1

Introduction and Applications of Nanotechnology

1.1 Nanotechnology: Introduction and Brief Historical Overview

Nanotechnology is a scientific field that deals mainly with materials and is very close to material science. As defined by the Royal Society in London, "*nanotechnologies are the design, characterization, production, and application of structures, devices, and systems by controlling shape and size at nanometer scale*" while according to the National Nanotechnology Initiative (NNI; http://www.nano.gov/node/1113) "*nanotechnology is the understanding and control of matter at the nanoscale, at dimensions approximately 1 and 100 nm, where unique phenomena enable novel applications*." The term *nano*technology was introduced by Professor Norio Taniguchi (Tokyo University of Science). The prefix *nano* is used by the International System of Units (SI) to denote one billionth and so one nanometer (nm) equals one billionth of a meter ($10^{-9} = 0.000000001$). Prof. Gregory Gregoriadis, a pioneer in the field of pharmaceutical nanotechnology, explains that the prefix *nano* comes from the Greek word *νάνος* (meaning "dwarf," something very small) with the second part of the word nanotechnology coming from the Greek word *τεχνολογία* (technology). Nanotechnology concerns the use of principles and methods of mechanics, electronics, material science, physics, and particularly thermodynamics and biophysics with the purpose of producing systems that exhibit new physicochemical and thermodynamic properties due to their size and to specific interfacial phenomena with biomaterials and biostructures, such as proteins and living cells.

An article published in 2006 by M. Saladin El Naschie suggests that nanotechnology could be characterized as the art of making tiny devices that approach the molecular dimension. The author defines nanotechnology as the application of the technology in the *gray*

Nanotechnology in Therapeutics: Basics and Trends, First Edition. Costas Demetzos.

area between classical and quantum mechanics (El Naschie 2006). This is because the properties of matter in the nanoscale are different and are related to the increasing ratio of the total surface area of the particles to their volume. In addition, the interfacial phenomena, the interactions between nanoparticles and between nanoparticles and biological entities, are related to their morphology and not to their Euclidian shape (*i.e.,* Euclidian geometry) creating new and unique properties in nanostructures. These properties can be utilized for various activities and applications not only in our daily life but also for the development of new therapeutic products and vaccines.

During the last 30 years, the presence of nanotechnology in many fields of science, such as physics, chemistry, biology, mathematics, and social sciences, has influenced their advancement. Moreover, the results and the achievements of nanotechnology are currently used in therapeutics, diagnostics, imaging, and fields such as

- Medicine
- Science of materials
- Economics (green nanotechnology)
- Informatics
- Clothing
- Environmental technology
- Electronics

as well as in social aspects and daily human activities.

Ultimately, nanotechnology is related to human ability to organize matter at the scale of individual atoms and molecules. It has the potential to transform medicine, informatics, drug development, and energy production and to produce raw materials for creating goods. A coordinated effort is required at both a European level and worldwide to make good use of nanotechnology for the benefit of man. Pharmaceutical nanotechnology refers to therapeutic products in which the particles have dimensions from a few tens of nanometers to the limit of 1 μm (1000 nm). In general, this term is dynamic and there have been many and constructive discussions related to it and mainly to defining the limits of the nanodimension. The nanodimension is not important when it comes to setting boundaries and of greater importance are the interfacial phenomena related to the morphology and not to Euclidean shape. Thus, the geometry of nanoparticles through the fractal approach can help us to understand their functionality and create more efficient nanosystems. There are many categories of nanoparticles that are used for the treatment of diseases as well as for vaccines that protect human beings against pathogenic agents. Nowadays, due to the pandemic (2020–2023) (SARS-CoV-2 virus), the development of many vaccines is based on nanodevices that carry and protect sensitive messenger RNA (mRNA) molecules from degradation. The applications of pharmaceutical nanotechnology are many, and nanoparticles, due to their very small size and large surface area-to-volume ratio, have increased efficiency and biocompatibility with the tissues of the human body, transporting therapeutic molecules or participating in the diagnosis of diseases. Improving the solubility of bioactive molecules, reducing their toxicity, targeted therapy, and other advantages are offered by nanoparticles with encapsulated therapeutic molecules because of their high-tech preparation and the scientifically rigorous criteria for their design and development. In general, pharmaceutical nanotechnology and nanotechnology in therapeutics include not only the well-known and defined structure nanomorphologies that we will introduce in this book but

also therapeutic macromolecules, such as antibodies, proteins conjugated with polymers, and other macromolecular structures.

Before moving on to the historical overview of nanotechnology, it is worth noting that the invisible world determined by prefixes *nano* and smaller dimensions, *i.e., pico-, femto-, atto-, zepto-* (1/1000 mathematical degradation of dimensions from the *nano-*) needs philosophical ways to tackle the borderline between visible and invisible dimensions. According to the Greek philosopher Cornelius Castoriadis (1922–1997), philosophy and science arose simultaneously in ancient Greece without a dividing line being drawn between them. As Einstein said ", […] *we are often blind trying to understand our nature*," while Heraclitus of Ephesus, a pre-Socrates philosopher, stated that "*nature likes to hide*."

However, it is a challenge to approach the natural laws that already exist and to rationally translate the "*cryptic codes*" at the nanoscale. The scientific tools that we have already on hand are based on the Newtonian and Euclidian principles and laws. Such tools are familiar to us in understanding the physical laws and the geometry of nature. This is not the only way of doing this. Nonlinearity and non-Euclidian geometry exist in the real cosmos such as the nanocosmos, but they are not visible to us (Demetzos 2022).

It seems that, in the end, an understanding of natural processes and the functionality of artificial nanostructures is important in the nanocosmos. What we need to do is to keep in mind that the positive entropy of a nanosystem should be controlled. Scientific achievements on nanotechnology give us a rational direction to produce nanosystems that can carry drugs or therapeutic elements. Our responsibility is to study the state of matter, the morphological characteristics, and the lyotropic behavior of nanoplatforms (Chapter 2) denoting the changes in their conformational polymorphism that are essential for their physical stability and their biological effectiveness (Demetzos 2022). The stability of nanosystems, their state of matter [*e.g.,* liquid crystalline state of matter (Chapter 2)] and their lyotropism, diffusion phenomena and interactions with biological object (*e.g.,* proteins), enable the scientists to understand their organization, the self-assembly process, and their thermodynamic content. The biomaterials from which the nanostructures are composed follow the natural processes and the laws of nature that are the controller of these complex processes and offer a high complexity (Chapter 2) of the nanosystem. The thermodynamical content of such nanosystems contributes to networks in a chaotic manner following nonlinear dynamics (Chapter 2) and cooperates harmoniously to produce the predominant statistical effect in every changing dynamic creation. The liquid crystalline state of matter as the predominant state, not only of biological objects but also in artificial nanotechnological platforms, has been chosen to transfer information in between nanoparticles of the "soup" of the dispersion nanosystem, and this is the way that should be explored to understand the nanodimension and its significant contribution in therapeutics. Finally, we argue that:

> *The key point is the harmony in all natural behaviors to maintain the physicochemical and thermodynamic balance of the nanosystem, promoting the non-equilibrium state in all activities.*

Because of the historical overview of the evolution of nanotechnology (Table 1.1), we must mention the first scientific report of nanotechnology that has been presented in a fundamental speech of Prof. Richard Feynman entitled "*There's plenty of room at the bottom*"

Table 1.1 *The timeline in the evolution of nanotechnology and of nanomedicines.*

1905	Einstein publishes his study on the dimension of sugar molecule, approximately 1 nm
1959	Prof. R. Feynman, in his lecture at the annual meeting of American Association of Physical Sciences, claims that *There is Plenty of Room at the Bottom*
1974	Prof. Norio Taniguchi introduces the term nanotechnology
1981	Dr. E. Drexler designs molecular machines that mimic enzymes and ribosomes
1984	The first description of the term "dendrimer" by Prof. D.A. Tomalia and the preparation method of PAMAM dendrimers
1991	The discovery of carbon nanotubes (CNTs)
1994	Drug delivery nanosystems (DDnSs)
1995	FDA approved Doxil® (liposomal doxorubicin)
1997	FDA approved AmBisome® (liposomal amphotericin B)
1998	DNA nanoparticles to control gene delivery
2000	The first Food and Drug Administration (FDA) approval of medicinal product based on the technology of Liquid Crystals (NanoCrystal® Technology) and the solid dose formulation of the immunosuppressant sirolimus – Rapamune®
2005	FDA approves Abraxane®, the nanotechnological formulation of paclitaxel
2008	In market: PEG-Certolizumab pegol (trade name, Cimzia®) anti-TNF Fab for rheumatoid arthritis and Crohn's disease
2012	Biomimetic Drug Delivery nanoSystems: the first publications in literature
2015	Clinical trials of ThermoDox® (*lyso-thermosensitive liposomal doxorubicin*) (Regenold et al. 2022)
2015	FDA approves Onivyde® (irinotecan liposomal) for advanced pancreatic cancer
2021	FDA and European Medicines Agency (EMA) approve the mRNA-LNP vaccine against SARS-CoV-2
2021	FDA and EMA approve (rolling review) the first recombinant nanoparticle vaccine (Nanoxovid®-NYX-CoV2373)
2023	EMA approves Zolsketil® (pegylated liposomal Doxorubicin) as "hybrid medicine"
2023	EMA approves Celdoxome® as "hybrid medicine"

during the American Physical Society dinner in 1959. Prof. Feynman differentiates the methodologies for constructing nanodevices as top-down and bottom-up technologies.

The term nanotechnology was introduced by Prof. Norio Taniguchi. He stated in his thesis entitled "*On the basic concept of Nano*technology" that the nanodimension was responsible for the formation of materials and devises at nanoscale. Eric Drexler in 1980s redefines the term nanotechnology in his book "*Engines of Creation*: *The Coming Era of Nanotechnology*" published in 1986. Drexler tried to introduce the self-assembly process as the phenomenon that produces very small devices in diameter, which could be functional. This approach was very interesting because the term nanotechnology was well adapted to the usefulness of nanodevices in daily human activities and in health sciences. His thesis entitled "*Nanosystems*: *Molecular Machinery Manufacturing and Computation*" describes all the necessary activities from a technical point of view for producing tiny machines (Drexler 1992). The basic principles of nanotechnology deal with the physicochemical characteristics of matter at the nanoscale considering physical parameters that can be used to characterize nanoparticles such as size, size distribution, ζ-potential, and

conductivity. In addition, well-established theories such as **DLVO** (named after **D**erjaguin and **L**andau, **V**erwey, and **O**verbeek, classic and extended) (Chapter 2) and techniques such as microscopy (optical, scanning probe, electronic, atomic force microscopies, which are the most applicable, among others) (Chapter 2), light scattering techniques, and calorimetric approaches are the main tools that could be used to evaluate the behavior of nanoparticulates. We must remember that DLVO theory deals with the stability of nanocolloidal dispersed systems. It should be mentioned that the physicochemical properties of the media in which nanoparticulate systems are dispersed (such as pH, ionic strength, and osmolarity) are considered crucial parameters that should also be evaluated because they are the key points for the physical stability of a nanosystem, especially in biological media.

