doi:10.2533/chimia.2022.236 Chimia 76 (2022) 236–241

Tailoring Design of Nanomaterials and Systems to Individualize Patient Treatments

Marija Buljan* and Peter Wick

Abstract: Nanomedicine encompasses usage of materials smaller than 100 nm for diagnosis, monitoring and treatment of disease. A frequent application of these materials is in reformulation of active drugs, which were previously approved for clinical use. As illustrated with chemotherapeutics, delivery of a drug within a nanocarrier can represent a clear clinical benefit as it can increase its targeted uptake and reduce the off-target toxicities. Matching nanomedicine treatments with patient-specific biomarkers provides an exciting prospect for moving the field towards precision medicine. In parallel, a strong potential for personalized treatments comes from employing nanomaterials for the delivery of patient-tailored biologically active molecules. Recent research and clinical data have highlighted mRNA and siRNA molecules, as well as short peptides, as powerful new drug classes that can be designed according to patient profiles and effectively delivered within nanoparticles. Particles used for therapeutic delivery are based on biodegradable and safe materials, frequently lipids and polymers, which can be further functionalized into more complex forms. Currently, there is a strong interest in developing specific nanocarrier formulations which can achieve optimal delivery of active molecules to targeted cells while reducing unwanted side-effects. Here, we discuss recent developments and future perspectives in the nanomedicine field and specifically highlight innovative approaches for the personalized patient treatments.

Keywords: Cancer immunotherapy · mRNA therapeutics · Nanocarriers · Nanomedicine · siRNA therapeutics

Dr. Marija Buljan leads the group 'Multi-omics for healthcare materials' at Empa. Previous to this, she worked as a researcher at the ETH Zurich, DKFZ Heidelberg and MRC LMB Cambridge. She has a degree in Computational biology from the University of Cambridge, which she obtained at the Sanger Institute. Her group is using modern omics technologies and advanced data analytics to inform the design of new materials for precise immunoengineering applications. Dr. Buljan is an associated group leader at the Swiss Institute of Bioinformatics and a member of the national advisory board for the Swiss Personalized Health Network.

Dr. Peter Wick heads the research laboratory for Particles-Biology Interactions at the Federal Laboratories on Materials Science and Technologies Empa in St. Gallen since 2010. He got his PhD degree in 2002 at the University of Fribourg, Switzerland. His general research interest is to study the interactions of nanomaterials with human barrier tissue *in vitro* and *ex vivo* with the purpose to obtain detailed mechanistic understanding about their uptake, accumulation, biotransformation, transport and effects. He is member of the EDQM working group for NBCs, member of the Swiss National COVID-19 Science Task Force and coordinator of the Swiss National Contactpointnano.ch.

*Correspondence: Dr. M. Buljan, E-mail: marija.buljan@empa.ch
Empa - Swiss Federal Laboratories for Materials Science and Technology, CH-9014 St. Gallen

1. Nanomaterials and Precision Medicine

The use of materials in medical treatments, such as in joint replacements or trauma surgery, has had a pivotal role in improving the independency and overall life quality of patients with different conditions. Down-sizing the material at the nanoscale level implies the design and synthesis of components that are at the same scale as cellular constituents, and interactions of these materials with living cells create new possibilities for innovation. In parallel, the concept of personalized- or precision medicine has been moving from medical research to the clinical routine. Approaches which optimize the right drug and right dose for the patient administered at the right time, are slowly being appreciated as a necessary replacement of 'one-size-fits-all' strategies. For their practical implementation, it will be instrumental to take into account the patient's-omic fingerprints as well as the patient's health history. This will enable stratification of patients in 'similar' subgroups for which the treatments will have an increased efficacy and reduced side effects. Sequencing technologies and novel developments in bioinformatics, together with advances in multiscale- and multilayer data integration, will create a novel quality of medical care. Combining material research and development with the possibilities of precision medicine will leverage nanomaterials and systems to the next level. In this perspective, we aim to explore the interplay between material developments and personalized medicine and discuss how future nanomedicine can help to address clinical needs and individualize patient treatments.

2. Nanomedicines: From Drug Delivery to Vaccines

Nanomedicine encompasses usage of nanomaterials, *i.e.* particles typically smaller than 100 nm, for diagnosis, monitoring or treatment of disease.[1] Most frequently, its applications are in bioimaging and drug delivery. As a drug class, nanomedicines, among others, include polymer-based nanoparticles (NPs), inorganic NPs, and diverse lipid-based carriers. In particular, lipid-based

