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1 Nanomedicine at a glance

1.1 Introduction

Medical doctors can efficiently diagnose and treat patients because of the broad experience available. Generally, the medical experts have hardly any deep understanding of nanoscience and nanotechnology. In some cases, however, they apply nanotechnology-based drugs, implants, and devices to reach the envisioned success. In our everyday life, we do make similar experiences, as we are using toothpaste and sun protection; both rely on nanometer-sized ingredients, without realizing that nanomedicine is employed. Nanomedicine, however, is a term often related to some danger for our health. Although there is no proof, people believe that nanotechnology could become harmful and the application should be better avoided. This chapter, therefore, summarizes selected examples, which elucidate the potential of nanoscience and nanotechnology for the treatment of common diseases, including caries, incontinence, and cardiovascular diseases.

Here, nanomedicine is defined as the science and technology of diagnosing, treating, and preventing diseases and traumatic injuries; of relieving pain; and of preserving and improving health using the nanometer-sized components [1]. Boisseau and Loubaton have introduced the term nanotechnology-enabled medicine, which might be the better choice compared to the simple word nanomedicine [2]. Recent publications prefer the term nanoscience and nanotechnology for human health, which covers the entire interdisciplinary field without pronouncing medicine [3].

1.2 Nanoscience and Nanotechnology for Oral Health

It should be noted that the subject has been covered in previous books [4–6]. Therefore, the following part is based on the knowledge already available.

1.2.1 Natural Nanomaterials Within the Oral Cavity

The human tissues consist of anisotropic and hierarchically ordered nanostructures. For example, the crowns of the 32 teeth embrace the hardest tissue of the human body – the enamel. It consists of nanometer-sized, ordered hydroxyapatite crystals. This natural material is about three times tougher than the geological hydroxyapatite

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and much less brittle than the hydroxyapatite sintered at elevated temperatures [7]. The unique mechanical properties stem from the organization of the crystallites in an ordered fibrous continuum in three-dimensional space, where the needle-like crystallites are aligned to form microscopic bundles or rods, sheeted by organic material. These are in return oriented in specific directions depending on their location within the crown. The design is not only restricted to the enamel but also includes the dentin located below the enamel, which is composed of a mineralized collagenous matrix more akin to bone. The softer dentin counteracts the enamel's high brittleness. The result is a high-performance composite structure that maintains its functionality – mastication – over decades under heavy cyclical loads and adverse chemical conditions [8]. Where these two materials meet, they gradually merge in a complex interplay of highly mineralized and collagen-rich regions [9]. Although many research activities have been devoted to understand the impact of the dentin–enamel junction on the mechanical properties of the crown, the role of this complex interface in the tooth's functionality is still under discussion [9, 10]. Especially the organization on the nanometer level seems to play a critical role [11]. Whereas the hydroxyapatite crystals in the enamel are oriented toward the crown surface and the dentin–enamel junction, in the dentin they are oriented parallel to the junction. The orientation of the enamel's crystallites at the crown surface permits an effective way to remineralize the top layer of the crown after the food-related demineralization phase. Such a mineralization cycle occurs for several times during day and, if balanced, the natural teeth last healthy for several decades. An imbalance toward the acidic conditions within the oral cavity, however, leads to destruction within short periods of time. Currently, no engineering process to biomimetically repair or ex vivo recreate the human crowns has been identified. Nevertheless, the state-of-the-art nanoimaging allows for the identification of the design rules to build bioinspired dental fillings [12].

1.2.2 Dental Fillings

The restoration of teeth has been significantly improved during the last century. Many of us do remember the gold crowns and the amalgam fillings, which have been replaced during the twenty-first century by zirconia crowns and polymer-based composites, respectively. Although the restoration materials and related procedures for crown repair have been steadily improved, their life span is limited and does not reach the level of the natural tissue [13, 14]. This means that after about two decades the fillings have to be replaced by larger ones or even by inlays or artificial crowns. The treatment of the root canal is usually the next step, before posts and dental implants become necessary. The costs involved are significant, and alternatives are desirable. One possible approach consists in the development of anisotropic restoration materials that mimic the complex ultrastructure of human teeth [12]. Ideally, such materials will improve bonding to the tooth material as well as better match physical properties, including Young's and shear moduli as well as the thermal expansion of the tooth's components, providing longer life span of the restoration.

