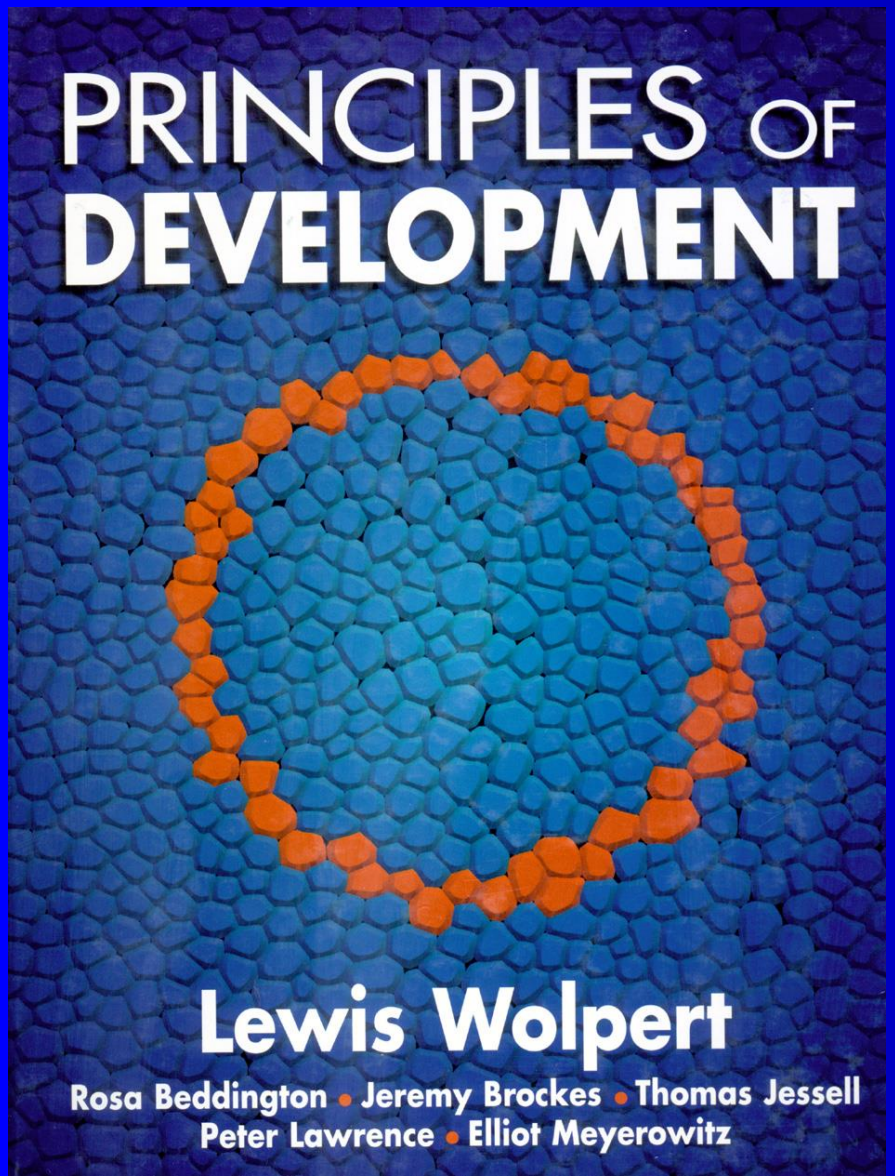
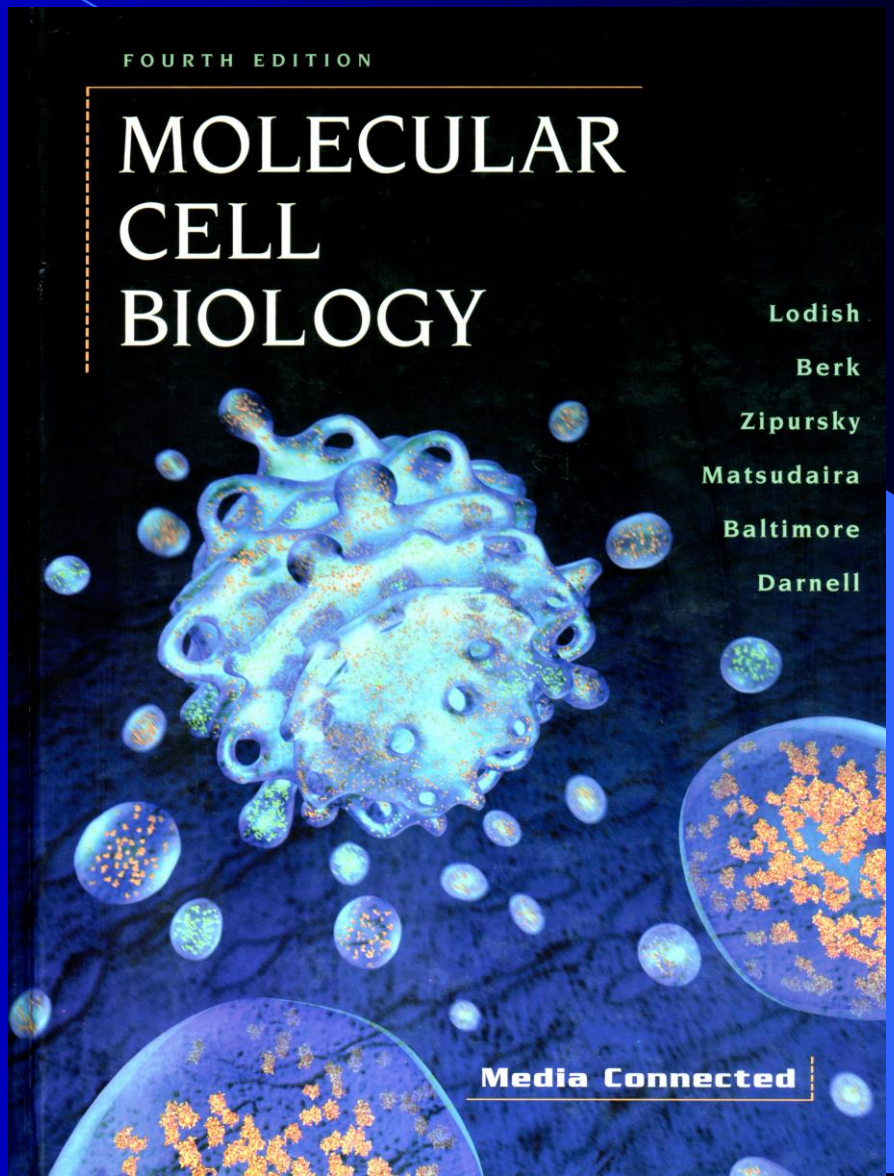
Gene Regulation in Mammalian Development

