Chapter 5
Nanodentistry

Simone E. Hieber and Bert Müller

Abstract Nanodentistry is defined as the application of nanotechnology to diagnose, treat, and prevent oral and dental disease. These approaches intend to preserve and improve the dental health. Nanotechnology deals with structures in the range of 1–100 nm and focuses on the development of materials with novel properties often not present in nature. As a result, it is considered as a key technology of the twenty-first century and promised to deliver innovative methods to medicine in general and to dentistry in particular. Clinical studies already deal with nanotechnology-based tooth treatments and innovative nanocontainers for local drug delivery for more efficient treatments. Nanotechnology has already started to have a significant impact in dentistry namely in periodontology, implantology, prosthetic dentistry, orthodontics, and endodontics. Nanotechnology will offer sophisticated methods for diagnosis, therapy, and prevention, so that a new era in medicine becomes reality, often termed nanomedicine. These tools will also create the field of nanodentistry, which finally results in an interdisciplinary challenge to efficiently educate and train all specialists in dentistry and related materials science.

5.1 Introduction

Nanotechnology is based on structures that are ten thousand times smaller than the diameter of a human hair. It allows not only the fundamental investigation on the molecular level, but also the development of nanostructured materials with novel fascinating properties. As a result, nanotechnology is considered as a key technology of the twenty-first century, where innovative solutions can be expected for many

S.E. Hieber · B. Müller (✉)
Biomaterials Science Center, University of Basel, c/o University Hospital Basel, 4031 Basel, Switzerland
e-mail: simone.hieber@unibas.ch; bert.mueller@unibas.ch

S. Logothetidis (ed.), *Nanomedicine and Nanobiotechnology*,
NanoScience and Technology, DOI 10.1007/978-3-642-24181-9_5,

medical and dental problems. Nanocontainers for local drug delivery offer powerful tools for an efficient treatment with less negative side effects. Intelligent implants and devices based on nanotechnology will conquer the market and change dental treatments significantly as it already occurred to the field of materials science and medical imaging.

5.2 Nanodentistry

"Nanodentistry" can be defined as the science and technology of diagnosing, treating, and preventing oral and dental disease, relieving pain, and of preserving and improving dental health, using nanoscale-structured materials [1]. The nanotechnology considers generally scales between 1 and 100 nm leading to new properties and functionality of materials that differ fundamentally from what is known from meter, millimeter, and micrometer scales. Nanostructures behave often differently than macroscopic or microscopic ones. The surface of the nanoparticles dominates the materials properties, which are usually given by the bulk. For example, the color of a polymer depends on the size of the components. The nanomaterials are not only promised to improve the properties and functionality of medical products but also to lead to completely new products including drugs. In particular, nanomaterials will be part of engineered products, such as implants, devices, and diagnosis tools.

The term nanodentistry was introduced to a larger community by the cover story of Freitas Jr. in the Journal of the American Dental Association more than a decade ago [2]. He developed his vision to use dental nanorobots for orthodontic realignments in a single office visit, for dentition regeneration and oral health maintenance. He also elucidated the role of nanomaterials and tissue engineering. Finally, he pointed out that properly configured dentifrobots will identify and destroy pathogenic bacteria residing in the plaque and elsewhere. He launched the new era in dental medicine, termed nanodentistry.

5.3 Imaging

The fundamental knowledge of the human tissues on the nanometer scale is required to take advantage of these innovative technologies for patients in an efficient manner. Radiologists can make visible the human body down to a spatial resolution of a fraction of a millimeter using computed tomography. The resulting datasets are so huge that the data processing cannot be performed manually and requires a handling by means of appropriate software.

