International Efforts in Nanoinformatics Research Applied to Nanomedicine

D. de la Iglesia[1]; V. Maojo[1]; S. Chiesa[1]; F. Martin-Sanchez[2]; J. Kern[3]; G. Potamias[4]; J. Crespo[1]; M. Garcia-Remesal[1]; S. Keuchkerian[5]; C. Kulikowski[6]; J. A. Mitchell[7]

[1]Biomedical Informatics Group, Departamento de Inteligencia Artificial, Facultad de Informatica, Universidad Politecnica de Madrid, Madrid, Spain;
[2]Department of Medical Bioinformatics. Institute of Health "Carlos III", Madrid, Spain;
[3]Department of Medical Statistics, Epidemiology and Medical Informatics, Andrija Stampar School of Public Health, Zagreb University Medical School, Zagreb, Croatia;
[4]Institute of Computer Science, FORTH, Heraklion, Crete, Greece;
[5]HealthGrid Organization, Clermont-Ferrand, France;
[6]Department of Computer Science, Rutgers, The State University of New Jersey, New Brunswick, NJ, USA;
[7]Biomedical Informatics Department, University of Utah, Salt Lake City, UT, ,USA

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Summary

Background: Nanomedicine and nanoinformatics are novel disciplines facing substantial challenges. Since nanomedicine involves complex and massive data analysis and management, a new discipline named nanoinformatics is now emerging to provide the vision and the informatics methods and tools needed for such purposes. Methods from biomedical informatics may prove applicable with some adaptation despite nanomedicine involving different biophysical and biochemical characteristics of nanomaterials and corresponding differences in information complexity.

Objectives: We analyze recent initiatives and opportunities for research in nanomedicine and nanoinformatics as well as the previous experience of the authors, particularly in the context of a European project named ACTION-Grid. In this project the authors aimed to create a collaborative environment in biomedical and nanomedical research among countries in Europe, Western Balkans, Latin America, North Africa and the USA.

Methods: We review and analyze the rationale and scientific issues behind the new fields of nanomedicine and nanoinformatics. Such a review is linked to actual research projects and achievements of the authors within their groups.

Results: The work of the authors at the intersection between these two areas is presented. We also analyze several research initiatives that have recently emerged in the EU and USA context and highlight some ideas for future action at the international level.

Conclusions: Nanoinformatics aims to build new bridges between medicine, nanotechnology and informatics, allowing the application of computational methods in the nano-related areas. Opportunities for world-wide collaboration are already emerging and will be influential in advancing the field.

Correspondence to:
Diana de la Iglesia
Lab. 3204, DIA, Facultad de Informatica, UPM
Campus de Montegancedo
28660 Boadilla del Monte
Madrid
Spain
E-mail: diglesia@infomed.dia.fi.upm.es

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1. Introduction

1.1 Nanomedicine

Nanomedicine is a new field arising from the application of nanotechnology in health care and research [1]. The US National Institutes of Health define nanomedicine as a "*highly specific medical intervention at the molecular scale for curing disease or repairing damaged tissues*" [2, 3]. In general terms, nanomedicine can be considered as the application of nanotechnology to the medical domain.

While nanotechnology was already proposed in 1959 by the Nobel Feynman at Caltech [4], in a speech entitled: "There's plenty of room at the bottom", it took almost three decades to fulfill the biological and medical promises and challenges already implicit in Feynman's vision. The development of novel nanoscientific and nanotechnological approaches allowed the development of new nanoparticles and devices and the study of their effects. The application of these new materials and devices to humans has rapidly evolved in the past decade, creating the new area of nanomedicine.

The possibilities of nanomedicine for biomedical research and practice are impressive, ranging from the improvement of pharmaceutical products – making them more effective and aiming to reduce their contraindications – to the creation of new diagnostic devices and procedures or the development of new techniques and materials for tissue replacement and repairing

in the area of regenerative medicine. Furthermore, nanoparticles recently started to be widely considered for medical practice as diagnostic and therapeutic tools in order to understand, detect and treat diseases. But, for such new clinical applications, secondary effects such as nanotoxicity – both in animals and the environment – must be carefully analyzed before nanoparticles are approved for their use in clinical routine. To understand the toxicity of nanoparticles it is important to consider them as particles of very tiny size enabled to circulate through the blood, lymph or other paths in human, animal or any biological organism [5]. Exposure to them could have some unwanted consequences, some adverse effect, some temporary or permanent toxic result. Given the complexity of interactions and secondary effects that may appear, the implication of informatics tools and systems – such as health electronic records – will be important to address information management in this area.

At the time of writing, 28,782 papers appear indexed in Medline under the term "Nanoparticle" and 1380 papers under "Nanomedicine" (▶Fig. 1), the oldest one of the latter being published in 1999 [6]. Nevertheless, many other examples can be found in the literature, although they have not been indexed under the MeSH term "Nanomedicine". For instance, as cited in [1], Douglas et al. presented in 1987 one of the first published examples of what can be considered now as nanomedicine [7]. ▶Table 1, modified from [1], shows a historical reconstruction of some milestones in the area.

Such large number of papers in a field that is still largely unknown to many biomedical researchers indicates its tremendous potential impact in modern and future biomedical science and technology. At the same time, it also points out a new trend, where enormous amounts of information will have to be efficiently managed by a whole set of informatics tools and new approaches for intelligent management of information and knowledge. These requirements have been earlier discussed elsewhere [23], including the essential commitment of the scientific community with innovative research on molecular medicine, which now can be extended to nanomedicine – as we suggest in this paper. This reference, and others, highlights the necessary developments of novel informatics standards and tools – such as databases, simulation models, adapted EHRs, ontologies, etc. – for managing and structuring biomedical knowledge at various biological levels. In this regard, expanding this information at the nano level might surely be a new challenge for biomedical informaticians.

