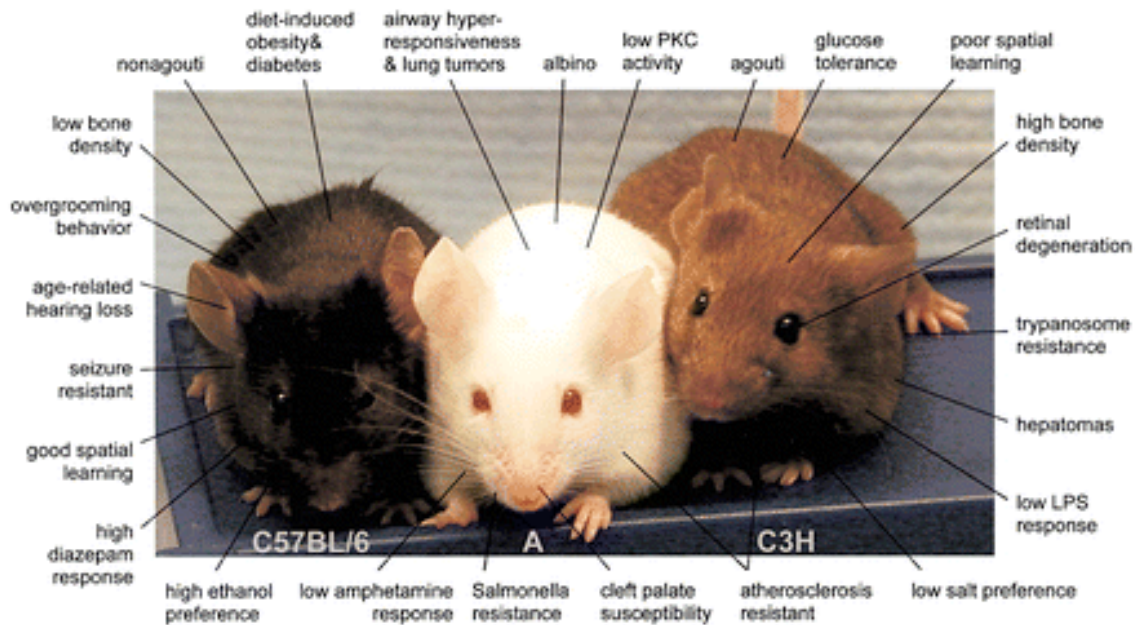


## Mouse (*Mus musculus*)

- 19 chromosomes, X, Y



### Inbred strains:

- » Created by 20 consecutive generations of brother-sister mating
- » All same sex members of an inbred strain are genetically identical (clones)
- » Members of an inbred strain are homozygous at every locus in the genome
- » Very useful for dissecting the genetic and environmental factors that affect quantitative traits
- » Inbred individuals tend to be less vigorous than outbred individuals (inbreeding depression) due to the effects of deleterious recessive alleles

### Technologies for manipulating the genome

#### 1) *Transgenic Mice*

- random integration of recombinant DNA into any chromosomal location  
Purpose:
  - Analysis of regulatory elements governing tissue-specific or hormonally (behaviorally, drug-induced?) gene expression.
  - Analysis of phenotypic consequences of altered gene expression:
- Over-expression of normal gene product  
“Gain-of-function”  
Expression of mutant proteins, including dominant-negative forms that inhibit or impair normal gene function
- Use for insertional RANDOM mutagenesis. The mutated gene is “tagged” and

can be cloned rapidly => gene discovery

2) *Gene targeting*- modification of the mouse genome at precise chromosomal location

Applications:

- 1) Derivation of null alleles
- 2) Derivation of allelic series and point mutations
- 3) Chromosomal engineering (translocations, megabase deletions)
- 4) Conditional gene ablation
- 5) High throughput genetics

