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Nanomedicine: a socio-technical system

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ABSTRACT

Recently, nanotechnology has put forward considerable opportunities for healthcare–including novel diagnostic and therapeutic prospects–leading to the emergence of nanomedicine. Together with such technological advancements, social science research has placed increasing attention to this emerging and complex discipline. Still missing, however, is a systematized, coherent understanding of nanomedicine as a discrete socio-technical system. By charting the extant literature and drawing on insights from science, innovation, technology, and organizational studies, we review the field of nanomedicine and pinpoint key thematic areas in which the field unfolds. Collectively, our work advances both theoretical and practical aspects as to why and how nanomedicine may be best understood as an idiosyncratic setting for the advancement of novel social science research inquiries.

1. Introduction

In the past few decades nanotechnology research–'the intentional design, characterization, production, and application of materials, structures, devices, and systems by controlling their size and shape in the nanoscale range (i.e., 1–100 nanometers)' (Kim et al., 2010)–has prospered worldwide. Nanotechnology developments have also rapidly converged into healthcare research and practice. Some examples of such innovations include manipulating chemo-physical proprieties of bioactive particles (e.g., Al-Jamal and Kostarelos, 2011; Zhang et al., 2008), exploring clinical applications of ground-breaking materials like graphene (e.g., Feng and Liu, 2011; Mao et al., 2013), and crafting miniaturized devices such as bio-cells powering medical tools (e.g., Zebda et al., 2013). This thriving scenario has promoted the emergence of nanomedicine, the application of nanoscience to medicine, as a scientific field in its own right (Freitas, 2005; Moghimi et al., 2005). Since its inception, indeed, nanoscientists have converged in considering nanomedicine as a research area which is well-distinct from the parental discipline of nanotechnology (e.g., Boisseau and Loubaton, 2011). In other words, nanomedicine has emerged to be more than just a semantic jargon, with dedicated research exceeding the thousands of peer-reviewed articles published each year, and granted patents rising so steeply to include about 4% of those focused on nanotechnology research worldwide (Wagner et al., 2006).

Correspondingly, social science inquiries have developed a strong interest in nanotechnology since the early stages of its development (e.g., (Macnaghten et al., 2005)Shapira et al., 2010). Yet they have also produced fewer comprehensive analyses specifically focused on nanomedicine thus far. This circumstance is rather surprising given that several calls have already prompted social scientists to thoroughly investigate the idiosyncrasies of nanomedicine (e.g., Cacciatore, 2014; Cormick, 2012). For one key argument, (Satalkar et al., 2016) contend that only a shared and consistent scholarly position on nanomedicine–as a distinct area form nanotechnology as a whole–can assist trust-building while curtailing miscommunication and fears of nanomedicine among societal stakeholders. Thus, important research questions for social scientists have remained unaddressed: Can nanomedicine represent a distinctive research context for social sciences? And, if so, why and along which dimensions? And, what theoretical, empirical, and practical agenda may this understanding promote?

In this article, we address these research gaps by putting forward an evidence-based, systematic literature review that analyzes nanomedicine by situating it within sociotechnical theory (e.g., Cooper and Foster, 1971; Emery and Trist, 1960). Drawing on this theoretical framework, and supporting it with strands of organizational, innovation, and science and technology studies, we aim to both synthetize and systematize the extant literature on key aspects of nanomedicine towards exposing several thematic areas able to cross fertilize research

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exchanges between social and nanomedical scientists.

We unfold our contribution as follows. First, by drawing parallels with nanotechnology and biotechnology, we motivate nanomedicine as a distinctive socio-technical system. By this exposition, we mean that nanomedicine, its innovations, and practices hold their idiosyncratic meanings, while being embedded within social discourses, society, and forms of organization, and intersect in their meaning with those broader social dimensions (e.g., Cherns, 1976; Geels, 2004; Trist, 1978Trist et al., 1990). Indeed, undertaking a socio-technical analysis offers a valued theoretical perspective to foster knowledge on emerging healthcare and biomedical settings (e.g., Gardner and Webster, 2016; Greenhalgh and Stones, 2010). Next, we explain the methodology and the evidence-based approach that we undertook in this work. We consulted expert nanomedical scientists who informed our literature search and systematization criteria; then, we describe the steps we performed to review the literature. Third, we isolate core themes arising from the retrieved literature that advance knowledge on the dynamic associations among technological and social aspects of nanomedicine, as well as the benefits and risks of nanomedicine for society. Overall, these conceptual areas capture: (i) the transdisciplinary nature of nanomedicine; (ii) the products, processes, and loci of innovation in which nanomedicine unfolds; (iii) the opportunities for sustained public engagement; and (iv) key regulatory and policy challenges and recommendations. Finally, we conclude this paper by discussing the contribution that an integrative socio-technical view of nanomedicine holds for both theory and practice.

2. Nanomedicine: a distinct field of research

Since its emergence, social scientists have placed considerable interest in understanding and investigating nanotechnology as a socio-technical system (Delgado et al., 2011). A socio-technical scheme embraces intertwined elements of artefact and societal sub-systems (e.g., institutions, routines, and politics), whose dynamic patterns make it often convoluted and resilient to profound transformation (Geels and Kemp, 2007; Frantzeskaki and Loorbach, 2010). Technology affects societal structures, which involve social actors, institutions, and their interactions; these in turn shape technical configurations and innovations (Dolata, 2009; Geels, 2004). While these regimes are rather stable, they are also porous. This is because they are consistently faced with either internal or external pressures covering broader factors and events within and beyond the regime itself (Geels and Schot, 2007). These demands influence the system's dynamics and generate disruptions, often destabilizing existing *modus operandi* while offering opportunities of co-evolution of both technological innovation and social structural change (Geels and Kemp, 2007).

Informed by the case of biotechnology—in which the discussion on the social dimension generated significatively later than the implementation of the technological innovations—researchers have been attentive to develop a conversation between the social and technological aspects of nanotechnology synchronously (Wolfson, 2003). Indeed, biotechnology (in particular in relation to genetically modified nutriments; Krimsky and Wrubel, 1996), did not achieve a smooth transition from the laboratory to society, and remained characterized by strong public resistance which is still present these days (Guida, 2021). Thus, the scholarly community as a whole has developed awareness that the introduction of a new technology to the 'lay-public' can be profoundly affected, unless the entire socio-technical sphere in which it operates is fully evaluated to begin with.