We must point out two basic scientific fields that efficiently contribute to the evaluation processes of nanosystems. The first one is the *biophysics* and the second one is the *thermodynamics* or even better the *bio-thermodynamics*. These two approaches are considered complementary to chemistry, applied mathematics, engineering, and nanotechnology to efficiently approach behavior of nanoparticles. In addition, the nature of biomaterials that are used to construct nanosystems is of great importance and issues such as cooperativity between biomaterials, biodegradability, and biocompatibility should be taken into consideration during the evaluation process of nanosystems.

It is well documented in the literature and is obviously an acceptable concept that there are two main directions for developing new therapeutic products. The first one deals with the activities to identify new bioactive molecules that are well-known as active pharmaceutical ingredients (APIs) using approaches such as synthesis, hemi-synthesis or isolation from natural sources. The second direction concerns the formulation process to develop new medicines, while the bioactive molecule (*i.e.,* drug) remains the same.

However, new and innovative drug delivery nanosystems are an emerging approach, and they act as vehicles that deliver the drug payload to its target tissues in a more precise way than that of the free drug. Nanotechnology can offer nanosystems that are able to incorporate bioactive molecules, biological factors, or genes and to precisely transport them to the target tissues reducing their side effects.

There is a great number of drug delivery nanosystems (DDnSs) (Fig. 1.1) consisting of different, in their nature, biomaterials. The mostly used biomaterials that meet the requirement for the drug development process are

- Lipidic drug carriers
- Polymeric drug carriers
- Mixed drug carriers that may be divided into *hybrid* and *chimeric* DDnSs (Chrysostomou et al. 2022; Tsakiri et al. 2022).

Table 1.1 presents the timeline milestones in the evolution of nanotechnology and of nanomedicines.

As nanotechnology deals with the development of devices between 1 and 1000 nm in size, the applications extent over several fields that make up nanomedicine. The incorporation of active ingredients into nanodevices as colloidal dispersions provides new properties different from those of the biomaterials that they consist of. Moreover, the high surface-to-volume ratio increases the effective interactions with the tissue promoting the healing properties of the encapsulated active substance. We must point out that nanotechnology applies

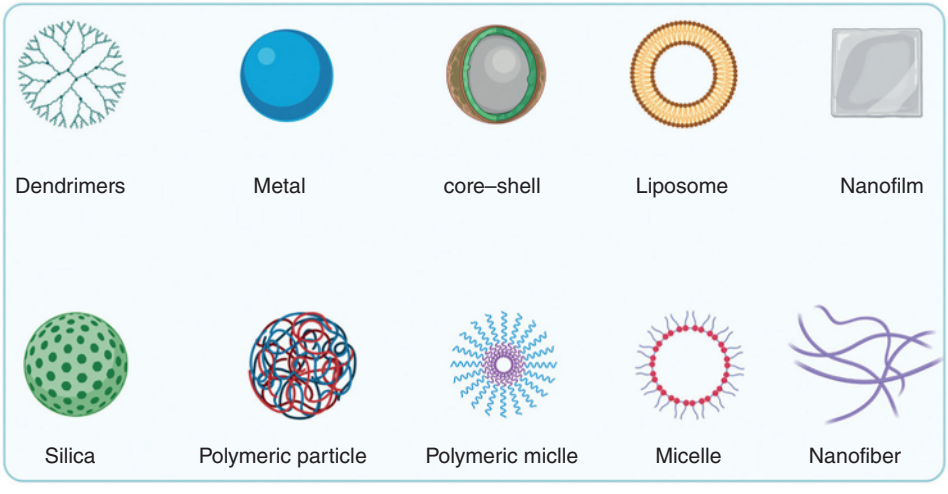

Figure 1.1 *Different drug delivery nanosystems. Source: Makvandi et al. (2021)/John Wiley & Sons/CC BY 4.0.*

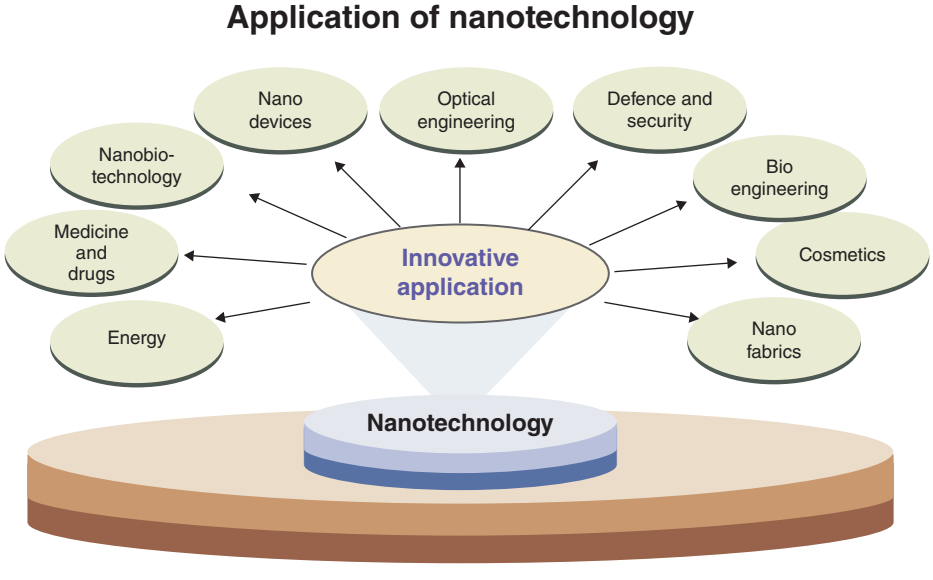

Figure 1.2 *Applications of nanotechnology in several fields. Source: Haque (2013)/Oriental Journal of Chemistry/CC BY 4.0.*

well to electronics, environment, food, and food supplements as well as in physical sciences, engineering, and bioengineering. It is worth mentioning that the nanomedicine market globally was valued at USD 135 billion in 2015 and is expected to reach USD 350.8 billion by 2025 (Shah et al. 2020).

The main sectors of nanotechnology applications are briefly presented in Fig. 1.2.

1.2 An Overview of Nanomedicines

Nanodevices made from biocompatible and biodegradable materials are on the same magnitude with biological entities. So is the size of nanodevices that can be used to transport bioactive molecules smaller than that of our cells? Nanodevices with a dimension of less than 10 nm can enter our cells. Even smaller nanodevices can additionally penetrate biological barriers. Due to their small size, nanodevices also interact with surface macromolecules, but also, due to their surface properties, they function as artificial biological entities, affecting biological cascades, with the aim of treating diseases or the elimination of disease factors, such as viruses and bacteria. The development of nanodevices that mimic the behavior of biological entities is of great interest and the pharmaceutical industry finances research programs or participates in competitive European programs in collaboration with universities and research institutes, with the aim of developing new therapeutic or preventive products. The collaboration of scientific fields, such as Pharmaceutical Chemistry, Pharmacognosy, Computational Chemistry, Biotechnology, and Molecular Genetics, but also new emerging sciences and technologies, such as artificial intelligence (AI) and machine learning (ML), will contribute to the development of new therapies. We should mention that the formulation of the bioactive molecules, through Pharmaceutical Technology and Nanotechnology, is a prerequisite for the final therapeutic effect. Technological advances with nanomaterials will improve the biocompatibility of implants after coating.

Nanotechnology is making an effective contribution to cancer therapies (Chapter 4). The effort to treat various types of cancer is ongoing, and clinical trials for therapeutic vaccines against breast cancer, colon cancer, and melanoma, aggressive, mostly metastatic cancers, are expected to lead to therapeutic success soon. Therapeutic vaccines (Chapter 6) will stimulate the immune system to produce antibodies that will target specific cancer cells by recognizing specific proteins on their surface. The antibodies that will be produced by the patient's body will "attack" and destroy the cancer cells. With these developments and the collaboration of nanotechnology and biotechnology, as well as other classic and emerging technologies, not only will social health benefit but also prospects for the treatment of diseases based on immunotherapy will be created.

The main directions that have been recognized as essential in producing new pharmaceutical products are the following:

- Every day hygiene following diverse procedures for protection against infectious diseases and contaminations that could prevent serious types of bacterial and viral infections.
- The imaging and diagnostic fields have been involved in designing and developing new nanodevices that need small amount of sample and give more precise and accurate results. In addition, the convergence of nanotechnology, pharmaceuticals, and medicine is expected in the future to make it possible to detect a single molecule or a cell in a complex biological environment. The above will contribute catalytically to the early diagnosis and effective treatment of cancer.
- The bioavailability and the pharmacokinetics of drugs are affected by the release profile of the drug from the final formulation. The controlled release profile can improve the therapeutic effect of the encapsulated drug into the nanosystem. In addition to addressing the limitations associated with drug use, such as low solubility, rapid degradation, and

elimination from the organism, as well as relatively short biological activity and the inability to overcome biological barriers, it is evident that controlling the release profile via nanosystems improves therapeutic outcomes. We must point out that substances capable of distinguishing molecular changes and preventing the mutation of precancerous cells into cancerous ones are recognized as essential directions in the field of discovering new medicines.

- Research tools that will enable researchers to quickly identify new targets and predict drug resistance are also important directions for improving the therapeutic effect of innovative health products.

Proteins and peptides are known to be the building blocks of life and living beings and their functionality has the effect of maintaining normal functions in humans and, consequently, human health. It is obvious that the use of proteins and peptides with the aim of their therapeutic utilization and combination with nanotechnology can result in the creation of important therapeutic products. The effectiveness of protein therapies has led to many beneficial applications and the treatment of diseases such as diabetes mellitus, metabolic diseases, and infections. The problem with proteins, and with macromolecules in general, is mainly related to the stability of their three-dimensional conformation. The attempt to apply nanodevices for the protection of protein molecules has shown results by improving not only their stability but also their pharmacokinetic parameters. Their administration without their entrapment in advanced excipients as delivery systems, such as nanoparticles of various types, whether lipidic or polymeric (*e.g.,* nanogels, polymersomes, and lyotropic liquid crystals), creates problems related to their effectiveness, due to their low stability. The protection of their morphology during their entrapment in a nanoparticle and the preservation of their functional behavior and structure when they are released from the nanoparticles are conditions for their therapeutic action. Table 1.2 presents the commercially available nanotherapeutic products that have been approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA).

