AIP Conference Proceedings

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Cite as: AIP Conference Proceedings **1990**, 020001 (2018); https://doi.org/10.1063/1.5047755

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Deployment and Exploitation of Nanotechnology Nanomaterials and Nanomedicine

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Abstract. Since around 50 years ago, the academic world is developing knowledge and technology to understand and to control matter at the nanoscale in order to exploit the peculiar mechanical, electrical, optical and magnetic properties emerging when a discrete number of atoms is assembled in structures which must be described according to the weird rules of quantum mechanics. This huge know how, commonly named Nanotechnology, was nucleated according to deployment strategies mainly defined and funded worldwide by governmental institutions in order to create the base for their further industrial exploitation and to provide an expectedly large socioeconomic impact. In the following, we will give a brief overview of the main applications of nanomaterials and an estimate of their value, based on the forecasts provided by some market research companies. In particular, we will briefly disclose the application of nanomaterials in the fields of Electronics & ICT, Energy and Environment, and, in particular, in the highly rewarding field of Nanomedicine. Further, we will highlight some key aspects of the deployment policies undertaken around the world which still are a key prerequisite for a full exploitation of the potential of Nanotechnology.

INTRODUCTION

In 1959, decades before Nanotechnology was even defined, Richard Feynman said in a visionary lecture “in the great future we can arrange the atoms the way we want” [1]. This vision set in motion the Nanotechnology race [2]. In parallel, with technical achievements in the field of manipulating and observing the nanoworld, since the ‘80s there was a growing understanding of the behaviour of matter at the nanoscale and of methods to make nanoparticles. Since its first steps, Nanotechnology showed its potential to: i) revolutionise many field of our lives by impacting any manufactured item, and ii) help societies achieve the shared goal of improving efficiency and accelerating progress in a wide range of economic sectors such as, for example, medicine, manufacturing and energy. As a result of significant public and private investments in Nanotechnology during the past decades, Nanotechnology matured to a point of showing significant results in terms of exploitation. The assessment of the exploitation of Nanotechnology is a challenge due to the broad economic sectors impacted by Nanotechnology, ranging from goods to services and manufacturing techniques. Therefore, there exists a large and varied amount of

NANOINNOVATION 2017
AIP Conf. Proc. 1990, 020001-1–020001-25; https://doi.org/10.1063/1.5047755
Published by AIP Publishing. 978-0-7354-1706-9/$30.00

data on Nanotechnology exploitation that may be difficult to analyse meaningfully [3]. This paper starts describing the main first steps of the Nanotechnology history and then provides an analysis of Nanotechnology exploitation, discussing the many data with a specific focus on Nanomedicine. It then follows a description of the main deployment policies adopted by many countries. In conclusion, this paper wants to analyse exploitation data and deployment policies in the Nanotechnology area in order to guide further investment and policy decisions of the different actors of the Nanotechnology ecosystem and promote the continued responsible development of Nanotechnology.

NANOTECHNOLOGY

Originating from the Greek word meaning "dwarf", the prefix "nano" signifies one-billionth. Technology is a term, etymologically derived from the Greek words "teknè" and "logos", meaning the know-how of doings things. In contemporary language, it refers to all activities to convert scientific discoveries into practical use, therefore in "industrial" applications [4]. More in details, technology allows understanding the principles that underlie how things (i.e. materials) behave and is aimed at changing the world to suit us better [5]. The term "Nanotechnology" has his roots in precision engineering [6] and was first coined in 1974 by Norio Taniguchi who defined it as "the production technology to get the extra high accuracy and ultrafine dimensions, i.e. the preciseness fineness of the order of 1 nm". It mainly consists of processes of separation, consolidation and deformation of materials by one atom or one molecule [7]. As far as the modern history of Nanotechnology concerns, the first step can be considered the invention by Max Knoll and Ernst Ruska, at the Berlin Technische Hochschule, of the electron microscope, a technique for observing the matter at the nanoscale. In 1931, thanks to their discovery, they overcame the barrier to higher resolution that had been imposed by the limitations of classical optical instruments, therefore allowing the future imaging of nanoparticles [8]. In 1959 Richard Feynman, the scientific father of Nanotechnology, presented at Caltech a visionary lecture where he introduced a process to manipulate individual atoms/molecules and the unique properties related to this scale [1]. In 1968 a technique was invented to deposit single atomic layers (Molecular Beam Epitaxy) and in 1989 the first example was shown of manipulation at the atomic scale by writing the letters of the company IBM on a copper surface with individual Xenon atoms. As far as the development of techniques to observe the matter at the nanoscale is concerned, the Scanning Tunneling Microscope (STM) was invented in 1981 and the Atomic Force Microscope (AFM) in 1986. These instruments opened the doors of the nanoworld to scientists and revolutionised the imaging and manipulation of surfaces at the nanoscale. If the electron microscope may be likened to a kind of ultra-powerful eye, the STM and the AFM may be described as a sort of delicate finger that investigates matter by prodding it [9]. The first process to make nanoparticles was patented in 1978 as a first step in nanochemistry, that means discovery and design of new nanomaterials, and the carbon fullerene was discovered in 1985. Nanochemistry has become a growing industry (i.e. industrial production of nano-silica, silver and titanium for the building and catalyst industry) exploiting the almost infinite possibilities of designing nano-objects, and has found a wide range of applications, from electronics to the health sciences. In the '70s thanks to recombinant DNA technology it became possible to insert extra genes into cells and make them produce for example drugs like insulin. Nowadays, Nanotechnology also draws inspiration from Nature by using similar principles to generate macromolecules, such as drugs or biofuels or nano-assemblies, with applications ranging from medicine to automotive or aerospace [10].

A last example, but no doubt one of the most spectacular of all, is the development of microelectronics. The extraordinary expansion in this field at the end of the twentieth century brought the pursuit of ever smaller devices into the limelight. The evolution of this miniaturisation has been brought about by the tremendous advances in the semiconductor industry and the ability to produce smaller and smaller integrated circuits (ICs) [11]**.**

Nowadays, there are many definitions of the term "Nanotechnology", but common elements to all of them are: the scale (1-100 nm or less), the exploitation of size-dependent properties that are unique at this scale (importance of miniaturization), the manipulation of nanoscale structures/materials/processes, and the creation of nanoscale-enabled devices for specific technological applications [12]**.** Nanotechnology is not just the business of miniaturising matter, as it is often referred to as a cross-cutting or key-enabling technology since it can pervade virtually all technological sectors enabling novel applications [13]. It is of systemic relevance, multidisciplinary and trans-sectorial, i.e. at the cross-roads of different technologies and disciplines such as physics, chemistry and biology [14]. Thanks to its aim of understanding and controlling matter at dimensions between approx. 1 to 100 nm, Nanotechnology involves imaging, measuring, modelling and manipulating matter at this length scale where unique phenomena enable novel applications [15]. The value proposition of Nanotechnology, providing opportunities to scientists as well as entrepreneurs, is the unique behaviour at the nanoscale of materials properties - chemical (i.e. reactivity), electrical (i.e. conductivity), optical (i.e. transparency), mechanical (i.e. hardness). In fact, when moving from the macroscale to the nanoscale we gain access to a set of different properties due to quantum effects that derive from the interaction of matter and energy at the nanoscale [16]. More in details, at the nanoscale electromagnetic forces and the movement of electrons become the dominant factor, and radically new properties emerge due to quantum effects.

As it is well known, in order to progress technological developments need to be disseminated and communicated. Such an activity as well as the promotion/popularization of the technological significance of nanoscale phenomena and devices was launched in the ’80s by K.E. Drexler who was the author of the first scientific paper [17], the first book [18] and the first doctoral dissertation on Nanotechnology. Together with C. Peterson, Drexler founded the Foresight Institute, aimed at facilitating the communication of advances in Nanotechnology that are most likely to transform our future. As time went by, different areas of understanding and manipulating the nanoscale came together to form the field of nanoscience, or Nanotechnology when we speak of applications, with the unifying feature of the length scale at which the different phenomena take place. In conclusion, we can state that nowadays, thanks to the aforementioned development of new tools and techniques as well as to the discovery of new properties and materials, Nanotechnology is already influencing many industrial fields ranging from health to electronics with more than 2,000 Nanotechnology consumer products [19].

NANOTECHNOLOGY AS A DRIVER FOR DISRUPTIVE INNOVATION: PERVASIVITY AND ECONOMIC IMPACT

Innovation has come to mean specifically the process whereby new products are introduced into the commercial sphere. Innovation is defined as “the technical, designing, manufacturing, management and commercial activities involved in the marketing of a new (or improved) product or the first commercial use of a new (or improved) process or equipment” [20]. *Disruptive innovation* is an innovation that creates a new market and value network and eventually disrupts an existing market and value network, displacing established market-leading firms, products and alliances [21]. A disruptive process can take longer to develop than a conventional one and the risk associated to it is higher than other more incremental or evolutionary forms of innovations, but once it is deployed in the market, it achieves a much faster penetration and a higher degree of impact on the established markets [22]. Technologies for disruptive innovation, by definition, are qualitatively different from those in existence at the moment of their emergence.

Inevitably, being concerned with building matter up atom-by-atom, Nanotechnology is a *universal technology* with enormous breadth which can be applied to virtually any manufactured artefact [23]. Universal technologies form the basis of new value creation through disruptive innovation for a broad range of industries. Nanostructured materials are incorporated into nanoscale devices, which in turn are incorporated into many products. The pervasive presence of computing is *enabled* by Nanotechnology. The fact that the feature sizes of components on semiconductor microprocessor chips are now smaller than 100 nm, and hence within the nanoscale, means that practically the entire realm of information technology has now become part of Nanotechnology. Nanotechnology is, therefore, becoming *pervasive*.

