Available online at www.sciencedirect.com

ScienceDirect

Procedia Manufacturing 30 (2019) 544–551

Procedia MANUFACTURING

www.elsevier.com/locate/procedia

14th Global Congress on Manufacturing and Management (GCMM-2018)

Recent Developments in the Field of Nanotechnology for Development of Medical Implants

Tejasri Yarlagadda[a], Sarthak Sharma[b], Prasad KDV Yarlagadda[c] and Jyoti Sharma[d]*

[a]*School of Biomedical Sciences, Faculty of Health, Queensland University of Technology, Brisbane, Australia*
[b]*School of Clinical Sciences, Faculty of Health, Queensland University of Technology, Brisbane, Australia*
[c]*Faculty of Science and Engineering, Queensland University of Technology, Brisbane, Australia*
[d*]*Department of Science and Technology, Ministry of Science & Technology, India*

Abstract

Nanoengineering is an emerging field with combination of all traditional branches of science. Development in nanoengineering is opening avenues in the field of health specially development of prostheses & implants, diagnostics and drug delivery. Application of nanoengineering is used to discover and design materials for better biocompatibility with a high degree of specificity. Present paper introduced ongoing research in the application of nanotechnology and its use in development of antibacterial, rigid and functional implants.

Key Words: Nanoengineering, implants, nanomaterial, antibacterial

* Corresponding author *E-mail address:* jyotisharma.dst@gmail.com or j6.sharma@qut.edu.au

1. Introduction

Nanotechnology is application of multidisciplinary science to produce significant scientific and technological advances in diverse fields including medicine and physiology. It is made up of two words, the prefix nano comes from the Greek word nanos, which means one-billionth part of something and described as engineering and manufacturing with technology word at the smallest level (1-100nm) [1]. In a broad sense, nanotechnology is involved in designing, synthesis and application of materials whose smallest functional organization in at least one dimension is on the nanometer scale, ranging from a few to several hundred nanometers.

2351-9789
10.1016/j.promfg.2019.02.077

Worldwide funding agencies are investing a large amount of funds on development of nanotechnologies and devices. Apart from other fields, three applications of nanotechnology are in demand and particularly suited to biomedicine: diagnostic tools, drug delivery, prostheses & implants. This paper provides a unique comprehensive overview of the most relevant achievements and new developments in the field of prosthesis and implants. Nanomaterials and their possible impact on the fabrication of a new generation of reliable and long-lasting implants in the field of orthopaedic for joint replacement, dental, cardiac, podiatry and so on. Special emphasis is given to the role of use of nanomaterials as scaffolds to induce a more favourable interaction between implants and human cells. These nanostructured materials have opened an exciting avenue in the designing of implants which are biocompatible, long lasting, tough and bacterial & mechanically resistant. However, there is need to understand the long-lasting health effects of nanomaterials and need to do extensive research regarding clinical safety.

2. Tissue Engineering & Regenerative Medicine

Tissue engineering (TE) is the application of principles and methods of engineering & life sciences to create living tissue to replace or repair skin of a failing organ or a damaged or missing body part [2]. The term tissue engineering was first presented to the broad scientific community in 1993 by Langer and Vacanti [3] for the development of biological substitutes that maintain, improve or restore tissue function. Tissue engineered products (TEPs) typically are a combination of three components, i.e. isolated cells, an extracellular Matrix (all cells surrounded by a complex mixture of non-living material) and signal molecules, such as growth factors.

The term 'scaffold' provides new possibilities for the extracellular matrix by maintaining a three-dimensional space for the formation of new tissues with appropriate function. It is well known that the interaction of the cells and the extracellular matrix is of great importance for the intended function of the final product. Polymers having excellent physical properties such as high surface area, high porosity, interconnectivity pores of the nanofibre matrices with well-controlled degradation rates and biocompatibility of the base polymer make it an ideal candidate for developing scaffolds for tissue engineering [4] .

3. Nano Materials and implants

There are entirely different physical and chemical properties of conventional macro-materials as compare to smaller nanosized particles specially phenomena such as the quantum size effect become more prominent when particulate matter decreases to 100 nm or smaller [5]. The basic concept of large surface area to volume ratios allows nanophase materials for more favourable interactions with surrounding structures. Several researches shown that nanocrystalline layer encourages the growth and bonding of the surrounding bony tissue. In vitro research has also shown that bone-forming cells (osteoblasts) adhere better and deposit more calcium on materials with a grain size in the nanometre range than on conventional materials with a grain size in the micrometre range [1]. Proper, coordinated function of both types of cells is essential for the formation and maintenance of healthy bony tissue and, therefore, for strong bonding between the implant and the surrounding bone [6]. This is extremely important for implants that are attached without the use of bone cement.

