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Review

Biomedical Applications of Titanium Alloys Modified with MOFs—Current Knowledge and Further Development Directions

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Abstract: MOFs (Metal–Organic Frameworks) are so-called coordination polymers with a porous crystalline structure. In this review, the main emphasis was placed on these compounds' use in modifying titanium implants. The article describes what MOFs are, gives examples of ligands used in the synthesis of MOFs, and describes a subgroup of these materials, i.e., Zeolitic imidazolate frameworks. The article also lists the basic biomedical applications of these compounds. This review shows the significant impact of titanium surface modification with Metal–Organic Frameworks. These modifications make it possible to obtain layers with antibacterial properties, better corrosion resistance, increasing cell proliferation, faster bone growth in vivo, and much more. The presented work shows that the modification of titanium with MOFs is a very promising method of improving their properties. We hope that the prepared review will help research groups from around the world in the preparation of implants modified with Metal–Organic Frameworks with enhanced properties and utility applications.

Keywords: MOFs; ZIFs; titanium implants; biomaterials; osseointegration

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1. Metal-Organic Frameworks (MOFs)

Metal–organic frameworks (MOFs) or porous coordination polymers are crystalline materials that have attracted the interest of a large number of scientists from around the world in recent years. It is one of the fastest-growing groups of materials, with about 100,000 structures obtained so far [1]. They consist of metal ions (e.g., Zn^{2+}, Co^{2+}, Ni^{2+}, Fe^{3+}, Cr^{3+}, and Zr^{4+}) and organic ligands with various functional groups (e.g., carboxyl or amino groups). Most of the ligands used are of synthetic origin (e.g., terephthalic acid, 2-amino terephthalic acid, 4,4′-biphenyl dicarboxylic acid, 1,1′,2′,1″-terphenyl-4,4′,4″,5′-tetracarboxylic acid, 6-(4-carboxylphenyl)nicotinic acid, 5-propoxy-isophthalic acid), while some are also of natural origin (e.g., gallic acid, L-glutamic acid, adenine or porphyrins) [2–10]. Examples of ligands used in the synthesis of MOFs are shown in Figure 1. Such great interest in this class of materials is due to their unique properties. They have a large specific surface area. There are some MOFs with a specific surface area greater than 7000 $m^2 \cdot g^{-1}$. It is possible to obtain networks with different porosity from 3 to 100 Angstroms. Many existing MOFs have excellent thermal stability, up to 600 °C, and chemical stability in solutions of strong acids or bases [11–13]. In addition, the physicochemical properties of Metal–Organic Frameworks can be easily modified. This can be done by, e.g., modification with silanizing agents, creation of open metal sites, or chemical modification of the ligand [14,15]. The presented properties and a large number of available MOFs have led to an increase in their application potential in various fields. One of the fields of their application is the storage of gases such as hydrogen or methane. They can also be used as molecular sieves for separating gas mixtures such as C_2H_4/C_2H_2 [16]. Some of these structures are studied for application in electrochemistry. They can be used, for example, as positive and negative electrodes in Li-ion batteries. Another application in electrochemistry is electrocatalysis where MOFs can be used in, e.g., hydrogen evolution reactions [17]. MOFs can also be used to construct electrochemical sensors, e.g., to detect pesticides or heavy metal ions [18,19]. Another application of these materials is photocatalysis; MOFs based on titanium ions have special properties in this aspect. According to the literature, they have outstanding photocatalytic and optoelectronic properties [20]. They are also used as "traditional" catalysts for chemical reactions [21].

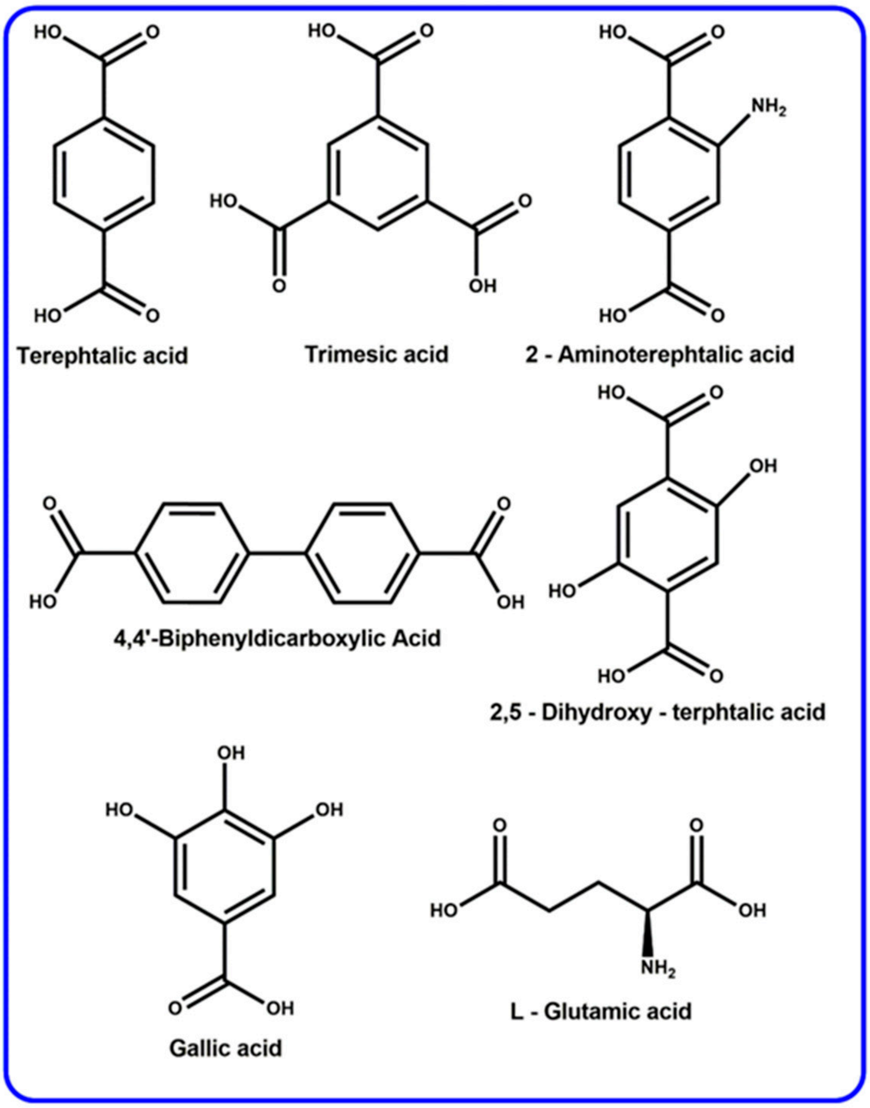

Figure 1. Commonly used synthetic and natural linkers in the synthesis of MOFs.