A higher spatial resolution can only be achieved by means of postmortem methods. Microtomography is an established method in materials science and reaches a spatial resolution down to the submicrometer range. It allows the nondestructive

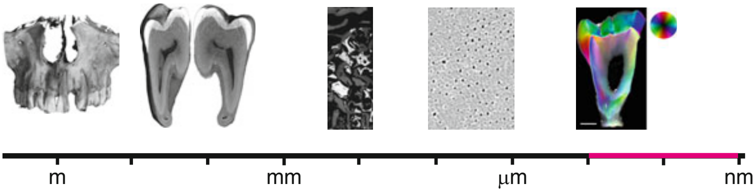

Fig. 5.1 The scales ranging from the size of a human down to the molecular level in the field of dental medicine (nanotechnology length scale given in *red*)

three-dimensional imaging of human tissues as recently demonstrated by the visualization of individual ganglion cells [3] or Purkinje cells [4] leading to complementary information to conventional histology. The resulting three-dimensional datasets are several orders of magnitude larger than the typical clinical tomograms and require the handling by an expert. As a result, the nanometer-sized structures are invisible for the conventional X-ray tomography methods.

Electron microscopy offers an alternative to image nanostructures. However, it can only reproduce surfaces of the specimens and requires vacuum conditions. The wet tissues cannot be investigated in physiological state. In general, however, electron microscopy techniques deliver valuable images particularly for the qualitative analysis.

Scanning probe microscopy techniques enable imaging in fluids, but only provide two-dimensional images of small surface areas. Reasonable areas on human tissues require long scanning times.

X-ray scattering and diffraction methods allow experiments in fluids. The resulting data are exact mean values of the illuminated area. These methods are very useful to quantify nanostructures in human tissues such as collagen fibers or apatite crystallites. Using a focused X-ray beam of about 10 or 100 μm in diameter, which can be scanned along a tissue specimen, one can combine the scattering data uncovering the nanometer range with the less detailed real-space raster. In this way, one obtains fascinating colorful images yielding the spatial distribution of abundance and orientation of all present nanostructures as exemplarily indicated in Fig. 5.1 by a 300-μm-thick tooth slice.

Figure 5.1 shows a logarithmic scale from 1 m down to 1 nm. The incorporated images are characteristic for the length scale. Nanomedicine can significantly influence the entire human body, but is based on phenomena in the red-colored range between 1 and 100 nm. As a result, the methods, such as small-angle X-ray scattering (SAXS) [5], will play an important role for the characterization of human tissues and the future development of biomimetic, nature analogue implants [6]. The images incorporated in Fig. 5.1 show a dataset from clinical CT representing the hard tissues of a part of the human head, conventional micro computed tomography data of a tooth, two virtual cuts through tomograms obtained by synchrotron radiation-based micro computed tomography of a biopsy from bone augmentation treatments [7,8] and a dentin specimen with resolved dentinal tubules [9], and finally the scanning SAXS pattern mentioned above. More details are given in another chapter in the present book [10].

To illustrate the Herculean task to build a human being atom by atom, we estimate the number of atoms within our body. Assuming that the body basically consists of water (molar mass 18 g/mol), we obtain for a human body of 90 kg a number of 3×10^{27} atoms. This huge number cannot be captured by our imagination. Restricting the consideration to the number of atoms within an individual biological cell or the number of cells within our body, one obtains numbers of the order of 10^{14}, which is still an unimaginable number. Note, it is thousand times larger than the number of stars in the Milky Way. You can find more analogies on the nanometer scale given for dentists in [11]. Conclusively, the three-dimensional visualization of the human tissues has progressed significantly and will face demanding challenges for interdisciplinary research teams in future.

5.4 Roadmap

Figure 5.2 shows a roadmap illustrating the likely progression of successful research activities in the field of dentistry applying nanotechnology. Nowadays, implant surfaces are micro- and nanostructured to improve the bone-implant interface. One uses procedures such as etching and sandblasting without knowing the best conditions. The recipes are based on experience of engineers and medical specialists. Especially the tailoring of the nanostructure could significantly improve the inflammatory behavior of the bone implants [12]. In bone, we do find apatite crystallites, which are assumed to exhibit a similar functionality. Multifunctionality of biomaterials is already observed in several cases. A degradable poly(D,L-lactic-co-glycolic acid) membrane, for example, covers the wound after tooth extraction and the degradation products act antibacterial and, therefore, avoid infections. The full potential of multifunctionality, however, is not exhausted yet. Therefore, numerous examples will be developed during the next decade.

