Advances in Clinical Medicine 临床医学进展, 2022, 12(12), 11194-11201
Published Online December 2022 in Hans. http://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2022.12121614

Hans汉斯

抗菌生物材料在骨感染中应用的研究进展

李　森[1]，苑　龙[1]，李万祥[1]，延易泽[1]，崔心广[1]，卞继超[2]，王国栋[2*]

[1]济宁医学院临床医学院，山东　济宁
[2]济宁医学院附属医院关节与运动医学科，山东　济宁

收稿日期：2022年11月12日；录用日期：2022年12月6日；发布日期：2022年12月14日

摘　要

骨感染是目前骨科常见并且难以治愈的疾病。其主要的病原菌是金黄色葡萄球菌，感染过程中主要特征是生物膜的形成，这也是病菌难清除的主要原因。骨感染常常伴有骨缺损，这需要有创手术并可能发生反复感染，这给病人带来了极大的痛苦。新兴的抗菌生物材料因其良好的生物相容性及抗菌能力而受到关注。利用3D打印技术和金属离子、纳米材料、水凝胶等物质的结合可以生产出不同的抗菌生物材料。这些材料有着不俗的抗菌能力但也有着明显的缺点。本文主要对负载金属涂层的抗菌植入物、灌注抗生素的支架及抗菌水凝胶进行了简要说明。

关键词

骨感染，3D打印，抗菌生物材料，综述

Research Progress on the Application of Antibacterial Biomaterials in Bone Infection

Sen Li[1], Long Yuan[1], Wanxiang Li[1], Yize Yan[1], Xinguang Cui[2], Jichao Bian[2], Guodong Wang[2*]

[1]School of Clinical Medicine, Jining Medical University, Jining Shandong
[2]Department of Joint and Sports Medicine, Affiliated Hospital of Jining Medical University, Jining Shandong

Received: Nov. 12th, 2022; accepted: Dec. 6th, 2022; published: Dec. 14th, 2022

Abstract

Bone infection is a common and difficult disease in orthopedics department. The main pathogen is *Staphylococcus aureus*, and the main feature of the infection process is the formation of biofilm, which is also the main reason for the difficult removal of bacteria. Bone infections are often ac-

*通讯作者。

文章引用: 李森, 苑龙, 李万祥, 延易泽, 崔心广, 卞继超, 王国栋. 抗菌生物材料在骨感染中应用的研究进展[J]. 临床医学进展, 2022, 12(12): 11194-11201. DOI: 10.12677/acm.2022.12121614

companied by bone defects that require invasive surgery and can lead to repeated infections, which can be extremely painful for patients. The emerging antibacterial biomaterials have more attention because of their good biocompatibility and antibacterial ability. Different antibacterial biomaterials can be produced by combining 3D printing technology with metal ions, nanomaterials, hydrogels and other substances. These materials have excellent antibacterial properties but also have obvious disadvantages. In this paper, antibacterial implants loaded with metal coating, stents infused with antibiotics and antibacterial hydrogels were briefly described.

Keywords

Bone Infection, 3D Printing, Antibacterial Biomaterials, Review

1. 引言

严重创伤、开放性手术切除、病毒以及细菌感染引起的骨缺损的发生率越来越高，其中感染性骨缺损在临床治疗中病程长，预后差，是目前临床上的一个难题[1] [2]。感染性骨缺损的主要病因有两个，一是严重的开放性骨折，约有 5%~30%的损伤最终会发展为感染性骨缺损；二是手术后期继发慢性骨感染的骨缺损，约占 2%~5% [3]。目前临床治疗感染性骨缺损的方法有开放颗粒骨修复、假体技术、骨转移手术等，然而，这些方法缺乏持续有效的抗生素治疗，并伴有反复感染[4] [5] [6]。同时分别以聚甲基丙烯酸甲酯[poly(methyl methacrylate)]和硫酸钙(calcium sulphate)为代表的不可生物降解和可生物降解两类抗生素释放系统治疗骨感染的效果逐渐不佳[7] [8]。骨组织工程为感染性骨缺损的治疗提供了新途径，生物材料在骨组织再生中起着至关重要的作用，是新骨生长的重要支架[9]。近年来报道了几种新型治疗骨感染的生物材料包括金属离子[例如，金属颗粒和金属纳米颗粒(NPs)]、生物陶瓷[例如，生物活性玻璃(BG)、羟基磷灰石(HA)和磷酸三钙(TCP)]、多肽(抗菌肽)、聚己内酯(PCL)、聚乳酸－羟基乙酸共聚物(PLGA)、聚乳酸(PLA)和壳聚糖(CS) [10]。3D 打印技术的进步使构建新型定制的支架成为可能，这些支架能够以受控的方式输送药物和补充缺损骨。从而有可能改变目前治疗骨缺损和感染的方式[11]。3D-打印技术可以制备金属支架还可以制备用于控制感染和骨再生治疗的抗菌水凝胶支架[10]，如以壳聚糖－聚氧化乙烯－磷酸甘油和氧化锌纳米颗粒(NZNO)为材料，设计了一种 pH 依赖性的 3D 打印水凝胶支架，用于抑制细菌生长[12]。骨修复支架是骨组织工程的核心部件，其可以为细胞提供合适的粘附和增殖环境，并随着支架生物材料的降解，细胞外基质的沉积可以修复骨缺损的部分[13] [14] [15]。不断开发新的生物材料用于支架的建立，这是骨组织工程在临床应用的有效方法之一。

