Hélène Malhaire and Frédéric Lagarce*

Is the translational approach becoming a reality in nanomedicine?

The key points of the 2nd translational nanomedicine conference, Angers, August 2014

Abstract: This paper summarizes the key points discussed at the international conference held in Angers (France) on translational nanomedicine. During 3 days, more than 150 attendees presented their works and discussed through plenary sessions on how to translate to the clinics the discoveries found at lab scale. The importance of interdisciplinary works has been emphasized. New promising strategies inspired by biology were presented, such as bacteriophage associated silicon particles (BASP) in cancer therapy. Green nanotechnology, which limits the use of potentially toxic excipients to the benefit of natural compounds, is growing. Although there are various financial helps for the research and the training of next generations of researchers, the difficulties to find funding to go to the clinics has been illustrated by the squalene-conjugated nanoparticles that find no industrial support. Large-scale production of nanomedicines is also challenging to implement and pharmaceutical companies are developing new large-scale production tools to reach the patient bedside. Last but not least, regulation requirements and patenting have been forced to evolve and adapt to these particular vectors. As a conclusion, transversal collaborative research and a design of nanomedicine based on simplicity are two important levers to help these promising drugs to reach the patient.

Keywords: clinics; nanomedicine; pharmaceutical industry; translational research.

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Introduction

After a first edition held in Newark (Delaware, USA), the second international symposium in Angers (France) brought together the flagship of several disciplines namely formulation, large scale production, PK/PD, non-clinical toxicology, from academia and private companies, clinicians and regulatory bodies in order to share and work in a translational way to allow the market access for nanomedicines. Indeed, this research field leads to countless scientific papers but still too few of these new drug products reach the patient bedside. Thus, the discussion was focused on how to perform efficient translational research in nanomedicine and many questions were raised by the participants. Here are the key points highlighted during the conference.

Interdisciplinary work

To deal alone with one’s own concerns is obsolete. It is now necessary to work in an interdisciplinary manner. The European Commission and the National Institute of Health have thus encouraged the research to involve all the actors from the early stages until market access, and even during post-marketing surveillance. Other fields of knowledge might also contribute a lot. Indeed, Ruth Duncan from the European Medicines Agency has highlighted that geologists have assessed nanotoxicology through pollution impact (e.g., dust, diesel exhaust nanoparticles) on biology for years and the food industry as well as cosmetology is more and more interested by nanomaterials. However, to promote the sharing of this knowledge, the terminology should be reviewed in order to make it common. Furthermore, a clear definition of nanoparticle has to be provided.

New strategies to enhance nanomedicine efficiency

Research on cancer, the world’s top “economic killer”, has contributed a lot to the expansion of nanotechnologies.
Parasitology, endocrinology and pain have been as well pretty creative in the nanoscale field. However, this growth has crested and is now facing new issues. Indeed, regarding cancer, the mean 5-years relative survival in US for the years 2003–2009 varies between 77% with a primary tumor and only 21% with a distant form (direct extension or metastasis) (1). The global idea is now to tackle issues with new strategies and a common thinking including all expertise fields in health (i.e., chemists, physic engineers, biologists, clinicians and patients but also regulatory body). Besides, it is from the knowledge on bacteriophage, that bacteriophage associated silicon particles (BASP) and adeno associated virus and phage (AAVP) targeted phage have been developed and have shown promising results for tumor specific and selective targeting (2–4). The interest is also to develop multifunctional products like theranostic tools for an early detection, a simultaneous treatment and an efficient as well as personalized follow-up. Plus, targeting (passive, active and/or magnetic) and controlled release can limit side effects and toxicity and improve therapeutic efficiency. It was however highlighted by the participants that developing complex nanocarriers, whose production might be equally complex and not compatible with a large scale production, could impede the translation to the clinics.