Early positioning papers on nanotechnology purposively aimed at ensuring that nanotechnology was not going to get the same backlash of biotechnology as it reached society (Barben et al., 2008). Nanotechnology was presented as a wider "general purpose technology" (Gambardella and McGahan, 2010), operating within a socio-technical regime, and acting as the ground for technological innovations across a range of sectors as well as a connection for other enabling technologies (Kautt et al., 2007; Linton and Walsh 2008; Mangematin and Walsh, 2012). As a result, nanotechnology has seen earlier and more significant interest and investments than biotechnology, with start-ups and SMEs positioning themselves as expert suppliers while research organizations forming coalitions with industrial partners to both develop and commercialize innovation (e.g., Mangematin et al., 2011; Rothaermel and Thursby, 2007). Concurrently, new centers and scientific communities were created (Kautt et al., 2007) and, at the product level—rather than focusing on mostly generating ex-novo products (as in the early waves of biotechnology)—innovations were embedded in pre-existing products and production processes.

Altogether, these activities rapidly confirmed the idea of nanotechnology as a general-purpose technology that, being embedded within a socio-technical regime, could both shape a wide array of scientific aspects and influence the way in which innovations, production, and processes were perceived by society. Thus, on the one hand, nanotechnology has been embraced by society with its full technological potentials: From the improvement in the inanimate world (e.g., nanofibers to advance IT communications) to, as we shall see in the following sections of this paper, the ability to tackle many healthcare challenges. On the other hand, its breadth has confronted the expected boundaries of the socio-technical regime, making it apparent that each individual area of nanotechnological application has its own specific features, issues, and corresponding concerns in the social sphere.

One of the most challenging domains has turned out to be nanomedicine, which nanotechnology scholars have almost instantaneously demarcated as a self-standing scientific field (Freitas, 1998). In essence, nanomedicine is the application of nanoscience and nanotechnology–in terms of both methods and products (Duncan, 2004; European Science and Technology Observatory, 2006)–to the problems of medicine (European Science Foundation, 2005;). The 'nanomedicine revolution' (Ventola, 2012) developed since the early 1990s, thanks to the establishment of the first FDA-approved nanotherapeutic innovations for clinical use (i.e., the chemotherapy drug Doxil© in 1995), of the first nanotech company (i.e., Zyvex© in 1997), and the blossoming of nanoscientific research (Bawa, 2011; McGrady et al., 2010). Over the past two decades, further advances in scientific research have matured to enable the translation and exploitation of their insights into a wide range of medical scenarios, spanning from tackling cardiopathies to cancer treatments (e.g., Godin et al., 2010; Seigneuric et al., 2010). As it happened for nanotechnology as a whole, these developments have rapidly led to the appearance of hundreds of products and processes, generating a multibillions market and large public policy initiatives and investments (see e.g., Hobson, 2009; Flynn and Wei, 2005). For instance, the US National Institute of Health (NIH) released a roadmap to nanomedicine and established a network of Nanomedicine Development Centers (Zerhouni, 2003). Likewise, in 2013, the European Commission promoted a framework for academics and industry researchers to jointly boost innovation in nanomedicine, which was followed by a dedicated agenda in the Horizon 2020 program (Hafner et al., 2014).

Together with growing innovations, nanomedicine has also promoted opportunities for reflections involving society at large (Best and Khushf, 2006). Yet, somehow surprisingly, social science research has generally addressed these arising issues within the same discussion conducted for nanotechnology as a whole. In other words, while nanoscientists have clearly defined nanomedicine as a different domain from nanotechnology, their social peers have understood the field as being firmly anchored to its parental domain, in a sort of conceptual path-dependency. Thus, in the recent past, mounting calls to extend the conversation in nanomedicine at the nexus between the social and technological have emerged. For instance, nanoscientists have made clear that nanomedical processes and products rely on features of the matter different from those manifested at higher scales (National Research Council, 2013). However, these features are still not completely understood, in particular when considering their effect on the human body and people's health, thus requiring a wider scholarly exchange. Moreover, due to a limited theorization of nanomedicine as a singular socio-technical regime, symptoms of technological insecurity have emerged (e.g., Scheufele et al., 2009) which have often translated into regulatory (Gaspar, 2007) and ethical (Resnik and Tinkle, 2007) concerns. This uncertainty has also augmented tensions within the field's institutional and disciplinary boundaries (Kostarelos, 2006; Porter and Youtie, 2009) and with respect to organizational dynamics and relationships between academia, policy, and industry (Barirani et al., 2013; Beaudry and Allaoui, 2012; Haberzettl, 2002). Similarly, queries about organizational, processes, and innovations themselves have spurred, challenging the understanding of whether it was even possible to apply the 'general-purpose technology' framework used in nanotechnology to the features of nanomedicine. In sum, nanomedicine has swiftly developed beyond the margins of a medico-technological context alone. Relations among nanomedicine actors, institutions, policy, and society as a whole, have become complex and interdependent, creating a scenario characteristic of healthcare socio-technical systems (e.g., Gardner and Webster, 2016; Greenhalgh and Stones, 2010; Webster, 2002).

Yet, to the best of our knowledge, a coherent work that reviews the interfaces between social and technological in nanomedicine, one that highlights key areas of concern, emerging questions, and prompts to fertilize novel research, is currently missing. As we shall now elaborate, this article addresses this need by following a systematic approach that takes into account the existing literature on the opportunities and issues that nanomedicine offers to science and society within its own socio-technical regime. Overall, as Petticrew and Roberts (2008) indicate, such a review effort can help to clarify remaining research questions, identify major gaps in the literature, and provide important directions for future research and practice.