1.2.3 Dental Implants

Dental implants are inserted into the jaw and form a stable interface with the surrounding bony tissue. This part of the implant's surface is made rough by means of sand-blasting and etching to reach osseointegration. Here, the roughness on the micro- and nanometer scales is equally important. It has been demonstrated that the nanostructures are especially vital to avoid the inflammatory reactions [15–17].

The other part of the implant is usually smooth and serves for the artificial crown fixation on top. The only current main challenge is the formation of a satisfactory interface between the crown and the soft tissue of the gingiva.

In general, the currently available dental implants remain stable with a success rate close to 100%, and further breakthroughs in nanostructured implants are not expected any more.

Before placing an implant, it is necessary to check for the bone volume and quality. In the case of insufficient bone availability, the bone has to be augmented to guarantee the stability of the implant. A variety of calcium phosphate-based bone graft materials of well-established suppliers are on the market [18], which are used to strengthen the jawbone within months and subsequently allow for a proper fixation of the implant. These calcium phosphate phases should be upgraded to accelerate the jawbone formation.

1.2.4 Challenges of Nanotechnology in Oral Health

Depending on the pH value within the oral cavity, cyclic de- and remineralization of the enamel surface region takes place through diffusion of ions, maintaining tooth crowns in an intact state (see Figure 1.1). If a disequilibrium between the two processes occurs in favor of demineralization, tooth decay occurs. Conversely, artificially supporting the remineralization process can result in tooth repair. The biomimetic repair of the damaged crowns, however, is hardly solved and understood. Ion delivery is a concentration-mediated dynamic process, and such a material flow is more evasive to classical pharmaceutical approaches. In everyday life, we use a more or less nanotechnology-based toothpaste together with a more or less sophisticated brush mainly to clean the crowns usually twice a day. The toothpaste often also provides nanometer-sized species, which promote the remineralization of the crown's surface, and thus, the regeneration processes. Therefore, the small damages that are optically

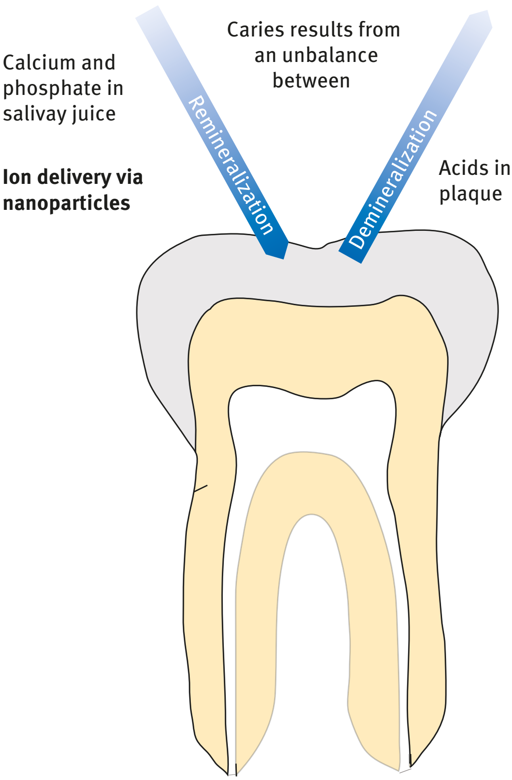

Figure 1.1: The enamel, given in gray, has direct contact to the oral cavity. Therefore, in acidic environment a demineralization takes place, which is converted by changes in the pH value.

invisible can be repaired. The penetration depth of these species is, however, limited, restricting their efficiency to surface incipient lesions. For slightly larger damages, termed white spots, which are visible because of their few hundred micrometers depth, products that are reported to improve the natural regeneration capacity of the crowns are on the market [19, 20]. Their mode of action, however, is not fully understood, since there is no driving force known that pushes the calcium ions into the layers far from the crown surface.

If the caries lesion reaches a critical size, remineralization is currently no longer possible. Here, the highly active inorganic bioactive nanoparticulate glasses are promising candidates to promote remineralization in deeper decayed layers. These materials have already been implemented to produce *bioactive* restorations with an antibacterial effect, reducing bacterial population in affected dentin [21]. Currently, however, the dentist mechanically removes the diseased region as well as some surrounding unaffected tissue, before an isotropic and, therefore, not biomimetic dental filling is implemented. Although the filling materials and their preparation procedures have constantly been improved, we do not know any procedure to build a filling with a micro- and nanostructure similar to that of enamel and dentin including their interface. Here, interdisciplinary teams of experts in dentistry and nanotechnology have to invent suitable compositions of materials and appropriate procedures to be compatible with a chair-side patient treatment in order to reach a crown repair in a biomimetic fashion.