The last mentioned application of MOFs is the adsorption of impurities such as toxic dyes from aqueous solutions [22]. These structures also have many biomedical applications, which will be discussed later in the article. To date, many review articles have been published on the biomedical applications of MOFs. For example, articles published by Chen and Keskin et al. [23,24]. The first article describes the applications of Ti-based MOFs in the biomedical field, however, it focuses mainly on drug delivery systems and the development of antibacterial materials. The second paper also focuses on other applications such as drug delivery systems and the use of MOFs as imaging agents. A recently published paper by Sharabati et al. also focused mainly on drug delivery and imaging in diseases such as cancer, viral infections, diabetes, bacterial infections, and lung diseases [25]. In the next article on the biomedical applications of MOFs, only MOFs based on porphyrins were discussed, and so far they have not been used in the modification of titanium. The last mentioned work published by Sun et al. also applies only to the delivery of drugs [26,27].

2. Zeolitic Imidazolate Frameworks (ZIFs)

Zeolite imidazolate frameworks (ZIFs) are one of the subgroups of MOFs that are of great interest to the scientific community. These materials, like all MOFs, consist of an organic ligand and an inorganic metal cation. The ligand is based on an imidazole skeleton, and the metal cation is most often Zn^{2+} or Co^{2+} [28–31]. Examples of the ligands used to synthesize various ZIFs are presented in Figure 2. The scheme of combining metal ions and ligands can be schematically presented as follows: Me^{2+}-IM–Me^{2+}. This bond has an angle of 145° The bonding scheme is shown in Figure 3.

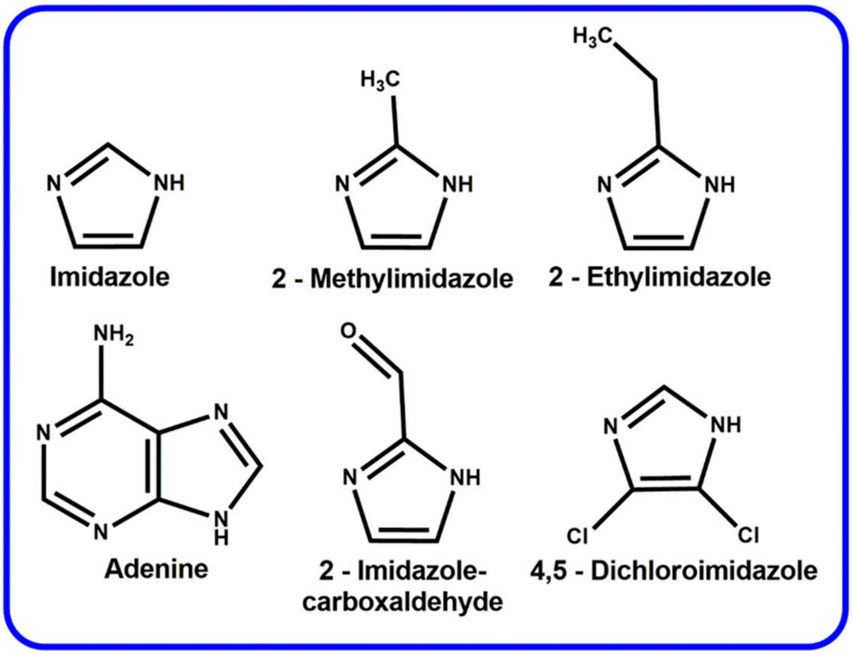

Figure 2. Examples of imidazolate-based ligands for the synthesis of Zeolitic imidazolate frameworks [32].

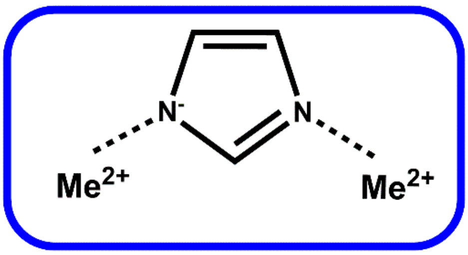

Figure 3. Bonding scheme of metal ions with imidazole ligands.

Such a bonding angle makes these materials similar in structure to zeolites. This is why they are so popular. In this material, metal cations, e.g., zinc, play the role of silicon atoms, while the linker plays the role of oxygen atoms [33,34]. This type of connection of atoms makes them have unique properties, as in the case of MOFs. They have a large specific surface, high porosity, and tunable surface properties. They are also characterized by good chemical stability (especially in an alkaline environment) and thermal stability [34]. Like MOFs, ZIFs have many applications in various branches of chemistry [28]. They are used, for example, in the separation of gas mixtures such as H_2/CO_2 or N_2/H_2 [35,36]. ZIFs are also used to prepare so-called mixed matrix membranes (MMMs). These membranes are used for gas or liquid separation. ZIFs can also be used to create catalysts, for example, transesterification or acylation reactions [28]. ZIFs as materials with a large surface areas and porosity are also a great support for obtaining catalysts by incorporating, for example, active metal oxides [37]. As in the case of MOFs, ZIFs also possess many biomedical applications, which will be discussed in the next section.

