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GROUNDBREAKING TECHNOLOGICAL APPLICATIONS OF NANOTECHNOLOGY IN BIOMEDICINE: DETECTING EMERGING PATHWAYS FROM SCIENTIFIC AND TECHNOLOGICAL OUTPUTS

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Groundbreaking technological applications of nanotechnology in biomedicine: detecting emerging pathways from scientific and technological outputs

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ABSTRACT: The purpose of this paper is to measure and analyze the rate of scientific and technological advances of nano-technological research in biomedicine. The approach, based on models of growth, shows the current evolutionary trends of nano-research that may underpin future patterns of technological innovation in biomedicine. In particular, results show that biosensors, nanoparticles, quantum dots, carbon nanotube and nanomicelle have innovative applications in diagnostics and target therapies that have been generating a revolution in clinical practice. The present study also shows two main implications of determinants that have been supporting continuous application of nanotechnology in biomedicines such as the patterns of technological innovation driven by converging research fields and a learning process. These factors have been paving the way to innovative nanomedical drugs applied in biomedicine that lead to longer, better and healthier living of patients and therefore of societies.

Keywords: Nanotechnology, Nanoscience, Emerging Technology, Biomedicine, Nanomedicine, Nanoparticles, Quantum dots, Therapeutics, Diagnostics, Drug delivery.

JEL Codes: O30, C53, I10.

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SUMMARY

INTRODUCTION

Scientific research and patents are crucial competitive assets of nations in the current knowledge era. They are generated within the national system of innovation[1] in order to support the "competitive advantage" of countries (Porter, 1990) (see also Aghion and Howitt, 1998; Coccia, 2008). Scientific research focused on bio-nanotechnology is a current vital research field that has been supporting innovation and change in modern biomedicine and biomedical engineering (Islam and Miyazaki, 2010; Rafols and Meyer, 2007; Rafols and Meyer, 2010). In fact, nanostructured materials, also in connection with biomolecules, have a high potentiality of development for biomedical purposes by applications in new therapeutic instruments, diagnostic methodologies, etc. (*cf.* Lim *et al.*, 2010). No and Park (2010) argue that the interaction of biotechnology and nanotechnology, using patent citations, may provide main signals for future patterns in nano-biomedicine (*cf.* Bárcena *et al.*, 2009; Sylvester and Bowman, 2010).

The purpose of this paper is to analyze the evolutionary growth of knowledge in nanotechnology research by a model that measures and assesses the rate of scientific and technological advances in biomedicine and nanomedicine. This approach uses data of articles and patents, and provides main information to understand current leading scientific areas in the field of nanotechnology that have been generating a revolution in clinical practice. In particular, this technological analysis is important to explore future nano-biomedical pathways that will improve human health and quality of life.

Next section describes the theoretical framework, showing the most important features of nanotechnologies applied to the bio-medical field. The third section describes data mining strategy and research methodology, while the fourth part shows the main findings. The last section discusses the results, showing trends that seem to be emerging in nanotechnology applied in biomedicine.

[1] The national system of innovation (NSI) refers to the complex network of agents, policies, and institutions supporting the process of technical advance in an economy (Lundvall, 1992). The narrow definition of NSI would include the subsystem research sector represented by universities, research laboratories, while the broad NSI includes many subsystems such as finance, firms, government, and so on. The efficiency of this broad NSI supports economic growth patterns.

1. THEORETICAL FRAMEWORK

Biomedicine is one of the key scientific fields where nanotechnologies are providing vital innovative applications. Nanostructured materials show high sensibility, stability and biocompatibility and are applied to improve the performance of diagnostic or therapeutic tools[2]. Kim *et al.* (2010, p. 2434) state:

> Nanomaterials are now being designed to aid the transport of diagnostic or therapeutic agents through biologic barriers; to gain access to molecules; to mediate molecular interactions; and to detect molecular changes in a sensitive, high throughput manner. In contrast to atoms and macroscopic materials, nanomaterials have a high ratio of surface area to volume as well as tunable optical, electronic, magnetic, and biologic properties, and they can be engineered to have different sizes, shapes, chemical compositions, surface chemical characteristics, and hollow or solid structures. These properties are being incorporated into new generations of drug-delivery vehicles, contrast agents, and diagnostic devices.