2. 骨感染

2.1. 主要病原菌

骨感染的主要病原菌是革兰氏阳性球菌，包括葡萄球菌和肠球菌，而金黄色葡萄球菌是最流行和最具破坏性的病原菌[16] [17]，其中耐甲氧西林金黄色葡萄球菌(MRSA)因产生和释放细胞毒素而成为毒性最强的病菌[18]。链球菌、厌氧菌如痤疮丙酸杆菌和革兰阴性厌氧杆菌如大肠杆菌、奇异变形杆菌也可引起感染[10] [19]。

2.2. 感染机制

骨感染的机制包括三个过程：病原体被成骨细胞内化、生物膜的形成和骨质破坏[10]。以金黄色葡萄球菌为例，在骨环境中，金黄色葡萄球菌对非专业吞噬细胞的入侵称为宿主介导的摄取，并在内化过程中，金黄色葡萄球菌通过进入宿主细胞来逃避抗生素和宿主免疫反应[10]体外研究显示金黄色葡萄球菌在成骨细胞[20] [21] [22]、破骨细胞[23]和骨细胞[24]内入侵和存活，其中成骨细胞对金黄色葡萄球菌的内化与病原菌在成骨细胞表面的细胞壁锚定(CWA)和纤维连接蛋白结合蛋白(Fnbps)的表达密切相关[22] [25]。Fnbps 作为成骨细胞和金黄色葡萄球菌的桥梁连接金黄色葡萄球菌细胞表面 FnbpsA 或 FnbpsB 与宿主细胞 $\alpha5\beta1$，触发细胞骨架重组和细菌细胞摄取[26] [27]。纤维连接蛋白先和金黄色葡萄球菌表面的 Fnbps 结合，再通过整合素 A5B1 与成骨细胞连接，这是病原菌入侵宿主细胞的主要过程之一[28] [29]。金黄色葡萄球菌感染机制的最重要特点是生物膜的形成，生物膜的发育可分为细菌粘附、细菌聚集、生物膜成熟和细胞脱离四个阶段[30]。黏附素和细胞壁蛋白介导的细胞相互作用，使金黄色葡萄球菌聚集在一起，形成生物膜[10]。在生物膜成熟过程就是生物膜基质产生的胞外聚合物质进一步增加和金黄色葡萄球菌的进一步聚集[10]。金黄色葡萄球菌进入细胞后，通过促进肿瘤坏死因子相关凋亡诱导配体(TRAIL)的表达，从而降低成骨细胞的活性，从而触发蛋白酶 caspase-8 激活、成骨细胞凋亡和骨质破坏，此外，受感染的成骨细胞分泌的细胞因子、趋化因子和生长因子等也参与骨质破坏[31] [32]。