3. Methods

To examine the nature, extent, and scope of nanomedicine as a socio-technical system, we undertook a reviewing approach over multiple iterative stages (Arksey and O'Malley, 2005; Levac et al., 2010; Khan et al., 2001). First, as a part of a wider research project we have been conducting on nanomedicine, we established prolific dialogues with several external informants, mostly prominent nanoscientists and directors of world-leading nanocenters (Table 1). These respondents help guide the rationale of our literature search and analysis. During the initial semi-structured interviews, we probed them with questions covering both the definition of the field (e.g., *How would you define nanomedicine?)* and its socio-technical nature (e.g.,*What are the key areas in which nanomedicine and society intersect, and in what ways?*)

Based on such dialogues, we performed a systematic literature review based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework (Moher et al., 2009). The PRISMA framework consists of a statement comprising a 27-item checklist and a four-phase flow diagram (Fig. 1). The aim of the PRISMA framework is to help authors improve the reporting of reviews in a standardized format, and readers better appreciate the search approach employed by researchers.

Table 1
Overview of the External Informants Consulted.

Informant	Disciplinary background	Current position/ role	Institution (location)
1	Physics	Director	Strasbourg, France
2	Chemistry	Director	Boston, MA
3	Physics	Managing director	London, UK
4	Physics	Managing director	Zurich, Switzerland
5	Physics	Director	Stanford, CA
6	Chemistry	Area director	Brighton, UK
7	Chemistry	Managing director	Dublin, Ireland
8	Chemistry	Beamline manager	Trieste, Italy

Our search involved an extensive review of the published and gray literature to identify key attributes of 'nanomedicine.' Thus, we tailored the entire search to probe for overarching concepts and relations pertaining to the wider domains of social science and medical nanotechnology. The intent was to ensure a wide coverage of the socio-technical aspects occurring in nanomedicine.

We conducted our search in three comprehensive electronic databases (i.e., Medline PubMed, Scopus, Web of Science), examining the reference lists of selected papers, and hand searching key nanotechnology journals (e.g., *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology; Nanomedicine*) and additional sources (e.g., International Council on Nanotechnology). The database search terms that guided our search were pooled with Boolean operators (AND, OR) and included among others: 'nanomedicine;' 'social issues;' 'organizations;' 'nanocenter;' 'nanofacility;' 'innovation;' 'disciplines;' 'institutional dynamics;' 'public engagement;' 'regulation;' 'policy;' 'policy-making;' 'patient safety;' and, 'drugs.' The choice of keywords was supported by the recursive interactions with the external informants.

Our initial search yielded 2528 citations written in English, for the period comprised between January 1998 and June 2019. This interval spans from the first appearance of the word 'nanomedicine' in a scientific publication (Freitas, 1998) to the moment in which our initial search was conducted. Subsequently, we updated and advanced our search in December 2020, for the period comprised between January 2004 and December 2000, which allowed us to retain 36 additional articles for analysis (Fig. 1). When initially reviewing the articles, we understood that the social features of nanotechnology as a whole became prominent in the literature only in the mid-2000s. Indeed, socio-technical aspects of nanotechnology emerged worldwide only in 2003/2004, following the US Congress enacting the 21st Century Nanotechnology Research and Development Act promoted by President Clinton. This act provides a statutory foundation for the National Nanotechnology Initiative (NII), established programs, assigned agency responsibilities, and promoted research agendas. Similarly, in 2004, the European Commission adopted the document "Towards a European Strategy for Nanotechnology," which proposed institutionalizing nanoscience efforts within an interconnected strategy.

During the review process, for the evaluation of the search quality, precision and recall were estimated following the suggestions given by Egghe (2008). Precision is a measure that shows how many of the retrieved articles are relevant to our goal. To compute it, we considered a sample of 50 articles that were randomly selected via a function computed in Microsoft Excel, finding 42 thereof to be relevant. The other entries mainly described opinion or specific applications and were considered as partly relevant. We decided to accept this precision and forego additional data cleaning. We also computed recall as a measure of how many works contained in the database as a main unit could be found by the search, which amounted to 0.64.

We independently screened the retrieved publications for titles and abstracts to select unambiguous systematic and conceptual publications of relevant views and research. We selected articles (authors' concordance rate $\kappa = 0.74$) if the content was (i) closely relevant to both nanotechnology and healthcare, and (ii) included one or more explicit mentions of themes proper to medical social science scholarship, such as, 'social issues,' 'public engagement,' and 'patient safety,' and appropriate variants. Equally, the titles and abstracts of all retrieved sources were screened and subjected to the following exclusion criteria: (i) lack of social science theoretical/practical components; and, (ii) book reviews.

We then independently assessed full-text articles and filtered concepts for further analysis. In this step, we focused on how roundly the articles were defined and differentiated in the literature; we were supported by an external coder who was blind to this paper's specific goals. In conclusion, 182 representative articles were included for final analysis (overall concordance rate $\kappa = 0.84$). Notwithstanding possible individual biases, we came to agreement on all ambiguous cases (Table 2).

