Title

Challenges of clinical translation in nanomedicine: A qualitative study

Authors

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Abstract:

Clinical translation of breakthroughs in nanotechnology and nanomedicine is expected to significantly improve diagnostic tools and therapeutic modalities for various diseases. This will not only improve human health and well-being, but is also likely to reduce health care costs in the long run. However, clinical translation is a long, arduous, resource intensive process that requires priority setting, resource mobilization, successful national and international collaboration, and effective coordination between key stakeholders. The aim of this paper is to describe various challenges faced by the stakeholders involved in translational nanomedicine while planning and conducting first in human clinical trials. We draw on insights obtained from 46 in-depth qualitative interviews with key stakeholders from Europe and North America.

Key words:

translational research, nanomedicine, first in human (FIH) trials, challenges, qualitative research

Background

Translation of basic science research into clinical applications is known as translational research, and is crucial to improve human health and well-being.¹ Translational research facilitates the availability of improved diagnostic tests and treatment options, enabling early diagnosis, better treatment, and a consequent decrease in disease related morbidity and mortality. However, less than 10% of basic science research gets translated into clinical applications with a large proportion of promising experimental therapies not crossing the “valley of death”.² This makes translational research a long, ineffective, and expensive enterprise which significantly increases health care costs.³ In 2004, the US Food and Drug Administration (FDA) launched the Critical Path Initiative with the aim to improve the availability of new diagnostic and therapeutic modalities by systematically addressing some of the key obstacles in existing translational research processes.⁴

First in human (FIH) trials mark a critical juncture in translational research because it is at this point that experimental products get tested in human beings for the very first time. Though translational research in general involves significant levels of uncertainty, it peaks during FIH trials.⁵ FIH trials get further complicated when the products under evaluation involve cutting edge medical technologies such as nanomedicine, synthetic biology, gene therapy, or cell therapy due to a lack of clarity on the mechanism of action and the exact target of the experimental product, and limited reliability and validity of preclinical animal models.⁶

The aim of this paper is to describe and discuss the challenges faced by stakeholders involved in translational research in nanotechnology. We chose medical applications of nanotechnology as a prototype and decided to focus on FIH trials. Nanotechnology has the potential to develop highly accurate and sensitive diagnostic tests,⁷ targeted therapies,⁸ and theranostic applications.⁹ At the same time, there is a national and international focus on funding and research in nanomedicine with the hope that it will revolutionize our

understanding of diseases and advance our means to treat them.¹⁰ Thus, researchers working in translational nanomedicine have to deal with high levels of uncertainty, the novelty of the technology, limited prior experience with nanoformulations and toxicity assessment, challenges in applying for and obtaining regulatory and ethics approval, increased media hype and heightened requests for scrutiny, while keeping in mind the unmet and pressing needs of patients living with chronic and terminal illnesses.

A number of researchers and experts have reflected on the challenges of translational research in nanomedicine from the perspective of underlying science, drug delivery mechanisms and interactions of nanoparticles within complex biological systems.¹¹⁻²³ If not addressed, these challenges could significantly limit the potential of nanotechnology in improving health outcomes. For example, the transport and interactions of nanoparticles with cell layers in in-vitro studies and with subcutaneous tumors in animal studies are different from how the same nanoparticles could penetrate and diffuse in a three dimensional solid tumor within the human body with its variable composition of stromal tissue, blood vessels, tissue necrosis and cancerous cells.^{11,12} This poses challenges in extrapolating results of in-vitro and animal experiments to early human trials.²¹ Another challenge that particularly relates to cancer nanomedicine is heterogeneity of tumors and diversity in cellular expression within a particular tumor.¹⁸⁻²² Inadequate diffusion of chemotherapeutic agents into deep tumor spaces has been linked with resistance against certain anti-cancer drugs.²¹ Some have questioned the extreme reliance of many researchers on enhanced permeation and retention effect (EPR) as the passive targeting strategy to improve accumulation of chemotherapeutic agents using nanotechnology based drug delivery systems.^{15,18,19} A number of researchers have advocated for imaging studies that could preselect patients with tumors that demonstrate stronger EPR effect or use of specific biomarkers that predict the response to planned intervention but that involves higher costs in clinical trials.^{12,13} Concerns have also been raised about the efficiency with which a drug can be released from the nanocarrier into the

