Isotopes in Nanoparticles

Fundamentals and Applications

edited by
Jordi Llop Roig
Vanessa Gómez-Vallejo
Peter Neil Gibson

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PAN STANFORD PUBLISHING

CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

Version Date: 20160308

International Standard Book Number-13: 978-981-4669-09-2 (eBook - PDF)

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and the CRC Press Web site at
http://www.crcpress.com

This book is dedicated to Prof. Manuel Martín Lomas, founding director of CIC biomaGUNE. Dr. Llop and Dr. Gómez-Vallejo are grateful for his mentoring and guidance.

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Contents

Preface

Recent developments in nanoscience have given rise to concerns about the possible negative impact of nanomaterials (NMs) on human health and the environment. On the other hand, the application of nanomaterials in the medical field as drug delivery vehicles, contrast agents, or scaffolds for tissue engineering has grown in parallel with industrial use. NMs are extremely difficult to detect and quantify once distributed in a biological system, and one approach to overcome this problem is to label NMs with (radio)isotopes, enabling ultra-sensitive detection using different techniques.

This unique book is the result of several years of work devoted to labeling nanomaterials for nanosafety and nanomedicine studies. The aim is to share the considerable cumulative experience of the authors by describing the state-of-the-art and future perspectives on the labeling of NMs for toxicological, imaging, and safety studies.

The book is presented in three main parts. The first part (Chapters 1–7) provides a general background to the topic, including synthesis and properties of the most commonly used NMs (Chapters 1–5), a general introduction to radioactivity and the reasons why radiolabeling is required (Chapter 6) and a description of the main imaging techniques that can be used to study radiolabeled NMs *in vivo* (Chapter 7). The second part of the book (Chapters 8–15) covers the different strategies reported so far for the preparation of radiolabeled NMs using positron and gamma emitters (Chapters 8–14) and the radiolabeling of NMs for therapeutic purposes (Chapter 15). The third part of the book contains three more chapters. Chapter 16 discusses the radiochemical integrity of the radiolabeled NMs, Chapter 17 covers the labeling of NMs using stable isotopes, and Chapter 18 discusses some operational health and safety issues related to the preparation and use of radiolabeled NMs.

The book, which aims to be a comprehensive resource for both the specialist and the non-specialist reader, covers a hot an emerging topic and is intended to become a point of reference for all those working in the field of nanotechnology.

Finally, special acknowledgements go to all authors who contributed to this book. The editors gratefully acknowledge editorial assistance from Nextgenediting (http://www.nextgenediting.com) and the projects MAT2013-48169-R (Spanish Ministry of Economy and Competitiveness) and FP7-NMP-2010-LARGE-4-263307 (European Commission) for financial support.

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Chapter 1

Introduction

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Recent developments and technical advances in nanotechnology and nanosciences have given rise to concerns about the possible negative impact of nanomaterials (NMs) on human health and the environment. The increased use of NMs in everyday products and a number of industrial processes exacerbate this worry. Large-scale production of NM-based products and devices is by no means a fantasy, and nanotechnology is already present in myriad household products including textiles, construction materials, electronics, surface coatings, fuels, and solar cells. The application of nanotechnology to the medical field, particularly for the treatment of complex diseases in which conventional medicines lack treatment or diagnostic efficacy, has grown in parallel with industrial use. NMs are rapidly emerging as promising drug delivery vehicles, contrast agents, or scaffolds for tissue engineering.

However, the toxicological evaluation of NMs due to either unintended or deliberate exposure is challenging. NMs are complex and variable, and a lack of long-term studies and technical

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ISBN 978-981-4669-08-5 (Hardcover), 978-981-4669-09-2 (eBook)
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limitations in tracking and quantifying NMs in organisms and cells hampers progress.

Studying the translocation and eventual fate of NMs is fundamental to comprehending possible toxicological mechanisms. The toxicological effects of NMs will depend on a number of different factors, such as the organs that the NMs reach and their dose. Fate and translocation studies are particularly important in medical applications of NMs, in which their capacity to target selected organs and subcellular domains needs to be established.

On exposure, NMs can translocate into the body by crossing the epithelial barriers provided by the skin, the gastrointestinal tract, the upper respiratory tract, or the lungs. For medical purposes, NMs may also be administered parenterally or intravenously. Once in the circulatory system, NMs redistribute and must cross an endothelial barrier to translocate into remote tissues or organs. The biokinetics, biodistribution, and tissue and cellular interactions of NMs are complex and are influenced both by the nature of the NMs and their surface functionalisation.

NMs eventually gain access to the inside of the cell. In order to understand the biochemical action(s) of NMs, mechanisms of cellular uptake, intracellular localisation, and intracellular processing need to be characterised.

The intracellular actions of NMs are influenced by their physical state including their aggregation, interaction with biomolecules in different cellular environments, formation of protein/lipid coronas, and dynamics. At the cellular level, NMs can be present as single entities or as aggregates, and the degree of aggregation can change during their residence time in the cell. The aggregation state of NMs affects their interaction with other intracellular molecules (such as proteins, nucleic acids, and lipids) and also their localisation and intracellular trafficking. Moreover, NM aggregation has an impact on their toxicological action and, in cases where the NMs are intended for medical use, the aggregation state and how this varies over time also influences clinical efficacy.

Many of the difficulties in tracing NMs in the cell and body stem from their complexity, the wide variety of different NMs available, and a lack of suitable generalisable techniques. NMs can be broadly classified as organic/polymeric, carbon, inorganic,

and hybrid. Organic/polymeric NMs are most frequently used in nanomedicine. Inorganic NMs, such as metal and metal oxide NMs, have highly variable surface to volume ratios and shapes (e.g., spherical, nanorods, nanowires, stars, triangles).

The complex nature of the interactions between NMs and biological molecules, cells, and organisms is strongly related to their surface properties and stability in biological fluids. Organic, self-assembling NMs can easily degrade into their component molecules *in vivo*, while many metal and metal oxides can dissolve to generate ions that negatively affect cellular homeostasis. Metal and metal oxide NMs can also have highly reactive surfaces that interfere with biological reactions by acting as catalysts and/or oxidising/reducing agents. Carbon-based NMs, unless oxidised, do not degrade easily and tend to form large aggregates and fibrillar structures.

To trace NMs at the intracellular and body level and to study their fate and interactions with biomolecules requires a combination of different experimental techniques, the exact details of which depend on the nature of the material and its surface characteristics. It also requires the proper design, engineering, and labelling of the NMs to be traced.

In vivo translocation studies of NMs require sophisticated, and often difficult, techniques. In most scenarios, the NMs are extremely difficult to detect and quantify once distributed in a biological system. One way to overcome this problem is to label NMs with radionuclides, which enables ultra-high sensitivity detection in biological systems using positron emission tomography (PET) or single-photon emission computerised tomography (SPECT), as routinely performed for pharmaceuticals. However, incorporation of radionuclides into NMs is far from trivial and usually requires laborious procedures. To date, different strategies have been developed to incorporate radionuclides into NMs that depend on their chemical composition. One common NM labelling strategy is to attach an appropriate radiolabelled tag to the surface of the NM. Other strategies are based on the incorporation of the radioactive isotope into the NM core without significantly changing its surface properties.

This unique book is the result of several years of work devoted to radiolabelling nanomaterials for nanosafety and nanomedicine

studies in a number of European projects. The aim is to share the considerable cumulative experience of the authors by presenting state-of-the-art and future perspectives on the labelling of NMs for toxicological, imaging, and safety studies.

