

Stem Cells for Pre-clinical Imaging

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Stem Cell Research and Regenerative Medicine

Introduction

With the potential to treat a wide range of disease, from organ damage to congenital defects, stem cell research and tissue engineering form the underlying basis of regenerative medicine. Significant advances in the science of skin regeneration, for example, have now made it possible to develop and grow artificial skin grafts in a

lab for treatment of burn victims. Other therapeutic applications include the use of stem cells to treat and repair central nervous system diseases such as ischemia and cerebral palsy, cardiovascular diseases, as well as autoimmune diseases including type I diabetes. However, critical research addressing safety concerns, exploring therapeutic function, and assessing mechanisms of action must be completed prior to human adoption. IVIS® technology is being widely used to explore stem cell research outcomes in preclinical small animal models, which serve as key test pre-cursors to human clinical trials.

Role for Optical Imaging

Optical imaging technology has emerged as an established tool to assess efficacy and treatment outcomes of cell-based therapeutics in preclinical models. The IVIS technology provides vital clues into the viability and behavior of stem cells post transplantation, aiding the prediction of how these cells might behave in humans. A representative sample of stem cell applications, out of more than 250 peer-reviewed citations, is outlined in the following pages. Below is a table showing the various stem cell and progenitor populations that have been imaged on the IVIS imaging system.

Different Stem Cell Types (Murine/Human)

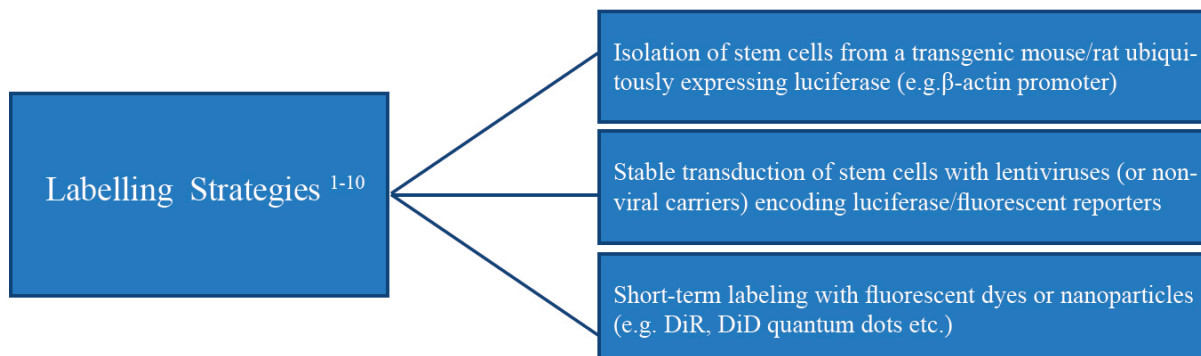
- Embryonic Stem Cells^{1, 2, 11-56}
- Neural Stem Cells^{17, 18, 57-62}
- Mesenchymal Stem Cells^{4, 5, 63-10}
- Hematopoietic Stem Cells¹⁰²⁻¹⁰⁸
- Muscle Stem Cells^{19, 109-111}
- Adipose-derived Stem Cells^{96, 112, 113}

Progenitor Populations

- Different Stem Cell Types (Murine/Human)
- Embryonic Stem Cells^{1, 2, 11-56}
- Neural Stem Cells^{17, 18, 57-62}
- Mesenchymal Stem Cells^{4, 5, 63-101}
- Hematopoietic Stem Cells¹⁰²⁻¹⁰⁸
- Cancer Stem Cells¹²⁶⁻¹³⁸

Labeling Strategies

Stem cells are required to be labeled with appropriate bioluminescent or fluorescent reporters to be imaged noninvasively in vivo. The following strategies for labeling stem cells with proteins and/or chemical conjugate dyes have previously been used with great success.



Applications

Characterization of stem cell behavior and homing patterns.

Stem cell therapies have been proposed as a putative treatment for arthritis, evidenced by clinical trials currently underway. Pre-clinical models often serve as a 'go' or 'no go' decision point, as potential therapies are often validated and characterized in murine models of disease prior to testing them in human subjects. Two critical points of characterization are their route of administration and their subsequent homing and localization into diseased tissue.

In this study by Sutton et al, featured in the Optics Express, December 2009 issue⁶, mesenchymal stem cells labeled with a fluorescent dye (DiD) were intra-peritoneally injected into athymic polyarthritic rats and shown to preferentially accumulate within arthritic ankle joints in vivo. The IVIS has served as a vital tool for imaging stem cell viability, migration and targeting of diseased tissue in various models^{5, 29, 60, 72, 139, 140}.

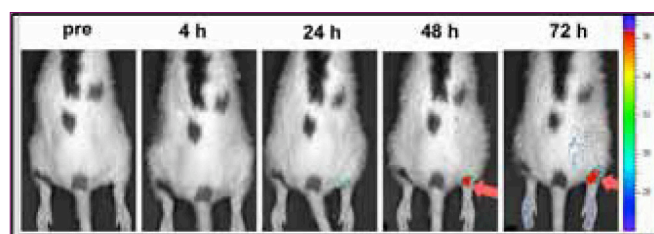


Figure 1. Imaging the accumulation of fluorescent mesenchymal stem cells in arthritic ankle joints (Sutton et al, Opt. Express, 17, p24403, 2009).

