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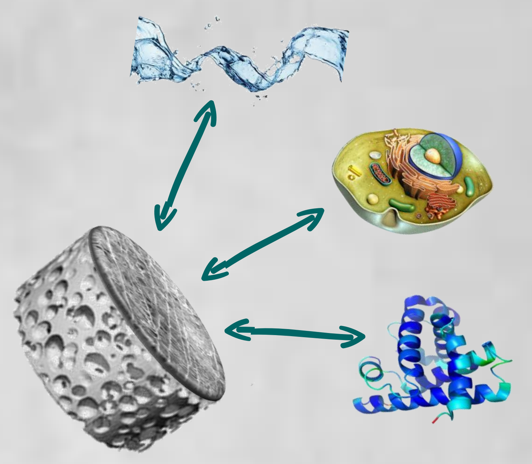
Surface modifications of titanium and titanium alloys to improve their properties for biomedical applications

Serena De Santis, G. Sotgiu, F. Porcelli, M. Orsini

Department of Engineering, Roma Tre University, Rome

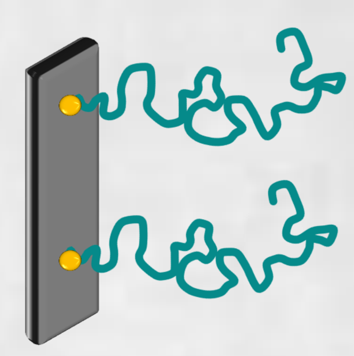
Titanium (Ti) and its alloys are widely used biomaterials for tissue regenerative medicine, because of excellent biocompatibility and favorable mechanical properties. However, titanium-based implants are often subject to complications such as loosening of the implant-host interface due to unsatisfactory cell adhesion and susceptibility of implants to bacterial infections. It is the surface of a biomaterial which first comes into contact with the living body when the biomaterial is placed in it, thus guiding the response of the living body. Thus, by suitably manipulating the surface properties of these materials, through coatings or functionalization, it is possible to improve their cell-host response while inhibiting pathogenic microbial adhesion [1].



Here we show how titanium surface properties can be improved by the covalent tethering of and antibacterial, quaternizable polymer and by a simple drop casting coating with an active oxide.

Polymer grafting

Polymers are very versatile materials, capable of regulating protein adsorption and cell adhesion and of protecting materials from bacterial and protein fouling [2].
We **covalently bonded** well-defined **polymer brushes** of Poly[2-(Dimethylamino)ethyl Methacrylate] (**PDMAEMA**) onto titanium surfaces by attaching the end-functionalized polymer incorporating an azide anchor ("grafting to") and by an in-situ polymerization directly initiated from the properly functionalized surface ("grafting from") (Fig 1).
Polymers of the *same length* with very low values of polidispersity were prepared.



PDMAEMA grafted on titanoim surface: Ti-PDMAEMA

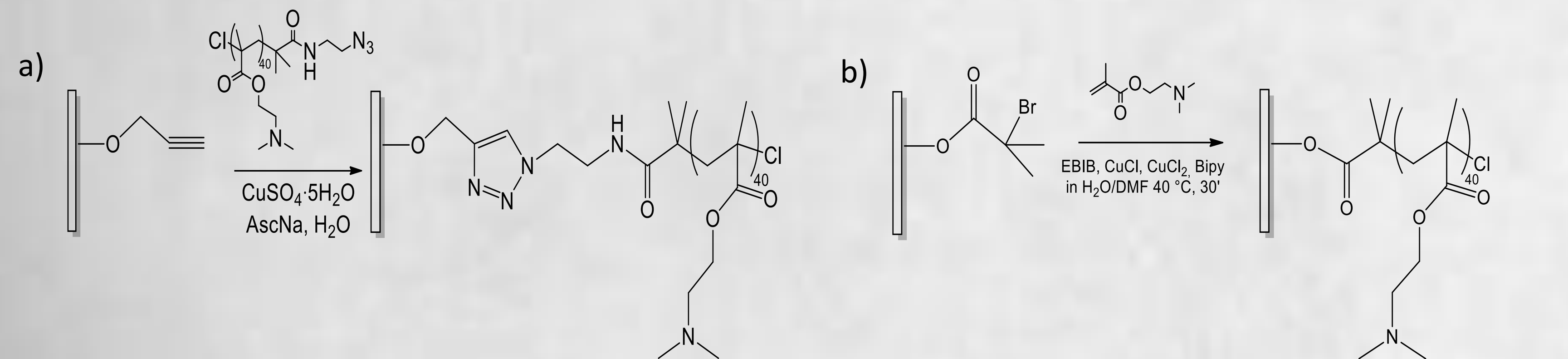


Fig 1. Reaction Schemes for the "grafting to" approach realized trough click chemistry (a) and for the "grafting from" one realized by SI-ATRP

The surface obtained by **click chemistry** had a lower areal density of grafted chains having a *globular conformation* of the solvated brushes, close to that expected for a bulk solution polymer. Surface initiated **Atom Transfer Radical Polimerization** (ATRP) led to high grafting density with *stretched chains* extended in the direction normal to the surface.