C.-L. Chien, 2002





I. Growth of mammals is dependent on growth factors

Fibroblast growth factors (FGFs):

***FGF-4: Requirement of FGF-4 for postimplantation mouse development. (Science 267:246-249, 1995)**
***FGF-5: FGF5 as a regulator of the hair growth cycle: evidence from targeted and spontaneous mutations. (Cell 78:1017-1025, 1994).**
***FGF receptor-1: fgfr-1 is required for embyonic growth and mesodermal patterning during mouse gastrulation. (Genes Dev. 8:3032-3044, 1994)**
***FGF receptor-3: Skeletal overgrowth and deafness in mice lacking fibroblast growth factor receptor 3. (Nature Genetics 12: 390-397, 1996)**
Fibroblast growth factor receptor 3 is a negative regulator of bone growth. (Cell 84:911-921, 1996)

Insulin-like growth factors (IGF):

IGF- I: knock out animal model shows that IGF-1 play an important role in the embryonic development. (Cell 75:73-82, 1993)

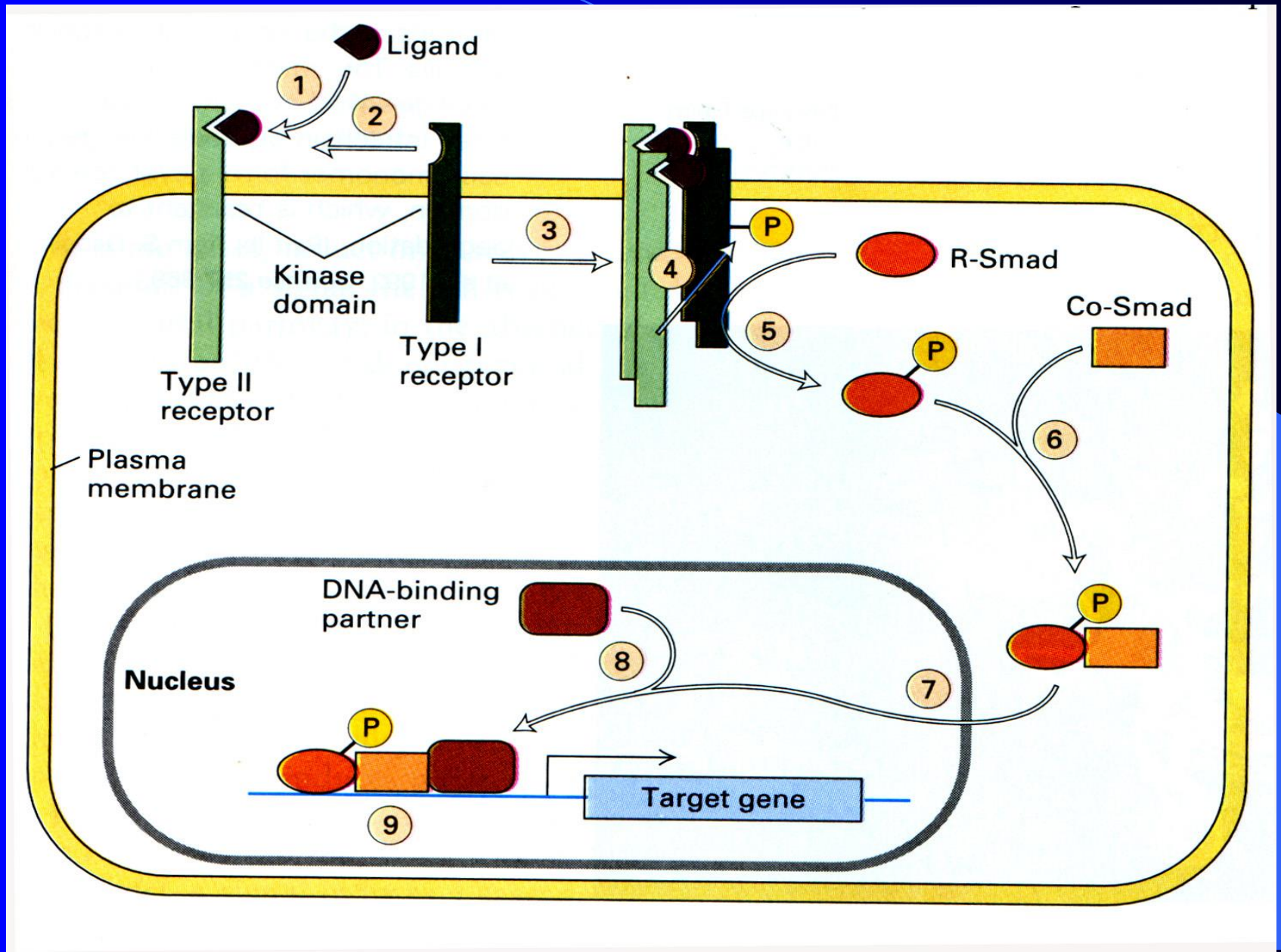
IGF- II: Knockout mice developed relatively normal, but weigh only 60% of the normal newborn body weight. (Nature 345:78-80, 1990)

Transforming growth factors (TGF):

*TGF α: Mice with a null mutation of the TGF α gene have abnormal skin architecture, wavy hair, curly whiskers and often develop corneal inflammation. (Cell 73:249-261, 1993)
TGF α deficiency results in hair follicle and eye abnormalities in targeted and waved-1 mice. (Cell 73:263-278, 1993).