One of the forthcoming challenges is associated with the realization of organs or essential parts of them. Maybe the first prototypes are extracorporal devices, but with increasing miniaturization, implantation becomes more and more likely.

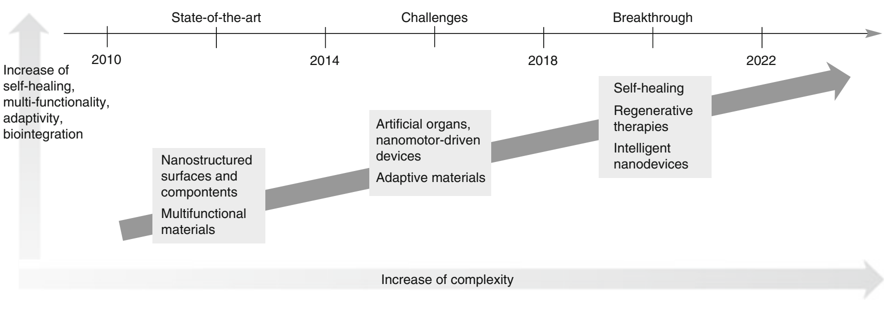

Fig. 5.2 Roadmap of possible nanotechnology approaches toward breakthrough in nanodentistry

Nanomotors may drive orthodontic treatments and distractors or extraction tools with superior precision. In a next step, regenerative therapies should be established to support self-healing for the wide variety of patients avoiding negative side effects.

Biomedical engineers will improve the multifunctional biomaterials to more complex and adaptive ones, so that potential stress-shielding and other nondesired phenomena are kept away from the affected parts of the body. Along with these demanding research tasks, engineers will develop intelligent nanoscale systems promoting the self-healing potential of the human body. Regarding the current state-of-the-art, we expect a breakthrough around the year 2020 associated with a substantial increase of complexity. After the breakthrough, simplifications are expected to lower the degree of complexity and to reduce the costs of nanotechnology-based devices. The application of intelligent nanodevices or nanorobots [1] will not only optimize the multifunctionality, the adaptation and the integration of implants, but also enable the desired self-healing capabilities guided by well-educated and well-trained surgeons and dentists.

5.5 Biomaterials Science

The common biomaterials are ceramics, metals, and polymers or any kind of combination (see Fig. 5.3). Using nanotechnology, one can integrate patterns on the nanometer scale at the surfaces and within the volume of the materials to accomplish the dedicated functionality. Nanostructures can optimize the biocompability of implants or carry drugs towards the target. Reactive nanostructures will emerge in diagnosis, monitoring, and therapy to improve the patient treatments. Numerous activities will fertilize the basic research of bio-nanomaterials.