A very *thin continuous polymeric film* was formed on titanium surfaces, showing different morphologies also linked to the different pre-treatment required to enable the first functionalization steps: the "clicked" surface showed a **regular nanoroughness**, while the polymerization technique produced a *smoother top* also with respect to the native material

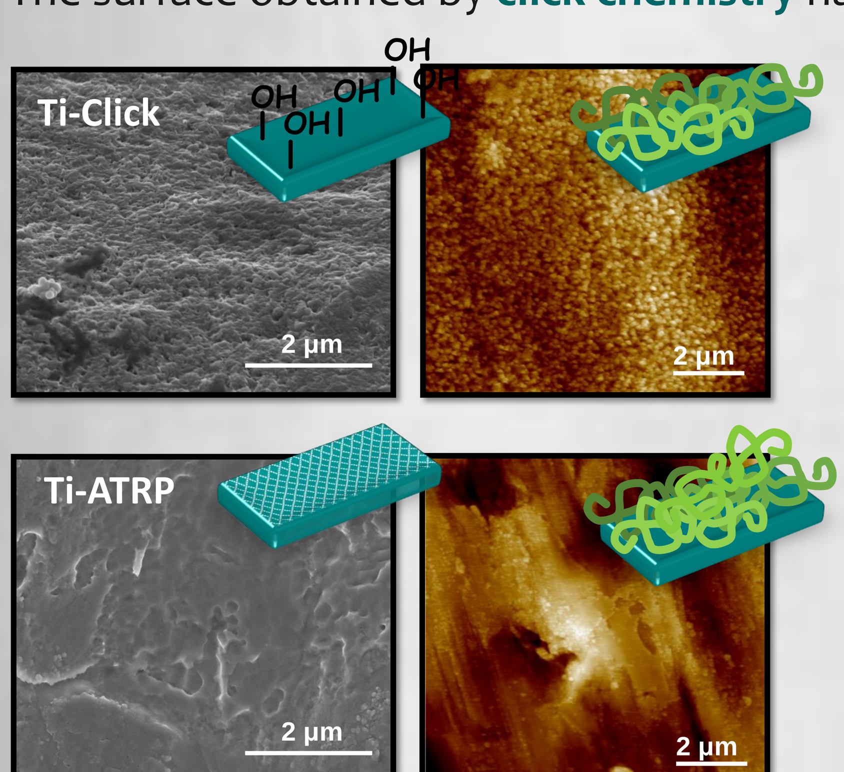


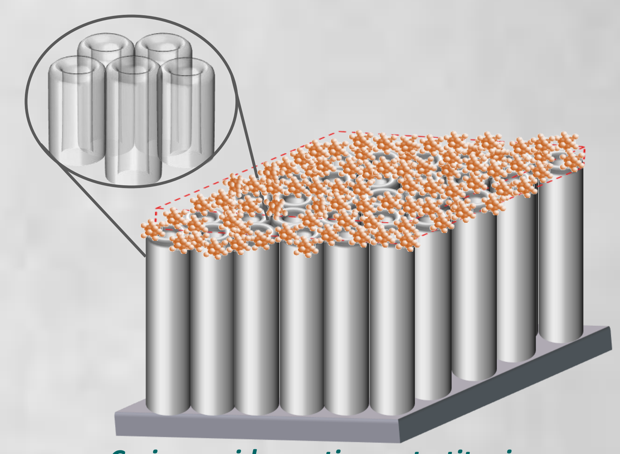
Fig 2. SEM (left) and AFM (righ) images of Ti-PDMAEMA surfaces obtained by graft to (top) and graft form (bottom).

Also the surface **wettability**, which plays a large role in the onset of protein adsorption and cell adhesion, is *differently affected* by the two grafting procedures, despite using the very same polymer: a high degree of hydrophilicity was reached with the graft to approach while the graft for one resulted in only moderate hydrophilic surface effect.

Fig 3. Water contact angle measurments on Ti-PDMAEMA surfaces obtained by grating to (left) and grafting from (rigt) approaches.

