Journal of Controlled Release 326 (2020) 164–171

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Delivering the power of nanomedicine to patients today

Matthieu Germain[a,*,1], Fanny Caputo[b,1], Su Metcalfe[c], Giovanni Tosi[d], Kathleen Spring[e], Andreas K.O. Åslund[b], Agnes Pottier[f], Raymond Schiffelers[g], Alexandre Ceccaldi[f], Ruth Schmid[b]

[a] Curadigm SAS, 60 rue de wattignies, 75012 Paris, France
[b] Department of Biotechnology and Nanomedicine, SINTEF Industry, 7465 Trondheim, Norway
[c] LIFNano Therapeutics, 10 Fendon Road, University of Cambridge Clinical School, Cambridge CB1 7RT, UK
[d] Nanotech Lab, Te.Far.T.I., Department of Life Sciences, University of Modena and Reggio Emilia, Via Campi 103, 41124 Modena, Italy
[e] Gesellschaft fuer Bioanalytik Muenster e.V., Mendelstrasse 17, 48151 Muenster, Germany
[f] ETPN association, 64-66 rue des archives, 75003 Paris, France
[g] Department of Clinical Chemistry and Haematology, University Medical Centre Utrecht, 3584, CX, Utrecht, the Netherlands

ARTICLE INFO

Keywords:
Nanomedicine
Clinical translation
Nanotechnology
Healthtech
Regulatory
Standardization

ABSTRACT

The situation of the COVID-19 pandemic reminds us that we permanently need high-value flexible solutions to urgent clinical needs including simplified diagnostic technologies suitable for use in the field and for delivering targeted therapeutics. From our perspective nanotechnology is revealed as a vital resource for this, as a generic platform of technical solutions to tackle complex medical challenges. It is towards this perspective and focusing on nanomedicine that we take issue with Prof Park's recent editorial published in the Journal of Controlled Release. Prof. Park argued that in the last 15 years nanomedicine failed to deliver the promised innovative clinical solutions to the patients (Park, K. The beginning of the end of the nanomedicine hype. *Journal of Controlled Release, 2019;* 305, 221–222 [1]. We, the ETPN (European Technology Platform on Nanomedicine) [2], respectfully disagree. In fact, the more than 50 formulations currently in the market, and the recent approval of 3 key nanomedicine products (e. g. Onpattro, Hensify and Vyxeos), have demonstrated that the nanomedicine field is concretely able to design products that overcome critical barriers in conventional medicine in a unique manner, but also to deliver within the cells new drug-free therapeutic effects by using pure physical modes of action, and therefore make a difference in patients lives. Furthermore, the > 400 nanomedicine formulations currently in clinical trials are expecting to bring novel clinical solutions (e.g. platforms for nucleic acid delivery), alone or in combination with other key enabling technologies to the market, including biotechnologies, microfluidics, advanced materials, biomaterials, smart systems, photonics, robotics, textiles, Big Data and ICT (information & communication technologies) more generally. However, we agree with Prof. Park that " *it is time to examine the sources of difficulty in clinical translation of nanomedicine and move forward* ". But for reaching this goal, the investments to support clinical translation of promising nanomedicine formulations should increase, not decrease. As recently encouraged by EMA in its roadmap to 2025, we should create more unity through a common knowledge hub linking academia, industry, healthcare providers and hopefully policy makers to reduce the current fragmentation of the standardization and regulatory body landscape. We should also promote a strategy of cross-technology innovation, support nanomedicine development as a high value and low-cost solution to answer unmet medical needs and help the most promising innovative projects of the field to get better and faster to the clinic. This global vision is the one that the ETPN chose to encourage for the last fifteen years. All actions should be taken with a clear clinical view in mind, " *without any fanfare*", to focus "*on what matters in real life*", which is the patient and his/her quality of life.

This ETPN overview of achievements in nanomedicine serves to reinforce our drive towards further expanding and growing the maturity of nanomedicine for global healthcare, accelerating the pace of transformation of its great potential into tangible medical breakthroughs.

* Corresponding author at: Curadigm SAS, 60 rue de wattignies, 75012 Paris, France.
E-mail address: matthieu.germain@curadigm.com (M. Germain).
[1] These authors contributed equally.

https://doi.org/10.1016/j.jconrel.2020.07.007
Received 9 April 2020; Received in revised form 6 July 2020; Accepted 7 July 2020
Available online 15 July 2020

1. Introduction

For decades the field of nanomedicine has promised to revolutionize treatment outcomes for millions of patients. Has nanomedicine succeeded in meeting the initial expectations, making a real difference for patients or is it still only delivering "*lofty promises*" of what "*we hope it might do someday*"? In his editorial in the Journal of Controlled Release [1], Prof. Park argues that the field of nanomedicine has been clearly overrated, that it was overly focused on cancer therapy and that its promises probably never will be realized. Based on these conclusions, he suggests that the massive resources, time and financial investments allocated to the field of nanomedicine should be refocused on other priorities. It may be true that the publicly funded research investment in the field is decreasing. For example, the US National Cancer Institute (NCI) recently announced that, after 15 years, it will stop funding the Centers of Cancer Nanotechnology Excellence (CCNEs). But the reason for setting aside this funding mechanism was not the failure of the nanomedicine field. On the contrary, the program was supposed to only support emerging technologies, while nanomedicine is now considered resilient enough to compete in other standard funding mechanisms. Moreover, Prof. Grodzinski in response to Park, pointed out that the CCNEs program was very successful, not only producing > 3400 nanomedicine publications, but also generating concrete results, such as the creation of > 100 start-up companies, and products entering > 30 clinical trials in the US [3]. The Nanomedicine and Nanoscale Delivery (NND) focus group of the Controlled Release Society (CRS) also recently joined the discussion, arguing in favor of the solid progresses made by nanomedicine [4].