The book can be considered in three main parts. The first (Chapters 1–7) provides the reader with a general background to the topic. Chapters 1–5 cover the synthesis and properties of the most commonly used NMs: metal and metal oxide nanoparticles, carbon-based NMs, and organic nanoparticles. This general description of NMs provides the reader with the basic knowledge necessary to understand the labelling strategies available and the complexities that can be expected when approaching the problem. A large collection of references is provided to facilitate further reading. Chapter 6 provides a general introduction to radioactivity and the reasons why radiolabelling is required, along with some key parameters that must be taken into consideration when selecting the most appropriate isotopes. Chapter 7 provides a description of the main imaging techniques that can be used to investigate radiolabelled NMs *in vivo*.

The second part of the book covers the different strategies reported so far for the preparation of radiolabelled NMs: Chapter 8 details the radiolabelling of NMs with radiometals; Chapter 9 provides a description of the labelling alternatives when using radiohalogens and the short-lived positron emitters ^{13}N and ^{11}C; Chapter 10 covers the different labelling strategies described to date for the preparation of radiolabelled liposomes; Chapters 11–13 cover the preparation of labelled NMs by direct activation (including ion beam activation, neutron activation, and recoil labelling); and Chapter 14 introduces the main calculation tools that can be applied to isotope production by beam activation. Finally, Chapter 15 covers the preparation of radiolabelled NPs for therapeutic purposes.

The third part of the book contains three more chapters. Chapter 16 discusses one of the main issues arising when using radiolabelled NPs for *in vivo* investigations: the radiochemical integrity of the labelled species. Chapter 17 covers the labelling of NMs using stable isotopes while Chapter 18 discusses some operational health and safety issues related to the preparation and use of radiolabelled NMs.

This book aims to be a comprehensive resource for both the specialist and non-specialist reader. The importance of the topic in the context of the safety evaluation of NMs and their assessment in biomedical applications makes this book a point of reference for all those working in the field of nanotechnology, and especially researchers or graduate students developing NPs for potential industrial applications or use in the biomedical arena.

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Chapter 2

Inorganic Nanoparticles

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This chapter is intended as an introductory overview of the vast subject of inorganic nanoparticles (INPs), drawing focus on some of the more common synthesis techniques, such as the wet chemistry methods, and on some of the characteristics of inorganic nanoparticles and their applications. A broad brushstroke approach to the subject matter was chosen in the hope of providing researchers in the radiolabeling and tracer fields with a guide to current trends in the synthesis of INPs over the broad landscape and backdrop of nanoscience and nanotechnology. We hope that the material and references presented herein will assist the reader in selecting possible INPs of potential interest and aid in suggesting potentially new opportunities for research and applications in the field of radiolabeled nanoparticles. As many reviews, books,

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and articles as possible were consulted for the preparation of this chapter.

2.1 Introduction

The physics and chemistry of materials at sizes approaching those of atomic dimensions, i.e., of nanostructures and nanoparticles (NPs), are spawning new research strategies and paradigms in physics, chemistry, biology, materials science, and engineering. The unusual nature of such materials was noted in antiquity. Witness, for example, the glazes for early dynasty Chinese porcelain [1] and the unusual optical properties of the Roman Lycurgus cup [2]. During the 70s and 80s of the past century, studies in physics and chemistry started to focus attention on matter, then called ultra-fine particles (or inhomogeneous media when dispersed in a matrix), in the range of ~1 to 100 nm that displayed unusual and often unexpected electrical, optical and magnetic properties [3–8]. During the past two decades, inter- and multidisciplinary research has been broadening the scope of that attention to computation, systems, processes, manipulation, sensing, control, and analytical capabilities at the nanoscale [9–12]. These advances are presently fuelling further initiatives and growth in the rapidly growing disciplines of nanoscience and nanotechnology as the convergence of knowledge continues [13, 14]. Combined, research from these disciplines continues to impact discovery, development and change in societally important technology sectors such as electronics and photonics [15–17], telecommunications [18, 19], medicine [20–29], energy [30–32], catalysis [33], manufacturing [34], advanced materials, such as metal-NP plasmonics [35] and self-organizing nanoscale systems [36–38], and the environment [39–42]. Clearly, the nanoscale will provide numerous opportunities and challenges for innovative research and applications in the study and use of radiolabeling and tracer techniques. A “crash course” in nanotechnology is available for those wishing to have an overview [14a], as is the EC co-funded “roadmap” report on nanoparticles 2005 [14b] and a recent overview of nanochemistry [14c].

At the nanoscale, the size of matter is dimensionally smaller than the characteristic length of a number of physical properties. As a consequence, the new and sometimes unexpected properties

of the nanoscale materials, as compared with those of the bulk, result from quantum confinement effects. Matter in the nanometer regime also has a high ratio of surface atoms to bulk atoms as the surface-area-to-volume ratio of the matter increases. Consequently, the electronic states of the surface and near-surface atoms become important as does any spill-out of electronic density, for example, outside of a NP. Nanoparticles and nanoscale materials of inorganic, bioceramic, carbon, and organic materials are the subjects of the introductory Chapters 2–5, respectively, and are the kinds of matter that will continue to contribute to the evolution of platforms, scaffolding, hierarchical and integrated structures during the next decades.

2.1.1 Nanomaterials and Nanoparticles

Nanomaterials generally have at least one dimension small enough to experience quantum confinement effects, usually in the size range of 1 to 100 nm. Thus, many materials of different compositions and shapes may be included, such as 3D clusters of atoms, compounds and materials, generally referred to as NPs, 2D sheets of clays, rings, dendrimers, graphenes, and graphene quantum discs, 1D materials, such as rods, tubes, wires, and filaments, and 0D "nanoparticles," such as knots and quantum dots (QDs). Nanoparticles generally contain about 10^2 to 10^7 atoms. In the literature, some of the 2D and 1D materials, when small enough, are referred to as NPs, especially when dispersed in a medium.

2.1.2 Chapter Scope

The aim of this chapter is to present a broad overview of INPs by introducing some of the synthesis techniques used to make them, some characteristics, and some representative applications. The discussion is meant to be illustrative rather than exhaustive and in this sense is selective and a bit arbitrary. Hence the reference list includes many books and review articles to which the reader is referred. No attempt is made to be comprehensive or all inclusive given the enormity of the literature and limited space of the chapter. The words synthesis, preparation, and methodology are used interchangeably.

2.1.3 Challenges

The challenges facing anyone wishing to prepare and use nanoparticles are many and depend foremost on the objective of the research or application and on the end use of the nanomaterial. Variables such as particle size, shape, distribution, composition, stoichiometry, phase, homogeneity, topology, and surface attributes, such as functionalization, dispersibility, the presence or absence of dispersing or capping agents, and, in some cases, biocompatibility, all deserve careful consideration as do issues of nanoparticle safety and environmental effects.

2.2 An Overview of Inorganic Nanoparticle Synthesis

Overall, there are three approaches or strategies to synthesizing nanoparticles. They can be synthesized by building the structures from the constituent atoms or molecules, i.e., from the bottom up, or, by breaking down large-scale structures to the nanoscale, i.e., from the top down. The third approach is a combination of the bottom-up and top-down strategies. Each approach can involve different synthesis techniques and even different strategies in execution of the techniques.