CeO_2 coating

We realize a ***CeO_2 coatings*** on TiO_2 nanotubes (TiNT) to exploit both the *antioxidant* and *antibacterial* activity of cerium oxide together with the nanotopographical features of titanium nanotubes which can induce human Mesenchymal Stem Cells differentiation into osteoblasts [3].



Cerium oxide coating onto titanium nanotubes: TiNT-CeO_2

We deposited 1, 3, 6, 9 and 12 CeO_2 layers onto highly ordered self-assembled layers of vertically oriented TiO2 nanotubes with diameters of about 100 nm.
All coatings kept unaltered the nanostructuring introduced by the nanotubes, with a progressive slight reduction of their internal diameter due to the accumulation of CeO_2. The oxide layer was homogeneously distributed over the entire surface and showed, an increasing density with the increase in the number of layers.

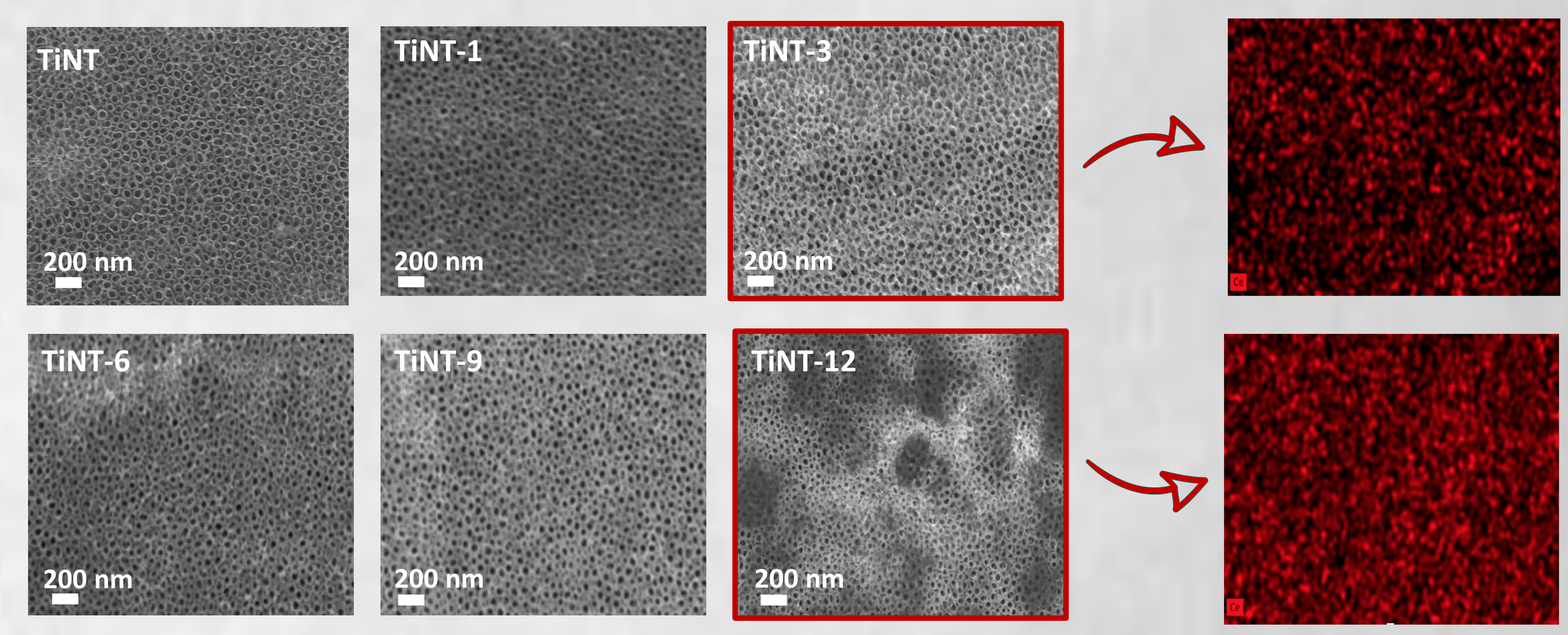


Fig 4. SEM micrographs of TiNT-CeO_2 at increasing number of depositions (left) and EDX map showing Cerium distribution.