target cells, its penetration into tumor cells and its availability in tumor tissue for sufficient time to act before being cleared from the site.¹⁸ Some other challenges that could limit the translational potential of nanomedicines are related to regulatory pathways, and particularly to classification of products given that many of these products are multimodal hybrid structures, may contain therapeutic and diagnostic components and involve significant knowledge gaps and uncertainty regarding long term safety.^{11,14} Characterization of nanomedicines and upscaling their production for clinical trials is also challenging due to batch to batch variation and unsuitability of classical methods to test impurities.^{11, 13, 15} In this manuscript, our goal is to document various challenges in translational nanomedicine by exploring the experiences and perspectives of key stakeholders who have either conducted a FIH trial or are planning one, and to propose possible solutions. We will focus on the non-technological challenges that influence translational nanomedicine.

Methods

Qualitative research methods are employed to investigate topics where previous empirical research has been scarce.²⁴ We used semi-structured, in-depth interviews for this exploratory research project. We drew up a list of open ended questions to facilitate conversations with expert stakeholders involved in translational nanomedicine. This enabled respondents to freely narrate their experience and bring up topics, themes, and challenges that they deemed relevant. Three pilot interviews (with colleagues experienced in qualitative research and ethics of new technology) were carried out at the beginning of the project to validate and refine the interview guide, but were excluded from analysis. The research project, including the interview guide (attached in an annex), was approved by the ethics commission of Basel Land and Basel Stadt (EKBB) in January 2013.

We identified key stakeholders in translational nanomedicine through literature search and PS's participation in nanomedicine conferences such as CLINAM Basel, Swiss

Nanoscience Convention and a meeting of the European Technology Platform (ETP) - Nanomedicine. These European conferences attract key stakeholders and researchers in nanomedicine from around the globe and reflect collaborative efforts made by the EU, the US and other countries to accelerate translational research in nanomedicine. Rather than focusing on a homogeneous study population, we used purposive sampling to obtain maximum variation in views and experiences of respondents.²⁵ We contacted them either via email or in person during conferences and explained the aim of the research project, the process to be followed, and ways in which their confidentiality and anonymity would be ensured. We realized that building a relationship of trust with the respondents was crucial given that many of them were working on cutting edge research, were concerned about information they would share with us, and most importantly wanted to know how the data from the interviews would be used.

PS carried out 46 stakeholder interviews in English between October 2013 and November 2014. She obtained oral informed consent from each respondent before starting the interview. Whenever possible, she conducted interviews in person as this helped create a better rapport with respondents. She carried out 26 interviews either via telephone or Skype when it was not possible to arrange timely travel to the location of the respondents. In line with qualitative research methods, we stopped recruitment when theoretical saturation was reached. Theoretical saturation is a point in time when the research team believes that in spite of interviewing more respondents, no new themes emerge for research questions being investigated.²⁶ All interviews were transcribed in full and we sent the transcript to each respondent to check the accuracy of technical details. Together with DS, PS analyzed all interviews by creating systematic codes and sub-codes, building them further into themes that were related to particular research question. Codes and themes were discussed within the larger research and author team to improve the rigor of the qualitative data analysis. Our goal is to discuss the range of views and experiences rather than the frequency of similar views. So

instead of quantifying the results, we describe them in general terms (e.g. “a few,” “some,” “many,” “all”). For elaborating specific challenges in translational research, we chose the most comprehensive and detailed quotation from the respondents instead of providing four to five quotations from different respondents who expressed similar views or experiences. We have described the methodology of our research projects in greater details elsewhere.²⁷

Results

Our respondents were located in Switzerland, Germany, The Netherlands, Denmark, Norway, Austria, Hungary, Spain, Portugal, the United Kingdom, Israel, the United States and Canada. Their professional roles/affiliations and geographic distributions are shown in Figure 1 and Figure 2. Respondents were trained in medicine, molecular biology, biochemistry, material science, physics, toxicology, organic chemistry, pharmaceutical science, law, and ethics and had at least seven years of work experience in their respective field. Out of 21 investigators (affiliated with universities, SMEs or large pharmaceutical industries), 11 had conducted a FIH nanomedicine trial while the remaining 10 were in various stages of preclinical research. Nine out of 21 investigators were working on nanotechnology based cancer drugs, seven on immune mediated diseases and five were targeting infectious diseases. While the majority of our respondents were working with various types of liposomes (immunoliposomes, pH sensitive liposomes, thermosensitive liposomes), others had experience with gold and silver nanoparticles, super paramagnetic iron oxide particles, polymeric micelles, and SiRNA. The diversity in disciplinary background, geographic locations, and professional roles enabled us to gather views and experiences across a broad range of topics related to translational nanomedicine. To ensure anonymity of the respondents, we will use respondent numbers (e.g. R1, R2...) while describing results of this study. Nanomedicine is a small and close-knit community and detailed description of respondents in terms of their location or professional

role can reveal their identity. Though this limits extent of our analysis, we believe that this is the most practical solution for our concerns regarding anonymity of respondents.

