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Nano particle targeting assessed by novel photo acoustic and pet imaging: Internal normalization by multi spectral imaging

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There is an increased demand for fast and inexpensive methods to determine cancer phenotypes and morphologies. Current *in vivo* diagnostic imaging modalities utilizing X-ray CT, MRI, and PET scans are limited to black-white images that cannot be used to differentiate multiple disease marker contrast agents at a time. In addition, targeting studies in which each nanoparticle (NP) type must be individually administered to an animal result in large numbers of animals that must be used in a study to obtain reliable statistics. This requires both significant time and expense. Photoacoustic (PA) imaging, a hybrid light and sounds imaging technique, has shown to be a safe and inexpensive diagnostic technique with high spatial resolution in 3D. Traditional PA contrast agents, however, tend to have broad absorption peaks in the NIR range which renders it difficult to simultaneously image more than one signal at a time in deep tissue. Here we present the formulation of a series of PA active NPs with sharp and separable absorbance profiles in the NIR range for simultaneous multiplexed imaging. PA dyes are encapsulated inside NPs using the controlled self-assembly mechanism, Flash nanoprecipitation (FNP). Four new contrast agents, with sharp absorbance maxima between 600-900 nm, were created by encapsulating a variety of phthalocyanine derivatives. We were able to simultaneously detect the concentrations of contrast agents mixed together with >95% deconvolution efficacy. As a proof of concept, we co-injected RGD modified NPs and non-modified NPs with different labeling agents and tracked NP biodistributions for both particles simultaneously. Using this technology, we accessed the effect of NP ligand modification on both targeting efficacy onto the tumors and off targeting accumulation in the liver using a single animal model. Over modification of the NPs resulted in rapid liver clearance and poor accumulation in the tumor; at low modifications, the tumor to liver accumulation ratio is 9.9±4.2, while at high RGD modifications the tumor to liver accumulation ratio is 52±22. The ability to simultaneously inject control particles and targeted particles, and to follow their fate greatly enhances the ability to design targeted nanoparticles. The same phthalocyanine dyes effectively chelate PET active cations to enable whole animal PET imaging. The FNP technology enables the production of both NPs that enable PAI and PET imaging.

Recent Publications

1. Lu H D et al. (2017) Assembly of macrocycle dye derivatives into particles for fluorescence and photoacoustic applications. ACS Combinatorial Science. 19(6):397-406.
2. Lu H D et al. (2015) Modulating vibrio cholerae quorum-sensing-controlled communication using autoinducer-loaded nanoparticles. Nano Letters. 5(4):2235-2241.
3. Lu H D et al. (2017) Copper loading of pre-formed nanoparticles for PET-imaging applications. ACS Applied Materials & Interfaces. 10(4):3191-3199.
4. Lu H D et al. (2017) Real-time and multiplexed photoacoustic imaging of internally normalized mixed-targeted nanoparticles. ACS Biomaterials Science & Engineering. 3(3):443-451.
5. Lu H D et al. (2017) Nanoparticle targeting of grampositive and gram-negative bacteria for magnetic-based separations of bacterial pathogens. Applied Nanoscience. 7(3-4):83-93.

Biography

Robert K Prud'homme is a Professor in the Department of Chemical and Biological Engineering at Princeton University, USA. He is the Founding Director of the Program in Engineering Biology. His research program focusses on polymer self-assembly applied to drug delivery. The development of Flash Nanoprecipitation (FNP) in his laboratory enabled the encapsulation of poorly soluble drug compounds and oligonucleotides for therapy directed towards cancer, TB, and injections. FNP is a scalable and continuous process that is enables integrated processing and spray drying for low cost oral and aerosol formulations. Under sponsorship by the Bill and Melinda Gates Foundation, the process is being adopted to formulate new compounds coming from TBA, MMV, and DNDi.

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