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Editorial

Celebrating Women in the Pharmaceutical Sciences

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This Virtual Issue highlights the work of some of our most creative and successful woman pharmaceutical scientists across academia and the pharmaceutical industry. The editorial team at Molecular Pharmaceutics is delighted to take this opportunity to feature the research of some of the disciplines' most prominent and trailblazing women scientists.

Unfortunately, it is well recognized within the STEM disciplines, which encompass the pharmaceutical sciences, that a lack of gender parity is still a prevalent issue.[1,2] The current rate of change toward gender parity is unacceptably slow. According to a 2020 World Economic Forum report, it will take a shocking ~100 years to close the global gender gap.[3] To accelerate progress toward equality, we need specific and aggressive action, rather than passive acceptance of the current dynamics with incremental changes.

With this in mind, we make a few suggestions for some things that everyone can do to support women pharmaceutical scientists, with the ultimate goal of closing gender gaps. Women scientists need allies and coaches, and these need to come from the entire scientific cohort, both men and women. Nominate women for awards. Perhaps make it a yearly resolution to nominate a minimum of 3 women for an award, including graduate students, postdoctoral associates, faculty and work colleagues, collaborators, etc. If you are organizing a session at a conference, make sure you have women on the organizing committees and invite women speakers and moderators. If you are a speaker, encourage the session organizers to invite women, especially if they are underrepresented within the session. Consider refusing to speak if women are not adequately represented at a session. Do mentor women scientists. The support provided by mentorship is essential to help women scientists achieve their full potential.[4] Ensure that there is gender balance on important decision-making committees and panels (hiring, promotion, proposal review, financial allocation, etc.), but do not overburden women with low-importance service committees. Be an active bystander: call out people in meetings who interrupt or talk over women, and intervene if women presenters face aggressive and dismissive questioning at conferences. Do not allow the voices and suggestions of women to be ignored in meetings. Promote the work of women scientists by citing their papers, talking about their work, and inviting them to give presentations. Recognize that you may be subject to implicit bias and take steps to counteract it. Implicit bias against women is an issue for both women and men and leads to subtle acts of discrimination such as less enthusiastic letters of recommendation relative to counterparts who are men or the automatic assumption that the man in the room is the senior person.[5] Nominate women for leadership positions including within the workplace, in professional organizations, and for editorial roles.

These suggestions may make readers of both genders uncomfortable. However, staying in our comfort zone is not going to bring about change, so we should be at ease with being uncomfortable.

Now we turn to the recent wonderful and impactful contributions of women pharmaceutical scientists highlighted in this Virtual Issue.

The field of nanomedicine has seen a rapid pace in research on different fronts, including the development of new nanomaterials, pharmaceutical procedures, and/or alternative routes of administration that can tackle the roadblocks hindering effective drug, gene, and vaccine delivery and targeting. Although most literature in this area has focused on oncological conditions, recent attempts have found justification and evidence for the use of nanomedicine in other pathological conditions including infectious diseases and various inflammatory conditions. In cancer therapy, novel nanoparticle designs have been adopted as a means to provide efficient delivery of individual chemotherapeutics for the treatment of hard-to-treat cancers. In this context, triple-negative breast cancer (TNBC) has been the subject of several efforts. Women scientists have played a central role in the scientific advancement of the field of nanomedicine and continue to make significant and innovative contributions in this regard.

In a recent elegant study, Stavroula Sofou et al. of Johns Hopkins University developed lipid nanocarriers of cisplatin that can adhere to the extracellular matrix (ECM) in the tumor and/or release their cisplatin cargo in the extracellular space for better tumor penetration (DOI: 10.1021/acs.molpharmaceut.9b00812). Their results provided evidence for the positive contribution of both extracellular cisplatin release along with nanocarrier ECM adhesion in the enhanced anticancer activity of cisplatin in TNBC. In this context, the contribution from the extracellular cisplatin release on the anticancer activity of nanoparticles was found to be more significant than that of nanocarrier ECM adhesion. In another attempt to design nanocarriers for the treatment of hard-to-treat cancers, Sabrina Oliveira and co-workers from Utrecht University developed

EGFR nanobody-modified polymeric micelles loaded with *meta*-tetra(hydroxyphenyl)chlorin (*m*THPC) for photodynamic therapy of head and neck cancer (DOI: 10.1021/acs.molpharmaceut.9b01280). The results showed the effectiveness of this approach in preferential targeting of EGFR-expressing cancer cells *in vitro*, without any negative impact from the nanobody ligand on the pharmacokinetic profile and stealth properties of the nanocarrier.

