Proceedings of the World Congress on Recent Advances in Nanotechnology (RAN'16)
Prague, Czech Republic – April 1 – 2, 2016
Paper No. ICNB 102
DOI: 10.11159/icnb16.102

Fluorescent Nanodiamonds Enable Tracking of Prospectively Isolated Lung Stem Cells *in Vivo*

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Extended Abstract

Lung stem/progenitor cells play protective roles in epithelial repair and tissue homeostasis. However, direct isolation of these cells is challenging and little is known about their homing capacity in vivo and they are also potentially useful in regenerative therapy such as repairing damaged or lost lung tissues in patients. Several optical imaging methods and probes have been used to track how lung stem cells incorporate and regenerate themselves *in vivo* over time; however, they are limited by photobleaching, toxicity, and interference from background tissue autofluorescence. But recently we had developed a new and prospective isolation method using glycoproteomics analysis to obtain lung stem cells. We also showed that lung stem cells can be isolated for expansion in culture using a new glycoprotein marker, together with CD45 and CD54, and subsequently tracked *in vivo* with novel fluorescent nanodiamonds (FNDs) as a long-term biolabel. Here, we show subsequently that these isolated cells possess the abilities of cell expansion and sequential differentiation into type II and then type I pneumocytes. And we show that labeling of lung stem cells with FNDs does not eliminate the cells' abilities of self-renewal and differentiation into type I and type II pneumocytes. The FND labeling in combination with fluorescence-activated cell sorting, fluorescence lifetime imaging microscopy, and immunostaining can identify transplanted $CD45^{-}CD54^{+}CD157^{+}$ lung stem cells *in vivo*, and allows tracking of their engraftment and regenerative capabilities with single cell resolution. Time-gated fluorescence imaging of the FND-labeled lung stem cells in mouse tissue sections indicates that they reside preferentially at the bronchoalveolar junctions of lungs, especially in naphthalene-injured mice 7 days after intravenous transplantation. Our results demonstrate not only the remarkable homing capacity and regenerative potential of the isolated lung stem cells, but also the ability of finding rare lung stem cells in vivo using FNDs and time-gated imaging technologies.