1.3 Nanomedicine

Nanotechnology has triggered the emergence of a huge variety of research activities. In the European Union (EU), it has been recognized that new nanotechnological medicines are considered a key enabling technology (KET) that can provide effective treatment in human diseases. It is of importance to mention that nanotechnology, as applied to medicine, brings significant advances in therapeutics, imaging, and the diagnosis of diseases. Nanomedicine is a sector of nanotechnology that provides new insights in therapeutics and *in vitro* and *in vivo* diagnostics including the delivery of bioactive molecules to the target tissues as well as in regenerative medicine. In terms of therapeutics, nanomedicine contributes to the control of pharmacokinetics and to the control of the pharmacodynamics of drugs by maximizing bioavailability and efficacy, by overcoming obstacles arising from the inability of biomolecules to cross biological membranes, from low solubility, from fast clearance rates, etc. An unmet need for the approval of new nanomedicines is to have an established and acceptable definition to avoid controversial discussions among scientific societies and regulatory agencies. It is well-known that the properties of the biomaterials from which

Table 1.2 *Commercially available nanomedicines.*

Type of formulation	Nanosystem type	Product name	Active ingredient(s)	Company	Approving organization and approval date	Indication(s)
Lipid-based nanomedicine	Liposome	Doxil®	Doxorubicin hydrochloride	Johnson and Johnson	FDA (1995) EMA (1996)	Metastatic ovarian cancer, HIV-associated Kaposi's sarcoma, multiple myeloma
	Lipid complex	Abelcet®	Amphotericin B	Liposome Co	FDA (1995)	Aspergillosis in patients refractory to or intolerant of conventional amphotericin B and for invasive fungal infections
	Liposome	DaunoXome®	Daunorubicin citrate	Galen Ltd.	FDA (1996) EMA (1996)	HIV-associated Kaposi's sarcoma
	PEGylated liposome	Caelyx®	Doxorubicin hydrochloride	Janssen Pharmaceutica NV	EMA (1996)	Metastatic breast cancer, ovarian cancer, AIDS-related Kaposi's sarcoma
	Unilamellar liposome	AmBiosome®	Amphotericin B	NeXstar Pharmaceuticals	FDA (1997) EMA (2006)	Fungal infections in febrile neutropenic patients; Aspergillosis, candidiasis, and cryptococcosis infections refractory to amphotericin B
	Liposome	Inflexal® V	Inactivated influenza virus vaccine	Crucell (former Berna Biotech Ltd.)	EMA (1997)	Prevents influenza infection
	Lipid surfactant	Curosurf®	Pulmonary surfactant	Chiesi Farmaceutici	FDA (1999)	Respiratory distress syndrome (RDS)
	Liposome	Myocet®	Doxorubicin hydrochloride and an anthracycline cytotoxic agent	Teva Pharmaceutical Industries Ltd.	EMA (2000)	Metastatic breast cancer
	Liposome	Visudyne®	Verteporfin	QLT Photo-Therapeutics	FDA (2000) EMA (2000)	Severe eye conditions like macular degeneration, decreased vision, ocular histoplasmosis, pathologic myopia

(*Continued*)

Table 1.2 *(Continued)*

Type of formulation	Nanosystem type	Product name	Active ingredient(s)	Company	Approving organization and approval date	Indication(s)
	Liposome	Depocyt®	Cytarabine	Pacira Pharmaceuticals	FDA (1999) EMA (2001)	Intrathecal treatment of lymphomatous meningitis
	Liposome	DepoDur®	Morphine sulfate	Endo Pharmaceuticals	FDA (2004) Disc EMA (2006)	Postoperative analgesia
	Liposome	Mepact®	Mifamurtide	Takeda France SAS	FDA (2001) EMA (2009)	High grade nonmetastatic osteosarcoma and myosarcoma
	Liposome	Marqibo®	Vincristine	Talon Therapeutics	FDA (2012) Disc EMA (2012)	Philadelphia chromosome-negative acute lymphoblastic leukemia in adult patients
	Liposome	Lipodox®	Doxorubicin hydrochloride	Sun Pharmaceutical Industries Ltd. (SPIL)	FDA (2013)	Kaposi's sarcoma, ovarian cancer, multiple myeloma
	Liposome	Onivyde®	Irinotecan	Merrimack Pharmaceuticals	FDA (2015)	Metastatic pancreatic cancer
	Liposome	Lipusu®	Paclitaxel	Luye Pgarna	FDA (2016)	Lung squamous cell carcinoma
	Liposome	Onpattro®	Patisiran sodium	Alnylam Pharmaceuticals, Inc.	FDA (2018) EMA (2018)	Polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults
	Liposome	Pfizer-BioNTech vaccine	mRNA vaccine	Pfizer Pharmaceuticals	FDA (2020)	Prevention of COVID-19 infection
	Liposome	Moderna Vaccine	mRNA vaccine	ModernaTx Inc.	FDA (2020)	Prevention of COVID-19 infection
Polymer-based nanomedicine	Nanoemulsion	Diprivan®	Propofol	AstraZeneca LP	FDA (1989) EMA (2001)	Anesthetic agent for induction and maintenance of anesthesia. For sedation of patient under critical care and those requiring mechanical ventilator

Polymer-protein conjugate	Adagen®	Adenosine deaminase	Enzon Pharmaceuticals Inc.	FDA (1990)	Adenosine deaminase-severe combined immunodeficiency disorder
Polymer-based	Oncaspar®	L-Asparaginase	Enzon Pharmaceuticals Inc.	FDA (1994) EMA (2016)	Acute lymphoblastic leukemia
Micelle	PegIntron®	PEGylated interferon alpha-2B	Merck & Co. Inc.	EMA (2000) FDA (2001) Disc	Hepatitis
Polymer-protein conjugate	Neulasta®	Filgrastim	Amgen, Inc.	FDA (2002)	Neutropenia
Polymer-protein conjugate	Pegasys®	PEGylated interferon alpha-2A	Genentech, Inc.	FDA (2002) EMA (2002)	Hepatitis B and Hepatitis C
Polymer-protein conjugate	Somavert®	Recombinant human growth hormone receptor antagonist	Pfizer, Inc.	EMA (2002) FDA (2003)	Acromegaly
Nanoemulsion	Restasis®	Cyclosporine	Allergan	FDA (2003)	Chronic dry eye
Nanoemulsion	Estrasorb®	Estradiol	Novavax, Inc.	FDA (2003)	Treatment of moderate to severe vasomotor symptoms in postmenopausal women
Polymer-protein conjugate	Macugen®	Pegaptanib sodium	Pfizer, Inc.	FDA (2004)	Wet age-related macular degeneration
Micelle	Genexol-PM®	Paclitaxel	Lupin Ltd.	FDA (2007)	Breast cancer
Polymer-protein conjugate	Mircera®	Epoetin beta	Vifor pharma	EMA (2007) FDA (2007)	Renal anemia
Polymer-peptide conjugate	Cimzia®	Certolizumab pegol	UCB	FDA (2008) EMA (2009)	Rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis

(*Continued*)

Table 1.2 *(Continued)*

Type of formulation	Nanosystem type	Product name	Active ingredient(s)	Company	Approving organization and approval date	Indication(s)
	Polymer-protein conjugate	Krystexxa®	Pegloticase	Savient Pharmaceuticals	FDA (2010)	Severe and treatment-refractory chronic gout
	Polymer-protein conjugate	Plegridy®	Peginterferon beta-1a	Biogene	FDA (2014)	Relapsing remitting multiple sclerosis in adults
	Polymer-protein conjugate	Adynovate®	Recombinant antihemophilic factor	Baxalta US Inc.	FDA (2015)	Hemophilia A
	Polymer-protein conjugate	Rebinyn®	Recombinant coagulation factor IX	Novo Nordisk Inc.	FDA (2017)	Hemophilia B
	Polymer steroid mixture	Zilretta®	Triamcinolone acetonide	Flexion Therapeutics	FDA (2017)	Knee osteoarthritis
	Micelle	Apealea®	Paclitaxel	Oasmia Pharmaceutical AB	FDA (2018)	Ovarian cancer, peritoneal cancer, fallopian tube cancer
Nanocrystals	Nanocrystal	Avinza®	Morphine	King Pharma	FDA (2002)	Chronic pain
	Nanocrystal	Ritalin LA®	Methylphenidate hydrochloride	Novartis	FDA (2002)	Attention deficit hyperactivity disorder in children
	Nanocrystal	Zanaflex®	Tizanidine hydrochloride	Acorda	FDA (2002)	Muscle relaxant
	Nanocrystal	Emend®	Aprepitant	Merck & Co. Inc.	FDA (2003)	Antiemetic
	Nanocrystal	Tricor®	Fenofibric acid	Abott Laboratories	FDA (2004)	Antihyperlipidemia
	Nanocrystal	NanOss®	Hydroxyapatite	RTI Surgical	FDA (2005)	Bone substitute
	Nanocrystal	Megace® ES	Megestrol acetate	Par Pharmaceuticals	FDA (2005)	Anorexia, cachexia and AIDS-related weight loss
	Nanocrystal	IVEmend®	Fosaprepitant dimeglumine	Merck & Co. Inc.	FDA (2008) EMA (2008)	Antiemetic

	Nanocrystal	Focalin® XR	Dexmethylphenidate hydrochloride	Novartis	FDA (2008)	Attention deficit hyperactivity disorder in children
	Nanocrystal	Invega®	Paliperidone palmitate	Janssen Pharmaceuticals	FDA (2009)	Schizophrenia
Inorganic nanoparticles	Iron nanoparticles	Dexferrum®	Iron dextran	American Regent	FDA (1996)	Iron deficiency in chronic kidney disease
	Iron nanoparticles	Venofer®	Iron sucrose	Lutipold Pharmaceuticals, Inc.	FDA (2000)	Iron deficiency in chronic kidney disease
	Hafnium oxide nanoparticles	Hensify®	Hafnium oxide	Nanobiotix	EMA (2019)	Locally advanced squamous cell carcinoma
Protein based nanoparticles	Engineered fusion protein nanoparticle	Ontak®	Denileukin diftitox	Eisai Co., Ltd.	FDA (1999)	Leukemia, T cell lymphoma
	Albumin nanoparticle	Abraxane®	Paclitaxel	Eli Lilly	FDA (2005) EMA (2008)	Metastatic breast cancer

Source: Thapa and Kim (2023)/with permission of Springer Nature.

nanomedicines are composed have different physicochemical properties and biological behavior from those of the final nanomedicinal formulations. Concerns regarding their safety have emerged due to the lack of a consensus based on the scientific evidence.

