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Porous tantalum and tantalum oxide nanoparticles for regenerative medicine

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For centuries, inflammatory/foreign body reactions have plagued the attempts of clinicians to use metals for tissue and bone reconstructions. Since corrosion contributes to the rejection of metal by the body, an extremely bioinert metal—tantalum—has been successfully used in medicine. The outstanding biocompatibility and flexibility of tantalum established the basis for a growing cadre of clinical applications. One important application which benefited from the introduction of powder (particle) metallurgy is use of tantalum as bone implants. Porous materials have re-shaped the landscape of bone implants, as they allow for bone ingrowth and biological fixation, and eliminate implant loosening and related treatment failures. The unique bone-mimicking properties of porous tantalum enabled the use of tantalum as a material for bulk implants, and not only for coatings, as is the case with other porous metals. Moreover, porous tantalum also facilitates the ingrowth of soft tissue, including the formation of blood vessels that were found to assemble on the surface and within the structure of the porous tantalum. Also, since tantalum is strongly radiopaque due its high atomic number, this property is widely employed for marking in orthopedics and in endovascular medical devices. Another important development was the production of nanoparticles based on tantalum. These particles have been shown to be superior to iodinated contrast agents for blood pool imaging applications due to their longer circulation time. Their properties are similar to gold nanoparticles, but are far more cost-effective, and thus, well-positioned to replace gold in regenerative medicine for labeling and tracking of cell grafts through x-ray-based imaging. However, the amount of tantalum nanoparticles that can be taken up by stem cells is not enough to make individual cells visible in x-ray images. Thus, alternative strategies are needed, such as hydrogel or nanofiber scaffolds, which can be loaded with higher concentrations of nanoparticles, to increase the precision of cell deposition and allow tracking under x-ray guidance.

Key words: tantalum, porous tantalum, tantalum oxide, x-ray, nanoparticles, regenerative medicine

INTRODUCTION

Surgeons have long been interested in taking advantage of the properties of various metals for the reconstruction of body defects. The use of gold plates by Petronius in 1565 to repair cleft palates is a testimony to the high demand for metals in medicine, and, at the same time, a proof-of-principle that these are a viable option. However, the use of metals quickly gained a poor reputation since they were associated with inflammatory/foreign body reactions and often resulted in pain and discomfort for patients. It was discovered that these unfavorable effects occurred due to an electrochemical process known as corrosion. With this discovery, the obvious step has been to utilize metals that are extremely resistant to corrosion, such as tantalum. The favorable feature of tantalum is the formation of a thin, impenetrable oxide film on the metal surface that prohibits access of damaging substances, including acids and alkalies. In other words, oxidation of tanta-

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Table I

Tantalum Forms and Applications

Form	Properties	Applications	Defects
Porous Tantalum	Highly porous [19] Anticorrosive [22] Cost effective [23] Biocompatible [32]	Orthopedics [25] Dentistry [28] Tissue regeneration [37]	Heterogeneity of pore size [19]
Tantalum Nanoparticles	Anticorrosive [22] Biocompatible [40] Cost effective [44] Multi-functionality [47]	Contrast agents for: MR [40], X-Ray CT [41] Hydrogel composite component [51]	Aggregation [44]

lum renders the metal biocompatible. Since tantalum is very strong and ductile, it was initially employed for the production of surgical sutures (Burke 1940). The long-term, favorable outcome, devoid of any inflammatory/foreign body reaction, encouraged surgeons to use it for more complex applications. During World War II, tantalum began to be widely used for cranioplasty of skull defects following battlefield injuries (Woodhall and Spurling 1945). It was highly valued because, unlike any other implantable materials, it had all the advantages of a traditional bone graft. Subsequently there was an expansion of tantalum usage including mesh for hernia surgery (Koontz 1947), foil for peripheral nerve reconstruction (Norcross and Bakody 1947), and tubes for frontal sinus reconstruction (Harris 1948), as well as for blood vessel anastomoses (Weissand Lam 1950). These early studies demonstrated the outstanding biocompatibility and flexibility of tantalum, establishing a basis for a growing body of clinical applications (Table I). Later on, Titanium has been introduced to reconstructive medicine as a less expensive substitute (Leventhal 1951, 1957, Beder and Eade 1956). Currently the price for tantalum is above \$100/kg, what compares to only \$10/kg of titanium and over \$1000 for ounce of gold.