The debate is open: are we at the beginning of the end of the nanomedicine hype, as suggested by Prof. Park, or are we just at the end of the beginning which will guide nanomedicine into a new, more mature phase? To answer this question, we propose to first proceed as described in the citation used by Prof. Park himself: "*Innovators who seek to revolutionize and disrupt an industry must tell investors the truth about what their technology can do today, not just what they hope it might do someday*." We will argue in section one, how, in our opinion, nanomedicine has already made a concrete difference in the treatment of cancer and of other diseases. Then, in section two we will discuss the bottlenecks that are still delaying nanomedicine's efficient translation into the clinic, we will describe the main on-going European and international initiatives to sustain the field alone or in combination with other key enabling technologies (KETs). Finally, we will conclude on the potential role that European infrastructures may play in the future, notably within the framework of the upcoming Work Programme Horizon Europe led by the European Commission (E.C.).

2. Section one: How nanomedicine is improving therapeutic outcomes

It is very often claimed that nanomedicine failed to meet the initial expectations in drug delivery, since less than 1% of the active pharmacological ingredient (API) is locally released, e.g. in cancer treatment in the tumoral tissues [5,6]. As pointed out by Scott Mc-Neil, former Director of the Nanotechnology Characterization Laboratory (NCL) of the NCI, the average amount of the API delivered locally may not be the only parameter to judge the success of nanomedicine in cancer therapy, since other pharmacological parameters, as peak drug concentration, clearance rate and half time elimination may be significantly improved, increasing the therapeutic outcome and also reducing side effects [7]. More importantly, the nanomedicine success cannot be judged only by considering the delivered dose, since nanoparticles are not acting only as passive drug carriers. In the last three years, three new formulations were approved, Vyxeos, Onpattro and Hensify, clearly demonstrating that a new generation of nanomedicine formulations has successfully reached the market, opening new clinical perspectives based on their unique physico-chemical properties.

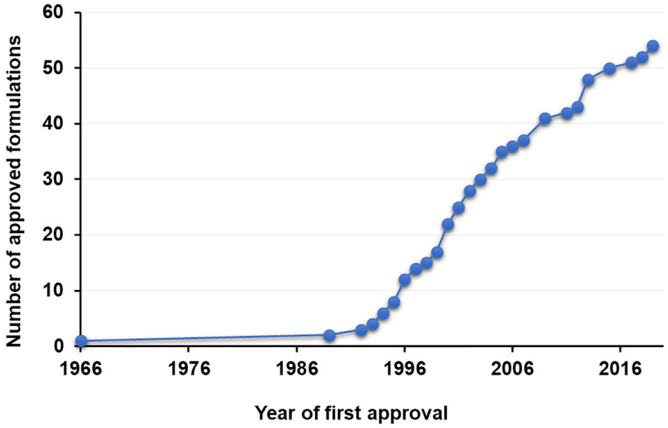

Fig. 1. Evolution of the approved nanomedicine formulations (cumulative number/year). First year of approval reported for formulations approved by multiple agencies (e.g. EMA and FDA).

3. The new generation of nanomedicine who made it to the market

Currently more than 50 nanomedicine formulations have been approved for clinical use, as recently reviewed by multiple authors [8–10]. These marketed nanomedicine formulations are approved for cancer treatment, iron-replacement therapies, anesthetics, fungal treatments, macular degeneration, and for the treatment of genetic rare diseases [8]. Nano/microparticle imaging agents have also been included in the statistics. The majority of approved NP classes are represented by liposomes, iron colloids, protein-based NP, nano-emulsions, nanocrystals and metal oxide nanoparticles. The three new formulations mentioned in the previous section, not only show that the number of formulations approved are steadily increasing (Fig. 1), but that new generations of nanomedicine are now reaching the market.

Vyxeos was approved in 2017 by the FDA for the treatment of acute myeloid leukemia [11]. It allows the simultaneous delivery of two drugs, cytarabine and daunorubicin, at a synergic fixed 5:1 ratio to increase treatment efficacy with a lower cumulated dose. Due to differential pharmacodynamics and biodistribution of drugs, a temporal and spatial controlled delivery of this optimal ratio cannot be reached by any other approach than by the encapsulation of the chosen mix of drugs in a nano-object. It is easy to envision that such a success will be reproduced with various drug combinations.

