moreover, cerium oxide nanoparticles are often used as an antibacterial material. However, there were few researches focusing on the antibacterial properties of Ce$^{3+}$ and Ce$^{4+}$ ions, instead of their corresponding oxide, as potential antibacterial coatings. Thus in this work, we loaded Ce ions into the porous structure of the ZIF-8 nanoparticles and co-deposited them with hydroxyapatite as a composite coating onto anodized titanium dioxide nanotubes array in order to test whether it can improve the anti-corrosion and antibacterial properties of the materials without affecting the biocompatibility.

KEYWORDS
antibacterial property, biocompatibility, corrosion resistance, hydroxyapatite, metal-organic framework, rare earth element

1 | INTRODUCTION

For recent decades, titanium is one of the most widely used orthopedic implants due to its excellent biocompatibility, superior corrosion resistance and desirable mechanical properties. [1] However, there are still some flaws for bare titanium such as peri-implant inflammation, bacte-
proliferation.\cite{5} In addition, TiO\textsubscript{2} nanotubes can be easily synthesized on Ti surface by using electrochemical anodization method.\cite{6} Therefore, TiO\textsubscript{2} nanotubes can be a cheap and convenient base for biocompatible coatings to deposit. Hydroxyapatite (HA), as the main inorganic component of human bones and teeth,\cite{7} has a very strong affinity for titanium dioxide.\cite{8} Moreover, further biological characteristics shows that it has non-immunogenicity, non-inflammatory behavior, good biocompatibility, high osteoconductivity and osteoinductivity.\cite{9} Thus, it is a desirable coating material on TiO\textsubscript{2} nanotubes in order to enhance the biocompatibility of titanium substrate implant.\cite{10}

Metal-organic frameworks (MOFs) are well-aligned nanoporous crystals\cite{11} which have already been used in gas storage,\cite{12} sensor\cite{13} and catalysis.\cite{14,15} Furthermore, MOFs can be applied to biomedical field thanks to the large superficial area, ordered pores array and biocompatible metallic ion composition.\cite{14} Ruyra et al., investigated the toxicity of 16 representative MOF nanoparticles and found that Zn-based and Fe-based MOFs had low cytotoxicity.\cite{16} Zeolitic imidazolate framework-8 (ZIF-8) is a Zn-based MOF which is made of Zn\textsuperscript{2+} as the coordination center and 2-methylimidazole as the ligands.\cite{17} As one of the essential elements in human body, zinc exhibits satisfactory osteogenic activity and antibacterial effects.\cite{18} Thus, it can be a desirable platform for Ce\textsuperscript{3+} ions to load.

Cerium has been used as an implanted alloy additive for many years. It can enhance the mechanical properties of the alloy and restrain the corrosion of the implant.\cite{19} Moreover, cerium oxide nanoparticles are often used as an antibacterial material.\cite{20} However, there were few reports focusing on the antibacterial properties of Ce\textsuperscript{3+} ions as potential orthopedic Ti-based implants. Therefore, this paper aims to introduce a new material based on Ti and TiO\textsubscript{2} nanotubes and using Ce\textsuperscript{3+}, zeolitic imidazolate framework nanoparticles and hydroxyapatite as composite coating. This novel biocompatible composite coating provides an appropriate option for the orthopedic application of titanium-based implants.