The present paper analyzes the scientific and technological evolution of knowledge of some nanotechnologies in biomedicine. Thus, in order to better frame the research design, we describe, briefly, the main characteristics of some vital nanotechnological research topics that we are going to analyze to pinpoint technological trajectories.

Nanoparticles for therapeutics and diagnostics

Nanoparticles (NPs) are a key element for the development of nanotechnologies in the biomedical field (Chen *et al.*, 2011; He *et al.* 2010). NPs are nanoscopic spheres ranging in diameter up to some tenths of nanometers[3] that can be made of metals, metallic salts or oxides, or can have a biological origin. Several NPs are used as contrast agents in Magnetic Resonance Imaging (*in vivo* anatomical imaging) for

[2] Cf. Hu et al., 2011; Sekhon et al., 2010; Sekhon et al., 2010b; Willner and Willner, 2010.

[3] A nanometer (nm) is equal to one millionth of millimeter.

diseases of the vascular system and of the heart. Iron oxide nanoparticles present peculiar magnetic properties (superparamagnetism). Up-to-date research has showed that Iron oxide nanoparticles are non toxic, have minimal impact on cell viability and function (*cf.* Bárcena *et al.*, pp. 591ff). NPs are also able to target selectively the object of the analysis due to the addition of specific surfactants. Some NPs can also fluoresce and are applied as probes for optical imaging techniques. In fact, Gold nanoparticles or rare earth doped particles fluoresce once irradiated with particular wavelengths, such that they are used for optical imaging of proteins and genes. Several dye-containing or dye-doped nanoparticles – such as Silica nanoparticles or Calcium phosphate nanoparticles – are important for *in-vivo* or *ex-vivo* near infrared fluorescence imaging of cancers (Coto-García *et al.*, 2011).

Quantum dots for diagnostics and therapeutics

A specific subset of NPs is represented by Quantum Dots (QDs) (Obonyo *et al.*, 2010; Byers *et al.*, 2011; Rosenthal *et al.*, 2011). QDs (which have generally a diameter of 2 - 10 nm) are produced including a spherical core of a semiconductor in a shell of another semiconductor with a different band gap. This allows to control their electronic and light emission properties. The bioconjuation of the surface of QDs with biomolecules (*e.g.* antibodies, oligonucleotides, DNA, etc.) gives the property of targeting them onto specific locations in the body to kill, for example, tumor cells. QDs can also be used in diagnostics. Irradiation with specific wavelength generates the fluorescence of QDs that is an effective approach to find out the location of solid cancers. QDs are also used for therapeutic purposes, for instance in Photodynamic Therapy: irradiation with low energy electromagnetic waves allows QDs to excite oxygen molecules present in the body via an electronic process; excited oxygen is very reactive and causes the death of tumor cells and not of normal cells.

Cyanine dies-loaded nanoparticles for diagnostics

A relevant position in this scientific research is played by Cyanine dyes (Miletto *et al.*, 2010; Mortati *et al.*, 2011; Alberto *et al.*, 2009), a class of organic colored molecules presenting strong fluorescence features and high biocompatibility towards the human body (Shi *et al.*, 2010).

Carbon nanotubes as drug carrier

Nanostructured materials are also used for carrying drugs: porous inorganic nanoparticles can be loaded with effective drugs, which are contained into organic nanomicelles that by apt bioactive systems target body cells presenting illness. Carbon nanotubes are a typology of nanostructured materials studied to delivery drugs against cancers (Ezzati Nazhad Dolatabadi *et al.*, 2011). In fact, their tubular structure allows both carrying drugs and protecting them towards external agents. More in general therapeutic applications involving nanotechnological materials combined with cytotoxic (antineoplastic or chemotherapies) agents are a key area of development for science and technology (Shapira *et al.*, 2011).