*TGFβ1: Defective haematopoiesis and vasculogenesis in transforming growth factor β1 knockout mice. (Development 121: 1845-1854, 1995)

TGF-β Signal Pathway (movie)

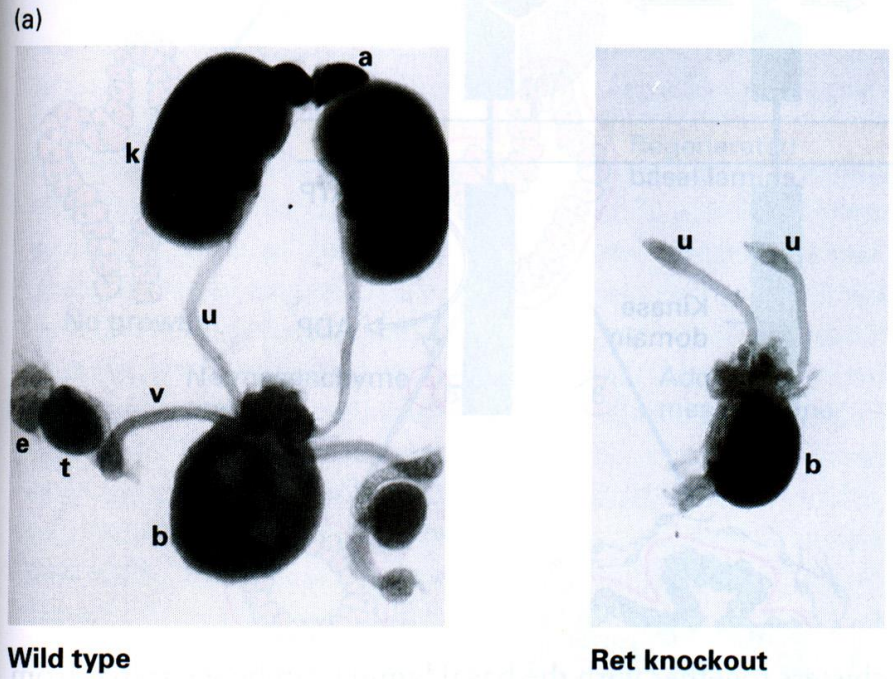


Nerve growth factors:

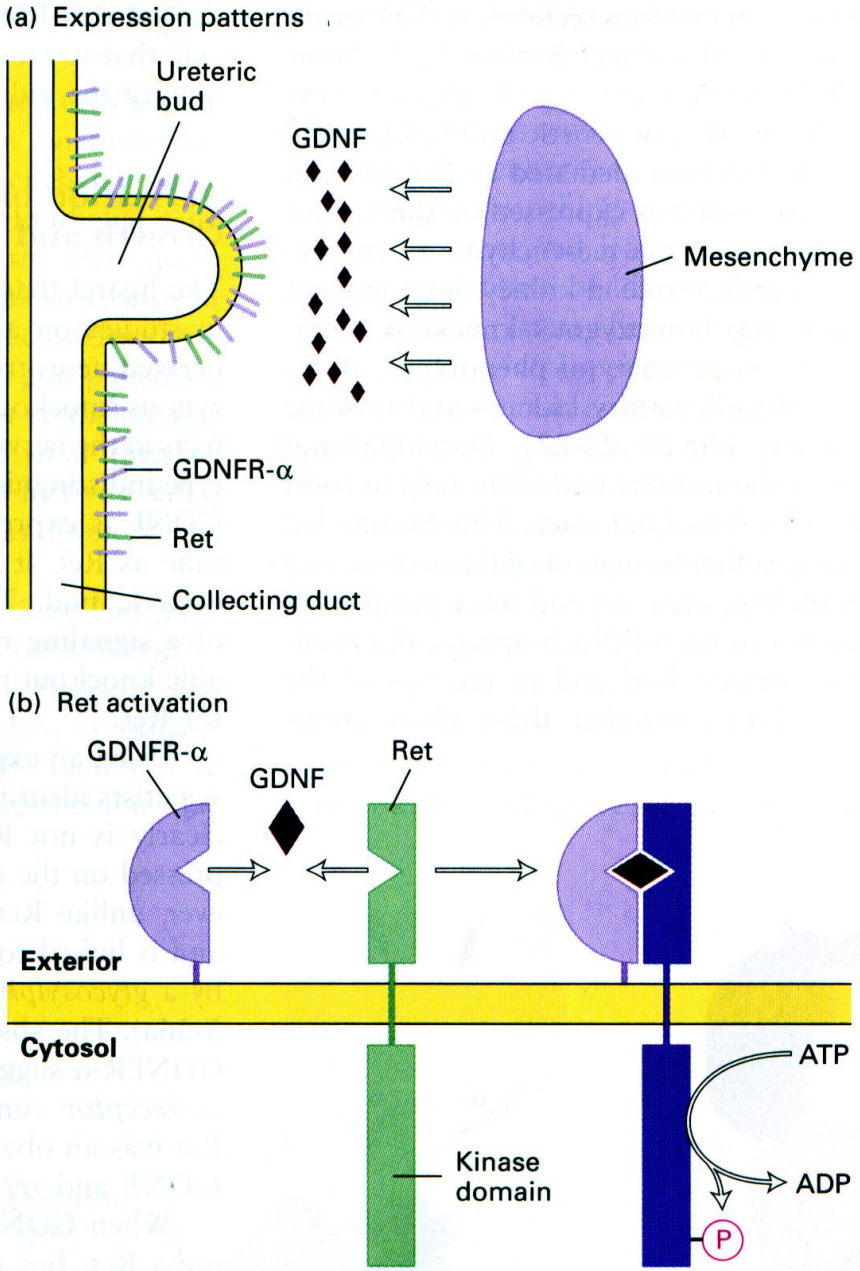
***NGF:** Mice lacking nerve growth factor display perinatal loss of sensory and sympathetic neurons yet develop basal cholinergic neurons.
(Cell 76:1001-1011, 1994).
***BDNF:** Targeted disruption of the BDNF gene perturbs brain and sensory neuron development but not motor neuron development.
(Cell 76: 989-999, 1994)
***GDNF:** Defects in enteric innervation and kidney development in mice lacking GDNF.
(Nature 382:73-76, 1996)
Renal and neuronal abnormalities in mice lacking GDNF.
(Nature 382:76-79, 1996)