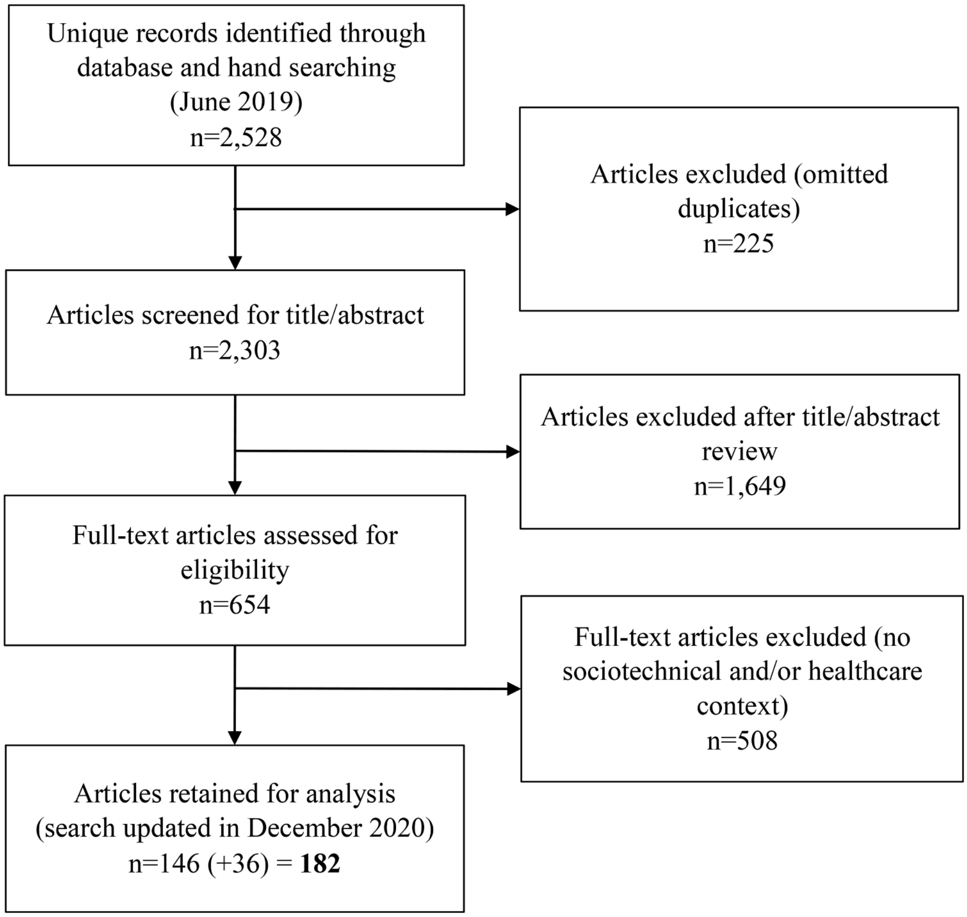

Fig. 1. PRISMA Search Strategy.

Table 2
Articles Analyzed from Database Search.

Database	Search parameters	Shortlisted sources	Thematic areas			
			Transdisciplinarity	Innovation	Public Engagement	Regulations and Policy
Web of science	Topic (i.e., title, abstract, author, keywords)	61	16	9	21	15
Scopus	Title, abstract, keywords	57	18	10	12	17
Medline pubMed	Anywhere (e.g., abstract, author, document text, document title)	64	11	29	19	5

Once finalized the review pool, we distilled a socio-technical perspective on nanomedicine that integrates four key thematic areas emerging from the selected literature. The bibliographic features of the shortlisted articles were clustered into emerging conceptual themes following the charting approach recommended by Arksey and O'Malley (2005). These concepts were critically reviewed and developed as a team by the authors, mostly during face-to-face meetings, to outline the preparation of the paper.

Finally, we confirmed the importance and relevance of these themes by further consulting nanomedical professionals . This approach was aimed at confirming core areas and dynamics of nanomedicine of relevance for social research, as recognized by practitioners. Our intent here was not to be encyclopaedical, rather to appreciate key issues and concepts in nanomedicine that are deemed worth of discussion by both social and technological scholars. Similarly, the distinctions between the themes that we present in the next sections of this article are not meant to be resolutions with firm borders, as they may overlap at several points. Even with such permeability, we believe that their features are robust enough to capture the majority of the ongoing dialog in nanomedicine and promote open, stimulating questions for future research.

4. Findings

4.1. Overview of the retrieved articles

The selected literature reveals an increasing, steady trend in publications in nanomedicine from 2004 to 2020 and a concentration of research coming primarily from Western countries, China, Japan, and India ($n = 162$). The retrieved papers were published for the majority in nanotechnology ($n = 117$) and ethical ($n = 33$) outlets. When analyzing the topics used to describe nanomedicine, diagnostic and therapeutic innovation were the most present subjects and examples ($n = 103$).

As regards the themes retrieved, our analysis of the literature reveals four clusters in which nanomedicine develops. These dimensions include: (i) the transdisciplinary nature of nanomedical technology and innovation; (ii) the products, processes, and loci of innovation in which nanomedicine unfolds; (iii) the opportunities for sustained public engagement; and, (iv) key regulatory and policy challenges and recommendations. We present and discuss each of these areas in the following sections.

4.2. Transdisciplinarity

Nanomedicine is based on a set of technological platforms that promote the creation of novel medical knowledge by building upon several underlying disciplines as enabling background (Bates, 2014). On the one hand, scientometric research has revealed contrasting views on whether such interdisciplinarity may comprise 'mono-disciplines,' that barely share anything more than the word 'nano' (Porter and Youtie, 2009; Rafols and Meyer, 2010; Wang et al., 2013). On the other hand, scholars have argued that nanomedicine's disciplinary connotation offers a concrete discourse to promote a number of distinct subjects, such as nanoneuroscience, nanotoxicology, and so forth (e.g., Oberdörster et al., 2005). Aiming to resolve this tension, the European Science Foundation (European Science and Technology Observatory 2006) outlined five 'disciplines of nanomedicine'. These domains include analytical tools; nanoimaging; nanomaterials and nanodevices; novel therapeutics and drug delivery systems; and clinical, regulatory, and toxicological issues (European Science Foundation, 2005). This proposition has supported a systemic institutionalization of nanomedicine, accompanied by increasing governmental resources, prospering of research facilities, and flourishing of dedicated scientific endeavors. However, it has also opened divergent perspectives on the field's boundaries (Boulaiz et al., 2011; Tsai-hsuan Ku, 2012).

Fundamentally, nanomedicine is a transdisciplinary reality. If interdisciplinarity concerns the spillover of methods among disciplines but stays within a defined framework of disciplinary research, transdisciplinarity is simultaneously 'between, across, and beyond' each constituting discipline so that their convergence leads to a persistent and systematic scientific regime (Nicolescu, 2012). That is, transdisciplinarity occurs wherever it is not possible to define or attempt to solve problems within the defined boundaries of 'traditional' disciplines (Wickson et al., 2006).