2.2.1 The Bottom-Up Approach: From Small to Large

Commonly, the bottom-up approach employs wet chemical or liquid phase techniques as discussed in Section 2.3. These techniques include precipitation, co-precipitation, hydrolysis, sol-gel, spray pyrolysis, templating, microwave-assist, and electrochemical, sonochemical, and solvothermal methods, and synthesis in microemulsions and supercritical fluids. Many of these techniques are referred to or illustrated in this chapter (see Sections 2.3 to 2.5). A recent overview of wet production methods was presented by Bensebaa [43a].

With a view toward biotechnology applications, Kharissova et al. recently reviewed “green” synthesis techniques for making NPs using natural products such as polyphenols in plant extracts as chelating or reducing agents in a one-step process without the direct addition of surfactants or capping agents [43b].

Besides the liquid-phase techniques used in the bottom-up approach, high-purity nanoparticles can be synthesized using gas-phase techniques, which are convenient for continuous processing. Kruis et al. review and evaluate many of the gas-phase techniques such as homogeneous gas phase nucleation, laser, flame, and plasma reactors, sputtering, and aerosols [44]. Surface growth under vacuum conditions using such techniques as chemical vapor deposition, molecular beam epitaxy, electron beam plasma, magnetron sputtering, and laser deposition may be employed to produce nanoparticles in film form and in different matrices. Gas phase and vacuum techniques per se are not discussed further.

2.2.2 The Top-Down Approach: From Large to Small

Breakdown or top-down strategies can involve mechanical processes such as dry and wet grinding, ball milling, mechanical alloying, sonication, and severe plastic deformation. In the early 60s, NASA first prepared highly stable magnetic colloids, now known as ferrofluids, by grinding mixtures of natural magnetite, oleic acid and a hydrocarbon for periods of up to nine months [45]. Today, bottom-up approaches can provide ferrofluids within minutes to hours. Breakdown can also be achieved by laser ablation, especially for noble metal NPs in water and organic solvents where surfactant-stabilizing molecules are not needed [46]. Redel et al. reported a fast, green synthesis of metal oxide NPs using a more traditional approach of metal powder reduction by chemical means. A controlled oxidative dissolution process of micrometer size bare metal powders using aqueous 30% hydrogen peroxide and acetic acid produced high-purity aqueous dispersions of 3–8 nm metal oxide NPs [47]. The method appears to be widely applicable to the synthesis of metal oxide NPs. Although simple and straightforward, these reactions are very exothermic and must be carried out with extreme care and with the use of instant ice-bath cooling and other safety considerations.

In the top-down approach, mechanical alloying is also a viable technique, for example, in preparing mixed nanoscale chalcogenides, and can be used to prepare non-equilibrium phases of nanostructures [48]. Ferrando et al. reviewed metal alloys form theory to applications of alloy clusters and NPs [49]. Severe plastic deformation (SPD) has been employed in recent years for the

production of nanocrystalline particles. Data for several different SPD methods were evaluated to determine the refining efficiency and capabilities of the top-down synthesis methods [50].

2.2.3 Combined Approaches

Cryochemical synthesis techniques illustrate the combination of a top-down and bottom-up strategy where the high temperature vaporization of bulk elements or compounds is followed by condensation of the vapor in cold matrices of inert gases or selected molecular reactants to form NPs consisting of atom clusters [51]. As an example of a process that involves a bottom-up and top-down strategy, Ziolo et al. synthesized magnetic NPs in a polymer matrix, which was used to control the NP size, shape, and distribution of the NPs in the matrix [7]. The polymer nanocomposites were then milled for a few hours in water or alcohols to produce aqueous ferrofluids with shelf lives >30 years [8a–f]. Although no surfactant or stabilizing agents were used in the process, the long-term stability of the aqueous ferrofluids resulted from the polyelectrolytic nature of the oligomers that resulted from the breakdown of the polymer matrix during ball milling. Some discussion of the advantages and disadvantages of bottom-up and top-down methods of syntheses are discussed by Sergeev and Klabunde [52].

2.3 Synthesis of Some Specific NP Materials

2.3.1 Metal Oxide NPs

In a general overview of traditional and emerging synthesis approaches to nanostructured metal oxides, Corr discusses a broad range of synthesis techniques covering many different metal oxides [53]. The techniques include decomposition of precursors, chemical vapor methods, template synthesis, co-precipitation, and microwave-assist to name but a few. In a follow-up article, Corr discusses the characterization of NPs to probe more extensively their structure property relationships and of NP hybrids for synergistic relationships and applications [54]. It is important to note that in some cases, as pointed out by Corr, carefully constructed

hybrid nanostructures can promote a synergetic relationship between the composite constituents.

In the case of metal oxides, such as those, for example, of Al, Ti, Fe, Zn, Zr, Sn, alkaline earths, Ce, etc., that are prepared in aqueous solutions by hydrolysis and precipitation, the cations involved in the synthesis often undergo complex and extensive hydrolysis to form a wide variety of hydrolysis products. Baes and Mesmer provide a useful reference for the identity and stability of the many hydrolysis products [55].

2.3.1.1 Zinc oxide NPs

Zinc oxide NPs have received much attention in the literature because of the diversity of their applications, including biological applications, and have been prepared by a variety of techniques [56–75]. Zinc oxide NPs with tunable emission colors and good water stability were synthesized through an ethanol-based precipitation method. The emission colors could be tuned by adjusting the pH of the precipitating solution, Fig 2.1. The ZnO NPs were then encapsulated with silica to form ZnO@silica core–shell NPs, sometimes referred to as nanostructures, as in Chapter 3, to improve the water stability of the ZnO nanoparticles while retaining the fluorescence of the NPs in the core–shell form. The core–shell NPs exhibited low cytotoxicity and were promising in cell-labeling applications [56].

A problem of zinc oxide particles for fluorescent labeling for cellular imaging is their low stability in water. Zhang et al. synthesized ZnO@silica NPs modified with surface hydrophilic amino groups through a three-step silanization process to produce ZnO NPs that are stable in water, phosphate buffer saline, and Roswell Park Memorial Institute (RPMI) cell culture medium 1640. The aqueous solutions showed high quantum yields with blue, green, and yellow emissions and were stable for cell imaging experiments [71]. Zhao et al. reported two facile synthesis routes for the preparation of water-stable ZnO NPs with blue and yellow fluorescence. In one preparation, zinc nitrate and oleic acid were dissolved in triethylene glycol. The mixture was heated to 240°C with stirring and concomitant ester elimination. In the second method, zinc acetate was hydrolyzed in ethanol with KOH at room temperature. The resulting NPs were then stabilized with

3-aminopropyltriethoxysilane, which improved their water stability [69]. High stability of ZnO nanocrystals in the aqueous phase was also reported by Zhang et al. [72].

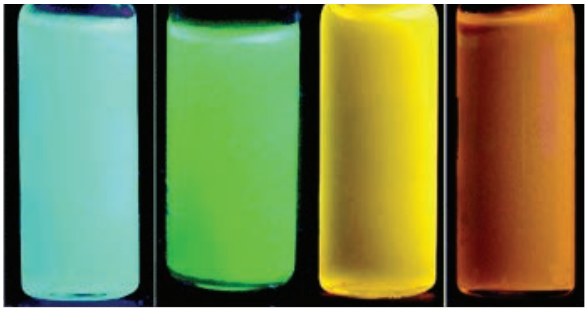

Figure 2.1 Fluorescence emission of ZnO nanoparticles in ethanol under 365 nm excitation at, from left to right, pH 12, 10, 8, and 6. Reprinted with permission from [56]. Copyright © 2010, American Chemical Society.