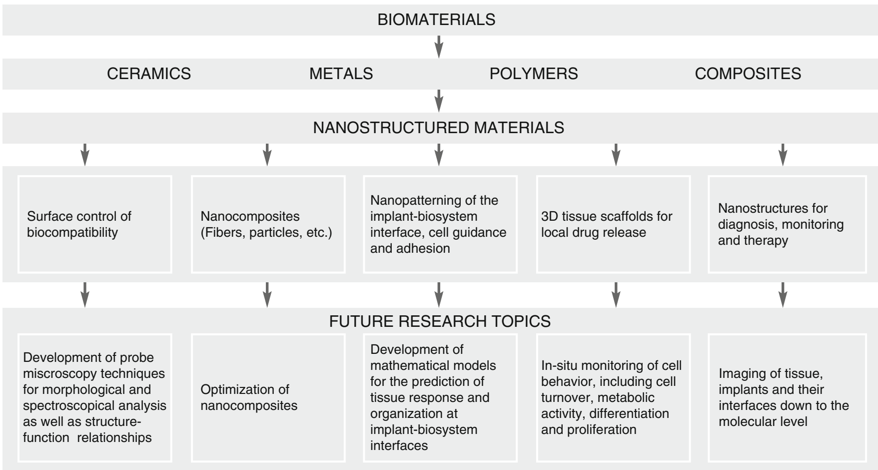

Fig. 5.3 Materials science for nanodentistry

For example, scanning probe microscopy techniques will enable the morphological and spectroscopic analyses of tissues to understand the structure–function relationship on the atomic scale. To improve the properties of the individual materials and their combinations sophisticated mathematical simulations will be expanded to predict the tissue response and the self-organization at the implant–biosystem interfaces down to the molecular level. Moreover, physics-based in vivo measurements supporting cell biologists will reveal the cell behavior with respect to metabolism, cell differentiation, and proliferation especially at the interface between the man-made material and the biosystem. For this purpose, high-resolution imaging facilities, as discussed above, will become more and more important to reveal the nanostructures of tissues, implants, and their interfaces with the necessary precision.

5.6 Major Research Topics

The German BMBF program in nanotechnology involved grants of in total 24 million Euros for German research projects in 2005. The 7th Research Program of the EU supports projects in nanomedicine with 100 million Euros during the period 2007–2013. More than a third of this amount was granted for cancer research, followed by regenerative medicine and imaging. Consequently, one expects that especially the nanotechnology will become a cross section and key technology in diagnosis and therapy of all kinds of cancer including those in the oral cavity. Researchers work for designated nanodevices that allow diagnosing cancer already in the early stage and deliver the drugs directly to the affected cells. Nanodevices will detect cancer-specific biomolecules in vivo faster and more precise than nowadays in committed laboratories.

Moreover, the research will focus on the development of biosensors for monitoring purposes, which includes different quantities related to the oral cavity such as halitosis. The techniques require an improvement of the micro- and nanoscopic methods as shown in Fig. 5.4. These methods play a predominant role for the three-dimensional visualization of nanoscale features, the development of nanocomposites as biomimetic, anisotropic implants [6], and the monitoring of biological processes in real time.

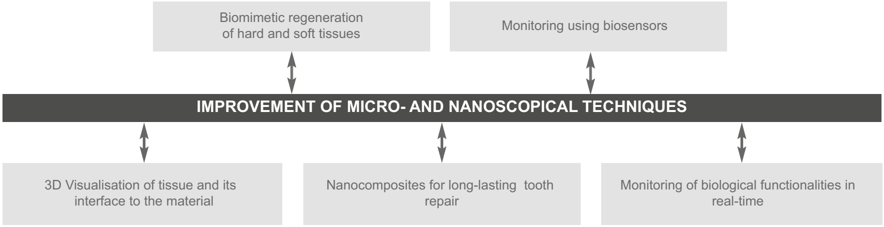

Fig. 5.4 Major research topics in nanotechnology for Cancel dental dentistry

5.7 Applications of Nanotechnology in Dentistry

Figure 5.5 shows selected applications of nanotechnology in the field of dentistry. Filling materials for reconstructions, dental root implants, bone augmentation, and dentin remineralization already take advantage of nanotechnology today, but have increasing growth potential. Today's dental materials will be replaced by nature analogue, anisotropic tooth restorations. It is, however, still unclear how the anisotropic biomaterials can be oriented. The nanostructures in dentin are orthogonally oriented to the ones of the same size in the enamel. In this way, the dentin–enamel junction acts as crack barrier [13]. The calcium phosphate phases for bone augmentation gain more and more importance along with the increase in age of the population. The resorbable calcium phosphate phases or bioglasses support the growth of the natural bone being applied to larger and larger defects. The materials have to be optimized on the micro- and nanometer scales to tweak the biocompability, the bioactivity, and the osteoconductivity promoting tissue regeneration and resisting the mechanical loads.

The tooth implants of established manufacturers are inserted with a high success rate. A broader distribution is hindered by their high costs, peri-implantitis, and time-consuming osteointegration until first loading. We expect products of even