To overcome these concerns, it is necessary to draw up a sustainable framework to define terms such as nanomaterial, nanodevice, nanomedicines, and many others, considering not only the active substance (*i.e.,* drug) but also the advanced excipients that are the building blocks of the nanocarrier. According to Soares (Soares et al. 2018), "[…] *the EMA working group introduces nanomedicines as purposely designed systems for clinical applications, with at least one component at the nanoscale, resulting in reproducible properties and characteristics, related to the specific nanotechnology application and characteristics for the intended use (route of administration, dose), associated with the expected clinical advantages of nano-engineering*."

In the same article by Soares (Soares et al. 2018) "[…] *Food and Drug Administration (FDA) has not established its own definition for "nanotechnology," "nanomaterial," "nanoscale," or other related terms, instead adopting the meanings commonly employed in relation to the engineering of materials that have at least one dimension in the size range of approximately 1 nanometer (nm) to 100 nm. Based on the current scientific and technical understanding of nanomaterials and their characteristics, FDA advises that evaluations of safety, effectiveness, public health impact, or regulatory status of nanotechnology products should consider any unique properties and behaviors that the application of nanotechnology may impart*." The article proposes that there are three fundamental issues that should be taken into consideration considering the nanoparticle characterization, namely,

- Size of the nanoparticle [*e.g.,* liposome, lipid nanoparticle (LNP), polymeric nanoparticle, etc.]
- Size distribution of the nanoparticle [polydispersity index (PDI)], and
- Surface area (Soares et al. 2018)

The approval process for nanomedicines follows the common and traditional framework of benefit/risk analysis. The ambitious and challenging approach is to evaluate the follow-on nanomedicine with the prototype nanomedicine at the time of the patent expiration, considering the morphological, physicochemical, and thermodynamic properties of the nanoparticles that incorporate the drug. The nonbiological complex drugs (NBCDs) follow a regulatory process that is still ongoing and under evaluation (Soares et al. 2018).

The World Health Organization (WHO) is an autonomous international intergovernmental organization, a specialized agency of the United Nations (UN) that deals with international public health issues. It was officially founded in 1948 and is based in Geneva. It is a member of the United Nations Development Group. The "constitution" of the WHO was signed by 61 countries on 22 July 1946, while the first meeting of the World Health Assembly ended on 24 July 1946. Since its establishment, it has played an important role in the eradication of smallpox. Its current priorities include addressing transmutable diseases, particularly acquired immunodeficiency syndrome [(AIDS) human immunodeficiency virus (HIV)], Ebola virus, malaria, and tuberculosis, reducing the impact of non-transmutable diseases, sexual health and reproduction, development and ageing, healthy eating, and food safety. The current definition of Health is mentioned in the preamble to the WHO statute was adopted by the International Health Conference (New York, 19–22 June

1946) was put into force on 7 April 1948 and remains unchanged: "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (https://el.wikipedia.org/wiki).

Medicine is a science and art that deals with the research and application of methods and techniques for the prevention, diagnosis, and treatment of human diseases. It is considered one of the most ancient practical sciences, having its first applications in the beginnings of human society itself. Up to two centuries ago, it was considered exclusively an art, a terminology by which it would also appear in Hippocratic Oath (https://en.wikipedia.org/wiki/Hippocratic_Oath).

The correlation between nanotechnology and medicine, or rather the applications of nanotechnology in medical practice, has biology as a communication channel but also the nanodimension. In the nanodimension, the phenomena of life in the microcosm evolve with harmony and order, and in this world which is invisible to us, but is alive, the natural laws and the evolution of species of our planet are revealed. We must discover this invisible cosmos, converse with it, translate it, and understand its workings. Nature, as we know, does not reveal detailed information about the processes that evolve and about the structural events that contribute to its evolution. "*Nature likes to hide*" (Heraclitus, op. 123). Most of the time, nature presents us in its own way the information that its complex bionetworks use, as projections to our macrocosm. Science must analyze these "messages" and present the natural laws translated, based on our human capabilities. Man cannot have absolute knowledge, he only has an opinion, because according to the cosmogony of Xenophanes of Colophon (570 BCE–470 BCE), what people say is nothing but "suppositions," that is, something that may resemble the truth. In passage 16 (1–2) Xenophanes of Colophon says, "*The gods did not show all from the beginning, but people, by searching, will probably find them*." So here, in our opinion, in an invisible world, in the nanoworld, natural laws and the evolution of species appear, as we mentioned, and science comes to give us the perspective of these laws, in our world, in the macrocosm.

Medicine as a science and art, and nanotechnology as an interdisciplinary field where sciences meet, combines to give us the application of sciences that deal with the nanodimension in the service of human health. Nanomedicine is therefore the field where the nanodimension meets the biological invisible phenomena related to our health, it "copies" biological behaviors and biological entities and reproduces them technologically for the benefit of human health.

Nanomedicine is a term that was used by Freitas (2005) as an extension of the thoughts of E. Drexler and his collaborators.

In his publications, along with others, he reported the practical application of nanodevices in many fields of medicine. The term nanomedicine integrates many fields that refer to medical technology and especially nanotechnology. Table 1.3 (Freitas 2005) presents a partial nanomedicine technologies taxonomy.

We may also mention that nanomedicine includes the applications of nanotechnology in medical practice and medical procedures. Thus, the administration of therapeutic nanodevices that carry bioactive molecules is a constantly evolving field and solves many problems that exist during the administration of low molecular mass drug molecules. Nanodevices, by encapsulating bioactive molecules, increase their solubility in the case of hydrophobic drug molecules, facilitate their transport through natural barriers of the human body, and help in targeted therapy by reducing their potential toxicity. Finally, they improve

Table 1.3 *Partial nanomedicine technologies taxonomy.*

Raw nanomaterials	**Cell simulations and cell diagnostics**	**Biological research**
Nanoparticle coating	Cell chips	Nanobiology
Nanocrystalline materials	Cell simulators	Nanoscience in life sciences
Nanostructured materials	**DNA manipulation, sequencing, diagnostics**	**Drug delivery**
Cyclic peptides	Genetic testing	Drug discover
Dendrimers	DNA microarrays	Biopharmaceutics
Detoxification agents	Ultrafast DNA sequencing	Drug delivery
Fullerenes	DNA manipulation and control	Drug encapsulation
Functional drug carriers		Smart drug
MRI scanning (nanoparticles)	**Tools and diagnostics**	
Nanobarcodes	Bacterial detection system	**Molecular medicine**
Nanoemulsions	Biochips	Genetic therapy
Nanofibers	Biomolecular imaging	Pharmacogenomics
Nanoparticles	Biosensors and biodetection	
Nanoshells	Diagnostic and defense applications	**Artificial enzyme and enzyme control**
Carbon nanotubes	Endoscopic robots and microscopes	Enzyme manipulation and control
Noncarbon nanotubes	Fullerene-based sensors	
Quantum dots	Imaging (cellular, etc.)	**Nanotherapeutics**
	Lab on a chip	Antibacterial and antiviral nanoparticles
Artificial binding sites	Monitoring	Fullerene-based pharmaceuticals
Artificial antibodies	Nanosensors	Photodynamic therapy
Artificial enzymes	Point of care diagnostics	Radiopharmaceuticals
Artificial receptors	Protein microarrays	
Molecularly imprinted polymers	Scanning probe microscopy	**Synthetic biology and early nanodevices**
Control of surfaces	**Intracellular devises**	Dynamic nanoplatform "nanosome"
Artificial surfaces-adhesive	Intracellular assay	Tecto-dendrimers
Artificial surfaces-nonadhesive	Intracellular biocomputers	Artificial cells and liposomes
Artificial surfaces-regulated	Intracellular sensors/ reporters	Polymeric micelles and polymerosomes
Biocompatible surfaces	Implants inside cells	
Biofilm suppression		
Engineered surfaces		**Biotechnology and biorobotics**
Pattern surfaces (contact guidance)	**BioMEMS**	Biologic viral therapy
Thin-film coating	Implantable materials and devices	Virus-based hybrids

Table 1.3 *(Continued)*

	Implanted bioMEMS, chip, and electrodes	Stem cells and cloning
Nanopores	MEMS/nanomaterials-based prosthetics	Tissue engineering
Immunoisolation	Sensory aids (artificial retina, etc.)	Artificial organs
Molecular sieves and channels	Microarrays	Nanobiotechnology
Nanofiltration membranes	Microcantilever-based sensors	Biorobotics and biobots
Nanopores	Microfluidics	**Nanorobotics**
Separations	Microneedles	DNA-based devises and nanorobots
	Medical MEMS	Diamond-based nanorobots
	MEMS surgical devises	Cell repair devises

Source: Freitas (2005)/with permission of Elsevier.

the pharmacokinetic parameters and protect them from possible physicochemical alterations. We can categorize nanomedicine in directions related to their therapeutic or even diagnostic applications.

Artificially prepared nanosystems or nanodevices such as polymeric and lipid nanoparticles (Table 1.4), and artificial exosomes based on polymers or lipids or their mixtures, the so-called chimeric particles, and natural nanoparticles, such as viruses, can be used as nanocarriers for the transport of therapeutic macromolecules, *e.g.,* proteins, lipoproteins, and exosomes (extracellular vesicles, EVs), which can be released by eukaryotic cells, bacteria or even fungi. Exosomes, as natural nanostructures, are composed of phospholipids and play an important role in communication networks by transferring information between cells. It seems that research activity concerning exosomes as drug delivery systems is constantly developing because, as natural nanoparticles, they can overcome the natural tissue barriers in the human body, thereby transporting biomolecules for treatment. They also possess the advantage of possible targeting due to their surface macromolecules and their stability during their circulation in the body (biological stability).

All of these are extremely useful as nanotechnological platforms in medicine and can be characterized as nanomedical systems for the treatment or diagnosis of diseases.

