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Biomedical Applications of Nanodiamonds in Microbiology

Norouzi, Neda

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Chapter I

General Introduction

1.1 Introducing Nanodiamond Materials

In the past years, nanodiamonds (NDs) have attracted increasing attention due to their unique properties and interesting qualities that arise in diamond particles in the nanometer range (5-200 nm). To name just a few outstanding properties based on the literature, ND particles can be either a super hardness thermal conductor, an excellent electrical insulator, or a chemically inert nanosensor with exceptional optical properties and excellent biocompatibility.

Various techniques exist to produce NDs resulting in materials with fundamentally different physical properties and biocompatibility. Nanodiamonds differ in size, shape, and surface chemistry, which is responsible for their highly-valued utilization in a large variety of fascinating applications (Figure 1-1). Thus, it is very crucial to specify which material is used. [1,2] There are two widely-used diamond materials commercially available for research and industry applications, which we used in this thesis.

This introductory chapter will briefly describe detonated nanodiamonds (DNDs) and milled nanodiamonds (HPHT NDs). However, we will carefully differentiate between different diamond materials during the entire thesis. This is often neglected in the literature and can lead to major confusion and/or conflicting results. The bioapplications of NDs in microbiology, which have been explored in this thesis, are described here. The main focus is on the potential of milled HPHT NDs as nanosensors to detect free radicals in the bacteria upon stress. Moreover, a new composite material, diamond coated black silicon surfaces, is introduced. Their potential as antibactericidal surfaces was investigated in this thesis since biocompatibility and antimicrobial activity often have conflicting functions.

1.1.1 Detonation Nanodiamonds(DNDs)

Detonation nanodiamonds(DNDs) are tiny nanoparticles (~5 nm) that are obtained by the oldest method involving a controlled explosion of carbon-rich explosives [typically TNT-like compounds]. [3] These nanoparticles found their way very soon into drug delivery applications due to their small size, round shape, and high surface-to-volume ratio. [4] Additionally, they are relatively chemically inert but still reactive enough to allow functionalization.

Therefore, these properties will enable the attachment of large quantities of drugs and lead to reproducible particle sizes.

On the other hand, a high number of impurities and defects plus the small size of these nanodiamonds make them less likely to host stable fluorescent defects. Consequently, they are not usually the candidate diamond material for labeling or sensing applications. However, some recent developments might render DNDs more attractive for these applications as well. [5,6]

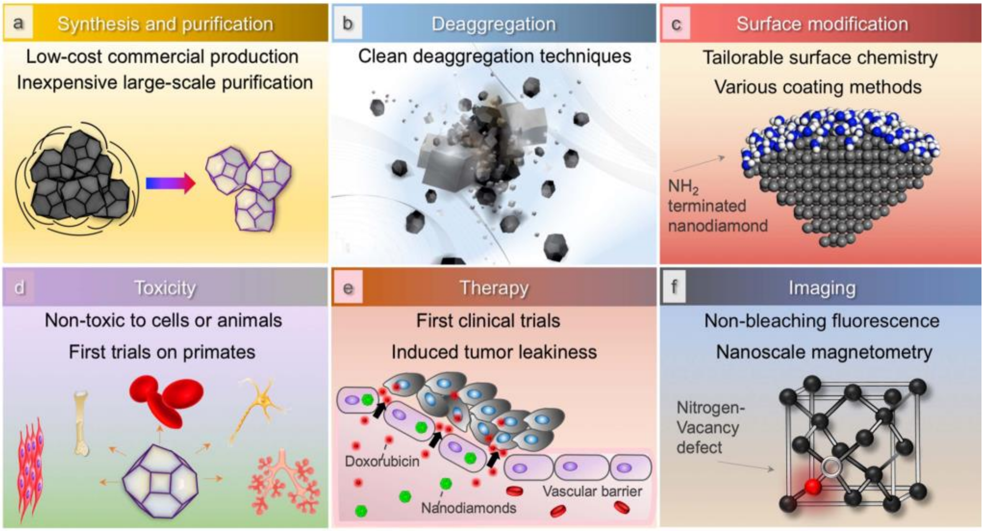

*Figure 1-1. Steps towards nanodiamond theragnostic: (**a**) synthesis and purification, (**b**) deaggregation, (**c**) surface modification, (**d**) toxicity evaluation, (**e**) nanodiamond-based therapy, and (**f**) biomedical imaging.* [7]

