

## Data Sheet for JAX<sup>®</sup> Mice Strain NONcNZO10/LtJ

<b>Stock Number</b>	<b>Strain Name</b>
<b>004456</b>	<b>NONcNZO10/LtJ</b>
Common Name	RCS-10
Type	Recombinant Congenic
H2 Haplotype	<i>nb1</i>
Donor Strain	NZO/HILt
Background Strain	NON/Lt
Appearance	albino
Related genotype:	<i>A/A Tyr<sup>c</sup>/Tyr<sup>c</sup></i>



**JAX<sup>®</sup> Mice Strain NONcNZO10/LtJ**

### Advantages:

Obesity in NONcNZO10/LtJ reflects most human obesities because it is:

- polygenic, not monogenic
- moderate, not morbid obesity

As in most humans with obesity/Type 2 diabetes syndromes, these mice:

- have a normal leptin/leptin receptor axis
- are not hyperphagic
- do not exhibit hypercorticism
- show no obvious thermoregulatory defects
- have normal reproductive ability

Development of diabetes syndrome occurs when these mice are on a chow diet containing 4-6% fat. Diets of higher fat content, although untested, probably accelerate onset of hyperglycemia.

### Uses:

This strain represents a model of polygenic obesity and obesity-induced diabetes (diabesity) and may be useful for pharmacogenetic analysis.

### Strain Description

- Hyperglycemia (males) between 12-16 weeks  
   > 85% diabetic by 24 weeks
- Increased serum triglyceride levels (males)
- Moderate obesity (both sexes)
- Pancreatic islet atrophy
- Moderate to severe liver steatosis
- Females are normoglycemic; may be used as controls
- Good reproductive efficiency
- Serum insulin and leptin values are lower than NZO/HILt, and are moderately elevated above NON/Lt males



Reifsnyder PC, Churchill G, Leiter EH. Maternal environment and genotype interact to establish diabetes in mice. *Genome Res* 2000; 10:1568-78.

Reifsnyder PC, Leiter EH. Deconstructing and reconstructing obesity-induced diabetes (diabetes) in mice. *Diabetes* 2002; 51:825-32.

Taylor BA, Wneck C, Schroeder D, Phillips SJ. Multiple obesity QTLs identified in an intercross between the NZO (New Zealand obese) and the SM (small) mouse strains. *Mamm Genome* 2001; 12:95-103.

Watkins SM, Reifsnyder PC, Pan H-J, German B, Leiter EH. Lipid metabolome-wide effects of the peroxisome proliferator-activated receptor gamma agonist rosiglitazone on a new mouse model of type 2 diabetes. *J Lipid Res* 2002; 43:1809-17.

#### Additional Web Information

New Polygenic Obesity Mouse Models. JAX Notes<sup>™</sup>, Fall 2002; 487:10-11. <http://jaxmice.jax.org/library/notes/487n.html>

The Leiter Laboratory web page at The Jackson Laboratory. The current genome-wide scan profiles for all ten

NONcNZO strains can be viewed at Dr. Leiter's Web site. [http://www.jax.org/staff/leiter/labsite/type2\\_genomics.html](http://www.jax.org/staff/leiter/labsite/type2_genomics.html)

## **Endocrine Profiles in Mice with Type 2 Diabetes—a Collaborative Study with Linco Research, Inc. and Dr. Edward Leiter**

A collaboration between the research laboratory of Dr. Edward H. Leiter at The Jackson Laboratory (Bar Harbor, ME) and LINCO RESEARCH, INC. (St. Louis, MO.) was established to use endocrine profiling to distinguish two recently-developed mouse models for the study of polygenic obesity/type 2 diabetes. The LINCO Research, Inc. LINCOPlex<sup>®</sup> multiplex technology permitted simultaneous determination of multiple endocrine analytes in a small volume (20 µl) of plasma, thus enabling The Jackson Laboratory research team to repetitively sample the same individuals during the prodromal stages, which are characterized by either uncomplicated obesity or a diabetes-precipitating obesity. This technology provided new insight into the pathogenic basis for the diabetogenic obesity.

The mice tested included NONcNZO10/LtJ (line 10) and NONcNZO5/LtJ (line 5); two new polygenic models developed by selectively combining multiple genes from two inbred strains (NZO/HILtJ and NON/LtJ) with independent type 2 diabetes and/or obesity susceptibilities. Plasma endocrine hormones (insulin, leptin), adipokines (adiponectin, resistin), plasminogen activator inhibitor-1 (PAI-1), as well as a cluster of cytokines implicated in obesity/diabetes were analyzed in groups of 3-5 mice of each strain (both sexes). Sampling points were at ages 4, 6, 8, 10, 12, 14, and 16 weeks. This time course covered the post-pubertal window at 12-16 weeks when line 10 males transited from normoglycemia (plasma glucose <250 mg/dl) to chronic hyperglycemia (plasma glucose > 250 mg/dl). Body weights and plasma glucose values were recorded at each sampling point for correlation with the endocrine/adipokine values.

The LINCOPlex<sup>®</sup> assays (mouse adipokine 8-plex panel) revealed an important difference in the diabetes-resistant line 5 and the diabetes susceptible line 10: an unusual delay in the ability of line 10, but not line 5 males to compensate for obesity development with an early increase in plasma insulin. In Line 5 males, the LINCOPlex<sup>®</sup> assays showed a transient spike in plasma insulin over the 6- 8 week time points coinciding with maintenance of normal plasma glucose values despite progressive weight gain and development of moderate obesity by 16 weeks of age. Although obesity development occurred at the same rate in Line 10 males, they failed to show the early spike in plasma insulin. Rather, moderate plasma

insulin elevations occurred only after plasma glucose concentrations had increased at a late post-pubertal stage (12 weeks). According to Dr. Edward Leiter, this suggests that an intrinsic pancreatic beta cell defect in line 10 distinguishes its diabetes.

Consistent with their development of increased adiposity, both line 5 and line 10 males exhibited higher mean plasma leptin concentrations than did parental NON/Lt males. However, these increases were relatively modest. Hyperleptinemia, like hyperinsulinemia, is not extreme in either line. In the case of the diabetes-developing line 10, the LINCoplex<sup>®</sup> assays demonstrated that plasma leptin, like plasma insulin, follows rather than precedes the initial period of rapid weight gain occurring in the pre- and peri-pubertal period.

These two new models, because of their polygenic etiology and their more moderate obesity, and plasma hormone concentrations, more accurately reflect the more prevalent form of type 2 Diabetes in humans, and thus should prove an important addition to the monogenic obesity mutation stocks currently distributed by The Jackson Laboratory. The LINCoplex<sup>®</sup> mouse adipokine panel, powered by the Luminex xMAP technology, now makes it possible to simultaneously analyze several endocrine hormones as well as cytokines in a single, small volume of mouse serum or plasma sample and thus, provides a useful tool for characterization of various mouse phenotypic models.