3. 抗菌生物材料

3.1. 负载金属涂层的抗菌植入物

骨科植入物有着优异的生物相容性、降解性、孔隙率和机械强度，但缺乏抗菌能力[33]，因此研究了结合固有抗菌材料如金属离子或金属 NP 的涂层的方法来添加具有抗菌作用的附加层[10]。抗菌材料的涂层可以抑制浮游病原菌对细胞的粘附，然后使用物理或化学方法杀死病原菌。银、铜、锌和镁等金属离子可有效抑制革兰氏阳性和革兰氏阴性细菌的生长，因此被广泛用作涂层或与骨科植入物结合[34] [35] [36] [37]。Yunan Qing 等人通过选择性激光熔化制造了一种高度多孔的不锈钢部件，该部件通过原位水热结晶方法进行了银负载涂层的 3D 打印，并用扫描电子显微镜研究了其表面的形态，研究结果显示该部件抑制了金黄色葡萄球菌和大肠杆菌的生长并有着优异的骨整合能力[34]。Jian Wang 等人利用锌水热制备了负载锌的蒙脱石(Zn-MMT)涂层并印刷在镁合金 AZ31 上，该植入物在体外抑制细菌生长，但它有着较差的骨再生能力[36]。抗菌能力和成骨能力对于骨科植入物都是非常重要的。例如 Bailong Tao 等人采用阴极电泳沉积(EPD)方法制造的涂有氧化石墨烯－锌/甲基丙烯酰基明胶苯基硼酸(GO-Zn/GelMA-PBA)的 Ti 基植入物，该植入物不仅抑制细菌粘附并防止生物膜形成，而且还增强了成骨细胞的粘附、增殖和分化[38]。为了增强植入物的抗菌特性，设计了了金属－有机骨架－金属离子组成的化合物与有机配体规律结合的方案，它可以在早期释放大量的金属离子来抗菌[10]。Xinkun Shen 等人发现由于碱性微环境和涂层降解而释放的化合物使得涂有混合 Mg/Zn-有机框架的 Ti 表面有着出强大的抗菌能力[39]。银通过包围和破坏细菌细胞膜来抗菌，但其也会增加细胞毒性[10]。H. Bakhsheshi-Rad 等人利用空间保持器技术制造的含银可生物降解多孔镁基支架抗菌能力随着银离子浓度的增加而增加，其细胞毒性也随之增加[40]。因此，不单单是银，其它金属颗粒的细胞毒性都需要在体内和体外进行充分的评估后再投入临床使用。

3.2. 灌注抗生素的支架

骨组织工程是一种特别有发展前景的骨再生和控制感染方法。利用常规方法(如溶液浇注/颗粒浸出法、冷冻干燥/相分离法、烧结微球法等)和 3D 打印技术开发有抗菌能力和成骨性能的支架，该支架能帮助新

骨整合到缺损区域，同时可以模仿天然骨的细胞外基质(ECM)，促进细胞黏附、增殖[41]，随着支架生物材料逐渐降解，它被新的骨组织取代，直到骨修复过程完成[42] [43]。理想的支架需要包括以下几点：优异的生物相容性、可降解性、促进组织向内生长的宏观孔和微观孔以及一定的力学强度。由于治疗过程中生物膜的形成，骨感染的治疗效果普遍较差[44]，而灌注抗生素的支架不仅改善了该问题，还可以进一步促进骨生成。同时，这些支架减少了与传统口服和静脉内全身给药相关的副作用[10]。PCL 因其良好的机械强度、低熔点、可降解性和无毒降解产物而成为一种常见的有机支架材料[45] [46]。其熔点低的特性使支架可以灌注利福平和罗红霉素等不耐热的抗生素[10]。但 PCL 的疏水性和低吸水能力阻碍了细胞的粘附和生长[47]。亲水性的表面是细菌黏附和生物膜形成的基础[48]。聚乙二醇(polyethylene glycol)是一种亲水性和生物相容性材料，其本身没有抗菌作用，但利用其亲水性可以抑制细菌的黏附[49]。因此利用熔融电流体动力 3D 打印技术制造了灌注有罗红霉素的纤维 PCL/PEG 支架，该支架不仅有优异的抗菌能力，还可以促进人成骨细胞样细胞(MG63)的生长[50]。目前已经研究出可以灌注抗生素并含有 HA，CaS，TCP 和 BG 的生物陶瓷支架。HA 作为骨的主要无机成分，已被用于修复颌面部和椎骨创伤[51] [52]。作为 HA 的衍生物纳米羟基磷灰石(n-HA)与聚合物和抗生素结合后同时具有抗菌和促进骨生长的能力[10]。经过研究发现细菌通过入侵并驻留在宿主细胞来逃避抗生素，这是因为宿主细胞中的药物浓度无法控制感染。新兴的纳米材料具有极强的穿透细胞的能力和高载药能力，可以明显提高药物的使用效率和规避细菌的耐药机制[53]。例如 Luciano Benedini 等人制备出海藻酸钠(ALG)和 n-HA 组成的复合材料用来负载环丙沙星(CIP)，通过实验发现该复合材料有着良好的机械性能，生物粘附能力以及可以持续的释放 CIP [54]。研究发现，纳米载体，如 MSNs，是优良的药物递送系统，它可以维持药物活性，延长释放周期并且可控[55] [56]。利用新兴的纳米材料和 3D 打印技术结合生产具有抗菌活性的新型骨修复材料，以防止感染性骨缺损这在未来有巨大的发展前景。

