Journal of Oral Health & Dentistry
JOHD, 1(2): 42-43
www.scitcentral.com
ISSN: 2638-499X
Short Communication: Open Access

Double-Labeled Transgenic Mouse Model Facilitates Stem Cell Research

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Received August 24, 2018; Accepted September 29, 2018; Published October 28, 2018

INTRODUCTION

A double-labeled transgenic mouse was created in our lab. The male ACTB-EGFP mice (Jackson Lab) mouse was cross-bred with a homozygote mBSP9.0Luc female mouse [1]. We named the mice with both Luc and GFP genes as mBSP9.0Luc/β-ACT-EGFP. The production of the mouse line and the unique features of the cells are illustrated in **Figure 1A**. Using the Xenogen 200 IVIS Imager we could identify pups that were positive for both genes in the offsprings (**Figure 1B**, left panel). Bone marrow stem cells (BMSCs) isolated from mBSP9.0Luc/β-ACT-EGFP was cultured and examined [2]. BMSCs possess the pluripotency to differentiate into a variety of cell types, including osteoblasts, chondrocytes, and adipocytes. The cells were cultured in osteogenic medium showing luciferase expression after introduction of luciferin substrate indicating an osteogenic differentiation of the BMSCs. Non-osteogenic treated cells only showed GFP fluorescent light (**Figure 1B**, right panel).

To test the sensitivity of the IVIS system in detecting signals in a live animal we have performed another round of pilot study using the BMSCs isolated from mBSP9.0Luc/β-ACT-EGFP transgenic mice. After transplantation into the calvarial and mandibular defects in nude mice for 2 and 7 days, respectively, we anesthetized the mice and placed them in the Xenogen imager and luciferase and EGFP expressions were measured using an IVIS Imaging System 200 Series in the live animals as we did previously [3,4]. Shown in **Figure 2** were the representative images displaying strong luciferase and GFP signals in the wound sites.

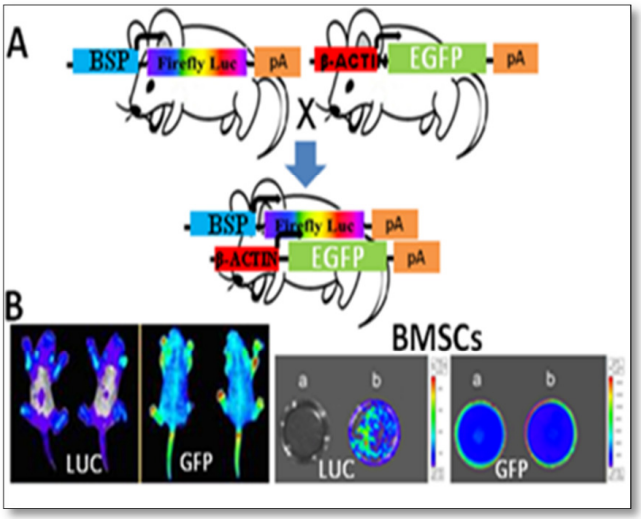

Figure 1. A) Schematic representation of the double labeling mouse with transgenes of murine BSP promoter linked with a luciferase reporter gene (shown as a multicolored band), and beta-actin promoter driving EGFP (shown as a green band). B) Left panel, offspring of the cross-breeding between an ACTB-EGFP transgenic mouse (male, +/-) and a mBSP9.0Luc transgenic mouse (female, +/+) scanned by Xenogen IVIS imaging system); Right panel, BMSCs from BSP-Luc/ACT-GFP mice with double markers were cultured for 7 days in non-osteogenic maintenance medium (a) or osteogenic medium (b), respectively, and were visualized by an IVIS imaging system.

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Citation: Zhang J, Li S, Chen J & Tu Q. (2018) Double-Labeled Transgenic Mouse Model Facilitates Stem Cell Research. J Oral Health Dent, 1(2): 39-41.

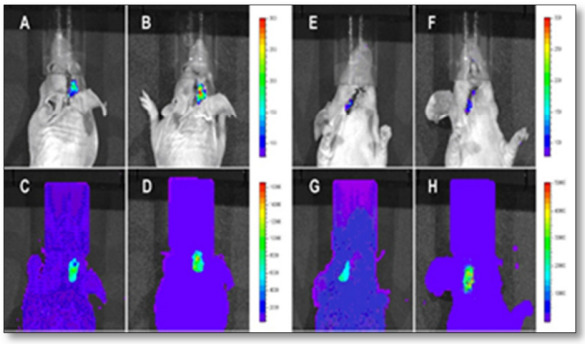

Figure 2. Representative images of evaluation of bone regeneration in cavarial (A-D) and mandible (E-H) defects by using a Xenogen *in vivo* imaging system. A defect of 4 mm in diameter was created on the right side of calvarial bone of nude mice. In a mandible group an ostectomy of 2 × 2 mm was made in the right side of mouse mandibles. Collagen sponge scaffolds with the BMSCs from BSP-Luc/ACT-GFP were implanted over the defects, respectively. Luciferase expression was detected at day 2 (A and E) and day 7 (B and F) post-surgery. GFP fluorescent signals were also visualized at the same time point (C and G for 2 days; D and H for 7 days after implantation).

These double-labeled cells are unique and useful for bone tissue engineering and regeneration studies. One genetic marker is a luciferase reporter gene driven by a mouse BSP promoter that regulates the expression of BSP that is specific to mineralized tissues [1,5-7]. The other genetic marker is GFP driven by a β-actin promoter and a cytomegalovirus enhancer. By scanning the mouse using Xenogen IVIS *in vivo* imaging system which allows real-time, non-invasive exploration of genes and cells in living animals, GFP imaging is used to track the fate and migration of transplanted BMSCs, whereas luciferase imaging serves as a marker for osteogenic differentiation of the transplanted BMSCs because the luciferase-mediated bioluminescence will only be appearing in newly formed bones. This mouse model will greatly facilitate stem cells research as it permits the determination of where these cells originate and how they undergo osteogenic differentiation.

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