But what could be the combination of medicine with nanotechnology give us as additional health products that would help in the treatment of diseases and human health in general? The development of new nanoscale instruments that will be able to analyze very small amounts of samples is an important development toward the diagnosis of diseases. Also, the rapid and simultaneous examination of several samples based on the nanodimension, such as removable nanorods, but also the simultaneous monitoring of tissues and organs can yield enormous benefits and rapid diagnosis of diseases, which is lifesaving for humans. Personalized therapy and precision medicine can offer significant benefits to the patient. Personalized pharmacotherapy, based on the rapid simultaneous measurement of the expression of biomarkers associated with several diseases, can exclude pathogenic

Table 1.4 *Main types of nanosystems.*

Nanoparticles
Lipidic and polymeric
Liposomes
Polymeric nanoparticles
Polyplexes
Lipopolyplexes
Lipid nanoparticles (LNPs)
Solid lipid nanoparticles (SLNs)
Nanostructured lipid carriers (NLCs)
Niosomes
Polymerosomes
Micelles
Nanogels
Inorganic
Nanocrystals
Quantum dots
Magnetic nanoparticles
Gold nanoparticles
Fullerenes
Silica nanoparticles
Magnetic nanoparticles
Carbon nanotubes
Nanofibers
Nanowires
Carbon nanofibers
Composite nanostructures
Nanoemulsions
Nanoliposomes
Nanocapsules
Nanoshells
Nanovesicles
Nanopipettes
Nanoneedles
Nanochannels
Nanopores
Nanofluidics

factors and even detect genetic predisposition in some diseases, leading to early diagnosis and protection. Implants, tissue regeneration, targeted delivery of therapeutic products, reconstructive surgery, and bionanomaterials with healing potential, along with biomaterials possessing new biocompatible and biodegradable properties, especially in treating cardiac diseases, can significantly contribute to both protection and therapeutic treatment against disease factors. The simultaneous diagnosis and treatment of diseases through the combination of treatment and imaging (Chapter 5), *i.e.,* the imaging of cancer tumors with great precision and the simultaneous administration of therapeutic products, is an important advancement in the treatment of serious diseases.

It is of importance that DDnSs can cross/pass through barriers [*e.g.,* blood–brain barrier (BBB)] in the human body maintaining their integrity. The basic concept of encapsulating bioactive molecules into DDnSs is a way to improve the effectiveness of the encapsulated drug. Thermodynamics (Chapter 2) and biophysics of their surface properties, the ζ-potential, the size, and the size distribution as well as their thermodynamical content, affect their stability and dictate their interaction and interfacial phenomena with the cell membranes.

The disadvantages that should be mentioned are

- poor encapsulating capacity of the bioactive substance
- unpredictable gelation tendency
- high water content, and
- the partitioning effect (Dianzani et al. 2014; Arif et al. 2015; Hashim et al. 2020).

Regarding skin, it has been shown that DDnSs could be used to repair skin and may improve the controlled release and the bioavailability of the active substance (Karypidis 2021).

We should also mention at this point that dermatological diseases related not only to the aesthetics of the skin but also to health issues are very important. Exposure to the environment and to infections can lead to local skin diseases, destroying the physiology and anatomy of the skin. Thus, chronic lesions and wounds affect more than 1.5% of the population in Europe and the United States, while diabetic ulcers affect 12–25% of diabetic patients. It is therefore necessary to develop effective dermatological products that are also safe for the treatment of skin wounds and injuries. Treatments must be effective and require high selectivity, compatibility with skin tissue and patient compliance with treatment. Classic treatments lead to problems and reduced healing in up to 70% of cases (Karypidis 2021). The nanomedical approach to these diseases seems to have advantages, reduces systemic treatment, and helps patient compliance with the choice of using different nanoparticles designed to treat acute and chronic dermatological diseases. The literature refers to various healing strategies that include transport of drug molecules, tissue growth factors, and mechanical tissue regeneration with the creation of scaffolds that promote skin regeneration (Table 1.5). The applications of different growth factors, interleukins, etc., are mentioned in the literature (Karypidis 2021). Regenerative medicine in the case of the skin offers advantages with the application of stem cells, while scaffolds for transporting inorganic nanoparticles, *e.g.,* silver, are used as potential antimicrobial products by alleviating inflammation. Finally, autoimmune skin problems and skin cancers with the use of nanotechnology liposomal products that carry cytostatic drugs, *e.g.,* methotrexate against psoriasis and anticancer drugs against skin cancers, respectively, also seem to be effective.

Skin healing and regeneration is a challenge concerning the topical applications of DDnSs. Lipidic nanocarriers have advantages such as:

- Their self-assembled complex structure composed of advanced excipients (Chapter 7) promotes their favorable lyotropism leading to their integrity and effective interaction with the skin cell membranes.
- The flexibility and deformability (*e.g.,* transfersomes) of the final formulation leads to the effective transportation of the active substance to the desired site.
- The controlled release properties, the homogeneous dispersion, and the responsiveness to the external stimuli (*e.g.,* pH, ionic strength, temperature), depending on the biomaterials that were used, increase their effectiveness (Karypidis 2021).

Table 1.5 *The table presents the type of nanosytems delivery platform of the active compound and the main effect on skin regeneration and healing.*

Nanodrug delivery system	Active drug/agent	Effect
Liposomes with silk fibroin hydrogel core	bFGF	Protection and prolongation of EGF function at the skin repair site
Liposomes	Madecassoside	Increased bioavailability at the skin site and prolongation of action
Liposomes	Curcumin	Increased antioxidation and revascularization
Liposomes	Calcipotriol	Psoriasis treatment, less adverse effects
Liposomes	Methotrexate	Psoriasis treatment, higher concentration
Liposomes	Vincristine, cisplatin, doxorubicin	Skin cancer treatment, effective wound healing
Liposomes	Tretinoin clindamycin and benzylperoxide	Acneic skin treatment and remodeling, prolonged release
Liposomes	Finasteride	Androgenic alopecia enhanced treatment without systemic effects
Deformable liposomal ointment	Retinoic acid EGF	Improved proliferation and cell migration (keratinocytes viability)
Liposome/gelatin methacrylate	SDF1ananocomposite hydrogel	Keratinocyte and fibroblast migration enhancement
Anionic liposomes	Ascorbic acid	Increased skin permeation, retention and enhanced collagen synthesis by fibroblasts
Cationic elastic liposomes	EGF, PDGF-A, IGF-I	Prolongation and acceleration of growth factor function, diabetic wound healing enhancement
Ethosomal gel	Thymosinβ-4	Improved and prolonged skin permeation
Liposomes	Papain	Protease like skin fibrosis protection, improved remodeling
Liposomes	Ceramide 3 and 6, cholesterol and stearic acid, indomethacin	Drug bioavailability increase at the skin repair site
Deformable liposomes	EGF	Improved and prolonged EGF function on newly formed epithelium
Niosomes	Catalase	Enhancement of the rate (and total time) of wound healing, by protecting against oxidative stress
Liposomes	Mangiferin	Increased adhesiveness, decreased hypoxia induced apoptosis, lowering inflammation
Glycyl-L-histidyl-L-lysine (GHK)-Cu-liposomes	Human umbilical vein endothelial cells	Increased expression of angiogenesis-related factors and faster burn wound healing
Liposomes	Dihydroquercetin	Stabilization of the endogenous antioxidant system

Table 1.5 *(Continued)*

Nanodrug delivery system	Active drug/agent	Effect
Liposomes	Tocopherol	Improved skin permeation, accelerated wound closure, enhanced fibroblast migration
Liposomes	Kynurenic acid	Prevention of aberrant scar formation
Liposomes in a gelatin membrane	Usnic acid	Organized scar tissue repair with no fibrosis, fast wound contraction, and closure, richer granulation tissue and faster healing time
Solid lipid nanoparticles (SLNs)	Irbesartan	Improved bioavailability of the drug resulting in improved blood supply
SLNs	Curcumin	Increased antioxidation and revascularization
SLNs	Silver sulfadiazine	Steady controlled release, reduction of toxic effects on fibroblasts
SLNs	Retinoic acid	Improved proliferation and cell migration
SLNs	Chamomileoil	Improved hydration, natural antioxidation mechanisms
SLNs	LL37	Enhanced antibacterial properties
SLNs	SerpinA1	ECM organization and production favoring wound healing
SLNs	Quercetin	Healing acceleration, SMAD7 protein cascade and TGF-b pathway down-regulated
Nanostructured lipid carriers (NLCs)	Phenytoin	Avoidance of skin irritation and dryness
NLCs	Curcumin	Increased antioxidation and revascularization
NLCs	Simvastatin	Sustained release and tissue oxygenation
NLCs	Melatonin	Prolonged protected release
NLCs	Pioglitazone	Increased angiogenic and strong anti-inflammatory effects by regulating matrix metalloproteinases
NLCs	Essential oils	Regulation of toxicity and decrease of inflammation by cytokines
NLCs, SLNs, liposomes	siRNA	Efficient transfection, prolonged protection from enzymatic degradation
Nanoemulsions	Antitumor, anti-inflammatory agents	Increased bioavailability, large surface protected coverage
Chitosan polymeric nanoparticle/hydrogel	Insulin	Significant loading capacity, improved skin glucose metabolism reduced glycation
Fibrin gel/chitosan nanoparticles	rhEGF	Improved cell migration and proliferation, increased local concentration

(*Continued*)