Nano-biosensors

Biosensors are a promising application of nanotechnology, as they play a critical role for modern biomedical technologies. In particular, biosensors are, basically, devices able to detect specific biological molecules and to convert their presence in an electric signal that can be analyzed for diagnosis (Bounichy and Mousa, 2011; Sanvicens *et al.*, 2011). A key application is the detection of cancers in the human body as well as to find out pharmaceuticals in concentrations well beyond those detectable by traditional methods. Biosensors in diagnostics rely much on modern nanotechnological applications: for instance the use of single wall carbon nanotubes has enhanced the ability of detection of electrochemical biosensors that are able to find out cancers and their metastases.

Gold nanoparticles for Plasmon Photothermal Therapy

Another main advanced therapy for cancer, based on nanostructured/nanodimensioned materials, is the Plasmon Photothermal Therapy. In this case, Gold nanoparticles and Gold nanorods[4], because of the electronic structure of the particle/rod, have the feature of heating themselves when exposed to strong electromagnetic radiations, like those emitted by lasers (Ratto *et al.*, 2011; Ungureanu *et al.*,

[4] Nanorods are a specific morphology of nanoscaled objects. The main difference from nanoparticles is their elongated shape. Each of their dimensions range from 1 to 100 nm. They may be synthesized from metals or semiconducting materials.

2011). This biomedical procedure uses the heat for killing cancer cells (El-Sayed *et al.*, 2006).

Nanoparticles for immunotherapy

Immunotherapy is another new frontier for future therapeutic treatment of cancer. In particular, the combination of nanotech objects and lymphocytes, such as T-cells[5], may be vital for new applications of these methods for effective cancer treatments (Hamdy *et al.*, 2011; Hung *et al.*, 2011).

Some edge areas of bio-nano-medical applications (closer to molecular biology) are still at the stage of first experimental trials, such as the combination between nanovector and si-RNA or mi-RNA[6].

These main topics of nanotechnology play a vital role in biomedicine. Next section describes the methodology to investigate their rates of growth in order to understand the current patterns of development that may drive the future therapy and diagnosis in medical practice.

2. DATA MINING STRATEGY AND METHODOLOGY OF RESEARCH

This paper uses Scopus (Scopus 2011) database and data mining is performed with a series of queries based on complex search subjects of keywords and Boolean operators. Data mining is performed in the time horizon 2000 – 2010 for scientific research products (e.g. articles) and for patents across key nano-bio-medical topics. Data on scientific products, which represent a proxy of scientific activity, are retrieved via the "Advanced search" window of Scopus website, using the "Article title, abstract, keyword" tag in the search window. Data on patents that indicate a proxy of technological activity, are retrieved in the SciVerse Scopus instrument with a full text query[7]. Tests are made before performing the final queries. Syntax of these queries is checked in order to obtain best results in terms of number of occurrences. The queries are dived in two main groups. *The first group* concerns general terms related to scientific fields of nano-bio medicine. The aim is to measure the general rate of scientific and technological growth of nanotechnology in biomedical sciences. *The second group* is focused on specific analysis of subfields or techniques: the bio-nano-medicine applied mainly in diagnostic and therapeutic techniques. The queries of this group are able to provide data to analyze specific trends of several important scientific-technological topics in nano-bio-medicine, as well as to explore specific topics that are (either or both):

- in some way on the edge of basic research activities;
- very promising for future results in biomedical applications;
- liable of generating a huge quantity of innovative activities.

Appendix 1 presents a short description of these queries.

