Docket #: S03-250

Somatic Recombination with MADM (Mosaic Analysis with Double Markers) - ackson Labs mouse strains 013749 and 013751

Stanford scientists in Dr. Liqun Luo's laboratory have developed a patented method for site-directed somatic cell recombination and concurrent labeling of "knock in" cells. The technique, mosaic analysis with double markers (MADM), allows for highly sensitive detection of recombination events down to the single-cell level. This enables researchers to study gene function in particular tissues and developmental stages, mimic loss of heterozygosity in cancers, and generate specific mutant mouse models.

Stage of Research
The inventors have used MADM to achieve tumor-suppressor gene inactivation and concurrent labeling of sporadic mutant cells in mice, closely mimicking the loss of heterozygosity that occurs in human cancers. The inventors continue to develop the MADM technology on several other mouse chromosomes with improved transgenes.

Applications

- **Research of mutant mouse models:**
  - uniquely mark homozygous mutant cells and their wild type siblings with two different colors in the same animal
  - analyze naturally occurring mutants instead of just mutations made through gene targeting
  - identify individual labeled mutant cells due to efficiency of mitotic recombination

    - generate conditional knock out mice to mimic sporadic loss of tumor suppressor genes in human cancers
- **Research of wild type mice:**
    - study stem cell behavior
    - label individual cells to analyze normal biological processes

Advantages

- **Specific labels** - with either GFP or RFP in a regulated manner
- **Efficient**
- **Cost effective**
- **Permanent label** - marker stays on permanently (controlled by a ubiquitous promoter) during the life span of the cell

Publications

- "Mosaic analysis with double markers reveals tumor cell of origin in glioma." Liu C, Sage JC, Miller MR, Verhaak RG, Hippenmeyer S, Vogel H, Foreman O, Bronson RT, Nishiyama A, Luo L, Zong H. *Cell*. 2011 Jul 22;146(2):209-21. doi: 10.1016/j.cell.2011.06.014. Epub 2011 Jul 7.
- "'Mosaic mouse' technique offers powerful new tool to study diseases, genetics.", *Stanford Report*, May 6, 2005. Muzumdar MD, Luo L, and Zong H
- "Modeling sporadic loss of heterozygosity in mice using Mosaic Analysis with Double Markers (MADM)." *PNAS* 104(11): 4495-500 (2007).
- "Mosaic Analysis with Double Markers in Mice." Hui Zong, J. Sebastian Espinosa, Helen Hong Su, Mandar D. Muzumdar, and Liqun Luo *Cell*, Vol 121, 479-492, 6 May 2005.
- "Dendrite morphogenesis depends on relative levels of NT-3/TrkC signaling." Joo W, Hippenmeyer S, Luo L *Science* 346(6209):626-9, October 2014.
- Ali SR, Hippenmeyer S, Saadat LV, Luo L, Weissman IL, Ardehali R *PNAS* 111(24):8850-5, June 2014.
- "Mosaic Analysis with Double Markers Reveals Cell-Type-Specific Paternal Growth Dominance." Hippenmeyer S, Johnson RL, Luo L *Cell Reports* Epub, February 2013.
- "Extensions of MADM (mosaic analysis with double markers) in mice." Tasic B, Miyamichi K, Hippenmeyer S, Dani VS, Zeng H, Joo W, Zong H, Chen-Tsai Y, Luo

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- ”Genetic mosaic dissection of lis1 and ndel1 in neuronal migration.” Hippenmeyer S, Youn YH, Moon HM, Miyamichi K, Zong H, Wynshaw-Boris A and Luo L *Neuron* 68(4):695-709, November 2010.
- ”Uncoupling dendrite growth and patterning: single-cell knockout analysis of NMDA receptor 2B.” Espinosa JS, Wheeler DG, Tsien RW, Luo L *Neuron* 62(2): 205-17, April 2009.
- ”Timing neurogenesis and differentiation: insights from quantitative clonal analyses of cerebellar granule cells.” Espinosa JS and Luo L *The Journal of Neuroscience* 28(10): 2301-12, March 2008.

Patents

- Published Application: 20050125850

Innovators

- Liqun Luo
- Hui Zong

Licensing Contact

Brenda Martino

Biological Materials Specialist

Email