3. Biomedical Applications of MOFs

As mentioned earlier, due to their excellent properties, MOFs have many biomedical applications. These are, for example, drug delivery, gene delivery, and delivery of gasses (nitric oxide) necessary for many biochemical processes, bioimaging, biosensors, and scaffold materials [24,38]. Some of these applications will be briefly explained in this review.

The first application described will be for drug delivery and gene delivery. MOFs can retain various drugs in their structure, which undergo intelligent, slowed release in the body. This often happens under the influence of appropriate conditions, such as reduced pH of the tumor or the presence of glutathione. For this purpose, various MOFs are employed. One of the most commonly used networks for this purpose is ZIF-8. For example, Kaur et al. prepared ZIF-8 containing an encapsulated anticancer drug—6-mercaptopurine [39]. Drug release studies have shown that the drug is released under the influence of reduced tumor pH. Another example of using this network in drug delivery is presented by Zheng et al. [40]. In this work, authors prepared ZnO@Zif-8 core-shell nanoparticles loaded with an important anticancer agent—doxorubicin. The work also shows that this system has the ability to release the drug in an environment with a reduced pH. Another network that has been proposed for drug delivery applications is the UiO-66. In this work, Gong et al. prepared MOF containing free SH_2 groups in the linker structure [41]. These groups were used to attach 6-mercaptopurine to it via a covalent disulfide bond. The results showed that the release of the drug is possible only in the presence of glutathione, which is present in increased amounts in cancer cells. MOFs can also be used to deliver protein drugs and modify the genome. In the work presented by Yang et al., authors synthesized ZIF-90 loaded with cytotoxic protein for cancer therapy and genome-editing protein Cas9 [42]. The results of their research showed that both proteins are released under the influence of adenosine triphosphate (ATP), which is present in large amounts in the intracellular fluid. All these results suggest that MOFs can be used for the delivery of various types of drugs.

Properly constructed MOFs are also used in photodynamic therapy. Photodynamic therapy consists of the fact that photosensitizers under the influence of light radiation generate various reactive oxygen species (ROS), such as singlet oxygen or hydroxide radicals [43]. For instance, Lu et al. prepared a MOF consisting of Hf^{4+} ions and a porphyrine-based ligand [44]. The ability of porphyrins to generate ROS is well known, however, their combination with metal ions increases the amount of ROS generated. In this work, it was almost twice as large. In the next paper, the authors show that the use of an MOF based on Mn^{2+} ions has the ability to generate oxygen from H_2O_2 present in cells [45]. In a paper published by Sharma et al., the possibility of delivering the photosensitizer through encapsulation in the MOF structure is also shown [46]. In their work, a MOF based on Cu^{2+} ions and gallic acid was used for this purpose. Their work shows that material loaded with methylene blue has the ability to generate more ROS than material without it.

MOFs can also be used as imaging agents. For instance, Ryu et al. prepared two types of MOFs named UiO-67 and MOF-801 loaded with two fluorescent dyes, Resorufin and Rhodoamine-6G, respectively [47]. Both frameworks were functionalized with the targeting agent galactosamine. The test results showed that the prepared particles have high biocompatibility towards two human cell lines and are excellent as fluorescent imaging agents. In the next work, Rieter et al. prepared an MOF consisting of gadolinium ions and 1,4-benzenedicarboxylic acid [48]. The synthesis was carried out in the inverted microemulsion system, which resulted in obtaining a material with the morphology of nanorods. The obtained materials were tested for use as a contrast agent in nuclear magnetic resonance imaging. The obtained results showed that the prepared material has high values of R1 and R2 relaxivities per mM of material and is suitable for use as a contrast agent. Zeolitic imidazolate frameworks are also used for the preparation of imaging agents. Zhao et al. presented the synthesis of ZIF-8 doped with manganese ions [49]. The obtained material was tested for use as a contrast agent in nuclear magnetic resonance. The results of the study showed that such material has the ability to act as a contrast agent and is additionally characterized by low cytotoxicity against the human 4T1 cell line.

MOFs are also used to obtain scaffolds with different properties. For example, Guerrero et al. prepared a kidney scaffold consisting of ZIF-8 and (poly[isobutylene-alt-maleic anhydride]-graft-dodecyl) [50]. The prepared material was tested for retention of two uremic toxins, p-cresyl sulfate, and indoxyl sulfate. The results of these studies showed a high retention rate for p-cresyl sulfate and less for indoxyl sulfate. However, they also showed the great potential of using organometallic lattices in kidney scaffold construction. In another paper, Karakeçili et al. prepared a chitosan scaffold loaded with ZIF-8 and encapsulated with the antibiotic vancomycin [51]. The test results showed an excellent antibacterial effect of the prepared material. They also showed that the release of the antibiotic is to some extent pH-dependent as in an acidic environment more percentage of the drug is released. The authors also conducted biocompatibility studies on the MC3T3-E preosteoblast cell line. The results of these studies showed that the prepared material increases cell proliferation and alkaline phosphatase activity. This means that this material has great potential in the treatment of bone diseases. Han et al. prepared a bio-glass scaffold also functionalized with ZIF-8 loaded with vancomycin [52]. The prepared scaffold, as in the previous work, also showed pH-dependent release. In this work, the authors also managed to confirm that the prepared scaffold increases cell proliferation and has strong antibacterial properties.

MOFs can also be used to create biosensors. Biosensors are devices consisting of a biological recognition element, which can be, for example, enzymes or DNA fragments, in close contact with the transducer [53]. For instance, Sheta et al. prepared an electrochemical biosensor consisting of a composite that consisted of polyaniline and an Ni-based MOF [54]. The material was also modified with DNA aptamers capable of detecting the hepatitis-C virus. The authors managed to obtain a sensor characterized by a low detection level (0.75 fM) and the ability to detect the virus in real biological samples. In another work, the authors prepared a fluorescent biosensor consisting of zirconium porphyrin-based MOF (PCN-222) for the detection of the antibiotic chloramphenicol. This material was also functionalized with appropriate aptamers. The prepared sensor was characterized by a low detection limit of $0.08\ pg \cdot mL^{-1}$ and a wide measurement range of $0.1\ pg \cdot mL^{-1}$–$10\ ng \cdot mL^{-1}$. This sensor also could detect the antibiotic in real milk samples [55].