POROUS TANTALUM FOR BONE REGENERATION

The introduction of powder (particle) metallurgy resulted in porous materials which re-shaped the landscape of bone implants as porous materials allow for bone ingrowth, regeneration and biological fixation and eliminated implant loosening and related treatment failures (Matassi et al. 2013). However, these porous materials have their own challenges; for example porous titanium possesses relatively low resistance to corrosion and as such requires a coating (Dabrowski et al. 2010). It is also not strong enough, as a bulk implant, to bear the physiologic load of bones (He et al. 2013), and until now medical grade bulk implants made of porous titanium were not available on the market. However these have been used as metaphyseal sleeves for tibial defects in revision of total knee arthroplasty (Barnett et al. 2014), and were shown to be superior to hydroxyapatite scaffolds in a rabbit radius nonunion model (Zhang et al. 2014). In this regard, porous tantalum, although more expensive than titanium has several advantages, such as a much higher living cell density on the surface, excellent cellular adherence and growth, and allowing abundant extracellular matrix formation (Balla et al. 2010a), with new bone occupying up to 80% of the pores (Bobyn et al. 1999), which has allowed for successful commercialization (Trabecular Metal™, Zimmer®). Porous tantalum was even shown cheaper and more effective than autograft plus plate for anterior cervical fusion (Fernandez-Fairen et al. 2012). In addition, the novel, LASER-based methods of manufacturing porous tantalum enable production of bulk materials for implants with unique characteristics, such as optimal mechanical properties corresponding to the strength of human cortical bone (Balla et al. 2010b). Porous tantalum has a trabecular geometry that is useful for simulating osseous tissue, as well as an open cellular structure (Fig. 1). It is 75–85% porous and contains interconnecting pores throughout. With these properties, tantalum has a modulus of elasticity similar to that of cancellous bone (Cohen 2002, Malkani et al. 2009). In contrast to large-pore materials, the smaller pore sizes of tantalum result in significant ingrowth of bone into implants and increased contact between the bone and tantalum struts made of the porous material (Fig. 2). Mechanical testing has revealed that the amount of shear strength of the ingrowth increases over time. Porous tantalum also provides a significantly higher amount of fixation strength compared to conventional metals (Ducheyne et al. 1980, Bobyn et al. 1999). Based on *in vitro* studies, a porous Titanium-Niobium alloy has just been reported as a cost effective alternative to porous Tantalum with corrosion resistance and strength exceeding pure Titanium (Xu et al. 2013), but direct comparisons of the alloys performance to Tantalum *in vivo* are still needed.

Porous tantalum also has high stability and healing potential, as evidenced by hip, knee, and spine surgeries, as well as with foot and ankle surgery (Frigg et al. 2010). Prior to porous tantalum, autografts, allografts, and xenografts were the prime structural components used to fill the gaps following reconstructive surgery. All three of these posed disadvantages, such as donor-site morbidity, failure to integrate with the bone, low stability, and potential risk of transmission of infectious diseases (Jager et al. 2005). Porous tantalum blocks have been used after reconstructive foot and ankle surgery for bone ingrowth. Tantalum helps to fuse the gaps between bone structures, without any of the complications that conventional methods present. The tantalum blocks were found to provide even better bone fusion rates than structural bone grafts in several different clinical applications (Wigfield et al. 2003, Levine et al. 2006, Fernandez-Fairen et al. 2010). The cost of porous tantalum blocks are also similar to previous methods, which makes this material a perfect substitute for a porous material graft that does not provide as much stability (Frigg et al. 2010).