In 2018 Onpattro, the first lipid-based nanoformulation encapsulating siRNA, was approved for the treatment of transthyretin amyloidosis [12], a rare disease. This approval is a great achievement, nanomedicine being the first technology platform answering the needs of nucleic acid delivery and finally making it available for patients. Indeed, nucleotide-based drugs have an enormous therapeutic potential but pose specific delivery challenges. In fact, nucleotides are rapidly degraded in vivo and have little or no possibility to reach the target region. Furthermore, they are negatively charged and uptake into cells is electrostatically hindered. Hence, nucleotide drugs need both protection and a trojan horse to enter cells. The design of Onpattro combines an efficient encapsulation of siRNA with prevention of its degradation in vivo but also with the ability to perform endosomal escape and delivery of siRNA within the cell cytoplasm. Considering the high number of ongoing clinical trials based on nanomedicines encapsulating nucleic acids, including mRNAs, several new products will be expected to reach the market in the near future. The current global Covid-19 pandemic highlights that a vaccine, based on mRNA encapsulation in lipid-based nanoparticles, could now be developed with unprecedented speed. Importantly, the therapeutic potential of mRNA is vastly larger, and can provide solutions in multiple areas including cancer vaccines and immune activation, in-body production of patients'

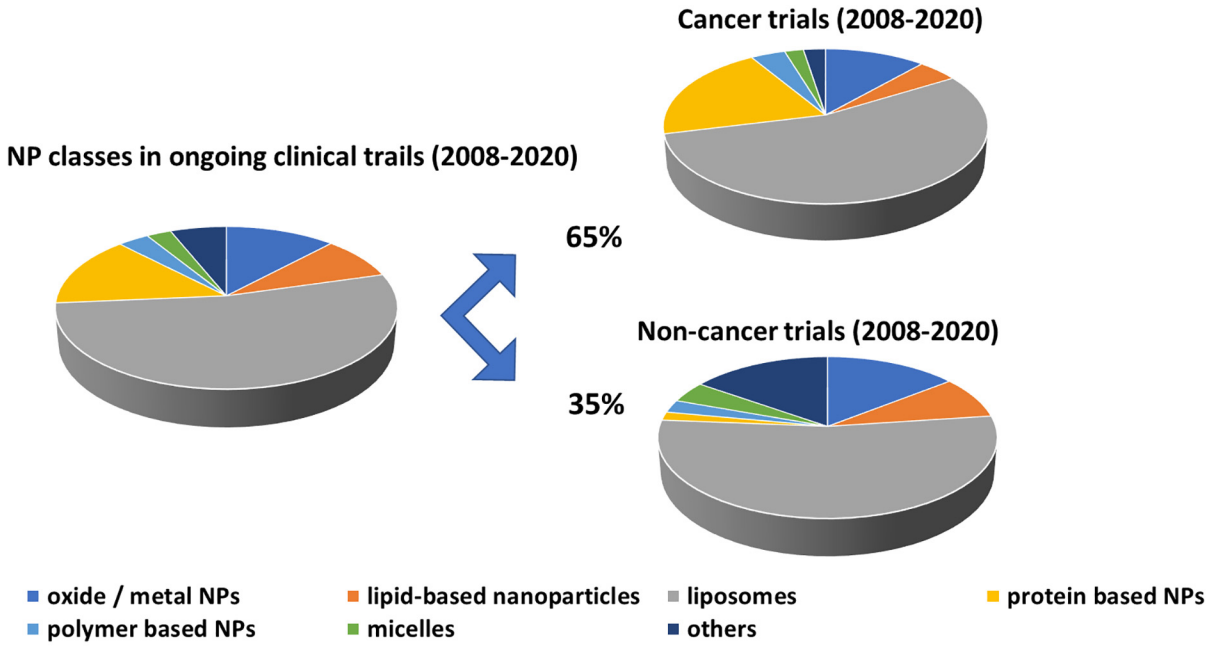

Fig. 2. Nanoparticle classes investigated in ongoing clinical trials. The analysis was performed on 409 clinical trials from 2008 to 2020 (active, ongoing or recruiting), identified in the clinicaltrials.gov database in May 2020. Search limited to trials identified with the following keywords: nanoparticle, liposome, liposomal, lipid, vaccine, micelle, nanocrystal, virus like particle, silica particle, iron oxide, extracellular vesicle, dendrimer, nanobubble, lipoplex, gold nanoparticle. These keywords were used alone or in association with other diseases or technologies specific keywords: COVID-19, mRNA, nucleic acid, cancer. Only trials using nanoparticles were selected, eliminating doubloons arising from multiple searches. Repartition of nanoparticle types is presented for all ongoing clinical trials, for cancer related applications (65% of the total) and for all applications outside oncology (35% of the total). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

own therapeutic antibodies, protein replacement therapies and regenerative medicine. Importantly, delivery of nucleic acids could be used for any kind of permanent gene therapy of, conceivably, any genetic disorder by encoding of the CRISPR/Cas9 complex [13]. Therefore, we believe that Onpattro is only the very beginning of a paradigm shift in the treatment of various therapeutic areas including oncology, but also rare diseases, genetic or infectious diseases.

Nanomedicine cannot be considered simply as a drug delivery system anymore since nanomaterials themselves may become the active therapeutic ingredient. Nowadays, radiotherapy's efficacy is limited by the tolerance of normal tissues adjacent to the tumor which reduces the energy dose that can be administered safely the patient. Nanotechnologies have created a new profile of material interactions with cell biology. The use of a new class of radiation-enhancing nanoparticles could be a breakthrough approach for the local treatment of solid tumors that are treated with radiotherapy. NBTXR3 is a first-in-class nanoparticle composed of functionalized crystalline hafnium oxide (HfO2). NBTXR3 nanoparticles were chosen for clinical development because of their excellent ratio for x-ray absorption and acceptable safety. Once activated by ionizing radiation, NBTXR3 administered intratumorally yields a cell-localized high energy deposit and increased cell death compared with the same dose of radiation alone, without adding toxicity to the surrounding tissues. This innovative approach proposes to broaden the therapeutic window of radiation therapy by opening the possibility to bring physics at the heart of the cells without changing radiotherapy practice. NBTXR3 obtained its CE mark for the treatment of locally advanced soft tissue sarcoma in 2019 and the results from its phase 2–3 clinical trial were recently published [14].

