Emerging nanotechnological research for future pathways of biomedicine

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Abstract: The purpose of this paper is to measure and analyse the rate of scientific and technological advance of some emerging nanotechnological research fields in biomedicine to detect path-breaking technological trajectories. The approach, based on exponential models of growth, shows the current evolutionary trends of nano-research that may underpin future patterns of technological innovation in biomedicine and nanomedicine. In particular, results show that biosensors, quantum dots, carbon nanotubes and nanomicelles have innovative applications in diagnostics and targeted therapies for cancers that have been generating a revolution in clinical practice. The present study also detects two main determinants that have been supporting continuous diffusion of nano-technology in biomedicine: convergence of genetics, genomics and nanotechnology and multiplicity of learning processes in clinical research/practice. These drivers have been paving groundbreaking pathways in biomedicine that can lead to longer, better and healthier living of societies in not-too-distant future.

Keywords: nanotechnology; nanoscience; emerging technology; biomedicine; nanomedicine; nanoparticles; NPs; quantum dots; QDs; drug delivery.
1 Introduction

Scientific research production is a crucial competitive asset of nations in the current knowledge era (Coccia, 2012c). In general, Research and Development (R&D) is generated within the national system of innovation in order to support the ‘competitive advantage’ of countries (Porter, 1990; see also Coccia, 2008). Scientific research focused on bio-nanotechnology is a current vital research field that is supporting innovation and change in modern biomedicine and biomedical engineering (Islam and Miyazaki, 2010; Rafols and Meyer, 2007, 2010; Coccia, 2012b). In fact, nanostructured materials have a high potentiality of development for biomedical purposes through groundbreaking applications in new therapeutical instruments and diagnostic methodologies (cf., Lim et al., 2010; Coccia and Finardi, 2012). No and Park (2010), using patent citations, argue that the interaction of biotechnology and nanotechnology may provide important signals for future patterns in nanobiomedicine (cf., Bárcena et al., 2009; Sylvester and Bowman, 2010; Coccia, 2012b).

The purpose of this paper is the analysis of the evolutionary growth of knowledge in emerging nanotechnology research fields in bio-medicine using an exponential model that measures and assesses the rate of scientific and technological advances. The methodology is based on published scientific outputs (articles, proceedings, etc.) in order to detect and analyse the directions of emerging scientific fields in the converging area of nanotechnology and biomedicine that has been generating a revolution in clinical practice. In particular, the study reported here is important to explore emerging
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nanotechnology pathways that have been changing biomedical sciences and are improving human health and quality of life.

Next section contains the theoretical framework, describing the most important features of some nanotech biomedical applications. The third section describes the research methodology, while the fourth section shows main findings. Last section discusses the results, showing trends that seem to support emerging research fields of nanotechnology applied to biomedicine.

2 Theoretical framework

Biomedicine is one of the key scientific fields where nanotechnologies are providing vital innovative applications that have been generating a revolution in clinical practice (Coccia and Finardi, 2012; Coccia et al., 2012; Coccia, 2012b). Several biomedical devices, implementing nanostructured materials, have innovative applications either in diagnostics or in therapeutics.2

In fact, 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 tuneable 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.”

Groundbreaking nanomaterials have various degrees of stability and biocompatibility, and may even present toxicity3 depending on the specific properties and chemical composition. As a matter of fact, stability and biocompatibility of nanomaterials are ongoing issues in preclinical and clinical applications. For instance, Feliu et al. (2012) analyse stability and biocompatibility of a library of polyester dendrimers in comparison to polyamidoamine dendrimers. They: “evaluate material stability as a function of pH, temperature, and time, demonstrated that the stability of the 4th generation hydroxyl functional bis-MPA [methylol-propionic acid] dendrimer increased at acidic pH. Taken together, bis-MPA dendrimers are degradable and non-cytotoxic to human cell lines and primary cells” (p.1970). Jaganathan and Godin (2012) analysed the effects of silicon and silica nano- and micro-particles on cells and organs based on four main exposure routes (intravenous, pulmonary, dermal and oral). They also discuss the improving and standardising biocompatibility assessment for nano- and micro-particles.