Insert Figure 1 on professional affiliation and geographic distribution here.

Financial challenges

Academic researchers and members of small and medium size enterprises (SMEs) experienced difficulty in securing the required finances. University researchers begin their basic science research with grants but developing it further into clinical trials requires additional funds. A researcher who conducted an FIH nanomedicine trial in a university hospital without an external sponsor told us that most of his team worked on this trial in their spare time. Scaling up good manufacturing practice (GMP) production at higher dose levels for this FIH trial required 9 to 10 production cycles, each cycle requiring one complete week of work for five to six people. He stated that without any industry support, his team could not scale-up production and move further into phase II trials.

Scaling up GMP production of highly specialized nanomedicine products also requires substantial financial resources as described by a representative of a contract manufacturing organization (CMO).

.. the supply chain can be a challenge because we are working in a niche, and can't get the raw materials from 10000 different suppliers. (...) we need to get all the documents needed for GMP production such as the Bovine Spongiform Encephalitis (BSE) certificate or certificate of origin for each raw material. (...) sometimes the client does not want to invest too much money at the beginning but wants from us the highest quality. And high quality needs full traceability right from the beginning. **R27**

Another university researcher further elaborated why one needs money to conduct a trial in a public institution.

You need money to compensate volunteers, for the time they invest or the night they need to spend in the hospital (...) and you need money for insurances, because you need to cover any possible side-effects that you could cause to the volunteers. So, even if all the people involved are not requesting any payment, you need money. **R41**

Some university researchers secured more money by launching SMEs. SMEs play a crucial role in translational research but they continue to face funding challenges as well as pressure to complete trials quickly.

And for a small company like ours, time is maybe the most important thing because ...we have to show that we progress. We have limited amount of money from investors which does not last that long and before we can get more money from them we have to show that we have done something. And then we can't have two or three patients a year and then wait for five years to complete the study. That's impossible. Time is maybe the most important issue -to be able to get patients in as quickly as possible. **R34**

Several respondents mentioned that lower than expected patient recruitment prolonged trials and made them more expensive. Low recruitment was attributable to various reasons as described in the Table 1.

Insert Table1 on slow/low patient recruitment

While a large majority of nanomedicine has been developed for cancers, some respondents were working on other diseases such as arthritis, atherosclerosis, and diabetes. Unlike cancer trials, the primary and secondary endpoints for these trials are different and often require sophisticated imaging techniques within protocols, making the trials more expensive.

In cardiovascular diseases, to look at these trials, they usually include 10000 patients with general cardiovascular drugs but with nanomedicine it is not possible, it is too expensive. We want to look at vessel wall, (...) rather than looking at the morbidity or mortality. That is a real challenge. These are very technical procedures so in addition to getting approval for a trial, you also have to integrate these imaging end points. And that makes it even more complex and even more expensive. **R28**

Interviewees mentioned that many national and international funding bodies continue to heavily invest in nanotechnology and nanomedicine through collaborative funding schemes and by establishing centers of excellence. Many respondents said they benefited from these opportunities but a few questioned the 'rationale of priority setting' at the policy level and the

utility of spreading available money across many players in the field which they considered inefficient.

Researchers in large pharmaceutical industries also reported difficulties in attracting companies' attention towards their nanomedicine projects.

Companies are not investing. If they have their own product already in the market they will not invest because they don't want to take risks. And new companies are very focused on their own products. The big pharma is buying products only if it is in advanced clinical status and very promising. **R24**

Another respondent explained how the pharmaceutical industry's traditional approaches to drug development do not encourage novel approaches in therapy and cure.