Other examples of the difference made by nanomedicine can be found in liposomal marketed products in various therapeutic areas [15]. The final aim of this paper is not to provide an exhaustive list of products, but rather to highlight and focus on some of them, e.g. Visudyne, a liposomal formulation of verteporin, used in the treatment of age-related macular degeneration (AMD) by photodynamic therapy [16]. Encapsulation of verteporin is required since this molecule undergoes self-aggregation in aqueous medium, limiting its bioavailability. Ocular delivery is very challenging due to the presence of biological barriers (cornea, aqueous humor, etc.) which reduce the bioavailability of topically or intraocularly administered therapeutic agents. This situation demands frequent therapeutic agent administration which could limit the treatment especially for invasive intra-ocular administration which can cause intraocular bleeding associated with pain and discomfort that results in poor patient compliance. This demonstrates that nanomedicine has also made a difference in this therapeutic area by offering the possibility to improve therapeutic agents' bioavailability for intraocularly and topically administered drugs and sustained drug release which reduces the frequency of drug administrations. Such benefits explain why there are already 10 nanomedicine-based products marketed for ocular treatment [17].

Imaging also benefits from nanomedicine's properties. For example, Magtrace is made of magnetic iron nanoparticles enable tracing of the sentinel node in breast cancer without the use of radiomarkers, resulting in a more efficient biopsy and detection of cancer cell migration [18].

4. Who's next? Innovative formulations in pre-clinical and clinical development

By analyzing the active or recruiting clinical trials in the clinicaltrials.gov database we were able to identify 409 clinical trials focusing on therapy and diagnostics involving nanomedicines. From the beginning of 2018, more than 247 new clinical trials (active or recruiting) have been started. Interestingly, in May 2020 at least 3 trials were already started on vaccines for COVID-19 based on lipid-based nanoparticles and this number will probably increase significantly in the upcoming months. The most common formulations under investigation are still liposomes and protein based-nanoparticles, e.g.

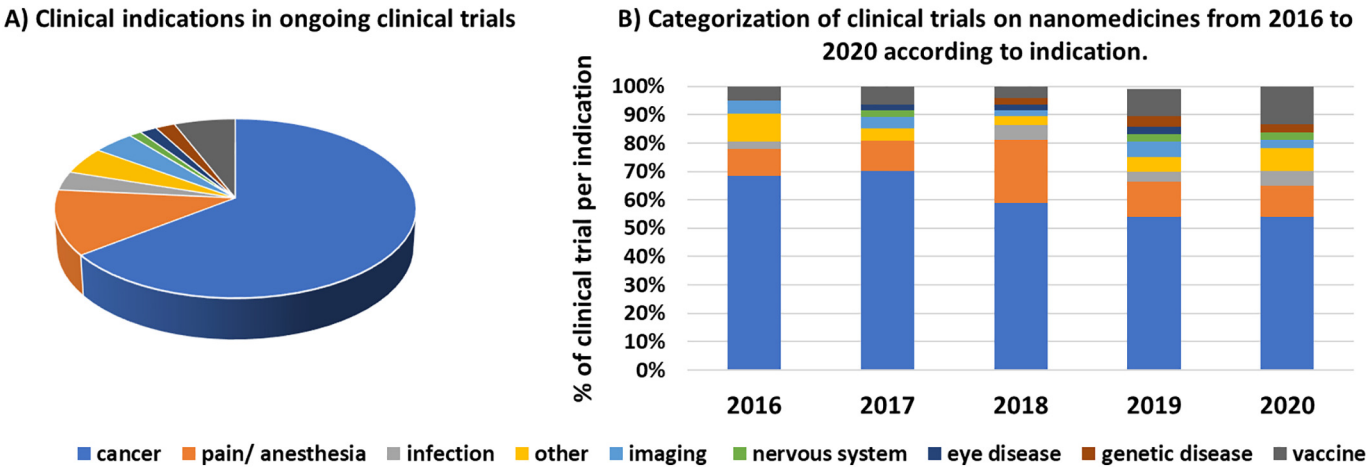

Fig. 3. Categorization of clinical trials based on nanomedicine formulation per indication: A) analysis on all the 409 trials and b) repartition per year in the 2016-May 2020 period (333 trials). The analysis was performed on 409 clinical trials (active, ongoing or recruiting), identified in the clinicaltrials.gov database in May 2020. Search limited to trials identified with the following keywords: nanoparticle, liposome, liposomal, lipid, vaccine, micelle, nanocrystal, virus like particle, silica particle, iron oxide nanoparticle, extracellular vesicle, dendrimer, nanobubble, lipoplex, gold nanoparticle. These keywords were used alone or in association with other diseases or technologies specific keywords: COVID-19, mRNA, nucleic acid, cancer. Only trials using nanoparticles were selected, eliminating doubloons arising from multiple searches. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Nab-paclitaxel/Abraxane, but since 2015 the number of other types of nanomedicines reaching clinical testing has drastically increased with new innovative concepts such as lipid-based nanoparticles for nucleic acid delivery or metal oxides as radio-enhancers. Multiple trials are also ongoing on polymeric nanoparticles, virus like particles, and micelles, as represented in Fig. 2.

