Near-Infrared FRET imaging reveals the fate and integrity of lipid nanocarriers in healthy and tumor-bearing mice

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Lipid nanocarriers emerged as promising candidates for drug delivery and cancer targeting because of their low toxicity, biodegradability and capacity to encapsulate a drug or a contrasting agent [1]. However, because of poor understanding of their *in vivo* fate and integrity, their translation from laboratory to biomedical applications is limited. In this work, we exploited the Förster Resonance Energy Transfer (FRET) technique for real time investigation of their stability *in vivo*. Using our recently developed approach of hydrophobic counterion (TPB),[2] we encapsulated two lipophilic NIR cyanine dyes (Cy 5.5/TPB and Cy 7.5/TPB) inside a lipid nanocarrier of 100 nm size.[3] After validation of our FRET nanocarriers in vitro, they were retro-orbitally injected into healthy and tumor bearing mice. Using two-color whole animal NIR imaging, we could quantify the content of the nanocarriers and their integrity directly in blood circulation, liver and tumor xenografts of living mice. This methodology reveal that the particles remain stable in the blood circulation for at least 6h. they accumulate in tumor rapidly in nearly intact form (77% after 2h) through permeability and retention effect (EPR), and then disintegrate with half-life of 4.4 h. In conclusion, we developed a FRET approach that allows directly visualization and quantification of nanocarrier integrity in vivo.

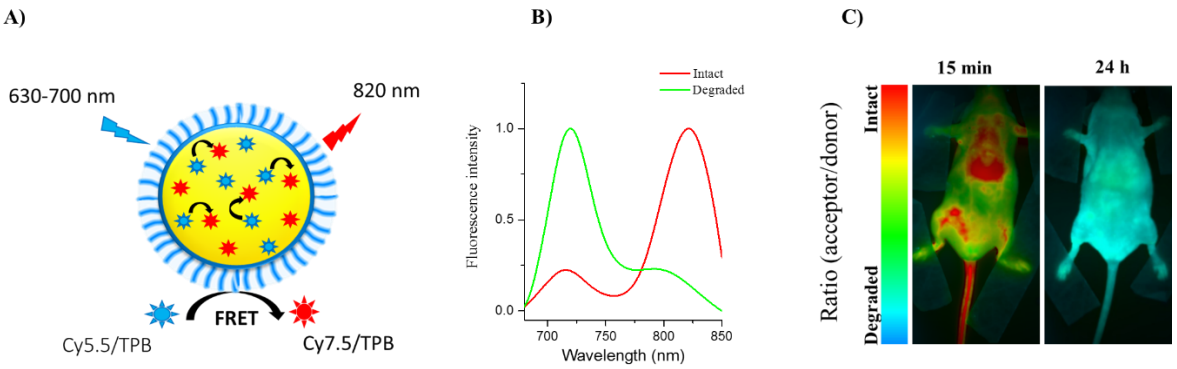

Figure 1. (A) Schematic presentation of FRET system inside lipid nanocarrier encapsulating NIR cyanine dyes. (B) Emission spectra of intact nanocarriers in water and after addition of dioxane. (C) NIR in vivo imaging in living mice using 100-nm FRET nanocarriers at 15min and 24 h.

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2) Kilin VN, Anton H, Anton N, Steed E, Vermot J, Vandamme TF, Mely Y, Klymchenko AS. Counterion-enhanced cyanine dye loading into lipid nano-droplets for single-particle tracking in zebra fish *Biomaterials*, 6 (**2014**), pp. 4950–4957.
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