Engineering Metal-Phenolic Capsules for Controlled Pulmonary Delivery

Yi Ju,[1,] Christina Cortez-Jugo,[1] Ting-Yi Wang,[2] Leslie Y. Yeo,[3] Christoph E. Hagemeyer,[2] and Frank Caruso[1]*

[1]ARC Centre of Excellence in Convergent Bio-Nano Science and Technology, and the Department of Chemical Engineering, The University of Melbourne, Parkville, Victoria 3010, Australia.

[2]Nanobiotechnology Laboratory, Australian Centre for Blood Diseases, Monash University, Melbourne, Victoria 3004, Australia.

[3]Micro/Nanophysics Research Laboratory, School of Engineering. RMIT University, Melbourne, Victoria 3001, Australia

Presenting and Corresponding Author E-mail Address: y.ju@unimelb.edu.au

Lungs represent an attractive route for therapeutic administration. The ability to control the deposition of particulate drug carriers in the lungs is important to achieve high delivery efficacy, and this can be accomplished by particle engineering—specifically by tuning the aerodynamic properties of the particles through their aerodynamic diameter. To this end, variations in particle shape and size have been previously investigated, mainly for dry particle formulations, but there have been few studies on liquid formulations. Given that the inhalation device plays a major role in determining the aerosol aerodynamic behavior in liquid formulations, particle engineering adds scope to finely tune the aerodynamic diameter of particles that may encapsulate drugs not amenable to drying. This may allow control of the bio–nano interactions at the deposition site of the particles and their ultimate performance.

Drug delivery systems based on metal–phenolic networks (MPNs),[1] which are formed upon coordination of metal ions to phenolic compounds, have emerged as promising candidates for biomedicine owing to their distinct properties, including pH responsiveness, high biocompatibility, and multifunctionalities.[2-4] In a recent study, we nanoengineered and nebulized MPN capsules, loaded with small molecule to macromolecular drugs, and we examined the interactions of the capsules in lung cell lines, a mechanical human lung model and in a small animal (mice).[5] The capsules, composed of materials generally recognized as safe by the FDA (tannic acid and Fe^{III}), were nebulized without significant loss of encapsulated cargo. Importantly, tuning the aerodynamic diameters of the capsules by increasing the capsule shell thickness facilitated precise control of capsule deposition, corresponding to a shift from the alveolar region to the bronchi regions of the lungs, as assessed using a human lung model, Furthermore, we examined the pulmonary biodistribution of the capsules at both organ and single-cell levels by mass cytometry. These studies show the biocompatibility and biodegradability of MPN capsules in murine lungs, and combined with their robustness to nebulization, capacity for cargo loading, and tunable aerodynamic behavior as demonstrated in this study, make these capsules attractive candidates for controlled pulmonary delivery.

References

[1] H. Ejima, J. J. Richardson, K. Liang, J. P. Best, M. P. van Koeverden, G. K. Such, J. Cui, F. Caruso, *Science* **2013**, *341*, 154.

[2] Y. Ju, J. Cui, M. Müllner, T. Suma, M. Hu, F. Caruso, *Biomacromolecules* **2015**, *16*, 807.

[3] Y. Ju, J. Cui, H. Sun, M. Müllner, Y. Dai, J. Guo, N. Bertleff-Zieschang, T. Suma, J. J. Richardson, F. Caruso, *Biomacromolecules* **2016**, *17*, 2268.

[4]. Y. Ju, Q. Dai, J. Cui, Y. Dai, T. Suma, J. J. Richardson, F. Caruso, *ACS Appl. Mater. Interfaces* **2016**, *8*, 22914.

[5] Y. Ju, C. Cortez-Jugo, J. Chen, T.-Y. Wang, A. J. Mitchell, E. Tsantikos, N. Bertleff-Zieschang, Y.-W. Lin, J. Song, Y. Cheng, S. Mettu, M. A. Rahim, S. Pan, G. Yun, M. L. Hibbs, L. Y. Yeo, C. E. Hagemeyer, F. Caruso, *Advanced Science* **2020**, DOI: 10.1002/advs.2019026501902650.