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Introduction

> The impact of nanotechnology on health, wealth and the standard of living for people will be at least the equivalent of the combined influences of microelectronics, medical imaging, computer-aided engineering, and man-made polymers…
>
> Richard Smalley, Nobel laureate 1996

If asked to define nanotechnology, almost everybody bold enough to do it would say that it is the study of materials with sizes of 1–100 nm. Since its murky origin in the 1950s physics, it made big strides ahead finding applications in fields like materials science, engineering, medicine, pharmaceutics, cosmetics, and many others. It started by capitalizing on the unique properties of materials with nanometer sizes, many of which are different from those of the bulk material with the same chemistry. The high surface to volume ratios, increasing exponentially with decreasing size, make for similar increases in reactivities, for some novel properties, and even, sometimes, for shape-dependent behavior.

This field, the epitome of interdisciplinarity, emerged where many disciplines came together blurring frontiers and establishing an incredibly fast-growing new discipline based on materials having very small dimensions. And growing it blurred the well-defined numbers in the definition, imparting flexibility and refusing to fit into predetermined molds and scenarios. It did so also because it is the best field to explore life, since life itself happens at the nanolevel, somewhere between how big atoms are and, at the other limit, the size of a bacterium. Working at the interface between nanotechnology and biology makes a lot of sense, and some bionanomaterials have been known for a long time (pigments, viruses). Numerous other nanomaterials have been discovered or synthesized more recently and, due to their amazing properties, were claimed, tested, and many times adopted by different fields. The advantages they offer, such as enhanced stability of unstable species (antioxidants, volatile compounds) by encapsulation, increased bioavailability, targeted approach which reduced doses of medication, and the possibility to tailor them to different applications, made nanomaterials look attractive to specialists in many domains. For the pharmaceutical industry, the appeal is tremendous as it is for the cosmetic industry and for regenerative medicine. But the cosmetic industry, less hindered by regulation, has been more dynamic in adopting them, while the pharmaceutical and the medical field are lagging behind due to the arduous and lengthy process which is required for FDA approval. The increasing client base which is represented by an aging population makes potential applications of nanomaterials even more numerous and more desirable. There are growing demands for antiaging skin care products, for medications for skin conditions (especially degenerative ones) and for chronic wounds, and for materials able to regenerate tissues.

This book focuses on nanomaterials from the organic world, synthetic ones, materials from biological sources, or hybrids thereof. Nanoparticles made from inorganic materials (titanium oxide, carbon nanotubes, etc.) which received a lot of attention in the scientific literature, some of which found well-established commercial applications (such as sunscreens), are not included herein. After discussing the special properties of materials at the nanosize and their interactions with other entities and with their environment, this book visits briefly the structure of skin and its function as a barrier. Short descriptions of its layers and of their roles are given, as is a discussion of the skin aging process, with special attention to photoaging. Wounds (chronic and acute), burns, the great toll they take on healthcare costs, and the importance of skin regeneration are discussed in another chapter. Modalities to deliver different compounds to the skin (topical, transdermal) are introduced qualitatively, with short discussions of quantitative aspects, and comparisons are made. A chapter is dedicated to nanoparticles and to different types of nanocarriers (nanoemulsions, micelles, dendrimers, gels, etc.), sources, preparative processes, comparative discussion of properties, and applications. A special chapter is focused on nanomaterials as a solution to enhance bioavailability of active principles to the skin.