Nanotechnology may trigger an unprecedented revolution whenever the ultimate goal of Nanotechnology is reached: the development of Atomically Precise Manufacturing (APM) which, according to the visionary engineer Eric Drexler, *is* Nanotechnology [18, 24]. Atom-by-atom manufacturing certainly is inspired by nature [25, 26]: Nature shows that molecular machines can be programmed by instructions encoded in DNA to build complex, atomically precise structures, including components that fit together precisely [27]. Nature also shows that molecular machines can join and position a wide range of reactive molecules, guiding their encounters in order to build atomically precise biomolecular structures and machine components. Similar machines could be used to join, position, and combine an even wider range of reactive molecules, even outside the realm of biology, and thereby build a greater range of atomically precise structures, including machine components that are more densely bonded and hence more robust. These more robust next-generation components could be used to build higher performance production machinery, which in turn could be used to build a yet wider range of components, and from these components yet more capable production machines, and so on, extending toward a horizon far beyond biology. According to Drexler, large scale, high-throughput APM is the heart of advanced Nanotechnology and in the coming years it has the potential to transform our world. APM may open the door to extraordinary improvements in the cost, range, and performance of products. Their range of applications extends beyond the whole of modern physical technology, spanning ultra-light structures for aircrafts, billion-core laptop computers, and microscopic devices for medical use, including devices able to recognize and destroy cancer cells. APM may replace enormous, polluting factories with clean, compact machines that can make better products with a more frugal use of energy and material resources.

APM certainly is yet to come but it has to be underlined that:

- researchers now routinely use scanning probe instruments to image and place individual atoms and to manoeuvre and join individual molecules [28]: this level of control has demonstrated the principle of mechanically directed atomically precise fabrication;
- organic chemists have built steadily larger and more complex structures along with motors and other machines: their techniques now provide a rich toolkit for building molecular systems, while inorganic chemists and materials scientists have expanded a complementary toolkit of nanoscale structures;
- protein engineering has flourished [29], supported by computer-aided design software, and now enables the routine design of intricate, atomically precise nanoscale objects, including structural components and functional devices [29, 30];
- structural DNA Nanotechnology has emerged and now enables rapid and systematic fabrication of addressable, atomically precise frameworks on a scale of hundreds of nanometers and millions of atoms;
- quantum methods in chemistry have advanced together with the power of computers and algorithms, providing powerful, physics-based tools for modelling and molecular engineering [30];
- molecular mechanics methods in chemistry can now describe the structure and dynamics of molecules on scales that reach millions of atoms, a range that enables the design and development of complex, atomically precise systems [31].

The awareness of the potential impact of APM may justify the assignment of the 2016 Nobel Prize in Chemistry to Jean-Pierre Sauvage, Fraser Stoddart and Bernard Feringa “for the design and synthesis of molecular machines” [32] which certainly are on the APM development track.

Jim Tour, a scientist and serial entrepreneur at Rice University, named among *the 50 Most Influential Scientists in the World Today* by TheBestSchools.org in 2014, listed in *The World’s Most Influential Scientific Minds* by Thomson Reuters ScienceWatch.com in 2014, believes that “it will take 100 to 200 years to fabricate everything from the bottom up using molecular machines” [33].

Even if APM may represent the long-term, final goal of Nanotechnology, there are countless applications of Nanotechnology that are already providing or may provide in the near term a huge impact on the socio-economic ground at global level.

THE NANOTECHNOLOGY VALUE CHAIN: NANOMATERIALS AND THEIR APPLICATIONS

Figure 1 shows the Nanotechnology global value chain (GVC) framework, as proposed by Frederick Stacey of the GVC Center of Duke University (NC, USA), who developed the GVC approach to analyze the innovation to commercialization life cycle of an enabling technology such as Nanotechnology.

The Nanotechnology GVC may be helpful to identify how the actions and relationships between public and private stakeholders affect the development, location, and competitiveness of an industry and to provide an estimate of the value of a specific element of the chain.

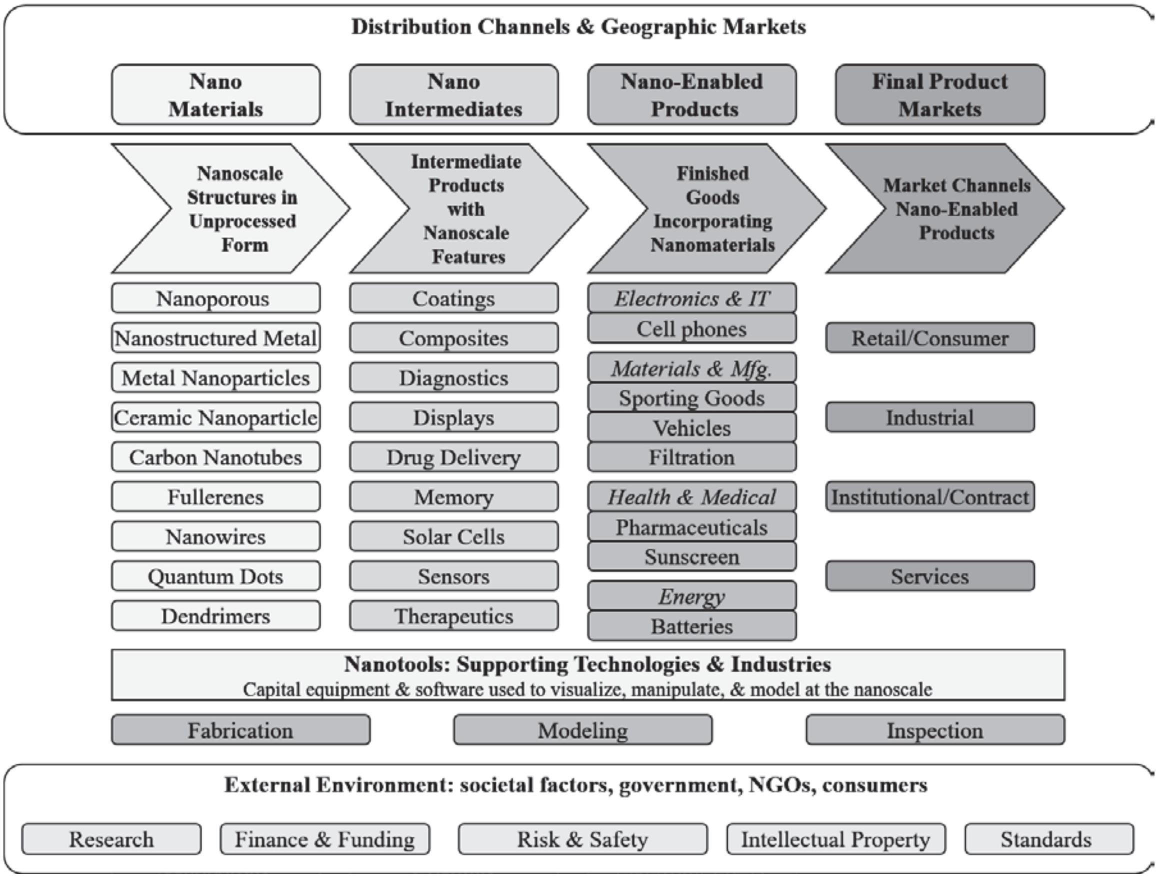


FIGURE 1. The Nanotechnology Value Chain (adapted from [34]).

In the following, we will give a brief overview of the main applications of nanomaterials and an estimate of their value (e.g. the value of quantum dots - QD), based on the forecasts provided by some market research companies, without discussing the whole value generated through the exploitation of Nanotechnology across the rest of the Nanotechnology value chain (e.g. the value of QLED displays).

In particular, we will briefly disclose the application of nanomaterials in the fields of Electronics & ICT, Energy and Environment, leaving more space to consider the impact and the emerging business of Nanomedicine.

THE GLOBAL NANOMATERIALS MARKET

According to a report issued by Zion Market Research in 2017 [35], the global nanomaterials market is valued at USD 7.3 billion in 2016 and is expected to reach USD 16.8 billion in 2022, growing at a CAGR of 15.5% between 2017 and 2022. North America dominated the nanomaterials market in 2016 mainly due to the increasing demand from the packaging industry in North America and to the extensive application of nanotubes in various industries such as electronics & ICT, pharmaceutical and chemical products. Europe was one of the leading players in the global nanomaterials market, accounting for a significant market share in 2016 while an increasing demand is expected over the next 5 years due to several emerging applications in the European healthcare industry. The Asia Pacific nanomaterials market size is likely to experience the highest growth over the next 5 years due to the rapid increase in population in India and China, which has significantly propelled the growing construction industry. Latin America, Middle East, Africa and Saudi Arabia are also expected to witness strong growth over the next 5 years.

According to Inkwood Research [36], the global nanomaterials market (nanotubes, nanoparticles, nanowires, nanoclays and nanofibers) is projected to grow from USD 4.7 billion in 2017 to USD 13 billion by 2024, with a CAGR of 15.6% between 2017 and 2024. Nanoparticles (metals, metal oxides, quantum dots and nanofibers) represent the largest market share while nanofibers are expected to grow with the highest CAGR during the forecast period. Growing demand and usage in aerospace and automotive applications, increasing usage in the healthcare industry and growing applications in water treatment are major drivers for the nanomaterials market. The demand and application of nanomaterials in the healthcare industry are consistently increasing, especially in the Nanomedicine field. With increasing demand for improved fuel efficiency and reduced exhaust emissions, automotive manufacturers have increased their usage of nanofibers and carbon nanotubes for the production of lightweight engines and their components. Nanosilver is one of the most extensively used materials in water treatment applications.

The global nanomaterials market, not including carbon black nanoparticles used to reinforce tires and other rubber products, photographic silver and dye nanoparticles and activated carbon used for water filtration, was valued by Research and Markets at USD 4 billion in 2015 and is expected to reach USD 11 billion by 2020, at a CAGR of 22.4% between 2017 and 2022 [37].

Mordor Intelligence provides a forecast over the period 2017-2022 very similar to that published by Research and Markets: the global nanomaterials market was valued at about USD 4.1 billion in 2015 and is expected to reach USD 11.3 billion by 2020, at a CAGR of over 22% during the forecast period [38].