In the past, the industry was prepared to produce chemicals; chemicals to kill some bacteria (...). Here in nanomedicine, we are confronted with something that is even more different. (...) We will need to rethink and produce. (...) Usually a pharmaceutical company would like to sell a product that is in a box and that has a very long shelf life. **R29**

Instead, stakeholders perceive large pharmaceutical companies to be interested in buying truly promising products developed by SMEs only after they have a strong 'proof of concept' in man. Which products developed by SMEs will gain the interest of large pharmaceutical companies and investors depends on their potential market share, competitive edge over existing products, and unmet treatment needs as shown in Table 2.

Insert Table 2 on market interest

Finally, availability of patent protection for products under investigation was mentioned as another crucial point that determines investors' interest and researchers' chances of success in procuring the necessary funding to take the product further into clinical translation, as shown in Table 3.

Table 3 Patents and IPs

Ethical challenges

Risk/benefit evaluation serves as the foundation of ethical review. Most FIH trials in nanomedicine are conducted in patients who have exhausted all other treatment options. Due to the design of these trials, patients are unlikely to receive therapeutic benefits but the data gathered is valuable in terms of knowledge gained. In early clinical trials of cutting edge medical technology such as nanomedicine, assessing risks, benefits/harms, and knowledge gain poses significant challenges.

The biggest single challenge is the problem of risk. Now in life and in all sectors of human activity, (...) we encounter risk that is in a sense calculable. And when you are working within a realm that is highly novel like gene therapy or novel stem cells approaches or nanomedicine, you are dealing with circumstances where it is very difficult to calculate the risk. And it is also unclear what the appropriate evidence to be used is, on which one can base their risk decisions. In addition it's also difficult to calculate utility, to calculate value. And it's hard to know which kind of evidence to draw on to calculate the value. So it's a realm that is ripe with arbitrary decision-making (...) And because there is no clear well-developed framework or structure for making the risk benefit decisions, one of the biggest challenges is trying to control or limit extent to which decision-making is utterly arbitrary. **R42**

Our respondents were divided on role of ethics committees in translational nanomedicine. Some had smooth interactions with ethics committees while others perceived them to be risk averse and paternalistic, thus slowing down translational research. Some of our respondents believed that ethics committees do not intentionally block translational research but their role requires them to be "cautious" and to strictly follow available guidelines to ensure human subject safety. Others criticized the tendency of ethics committees towards what they considered to be "exaggerated caution", especially when there were no treatment options for the suffering patient population; argued for meaningful patient involvement in the ethical evaluation of trials; and highlighted the need for a broad stakeholder discussion.

Long term implications of new medical technologies are often poorly understood. This in turn, possibly creates a climate erring on the side of caution. (...) there is a perception that maybe the ethical choice is to do nothing rather than to allow the proposed trial to go ahead. Whereas from a patient perspective, those living with or caring for someone with a life limiting disease (...) would like to have the opportunity to make that choice for themselves. The regulators and ethics committees tend to be cautious as they have a role in protecting patient safety. But the balance between benefit and risk needs to swing. (...) If you are dealing with people with a life limiting

disease, then they may have a different view on the amount of risk that they are willing to be exposed to in the return for the possibility of a benefit which they would value. So it is important to look at the issues from the perspective of patients as well.**R36**

Physicians interviewed in this study agreed that patients had an important role to play in translational research. But they also described their struggle to explain to patients the trial design, risks and the unlikely possibility of benefit from the trial. One of their major challenges was to provide technically correct information without completely destroying patients' hope. They often wondered if patients really fully understood the procedure and provided truly informed consent.

What I personally find a bit difficult is that you have to explain the trial to the patients. (...) patients may be hopeful that the trial is doing something good, (... but) as an investigator you (...) know chance of 10% or 20% of any benefit. (...) And you have to tell them, (...) you won't have any benefit, but you will have toxicity. I think it's quite a difficult discussion, because you don't want to take away any hope from the patients, but at the same time you have to tell them that there is a fair chance it's not going to help. **R3**

Regulatory challenges

All respondents acknowledged the critical role played by drug regulatory authorities in early clinical translation. Most of them had established contact with the authorities early on in trial planning and found it extremely useful to keep regulators "on board." They felt that the scientific advice and pre Investigational New Drug (IND) consultations with the authorities were extremely valuable for them to prepare for their trial. But they also criticized regional and national differences within and between regulatory authorities and their individual requirements, which were often quite distinct. This posed a significant challenge for researchers running multicentric international trials. Depending on local regulatory requirements, they sometimes needed to amend their protocols but then ended up with different protocols at different sites.