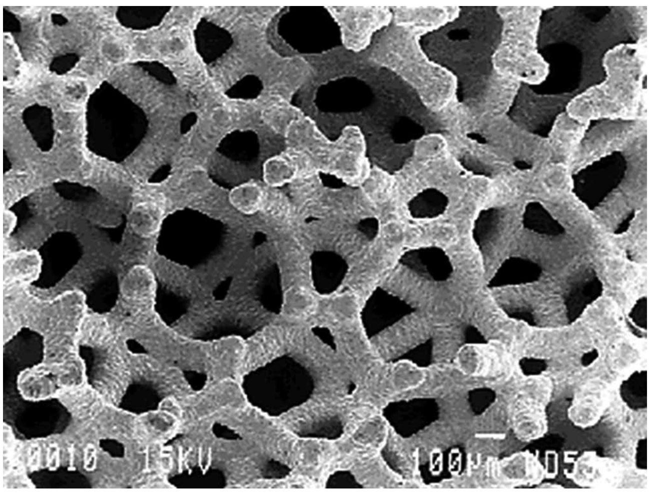

Fig. 1. Structure of porous tantalum. SEM of porous tantalum with small pores and high interconnectivity and porosity. [Reprinted with permission from Hacking et al. (2000) Fibrous tissue ingrowth and attachment to porous tantalum. J Biomed Mater Res 52: 631–638. Copyright (2014) John Wiley & Sons, Inc.]

In another study, porous tantalum has been used as the midsection of a dental implant instead of a titanium alloy, which is a standard for this application. Porous tantalum was designed to be structurally similar to trabecular bone and the expectation was that a tantalum material would provide long-term stability and facilitate bone growth into the implant. There was significant growth in and around the porous section, however, no difference in long-term stability between traditional threaded titanium alloy and porous tantalum was found thus, for purposes of dental implants, porous tantalum might be not beneficial over currently existing technologies (Kim et al. 2013).

Tantalum-based materials also show a capacity for interconnectivity with existing bone structures in the body and a homogenous shape and size range. This allows the biomaterial to be produced in bulk for implants in reconstructive orthopedics (Bobyn et al. 2004). After implanting the porous tantalum, different pore sizes are evaluated for growth, and porosity is a key feature that is at the center of all the advantages of this material (Matsuno et al. 2001). This feature stimulates extensive bone growth, faster ingrowth into the implant and, effectively, greater interface stability, which has proven beneficial in many implants (Zou et al. 2004). In addition, the biocompatibility of the implant materials has been highly increased after the introduction of tantalum-based porous materials (Black 1994).

Radiopacity is a highly desired property for most biomaterials, especially for dentistry. With regard to dental materials, radiopaque transplanted materials can be distinguished from the surrounding tooth structures. They can also be used to detach marginal overhangs as well as determine if there is contact with adjacent teeth (Chan et al. 1999). Use of radiopaque materials can also expedite the removal process of foreign dental implants from soft tissue. Materials in dentistry currently consist of silver amalgam mixtures, which are highly radiopaque, but they undergo hydrolysis and degrade easily. One solution to this problem is the use of a homogenous heavy metal. Tantalum is an inherently radiopaque element because of its high atomic number (72), and can easily be formed into the required size structures. The conclusion of many studies listed in this review was that, due to its chemical inertness, tantalum oxide has a low toxicity and, because it is radiopaque, enables the gathering of important diagnostic information reliably, making it a highly attractive material for regenerative and restorative medicine.

POROUS TANTALUM FOR REGENERATION OF SOFT TISSUE AND TENDONS

Porous tantalum also facilitates the ingrowth of soft tissue, including the formation of blood vessels that were found to assemble on the surface and within the structure of the porous tantalum. As a result, tissue maturity and vascularity increase as time progresses (Hacking et al. 2000). Porous biomaterials have been studied for the past two decades for their ability to stimulate soft tissue ingrowth (Salzmann et al. 1997). Many of these porous materials were metal-based and were used in orthopedic procedures for ligament and tendon attachment or for implants to fill the bone gap after tumor removal (LaBerge et al. 1990). Fibrous tissue has been shown to heal with the presence of small pores, high porosity, and high interconnectivity (Hacking et al. 2000). Tantalum-based porous biomaterial has already been shown to successfully aid in bone ingrowth in implants, but it has also shown promise in tissue regeneration.

In one study in canines, tendons were surgically attached between porous tantalum washers (Reach et al. 2007). The ingrowth of tendon tissue was analyzed to determine the tendon-to-implant fixation strength and compared to tendon-to-bone strength. Mechanical testing reveled that tendon strength increased each week following surgery, with the stiffness similar to that of a normal tendon. Histological examination revealed that, over time, there was an increase in the density of tendon growth on the tantalum washers.

