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Sound Understanding of Environmental, Health and Safety, Clinical, and Market Aspects is Imperative to Clinical Translation of Nanomedicines

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Nanotechnology has transformed materials engineering. However, despite much excitement in the scientific community, translation of nanotechnology-based developments has suffered from significant translational gaps, particularly in the field of biomedicine [1]. Of the many concepts investigated, very few have entered routine clinical application. Safety concerns and associated socioeconomic uncertainties, together with the lack of incentives for technology transfer, are undoubtedly imposing significant hurdles to effective clinical translation of potentially game-changing developments. Commercialization aspects are only rarely considered in the early stages and in many cases, the market is not identified early on in the process, hence precluding market-oriented development. However, methodologies and in-depth understanding of mechanistic processes existing in the environmental, health and safety (EHS) community could be leveraged to accelerate translation. Here, we discuss the most important stepping stones for (nano)medicine development along with a number of suggestions to facilitate future translation.

The number of new nanotechnology-enabled approaches to solve unmet medical needs is vast with numerous proof-of-concept studies completed successfully and many more under way. Many of these attempts, irrespective of how clever and effective they are, unfortunately finish with the publication of the paper, inevitably resulting in the academic pressure to return to the bench to establish preclinical proof of concept once again with an entirely new material. Most academic researchers are evaluated based on published papers and third party funding, but not on successful technology transfer. As such, it is frequently unappealing to invest time into translating research

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findings, which is excacerbated by the need for academics to step outside of their comfort zone to assume a viewpoint encompassing clinical, regulartory and market aspects.

Additionally, there is a need to develop methodologies that enable a more holistic understanding of the field, and particle biology interactions in particular, which can then be fed into risk/benefit models to evaluate whether a nanotechnology-enabled solution outperforms other approaches. The number of publications focussing on nanoparticle toxicology and side effects has risen exponentially in recent years as the result of many drivers, and not necessarily because of overt new hazards but also because of significant public research funding. While such studies should specifically focus on product-associated risks in order to bring immediate value to product development, the nanomedicine community can benefit tremendously from methods developed previously by the EHS community. Studies comparing biological effects of different nanomaterials could contribute to a more comprehensive understanding of particle interactions with biological entities, which could then be used for a safe design of nanomaterials. Over the past decades, massive amounts of data have been collected. However, the interconnections of these data points is mostly lacking, which limits holistic understanding. One reason for this is the nature of nanomaterials themselves; in contrast to small molecule drugs, they cannot be easily characterized down to atomic level. For classical small molecule drugs, the atomic connectivity is clearly defined by the International Union of Pure and Applied Chemistry (IUPAC) who have developed a universal nomenclature that allows bijective identification of a compound and thus harmonization and classification of data points. When moving to nano-drugs however, this cannot be easily accomplished and requires detailed understanding of the nanomaterials as well as the pharmacophore. Even though major advances have been achieved in the physicochemical characterization of nanostructures, we are far away from a bijective identification of nanomaterials. Batch-to-batch variability, compounded by lab-to-lab variability, are of significant magnitude and demonstration of equivalency becomes critical [2]. Standard procedures cannot be readily translated to nanomaterial evaluation due to the distinctly different physicochemical characteristics of particles as opposed to small molecules or bulk materials [3], leading to assay interference and skewed data. Hence, a modular set of sound methodologies to assess nano-drug properties and biological effects is needed.

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Appropriate physical, chemical and biological (*in vitro* and *in vivo*) characterisation requires a large panel of analytical techniques run by experienced personel. Before the establishment of the National Cancer Institute Nanotechnology Characterization Laboratory (NCI-NCL, ncl.cancer.gov) in the US in 2005, the sponsors had little choice other than to assemble a panel of experts in physicochemical characterization, sterility, microscopy, immunotoxicity, *etc*, at great effort and expense. To date, NCI-NCL is the first and by far most advanced center performing the analytical cascade required by the Food and Drug Administration (FDA) according to standards defined in cooperation with the National Institute of Standards and Technology (NIST). This facility was unique until 2015 when the European Nanomedicine Characterisation Laboratory (EU-NCL, www.euncl.eu), was founded by the European Commission under its Horizon 2020 Infrastructure programme. NCI-NCL and EU-NCL cooperate very closely to harmonize assay cascades and data comparisions. Having two large infrastructures linked by a strong transatlantic cooperation, in addition to access to GMP production facilities, constitutes an initial step towards a global open market for nanomedicines.