About 25% of the nanoproducts introduced into the market incorporate titanium dioxide, silver, or silicon dioxide nanoparticles [39]. Titanium dioxide and silicon dioxide are the most consumed metal and non-metal oxide based nanomaterials. Consumption of silicon dioxide was 198,000 tons in 2015 and is projected to reach 786,000 tons by 2022, at a CAGR of 21.8%. Silver nanoparticles are considered by Global Market Insights Inc. analysts to be the most widely commercialized nanoparticles, accounting for over 50% of the global nanomaterial consumer products in 2015 [40] with expectation of market growth at a CAGR of nearly 13% in 2016-2024 [41]. Due to its antimicrobial properties, nanosilver is among the most popular nanomaterials used in manufacturing consumer products by numerous industries, mostly electronics, IT, healthcare and beauty, textiles (20% of the world silver nanoparticles market). Main areas of application for silver nanoparticles are healthcare and the life sciences, the food and beverages packaging industry (improved packaging and active packaging), electronics and the IT sector.

The global markets for nanoclay and nanocellulose also demonstrate stable growth of the indicators based the widening range of their industrial application [42]. According to the Transparency Market Research (TMR) forecasts, the market revenue of nanoclay is expected to grow at a CAGR of 24.9%, and of nanocellulose at 19% until at least 2020 [43, 44].

TABLE 1. Selected nanomaterials markets [40-44].

Nanomaterial	Global market revenue in 2016 (USD billion)	Expected global market revenue by 2021 (USD billion)	Expected CAGR in 2016-2021 (%)
Silver nanoparticles	1.1	3.0	13
Nanoclays	0.7	2.1	24.9
Nanocomposites	1.6	5.3	26.7
Quantum dots	0.61	3.4	41.3
Nanofibers	0.39	2.0	38.6
Nanoscale ceramic powders	14.6	22.3	8.9

By the end of January 2018, the Nanowerk Nano Catalog [45] contains 3,601 nanomaterials, including 582 nanotubes, 2,453 nanoparticles, 117 graphene items, 231 quantum dots, 99 fullerenes, 77 nanowires and 42 nanofibres from more than 150 suppliers worldwide, while the StatNano Nanotechnology Products Database [46] has monitored 108 nanomaterials produced by 1,555 manufacturers in 53 countries and applied by 15 industries in 897 product types.

BASF, Evonik Industries, Covestro, Arkema, Nanocyl, Showa Denko, Air Products PLC, Cnano Technologies, Nanophase, and Glonatech SA are some of the major players in the global nanomaterials market.

Here are some specific applications of nanomaterials.

Electronics & ICT

Nanotechnology is impacting and will continue to impact on computer processing, memory, data storage and display technologies. The *transistor count* is the number of transistors on an integrated circuit (IC). As of 2016, the largest transistor count in a commercially available single-chip processor, the Intel Broadwell-EP Xeon, is over 7.2 billion. This chip is fabricated on a 456 mm^2 die through a 14 nm node process (a *node* is the average half-pitch *i.e.* half the distance between identical features of a memory cell). Moore's law - an empirical observation rather than an actual physical law - holds that the transistor count doubles every 18 to 24 months. Microelectronics has progressed along this path for nearly forty years. Within the next 10 years, however, silicon electronics will be unable to increase computing speed at the current rate [47]. Stray signals on the chip, thermal instability caused by densely packed transistors and excessive fabrication costs are predicted to crash the silicon wave. Semiconductor and computer companies such as Hewlett-Packard (HP), Intel, and IBM have already begun to research the possibility of using Nanotechnology to build chips in the future.

Data storage - A very recent example of how Nanotechnology may provide a revolution in data storage is given by the work by Sander Otte at Delft University of Technology in the Netherlands [48]. In fact, the advent of devices based on single dopants, such as the *single-atom transistor* [49], the *single-spin magnetometer* [50, 51] and the *single-atom memory* [52], has motivated the quest for strategies that permit the control of matter with atomic precision. Manipulation of individual atoms by low-temperature scanning tunneling microscopy [53] provides ways to store data in atoms, encoded either into their charge state [54], magnetization state [55-57] or lattice position [58]. The challenge now is the controlled integration of these individual functional atoms into extended, scalable atomic circuits. Otte and his colleagues assembled arrays of chlorine atoms on a nanometre-sized copper surface. They used a scanning tunnelling microscope to manipulate the atoms and vacant spaces on the surface, creating many different arrangements that encode information. The researchers used these arrays to build a 1-kilobyte rewritable data-storage device with an information density as high as *78 terabits per square centimetre*. A scaled-up device could store the entire US Library of Congress in a cube just 100 μm wide, according to the authors.

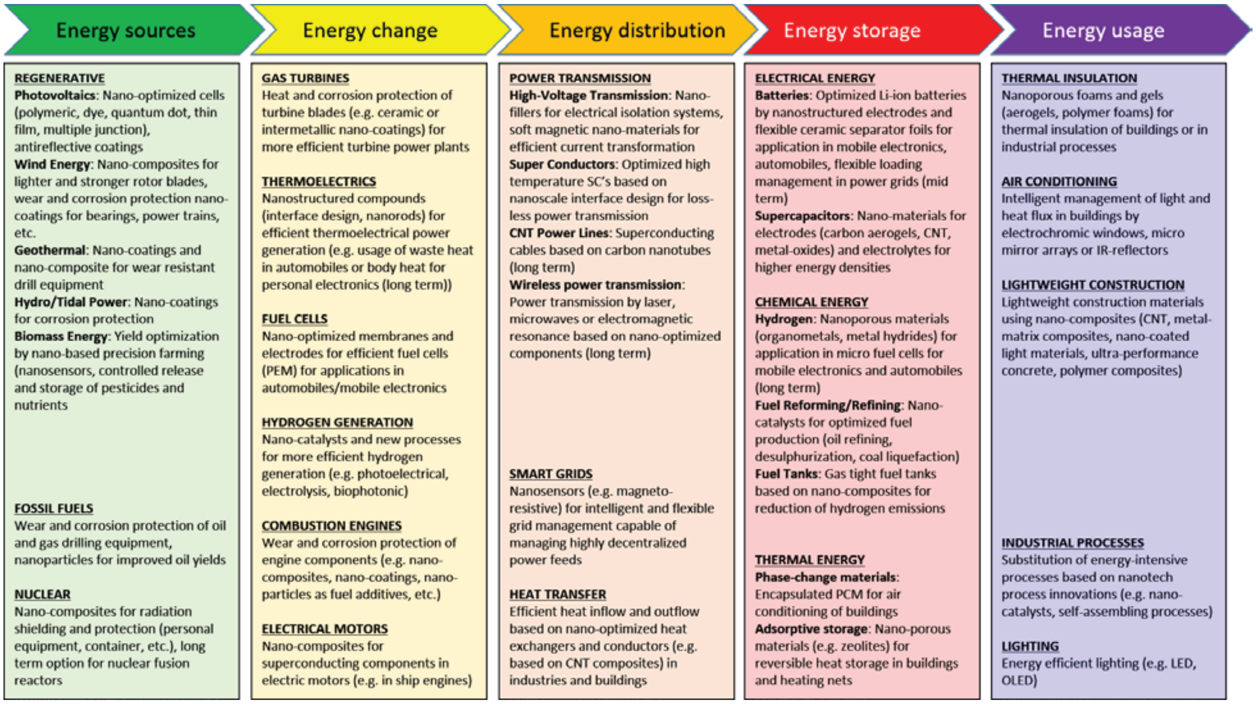
More-than-Moore computing - One of the more disruptive *more-than-Moore* approaches to computing is provided by *advanced nanophotonics*. In particular, *microcavity polaritons* may offer a way to undertake disruptive innovation towards next generation on-chip optical components (such as switches and routers), all-optical computing and quantum computing. Typically, microcavity polaritons consist in a very thin layer (1-10 nm) of a III-V semiconductor, such as GaAs, sandwiched between two high-reflecting distributed Bragg reflectors (DBRs) made of multiple thin layers (5-10 nm) of alternating materials with varying refractive index, such as TiO_2 and SiO_2. The exploitation of the strong nonlinearities provided by the excitonic component of the polariton quasiparticles recently enabled the Advanced Photonics Group of CNR NANOTEC in Lecce (Italy) to realize the *first all-optical polariton transistor-gate* [59]. Further research in this field, aimed at engineering new kinds of electronic excitations with unique quantum coherence properties, long correlation both in space and time and robustness to environment-induced decoherence may soon enable the birth of *practical quantum computing systems* [60].

Displays - An organic light-emitting diode (OLED) is a light-emitting diode (LED) in which the emissive electroluminescent layer is a film of an organic compound that emits light in response to an electric current. This layer of organic semiconductor is situated between two electrodes. OLEDs are used to create digital displays in devices such as television screens, computer monitors, portable systems such as mobile phones, handheld game consoles and PDAs. OLEDs enable a greater contrast ratio and wider viewing angle compared to LCDs, because OLED pixels emit light directly. At present, OLED films are applied to the anode layer with conventional vapor deposition but in the next future displays may be fabricated through roll-to-roll printing process, enabling the realization of bendable, rollable and foldable displays that will represent a breakthrough innovation in the display market. Fabrication of OLED displays certainly belong to Nanotechnology, as these devices are made by several very thin (1-10 nm) layers of organic and inorganic materials and a major hurdle in industrial OLED production is the strict *control* of layer thickness in the range of ± 1nm. Public and private investments in the development of technology to manufacture flexible OLED displays have been and still are huge [61] and the business potential is extremely high. Samsung Display, which invested USD 1.7 billion in the first half of 2016, made an additional investment worth USD 2.5 billion by the end of 2017. The company has made such a decision because it believes that demand of flexible OLED will rapidly rise from 2017 due to favourable factors, such as provision of OLEDs for new iPhones and foldable displays [62]. IDTechEx estimates that the market for all types of OLED displays, which has reached USD 16 billion in 2017, will grow to USD 57 billion in 2026, while plastic and flexible displays will grow rapidly from a USD 2 billion market in 2016 to USD 18 billion by 2020 [63].

Quantum dots (QD) also represent a growing opportunity towards high-mobility transistors and circuits, high-quantum-yield photodetectors and light-emitting devices, and high-efficiency photovoltaic devices [64].