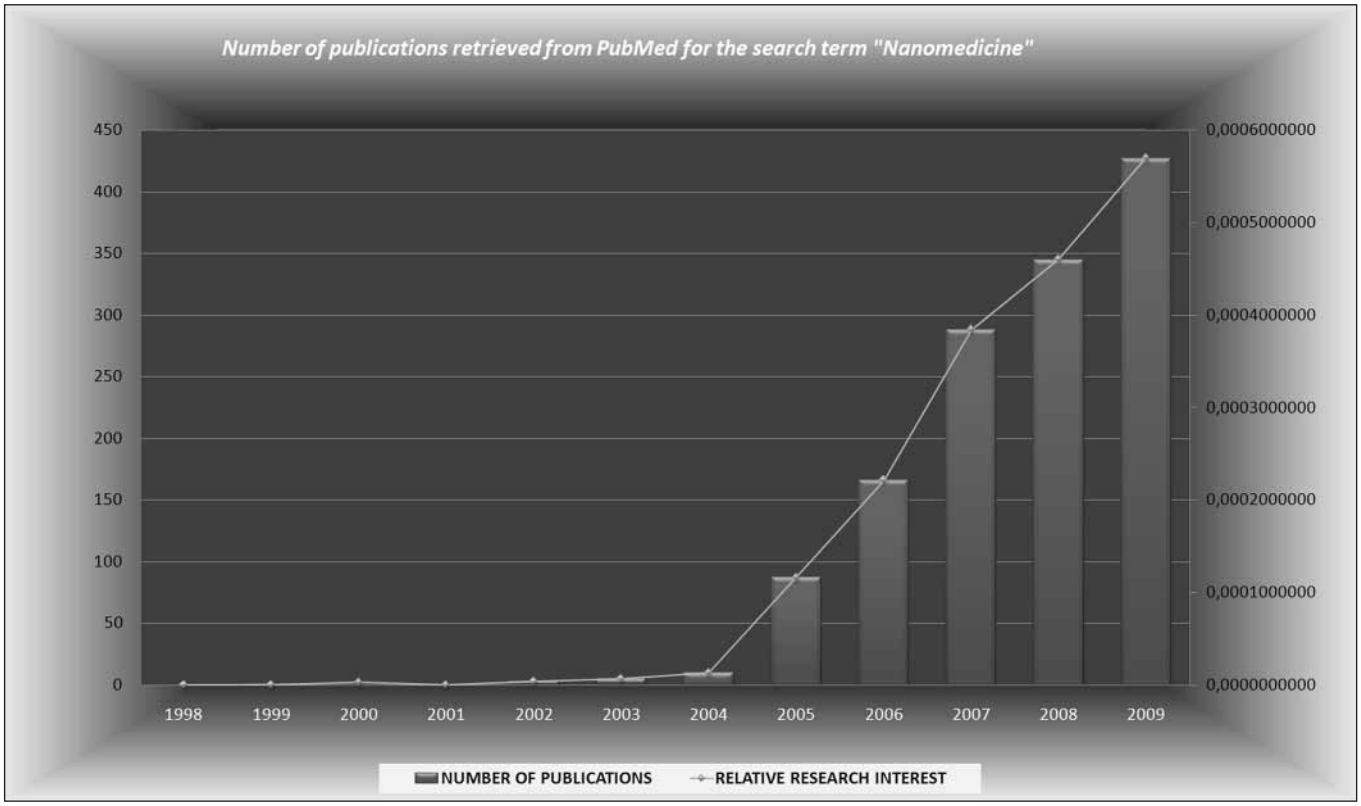

Fig. 1 Number of publications retrieved from PubMed for the search term "Nanomedicine" from 1998 to 2009. Note: These statistics offer a bibliometric analysis showing the growth of publications over time, using this term. Time lines show the absolute count of papers over time for the term "Nanomedicine" ("NUMBER OF PUBLICATIONS") and the relative growth in comparison to the growth of whole PubMed ("RELATIVE RESEARCH INTEREST"). In addition, there are papers which could be now associated to nanomedicine which actually do not include such term. Thus, the actual numbers could be higher.

Table 1 Relevant achievements on nanomedicine since 1978 to present days

Authors	Topic	Year of publication
Kreuter [8]	Nanoparticle-based drug delivery	1978
Rogers [9]	Advances in nanoparticle-based drug delivery and therapies	1982
El-Samaligy et al [10].	Nanocarriers	1983
Douglas et al [7]	Targeting cancer cells with nanoparticles coated with monoclonal antibodies.	1987
Nilsson [11]	Nanoparticle-based immunoassays	1989
Violante [12]	Diagnostic imaging	1990
James et al [13]	Doxil, a liposomal formulation of doxorubicin with lower toxicity, approved by the FDA for Kaposi's sarcoma	1994
Truong-Le et al [14]	DNA-gelatin nanospheres for controlled gene delivery	1998
Freitas [15]	Vision of nanomedicine	1999
Bogunia-Kubik et al. [16]	DNA-based computational approaches for Nanomedicine	2002
Roco [17]	National Nanotechnology Initiative approved in the USA	2003
Freitas [18]	Biocompatibility of nanomaterials	2003
Allen et al. [19]	Nanoparticle-based drug delivery	2004
Jain et al. [20]	Thorough analysis of impact of nanotechnology on healthcare	2006
Liu et al. [21]	Cancer therapy and diagnosis based on nanoparticles	2007
Gewin [22]	New nanotechnology applications on medicine	2009

To improve the efficiency of research on nanomedicine-related areas, the scientific community should approach the problem considering various points of view, such as for instance:

- Organize the current available material. It is important to create indexes of current research initiatives and the available resources that can be used and shared by research groups.
- Focus research efforts on specific high-impact research directions. Some topics can be considered more relevant for a rapid progress of the area (▶Fig. 2). Research effort should be focused on these themes.
- Reuse techniques and methods that have proved to be successful in areas like biomedical informatics or systems biology – regarding issues like standardization, interoperability, modeling or ontological development – in order to establish the necessary multidisciplinary approach, as pointed out by Blobel [24].