GDNF KO:

Defects in kidney development

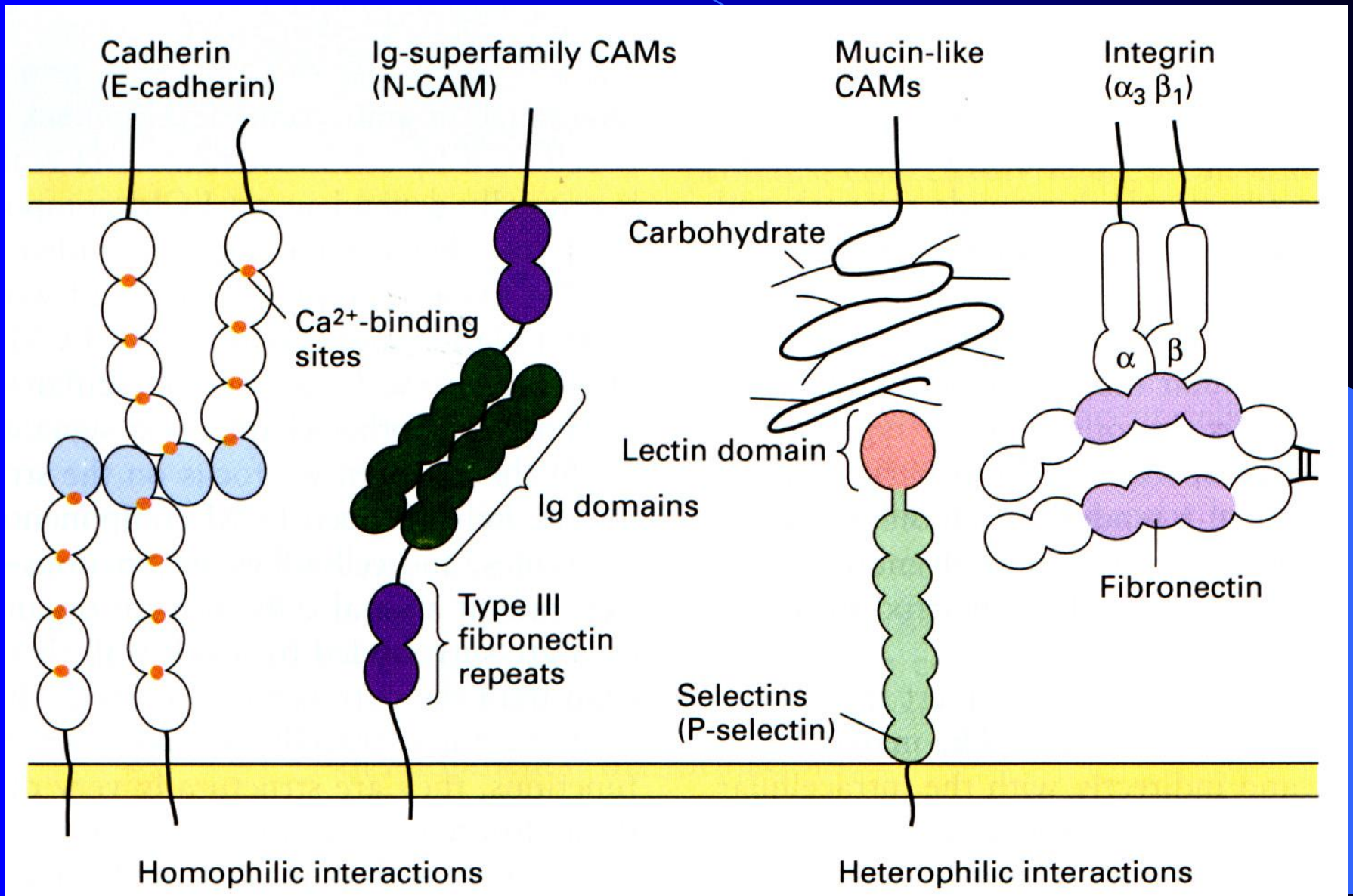


▲ **FIGURE 23-22 Knockout mutations in *ret* produce severe defects in kidney morphogenesis in mice.** (a) Urogenital systems