Energy

Nanotechnology has the potential to enhance energy efficiency across all branches of industry and leverage the economic returns from renewable energy production through new solutions. Nanotechnology innovations could impact each part of the value-added chain in the energy sector, shown in Fig. 2.



Energy sources

REGENERATIVE
Photovoltaics: Nano-optimized cells (polymeric, dye, quantum dot, thin film, multiple junction), antireflective coatings
Wind Energy: Nano-composites for lighter and stronger rotor blades, wear and corrosion protection nano-coatings for bearings, power trains, etc.
Geothermal: Nano-coatings and nano-composite for wear resistant drill equipment
Hydro/Tidal Power: Nano-coatings for corrosion protection
Biomass Energy: Yield optimization by nano-based precision farming (nanosensors, controlled release and storage of pesticides and nutrients

FOSSIL FUELS
Wear and corrosion protection of oil and gas drilling equipment, nanoparticles for improved oil yields

NUCLEAR
Nano-composites for radiation shielding and protection (personal equipment, container, etc.), long term option for nuclear fusion reactors

Energy change

GAS TURBINES
Heat and corrosion protection of turbine blades (e.g. ceramic or intermetallic nano-coatings) for more efficient turbine power plants

THERMOELECTRICS
Nanostructured compounds (interface design, nanorods) for efficient thermoelectrical power generation (e.g. usage of waste heat in automobiles or body heat for personal electronics (long term))

FUEL CELLS
Nano-optimized membranes and electrodes for efficient fuel cells (PEM) for applications in automobiles/mobile electronics

HYDROGEN GENERATION
Nano-catalysts and new processes for more efficient hydrogen generation (e.g. photoelectrical, electrolysis, biophotonic)

COMBUSTION ENGINES
Wear and corrosion protection of engine components (e.g. nano-composites, nano-coatings, nano-particles as fuel additives, etc.)

ELECTRICAL MOTORS
Nano-composites for superconducting components in electric motors (e.g. in ship engines)

Energy distribution

POWER TRANSMISSION
High-Voltage Transmission: Nano-fillers for electrical isolation systems, soft magnetic nano-materials for efficient current transformation
Super Conductors: Optimized high temperature SC's based on nanoscale interface design for loss-less power transmission
CNT Power Lines: Superconducting cables based on carbon nanotubes (long term)
Wireless power transmission: Power transmission by laser, microwaves or electromagnetic resonance based on nano-optimized components (long term)

SMART GRIDS
Nanosensors (e.g. magneto-resistive) for intelligent and flexible grid management capable of managing highly decentralized power feeds

HEAT TRANSFER
Efficient heat inflow and outflow based on nano-optimized heat exchangers and conductors (e.g. based on CNT composites) in industries and buildings

Energy storage

ELECTRICAL ENERGY
Batteries: Optimized Li-ion batteries by nanostructured electrodes and flexible ceramic separator foils for application in mobile electronics, automobiles, flexible loading management in power grids (mid term)
Supercapacitors: Nano-materials for electrodes (carbon aerogels, CNT, metal-oxides) and electrolytes for higher energy densities

CHEMICAL ENERGY
Hydrogen: Nanoporous materials (organometals, metal hydrides) for application in micro fuel cells for mobile electronics and automobiles (long term)
Fuel Reforming/Refining: Nano-catalysts for optimized fuel production (oil refining, desulphurization, coal liquefaction)
Fuel Tanks: Gas tight fuel tanks based on nano-composites for reduction of hydrogen emissions

THERMAL ENERGY
Phase-change materials: Encapsulated PCM for air conditioning of buildings
Adsorptive storage: Nano-porous materials (e.g. zeolites) for reversible heat storage in buildings and heating nets

Energy usage

THERMAL INSULATION
Nanoporous foams and gels (aerogels, polymer foams) for thermal insulation of buildings or in industrial processes

AIR CONDITIONING
Intelligent management of light and heat flux in buildings by electrochromic windows, micro mirror arrays or IR-reflectors

LIGHTWEIGHT CONSTRUCTION
Lightweight construction materials using nano-composites (CNT, metal-matrix composites, nano-coated light materials, ultra-performance concrete, polymer composites)

INDUSTRIAL PROCESSES
Substitution of energy-intensive processes based on nanotech process innovations (e.g. nano-catalysts, self-assembling processes)

LIGHTING
Energy efficient lighting (e.g. LED, OLED)

FIGURE 2. Examples for potential applications of Nanotechnology along the value chain in the energy sector (adapted from [64]).

Energy sources - Nanotechnology provide essential improvement potentials for the development of both conventional energy sources (fossil and nuclear fuels) and renewable energy sources like geothermal energy, sun, wind, water, tides or biomass (see Fig. 2). *Nano-coated, wear resistant drill probes*, for example, allow the optimization of the lifespan and efficiency of systems for the development of oil and natural gas deposits or geothermal energy and thus cost savings. Further examples are *high-duty nanomaterials for lighter and more rugged rotor blades* of wind and tidal turbines as well as *wear and corrosion protection layers* for mechanically/chemically stressed components (bearings, gear boxes, etc.) [65]. Nanotechnologies will play a decisive role in the intensified use of solar energy through the development of nano-optimized cells (polymeric, dye, quantum dot, thin film, multiple junction) and nanostructured antireflective coatings for *photovoltaic systems* [66]. In the long run, the utilization of nanostructures, like *quantum dots and wires*, could allow for solar cell efficiencies of over 60% [66].

Energy conversion - The conversion of primary energy sources into electricity, heat and kinetic energy must be efficient. Efficiency increases, especially in fossil-fired gas and steam power plants, could help avoid considerable amounts of carbon dioxide emissions. Higher power plant efficiencies, however, require higher operating temperatures and thus heat-resistant turbine materials. Improvements are possible, for example, through *nano-scale heat and corrosion protection layers for turbine blades* in power plants or aircraft engines to enhance the efficiency through increased operating temperatures [67] or the application of lightweight construction materials (*e.g.* titanium aluminides) [68]. *Nano-optimized membranes* can extend the scope of possibilities for the *separation and climate-neutral storage of carbon dioxide* for power generation in coal-fired power plants, in order to render this important method of power generation environmentally friendlier in the long run [69]. The energy yield from the conversion of chemical energy through *fuel cells* can be stepped up by nano-structured electrodes, catalysts and membranes, which results in cheaper applications in automobiles, buildings and the operation of mobile electronics [70]. *Thermoelectric energy conversion* seems particularly promising. Nano-structured semiconductors with an optimized boundary layer design contribute to increases in efficiency that could pave the way for a broad application in the utilization of waste heat, for example in automobiles, or even of human body heat for portable electronics in textiles [71].

Energy distribution - Regarding the *reduction of energy losses in current transmission*, hope exists that the extraordinary electric conductivity of nanomaterials like carbon nanotubes can be utilized for applications in electric cables and power lines [72]. Furthermore, there are nanotechnological approaches for the optimization of *superconductive materials* for lossless current conduction [73].

Energy storage - The utilization of nanotechnologies for the enhancement of electrical energy stores like *batteries* and *super-capacitors* is very promising [74]. Due to the high cell voltage and the outstanding energy and power density, the *lithium-ion technology* is regarded as the most promising variant of electrical energy storage. Nanotechnologies can improve capacity and safety of lithium-ion batteries decisively, as for example through new ceramic, heat-resistant and still flexible separators and high-performance electrode materials [75]. In the long run, even *hydrogen* may be a promising energy store for environmentally-friendly energy supply. Apart from necessary nanostructure adjustments, the *efficient storage of hydrogen* is regarded as one of the critical factors of success on the way to a possible hydrogen management. Current materials for chemical hydrogen storage do not meet the demands of the automotive industry, which requires a hydrogen-storage capacity of up to ten percent in weight. Various nanomaterials, *inter alia* based on *nanoporous metal-organic compounds*, show development potential, which seems to be economically realizable at least with regard to the operation of fuel cells in portable electronic devices [76]. Another important field is *thermal energy storage*. The energy demand in buildings, for example, may be significantly reduced by using *phase change materials* such as latent heat stores [77]. Interesting, from an economic point of view, are also adsorption stores based on *nanoporous materials like zeolites*, which could be applied as heat stores in district heating grids or in industry [78].

Energy usage - To achieve sustainable energy supply, and in parallel to the optimized development of available energy sources, it is necessary to improve the efficiency of energy use and to avoid unnecessary energy consumption. This applies to all branches of industry and private households. Nanotechnologies provide a multitude of approaches to energy saving. Examples are the reduction of fuel consumption in automobiles through *lightweight construction materials* on the basis of nanocomposites, the optimization in fuel combustion through wear-resistant, lighter engine components and nanoparticulate fuel additives or even nanoparticles for optimized tires with low rolling resistance [79]. Considerable energy savings are realizable through *tribological layers* for mechanical components in plants and machines [80]. *Building technology* also provides great potential for energy savings, which could be tapped, for example, by *nanoporous thermal insulation materials* suitably applicable in the energetic rehabilitation of old buildings [81]. In general, the *control of light and heat flux by nanotechnological components*, like for example switchable glasses, is a promising approach to reducing energy consumption in buildings [82].

Environment

Nanotechnological products, processes and applications are expected to contribute significantly to environmental and climate protection by saving raw materials, energy and water as well as by reducing greenhouse gases and hazardous wastes. Here are some specific examples of Nanotechnology applications that benefit the environment.

Battery disposal - Many batteries still contain heavy metals such as mercury, lead, cadmium and nickel, which can contaminate the environment and pose a potential threat to human health when batteries are improperly disposed of. Not only do the billions upon billions of batteries in landfills pose an environmental problem, they also are a complete waste of potential and cheap raw materials. Researchers have managed to *recover pure zinc oxide nanoparticles* from spent Zn-MnO_2 alkaline batteries [83].

Waste clean-up - Scientists are working on Nanotechnology solution for *radioactive waste clean-up*, specifically the use of titanate nanofibers as absorbents [84] for the removal of radioactive ions from water. Researchers have reported that the unique structural properties of titanate nanotubes and nanofibers make them superior materials for the removal of radioactive cesium and iodine ions in water [85]. Conventional clean-up techniques are not adequate to solve the problem of *massive oil spills*. Although the application of Nanotechnology for oil spill clean-up is still in its nascent stage, it offers great promise for the future. In the last few years, there has been a particularly growing interest worldwide in exploring ways of finding suitable solutions to clean-up oil spills through the use of nanomaterials [86-90].