In this context, the new discipline named "nanoinformatics" has recently emerged, as discussed in more detail below.

1.2 Nanoinformatics

In 2007, a conference held in Virginia with support from the US National Science Foundation established the foundations of nanoinformatics [26]. At this conference, nanoinformatics was defined as "the development of effective mechanisms for collecting, sharing, visualizing, modeling and analyzing data and information relevant to the nanoscale science and engineering community". This includes those data that can be relevant such as literature, physical-chemical properties, biological, clinical and toxicological effects [27].

In the same year, a project was submitted to the European Commission and began in 2008. This project, called ACTION-Grid – where the authors participate – aimed to establish links between biomedical informatics, the Grid and the new field of nanoinformatics. In this regard, it has been the first initiative in nanoinformatics at the European level. It has also been aimed at expanding international cooperation in the field. Partners and experts from Europe, the Western Balkans, Africa, Latin America and the USA participate in the project.

2. Information Management in Nanomedicine

As stated before, nanoinformatics aims to improve the efficiency of nanomedicine-related research applying informatics methods and tools to nanomedical data and results (▶Fig. 3). This section provides a brief overview of these techniques and methodologies, some of them previously used in biomedical informatics research and recently applied to the nano context, such as ontologies, data and text mining approaches, modeling and simulation techniques and methods, development of standards to facilitate the interoperability and integration of heterogeneous data.

In nanoinformatics, *ontologies* can be considered as a semantic framework representing the nanomedical domain. This model contains a myriad of nanomedical concepts, categories and relations that can be used as a controlled terminology for data management and analysis, allowing different research tasks – such as the annotation of experimental data or the integration of heterogeneous data sources. Considering the extensive biological and medical vocabulary and the wide range of names and terms for the same concept in this area, ontologies provide a mechanism to standardize the representation of the nanomedical domain that can be very useful to disseminate information and knowledge in a machine-readable format and to express the metadata related to nanoinfor-

matics resources in a semantically interoperable way. Nowadays, there are some relevant initiatives to develop nanomedical ontologies, like the NanoParticle Ontology (NPO) [28, 29], developed by researchers of the National Cancer Institute to promote nanomedical informatics or the Atlas of Nanotechnology [30].

Besides the domain knowledge representation, nanoinformatics can address another relevant challenge for nanomedicine: the management of high volumes of data and information generated on nanomedical research. This requires methods to improve the efficiency on information search and retrieval, such as those provided by *data mining* – extraction of data from large databases to discover new knowledge about reactions, chemical properties of nanoparticles, nanomaterials, nanotoxicity, physical interactions, nanocarriers, etc. – and *text mining* – extraction of information from unstructured sources through the application of clustering, pattern discovery, feature generation, information extraction, web mining, etc. techniques. Text mining enhances automatic approaches to allow researchers to rapidly collect and manage nanomedical data and information.

Top Terms	Publications
Nanomedicine	1,164
Humans	857
Nanoparticles	831
Pharmaceutical Preparations	700
Animals	657
Nanotechnology	466
Therapeutics	439
Nanostructures	426
Neoplasms	406
Drug Delivery Systems	391
Drug Carriers	312
Tissues	296
Proteins	291
Mice	249
Evaluation Studies as Topic	239
Polymers	233
Medicine	231
Particle Size	225
Genes	204
Technology	193

Fig. 2 Top MeSH terms on nanomedicine publications. Source: Search for the term "Nanomedicine" on the scientific literature by using the tool GoPubMed [25]