Even if nanomedicine is still highly focused on oncology, there is a clear shift towards other clinical applications: while clinical trials for cancer treatments remain above 50%, the number of clinical trials is increasing in other indications including pain treatment, infection, and vaccination. Furthermore, new indications/areas for treatment are emerging encompassing diseases related to neural system diseases, eye diseases and genetic diseases (Fig. 3).

5. The direction of cancer nanomedicine

65% of currently ongoing clinical trials are focused on cancer applications. To beat cancer, nanomedicine can offer great contributions for better treatments and early diagnosis. It is important to stress that even if the main goal remains to reduce or eradicate cancer, it is equally important to improve the quality of life of patients during treatment, helping to reduce the, often devastating, side effects. This is also where nanomedicine can significantly contribute. Nanomaterial's potential to deliver drugs locally, ensuring the therapeutic outcome by also reducing side effects is thus very important in cancer applications [5]. In this perspective, anti-cancer vaccines and personalized immuno-therapy (nucleic acids-based technologies) can notably be developed by nucleic acids-based technologies encapsulated in nanoparticle drug delivery systems. Multiple clinical trials are currently ongoing on lipid-based nanoparticles and on lipoplexes. Radio-enhancers like NBTXR3, could be a revolutionary concept for treating solid tumors, by locally enhancing the delivered dose of radiation. Stimuli-responsive nano-carriers with hyperthermia, are another innovative concept explored in clinical trials with the same purpose. For example, Thermodox, a heat sensitive liposome loaded with doxorubicin [19], is under clinical investigation in the OPTIMA Phase III Study for Primary Liver Cancer in combination with hyperthermia. In this clinical application, the combination of a stimuli-responsive nano-carrier with hyperthermia treatment, would allow a better temporal and spatial control of drug release, improving the therapeutic outcome with a lower dose.

Nanomedicine can also support early cancer diagnosis by providing ultrasensitive contrast agents. Several examples of nano-sized systems for diagnostic are currently investigated in clinical trials, including iron oxide nanoparticles for PET/MRI, and liposome/nanoparticle [18] mediated delivery of contrast agents (99Tc or 111In as examples) to be used in scintigraphy, SPECT or PET analysis.

6. Nanomedicine is not only focusing on cancer

Among the trials identified, 35% are investigating the use of nanomedicine for other clinical applications than cancer, demonstrating that nanomedicine could make a difference in other therapeutic areas, such as the central nervous system (CNS). Based on their unique physico-chemical properties (e. g. size, targeting agent coupling), nanomedicines are able to act on / pass through the blood brain barrier (BBB) and deliver the treatment more efficiently within the CNS. Tailored nanomedicines can pass through the BBB via transcytosis or endocytosis. Relevant preclinical results were obtained in various animal models of brain diseases as gliomas [20], Huntington's [21], Alzheimer's [22–24] or neurometabolic diseases [25–27]. Strategies based on transcytosis will typically give access to CNS delivery of small molecules but also nucleic acids or proteins via systemic and non-invasive administration [28]. Also, there is ongoing research to modulate nerve electrical activity or stimulate neural growth using gold nanoparticles combined with laser activation [29]. Such approaches open opportunities for the treatment of neurodegenerative diseases such as Parkinson's or Alzheimer's disease.

Furthermore, nanomedicine can become a key player in cross-sectoral and cross-technological solutions for healthcare. The unique properties of nanoparticles (electrical, mechanical, acoustic, optical) open new opportunities when combined with other technologies in health. Some examples of cross-technological solutions have been cited above. Furthermore, sensors should also be mentioned since their sensitivity, speed and miniaturization may be improved by nanomedicine. Such nanosensors will be suitable for more sensitive biomarker detection in a large panel of diseases (e. g. cancer, CNS and infectious diseases). A review of Munawar et al. gives a good overview of the potential of nanoparticles for nanosensors [30]. Typical applications of nanosensors are found in the monitoring and control of pandemics and plagues. There are now diagnostic tools that have been approved for diseases such as Ebola and the Zika virus, which had the potential to develop into global pandemics without nanotechnology-based products.

7. Nanomedicine: A platform for designing better medical solutions

One major advantage of nanomedicines as designed objects over other medicinal products is their high level of uncoupling between their functional requirements (therapeutic effect & targeted delivery for instance) and their design parameters (nanoparticle & drug for instance), as could be described by the general theory of axiomatic design by Nam P. Suh in the 1990's [31]. In other terms, a very interesting feature of nanomedicines is to offer the characteristics of a generic platform in which modules can be replaced, improved or re-designed without the need to re-design the whole product from the beginning every time its function needs to evolve. For instance, by keeping the same nanoparticle structure, but only changing the drug it carries, any other therapeutic agents inside the particle or through fine tuning of the coating of the particle, one can adapt the product to new applications or subtypes of patients with the same disease, with better efficiency, and while keeping some advantages inherent with the core particle itself. *Re*-design of the whole product could also be done by functions uncoupling in two distinct nanoparticles. Decreasing the notion of compromise between the required physico-chemical properties allows a more efficient delivery of these functions improving the treatment benefit / risk ratio [32]. This is indeed not the case for small organic molecules & biologicals that need to go through a high number of constraints for each new application. Answering these new constraints require modifications in the drug design to optimize a specific function but such modifications may also lead to degradation of other functions in the same time. Indeed, each new nanomedicine has to follow a full clinical development and no specific regulation at this stage is available for them. Still, despite nanomedicines are often regulated as drugs, they are different from classical drugs. As complex manufactured objects offering tunable functions that can interact at sub-cellular level, nanomedicines are platforms to design & deliver better medical solutions, with personalized treatment capacities.