formulations represent a dominant class among the nanomedicines approved for clinical use, a category that so far comprises around 50 drug products in total.[2] The majority of the approved drugs relate to reformulations of active pharmaceutical ingredients, which were previously approved as standalone therapeutics. However, delivery of these drugs within a nanomedicine formulation was able to improve their pharmacokinetics and safety, or it enabled more convenient or less frequent drug administration. When it comes to cancer nanomedicines, the dominant class of approved drugs is again represented by liposomal formulations of small-molecule chemotherapies, which reduce the drugs' off-target toxicities. To improve *in vivo* applications, surfaces of the formulated liposomes, but also surfaces of polymeric NPs, are often coated with polyethylene glycol (PEG), a hydrophilic polymer which improves a particle's stability and systemic circulation time, while in parallel decreasing its immunogenicity and aggregation, as well as decreasing its phagocytosis by the circulating and tissue resident immune cells.[3] PEG can be attached to the surface through cleavable linkers so that the NPs can stay PEGylated in the circulation, but lose this protective polymer shell upon the changes in pH or upon specific enzymatic activities.[3] For instance, in the case of cancer drugs the latter can be triggered with a low pH associated with the acidic tumor microenvironment or through the activity of metalloproteases that are often secreted by tumors for the remodeling of extracellular matrix.[4] Of note, other polymers may also be applied for coating, but PEG is currently most commonly used due to being regarded as safe and due to the previous clinical approval of a variety of PEGylated NP drugs.[5]

In addition to lipid-based NPs, biodegradable polymers are another choice of materials for nanocarriers and for an effective delivery of small drugs, peptides and nucleic acids. The polymers can be synthetic, such as poly lactic-co-glycolic acid (PLGA), poly DL-lactic acid (PLA), poly glycolic acid (PGA) or poly β-amino esters (PBAE)s, or they can originate from natural materials, like chitosan or gelatin.[6] What matters is that neither the biodegradable polymers nor their degradation products cause toxicity, but instead, the polymers can be naturally degraded and their products safely processed in the body. The advantages of these polymers are that (i) they are stable in the circulation system; (ii) they are not strongly immunogenic and (iii) they are often able to avoid phagocytic clearance. For instance, PLGA has been approved by the Food and Drug Administration already 30 years ago for medical applications. PLGA is a copolymer of hydrophobic polylactic acid (PLA) and hydrophilic polyglycolic acid (PGA).[7] The ratio of PLA to PLGA regulates the degradation rate of PLGA, a property which can be used to control the release of incorporated drugs.[6,8] In addition, its surface can be easily modified to incorporate a targeting ligand. This, together with a low immunogenicity and biodegradability, make PLGA an attractive material for different drug delivery applications. However, there are only a relatively few approved delivery therapeutics based on PLGA. This is explained with the fact that acidic PLGA monomers are not suitable carriers for many drugs and bioactive molecules, as well as with non-trivial challenges in controlling the drug release.[6]

Mechanisms for the cellular uptake of NPs depend both on a particle's physicochemical properties as well as cell characteristics. The uptake can be broadly categorized as (i) endocytosis-based, which is a more frequent route and includes clathrin and caveolin-mediated endocytosis, as well as phagocytosis, and (ii) direct cellular entry, which includes a direct translocation of smaller particles across the cell's membrane as well as lipid fusion followed by a cargo unload.[9] Importantly, through the modification of an NP's surface and addition of targeting ligands, the uptake by the specific, targeted cells can be strongly increased. The ligands can be specific molecules that bind to receptors or other proteins expressed on the cells of interest, such as monoclonal antibodies and antibody fragments, peptides or antibody mimics, but also other molecules, such as mannose sugars, which are frequently added to the particles that should be recognized by mannose receptors on macrophages or dendritic cells.[10] Building on the concepts successfully introduced in the field of antibody-drug conjugates, nanotechnology studies have shown that it is also possible to modify the surface of NPs and conjugate antibodies specific for antigens expressed on tumor cells. In this way, after the particle has been recognized, its cargo, which can be cytotoxic, is delivered more specifically to targeted tumor cells. A pertinent example is a delivery of cytotoxic microtubule inhibitors conjugated to the Her2 antibody. This antibody-drug conjugate is specifically designed for a delivery to breast cancer cells which highly express the Her2 receptor, but which have become resistant to the antibody treatment alone.[5] This example also illustrates the next important road in the development of nanomedicines: tailoring the treatments to specific patient profiles (Fig. 1). In addition to the above-mentioned design of particles that target antigens specifically present on the disease cells of individual patients, another major promise for personalized nanomedicine comes from a better definition of biomarkers relevant for predicting a patient's response to treatments and hence more rational applications of nanomedicines to the stratified patient populations.[2,11] Furthermore, building on the recent success of vaccine nanomedicines that showed huge advantages during Covid pandemics,[5] a prospect for personalized cancer vaccines is receiving increased attention (Fig. 2).

Cancer vaccines aim to immunize the patient by using information on their individual tumor mutations. The rationale of this approach is that by training the immune system with peptides, which are specifically exposed on tumor cells, it is possible to elicit a stronger immune response to the tumor. Preclinical data and first clinical trials of personalized cancer vaccines have indicated safety and feasibility of this approach and confirmed its immunotherapeutic activity.[12] Since the effective and immunogenic vaccines, both cancer and traditional ones, often encompass heterogeneous cargo with different physiochemical properties and biodistributions, co-encapsulation of individual components in polymer particles or lipid carriers represents a practical administration route and it highlights an important application for biomaterials.[12] In addition to vaccines, there is a high potential of using biomaterials as carriers for different siRNA and mRNA drugs, which are starting to emerge as effective and promising disease treatments. Furthermore, several recent studies have highlighted the value of nanomedicine approaches for cancer immunotherapy treatments, either by engaging the immune system directly through antigen presentation[10b] or by modifying tumor microenvironment composition.[10a,11] Of note, approved nanomedicines also include particles whose treatment activity does not come from the cargo, but from the material properties themselves, such as hafnium oxide NPs that enhance the response to radiotherapy.[13]