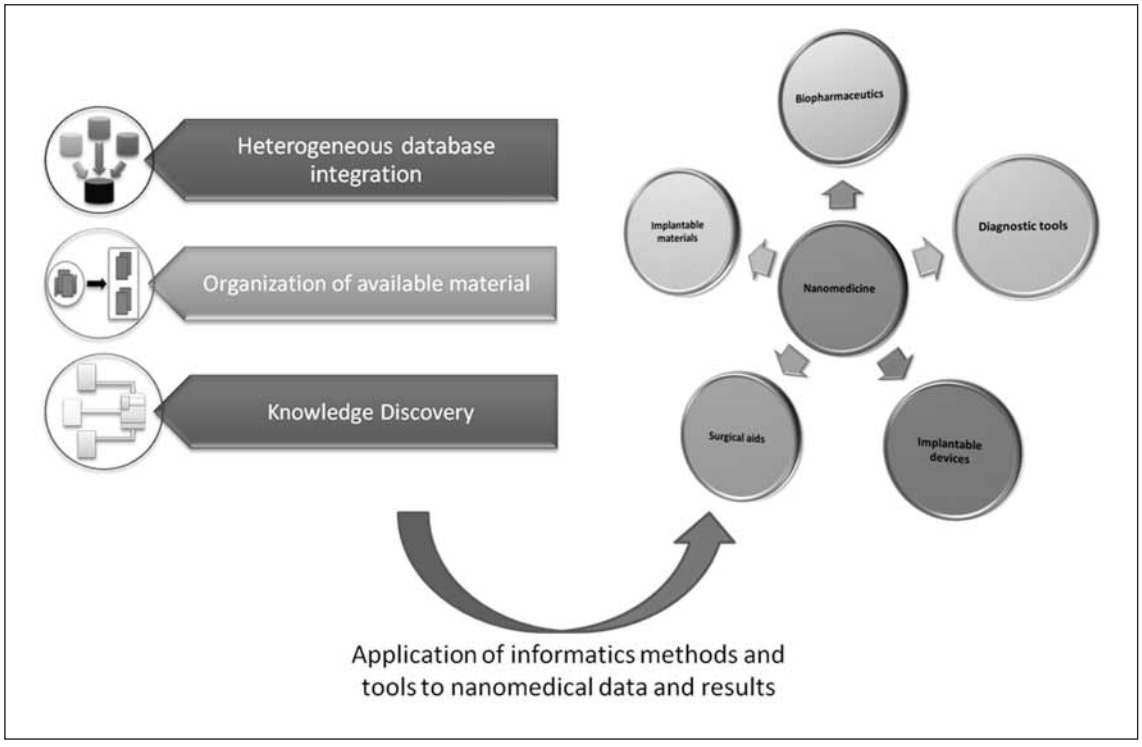

Fig. 3 Medical nanoinformatics

In addition, researchers typically need to link data from many online sources to generate data sets for further analysis. These data may reside on different servers using different access methods and data formats. The scientific community is currently demanding resources for data integration. This demand requires a big effort on the development of *standards*, which will allow *interoperability* between available nanoinformatics resources, facilitating information exchange. Standardization is necessary to address multidisciplinary research on nanomedicine, which involves links with areas like chemistry, genomics, medicine, physics, molecular biology, mathematics and computer science. Examples of standardization efforts in nanotechnology are those conducted by the Nanotechnology Standards Panel (NSP) of the American National Standards Institute (ANSI) or the International Organization for Standardization Technical Committee on Nanotechnologies (ISO/-TC 229), initiatives focused on environmental, health, and safety standards.

In this context, one of the main challenges of translational research on nanoinformatics is linking nanomedical information with patient clinical data. The integration of nanomedicine and implantable technology solutions with electronic health records (EHR) is just now starting to emerge. The projection is that in the next decade implantable medical sensors that can actually feed data to EHR systems will be more widely utilized. Advanced drug delivery systems are expected to become commercially available, including implantable nanomedicine devices that automatically sense drug levels and administer medication. In the coming decade nano- and implantable devices are expected to be more interactive in nature, having the capability to securely transmit information to EHR systems so clinicians can view it and issue directions to the implantable device [31].

Finally, it has to be highlighted the tremendous effort of the scientific community in the development of *modeling and simulation* tools for their use in nanomedicine. For instance, the initiative NanoHub [32] – supported by the US National Science Foundation – comprised a large set of online tools for simulation of quantum mechanics, nanomaterials production processes, nanoparticles behavior, nanofluidics, etc. Whereas current approaches are focused on modeling and simulating biological processes in the context of physiology and systems biology, new challenges lie ahead for linking such research with deeper analysis at the molecular and atomic level. In such direction, there are great challenges for expanding towards the nano level current initiatives like the European Virtual Physiological Human, described in the next section.

3. European Research Initiatives

There are currently various European initiatives that are already linked —directly or indirectly— to define the role of nanoinformatics in supporting research and developments in nanomedicine —and biomedicine, in general. We summarize below some of the initiatives where the authors are already contributing to such scientific vision.

3.1 The Virtual Physiological Human

The Virtual Physiological Human (VPH) [33], an initiative recently launched by the European Commission, aims to develop a methodological and technological framework that will facilitate collaborative and interdisciplinary research on the human anatomy and physiology. In general terms, the VPH envisions the human body as a complex system, that can be analyzed and simulated through the development of *in silico* integrative models, considering any level of complexity of the biological scale – from the whole body down through the organs to the cells and molecules.

The VPH framework consists of a set of research projects and support initiatives to address the key scientific and research issues associated to the "physiome". The physiome has been described as "*an umbrella term that refers to human modeling with mathematics and computational methods, accommodating cross-disciplinary science (chemistry, biology, physics) and a breadth of dimensional and temporal scale (sub-cellular to organs, sub-microsecond to tens-of-years)*" [34].

3.2 ACTION-Grid

ACTION-Grid [35] is a European Commission-funded support action, mentioned above, which has introduced the nano or atomic dimension into the VPH framework by supporting the establishment of the basis and foundations for nanoinformatics. One of their main objectives is to develop a white paper to suggest a roadmap with recommendations and priorities for nanoinformatics and international collaborations [36–38].

3.3 An Inventory of Informatics Resources

As stated above, nanomedicine implies an important information management problem that can be addressed by nanoinformatics. The latter involves the development of effective tools/technologies/methods for collecting, standardizing, integrating, analyzing and visualizing information relevant to nanomedicine including those data that can be relevant such as literature, physical-chemical properties, biological, clinical and toxicological effects [27]. In such context, researchers at the Biomedical Informatics Group, Universidad Politecnica de Madrid (UPM), have developed a method for the automatic creation of an index of bioinformatics resources [39, 40]. This collection of tools, databases and services (in general "resources") is an index of resources, created automatically from a set of scientific documents describing resources retrieved from internet. Each of these documents is analyzed and processed to extract relevant information. The method used to process documents is based on four steps: i) The document is divided in sections corresponding to the title, the abstract and the article body. ii) Then the algorithm preprocesses the sentences belonging to the title and the abstract sections, eliminating stop words and reducing the remaining words to their root form. iii) The preprocessed text is given as input to a transition network that,

applying morphological and syntactic patterns, extracts the name and the functionalities of the resource described in the paper given as input. iv) Finally, a second transition network uses the previous extracted information to classify the considered resource. The first prototype of this method receives scientific articles as input and populates a database with the relevant information.

Currently this method – initially designed to discover and annotate bioinformatics resources – is being adapted to be applied to the nanomedicine domain. The objective is to be able to process scientific articles about nanomedicine and extract relevant data about resources used in this field. Preliminary results are already available, contributing to the construction of the resources index [41].

