

Docket #: S08-154

Mitochondrial aldehyde dehydrogenase 2*2 (ALDH2*2) knock-in gene targeting mice-an experimental model for a prevalent human genetic disorder in East Asians

A common dominant negative allele, *Aldh2*2*, exists in the human population. The *ALDH2*2* mutant retains only about 1-3% of the enzymatic activity of a corresponding wild-type *ALDH2* and affects >40% of the East Asian population (including Japanese, Chinese, Taiwanese and Koreans with an estimated > 1 billion affected individuals). Reduced *ALDH2* activity has been associated with a range of human metabolic disorder and diseases. Accumulation of biogenic/xenogenic aldehydes in *ALDH2*2* individuals are known to cause sensitivity to alcohol intoxication (hangover), ischemic tissue damage, free-radical induced damage in an organ, such as acute myocardial infarction, heart failure, stroke, Alzheimer disease, Parkinson's disease, other neurodegenerative diseases, alcohol-induced liver cirrhosis, cancers of upper digestive track, insensitivity to nitroglycerin treatment, and hyper-sensitivity to certain drug metabolism.

This invention creates an identical genetic model for animal research specifically for human subjects carrying the *ALDH2*2* allele. No such genetically engineered animal exists currently. This mutation affects an estimated >1 billion people.

This invention offers an innovative idea for testing of drug/pharmaceuticals sensitivity and treatment in human *ALDH2*2* carriers. Currently the usage of most of the prescribed pharmaceuticals does not take into account of human genetic polymorphism. This is an important aspect in research and application of pharmacogenetics. We also provide in vitro data to indicate that *ALDH2*2* enzyme may be

sensitive to some drugs that are previously unknown or have not yet been described in the literature.

Applications

- To provide a proper human analog of the E487K (ALDH2*2) using a genetic mouse strain.
- Ideal animal model for commercial drug testing, treatment and drug discovery.

Advantages

- The knock-out mice represents complete inactivation of the ALDH2 gene (via gene interruption) and the naturally occurring ALDH2*2 allele in the large human population.
- The ALDH2*2 knock-in mice are completely identical to the human ALDH2*2 carriers. The mice segregate to both heterozygous and homozygous genotypes as in the human population
- It is a superior experimental system and innovation for the valuable research purposes. In addition, the partially inactive enzyme offers the opportunity for the discovery of small drug molecules.

Innovators

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