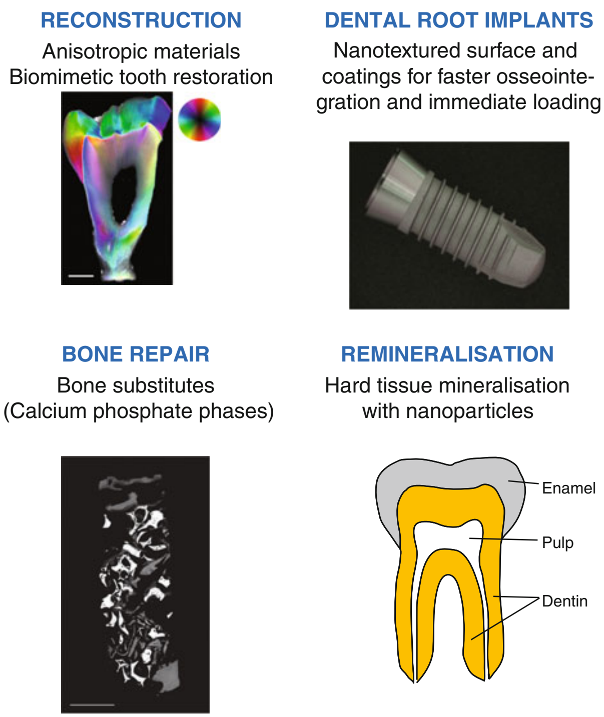

Fig. 5.5 Applications of nanotechnology in dentistry

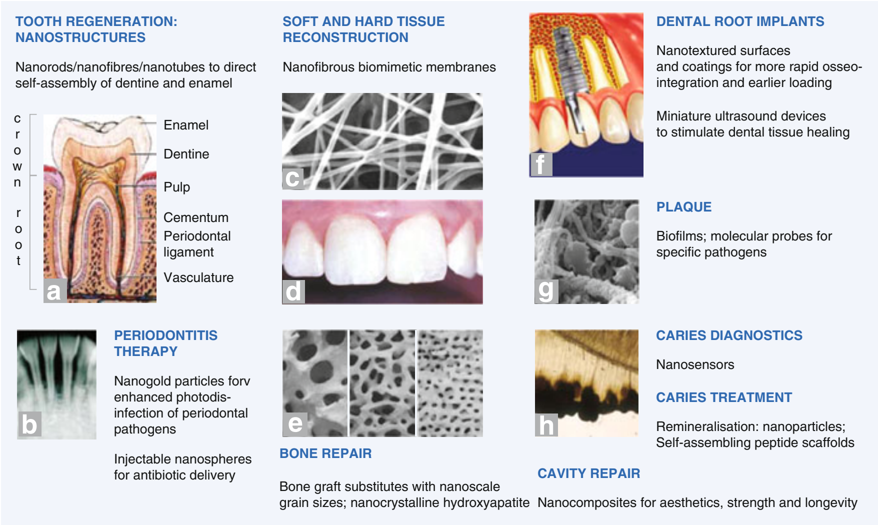

Fig. 5.6 Overview of several applications of nanotechnology in dentistry. (**a**) Anatomy of the tooth; (**b**) Radiograph showing bone loss in periodontal disease; (**c**) A nanofibrous membrane for soft tissue repair to mimic the natural extracellular matrix; (**d**) Composite fillings must match as closely as possible the color and translucency of natural teeth; (**e**) Hydroxyapatite scaffolds for bone repair; (**f**) Diagramme (DENTSPLY Friadent), of a dental implant showing osseointegration; (**g**) Scanning electron microscope image of dental plaque showing mixed bacterial biofilm and cells. (**h**) Tooth section showing caries developing in the enamel (copyright [1])

higher quality standards and significantly lower costs due to the fabrication progress in the coming years. This especially comprises the micro- and nanostructures surfaces that guarantee the osteointegration.

The remineralization of tooth hard tissues will be one of the main tasks of nanotechnology in the aging industrial societies. Nanoparticles are already used in "sensitive" toothpastes. In the near future, damaged teeth (by caries) will be remineralized applying mature ceramic nanoparticles.

Figure 5.6 contains further applications: more or less complex nanostructures for self-assembly of tooth hard tissues, periodontitis therapies by means of nanoparticles/nanophotonics, plaque monitoring, and caries diagnosis and treatment. Note caries is the most frequent dental disease known to damage the enamel, the dentin, and the cementum through the production of acidic species that dissolve the ceramic tooth components. Regrettably, the destroyed tooth structures almost do not regenerate, although remineralization of slight carious lesions occurs under optimized dental hygiene conditions.