The vast sample, represented by 42,800 occurrences of articles and 213,732 of patents, is the basis to apply the model in order to measure the rate of scientific and technological advances of nanotechnology in biomedicine. First of all, the data has been analyzed by descriptive statistics and a correlation analysis. After that, the following *assumptions* are stated to apply the model:

1. ${}_{a}P$ is the number of articles/patents in the specific research field at 2000

2. ${}_{t}P$ is the number of articles/patents in the specific research field at 2010

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[5] T cells or T lymphocytes belong to a group of white blood cells known as lymphocytes, and play a central role in cell-mediated immunity. The abbreviation T stands for thymus, since this is the principal organ responsible for the T cell's maturation.

[6] Small interfering RNA (siRNA), sometimes known as short interfering RNA or silencing RNA, is a class of double-stranded RNA molecules, 20-25 nucleotides in length, that play a variety of roles in biology. MicroRNAs (miRNAs) are short ribonucleic acid (RNA) molecules, on average only 22 nucleotides long and are found in all eukaryotic cells, except fungi, algae, and marine plants.

[7] Technology is based on inventions and innovations. Invention is a commercially promising product or service, based on new science and/or technology that meets the requirements for a patent application and/or the patent is already granted. On the other hand, innovation, which already has a valid and granted patent, is the successful entry of a new science or technology-based product into a particular market. In particular, innovations are protected by patents, which indicate the current innovation of industries and also commercially promising inventions.

3. t is the period analyzed and it is equal to 10 years

4. this basic scientific research might generate over the Forecast horizon (*e.g.* from 2011 onwards) new patterns of nano-technological innovations in biomedicine.

5. articles are a proxy of the scientific activity, whereas patents are a proxy of the technological activity of the research field.

Since these critical scientific areas have a considerable acceleration in their production activity, the model is based on an *exponential* function (*cf.* Livi Bacci, 1999, chp. 3):

$${}_tP = {}_0P \cdot e^{rt}$$

where e is the base of natural logarithm (2.71828…).

Hence $\frac{{}_tP}{{}_0P} = e^{r\,t}$;

$$Log\frac{{}_tP}{{}_0P} = r \cdot t\,;$$

$$r = \frac{Log\left(\frac{{}_tP}{{}_0P}\right)}{t}. \qquad [1]$$

r= rate of scientific and technological advances of nano-research in biomedicine.

This model can be used to assess the evolutionary growth of knowledge in the short run[8] and can offer an analytical framework for understanding the current patterns of nano-technological innovations that can drive the future progress in biomedicine in fast-changing scenarios.

3. FINDINGS AND DISCUSSION

Table 1 shows, *ceteris paribus*, the rates of growth of general nanotechnology trends in biomedicine. All rates are rather high; in particular the rates based on the use of biocompatible materials show the highest rate of growth both in journal articles (56.93%) and patents (46.72%). This means that these key research areas have been generating an accumulation of knowledge that can underpin the pathways of innovative applications of nanotechnology in biomedicine.

Table 1: rates of growth in MAIN nano-research fields in biomedicine over 2000-2010

Main nanotechnology research fields in biomedicine	**Rate of scientific growth (articles) %**	**Rate of technological growth (patents) %**
1. (bionanotechnology OR (bio nanotechnology) OR (bionano technology) OR nanobiotechnology OR (nano biotechnology) OR (nanobio technology)); *occurrences: 3426 articles, 13,542 patents*	37.39	21.08
2. (nanobiomaterial OR (nano biomaterial) OR (nanobio material) OR bionanomaterial OR (bio nanomaterial) OR (bionano material)); *occurrences: 1183 articles, 1784 patents*	49.56	31.31
3. ((biocompatible nanomaterial) OR (biocompatible nanomaterials)); *occurrences: 877articles, 499 patents*	56.93	46.72
4. ((biomedical AND nano) OR (bio AND medical AND nano) OR (bionano AND medical) OR (biomedicine AND nano) OR (bio AND medicine AND nano) OR (bionano AND medicine)); *occurrences: 7554 articles, 30,563 patents*	43.94	27.38

[8] See Diebold (2004) for a general description of other forecasting methods.