To illustrate this concept further, let us consider the example of the bio-barcode assay innovation, a low-cost method of detecting disease-specific biomarkers. This process, which attaches 'recognition particles' and 'molecular amplifiers' to gold nanoparticles, has proven more sensitive than traditional assays for the same target. The process can be adjusted to detect almost any molecular biomarker (e.g., Georganopoulou et al., 2005). Transdisciplinarity here occurs between chemical physics and molecular biology, in the underlying interactions between biological ligands and nanoparticles. Similarly, transdisciplinary occurs across disciplines by integrating and converging such basic insights with a precise biomedical problem: the concentration of amyloid-β-derived ligands, a potential pathogenic Alzheimer's disease marker. Lastly, transdisciplinary can be manifested beyond disciplines by extending the tool's potential to the detection of other bio-targets and overall redefining a traditional diagnostic approach with an innovative and cheaper tool. Moreover, the opening up of potentially novel healthcare scenarios and wider public discussions necessarily brings into the conversation public health and medical audiences as direct stakeholders of this innovation (see also Sections 4.4. and 4.5).

As nanomedicine's transdisciplinarity enables a powerful epistemic strategy on the technological side (Del Cerro Santamaría, 2014), the research potential of the nanomedical system emerges at the social level. Given the significant diversity of interests and research agendas that each grounding discipline holds, the network of expertise in nanomedicine becomes increasingly relevant. The composite disciplinary status of nanomedicine means that the field's boundaries cannot be defined through accounts of actors' distinct expertise and networks (Cattani and Rotolo, 2014; Leydesdorff, 2007). The relationships among actors change over time and are in constant development. As recognized in the wider sociology of technology literature–e.g., social construction of technology (Bijker, 2009; Kline and Pinch, 1996), actor-network theory (Callon, 1999; Latour, 1987), and large-technical systems theory (Hughes, 1987; Summerton, 1994)–actors produce and reproduce, through their daily routines, their micro-level scientific practices, as well as the social relations and organizational forms in which these practices are embedded. In other words, their activities create linkages between different parts of the socio-technical system of nanomedicine. Status and interactions among actors are dynamic and extend to both internal and external players, including researchers, people affected by the research, the general public, and industry stakeholders. These interactions show that nanomedicine exists as an integrated process of flexible disciplinary boundary conditions, constructed under specific contexts, and ultimately relying on the interests and needs of these actors altogether.

This aspect points to another relevant feature for a social science discourse. While transdisciplinarity has been mainly approached from a philosophical viewpoint thus far, still little has been said on how it is grounded, factually, in research practice (Del Cerro Santamaría, 2014). As such, the transdisciplinary margins of nanomedicine provide unique opportunities to investigate the processes by which knowledge is generated and exchanged. This context allows for social sciences to explore the daily practices of scientists. For example, researchers can ascertain ways in which nanomedicine professionals reproduce and create the meanings of their own trans-discipline. As a result, social inquires can observe how actors may contest, challenge, and create new ways of thinking and doing, as well as new forms of personal relationships (Massaro and Jong, 2011). This research avenue could, therefore, shed light on how trandisciplinarity is conducted 'on the ground.' The empirical analysis of these practices can also reveal how, and why, scientists may become 'nanoexperts.' This theoretical gain could be obtained even in research environments supportive of classic mono-disciplinary trainings, as well as in emerging transdisciplinary fields such as 3D Printing or Artificial intelligence (AI) (Aversa et al., 2016). Moreover, since the pressures exercised and opportunities occurring from the technology shape both research relationships and personal identities, social studies can investigate further in what ways researchers profile their roles by modulating cognitive, institutional, and external factors (Kurath, 2009), and the tensions among these elements.

Overall, these considerations raise intriguing questions about the processes through which transdisciplinarity is defined and analyzed in relation to socio-technical drivers and in health-research settings. Most of all, they indicate that outlining the boundary definition of nanomedicine is an important theoretical and empirical issue worthy of future exploration.

4.3. Products, loci, and processes of innovation

The examination of how and where nanomedicine innovations actually take place is another aspect deeply interconnected with the development of the field. Just as the underlying disciplines composing nanomedicine are multifaceted, so are the innovations and the organizations performing the needed research. Despite the increasing number of products put in the market every year, nanomedical innovations can be grouped in the following six clusters (see Wagner et al., 2006): (i) drug delivery; (ii) therapeuticals; (iii) in vivo imaging; (iv) in vitro diagnostic; (v) biomaterials; and, (vi) active implants.

Drug delivery pertains to nanoscale products, such as liposomes polymer nanoparticles, and nanosuspensions developed to improve the bioavailability of therapeutics (Nalwa, 2014; Tran et al., 2017). In other words, drugs in which a molecule is joined with a nanoparticle to expand its clearance properties would be considered as nanomedicine-based drug delivery. When referring to therapeuticals, the literature indicates those nanoscale products such as fullerenes are used in the treatment of diseases that given their structure have unique clinical effects, and as such differ from traditional small-molecule drugs (Dellinger et al., 2013). In vivo imaging regards nanoparticle contrast agents, particularly for magnetic resonance imaging and ultrasound, offering better contrast and biodistribution (Man et al., 2018), while in vitro diagnostics comprises sensors based on nanotubes, nanowires, or atomic force microscopy (AFM) applied to diagnostic devices (Vaddiraju et al., 2010). The objective of these devices is to improve the sensitivity and/or reduce production costs; examples include carbon nanotube–based sensors for monitoring vital parameters and atomic force microscopy for the detection of viruses involved in infections (Saji et al., 2010). Finally, biomaterials and active implants are the last types of innovations occurring in nanomedicine. Biomaterials refer to self-assembling particles or other types of nanomaterial that improve the mechanical features and the compatibility of biomaterials for medical implants; examples include dental fillers, coatings, and bone substitutes (Hasirci et al., 2006). Active implants are instead materials that improve biocompatibility of device housings (Liu and Webster, 2007), such as Biophan©'s (Henrietta, NY, USA) magnetic nano–based coating that makes implants safe for use with resonance imaging.