This fundamental knowledge of the tooth's nanostructure should be applied for introducing biologically inspired dental fillings. It is the aim to realize dental materials with a nanometer-scale architecture similar to the ones in enamel and dentin [9]. After caries significantly damaged the tooth's hard tissues, the dentist removes the damaged part and rebuilds the crown using conventional isotropic

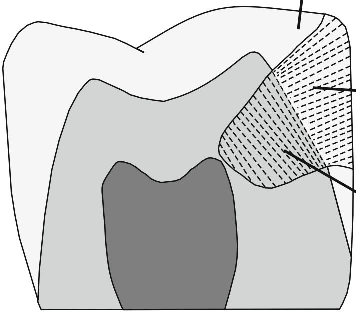

Fig. 5.7 Bioinspired, nature analogue dental fillings

composites that do not resemble the anisotropic nanostructure of human teeth. The use of such shrinking material is the reason, why the dentist regularly removes more enamel than necessary. Overhangs, as shown in Fig. 5.7, are avoided to prevent crack formation. Therefore, nonshrinking nature analogue fillings are highly desirable to achieve better restoration quality by less invasive treatments. The key challenge in achieving such nanotechnology-based fillings lies in the arrangement of the nanometer-sized building units. Here, the following approaches to mimic the hard tissues of the human teeth can be foreseen. Crystalline growth, which take place at nonequilibrium conditions with temperature or concentration gradients, result in strongly anisotropic nanostructures [12]. Unfortunately, such processes are demanding and seem to be impractical for patient treatments. Alternatively, nanofiber composites as already successfully built-in in dental posts can be applied. The appropriate orientation of the fibers, however, is not solved. Nanometer-sized arrangements of charged or dipolar units such as dedicated nanorods or nanotubes could give rise to parallel arrangements of the anisotropic nanostructures. The dashed lines in Fig. 5.7 symbolize the potential arrangements of charged nanorods. Because of the positive or negative charges, the nanorods show repulsive interactions leading to more or less parallel equidistant alignments [14]. Such dental restorations will have excellent resistance to thermal and mechanical shocks as recognized from the hardest substance in our body – the nanostructured enamel.

5.8 Challenges

Figure 5.8 shows the main challenges in nanomedicine/nanodentistry from current point of view. Assessment tools for nano-biomaterials are important to judge the toxicity and the biocompability and to pursue the personalized medicine with respect to material incompatibilities. Nanomarkers are developed to deliver more accurate test results for diagnosis down to the cellular level and below. Nanocontainers will enable local drug delivery for therapies preventing undesired side effects. Nanomaterials have already been used to stimulate the healing as

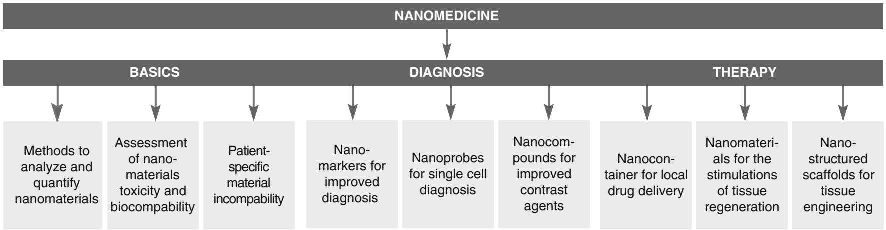

Fig. 5.8 Selection of challenges in nanomedicine/nanodentistry

demonstrated in first clinical trials. Nanostructured scaffolds for cell guidance are the basis in contemporary tissue engineering. Likewise, these scaffolds can be applied to stimulate tissue formation in vivo. As a result, nanomedicine in general and nanodentistry in particular will affect the basic dental science, the diagnosis and the therapy of oral diseases as well as maintain the oral health.