3.3. 抗菌水凝胶

3D 打印水凝胶材料不仅具备现有修复材料的大部分性能，还具有独特的延展性、水溶胀性，高氧渗透性，组织相容性，水凝胶不仅容易负载抗菌剂，还易于释放此药剂[57] [58]。3D 打印多孔钽(3D-P-P-TA)是一种新药物传递方法，与羟基磷灰石和磷酸钙(CAP)支架相比，采用水凝胶表面包覆技术改性的 3D-P-P-TA 提高了靶向给药系统(DDSS)的效率[59]。庆大霉素是一种广谱抗生素，Urszula Posadowska 等人将庆大霉素掺入结冷胶和丙交酯–共乙交酯(PLGA) np 组成的水凝胶中，结果发现庆大霉素的释放浓度得到了提高，这种材料可以改善庆大霉素在低血浆浓度下应用效率低的问题[60]。通过将纳米导电材料添加到水凝胶基质中，可以制造出可注射的导电水凝胶，目前纳米银更为常见[61]。例如，利用 β-TCP、透明质酸和玉米丝提取物-Ag np 合成的热敏可注射水凝胶支架，这种支架显示出对良好的抗菌活性，且无细胞毒性[62]。但该技术仍有许多问题，比如因为革兰氏阳性细菌细胞壁中肽聚糖的存在，导致水凝胶对其抗菌能力比革兰氏阴性细菌弱[63]，金属离子的物理和化学不稳定性也会阻碍水凝胶的性能，因此对金属离子和水凝胶的作用需要更多的研究。

4. 总结和展望

本文对新兴的抗菌材料进行了说明，简要叙述了它们在抗骨感染中的应用。这些生物材料在保持良好生物相容性的同时具有抗菌活性。纳米技术作为先进的生物材料已经成为了抑制细菌黏附和生物膜形成的重要方法，然而其与金属粒子结合的复合物有着细胞毒性，需要进步一研究金属粒子在控制骨感染方面的局限性。作为灌注了抗生素的支架提高了药物运送效率并促进成骨，但这些过程涉及的生长因子信息传导和细胞反应需要进一步的探索。负载银的水凝胶有着不俗的抗菌能力，但它有着生物相容性低

和抗生素剂量依赖的缺点，大量的使用抗生素还会导致细菌产生耐药性，新发现的结合抗菌肽和生物提取物水凝胶可能会成为改善这些问题的方法。未来的研究方向可以关注在体内/体外的临床评估以及抗菌剂运送系统的研究上。寻找到更新的生物材料或许是攻克骨感染最有效的方法。

基金项目

国家自然科学基金(81871814)。

参考文献

[1] Lu, H., Liu, Y., Guo, J., *et al*. (2016) Biomaterials with Antibacterial and Osteoinductive Properties to Repair Infected Bone Defects. *International Journal of Molecular Sciences*, **17**, 334. https://doi.org/10.3390/ijms17030334

[2] Mehnath, S., Ayisha Sithika, M.A., Arjama, M., *et al*. (2019) Sericin-Chitosan Doped Maleate Gellan Gum Nanocomposites for Effective Cell Damage in *Mycobacterium tuberculosis*. *International Journal of Biological Macromolecules*, **122**, 174-184. https://doi.org/10.1016/j.ijbiomac.2018.10.167

[3] Guo, X., Chen, M., Feng, W., *et al*. (2011) Electrostatic Self-Assembly of Multilayer Copolymeric Membranes on the Surface of Porous Tantalum Implants for Sustained Release of Doxorubicin. *International Journal of Nanomedicine*, **6**, 3057-3064. https://doi.org/10.2147/IJN.S25918

[4] Zeng, H., Pang, X., Wang, S., *et al*. (2015) The Preparation of Core/Shell Structured Microsphere of Multi First-Line Anti-Tuberculosis Drugs and Evaluation of Biological Safety. *International Journal of Clinical and Experimental Medicine*, **8**, 8398-8414.

[5] Li, K., Zhu, M., Xu, P., *et al*. (2015) Three-Dimensionally Plotted MBG/PHBHHx Composite Scaffold for Antitubercular Drug Delivery and Tissue Regeneration. *Journal of Materials Science*: *Materials in Medicine*, **26**, 102. https://doi.org/10.1007/s10856-015-5455-x

[6] Liu, Y., Zhu, J. and Jiang, D. (2017) Release Characteristics of Bone-Like Hydroxyapatite/Poly Amino Acid Loaded with Rifapentine Microspheres *in Vivo*. *Molecular Medicine Reports*, **16**, 1425-1430. https://doi.org/10.3892/mmr.2017.6747

[7] Qayoom, I., Verma, R., Murugan, P.A., *et al*. (2020) A Biphasic Nanohydroxyapatite/Calcium Sulphate Carrier Containing Rifampicin and Isoniazid for Local Delivery Gives Sustained and Effective Antibiotic Release and Prevents Biofilm Formation. *Scientific Reports*, **10**, Article No. 14128. https://doi.org/10.1038/s41598-020-70726-3