2 | RESULTS AND DISCUSSION

In order to obtain the differences between Ti, Ti-TiO\textsubscript{2}, HA/TiO\textsubscript{2}-Ti, ZIF@Ce/TiO\textsubscript{2}-Ti and ZIF@Ce-HA/TiO\textsubscript{2}-Ti, SEM was applied to observe the surface morphology intuitively. It can be seen in Figure 1A that natural surface oxide layer on the bare Ti tended to break while the TiO\textsubscript{2} nanotubes arrays on the TiO\textsubscript{2}-Ti was regular and integrated (Figure 1B). TiO\textsubscript{2} nanotubes arrays produced by electrochemical anodization method can enhance the anti-corrosion ability reduce the possibility of stress deformation.\cite{21} Furthermore, it provided a more ideal platform for ZIF nanoparticles and hydroxyapatite to deposit in subsequent steps. As shown in Figure 1C,D. The morphology of the cube-shaped ZIF nanoparticle remained the same even after depositing to the surface of Ti-TiO\textsubscript{2} directly, which means ZIF nanoparticles will not be destroyed by the voltage required for electrodeposition. The surface morphology of HA/TiO\textsubscript{2}-Ti was shown in Figure 1E while the ZIF@Ce-HA/TiO\textsubscript{2}-Ti was exhibited in Figure 1F for a more obvious contrast. It is apparently that the codeposition with Ce doped ZIF nanoparticles will not affect the growth of hydroxyapatite. The zoom in photograph in Figure 1G demonstrate that some ZIF nanoparticles even acted as nucleation center of hydroxyapatite during the process of co-deposition so that the needlelike hydroxyapatite covered the nanoparticles completely, which made it looked like waxberries. This provided a desirable platform for the nanoparticles to be anchored so that the Zn and Ce ions can release after the hydroxyapatite coating is partially dissolved in the body. The Figure 1H exhibited the surface morphology of ZIF@Ce-HA/TiO\textsubscript{2}-Ti.
immersed for 9 days after ICP experiment. It can be seen that the basic structure of hydroxyapatite remains almost the same as the new synthesized one (Figure 1F). So it can be concluded that the Ce doped ZIF hydroxyapatite coating has satisfactory durability and endurance.

Besides, in order to exhibit the distribution of Ce atoms in the ZIF-8 nanoparticles after doping, TEM and its corresponding mappings were shown in Figure 2A-F. Comparing Figure 2A and F, the bright dots in Figure 2A were the Ce atoms, which suggests that Ce atoms had been successfully doped into the ZIF-8 nanoparticles.

In order to investigate the specific surface area and pore structure of ZIF@Ce, N2 adsorption–desorption was carried out. As shown in Figure 3A, the shape of the isotherm is a type II curve with an H3-type hysteresis loop, suggesting the slits of ZIF@Ce formed by the accumulation of flaky particles. Besides, the calculated Brunauer–Emmett–Teller (BET) surface area of ZIF@Ce was about 51.2224 m²g⁻¹ (Figure 3A) with a BJH adsorption average pore diameter of 7.0090 nm (Figure 3B). The slit pore structure formed by the lamellae particles can absorb Ce ions hierarchically during the stirring process, so it can release antibacterial Ce ions faster in the first days than the following days, which was conducing to dealing with postoperative rehabilitation of the critical period.

The XRD patterns of simulated ZIF-8 and synthesized ZIF-8 had been recorded in Figure 3C The angle of the peaks of the two were basically the same, which indicated that the ZIF-8 was successfully synthesized. Besides, the XRD patterns of Ti, TiO₂-Ti, ZIF@Ce/TiO₂-Ti, HA/TiO₂-Ti and ZIF@Ce-HA/TiO₂-Ti were shown in Figure 3D. It can be observed intuitively that the typical peak at 38.4°, 40.2°, 53.0°, 62.9°, 70.7°, and 74.2° indicated the (002), (101), (102), (112), (200) face of Ti base (JCPDS No: 44-1294) while the diffraction peaks at 16.9°, 25.9°, 28.2°, 28.9°, 31.8°, 32.2°, 49.5°, and 53.3° corresponded to HA (101), (002), (102), (120), (121), (112), (123) and (004), respectively (JCPDS No: 84–1998). The peaks of TiO₂ was not detected which indicated that the TiO₂ nanotube arrays were made of amorphous TiO₂. In addition, the ZIF-8 peaks were also invisible since the amount of nanoparticles deposited on the surface was too low compared with the amount of HA. However, they can be detected by the following characterizations.