3. Innovations in Active Molecules for Nanomedicine Strategies

Traditionally, active pharmaceutical ingredients that could be reformulated and delivered within NPs encompassed small drugs, peptides and proteins. Since few years, the long-discussed use of small interfering RNAs (siRNAs) for gene silencing and mRNAs for gene delivery has started demonstrating first successful clinical applications and has raised a broad interest within the biomedical community. Even though siRNAs have been considered as a highly attractive and easily adaptable tool for gene silencing since their discovery, the fact that these molecules are not stable, together with their immunogenicity and an ability to elicit a variety of off target effects, has represented a major application drawback. Moreover, for the majority of conditions, their effec-

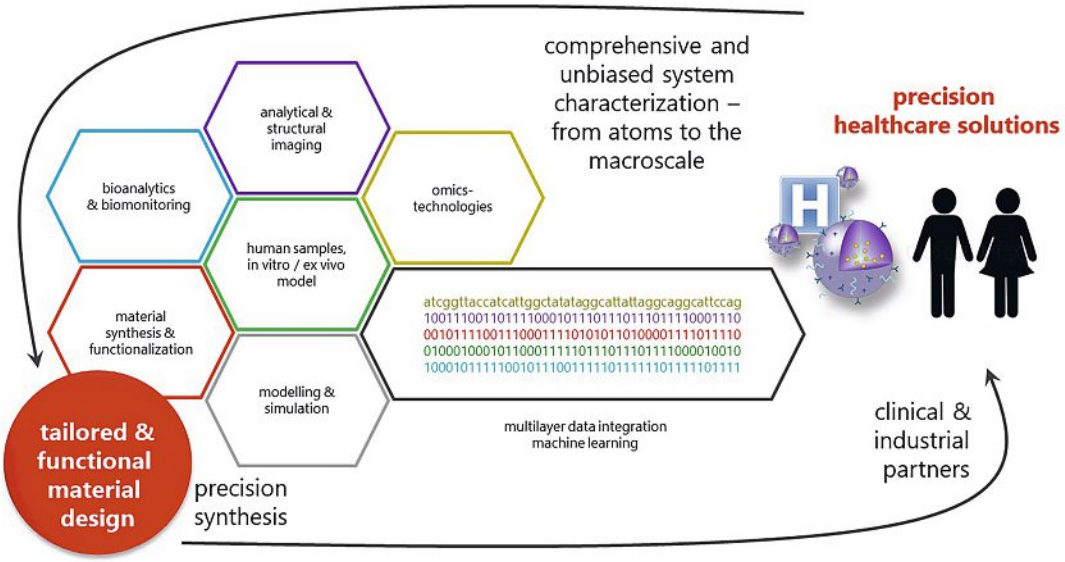

Fig. 1. Tailoring nanomaterial design for individual patient's treatment needs the orchestration of seven pillars indicated here as hexagons, whereas '-omics' technologies, multilayer data integration and machine learning are new boosters.

tive delivery to targeted cells represents an important challenge. Not surprisingly, the major potential for the siRNA application comes from using NPs as their delivery systems. The first siRNA therapeutic Patisiran (Onpattro) is based on an NP and it was approved in 2018 for the treatment of the hereditary transthyretin amyloidosis.[14] Patisiran uses a lipid-base formulation to pack an siRNA that downregulates the mRNA encoding the transthyretin protein, which is abundant in liver. The drug's success in patient treatments has partly also reflected the fact that the used lipid NPs preferentially accumulate in liver.[14] Importantly, Patisiran's approval has encouraged other efforts that are aiming to use siRNA not only for the treatment of different liver diseases[15] and liver cancer, but also for the treatment of cancer in general[16] as well as other conditions, spanning from inflammatory conditions to diseases of the central nervous system.[17] For the latter, the treatments have largely been designed around a local delivery of NPs,[17] mostly through spinal cord injections.[17] Furthermore, conditions that allow for drug topical applications, such as skin, eye and pulmonary diseases[17] are also of a strong interest for NP-based drug delivery. The currently ongoing studies are in parallel interrogating the optimal siRNA targets as well as most effective delivery mechanisms. This is nicely illustrated with a recent work on siRNA nanocarriers designed for triple negative breast cancer.[16] The interdisciplinary approach applied there first used computational analyses and identified POLR2A as an essential gene that, due to its co-deletion with PT53, was estimated to be hemizygous in nearly half of the patients. To deliver the siRNA targeting POLR2A, the authors designed an NP in which the shell was composed of the PLGA polymer and dipalmitoylphosphatidylcholine phospholipid, whereas the core, together with siRNA, contained a modified chitosan that bound CO_2. The particle was pH-sensitive: the lower pH, typical for endosomes and lysosomes, was able to activate the release of CO_2 from chitosan, which then caused NP ruptures, triggered endosomal escape, and increased siRNA release in the cytoplasm. In this way, the siRNA bioavailability could be improved and endo/lysosomal degradation avoided, which resulted in significantly slower tumor growth in mice treated with the NP.[16]