5.9 Future Risks

Nanotechnology involves not only benefits, but also serious risks that are not completely investigated. The toxicity of nanoparticles has to be assessed. The size of the particles leading to the interesting properties can also be a risk for human health. Nanoparticles undermine the human immune system and have almost unlimited access to the entire body [15]. Sensitive organs such as the brain can suffer from them. Moreover, the interactions with the immune system have to be investigated in detail. An open question exists concerning the final stage of the particles: Do they drop out or do they accumulate in specific organs? Biodegradable substances should decompose and leave the body. Nonbiodegradable particles often accumulate in organs as liver [15]. Up to now, we cannot estimate the long-term effects of nanotechnology. The impact on our environment has also to be uncovered in a similar manner as we do it today for drugs. The nanoparticles can contaminate water, soil, and air. The environment is faced with man-made particles becoming a new class of pollution [15]. Besides the investigation of the side effects, its report to the public will be important to achieve the acceptance of nanomedicine and nanodentistry.

5.10 Tailoring Biocompatibility of Implants by Nanostructures: Benefitting Patients

At first glance, one may expect that biocompatibility is considered as a specific material property, such as color or heat conductivity. Biocompatibility, however, is a strange term, not as well defined and standardized as typical material properties.

Nonetheless, we do have a certain understanding of biocompatibility. Consulting a dictionary, one finds: "Biocompatibility is the ability of a material to perform with an appropriate host response in a specific application" [16]. Using such a definition, however, the engineers and natural scientists are lost since biocompatibility not only depends on the specific solid-state material but also on the surrounding tissue. How one deals with a term such as biocompatibility, which does not even have a dedicated unit? One of the related questions concerns the roughness of titanium bone implants. This roughness generated by sandblasting and etching guarantees the osteointegration experimentally proven for million times. The details on the preparation procedures belong to the secrets of the implant suppliers. The measurement of the roughness, however, is more than challenging, since one cannot simultaneously determine it on the micro- and nanometer scales. Certainly, different techniques do exist, suitable for length scales of interest, but there is no unique parameter for surface roughness – with one exception – the Wenzel ratio, which is the actual surface divided by the projected one. In fact, nobody had measured this on the atomic level until it was realized that Ge nanopyramids on Si(100) with their well-defined facets, termed hut and dome clusters, can be counted to derive the Wenzel ratio [17]. This Wenzel ratio was correlated to biocompatibility measurements. First, the dynamic contact angles were measured on the surfaces with different nanopyramid densities, but the effect was only marginal. Second, absorption studies with the most important proteins (albumin and globulin) as well as in vitro cell experiments were carried out. Here, huge effects were uncovered. While the monocytes were exclusively damaged on the surfaces without nanopyramids, the rough surfaces (with many nanopyramids) had a very positive effect on inflammatory reactions [18]. This observation gave evidence that biocompatibility of medical implants can be tailored using nanostructures. Therefore, we obtained not only a positive message for the patients but also for the engineers and natural scientist.

Several parameters (see Fig. 5.9) are identified to intentionally manipulate the biocompatibility of bone implants. Each of the parameters (surface morphology

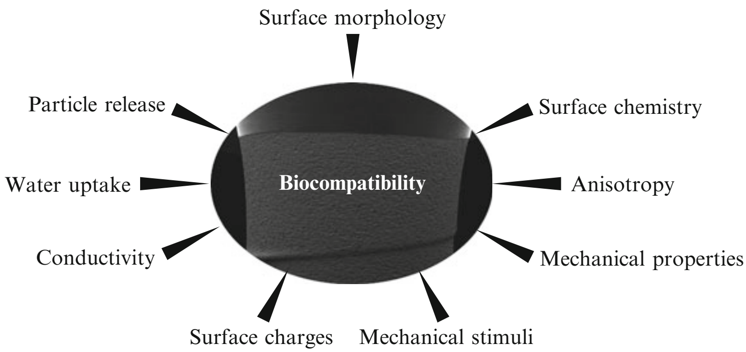

Fig. 5.9 Many parameters are used to tailor the biocompatibility of medical implants

and chemistry, mechanics, local and global electrical charges, uptake and release of atoms, molecules, and particles) can be used to improve the implant's functionality and also depends on the host tissue or the implantation site, as stated in the definition mentioned above – a lot of fascinating challenges for future generations of nanoscientists and nanoengineers [19].