[8] Cyphert, E.L., Lu, C.Y., Marques, D.W., *et al*. (2020) Combination Antibiotic Delivery in PMMA Provides Sustained Broad-Spectrum Antimicrobial Activity and Allows for Postimplantation Refilling. *Biomacromolecules*, **21**, 854-866. https://doi.org/10.1021/acs.biomac.9b01523

[9] Khalaf, A.T., Wei, Y., Wan, J., *et al*. (2022) Bone Tissue Engineering through 3D Bioprinting of Bioceramic Scaffolds: A Review and Update. *Life* (*Basel*), **12**, Article No. 903. https://doi.org/10.3390/life12060903

[10] Chen, Z.Y., Gao, S., Zhang, Y.W., *et al*. (2021) Antibacterial Biomaterials in Bone Tissue Engineering. *Journal of Materials Chemistry B*, **9**, 2594-2612. https://doi.org/10.1039/D0TB02983A

[11] Cui, M., Pan, H., Li, L., *et al*. (2021) Exploration and Preparation of Patient-Specific Ciprofloxacin Implants Drug Delivery System via 3D Printing Technologies. *Journal of Pharmaceutical Sciences*, **110**, 3678-3689. https://doi.org/10.1016/j.xphs.2021.08.004

[12] Ramesh, S., Kovelakuntla, V., Meyer, A.S., *et al*. (2020) Three-Dimensional Printing of Stimuli-Responsive Hydrogel with Antibacterial Activity. *Bioprinting*, **24**, e00106. https://doi.org/10.1016/j.bprint.2020.e00106

[13] Siddiqui, N., Asawa, S., Birru, B., *et al*. (2018) PCL-Based Composite Scaffold Matrices for Tissue Engineering Applications. *Molecular Biotechnology*, **60**, 506-532. https://doi.org/10.1007/s12033-018-0084-5

[14] Chen, X., Gleeson, S.E., Yu, T., *et al*. (2017) Hierarchically Ordered Polymer Nanofiber Shish Kebabs as a Bone Scaffold Material. *Journal of Biomedical Materials Research Part A*, **105**, 1786-1798. https://doi.org/10.1002/jbm.a.36039

[15] Barba, A., Maazouz, Y., Diez-Escudero, A., *et al*. (2018) Osteogenesis by Foamed and 3D-Printed Nanostructured Calcium Phosphate Scaffolds: Effect of Pore Architecture. *Acta Biomaterialia*, **79**, 135-147. https://doi.org/10.1016/j.actbio.2018.09.003

[16] Arciola, C.R., Campoccia, D., Montanaro, L. (2018) Implant Infections: Adhesion, Biofilm Formation and Immune Evasion. *Nature Reviews Microbiology*, **16**, 397-409. https://doi.org/10.1038/s41579-018-0019-y

[17] Masters, E.A., Ricciardi, B.F., Bentley, K.L.M., *et al*. (2022) Skeletal Infections: Microbial Pathogenesis, Immunity

and Clinical Management. *Nature Reviews Microbiology*, **20**, 385-400. https://doi.org/10.1038/s41579-022-00686-0

[18] Sarkissian, E.J., Gans, I., Gunderson, M.A., *et al*. (2016) Community-Acquired Methicillin-Resistant *Staphylococcus aureus* Musculoskeletal Infections: Emerging Trends over the Past Decade. *Journal of Pediatric Orthopaedics*, **36**, 323-327. https://doi.org/10.1097/BPO.0000000000000439

[19] Kernéis, S., Plainvert, C., Barnier, J.P., *et al*. (2017) Clinical and Microbiological Features Associated with Group B Streptococcus Bone and Joint Infections, France 2004-2014. *European Journal of Clinical Microbiology & Infectious Diseases*, **36**, 1679-1684. https://doi.org/10.1007/s10096-017-2983-y

[20] Ahmed, S., Meghji, S., Williams, R.J., *et al*. (2001) *Staphylococcus aureus* Fibronectin Binding Proteins Are Essential for Internalization by Osteoblasts But Do Not Account for Differences in Intracellular Levels of Bacteria. *Infection and Immunity*, **69**, 2872-2877. https://doi.org/10.1128/IAI.69.5.2872-2877.2001

[21] Ellington, J.K., Harris, M., Webb, L., *et al*. (2003) Intracellular *Staphylococcus aureus*. A Mechanism for the Indolence of Osteomyelitis. *The Journal of Bone and Joint Surgery*. *British Volume*, **85**, 918-921. https://doi.org/10.1302/0301-620X.85B6.13509