These nanomedical innovations are as complex as the research laboratories that produced them, with nanofacilities–centers provide nanoscale fabrication, manipulation, characterization, services, and training—representing unique paradigms of the organizational complexity of a novel generation of scientific workrooms (Ensor, 2006). These laboratories are shaped by their abilities to converge disciplines and share knowledge and expensive instrumentation, like AFMs or cleanrooms. These centers also act as hubs of interface between academia and industry, promote commercialization of nanomedical products, and engage with the public. As parts of the complex system to which they belong, these workspaces grow around a number of individual actors, groups, embedded industrial laboratories, and service facilities (Avenel et al., 2007). As such, these facilities represent meta-organizations: organizations composed of interacting organizational systems (Gulati et al., 2012).

These forms of administration are largely characterized by a set of features that allow them to differentiate themselves from individual-member organizations (Ahrne and Brunsson, 2008). They are arranged in terms of collective actions around interdependencies and collaborations with mechanisms of knowledge sharing, all of which are the supports of their procedural dynamics (e.g., Alter and Hage, 1993; Greenwood et al., 2002). Research has already proposed that these arrangements are forms of alliances that surpass the structures and operational elements of traditional organizations (Amburgey and Rao, 1996), and whose members are legally autonomous and linked by a system-level goal (Gulati et al., 2012). Thus, it occurs that nanomedical organizations represent complex organizational forms and display distinctive characteristics, such as flexible boundaries, multi-stratifications, and horizonal control processes. Consequently, these organizations are more loosely defined than in individual-based firms and resource allocations closely depend on single members rather than on the meta-organization itself.

These characteristics promote several research intuitions. For one, a nanofacility's management and structures face challenges in placing collaborations across individuals, groups, and internal and external partners. These relationships are indeed intricate. All actors involved may share a key goal, such as that of addressing a clinical challenge, yet each of the parties also preserves their individual biases (Massaro, 2012; O'Mahony and Bechky, 2008). Typically, the more diverse the backgrounds of the participants, the more pronounced the divisions within the nanofacility. This conflict resonates at the micro as well as at the macro level, where nanocenters engage with industry. It is, thus, not surprising that nanomedical organizations are facing several concerns in the outreach as well as the commercialization of their products. For instance, in order to minimize inherent costs and risks during a drug's development, firms have increasingly outsourced pre-clinical testing to academia (Balogh, 2011). This situation has occurred because nanotechnology firms often lack flexible business models and strategies, thereby failing to trigger a more supportive and wider industrial interest (Flynn and Wei, 2005; Lorenzoni and Lipparini, 1999; Morigi et al., 2012). Firms with ventures in nanomedicine may face impediments in production scale-up or health and safety concerns. In particular, this impact occurs if the firms do not interface with academia to understand the authentic research dynamics that the field carries. The difficulties are multiple and complex (Germain et al., 2020), including: (i) lack of mutual training in management and nanotechnology; (ii) difficulties in performing pre-clinical assessments due to lack of protocols or access to characterization facilities; (iii) problems in scale-up and manufacturing; and, (iv) uncertainty and fragmentation in the regulatory framework, especially for the most complex products that combine multiple technologies.

The existence of nanocenters, as hubs for nanomedical research, has sought to respond to this request and mitigate these difficulties. But can these centers ease such tensions? Could the linkages between universities and industry become more effective when they exist together within nanomedical meta-organizations? Evidence shows the existence of industrial commercial laboratories situated within nanocenters may enrich the dynamics sustaining universities' technology transfer offices (Nikulainen and Palmberg, 2010). These partnerships may also further knowledge on the mechanisms of organizational design (Kimberly and Evanisko, 1981) and of institution building in the context of rapid technological change (Bloom and Wolcott, 2013).

Moving forward, nanomedicine offers several openings for future research interested in the interface with innovation scholarship. Thus, research will find a fruitful context to better understand different scopes of innovation. These may refer to patent intensity, product and service development, supply chain and networks, open and downstream boundary spanning innovation, infrastructural support, and provisioning, among others (Table 3).

4.4. Public engagement: health issues and risks

Nanocenters are promoting public outreach and educational engagement. Several prominent initiatives are already in place. For instance, the Science Galleries at Dublin's CRANN nanocenter promotes nanoscience as a form of art for the lay public (CRANN, 2015); integrated hospitalized structures have been created in many nanocenters to encourage hands-on engagement of patients (Brighton, UK). Given this evidence, it is appropriate to analyze why public engagement is becoming a priority for nanomedicine and in what ways this feature can contribute to advancing social research. Are there underlying propositions in the nanomedical world promoting the urge for this outreach? Or, does it just signify that nanomedicine has implemented lessons from former technological revolutions, like the biotechnology one (Mehta, 2004)?

Addressing these questions cannot be separated from recognizing the technological evidence that nanomaterials' properties are essentially different from their counterparts situated at a larger scale (National Research Council, 2002). Gold and silver are basic examples. Macroscopically inert and unreactive, at the nanoscale gold acts as a highly effective catalyst and silver displays bioactive properties (Della Rocca, Liu, and Lin, 2011). Because these features are not yet fully understood, as concerning nano drugs and devices, nanoscientists have to deal with a diffuse technological uncertainty in society, as well as with their own concerns on how technical communication should best be conducted (Cacciatore et al., 2011). Specifically, there are several reservations on whether nanomedicine-based devices, therapeutics, and diagnostic tools are entirely safe (Riehemann et al., 2009; Sanhai et al., 2008). Health hazards of nanomaterials are not easy to determine. This issue arises given that long-term toxicity studies on humans are still limited. In a similar fashion, the behaviors of nanomaterials in complex biological systems, like the human body, are largely unpredictable *a priori*, and the safety profiles of these materials may not reflect that of the same chemical entity of larger size (Nijhara and Balakrishnan, 2006).

These factors signal a foremost issue for healthcare practitioners and

Table 3
Scoping Research Questions for Innovation Research in Nanomedicine.

