Docket #: S02-299

p53-VP16 chimera knock-in mouse

Researchers in Dr. Laura Attardi's lab have created a knock-in mouse strain which generates a form of p53 that is not subject to degradation by the proteasome. p53 is a tumor suppressor protein that senses and responds to cellular stress and is crucial for genomic stability and thus is involved in preventing cancer. In this mouse the wild-type p53 locus is replaced with a p53-VP16 fusion; such that the p53 transactivation domain is replaced with that of the VP16 transactivator protein. The p53-VP16 is silenced through an upstream floxed transcriptional stop element until Cre recombinase is expressed and the transcriptional stop element is excised. Furthermore, the Mdm-2 ubiquitin ligase binding domain has been removed thereby increasing the stability of p53. This mouse will serve as a useful model for investigating and developing p53-based cancer therapeutics.

Stage of Research
The inventors demonstrated, through analysis of mouse embryo fibroblasts derived from these mice, that upon activation of the p53-VP16 gene there is very potent growth suppression. In addition, they have shown that this fusion protein is like wild-type p53 in its ability to activate p53 target genes.

Applications

- Basic and pre-clinical research tool for:
  - Development of cancer therapeutics.
    - Including potential for development of the fusion protein as a therapeutic for tumors lacking p53.
  - Study of p53 activities and function.

Advantages

- Mice can show proof-of-principle efficacy in tumor suppression/regression in vivo.
- The p53-VP16 fusion protein, as compared to wild-type p53,:
    - Has the same growth suppression and target gene activation activities.
    - Is more stable.
    - Is more potent.
    - Has the potential to be a more effective cancer therapeutic.

Publications

- Johnson TM, et al. Knockin mice expressing a chimeric p53 protein reveal mechanistic differences in how p53 triggers apoptosis and senescence. Proc. Natl. Acad. Sci. USA 2008;105:1215-1220.

Innovators

- Laura Attardi
- Tyler Jacks

Licensing Contact

Brenda Martino

Biological Materials Specialist

Email