In case of intracellular pharmacological target, especially in gene therapy, the drug delivery system may have to present particular features. Indeed, the pathway to this target is fraught with pitfalls from crossing the lipid bilayer to overcoming the endosome degradation and sequestration. Despite the lack of knowledge to study and understand the fate of nanomedicine after cell internalization, some techniques have already shown promising results. Photochemical internalization or specific designs of peptide have thus been proposed to oppose these difficulties and enhance the gene delivery efficiency. Scientists have also investigated the ocular administration of nanomedicines. Mucosal-penetrating particles (MPP) have thus been designed to overcome the fast clearance peculiar from the eye and have already reached phase III human clinical trial (5). These new tracks have to associate PK/PD studies in the early stages, since biodistribution is of prime importance in the “go/no go” decision process. Besides, in vitro/in vivo studies have also evolved. On one hand, 3D cell culture mimics in a more relevant manner the in vivo cell behavior and allowed a better estimation of the nanoparticle impact. On the other hand, some researchers have reservations with transplanted tumor into immunodeficient mouse models to address treatment efficiency in cancer. This could explain the lack of correlations between in vitro and in vivo or between animals and human trial. A real and spontaneous tumor that behaves similarly in human could be more relevant. Since dogs have the same diet, the same lifestyles and are likely to suffer from the same diseases as humans, they arouse a keen interest, especially in cancer research (6, 7). This is why veterinarians and their cancer patient are more and more involved. However, since cancer expression might be different from a species to another, the model has to be carefully chosen. Furthermore, double-blind evaluation has been recommended by Jean-Christophe Leroux from the institute of Pharmaceutical Sciences in Zürich to enhance the reliability of these preliminary non clinical studies performed in universities and ease the translation to the pivotal clinical trials.

Emergence of green nanotechnology

Since toxicology is one of the major drawbacks of nanomaterials for market access, green technology and natural biocompatible components are more and more investigated to replace more toxic components. In this sense, preexisting techniques of nanoparticle preparation have evolved to limit the use of organic solvents. Supercritical fluids that combined the dissolving properties of a liquid and the low surface tension of a gas, has therefore been introduced in nanoprecipitation, liposomes formation, spray-drying and emulsion-evaporation methods to give birth to supercritical assisted injection in liquid antisolvent (SAILA), supercritical antisolvent (SAS) precipitation, supercritical assisted liposome (Super Lip) formation, supercritical assisted atomization (SAA) or supercritical fluid extraction of emulsions (SFEE), respectively (8–10). The desire is also to return to nature and natural compounds such as polyphenols from tea leaves (EGCG), mangiferin from mango peel, essential oils as well as zein from corn, which have shown interesting results in stabilization, active targeting or pharmacological action (11, 12). Gold radioisotope has been used as a promising tool for imaging and personalized follow-up.

The long way from the lab bench to the patient

Squalene and terpenes have been conjugated with a drug to spontaneously form nanoparticles (13). This technology is simple and avoids the use of an organic solvent. Moreover,
the high drug loading limits the amount of excipients that enter in the organism and therefore their potential toxicity (14, 15). In spite of these advantages and although the system is ready to undergo clinical trial, funding is still missing. This highlights the gap that remains between the lab scale and the marketing. The pharmaceutical industry is not keen to invest money in risky phase I or phase II clinical trials. This issue seems more important in Europe. To access the market, the strategy is to set-up spin-off companies from the university labs. In this respect, financial aspect and intellectual property have to be considered early. Since nanomedicine is different from conventional medicine drugs, research takes longer, and the approval request as well as patenting should be different. Besides, the IP patent lawyer Tani Chen from Wolf Greenfield in Boston has highlighted that badly protected or unprotected innovations are often not commercialized because of the inability of businesses to protect and recover their investments. It is therefore of prime importance to think about how to properly fill a patent with the broadest scope possible.