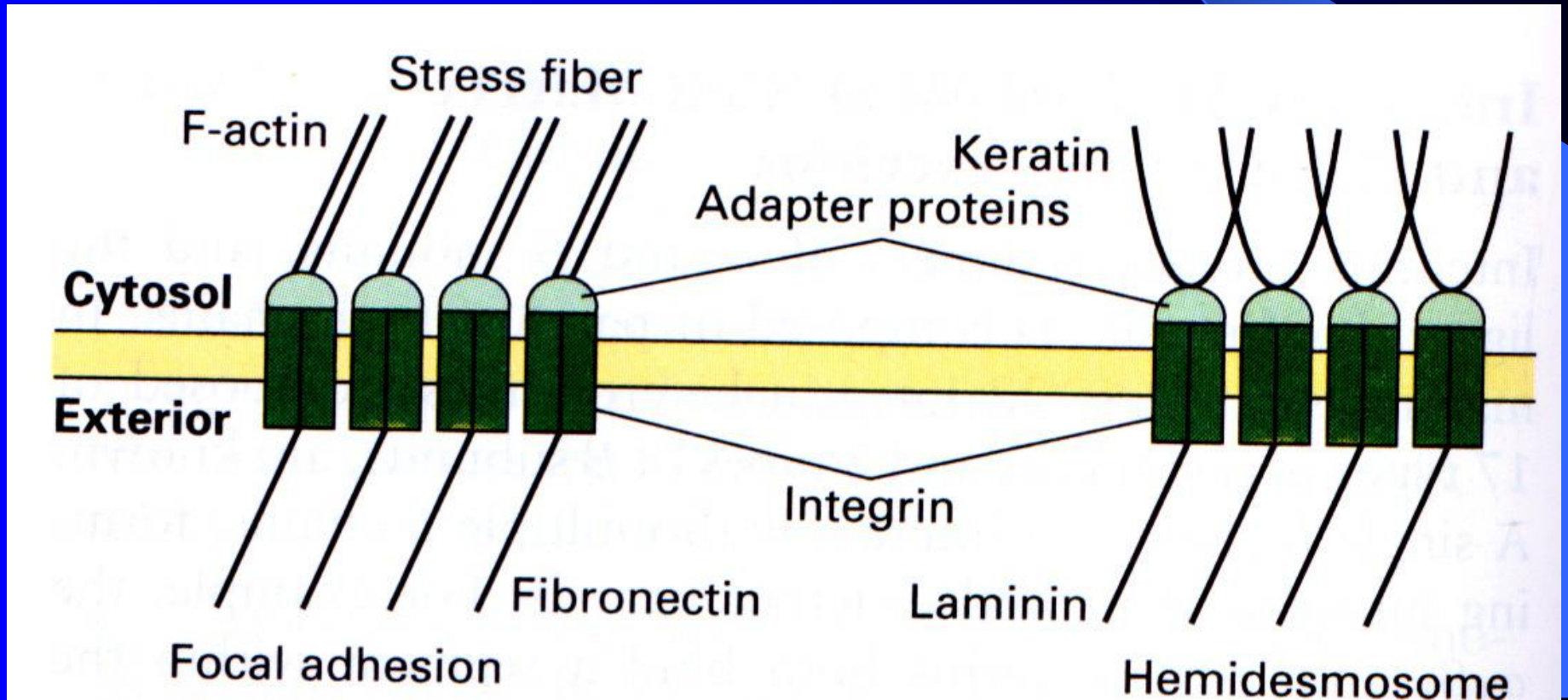
II. Cell adhesion:

play important roles in the early embryonic development



Fibronectin

Defects in mesoderm, neural tube and vascular development in mouse embryos lacking fibronectin. (Development 119:1079-1091, 1993)



α5 integrin:

Embryonic mesodermal defects in α5 integrin-deficient mice. (Development 119:1093-1105, 1993)

β1 integrin:

Deletion of β1 integrins in mice results in inner cell mass failure and peri-implantation lethality. (Genes & Dev. 9: 1883-1894, 1995)

Consequence of lacking of β1 integrin gene expression in mice. (Genes & Dev. 9: 1896-1908, 1995)

E-cadherin: A targeted mutation in mouse E-cadherin gene results in defective preimplantation. (PNAS 92:855-859, 1995)

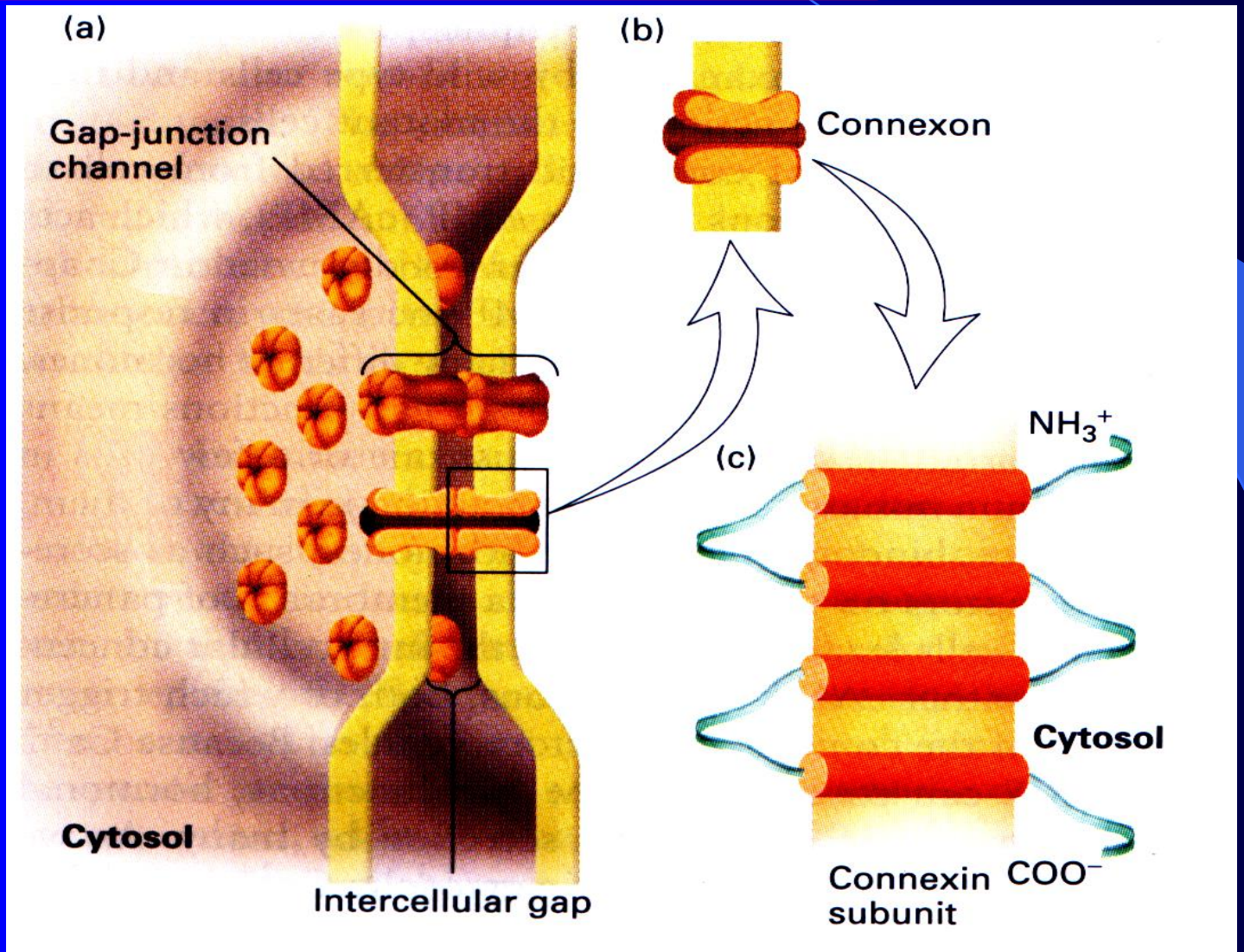
TABLE 22-1 Major Cadherin Molecules on Mammalian Cells