1.1.2 Fluorescence Nanodiamonds(FNDs)

By milling larger bulk diamonds under high pressure and high temperature, very different particles are obtained called high pressure high temperature nanodiamonds (HPHT NDs). They have flake-like shapes available in many different sizes [8]. The milled NDs are usually used for their comparably low price, exceptional biocompatibility, and a very broad size distribution. The particle sizes can be adjusted by grinding down the materials to the desired dimensions using different centrifugation speeds. [9]

Moreover, they are purer and contain fewer defects than DNDs. Depending on the size of HPHT nanoparticles, they can naturally host stable fluorescent defects, for instance, nitrogen-vacancy (NV) centers which thus allows for using them for quantum sensing applications. The number of defects in one diamond particle can be increased by irradiation of HPHT diamonds. These are commercially available as fluorescent nanodiamonds (FNDs). Interestingly, since these fluorescent defects are protected in the crystal lattice, FNDs have the advantage that they never bleach. Since they change their optical properties depending on their magnetic surrounding, they can be used as promising nanoscale quantum sensors to detect, for instance, magnetic or electric fields,[10–12] temperature, [13,14] pressure, and particularly-for one of the described applications in this thesis – free radical molecules. [15,16] Their brightness increases by increasing NV centers;, recently, these defects have also been used as stable optical labeling and imaging applications. [17]

1.2 Nanodiamonds Potential in Microbiology

Infectious diseases caused by bacteria(Prokaryote) pose a major threat to human health. Furthermore, antibiotic resistance is one of the most daunting challenges for health care in modern societies. An increase in the risk of death and prolonged hospitalization makes bacterial infections even more alarming in the 21st century. Diamond nanoparticles have demonstrated to be promising materials in various biomedical settings. These nanoparticles have diverse applications based on their different structures and properties. Several aspects and (bio)applications of nanodiamonds have been reviewed. [1,2,7,18] There are also a few articles about bio-applications of FNDs as nanosensors to free radical detection in the biological environment, [15,19] however, primarily focused on Eukaryote cells. In the following subsections, two of the applied potential of NDs in microbiology will be described, which have been considered in this thesis.

1.2.1 Diamond Magnetometry for Sensing Free Radicals

Free radical generation occurs in all antibiotic classes during the killing process regardless of the antibiotic's working mechanism. [20] However, detecting free radicals in biological systems is challenging due to their short half-lives and low baseline concentrations. [21] We believe that understanding the underlying mechanism of drug-cell interaction could contribute to the control of this problem. It has been reported that free radical plays a role in drug-cell interaction at the molecular level. [20,22] Thus we are particularly interested in free radical formation. However, very little is known about this factor due to a lack of methods to assess radical formation at the nanoscale in microbiology. It is therefore necessary to develop sensitive methods allowing to detect free radicals in microbiological environments in real-time.