A number of chapters are dedicated to the study of different classes of bionanomaterials based on their natural sources. Due to their characteristics (natural, biodegradable, and able to encapsulate both hydrophilic and lipophilic species), lipid (and solid lipid) nanoparticles are discussed in a separate chapter together with their applications for the skin and the enhancements they afford. Antioxidants are valuable agents for health in general and for the skin in particular (care and treatment), but their reduced stability limits their actual benefits. Encapsulation in nanocarriers is a viable solution for this, and it is discussed, together with examples, in a separate chapter. Chitosan, an inexpensive polymer from natural sources, found many applications during the last 20 years. Due to its antimicrobial and antimycotic properties, and to the facility of preparing nanochitosan, it offers a huge potential for medical and cosmetic applications, some of which are already in use, and a chapter of the book discusses them. Also natural, available from many sources, inexpensive, and with special mechanical properties, nanocellulose found many applications, alone or in hybrid materials, and it is discussed in a separate chapter. Bionanomaterials from plant sources have received great attention from scientists due to their healing properties, antioxidant effects, and biodegradability. Their poor chemical stability and limited bioavailability have been addressed by encapsulation in nanocarriers, and a chapter is dedicated to this discussion. Regenerative medicine is a topic of high interest in general and of particular importance for dermatology. This makes the chapter focused on nanofibers, nanoscaffolds, and skin regeneration an important one for the scope of the book. A separate chapter discusses bionanomaterials based on peptides and proteins and briefly mentions the importance of those based on small interfering RNA (siRNA) species in the treatment of skin conditions.

The history of nanomaterials is not long enough for their long-term effect to be known and for their toxicity to be assessed over time. After the hype and enthusiasm of the beginnings when everything nano was adopted and praised, hazards started to be reported, and the public opinion shifted to the other extreme. A later chapter discusses what is known versus what is not yet clear about the toxicity of nanomaterials and evaluates benefits against risks as known so far. Finally, the last chapter of the book discusses some of the ethical, regulatory, and social issues linked to using nanomaterials in skin regeneration.

Discussion and growth in the field of nanomaterials need specialists in many domains. Not all the disciplines are preoccupied to provide adequate training in this field which makes dialogue difficult or even lacking sometimes. This small book hopes to be a modest start of the discussion for newcomers and for some experts interested in collaborating at a place where their disciplines come together.

"Science is the only possible adventure of our times..."
One of our fathers—sometime during the second half of the twentieth century
"..., and technology...."
The authors—sometime at the beginning of the twenty-first century

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Mihaela D. Leonida dedicates her part of this book to the memory of her parents who taught her that science cannot be hijacked by history and that a scientist has to make a mark not only in his/her field but in culture as well. She is very grateful to them and to Jim for his infinite patience, unwavering support, and willingness to participate in any cultural endeavor.

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Mihaela D. Leonida is a professor of chemistry at Fairleigh Dickinson University, Metropolitan Campus, in Teaneck, NJ (mleonida@fdu.edu). She received an M.S. and a Ph.D. in chemical engineering from Polytechnic University in Bucharest, Romania, and a second Ph.D. in chemistry from Wesleyan University in Middletown, CT. While teaching, she has mentored research with over 60 students.

Her scientific interests are broad, from "wiring" enzymes to bionanomaterials with antimicrobial and anti-proliferation activity, to detecting art forgeries, to materials and techniques used by artisans of times past. She spent a sabbatical leave doing research and lecturing at l'Universite de Quebec a Montreal and at McGill University and was invited to lecture and collaborate on an interdisciplinary project at the Ecole Polytechnique de l'Universite de Nantes. In 2010, she spent one semester as a senior Fulbright scholar lecturing (about modified enzymes and materials in art) and doing research at the Polytechnic University in Bucharest. She has authored/coauthored five books, two textbooks, and several book chapters. Dr. Leonida published over 60 papers in scientific journals (among which are *Journal of Organic Chemistry, Analytical and Bioanalytical Chemistry, Nonlinear Optics and Quantum Optics, International Journal of Nano and Biomaterials, Phytomedicine, Études et Documents Balkaniques et Mediterranéens, International Journal of Bio-Chromatography, Bioorganic & Medicinal Chemistry Letters, Tetrahedron Letters, Revue Roumaine de Chimie, Review of Museums and Historical Monuments, Current Nanoscience, The Protein Journal*) and made over 80 presentations at scientific conferences. She gave over 30 invited lectures at different venues in the USA, Canada, France, and Romania. Her strong interest in varied materials led to lifelong connections and collaborations with researchers from different fields. Most of her interests, work, and lectures are focused on interdisciplinary topics. She is actively involved in the American Chemical Society, at the local and national level.