4. MOFs in Modification of Titanium Alloy

Bone diseases are one of the most common diseases in the world. Examples of bone diseases are osteoporosis, rheumatoid arthritis, and bone cancer. Elderly people and postmenopausal women, in the case of osteoporosis, are particularly at risk. The presence of any of these diseases can lead to increased bone fragility, which often leads to serious fractures. In some cases, the fusion of the bone is impossible, which leads to the fact that the bone must be replaced with an implant [56]. To date, many different materials have been proposed for this purpose: metals such as tantalum or titanium, ceramics, or polymers. The most frequently chosen material, however, is a biomedical titanium alloy with the designation Ti6Al4V. This material has excellent mechanical properties, good biocompatibility, and is practically completely resistant to corrosion in human body fluids. Literature reports show that this material additionally has a very high survival rate. Like any material, this also has several disadvantages. Despite this, titanium is bioinert, i.e., it does not cause allergic reactions and is not toxic, although it is still recognized by the body as a foreign body. This action causes inflammation in the body, which negatively affects the process of osseointegration, and thus bone reconstruction [57,58]. In addition, there is a possibility of bacterial or fungal infection after the implantation operation, which is another serious disadvantage [59,60].

All these disadvantages cause scientists around the world to modify the surface of titanium implants in order to obtain a material with better properties such as the increased proliferation of osteoblasts, and antibacterial or accelerated growth of hydroxyapatite. The properties of the resulting layers depend on many different factors such as surface energy, hydrophilicity, surface topography, and porosity [61]. To date, many different materials have been used for this purpose. For instance, titanium dioxide is modified with different alkali earth metal ions, titanates layer with different cations or zeolites [62–66]. MOFs are also used for this purpose, and layers prepared with their use will be discussed in this review. Examples of applications of titanium implants covered with MOFs are presented in Figure 4. As mentioned, many parameters affect osseointegration, such as wettability, surface porosity, and roughness. Scientific research proves that osseointegration is faster when the surface of the implant is hydrophilic [67]. Modification of metallic and polymer surfaces with MOFs allows to an increase in their water contact angle and thus hydrophilicity [68]. In addition, high porosity and surface roughness are needed for effective and fast osseointegration [61]. These are the parameters that MOFs also provide. Unfortunately, MOFs can also have disadvantages such as ion leakage and the ligands used for their synthesis.

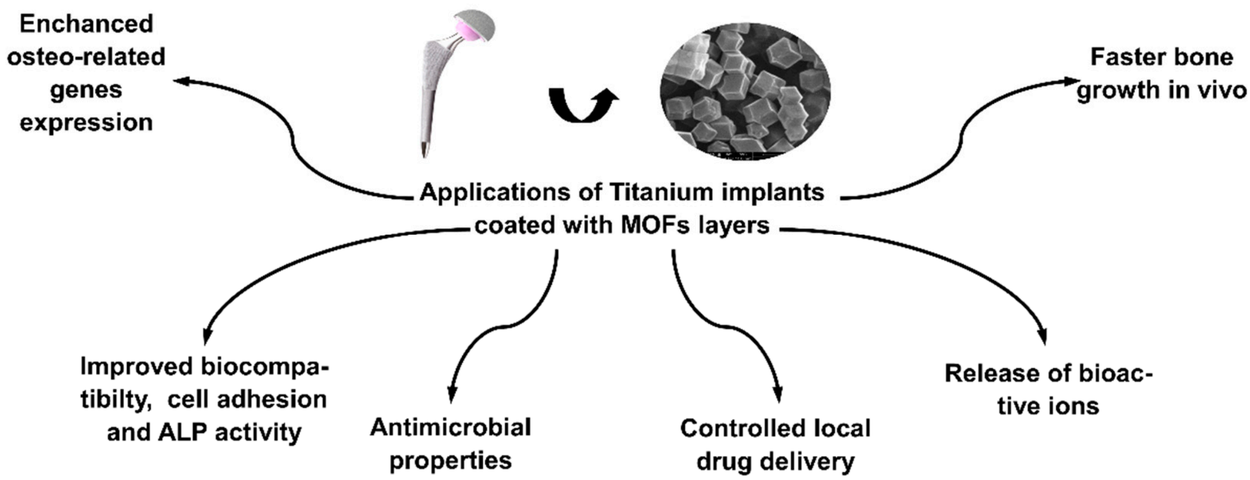

Figure 4. Examples of the applications of MOFs as a coating on titanium alloy.

In the first paper presented, Zhang et al. prepared a titanium alloy modified with ZIF-8 by a simple hydrothermal approach [68]. In their research, the authors proved that the modified material is biocompatible with the MC3T3-E1 cell line. The work also examined the release of zinc ions from the prepared layer, and it was found that only amounts of zinc ions are released. The effect of the synthesized layer on extracellular matrix mineralization (ECM) and collagen production was also investigated. The results show that ZIF-8-coated titanium materials significantly increased extracellular matrix mineralization and collagen production. To confirm the positive effect of the modification on accelerated osseointegration, alkaline phosphatase activity and the expression of osteo-related genes were also tested. In all the tests performed, the titanium coated with ZIF-8 showed an increase in the above-mentioned parameters. The authors also performed in vivo studies using mice. The study confirmed the results of in vitro tests. It was proved that in mice implanted with ZIF-8-modified titanium, more mature collagen and more mineralized bone matrix were formed. Figure 5 shows the scheme of the surgery and results of the in vivo study of the collagen and mineral matrix formation.

