Applications of transgenic technology

Transgenic animals are divided into **5** classes based on their purposes -

a) Disease models
b) Transpharmers
c) Xenoplanters
d) Food sources
e) Biological models

Disease models

- Animals that have been genetically altered to express some aspect of human disease.
- Etiology of complex diseases & to develop potential therapies without the use of human subjects.
- Eg. AIDS mouse, Alzheimer's mouse, Oncomouse.
  Other models - HTN, DM, CAD etc

Oncomouse

- 1st patented transgenic animal
- Created by Philip Leder and Timothy Stewart of Harvard University in 1984.
- To study cancer formation and to screen anti-tumor drugs
- 13 different strains were engineered to contain a human oncogene that causes tumor formation .

Transgenic models for Diabetes

- For studying the genes, & their role in peripheral insulin action.
- Models of insulin secretion –
  Glucokinase,
  hepatic glucose production in T2 diabetes
- Transgenic mouse model → IDDM
  (by retroviral vector method)
- Others –
  β receptor knockout mouse,
  Uncoupling protein (UCP1) knockout mouse,
  Acute & chronic models for antidiabetic agents

Transgenic models for Atherosclerosis

- **Plasma cholesterol** homeostasis –
  Receptor-mediated endocytosis of lipoproteins.

Atherosclerosis

High susceptibility	**Low susceptibility**
➢ LDL gene knock-out mice	➢ LDL overexpression
➢ Apo A overexpression	➢ Apo A knock-out mice
➢ Apo E knock-out mice	➢ Apo E overexpression
- ↑ plasma cholesterol	– ↓ plasma cholesterol

Transpharmers

- Transgenic animals which are genetically engineered to produce a human pharmaceutical (recombinant protein) in their saliva, milk, urine, or blood. - "Pharming"

- 1920s: Insulin extracted from pig pancreas
- Early 1980s: human insulin prepared in recombinant bacteria
- Synthesis of complex proteins requiring post-translational modifications to remain stable
  - **Mammalian cells**

Eg for Human RPs synthesized by transgenic technology

RP (construct)	TA/method of production
Albumin (native gene)	Cow/NT
α-fetoprotein (native gene)	Goat/NT
Butyrylcholinesterase (cDNA)	Goat/NT
Granulocyte colony-stimulating factor (native gene)	Goat/NT
Growth hormone (native gene)	Goat/NT
Antithrombin (cDNA)	Goat/MI
Coagulation Factor IX (mini-gene)	Mouse/MI
Tissue plasminogen activator (cDNA)	Goat/MI
Coagulation Factor IX (cDNA)	Goat/MI
Growth hormone (native gene)	Cow/NT
Granulocyte colony-stimulating factor (native gene)	Mouse/MI
Erythropoietin(cDNA)	Mouse/rabbit/MI
Lysostaphin (native gene)	Cow/NT
Lysostaphin (cDNA)	Mouse/MI
C1-esterase inhibitor (native gene)	Rabbit/MI
Coagulation Factor IX (cDNA)	Pig/MI
Coagulation Factor VIII (cDNA)	Rabbit/MI

Examples of mAb production in transgenic animals (TAs)

Antibody binding antigen	TA/constructs
CD6-receptor	Mouse/two native genes
Envelope glycoprotein S (gastroenteritis coronavirus)	Mouse/two native genes
Envelope glycoprotein S (gastroenteritis virus)	Mouse/two cDNA
BR96 anti-Lewis Y	Mouse/two native genes
BR96 anti-Lewis Y	Mouse/two native genes
CD20-receptor	–"–
Surface antigen (Hepatitis A virus)	–"–
Surface antigen (Hepatitis B virus)	–"–

Xenotransplanters

- Transgenic animals that are genetically modified to have organs that can be transplanted into humans.
- Do not express key foreign antigens.
- Promising alternative to human donors.

- Pig is the only animal used.
  - its physiology closely matches that of humans
  - much less expensive than monkeys & other primates

- Pigs have α-1,3-galactose (αGal) on the surface of their cells, produced by enzyme α-1,2 galactosyltransferase (GGAT1)
  - absent in humans → rejection

- **GGAT1-knock out pigs** – much lower incidence of rejection (in monkeys)

- Porcine heart valves successfully transplanted into human hearts (liver, lungs, kidneys being tested)

- Risk of transmission of porcine viruses - ↓ by pre-screening

Food sources

- Creation of animals that grow larger without much food
  → more efficient, cost effective food source.

- Ethical and safety concerns – not yet produced commercially as food sources.

- Only for research purposes.

Transgenic biological models

- Created to increase our knowledge about the **function of a protein**
  - by overexpressing the gene encoding that protein, or knocking it out

- In biology & genetic studies

- Eg. ANDi, Smart mouse & Youth mouse.