The present paper analyses the evolutionary growth of the knowledge of some emerging research fields of nanotechnologies in biomedicine as well as the most promising applications that may strongly improve older technologies or enable new pathways for biomedical diagnosis or therapy.

In order to better frame the research design, we describe, briefly, the main characteristics of some vital nanotechnological research topics in applied biomedicine that we are going to analyse. In particular, we describe some nanomaterials for
biomedical applications [e.g., nanoparticles (NPs), quantum dots (QDs) and carbon nanotubes] and relevant topics of nanobiosensoring.

2.1 Nanoparticles in biomedicine

NPs are a key element for the development of nanotechnologies in the biomedical sciences (Chen et al., 2011; He et al., 2010). NPs are nanoscopic spheres ranging in diameter up to some tenths of nanometers4 that can be made of e.g., silica, metals, metallic salts or oxides, or can have a biological origin. NPs can be used as contrast agents in Magnetic Resonance Imaging (in vivo anatomical imaging) for diseases of the cardio-vascular system. Iron oxide NPs present peculiar magnetic properties (superparamagnetism) and current research has showed that iron oxide NPs are non-toxic, with minimal impact on cell viability and function [cf., Bárcena et al., (2009), p.591 ff]. NPs can be designed to selectively target the specific tissue/organ in order to treat diseases, such as in localised drug delivery strategies for cancer treatment (Wolinsky et al., 2012). Kumar and Mohammad (2011, p.789 ff) show: “magnetic nanoparticle-based hyperthermia to generate local heat resulting in the release of drugs either bound to the magnetic nanoparticle or encapsulated within polymeric matrices”. They highlight the potential opportunities for the combination of hyperthermia-based therapy and controlled drug release paradigms towards successful applications in personalised medicine. Zhang et al. (2012) show that peptides5 are an important class of components in nanomedicine that can be used either alone or in combination with nanomaterials of every reported composition. Their functions in cancer nanomedicine include serving as drug carriers, as targeting ligands, and as protease-responsive substrates for drug delivery.

In addition, functionalising the surface of NPs with specific and appropriate ligands can allow their use as drug carriers to target them selectively to the tissue/organ affected by cancer (Pöselt et al., 2012; Shukoor et al., 2012, 2011). Some NPs can also fluoresce and are applied as probes for optical imaging techniques. In fact, Gold NPs or rare earth doped particles fluoresce once irradiated with particular wavelengths, such that they are also used for optical imaging of proteins and genes. Several dye-containing or dye-doped NPs – such as Silica NPs or Calcium phosphate NPs – are important for in-vivo or ex-vivo near infrared fluorescence imaging of cancers (Coto-García et al., 2011; Ray et al., 2011).

NPs and nanomicelles can also act as carriers for drugs, which can be contained into organic nanomicelles or porous inorganic NPs that, by apt bioactive systems, can target tumoral cells of the body (see Yao et al., 2011; Goel et al., 2010)

2.2 Gold NPs for plasmon photothermal therapy to treat cancers

A novel advanced therapy for cancer, based on the use of NPs or nanorods, is the plasmon photothermal therapy. Gold NPs and gold nanorods,6 due to their electronic structure, heat themselves when exposed to strong electromagnetic radiations, like those emitted by lasers (Ratto et al., 2011; Ungureanu et al., 2011). This biomedical procedure uses heat to kill cancer cells (El-Sayed et al., 2006).