Thin layer of nanocrystalline structure on artificial implants such as artificial hips, which are usually made of titanium or alloys of cobalt and chromium could help to reduce the problems of wear or implant loosening. This nanocrystalline structure is harder, smoother, good binder and consequently results in more resistance of wear of the artificial socket, which is generally made of a special type of polyethylene. Hydroxyapatite is a natural component of bone, 70% of which consists of the mineral hydroxyapatite, with the remaining 30% consisting of organic fibres (collagen). Coating of hydroxyapatite with a grain size in the nanometer, rather than the micrometer scale as earlier makes it more biocompatible and more like that of natural hydroxyapatite in bone which likewise has a nanocrystalline structure (grain size less than 50 nm). Nanoparticles of hydroxyapatite can also be used to repair the bony tissues of damaged bones which was first demonstrated in Maastricht University Hospital in 2000 to use an artificial hip with a hydroxyapatite nanocrystalline layer. Apart from hydroxyapatite, diamond and metal ceramic are other materials which are in use to make implants [1].

Nanoparticles including calcium triphosphate, bioactive glass, hydroxyapatite, synthetic chitin, chitosan and biodegradable polymers have been fabricated into porous three-dimensional scaffolds for bone repair and regeneration purposes. This approach not only allows for mimicking bone in composition but the incorporation of nanoceramics enhances the material's mechanical strength and nanopographic features. The utilization of polymer ceramic matrices containing single or multi-walled carbon nanotubes offers high tensile strength, high flexibility and low density that can be exploited to develop more successful orthopedic implant materials.

The mechanical properties and biocompatibility of implants can also be improved by providing the material which is used to make the implants with a nanostructure. Thin layer of titanium dioxide with nanopores and slow released copper ions gives an antiseptic effect which helps to reduce bacterial infections which is common complication with implants [7]. Another possibility is to make the implants from nano powders of titanium dioxide or aluminium oxide using a sinter process. Promising alternative materials include organic polymers with a nanostructure and composite materials of organic polymers into which nanofibres of carbon or nanoparticles of titanium, aluminium, or hydroxyapatite have been mixed [8]. The advantage of the organic polymers is that they dissolve gradually while new bony tissue is being formed and imitate the natural extracellular matrix. [9]. The orthopaedic applications are closest to being used on patients, but biodegradable scaffolds of nanofibres consisting of natural or synthetic organic polymers are already used to cultivate other tissues, such as cartilage, muscle tissue, nerve tissue, and vascular tissue *in vitro* [10]. Researchers recently succeeded in using nanofibres to regenerate brain tissue *in vivo*. Scaffold-forming nanomaterial may be possible to use the method in the future to repair damaged human nerve tissue. Stents are small tubes of woven threads which are common to use to dilate blood vessels. However, inflammation reactions often occurring cause closing in stents again. This problem is addressed by applying radioactive substance coating on aluminium oxide with nanopores. These nanopores helps to slow release of radioactive material which prevents the stents from clogging. Though, there is need to check functionality and safety of these stents. Research is also underway to explore an opportunity for conformational changes in blood proteins caused by their contact with the stent wall due to coating of titanium compounds [11].

3.1 Arthroplasty

Nanotechnology in arthroplasty is focusing on the development of implantable materials that can function safely and effectively while extending the average lifespan of implants and preventing infection. Nanotextured implant surfaces have augmented the function and growth of osteoblasts to increase implant osseointegration [12]. Specifically, the technique of severe plastic deformation (SPD), which breaks down the coarse grains of metals into the nanoscale range by exposing the metal to a complex high stress state, has demonstrated the ability to improve the biocompatibility and mechanical properties of titanium implants [13]. The use of ultra-high molecular weight polyethylene (UHMWPE) implants has been limited in the field of arthroplasty due to concern for potential fracture. However, due to its favourable biocompatibility properties and wear resistance, there has been increased interest in improving the mechanical strength of UHMWPE through nanotechnology. The addition of carbon nanotubes to this material to create a novel composite has demonstrated translational success and may eventually have utility as an acetabular lining or tibial component [14]. Altering an implant's surface nanostructure has the potential to increase resistance to static and dynamic fatigue, improve functionality, and increase implant survivorship.