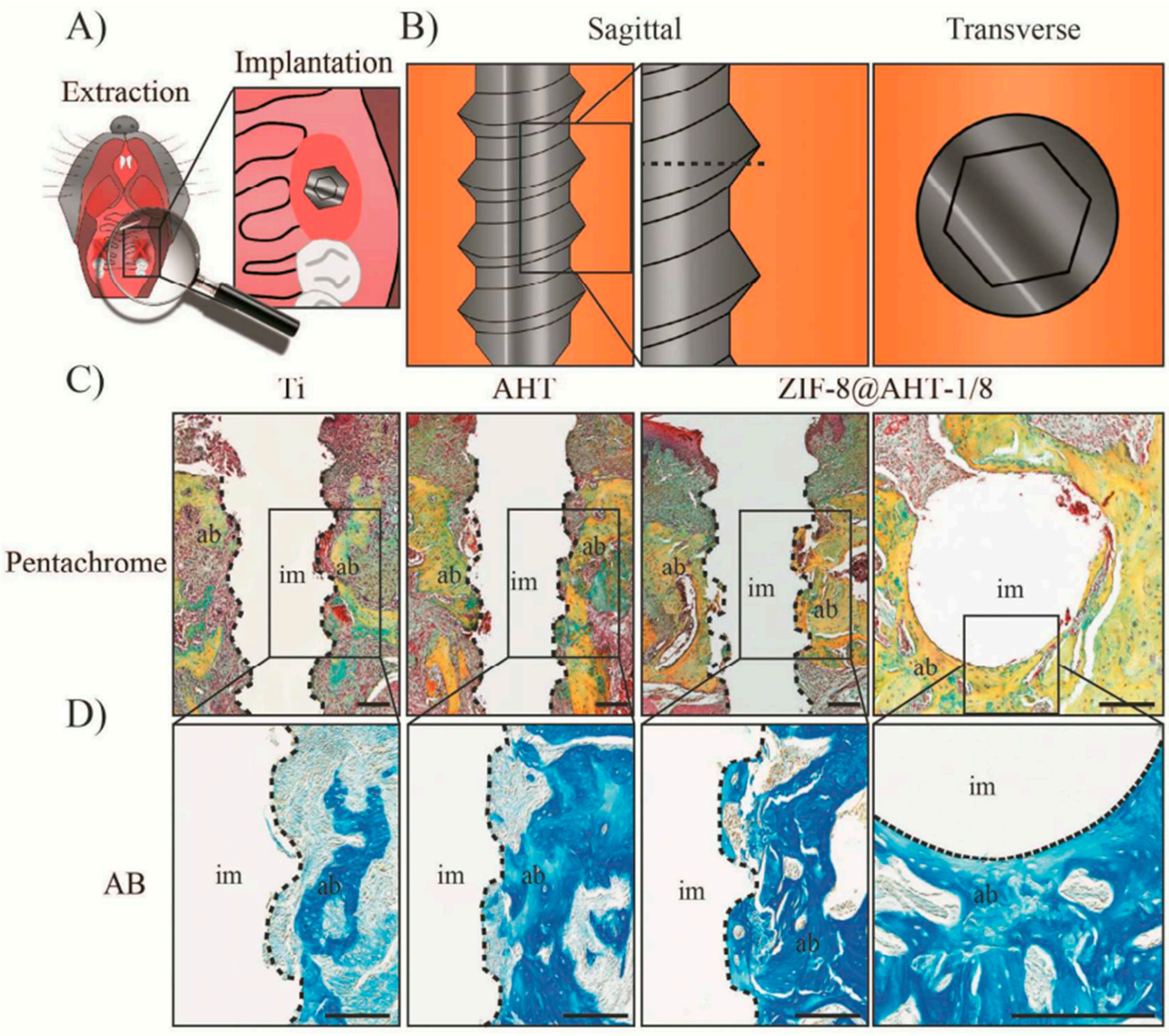

Figure 5. (**A**) Schematic of the surgery; (**B**) Sagittal and transverse direction of the implants placed into osteotomies; (**C**) Pentachrome staining, and (**D**) Aniline blue staining of Ti, AHT, and ZIF-8@AHT-1/8. Scale bar representing 100 μm; n = 6 per group. Reprinted with permission from [68]. Copyright 2023 American Chemical Society.

In another work, Chen et al. prepared titanium alloy plates modified with nano and micro ZIF-8 films [69]. Both layers were synthesized by different methods. In order to obtain the ZIF-8 nanolayer, the secondary growth method was used, while the in situ synthesis method was used to obtain the microscale ZIF. Various parameters such as the morphology of the obtained layers, MG63 cell proliferation, alkaline phosphatase activity, osteocalcin production, and cell adhesion were investigated in the work. SEM photos of both films confirmed the receipt of layers of the assumed size. It was found that particle size in the nanolayer ranged from 200–300 nm while the particle size in the microlayer was found to be over 10 um. Biocompatibility studies have shown that the ZIF-8 microlayer has cytotoxic properties while the nanolayer is biocompatible. This is due to the fact that on a micro-scale, the ZIF-8 releases much larger amounts of zinc ions, which in too high concentrations cause a cytotoxic effect, which has been confirmed by the authors. The results of biocompatibility tests and zinc release from both layers are shown in Figure 6.

The study of ALP activity showed that the nanolayer significantly increases its activity in relation to unmodified titanium. The work also examined the antibacterial activity against the S. Mutans strain. It was found that the prepared layer shows remarkable antibacterial activity against this strain.