For the dentin, recent studies have shown that even after severe demineralization due to caries the overall nanostructural framework of the crown tissue remains intact [22–24]. As a result, the remineralization of moderate carious lesions can become feasible soon.

1.3 Nanotechnology-Based Artificial Muscles for the Treatment of Severe Incontinence

1.3.1 Anatomy and Function of the Natural Continence Organ

From an engineering point of view, the continence organ acts as a simple switch. Usually the hollow organ is closed and just to pass water or for defecation the hollow organ is opened for a restricted period of time.

In the case of fecal continence, the closeness of the anus depends on the intact continence organ consisting of the internal anal sphincter and the external anal sphincter, the hemorrhoid cushion, and the puborectal muscle. The puborectal muscle surrounds the rectum and pulls it toward a ventral bone of the pelvis. When the puborectal muscle is activated, the rectum is closed, and feces cannot descent from the rectal ampulla to the anal canal. For defecation, the puborectal muscle is relaxed, the rectum straightens, and feces descent. Compared to the technical analogue, the anatomy and the function of the continence organs is complex. Therefore, it is not advised to build the medical device as an exact copy of the natural counterpart. Instead, the implant should be as simple as possible, but provide the full functionality of the natural continence organ.

1.3.2 Lack of Biomimetic Artificial Sphincters

Patients suffering from severe incontinence like to improve their quality of life even if the currently available devices are suboptimal. Most of these artificial muscles generate a constant pressure onto the hollow organ [25, 26]. If this pressure is low, the patients still loose urine and feces. If the pressure onto the hollow organ is high, rejection responses generally occur and atrophy as well as erosion give rise to further critical interventions often resulting in definitive removal of the medical device [25, 26].

The main reason for the disappointment is the missing feedback via the nervous system. Therefore, the artificial muscle should comprise not only the actuator but also a sensory feedback, which should be as fast as in the healthy situation. Millisecond response times are desired.

The device should be autonomous, that is, it should contain not only a battery with limited life time but also a component for energy harvesting from the human body.

As a consequence, the artificial muscle for incontinence treatment is a rather complex device that should reliably operate as actuator, sensor, and energy harvester, simultaneously.

1.3.3 Possible Physical Principle for the Biomimetic Artificial Sphincters

Currently, dielectric elastomer transducers (DETs) are promoted as powerful devices to simultaneously work as actuator and sensor. There are also applications as energy harvester. Thus, these physical principles can also be applied in the field of medicine (see Figure 1.2). The major drawback, however, is the operation voltages, which are usually in the kilovolt range and are reduced to several hundred volts in best cases [27]. As the power required to operate the artificial muscle is relatively large, the operation voltages have to be reduced to the well-known battery ranges of a few volts. Such a reduction is possible by a significant increase of the elastomer's permittivity [28, 29] and by reducing the elastomer film thickness to the nanometer range [30]. The preparation of such materials and films, however, is a critical challenge [31, 32].

1.3.4 Nanometer-Thin DETs for Artificial Muscles

Today, elastomer thin films or membranes with a thickness of several hundred nanometers and an appropriate elasticity can be fabricated [33]. The electrical contacts on both sides on the membranes, however, exhibit Young's moduli orders of magnitude larger than the elastomer membranes. These electrodes dominate the overall mechanical properties, although they are more than one order of magnitude thinner. As a consequence, research teams search for soft electrodes, which include conductive polymers and liquid metals. Nonconfluent metal films with a thickness above the percolation threshold, for example 7-nm-thin gold films, are a promising alternative [34].