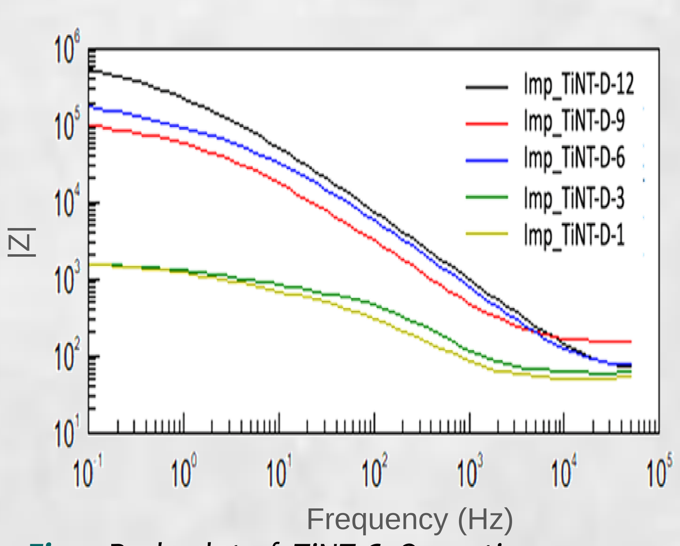


Fig 5. Bode plot of TiNT-CeO_2 coatings.

The corrosion resistance is an important factor contributing to the ultimate behavior of biomedical implants, affecting their stability and biosafety. A growing corrosion protection capability is achieved increasing the number of CeO_2 layers, with a steep increase of about two order of magnitude going from 3 to 6 subsequent deposition.

The ability of cells to adhere and proliferate on a biomaterial is critical to the success of an implant. The presence of CeO_2 on the surface of titanium substrates not only allowed, but further promoted the growth of fibroblasts, chosen as a cell model because of their participation in wound healing and fibrotic diseases. After 48h cells appeared *elongated* without signs of suffering.

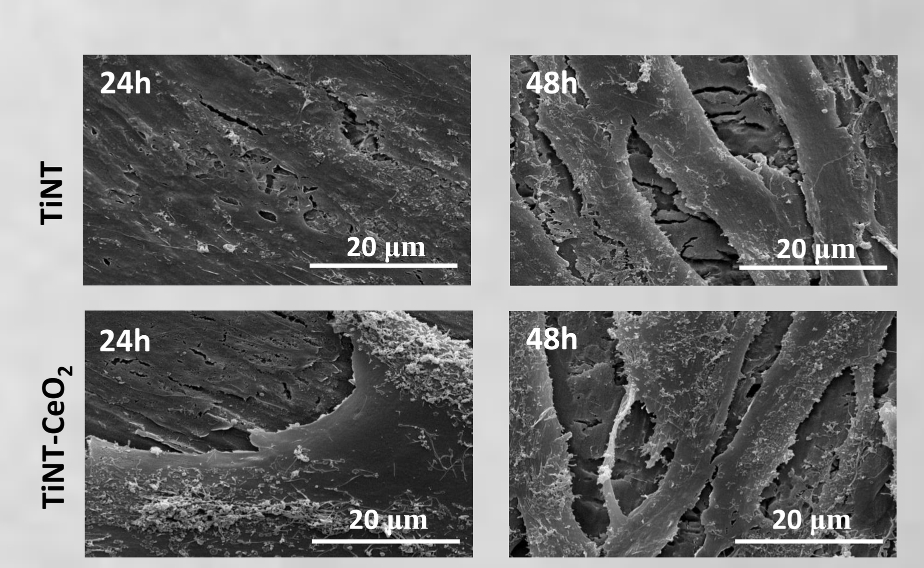


Fig 6. SEM micrographs of fibroblasts seeded onto TiNT (top) and TiNT-CeO2 substrates showing good cell proliferation at 24 and 48h

The optimization on surface of biomaterials for biomedical applications remains a scientific and technological challenge. Here we presented two promising examples of surface modifications able to affect important parameters of the material such as biocompatibility, corrosion resistance, wettability, cell adhesion and proliferation.

Surface properties of medical devices can thus be finely tuned without disrupting bulk properties of materials to address the specific needs of any different application.

[1] H. Chouirfa et al. **Review of titanium surface modification techniques and coatings for antibacterial applications** *Acta Biomaterialia*, **2019**, *83*, 37-54
[2] C. Battocchio et al. **Chitosan functionalization of titanium and Ti6Al4V alloy with chloroacetic acid as linker agent** *Materials Science & Engineering C*, **2019**, 99, 1133–1140.
[3] A.N. Gravina et al. **Bioactivity enhancement of cerium-containing titanium oxide nanotubes. Relationship between surface reactivity and nanostructuring process.** *Surface & Coatings Technology*, **2019**, *378* 124968