Another study involved the use of porous tantalum to create constructs that resemble porous surfaces with a beaded layer. This type of surface is necessary for the utilization of porous tantalum for soft tissue growth. Soft tissue can adhere to the rough tantalum block surface without complications. Histological tests revealed the attachment of new growth to the site of the implant, and mechanical testing revealed proper attachment strength (Hacking et al. 2000).

Mechanical testing is also conducted to test whether the mechanical properties of the tissue growing into the implant are comparable to innate tissue in the body. Soft tissue rupture tests were conducted to determine where the point of separation occurred. In all the tests, tissue would rupture near an area that was separate from the implant region. This suggests that the implant is as strong as, or stronger than, the surrounding natural tissue. Histological analysis also revealed the presence of blood vessels and neovascularization (Soballe et al. 1992). Further histology revealed that the ingrown soft tissue is densely and intimately attached to the tantalum surface. As time progressed, the density, structural organization, and vascularity all increased with the developed ingrown tissue (Hacking et al. 2000). All of these beneficial characteristics allow the implant model to maintain a tensile strength that is similar to different types of animal soft tissue. Porous tantalum also offers more porosity compared to conventional metal-based porous material. This characteristic is required for tissue ingrowth because fibrous tissue is more cellular, compared to osseous tissue. The porous tantalum is able to provide the volume that soft tissues require for growth (Squier and Collins 1981). The tantalum-based biomaterial has proven to be equally as useful for soft tissue generation as it is for osseous tissue ingrowth. Porous tantalum is able to

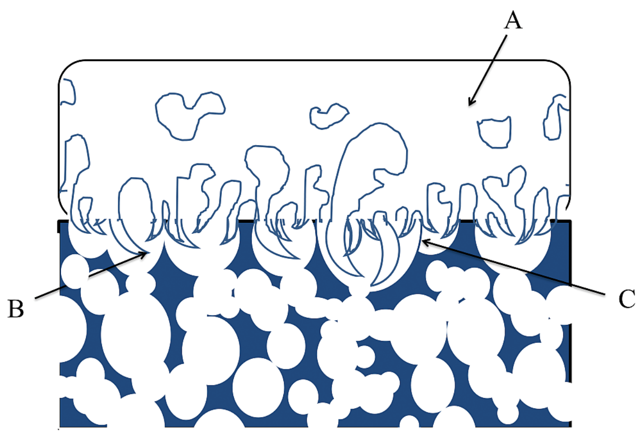

Fig. 2. Stable bone growth. Graphic representation of stable bone ingrowth on porous tantalum scaffold pores with (A) bone layer, (B) bone ingrowth, and (C) porous tantalum scaffold pores.

match the stability, growth rate, and complete functionality that innate tissue provides (Reach et al. 2007).

TANTALUM NANOPARTICLES

One of the recent major advances in tantalum applications was the production of nanoparticles. Tantalum nanoparticles have been experimentally used over the past two decades, including for assessment of biocompatibility and for detection with magnetic resonance (MR) (Weissleder et al. 1990). Bioinert tantalum oxide nanoparticles are also commonly used as nanoprobes for X-ray computed tomography (CT) imaging (Bonitatibus et al. 2010). As described above, the advantages of tantalum due to its corrosion-resistant oxide layer were appreciated with its early applications in orthopedics.

Many different inorganic nanoparticles have been used in medical imaging with the composition dependent on imaging modality (Barnett et al. 2007). X-ray computed tomography is an imaging technique that