In order to investigate the compound surface including the chemical composition and element bonding configurations, X-ray photoelectron spectroscopy (XPS) was carried out for ZIF@Ce. As shown in Figure 3E, the existence of C, N, O, Zn and Ce with the atomic contents of C-58.51%, N-15.59%, O-15.44%, Zn-7.65% and Ce-2.81% was determined. In the Ce 3d spectra (Figure 3F), the peaks observed at 881.89 and 898.02 eV can be ascribed to Ce⁴⁺ 3d₅/₂ and Ce⁴⁺ 3d₃/₂, respectively. And the peaks at 884.42 and 900.54 eV can be ascribed to Ce³⁺ 3d₅/₂ and Ce³⁺ 3d₃/₂. More importantly, satellite peaks were observed at 888.81 and 904.54 eV for Ce3d₅/₂ and Ce3d₃/₂, which exhibited higher binding energy than Ce⁴⁺ and Ce⁴⁺. This meant that except the Ce ions that were physically adsorbed on the surface of the ZIF-8 porous nanoparticles, there was another chemical environment of Ce ions that were chemically adsorbed within the ZIF-8 lattice, which was consistent with the conclusion drawn by XRD (Figure 3C). It was probably that the empty d orbitals of Ce atoms and lone pair electrons on pyridine N were forming coordination bonds. On the other hand, Figure 3G shows the high-resolution spectrum of Zn 2p. The positions of the Zn 2p₁/₂ and 2p₃/₂ peaks of ZIF@Ce (1021.89 and 1044.95 eV) shifted positively in comparison to the standard binding energy of Zn (1012.8 and 1044.8 eV), indicating that the Ce atoms filled some vacancies which used to be the Zn atoms.

In order to test the corrosion performance of the material in vitro, electrochemical experiments were carried out. Figure 4A shows the Tafel plots of Ti, TiO₂-Ti, HA/TiO₂-Ti and ZIF@Ce-HA/TiO₂-Ti. It can be observed that ZIF@Ce-HA, TiO₂-Ti, HA/TiO₂-Ti, TiO₂-Ti and Ti had decreasing corrosion current densities and increasing corrosion potential, which meant corrosion resistance ability of samples increased gradually. The Figure 4B exhibits corrosion current density and corrosion potential of all samples in details. The bare Ti had the lowest corrosion potential at -0.173 V (vs. SCE) and the highest corrosion current density of 10⁻⁶.626 A⋅cm⁻² while the ZIF@Ce-HA/TiO₂-Ti had the highest corrosion potential at 0.281 V (vs. SCE) and the lowest current density of 10⁻⁸.354 A⋅cm⁻². Besides, EIS spectra were also carried out for qualitative analysis of the resistances of different samples. As shown in Figure 4C, the impedance was ZIF@Ce-HA/TiO₂-Ti > HA/TiO₂-Ti > TiO₂-Ti > Ti, which was consistent
with the result of electrochemical polarization curves. In all, the ZIF@Ce-HA/TiO$_2$-Ti had the best corrosion resistance of all samples even better than HA/TiO$_2$-Ti, which provided a favorable condition for the implantation of ZIF@Ce-HA/TiO$_2$-Ti in vivo. Therefore, the doping of ZIF@Ce can enhance the anti-corrosion ability of the HA coating, reduce the risk of secondary deformation in the body due to corrosion and lower the possibility of postoperative inflammation on account of hydrogen precipitation.

The release behavior of Ca, P, Zn and Ce ions were monitored by ICP. All the data in Figure 4D has been calibrated using blank SBF groups and HA/TiO$_2$-Ti sample. Generally, ZIF@Ce-HA/TiO$_2$-Ti exhibited an initial ions release burst in the first few days. In the next few days, the speed of ions release by the sample slowed down, which meant that the ions were released constantly. This could also be explained that the HA coating covered ZIF@Ce nanoparticles and make it hard for ZIF@Ce to fall off so that it can release Ce ions more sustained.

In order to evaluate the antibacterial activities of Ti and ZIF@Ce-HA/TiO$_2$-Ti in vitro, plate-counting method was applied to the gram-negative *Escherichia coli* and gram-positive *Staphylococcus aureus*. The result was shown in Figure 5A-D, which exhibited that the amount of colonies in the culture medium of the ZIF@Ce-HA/TiO$_2$-Ti was much less than that of the Ti sample in both *E. coli* and *S. aureus* petri dish. The results obtained from multiple experiments were collected in Figure 5E. It indicated that ZIF@Ce-HA/TiO$_2$-Ti had the antibacterial ratio at 89.81% against *E. coli* while at 87.77% against *S. aureus*, which suggested that the ZIF@Ce-HA/TiO$_2$-Ti had an ideal broad-spectrum antibacterial property. This antibacterial layer might greatly reduce the risk of bacterial infection after implantation.
The biocompatibility of coatings on implants was also detected by cell viability test. As shown in Figure 5F, no statistically significant difference of cell viability was monitored at the surfaces of the samples on the 24 hours, 48 g and 72 hours ($P > 0.05$) detected by CCK-8 method. It indicated that the ZIF@Ce-HA/TiO$_2$-Ti demonstrate the same biocompatibility to the L929 cell growth comparing to HA/TiO$_2$-Ti, which meant that the ZIF@Ce-HA/TiO$_2$-Ti synthesized in this paper can eliminate the bacteria without damaging the normal cell. This is a prerequisite for the ZIF@Ce-HA/TiO$_2$-Ti to be implanted as a bone implant in vivo.