Quite unexpectedly, the long-awaited breakthrough in the field of nanotechnology for medicine may come from nanomedicine use in the SARS-CoV2 vaccine development. With at least two nanotechnology products having received emergency use authorization by regulatory authorities and many more under preclinical and clinical development, the importance of research in the area of vaccine development and nucleic acid delivery using nanotechnology approaches is coming to its fruitful realization. Under the general area of nano for gene delivery, here we highlight the innovative approach of Ester Kwon and Sangeeta Bhatia (DOI: 10.1021/acs.molpharmaceut.0c00714) in the development of "peptide spiders" for effective delivery of siRNA in cancer. In this interesting architecture, they have used chemical conjugation of a_Vb_3 integrin targeting peptide with the binding capacity to tumor and stroma cells, i.e., iRGD, along with a cell-penetrating peptide, through reducible or nonreducible linkages to a multiarm PEG backbone. Taking advantage of the increased avidity of the peptide constructs on the PEG backbone, they proved the superiority of the "peptide spiders" with nonreducible linkages in siRNA transfection in an MDA-MB-435S tumor model, *in vivo*. In the area of vaccine development, and in a pioneering effort toward the development of lung cancer vaccines, Rita Vanbever of the Université Catholique de Louvain studied the potential of two different cationic nanoliposomes in delivery of antigens and adjuvants to dendritic cells versus alveolar macrophages residing in the lung (DOI: 10.1021/acs.molpharmaceut.9b00033). Their findings showed that the majority of the cationic nanoliposomes under study were taken up by alveolar macrophages, *in vivo*, hindering access to dendritic cells, which are considered to be more efficient in antigen presentation. In a similar line of research, Azita Haddadi and co-workers from the University of Saskatchewan investigated poly(D,L-lactic-*co*-glycolic-acid) (PLGA) nanodelivery systems of a model antigen, ovalbumin, along with monophosphoryl lipid A adjuvant, modified on its surface with anti-CD205 targeting ligand for dendritic cell targeting (DOI: 10.1021/acs.molpharmaceut.8b00700). The results showed a positive contribution from the use of anti-CD205 ligands particularly following chemical conjugation to the surface of PLGA nanoparticles in increasing the proliferation of cytotoxic CD8 T cells following vaccine inoculation in relevant mice models for the OVA antigen, suggesting new potential strategies for the design of nanovaccines with improved performance.

The current *status quo* and problems associated with large-scale production and distribution of nanobased COVID vaccines have once again emphasized major roadblocks against the widespread use of nanomedicine. In this context, controllable technologies such as microfluidics can provide a scalable alternative production strategy with more reproducibility. We highlight interesting research by Yvonne Perrie and collaborators, who used this approach to produce cationic liposomal adjuvants, which showed analogous biodistribution and immunogenicity compared to those produced by the small-scale lipid hydration method (DOI: 10.1021/acs.molpharmaceut.9b00730).