A further specificity in the delivery of nucleotide cargo can be achieved by active targeting through surface modifications with specific ligands or through modulation of NP composition. Prominent examples for the former include antibodies, peptides, and molecules that target tumor or cell-type specific receptors, such as folic acid that targets folate receptors overexpressed on different tumor types. The effect of the NP composition on the delivery is illustrated with biodistributions of different lipid NPs. For instance, NPs with ionizable lipids typically form a protein corona in the bloodstream. One of the proteins in the corona, ApoE, is known to bind to receptors overexpressed on hepatocytes, which further increases liver uptake of these NPs.[17] Therefore, when the NPs should be delivered to the liver, formation of protein corona can be beneficial, and only a small amount of PEG modification can be applied. However, for the targeting to other organs and cell types, increased PEG fraction and active targeting are more likely to increase the NP uptake. Of note, even though initial development of lipid NPs focused on cationic lipids, which can encapsulate negatively charged RNAs, ionizable lipids that are positively charged only at acidic pH showed a higher transfection efficacy, reduced toxicity and a high competency for endosomal escape.[18]

Recent fast developments of mRNAs vaccines against SARS-CoV-2 were partially possible due to the decades of nanotechnology research in the field of NP delivery systems. In general, many of the nanocarriers which were initially developed for siRNA can also be utilized for an mRNA delivery. However, these applications often ask for optimizations in the particle compositions. In some instances, changes in formulations that increase mRNA expression do not necessarily effect efficiency of siRNA silencing.[17] Even though lipid NPs dominate also as mRNA delivery systems, cationic polymers have also been widely used for it. The latter include poly(L-lysine), DEAE-dextran, PBAE and chitosan. Complexes formed between these polymers and nucleic acids can be based on electrostatic interactions and produced through self-assembly. In addition to the simple formulations, co-formulations of different polymers as well as lipid-polymer hybrid NPs, which integrate the complementary properties of lipid and polymeric nanomaterials, are often used.[19] For instance, lipid conjugated PBAEs and poly(glycoamidoamine) were applied for a simultaneous delivery of mRNA and siRNA molecules.[20]

In addition to modifications in nanocarrier compositions, introduction of mRNA therapeutics also asks for specific mRNA modulations that are needed for its effective translation with the cell's machinery. The aim of these changes is to ensure optimization of the mRNA's translational efficiency and to improve the

molecule's intracellular stability, as well as to reduce its immunogenicity. This is mainly achieved through modifications of the mRNA's structural elements: 5' cap, 5'- and 3'-UTRs and poly(A) tail, as well as an optimized codon usage.[21] Delivery of mRNA therapeutics is facing similar limitations as siRNA delivery, as after an intravenous injection, most accessible target cells are those in the liver, in the blood or in the reticuloendothelial system of the spleen, bone marrow and lymph nodes.[21] However, there is ongoing research into the mechanisms for overcoming this and achieving more targeted delivery of mRNAs to specific organs and cell types. Overall, the overarching goal of the ongoing studies has been to capitalize on the potential of mRNAs to be used for the protein replacement and supplement therapies which, among others, can be applied for oncology, cardiology, endocrinology, as well as for pulmonary diseases.[17,21] Different studies have used nanomaterials for the delivery of therapeutic mRNAs: for instance, hyperbranched PBAEs were successfully used in preclinical models for mRNA delivery to the lungs by inhalation[20] and PBAE/PEG–lipid NPs were capable of assisting mRNA delivery to the lungs after intravenous administration in mice.[22] Nevertheless, till now, the major clinical progress in the application of mRNA-based therapies has been in their use as vaccines for infectious diseases and cancer immunotherapies. With regard to cancer immunotherapies, mRNAs synthesized from patient-specific mutation profiles and applied as vaccines in clinical trials were able to strongly enhance T cell immune response to tumors.[23] Results of these clinical trials have shown that personalized cancer vaccines were able to achieve a sustained progression-free survival, thus suggesting they could represent a path to patient-tailored immunotherapies.

In addition to lipid NPs and polymers, other materials, including mesoporous silica, carbon nanotubes and graphene oxide are being explored as potential nanocarriers.[24] Furthermore, due to the high biocompatibility, a special attention has been given to exosomes.[25] Exosomes are vesicles released from cells, which naturally have a role as nucleic acids and protein carriers, and are therefore expected to represent safe and efficient delivery vehicles.[26] However, their uniformed synthesis still represents a formidable challenge. In general, delivery of nucleic acids, both siRNA and mRNA, *via* NPs represents an unprecedented opportunity for precise and personalized medicine applications (Fig. 2); one can deliver nucleic acids targeting different genes at the same time, it is possible to target patient-specific defects, such as missing proteins (with mRNA) or target gene copies with disease mutations, alternative splicing isoforms or fusion transcripts (with siRNA), as well as so far undruggable genes and pathways (using both mRNA and siRNA drugs). Finally, in the future, delivery of gene editing therapeutics[27] is likely to also benefit from the expected advancements in nanotechnology (Fig. 2).