8. Nanomedicine: Clinical success rate

We have described in the last paragraphs examples of concrete outcomes of the nanomedicine field and new exciting products to come. But what is the average approval rate of nanomedicines compared to classical drugs? Is there a difference in different fields, e.g. in oncology vs other clinical applications?

He et al. calculated the success rate of nanomedicine formulations in oncology for the different clinical phases [33]. They showed that the success rate of nano-enabled cancer drugs in phase 1 is 94%, and this is attributed to their good safety profile often couple to the improved pharmacokinetic for the drug. Phase 2 and 3 success rates are respectively of 48 and 14%. With an estimated total success rate from phase 1 to approval of 6%; thus, nanomedicines perform better than conventional drugs in oncology, which have a success rate of 3.4 [34]. However, Prof. Park is right in saying that nanomedicine has been mainly focused on cancer, and that the clinical outcome for other clinical applications has been poor. Why is it that, outside of oncology, only a few nanomedicines reach clinical trials and market approval? We need to enable and support clinical development of new promising formulations for diseases that is not related to oncology [35]. But what should we do to support the entry of new promising formulations of nanomedicines into clinical trials?

9. Section two: Addressing the gaps to accelerate nanomedicine translation into the clinic

The difficulties in clinical translation of nanomedicine are multiple and complex. Among them are: (i) lack of education in business management, especially at the academic level, (ii) difficulties in performing the pre-clinical characterization and safety assessment from early stages, due to lack of protocols and lack of access to characterization facilities, (iii) difficulties in scale-up and GMP manufacturing and (iv) uncertainty and fragmentation in the regulatory framework, especially for the most complex borderline products that combining multiple technologies [4,36].

The European Technology Platform on nanomedicine (ETPN) [2] is a think tank created in 2005 and set up together with the European Commission (E.C.) to address the application of nanotechnology in healthcare. The ETPN believes that involving industry will accelerate the development of promising ideas and provide the effective and safe healthcare products that patients need. Today, it gathers more than 130 member institutions from 27 different countries, representing the whole value chain of healthcare from academia, SMEs, industry, healthcare providers to national associations, scientific societies and policy makers. The ETPN has supported strong and smart public funding of the most promising R&D topics – “where Nanomedicine can bring something more” – through strategic inputs coming for all stakeholders, towards the E.C. for the last fifteen years. Complementarily, the ETPN acts also as a driving for force for industrialization of nanomedicine in Europe since 2014, detecting the best innovations of the field and facilitating their transfer from innovative design to clinical development through the nanomedicine Translation HUB, a global set of premium

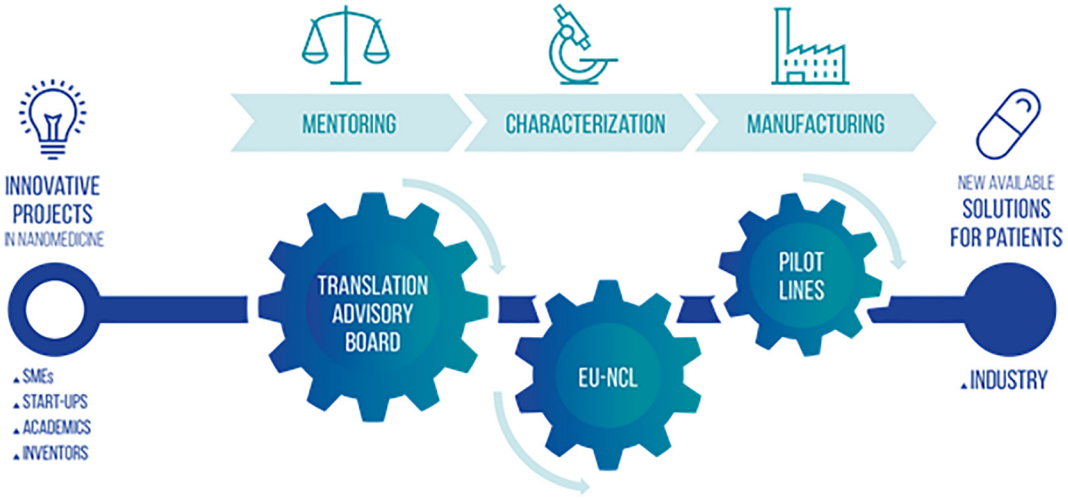

Fig. 4. The Nanomedicine Translation Hub: Developed infrastructure to accelerate the development of the best nanomedicine projects from innovative design to clinical development. Translation HUB is not a linear process and innovative projects can benefit of each pillar independently.

services, free-of-charge for the beneficiaries. This Hub is composed of three main pillars, custom mentoring, product characterization and GMP manufacturing, as represented in Fig. 4.