2.3 NPs for immunotherapy in anti-cancer treatments

Immunotherapy is another new frontier for future therapeutic treatment of cancer. In particular, the combination of NPs and lymphocytes, such as T-cells,7 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-nanomedical applications (closer to molecular biology) are still at the stage of first experimental trials, such as the combination between nanovector and siRNA or miRNA.8

2.4 Quantum dots in biomedicine

QDs are a specific subset of NPs (see Obonyo et al., 2010; Byers and Hitchman, 2011; Rosenthal et al., 2011). QDs have generally a diameter of 2 to 10 nm and 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 most interesting applications of QDs in medicine are, for instance, the nanodiagnoscics, imaging, targeted drug delivery, and photodynamic therapy (Jain, 2012; Chatterjee et al., 2008; Azzazy et al., 2007). Moreover, the bioconjugation 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, tumour cells. In diagnostics, QDs can utilise the specificity of monoclonal antibodies (mAbs) for targeting, though QD-mAbs conjugates are not always well-suited for this purpose because of their large size. Sukhanova et al. (2012, p.516 ff) show a new generation of ultrasmall diagnostic nanoprobes to overcome these problems. In addition, QDs fluoresce when irradiated with specific wavelengths; in this way it is possible to locate solid cancers.

QDs are also used for therapeutic purposes. Semiconductor QDs (e.g., metal or polymer NPs, and lipids micelles) have emerged with promising applications for early detection and therapy of cancers (Juženas et al., 2008). Another relevant application is 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 tumour cells and not of normal cells. Some researchers have also developed photosensitised QDs for production of radicals upon absorption of visible light; this approach is suitable to treat superficial tumours, whereas ionising radiation (X-rays and gamma rays) penetrates much deeper and offers a huge advantage in treating patients with tumours in internal organs (Juženas et al., 2008 and cf. also Cheng and Burda, 2011; Paszko et al., 2011; Fowley et al., 2012; Charron et al., 2012).

2.5 Cyanine dyes-loaded NPs for diagnostics and cancer treatments

Cyanine dyes are a class of organic coloured molecules presenting strong fluorescence features and high biocompatibility towards the human body (Miletto et al., 2010; Mortati et al., 2011; Alberto et al., 2009; Shi et al., 2010). Cyanine dyes present an electron deficient conjugated methine chain between two nitrogen atoms (usually inserted in heterocyclic groups).

Cyanine dyes can be used non-invasively to improve cancer detection, prognosis, and treatment: they can be inserted in apt NPs (usually made with mesoporous structures) to detect tumour and tumour metastases in vivo, cancer cells in pathological specimens, and circulating cancer cells in blood (Shi et al., 2010).

In addition, it has been discovered (with the use of confocal fluorescence imaging) that some specific Cyanine dyes present selective uptake by cancer cells, and spare
normal fibroblast cells, thus suggesting tumour cell targeting (Henary et al., 2012). Moreover, cytotoxic activity of such dyes has also been shown by Henary et al. (2012).

Cyanine dyes presenting longer chain absorb and fluoresce in near-infrared (NIR): recent development of NIR dyes (including cyanine dyes, squaraines, phthalocyanines, porphyrin derivatives) has marked a significant progress, with much improved chemical stability and photostability, high fluorescence intensity and long fluorescent life. These dyes hold promise as suitable agents for biomedical imaging. Newly developed NIR dyes have potential applications in cancer targeting and imaging. In addition, newly developed multifunctional NIR dyes will broaden current concept of tumour targeted imaging and hold promise to make an important contribution to the diagnosis and therapeutics for the treatment of cancer (Luo et al., 2011).

2.6 Carbon nanotubes as drug carrier for cancer therapy and as biosensors in cancer diagnostics

Carbon nanotubes are an allotropic form of carbon, having cylindrical structure. Their properties are outstanding under several characteristics: mechanic, electric, etc. A main feature is also the possibility of being used to deliver drugs, for instance against cancers (Ezzati Nazhad Dolatabadi et al., 2011). In fact, their tubular structure allows both carrying drugs and protecting them towards external agents. Therapeutic applications of carbon nanotubes combined with cytotoxic (antineoplastic or chemotherapies) agents are a key area of development for biomedical sciences (Shapira et al., 2011).