3.2 Active Implants

Active implants for administering medicines, such as insulin and morphine pumps have been in use for a long time. To administering medicines at target areas at varying rate, research on implantable microchips for the storage and controlled release of active substances are in process [15-17]. The release could also be controlled by a biosensor that responds to physiological parameters. [1]. The other group of active implants comprises neural prostheses, which are intended to repair or take over nerve functions. Cochlear implants (for restoring hearing), pacemakers and defibrillators (for regulating the heart beat), bladder stimulators (for controlled emptying of the urinary bladder by spinal cord lesion patients), deep-brain stimulators (to combat tremor in patients with Parkinson's disease), as well as peroneus stimulators (to combat drop foot) are few examples which are currently in used [1]. Nanotechnology may play an important role in their improvement and further development with increasing functionality, fixation in the surrounding tissue, and biocompatibility by modifying the surface at the nanoscale [18]. The nanostructure increases the electrodes' surface area by a factor of one hundred, which is necessary for proper signal transfer from the electrodes to the tissue [19]. The microelectrodes of neuro prostheses that register electrical signals in the brain often only work for a few weeks. They do not usually become defective, but the surrounding tissue gets damaged and nonconductive scar glial-cell tissue grows. In vitro research has shown that a nanoporous surface structure reduces glial-cell adhesion and promotes the formation of outgrowth of nerve cells [20]. A possible explanation for the stimulating effect on the nerve cells is that they are naturally embedded in an extracellular matrix with a nanostructure of microtubule and laminin. To combat rejection reactions or infections, nano coatings can be applied that release medicines gradually [21]. An antiseptic layer based on silver nanoparticles is already being used in Germany on cochlear implants [22]. Other examples of contributions made by nanotechnologies to active implants include the membranes with nanopores in microchips for drug delivery [23] and batteries with a higher energy-storage capacity [24].

3.3 Dental Implants

Nanotechnology opens a new spectrum of possibilities for advancement in implant dentistry to make implant surfaces more biocompatible. The surgery for dental implantation is critical as there are high chances of infections in gingival tissue after implantation. Mimicking of nanometre scale ECM components of typical dimensions of 10–100 nm may improve the bone – implant interface which is the most frequent cause for failure for insufficient bone formation around the implant surface [25].

Dental implant therapy has been one of the most significant advances in dentistry in the past three decades. However, another challenge for the dental surgeons is achieving osseointegration. Failure to achieve osseointegration can be attributed to one or more implant, local anatomic, local biologic, systemic or functional factors. Surface profiles in the nanometre range play an important role in the adsorption of proteins, adhesion of osteoblastic cells and thus the rate of osseointegration. Many in vitro and animal studies have shown that nano surface modifications enhance surface properties of titanium dental implant that result in rapid osseointegration and faster bone healing [26]. Nanoscale surface structuring, surface chemistry and wettability are three key factors for the development of improved devices. Nanoscale surface structuring and surface chemistry would require nanoscale processes to optimize cell colonization and control & optimize the chemical surface properties of an implant material. However, engineered nanomaterial would play a role in increasing wettability due to the observation that cell adhesion and subsequent activity are generally better on hydrophilic surfaces [27].

3.4 Nanotechnology in Podiatry

How nanotechnology is playing critical role to help Podiatrist in saving our foot due to diabetes? Ohio State University and Boston University have created what could be considered one of the earliest therapeutically useful nanomedical devices. They created a tiny silicon box that contains pancreatic beta cells taken from animals. The box is surrounded by a material with a very specific nanopore size (about 20 nanometres in diameter). These pores are big enough to allow for glucose and insulin to pass through them, but small enough to impede the passage of much larger immune system molecules. These boxes can be implanted under the skin of diabetes patients. This could temporarily restore the body's delicate glucose control feedback loop without the need of powerful immunosuppressants that can leave the patient at a serious risk of infection [28].

The idea of artificial pancreas was developed in 1974. The problem of size of this organ didn't allow the scientists to convert it in workable model. However, now an American company, Medtronic MiniMed, has been working on a device called Long Term Sensor System (LTSS), which links an implantable long-term glucose mini sensor with an implantable insulin mini pump by using this concept [29]. Discovery of 'Smart Cells' may be another solution to control diabetes. The author says "*When glucose rises in the bloodstream, it will eat away SmartCell's structure. As the SmartCell protein matrix breaks down, insulin is released. The more glucose is present, the faster matrix will erode.*" This technology may stop endless blood testing and multiple shoots. Advancement in the field of drug delivery, non-invasive glucose monitoring via implanted nanosensors, nano-encapsulation technology to achieve better insulin delivery, nanomedicine-oriented applications of antiseptics, disinfectants and antibacterial therapeutics, development of nanofibers, which mimic collagen fibrils that may be beneficial in treating burn wounds may demonstrate potential treatments in the field of podiatry [30-33].