ZnO NPs can also be synthesized by the microwave decomposition of zinc acetate using an ionic liquid, 1-butyl-3-methylimidazolium bis(trifluoromethyl-sulfonyl) imide, as a green solvent, as shown by Jalal et al. [57]. The resulting ZnO NPs, were then dispersed in glycerol using ammonium citrate to form a ZnO nanofluid that showed antibacterial activity toward *E. coli*.

2.3.1.2 Titanium dioxide NPs

Several methods have been used for the preparation of nanocrystalline titanium dioxide, TiO_2, which, among other uses, is an important photocatalyst and pigment with many environmental applications. These methods include the sol-gel method discussed in Chapter 3, microemulsion techniques [76, 77] and chemical precipitation by hydrolysis [78]. For the room temperature synthesis of titanium dioxide in the rutile and anomalous pseudobrookite phases, using a microemulsion technique, see Keswani et al. and references therein [76]. Abbas et al. reported the radiolabeling of TiO_2 NPs for radiotracer studies [79]. TiO_2 NPs were prepared in $[^{18}O]H_2O$ by precipitation under basic conditions using $NH_{3(g)}$ to prevent the incorporation of ^{16}O, for use in ^{18}F labeled TiO_2 NPs for bio distribution studies [80].

2.3.1.3 Aluminum oxide NPs

Different phases of aluminum oxide nanoparticles can be synthesized, for example, by sol-gel (see Chapter 3), hydrothermal, sputtering, and laser ablation techniques. Aluminum oxide NPs, for example, were synthesized in water using the latter technique with Al powder as a target and a long-pulsed Nd:YAG laser [81]. Pang et al. synthesized Al_2O_3 NPs using oil-in-water microemulsion techniques to obtain as-prepared NPs about 8 nm in size, which then yielded oxide NPs about 15 nm in size after calcination [82].

A facile and direct precipitation method using aluminum chloride and ammonia gas bubbled in water was used by Pérez-Campana and Llop et al. to prepare ^{18}O-enriched Al_2O_3 NPs of various sizes that were subsequently converted to ^{18}F-labeled positron emitting NPs by proton irradiation for *in vivo* bio distribution studies [83, 84].

2.3.1.4 Other metal oxide NPs

Iron oxides NPs are discussed in Section 2.3.4. The sol-gel synthesis of NP metal oxides, such as those of Al, Ti, Si, and Ni, and of mixed metal oxides, such as barium titanate and other complex metal oxides, are discussed in Chapter 3. A brief introduction to the sol-gel process can be found in Wright and Sommerdijk [85].

2.3.2 Noble Metal NPs

The noble metals, particularly those of gold and silver, continue to emerge as key materials in biological imaging, plasmonic sensing, medical therapeutics, and nuclear medicine and appear to offer potential for new opportunities in radiolabeling and tracing research and applications. Aside from biological and medical applications, it is interesting to note that a single 1.63 mm diameter, Epoxy/^{198}Au tracer-particle bead was successfully tested for its applicability to indicate shed fouling in the stripper section of a fluid-coker [86].

Chen et al. provide a comprehensive discussion of the green synthesis of noble (Au, Ag, Pt, Pd, Ru, Rh) and other metal (Cu, Ni, Co, Mn, Zn, Fe) NPs with microwave irradiation and also consider the role of biocompatible and polymer surfactants for each of the

metals [87]. A low-cost, versatile, and reproducible large-scale synthesis of organoamine-protected Au and Ag NPs in the 6–21 and 8–32 nm size range, respectively, was reported by Hiramatsu and Osterloh [88].

Michael Faraday first prepared NP gold sols by reducing $AuCl_4^-$ in a two-phase system with phosphorous in CS_2 [89]. The preparation of Au NPs in water is easily done using chlorauric acid, $HAuCl_4$, or its salts, and reducing them, for example, with salts of sodium borohydride, metabisulfite, or citrate in the presence of a surfactant or capping agent such as the citrate ion. Frens used this approach with sodium citrate to produce nearly monodisperse gold NPs of different particle sizes of < 200 nm. The approach is limited, however, in that the gold cannot be directly capped with hydrophobic ligands or surfactants [90]. A different approach was used by Lu et al., who reported controlled growth of Au NPs with a narrow size distribution using Au(I) salts, such as AuBr and AuCl, and their relatively low stability in the presence of alkylamines [91]. Au NPs were prepared using AuCl and oleylamine heated in chloroform at 60°C without the need for a reducing agent.

Wilcoxon and colleagues introduced and pioneered a two-phase method for the preparation of specific sizes of metal NPs including Au using inverse micelles that allowed for capping by hydrophobic surfactants [92, 93]. Using a modification of this two phase method, Brust et al. prepared 1–3 nm thiol-capped Au NPs in water-toluene by reducing $AuCl_4^-$ with sodium borohydride in the presence of the alkanethiol [94].

As is the case for gold, silver NPs can also be prepared by reduction methods. Monodisperse samples of silver nanocubes, for example, were synthesized in large quantities by reducing silver nitrate with ethylene glycol in the presence of poly(vinypyrrolidone) [95]. Similarly, Guzman et al. reduced $AgNO_3$ with hydrazine hydrate to form small silver agglomerates in powder form for antibacterial activity studies. The Ag NPs themselves had diameters of 20–40 nm [96]. Reducing agents obtained from natural sources rich in antioxidants were used by Rodríguez-León et al. to form Ag NPs in the 2–40 nm diameter range. The NPs grow in a single-step method at room temperature with no additional energy input as shown in Fig. 2.2 [97a]. *In vivo* plant biosynthesis of metal NPs has also been studied [97b].

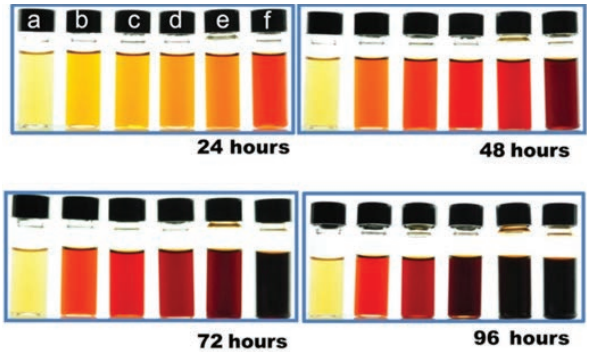

Figure 2.2 Change in color indicating growth of Ag NPs at different reaction times using *R. hymenosepalus* extract; vials (a) through (f) represent increasing concentrations of Ag NPs. Reprinted with permission from [97a]. Copyright © 2013, Springer.

2.3.3 Colloidal Semiconductor Quantum Dots

In one of their most commonly known forms, quantum dots (QDs) are nanocrystals of semiconductor materials that exhibit a sharp density of states due to quantum confinement. Examples of QD nanocrystals include such materials as the noble metals, particularly those of Au, Ag, and Pt, and binary compounds, such as CdS, CdTe, PbS, ZnSe, InAs, and InP, among many other known QD materials. The particles generally are a few nanometers in size, generally <5 nm, but some <10 nm, and are composed of a few hundreds to a few thousands of atoms. In very small size, where the particle radii are smaller than their exciton Bohr radius, QDs have electrical and optical properties that are highly tunable [98].