Molecule	Predominant Cellular Distribution
E-cadherin	Preimplantation embryos, non-neural epithelial tissue
P-cadherin	Trophoblast
N-cadherin	Nervous system, lens, cardiac and skeletal muscle

SOURCE: M. Takeichi, 1988, *Development* **102**:639; M. Takeichi, 1991, *Science* **251**:1451; H. Inuzuka et al., 1991, *Neuron* **7**:69; and M. Donalies et al., 1991, *Proc. Nat'l. Acad. Sci. USA* **88**:8024.

Connexin 43:

Cardiac malformation in neonatal mice lacking connexin 43. (Science 267: 1831-1834, 1995).



VCAM-1:

Defective development of the embryonic and extraembryonic circulatory systems in vascular cell adhesion molecule (VCAM-1) deficient mice.
(Development 121: 489-503, 1995)

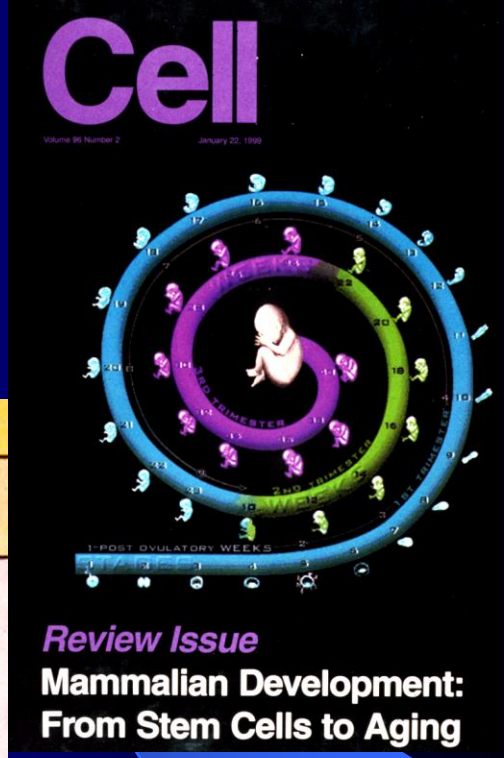
Targeted disruption of the murine VCAM-1 gene: essential role of VCAM-1 in choriollantoic fusion and placentation. (Genes & Dev. 9: 1-14, 1995).

Aging and Senescence

The life span, length of gestation, and age at puberty for various mammals

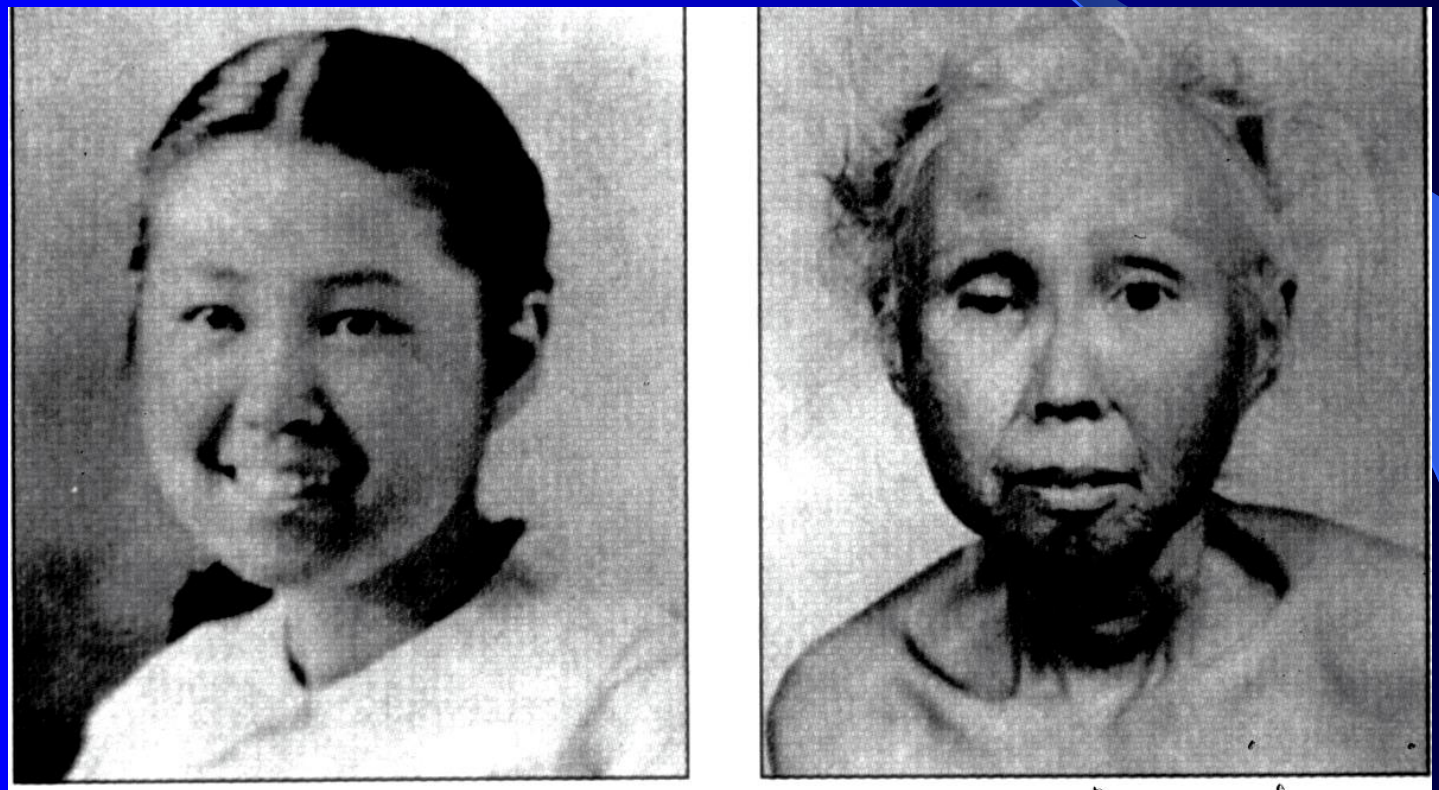
Longevity and time to attain reproductive maturity at puberty for various mammals