Topics	Research questions	References
Patent intensity	Do smaller nanomedical firm foreign patents differ from those of their larger counterparts? As nanomedicine develops as a socio-technical system, will patents become easier to be approved and more valuable to firms?	(Fernández-Ribas, 2010)
Technological transfer	To what extent channels for technology transfer from public research to firms are established and can be supported further in nanomedicine?	Nikulainen and Palmberg, 2010
Networks of innovation	Can understanding the knowledge-diffusion networks of patent inventors help nanomedical organizations effectively use their investment to stimulate commercial science and technology development?	Jiang et al., 2015
Product and service development	How is nanomedical product and service development embedded in community cultures? Are there distinctive community cultures around intensive versus extensive knowledge-generating patents?	Wry et al., 2010
Technological uncertainty	In what ways can the social uncertainties posed by a nanomedical product be characterized through the identification of risks and opportunities in early stages of product development?	Wardak et al., 2008
Global innovation	What is the effect of international responses to nanomedicine on product development? What is the role of shared international models and practices?	Marchant and Sylvester, 2006
Supply chain	Why and in what ways risk governance affect the nanomedical supply chain? Has the establishment of nanocenters offered a more effective set-up to scale-up industrial processes in the pharmaceutical supply chain?	Renn and Roco, 2006
Innovation expertise	How and why do experts and lay audiences form difference attitudes toward nanomedicine?	Su et al., 2016
Open innovation	How can we develop nanomedical products under open innovation?	(Eaton et al., 2015)

nanotechnologists: The necessity of validating accurate systems to assess the safety and impact of nanomedicine on humans' health, as well as having appropriate infrastructure in place to conduct these assessments (Bauer et al., 2008). Given these modalities require specialized equipment not easily accessible (Nel et al., 2009; Oberdörster, 2010), networks of experts are now calling for unified frameworks on 'nanosafety' (Krug, 2014). Scientific accountability to society on nanomedicine has become priority and there is a shared awareness of the 'Pandora's Box' that nanomedicine's uncertainties can potentially open. On the one hand, it is argued that the field should remain a neutral-value scenario. Conversely, the wider public may be unprepared to understand the complexity of emerging technologies and sciences, by being either (overly) skeptical or enthusiastic (Macoubrie, 2004; Scheufele and Lewenstein, 2005).

These concerns about safety and public understanding blend into scientists' actions to include the public at large in scientific discussions around nanomedicine. The emblematic interrelation of nanocenters with the public, together with sustained calls for transparency of information and open-access dissemination of results, are signaling that nanoscientists are paying concrete attention to the public agenda (Cobb, 2005). Two main elements emerge from this context. First, scientists have a strong interest in differentiating nanomedicine from other technologies. For instance, while social science research examining nanomedicine may be prone to drawing similarities with biotechnology, nanoscientists warn that such dialogues between the public and nanoscientists will have to be analyzed with the consideration that these technologies are different in substantive ways (Currall, 2009). Second, nanoscientists are increasingly aware of the ways in which public concerns can shape a technological field. Additionally, they realize that restricting decision-making to technological actors only is a risky path for the development of the field (Currall et al., 2006).

Importantly, these insights provide the ground to further integrate constructive and real-time technological approaches (Guston and Sarewitz, 2002), both socially-oriented critiques that focus on how 'technics' often make unspoken suppositions about the social uses to which the technology will be put. The conversation as pertains the public engagement in nanomedicine may then represent a significant shift in the discourse. For instance, this change could involve what conditions, which actors, and what and whose aims will shape the social components of the socio-technical system (Bijker and Law, 1992; Grint and Woolgar, 2013).

For one practical example, a corollary of this discussion involves doctor-patient relationships. A pilot study by the European Technology Platform on Nanotechnology (ETPN) shows that patients have generally low awareness of the opportunities and challenges of nanomedicine (Mühlebach et al., 2015). However, the patients are demanding more and more information from clinicians regarding the safety and risks of nanomedicine, as well as a high level of preparedness from healthcare professionals. To meet these requests, the NanoMed 2020 Action, a targeted European-funded project, is working toward new recommendations and guidelines (Eaton et al., 2015). At the same time, these issues are introducing significant questions that still need to be addressed, such as: Are 'citizen-consumers' exercising constructive influence on the development of nanomedicine? How shall public engagement coexist with the scientific independence of nanomedicine? Lastly, given that public engagement is highly interfaced with policy infrastructures, to what extent will decision-makers mirror these socio-technical considerations?

4.5. Policy, regulatory, and ethical concerns

Legislative and regulatory artefacts are key means to shaping the dynamics of fields in which science and society interface (Hughes, 1986). As with nanomedicine, policy creates the conditions to ensure that research is conducted and exploited according to rigorous scientific and ethical principles (Glenn and Boyce, 2008). This effort, however, does not arise without hurdles. For instance, one of the main areas where unpredictable problems emerge is in the definition of nanomedicine's hazardous potential. Thus far, nanomaterials have been considered like their larger scale counterparts regarding their safety. For example, carbon nanotubes and fullerenes have been treated like graphite. Graphite is a different allotrope of carbon and their physical, bio-chemical, and most likely, hazardous properties are different (Baughman et al., 2002). This issue alone has led to various concerns on the regulatory framework required for bringing nanomedicine products into clinics, such as for clinical trials. These concerns include the absence of unified standards for defining hazardous properties and the still unaddressed uncertainties surrounding the manufacturing processes of nanodrugs. Thus, mounting questions have emerged: At what stages in the research and development (R & D) process should policy realistically intervene, raise issues of public accountability, and frame appropriate regulations? And, on whose terms should such aspects be debated?

If 'precautionary principles' may well be the standard approach for regulatory agencies regarding nanomedical products, the overall lack of guidelines and consensus on how stringent the risk assessment should be in nanomedicine complicates the scenario (Da Cruz Vilaça, 2004). There is no agreement, yet, on how much and what kind of risk and uncertainty are acceptable. Additionally, there is no congruence as to how to determine if costs and benefits balance the risks, and what kind of evidence is sufficient to justify precautionary actions. Will, then, absolute precaution–meaning that nothing will be authorized unless there is full evidence of complete safety–prevent nanomedical advancements? Or, instead, is the precautionary principle to be understood and investigated as a risk management exercise rather than a risk assessment instrument?