QDs were discovered in glass in the early 80s by Ekimov with an interpretation as to their role in colored glasses [99]. At about the same time, Brus and associates discovered QDs in colloidal liquids and attributed their color to quantum effects [5, 6].

An overview of the various synthesis techniques for colloidal QDs, is presented by Kim et al. [100]. A primer on QDs, including syntheses, was reported by Murphy and Coffer [101]. Drummen has reported on the synthesis of QDs and applications in biomedicine and the life sciences [102]. Bawendi et al. presented a review on the quantum mechanics of QDs [98].

Weiss presented a discussion on the use of organic molecules in the preparation of colloidal quantum dots as tools to control growth, surface structure and redox activity of these materials [103]. Wang et al. provided a direct synthesis of water soluble CdTe: Zn^{2+} QDs that potentially may be applied to the synthesis of other QD chalcogenides [104].

For recent articles on the synthesis, properties, and applications of colloidal QDs, the reader is referred to the Web site of the International Conference, "*30 Years of Colloidal Quantum Dots,*" held in Paris, France, May, 2014 [105].

2.3.4 Magnetic Nanoparticles

Magnetic nanoparticles constitute an important class of nanostructured materials that can be manipulated with hand-held magnets or by otherwise applied magnetic fields. Some of the more common magnetic NPs consist of metals such as Fe, Co, Ni, and Gd, their oxides, mixed metal oxides, and alloys. The breadth of their potential in applications at the nano and higher scales is enormous and continually growing with research impacting areas such as multifunctionality, device sophistication and hierarchical magnetic nanostructures.

Applications of magnetic NPs includes areas such as catalysis, biomedicine, drug delivery [21, 106, 107], therapeutics, sensors, MRI contrast agents [107–111], particle imaging, data storage, and environmental remediation, including water filtration [39, 112].

The simpler magnetic NPs are easily synthesized by wet chemical methods [113] and may be used to form, for example, additional nanostructured materials, such as magnetic polymer nanocomposites or the core or shell of bi-functional core–shell nanoparticles.

Some of the most studied magnetic nanoparticles are magnetite, Fe_3O_4, and maghemite, γ-Fe_2O_3, which display relatively high saturation magnetization moments [114]. These and other oxides of iron have been prepared by a host of different and reliable methods [113, 115]. Magnetite can be prepared by mixing aqueous solutions of stoichiometric amounts of Fe(II) and Fe(III) salts (such as chlorides, nitrates or sulfates) and simply controlling the pH, temperature and stirring rate. This co-precipitation

method was used early on by Masart [116], for example, to prepare ionically stabilized aqueous ferrofluids. By adjusting the molar ratio of ferrous to ferric ions in aqueous solutions, Osaka et al. synthesized Fe_3O_4 NPs in controlled sizes from 10 to 40 nm potentially suitable for drug delivery systems [106]. Iron oxide particles with mean diameters ranging from 7 to 20 nm were synthesized by Carvalho et al. [117]. A novel and simple non-aqueous route for the preparation of nanocrystalline magnetite was reported by Pinna et al., using the decomposition of ferric acetylacetonate in benzyl alcohol to make particles from 12 to 25 nm in size [118].

The saturation magnetization of magnetic nanoparticles is typically lower than that for the same material in the bulk state. The lower values generally result from magnetically disordered surface states of the NPs with their high surface-area-to-volume ratios and by the presence of attached surface ligands or capping agents [119].

The effect of surface modification with amine and carboxylate groups on the magnetic properties of iron oxide colloids for applications in the biomedical field was reported by Yuan et al. [109]. It was also shown that the composition and magnetic properties of iron oxide NPs can be influenced by the synthesis method and size of the magnetic nanoparticles [117]. The magnetic relaxation of polymer-coated NPs in aqueous solution was reported by Keshavarz et al. [120]. Cao et al. reported the preparation and radiolabeling of surface-modified magnetic nanoparticles with rhenium-188 for magnetic targeted radiotherapy [121]. Glaus reported on the development and analysis of radiolabeled magnetic NPs for positron emission tomography (PET) and magnetic resonance imaging (MRI) [108].

In nanocrystalline form, magnetic NPs generally exhibit superparamagnetism (SPM) above a critical temperature called the blocking temperature. In a practical sense, an ensemble of single domain SPM nanoparticles can be attracted to a magnet where the particles, each with their own magnetic moment, align in a magnetic field. The ensemble, however, possesses no permanent magnetism or magnetic memory above the blocking temperature due to thermal effects that keep the particles randomly oriented [114, 119]. SPM iron oxide NPs, or SPIONs, are emerging

as potentially important magnetic nanoplatforms for drug delivery. Wahajuddin and Arora present a practical review of the preparation of SPIONs, their utility as drug delivery vehicles and concerns that need to be addressed before they can be moved from bench top to bedside [21]. A recent book by Stroeve, Milani, and Arbab covers the synthesis, surface engineering, cytotoxicity, and biomedical applications of SPIONs [122].

A facile, one-pot hydrothermal synthesis and surface functionalization of branched polyethyleneimine-coated Fe_3O_4 nanoparticles for biomedical applications was reported by Cai et al. [123]. Suspensions of magnetic nanoparticles with glycopeptide coatings affording high sugar unit density were obtained via ring-opening polymerization of *N*-carboxyanhydride, followed by step-glycosylation [124]. Chitosan-coated iron oxide nanoparticles are receiving increased attention for biomedical applications. The chitosan-coated magnetic NPs prepared by Unsoy et al. were found to be non-cytotoxic on cancer cell lines SiHa and HeLa [107].

2.4 Non-Aqueous, Microwave-Assist and Other Synthesis Routes

Most of the wet chemistry methods for the synthesis of INPs use water as a reaction medium. Non-aqueous routes, however, are available that offer equally viable preparations of INPs. Additionally, microwave-assisted reactions are showing great promise for the preparation of INPs in both aqueous and non-aqueous media.

2.4.1 Nanoparticle Synthesis by Non-Aqueous Routes

As in the case of NP synthesis in aqueous routes, syntheses using non-aqueous routes offer ways to control and tailor particle size, shape, and surface attributes, and can be performed at ambient temperatures in common solvents such as alcohols, ketones, and amines, while other methods may require higher temperatures and the use of solvothermal methods up to 250°C.

The reader is referred to the numerous works of Niederberger and associates that report on the synthesis of NPs by non-aqueous

routes, some of which are referenced herein [118, 125–142]. These works include reviews on the synthesis, assembly and formation mechanisms of metal oxide nanocrystals [129, 140], and on non-aqueous sol-gel routes to metal oxide NPs [127]. Materials covered in these works include perovskites, such a $BaTiO_3$, $SrTiO_3$, and mixed titanates [128], zirconium and titanium dioxides [131, 133], semiconducting metal oxides for gas sensing [132], and the oxides of indium and zinc [137a,b], manganese [137c] and molybdenum [142]. For the preparation of multimetal and doped metal oxide nanocrystals using a benzyl alcohol route, see Pinna et al. and references therein [143]. For an overview of nanoparticles in organic solvents, including synthesis, characterization, reaction mechanisms, assembly, properties, and applications, see Niederberger and Pinna [141]. Recent trends in the synthesis of metal oxide nanoparticles through reverse microemulsions in hydrocarbon media were recently reviewed by Khadzhiev et al. [144]. Surfactant-free non-aqueous synthesis of metal oxide NPs [130a,b] and nanorods and wires [130c] has also been demonstrated.