First, the HealthTech TAB (Translation Advisory Board) [37] is a unique mentoring service in Europe, boosting selected HealthTech inventions to transform them into successful businesses. It is funded and managed by the NOBEL Project which is funded by the European Commission under the Horizon 2020 research and innovation program. The HealthTech TAB gives access to world-class expertise from former managers from Pharma and Medtech industry, successful entrepreneurs, heads of innovation agencies, etc. Together, they offer custom support to innovative project holders on specific issues for which they usually lack skills: IP management, regulatory aspects, business development, market access, scale-up, team building, fund raising, etc. Application for the TAB is open to all: start-up, SMEs, academics, individual entrepreneurs, industry, etc. This service is free-of-charge for its beneficiaries, as a service funded by the E.C. through the NOBEL Project. The HealthTech TAB has already supported +110 projects and helped its beneficiaries to raise +15 M€ in fundraising.

Another pillar of the Translation HUB is the European Nanomedicine Characterization Laboratory (EUNCL) [38], a trans-European, transdisciplinary characterization infrastructure founded in 2015, providing a comprehensive and integrated set of preclinical characterization assays for the nanomedicine formulations, including physical, chemical, in vitro and in vivo biological testing. EUNCL supports European stakeholders to advance the translation of their products into the clinic, e.g. advancing from TRL 3 to TRL4 or higher. Since 2015 EUNCL has operated thanks to E.C. H2020 funding and has supported more than 30 nanomedicine developers, including SMEs, big pharma and universities, in the safety and quality assessment of their formulation. More than 30 Standard Operating Procedures (SOP) have been validated and shared with the community (http://www.euncl.eu/about-us/assay-cascade/).

Finally, the Nanomedicine formulation could also benefit of one of the three medium scale product lines regrouped in the third pillar funded by Europe: Nanofacturing, Nanopilot and Maciviva. These have been established for scaling up existing good manufacturing practice (GMP) pilot lines to a medium-scale sustainable manufacturing process for solid core nanopharmaceuticals and other medical nanobiomaterials were funded. Interestingly, as a logical continuation of these first publicly funded efforts to ensure easier scale-up of manufacturing for nanomedicines in GMP conditions, a new industry offer provided by contract development and manufacturing organizations has recently appeared in Europe, proving both the high relevance and clear need of this approach for technology providers in nanomedicine.

10. The need for a harmonized international regulatory framework for regulating physical-chemical and biological characterization of nanomedicines

Nanomedicines are not officially regulated differently from small traditional drugs. To be successfully translated into the market FDA and EMA both require that nanomedicines meet the same safety, efficacy and pharmaceutical quality criteria applied to all drug products [39]. However, due to their unique and hybrid nature, the quality assessment of nanomedicine formulations pose substantial analytical challenges when compared to small molecular or biological drugs (e.g. antibodies). In fact, in addition to the measurement of identity, strength, potency, stability and impurities, bacterial endotoxins and bioburden of the different chemical ingredients, additional physico-chemical properties must be assessed for the final drug product (the final nanomedicine formulation). These assessed properties include particle size, size distribution and polydispersity, surface charge, drug loading and drug release profile, complex core-shell chemical and physical structure, chemical and size stability during storage and when in contact with biological media [40]. To add a layer of complexity, classical characterization methods are often not applicable to nanomaterials. Furthermore, more complex methodological approaches are needed in order to understand how nanomedicine properties could impact their safety and efficacy profiles (e.g. determined by their immunological effects, biodistribution, pharmacokinetics, metabolism, and degradation profile) in order to determine the specific critical quality attributes (CQAs) of each system.

The US National Cancer Institute Nanotechnology Characterization Laboratory (NCI-NCL, ncl.cancer.gov/about-ncl) and the European Nanomedicine Characterization Laboratory (EUNCL, euncl.eu) have unbiasedly supported nanomedicine developers, by providing access to their multidisciplinary characterization facilities, and also by promoting knowledge and educational exchange within the community. The two laboratories have jointly worked with other H2020 consortia (e.g. REFINE and SAFE-N-MEDTECH), regulatory bodies (EMA and FDA), metrology institutes and standard authorities (ASTM E56) in order to develop new standards and to promote a harmonized approach between Europe and the US. Unfortunately, despite their efforts, due to the complexity to standardize characterization approaches on various very specific nanomaterials, currently only a few standard methods for nanomedicine characterization exist. Major gaps have been identified in the lack of standardized methods to measure: (i) drug loading (free vs. encapsulated drug), (ii) particle stability in plasma, including drug release kinetics, (iii) surface properties and surface interactions with the biological environment and (iv) particle interactions with the immune system [41–43].