For what about the use of carbon nanotubes in biosensors for cancer diagnostics, Kim et al. (2009) present a simple and sensitive method for the real-time detection of a prostate cancer marker through label-free protein biosensors based on a carbon nanotube field effect transistor (see and cf. Kim et al., 2012). Instead, Bareket et al. (2010) report the development of an electrochemical biosensor based on carbon nanotubes for detection of formaldehyde released from a cancer cell line treated with formaldehyde-releasing anticancer prodrugs (see Yang et al. (2012) for pancreatic cancer). In addition, Tasviri et al. (2011) show an interesting application for diagnosis and therapy of diabetics: carbon nanotubes coated with amine-functionalised TiO₂ were used for glucose oxidase absorption in a novel biosensor for glucose determination.

2.7 Nanobiosensors for diagnosis

Nanobiosensors are a promising application of nanotechnology in modern biomedical technologies (Sadana and Sadana, 2011a, 2011b). In particular, biosensors are, basically, devices able to detect specific biological molecules and to convert their presence in an electric signal that can be analysed for diagnosis (Bounichy and Mousa, 2011; Sanviccens et al., 2011). Biosensors in diagnostics are starting to rely on nanotechnological applications: for instance the use of single wall carbon nanotubes can enhance the ability of detection of electrochemical biosensors. Key applications of nanobiosensors are the detection of DNA and of pharmaceuticals or other substances in very low concentrations (cf., Kurkina et al., 2011; Zhu et al., 2012).

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 technological innovation that may drive the future therapy and diagnosis in biomedical practice.
3 Data mining strategy and methodology of research

This paper uses Scopus database (Scopus, 2012) and data mining is performed with a series of queries based on complex search subjects of keywords and Boolean operators. Data mining is performed over the time horizon 2000 to 2010 for scientific research products (e.g., articles, proceedings, books, etc.) across key nanotechnology research fields applied in biomedicine. Data on scientific products represent a proxy of scientific activity in progress and are retrieved via the ‘Advanced search’ window of Scopus website, using the ‘Article title, abstract, keyword’ tag. Tests have been made before performing the final queries. Syntax of these queries is checked in order to obtain accurate and fruitful results in terms of number of occurrences. The queries are divided in two main groups.

- **The first group** concerns general terms related to macro emerging research fields of nanobiomedicine. In particular, the aim is to detect general directions of emerging nanoresearch fields and to measure the general rate of scientific and technological growth of nanotechnology in biomedical sciences.

- **The second group** is focused on emerging specific fields of nanomedicine applied mainly in diagnostics and therapeutics. This specific analysis is able to detect technological trajectories of several important nanoresearch fields in biomedicine, as well as to explore specific scientific fields that are:
  a) the edge of basic research activities
  b) very promising for future biomedical applications
  c) liable of generating a huge quantity of innovative activities.

Appendix presents a short description of these queries.

The data, represented by 48,332 occurrences of articles (from general and specific queries, see note of Table A1), show trends with a considerable acceleration across different research fields. These data have an apt structure to apply an exponential model in order to measure the rate of scientific and technological breakthroughs of nanotechnology applied in biomedicine (cf., Livi Bacci, 1999; Coccia, 2012a, 2012b). The following assumptions are stated to apply the model:

1. \( \alpha P \) is the number of articles in the specific research field at 2000
2. \( \beta P \) is the number of articles in the specific research field at 2010
3. \( t \) is the period analysed and it is equal to ten years
4. this basic scientific research might generate over the Forecast horizon (e.g., from 2011 onwards) new patterns of nanotechnological innovations in biomedicine.
5. articles are a proxy of the scientific activity in progress.

The exponential model is:

\[ \beta P = \alpha P \cdot e^{\tau} \]

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

Hence,

\[ \frac{\beta P}{\alpha P} = e^{\tau} \]
\[
\log \frac{P}{uP} = r \cdot t;
\]

\[
\log \frac{\frac{P}{uP}}{P} = \frac{1}{t}.
\]

(1)

\(r\) = rate of scientific and technological advances of nanoresearch in biomedicine.

This model can be used to assess the evolutionary growth of knowledge in the short run and can offer an analytical framework for understanding the current direction and intensity of the patterns of nanotechnological innovations that can drive the future progress in biomedicine.