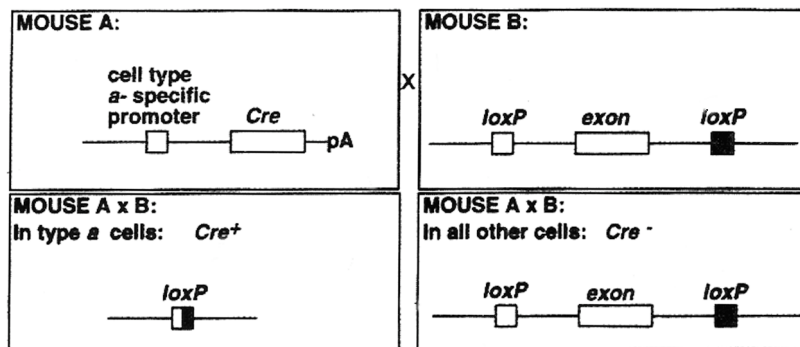
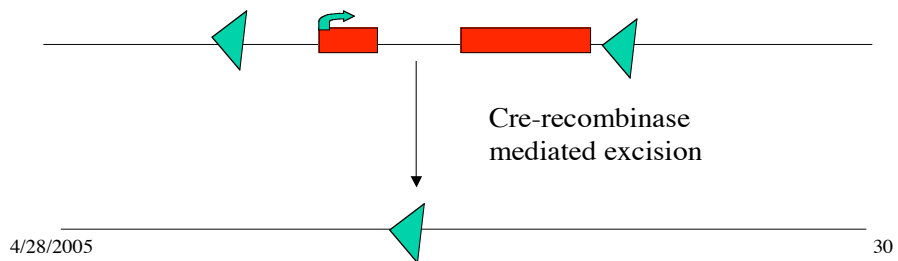
Making “mosaic” mice: tissue-specific and inducible manipulation of the genome

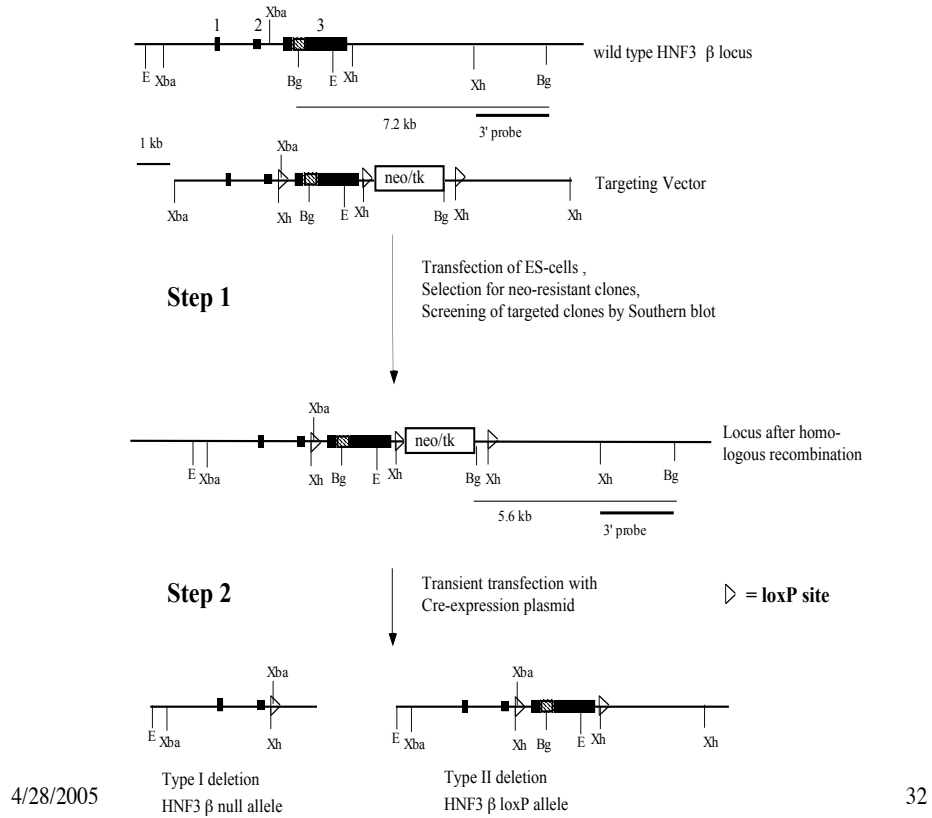
**Purpose:** To overcome embryonic or perinatal lethality of null mutations that prevent the analysis of a gene’s function in tissue of interest

The Cre/loxP system from bacteriophage P1

*loxP*: DNA site, or “locus of crossing over”,  
34 bp sequence NOT NORMALLY present in the mouse genome

*Cre*: recombinase enzyme (single polypeptide) that cuts and ligates DNA ONLY at *loxP* sites





## Types of Cre-recombinase mice

### A) tissue-specific, constitutive

- conventional transgenic (CaMK-II promoter)
- YAC or BAC transgenics
- place into gene of choice by gene targeting (see above)

### B) Inducible systems:

- tetracycline-inducible system (3 mice)
- interferon-inducible Cre (2 mice, no control over tissue-specific expression)
- steroid-hormone receptor/Cre fusion proteins expressed under tissue-specific promoter (RU486 or tamoxifen)