Table 1.5 *(Continued)*

Nanodrug delivery system	Active drug/agent	Effect
chitosan nanoparticles/PCL/ gelatin polymeric nanofibrous scaffold	Curcumin	Decreased cytotoxicity, increased angiogenesis and antioxidation, improved stability and prolonged presence at the skin repair site
Phosphorylated chitosan polymeric nanoparticles	Quercetin	Cytokines, growth factors signaling pathways promoting markedly improved skin repair
Chitosan polymeric nanoparticles	GM-CSF	High capacity, solubilization, gradual and structured release
PLGA polymeric nanoparticles	Curcumin	Faster and better granulation tissue formation and re-epithelization
PLGA polymerosomes	LL37	More efficient angiogenesis and anti-inflammatory and antibacterial function
PEG/PVP polymeric nanoparticles/hydrogel	Simvastatin	Efficient solubilization and inhibition of 3-hydroxy-3-methyl-glutaryl-CoA reductase
Chitosan polymeric chains	Titanium oxide nanoparticles/oleic acid	Nanofilm production enhanced antibacterial effects
Keratin nanoparticles	Keratinic structure	Superior safety and biocompatibility, and significantly improved dermal repair and granulation tissue formation
Cellulose, chitosan, and alginate polymeric biofilms loaded with ZnO	Nanobiofilms	Highly improved local concentration and local bioavailability
Cellulose nanocrystals, gelatin, hyaluronic acid composite hydrogel	Dressing	Protection, moisture wound healing, less chronicity and inflammation
Hydroxyethylcellulose scaffold	AgNP	Inhibition of the production of pro-inflammatory cytokines by keratinocytes
AgNP	Dressing	Wound protection, antibiotic function, burn injuries repair enhancement, deeper penetration
Collagen/chitosan scaffolds	AgNP	Accelerated fibroblasts migration and macrophage activation
Chitosan/silk fibroin	AgNP/exosomes	New collagen organized deposition, angiogenesis, fluid-electrolyte balance and antimicrobial protection
Cellulose nanocrystals	AgNP	Long term safety and toxicity of prolonged application
Complex nanofabrication of oxidized cellulose/a cellular dermal (porcine) matrix	AgNP	Lower immunogenicity, structural support, antibacterial protection, high thermal and chemical stability

Table 1.5 *(Continued)*

Nanodrug delivery system	Active drug/agent	Effect
Thermoresponsive gel	AuNP/DsiRNA	Increased functional angiogenesis in diabetic wound skin repair, stable depot, thermoresponsive
AuNPs	Epigallocatechin	Collagen synthesis promotion, stable depot, prolonged presence
AuNPs	Alpha-lipoic acid	Promotion of healing, remodeling, and repair through receptor for advanced glycation end-products (RAGE)
AuNPs	VEGF	Protected increase of bioavailability of the growth factor
AuNPs	Acalyphaindica	Inflammation acceleration/termination, more efficient proliferation phase
AuNPs	Flavonoids	Increased ECM synthesis and angiogenesis
PEG chains/AuNPs	MicroRNA-378a	Enhancement of fibroblast migration and differentiation
Cellulose matrix/ AuNPs	4,6-Diamino-2-pyrimidinethiol	Enhanced biocompatibility release, hemostasis, water-electrolyte balance, mechanical stability
Bioactive glass	AuNPs	Mechanical and structural stability, skin repair site organization
PCL scaffold	AuNPs/PEG	Rapid internalization, cell migration, proliferation and effective organization
Hydrogel	Cerium oxide NPs (CNPs)	Increased auto-regenerative bacteriostatic and antioxidant properties
CNPs	microRNAmiR-146a	Efficient synergistic transfection favoring skin regeneration
CNPs	L-Arginine	Accelerated hemostasis, potent ROS and infection protection
Polymeric PCL-gelatin nanofibers	CNPs/curcumin	Marked angiogenetic, proliferating, antioxidant effects in multiple skin repair stages
Poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate)	CNPs/curcumin	Marked angiogenetic, proliferating, antioxidant effects in multiple skin repair stages
Polyacrylamide hydrogel	CNPs/MSCs	Marked angiogenetic, proliferating, antioxidant effects in multiple skin repair stages
Chitosan/PVA	ZnO nanoparticles (ZnNPs)	Generation of ROS, cell migration and proliferation leading to improved wound repair
Bilayered scaffold of PCL/gelatin	ZnNPs/amoxicillin	Firm antibacterial barrier, antioxidative-revascularization-dermal regenerating surface

(*Continued*)

Table 1.5 *(Continued)*

Nanodrug delivery system	Active drug/agent	Effect
Nanocomposites prayK-carrageenan-polydopamine	ZnNPs/L-glutamic acid	Increased therapeutic potential in diabetic wound healing
Porous silk fibroin/ collagen scaffold	ZnNPs	Reduced inflammation and fast granulation tissue formation
Network hydrogel (poly(*N*-hydroxyethyl acrylamide)/agar)	ZnNPs	Superior water retention, improved skin tensile strength, tissue adhesion, antibacterial effect
Polyvinylpyrrolidone/ PCL electrospun nanofibers	ZnO/Ag/nanoparticles	Reduced cytotoxicity, superior antibacterial effect
Graphene oxide (GO)	Reduced grapheme oxide (rGO)	High angiogenic properties but unknown degree of toxicity
rGO	Isabgol	Accelerated wound contraction and reduced epithelialization time
Hydrogel	rGO	Improved keratinocytes proliferation and migration
Chitosan complex	Single wall/multiwall carbon nanotubes (CNTs)	Improved the re-epithelialization but showed increased fibrosis in some wounds
GO nanosheets	Ag/Cu bimetallic nanoparticles	Minimized cytotoxicity and enhanced antibacterial effect
Carbon nanodiamonds	—	High rate of passage and fast concentration increase in the hair follicles
Chitosan hydrogel/a cellular dermal matrix	Carbon nanodots/ hAMSC	Significant angiogenetic, proliferative and ROS scavenging effects
Silicon carbon nanohybrids	—	Enhanced wound closure, superior bacterial inhibition
Hybrid nanocomplex of PVA nanofibers	Carbon nanotubes/ rhEGF	Stability, mechanical support, water retention and safety, controlled release, cytotoxicity
Mesoporous silica nanoparticles(MSNs)	Ampicillin	Highly pH responsive, fighting bacterial resistance
MSNs	Curcumin	Inhibited inflammation and protected the wound site from falling to chronicity promoting angiogenesis and fibroblast proliferation
MSNs	Ag	Increased bactericidal load, managing drug resistance
MSNs	Bismuth and Ag	Treatment for multidrug-resistant bacteria even with planktonic and biofilm abilities
MSNs	Cerium oxide	Adhesive properties enhanced, faster wound closure and faster uneventful skin remodeling

Table 1.5 *(Continued)*

Nanodrug delivery system	Active drug/agent	Effect
Mesoporous bioactive glasses (MBGs)	Cu/cellulose-based aerogel	Up-regulation of proangiogenic fibroblast genes, antibacterial protection
MBGs	Cu	Up-regulation of proangiogenic fibroblast genes, antibacterial protection
MBGs	Cu/cellulose scaffold	Up-regulation of proangiogenic fibroblast genes, antibacterial protection
Polycaprolactone (PCL)	Collagen-based scaffolds	Increased mechanical strength and closure
PCL/poloxamer nanofiber scaffold	—	Approximation of skin mechanical properties
PLGA nanofibers	Cellulose nanocrystals (CNC)/neurotensin	Decrease in proinflammatory status, modulation of keratinocyte function
Chitosan nanofiber	Collagen	Accelerated skin repair but increased aberrant scarring
5-Methylpyrrolidinone chitosan (MPC)	Collagen	Better results than chitosan nanofiber
PCL	Oxygen loaded in inorganic salt	Sustained oxygen release to the damaged tissue
PCL thermostable multilayer nanofibrous scaffold	Mupirocin	Stable prolonged antimicrobial effect
Nanofibrous scaffold	Astragulus	Microvascular restoration
PCL-collagen scaffold	Elastin	More efficient fibroblast and keratinocyte migration and remodeling
Zn-polyP (inorganic polyphosphate polymer)	—	Substrate for ATP production, enhancement of metabolic activity of all cellular types
Chitosan hydrogel	Biomimetic peptide part of laminin	Improved cellular mobility and adhesion as well as *in vivo* angiogenesis and proliferation
Type I collagen scaffold	Integrin molecules, laminin fragments	Migration adhesion and proliferation of keratinocytes, fibroblast s and myofibroblasts
Nanofibrous PCL scaffold	EGF	Better adhesion, migration and proliferation but not as high as EGF loaded nanoparticles
Nanofibrous PCL scaffold/poly(vinyl alcohol) (PVA)	EGF	More efficient *in vivo* re-epithelization
Thin membranous collagenous scaffold	PCL	Faster skin repair and collagen synthesis
Thin membranous collagenous scaffold	Ultra-thin silk fibroin nanofibrous scaffold	Faster skin repair and collagen synthesis
Silicon carbon nanohybrids	—	Enhanced wound closure, superior bacterial inhibition

(*Continued*)

Table 1.5 *(Continued)*

Nanodrug delivery system	Active drug/agent	Effect
Hybrid nanocomplex of PVA nanofibers	Carbon nanotubes/ rhEGF	Stability, mechanical support, water retention and safety, controlled release, cytotoxicity
Mesoporous silica nanoparticles (MSNs)	Ampicillin	Highly pH responsive, fighting bacterial resistance
MSNs	Curcumin	Inhibited inflammation and protected the wound site from falling to chronicity promoting angiogenesis and fibroblast proliferation
MSNs	Ag	Increased bactericidal load, managing drug resistance
MSNs	Cerium oxide	Adhesive properties enhanced, faster wound closure and faster uneventful skin remodeling
Mesoporous bioactive glasses (MBGs)	Cu/cellulose-based aerogel	Up-regulation of proangiogenic fibroblast genes, antibacterial protection
MBGs	Cu	Up-regulation of proangiogenic fibroblast genes, antibacterial protection
MBGs	Cu/cellulose scaffold	Up-regulation of proangiogenic fibroblast genes, antibacterial protection
Polycaprolactone (PCL)	Collagen-based scaffolds	Increased mechanical strength and closure
PCL/poloxamer nanofiber scaffold	—	Approximation of skin mechanical properties
PLGA nanofibers	Cellulose nanocrystals (CNC)/neurotensin	Decreasing the proinflammatory status, modulates keratinocyte function
Chitosan nanofiber	Collagen	Accelerated skin repair but increased aberrant scarring
PCL	Oxygen loaded in inorganic salt	Sustained oxygen release to the damaged tissue
PCL thermostable multilayer nanofibrous scaffold	Mupirocin	Stable prolonged antimicrobial effect
Nanofibrous scaffold	Astragulus	Microvascular restoration
PCL-collagen scaffold	Elastin	More efficient fibroblast and keratinocyte migration and remodeling
Zn-polyP (inorganic polyphosphate polymer)	—	Substrate for ATP production, enhances the metabolic activity of all cellular types
Chitosan hydrogel	Biomimetic peptide part of laminin	Improves cellular mobility and adhesion as well as *in vivo* angiogenesis and proliferation
Type I collagen scaffold	Integrin molecules, laminin fragments	Migration adhesion and proliferation of keratinocytes, fibroblasts and myofibroblasts

Table 1.5 *(Continued)*

Nanodrug delivery system	Active drug/agent	Effect
Nanofibrous PCL scaffold	EGF	Better adhesion, migration and proliferation but not as high as EGF loaded nanoparticles
Nanofibrous PCL scaffold/poly (vinyl alcohol) (PVA)	EGF	More efficient *in vivo* reepithelization
Thin membranous collagenous scaffold	PCL	Faster skin repair and collagen synthesis
Thin membranous collagenous scaffold	Ultrathin silk fibroin nanofibrous scaffold	Faster skin repair and collagen synthesis
Nanofibrous PLGA scaffold	—	Deterioration of wound healing and repair

Source: Adapted from Karypidis (2021).