In addition, systems to globally analyse data along with its quality and completeness need to be established [4]. Such systems work remarkably well for areas that can be described sufficiently well by a nomenclature that is built on bijective building blocks (such as atoms in small molecule drugs, amino acid sequences in proteins or base sequences in genomic data). These building blocks and their connectivity must define the identity of the specimen in a bijective manner. This is intrinsically challenging for more complex systems, especially when they consist of multiple phases (*e.g.*, polymeric, inorganic, lipid, drug *etc*) and/or are highly susceptible to environmental changes [5, 6]. The challenge is to find a level of minimal characterisation that describes the system sufficiently well to enable retrospective confirmation and prediction of responses under different conditions, which can then be validated experimentally [7]. A landmark study by the NCI-NCL spearheaded by McNeil and colleagues has recently attempted to quantify major nanomaterial characteristics and correlate them with relative benignity. This data can then be fed into a searchable database of nanoparticle charateristics and could be of use for *ab initio* designed nanoparticles in both an EHS and nanomedicine context. This has obvious benefits for researchers developing new, engineered, nanoparticles, and may enable a “safety by design” approach where developers may learn from

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exisiting research. A number of efforts are under way to create resources for developers in the field [8]. One example of an established database is the DaNa project Knowledge Base Nanomaterials, which was founded in 2009 (www.nanoobjects.info) and provides information about the use of environmental, health and safety (EHS) data of around 25 industrially relevant nanomaterials and their recpective applications. Such databases may provide a framework for rational approaches to research and development and generation of hypotheses for further exploration, however, it is important that innovation so that an evolving diversity of materials continue to emerge.

More robust characterisation methods and databases to explore particle-biological interactions may also enable a framework to be developed for nanomaterial pharmacokinetics and distribution. Nanomaterial exposure may occur via a number of different routes (e.g. oral, parenteral, topical or inhaled) and there are different considerations for each. Notwithstanding, oral delivery of conventional small molecule drugs presents an excellent example of how molecular descriptors can be extremely useful in lead selection through the application of Lipinski's rule of 5 or its various evolutions [9]. In the past 3 decades, physiologically-based pharmacokinetic (PBPK) modelling has proliferated for conventional small molecules and is now almost routinely used in development and post-licensing environments [10]. PBPK modelling requires a thorough understanding of the precise mechanisms that underpin absorption, distribution, metabolism and elimination (ADME) as well as the necessary *in vitro* ADME tools to provide robust and translatable readouts. As such data continues to emerge, PBPK modelling may become an increasingly valuable tool in the development of nanomedicine-based formulations and will accelerate preclinical development. While such databases and modelling may aid the design of safe nanomedicines, experimental demonstration will still be imperative in the industrial development process.

Among the nanomedicine-based products which have successfully been commercialized, the majority are based on platform technologies, such as the most mature liposome technology. The other marketed nanomedicines are based on polymeric nanostructures, and on iron oxide nanoparticles [11-13]. Most recently, the field has transitioned to more exotic materials, and nanomedicines based on HfO_2 (NBTXR3, Nanobiotix) have been submitted for market approval.[12] However, the biggest hurdle in translating nanomedicines remains to be commercialization. Developing a nano-based drug

requires academics to step out their comfort zone and to take considerable financial risks, which imposes a double disincentive to entrepreneurs. Close collaboration between academia, industry, governmental institutions and the regulatory agencies, transfer of methodological know-how from the EHS community and identification of promising, developable nanomedicines is thus essential for successful future translation so that the benefits can ultimately be realised for patients.