In this context EMA has recently published a Regulatory Science Strategic Reflection to 2025. One of five strategic goals and core recommendations proposed is "*Enabling and leveraging research and innovation in regulatory science*", which includes to "Identify and access the best expertise across Europe and internationally" and "*Disseminate and exchange knowledge, expertise and innovation across the network and to its stakeholders*". ETPN is aware of the clear need to support the EMA strategic aims to guarantee access to the best expertise across Europe including infrastructure such as the EUNCL and novel initiatives such as the Open Innovation Test Bed for nano-pharmaceuticals production to support the development of a harmonized regulatory framework for nanomedicine and borderline products combining different technologies in one cross-technological solution. In this context, ETPN will support the continuation of the activities of the European Nanomedicine Characterization Laboratory (EUNCL) as part of the ETPN Translational Hub by reaching out for opportunities to pursue continuous public funding which is needed to support developers to bring their products to the market. Moreover, ETPN will support international initiatives aiming to reduce the current fragmentation of the standardization and the regulatory body landscape, e.g. by leading the emerging EU-US Community of Research (CoR) in Nanomedicine, with an international collaborative group called "EU-US Collaboratory" under its umbrella. This initiative includes academia, R&D, regulators, metrology and industrial experts, and has been created in order to address the lack of validated harmonized and standardized physical-chemical measurements of nanomedicines under the leadership of the National Institute of Standard and Technology (NIST) from the US side and the Joint Research Centre of the European Commission on the European side [44].

11. Nanomedicine as a cross-sectoral and cross-technological solution for healthcare

The ETPN has recently made efforts to strengthen the European ecosystem for smart health technologies within the NOBEL project. From precision engineering to smart connected HealthTech, and from academic research to the clinic, NOBEL is creating a European HealthTech ecosystem, for the convergence of nanomedicine with photonics, robotics, biomaterials, smart systems, digital health and textile. NOBEL has three main missions: (i) to build an ecosystem, as a

unique meeting place for all stakeholders from academia to industry, SMEs, clinicians and policy makers; (ii) to shape a common vision for the future of HealthTech in Europe, the Continuum of Integrated Care, incorporating the separate roadmaps of individual technologies, and showing how concretely these medical technologies may improve the whole journey of patients, for a more, preventive, predictive, personalized and sustainable medicine; (iii) to accelerate the transfer to market of the most useful disruptive medical innovations, through the funding of the HealthTech TAB.

By coordinating the NOBEL project since 2017, the ETPN pursues its successful contribution to bring healthcare solutions faster to the market and foster the strategic cross-sectorial approach and intensifies crosstalk between different technology communities which is needed to synchronize cross-technology innovation and developments necessary to advance, e.g. functionalized surfaces for regenerative medicine approaches or smart biosensors to ensure distant monitoring of patients and attenuate the acute phase of a disease. Nanomedicine as a horizontal and essential complementary technology with broad applications in many medical fields of the Continuum of Integrated Care will continue to be at the front of innovation in healthcare and the ETPN will support and foster nanomedicine in this new vision. The ETPN is strongly willing to keep on playing a key role in shaping the future of health technologies in Europe, encouraging their synergy in a medical problem solving approach rather than a techno-push approach, for more preventive, patient-centered and sustainable health care. Indeed, patients, and citizens in general, do not care about technology for the sake of it. They care about quality of life.

12. Conclusions

From an ETPN perspective, nanomedicine unquestionably makes a difference for patients. Even if we agree with Prof. Park that nanomedicine was overpromoted a few years ago as an immediate revolution and several promises of nanomedicine are still not achieved, we are entering a new period turning from academic development to proven clinical value. We need to be constructive in our approach and focus on the gaps to fill to accelerate nanomedicine translation into a more mature phase. The ETPN will continue to support nanomedicine development using its different platforms towards the integration of knowledge, communication, and cooperation between different stakeholders (including academia, industry, clinics, training patients/people and related associations), providing instruments to support clinical translation of new products and contributing to shape the nanomedicine and smart health technologies landscape in Europe and in the coming European research funding program Horizon Europe. ETPN is also actively supporting formation of open-minded young researchers in the field, which will be the future protagonists of ideas and innovations for the sustainable development of nanomedicine. European support to nanomedicine needs to remain a priority in the next Horizon Europe program, so this technology can continue to contribute with cutting-edge science and innovation as a provider of new solutions to tackle complex medical challenges. The ETPN is therefore actively contributing and will reinforce its participation in to future European initiatives, including Europe's Beating Cancer plan, the Mission Cancer, the Cluster Health, and the innovative European Partnership for Innovative Health (Public Private Partnership) which is a new and unique occasion to finally see the medtech, pharma and biotech industries work together in Europe. Nanomedicine will open new possibilities to support the development of early diagnostic tools and better treatments, in a new, more patient centered, era. But, nanomedicine should not act as isolated technology and the ETPN will continue to be a driving force in shaping a cross-technology environment, where nanomedicine interacts with other technologies to design cross-technological, multidisciplinary medical solutions for the benefit of the patients.

Declaration of Competing Interest

Matthieu GERMAIN and Agnes POTTIER are co-inventors of patent applications related to Hensify product (Nanobiotix) described in this article. Alexandre CECCALDI is employee of ETPN. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

Credit authors statement

- Matthieu GERMAIN: Writing - Original Draft. Review & Editing
- Fanny CAPUTO: Writing - Original Draft. Review & Editing
- Su METCALFE: Writing - Original Draft. Review & Editing
- Giovanni TOSI: Writing - Original Draft. Review & Editing
- Kathleen SPRING: Writing - Original Draft. Review & Editing
- Andreas K. O. ÅSLUND: Writing - Original Draft. Review & Editing
- Agnes POTTIER: Review & Editing
- Raymond SCHIFFELERS: Review & Editing
- Alexandre CECCALDI: Review & Editing
- Ruth SCHMID: Review & Editing

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