3.4 Lab-on-Chip and Proteomics-based Discovery of Biomarkers

The importance of lab-on-chip technology, and of the engaged proteomics-based discovery of biomarkers is made evident, among others, by a special issue of the *Nature* journal [42], and reports related to microfluidic-based diagnostic technology [43]. A biomarker is an identified protein, which is correlated with the state of a particular disease or condition [44]. Biomarkers can be used for the detection, diagnosis, treatment, monitoring, and prognosis of many different diseases, as well as in the drug discovery process for the assessment of new drug candidates.

Proteomics approaches for the discovery of biomarkers are based on differential protein expression and founded on the following assumption: *changes in protein concentrations between control and pathological samples are indicative and provide significant cell pathway, signaling, and biomarker information.*

Biomarker discovery is moving away from the idealized single, cancer-specific biomarker such as prostate-specific antigen. Since 2002, a growing confluence of scientific data and results point to combinations of blood-borne markers, using MS profiling techniques as well as tissue MS profiling strategies [45], and multiplexed immunoassay [46] providing superior results than single markers alone. Despite decades of effort, most single biomarkers have not reached the level of cancer specificity and sensitivity required for routine clinical use in early detection and screening purposes.

Human blood serum and plasma contain a large variety of proteins, and their relative abundance and modification may precisely reflect the disease status of organs and tissues. One major breakthrough comes from the utilization of multi-protein disease markers instead of single protein analytes and the detection of all the isoforms of the selected proteins. Recent advances in MS-based proteomic technologies coupled with bioinformatics may revolutionize medical diagnosis and cancer screening. However, the application to diagnostics is still at its beginning [47]. The need for new and relatively simple devices to allow for the translation of these research results to clinical practice is urgent. In such direction, new nano-related approaches have been already proposed.

An indicative example of a relative R&D approach in the field is the work carried out in the context of the LOCCANDIA [48] (Lab-On-Chip based protein profiling for CANcer DIAgnosis) European project. The work concerns the validation of an application targeting plasma protein profiling for early pancreatic cancer diagnosis by means of developing an innovative nanotechnology-based (lab-on-a-chip) platform integrated in a full proteomics analysis chain [49]. The model combines three main workflows, from blood sample to diagnostic information, combining bio-, nano- and information-related technologies: a) The 'bio' module of the analysis chain gets as input blood sample, and provides the 'nano' part with a selected protein mixture that will be further analyzed. b) The 'nano' module is the part related to the dedicated lab-on-chip device, mass spectrometry (MS) experiment and analysis of related MS data. This module is divided in several sub-modules: target protein mixture treatment, digestion, liquid chromatography, electrospray ionization, and mass spectrometry. c) The 'info' part is related to the supporting information technology infrastructure. It is used by the LOCCANDIA Information Management System (LIMS), a web application for storing, analyzing and manipulating both proteomic and clinical data, i.e., an integrated clinico-proteomics information management system [50]. Thus, the objective of this platform is to link clinical and proteomic information towards the project's objective of early pancreatic cancer diagnosis.

The client-server architecture of LIMS comprises different parts: i) data preprocessing, to standardize data and correct time delays among spectrograms by applying techniques such as baseline adjustment, normalization and kernel smoothing; ii) proteomic profile reconstruction, a functional model for the quantification (from mass-spectrogram peaks) of targeted protein concentration levels [51], by associating the concentration profile of the unknown molecular measurements with the measurements of spectrograms; iii) classification, to predict patient outcomes discerning healthy individuals from pancreatic cancer patients by the application of machine learning algorithms (support vector machines and logistic regression) to a set of selected proteomic and clinical data. The classification module produces images and Excel files that hold the predicted health status of the patient.

LIMS encompasses an advanced data-mining module for the analysis of MS data and the discovery of biomarkers (i.e., protein concentration levels). A major challenge in the systematic capture of protein expression data is the diversity of experimental technologies and data formats in the field. Various XML (eXtensible Markup Language) standards for proteomics have been developed in order to facilitate the capture, analysis, and distribution of proteomics data, such as mzXML [52, 53], a XML-based common file format for proteomics mass spectrometric data. The intent of mzXML is to encapsulate unprocessed, raw peak lists. Therefore, mzXML is the data format used as a data input on the profile reconstruction module.

Thus, innovation in LOCCANDIA is based on the seamless integration of bio, nano and information processing stages for the development of a novel integrated diagnostic system. As a result, an innovative integrated clinico-proteomics computational

environment has been developed, combining standard-based informatics systems and best-of-breed computational modules to support the LOCCANDIA integrated lab-on-chip-based diagnostic device. Other main research outcome of the LOCCANDIA project will be an optimized chromatography-electrospray lab-on-chip dedicated to protein profiling for cancer diagnosis.

3.5 Micro- and Nanoarrays

Microarrays represent a bridging development between micro- and nanotechnology. There are several aspects related with microarray technology that are located at the boundaries of nanotechnology or that can be considered directly as such. At the microarray laboratory of the Medical Bioinformatics Department of the Instituto de Salud Carlos III (BIOTIC) researchers have been working for several years in this scientific and technological interface between micro- and nanotechnologies. For instance, the group has developed and standardized a combined nested PCR and microarray-based approach for the simultaneous detection and genotyping of adenovirus serotypes causing respiratory tract infection by using generic and specific probes [54]. This approach enables a rapid clinical diagnosis since: i) the hybridization conditions have been simplified; and ii) the microarray design allows a visual identification of the serotype detected by showing a characteristic hybridization pattern for each adenovirus. An information retrieval software, BussuB [55], has been also developed to simplify the identification of the best target DNA sequences. This software determines the gene region within DNA or RNA genomes where the probes must be designed to be used in a microarray system with both high specificity and sensitivity.