[22] Josse, J., Velard, F. and Gangloff, S.C. (2015) *Staphylococcus aureus* vs. Osteoblast: Relationship and Consequences in Osteomyelitis. *Frontiers in Cellular and Infection Microbiology*, **5**, 85. https://doi.org/10.3389/fcimb.2015.00085

[23] Roper, P.M., Shao, C. and Veis, D.J. (2020) Multitasking by the OC Lineage during Bone Infection: Bone Resorption, Immune Modulation, and Microbial Niche. *Cells*, **9**, 2157. https://doi.org/10.3390/cells9102157

[24] Yang, D., Wijenayaka, A.R., Solomon, L.B., *et al*. (2018) Novel Insights into *Staphylococcus aureus* Deep Bone Infections: The Involvement of Osteocytes. *mBio*, **9**, e00415-18. https://doi.org/10.1128/mBio.00415-18

[25] Foster, T.J., Geoghegan, J.A., Ganesh, V.K., *et al*. (2014) Adhesion, Invasion and Evasion: The Many Functions of the Surface Proteins of *Staphylococcus aureus*. *Nature Reviews Microbiology*, **12**, 49-62. https://doi.org/10.1038/nrmicro3161

[26] Edwards, A.M., Potts, J.R., Josefsson, E., *et al*. (2010) *Staphylococcus aureus* Host Cell Invasion and Virulence in Sepsis Is Facilitated by the Multiple Repeats within FnBPA. *PLOS Pathogens*, **6**, e1000964. https://doi.org/10.1371/journal.ppat.1000964

[27] Edwards, A.M., Potter, U., Meenan, N.A., *et al*. (2011) *Staphylococcus aureus* Keratinocyte Invasion Is Dependent upon Multiple High-Affinity Fibronectin-Binding Repeats within FnBPA. *PLOS ONE*, **6**, e18899. https://doi.org/10.1371/journal.pone.0018899

[28] Alva-Murillo, N., López-Meza, J.E., Ochoa-Zarzosa, A. (2014) Nonprofessional Phagocytic Cell Receptors Involved in *Staphylococcus aureus* Internalization. *BioMed Research International*, **2014**, Article ID: 538546. https://doi.org/10.1155/2014/538546

[29] Horn, J., Stelzner, K., Rudel, T., *et al*. (2018) Inside Job: *Staphylococcus aureus* Host-Pathogen Interactions. *International Journal of Medical Microbiology*, **308**, 607-624. https://doi.org/10.1016/j.ijmm.2017.11.009

[30] Zhang, T., Wei, Q., Zhou, H., *et al*. (2020) Sustainable Release of Vancomycin from Micro-Arc Oxidised 3D-Printed Porous Ti6Al4V for Treating Methicillin-Resistant *Staphylococcus aureus* Bone Infection and Enhancing Osteogenesis in a Rabbit Tibia Osteomyelitis Model. *Biomaterials Science*, **8**, 3106-3115. https://doi.org/10.1039/C9BM01968E

[31] Raynaud-Messina, B., Verollet, C., Maridonneau-Parini, I. (2019) The Osteoclast, a Target Cell for Microorganisms. *Bone*, **127**, 315-323. https://doi.org/10.1016/j.bone.2019.06.023

[32] Alexander, E.H., Rivera, F.A., Marriott, I., *et al*. (2003) *Staphylococcus aureus*-Induced Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand Expression Mediates Apoptosis and Caspase-8 Activation in Infected Osteoblasts. *BMC Microbiology*, **3**, Article No. 5.

[33] Wang, N., Fuh, J.Y.H., Dheen, S.T., *et al*. (2021) Functions and Applications of Metallic and Metallic Oxide Nanoparticles in Orthopedic Implants and Scaffolds. *Journal of Biomedical Materials Research Part B*: *Applied Biomaterials*, **109**, 160-179. https://doi.org/10.1002/jbm.b.34688

[34] Qing, Y., Li, K., Li, D., *et al*. (2020) Antibacterial Effects of Silver Incorporated Zeolite Coatings on 3D Printed Porous Stainless Steels. *Materials Science & Engineering C*, *Materials for Biological Applications*, **108**, Article ID: 110430. https://doi.org/10.1016/j.msec.2019.110430

[35] Vu, A.A., Robertson, S.F., Ke, D., *et al*. (2019) Mechanical and Biological Properties of ZnO, SiO_2, and Ag_2O Doped Plasma Sprayed Hydroxyapatite Coating for Orthopaedic and Dental Applications. *Acta Biomaterialia*, **92**, 325-335. https://doi.org/10.1016/j.actbio.2019.05.020