Water purification - The potential impact areas for Nanotechnology in water applications are divided into three categories - *treatment and remediation, sensing and detection, and pollution prevention* - and the improvement of desalination technologies is one the key areas. Nanotechnology-based water purification devices have the potential to transform the field of desalination, for instance by using the *ion concentration polarization* phenomenon [91]. Another, relatively new method of purifying brackish water is *capacitive deionization* (CDI) technology. The advantages of CDI are that it has no secondary pollution, is cost-effective and energy efficient. Nanotechnology researchers have developed a CDI application that uses graphene-like nanoflakes as electrodes for capacitive deionization [92]. They found that the graphene electrodes resulted in a better CDI performance than the conventionally used activated carbon materials.

Greenhouse effect: CO_2 capture - Before CO_2 can be stored in Carbon dioxide Capture and Storage (CCS) schemes, it must be separated from the other waste gases resulting from combustion or industrial processes. Most current methods used for this type of filtration are expensive and require the use of chemicals. Nanotechnology techniques to fabricate *nanoscale thin membranes* could lead to new membrane technology and change this [93].

Pollution: H_2 as an alternative to fossil fuels - Companies developing hydrogen-powered technologies like to wrap themselves in the green glow of environmentally friendly technology that will save the planet. While hydrogen fuel indeed is a clean energy carrier, the source of that hydrogen often is as dirty as it gets. The problem is that you can't dig a well to tap hydrogen, but hydrogen has to be produced, and that can be done using a variety of resources. The dirtiest method - at least until highly efficient carbon capture and sequestration technologies are developed - is the gasification of coal. By far the cleanest method would be *electrolysis by renewable energy*: using renewable energy technologies such as wind, solar, geo- and hydrothermal power to split water into hydrogen and oxygen. *Artificial photosynthesis,* using solar energy to split water in order to generate hydrogen and oxygen, can offer a clean and portable source of energy supply as durable as the sunlight [94]. Working at the nanoscale, researchers have shown that an inexpensive and environmentally benign *inorganic light harvesting nanocrystal array* can be combined with a low-cost electrocatalyst that contains abundant elements to fabricate an inexpensive and stable system for photoelectrochemical hydrogen production [95].

Nanomaterials for environmental applications - On September 2015, BCC Research issued a report to estimate the value of different types of environmental remediation using different types of nanomaterials for the following applications: i) Environmental amendment, ii) Environmental protection, iii) Environmental maintenance and iv) Environmental enhancement. The *global Nanotechnology market in environmental applications* reached USD 23.4 billion in 2014 and is expected to reach about USD 41.8 billion by 2020, registering a CAGR of 10.2% from 2014 to 2020 [96].

Nanomedicine

Nanomedicine has been defined as “the application of nanoscale material in medicine that takes advantage of the nanomaterial’s unique properties” [97]. It is this emphasis on the specific properties associated with the nanoscale that distinguishes Nanomedicine from classical life science disciplines like molecular biology, biochemistry etc., which also study nanoscale materials such as nucleic acids and proteins, but from a different perspective. For example, Nanomedicine focuses on how DNA may be used to build novel structures for diagnostics or therapeutics (e.g. DNA origami) rather than on its information content and the way it is replicated and transcribed.

The domain of Nanomedicine is really vast, so we shall give here only few examples of the latest results which we believe have stronger potential for disruptive innovation in the clinical practice, grouping them in 3 main areas (Table 2).

TABLE 2. Main areas of potential disruptive innovation in Nanomedicine.

Nanotechnologies for *ex-vivo* diagnostics
Nanotechnologies for *in vivo* imaging and therapy
Nanotechnologies for tissue engineering and wearables for health

***Nanotechnology for ex-vivo diagnostics* -** *Ex-vivo* applications with non-implantable devices place few limits to the Nanotechnology arsenal, since materials and methods may be used that are not be suitable for *in vivo* use (e.g. due to long-term toxicity, need of proximity detectors, etc.), and generally do not require clinical trials, unless they are designed to play a role in patient-care decisions.

The main application is for molecular diagnostics. Biomarkers (i.e. DNA/RNA/miRNA, proteins, etc.) are a cornerstone of precision medicine, not only for early diagnosis, but also to refine disease classification, identify prognostic factors, predict drug response and monitor disease progress/recurrence. Typical examples are the estimation of residual tumour burden after first-line therapy, or the preclinical detection of life-threatening infections (Ebola, HIV, HCV) or of major degenerative processes (atherosclerosis, Alzheimer, Parkinson, etc.). The sensitivity of current clinical lab tests is in the pico-molar range (corresponding to approx. 10^8 molecule per ml of sample). However, as both the number and the concentrations of clinically useful indicators expand due to intensive discovery efforts, a higher sensitivity is required.

The main drivers of Nanotechnology in this area are fourfold: i) to improve sensitivity by several orders of magnitude to femto/atto-molar (the latter corresponding to approx. 10^3 molecules/ml), whilst expanding the dynamic range, i.e. provide linear responses over several logs of concentration, even in complex samples (e.g. blood); ii) to increase multiplexity, i.e. carry out multiple separate assays in parallel, in order to derive highly informative molecular fingerprints of a patient; iii) to provide faster results, on a time scale of minutes, whilst reducing costs by minimizing the consumption of expensive reagents and the amount of sample; iv) to increase robustness and enable user-friendly operation outside sophisticated facilities even by unskilled/untrained operators, e.g. the patients themselves. These results depend on a combination of factors. First, miniaturized biosensors (e.g. resonant cantilevers, or nanowires/nanotubes/nanofibers used as gates in field-effect transistors, FETs) maximize signal-to-noise due to large surface to volume ratios. Second, nanobiosensors are readily integrated onto microfluidic and microelectronic circuits, with which they often share materials and fabrication principles, to provide an interface to the biological sample on the one hand, and to control and read-out systems on the other. This compact and miniaturized architecture (LabOnChip or LoC) can reduce the sample volumes required for analysis to sub-μl, whilst simplifying the implementation of even inherently complex, high-sensitivity detection schemes, such as those requiring careful coupling of lasers and optical detectors [98]. Third, miniaturization and on-chip fabrication open the way to scalability, i.e. the implementation of vast arrays of parallel biosensors for highly multiplexed analysis, as well to mass manufacturing.

A number of high-performance systems based on miniaturized detectors, often in combination with microfluidics, have been described [99], albeit only a few have been subjected to thorough clinical validation. Amongst these are biobarcode assays based on gold or semiconductor nanoparticles [100] and FETs based on molecularly-modified Si nanowires for the detection of volatile organic compounds (VOCs) in breath [101]. A relatively recent development is the implementation of digital quantitation (digital PCR, digital ELISA) based on a binary output: a sample is subdivided into smaller aliquots each containing from none to few molecules of the target analyte, and each aliquot is tested just for the presence or absence of the target irrespective of its amount. Assuming a Poisson distribution, the mean concentration of the analyte is estimated from the fraction of negative aliquots.

With optical reporters, the results may be read using a mobile phone camera and relayed wirelessly to a cloud server for remote analysis [102]. By parallel analysis of aliquots of varying size, digital quantitation may be adapted to a wide dynamic range, and has proven very robust due to its relying on binary outputs, hence may be particularly suitable for home/field testing.

LoCs have also been designed to meet a requirement to count and isolate rare cells or particles. Circulating Tumour Cells (CTC) are an early indicator of tumour persistence or progression and may provide personalized drug resistance data. The iCTC (immobilised Circulating Tumour Cells) chip consists of an array of microposts functionalised with a CTC-specific reagent. It was shown to capture CTC in concentrations as low as 1–10 per ml in the presence of a billion-fold excess of normal blood cells, enabling their further molecular/functional characterization [103]. In magnetic ranking cytometry (MagRC) an array of variably sized micromagnets in a microfluidic chip provides an increasing local magnetic force along the channel. CTCs bound to different numbers of magnetic nanoparticles, according to the level of a surface marker, are trapped at different positions along the chip, enabling their efficient sorting at single-cell resolution even at low levels (10 cells per ml) in whole blood [104]. LoCs have also been devised for microvesicles, a heterogeneous class of cell-derived particles in the size range from 50 nm to 1 micron and an important source of biomarkers related to the cell of origin. A microfluidic chip for the labelling of surface markers on microvesicles with magnetic nanoparticles (MNP) and their quantitation via micronuclear magnetic resonance (μNMR) was shown to differentiate microvesicles from glioblastoma multiforme (GBM) and non-tumor cells, and to enable prediction of treatment outcomes [105].

Amongst the most striking examples of nanotechnologies for *ex-vivo* diagnostics are devices for nucleic acid sequencing. The current gold standard (next-generation sequencing, NGS) has made genome sequencing widely affordable, however it has limitations since it requires both amplification and expensive reagents, and produces relatively short reads, making the whole genome assembly a computationally intensive task. These are overcome by two different nanotechnologies: in the first, light confinement to a few zeptoliter volume by a nanofabricated zero-mode waveguide enables sensing single DNA molecules as they are copied nucleotide by nucleotide. This technology, which is commercialised by Pacific Biosciences, is claimed to provide average reads > 10,000 nucleotides, with 99.999% consensus accuracy, unbiased coverage and the potential to identify epigenetic modifications. In a different approach, a single nanopore, or arrays of nanopores are fabricated of a size comparable to a nucleobase, and used as resistive-pulse sensors: their ionic conductance is sampled during the electric field-induced transfer of DNA/RNA. Protein-lined nanopores form the basis of the technology commercialised by Oxford Nanopore Technologies (MinION and related), whilst solid-state nanopores have also been described, fabricated in inorganic/organic substrates like SiN and graphene, which exploit the latter's conductive properties. The MinION is reported to enable long read lengths (hundreds of kb), to stream data in real time and to require minimal sample preparation or accessory instrumentation (it has been used even in a jungle). However, questions on its accuracy have been raised. Nanopore technology is also being developed for sensing proteins and small analytes [106, 107].