Additionally, the main efforts carried out up to now have been focused on two different directions. The first one is oriented towards improving the chemical quality used on the surfaces of the microarrays. Surface chemistry is a key issue for microarrays because the efficiency of the process of binding biological molecules to the microarray relies on an optimal design of chemical interactions at this level. The group has been testing different methodologies for treating glass slides to increase their affinity for the biological molecules that are more frequently immobilized (nucleic acids and proteins). The second approach is represented by the use of biological machinery and robotics for the in-situ synthesis of biological molecules on the microarray surface. The basis for this approach relies on the immobilization of biological molecules that can act as a substrate for the synthesis. This technology has been applied for the development of diagnostic assays [56] and the detection of microbial pathogens. In these assays the immobilized probes are DNA molecules that can be extended by the use of a polymerase (an enzyme responsible for the DNA synthesis within the cells). In our applications this newly synthesized DNA is detected by fluorescence and allows us to identify the organism present in the sample. This approach based on the application of peptide microarrays and bioinformatics analysis tools – such as, for instance, BRB array tools [57], databases, laboratory information management systems and MIAME standard –, has been used for analyzing complex humoral responses, such as those produced during HIV infections. It could serve as basis for developing predictive models that could be useful in diagnostics and analysis of immune responses. The same principle is planned to be used shortly for the generation of synthetic DNA for other purposes.

3.6 Knowledge Management in Nanomedicine

Knowledge management is a key component that facilitates to researchers in different fields the classification and access to different resources. In such area, BIOTIC has been working in structuring a framework to accommodate and organize the increasing number of available resources (systems, methods, data, software tools and standards) in nanomedicine [58]. The in-house knowledge management system (BIKMAS) that BIOTIC has been using for several years [59] has been recently adapted to be able to incorporate and process all the new information coming from nanomedicine research and development. Using this new version of the software, it is possible to provide partners with up-to-date information related to advances of the application of nanotechnology in medicine.

Especially remarkable in this regard is our role as knowledge managers in the recently funded "Ibero American Network of Convergent Technologies in Health Applications" (Ibero-NBIC). This represents a new collaborative endeavor that is promoted by Cooperation Programs (CYTED), a public agency. Ibero-NBIC gathers 13 research groups from six Latin-American countries (Spain, Portugal, Chile, Argentina, Brazil and Uruguay).

Within such knowledge management and nanoinformatics approach, researchers at BIOTIC are also working in Nano-Sost, a strategic research project funded by the Spanish Ministry of Science and Innovation that brings together 21 private and public partners in different research areas with the aim of setting up the scientific basis and the information and knowledge – including databases, ontologies, simulation tools, etc. – that are needed for a safe use of nanoparticles and nanostructured materials in order to promote industrial applications ensuring safety of employers and consumers. Similarly, we are working at BIOTIC on a model called INFO-POC that stands for Information-enhanced Point-Of-Care diagnostic system. This research aims to demonstrate the concept of convergence among converging technologies: nano bio info cogno (NBIC) technologies, with the goal of creating a new research framework for the development of diagnostic methods at the point of care, in the context of genomic medicine.

These results, previously began in a Spanish national network called COMBIOMED [60], will be integrated with computerized protocols for diagnosis, treatment and management of patients with particular genetic (cancer) and infectious diseases.

3.7 NMP Programme

The NMP Programme (nanosciences, nanotechnologies, materials and new production technologies) [61] is another

initiative within the 7th Framework Programme of the EC. The program consists of three different thematic activities: i) nanosciences and nanotechnologies; ii) materials; and iii) new production technologies; each one of them divided in different research lines related to the nano areas.

In this initiative, the European Commission provides support and funding for very diverse topics, such as, for instance: research on the impact of nanoparticles on health and the environment, methodologies for the management of the risks of nanoparticles, research on green nanotechnology, chemical engineering, development of materials for energy storage, modeling work on crystalline materials, industrial models for sustainable and efficient production, intelligent management of information generated in nanomedicine research, and others.

3.8 European Technology Platform on Nanomedicine

The European Technology Platform (ETP) on Nanomedicine [62] was launched in 2006 by the European Commission, in collaboration with the industry, to promote collaborative research on this area. The ETP is mainly made up of industrial and academic stakeholders in the nanomedicine field, such us big companies, small and median enterprises (SMEs), industrial associations, research organizations, academia and hospitals. The objectives of the platform include: identifying the priority areas on nanomedicine, obtaining additional public and private investment for research and promoting innovation in nanotechnologies for medical use. One of the main outcomes of this initiative is the publication of a strategic research agenda [63], offering a clear vision in nanomedicine. The document also pointed out the need of computational technologies and tools – i.e. analysis and management of data, modeling and simulation, imaging techniques, diagnostics systems, etc. – to facilitate nanomedical research and its application.

3.9 ICT European Infrastructures for Nanomedicine and Medical Informatics

Bioinformatics, medical informatics and nanoinformatics have developed a common framework through their common need for computational capacity and access to computational resources. The applications made by each of these communities further enhance the vision for platforms, interoperable software and ICT infrastructures to support their efforts. Converging technologies and needs created the environment for grid infrastructures and high-performance computing (HPC) resources and worldwide networks to further increase their interoperability through projects and collaborations (such as EGI, the European Grid Initiative), thus supporting the idea that medical communities should increase collaboration with ICT infrastructures to create innovative and economically viable solutions.

The new area of grid computing can be divided in three branches, namely: data and computational grids, collaboration grids and knowledge grids [64], which create a favorable environment for knowledge exchange, data processing, computational and collaboration needs for the nanoinformatics requirements.

Current projects and major infrastructure projects – such as EGI, EGEE (Enabling Grids for E-SciencE) [65], DEISA (Distributed European Infrastructure for Supercomputing Applications) [66], NorduGrid [67], OSG (Open Science Grid) [68] and caBIG [69] – already provide an environment for biomedical informatics, where services are offered to facilitate the use of the different computational resources developed by research communities. Such environment can be especially adequate for the large computational needs linked to nanoinformatics and nanomedicine.