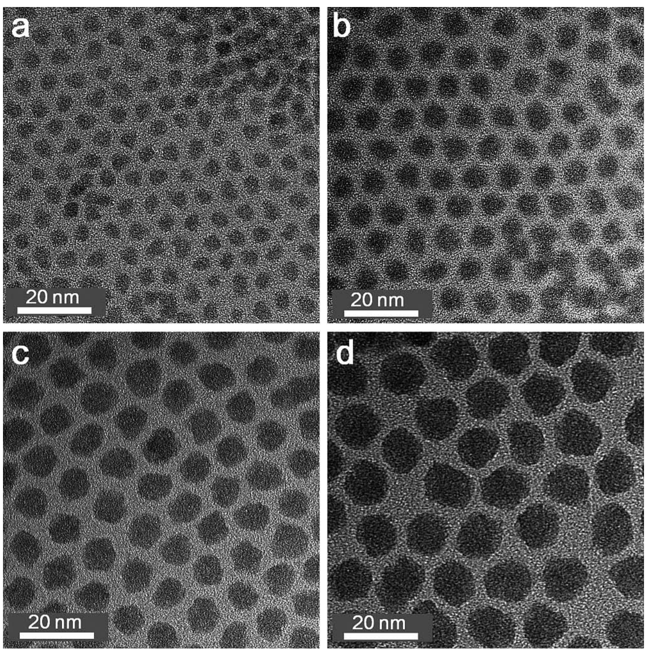

Fig. 3. Size-controlled synthesis of TaO_x nanoparticles. (a–d) TEM images of 6, 9, 13, and 15 nm-sized TaO_x nanoparticles in microemulsion. [Reprinted with permission from Oh et al. (2011) Large-scale synthesis of bioinert tantalum oxide nanoparticles for X-ray computed tomography imaging and bimodal image-guided sentinel lymph node mapping. J Am Chem Soc 133: 5508–5515. Copyright (2014) American Chemical Society.]

allows for the use of contrast agents to enhance soft tissue visualization. Iodine-based contrast agents are commonly used, but their short clearance times from blood circulation are not advantageous for targeted imaging studies (Yu and Watson 1999). Nanoparticle-based contrast agents are more desirable because they can provide strong contrast and can be designed for long blood circulation times. These nanoparticles can also be functionalized to facilitate the targeted delivery of contrast agent (Oh et al. 2011). CT requires a relatively high concentration of contrast agents to produce satisfactory signal contrast in images; however, excessive aggregation of nanoparticles can lead to toxicity. This toxicity can be avoided through improving nanoparticle colloidal stability, which is achieved with proper functionalization.

Prior to the synthesis of tantalum nanoparticles, gold (Au) nanoparticles were evaluated as x-ray contrast agents. Au particles were easy to synthesize, but their high cost made it difficult for them to be used for large-scale clinical applications. However, they have been evaluated as molecular targeting and cell tracking agents using CT (Hainfeld et al. 2011, Menk et al. 2011). More recently, tantalum oxide nanoparticles have been investigated, and shown to provide good CT contrast along with high viability of labeled cells (Lee et al. 2012). The properties of tantalum are very similar to gold, including a high attenuation coefficient, but tantalum is much more cost-effective (Oh et al. 2011). The anticorrosive properties of tantalum oxide are also important for medical imaging. However, when non-functionalized tantalum oxide nanoparticles are used for CT imaging, there is quick renal clearance, which is detrimental to proper imaging thus functionalized nanoparticles better fit. Although tantalum has a lower contrast enhancement (Hounsfield Units) compared to gold, it still is superior to traditional iodine-based contrast agents.

One way to extend the circulation period is by synthesis of tantalum oxide (TaO_x) nanoparticles *via* a microemulsion method (Fig. 3). Functionalization of the particles results in improved targeted delivery. In addition the use of a microemulsion method enables the production of hybrid nanoparticles that combine different contrast materials, which facilitates multimodal imaging (Fig. 4). Tantalum oxide-based nanoparticles were synthesized for CT and MRI dual modalities. The particles were made with an iron oxide core with a tantalum (V) ethoxide shell. These nanoparticles are biocompatible and are known to have relatively high blood circulation times. For this reason, they can be used with MRI in order to provide soft tissue contrast. MRI is often paired with Computed Tomography (CT) scans in order to distinguish the oxygenated region from the hypoxic region of a tumor. The tantalum component of nanoparticles allowed for detailed evaluation of vasculature including tumor, and iron oxide component was shown to differentiate between oxygenated and hypoxic regions. The oxygenated regions appeared dark due to abundance of nanoparticles, while the hypoxic get only grey due to limited nanoparticle inflow. Such distinction is important since it is difficult to deliver anti-cancer drugs to low perfusion, hypoxic regions (Lee et al. 2012).