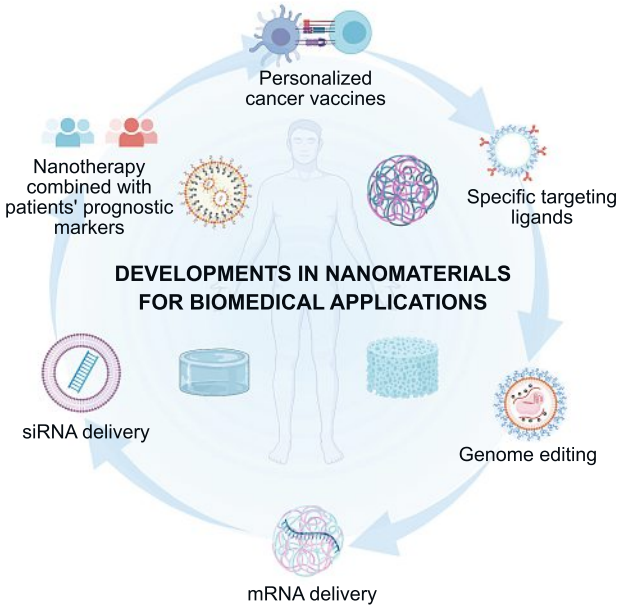

Fig. 2. Opportunities for personalized precision medicine treatments with the usage of nanomedicine.

4. Nanomedicine for Cancer Immunotherapy

Nanomedicine has a high translational potential for different disease modalities. One of the currently particularly active research areas is nanomedicine for cancer immunotherapy. Important possible applications of this work are in reducing toxic side effects of the existing therapies and in designing innovative therapies applicable to more patients.[28] Apart from the exciting prospects brought about with the development of the abovementioned mRNA cancer vaccines, a variety of other strategies have been implemented to provoke and sustain organism's immune response to cancer. For instance, PLGA NPs functionalized with immune potentiators have been recently used for the delivery of the Melan A/MART-1 peptide to dendritic cells in the mouse models of melanoma.[10b] The used peptide is often expressed by melanoma cells, and the functionalized PLGA particles were delivered to the cells either through a phagocytic uptake, or through ligand binding. In the latter case the NPs were additionally functionalized with the mannose sugar that targeted a mannose receptor, which is highly expressed in dendritic cells and macrophages. Ligand-based uptake was shown to be more effective than phagocytosis, and the NP internalization led to an increased infiltration of CD8+ T cells into tumors. Importantly, in combination with the immunotherapy checkpoint inhibition and modulation of the tumor microenvironment composition (through ibrutinib administration) the described treatment led to tumor remission and prolonged survival in mouse models. Other studies have focused more specifically on the reprogramming of immunosuppressive cells in tumor microenvironment. For instance, some of the studies utilized the fact that macrophages in tumor microenvironment (TME) have plastic phenotypes and can polarize either towards tumor-supportive immunosuppressive or towards tumor-fighting inflammatory states.[29] Among others, two recent *in vivo* preclinical studies succeeded in shifting the balance towards inflammatory macrophages in TME by using innovative nanomaterial solutions. The first approach relied on the delivery of a small drug, which is known to act as an agonist of an inflammatory macrophage receptor TLR7/8 and which was packed within a sugar-based β-cyclodextrin NP.[30] The second relied on the delivery of an mRNA for a transcription factor that promotes expression of genes involved in inflammatory pathways. The mRNA was packed within a cationic PBAE polymer.[10a] The latter NP was additionally also functionalized with mannose to increase its uptake by immunosuppressive macrophages. Importantly, treatment with either of the two particles resulted in the significant decrease of tumor growth in mouse cancer models and was suggested as a possible route for combinatorial treatments in cancer immunotherapy. In addition to these two studies, a number of other strategies for macrophage reprogramming has been proposed. For instance, macrophage reprogramming was also achieved through the delivery of a cytokine Interleukin 12 (IL-12) packed in a pH-sensitive PBAE NP that released the cytokine in the acidic tumor microenvironment.[31] The cytokine IL-12 was selected for reprogramming as it is usually produced in response to antigenic stimulation.

In addition to the efforts focused at macrophage reprogramming, or dendritic cells simulation, nanomedicine approaches have also been applied for the regulation of T cell functions.[32] For instance, a recent study was able to increase the efficacy of