Instead, table 2 shows, *ceteris paribus*, the rates of scientific/technological advances of nano-research in specific biomedical subfields of diagnostics and therapeutics. Average rate of scientific advances across these key research fields is 37.6% (*st.dev.* 10.4), whereas the average rate of technological advances is 23.8% (*st. dev.* 2.5). Of course, coefficient of correlation between rates of scientific and technological growth (of nano-bio-medicine applied in diagnostics and therapeutics) is positive and equal to 55.5% (*sig. at the 0.05 level*). This means that scientific and technological advances have similar and interwoven patterns of growth within the "techno-economic paradigms of nanotechnology" (*cf.* also Coccia *et al.*, 2011).

Although table 1A (appendix) shows that some converging research fields have a higher number of patents and/or articles, the rate of growth is lower than in smaller research fields (cf. Table 2). In fact, smaller research fields have a low number of occurrences because they are at the early stage of development, though they are characterized by high intensity of knowledge growth, representing promising emerging nanotechnologies for biomedical sciences.

Table 2 –Rate of scientific and technological advances of vital biomedical nanotechnology over 2000-2010

Nano-research research fields in biomedicine	% Rate of scientific growth (articles)	% Rate of technological growth (patents)
Vital nanotechnology for diagnostics		
((biosensor OR (bio sensor)) AND (nanotechnology OR nanotech))	39.93	32.36
(((quantum dot) OR (quantum dots)) AND (diagnostic OR diagnosis))	38.59	20.73
(magnetic AND (nanoparticle OR nanoparticles) AND imaging)	35.09	25.16
((nanoparticle OR (nano particle) OR nanoparticles OR (nano particles)) AND (diagnostic OR diagnosis))	33.34	19.94
(cyanine AND (nano*) AND (imaging OR (optical imaging)))	31.35	10.44
((nano*) AND (fluorescence imaging))	28.92	16.45
(((quantum dot) OR (quantum dots)) AND (imaging OR (optical imaging)))	27.74	21.20
Nanovector	15.07	8.41
Vital nanotechnology for therapeutics		
(((quantum dot) OR (quantum dots)) AND (therapeutic OR therapy))	57.76	21.77
((tumor OR cancer) AND (quantum dot))	53.88	20.11
(nanomicelle)	53.65	--
(((carbon nanotube) OR (carbon nanotubes) OR nanotube OR CNT) AND (drug delivery)))	53.29	26.74
(plasmon photothermal therapy)	41.65	25.58
((nanotechnology) AND (cytotoxic drugs))	37.79	34.84
((nanotechnology OR nanoparticle OR nanoparticles) AND (T-cell))	37.61	53.71
((nanoparticle OR (nano particle) OR nanoparticles OR (nano particles)) AND (therapeutic OR therapy))	35.05	18.68
((nanotechnology) AND (mi-RNA));	34.66	--
((nanotechnology) AND (si-RNA));	32.97	--
(RNA oligonucleotide nanoparticle delivery);	32.60	28.69
((nanoparticle OR (nano particle) OR nanoparticles OR (nano particles)) AND (drug delivery))	30.47	19.29

Table 2 shows that in *diagnostics* the higher rate of scientific growth is given by nanotech applications to biosensors (nano-biosensoring, 39.9% for articles and 32.36% for patents) and by the use of Quantum Dots (38.59% for articles and 20.73% for patents). The application of magnetic nanoparticles for imaging techniques (35.09%) is another key area with high rate of scientific growth (measured by articles in journals); this result is reinforced by the high rate of technological advances measured by patents (25.16%). Bárcena *et al.* (2009, p. 591) state that: "superparamagnetic iron oxide nanoparticles were found nontoxic and used as magnetic resonance imaging contrast agents, in molecular and cellular imaging applications […] drug delivery via magnetic targeting, hyperthermia, and labeling/tracking of stem cells have also been explored as potential therapeutic options."