***Nanotechnologies for in vivo diagnostics and therapeutics* -** The materials and technologies required for *in vivo* applications are more constrained than *ex-vivo*. First of all they are subject to pre-clinical and clinical validation. Whilst the FDA has yet to establish a specific regulatory framework for Nanomedicine, recent draft guidelines highlight the importance of nanomaterial characterization, which requires a comprehensive understanding of physicochemical parameters, and the reproducibility and scalability of the manufacturing process. Second, the enormous variety of targets (cell types/molecules) in an organism requires a very stringent specificity. Third the existence of anatomical and physiological barriers makes some targets difficult to reach, whilst deep locations are difficult to image and/or resolution is limited due to scattering.

Nanoparticles (NP) are ideal for many *in vivo* medical applications because, whilst they have similar sizes to biological molecules, their physicochemical properties (size, shape, elasticity, surface chemistry, etc.) may be finely controlled to yield unique functionalities (e.g. optical, electrical, magnetic) and specific interactions with biomolecules and cells, which may be highly customised to a condition/patient (personalized medicine). The main aim of using NP for drug delivery is to improve the therapeutic index (ratio of effective to toxic dose). This may be achieved by a variety of mechanisms: i) improved pharmacokinetics, by providing better stability and solubility, longer half-life, wider biodistribution (e.g. promoting crossing of epithelial and endothelial barriers, stromal penetration), accumulation at the target site (tissue, cell or organelle), conditional drug release dependent on local factors (e.g. pH, temperature, etc.); ii) co-delivery of multiple synergic drugs in precisely defined ratios, e.g. to minimise drug resistance, or of therapeutic with imaging agents, to enable real-time monitoring of *in vivo* efficacy; iii) enhanced immunogenicity, e.g. for synthetic vaccines; iv) the inherent therapeutic properties of some nanomaterials: NanoTherm (15 nm magnetic NP), approved in Europe for glioblastoma, acts by inducing localised hyperthermia upon application of an alternating magnetic field.

The first example of a nanoformulation to receive FDA approval was liposomal doxorubicin (Doxil), followed by albumin NP-bound paclitaxel (Abraxane). In addition to liposomes and proteins, NP have been made of lipid micelles, organic polymers and micelles (including dendrimers), metals and their oxides, silica, semiconductor nanocrystals, nanotubes, graphene, hydrogels and nanodiamonds. Whereas NP have up until now mainly been used as nanocarriers of classical chemotherapeutics, most clinically approved nanoformulations reduce toxicity rather than enhancing therapeutic efficacy. An emerging trend is to use NP for the delivery of molecularly targeted agents (e.g. kinase inhibitors) and nucleic acids (antisense or DNA inhibitor oligonucleotides, siRNA, miRNA). The applications that have catalysed most attention, and make up the lion's share of academic publications, are for cancer [108], although results in cardiovascular medicine, infectious disease and other areas have also been reported. NanoMega Medical Corp. (USA) has filed a patent for a chitosan-stabilised nanoparticle promoting increased gut absorption, and hence oral delivery of insulin for diabetes.

A number of sophisticated systems have been devised and published in high profile scientific journals. Amongst the most notable latest examples are the development of nanorobots for the transport of molecular payloads and their release upon activation by a built-in logic gate (the combined presence of a specific pair of molecules on the target) [109], of cooperating nanosystems, whereby the interaction of one class of NP with the target (tumour) amplifies the effects of a second class of NP, and of nanosystems that self-assemble and disassemble to optimize transport [110]. However, few studies have advanced beyond the research laboratory, and clinical trials have often been disappointing. One notable example is that of BIND-014, a targeted NP for the therapy of solid tumours, which contributed to the demise of its parent company, BIND Therapeutics. This has led to the suggestion that the role of Nanotechnology in medicine needs re-evaluation, and to the proposal of a new 30-year roadmap for Nanomedicine 2.0 [111].

NP are also actively explored as platforms for synthetic vaccines for immune stimulation (cancer immunotherapy, infectious disease) or immunosuppression (autoimmune disease). Recent examples are NP that enhance the function of antigen presenting cells leading to strong anti-tumour T cell cytotoxicity [112, 113]. A number of biotechnology/pharmaceutical companies are pursuing NP-based vaccines [114].

As for imaging, particular interest has recently been focused on multimodal techniques for both pre- and intra-operative mapping, e.g. of sentinel lymph node used in cancer staging, or to ensure clean resection margins. Preoperative scans must be easily and accurately co-registered with the anatomical sites accessed during surgery, often by minimally invasive endoscopic tools. A recent example is represented by dual modality C-dots, ultrasmall (6 to 7 nm) silica NP with optimized renal clearance and homing to lymphatics, which contain a NIR-active tracer and a PET radiotracer as well specific targeting moieties, and were approved by the FDA in 2010 for human testing [115]. Nanobiotech start-up Lumicell is developing the LUM Imaging System based on LUM015, a NIR fluorescent probe that is activated by cathepsins (biomarkers of some tumours), and a hand-held, wide-field, single-cell resolution imaging device to fit into a lumpectomy site, with dedicated software to produce real-time images. It is in late-stage development for breast cancer, with an advanced clinical trial recently approved by the US FDA, whilst it is also under investigation for other cancers [116].

Theranostics integrate diagnostic and therapeutic functions into a single NP formulation, which offers the means to correlate PK and biodistribution with the extent and progression of disease, and is likely to become an essential aid to personalized treatment. Examples include combined imaging by MRI, optical and ultrasound with photothermal therapy or with controlled delivery of chemotherapeutic or thrombolytic agents [117].

***Nanotechnologies for tissue engineering and wearables for health* -** Organ failure due to vascular pathology, degeneration, senescence, or trauma are amongst the leading causes of morbidity. Organ transplantation is limited by available donors, high costs and significant side effects. Alternative approaches aim at stimulating tissue regeneration, which depends both on adequate cellular sources and their 3D microenvironment. Since this microenvironment (extracellular matrix, ECM) is a complex and dynamic nanocomposite, Nanotechnology is being used to design nanostructured scaffolds to improve the performance of engineered tissues. Quite apart from *in vivo* regeneration, Nanotechnology-based *in vitro* reconstruction of miniaturized organs/tissues in microfluidic platforms (OrganOnChip) is being pursued to facilitate preclinical drug development and identify personalised therapies [118].

Transplantation of cardiac patches made with anisotropically nanopatterned hydrogels enhances the growth and integration of transplanted cells with the host tissue [119]. Integration of cardiomyocytes in a nanofiber scaffold on a flexible, freestanding nanoelectronic mesh enables both the recording of cellular electrical activities and on-demand electrical stimulation leading to synchronised contraction. Deposition of biochemical factors embedded in an electroactive polymer at selected nodes of the nanoelectronic mesh allows localised release [120]. Carbon nanotubes, nanofibers and graphene are actively explored for nerve tissue regeneration and stimulation [121].

Electrophysiological recordings through the skin (electrocardiograms, electromyograms and electroencephalograms) are widely used in clinical diagnostics, and may be employed to control human–computer interfaces. However, they are currently performed with bulky, paste-on, wired electrodes that are uncomfortable and unsuitable for chronic recording. Nanotechnology is used to design and realise ultrasoft devices ("epidermal electronics", "electronic tattoos" or "electronic skin") that can be applied to the skin and integrate sensors to record electrical activity and other physiological parameters (blood pressure, temperature, oxygen, blood sugar and hydration levels) [122]. In order to be suitable for extended/chronic operation, these devices must show high conformability to curved and mobile surfaces, be lightweight, mechanically robust, air and water-vapour permeable, and prevent dermatological irritation, even on chronic operation. A substrate-free nanoelectronic mesh has been produced that can be directly laminated onto the skin and is ultrathin, stretchable, highly gas-permeable and inflammation-free. It was shown to provide faithful electromyogram recordings and may be engineered to detect touch, temperature and pressure, and to relay signals wirelessly [123]. A wearable stretchable patch for diabetes monitoring and feedback therapy has been realised combining nanostructured graphene and a gold mesh. It integrates glucose and pH sensors with a heater and polymeric microneedles that can be thermally actuated to deliver Metformin and reduce blood glucose levels in mice, and wirelessly transfers data to remote mobile devices [124]. In the near future, it is likely that these devices will also integrate components for harvesting mechanical and thermal energy from the body to enable sustainable self-powering [125], and will find widespread application, apart from remote medical monitoring, in smart devices for personal wellness, a fast emerging trend whereby, based on regular measurements of the health status, lifestyle, exercise, and diet adjustments are made.

Scientific challenges of Nanomedicine - In 2000 the first Implementation Plan for the US National Nanotechnology Initiative identified a number of grand challenges. In particular, in the Advanced Healthcare, Therapeutics and Diagnostics sector these were:

- biosensors and new imaging technologies to enable earlier detection of cancer and other diseases;
- targeted gene and drug delivery systems;
- more effective, less expensive diagnostics and therapeutics using rapid gene sequencing;
- novel biocompatible materials that improve the retention time of artificial organs;
- vision and hearing aids;
- use of tiny "smart" medical devices for treatment modes that will minimize collateral damage of human tissues.

As discussed in the previous section, significant advances have been made towards these aims, although clinically-ready solutions are still scarce. Further progress is to be expected in these as well as in additional areas with major disruptive potential like single-cell biology and immunotherapy [126]. Since nanosystems operate in the same dimensional range as the fundamental units of life (from macromolecules to cells) and afford an exceptional flexibility of design and functions, it has been argued that Nanotechnology is the future of medicine [111].

As regards *ex-vivo* applications, major challenges in the short/medium term are [127]:

- to implement full automation, including the connection of sample processing, analysis and readout steps. This will guarantee accurate results without requiring highly trained operators, and minimise costs fostering widespread usage at Points of Care or in poor/remote locations without laboratory facilities. It may be particularly crucial in improving healthcare standards for the 5 billion people in the developing world;
- to increase substantially the degree of multiplexing. In the future, molecular fingerprinting of disease, both for preclinical research and for clinical diagnostics, will likely be based on hundreds of biomarkers rather than the few currently demonstrated.