	Maximum life span (months)	Length of gestation (months)	Age at puberty (months)
Man	1440	9	144
Finback whale	960	12	—
Indian elephant	840	21	156
Horse	744	11	12
Chimpanzee	534	8	120
Brown bear	442	7	72
Dog	408	2	7
Cattle	360	9	6
Rhesus monkey	348	5.5	36
Cat	336	2	15
Pig	324	4	4
Squirrel monkey	252	5	36
Sheep	240	5	7
Gray squirrel	180	1.5	12
European rabbit	156	1	12
Guinea-pig	90	2	2
House rat	56	0.7	2
Golden hamster	48	0.5	2
Mouse	42	0.7	1.5



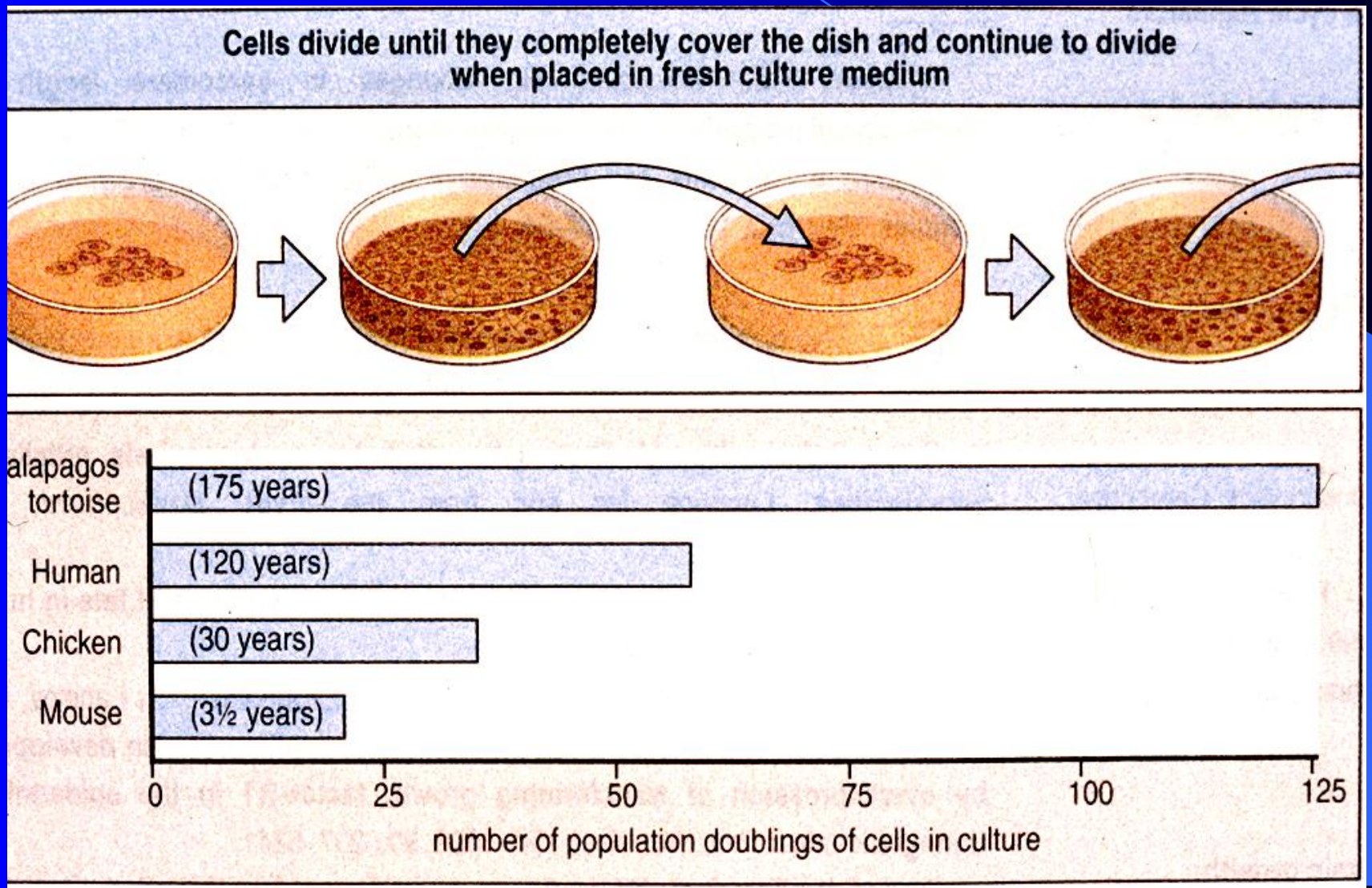
Werner's syndrome: a human genetic disease shows striking effects of premature aging

The gene affected in Werner's syndrome has been isolated and is thought to encode a protein involved in unwinding DNA. (Science 272: 258-262, 1996).