**Regulatory requirements for nanotechnology**

Regulation needs also to evolve. Since research on nanotechnology goes faster than the regulation evolution, the gap between them is increasing. New questions are arising. Polymer binder has been developed as sequestering agent in gluten intolerances: this polymer is able to complex with gliadin, a component presents in wheat as well as in other cereals and responsible for degradation of the gastrointestinal tract in gluten-sensitive patients (16, 17). Nanoparticles are therefore formed in situ and thus raise many regulation concerns. Since the.neo-formed nanoparticles are expected to remain in the lumen, should it be considered as a device? Nanotechnology field is emerging and not yet well implanted on the pharmaceutical market, thus representing a significant change in landscape. Belgian medicine agency has proposed to early involve the regulatory body in order to jointly prepare the document for drug approval. The main objective of the medicine agencies is to address the benefit/risk ratio rather than the technology per se. Although good opportunities might be missed if safety prevails, the opposite might be too risky. As with research, guidelines that legislate nanotechnologies should be decided in a multidisciplinary manner. Moreover, because of this lack in regulation, “conventional” toxicological approach as described in current guidelines for medicinal products in general has been accepted until now. However, assessment methods are more and more criticized, since nanoparticles interact in a specific manner with biological supports. The French medicine agency is therefore establishing a different view for nanomaterials distinguishing (i) medical imaging, (ii) vectorization of drug substances by introduction into the body and (iii) nanomedicines administered by a topical route for a local or a systemic effect.

During a roundtable held with representatives from the French and the Belgian medicine agencies, from the European Medicines Agency Ad Hoc Advisory Committee on Nanomedicine and from Aviesan—it has been agreed that the highest priority was to address the regulation lack at a global scale rather than at national scale. Time schedule has also been criticized but is due to drafting problems. On one side, regulatory bodies want to speed up the submission but on the other side, they are committed to assure the patients safety. The Ebola crisis is a good example of this dilemma between benefits and risks: what kind of emergency can shift the balance of safety concerns? Nanobiosimilars were also discussed. Since they can be compared to existing biocompatible and better-known compound, less toxicological data are required and the submission is therefore speeded up. However, to benefit from this facilitated approval request, the nanobjects should be as close as possible to the compared nanomaterials. Liposomes and lipid nanocapsules as well as micelles and copolymeric micelles are therefore not nanosimilars.

**Production key points**

Production is progressing as well as research and regulation. Indeed, the scaling-up step remains a tricky point that can impede the market access. Big pharma have thus identified key-points that could accelerate this process such as (i) the design of a stable commercial formulation, (ii) process scale-up taken into account from the beginning of research and (iii) cGMP manufacturing in aseptic environment. Sanofi has thus presented a new platform with a physico-chemical based approach to formulation and process engineering, a process development as well as scale-up and parenteral cGMP pilot facilities. But above all, the leitmotiv “keep it simple” is the best way to access an efficient industrial development. Certainly, the simpler the drug delivery system is, the quicker the scale-up process will be and the easier the production process and the quality controls will be.
Efficient funding and grouping for Nanomedicines

Last but not least, according to Piotr Grodzinski from the National Institute of Health (USA), good research is the result of good scientific expertise and funding. The European commission has made the same observation and has include nanotechnology among the six Key Enabling Technologies (KET) identified in Europe that are strategic to address competitiveness and grand societal challenges. The new EU Framework Programme Horizon 2020, has thus been planned with emphasis on innovation and clinical studies, to master and develop the required industrial and technological base indispensable for the delivery of smart, sustainable and inclusive European growth. The intent is also to train future researchers and to build the next scientific community, which will mix efficiency, expertise and translational thinking. Moreover, partnership between public and private entities is encouraged. In France, Aviesan is therefore gathering all the actors of the health research (public labs, small and medium enterprises as well as big pharmaceutical companies) around tomorrow’s field of interest. Trans-int illustrates also this new guideline at the European scale; this FP7 European project is the result of the narrow collaboration between European academia, teaching students, and small as well as big companies. The consortium is investigating the oral administration of macromolecules such as protein, the holy grail of the pharmaceutical industry, with a new approach that starts from understanding the barrier (i.e., the intestinal epithelium) to achieve the proper design of the carrier that will overcome the low oral bioavailability. The driving forces are a better understanding on mechanisms used by the carrier to cross the epithelial barrier, the training of young researchers, knowledge dissemination and, in economic terms, the growth of existing industries as well as start-up development.

