WG1 - DELIVERABLE D1.3

ROADMAP AND CONSENSUS PROTOCOLS FOR COST REDUCTION, YIELD OPTIMIZATION AND REPRODUCIBILITY OF THE CHEMICAL ENTITIES AND/OR RELEVANT NANOMEDICINES

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1. Identification of main common barriers for nanomedicine cost reduction, yield optimization, and chemical reproducibility

In the conceptions of roadmaps and protocols for nanomedicine cost reduction, yield optimiazione and chemical reproducility, the following points still constitute important bottlenecks:

Nomenclature, terminology and stardandization issues:

1. The lack of technical specifications, standard guidelines, best practices and specific nano-related measurements
2. The usage of different terminologies to indicate the same nanomaterial, nanoparticles and nanomedicines;
3. The absence of technical specifications issued by certified standard-setting entities (e.g., ISO, ASTM, etc.)

Commercial manufacturing and quality control:

1. The unsolved issues pertaining the separation of unwanted byproducts and/or other (e.g., biological) impurities from the final manomedicine
2. The lack of accurate mastering of nanomedicine manufacturing and control parameters
3. The impossibility of large scale current Good Manufacturing Practice (GMP) for certain nanomedicines
4. The existence of factual scalability problems concerning enhancing nanomedicine production rate to increase yield
5. The inherent impossibility of abating complexity and high fabrication costs for several nanomedicines
6. The intrinsic impossibility of reproducing nanomedicine size distribution and mass
7. The intrinsic batch-to-batch variability in the production process of nanomedicines
8. The intrinsic and/or potential instability of both the starting materials and the products

Toxicity and immunigenicity concerns:

1. Limited of *in vivo* data concerning bio/bio interactions (e.g., nanomedicines vs. biosurfaces and tissues
2. Incomplete preclinical characterization by mutliple-technique assessments
3. Limited biocompatibility and biodistribution data of nanomedicines
4. Lack of i) standards for in vitro screening platforms that provide relialbe predictions of in vivo performances, ii) data of nanomedicine/complement interactions, iii) data on cellular uptake and internalization pathways and mechanisms
5. Conflicting data issued by different agencies about toxicity effects of the same nanomedicine
6. High immunogenic reaction concerns – in particular for protein-based nanomedicines and biologics

7. Unpredictable activity and cytotoxicity of polydispersed nanomedicines
8. Unavailability of assays, tools and standardized technologies (including in silico techniques), and scaricty of clinical data to provide critical analysis and comparison of efficacy and side effects of nanomedicines
9. Limited data and reliability of ADMET detailed studies of nanomedicines

Economical issues concerning funding:

1. Perception of bad ROI of nanomedicines from investors and venture capitals
2. Long time scales from bench to bed acting as detrimental for ecomonical support of nanomedicine research
3. Novelty of subject for most of venture capitalists
4. Higher times and stakes for nanomedicines to enter the first-in-human (FIH) clinical trials (CTs)
5. Lack of important pharma investments in nanomedicines without the existence of a proof-of-concept in man; this is also connected to the lack of support by big pharma in fostering FIH CTs

Academic research:

1. Research often focused on poorly characterized and/or nonbiodegradable nanomaterials
2. Irreproducible basic and preclinical research
3. Focus on research and high impact journal publications rather than commercialization and production aspects
4. Lack of communication between basic and clinical scientists
5. Lacking of evidence of clinical validity and utility of the nanomedicine research being conducted
6. Lack of interdisciplinary-conducted research or of collaboratory spirit between industry and academy

Regulatory issues:

1. Confusion and future uncertainity due to “baby steps” undertaken by FDA/EMA and other regulatory agencies
2. Lack of technical and scientifical knowledge of governametal regulatory bodies to support risk-based regulations creating a significant regulatory void
3. National differences in regulatory requirements that pose serious challenges in international and multicentered translational aspects and trials

Other factors

1. The missing identification of key technological benefits in the early stages of the nanomedicine development and/or production