We ascertain that rates of scientific advances for therapeutic applications are higher (41.7%) than diagnostic applications (31.25%), whereas rates of technological advances are 19.33% (diagnostics) *vs.* 27.7% (therapeutics). Some topics in therapeutics do not have patenting activity because the nano-biotechnology applications are at the early stage of development (mainly in molecular biology - related research fields). The highest rates of scientific advances (measured by articles in journals) are for therapeutic applications of Quantum Dots (57.29% and 53.88%), carbon nanotubes for drug delivery (53.29%) and nanomicelles (53.65%). Nanomicelles have a polymeric structure to which ligands can be bound to target, for instance, specific viruses; they are mainly applied for destroying viruses and have generating a main shift of the paradigm in antiviral therapies changing the clinical practice. The scientific growth of therapeutic applications of magnetic nanoparticles is more than 35%. Bárcena *et al.* (2009, p. 612) describe some vital applications such as: "the magnetic fluid hyperthermia is a treatment for the eradication of cancer tissues using an alternating magnetic field. The magnetic waves are not absorbed by living tissue and permeate throughout the body." Plasmon Phototermal Therapy also shows a high growth in scientific and technological advances (41.65% and 25.58%, respectively).

Another high rate of technological growth (measured by patents) is by the edge biomedical-nano-research based on the combination of nanomaterials with T-cells (53.71%), applied mainly for cancer immunotherapy, and the use of nanotech materials associated to cytotoxic agents (34.84%). In particular nanomaterials in combination with T-cell biology are an apt technique to produce treatments that evade the immune system and deliver localized therapeutic payloads, minimizing the adverse reactions. These main nano-research fields are driving target cancer therapies in order to overcome drug resistance with traditional chemotherapy approaches. This nanomedicine based on new nanovehicles has been generating a revolution in modern clinical practice to treat a variety of cancers. Shapira *et al.* (2011, p. 150) claim that "NPs are being exploited for selective drug delivery to tumor cells, to cancer stem/tumor initiating cells and/or to the supportive cancer cell microenvironment, i.e. stroma or tumor vasculature."

These current rates of evolutionary growth of knowledge based on journal articles and patents allow to show insights in order to pinpoint some leading research fields of nanotechnologies that may drive future innovative application of nanotechnologies in bio-nanomedicine.

4. CONCLUDING REMARKS

This research shows how nanotechnologies have been affecting biomedicine with innovative applications for therapy and diagnosis. In fact, several specific nanomedical applications are effective strategies in diagnostics and therapeutics for delivering chemotherapeutic drugs, chemosensitizers, drug resistant proteins, etc. In addition, with the use of nanotechnology in biomedicine, cytotoxic drugs can be delivered to cancer sites more effectively and with lesser adverse reactions than traditional techniques. We review our main findings for nano-research and patents in biomedicine showing how the current fast-changing technological scenarios are characterized by following vital patterns:

1. In general: the rates of scientific growth of nanostructured and biocompatible materials in biomedicine (Table 1) are higher than others;
2. In particular: nanotechnology applied in *diagnostics* may be driven mainly by biosensors, nanoparticles, nanomicelles, and Quantum Dots; for instance, magnetic

nanoparticles are mainly applied for magnetic resonance imaging, gastrointestinal tract imaging, liver and spleen images, lymph nodes imaging, etc.

3. As far as nanotechnologies applied for *therapeutics* are concerned, leading roles will be played by: Quantum Dots, which have scientific growth rates greater than in diagnostic techniques, because of their effective applications to treat cancers, whereas their patenting activity lags behind other applications; nanotech applications to deliver cytotoxic drugs, which have also a high rate of growth in patenting activities (34.84%). Current cancer therapies based on traditional chemotherapy agents have several limitations because of drug resistance and new anticancer drugs based on nanomedicine are rapidly evolving, overcoming limitations of standard chemotherapy agents. In fact, NPs in combination with a cytotoxic drug can overcome the drug resistance proteins and enable to treat with effectiveness tumor and its metastases.