Even more important is the generation of the necessary forces. Such thin DETs can only produce forces, which are about four orders of magnitude below the forces necessary for the actuation of the artificial muscle for continence [30]. Therefore,

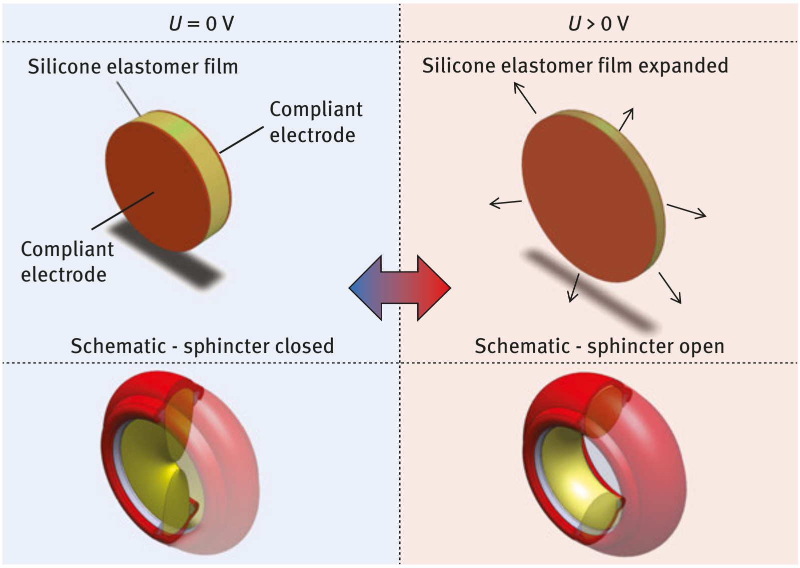

Figure 1.2: Operation principle of a low-voltage dielectric elastomer transducer: A several hundred nanometer-thin elastomer film, such as silicone, is sandwiched between two compliant electrodes. The elastomer is essentially incompressible but deformable. Therefore, the application of a voltage not only generates an electrostatic pressure, but reduces the thickness of the silicone film and is associated with an expansion parallel to the compliant electrodes. This actuation is fully reversible with response times of a few milliseconds. In the second row, a sphincter-like ring with a pre-stretched dielectric elastomer transducer (red color) and a liquid-filled cuff (yellow color) schematically shows the integration of the actuator into a prototyped implant.

multilayered nanostructures with a controlled thickness homogeneity have to be prepared. The related thin-film technology for both the elastomeric and the conductive films has to be developed.

Based on molecular beam deposition (MBD), the functional group density and chain length of polydimethylsiloxane (PDMS) can be tailored [35] and thus, enables to manipulate the elasticity and chemical integrity of the obtained nanometer-thin elastomer membranes [33, 36]. Elastomers with enhanced dielectric properties have been synthesized based on dedicated functional groups and subsequently thermally evaporated [37]. Furthermore, organic MBD enables to implement adhesion layers on the basis of thiol-functionalized PDMS – essential for the reliable binding of the gold electrode to the silicone layers [38]. Thiol-functionalized PDMS furthermore allows for photo-crosslinking [39]. Currently available deposition rates, however, are often below 1 µm per hour. As an alternative deposition technique, electrospray deposition (ESD) of PDMS with subsequent UV-based cross-linking has been introduced. The homogeneity of submicrometer-thin, ESD-prepared PDMS films, however, remains a challenge due to high defect level compared to MBD and the micrometer-rough film surface [40–42]. The homogeneous and soft polymer membrane with a thickness in the submicrometer range is the key for reliable low-voltage operation of multilayered DETs to qualify for artificial muscles.

In summary, although nanotechnology-based DETs seem to be technically feasible, several challenges have to be mastered: (i) fast and reliable elastomer membrane production, (ii) soft conductive film deposition, (iii) stable bonding between elastomer and electrode materials, (iv) thickness homogeneity of the elastomer and electrode better than 2%, and (v) self-healing capability of the device to tolerate a certain defect level.

1.4 Mechanically Responsive Nanocontainers for Targeted Drug Delivery

1.4.1 Emergency Treatment of Cardiovascular Diseases

It is well known that the formation of plaque in the arterial wall usually starts at the age of 20 years. The related cardiovascular disease, atherosclerosis, develops over years and decades. Abruptly, however, the plaque can rupture and can cause a myocardial infarction or stroke. Then, the time to treat the patient is critical. The shorter the time to medical treatment, the smaller the volumes of the heart muscle or brain tissue, which are lost. Currently available procedures are based on technologies such as endovascular devices for intra-arterial clot lysis, stent implantation, and arterial balloon dilatation – all of them are invasive and have to be performed in the catheterization room of a well-equipped hospital.