Assessment of safety and therapeutic potential in pre-clinical models

In 2009, the FDA cleared the way for the world's first clinical trial for embryonic stem cells in the context of spinal cord injury in the US¹⁴¹. Since then numerous such trials have been undertaken in other parts of the world with varying degrees of success. Due to the controversy widely surrounding embryonic stem cells, a new class of reprogrammed cells called "induced pluripotent stem cells" (iPS) have received considerable attention in the past few years since they are derived from adult cell populations and known to retain stem cell properties and function. However, prior to their adoption in human therapy, rigorous testing of their therapeutic efficacy and safety in pre-clinical mouse models is warranted. The IVIS plays a key role in such pre-clinical evaluations of iPS and numerous other stem cell types^{11, 13, 24, 37, 54, 58, 72, 78, 81, 96, 117, 121, 142-148}.

The example below is a 2010 report published by Tsuji et al in PNAS147. The researchers used IVIS to monitor the viability and therapeutic potential of IPS-derived neurospheres in a mouse model of spinal cord injury, suggesting that IPS can 'safely' promote locomotor function recovery in injured mouse models.

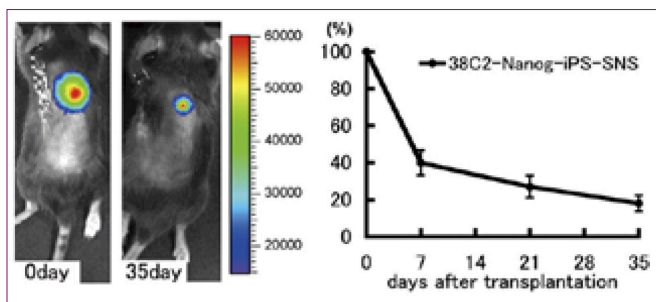


Figure 2. Imaging survival/viability of bioluminescent IPS-derived neurospheres in a mouse Model of spinal cord injury (Tsuji et al, PNAS, 107, p12704, 2010).

Exploration of molecular pathways and mechanisms of action.

Basic research that outlines key pathways and mechanisms by which stem cells survive, differentiate, migrate, and function are fundamental to our understanding of these cells^{14, 149, 150}. The combination of novel optical reporters, creative molecular biology, and imaging with IVIS technology has facilitated such comprehensive insight into these questions. One vital aspect of hematopoietic stem cell research is identification and definition of their 'niche,' a bone marrow microenvironment that both houses and regulates these cells (and their fate).

In a fascinating 2009 report published in Nature, Xie et al⁹ used ex vivo high-resolution microscopy alongside non-invasive (IVIS) imaging to identify and further characterize the stem cell 'niche,' its function, and HSC recruitment.

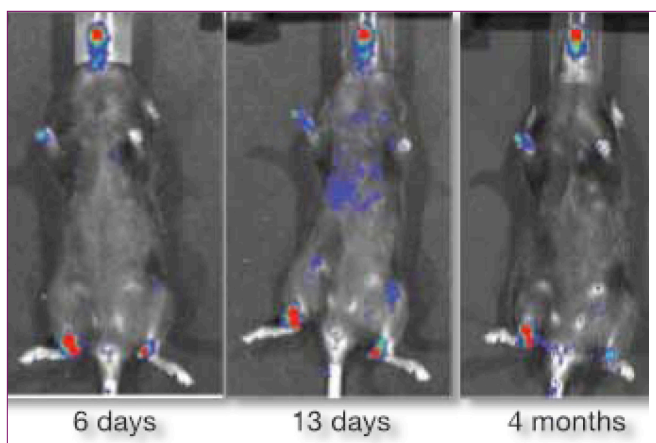


Figure 3. Bioluminescence imaging of hematopoietic stem cell recruitment to their niche in vivo, (Xie et al, Nature, 457, p97, 2009).

Identification and validation of complementary stem cell research technologies.

Several research areas including nanotechnology, biomaterials, and cell and tissue engineering complement stem cell research, and are equally invested in the promise of regenerative medicine. Collaborative developments in these fields have yielded biocompatible and biodegradable materials that coupled with growth factors and relevant biomolecules, provide the right 'scaffold' or environment to

guide stem cells to form functional desired tissues or organs in vivo. Often, the survival and function of seeded cells, as well as interactions between the biomaterials and host tissues can be explored using the IVIS system^{113, 116, 144, 151-156}.

In a 2008 report published in PNAS154, Jennifer Elisseeff's group at Johns Hopkins University used a combination of chondrocyte-secreted morphogenetic factors and hydrogels to commit mesenchymal stem cells (derived from human embryonic stem cells) into a chondrogenic lineage and eventually form cartilaginous tissue in mice. As seen in the figure below, they relied on IVIS imaging to validate the survival, viability and differentiation of MSCs seeded on a biodegradable polyester scaffold containing hydroxyapatite.

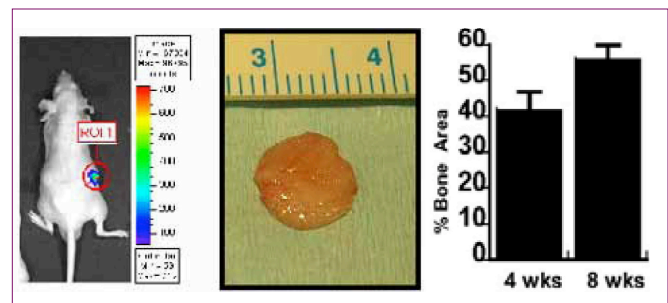


Figure 4. Imaging viability of bioluminescent mesenchymal stem cells seeded on a biodegradable scaffold (Hwang et al, PNAS, 105, p20641, 2008).

Conclusion

In summary, the IVIS is a valuable tool for stem cell research as it enables spatiotemporal and longitudinal monitoring of stem cell processes, cell viability and homing patterns, and therapeutic function in living animals. These preclinical readouts provide insightful cues to clinicians on the safety and efficacy of stem cell and regenerative medicine therapies to treat human disease.

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