As for *in vivo* applications, in order to overcome the generally disappointing results obtained so far in the translation to clinical settings, major albeit perhaps non-glamorous challenges in the short/medium term are [108, 111]:

- to elucidate and map in detail the interactions of nanoparticles with biomolecules, cells and organs. Many of the current views (e.g. the basis for the Enhanced Permeability and Retention (EPR) phenomenon leading to the passive accumulations of NP in tumours and at sites of inflammation) have not been adequately verified, which may explain the frustrating discrepancies between preclinical and clinical results. Moreover, only over the past few years has it been realised that, upon injection *in vivo*, NP take up a biological identity (consisting of adsorbed circulating proteins, the so called protein corona) which masks their synthetic identity and largely dictates their fate and effects. For the same NP, this biological identity may differ in different patients or disease stages. Systematic data collection and new modelling methods (QSAR) are needed to predict and control the determinants of an NP biological identity;
- to conduct systematic pharmacokinetics and biodistribution studies to provide the mechanistic basis for the reported end outcomes (e.g., survival data or tumour shrinkage);
- to develop novel techniques to analyze nanoparticles in complex tissues. A key step will be the large scale application of biomimetic microfluidic human OrganOnChip models that replicate the 3D hallmarks of physiological units (e.g. a nephron or a liver lobule) including vasculature, enabling faster, in-depth analysis at much reduced costs in systems potentially highly relevant to the human case. In addition, animal models must be used that closely mimic the human disease, such as high-fidelity patient-derived xenografts (PDXs), humanized and genetically engineered mouse models (GEMMs);
- to develop computational tools to simulate the behaviour of nanoparticles in the body, and widely accessible, structured databases to store and query the experimental data;
- to implement facile and reproducible synthesis of large NP libraries to enable systematic screening of optimal physicochemical parameters. Whilst traditional bulk techniques generally result in high polydispersity, better control over NP synthesis and drug loading is required, which may be provided by methods based on microfluidics [128] and PRINT (Particle Replication In Non-wetting Template) [129];
- to design NP synthesis so as to be scalable, whilst meeting Good Manufacturing Practice standards. Commercialization and clinical applications will likely require kilograms to tons of product, which in turn requires optimization of process and formulation parameters. Large-scale and reproducible synthesis will be harder for complex NP formulations comprising multiple functional units.

Longer term, Drexler, Peterson and Pergamit's grand vision of intelligent nanorobots patrolling the body, monitoring vital functions and intervening when and where needed to repair or replace defective structures, cells or molecules [3] seems to be within reach, albeit still some way off. A substantial amount of research has been aimed at developing micro- and nanorobots, with the first generation currently undergoing preclinical testing [130]. Much further work is required to develop efficient and biocompatible mechanisms for on-board powering, actuation and control, including perception and learning abilities. On the other hand, Nanotechnology-based body-computer interfaces will enable constant health monitoring and automatic intervention, whilst assisting patients with serious neural lesions to reacquire sensation or control of prosthetic limbs.

The business of Nanomedicine

The dominant research field in Nanomedicine is drug delivery, contributing 76% of the scientific publications, followed by *in vitro* diagnostics with a contribution of 11%. The countries of the European Union account for 36% of all nanomedical publications worldwide, compared to the US with a contribution of 32% and Asia with 18%. Most of the money being spent on nanomedical R&D comes from significant governmental funding programs and from established corporations. Both pharmaceutical and specialist companies are at the forefront of research into the medical applications of Nanotechnology. A comparison between Europe as a whole and the US shows that, despite a roughly comparable research output, the US leads in the number of patent filings, which indicates a more advanced commercialization status. In fact, US companies manufacture 45% to 50% of marketed Nanomedicine products, while European companies have a 35% share. Product pipelines suggest that this gap will widen, reflecting mainly the weak position of European nanomedical companies in the drug delivery sector, where they represent less than one quarter of all the companies in the field, compared to 60% for US companies. Of the approximately 200 companies identified as active in Nanomedicine worldwide, some three-quarters are startups and SMEs focusing on the development of Nanotechnology-enhanced pharmaceuticals and medical devices. Another 40-plus major pharmaceutical and medical device corporations have nanomedical products.

Nano-enabled medical products began appearing on the market over a decade ago and some have become best-sellers in their therapeutic categories. The main areas in which nanomedical products have made an impact are *cancer, CNS disease, cardiovascular disease and infection control*. At present, *cancer* is one of the largest therapeutic areas for nano-enabled products. These include Abraxane, Depocyt, Oncospar, Doxil and Neulasta. Cancer is a prime focus for nanopharmaceutical R&D, and companies with clinical-stage developments in this field include Celgene, Jazz Pharmaceuticals, Camurus, and Cytimmune. Treatments for *CNS disorders including Alzheimer's disease and stroke* also feature prominently in nanotherapeutic research, seeking to build on achievements already posted by products such as e.g. Copaxone. Enzon is among companies vigorously pursuing new product development in the field of *autoimmune-related inflammatory disease* and new products are expected to add to the continuing market penetration of existing therapies, contributing to annual growth rates around 15%. In addition, Nanotechnology has contributed to a wide variety of *anti-infective products*, from PEGylated interferons used in viral disease to nanocrystalline silver used topically in wound infections. Already on the market in the US and elsewhere are *wound dressings* that exploit the antimicrobial properties of nanocrystalline silver, a powerful antibacterial, effective even against problem organisms like MRSA. NanoBio is one of the companies actively involved in this field.

The business of nanomaterials (e.g. metal and metal-oxide nanoparticles, liposomes, polymers and polymer-drug conjugates, hydrogel nanoparticles, dendrimers, inorganic nanoparticles, nanoshells, nanotubes, etc.) used for *in vitro* and *in vivo* early disease diagnosis, preventive intervention (e.g. vaccines) and prophylaxis of chronic as well as acute disorders (e.g. therapeutics, regenerative medicine) mainly in the fields of clinical oncology, infectious diseases, clinical cardiology and orthopedics, was estimated by Grand View Research [131] at USD 140 billion in 2016 and is anticipated by the same company to reach USD 350 billion by 2025.

Therapeutics accounted for the largest share of market revenue in 2016 owing to the presence of nanoemulsions, nanoformulations or nanodevices that possess the ability to cross biological barriers. Within the same perimeter, Allied Market Research valued the global Nanomedicine market at USD 112 billion in 2016 to reach USD 260 billion by 2023, growing at a CAGR of 12.6% from 2017 to 2023 [132]. According to this study, the drug delivery segment accounted for a nearly two-fifths share of the global market in 2016: North America dominated the industry in 2016, accounting for 42% of total revenue. According to BCC Research, the Nanomedicine market for nanopharmaceuticals and nanodiagnostics will reach USD 293 billion by 2022 [133].

Even if the above estimates are affected by a rather high uncertainty, most of the experienced analysts in the field on Nanomedicine are forecasting a strong growth of the Nanomedicine business from about USD 110-140 billion in 2017 to about USD 260-290 billion in 2022/2023 and USD 350 billion in 2025.

All the above market research companies agree on some specific reasons that are driving the Nanomedicine business growth:

- the development of novel Nanotechnology-based drugs and therapies is motivated by the need for treatments that have fewer side effects and that are more cost-effective than traditional therapies, in particular for cancer;
- the application of Nanotechnology-based contrast agents for diagnosis and for monitoring the effects of drugs will also drive growth in the coming years;
- demand for biodegradable implants with longer lifetimes to restore function is anticipated to become significant;
- nanoformulations with triggered release for tailor-made pharmacokinetics, nanoparticles for local control of tumor in combination with radiotherapy, and functionalized nanoparticles for targeted *in vivo* activation of stem cell production are anticipated to drive R&D, resulting in revenue generation in the coming years;
- the oncology segment accounted for the highest revenue in 2016, with a one-third share of the global market, and is expected to maintain its dominance throughout the forecast period;
- the vaccines segment is expected to register a significant CAGR of 13.2% throughout the forecast period;
- the therapeutics segment accounted for about a fourth-sevenths share in the global market in 2016, the highest share during the forecast period: this is due to the high demand for therapeutics among patients and to the increasing incidence of chronic diseases;
- the neurological disease segment is expected to grow at a CAGR of 13.9% during the forecast period, owing to high demand for brain monitoring, therapeutic devices and drugs;
- the regenerative medicine segment is anticipated to grow at a CAGR of 13.8% during the forecast period;

- clinical cardiology is expected to witness the fastest growth through to 2025 owing to developments in nano-functionalized and modified surfaces for increased biocompatibility of implants and for the treatment of thrombosis.

DEPLOYMENT SCENARIOS

Today, knowledge in all its forms plays a crucial role in economic processes. Nations that develop and manage their knowledge assets effectively perform better, creating more jobs and income [134]. Nanotechnology provides an excellent opportunity for the development of knowledge-based economies having the revolutionary potential to open up new production routes and the capability to support a wide range of disciplines [135]. The deployment of new technologies is not an automatic, self-evident process. Rather, it is embedded in social relations and has to be backed by political measures [136]. The necessary and usually sufficient condition for the deployment of Nanotechnology is the creation and development of many ecosystems of innovation (EoIs), which are "environments" featuring complex relationships between actors or entities whose goal is to enable technology development and innovation, focused on "nano" topics [137]. In today's world where the only constant factor is change, there is no exact formula for creating an EoI. On the one hand they can be constructed through a state initiative in the form of a science and technology park (e.g. Grenoble). On the other hand, they can emerge in a self-organised fashion through the concerted efforts of institutional and economic actors (e.g. Silicon Valley) [138]. Due to the complexity of the EoI deployment process, government planning should gather the right enabling actors in the control room [139-141]. These actors, coming from University/Research Centres, Industry and Government must then collaborate as the core team leading the construction of an EoI for Nanotechnology [142]. For the EoI success it is crucial that they promote a favourable environment for nanotechnological innovation, particularly for start-ups, spin-offs and small- and medium-sized enterprises. At the same time, it is crucial that existing industry recognises the potential of Nanotechnology and adapts their strategy to profit from it.