3 | CONCLUSION

In summary, we successfully synthesized Ce doped ZIF-8 nanoparticles and co-deposited them with hydroxyapatite coating on titanium dioxide nanotubes array, which displayed desirable antibacterial, anticorrosive and biocompatible properties. More importantly, no toxic organic solvents or drugs have been introduced during the synthesis and production process. This provides an alternative way for the design of implant materials in vivo by using electrochemical method, which is time-saving and environmental-friendly.

4 | EXPERIMENTAL SECTION

4.1 | Reagents

Calcium nitrate tetrahydrate (Ca(NO$_3$)$_2$·4H$_2$O, Beijing Chemical Works, A.R.), ammonium phosphate monobasic (NH$_4$H$_2$PO$_4$, Beijing Chemical Works, A.R.), modified-simulated body fluid (SBF, Phygene Biotechnology Co. Ltd.), sodium nitrate (NaNO$_3$, Beijing Chemical Works, A.R.), ethyleneglycol (C$_2$H$_6$O$_2$, Beijing Chemical Works, A.R.), Ti sheet (Yitai Metal, China), hydrofluoric acid (HF, Beijing Chemical Works, A.R.), nitric acid (HNO$_3$, Beijing Chemical Works, A.R.), zincacetate dihydrate (C$_4$H$_6$O$_4$Zn·2H$_2$O, Beijing Chemical Works, A.R.), 2 - methylimidazole (C$_4$H$_6$N$_2$, Aladdin, 98%), cerium chloride heptahydrate (CeCl$_3$·7H$_2$O, Aladdin, 99.9%) were employed. All chemical reagents were used as received without further purification. All aqueous solutions were prepared with ultrapure water (resistivity of 18.25 MΩ cm).

4.2 | Physical characterization

Scanning electron microscopy (SEM) was performed on a HITACHI SU020 microscope. Transmission electron microscopy (TEM) and elemental mapping were
FIGURE 5 Typical images of cultivated Ti (A) or ZIF@Ce-HA/TiO₂-Ti (B) in E. coli and Ti (C) or ZIF@La-HA/TiO₂-Ti (D) in S. aureus colonies from the specimens after 24 hours of incubation. Statistics of bacterial colony (E) and cytotoxicity evaluation of L929 cells cultured on different samples performed on a FEI TALOS F200 microscope. X-ray photoelectron spectra (XPS) were recorded on a Thermo ESCALAB 250Xi with an excitation source of Al Kα radiation. X-ray diffraction (XRD) patterns were carried out using a Empyrean (PANalytical B. V.) with a Cu Kα radiation source ($\lambda_1 = 1.5406$ Å) operating at 40.0 kV and 40.0 mA, and the diffraction data were recorded in the $2\theta$ range of 5-80° with a scan rate of 5° per min. Gas adsorption–desorption analyses were conducted using N₂ as the adsorbent on a ASAP 2460 (Micromeritics). Inductively coupled plasma (ICP) data were collected from ICP OES 730 (Agilent Technologies Inc).

4.3 Synthesis of Ce³⁺ doped ZIF-8 (ZIF@Ce)

In a typical procedure, Zn(OAc)$_2$·2H$_2$O (0.35 g) was dissolved in 10 mL of deionized water to form solution A. 1.08 g of 2-methylimidazole (MeIM) was dissolved in 10 mL of deionized water to form solution B. Solution A was subsequently injected into solution B slowly under stirring for 1 minute and then stand for 24 hours at room temperature. The mixed solution was centrifuged and washed with deionized water three times and dried under vacuum at 60°C overnight to obtain ZIF-8.[22]

200 mg of the as-obtained precipitate (ZIF-8) was dissolved in 10 mL of deionized water and 10 mL 10 mg/mL CeCl$_3$·7H$_2$O aqueous solution was added into the former solution drop by drop then stirred for another 24 hours at room temperature. The precipitate was centrifuged and washed with deionized water three times and dried under vacuum at 60°C overnight to obtain Ce-doped ZIF-8 (ZIF@Ce).

