Animal models for neurological diseases
   Drug-induced animal model
   Transgenic animal model

Parkinson’s disease
   * selective loss of dopaminergic neurons in substantia nigra
   * motor function deficit
     constant tremor at rest
     muscle and limb rigidity
     limited initiation movement
     diminished spontaneous movements
Parkinson’s disease

Genetic factor: Two genes, alpha-synuclein and parkin, linked to PD.

- **classical PD**: presence of intracytoplasmic Lewy bodies
- Major component of Lewy body: filaments of **alpha-synuclein**.
- Two point mutations in alpha-synuclein are known genetic causes of PD.

**AR-JP** (autosomal recessive juvenile parkinsonism: rare form of PD)
- Onset: adolescence to young adult $\Rightarrow$ progression into incapacitation in 20-30 years
- Parkin: A large gene >500 kilobases with 12 exons
- Deletion of exons in AR-JP

Environmental factors also involved?
- **MPTP** (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) causes PD like-disorder.

*DIAGRAM: A toxic pathway of MPTP in the CNS. MPTP crosses the blood-brain barrier and enters neurons, astrocytes, and other cells. It is converted to MPP primarily by MAO-B in astrocytes. MPP is taken up into dopaminergic nerve terminals by a high-affinity dopamine transporter. MPP appears to be concentrated by mitochondria and can inhibit oxidative phosphorylation.*
Huntington’s disease
  Autosomal dominant disease
  Mid-life onset
  Loss of neurons in caudate and putamen
  Indiscriminate “release” of entire behavior
  ↓
  * random movement in various body parts at random sequences (chorea)
  * involuntary, repetitive writhing movement and abnormal postures (dystonia)
Alzheimer’s disease (AD)

Two major hallmarks of AD

1. Neurofibrillary tangles containing tau
   Tau: microtubule associated protein in axons
   stabilizes axonal microtubules in normal cells
   In AD: tau abnormally (hyper)phosphorylated
   aggregated into paired helical filaments
   loss of its ability to maintain the microtubule tracks

2. Senile neuritic plaques
   extracellular core of amyloid β peptide
   surrounded by degenerating neuronal processes

Risk factors
   Age
   presenilin -1 mutation (most cases)
   presenilin 2 mutation
   ApoE

Amyloid cascade hypothesis
   APP⇒Aβ40/42
Presenilins

- presenilin 1 (463 aa), presenilin 2 (448 aa)
- transmembrane protein (8 TM domains)
- localized in ER and possibly in Golgi
- a link between presenilin mutations and APP proteolysis

Fig. 1. Notch and amyloid precursor protein (APP) proteolytic processing. The domain structures of mouse Notch 1 and human APP/770 are indicated. APP and Notch are drawn approximately to scale. The regions that are important for proteolytic processing are magnified and the amino-acid sequences are displayed using the one-letter code. Notch 1 is cleaved in the ectodomain by furin and possibly also by Kuzbanian11,12, while APP is cleaved by α- and β-secretase, as indicated13. Both proteins are cleaved in their transmembrane domain by a γ-secretase-like activity that is controlled by presenilin 1 (Ref. 2, 6). In the case of APP two cleavage sites are predominant, one at residue 40 (γ40) and one at residue 42 (γ42) of the amyloid peptide sequence14. Asterisks indicate the localization of clinical mutations in the APP and presenilin-1 sequences. Abbreviations: ANK, ankyrin repeats; IAR, amyloid peptide; CHO, N-glycosylation site; EGF, epidermal growth factor repeats; KPI, kringle proteinase-inhibitor domain; LN, Lin Notch domain; C, signal peptide; P3, P3 peptide; PEST, PEST sequences; TM, transmembrane domain.
Transgenic mice as an animal model
specific change in a targeted gene
ex. gene knockout mice
Disruption of the targeted gene
Insertion of selection marker(s)
by homologous recombination

Fig. 1  The PNS procedure used to enrich for ES cells containing a targeted disruption of gene X. a. A gene X-replacement vector, that contains an insertion of the neo' gene in an exon of gene X and a linked HSV-tk gene, is shown pairing with a chromosomal copy of gene X. Homologous recombination between the targeting vector and genomic X DNA results in the disruption of one copy of gene X and the loss of HSV-tk sequences. Such cells will be X−, neo' and HSV-tk− and will be resistant to both G418 and GANC. b. Because non-homologous insertion of exogenous DNA into the genome occurs through the ends of the linearized DNA, the HSV-tk gene remains linked to the neo' gene. Such cells will be X−, neo' and HSV-tk− and therefore resistant to G418 but sensitive to GANC. Open boxes denote exons or flanking DNA sequences, closed boxes denote exons and cross-hatch boxes denote the neo' or HSV-tk genes.
Transgenic mice
1. Plasmid construct
2. Transfection of embryonic stem cells
3. Selection of successfully transfected stem cells
4. Implantation to female mice
5. Chimeric offspring (+/-)
6. Obtaining (-/-) transgenic mice by mating
Genetic therapies for neurodegenerative diseases

1. Direct delivery of genes in viral vectors
   - uptake of viral particles at the nerve terminal
   - retrograde transport to the nucleus
   - integration into genome (replication defective virus)
   - stable expression of the inserted gene

2. Grafting genetically engineered cells
   - production of neuroactive compound at the site grafted