Respondents planning to conduct trials in developing countries reported having received less support and guidance from regulatory authorities, which they attributed to the

fact that these authorities do not have much experience with nanoparticles and formulations and take a rather precautionary stand. Researchers using nanotechnology to work on therapies for neglected diseases particularly saw this as a significant challenge.

Respondents mentioned nanocharacterization and toxicological tests as another major challenge. European researchers mentioned this problem more often than their American colleagues. European scientists working on nanoparticles reported having been required to bring the tests and assays to prove that the particles under investigation are safe, but also acknowledged the EU's efforts to strengthen nanocharacterization capacity in Europe in collaboration with Nanotechnology Characterization Laboratory (NCL) of the United States.

(...) besides GMP-production, we have to show that the typical tox-tests which are developed for chemicals and molecules, are also useful for nanoparticles and if not we have to propose to drug regulatory authorities an alternative method to check the toxicity of the particles. This is the big, big hurdle. For example, a lot of tox-tests are based on colorimetric methods and iron oxide is brown. So a lot of colorimetric methods simply do not work for our particle. **R15**

While discussing FIH nanomedicine trials conducted in Europe in early 2000, one of our respondents highlighted the distinct regulatory pathways for drugs and devices. These regulations change over the course of time and can significantly affect the progress of certain products along the translation path.

(...) they are working now 20 years in this field. And at *that time* (emphasis in original) they were able to show that their particles are a device because they inject it directly into the tumor and particles stay in the tumor. With a device, much easier! Swiss and European authorities now handle nanoparticles even for diagnostic application as a medicament. So we have to do more preclinical work with the nanoparticles even if it's a device as compared to at the *earlier time* (emphasis in original). **R11**

Another respondent raised concerns about regulatory pathways to govern follow-on versions of licensed nanomedicines and nanosimilars.

...one of issues with either the biologics, the non-biologics and clearly as well with the nanomedicine is that the approach of the regulatory agencies is similarity approach than the sameness approach. Meaning that for follow-on versions, we will never have the same but some similar products, which could lead to question- what is similar enough to get a kind of therapeutic alternatives or therapeutic equivalence allowing

even to switch between the test and reference product or even interchange them? (...) This is big challenge and contrasts the generic paradigm. (...) one has to go to clinical head to head analysis for comparability evaluation which could finally make follow-on products not a cheaper alternative. **R32**

Discussion

Slow and scarce translational research is a global concern due to its adverse impact on the availability of affordable and effective treatment options. The financial, ethical, and regulatory challenges presented in this paper have been discussed extensively in the literature on translation of other cutting edge biotechnologies such as gene transfer,⁵ cell therapy,²⁸⁻³¹ and regenerative medicine,³²⁻³³ but our study is the first to actually investigate the experience of those involved in translational nanomedicine. This allowed us to understand the tensions underlying these challenges and to seek solutions which will be relevant for medical applications of any cutting edge biotechnology.

In spite of increased national and international collaborative funding schemes, all respondents of this study, irrespective of their affiliation with the universities, SMEs or large pharmaceutical companies, perceived it challenging to procure the necessary funds to initiate a FIH trial. Though many academic researchers are successful in basic science research, they often lack the capacity, experience and insight necessary to launch FIH trials.³⁴ Personnel experienced in clinical research are often in short supply in university hospitals due to existing high workload in patient care and priority on treatment over research. Furthermore, the turnover of hospital staff can adversely affect quality standards in clinical trials. These challenges significantly affect translational research in university settings in spite of availability of interdisciplinary expertise and access to patients. In this context, it is important to find ways to motivate academic researchers to continue working in translational research and create an environment in universities which is more conducive to conducting early clinical trials. Another approach could be to strengthen the capacity of academic medical centers to undertake translational research through dedicated funding schemes and

infrastructure development. Hospital pharmacies need to be strengthened to produce needed quantities of doses under GMP conditions. A certain percentage of hospital staff could be designated for clinical research. This would require innovative funding avenues that go beyond National Science Foundation grants which have reduced significantly in both size and number in recent years due to changes in policies for public funding in education and research.³⁵⁻³⁷ Philanthropic organizations could play a financial role in strengthening the translational research capacity of university hospitals and academic medical centers.