Finally, this theme puts forward some additional demands for the social sciences: Are the dominant frameworks on health risk and ethics adequate for addressing nanomedicine regulations on, for example, the commercialization of nanomedical products? Will the seemingly high cost of nanomedical products be justified by the level of technology, novelty, and superior performance compared to existing tools? Will new nanomedicine-based therapies exacerbate the discrepancies in healthcare accessibility? And will national healthcare systems be able to sustain such a high-expense technology and make it available to citizens in the future?

5. Discussion

In this article, we performed a review of the literature on the emerging field of nanomedicine highlighting core aspects that promote its theoretical understanding as a socio-technical system. Conceptualizing nanomedicine under this lens represents a valuable approach in both outlining healthcare settings and furthering social theories (e.g., Keating and Cambrosio, 2003; Knorr-Cetina and Mulkay, 1983; Latour 1987; Merton and Merton, 1968). Indeed, it enables reaching beyond a somehow deterministic top-down view of a transformative medical field to, instead, a focal set of disruptive innovations and processes. In so doing, this approach offers a contingent opportunity for the simultaneous merging of 'the technological' and 'the social' (Williams and Edge, 1996). As such, our socio-technical analysis reveals that the discussions on nanomedicine should not be developed just on the technology *per se* but, mostly, on the socio-technical system's functionality (Geels, 2004). That is, scholars and practitioners' discussions should extend to the relationships among the elements required to accomplish the societal roles of the system. These roles can encompass the artefacts, the identities of the social actors involved, the participating organizations, and, nanomedicine's wider cultural meaning.

Here, we took as a focal unit of analysis nanomedicine as a set of technologies embedded in multiple layers of social relations and organizational links. We disentangled it into four themes crucial to healthcare development, the employment of resources, and the use of technologies. While nanomedicine spreads over a breadth of parties–including individuals, universities, R & D units, private companies, and governments–the dynamic interplay among actors and their social practices create the emerging properties (e.g., the disciplines, organizations, and policies) of the system's functionality.

This aspect suggests that a fruitful technological system can arise only through its full integration with the social environment in which it develops (e.g., Geels, 2002; Jacobsson and Bergek, 2004; Rip and Kemp, 1998). This understanding allows researchers to trace and represent interactive dialogues, niches, and the broader scenery of elements at the macro-level (van den Ende and Kemp, 1999; Verbong and Geels, 2007). Nanomedicine is a highly interrelated system characterized by layered social features: These features span from individual's knowledge sharing processes and user's routines to organizational dynamics, social norms, and policy regulations.

5.1. Implications for theory and practice

Corroborating our theoretical contribution by employing a socio-technical perspective, we were also able to present a rare opportunity in terms of mapping a living historical context (Markard and Truffer, 2008). The current technological status of nanomedicine offers a vivid example of 'technoscience in-the-making' (Latour, 1987) with the possibility to assess and re-invigorate social science frameworks and explore empirical cases in a real-time fashion. Thus, nanomedicine as a socio-technical system is rich in 'matters of concerns' that may affect its implementation in healthcare practice (Gardner and Webster, 2016).

For these reasons, investigating nanomedicine within a socio-technical analysis allows for a variety of research questions, some of which were opened in the previous sections of this work already (see also Table 3). Similarly, this understanding could provide insights towards informing policy interventions. With such an open outlook, social inquiries can hold central value for the development of nanomedical research itself. Therefore, moving forward, by considering nanomedicine through a socio-technical perspective, researchers could converge different framings of a technology while approaching nanomedicine's ongoing issues. For one example, is the approval of a new nanodevice a technological issue, a public health issue, or a political, or essentially, a social problem? These types of characterization naturally point to different scholarly perspectives and expertise. However, only a joined social and technological framing will provide fuller answers to these issues, while reflecting the fluid nature of nanomedical advancements (Rein and Schön, 1994).

Practically, because specifying the boundary conditions of a socio-technological problem are not always a straightforward process, further development of nanomedicine will increasingly rely on how its advancements are characterized. Nanomedicine can be outlined by both its emergent properties and their dynamics (Sawyer, 2005). As such, it is only within socio-technical approaches that practitioners will find avenues to interpret uncertainties and better understand the mechanisms and processes of such a complex field. These efforts will inform decision-making, reveal the scope for targeted interventions, and potentially update debates on the effective governance of complex systems. Questions may thus revolve around how to best design nanotechnology centers that are capable of coping with technological uncertainty or how to engage with the general public so that the public understands and deals with the risks intrinsic to nanomedicine.

6. Conclusions

Nanomedicine is a recent, disruptive, and heterogeneous scientific field. It comprises complex social and technological connections, thereby requiring attention to the role of its social dimensions *vis-à-vis* the technical aspects in promoting and shaping its development. In this article, we reviewed this field to analyze why and how a socio-technological approach to nanomedicine may represent a valuable framework for social studies. We also discussed the role of social research in furthering a variety of key aspects of nanomedicine as a practice.

The current work shall however be understood in light of its limitations, including its foundational approach and the concentration on selected search queries. Nonetheless, we are hopeful that our analysis will open an investigative agenda promoting several future research directions. Further investigations may seek dedicated explorations of each of the themes presented here in the pursuit of additional topical areas in development. These topics could include, for instance, the nudging of public perceptions of nanomedicine or the interplay of formal and informal organizational structures of nanocenters. Other studies could be focused on the definition of ethical codes for nanomedical research and practice and may seek to enrich such insights with ethnographic and empirical studies. By pursuing these avenues, it will be important to consider that many of the themes developing around and impacting upon nanomedicine will be highly interrelated and overlap. For instance, public engagement in nanomedicine will necessarily be influenced by features such as the validity of information exchange between patients and health practitioners, and decision-making processes inside meta-organizations may include aspects such as prioritizing research on, for example, nanodrugs versus nanodevices.

In conclusion, nanomedicine entails a complex socio-technical structure. It combines both the social and scientific, as well as behavioral and technological elements, that connect together diverse people, places, and processes. Dealing with nanomedicine is not a purely technical task: Only a holistic perspective, merging investigations and adaptations within socio-technical systems, will advance knowledge on the interfaces between nanomedical developments and the social, organizational, and policy settings in which they appear.

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