In addition, there are several projects developing prospective ICT infrastructures in Asia, Africa, and Latin America and creating strong regional and worldwide networks for user communities' support. ESFRI (European Strategy Forum on Research Infrastructures) [70] projects are currently establishing the base for the sustainability of the main European research infrastructures. These prospective infrastructures, jointly with existing research infrastructures, are one of the prerequisites for interoperable solutions to biomedical informatics needs and constitute the link between the communities of users and services providers. Nanoinformatics will benefit with these existing and prospective infrastructures, as the community is seeking for collaborations that enable sharing of knowledge and information.

4. Other Initiatives in the International Context

4.1 Initiatives at the National Cancer Institute: caGrid and caNanoLab

caBIG [71] is a national-scale cancer biomedical informatics grid created by the National Cancer Institute (NCI) in 2004. It was created to address the need of cancer centers and research laboratories for sharing of data and analysis tools, combining strengths and expertise in a multi-institutional environment for cancer research. To reach this goal, the caBIG community is developing standards, policies, guidelines, common applications, and open-source tools and middleware infrastructures. This network is a compendium of applications, software tools, database technologies and web-based applications in the areas of: clinical trials management, biospecimens, imaging, genome annotation, proteomics, microarrays, pathways, data analysis and statistical tools, data sharing, infrastructures, vocabularies, and translational research. The caBIG infrastructure is based on grid computing technology that allows users to access a federated network of resources through standardized interfaces to solve informatics problems that are not solvable with conventional computing technology.

Within caBIG, caNanolab (the cancer Nanotechnology Laboratory Portal) [72] provides a collaborative framework for data sharing which facilitates the use of nanotechnology in biomedicine. The initiative offers support for efficient storage and retrieval of nanoparticles characterized by

the NCI Nanotechnology Characterization Laboratory (NCL), and involves the development of standards and controlled vocabularies for nanoparticle characterization.

Regarding nanoinformatics research, it must be mentioned the publication of the Nanotechnology Informatics White Paper [73], developed by researchers of the NCI National Characterization Laboratory. This white paper sets up the basis of the convergence between nanotechnology and biomedical informatics, focusing on its applications for cancer research.

4.2 National Nanotechnology Initiative (NNI)

The NNI is a US national program aiming to ensure US leadership in nanotechnology science and technology to improve healthcare. This initiative serves as the main communication and cooperative hub for federal agencies involved in nanotechnology research to collaborate towards advancing this complex and broad field. Over the last years, the NNI-participating agencies have funded the establishment and development of over 60 major interdisciplinary research facilities and centers equipped with the latest technology for nanoscale S&T research. Their main objectives are i) establishing a world-class nanotechnology R&D program, ii) create the required infrastructure and resources to advance nanotechnology, iii) foster the technology transfer by supporting the manufacturing of new products for commercial and public use, and iv) ensure a responsible development of nanotechnology.

4.3 The Alliance for NanoHealth (ANH)

The ANH [74] is a pioneering collaborative research initiative to use nanotechnology to bridge together different health-related scientific and technological areas including medicine, public health, biology, materials science and computer science and technology. The ANH aims to address unsolved problems in medicine using nanotechnology-based approaches. This includes, developing novel nano-resources and tools to battle against cancer, heart diseases or diabetes. Currently, the ANH is composed of eight top-class clinical and research institutions.

4.4 NIH's National Network of Nanomedicine Development Centers (N4DC)

The N4DC [75] is a US national research network funded by the NIH – and tightly related to the NNI effort described above – that comprises eight nanomedicine development centers (NDCs). The latter are composed by multidisciplinary scientific teams that include physicians, biologists, computer scientists, physicists, mathematicians, etc. Researchers at the NDCs aim to determine the physical properties of cellular and sub-cellular components following engineering-based approaches to better understand how biological machines are constructed and how they can be controlled and manipulated. This research will support the development of new technologies to prevent or treat diseases or to repair damaged tissue. This effort is also committed to train a new generation of multidisciplinary scientists in this emerging and exciting field.

4.5 Other International Initiatives: Asia

Even though most of the patent applications and research publications related to nanomedicine have been developed in the US – with a growing importance of the field in Europe – there are other countries that are also increasingly contributing to nanotechnology at an international context. For instance, the Asia Pacific Nanotechnology Forum (APNF) [76] provides, since 2002, a platform for networking across the Asia region. This initiative facilitates the coordination of nanotechnology development by promoting the creation of new programs and cross-regional collaborations among governments and policy makers, industry, R&D institutions, universities and leading researchers. In China, Japan, Korea and Taiwan the interdisciplinary research in biotechnology, nanotechnology and information technologies is particularly explicit in their R&D policies, covering topics such as diagnostics – molecular detection including biochips, lab-on-chips and protein chips; sensing; gene delivery and imaging –, targeted drug delivery systems, regenerative medicine – like stem cells and tissue engineering – and nanomedical devices.

Most notably, Japan is dedicating a significant percentage of its "start-up" investment to nanotechnology and nanomedicine and has established several research programs focused on nanomedicine [77]. As stated in the "Report on Mid- and Long-term Research and Development Strategy for Nanotechnology/Materials Science in Japan" [78], this country is currently conducting an ambitious research program, named "Nanotechnology & Material Science" with a total funding of around 480 million euros and prioritizing those areas related to life sciences, including drug delivery systems – nanoparticles, active targeting, nutrients delivery systems, nanocapsules –, molecular imaging, biosensors and medical implants, tailor-made diagnosis/therapy, nanomedical devices, lab-on-chip technologies and tissue engineering.

The Japanese government agencies have also created centers of excellence in nanotechnology. For instance, the Nanotechnology Researchers Network Center of Japan [79], which supports nanotechnology researchers especially in the area of drug delivery, and the Center for Nano-Bio Integration at the University of Tokyo [80], an interdisciplinary initiative for the integration of detection, diagnosis and therapy, both funded by the Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT).