5.11 Conclusions

Nanotechnology will lead to a new era of dental medicine that will change the current methods in diagnosis, treatment, and prevention of the different patients. As medicine advances and people live longer, nanodentistry will play an increasing role in enabling people to keep their natural teeth and oral tissues healthy and functioning forever. The scientists will understand in detail how the teeth grow, develop, and heal. The medical experts will understand the assembly of nanostructures in dentin and enamel to enable the development of biomimetic tooth repair and regeneration. Dentists will be able to reconstruct hard and soft periodontal tissues as well as to treat caries including biomimetic remineralization and repair of diseased teeth. In this manner, the role of well-educated and well-trained dentists will become more and more important.

Acknowledgments The authors would like to thank H. Deyhle for his contributions to the Figs. 1 and 5 and F. Schmidli for the image of the implant in Fig. 5.

References

1. H. Dosch, M. Van de Voorde (eds.), *Gennesys White Paper: A new European partnership between nanomaterials science and nanotechnology and synchrotron radiation and neutron facilities.* (Max-Planck-Institut für Metallforschung, Stuttgart, 2009)
2. R. Freitas, J. Am. Dent. Assoc. **131**, 1559 (2000)
3. A. Lareida, F. Beckmann, A. Schrott-Fischer, R. Glueckert, W. Freysinger, B. Müller, J. Microsc. **234**(1), 95 (2009)
4. G. Schulz, T. Weitkamp, I. Zanette, F. Pfeiffer, F. Beckmann, C. David, S. Rutishauser, E. Reznikova, B. Müller, J. R. Soc. Interface **7**(53), 1665 (2010)
5. B. Müller, H. Deyhle, D. Bradley, M. Farquharson, G. Schulz, M. Müller-Gerbl, O. Bunk, Eur. J. Clin. Nanomed. **3**, 30 (2010)
6. Y. Bar-Cohen (ed.), *Biomimetics: Nature-Based Innovation* (CRC Press/Taylor & Francis Group, Boca Raton, FL/London, 2010)
7. S. Gürel, C. Unold, H. Deyhle, G. Schulz, S. Kühl, B. Saldamli, J. Tübel, R. Burgkart, F. Beckmann, B. Müller, in *Proceedings of SPIE*, vol. 7804, p. 780401G, 2010
8. B. Saldamli, B. Müller, Sport-Orthopädie - Sport-Traumatologie **26**, 145 (2010)
9. H. Deyhle, O. Bunk, S. Buser, G. Krastl, N. Zitzmann, B. Ilgenstein, F. Beckmann, F. Pfeiffer, R. Weiger, B. Müller, in *Proceedings of SPIE* vol. 7401, p. 74010E, 2009
10. G. Schulz, H. Deyhle, B. Müller, in *Nanomedicine and Nanobiotechnology*, ed. by S. Logothetidis (Springer, Berlin, 2011)

11. T.L. Schleyer, J. Am. Dent. Assoc. **131**(11), 1567 (2000)
12. B. Müller, Surf. Rev. Lett. **8**, 169 (2001)
13. V. Imbeni, J. Kruzic, G. Marshall, S. Marshall, R. Ritchie, Nat. Mater. **4**, 229 (2005)
14. J.V. Barth, J. Weckesser, C.Z. Cai, P. Gunter, L. Burgi, O. Jeandupeux, K. Kern, Angew. Chem. Int. Ed. **39**(7), 1230 (2000)
15. A. Hett, *Nanotechnology: Small Matter, Many Unknowns*. Technical Report (Swiss Reinsurance Company, Zurich, 2004)
16. D.F. Williams, *Williams Dictionary of Biomaterials* (Liverpool University Press, Liverpool, 1999)
17. B. Müller, M. Riedel, R. Michel, S. De Paul, R. Hofer, D. Heger, D. Grützmacher, J. Vac. Sci. Technol. B **19**(5), 1715 (2001)
18. M. Riedel, B. Müller, E. Wintermantel, Biomaterials **22**(16), 2307 (2001)
19. B. Müller, Mater. Today **13**, 58 (2010)