4 Findings and discussion

Table 1 shows, ceteris paribus, the rates of growth of general nanotechnology trends in biomedicine. In particular, biocompatible materials show the highest rate of growth in journal articles (56.93%). 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>
<thead>
<tr>
<th>Main nanotechnology research fields in biomedicine based on combined keywords</th>
<th>Rate of scientific growth (articles) % based on equation (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (bionanotechnology OR (bio nanotechnology) OR (bionanotechnology) OR nanobiotechnology OR (nanobiotechnology) OR (nanobiology); occurrences: 3,426 articles)</td>
<td>37.39</td>
</tr>
<tr>
<td>2 (nanobiomaterial OR (nanobiomaterial) OR (nanobiomaterial) OR bionanomaterial OR (bionanomaterial) OR (bionanomaterial)); occurrences: 1,183 articles)</td>
<td>49.56</td>
</tr>
<tr>
<td>3 ((biocompatible nanomaterial) OR (biocompatible nanomaterials)); occurrences: 877 articles)</td>
<td>56.93</td>
</tr>
<tr>
<td>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: 7,554 articles)</td>
<td>43.94</td>
</tr>
</tbody>
</table>

Instead, Table 2 shows, ceteris paribus, the rates of scientific/technological advances in specific nanotechnological research fields applied in biomedicine (both diagnostics and therapeutics). Average rate of growth across these key research fields is 37.6% (st. dev. 10.4). Scientific advances support groundbreaking applications of emerging nanotechnologies in biomedical diagnostics and therapeutics that are interwoven technological trajectories within the macro “techno-economic paradigms of nanotechnology” (cf., also Coccia et al., 2012; Coccia and Finardi, 2012; Coccia, 2012b; Finardi, 2011, 2012).

Table A1 (Appendix) shows that some research fields have a higher number of articles, though the rate of growth is lower than emerging research fields (cf., also Table 2). In fact, some research fields have a low number of occurrences because they are
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still in the infancy, but they have high intensity of knowledge growth, representing emerging and groundbreaking nanotechnological research fields for biomedical sciences.

Table 2  Rate of scientific and technological advances of specific nanotechnology research fields in biomedicine over 2000 to 2010

<table>
<thead>
<tr>
<th>Nanotechnology research fields in biomedicine</th>
<th>% Rate of scientific growth (articles) based on equation (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vital nanotechnology for diagnostics</td>
<td></td>
</tr>
<tr>
<td>((biosensor OR (bio sensor)) AND (nanotechnology OR nanotech))</td>
<td>39.93</td>
</tr>
<tr>
<td>(((quantum dot) OR (quantum dots)) AND (diagnostic OR diagnosis))</td>
<td>38.59</td>
</tr>
<tr>
<td>(magnetic AND (nanoparticle OR nanoparticles) AND imaging)</td>
<td>35.09</td>
</tr>
<tr>
<td>((nanoparticle OR (nano particle) OR nanoparticles OR (nano particles)) AND (diagnostic OR diagnosis))</td>
<td>33.34</td>
</tr>
<tr>
<td>(cyanine AND (nano*) AND (imaging OR (optical imaging)))</td>
<td>31.35</td>
</tr>
<tr>
<td>((nano*) AND (fluorescence imaging))</td>
<td>28.92</td>
</tr>
<tr>
<td>(((quantum dot) OR (quantum dots)) AND (imaging OR (optical imaging)))</td>
<td>27.74</td>
</tr>
<tr>
<td>Nanovector</td>
<td>15.07</td>
</tr>
<tr>
<td>Vital nanotechnology for therapeutics</td>
<td></td>
</tr>
<tr>
<td>(((quantum dot) OR (quantum dots)) AND (therapeutic OR therapy))</td>
<td>57.76</td>
</tr>
<tr>
<td>((tumour OR cancer) AND (quantum dot))</td>
<td>53.88</td>
</tr>
<tr>
<td>(nanomicelle)</td>
<td>53.65</td>
</tr>
<tr>
<td>(((carbon nanotube) OR (carbon nanotubes) OR nanotube OR CNT) AND (drug delivery))</td>
<td>53.29</td>
</tr>
<tr>
<td>(plasmon photothermal therapy)</td>
<td>41.65</td>
</tr>
<tr>
<td>((nanotechnology) AND (cytotoxic drugs))</td>
<td>37.79</td>
</tr>
<tr>
<td>((nanotechnology OR nanoparticle OR nanoparticles) AND (T-cell))</td>
<td>37.61</td>
</tr>
<tr>
<td>((nanoparticle OR (nano particle) OR nanoparticles OR (nano particles)) AND (therapeutic OR therapy))</td>
<td>35.05</td>
</tr>
<tr>
<td>((nanotechnology) AND (mi-RNA))</td>
<td>34.66</td>
</tr>
<tr>
<td>((nanotechnology) AND (si-RNA))</td>
<td>32.97</td>
</tr>
<tr>
<td>(RNA oligonucleotide nanoparticle delivery)</td>
<td>32.60</td>
</tr>
<tr>
<td>((nanoparticle OR (nano particle) OR nanoparticles OR (nano particles)) AND (drug delivery))</td>
<td>30.47</td>
</tr>
</tbody>
</table>