Other emerging biomedical-nano-research fields are:

- Nanotech applications with the use of *T*-cells, that have a high technological rate of advance (53.7%) because of innovative applications to treat cancers;
- Drug delivery techniques performed with carbon nanotubes as carriers;
- Converging molecular biology and nanotechnology (nanovector and siRNA or miRNA, RNA oligonucleotide nanoparticle delivery); such converging nano-research is at the stage of trials and shows lower growth rates, though they have promising future applications in biomedicine. In particular they may play a main role as a new class of therapeutics based on nanoparticle drug delivery system. For instance, an innovative application is to treat the brain ischemic insult by carbon nanotube-mediated siRNA silencing (CNR 2011).

These results show that all analyzed new nano-research topics (including very specific areas such as Cyanine Dyes in optical imaging, Plasmon Phototermal Therapy or molecular biology-related areas) have high rates of growth driven mainly by current intensive scientific advances that create the background for underpinning technological advances in biomedicine.

The present study shows also that some nanotechnologies, such as magnetic nanoparticles, are playing a key role in diagnosis, though their applications for target therapy are still in a preliminary phase of development (*cf.* Bárcena *et al.*, 2009, pp. 162 ff). In fact, a lot of progress in the functionalization of these nanoparticles is focused on widening their diagnostic ability, though magnetic drug targeting by nanoparticles still presents several problems associated to humans. In addition, these scientific and technological advances of nanotechnology applied for biomedicine take place in several phases and there are significant time lags between the acquisition of information in clinical research and the development/ improvement of new applications of nanomedicine in clinical practice. In addition a fruitful role in developing innovative applications of nanotechnology in biomedicine is played by continuous learning process between clinical research and clinical practice in collaboration of medical staff and patients (Coccia, 2012). In particular, the steps of R&D are interwoven and blockbusters are best pursued in cooperation with end users (patients). It is important to note that advances of nanotechnology in biomedicine havebeen generating innovative drugs and diagnostic tools driven mainly by:

a) converging of different research fields and technologies such as the fruitful interaction between nanotechnology and molecular biology, which is a considerable boost to innovations in biomedicine that improve the clinical practice to treat drug resistant illnesses;

b) learning processes driven by the acquisition of skills through the interaction between clinical research and clinical practice based on participation of patients and medical staff (Coccia, 2012).

The continuous technical progress in biomedicine is supported by high intensity of scientific and technological knowledge growth of nanotechnology trajectories in association to advances in basic biomedical research, genomics, genetics etc. that has been paving revolutionary applications in clinical practice that will lead to longer, better and healthier living of modern societies.

APPENDIX

SHORT DESCRIPTION OF SEARCH TERMS

Diagnostic applications involving the use of nanotech items

- ((biosensor OR (bio sensor)) AND (nanotechnology OR nanotech)): this query explores the relations existing between biosensors and applications of nanotechnologies.
- (((quantum dot) OR (quantum dots)) AND (diagnostic OR diagnosis)): quantum dots (as above described) application in any diagnostic technique is explored by this query.
- (magnetic AND (nanoparticle OR nanoparticles) AND imaging): The use of magnetic nanoparticles in specific bioimaging techniques for diagnostic use;
- ((nanoparticle OR (nano particle) OR nanoparticles OR (nano particles)) AND (diagnostic OR diagnosis)): explores the use of nanoparticles for diagnostic purpose.
- (cyanine AND (nano*) AND (imaging OR (optical imaging))): the use of a specific type of fluorescent dyes (cyanine dyes) coupled to the use of nanostructured materials (mostly nanoparticles or nanotubes) for imaging diagnostic techniques;
- ((nano*) AND (fluorescence imaging)): this query explores the use of nanostructured materials (nanoparticles, nanotubes) in the diagnostic techniques involving fluorescence imaging
- (((quantum dot) OR (quantum dots)) AND (imaging OR (optical imaging))): in this case the search term is more specific with respect to the previous one, and collects data on the exploitation of quantum dots in all imaging diagnostic techniques (either optical or not).