5. Discussion

As seen above, the opportunities raised by the application of nanotechnology advances in fields like biomedicine will surely have a deep impact on science, technology and society.

In this context, nanoinformatics can become a key topic for future medical research activities. The scientific community should

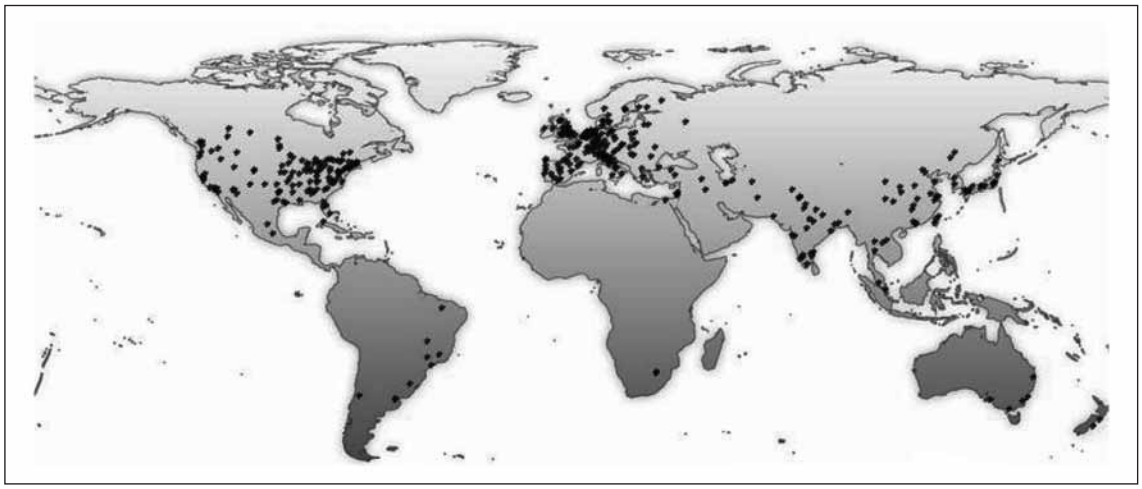

Fig. 4
Worlwide distribution of research on nanomedicine. Source: Search for the term "Nanomedicine" on the scientific literature by using GoPubMed [23]

facilitate and enhance synergies between this discipline and classical disciplines like medical informatics and bioinformatics. Lessons learned for various decades in these two disciplines [81] can be valuable to develop a sound agenda and strong foundations for nanoinformatics. Nevertheless, challenges remain in this scenario. During the last decade, biomedical informatics has emerged as an integrative discipline with a wide scope of interests, including areas such as "translational bioinformatics", focused on the medical implications of research carried out at the molecular and cellular level [82]. Various recent conferences have been focused on this topic – like the AMIA Summits on Translational Bioinformatics. Paradoxically, when the new term of genomic medicine seemed to get some strong attention for research and future developments, the new field of nanomedicine may well introduce new and deeper scientific challenges into the whole area of BMI [83]. In such context, the ACTION-Grid project has brought together researchers of three continents to analyze and put the basis for nanoinformatics, its role in nanomedicine and its potential links with BMI.

While BMI has been dealing with medicine and biology – two fields strongly linked for more than a century –, the new areas of nanomedicine and nanoinformatics introduce new topics and scientific issues that have been traditionally outside the core of BMI [84]. In such context, integrative approaches – e.g., integrating clinical and genomic databases, developing meta-ontologies that relate medical and genomic vocabularies and ontologies, or introducing genomic data into computerized medical records – that have been successfully addressed into BMI, cannot directly be extended towards lower biological levels at the nano dimension. As already reported elsewhere [36], a new term, *translational nanoinformatics*, coined by one of the authors (VM), presents challenges that may well lead to a new area of research at the nano level. This new area cannot be, therefore, just considered as a continuum of BMI, addressing different biological levels from populations to atoms. Different physical and biological characteristics at the nano level introduce new aspects for informatics that must be addressed before a mere integrative vision is considered [36].

Nanoinformatics is also having impact on educational programs, as shown by the recently published new IMIA recommendations on education in biomedical and health informatics. These recommendations include the topic "Medical Nanoinformatics" as one of the future areas to be addressed in future programs for educating health professionals [85].

6. Conclusions

Future achievements in nanomedicine will require new strategies and cooperative activities. In this regard, the use of information and communication technologies could help to launch and support medical research at the nano scale. (Medical) nanoinformatics aims to build new bridges between medicine, nanotechnology and informatics, allowing the application of computational methods to solve problems related at the (wide) intersection between medicine and nanotechnology. Nanoinformatics brings the opportunity to use current informatics tools to more effectively use the wealth of data and information that nanotechnology research is producing and introduce a novel, informatics-based approach to issues such as modeling and simulation of nanoparticles and their interaction within the human body, including aspects such as diagnosis, therapy, toxicity and others.

Challenges in the ethical, legal, social and economic constraints should also be considered. Several issues impact the technical, ethical, social and cultural, economical and organizational aspects ranging from the ownership of patients data, IPR issues, anonymization and pseudonymization of medical data.

In this paper we have reviewed various relevant initiatives in both the European and US contexts (▶ Fig. 4). Recent joint initiatives have been launched by the European Commission and different US agencies – e.g. linking the European NMP and the US EPA and NIH [86, 87] or fostering new developments for the European VPH to be carried out with US organizations, with support from the EC unit "ICT for Health". Besides the different research activities of the members of the consortium, one of the main goals of the authors in the context of their joint work is to deliver to the scientific community a white paper in

nanoinformatics – already in a draft form at the time of writing – that will include some specific recommendations for international cooperation. Such kinds of collaborative actions, that proved fundamental to advance various genomics projects, may be similarly needed for advancing nano-related research.

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