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Editorial: Nanomedicine – From bench to bedside

The current special issue on nanomedicine, which serves as a 10-year follow-up to the previous special issue in the same journal [1], is based on the Else Kröner-Fresenius Symposium on *Nanomedicine: From Bench to Bedside* held in Erlangen, Germany on October 7-9, 2024. Much has happened in the field of nanomedicine in the past decade [2]. This includes the recent introduction of messenger RNA (mRNA)-based vaccines against SARS-CoV-2, a milestone for mRNA therapeutics as well as for nanomedicine [3]. However, the field of nanomedicine, specifically, the translation of nanomedicines from the bench to the bedside, is not without its challenges. Indeed, nanomedicines, unlike traditional small molecules, are complex structures with features that are tunable and, therefore, in principle, exploitable [4]. However, this also poses several challenges related to batch-to-batch variability and manufacturing scalability. Hence, as pointed out in a recent perspective by leaders in the field, "close collaboration between academic researchers, industry partners, and regulatory agencies will be essential to facilitate the translation of structural nanomedicines from the bench to the bedside" [5].

Prof. Moungi Bawendi at Massachusetts Institute of Technology (MIT), a pioneer in the field of semiconductor nanocrystals (aka quantum dots), delivered the keynote lecture at the Else Kröner-Fresenius Symposium on Nanomedicine (Fig. 1). Bawendi [6] contributed a perspective on superparamagnetic iron oxide nanoparticles (SPIONs) to the current special issue, specifically, on zwitterionic dopamine sulfonate (ZDS)-coated SPIONs [7] as magnetic resonance imaging (MRI) agents with 'theranostic' properties (particles with therapeutic as well as diagnostic or imaging capabilities rolled into one).

Fig. 1. Prof. Moungi Bawendi, co-recipient of the Nobel Prize in Chemistry in 2023, speaking at the Else Kröner-Fresenius Symposium in Erlangen, Germany (October 2024). Photo: SEON.

Wegner and co-workers [8] at Fraunhofer Research Institution for Individualized and Cell-Based Medical Engineering (IMTE) in Lübeck provided a comprehensive review of 20 years of magnetic particle imaging (MPI) for capturing and localizing the signal of magnetic particles inside the body. During the past two decades, MPI has evolved into a well-established preclinical modality poised for translation into the clinical setting.

Joner and co-workers [9] at Technical University Munich discussed translational prospects of cardiovascular nanomedicine including advanced imaging techniques such as near-infrared fluorescence (NIRF) operating in tandem with intravascular ultrasound (IVUS) for the visualization of macrophage-rich and rupture-prone plaques in atherosclerosis. Alexiou and co-workers [10], University Hospital Erlangen, described the regulatory requirements for GMP-compliant production of iron oxide nanoparticles, focusing on a representative case study. Alexiou and co-workers [11], University Hospital Erlangen, also discussed next-generation microbial diagnostics based on magnetic iron oxide nanoparticles including the so-called critical offset magnetic particle spectroscopy (COMPASS) approach for rapid, point-of-care diagnostics [12]. Janko and co-workers [13], University Hospital Erlangen, demonstrated how SPIONs enable magnetic field-guided accumulation of chimeric antigen receptor (CAR)-T cells at tumor sites while also allowing for non-invasive tracking by MRI. Lyer and co-workers [14], University Hospital Erlangen, provided a panorama on micro- and nanobots and the implementation of artificial intelligence (AI) for a variety of biomedical applications.

The enhanced permeability and retention (EPR) effect is a classic concept in nanomedicine according to which macromolecules or particles of a certain size passively accumulate in solid tumors due to leaky blood vessels and poor lymphatic drainage. However, the animal tumor models used to study the EPR effect differ from tumors in patients, and the EPR effect is currently subject to reevaluation [15]. Kiessling and co-workers [16] at Aachen University argued that patient stratification is required to leverage the EPR effect, and they proposed that the accumulation of drugs can be improved by simultaneously targeting biological barriers in tumors. Qin and co-workers [17] at the Chinese Academy of Sciences (CAS) argued that the enhanced transcytosis and retention (ETR) effect is complementary to the EPR effect. The ETR effect implies a transcellular mode of transport that does not depend on vascular leakiness. The authors also highlighted the application of computational chemistry (modeling) tools for the prediction of tumor access mechanisms of nanocarriers [17].

The main route of entry of nanoparticles into the cell is *via*

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endocytosis [18]. Boccaccini and co-workers [19] at the University of Erlangen-Nuremberg provided a survey of recent studies on the cellular internalization of silica nanoparticles as well as their subsequent intracellular trafficking. RNA molecules display different mechanisms of action compared to conventional therapeutic approaches. However, both the carrier and the cargo (RNA) should be carefully considered. Aigner [20], University of Leipzig, discussed various classes of RNA molecules as drug candidates in oncology, including RNAs mediating loss-of-function, gain-of-function, or modulation of gene expression, along with various classes of nanocarriers (lipidic, polymeric, inorganic) available for RNA formulation. Lehr and co-workers [21], Saarland University, focused on mRNA delivery systems beyond conventional lipid nanoparticles including novel lipid formulations and hybrid (e.g., lipid-polymer) delivery systems for mRNA therapeutics.

Nanomaterials are not only drug carriers; the materials themselves may elicit biological effects. These 'ancillary' effects could give rise to unwanted adverse outcomes; conversely, if understood, these properties could also be exploited for therapeutic gain [22]. Nanotoxicology is tasked with understanding (describing and predicting) the potential adverse effects of nanomaterials and other advanced materials with respect to human health and the environment [23]. Machine learning (ML) has emerged as a powerful tool to improve toxicity predictions, and recent efforts have shown how ML can be applied in the development of safer and more effective nanomedicines [24,25].

Dobrovolskaia [26] at the Nanotechnology Characterization Laboratory (NCL) provided a perspective on immunotoxicological testing of nanomedicines, and cautioned that no ideal method or assay exists; instead, using orthogonal techniques to verify results and combining conventional and new techniques for immunotoxicity testing is required in order to ensure patient safety. Fadeel and co-workers [27], Karolinska Institutet, discussed biodegradation of nanomaterials and advanced materials by immune-competent cells and the environment. Degradation and/or excretion (clearance) of nanomaterials are key parameters for the safe and effective use of nanomedicines. Jaklenec and co-workers [28], Massachusetts Institute of Technology (MIT), addressed equitable access to medicines and vaccines and how next-generation delivery technologies such as microneedle array patches can overcome the current challenges.

Liang and co-workers [29], Chinese Academy of Sciences (CAS), summarized recent advances in nanopharmaceutical cancer therapy including theranostic nanomedicines, biomimetic nanomedicines, catalytic nanoparticles (nanozymes), nanovaccines, etc. Taken together, these emerging innovations are set to revolutionize precision oncology.

Overall, despite these remarkable developments, barriers to clinical translation remain. Recently, a group of industry, regulatory and clinical experts proposed a set of principles to guide the clinical translation of nanomedicines [30]. The DELIVER framework considers experimental, manufacturing, clinical, regulatory and business issues, but the need for continued fundamental research was also emphasized [30]. We do agree that the successful translation of nanomedicines requires a dialogue between stakeholders, similar to the one we witnessed at the symposium in Erlangen.

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