the adoptive T cells transfer by linking immunomodulators, which support the T cell expansion, to the cell surface in the form of a protein nanogel.[33] The nanogel was composed of immunomodulator proteins (IL-15), which can stimulate T cell proliferation, linked through the disulphide cross linkers. The authors used the observation that redox potential on T cell changes after the cells have been activated, leading to a higher cell surface reduction, which is able to promote disulphide cleavage and release of immunomodulators from the attached nanogels. Consequently, IL-15 stimulation was able to lead to a significantly increased expansion of the tumor-specific T cells. Importantly, toxic side effects of this treatment were significantly lower than the ones that would be faced with a systemic administration of IL-15 immunomodulators alone. In addition to the mentioned individual examples, a number of other biomaterial-based strategies has been developed for the delivery of immunostimulatory or immunosuppressive molecules to tumors.[31a] Furthermore, NP-based enhancers are also used for cancer immunotherapy treatments. They are standardly administered in combinatorial therapies together with immune checkpoint inhibitors and chemotherapy, photothermal therapy or radiotherapy. NP enhancers have a role in potentiating immunogenic responses triggered by cancer cell death[34] and in promoting the release of tumor antigens, which further triggers systemic antitumor responses. Importantly, immune responses trained this way can even eliminate metastases and prevent tumor recurrence.[34] Currently, multiple clinical studies are under way for diverse applications of NPs for the cancer immunotherapy, including combined cancer immunotherapy treatments.[10a,12,35] These efforts are likely to open new horizons in cancer nanomedicine, which will additionally directly have a high translational value for other disease modalities.

5. Conclusion

Nanomaterials hold a great promise as new therapeutic reagents and as delivery systems for active molecules. However, even for formulations with excellent preclinical results, one needs to bear in mind challenges associated with their robust and reliable production, and high criteria requirements for satisfying good manufacturing practices standards. Moreover, particularly nanomedicine treatments that rely on nucleic-acid based therapies bear a high risk of causing hematological and immunological toxicities.[36] For instance, Patisiran infusion needs to be accompanied with intravenous administration of corticosteroids and antihistamines for suppressing immune reactions (dexamethasone and H1 and H2 antagonists, respectively). Immunotoxicities strongly hamper clinical translation of nucleic acid-based therapeutics, but the potential of these approaches for treating an array of different diseases is enormous. We believe that in the next years, usage of nanomaterials and systems will gradually lead to individualized patient treatment and we will see an accelerated development and clinical employment of nanotherapeutics. In parallel, with the increasing availability of datasets that are giving insights into NPs physicochemical properties and their uptake, biodistribution and phenotypic outcome, both *in vitro* and *in vivo*, large scale data analyses and machine learning are likely to become instrumental in optimizing the particle design. Jointly, these developments are expected to expand the areas of nanomedicine applications and pave the route for more effective, precise and personalized disease treatments.

Acknowledgments

We would like to thank Prof. Scott McNeil for the helpful comments on the manuscript text and Prof. Inge Herrmann for her input to Fig. 1. Fig. 2 was created with BioRender.com.

Received: January 17, 2022

[1] S. Tinkle, S. E. McNeil, S. Muhlebach, R. Bawa, G. Borchard, Y. C. Barenholz, L. Tamarkin, N. Desai, *Ann. NY Acad. Sci*. **2014**, *1313*, 35, https://doi.org/10.1111/nyas.12403.

[2] T. Lammers, M. Ferrari, *Nano Today* **2020**, *31*, https://doi.org/10.1016/j.nantod.2020.100853.

[3] J. S. Suk, Q. Xu, N. Kim, J. Hanes, L. M. Ensign, *Adv. Drug Deliv. Rev*. **2016**, *99*, 28, https://doi.org/10.1016/j.addr.2015.09.012.

[4] a) A. A. Kale, V. P. Torchilin, *Bioconjug. Chem*. **2007**, *18*, 363, https://doi.org/10.1021/bc060228x; b) T. Terada, M. Iwai, S. Kawakami, F. Yamashita, M. Hashida, *J. Control. Release* **2006**, *111*, 333, https://doi.org/10.1016/j.jconrel.2005.12.023.

[5] S. R. Tracey, P. Smyth, C. J. Barelle, C. J. Scott, *Biochem. Soc. Trans*. **2021**, *49*, 2253, https://doi.org/10.1042/BST20210343.

[6] S. Su, P. M. Kang, *Nanomaterials (Basel)* **2020**, *10*, https://doi.org/10.3390/nano10040656.

[7] I. Bala, S. Hariharan, M. N. Kumar, *Crit. Rev. Ther. Drug Carrier. Syst.* **2004**, *21*, 387, https://doi.org/10.1615/critrevtherdrugcarriersyst.v21.i5.20.

[8] H. K. Makadia, S. J. Siegel, *Polymers (Basel)* **2011**, *3*, 1377, https://doi.org/10.3390/polym3031377.

[9] N. D. Donahue, H. Acar, S. Wilhelm, *Adv. Drug Deliv. Rev.* **2019**, *143*, 68, https://doi.org/10.1016/j.addr.2019.04.008.

[10] a) F. Zhang, N. N. Parayath, C. I. Ene, S. B. Stephan, A. L. Koehne, M. E. Coon, E. C. Holland, M. T. Stephan, *Nat. Commun*. **2019**, *10*, 3974, https://doi.org/10.1038/s41467-019-11911-5; b) J. Conniot, A. Scomparin, C. Peres, E. Yeini, S. Pozzi, A. I. Matos, R. Kleiner, L. I. F. Moura, E. Zupancic, A. S. Viana, H. Doron, P. M. P. Gois, N. Erez, S. Jung, R. Satchi-Fainaro, H. F. Florindo, *Nat. Nanotechnol*. **2019**, *14*, 891, https://doi.org/10.1038/s41565-019-0512-0.