[36] Zou, Y.H., Wang, J., Cui, L.Y., *et al*. (2019) Corrosion Resistance and Antibacterial Activity of Zinc-Loaded Montmorillonite Coatings on Biodegradable Magnesium Alloy AZ31. *Acta Biomaterialia*, **98**, 196-214. https://doi.org/10.1016/j.actbio.2019.05.069

[37] Tong, X., Shi, Z., Xu, L., *et al*. (2020) Degradation Behavior, Cytotoxicity, Hemolysis, and Antibacterial Properties of

Electro-Deposited Zn-Cu Metal Foams as Potential Biodegradable Bone Implants. *Acta Biomaterialia*, **102**, 481-492. https://doi.org/10.1016/j.actbio.2019.11.031

[38] Tao, B., Chen, M., Lin, C., *et al*. (2019) Zn-Incorporation with Graphene Oxide on Ti Substrates Surface to Improve Osteogenic Activity and Inhibit Bacterial Adhesion. *Journal of Biomedical Materials Research Part A*, **107**, 2310-2326. https://doi.org/10.1002/jbm.a.36740

[39] Shen, X., Zhang, Y., Ma, P., *et al*. (2019) Fabrication of Magnesium/Zinc-Metal Organic Framework on Titanium Implants to Inhibit Bacterial Infection and Promote Bone Regeneration. *Biomaterials*, **212**, 1-16. https://doi.org/10.1016/j.biomaterials.2019.05.008

[40] Bakhsheshi-Rad, H.R., Dayaghi, E., Ismail, A.F., *et al*. (2019) Synthesis and *In-Vitro* Characterization of Biodegradable Porous Magnesium-Based Scaffolds Containing Silver for Bone Tissue Engineering. *Transactions of Nonferrous Metals Society of China*, **29**, 984-996. https://doi.org/10.1016/S1003-6326(19)65007-7

[41] Pearlin, Nayak, S., Manivasagam, G., *et al*. (2018) Progress of Regenerative Therapy in Orthopedics. *Current Osteoporosis Reports*, **16**, 169-181. https://doi.org/10.1007/s11914-018-0428-x

[42] Roseti, L., Parisi, V., Petretta, M., *et al*. (2017) Scaffolds for Bone Tissue Engineering: State of the Art and New Perspectives. *Materials Science & Engineering C, Materials for Biological Applications*, **78**, 1246-1262. https://doi.org/10.1016/j.msec.2017.05.017

[43] Zhang, X. and Zhang, Y. (2015) Tissue Engineering Applications of Three-Dimensional Bioprinting. *Cell Biochemistry and Biophysics*, **72**, 777-782. https://doi.org/10.1007/s12013-015-0531-x

[44] Aragón, J., Feoli, S., Irusta, S., *et al*. (2019) Composite Scaffold Obtained by Electro-Hydrodynamic Technique for Infection Prevention and Treatment in Bone Repair. *International Journal of Pharmaceutics*, **557**, 162-169. https://doi.org/10.1016/j.ijpharm.2018.12.002

[45] Cobos, M., Ramos, J.R., Guzmán, D.J., *et al*. (2018) PCL/POSS Nanocomposites: Effect of POSS Derivative and Preparation Method on Morphology and Properties. *Polymers* (*Basel*), **11**, Article No. 33. https://doi.org/10.3390/polym11010033

[46] Gadalla, D., Goldstein, A.S. (2020) Improving the Osteogenicity of PCL Fiber Substrates by Surface-Immobilization of Bone Morphogenic Protein-2. *Annals of Biomedical Engineering*, **48**, 1006-1015. https://doi.org/10.1007/s10439-019-02286-1

[47] Aragón, J., Salerno, S., De Bartolo, L., *et al*. (2018) Polymeric Electrospun Scaffolds for Bone Morphogenetic Protein 2 Delivery in Bone Tissue Engineering. *Journal of Colloid and Interface Science*, **531**, 126-137. https://doi.org/10.1016/j.jcis.2018.07.029

[48] Sousa, C., Rodrigues, D., Oliveira, R., *et al*. (2011) Superhydrophobic Poly(L-lactic acid) Surface as Potential Bacterial Colonization Substrate. *AMB Express*, **1**, 34. https://doi.org/10.1186/2191-0855-1-34

[49] Buxadera-Palomero, J., Canal, C., Torrent-Camarero, S., *et al*. (2015) Antifouling Coatings for Dental Implants: Polyethylene Glycol-Like Coatings on Titanium by Plasma Polymerization. *Biointerphases*, **10**, Article ID: 029505. https://doi.org/10.1116/1.4913376