One of the recent advancement in podiatry is nanoemulsion treatment for onychomycosis (toenail fungal infection) [34]. Researchers at IBM and the Institute of Bioengineering and Nanotechnology in Singapore have found a way to make nanofibers from recycled plastic that know to attack only harmful fungal cells while leaving healthy human cells alone [32].

4. Bactericidal Effects: Biomimetics

The success of implants and tissue engineered constructs greatly depends on the biocompatibility of the material. Implants failure due to infection leads to increasing treatment cost, patient discomfort, increase antibiotics resistance, development of superbugs, revision surgery or death and lack of confidence in implant transplant. To overcome these issues, -researchers attempted to mimic the nano-texture bactericidal surfaces, observed in some plant, animal and insect species. Several fabrication techniques like lithography, hydrothermal synthesis as well as various sputter and vapour deposition techniques are in use to fabricate such nanostructures [35]. Best examples of nanotexture of naturally occurring surfaces are cicada and dragonfly wings, lotus leaves and shark skin. Nano-scale pillar structures on surfaces of cicada and dragonfly wings, nano and micro-scale hierarchical structure on lotus leaves and large number of nano-scale spatula found on gecko feet are responsible for bactericidal and self-cleaning properties (Figure 1) [36, 37].

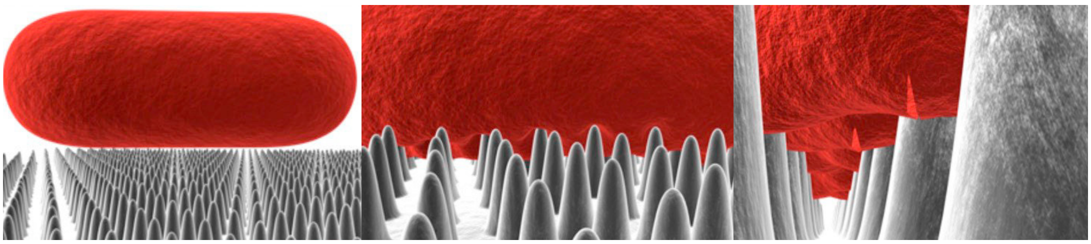

Figure 1: Rupture Mechanism of Bacteria Cells by Nanopillar Structures [37]. As bacterium cell is absorbed onto the surface, regions between pillars stretch the cell membrane, causing rupture

A large number of studies have aimed to reproduce the bactericidal behaviour of certain naturally occurring surfaces, using a variety of chemical and mechanical methods like lithography, polymer demixing, phase separation chemical etching, electrospinning and molecular self-assembly, for patterning implant surfaces and efficiently constructing scaffolds for tissue engineering have emerged. There is definite pattern to mimic these surfaces and provide a challenge to reproduce a universal surface pattern that incorporates the best features of various naturally occurring nano and micro-surfaces. Right combination of size, width, spacing, tip sharpness and height to width ratio may play major role in determining the best model to drive the bactericidal effects of textured surfaces [36].

5. Discussion

Nanotechnology is still advancing and need much more testing before appreciating its maximum potential in implant industry. In the future, we could imagine a world where medical nanodevices are routinely implanted or even injected into the bloodstream to monitor health and to automatically participate in the repair of systems that deviate from the normal pattern. Nanotechnology has the capability to inexpensively replace many conventional therapies and provide a multitude of novel applications. Nanotechnology offers more precise treatment modalities that may lead to more effective and longer lasting implants, decreased infection rates, and improved bone and tendon healing. However, nanotechnology is focusing on the development of implantable materials and their combinations that can function safely and effectively.