[11] I. de Lazaro, D. J. Mooney, *Nat. Mater*. **2021**, *20*, 1469, https://doi.org/10.1038/s41563-021-01047-7.

[12] M. S. Gebre, L. A. Brito, L. H. Tostanoski, D. K. Edwards, A. Carfi, D. H. Barouch, *Cell* **2021**, *184*, 1589, https://doi.org/10.1016/j.cell.2021.02.030.

[13] L. Maggiorella, G. Barouch, C. Devaux, A. Pottier, E. Deutsch, J. Bourhis, E. Borghi, L. Levy, *Future Oncol*. **2012**, *8*, 1167, https://doi.org/10.2217/fon.12.96.

[14] a) D. Adams, A. Gonzalez-Duarte, W. D. O'Riordan, C. C. Yang, M. Ueda, A. V. Kristen, I. Tournev, H. H. Schmidt, T. Coelho, J. L. Berk, K. P. Lin, G. Vita, S. Attarian, V. Plante-Bordeneuve, M. M. Mezei, J. M. Campistol, J. Buades, T. H. Brannagan, 3rd, B. J. Kim, J. Oh, Y. Parman, Y. Sekijima, P. N. Hawkins, S. D. Solomon, M. Polydefkis, P. J. Dyck, P. J. Gandhi, S. Goyal, J. Chen, A. L. Strahs, S. V. Nochur, M. T. Sweetser, P. P. Garg, A. K. Vaishnaw, J. A. Gollob, O. B. Suhr, *N. Engl. J. Med*. **2018**, *379*, 11, https://doi.org/10.1056/NEJMoa1716153; b) J. A. Kulkarni, D. Witzigmann, S. Chen, P. R. Cullis, R. van der Meel, *Acc. Chem. Res*. **2019**, *52*, 2435, https://doi.org/10.1021/acs.accounts.9b00368.

[15] M. M. Woitok, M. E. Zoubek, D. Doleschel, M. Bartneck, M. R. Mohamed, F. Kiessling, W. Lederle, C. Trautwein, F. J. Cubero, *Cell Death Dis*. **2020**, *11*, 343, https://doi.org/10.1038/s41419-020-2571-4.

[16] J. Xu, Y. Liu, Y. Li, H. Wang, S. Stewart, K. Van der Jeught, P. Agarwal, Y. Zhang, S. Liu, G. Zhao, J. Wan, X. Lu, X. He, *Nat. Nanotechnol*. **2019**, *14*, 388, https://doi.org/10.1038/s41565-019-0381-6.

[17] M. D. Buschmann, M. J. Carrasco, S. Alishetty, M. Paige, M. G. Alameh, D. Weissman, *Vaccines (Basel)* **2021**, *9*, https://doi.org/10.3390/vaccines9010065.

[18] a) D. Habrant, P. Peuziat, T. Colombani, L. Dallet, J. Gehin, E. Goudeau, B. Evrard, O. Lambert, T. Haudebourg, B. Pitard, *J. Med. Chem*. **2016**, *59*, 3046, https://doi.org/10.1021/acs.jmedchem.5b01679; b) M. Schlich, R. Palomba, G. Costabile, S. Mizrahy, M. Pannuzzo, D. Peer, P. Decuzzi, *Bioeng. Transl. Med*. **2021**, e10213, https://doi.org/10.1002/btm2.10213.

[19] W. Zhao, C. Zhang, B. Li, X. Zhang, X. Luo, C. Zeng, W. Li, M. Gao, Y. Dong, *Cell. Mol. Bioeng*. **2018**, *11*, 397, https://doi.org/10.1007/s12195-018-0536-9.

[20] Y. Dong, J. R. Dorkin, W. Wang, P. H. Chang, M. J. Webber, B. C. Tang, J. Yang, I. Abutbul-Ionita, D. Danino, F. DeRosa, M. Heartlein, R. Langer, D. G. Anderson, *Nano Lett.* **2016**, *16*, 842, https://doi.org/10.1021/acs.nanolett.5b02428.

[21] U. Sahin, K. Kariko, O. Tureci, *Nat. Rev. Drug Discov*. **2014**, *13*, 759, https://doi.org/10.1038/nrd4278.

[22] J. C. Kaczmarek, A. K. Patel, K. J. Kauffman, O. S. Fenton, M. J. Webber, M. W. Heartlein, F. DeRosa, D. G. Anderson, *Angew. Chem. Int. Ed*. **2016**, *55*, 13808, https://doi.org/10.1002/anie.201608450.