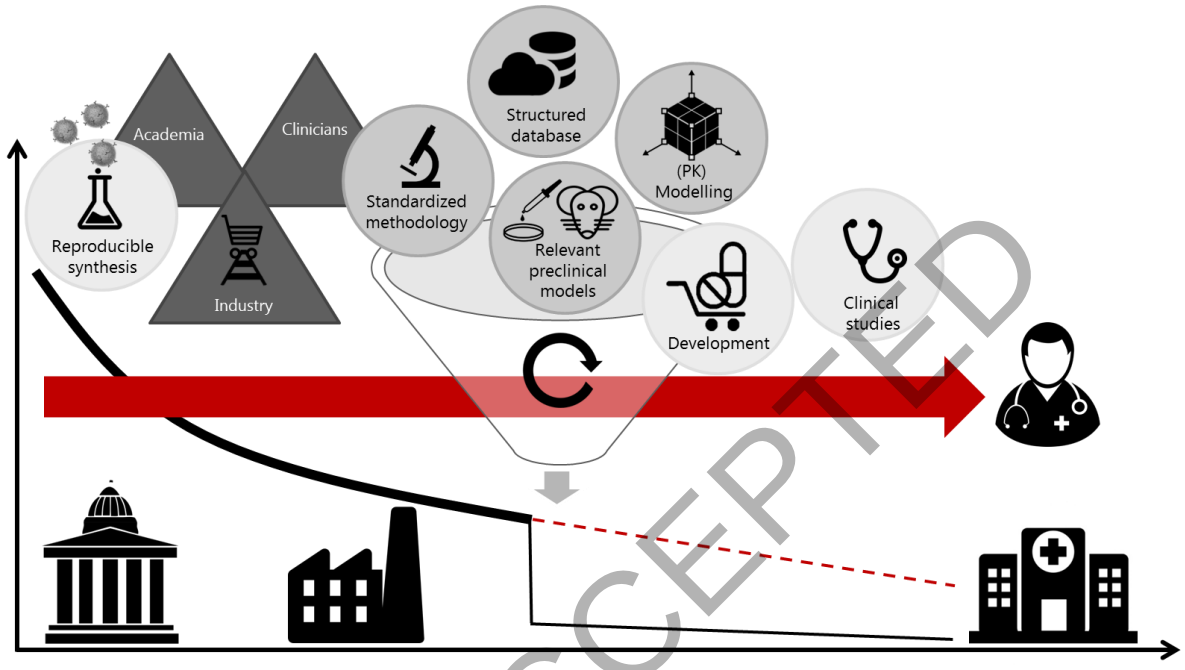

Figure 1: *Nanomedicine suffers from a significant translational gap; only very few nanomedicines are successfully translated into clinics. Standardized assay cascades adapted to nanomedicines, searchable databases in combination with modelling data for amore rational lead selection and identification of relevant preclinical models may contribute to accelerated translation. Close collaboration of academia with industry and clinical partners, and consideration of clinical, regulatory and market aspects are imperative for better translation.*

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References

1. Khorasani, A.A., J.L. Weaver, and C. Salvador-Morales *Closing the gap: accelerating the translational process in nanomedicine by proposing standardized characterization techniques*. International journal of nanomedicine, 2014. **9**, 5729-5751.
2. Rumble, J. and S. Freiman, *Describing nanomaterials: meeting the needs of diverse data communities.* Data Science Journal, 2012. **11**: p. ASMD1-ASMD6.
3. Stark, W.J., *Nanoparticles in Biological Systems.* Angewandte Chemie International Edition, 2011. **50**(6): p. 1242-1258.
4. Marchese Robinson, R.L., et al., *How should the completeness and quality of curated nanomaterial data be evaluated?* Nanoscale, 2016.
5. Robinson, J.M., M.L. Karnovsky, and M.J. Karnovsky, *Glycogen accumulation in polymorphonuclear leukocytes, and other intracellular alterations that occur during inflammation.* The Journal of Cell Biology, 1982. **95**(3): p. 933-942.
6. Murdock, R.C., et al., *Characterization of Nanomaterial Dispersion in Solution Prior to In Vitro Exposure Using Dynamic Light Scattering Technique.* Toxicological Sciences, 2008. **101**(2): p. 239-253.
7. Stefaniak, A.B., et al., *Nanoscale reference materials for environmental, health and safety measurements: needs, gaps and opportunities.* Nanotoxicology, 2013. **7**(8): p. 1325-1337.
8. Marchese Robinson, R.L., et al., *An ISA-TAB-Nano based data collection framework to support data-driven modelling of nanotoxicology.* Beilstein J Nanotechnol, 2015. **6**: p. 1978-99.
9. Lipinski, C.A., *Rule of five in 2015 and beyond: Target and ligand structural limitations, ligand chemistry structure and drug discovery project decisions.* Advanced Drug Delivery Reviews, 2016. **101**: p. 34-41.
10. Jamei, M., *Recent Advances in Development and Application of Physiologically-Based Pharmacokinetic (PBPK) Models: a Transition from Academic Curiosity to Regulatory Acceptance.* Current Pharmacology Reports, 2016. **2**(3): p. 161-169.
11. Min, Y., et al., *Clinical Translation of Nanomedicine.* Chemical Reviews, 2015. **115**(19): p. 11147-11190.
12. Svenson, S., *Clinical translation of nanomedicines.* Current Opinion in Solid State and Materials Science, 2012. **16**(6): p. 287-294.
13. Etheridge, M.L., et al., *The big picture on nanomedicine: the state of investigational and approved nanomedicine products.* Nanomedicine: Nanotechnology, Biology and Medicine, 2013. **9**(1): p. 1-14.