Table 2 shows that in diagnostics the higher rate of scientific growth is given by nanotech applications to biosensors (nanobiosensoring, 39.9%) and by the use of QDs (38.59% for articles). The application of magnetic NPs for imaging techniques (35.09%) is another key area with high rate of scientific growth (measured by articles in journals). 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”.

Average rates of scientific advances for therapeutic applications are higher (41.70%) than diagnostic applications (31.25% of nanoresearch fields). The highest rates of scientific advances (measured by articles in journals) are for therapeutic applications of QDs (57.29% and 53.88%), carbon nanotubes for drug delivery (53.76%) and nanomicelles (53.65%). In particular, nanomicelles have a polymeric structure to which ligands can be bound to target, for instance, specific viruses; main application is as antiviral that has been changing the clinical practice by a main shift of the paradigm in antiviral therapies. Instead, the scientific growth of therapeutic applications of magnetic NPs is more than 35%. Plasmon photothermal therapy also shows a high growth in scientific and technological advances (41.65%). 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”.

Another high rate of growth is based on the combination of nanomaterials with T-cells, applied mainly for cancer immunotherapy, and the use of nanotech materials associated to cytotoxic agents (37.61%). In particular, nanomaterials in combination with approaches of T-cell biology are an apt technique to produce treatments that evade the immune system and deliver localised therapeutic payloads, minimising the adverse reactions. These main nanoresearch fields are also driving target cancer therapies in order to overcome drug resistance of traditional chemotherapy agents. 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 allow to show some insights in order to pinpoint some leading research fields of nanotechnologies that may drive future groundbreaking applications in bio-nanomedicine.

We review our main findings showing how the current fast-changing technological scenarios are characterised 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 applications in diagnostics may be driven mainly by biosensors, magnetic NPs and nanomicelles; for instance, magnetic NPs are mainly applied for magnetic resonance imaging of gastrointestinal tract, liver and spleen, lymph nodes, etc.

3. As far as nanotechnologies applied for therapeutics are concerned, driving roles will be played by QDs, due to their effective applications to treat cancers. Hence, as current cancer therapies based on traditional chemotherapy agents have several limitations because of drug resistance, new anticancer drugs based on nanomedicine are rapidly evolving, overcoming limitations of standard chemotherapy. In fact, NPs in combination with a cytotoxic drug can overcome the resistance of proteins to drugs and enable to treat cancer and its metastases with efficacy.

Other emerging biomedical-nanoresearch fields are:
Nanotech applications with the use of $T$-cells for innovative cancers treatments.

Drug delivery techniques performed with carbon nanotubes as carriers.

Converging molecular biology and nanotechnology techniques (nanovector and siRNA or miRNA, RNA oligonucleotide nanoparticle delivery); such converging nanoresearch field is at the stage of trials and shows lower growth rates, though it has a promising future applications in biomedicine. In particular, it may play a main role as a new class of treatments based on nanoparticle drug delivery system. For instance, an innovative application is the treatment of brain ischemic insult by carbon nanotube-mediated siRNA silencing (CNR, 2011).