At pre-hospital level, the patient can systemically obtain a vasodilator drug often based on nitric oxides in the emergency vehicle. These drugs do not only widen the desired constricted artery but the entire blood vessel system. Because of the ensued blood pressure fall, which is a side effect, the maximal therapeutic doses of the administered medicine and the related success in an efficient treatment of the world-leading cause of death are restricted.

1.4.2 Constrictions in the Blood Vessel System

Constrictions within the vessel system, termed stenosis, diminish the blood flow to the end organ. As the cross section at the stenosis is significantly smaller than in the healthy situation, the blood velocity and the associated wall shear stress are substantially higher (see Figure 1.3) [43]. Recently, researchers proposed to take advantage of this behavior and to fabricate mechanoresponsive species, which release the vasodilator upon the disease-specific purely physical triggering [44, 45]. The preferential

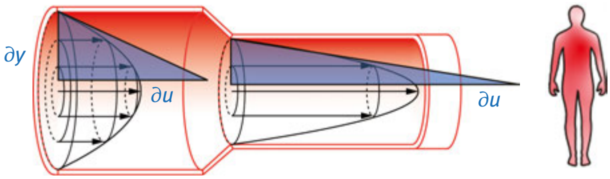

Figure 1.3: The shear stress in Newtonian fluid is proportional to the dynamic viscosity and the derivative of the velocity profile in direction of shear. If there is a disease-related constriction (stenosis) present, the flow of the velocity increases and the related wall shear stress may open the mechanoresponsive nanocontainer. The enclosed drug will be released near the stenosis and not in a systemic fashion.

release at the constrictions enhances the local concentration of the vasodilator and a considerably higher dose can be applied.

In order to determine the actual average wall shear stress at a critically constricted artery, the lumen has to be determined with necessary precision. In vivo examinations do not provide suitable data yet, as plaque-related artifacts and limited spatial resolution hinder the precise three-dimensional imaging. Therefore, the affected artery has to be identified and extracted for postmortem tomographic imaging, which also includes the decalcification. Once the three-dimensional data are available and the lumen segmented, flow simulations allow for the calculation of the local average wall shear stress values [46].

It is surprising that the most critical challenge relates to the localization of a critical stenosed artery, as the disease is the world-leading cause of death in the industrialized countries. Nonetheless, one can state that the threshold for the vasodilator release can be set one order of magnitude above the healthy situation, that is, to values above 20 Pa [47, 48].

1.4.3 Mechanoresponsive Vesicles for Targeted Vasodilator Release

Lipid bilayers can form various three-dimensional arrangements. Most interesting for medicine are liposomes or vesicles, where a bilayer membrane forms a sphere enclosing an aqueous inner cavity. As these vesicles are formed via self-assembly processes of phospholipids, synthetic molecules can substitute the natural phospholipids and this will lead to vesicles with unprecedented properties [49]. Using 1,3-diamidophospholipids, it is possible to formulate mechanoresponsive vesicles that are stable at rest but release their cargo upon mechanical stress. The threshold for release depends on the temperature and the applied stress. The vesicles need to be in the gel state, which is defined by the main phase transition of the bilayer membrane [44]. So far, mechanoresponsive liposomes, which do not release their cargo, for example the selected drug, at the healthy sites of an artificial blood vessel system, but yield the drug to the stenosed sites, have been developed. Their main phase transition temperature, however, lies slightly below body temperature. Therefore, their thermal stability is insufficient to successfully treat patients in an emergency vehicle [50].

These days, liposomal drugs are Food and Drug Administration approved and well established on the market, although adverse effects are noticed. The mechanoresponsive liposomes identified, however, show even less adverse effects than the established liposomal drugs [50, 51]. Therefore, a promising route for the acute treatment of myocardial infarction on the basis of nanotechnology has been discovered. It has to be further refined for the envisioned patient treatment.

1.5 Interdisciplinary Approaches for Nanoscience-Based Medicine

The three examples, that is, oral health, continence, and atherosclerosis therapy, demonstrate that nanomedicine is driven by the patient needs, managed by the medical doctors and dentists, but require close collaboration with a variety of engineers and natural scientists. This teamwork in the field of nanoscience and nanotechnology has given rise to a prominent improvement of the quality of life and has supported the great reduction of morbidity and mortality. Our society is in the era of the widespread use of nanotechnology for health and health care.

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