[23] a) U. Sahin, E. Derhovanessian, M. Miller, B. P. Kloke, P. Simon, M. Lower, V. Bukur, A. D. Tadmor, U. Luxemburger, B. Schrors, T. Omokoko, M. Vormehr, C. Albrecht, A. Paruzynski, A. N. Kuhn, J. Buck, S. Heesch, K. H. Schreeb, F. Muller, I. Ortseifer, I. Vogler, E. Godehardt, S. Attig, R. Rae, A. Breitkreuz, C. Tolliver, M. Suchan, G. Martic, A. Hohberger, P. Sorn, J. Diekmann, J. Ciesla, O. Waksmann, A. K. Bruck, M. Witt, M. Zillgen, A. Rothermel, B. Kasemann, D. Langer,

S. Bolte, M. Diken, S. Kreiter, R. Nemecek, C. Gebhardt, S. Grabbe, C. Holler, J. Utikal, C. Huber, C. Loquai, O. Tureci, *Nature* **2017**, *547*, 222, https://doi.org/10.1038/nature23003; b) U. Sahin, O. Tureci, *Science* **2018**, *359*, 1355, https://doi.org/10.1126/science.aar7112.

[24] M. S. Draz, B. A. Fang, P. Zhang, Z. Hu, S. Gu, K. C. Weng, J. W. Gray, F. F. Chen, *Theranostics* **2014**, *4*, 872, https://doi.org/10.7150/thno.9404.

[25] I. K. Herrmann, M. J. A. Wood, G. Fuhrmann, *Nat. Nanotechnol.* **2021**, *16*, 748, https://doi.org/10.1038/s41565-021-00931-2.

[26] a) W. Liao, Y. Du, C. Zhang, F. Pan, Y. Yao, T. Zhang, Q. Peng, *Acta Biomater.* **2019**, *86*, 1, https://doi.org/10.1016/j.actbio.2018.12.045; b) J. E. Pullan, M. I. Confeld, J. K. Osborn, J. Kim, K. Sarkar, S. Mallik, *Mol. Pharm.* **2019**, *16*, 1789, https://doi.org/10.1021/acs.molpharmaceut.9b00104.

[27] X. Zhang, B. Li, X. Luo, W. Zhao, J. Jiang, C. Zhang, M. Gao, X. Chen, Y. Dong, *ACS Appl. Mater. Interf.* **2017**, *9*, 25481, https://doi.org/10.1021/acsami.7b08163.

[28] W. Song, M. Das, X. Chen, *Trends Cancer* **2020**, *6*, 288, https://doi.org/10.1016/j.trecan.2020.01.011.

[29] Y. He, R. F. de Araujo Jr, L. J. Cruz, C. Eich, *Pharmaceutics* **2021**, *13*, https://doi.org/10.3390/pharmaceutics13101670.

[30] C. B. Rodell, S. P. Arlauckas, M. F. Cuccarese, C. S. Garris, R. Li, M. S. Ahmed, R. H. Kohler, M. J. Pittet, R. Weissleder, *Nat. Biomed. Eng.* **2018**, *2*, 578, https://doi.org/10.1038/s41551-018-0236-8.

[31] a) Y. Q. Xie, L. Wei, L. Tang, *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol.* **2018**, *10*, e1506, https://doi.org/10.1002/wnan.1506; b) Y. Wang, Y. X. Lin, S. L. Qiao, H. W. An, Y. Ma, Z. Y. Qiao, R. P. Rajapaksha, H. Wang, *Biomaterials* **2017**, *112*, 153, https://doi.org/10.1016/j.biomaterials.2016.09.034.

[32] M. Saeed, J. Gao, Y. Shi, T. Lammers, H. Yu, *Theranostics* **2019**, *9*, 7981, https://doi.org/10.7150/thno.37568.

[33] L. Tang, Y. Zheng, M. B. Melo, L. Mabardi, A. P. Castano, Y. Q. Xie, N. Li, S. B. Kudchodkar, H. C. Wong, E. K. Jeng, M. V. Maus, D. J. Irvine, *Nat. Biotechnol.* **2018**, *36*, 707, https://doi.org/10.1038/nbt.4181.

[34] a) Y. Fan, R. Kuai, Y. Xu, L. J. Ochyl, D. J. Irvine, J. J. Moon, *Nano Lett.* **2017**, *17*, 7387, https://doi.org/10.1021/acs.nanolett.7b03218; b) Z. Liu, W. Jiang, J. Nam, J. J. Moon, B. Y. S. Kim, *Nano Lett.* **2018**, *18*, 6655, https://doi.org/10.1021/acs.nanolett.8b02340.

[35] D. J. Irvine, E. L. Dane, *Nat. Rev. Immunol.* **2020**, *20*, 321, https://doi.org/10.1038/s41577-019-0269-6.

[36] a) K. A. Afonin, M. A. Dobrovolskaia, G. Church, M. Bathe, *ACS Nano* **2020**, *14*, 9221, https://doi.org/10.1021/acsnano.0c04753; b) M. A. Dobrovolskaia, S. E. McNeil, *Nat. Nanotechnol.* **2007**, *2*, 469, https://doi.org/10.1038/nnano.2007.223; c) M. A. Dobrovolskaia, S. E. McNeil, *Exp. Opin. Drug. Deliv.* **2015**, *12*, 1163, https://doi.org/10.1517/17425247.2015.1042857.

License and Terms

The definitive version of this article is the electronic one that can be found at https://doi.org/10.2533/chimia.2022.236