2.4.2 Nanoparticle Synthesis by Microwave-Assisted Routes

Research in microwave-assisted synthesis of inorganic NPs is progressing rapidly with the area offering many new avenues for exploration. The technique can involve wet and dry syntheses, the bottom-up and top-down approaches, and assists by sonication [145], not only in the breakdown from the macro scale, but also in the breakdown of nanoscale materials to form smaller nanoscale materials. The overall subject of microwave-assisted synthesis of INPs is discussed in a recent book by Horikoshi and Serpone [146].

New opportunities in microwave-assisted synthesis of INPs via liquid phase routes are discussed by Bilecka and Niederberger [136] and more recently by Niederberger for non-aqueous sol-gel chemistry, the polyol, and benzyl alcohol routes [147a], and for synthesis in ionic liquids [147a,b]. According to Niederberger, microwave chemistry offers unique opportunities that no other synthesis technique can provide [147a]. An overview of nanomaterials prepared by microwave irradiation is given by Baghbanzadeh et al. [148].

Microwave (MW) irradiation can provide rapid decomposition of metal precursors and be extended to produce NPs of various compositions, sizes, and shapes. Herring et al. offered a broad overview of metal oxide NPs synthesized by MW irradiation, including ZnO, TiO_2, CeO_2, transition metal oxides, and metal ferrite nanostructures [149]. Discussions also appear for MW-assisted synthesis of iron oxide NPs [150], metal NPs [87], particularly those of Au, Ag, Pt, and Pd, the solution synthesis of nanomaterials, [151] and different ways of NP synthesis through MW heating [152].

2.4.3 Microemulsion and Micellar Techniques

Microemulsion (ME) and micellar methods continue to provide valuable techniques for the synthesis of inorganic NPs. Studies using these techniques were presented earlier in this chapter [76, 77, 82, 92a,b, 144]. Eastoe et al. reviewed recent advances in NP synthesis with reversed micelles [153]. Microemulsion properties and applications [154], the formation and growth control in the synthesis of NPs in emulsions [155] and microemulsion dynamics and reactions in microemulsions [156] have also appeared. Inorganic micelles as efficient and recyclable micellar catalysts were recently reported by Zhang et al. [157].

2.5 The Role of NP Capping Agents and Functionalization

Various materials, whether in molecular, ionic, oligomeric, or polymeric form, are frequently used in nanoparticle syntheses to control critical aspects of the nanoparticles, such as their composition, phase, size, size distribution, shape, dispersibility, stability, homogeneity, and surface and near-surface chemical and physical properties. When used as such, these materials are known as capping or stabilizing agents, surfactants, ligands, chelates, shells and so on, depending on the literature source. Without the presence of such agents during synthesis, NPs can continue to grow in size and lose their nanoscale size-dependent properties. Although capping agents offer opportunities related to NPs, they

also introduce additional complexities to the study and application of NPs.

Typical capping materials can contain chemical functional groups, such as those found in organic acids, amines, alcohols, and thiols, and various ions, such as the citrate ion, $C_3H_5O(COO)_3^{3-}$. Bonding between the NP and capping agent can involve covalent or coordinate bonds, hydrogen or other secondary bonding, and van der Waals interactions. In a more general sense, the capping agent can be described as being chemisorbed or physisorbed on the NP. The stabilizing forces keeping the NPs from agglomerating in liquid media can be electrostatic and steric in nature. Weiss discussed the varied roles of organic molecules as tools to control the growth, surface structure, and redox activity of colloidal semiconductor quantum dots [103]. Particularly useful approaches to functionalizing NPs with biological molecules are reviewed by Sapsford et al. [158]. This broad review covers nanoparticle bioconjugation chemistries for noble metals, semiconducting quantum dots, metal oxides, transition and post-transition metal NPs, rare earth, alkaline earth, and zirconium, silicon, and germanium NPs. Capping agents and surrounding mediums are also important to consider for the fluorescence aspects of INPs. Philippot and Reiss discussed the synthesis of inorganic NPs for biological fluorescence imaging [159].

It is well known that the capping agents used to stabilize NPs and nanocrystals can dramatically affect their stability and reaction chemistry. However, the nature and associated subtleties of the ligand shell itself, as an integral part of the CNP, are just beginning to be examined in detail and a lot of work is needed in this area. The reader is referred to the particularly relevant theoretical and experimental study by Zherebetskyy et al., who clearly demonstrated the complexity of interactions that occur during the hydroxylation of the surface of PbS nanocrystals capped with oleic acid [160a]. Likewise, Valdez et al. presented a methodology to quantify the nature of the dodecylamine (DDA) capping shell of colloidal zinc oxide nanocrystals in a non-polar solvent and report three different binding regimes for DDA using NMR spectroscopy [160b]. The relative complexity of the capped nanoparticles (CNPs) is shown for the latter case in Fig. 2.3.

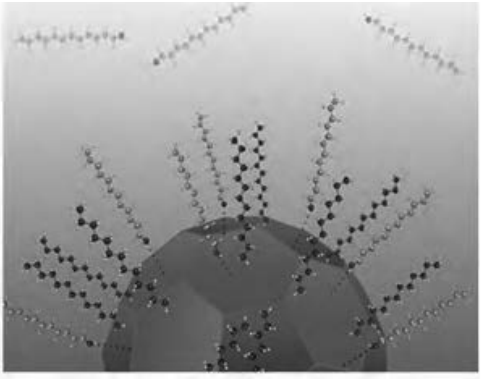

Figure 2.3 Particles of ZnO with associated capping agents. Adapted and reprinted with permission from [160b]. Copyright © 2014, American Chemical Society.

Clearly, the nature of the capping agent and that of the CNP itself is a crucial factor to consider in any studies of NPs and their applications. This is particularly evident, for example, in biological studies where the CNP can react with its medium, such as in the cases of cell culture media, living cells, and *in vivo* and *in vitro* tracing and labeling studies. CNP interactions are also important in the area of nanocatalysis. The removal of capping agents in the case of nanocatalysts and the utilization of capping agents in general for nanocatalysts was recently reviewed by Niu and Li [161]. In cases where no capping agent is used in the preparation of nanoparticles, such as in laser ablation, the medium itself can act as the stabilizing agent. The reader is referred to the many papers presented at the recent conference, ANGEL 2012, in Paris, France, on laser ablation and NP generation in liquids [46].

The geometry or morphology of the various capping or coating agents used on NPs can also influence the NPs' chemistry and performance. The coatings or capping agents, especially if oligomers or polymers, can vary and form, for example, brushes, close curl coatings, or open coatings. Pandey and associates gave a perspective view on polymer nanoparticle interactions and discuss how new developments in the field, through a concerted approach of theory, experiments and simulations, significantly expands our knowledge on the morphological behavior of such systems [162].

Regarding nanoparticles, their capping agents, and applications in general, we are in concert with what Nui and Li stated in their excellent article on nanocatalysts: "*While plenty of attention has been put on their inorganic cores that determine the intrinsic particle properties of nanoparticles, the influence of outside organic shells* (*e.g., capping agents*) *is relatively less examined*" [161]. The need is clear.

2.6 INP Applications and Opportunities

There now exists an enormous amount of literature on the application and uses of INPs in almost all societally relevant areas of technology. Concomitantly, the focus on nanoparticles in toxicology and the environment continues to grow. Following are a few specific areas that may be of potential interest to researchers in radiolabeling and tracing studies.