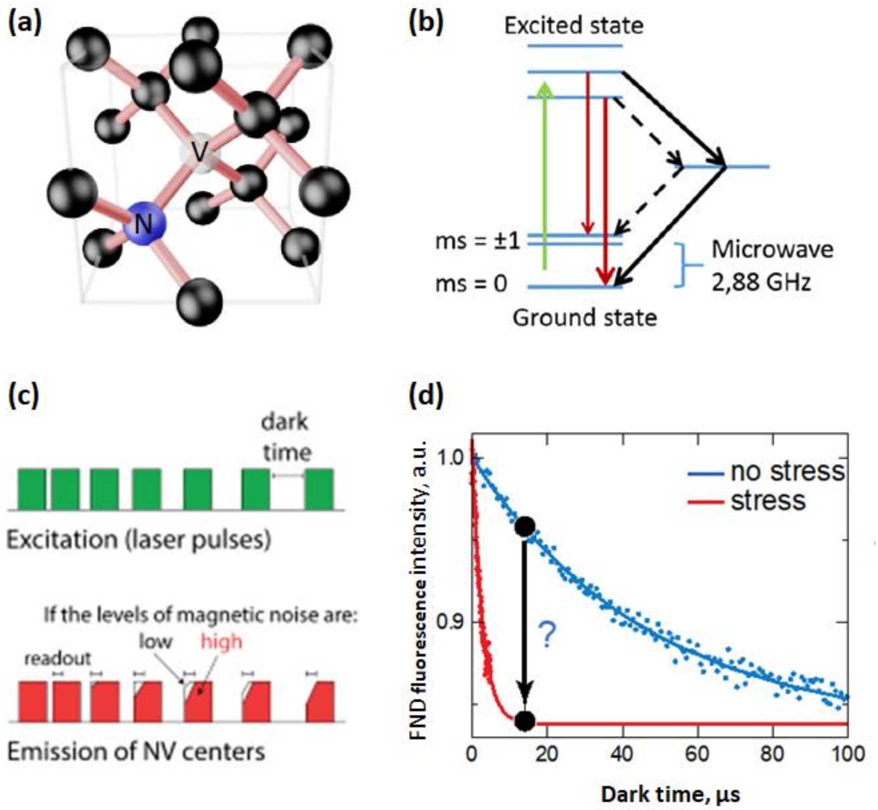

*Figure 1-2 NV centers in the diamond crystal structure (**a**) change their fluorescence properties, based on the environment (e.g., concentration of paramagnetic species, such as free radicals). If the NV-centers are pumped into a brighter ground state and then allowed to relax , their fluorescence intensity becomes lower with increasing dark times (**b**). These changes can be detected optically, using a laser pulsing sequence (**c**). The corresponding curves can be used to obtain the T1 relaxation constant. Longer T1s (blue; cells with no stress) correspond to slower relaxation. External factors, such as, free radicals in the close environment of the particle, cause faster relaxation and result in shorter T1s (orange; exposed cell with stressor) (**d**).* [23,24]

In this thesis, we have investigated free radical metabolism using a new diamond magnetometry approach. The technique is based on a defect(NV-center)(Figure 1-2 a) in FNDs, which can be used as a sensor for its surroundings. Its fluorescence strongly depends on the environment's magnetic fields. Consequently, the local magnetic resonance can be read out by measuring the fluorescence of the defect. Indeed, to measure free radical release NV centers are pumped into the ground state whereafter T1 measurements are done with a confocal microscope. [25] It has been recently demonstrated that it is possible to measure free radical formation in living eukaryotic cells. [15,16]

1.2.2 Diamond Thin Films

Over last two decades, chemical vapor deposition(CVD) technology has enabled the production of new inexpensive, high-quality coatings made from diamond as a scientific and commercial reality to obtain maximum translation from both *in vitro* to *in vivo* biomedical applications. Considering diamond as a highly desirable candidate material for biomedical applications offers important advantages. The highest benefit is its bioinertness or biocompatibility, meaning that there is minimal immune response when diamond is implanted into the body, and its electrical conductivity can be altered in a controlled manner, from insulating to near-metallic. Moreover, many academic and industrial research groups supply thin coatings of diamond on a silicon wafer using cost-effective CVD manner. The CVD process involves the reaction of a mixture of carbon-containing gas (usually methane) and hydrogen in a low-pressure reactor, followed by the deposition of carbon in the form of a crystalline diamond coating onto a suitable substrate material. The substrate can be a diamond , however, alternatively, if the substrate is made from another material, such as silicon, then the diamond is deposited as a thin coating or film, with thickness in nanometres, micrometres or even millimetres, depending upon the growth conditions and time.

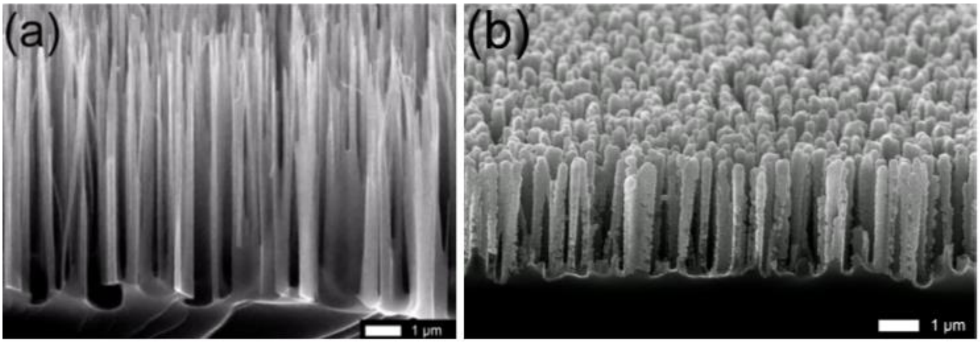

*Figure 1-3 Scanning electron micrographs of (**a**) a cross-section through a black Si sample, (**b**) a representative sample of black diamond*