FORMAMP, also funded by the 7th Framework Programme of the European Commission, exemplifies as well the new desire for collaboration between different fields of expertise and various European countries on common objectives: (i) reduce the alarming growth of multidrug-resistant bacteria and (ii) develop sustainable treatment strategies for infectious diseases based on antimicrobial peptides. Finally, NanoFar emphasizes the educational part; this Erasmus Mundus Joint Doctorate in nanomedicine and pharmaceutical innovation is dedicated to the formation of young worldwide scientists, through a fast-growth research field, namely the nanotechnology. Multidisciplinary thinking is thus promoted by European consortiums but it is important to be careful that partners do not remain in their box!

Conclusion

As a conclusion, this is the end of the linear thinking (research>regulatory body>clinicians>patients) that leads to countless scientific papers, but too few drug products on the market (18). Since we can learn a lot from patients and clinical reality, an interdisciplinary approach at all levels could accelerate the health care benefits to the society. It was also noticed by the participants that a side effect could reveal new therapeutic opportunities as this was previously observed with sildenafil (19). Boosting the publishing of unsuccessful results might as well help in moving faster forward. Plus, some have observed that the translational mindset could be applied to lab leadership with a joint management from basics to clinical practice. Lab, clinic, regulation and manufacturing are now evolving simultaneously and in collaboration forward a common terminology and new systems to overcome low bioavailability. Last but not least, natural products and design of simple systems have replaced the prosperous era of synthesis of the previous decades. Indeed, “make it simple” (few excipients, no organic solvent with a simple and mild method that can be easily transposable to industrial production) is probably the best way to reach the market and to ensure that patients benefit of new nanomedicines. In these conditions, translational nanomedicine could become a reality.

References


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**Bionotes**

**Hélène Malhaire**

LUNAM – Université d’Angers, F-49933 Angers, France; and INSERM U1066 – Micro et Nanomédicines Biomimétiques, 4 rue Larrey, Angers, France

Hélène Malhaire studied Pharmacy at the University of Angers, France; later she specialized in pharmaceutical technology and biopharmacy at the University of Paris-Sud, France, and received her Master’s degree in 2012. After completing her industrial pharmacist degree, she joined the Mint laboratory in Angers and has been working on her PhD under the supervision of Prof. Jean-Pierre Benoît and Prof. Frédéric Lagarce since then. She is collaborating with both academic and private partners as part of the European TRANS-INT project, focusing her research on the development and the characterization of nanoparticles as a novel oral delivery system for peptides.

**Frédéric Lagarce**

LUNAM – Université d’Angers, F-49933 Angers, France; INSERM U1066 – Micro et Nanomédicines Biomimétiques, 4 rue Larrey, Angers, France; and Centre Hospitalier Universitaire Angers, Pôle Pharmaceutique, Angers Cedex, France, frederic.lagarce@univ-angers.fr

Frederic Lagarce received his PhD in 2004, and is Professor of Pharmaceutical Technology and Biopharmaceutics since 2012 at the University of Angers in France. Being also a Hospital Pharmacist, his research is translational (from bench to bedside) and focused on cancer therapy, especially on bioavailability enhancement by playing on the interactions between drug products (mainly nanosystems) and living tissues. This field involves biological barrier crossing studies but also stability assessment of the active moieties and overcoming the acquired resistances to drugs. Finding new answers to medical needs using innovative drug formulations is what drives him every day to work.