Many university researchers have tried to overcome financial hurdles by establishing SMEs. In spite of having an increased chance of being funded by venture capitalists, SMEs struggle to procure enough funding to obtain a “proof of concept” in man. As our results show, the interest of venture capitalists in products heavily depends on their potential market share and returns on financial investment. This means that only products that can provide a good return on an investment are likely to get funded in the first place. This implies that treatment options for certain diseases or conditions that are financially lucrative are more likely to progress along the translational pathway, while treatment options for neglected and rare diseases will continue to remain on the periphery. Some universities have tried to overcome financial challenges by commercializing technology developed in-house through ‘tech transfer’ departments, but this leads to other intellectual and financial conflicts of interests³⁸⁻³⁹ when investigators and inventors become too closely involved in translation research as was the case in 1999 with the gene therapy trial for ornithine transcarbamylase deficiency.^{5, 40}

Large pharmaceutical companies are probably best placed to take on a major role in early translational research. However, as respondents of this study reported, the pharmaceutical industry seems to be rather reluctant to venture into early clinical translation of nanomedicine. Given the high uncertainty involved in novel technologies and financial stakes, they are willing to buy only promising products for which a “proof of concept” in man

has already been obtained. But it is extremely difficult for the academic researchers or SMEs to produce a “proof of concept in man” without substantial funding and technical support, thus creating a catch 22 situation. It might be worthwhile to think of ways to motivate large pharmaceutical companies to take a more facilitatory role in translational nanomedicine research.

Drug regulatory authorities undoubtedly play a major role in facilitating translational research in nanomedicine. As scientific knowledge evolves at a rapid pace they need to keep themselves up-to-date on all the technological developments in the field as well as advances in regulatory science.⁴¹ The US FDA and European Medicines Agency (EMA) differ in their definitions of nanomedicine and their requirements for the evaluation of new investigational drugs. Harmonization of regulatory procedures across different countries and jurisdictions is critical to facilitate translational research in nanomedicine.¹¹ If every national or regional drug regulatory authority has its own understanding of what constitutes a nanomedicine and what regulatory pathway such a product should follow, it becomes challenging for researchers to coordinate FIH trials in multiple jurisdictions. Some regulatory authorities might be seen as less restrictive and hence such countries can become “favorite” destinations for conducting FIH trials. It will also become more challenging to distinguish between drugs and devices as multiple technologies converge to produce medical applications; this has already occurred in regenerative medicine where nanostructures or scaffolds are used in combination with biological cells. Another challenge that lies ahead for drug regulatory authorities is the assessment of nanosimilars in comparison with the original drug produced with nanotechnology.^{11,42} Drug regulatory authorities will need to prolong and strengthen post marketing surveillance of nanomedicinal products to monitor long term toxicity profile in patients, especially for chronic diseases where patients will consume the drugs for a prolonged period. Finally, it is critical to build regulatory infrastructure in developing

countries so that they can locally assess and evaluate FIH trials for disease indications that are prevalent in their context.

It is essential to simultaneously establish strong ethical oversight to evaluate clinical research with investigational nanomedicinal products. In some countries, ethics committees only evaluate ethical aspects of FIH trails such as risk/benefit evaluation and readability of informed consent forms while in other countries, they are also expected to assess the scientific evidence upon which risk assessment is based. In both cases, it is critical that at least some members of the ethics committee are capable of critically examining the science and accuracy of preclinical evidence, and of undertaking comprehensive risk assessment in a context where uncertainty and ignorance regarding potential harms is significant.⁴³ In countries where few FIH trials in nanomedicines have already taken place, it might be worthwhile to develop national ethics oversight bodies that could assess proposals and systematically document the procedure of risk assessment as well as experience gained from these trials. That national experience and expertise could then percolate down to regional and institutional ethics committees through systematic training and knowledge transfer so that eventually such FIH trials can be evaluated in decentralized ethics committees. Data safety monitoring boards and robust reporting systems for adverse events need to be strengthened to ensure human subject safety.

Effective collaboration between pharmaceutical industry, SMEs, academics, drug regulatory authorities, ethics review committees, patient organizations, and policy makers is essential for strengthening translational research in nanomedicine.^{11,23} Professional organizations, such as CLINAM, Basel and ETP-Nanomedicine, have played a significant role in facilitating translational nanomedicine in Europe by generating multi-stakeholder debate, fostering effective collaborations within EU and globally, and actively engaging with policy makers with the aim to find solutions and speed up clinical translation.

