Imaging of Vaterite-based Drug Delivery Capsules in Vitro and in Vivo

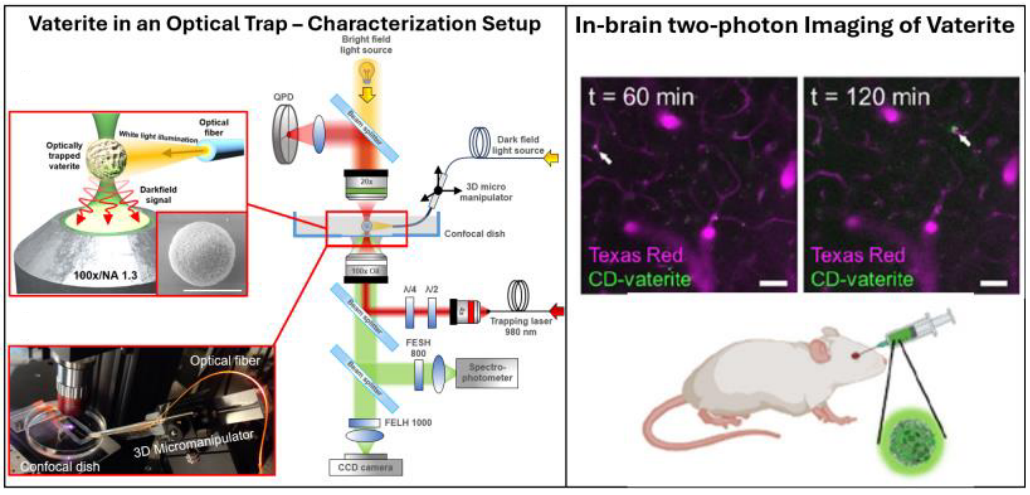
Pavel Ginzburg, Hani Barhom, Andrey Machnev,
Andrey Ushkov, Denis Kolchanov, and Pavel Bezrukov
Tel Aviv University, Israel

Abstract— Nano-engineered capsules for targeted drug delivery are an essential milestone on pathways to advance precision medicine concepts. As most phenomena occur in a liquid environment in vivo, understanding cargo-fluid interaction mechanisms in vitro becomes an important factor, which can control the drug release rates. In this contribution, we will introduce the concept of metamaterial drug delivery capsules, "golden" and "gilded" "vaterite", and demonstrate their unambiguous advantages in the future paradigm of light-driven theranostics. In particular, optomechanical drug delivery, one-photon and two-photon bioimaging, drug release, and thermal therapy with the aid of 'vaterite metamaterials' will be shown.

The presentation is based on our recent works [1–5] and on several new unpublished data (several manuscripts under review). On top of our published results, we will demonstrate novel light-driven functions, including realize, uptake acceleration, and cell treatment, underlying 'golden vaterite' advantages.

The fast-changing and evolving landscape of biomedical challenges motivates the continuous development of new functional platforms. Implantable devices made from biocompatible materials, capable of responding to optical signals and tailoring propagation of light waves can be employed in health monitoring applications and therapeutics [6]. The incorporation of such elements into living organisms can boost light-tissue interactions and shift conventional approaches towards precision medicine by opening new opportunities in sensing, photothermal therapy, photoacoustic tomography, and bioimaging. One of the grand challenges on those pathways is the miniaturization of biocompatible photonic structures along with providing multiple functionalities, such as monitoring of vital biological processes, light-responsive drug release, or local heating of a nanoscale area with the simultaneous measurement of its temperature.

We demonstrated a new mesoscopic approach to on-demand engineering of electric and magnetic resonances in submicron low-index vaterite spherulites by filling them with gold nano inclusions. This makes it possible to increase the effective permittivity of the structure and provide efficient light trapping. As an example of a potential thermal therapy application, we demonstrate an efficient laser heating of golden spherulites. Both water suspensions and individual spherulites, being illuminated with near-infrared light were investigated via time-resolved fluorometry and fluorescence-lifetime imaging microscopy (FLIM) and demonstrated an efficient local temperature elevation. Also, we have demonstrated a facile synthesis of meta-phenylenediamine CDs exhibiting robust optical fluorescence



(a) (b)

Figure 1: (a) Dark-field endoscopic setup for particle characterization. (b) In-vivo two-photon imaging of vaterite capsules inside the brain of a living mouse.

properties under both single-photon and two-photon absorption regimes. The interaction of the CD-vaterite composites with MDMDA-231 and C6-glioma cells was successfully investigated using one- and two-photon confocal microscopy. This was followed by injection and visualization of CD-vaterite composites in vivo in murine brain blood vessels for the first time. This allows for the tracking of particles in the bloodstream, thereby facilitating investigations involving blood vessels and the blood-brain barrier (BBB) and their disorders. Furthermore, with further optimization, this tool can allow real-time study of drug-cell interactions.

REFERENCES

1. Noskov, R. E., I. I. Shishkin, H. Barhom, and P. Ginzburg, "Non-Mie optical resonances in anisotropic biomineral nanoparticles," *Nanoscale*, Vol. 10, No. 45, 21031–21040, Dec. 2018, doi: 10.1039/c8nr07561a.
2. Noskov, R. E., et al., "Golden vaterite as a mesoscopic metamaterial for biophotonic applications," *Advanced Materials*, Vol. 33, No. 25, 2008484, Jun. 2021, doi: 10.1002/ADMA.202008484.
3. Barhom, H., et al., "Biological Kerker effect boosts light collection efficiency in plants," *Nano Lett.*, Vol. 19, No. 10, 7062–7071, Oct. 2019, doi: 10.1021/acs.nanolett.9b02540.
4. Bahrom, H., et al., "Controllable synthesis of calcium carbonate with different geometry: Comprehensive analysis of particle formation, cellular uptake, and biocompatibility," *ACS Sustain. Chem. Eng.*, Vol. 7, No. 23, 19142–19156, Dec. 2019, doi: 10.1021/acssuschemeng.9b05128.
5. Harpaz, D., H. Barhom, B. Veltman, P. Ginzburg, and E. Eltzov, "Biocompatibility characterization of vaterite with a bacterial whole-cell biosensor," *Colloids Surf. B: Biointerfaces*, Vol. 222, 113104, Feb. 2023, doi: 10.1016/J.COLSURFB.2022.113104.
6. Humar, M., S. J. J. Kwok, M. Choi, A. K. Yetisen, S. Cho, and S.-H. Yun, "Toward biomaterial-based implantable photonic devices," *Nanophotonics*, Vol. 6, No. 2, 414–434, Mar. 2017, doi: 10.1515/nanoph-2016-0003.