4.4 Preparation of TiO₂ nanotubes oxydic layer on Ti (TiO₂-Ti)

TiO₂ nanotubes were prepared on the titanium surface using the electrochemical anodization method. First, 15 mm x 10 mm x 0.1 mm titanium sheet was ultrasonic washed in 10 mL acetone, 10 mL ethanol and deionized water for 5 minutes, respectively. The titanium sheet was clamped on the electrode clamp and the exposed area was $1 \times 1$ cm$^2$. Then, the titanium sheet was immersed in the 10 mL HF:HNO$_3$:H$_2$O = 1:4:5 (volume ratio) solution for 15 seconds to remove the oxide layer. Then, the titanium was used as the anode while platinum electrode as the cathode. Next, the anodic oxidation process is carried out by a 60-volt constant voltage power supply with a mixture of 10 mL NH$_4$F (0.33 g) aqueous solution and 90 mL glycol as electrolyte for 120 minutes. After anodization, the sample was washed with deionized water and dried. Finally, the titanium with TiO₂ nanotubes on the surface was obtained and named as TiO₂-Ti.

4.5 Preparation of ZIF@Ce-HA/TiO₂-Ti

Surface modification of TiO₂-Ti was conducted by a CHI 660E electrochemical workstation with a two-electrode system, including a working electrode (TiO₂-Ti), a counter electrode (Pt foil, $1 \times 1$ cm$^2$) and a 50 mL aqueous solution containing 0.042 M Ca(NO$_3$)$_2$, 0.025 M NH$_4$H$_2$PO$_4$, 0.1 M NaNO$_3$ and 1 mL 5 mg/mL ZIF@Ce. Before the experiment, the whole electrolytic cell was placed in a thermostatic water bath at 60°C for 20 minutes. And it was maintained at 60°C throughout the process. The galvanostatic method was applied to electrochemically deposit a mixture of HA and ZIF@Ce onto TiO₂ nanotubes as coating. The chronopotentiometry (CP) experiment was carried out at 2 mA cathodic current for 60 minutes. After electrodeposition, the sample was rinsed with deionized water and dried. Then, the ZIF@Ce embedded HA coating
was successfully deposited on the surface of TiO$_2$-Ti, which was named after ZIF@Ce-HA/TiO$_2$-Ti. In addition, HA/TiO$_2$-Ti and ZIF@Ce/TiO$_2$-Ti were synthesized the same procedure as ZIF@Ce-HA/TiO$_2$-Ti except the addition of ZIF@Ce, Ca(NO$_3$)$_2$ and NH$_4$H$_2$PO$_4$, respectively for comparison.

### 4.6 Electrochemical measurements

The corrosion resistivity of Ti, TiO$_2$-Ti, ZIF@Ce/TiO$_2$-Ti, HA/TiO$_2$-Ti and ZIF@Ce-HA/TiO$_2$-Ti were determined by Tafel polarization and electrochemical impedance spectroscopy (EIS) in modified-simulated body fluid (SBF) at pH 7.4 and 37 ± 1°C. Electrochemical measurements were performed by a CHI 660E electrochemical workstation with a three-electrode system, including a working electrode (coated Ti specimens), a counter electrode (Pt foil, 1 × 1 cm$^2$) and a reference electrode (saturated calomel electrode (SCE)), respectively. The Tafel polarization curve were performed at a scan rate of 1 mV s$^{-1}$ from –0.4 to 1.2 V (vs. SCE) in SBF at pH 7.4 and 37 ± 1°C. Electrochemical impedance spectra (EIS) measurement was performed at open circuit potential with frequencies from 0.1 to 100,000 Hz and an amplitude of 5 mV.[23] In order to improve reproducibility, all electrochemical experiments were repeated at least three times and the result data were processed using Origin.

### 4.7 Ion release

The release of Ca, P, Zn and Ce from the samples was counted every 3 days. After immersion in the SBF (10 mL, pH 7.4) at 37°C for 3, 6, and 9 days, the supernatant liquid were collected. Then, the concentration of the metal ion released from the coating into the SBF solution was measured by inductively coupled plasma (ICP).