Tissue engineering leads to engineered tissues to provide more definitive solutions to tissue repair in clinics and aims to achieve this goal by the development of *in vitro* devices that would repair the damaged tissue *in vivo*. This will also help to overcome the limitations of 2D cultures where cell-cell and cell-ECM interactions reduces due to growth of cells under non-physiological and unnaturally polarized conditions. However, the interactions between cell-cell and cell-ECM can determine whether a given cell undergoes proliferation, differentiation, apoptosis or invasion. Consequently, 2D cultures do not recreate properly *in vivo* systems in terms of cellular communication, gene and protein expression pattern and diffusion of soluble molecules (oxygen, nutrients, growth factors, etc.). On the other side, Animal models are expensive, time-consuming, involve ethical controversies and unable to explain many parameters of human responses. As a result, 3D cultures have become an important tool of choice to observe the third dimension and fulfil the need for *in vitro* approaches that enable an accurate study of the molecular mechanisms.

Despite several breakthrough developments and technologies, we can’t ignore the harmful effects and threat by nanoscale materials. Airborne nanoscale materials can easily be deposited in the respiratory tract and can cause inflammatory response. The small size engineered nanomaterials are allowed to enter in or between the cells which can easily be transported to sensitive sites target sides of the body including bone marrow, spleen, heart, and brain. The shape, size, surface chemistry, physical and chemical properties of these particles are also known to increase inflammation and tissue damage.

6. Conclusion

Advancement in nanotechnology is helping us to overcome challenges in our daily routine life. Although, several technologies are at clinical stage and need to be tested at ground level. Healthcare providers may bless with nanotechnology for better diagnosis, specific drug target delivery and use of need based compatible implants. Nanotechnology may help the health specialists like orthopaedists, dermatologist, dentists and podiatrists to revolutionise the treatments in their specific fields. However, there is need to be taken care of hazardous toxins release through nanomaterial and nanoparticles.

ACKNOWLEDGEMENTS

Authors greatly acknowledge the Queensland University of Technology (QUT), Australia to provide all basic facilities and infrastructure. Dr. Jyoti Sharma would also like to thank Department of Science & Technology for necessary support and permissions.

REFERENCES

1. Shrivastava, S. and D. Dash, *Applying nanotechnology to human health: revolution in biomedical sciences.* Journal of Nanotechnology, 2009. **2009**.
2. Skalak, R. and C.F. Fox, *Tissue engineering: proceedings of a workshop, held at Granlibakken, Lake Tahoe, California, February 26-29, 1988*. Vol. 107. 1988: Alan R. Liss.
3. Langer, R. and J. Vacanti, *Tissue engineering. Science 260: 920-926.* TISSUE ENGINEERING: THE UNION OF BIOLOGY AND ENGINEERING, 1993. **98**.
4. Nair, L.S., S. Bhattacharyya, and C.T. Laurencin, *Development of novel tissue engineering scaffolds via electrospinning.* Expert opinion on biological therapy, 2004. **4**(5): p. 659-668.
5. Sichert, J.A., et al., *Quantum size effect in organometal halide perovskite nanoplatelets.* Nano letters, 2015. **15**(10): p. 6521-6527.
6. Park, G.E. and T.J. Webster, *A review of nanotechnology for the development of better orthopedic implants.* Journal of Biomedical Nanotechnology, 2005. **1**(1): p. 18-29.
7. Heidenau, F., et al., *A novel antibacterial titania coating: metal ion toxicity and in vitro surface colonization.* Journal of Materials Science: Materials in Medicine, 2005. **16**(10): p. 883-888.
8. Kay, S., et al., *Nanostructured polymer/nanophase ceramic composites enhance osteoblast and chondrocyte adhesion.* Tissue engineering, 2002. **8**(5): p. 753-761.
9. Zhao, B., et al., *A bone mimic based on the self-assembly of hydroxyapatite on chemically functionalized single-walled carbon nanotubes.* Chemistry of Materials, 2005. **17**(12): p. 3235-3241.
10. Vasita, R. and D.S. Katti, *Nanofibers and their applications in tissue engineering.* International Journal of nanomedicine, 2006. **1**(1): p. 15.
11. Huang, N., et al., *Hemocompatibility of titanium oxide films.* Biomaterials, 2003. **24**(13): p. 2177-2187.
12. Gusić, N., et al., *Nanobiotechnology and bone regeneration: a mini-review.* International orthopaedics, 2014. **38**(9): p. 1877-1884.
13. Serra, G., et al., *Nanostructured severe plastic deformation processed titanium for orthodontic mini-implants.* Materials Science and Engineering: C, 2013. **33**(7): p. 4197-4202.
14. Puértolas, J. and S. Kurtz, *Evaluation of carbon nanotubes and graphene as reinforcements for UHMWPE-based composites in arthroplastic applications: A review.* Journal of the mechanical behavior of biomedical materials, 2014. **39**: p. 129-145.
15. Santini, J.T., et al., *Microchip technology in drug delivery*. 2000, Taylor & Francis.
16. Santini Jr, J.T., M.J. Cima, and R. Langer, *A controlled-release microchip.* Nature, 1999. **397**(6717): p. 335.
17. Sutradhar, K.B. and C.D. Sumi, *Implantable microchip: the futuristic controlled drug delivery system.* Drug delivery, 2016. **23**(1): p. 1-11.
18. Ijzerman, M., et al., *Efficacy of topical nanoemulsion (NB-002) for the treatment of distal subungual onychomycosis: a randomized, double-blind, vehicle-controlled trial.* Journal of the American Academy of Dermatology, 2010. **62**(3): p. AB76.
19. Stieglitz, T., *Considerations on surface and structural biocompatibility as prerequisite for long-term stability of neural prostheses.* Journal of nanoscience and nanotechnology, 2004. **4**(5): p. 496-503.
20. Moxon, K.A., et al., *Nanostructured surface modification of ceramic-based microelectrodes to enhance biocompatibility for a direct brain-machine interface.* IEEE Transactions on Biomedical Engineering, 2004. **51**(6): p. 881-889.
21. Arruebo, M., et al., *Magnetic nanoparticles for drug delivery.* Nano today, 2007. **2**(3): p. 22-32.
22. Morrison, M., et al., *Nanotechnology and its Implications for the Health of the EU Citizen.* Publié par Nanoforum, décembre, 2003.
23. Tao, S.L. and T.A. Desai, *Microfabricated drug delivery systems: from particles to pores.* Advanced drug delivery reviews, 2003. **55**(3): p. 315-328.
24. Scrosati, B., *Nanomaterials: Paper powers battery breakthrough.* Nature nanotechnology, 2007. **2**(10): p. 598.
25. Tomsia, A.P., et al., *Nanotechnology approaches for better dental implants.* The International journal of oral & maxillofacial implants, 2011. **26**(Suppl): p. 25.
26. Le Guéhennec, L., et al., *Surface treatments of titanium dental implants for rapid osseointegration.* Dental