2. The availablity of limited infrastucture resources that quickly become obsolate due to the rapid advances in technology
3. The lack or the improper implementation of quality assurance (QA) guidelines for basic research
4. Thr lack of data tracing ability, including, e.g., full synthetic pathways and methodology, equipments employed, and where all relevant information/data are stored
5. Relative scarcity of workers trained in nano-based product development
6. Crisis of nanomedicine reproducibility performances due to shortcuts taken by manufacturers and researchers, contributing in irreproducibility of clinical results
7. True interdisciplinary still missing from nanomedicine translation leading to a persisting gap between the conception of new nanomedicine (bench) and regulatory clinical approval (bed)
8. Absence of researchers ability/willing to discriminate new chemical entities hits as the good the bad and the ugly
9. Lack or poor implementation of quality assurance (QA) guidelines for basic research
10. Lack of full data traceability, including equipments and conditionditions for experiment conductions and data storage.

Modern nanomedicine research is based on multiple synergistic stages, where success in targeting is not just about performance at the target site. There will be for instance loss of drug from the carrier by anticipated release or degradation, loss of the cargo/carrier complex through uptake into non-target sites, or reduced thermodynamic activity of the active principle once it is sequestered by proteins. The system may fail to reach the target in sufficient quantity, and payload release rate and the rate of diffusion of the free drug may be suboptimal to achieve therapeutic effects. It is one thing for a nanocarrier to reach a target tissue but another for its active cargo to be still bound to its vector and not lost *en route* or, conversely, bound to tightly that it is not released at the site of action. Recirculation of systems clearly provides further opportunity to engage with the target, but also prolongs the lifetime of the carrier in the circulation and, with most systems presently available, this increases the chances of drug leakage and premature drug loss if release is time-dependent, rather than triggered by some mechanism (e.g., pH variation or enzymatic reaction) close to the target.

2. Suggested procedures to possibly some major barriers at point 1

Concerning the points in the paragraph above, the following procedures could be adopted in trying to overcome the corresponding barriers:

- Create well defined classes of nanomaterials according to their chemical nature and characterization
- Develop consensus testing protocols to provide benchmarks for the creation of these classed of nanomaterials (both of synthetic and natural origin)
- Refine the current definition of nanomaterials, nanotechnology, nanodrugs, nanomedicines,

nanoscale and nanopharmaceuticals for regulatory purposes and, hence

- Create an uniform nomenclature for and/or working definition of nanomaterials
- Spend efforts in exploring and harmonize international regulatory bodies possibly involving all relevant stakeholders
- In addition to public and governamental bodies, include standard-setting organizations (ISO, ASTM, etc.) in these processes
- Create more effective and periodical international forums gathering all major public and private stakeholders for
    - A factual engagement in common policy dialogues
    - A jointed practical development/adoption of unique tools and techniques to characterize the nanoscale materials.
- Promote the broad adoption by vendors to offer only certified or validated reagents, including biological reagents, cell lines, antibodies, etc.
- Promote the utilization of such certified reagents by all principal investigators (PIS) as a documented best practice at all level of nanomedicine design and synthesis
- Ensure that all research funder policies require documented use of validated and uncontaminated reagents and annual reagent authentication throughout the entire nanomedicine production process and in time
- Ensure that procedures to document reagent validation and lack of contaminatioon are adopted by major journals
- Incentive the continue development of tools for reagents and procedures validation using e.g., genomic data
- Improve training program at the academic, clinical and industrial level to ensure that best practices are enforced in all areas – from core skills to advanced expertise
- Establish targeted training, coaching and certifications of established Pis to enforce the application of best practices along the entire nanomedicine production process (from bench to bed)
- In case of biological nanomedicines, define standard operating procedures for thier handling throughout the life cycle of the material under production
- Explore advanced manufacturing tehcnologies that enable more control over size and shape that allow using both covalent and noncovalent approaches to fabricate precisely defined nanomedicines and/or nanoscale drug delivery systems.
    - Top-down nanocolloid fabrication techniques such as photolithography and microfluidic synthesis offer a great opportunity to overcome the limitations of conventional bottom-up synthetic and/or fabrication methods
- Desing and adopt flexible and adaptive (*on demand*) manufacturing to increase market availability

- Implement the QA guidelined for basic research issued by the WHO or the RQA at every stage of nanomedicine production to safeguard data and ensure scientific rigor.