These results show that emerging nanoresearch fields (including very specific areas such as Cyanine dyes in optical imaging, Plasmon Photothermal Therapy or molecular biology-related areas) have high rates of growth driven mainly by intensive scientific advances that create the background for underpinning technological advances in biomedicine in the future.

Results also show that some applications of nanotechnologies, such as magnetic NPs, are playing a key role in diagnosis [cf., Bárcena et al., (2009), pp.162 ff]. In fact, a lot of progress in the functionalisation of such NPs is focused on widening their diagnostic ability, though they still present several problems associated to humans. In addition, these scientific and technological advances of nanotechnology for biomedicine are developed 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. A main determinant in developing innovative applications of nanotechnology in biomedicine is played by continuous learning processes between clinical research and clinical practice in collaboration of medical staff and patients (Coccia, 2012a). In particular, the steps of R&D are interwoven and blockbusters are best pursued in cooperation with end users (patients). In brief, it is important to note that breakthroughs of nanotechnology in biomedicine have been generating path-breaking drugs and diagnostic tools driven mainly by:

1. Converging research fields and technologies such as the fruitful interaction between nanotechnology and molecular biology, which is a considerable driver of innovations in biomedicine to treat drug resistant cancers
2. 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, 2012a).

## 5 Concluding remarks

The present study shows that the emerging nanoresearch fields in biomedicine, based on rate of scientific knowledge growth, are:

1. **in general**, nanostructured and biocompatible materials
2. **in particular**, in diagnostics, biosensors, magnetic NPs and nanomicelles
3. **in therapeutics**, nanomicelles, carbon nanotubes, plasmon photothermal therapy and nanotech applications with the use of $T$-cells.
Nanotechnologies have been affecting biomedicine with groundbreaking applications in oncology and virology. In fact, several specific nanomedical applications are effective strategies in diagnostics and therapeutics for delivering chemotherapeutic drugs, chemosensitisers, 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 effects than traditional techniques.

The continuous technical progress in biomedicine is supported by high intensity of scientific and technological growth from the convergence of nanotechnology, genetics, genomics and proteomics that accumulates knowledge and spurs the insurgence of ground breaking research fields. These path-breaking converging technological paradigms, driven by nanotechnology, have a pervasive diffusion in biomedical sciences by breakthroughs in clinical research that have been generating a revolution in clinical practice to treat (and we hope to cure) cancers and other diseases in order to lead to longer, better and healthier living of societies in not-too-distant future.

Acknowledgements

We would like to thank Ceris-CNR staff and Prof. S. Rolfo of the CERIS-CNR for supporting this research field. Ugo Finardi acknowledges the help and spur by Prof. S. Coluccia and L. Battezzati (University of Torino, Italy). The authors would like to thank two anonymous referees for fruitful comments and suggestions. Usual disclaimer applies.

The authors in parentheses (MC: Mario Coccia and UF: Ugo Finardi) have made substantial contributions to the following tasks of research: Conception (MC); Design (MC); theoretical framework (MC and UF); acquisition of data (UF); modelling and analysis of data (MC); interpretation of data (MC and UF); drafting of the manuscript (MC and UF); critical revision of the manuscript for important intellectual content (MC); statistical analysis (MC), supervision (MC).

References


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Notes
1 ‘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 of research sector represented by universities, research laboratories, etc., while the broad definition includes many subsystems such as finance, firms, government, and so on. The efficiency of this broad NSI supports economic growth patterns.
2 Cf., Hu et al. (2011), Sekhon and Kamboj (2010a, 2010b), and Willner and Willner (2010).
3 Cf., Jones and Grainger (2009).
4 A nanometre (nm) is equal to one millionth of millimetre.
5 Peptides are short polymers of amino acid monomers linked by peptide bonds. They are distinguished from proteins on the basis of size, typically containing fewer than 50 monomer units.
6 Nanorods are a specific morphology of nanoscaled objects. The main difference from NPs is their elongated shape. Each of their dimensions range from 1 to 100 nm. They may be synthesised from metals or semiconducting materials.
7 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.
8 Small interfering RNA (siRNA), sometimes known as short interfering RNA or silencing RNA, is a class of double-stranded RNA molecules, 20 to 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.
9 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 (Coccia, 2005a, 2005b, 2010).
10 See Diebold (2004) for a general description of other forecasting methods.