Poor aqueous solubility remains an enduring problem in drug delivery, driving creative research into how to achieve adequate absorption following oral administration. Women scientists are playing a pivotal role in developing and understanding solubility-enhancing formulations. Many formulation approaches exploit supersaturation, where the concentration achieved exceeds the saturation solubility of the crystalline form. However, using formulations to generate high levels of supersaturation is a double-edged sword, as higher supersaturation leads to an increased risk of crystallization. Naír Rodríguez-Hornedo from the University of Michigan highlights a strategy to fine-tune the supersaturation generated by cocrystal dissolution by considering the solubility advantage of the cocrystal, the critical supersaturation for nucleation, the drug dose, and the ability of surfactant additives to reduce the supersaturation to a lower, more kinetically stable value (DOI: 10.1021/acs.molpharmaceut.0c00713). This work provides mechanistic insight into how to rationally select excipients to achieve the best performance from a given cocrystal system. Continuing with the theme of supersaturation, work from Robin Bogner and colleague Na Li of the University of Connecticut underscores the need to consider the role of pH as a determining factor in the crystallization kinetics of the weak acid, indomethacin (DOI: 10.1021/acs.molpharmaceut.0c00539). Working at equivalent supersaturation, the authors made the intriguing observation that crystallization was, for some reason, slower in higher pH solutions—this has important implications when considering the pH variation of our gastrointestinal tracts. After exploring different mathematical models, the authors concluded that the ionized form of indomethacin hindered the integration of the growth unit (i.e., unionized indomethacin) by adsorption at the crystal surface, and hence reduced the crystal growth rate at higher pH values where a substantial fraction of the drug existed as ions. Amorphous formulations are also widely used to generate supersaturated solutions for absorption enhancement and can undergo complex phase behavior during dissolution, including crystallization at the surface-solution interface, which then slows down the drug release rate. Clare Strachan and collaborators applied nonlinear optical imaging techniques to take "pictures" of the drug surface solid form composition following exposure to an aqueous solution (DOI: 10.1021/acs.molpharmaceut.8b00840). Using a combination of sum-frequency generation and coherent anti-Stokes Raman scattering, different polymorphic forms were found to have crystallized at the surface of an initially amorphous indomethacin compact during the dissolution process, whereby the solid-state form was linked to the solution concentration—time profiles. An increasing number of protein therapeutics, such as monoclonal antibodies, have been successfully developed in recent years, and many of these formulations are amorphous. A key challenge with these formulations is retaining protein stability for the product shelf life, and hence formulation optimization is essential. Unfortunately, it can take months before it is apparent if the given formulation approach is working. Elizabeth Topp collaborated with Andrea Allmendinger and other scientists at Genentech to study one of their monoclonal antibodies using hydrogen/deuterium exchange as an approach to rapidly predict protein stability (DOI: 10.1021/acs.molpharmaceut.7b00504). Using this technique, they demonstra-

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ted an excellent correlation between the hydrogen/deuterium exchange results obtained after 2−4 weeks of storage with stability studies conducted over 2.5 years. Amorphous systems can be challenging to study experimentally, so applying molecular modeling can provide critical insight. Gabriele Sadowski from the Technical University Dortmund, in collaboration with colleagues from AbbVie, applied a thermodynamic model to predict liquid−liquid phase separation of an amorphous solid dispersion consisting of a drug and polymer during solvent evaporation (DOI: 10.1021/acs.molpharmaceut.0c00418). Using Raman spectroscopy, the authors were able to confirm the excellent predictability of the model, opening the door for *in silico* experiments to identify suitable solvents and processing conditions for optimized amorphous solid dispersion manufacturing using solvent evaporation-based processes such as spray drying. The power of molecular modeling is also highlighted in a study by Doris Braun and co-workers from the University of Innsbruck (DOI: 10.1021/acs.molpharmaceut.9b00419). Dapsone is a first-line therapy used to treat leprosy. Although this compound was first synthesized more than 100 years ago, Braun was able to find a new polymorph, which was confirmed to be the most thermodynamically stable crystal form by a combination of experiments along with crystal structure predictions and lattice energy modeling.

A key consideration in drug delivery is the interaction of the formulation with the body. Both formulations and biological targets are becoming increasingly complex, underscoring the importance of this interplay. This is nicely highlighted by the work of Natalie Trevaskis of Monash University (DOI: 10.1021/acs.molpharmaceut.0c00348), wherein the lymph node retention of high-density lipoproteins following subcutaneous injection was found to correlate with the surface composition of the lipoprotein, specifically, the magnitude of the negative charge. These findings are consequential since they inform targeting strategies of immunotherapies and vaccines via the use of high-density lipoproteins as carriers to lymph-resident immune cells. A wide variety of excipients is used across thousands of formulated products ingested by patients. Kathleen Giacomini from the University of California, San Francisco, evaluated the interaction of 136 excipients used in oral formulations with an intestinal efflux transporter (DOI: 10.1021/acs.molpharmaceut.9b00658). Certain dyes, surfactants, and flavoring agents were noted to exhibit inhibitory effects when screening experiments were conducted using membrane vesicles, but switching to a cell model showed minimal excipient-transporter interactions. This is an important study highlighting that the appropriate *in vitro* test needs to be conducted for translation to an *in vivo* environment. Efflux transporters, together with tight junctions, are also critical in protecting the brain from toxic chemicals. At the same time, this blood-brain barrier hinders the delivery of neurotherapeutic agents. In a perspective article, Margareta Hammarlund-Udenaes of Uppsala University (DOI: 10.1021/acs.molpharmaceut.0c00881) discusses the design and optimization of nanoformulations to achieve clinical success in brain treatment. The need for studies to evaluate the amount of unbound drug in the brain and plasma is highlighted as a critical gap to connect pharmacokinetics to pharmacodynamics. Another study emphasizing the need for improved *in vitro* testing approaches comes from the laboratory of Anette Müllertz, University of Copenhagen (DOI: 10.1021/acs.molpharmaceut.0c00307). *In vitro* studies of lipid-based formulations typically incorporate digestion by adding pancreatic enzymes to a solution containing bile salts and phospholipids to mimic intestinal conditions. By comparing two different lipid formulations that had been evaluated *in vivo*, Müllertz and co-workers demonstrated that it was important to include a gastric stage in the *in vitro* assessment in order to better predict the performance of each formulation.

