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Viewpoint

Nanomedicine toward 2040

Joseph J. Richardson and Frank Caruso*

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Nanomedicine as a research field has existed for about two decades, and it is therefore timely to discuss what the next 20 years in nanomedicine should accomplish to provide a scientifically grounded framework for sustained success. To further advance nanomedicine, emphasis should be on integration of hypothesis-driven research principles of medicine with the industrially relevant design principles of nanomaterials. The recently emerging but significantly successful field of immuno-oncology serves as an example of how fundamental research leads to translational success: mechanisms of action are first determined, followed by target molecule identification, and finally in vivo testing with appropriately designed and controlled studies.[1] From the materials science perspective, the rapid development of photovoltaics demonstrates how reproducibility is important to allow for field-wide objective comparisons to be made prior to industrial adoption.[2] The nanomedicine field could also benefit from delineating more clearly whether a study is addressing fundamental or translational questions.[3] Both should be encouraged, but focused, rigorous, and reproducible study designs are essential to facilitate scientific advances as well as comparative studies aimed at commercial outcomes.

REPRODUCIBILITY AND COMPARABILITY

Hypothesis-driven fundamental nanomedicine research needs to be reproducible to underpin translational outcomes. Standards within the field of nanomedicine have been proposed to improve documentation and experimental protocols to ensure reproducibility.[4,5] Improved reproducibility has the benefit of allowing researchers to build upon and compare against previously published studies, which is key to uncovering design principles and fundamental mechanisms in nanomedicine. This also has theoretical implications for facilitating the adoption of machine learning to guide research and predict outcomes.

Moreover, it is important for nanomedicine studies to be compared to the literature, which not only requires standards in reporting but also requires appropriate controls, including current clinical best practice. Elucidating which variables are most important for accurately comparing nanomedicine studies is essential for translational success, and identifying these should be an ongoing discussion for the nanomedicine research community. This will entail discussions around whether parameters, such as half-life, binding affinity, uptake, and endosomal escape efficiency, have predictive power for translation, while simultaneously searching for other ways to analyze and compare data for meaningful discoveries.

Reproducibility and comparison frameworks for other nanomaterial fields, such as batteries, membranes, and photovoltaics, and the real-world translation of these materials offer a glimpse of what nanomedicine can accomplish in the next 20 years.

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NECESSARY ATTRIBUTES FOR CLINICAL APPROVAL

Because nanomedicine has clear translational goals, i.e., FDA approval (or comparable), there are defined attributes that nanomedicines need to exhibit before they can be considered for approval. In terms of design principles relevant for nanomedicine researchers, the production process needs to be amenable to good manufacturing practice (GMP) and good laboratory practice (GLP), which means that the process should not only be reproducible but also be at least theoretically scalable.[6] Related to this, the production needs to be economically viable to the extent that the cost of clinical trials and manufacturing can actually be recovered.[7] The recent explosion in relatively expensive-to-manufacture biologics[8] suggests that the cost of goods is not an insurmountable hurdle, although the lack of abundance of the precursor materials could prove a bottleneck for some inorganic or hybrid nanomedicines.

Finally, nanomedicines should be chemically defined for both scientific and regulatory reasons, which in addition to

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their scalable and economic nature helps explain why approved therapeutic nanoparticles are dominated by liposomal systems.[9] From a scientific standpoint, having a chemically defined entity makes reproducibility relatively easier and allows for iteration and elucidation of the underlying science. Similarly, chemically defined materials facilitate the approval necessary to begin clinical studies. Collectively, these requirements suggest that more focus should be placed on relatively simple, safe, and economical building blocks for translational nanomedicine research until clearer design principles are uncovered through hypothesis-driven fundamental research.

MOVING FORWARD

As nanomedicine adopts a more rigorous approach to documentation (i.e., standards), a massive amount of analyzable data should be captured by the field as a whole. This in turn will allow for artificial intelligence and machine learning to identify trends in the data and predict which fundamental nano−bio interactions may be important in facilitating translation, which in turn can feed back into studies on the nanomedicine mechanisms of action. "Big Data" approaches are being seen in the pharmaceutical sector and are also finding application in the basic design of new materials for energy and environmental applications.[10] Therefore, some of the groundwork from the data science side has already been laid but the need for the generation of robust data remains. One technology that is facilitating the capture of useful and benchmarked data is high-throughput robotic screening. In other fields, synthesis and characterization can be performed in an automated fashion with hundreds to thousands of unique materials/molecules generated.[11] Although significant effort will be needed to design and optimize robotic systems for nanomedicine, the payoffs of such systems are expected to be immense, both scientifically and industrially.

Finally, while the last 20 years of nanomedicine has, to a large extent, been underpinned by materials design, it is likely that the next 20 years will see research driven more by clinical needs. The consensus is growing that translational studies should have a clear target indication, which requires expert input from clinicians. Often a vast amount of biomedical knowledge is required to understand how a specific disease could be realistically treated in the clinic, and we therefore believe that clinically directed research will increase in focus and scale. This will provide materials scientists with a mandate to design and assemble materials that meet clinical needs—a challenge that the field of nanotechnology, through its elaborate assembly and processing tools, is well positioned to address.

AUTHOR INFORMATION

Corresponding Author

Frank Caruso − *ARC Centre of Excellence in Convergent Bio-Nano Science and Technology, Department of Chemical Engineering, The University of Melbourne, Parkville, Victoria 3010, Australia;* orcid.org/0000-0002-0197-497X; Email: fcaruso@unimelb.edu.au

Author

Joseph J. Richardson − *ARC Centre of Excellence in Convergent Bio-Nano Science and Technology, Department of Chemical Engineering, The University of Melbourne, Parkville, Victoria 3010, Australia*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.nanolett.0c00620

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