Docket #: S00-167

Transgenic Biotracker Mouse

The transgenic biotracker mouse lines carry two or more broadly used reporters, and thus serve as sources for both labeled cells and tissues for transplantation and adoptive transfer experiments. The reporter transgene permits in vivo tracking of a living transplant in recipient animals as well as ex vivo analysis by traditional methods such as flow cytometry and microscopy (either confocal or fluorescence).

The biotracker mice contain multifunctional reporter gene constructs that are composed of the coding sequences for fluorescent proteins, such as GFP and luciferases (e.g. Luc from the firefly). The luciferases used in the current biotracker mice are either the native form, which emits yellow green light (max. 565 nm), or Stanford's red-shifted mutant, which emits in the orange-red range (max. 610 nm).

The biotracker mice serve as sources of traceable cells since the cells in these animals express reporters uniformly in hematopoietic cells and in all of the major tissue types analyzed thus far, including heart, muscle, skin, and pancreas (i.e. islet cells). The cells display both fluorescence (thus enabling analysis by flow cytometry or fluorescence microscopy) and luminescence (enabling in vivo measurements using in vivo bioluminescent imaging (BLI)). The use of both reporter functions enables cells to be traced ex vivo in a luminometer or by cytometery, or cells and/or entire organs to be detected in vivo with low light imaging systems such as those that employ intensified or cooled CCD-cameras.

Additionally, the mice are useful as an in vivo system to follow and assay the tissue distribution of novel luciferase substrates and/or methods designed to deliver small molecules to tissues. In the transplant models the labeled tissues allow monitoring of the success and immunoacceptance of the graft, and thus the mice can be used to test drugs that slow or prevent graft rejection in animal models.

Exemplary transplant applications include heart transplantation experiments. For instance, the heart of a heterozygous CMV-GFP-luc mouse was transplanted as a heterotopic xenograft into rats and monitored for luminescence and cardiac output (heart score) for six days. Similar studies were performed on pancreatic islets.

Further studies are ongoing on hematopoietic cells that were taken from the biotracker mouse and used to reconstitute immune deficient mice. The goal of these efforts is to monitor the differentiation and transfer of bone marrow, hematopoietic stem cells, and other members of the hematopoietic lineage (such as T- and B-cells).

Advantages

- Analysis by CCD camera: The transgenic mouse with a dual reporter allows monitoring of the cells in real time in vivo using low light imaging systems such as intensified and cooled CCD cameras. The mouse also enables analysis of individual cells by ex vivo assays based on fluorescence detection by any number of methods (microscopy, flow cytometry). The sensitivity of the in vivo imaging strategy that is used to detect the cell and tissue grafts allows detection of as few as 1000 cells in vivo (Edinger et al 1999, Sweeney et al. 1999).
- Tracking of live transplanted cells via ubiquitously expressed reporters: There are, at present, no other modalities that allow detection of such small numbers of engrafted cells and there are no other dual function reporter transgenic mice with constitutive and ubiquitously expressed reporters. BLI is rapid and comparatively inexpensive method for in vivo cellular and molecular imaging such that in combination with labeled tissues from lines of mice as described in this disclosure, high throughput assays that measure engraftment and survival can be used in drug screening.
- Inexpensive alternative to PET and SPECT imaging: The other methods for monitoring immune cell migration in situations of infection, neoplastic disease or normal development include PET and SPECT imaging, which require radiolabeled materials. BLI is an extremely sensitive and versatile imaging method that does not require radioactive materials, and when coupled with a source of labeled primary cells and tissues becomes a powerful tool for drug discovery.

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