Corr discussed some important applications of metal oxide NPs in the areas of sensors, water purification, catalysis, environment, energy, devices, and at the nano-bio interface. The latter is a particularly important area of study for the application of radiolabeling and tracer techniques, since more quantification studies are needed to better understand the complexities of the nano-bio interface [54].

Several books are available that discuss growth and properties of metal oxides and their applications and also of ZnO structures and devices [163]. Recent progress has demonstrated that nanostructured metal chalcogenide (MC) materials, such as metal sulfides, selenides, and tellurides, are promising candidates for advanced energy conversion and storage (ECS) devices. In a recent review, Gao et al. discussed 15 different liquid phase methods for the synthesis of MCs and their modification by other functional nanomaterials, such as carbon-based materials, noble metals, metal oxides, or by the MCs themselves [164]. ECS applications of the MC/modified-MC nanomaterials are then systematically summarized based on the number of successful cases.

A recent review by Zielińska-Jurek, summarized recent advances in the preparation and environmental application of

bimetallic TiO_2-based photocatalysts using Au, Pt, Ag, and Cu to enhance the photocatalysis of the TiO_2 template [165].

2.6.1 INPs in Potential Medical, Therapeutic and Toxicology Applications

The use of nuclear medicine and radiochemistry procedures continues to undergo rapid expansion with the increased use of imaging technologies, such as PET, MRI, and single photon emission computed tomography (SPECT), and with the advances in contributions from the life sciences in molecular biology, genetics, and proteomics [166]. In a theme issue of *Advanced Drug Delivery Reviews*, eds. Mattoussi and Rotello presented a sampling of what INPs, such as luminescent QDs, magnetic, plasmonic, and upconversion NPs, can provide in medicine and biology, which includes potential scaffolds for diagnostic, therapeutic and imaging agents [24].

As indicated earlier, INPs present potential platforms for drug delivery and therapeutics. Naahidi et al. reviewed the biocompatibility of engineered NPs for drug delivery [25]. Gottstein et al. addressed issues involving the precise quantification of NP internalization in measuring the impact of the physical and chemical properties on the uptake of NPs into targeted cells or into cells responsible for rapid clearance [167]. They addressed the issue of quantification with a mathematical model that integrates data from high-throughput flow cytometry measurements with data from confocal microscopy, as a potentially useful tool in biomedical nanotechnology studies. The method was then applied to measure the impact of surface coatings of vesosomes on their internalization by cells of the reticuloendothelial system.

The role of quantum dots from synthesis to applications in biomedicine and the life sciences is discussed by Drummen et al. [102]. Interest in nanoparticles [20] and QDs [168] for multimodal applications continues to gain momentum because of their potential for accurate and precise assessment of biological signatures. Gibson et al. discussed the radiolabeling of engineered NPs for *in vitro* and *in vivo* tracing applications using cyclotron accelerators [169].

Schütz et al. reviewed NP chemotherapeutic (CP) systems that have been developed for human therapy, considering the

components of the NPs, the therapeutic agents associated with the NPs, and the clinical indications for which the NPs were developed. The NP-CP systems reviewed are those that have been published, approved, and marketed, and that are currently in clinical use [170]. A recent review on the interaction of INPs with the skin barrier was presented by Labouta and Schneider [171]. The review briefly highlighted current applications and behavior of INPs in relation to the skin as well as qualitative and quantitative analysis of INPs present in the skin.

Engineered magnetic NPs for remediation and water treatment was reviewed by Tang and Lo with a focus on the necessity of enhancing the understanding of how these NPs react with contaminants and interact with the surrounding environment during applications [39]. Horie and Fujita discussed the toxicology of metal oxide nanoparticles [172].

The future promise of marine bio-nanotechnology in nano-medicines, foodstuffs, pharmaceuticals, and the fabric industries offers potential areas for radiolabeling research and tracing involving INPs. This topic was recently reviewed by Asmathunisha and Kathiresan [173].

2.7 Summary, Conclusions, and Outlook

In the present chapter, we present an introduction to a broad spectrum of examples that hopefully illustrate the enormous diversity that abounds in the area of nanoparticle research, along with selected examples of the many ways of synthesizing such nanoparticles as a potential guide to our readers.

The synthesis strategies and techniques presented will continue to provide new materials, which, when applied to specific cases, will hopefully lead to better understanding and control of the NP challenges mentioned in Section 2.1.3. For NP radiolabeling and tracer studies, there is not one best synthesis method or approach to making NPs, but rather may depend primarily on the research objective or application and end use of the nanomaterial.

Chemical functionalization of NPs will remain a powerful strategy for controlling the potential energy landscape of these particles, particularly as it relates to the particle-medium interface. The utilization of capping agents needs to shift from qualitative

exploration to quantitative investigation, and a lot of work needs to be done on understanding and identifying the specific binding sites associated with nanoparticles.

The entire field of nanoparticle research is undergoing change on a daily basis and at an ever-increasing rate. There is no doubt that the change, growth and development will continue well into the foreseeable future. The possibilities of labeling inorganic nanoparticles appear ready for creative ideas, new strategies, and applications in the many fields presented in the chapter. As labeling techniques in radiochemistry broaden and cyclotron availability increases, through miniaturization and automation, new opportunities, challenges, and needs will emerge.

Acknowledgements

The authors thank Layza Arizmendi-Galaviz, José A. Rodríguez González, and Raquel Ledezma-Rodríguez for help in preparing the manuscript. RFZ acknowledges support from the Air Force Office of Scientific Research, grant FA9550-10-1-0489.

References

1. Tite MS, Freestone IC, Bimson M (1984) A technological study of Chinese porcelain of the Yuan dynasty, *Archaeometry,* **26**(2), 139–154.
2. Freestone I, Meeks N, Sax M, Higgitt C (2007) The Lycurgus Cup—A Roman nanotechnology, *Gold Bull*, **40**(4), 270–277.
3. Activities in the mid-1970s in the United States began to appear in corporate research laboratories such as the then AT&T Bell Labs (Brus L and associates), Xerox Webster Research Center (Ziolo RF and associates), Exxon (Abeles B, Cody G and associates), and Eastman Kodak. Interestingly, it wasn't until later in the 20th century that the origin of the optical gain in silver halide photography was discovered to be a nanocluster of silver atoms. For a short review, see Belloni J (2003) Photography: Enhancing sensitivity by silver-halide crystal doping, *Radiat Phys Chem*, **67**, 291–296.
4. (a) Ziolo R, Gunther W, O'Horo M, Kellerman R, Ganguly B (7–9 September 1977) *Preparation and Properties of Low Optical Density, Superparamagnetic, Small Particle Iron Oxide Composites*,

presented at AIP Conference on Electrical Transport and Optical Properties of Inhomogeneous Media, Ohio State University, Columbus, OH; (b) Ziolo R, Gunther W, O'Horo M, Kellerman R, Ganguly B (1978) *ACS Abtracts Papers*, **175**, 28.