### 4.8 Evaluation of antibacterial activity

Plate-counting in a sterile environment was performed to evaluate the in vitro antibacterial activities of Ti and ZIF@Ce-HA/TiO$_2$-Ti against gram-negative Escherichia coli and gram-positive Staphylococcus aureus. The sterilization of samples, petri dishes and nutrient medium was performed in an autoclave under 121°C for 30 minutes.

The coating of A total of 100 µL of bacterial suspension with concentration of 10$^5$ colony forming units (CFU) mL$^{-1}$ was pipetted onto the surfaces of the samples including Ti and ZIF@Ce-HA/TiO$_2$-Ti, placed at the center of a petri dish surrounded by 1 mL of the PBS and allowed to stand at constant ambient humidity. After incubation at 37°C for 24 hours, the bacterial liquid was diluted 5-fold with PBS. Then, 50 µL of the as-diluted bacterial liquid was recultivated onto a standard agar culture plate. For further incubation, the recultivated suspension was uniformly dispersed. After 24 hours of incubation at 37°C, the colonies that resulted from the viable bacteria were counted. The antibacterial ratio was determined as “antibacterial ratio (%) = [(N$_0$ – N$_i$)/N$_0$] × 100%”, where N$_0$ is the average number of the viable bacterial colonies (CFU/specimen) on the nutrition agar plates for the control sample (Ti), and N$_i$ is the average number of the viable bacterial colonies (CFU/specimen) on the nutrition agar plates for the test samples (ZIF@Ce-HA/TiO$_2$-Ti).

### 4.9 Evaluation of cell viability

The experimental apparatus were all wiped with 75% alcohol cotton ball, then rinsed three times with deionized water, and dried in the incubator at 37°C. The samples including Ti and ZIF@Ce-HA/TiO$_2$-Ti were put into sterile plates and marked, and then transferred to the ultraclean table. After being irradiated and sterilized for 2 hours (turning over after 1 hour), the test pieces were transferred to new sterile plates and marked. The high glucose medium of sterile cells was added into the plate at a ratio of 3 mL:1 cm$^2$ and put into 37°C CO$_2$ constant temperature cell incubator for 24 hours to prepare the extract liquid.

Mouse fibroblasts (L929) were resuscitated by high glucose cell culture medium containing 10% fetal bovine serum and cultured at 37°C in CO$_2$ thermostatic cell incubator (5% of CO$_2$, 95% of humidity). The liquid was changed in the next day, and the morphology of the cells was observed under inverted microscope. The L929 cells in the logarithmic growth stage were digested with 0.25% trypsin, and placed in a 5 mL centrifuge tube. After centrifugation, the supernatant liquid was removed. An appropriate amount of h-DMEM high glucose medium was added to prepare cell suspension. Finally, the cell suspension diluted to 2 × 10$^4$ cell mL$^{-1}$.

100 µL of 2 × 10$^4$ cell mL$^{-1}$ L929 cell suspensions were added to the each well of 96-well plates. Then, the 96-well plates were labeled with blank group, control group (bare Ti) and experimental group (ZIF@Ce-HA/TiO$_2$-Ti) and placed in a 37°C CO$_2$ constant temperature cell incubator (5% of CO$_2$, 95% of humidity) for culture. After 24 hours, the supernatant liquid was discarded, and 100 µL of extract liquid was added to each well. The cell culture was terminated after 24, 48 and 72 hours. In dark condition, 10 µL of CCK-8 reagent was added to each well and incubated in 37°C CO$_2$ incubator for 2 hours. Finally, the
Optical density value at 450 nm wavelength was measured by a multifunctional enzyme marking instrument (synergy HT, BioTek).

ACKNOWLEDGMENTS
This work was supported by the National Key R&D Program of China (No. 2016YFC1102802), Natural Science Foundation of Jilin Province (No. 20200201020JC), Open Project of State Key Laboratory of Supramolecular Structure and Materials (No. sklssm202011).

DATA AVAILABILITY STATEMENT
Research data are not shared.

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How to cite this article: Zhang Z, Zhang Y, Liu Y, et al. Cerium doped ZIF nanoparticles and hydroxyapatite co-deposited coating on titanium dioxide nanotubes array exhibiting biocompatibility and antibacterial property. Nano Select. 2021;2:1225–1232.
https://doi.org/10.1002/nano.202000244