Poster Presentation Submission

Three-photon imaging of glioblastoma using defect-induced photoluminescence in biocompatible ZnO nanoparticles

Achyut J. Raghavendra[1,], *Wren E. Gregory[1,], Tyler Slonecki[2], Balakrishnan Pillai[1], Yongchang Dong[1], Indushekhar Persaud[4], Jared M. Brown[4], Terri F. Bruce[2], and Ramakrishna Podila[1, 5,] *

1. Laboratory of nano-biophysics, Clemson Nanomaterials Institute, Department of Physics and Astronomy, Clemson University, Clemson, SC 29634 USA
2. Clemson Light Imaging Facility, Clemson University, Clemson, SC 29634 USA
3. Department of Pharmaceutical Sciences, Skaggs School of Pharmacy and Pharmaceutical Sciences, The University of Colorado Anschutz Medical Campus, Aurora, Colorado, 80045, USA.
4. Clemson University School of Health Research, Clemson University, Clemson, SC 29634 USA.

Abstract: Although optical spectroscopy promises improved lateral resolution for cancer imaging, its clinical use is seriously impeded by background fluorescence and photon attenuation even in the so-called two-photon absorption (2PA) imaging modality. An efficient strategy to meet the clinical cancer imaging needs, beyond what two-photon absorption (2PA) offers, is to use longer excitation wavelengths through three-photon absorption (3PA). A variety of fluorescent dyes and nanoparticles (NPs) have been used in 3PA imaging. However, their non-linear 3PA coefficient is often low necessitating high excitation powers, which cause overheating, photodamage, and photo-induced toxicity. To address this demand we designed defected ZnO nanoparticles (ZnO NPs) for enabling a low-power 3PA paradigm at longer excitation and emission wavelengths, lower background noise, and improved spatial resolution (<1 um) at powers below 5 mW.

Keywords: three-photon imaging, ZnO nanoparticles, defects, photoluminescence

References

1. Liu, J. T. C., Meza, D. & Sanai, N. Trends in fluorescence image-guided surgery for gliomas. *Neurosurgery* **75,** 61–71 (2014).
2. Gioux, S., Choi, H. S. & Frangioni, J. V. Image-guided surgery using invisible near-infrared light: Fundamentals of clinical translation. *Molecular Imaging* **9,** 237–255 (2010).
3. Wyckoff, J., Gligorijevic, B., Entenberg, D., Segall, J. & Condeelis, J. High-resolution multiphoton imaging of tumors in vivo. *Cold Spring Harb. Protoc.* **6,** 1167–1184 (2011).
4. Yuan, B. & Rychak, J. Tumor functional and molecular imaging utilizing ultrasound and ultrasound-mediated optical techniques. *American Journal of Pathology* **182,** 305–311 (2013).
5. Kairdolf, B. A. *et al.* Intraoperative Spectroscopy with Ultrahigh Sensitivity for Image-Guided Surgery of Malignant Brain Tumors. *Anal. Chem.* **88,** 858–867 (2016).
6. Keating, J. *et al.* Identification of breast cancer margins using intraoperative near-infrared imaging. *J. Surg. Oncol.* **113,** 508–514 (2016).
7. Xu, C., Zipfel, W., Shear, J. B., Williams, R. M. & Webb, W. W. Multiphoton fluorescence excitation: new spectral windows for biological nonlinear microscopy. *Proc. Natl. Acad. Sci. U. S. A.* **93,** 10763–10768 (1996).
8. Yu, J. H. *et al.* High-resolution three-photon biomedical imaging using doped ZnS nanocrystals. *Nat. Mater.* **12,** 359–66 (2013).
9. Zagorovsky, K. & Chan, W. C. W. Bioimaging: illuminating the deep. *Nat. Mater.* **12,** 285–7 (2013).

10. Tong, L., Cobley, C. M., Chen, J., Xia, Y. & Cheng, J. X. Bright three-photon luminescence from gold/silver alloyed nanostructures for bioimaging with negligible photothermal toxicity. *Angew. Chemie - Int. Ed.* **49,** 3485–3488 (2010).
11. Rao, J., Dragulescu-Andrasi, A. & Yao, H. Fluorescence imaging in vivo: recent advances. *Curr. Opin. Biotechnol.* **18,** 17–25 (2007).
12. Wang, L., Nagesha, D. K., Selvarasah, S., Dokmeci, M. R. & Carrier, R. L. Toxicity of CdSe Nanoparticles in Caco-2 Cell Cultures. *J. Nanobiotechnology* **6,** 11 (2008).
13. Kauffer, F. A., Merlin, C., Balan, L. & Schneider, R. Incidence of the core composition on the stability, the ROS production and the toxicity of CdSe quantum dots. *J. Hazard. Mater.* **268,** 246–255 (2014).
14. Yu, J. H. *et al.* High-resolution three-photon biomedical imaging using doped ZnS nanocrystals. *Nat. Mater.* **12,** 359–366 (2013).
15. Gu, B., He, J., Ji, W. & Wang, H. T. Three-photon absorption saturation in ZnO and ZnS crystals. *J. Appl. Phys.* **103,** 9235–9247 (2008).
16. Sreeja, R., Sridharan, K., Philip, R. & Jayaraj, M. K. Impurity mediated large three photon absorption in ZnS:Cu nanophosphors. *Opt. Mater. (Amst).* **36,** 861–866 (2014).
17. Podila, R. *et al.* Evidence for surface states in pristine and Co-doped ZnO nanostructures: magnetization and nonlinear optical studies. *Nanotechnology* **22,** 095703 (2011).
18. Anand, B. *et al.* The role of defects in the nonlinear optical absorption behavior of carbon and ZnO nanostructures. *Phys. Chem. Chem. Phys.* **16,** 8168–77 (2014).
19. Egblewogbe, M. *et al.* Defect Induced Changes in the Linear and Nanotetrapods. *Mater. Express* **2,** 351–356 (2012).
20. Zhang, H. Y. *et al.* Use of Metal Oxide Nanoparticle Band Gap To Develop a Predictive Paradigm for Oxidative Stress and Acute Pulmonary Inflammation. *ACS Nano* **6,** 4349–4368 (2012).
21. Lee, S. *et al.* ZnO nanoparticles with controlled shapes and sizes prepared using a simple polyol synthesis. *Superlattices Microstruct.* **43,** 330–339 (2008).
22. Hong, H. *et al.* Cancer-targeted optical imaging with fluorescent zinc oxide nanowires. *Nano Lett.* **11,** 3744–3750 (2011).