Nuclear medicine continues to emerge as a major pharmaceutical focus for treating predominantly oncological diseases. The convergent advances in protein engineering, as well as new radionuclide therapies and companion diagnostics, have transformed the landscape for radiotherapeutics. The continued evolution of targeted α therapeutics drives significant interest in this field and a direct head-to-head assessment of the pharmacological activity of 225-Ac (α-emitter) and 177-Lu (β-emitter) radioimmunoconjugates was evaluated by Rebecca Abergel et al. using a monoclonal antibody targeted to δ-like 3 protein (DOI: 10.1021/acs.molpharmaceut.0c00703). While the α therapy showed enhanced efficacy in a small-cell lung cancer model compared to the β-emitter, the study highlighted the ever-important need to match the pharmacokinetic (PK) profiles of new drugs with the therapy. An elegant example of this feature was described by Cristina Müller and colleagues of ETH Zurich in her fundamental assessment of how albumin-binding groups present on the common prostate therapy, [^{177}Lu]Lu-PSMA probe, could be used to harness the innate biological environment to modulate PK (DOI: 10.1021/acs.molpharmaceut.0c00199). Being one of the most studied new probes in nuclear medicine, [^{177}Lu]LuPSMA offers a new gold standard for treating prostate cancer; concomitant advances in our fundamental understanding of how structure affects the function of these probes will ultimately improve the safety and efficacy of next-generation nuclear medicines. Antibody engineering also allows a deeper evaluation of the role of diagnostic probes in understanding immunotherapies. Through slight modification of the [^{89}Zr]Zr-DFO-antiCD8 monoclonal radioimmunoconjugate, Nerissa Viola and collaborators showed prolonged and enhanced detection of CD8+ immune cells could be monitored without tracer-dependent depletion (DOI: 10.1021/acs.molpharmaceut.0c00270). This was achieved through enzymatic cleavage of the N-linked biantennary glycans from the heavy chain of the IgG, leading to decreased recognition by the effector cells. The study highlights how simple protein structure modification decreases the perturbation of the system by the imaging probe and can lead to improved diagnostic outcomes.

While nuclear medicine has paved the way for a number of effective diagnostic and therapeutic agents, the role of MRI in disease management is also finding important new applications. This is of particular interest in the age of vaccine development (made even more poignant by the current COVID-19 crisis), where direct localization and accumulation of vaccines and adjuvants can give insight into mechanisms that improve potency. Camilla Foged of the University of Copenhagen and co-workers (DOI: 10.1021/acs.molpharmaceut.9b00908) described a gadoteridol-loaded liposome formulation that was engineered to facilitate MRI-guided delivery of the TB subunit vaccine, H56/CAF01. The MRI properties of the adjuvant system were significantly enhanced through the incorporation of the gadolinium-based relaxation agent and used to inform on the mechanism and delivery of the vaccine via intrapulmonary administration. This theranostic system offers

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significant new insight into the mode and site of action of novel vaccines.

We have highlighted the noteworthy research of some of our many women pharmaceutical scientists. We hope to see many more women entering and remaining in the field of drug formulation and delivery, driving the science of this important discipline. At Molecular Pharmaceutics, we are proud to represent a major hub for the dissemination of pioneering work in the pharmaceutical sciences and particularly celebrate the role that women researchers take in progressing our science.

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Notes

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