Limitations

To the best of our knowledge, this is the first exploratory qualitative study investigating challenges in translational nanomedicine. The results of this research provide interesting insights into stakeholder experience, but generalizability is limited due to qualitative methodology and purposive sampling technique. Those who agreed to be interviewed had a certain interest in the topic and hence their views might be different than those who refused participation. Our strategic focus on Europe and North America means that we missed direct views from other countries such as China, India, Australia, and Japan. However in light of globalization we would have expected at least some remarks of our interviewees to point out huge differences in Asia and Oceania, and have therefore reasons to believe that general challenges related to translational nanomedicine in those countries are largely similar.

Our study has identified key challenges in conducting translational nanomedicine research. We have suggested some ways to overcome these challenges. Further quantitative research with a global study population is warranted to systematically document differences attributable to national regulatory environments, funding opportunities, and experience of local ethics oversight.

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Fig. 1

Fig. 2

Table1. Challenges in patient recruitment

- (...) we agreed with the ethics committee to decrease the starting dose. But in the end that caused us a delay of a year because patients were hard to find. The dose level was so low that physicians were not keen on enrolling patients at low dose. **R2**

- One of the challenges, (...) is tumor heterogeneity. (...) we are taking advantage of the overexpression of a specific protein; we have to stratify the patients who actually overexpress on their tumors, that specific protein. And (...) it requires pretty strict and specific inclusion criteria or your particle won't work. **R16**

- The main challenge was that we did not get any patients. (...) the problem is our technology can only be used in a subset of patients. And you have to have quite strict inclusion/exclusion criteria. (...) It's logistically challenging (...). You have to have clinicians; a laser and everything which people are not used to using. This differs very much from hospital to hospital and the treatment such as ours involves different times and doctors. (...) So that's the challenge maybe especially for us because we have a technology that has to involve different kinds of medical professions and they do not always work well together. **R34**

Table2. Market interest

- I suppose the issues are rather market specific. ... In some diseases, there are some really effective drugs under development, so it will be better to avoid those or your drug may not be competitive. Cost is very important. **R10**
- (...) USP means there must be a clear advantage against today's solutions. There are many possibilities why it is better. It could be cheaper, it could be quicker, it could be smaller, it could be more effective...depends! It must be in some way clearly better than what we have. **R17**
- ...(one) problem is a lack of diversity. We have people developing very similar concepts for cancer. (...) The question of portfolio management as well is very difficult given the fact that many people abide the academic freedom. (...) a relatively small number of drugs go to the market each year. If thousand people are doing drugs for cancer using the EPR effect, 999 of them won't be successful. Unless, they are having a really good idea, they should not be going in this area.**R10**
- People focus on clinical studies but it not the goal and the end goal. For example if there are already three products on market, which work perfectly OK and you bring on the fourth, that product is not going to make any sales. So you have to know how the market is and your product has to be significantly better in some parameters than the products which are out there and also the cost has to be significantly reasonable. If the cost of your drug is astronomically high, then it won't sell.**R48**

Table3. Patents and Intellectual Property (IP) rights

- IP is quite weak on this. This is not patented (...) because there are so many steps involved which are already patented, on liposomes on antibodies, on construction. (...) there are more than 3000 conflicting patents so we were not able to have a strong patent and then you don't find funding from industry or interest of the investors. **R12**
- The technology is already very complicated because it involves also the heating equipment. So lot of companies will not be fond of that especially the pharma companies. And I believe that if it is not patented it will be really difficult to get the interest of pharma companies. **R8**
- I mean patents last only for twenty years. And if you don't have a patent then you use ten years of these years, probably even more to get a patent. Patents are often filed quite early in the preclinical studies and then you use some years for developing pre-clinically and then you use a lot of years for getting it approved clinically. And there are not that many years left. **R34**

Graphical abstract

Translational research is critical to improve health care but it is time and resource intensive.

We present the challenges experienced by stakeholders involved in translational nanomedicine in Europe and North America. Financial, regulatory and ethical challenges experienced by the stakeholders are not unique to nanomedicine and will be encountered in any cutting edge biotechnology. Hence we argue for systemic solutions rather than those specific to nanotechnology such as effective collaboration and communication across different stakeholders, streamlined drug regulatory pathways, comprehensive risk assessment and ethical evaluation, meaningful patient engagement and political commitment.