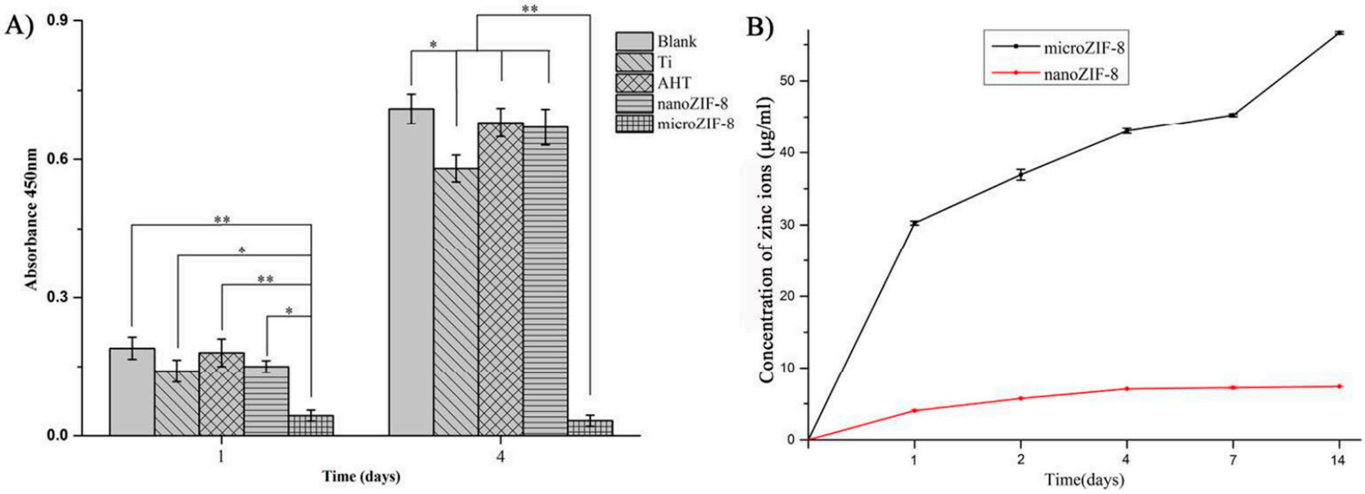

Figure 6. (**A**) Cell proliferation examined with a CCK-8 assay after MG63 cells were cultured for 1 and 4 days. * $p < 0.05$; ** $p < 0.01$; (**B**) Biodegradation of nanoZIF-8 and microZIF-8 films in 10% FBScontaining α-MEM. Reproduced with permission from [69].

Teng et al. prepared titanium also modified with ZIF-8 with immobilized iodine [70]. The scheme of this work is shown in the Figure 7. Prior to modification, the material was subjected to the micro-arc oxidation (MAO) process, on which ZIF-8 was then synthesized in situ. Iodine release studies show a dependence on pH; in an acidic environment, more iodine is released. In addition, the authors also showed that the prepared material can release immobilized iodine under the influence of near-infrared (NIR) light. It was found that NIR exposure act as an ON/OFF switch for iodine release. The material has also been subjected to antibacterial tests. It has been proven that it has antibacterial properties against the S. Aureus strain, especially when the samples were irradiated with NIR light. In vitro biocompatibility studies have shown that the material has no cytotoxic properties. In addition, in vivo studies were carried out. The bacteria-infected implants were implanted in mice. It was observed that, despite the material being infected, the post-operative wounds of the mice that had the modified implant healed without any complications, while the wound swelling was seen in the mice that had the infected material without the modification.

As you can see, great efforts are being made to obtain implant surfaces with antibacterial properties. One of the methods of achieving such an effect is the use of silver ions. Li et al. prepared a ZIF-8 layer modified with Ag+ ions on a titanium implant [59]. Studies using various techniques such as scanning electron microscopy, X-ray diffraction, or X-ray photoelectron spectroscopy, have proven the effective synthesis of the presented layer. The tests performed by the authors also showed that the modification is biocompatible, and increases the corrosion resistance and hydrophilicity of the surface. In addition, the layer loaded with silver ions significantly supports antibacterial properties.

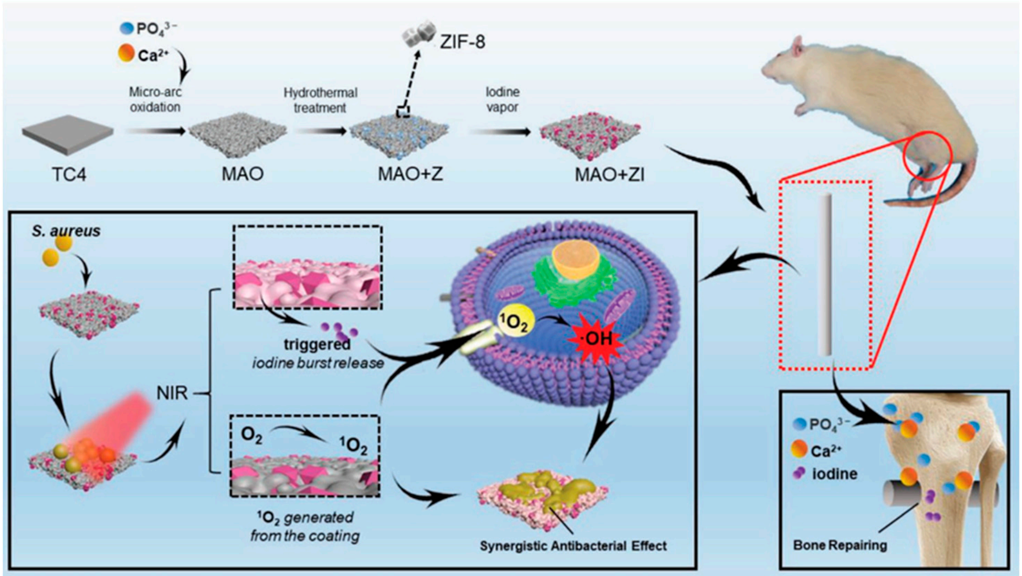

Figure 7. Schematic illustration of the synthesis process, hierarchical structure of MAO+ZI coating system, the antibacterial process (*S. aureus*) guided by NIR-triggered iodine burst release combined with one O_2 generated from the surface, and effective osseointegration enhanced by the Ca^{2+}, $PO_4{}^{3-}$ and iodine in vitro and in vivo. Reproduced with permission from [70].