[50] Bai, J., Wang, H., Gao, W., *et al*. (2020) Melt Electrohydrodynamic 3D Printed Poly(ε-caprolactone)/Polyethylene Glycol/Roxithromycin Scaffold as a Potential Anti-Infective Implant in Bone Repair. *International Journal of Pharmaceutics*, **576**, Article ID: 118941. https://doi.org/10.1016/j.ijpharm.2019.118941

[51] Watcharajittanont, N., Tabrizian, M., Putson, C., *et al*. (2020) Osseointegrated Membranes Based on Electro-Spun TiO(2)/Hydroxyapatite/Polyurethane for Oral Maxillofacial Surgery. *Materials Science & Engineering C, Materials for Biological Applications*, **108**, Article ID: 110479. https://doi.org/10.1016/j.msec.2019.110479

[52] Rodríguez-Vázquez, M. and Ramos-Zúñiga, R. (2020) Chitosan-Hydroxyapatite Scaffold for Tissue Engineering in Experimental Lumbar Laminectomy and Posterolateral Spinal Fusion in Wistar Rats. *Asian Spine Journal*, **14**, 139-147. https://doi.org/10.31616/asj.2019.0091

[53] Gupta, A., Mumtaz, S., Li, C.H., *et al*. (2019) Combatting Antibiotic-Resistant Bacteria Using Nanomaterials. *Chemical Society Reviews*, **48**, 415-427. https://doi.org/10.1039/C7CS00748E

[54] Benedini, L., Laiuppa, J., Santillán, G., *et al*. (2020) Antibacterial Alginate/Nano-Hydroxyapatite Composites for Bone Tissue Engineering: Assessment of Their Bioactivity, Biocompatibility, and Antibacterial Activity. *Materials Science & Engineering C, Materials for Biological Applications*, **115**, Article ID: 111101. https://doi.org/10.1016/j.msec.2020.111101

[55] Manzano, M. and Vallet-Regí, M. (2018) Mesoporous Silica Nanoparticles in Nanomedicine Applications. *Journal of Materials Science*: *Materials in Medicine*, **29**, 65. https://doi.org/10.1007/s10856-018-6069-x

[56] Wang, Y. and Gu, H. (2015) Core-Shell-Type Magnetic Mesoporous Silica Nanocomposites for Bioimaging and Therapeutic Agent Delivery. *Advanced Materials*, **27**, 576-585. https://doi.org/10.1002/adma.201401124

[57] Perera, K., Ivone, R., Natekin, E., *et al*. (2021) 3D Bioprinted Implants for Cartilage Repair in Intervertebral Discs and

Knee Menisci. *Frontiers in Bioengineering and Biotechnology*, **9**, Article ID: 754113. https://doi.org/10.3389/fbioe.2021.754113

[58] Li, S., Dong, S., Xu, W., *et al*. (2018) Antibacterial Hydrogels. *Advanced Science* (*Weinh*), **5**, Article ID: 1700527. https://doi.org/10.1002/advs.201700527

[59] Hua, L., Lei, T., Qian, H., *et al*. (2021) 3D-Printed Porous Tantalum: Recent Application in Various Drug Delivery Systems to Repair Hard Tissue Defects. *Expert Opinion on Drug Delivery*, **18**, 625-634. https://doi.org/10.1080/17425247.2021.1860015

[60] Posadowska, U., Brzychczy-Włoch, M., Drożdż, A., *et al*. (2016) Injectable Hybrid Delivery System Composed of Gellan Gum, Nanoparticles and Gentamicin for the Localized Treatment of Bone Infections. *Expert Opinion on Drug Delivery*, **13**, 613-620. https://doi.org/10.1517/17425247.2016.1146673

[61] De Mori, A., Hafidh, M., Mele, N., *et al*. (2019) Sustained Release from Injectable Composite Gels Loaded with Silver Nanowires Designed to Combat Bacterial Resistance in Bone Regeneration Applications. *Pharmaceutics*, **11**, Article No. 116. https://doi.org/10.3390/pharmaceutics11030116

[62] Makvandi, P., Ali, G.W., Della Sala, F., *et al*. (2020) Hyaluronic Acid/Corn Silk Extract Based Injectable Nanocomposite: A Biomimetic Antibacterial Scaffold for Bone Tissue Regeneration. *Materials Science & Engineering C, Materials for Biological Applications*, **107**, Article ID: 110195. https://doi.org/10.1016/j.msec.2019.110195

[63] Taglietti, A., Diaz Fernandez, Y.A., Amato, E., *et al*. (2012) Antibacterial Activity of Glutathione-Coated Silver Nanoparticles against Gram Positive and Gram Negative Bacteria. *Langmuir*, **28**, 8140-8148. https://doi.org/10.1021/la3003838