Therapeutic applications (e.g. against tumors) involving the use of nanotech items

- (((quantum dot) OR (quantum dots)) AND (therapeutic OR therapy)): the use of quantum dots for therapeutic purposes.
- ((tumor OR cancer) AND (quantum dot)): the use of above described quantum dots in cancer diagnosis and therapy;
- (((carbon nanotube) OR (carbon nanotubes) OR nanotube OR CNT) AND (drug delivery)): the use of carbon nanotubes for targeted drug delivery.
- (plasmon photothermal therapy): the above described thermal therapy involving nanostructures.
- ((nanotechnology) AND (cytotoxic drugs)): the object of the query is the combined used of nanotechnology retrieval and cytotoxic drugs for the cure of cancer;
- ((nanotechnology OR nanoparticle OR nanoparticles) AND (T-cell)): this query explores the combination of nanotech objects with T-cell (a type of lymphocytes) for the cure of cancer.
- ((nanoparticle OR (nano particle) OR nanoparticles OR (nano particles)) AND (therapeutic OR therapy)): the use of nanoparticles for therapies.
- ((nanotechnology) AND (mi-RNA)), ((nanotechnology) AND (si-RNA)), (RNA oligonucleotide nanoparticle delivery): these queries explore topics combining molecular biology and nanotechnology for therapeutic purposes;
- ((nanoparticle OR (nano particle) OR nanoparticles OR (nano particles)) AND (drug delivery)): the use of nanoparticles for targeted drug delivery.

Table 1A – Number of occurrences of vital biomedical nanotechnology research fields over 2000-2010

Nano-research research fields in biomedicine	Occurrences (articles)	Occurrences (patents)
Vital nanotechnology for diagnostics		
((biosensor OR (bio sensor)) AND (nanotechnology OR nanotech))	1404	1303
(((quantum dot) OR (quantum dots)) AND (diagnostic OR diagnosis));	1050	7389
(magnetic AND (nanoparticle OR nanoparticles) AND imaging)	2890	10,615
((nanoparticle OR (nano particle) OR nanoparticles OR (nano particles)) AND (diagnostic OR diagnosis))	3771	30,105
(cyanine AND (nano*) AND (imaging OR (optical imaging)))	75	3444
((nano*) AND (fluorescence imaging))	3363	28,753
(((quantum dot) OR (quantum dots)) AND (imaging OR (optical imaging)))	2592	9430
Nanovector	36	46
Vital nanotechnology for therapeutics		
(((quantum dot) OR (quantum dots)) AND (therapeutic OR therapy));	617	6028
((tumor OR cancer) AND (quantum dot))	1076	4205
(nanomicelle)	10	10
(((carbon nanotube) OR (carbon nanotubes) OR nanotube OR CNT) AND (drug delivery)))	1045	2806
(plasmon photothermal therapy)	78	76
((nanotechnology) AND (cytotoxic drugs))	152	478
((nanotechnology OR nanoparticle OR nanoparticles) AND (T-cell));	340	1324
((nanoparticle OR (nano particle) OR nanoparticles OR (nano particles)) AND (therapeutic OR therapy));	6466	39,227
((nanotechnology) AND (mi-RNA));	109	---
((nanotechnology) AND (si-RNA));	10	---
(RNA oligonucleotide nanoparticle delivery);	166	458
((nanoparticle OR (nano particle) OR nanoparticles OR (nano particles)) AND (drug delivery))	10,042,	34,421

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