According to Karypidis, "*the use of dual agents is also a significant area of future NDSs (NanoDrugSystems) research development. For example, β-catenin is defined as a dual function protein regulating and coordinating cell-to-cell adhesion and cell migration. Tissue sampling of β-catenin could serve as a prognostic marker in skin repair, as it can effectively identify the inhibition of epithelial cell and keratinocyte migration or the activation of fibroblast proliferation as well as sites of thickened, hyperproliferative and parakeratotic epidermis. It can also help diagnose chronic wounds by tracking aberrant proliferation and inappropriate differentiation of cells in the margins of skin defects. Additionally, skin repair and regeneration could be accelerated by loading the appropriate nanoparticulate system with β-catenin, or agents that up-regulate the production of β-catenin, while securing and prolonging its bioavailability at the skin defect site. Limitations include the non-standardized procedure of specimen collection and the need for identifying other co-agents that can modify β-catenin behavior, such as Asiaticoside Nitric Oxide gel which regulates β-catenin levels for efficient skin regeneration*" (Karypidis 2021).

The application of nanotechnology in the field of foods and food supplements/nutraceuticals should also be mentioned. There are a huge number of different formulations of vitamins, minerals, essential fatty acids, plant extracts, and amino acids. They are used to support specific physiological actions and not to treat or prevent human diseases or to modify and affect physiological functions (https://www.efsa.europa.eu/en/topics/topic/food-supplements). In order to improve the bioavailability of food supplements, nanoscaled formulations are being prepared and they are used to protect the products from degradation. The most frequently used food supplements are categorized as follows:

Vitamins. A, E, D, C, folic acid, riboflavin, and the pro-vitamin, carotene
Antioxidants. curcumin, astaxanthin, lycopene, resveratrol, quercetin, naringin, lutein, hydroxytyrosol, polyphenols, catechins, etc.
Probiotics. *lactobacillus* and *Bifidobacterium*

The bioavailability is increased by improving the solubility of the food supplement under gastrointestinal (GI) conditions or by increasing the transfer through the intestinal wall and by controlling the release profile of the food supplement within the GI tract. Liposomes are considered advanced excipients to solubilize food supplements, to protect them from the GI environmental conditions, and to improve their bioavailability. Their physicochemical characteristics such as size, size distribution, and surface properties are considered crucial for their effectiveness (Oehlke et al. 2014).

Food supplements are regulated by the European Food and Safety Authority (EFSA) and the FDA regulatory authority in the United States. The legislation in the European market concerning food supplements is the directive 2002/46/EC. This directive includes the lists of the vitamins and mineral substances that are used in manufacturing food supplements (Anadon et al. 2016, pp. 895–923). Compounds other than vitamins or minerals that could be used to produce food supplements are subject to Regulation (EC), No. 2015/2283 on novel food. This includes nanoformulations of this kind of compounds.

The EFSA is an independent source that provides scientific advice on food related risks. The advice helps also to protect consumers from risks in the food chain and covers food and feed safety, nutrition, animal health and welfare, plant protection, and plant health. According to the EFSA, four main pillars deal with the risk assessment of nanoformulations that are used as food supplement carriers.

- The physicochemical properties of the nanocarriers
- The interaction with the tissues
- The compounds from which the nanoparticles are composed
- The analysis of the composition of nanoparticles

The chemistry of the compounds is an important issue and deals with the safety of each compound. The size, the size distribution, and the surface properties are important for characterizing the nanoparticles as well as the techniques that were used for their development and production. *In vitro* studies should be performed to identify the safety of the compounds from which nanocarriers are composed, regarding their immunological, neurotoxic, and proliferative effect to the tissues. The risk assessment of nanocarriers, according to FDA requirements, includes good manufacturing practices (GMPs) concerning the manufacturing process, storage conditions, and the avoidance of any contamination or unexpected packaging and labeling of the final product (Migliore 2017).

Nanotechnology, regarding its application in the food sector, has an important role. The utilization of nanodevices to embed natural stabilizers plays a crucial role in preserving the physical integrity of food over time. These stabilizers help mitigate the effects of temperature variations caused by inadequate maintenance and prevent contaminations that could alter the pH, thereby leading to spoilage. This technology significantly contributes to enhancing the safety and maintaining the organoleptic properties of food products. It is also known that the entrapment of enzymes with nutritional value in nanosystems, such as liposomes, can increase their stability and control their release during food consumption but also during production and storage, until they are used by the consumer, protecting the enzymes from physicochemical degradation or alteration of their active and functional conformation. The addition of nanobiosensors in packaging materials creates safe products that can, through color changes, warn of food spoilage, thus protecting the consumer.

Furthermore, nanotechnology has an important role to play in the protection of the recipient from any adverse effects regarding vitamins, minerals, or other herbal products, by increasing their bioavailability, *i.e*., it offers a high concentration of the substance in the blood. Otherwise, the vitamin or trace elements are easily degraded by the body, forcing us to take a large amount to achieve the necessary levels. When incorporated inside the nanoparticle, they are protected from hydrolysis or physicochemical changes that normally occur when they enter the body. The entrapment of insoluble and lipophilic vitamins, such as vitamin D but also natural products, *e.g.,* antioxidants, such as curcumin, lipoic acid, results in more efficient absorption and consequently, higher levels of these molecules in the body. We should emphasize at this point that liposomal technology, *i.e.,* nanodevices and nanosystems, which are composed of lipid bilayers simulating our cell membranes, have a wide application and have significantly improved the absorption of vitamins and trace elements, offering a benefit to the consumer.

The growing interest for producing new food supplements includes the advantages of nanoscaled materials. Such nanomaterials can improve the bioavailability of the food supplement (*e.g.,* vitamin and trace elements) but special attention should be given to the possible hazardous properties of the nanocarrier. Thorough investigation is needed to ensure that the physicochemical and surface properties of nanocarriers do not cause any undesirable effects. The regulatory framework remains a challenge and more attention should pay to the risk assessment protocols that need to be integrated in different countries globally (Bailey 2020).

1.4 The Strategic Research and Innovation Agenda for Nanomedicine (SRIA) 2016–2030 (www.etp-nanomedicine.eu)

According to the European Medicine Agency (EMA), nanotechnology is "*the use of tiny structures less than 1000 nanometres across, which are designed to have specific properties. In medicine, nanotechnology has the potential to open new possibilities for the improvement of the properties of medicines, such as their solubility or stability, and the development of more efficient ways to deliver medicines and target them accurately in the body*." Furthermore, nanotechnology is "*the production and application of structures, devices, and systems by controlling the shape and size of materials at nanometre scale (range from atomic level at 0.2 nm up to around 100 nm)*" (Demetzos et al. 2020). Materials at molecular level that are used to produce nanodevices may have different properties and safety from the final self-assembled formulation at nanoscale. However, NBCDs (Demetzos et al. 2020) are medicines that are not belong to small pharmacologically active molecules (*i.e.,* low molecular mass drugs) and are not biological compounds such as macromolecules. In our point of view, it is better to characterize such formulations as nonbiological complex medicines (NBCMs), because of the advanced nanocarrier which could be defined as advanced excipient (Chapter 7) that encapsulates drugs (small molecules or macromolecules). Such medicines, *i.e.,* NBCMs, are composed of a drug and of an advanced excipient.

The Strategic Research and Innovation Agenda for Nanomedicine (SRIA), a collaborative work published by people involved in the European Technology Platform (ETP) Nanomedicine and in the ERA-Net EuroNanoMed, describes the in-depth discussion concerning the evolution of nanotechnology within the European Nanomedicine community.

Applications of nanotechnology for treatment, diagnosis, monitoring, and control of biological systems are referred to as nanomedicine and the umbrella term for the many scientific disciplines that have embraced the prefix *nano* in their applications is nanotechnology. The most important argument supporting the need for applying nanotechnology in health care is the fact that nanotechnology approaches scientifically the biological processes due to the scale of dimension and uses tools for analysis and manipulation of diseases, from cells to sub-cellular domains.

The scale of particles in the cosmos (invisible and visible) is presented in Fig. 1.3.

The SRIA for nanomedicine focuses on unmet needs regarding the health of the European community and promotes nanomedicine as a field for producing new and innovative diagnostic and therapeutic products. Moreover, the agenda facilitates interactions with other KETs and optimizes the implementation of the innovation process into the healthcare systems promoting the benefits for patients and industrial investment. Finally, the enhanced competitiveness of the European economy in the global market could be an asset.

The most important diseases that the WHO focuses on (see below) should be taken into consideration and require communication and collaboration between stakeholders from research, industry, and public authorities in order for society to benefit. The emerging ecosystem shows promise but requires social-economic implementations and the establishment of sustainable interactions among academic research groups, small and midsize enterprises (SMEs), and global healthcare providers. This collaboration aims to facilitate the distribution of new nanomedicinal products to the market, benefiting patients. The strategic documents that have been published in the last decade from the European Technology Platform on Nanomedicine (ETPN) (www.etp-nanomedicine.eu) are presented in Fig. 1.4.