Besides the enabling actors, since Nanotechnology is capital intensive – which means high spending for R&D activities/infrastructures, for the development and manufacturing of equipment for scale-up as well as for product commercialization - high capital investments with long term commitments are needed to deploy it. Further, it is also necessary to train and maintain sufficient levels of human capital. Such commitments have been and still are at present significant barriers to entry for firms or venture capitalist [143], despite the fact that private investment in Nanotechnology have strongly increased in the last decade. For this reason, all the initiative in Nanotechnology in the '90s has been taken by governments (e.g. EU, Asian countries, etc.) [144].

It was in 2001 that the United States became the first country to launch a National Nanotechnology Initiative (NNI) involving 27 department and agency units working together under the shared and challenging vision of a future in which the ability to understand and control matter at the nanoscale leads to a revolution in technology and industry to the benefit of society [145]. Within a few years more than one-third of all countries established their own initiatives using the NNI model [146]. Nowadays, there are more than 60 national programmes on Nanotechnology. In the decade from 2001 to 2010 governments all over the world invested more than USD 67 billion and in 2015 the total global investments (both public and private) reached a quarter of a trillion [147]. In the first decade of the third millennium, such funds have been invested in basic research and both hard (buildings, equipment), and soft (training of a new class of nano-researchers) infrastructure. Toward the end of the decade, the focus started to shift to commercial products and applications [148].

Another important factor for the deployment of Nanotechnology due to its multi-disciplinarity is the need of an open innovation approach in research [149]. In the early '90s many analysts suggested that, due to the huge investments required for its deployment, Nanotechnology would have been concentrated in few countries (nano divide). This hypothesis failed and Nanotechnology is now benefitting from a collaborative environment where anyone in the world can access and contribute to the innovation process. In fact, most of the world's nanoscience centres are connected and the real value of this framework is the knowledge-sharing network.

Besides funding for the development of world-class infrastructures (centers of excellence) and developing an EoI based on a knowledge-sharing network, the investment in human resources is of the utmost importance to ensure the deployment of Nanotechnology. In fact, one of the main novelties of Nanotechnology lies in bringing together scientists and engineers from a wide range of disciplines, therefore it is necessary to train such a new generation of researchers, engineers and related specialists.

Following the EU and US experience in fostering cross-disciplinary networks and partnerships, several universities all over the world have built new laboratories to serve as Nanoscale Sciences and Engineering Centers.

They provide a home for faculty from many departments, including physics, chemistry, biology, material science, computer science, neuroscience, genetics and others. This interdisciplinary effort has an impact on the traditional academic organization of strictly autonomous academic departments in separate scientific disciplines. It encourages the establishment of interdisciplinary formal courses, both at the undergraduate and graduate levels [150]. Due to both the multidisciplinary approach required by Nanotechnology and the need to increase the exploitation of its research results, a particular challenge is to provide master degree or PhD students with an educational approach that stimulates their entrepreneurial attitude [151, 152]. Course would need to be aimed at training young researchers with a technical-scientific degree in the field of Technological Innovation and Technological Entrepreneurship through extending a public-private partnership in education. The best approach, mainly based on the training-on-the-job method, may consist in developing different Business Cases into Business and Technology Plans for student teams [153]. Teachers will be mainly from academia to teach management, business and administration, finance or scientific topics, but also from the business world (e.g. managers, entrepreneurs, startuppers, venture capitalists) to recount their experience and mentor/coach students. The final outcome of the training courses would be a Business & Technology Plan, related to a business case proposed directly by the students or developed together with managers and/or mentors from the academia and the business world. Another educational challenge would be to start Nanotechnology education at secondary schools, since: i) "nano" is by now part of the daily environment and schools need to teach future consumers how to take full advantage of nano-enabled products in a safe and sustainable way, ii) career choices start in secondary school when decisions about study subjects are made. Besides, there is a need to develop novel teaching and assessment tools for secondary school programs in Nanotechnology.

In conclusion, Nanotechnology deployment requires the adoption of a model of: i) informal science education for the "general" audience on topics of emerging technologies and ii) strategic partnerships between research/education institutions and companies that benefit the goals of both.

NANOTECHNOLOGY AND SOCIETY

A range of views exist about the societal implications of Nanotechnology and the challenges it may pose [154]. Addressing ethical, legal and social aspects (ELSA) in a proactive manner is critical to ensure public trust in emerging technologies and to promote innovation and commercialization of their products whilst avoiding the feeding of irrational fears that sometimes accompany dramatic advances in scientific understanding [155, 156]. The success of a revolutionary project depends heavily on its public acceptance; in fact, public trust and acceptance of Nanotechnology will be crucial for its long-term development. Before year 2000, the majority of people in advanced industrialised states did not know much about Nanotechnology and, unfortunately, the situation has not improved much. This poses a problem to Nanotechnology players, because without a serious communication effort Nanotechnology innovation could face an unjustly negative public reception [135]. Therefore, an open public dialogue with citizens and consumers is necessary as a basis for an objective judgement on Nanotechnology and to remove baseless prejudice [157].

Nanotechnology is as exciting and challenging from a humanities and social science perspective as it is from a science and engineering perspective. But if in the latter case many efforts are on the way, in the former efforts have so far been inadequate [158]. Crucial components to achieve this goal are actions to support the responsible development of Nanotechnology by addressing environmental, health and safety (EHS) concerns, engaging in public education and outreach and addressing other ethical, legal and social issues. The correct approach is to take a broad, critical and constructive perspective on the relationship between technology, government, environment and society. This requires identifying societal and environmental problems that Nanotechnology innovation might help address as well as the non-technical barriers that may prevent Nanotechnology from succeeding and developing approaches to overcome these barriers in ways other than, but complementary to, technological innovation, e.g. by involving institutional structures, public and private policies and individual and cultural practices.

As far as the ethical profiles of emerging nanotechnologies are concerned, it must be highlighted that they are different depending on the applications: what is necessary is to develop tools and resources that assist individuals and organizations to make ethically informed decisions. There are several common misconceptions – such as i) too soon to tell, ii) goodness of technological innovation - regarding the social and ethical issues associated with emerging nanotechnologies that obscure their significance to responsible development.

In terms of sustainable development, nanomaterials and products containing Nanotechnology must be manufactured at a high rate, in large volumes, with reliable processes and at reasonable costs. As a result, a substantial new manufacturing infrastructure - one that includes everything from production of basic nanomaterials through to finished products, as well as process and end-of-life waste disposal - must be established, since hazards associated with nanomaterial release into the environment might occur.

In conclusion, a focus on Nanotechnology ELSA as well as Environmental and Health issues must be routinely integrated into mainstream Nanotechnology research and production activities to support a safer and more equitable progress of existing and future Nanotechnology generations [159].

NANOTECHNOLOGY IN EMERGING COUNTRIES

The development of Nanotechnology owes its progress to pioneering efforts in many nations. In many cases, the development started with a government initiative for public laboratories and/or university-based nanoscience centre(s) [160]. Nevertheless, every national Nanotechnology ecosystem has its own approach, and in this section some policy recommendations will be outlined. Since the ’90s many Nanotechnology projects were funded in the EU, USA and Japan. At the beginning of the third millennium many Asian and other emerging countries followed the USA National Nanotechnology Initiative launching national Nanotechnology programs to strengthen their capacity and sustain economic growth (e.g. Nigeria, Thailand, Philippines, South Africa, etc.). As already mentioned, in the first decade researchers mainly focused on basic discoveries, infrastructure building and training, but since the end of the decade the focus shifted to commercial products and applications mainly in countries with strong linkages between industry and academy [148].

In order to draw some policy recommendations, it is useful to summarize the actions of some countries for Nanotechnology:

- China: due to huge public funding for basic research and to a separation of basic research, industrial development and production, China achieved impressive results in terms of publications but not in terms of exploitation [161].
- South Korea: thanks to an early development of a Nanotechnology infrastructure where students, researchers and business leaders collaborated, South Korea has arguably produced the biggest commercial return from Nanotechnology [162].
- Brazil: as a result of the fact that the main public investment beneficiary is the scientific community, the transformation of knowledge into innovation still remains a challenge in Brazil, despite the fact that strong international partnerships with both technologically developed countries and Southern countries with similar resources have been established for many years [163].
- Israel: thanks to the development of problem-focused research groups through public-private partnerships, Israel has already produced many commercial products and technologies linked with Nanotechnology [164].
- Sri Lanka: thanks to a public-private partnership in Nanotechnology that funded many collaborations between the country’s largest industries and academia, Sri Lanka is developing a world-class nano-innovation ecosystem [165].
- Africa: countries lie South Africa, Kenya, Egypt, Nigeria, etc., despite periods of armed conflict and political turmoil are developing research infrastructure and human capital, and promoting collaborations with technologically advanced countries [3].
- India: public investment is being geared to create general scientific and technological capabilities without a set of concrete targets, therefore the results in terms of scientific publications are excellent but the firms/companies have yet to be involved [166].

CONCLUSIONS

The full potential on Nanotechnology remains to be exploited on the socioeconomic ground. Nevertheless, the economic impact of nanomaterials, at the top of the Nanotechnology value chain, is steadily increasing. Besides a huge variety of industrial applications of nanomaterials, their use in the field of Nanomedicine looks like to be one of the most rewarding.

The revolutionary impact of Nanotechnology across the whole value chain strongly depends on its deployment at a global level, which may depend on the following policy recommendations:

- state support is necessary to develop a Nanotechnology ecosystem of innovation through initially providing infrastructure (e.g. equipment), training students and promoting a culture of innovation [167],

- the promotion of international/multidisciplinary collaboration is fundamental to foster a collaborative environment for Nanotechnology development,
- the private sector participation is crucial both in terms of capital support (e.g. venture capitalists) and technological/market vision.

ACKNOWLEDGMENTS

We thank the organizers of NANOINNOVATION 2017 i.e. AIRI – Associazione Italiana per la Ricerca Industriale and Associazione NanoItaly, for giving us the opportunity and honor to introduce the Proceedings of NANOINNOVATON 2017 with the present paper.

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