With the rise in antibiotic resistant bacteria also comes a high demand for anti-bacterial, anti-fouling and bactericidal materials that are not based on antibiotics. One such substrate material that has recently been gaining popularity is black silicon (bSi), which is a synthetic nanostructured material that contains high-aspect-ratio nanoprotrusions, such as nanospikes or nanoneedles, on its surface produced through plasma etching. [26] It has now found applications in photovoltaics [27,28] and has recently been used for biomedical sensing applications. [29,30] Black silicon has an excellent bactericidal effect that can be tuned by varying the lengths and spacing of the nanoscale needles. [31]. However, silicon nano-needles are relatively fragile [32] and thus it would be desirable to improve their mechanical properties and durability. To this end, the black silicon needles were conformally coated with a thin (< 500 nm) layer of diamond using a chemical vapour deposition process (Figure 1-3). This new composite material has been labeled 'black diamond' (bD), [33] and it has been shown previously that these black diamond surfaces retain many of the bactericidal properties of black silicon while being chemically more inert and mechanically more robust [31,32,34]. Even though many studies have already been done using Gram negative bacteria, further investigations are still required to have a complete picture of the bactericidal properties.

1.5 Outline and aim of this thesis

Fluorescence imaging and magnetic resonance imaging (MRI) are potential imaging methods to visualize bacterial responses to drugs. [35,36] However, both techniques suffer from limitations in providing high-resolution data on free radical metabolism. While magnetic resonance techniques are element-specific, their sensitivity is very low, and thus, spatial resolution is limited to cubic milimeters down to a few cubic µm. Furthermore, very complex and expensive equipment is needed. On the other hand, fluorescence imaging is very sensitive (single photon detection is possible), which allows for high spatial resolution and relatively easy detection. However, the technique is not element-specific. [2]

The aim of the research in this thesis is to combine the advantages of both techniques. We are interested in achieving this by using nanodiamonds containing fluorescent defects. These function as sensors since they change their optical properties depending on their magnetic surroundings and thus enable optically reading out magnetic resonance signals. The idea is to use nanodiamonds and track their path. By recording the magnetic resonance in real-time, we hope to gain the time, exact location, and nature of free radical generation in bacteria in response to an antibiotic. Quantifying, identifying and localizing free radicals has been identified as the main bottleneck to understanding their working mechanisms and, as a consequence, translating free radical biology into medical advances. This project thus assessed free radical release in bacteria upon exposure to antibiotics by using Diamond Magnetometry.

Since the foremost step for using any materials for biological and medical purposes is determining their lack of toxicity and biocompatibility, [37] this project also aimed to systematically investigate the antimicrobial mechanism and biocompatibility of NDs and coatings. In the recent publication of our group, [38] we consider milled HPHT nanodiamonds' interaction with Gram-negative and Gram-positive bacteria for the first time. An initial study was performed to assess the interaction of partially oxidized monocrystalline nanodiamonds with *S. aureus* ATCC 12600 and *E. coli* ATCC 8739. The results showed that for *S. aureus*, these nanodiamonds' presence leads to a sharp reduction of colony-forming ability under optimal conditions. A different effect was observed on *E. coli*, whereas no significant adverse impacts of milled ND presence was observed. The mode of interaction was further studied by electron microscopy and confocal microscopy. The effects of NDs on *S. aureus* viability depended on many factors, including the concentration and size of nanoparticles, the suspension medium, and incubation time. In the following is the detailed outline of the chapters of this thesis:

- *Chapter 2* is a systematic experimental study of different strains, milled HPHT nanodiamonds sizes, and surface chemistries. The focus was on investigating in more detail the role of the cell wall type, bacterial ability in Extracellular Polymeric Substance (EPS) secretion and medium composition in the interaction of milled nanodiamonds with Gram-positive and Gram-negative bacterial strains. An overview of studies on the interaction of non-functionalized nanodiamond materials with bacteria, summarizing their methods and respective outcomes are presented in *chapter 2*.
- The possibility of free radical detection in bacteria during the stress condition using the new approach of diamond magnetometry is explored in *chapter 3*. The different concentrations of Vancomycin (antibiotic) and UV irradiation were used as stressors. It is hypothesized that exposure to antibiotics induces reactive oxygen species (ROS) production in bacterial cells. FNDs can sense the spin noise generated by free radicals in their surroundings and thus allow nanoscale magnetometry.
- Bactericidal surfaces are in high demand for biomedical and industrial applications. In *chapter 4*, we investigated if black diamond is useful for this application. The bactericidal and anti-bacterial properties of differently terminated bD and bSi were compared with flat surfaces (diamond or silicon) of the same termination. While Gram-negative bacteria were investigated in previous studies, in this chapter, we evaluated the ability to repel and kill Gram-positive bacteria (*S. aureus* and *S. epidermidis*) with a thicker cell wall that are more mechanically robust.

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