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Contents

Chapter 1
Bionanomaterials for the Skin: More than Just Size

Bionanomaterials are considered to be biological molecules (peptides, proteins/antibodies/enzymes, nucleic acids, lipids, mono-/oligo-/polysaccharides) with nano-size dimensions. Some hybrid entities containing a biological part in conjunction with an inorganic one are included in this type of materials as well. When used in skin applications, bionanomaterials may be functionally active (therapeutic agents, catalysts, skin care agents) or passive (used as vehicles, coatings, scaffolds).

Materials for skin care and for the treatment of skin disease contain active principles which can act only after penetrating into the skin structure. How effective they are depends on their transport across the outermost layer of the skin, the *stratum corneum* (SC), a rate limiting barrier, to reach an intercellular lipid matrix. It has been known for some time that materials having at least one external dimension in the nanorange (usually defined, arbitrarily, as 1–100 nm) are the best to accomplish this. Some authors consider separately nanoparticles (<999 nm) and nanomaterials (<100 nm) [1]. Discussions about size-based definitions of nanoparticles/nanomaterials appear in many publications and they may vary as to specifications (see Chap. 5). The problem with defining nanomaterials based on size is compounded by the overlap with the earlier definition for materials previously called colloids. Naturally occurring tattoo pigments, known and used for a long time, are an example of bionanomaterials used for skin, while many others were discovered and/or prepared recently.

Interest for small size structures is not new. Physicist Richard Feynman predicted more than 50 years ago, in 1959, that a new science will emerge and develop around studying and handling entities with dimensions between 1 and 100 nm. Miniaturization to reach nanoscale became the main pursuit of the beginning of the twenty-first century and "nano" is broadly and not accurately used as a synonym for downsizing.

This size, larger than an atom but smaller than an average bacterium (Fig. 1.1, [2–4]), is optimal for interacting with living entities since life itself takes place at the nano level. Critical size of nanoparticles varies from one application to another. But size is not all there is to them. Nanoparticles have high surface to volume ratios. If the area per mass unit increases 10^2 times when the size of the particles decreases

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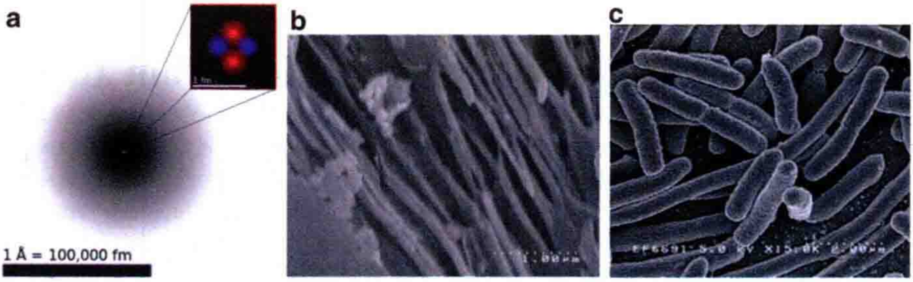

Fig. 1.1 (**a**) An atom [2]; (**b**) scanning electron micrograph of a chitosan-$CuSO_4$ nanoparticle [3]; (**c**) scanning electron micrograph of *Escherichia coli* bacilli [4]

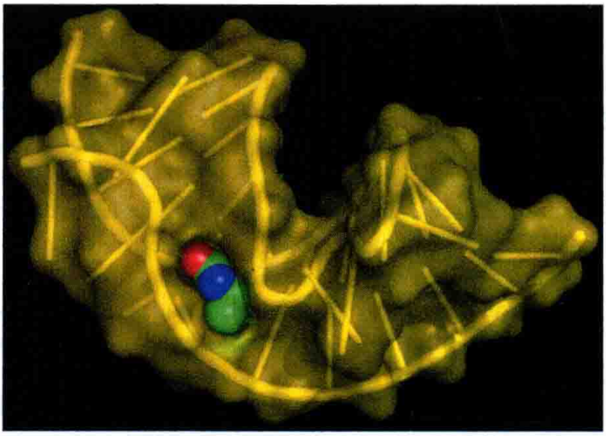

Fig. 1.2 Aptamer biotin [6]

from 1 μm to 10 nm, the number of particles per mass unit increases 10^6 times [5]. If the surface is functionalized with active groups, the reactivity per particle increases when the size decreases. Consequently, an increase in interactions with cells and tissue is expected and has been, indeed, observed.