Titanium implant modifications can also be used as local drug delivery systems. For example, ZIF-8-modified Ti6Al4V titanium alloy can be used as a local drug delivery system for an osteoporotic drug, risedronate (RSD). In this work, the authors proposed a new approach to the synthesis of MOFs on a titanium surface. Prior to modification, alloy was treated with NaOH to produce a layer of sodium titanate. Then, thanks to ion exchange, zinc titanate was obtained, which was modified with a linker (2-methylimidazole) to obtain a monolayer on the surface. The surface prepared in this way ensures excellent adhesion of ZIF-8 crystals, which were synthesized by the hydrothermal method. The material was used as an RSD carrier; it was proven that the drug is released from the surface of the material in constant amounts for 16 hours. Such material can be of great importance immediately after surgery. In addition, the uniformity of the occurrence of ZIF and RSD on the surface was confirmed by FT-IR microscopy [71].

Titanium coated with ZIF-8 loaded with the antibiotic levofloxacin was prepared by Tao et al. [72]. Figure 8 shows the scheme of the coating preparation and possible antibacterial pathways of the modified implant.

The layer was prepared using electrophoretic deposition. Covering titanium with this layer clearly increased the hydrophilicity of the surface. Zinc and drug release studies have shown that it is released gradually in a controlled manner over 240 h. In addition, titanium with a modified surface showed the highest biocompatibility and cell adhesion. The authors of this paper also studied the expression of osteo-related genes such as Runx2, Col1, OCN, and OPN. The expression values of all genes were higher for the samples modified with the ZIF layer. The samples were also antibacterial against E. Coli and S. Aureus bacterial strains. In vivo tests have shown that the material retains its antibacterial properties in these conditions, and additionally reduces the formation of inflammation around the implant.

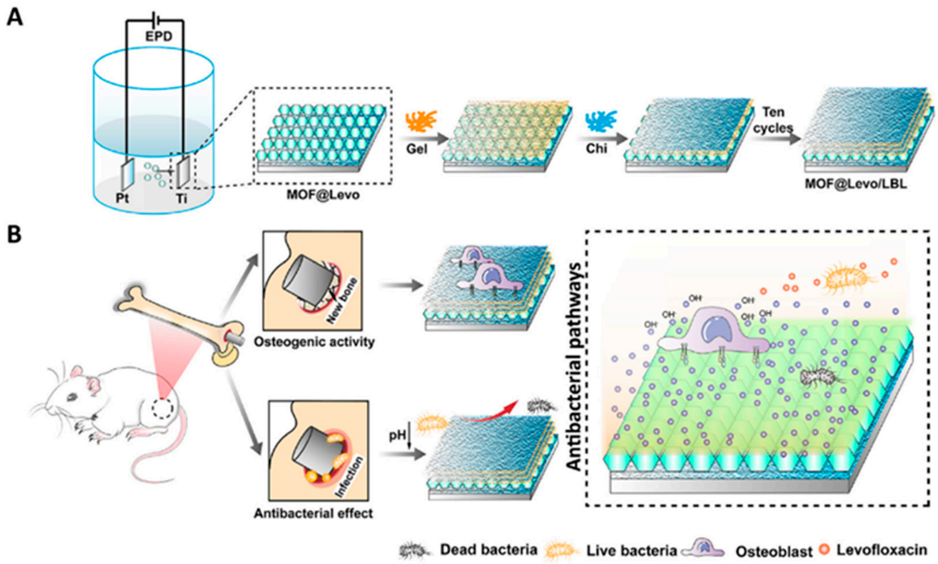

Figure 8. (**A**) Schematic illustration of ZIF-8@Levo coating onto Ti implant and (**B**) potential antibacterial pathways of the ZIF-8@Levo/LBL implant for infected femur treatment. Reproduced with permission from [72].

As also mentioned earlier, other MOFs can also be used to modify titanium. Shen et al. modified the implant with MOF-74, which had mixed metal cations [73]. The cations used were Mg^{2+} and Zn^{2+}. Using X-ray diffraction, it was possible to confirm the effective synthesis of the MOF. The hydrophilicity of the surface was also tested; it turned out to be very hydrophilic, with a water contact angle value below 10°. The prepared material was obtained with different ion ratios in the MOF. It was found that as the content of zinc ions increases, the thickness of the obtained coating decreases. This phenomenon is shown in Figure 9. The coating containing the most Zn^{2+} was also the most stable. Antibacterial tests showed a significant increase in the antibacterial effect compared to unmodified material. Tests on cells and in vivo were also performed. Studies have shown that the modified material increases ALP activity, collagen secretion, and mRNA expression of some osteo-related genes. The modified material was able to maintain its antibacterial properties in vivo and additionally increased the growth of healthy bone on the implant.

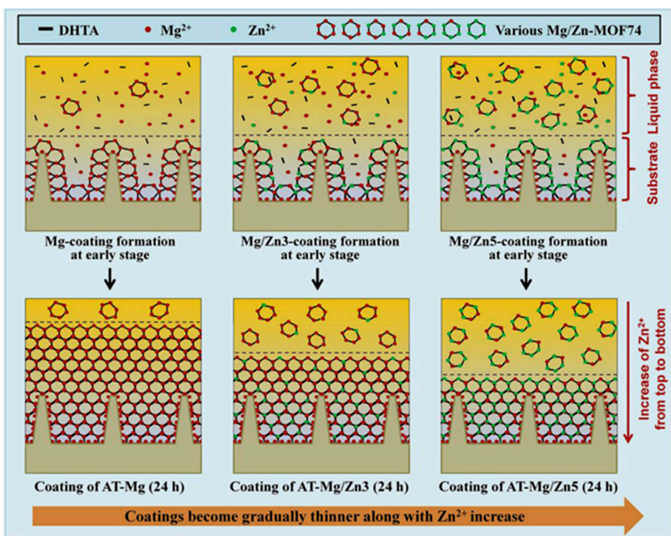

Figure 9. Illustration scheme of the formation of various Mg/Zn-MOF74 coatings on AT surfaces. Reproduced with permission from [73].