The main promising approaches for nanomedicine applications in the fields of diagnosis, therapy, and regenerative medicine may be categorized as follows:

In the field of therapeutics

- Nanotechnologies to cross biological barriers
- "Smart" nanocarriers

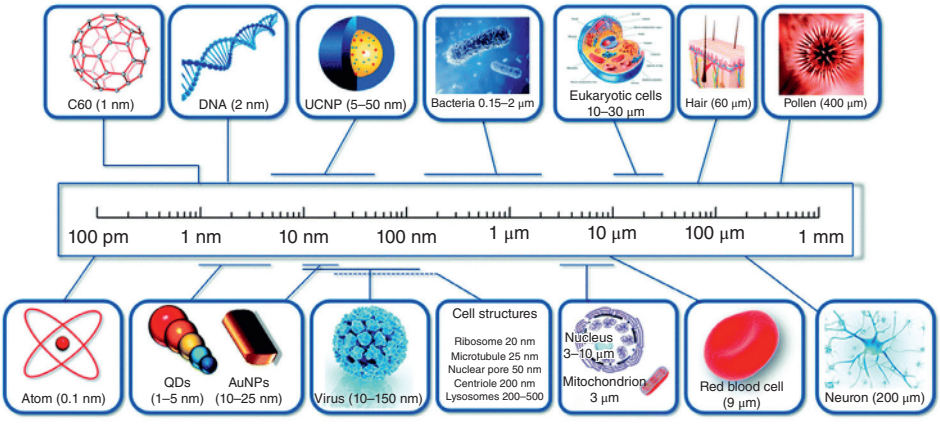

Figure 1.3 *Scale of particles from molecular to macroscopic level. Source: Bayda et al. (2019)/MDPI/CC BY 4.0.*

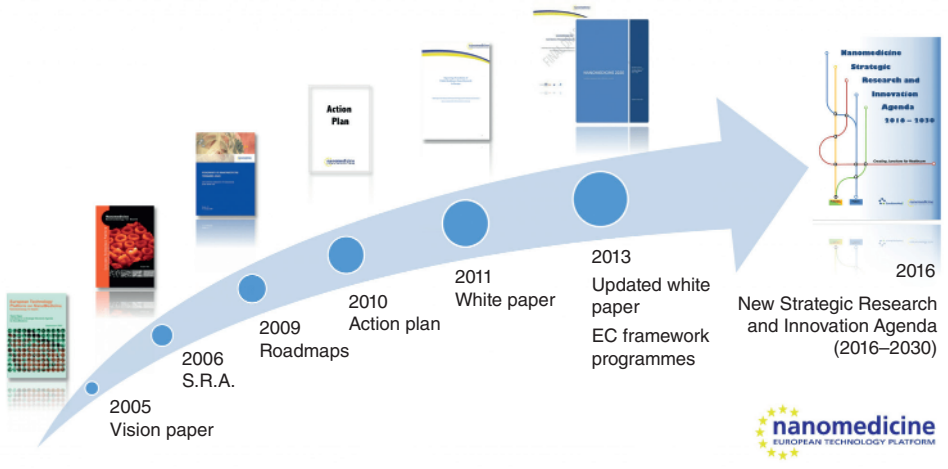

Figure 1.4 *Strategic documents published by the ETPN in last decade. Source: ETPN Association / www.etp-nanomedicine.eu / last accessed 24 February 2024.*

- Biocompatible nanoparticles
- Activable nanoparticles providing physical therapeutic effects
- Monitoring of therapeutic efficacy
- Theranostic nanoparticles and nanodevices carrying a drug and acting as diagnostic tool.

In the field of diagnostics and imaging
- Nanoenabled biomarkers, vectors, and contrast agents with high-sensitivity and specificity
- Nanotechnologies to cross biological barriers (BBB)
- High throughput systems
- Nanostructures surfaces for biosensors
- Noninvasive and painless monitoring

In the field of regenerative medicine
- "Smart" nanostructures and functionalized surfaces
- Scaffolds and nanoparticles for new and advanced therapeutic treatment
- 3D printing of cells and biomaterials for implants and/or reconstitution
- Intelligent biomaterials/bioactive materials
- Nanofunctionalization for increase biocompatibility of implants (www.etp-nanomedicine.eu).

The most important diseases that the WHO proposes to be considered into the research and development framework are embraced by the SRIA and presented below

- Noncommunicable diseases, such as atherosclerosis and cardiovascular diseases, cancer, and chronic obstructive pulmonary diseases, which account for 80% of deaths in Europe
- Neuro-degenerative and other neurological disorders
- Infectious diseases
- Diabetes and endocrine disorders
- Arthritis and osteoarticular pathologies

Rare diseases are considered a mixture of pathologies and 30 million of people in Europe suffer from more than 6000 different disease while the majority (80%) are genetic disorders.

The future challenges according to SRIA are

- to interface multibillion industries toward new value chains,
- to improve manufacturing of complex smart medical solutions,
- to accelerate adaptation of the regulatory systems to speed up developments toward a "fast but safe track" to innovation,
- to develop new business models for healthcare providers adapted to the new precision medicine trends,
- to embrace doctors, patients, and society in the implementation of new cross-KETs medical options to gain acceptance of these stakeholders (www.etp-nanomedicine.eu).

Summarizing,

The SRIA:

- offers the opportunity to assess the state of the art and to provide the larger nanomedicine community with research and innovation priorities for the next 15 years.
- integrating innovation aspects into the Strategic Agenda for Nanomedicine is of crucial significance for the ETPN as emphasizes the efforts of the European Community to tackle the challenges in translation to the market and to contribute to an emerging industrial sector in nanomedicine.
- focuses strongly on unmet clinical needs in selected diseases, highlighting thereby the potential of current and future nanomedical products to provide new, efficient, and effective solutions for healthcare.
- relies to a large extent on data and information collected through consultations with the 160 members of the ETPN and 150 researchers from clinical institutions having submitted applications to the EuroNanoMed calls.

In our view, scientific excellence in innovative medicines including nanoformulated medicinal products is an ongoing challenge in EU and globally. It is of interest that theranostics (Chapter 5), which is a part of personalized medicine at nanoscale, demonstrates new achievements and new approaches by using drugs or biomacromolecules to target receptors that are well-known biomarkers. The concept of the public–private partnership (PPP) (Gaspar 2007) is to bring together different scientific disciplines based on nanotechnological and biotechnological approaches. This bio-inspired therapeutic nanotechnology has the potential to provide new nanomedicines inspired by new biological targets.

References

Anadon, A., Martinez-Larrañaga, M.R., Ares, I. et al. (2016). Evaluation and regulation of food supplements: European Perspective. *Nutraceuticals* 895–923. https://doi.org/10.1016/B978-0-12-802147-7.00063-2.

Arif, T., Nisa, N., Amin, S. et al. (2015). Therapeutic and diagnostic applications of nanotechnology in dermatology and cosmetics. *Journal of Nanomedicine & Biotherapeutic Discovery* 5 (3): 1000134. https://doi.org/10.4172/2155-983X.1000134.

Bailey, R.L. (2020). Current regulatory guidelines and resources to support research of dietary supplements in the United States. *Critical Reviews in Food Science and Nutrition* 60 (2): 298–309. https://doi.org/10.1080/10408398.2018.1524364.

Bayda, S., Adeel, M., Tuccinardi, T. et al. (2019). The history of nanoscience and nanotechnology: from chemical-physical applications to nanomedicine. *Molecules* 25 (1): 112. https://doi.org/10.3390/molecules25010112.

Chrysostomou, V., Foryś, A., Trzebicka, B. et al. (2022). Amphiphilic copolymer-lipid chimeric nanosystems as DNA vectors. *Polymers (Basel)* 14 (22): 4901. https://doi.org/10.3390/polym14224901.

Demetzos, C. (2022). *The Voice of doi:Science, the Silence of Nature*. Lambert Academic Publishing.

Demetzos, C., Kavatzikidou, P., Pippa, N. et al. (2020). Nanomedicines and nanosimilars: looking for a new and dynamic regulatory 'Astrolabe' inspired system. *AAPS PharmSciTech* 21: 65. https://doi.org/10.1208/s12249-019-1573-y.

Dianzani, C., Zara, G.P., Maina, G. et al. (2014). Drug delivery nanoparticles in skin cancers. *BioMed Research International* 2014: 895986. https://doi.org/10.1155/2014/895986.

Drexler, E. (1992). *Nanosystems: Molecular Machinery Manufacturing and Computation*. Chichester: Wiley.

El Naschie, S.M. (2006). Nanotechnology for the developing world. *Chaos, Solitons & Fractals* 30 (4): 769–773.

ETPN - Nanomedicine European Technology Platform. www.etp-nanomedicine.eu

Freitas, R.A. Jr. (2005). What is nanomedicine. *Nanomedicine* 1 (1): 2–9. https://doi.org/10.1016/j.disamonth.2005.08.003.

Gaspar, R. (2007). Regulatory issues surrounding nanomedicine: settling the scene for the next generation of nanopharmaceuticals. *Nanomedicine (Lond)* 2: 143.

Haque, F.Z. (2013). Chemical hazards of nanoparticles to human and environment (a review). *Oriental Journal of Chemistry* 29 (4): 1399–1408. https://doi.org/10.13005/ojc/290415.

Hashim, P.W., Nia, J.K., Han, G., and Ratner, D. (2020). Nanoparticles in dermatologic surgery. *Journal of the American Academy of Dermatology* 83: 1144–1149.

Karypidis, D. (2021). Nano-drug delivery systems for skin repair and regeneration. MSc thesis. National and Kapodistrian University of Athens.

Makvandi, P., Josic, U., Delfi, M. et al. (2021). Drug delivery (nano)platforms for oral and dental applications: tissue regeneration, infection control, and cancer management. *Advanced Science (Weinheim, Baden-Wurttemberg, Germany)* 8 (8): 2004014. https://doi.org/10.1002/advs.202004014.

Migliore, A. (2017). On the new regulation of medical devices in Europe. *Expert Review of Medical Devices* 14 (12): 921–923. https://doi.org/10.1080/17434440.2017.1407648.

Oehlke, K., Adamiuk, M., Behsnilian, D. et al. (2014). Potential bioavailability enhancement of bioactive compounds using food-grade engineered nanomaterials: a review of the existing evidence. *Food and Function* 5: 1341–1359.

Regenold, M., Bannigan, P., Evans, J.C. et al. (2022). Turning down the heat: the case for mild hyperthermia and thermosensitive liposomes, nanomedicine: nanotechnology. *Biology and Medicine* 40: 102484. https://doi.org/10.1016/j.nano.2021.102484.

Shah, S., Dhawan, V., Holm, R. et al. (2020). Liposomes: advancements and innovation in the manufacturing process. *Advanced Drug Delivery Review* 154–155: 102–122.

Soares, S., Sousa, J., Pais, A. et al. (2018). Nanomedicines: principles, properties and regulatory issues. *Frontiers in Chemistry* 6: 1–15.

Thapa, R.K. and Kim, J.O. (2023). Nanomedicine-based commercial formulations: current developments and future prospects. *Journal of Pharmaceutical Investigation* 53: 19–33.

Tsakiri, M., Peraki, A., Chountoulesi, M. et al. (2022). Chimeric liposomes decorated with P407: an alternative biomaterial for producing stealth nano-therapeutics. *Journal of Liposome Research* 32 (1): 83–91.