Shape is another determinant of behavior at the nanosize level. Rutile, a crystalline form of titanium dioxide, is less reactive than anatase, another crystalline form of the same mineral while RNA aptamers (Fig. 1.2, [6]) have different binding affinities for one ligand, depending on their 3-D conformation [7]. Adding to these characteristics the fact that nanoparticles contain a larger number of particles per unit of mass and that they present quantum confinement effects,[1] they behave like materials with different properties from those in the bulk state. Examples thereof may be: melting points [8], solubilities [5], optical [9] and magnetic [10] properties.

Due to their properties nanoparticulate materials are valuable for treating skin conditions. Their selectivity for neoplastic cells, for instance, enables them to deliver drugs preferentially to tumors, displaying enhanced translocation and targeting effect compared to traditional medications. This makes them more effective and

[1]Observed for particles with sizes/diameters too small compared to the wavelength of the electron.

less likely to target healthy cells. Other benefits of using nanosized materials are: increased bioavailability of otherwise poorly soluble medicines, tunable properties, and possibility to use them in combination therapies [11]. Increased solubility translates into decreased doses, hence fewer/reduced side effects. The pharmacokinetic profiles of nanomaterials are different from those of the bulk materials, immunogenicity is reduced, while bioavailability is increased. The fact that their properties can be tailored to a certain application allows for combination therapies (delivery of multiple actives by multifunctional nanoparticles) and controlled release. At the present, due to advances in engineering, it is possible to combine the advantages of reduced size with imaging properties (which allow monitoring) and joint delivery (in conjunction with heat, light, sound) and thereby increase the beneficial effects of medicines delivered at the nanosize.

Due to their large surface and high surface energy nanomaterials have strong interactions with their environment which modulate their behavior (matrix effect). The fact that their size and chemical properties can be tailored allows scientists to estimate quantitatively the relationship between the resulting nanostructure and its activity. As a result, the interactions of nanoparticles with cells, subcellular units, and different macromolecules can be predicted. This is important especially when, trying to emulate nature, biomolecules are considered for synthetic routes leading to bionanomaterials. In the same direction, to emulate nature, bionanoparticles were used recently to create biomimetic nanoenvironments (similar to the extracellular matrix, ECM) for skin regeneration [12].

In skin care bionanomaterials can have different roles: active principles (protection, antimicrobial, moisturizing), nanocarriers (vehicles), ingredients in formulations (e.g. to modify rheological or optical properties). Vitamins, antioxidants, UV filters, anti-acne or anti-wrinkle agents are delivered to the skin in nanosized form. After reaching the targeted skin layer more efficiently than the bulk form of the same component, the nanoparticulate materials are processed and the active components work through the same pathways as in the bulk form. Their benefits for skin care are enhanced permeability, increased stability, controlled delivery profiles, improved efficacy, and, in hybrid materials, possible synergistic effects.

As a consequence of the increased solubility and deeper penetration of nanomaterials, the problem of their potential toxicity has to be seriously considered and evaluated. Skin is the first contact they make when used as medicines or in skin care, making their risk a very real one. Dermatitis, irritation, allergic reactions or tissue necrosis are possible effects. Also, due to their high surface to volume ratio, which is considered one of their main advantages (since it affords many surface active groups), the availability of active surface groups to interact with tissues and cells increases. Since toxicity is proportional to uptake, when nanoparticles accumulate in cells they may become toxic and trigger undesirable reactions. An example thereof is the case of species generating reactive oxygen species (ROS) which may damage DNA and other biomolecules. Some cells, like keratinocytes, can phagocytize small molecules but none can do the same to nanosized species. It is not always easy to assess the toxicity of nanoparticles due to the limitations of detection methods in vitro, in vivo, or at the cell level.