5. Rossetti R, Hull R, Gibson JM, Brus LE (1985) Excited electronic states and optical spectra of ZnS and CdS crystallites in the ~15 to 50 Å size range: Evolution from molecular to bulk semiconducting properties, *J Chem Phys,* **82**, 552–559.
6. Brus L (1986) Electronic wave functions in semiconductor clusters: Experiment and theory, *J Phys Chem,* **90**, 2555–2560.
7. (a) Ziolo RF, Giannelis EP, Weinstein BA, O'Horo MP, Ganguly BN, Mehrotra V, Russell MW, Huffman DR (1992) Matrix-mediated synthesis of nanocrystalline γ-Fe_2O_3: A new optically transparent magnetic material, *Science*, **257**, 219–223; (b) Ziolo RF, Giannelis EP, Shull RD (1993) Matrix-mediated synthesis and properties of nanostructured materials, *Nanostruct Mater,* **3**, 85–92; (c) Giannelis EP, Mehrotra V, Vassiliou JK, Shull RD, MacMichael RD, Ziolo RF (1994) Magnetic and optical properties of γ-Fe_2O_3 nanocrystals, in *Nanophase Materials—Synthesis, Properties, Applications* (Hadjipanayis GC, Siegel R, eds), *NATO ASI Series E: Applied Sciences*, Kluwer Academic Publishers, Dordrecht, pp 617–624.
8. (a) Ziolo RF (1984) Developer composition containing superparamagnetic polymers, US Patent 4,474,866, October 2; (b) Ziolo RF (1994) Magnetic materials with single-domain and multidomain crystallites and a method of preparation, US Patent 5,358,659, October 25; (c) Ziolo RF (1994) Method of preparing a stable colloid of submicron particles, US Patent 5,362,417, November 8; (d) Ziolo RF (1996) Method of preparing a stable colloid of submicron particles, US Patent 5,578,245, November 26; (e) Ziolo RF, Kroll EC Pieczynski R (1997) High magnetization aqueous ferrofluids and processes for preparing and uses thereof, US Patent 5,667,716, September 16; (f) Ziolo RF (1997) Magnetic and non-magnetic particles and fluids, US Patent, 5,670,078, September 23; (g) Ziolo RF (1999) Particle size reduction process, US Patent 5, 927, 621, July 27.
9. Hadjipanayis GC, Siegel RW (eds) (1994) *Nanophase Materials: Synthesis–Properties–Applications,* Kluwer Academic Publishers, Dordrecht.
10. Siegel RW, Hu E, Roco MC (eds) (1999) *Nanostructure Science and Technology,* Kluwer Academic Publishers, Dordrecht.

11. Timp G (ed) (1999) *Nanotechnology,* Springer-Verlag, New York.
12. Wolf E (2006) *Nanophysics and Nanotechnology*, Wiley-VCH, Weinheim.
13. (a) Chen H, Roco MC, Son J, Jiang S, Larson CA, Gao Q (2013) Global nanotechnology development from 1991 to 2012: Patents, scientific publications, and effect of NSF funding, *J Nanopart Res*, **15**, 1951, 21 pp; (b) Roco MC, Bainbridge WS (2013) The new world of discovery, invention, and innovation: Convergence of knowledge, technology, and society, *J Nanopart Res*, **15**, 1946, 17 pp.
14. (a) Martin-Palma RJ, Lakhtakia A (2010) *Nanotechnology: A Crash Course,* SPIE Press, Washington; (b) Perez J, Bax L, Escolano C (2005) NRM Project, 6th Framework Programme, http://nanoparticles.org/pdf/PerezBaxEscolano.pdf (20/08/2014); (c) Sergeev GB, Klabunde KJ (eds) (2013) *Nanochemistry,* 2nd ed, Elsevier, Amsterdam.
15. Hanson GW (ed) (2008) *Fundamentals of Nanoelectronics*, Pearson/Prentice Hall, New Jersey.
16. Stroscio MA (2008) Materials for nanoelectronics, in *Introduction to nanoelectronics: Science, Nanotechnology, Engineering, and Applications* (Mitin VV, Kochelap VA, Stroscio MA, eds), Chapter 4, Cambridge University Press, UK, pp 65–108.
17. Ohtsu M (ed) (2006) Progress in Nano-Electro-Optics V: Nanophotonic Fabrications, Devices, Systems, and Their Theoretical Bases, Springer, Netherlands.
18. Minoli D (ed) (2005) Nanotechnology Applications to Telecommunications and Networking, Wiley-VCH, Weinheim.
19. Ermolov V, Heino M, Karkkainen A, Lehtiniemi R, Nefedov N, Pasanen P, Radivojevic Z, Rouvala M, Ryhanen T, Seppala E, Uusitalo MA (2007) Significance of nanotechnology for future wireless devices and communications, in *Personal, Indoor and Mobile Radio Communications, PIMRC 2007, IEEE 18th Int Symp,* 1–5.
20. Xing Y, Zhao J, Conti PS, Chen K (2014) Radiolabeled nanoparticles for multimodality tumor imaging, *Theranostics,* **4**(3), 290–306.
21. Wahajuddin, Arora S (2012) Superparamagnetic iron oxide nanoparticles: Magnetic nanoplatforms as drug carriers, *Int J Nanomed,* **7**, 3445–3471.
22. Corr SA, Rakovich YP, Gun'ko YK (2008) Multifunctional magnetic-fluorescent nanocomposites for biomedical applications, *Nanoscale Res Lett,* **3**(3), 87–104.

23. Moreno-Vega AI, Gómez-Quintero T, Nuñez-Anita RE, Acosta-Torres LS, Castaño V (2012) Polymeric and ceramic nanoparticles in biomedical applications, *J Nanotech,* 936041, 10 pp.
24. Mattoussi H, Rotello VM, eds (2013) Inorganic nanoparticle platforms, *Adv Drug Deliv Rev*, **65**(5), 605–756.
25. Naahidi S, Jafari M, Edalat F, Raymond K, Khademhosseini A, Chen P (2013) Biocompatibility of engineered nanoparticles for drug delivery, *J Control Release,* **166**(2), 182–194.
26. Kango S, Kalia S, Celli A, Njuguna J, Habibi Y, Kumar R (2013) Surface modification of inorganic nanoparticles for development of organic–inorganic nanocomposites—A review, *Prog Pol Sci*, **38**(8), 1232–1261.
27. Cohen-Karni T, Langer R, Kohane DS (2012) The smartest materials: The future of nanoelectronics in medicine, *ACS Nano*, **6**(8), 6541–6545.
28. Etheridge ML, Campbell SA, Erdman AG, Haynes CL, Wolf SM, McCullough J (2013) The big picture on nanomedicine: The state of investigational and approved nanomedicine products, *Nanomedicine NBM*, **9**(1), 1–14.
29. Kim YY, Walsh D (2010) Metal sulfide nanoparticles synthesized via enzyme treatment of biopolymer stabilized nanosuspensions, *Nanoscale*, **2**(2), 240–247.
30. Nozik AJ (2010) Nanoscience and nanostructures for photovoltaics and solar fuels, *Nano Lett*, **10**(8), 2735–2741.
31. Whittingham MS (2008) Materials challenges facing electrical energy storage, *MRS Bull*, **33**, 411–419.
32. Nanoscience Research for Energy Needs (2004) Report of the National Nanotechnology Initiative Grand Challenge Workshop, March 16–18, http://www.whitehouse.gov/files/documents/ostp/NSTC%20Reports/nni_energy_rpt%202004.pdf (22/08/2014).
33. Kalidindi SB, Jagirdar BR (2012) Nanocatalysis and prospects of green chemistry, *ChemSusChem*, **5**(1), 65–75.
34. See Manufacturing at the Nanoscale, US National Nanotechnology Initiative, http://www.nano.gov/nanotech-101/what/manufacturing (20/08/2014).
35. Pelton M, Bryant GW (2013) *Introduction to Metal-Nanoparticle Plasmonics*, John Wiley & Sons, New York.