Moreover, it was recently published a method for inexpensive, large-scale synthesis of functionalized nanoparticles, potentially applicable for the wide range of clinical applications. Functionalized, stable and homogenous TaO_x nanoparticles with the range of 5–15 nm were synthesized by a microemulsion method. Silane-based components were used in this procedure because they are biocompatible and allow for easy tethering of fluorescent markers. This proved to be significant in multi-modality imaging and targeted delivery. In addition, the PEG-silane component was used to increase blood circulation time in the body by acting as an antifouling agent against reticuloendothelial system (RES) uptake. Such functionalized nanoparticles did not show any toxic effect unless dissolution or aggregation occurred (Oh et al. 2011). Properly synthesized particles have a homogeneous colloidal structure and their size can be controlled as required for a particular application (Fig. 3). In addition, since the tantalum oxide particles can be synthesized with an array of silane agents, they can be used as hybrid probes for excellent multimodal imaging results.

TaO_x nanoparticles can potentially be used for imaging of hydrogels by incorporating them during the gelation process using covalent or/and non-covalent strategies. Hydrogels have been known to be effective carriers of drugs for cell-based drug delivery applications (Schmidt et al. 2008). One such representative is a hydrogel with Hyaluronic acid-based (HA) hydrogels which was specifically designed for the regeneration of different types of tissues (Leach and Schmidt 2005). TaO_x can be cross-linked with the HA hydrogel to create a composite that can be used for efficient cell or drug delivery, where TaO_x acts as the contrast agent allowing to monitor biodistribution and half-life of bioactive compartments. Hydrogel and tantalum-based composites can also be used for simultaneous incorporation of drugs or stem cells since neither is detrimental. Hydrogel-carrying tantalum oxide nanoparticles have been shown to have better imaging properties than traditional contrast agents (Tang et al. 2013). Hydrogel composites have also been shown to be useful in the regeneration and repair of ruptured intervertebral discs (Benz et al. 2012).

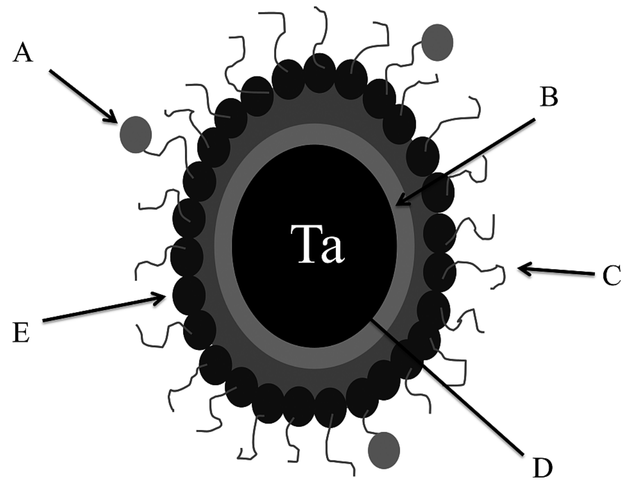

Fig. 4. Functionalized tantalum-based nanoparticle. Graphic representation of a functionalized tantalum nanoparticle capable of multi-modal imaging functions with (A) NIR fluorescence component, (B) silica, (C) Polyethylene Glycol (PEG), (D) Tantalum (CT) and (E) MRI lipid component.

CONCLUSIONS

Tantalum is a biomaterial with a long history of applications in medicine. Due to the beneficial properties of tantalum, interest in expanding potential applications is increasing. Novel fabrication techniques, such as production of porous implants, introduces new qualities of these materials, including outstanding biocompatibility and mechanical properties that are useful for tissue regeneration (Weeden and Schmidt 2007). Future applications include use of tantalum nanoparticles and hydrogel composites for targeted drug delivery purposes with the goal of treating diseases such as cancer and degenerative disc disease (Benz et al. 2012). Tantalum nanoparticles are low-cost, bioinert, and are known to be excellent X-ray contrast agents with low cytotoxicity, including imaging of tissue composites (Bonitatibus et al. 2010, Janowski et al. 2012).

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