Appendix

Short description of search terms

Diagnostic applications involving the use of nanotechnology

- ((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)): application of quantum dots 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 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 tumours) involving the use of nanotechnology

• (((quantum dot) OR (quantum dots)) AND (therapeutic OR therapy)): the use of quantum dots for therapeutic purposes.

• ((tumour OR cancer) AND (quantum dot)): the use of 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 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 lymphocyes) 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 A1  Number of occurrences of vital biomedical nanotechnology research fields over 2000 to 2010

<table>
<thead>
<tr>
<th>Nano-research fields in biomedicine</th>
<th>Occurrences (articles)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vital nanotechnology for diagnostics</strong></td>
<td></td>
</tr>
<tr>
<td>((biosensor or (bio sensor)) and (nanotechnology or nanotech))</td>
<td>1,404</td>
</tr>
<tr>
<td>(((quantum dot) or (quantum dots)) and (diagnostic or diagnosis))</td>
<td>1,050</td>
</tr>
<tr>
<td>(magnetic and (nanoparticle or nanoparticles) and imaging)</td>
<td>2,890</td>
</tr>
<tr>
<td>((nanoparticle or (nano particle) or nanoparticles or (nano particles)) and (diagnostic or diagnosis))</td>
<td>3,771</td>
</tr>
<tr>
<td>(cyanine and (nano*) and (imaging or (optical imaging)))</td>
<td>75</td>
</tr>
<tr>
<td>((nano*) and (fluorescence imaging))</td>
<td>3,363</td>
</tr>
<tr>
<td>(((quantum dot) or (quantum dots)) and (imaging or (optical imaging)))</td>
<td>2,592</td>
</tr>
<tr>
<td>Nanovector</td>
<td>36</td>
</tr>
<tr>
<td><strong>Vital nanotechnology for therapeutics</strong></td>
<td></td>
</tr>
<tr>
<td>(((quantum dot) or (quantum dots)) and (therapeutic or therapy))</td>
<td>617</td>
</tr>
<tr>
<td>((tumour or cancer) and (quantum dot))</td>
<td>1,076</td>
</tr>
<tr>
<td>(nanomicelle)</td>
<td>10</td>
</tr>
<tr>
<td>(((carbon nanotube) or (carbon nanotubes) or nanotube or CNT) and (drug delivery)))</td>
<td>1,045</td>
</tr>
<tr>
<td>(plasmon photothermal therapy)</td>
<td>78</td>
</tr>
<tr>
<td>((nanotechnology) and (cytotoxic drugs))</td>
<td>152</td>
</tr>
<tr>
<td>((nanotechnology or nanoparticle or nanoparticles) and (T-cell))</td>
<td>340</td>
</tr>
<tr>
<td>((nanoparticle or (nano particle) or nanoparticles or (nano particles)) and (therapeutic or therapy))</td>
<td>6,466</td>
</tr>
<tr>
<td>((nanotechnology and (mi-RNA))</td>
<td>109</td>
</tr>
<tr>
<td>((nanotechnology and (si-RNA))</td>
<td>10</td>
</tr>
<tr>
<td>(RNA oligonucleotide nanoparticle delivery)</td>
<td>166</td>
</tr>
<tr>
<td>((nanoparticle or (nano particle) or nanoparticles or (nano particles)) and (drug delivery))</td>
<td>10,042</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>35,292</td>
</tr>
</tbody>
</table>

Note: The total number of occurrences is 35,292 + 13,040 (from Table 1) = 48,332.