materials, 2007. **23**(7): p. 844-854.
27. Liu, H. and T.J. Webster, *Nanomedicine for implants: a review of studies and necessary experimental tools.* Biomaterials, 2007. **28**(2): p. 354-369.
28. Freitas, R.A., *Current status of nanomedicine and medical nanorobotics.* Journal of computational and theoretical nanoscience, 2005. **2**(1): p. 1-25.
29. Martinac, K. and Z. Metelko, *Nanotechnology and diabetes.* Diabetologia Croatica, 2005. **34**(4): p. 105-110.
30. Pickup, J.C., et al., *Nanomedicine and its potential in diabetes research and practice.* Diabetes/metabolism research and reviews, 2008. **24**(8): p. 604-610.
31. Yacoby, I. and I. Benhar, *Antibacterial nanomedicine.* 2008.
32. Hromadka, M., et al., *Nanofiber applications for burn care.* Journal of burn care & research, 2008. **29**(5): p. 695-703.
33. Smith, R.G. *Can Nanotechnology Have An Impact For Patients With Diabetes?* Podiatry Today, 2009. **22**, 16-19.
34. Ijzerman, M., Baker, J., Flack, M., & Robinson, P. , *Efficacy of topical nanoemulsion (NB-002) for the treatment of distal subungual onychomycosis: a randomized, double-blind, vehicle-controlled trial.* Journal of the American Academy of Dermatology, 2010. **62**(3): p. AB76.
35. Jaggessar, A., Mathew, A., Wang, H., Tesfamichael, T., Yan, C., & Yarlagadda, P. K., *Mechanical, bactericidal and osteogenic behaviours of hydrothermally synthesised TiO2 nanowire arrays. .* Journal of the mechanical behavior of biomedical materials, 2018. **80**(311-319).
36. Jaggessar, A., Shahali, H., Mathew, A., & Yarlagadda, P. K. , *Bio-mimicking nano and micro-structured surface fabrication for antibacterial properties in medical implants. .* Journal of nanobiotechnology, 2017. **15**(1): p. 64.
37. Pogodin, S., et al., *Biophysical model of bacterial cell interactions with nanopatterned cicada wing surfaces.* Biophysical journal, 2013. **104**(4): p. 835-840.