In another work, authors prepared Co^{2+}-based ZIF-67 modification on Ti implant. They used this MOF as a local delivery system for osteogenic growth peptide (OGP) [74]. As in the previous cases, the hydrophilicity of the implant increases after covering it with a layer of MOF. The prepared layer killed almost all bacteria from E. coli and S. Aureus strains. The authors proved that such a strong antibacterial effect is due to the presence of cobalt ions in the prepared layer. Biocompatibility studies have shown that the material does not cause cytotoxicity and even increases cell proliferation in relation to unmodified titanium. It was also found that it increased the expression of osteo-related genes. Thanks to the modification of the ZIF-67 alloy, it was also possible to increase ALP activity and collagen secretion. In vivo studies confirmed the results of in vitro studies. The implant retained its antibacterial properties and additionally increased the rate of bone growth and bone–implant contact ratio.

MIL-125 doped with rare earth Cerium ions was also used as a modification for the implant surface. The coating containing this MOF and hydroxyapatite was prepared using the galvanostatic method on titanium with a layer of TiO_2 nanotubes on the surface. Scanning electron microscopy images confirmed the formation of a uniform layer while energy dispersive X-ray spectroscopy and X-ray photoelectron spectroscopy confirmed the presence of cerium ions in the material. In this work, the corrosion properties were also assessed. The unmodified titanium had the lowest corrosion potential and the highest corrosion current density, while the titanium coated with a layer of MOF combined with HA had the highest corrosion potential and the lowest corrosion current density. Antibacterial tests showed almost complete inhibition of bacterial growth. The prepared layer was biocompatible and could slowly release bioactive calcium and phosphorus ions [75].

The last modification described in this article will be the work published by Wu et al. [76]. In their work, they synthesized a MOF on the surface of titanium called bio-MOF-1. It has a natural linker in its structure—adenine. Using scanning electron microscopy, X-ray diffraction, and FT-IR spectroscopy, it was possible to confirm the effective synthesis of the layer. Biological properties were also investigated in this work. Biocompatibility studies have shown that titanium modified with this MOF increases cell proliferation. It also significantly increases the activity of alkaline phosphatase and the expression of osteogenic genes. In vivo studies conducted additionally by the authors also show that the presented modification accelerates bone growth.

All methods of titanium alloy modification and their influence on the final properties are summarized in Table 1.

Table 1. The influence of MOF layers on the properties of titanium alloys is described so far in the literature.

Type of MOF	Influence of Modification on Material Properties	Ref.
ZIF-8	Biocompatibility, Zn^{2+} release, increased collagen production, improved extracellular matrix mineralization and alkaline phosphatase activity, faster bone growth in vivo.	[68]
ZIF-8	Biocompatibility, Zn^{2+} release, better cell adhesion, antibacterial activity	[69]
ZIF-8	Biocompatibility, NIR triggered iodine release, antibacterial effect	[70]
ZIF-8	Local controlled risedronate delivery	[71]
ZIF-8	Controlled levofloxacin delivery, improved osteo-related genes expression, biocompatibility, antibacterial	[72]
ZIF-8	Ag^{+} release, improved antibacterial effect, biocompatibility better corrosion resistance	[77]
ZIF-8	Controlled dexamethasone delivery, biocompatibility, enhanced ALP activity	[78]
MOF-74	Antibacterial, Zn^{2+} release, enhanced osteo-related genes expression, biocompatibility	[73]
ZIF-67	Osteogenic growth peptide delivery, Co^{2+} release, biocompatibility, antibacterial	[74]
Bio-MOF-1	Enhanced osteo-related genes expression, improved ALP activity, better cell proliferation, and faster bone growth in vivo.	[76]
MIL-125-Ti	Improved corrosion resistance, biocompatibility, Cerium release, Ca and P release, antibacterial	[75]

5. Conclusions and Possible Development Directions

This article shows that MOFs are a great material for modifying titanium implants. The prepared modifications enable the implant to acquire new properties. These are excellent biocompatibility, enhanced alkaline phosphatase activity, enhanced collagen production, better cell adhesion, and release of bioactive ions. In addition, the prepared layers also have the ability to increase the expression of osteo-related genes. The obtained coatings also have strong antibacterial properties against various strains of bacteria and better corrosion resistance. This review also shows that the modification of titanium with MOFs can be used as a carrier in the controlled release of drugs, e.g., antibiotics or anti-osteoporotic drugs. Numerous in vivo studies have also shown that the modifications accelerate bone growth in mice. Despite such good properties, there are still some challenges that need to be solved. One of the biggest concerns when using MOFs in medicine is ligand leakage. It is not entirely clear what amounts of ligand will be released by a titanium implant placed in the body for many years. Additionally, almost all papers cited in this review show that the ligand and ion are released. It should be remembered that the materials in these works were prepared on a small scale. On the other hand, the hip implant is much larger, which will result in the fact that the total amount of released substances will be greater. This shows that further research is needed on this topic.

Despite the high degree of research on the modification of titanium with MOFs, there are further possible directions of development. So far, MOFs synthesized on the surface of implants contain mainly synthetic ligands. The only one containing a natural linker is bio-MOF-1. However, this ligand also contains a second ligand (4,4′-biphenyl dicarboxylic acid) of synthetic origin in its structure. Thus, the next step in the research on the formation of MOF coatings on implants may be the synthesis of those containing only natural linkers. An example of a linker that would be suitable for this purpose is, for example, gallic acid, which has a proven ability to form MOFs and has antimicrobial properties. As can also be seen, the only metal ions used in the synthesis of MOFs are zinc and cobalt. However, there are many more metal ions with the ability to improve osseointegration, such as calcium, magnesium, or strontium [79]. These metals also have a proven ability to form MOFs [80,81]. These networks have, for example, anti-oxidative properties and are biocompatible. One example is MOF synthesized from Mg^{2+} ions and gallic acid. It was biocompatible against HL-60, RAW 264.7, and NCI-H460 macrophage cell lines [6]. Another element that affects osseointegration is lanthanum [82]. It also has the ability to create MOFs. This could be another new line of research. We hope that this review will help scientists from around the world create new modifications of titanium implants using MOFs.

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