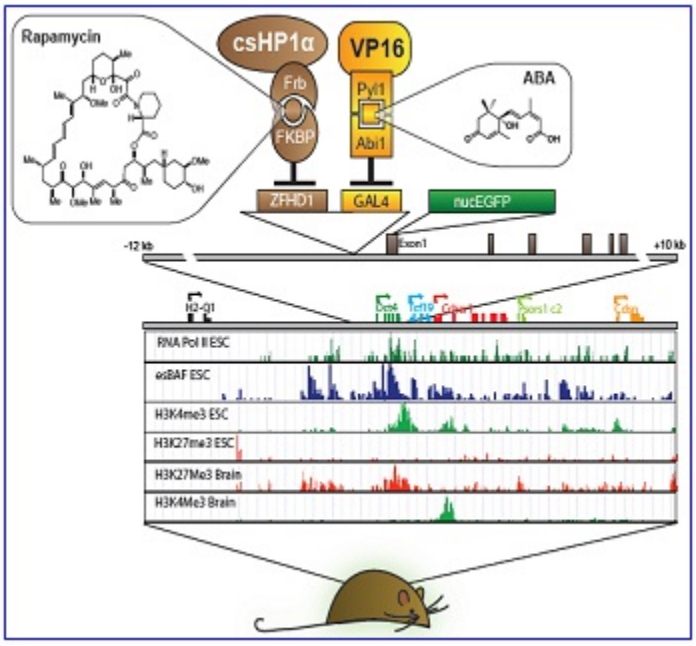
Docket #: S11-188

Chromatin in-vivo Assay (CiA) mouse

Researchers in Prof. Gerald Crabtree's laboratory have produced a mouse allowing high-throughput screening for activity and inhibition of virtually any chromatin modifier in any murine tissue. This technology – Chromatin in vivo Assay (CiA) System at Oct4 – provides temporal control to target chromatin-modifying activities and to study their effects on Oct4 transcription in the context of native chromatin architecture. We anticipate that the primary use of these mice and tissues derived from them will be to identify novel chromatin and transcriptional regulators. The approach can also be used to validate small molecules in the context of living animals. Finally, since the approach aims to modulate Oct4 transcription in pluripotent as well as differentiated tissues, it could be used to identify modulators of reprogramming and pluripotency in general.



The CIA:Oct4 mouse, was generated by targeting one allele of the Pou5f1 gene by homologous recombination to introduce two arrays of DNA binding sites (12XZFHD1 and 5XGal4) in the promoter region upstream of an in-frame EGFP reporter. Genomic screenshot shows high levels of active histone marks and the absence of repressive

marks at the active Oct4 locus in ES cells. The chromatin landscape of the Oct4 locus is transformed in differentiated tissues such as fibroblasts and brain as the locus is repressed.

Stage of Research
The inventors have produced the double knock-in CiA:Oct4 mouse and used it to study the initiation and propagation of epigenetic events as well as their interaction with specific transcriptional regulators.

This mouse model has been deposited at Jackson Labs stock number: 023515

Applications

- **Screening**
  - small molecules or siRNAs that can reprogram differentiated cells to **iPS cells**
  - small molecules or siRNAs that modulate any desired chromatin modification, such as those at fault in many **human cancers and diseases**
- **Reprogramming** - tool to define molecules contributing to reprogramming; **allows validation of small molecule modulators in the context of a developing mouse or embryo**

Advantages

- **High temporal control** - ability to add and remove any activity of interest in real time:
  - ability to separate order of events on gene expression, distinguish primary from secondary effects
  - ability to remove initiating event and if desired recruit a second event
- **Assay in living cells or mice** with kinetic measurements in a quantitative framework to elucidate rates of reaction
- **Model the pathways involved and validate therapeutic actions in the context of a living mouse**

Publications

- N.A. Hathaway, O. Bell, C. Hodges, E.L. Miller, D.S. Neel and G. R. Crabtree, Dynamics and Memory of Heterochromatin in Living Cells *Cell* June 14, 2012, Vol. 149, Issue 7, 1447-1460.

Patents

- Published Application: WO2013188406

Innovators

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