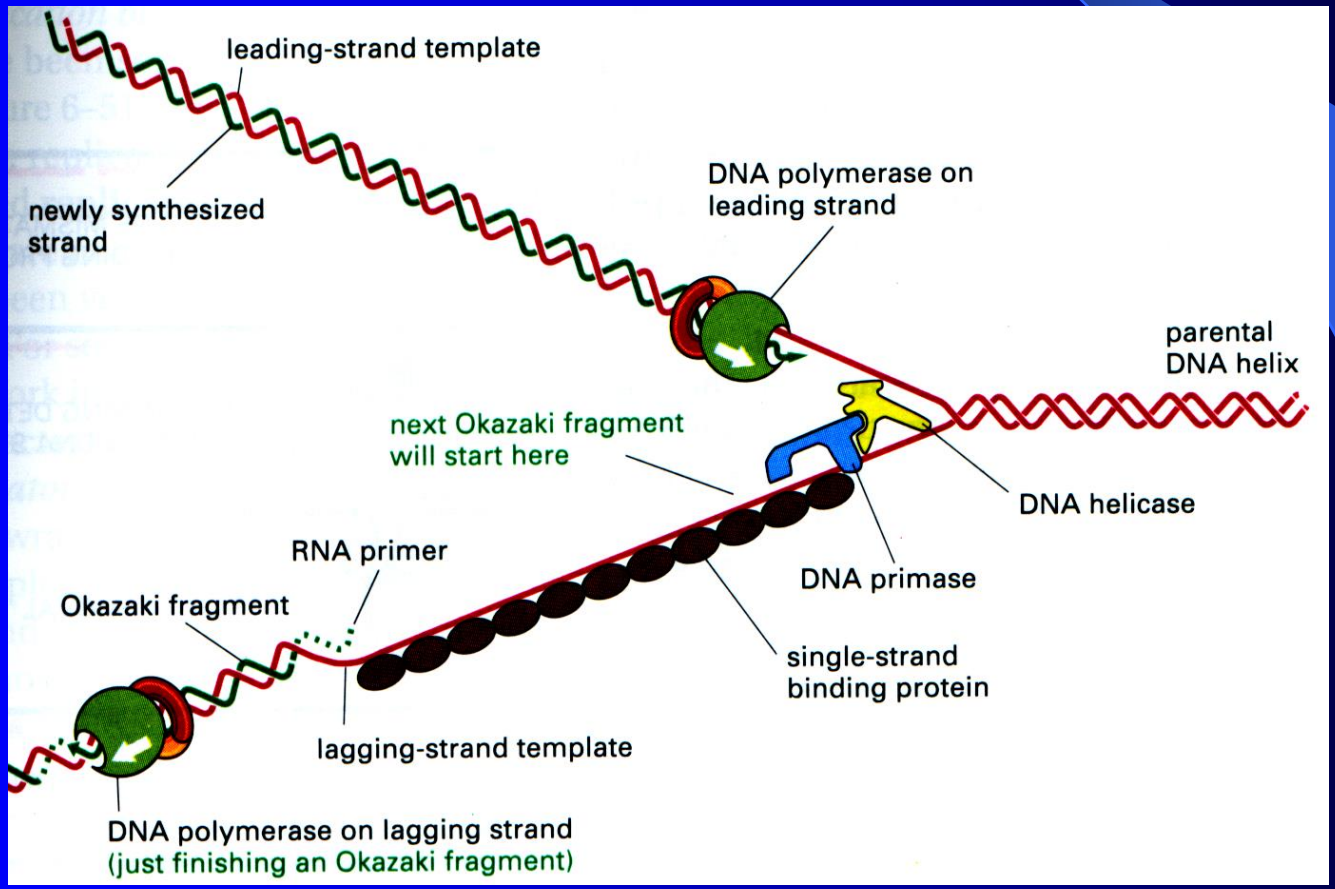


Taking its toll. As a teenager *(left)*, this Japanese American looked normal, but by age 48, the effects of Werner's syndrome were readily apparent.

Fibroblasts isolated from Werner's syndrome patients undergo fewer divisions in culture before becoming aging and dying than do fibroblasts from unaffected people of the same age.

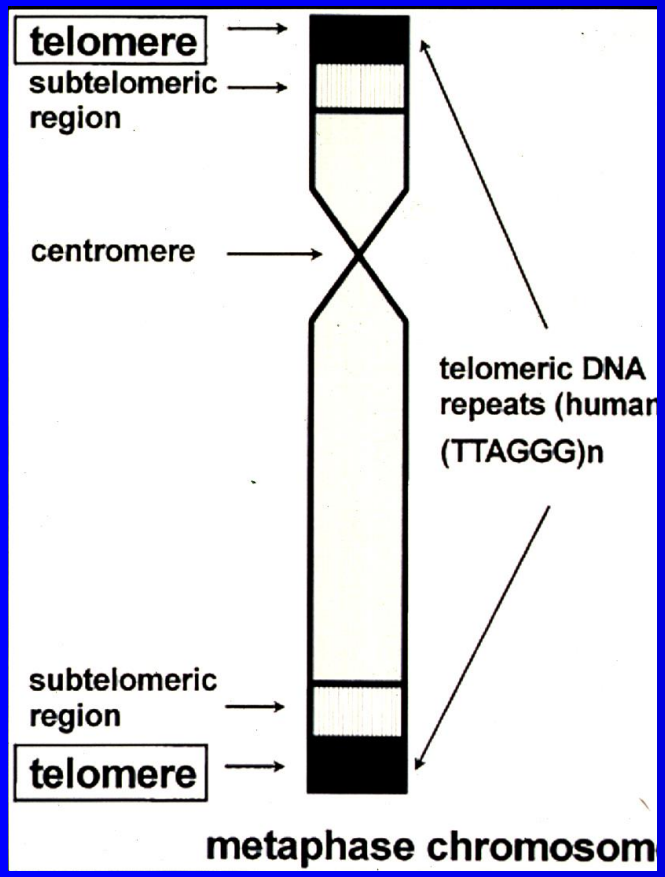


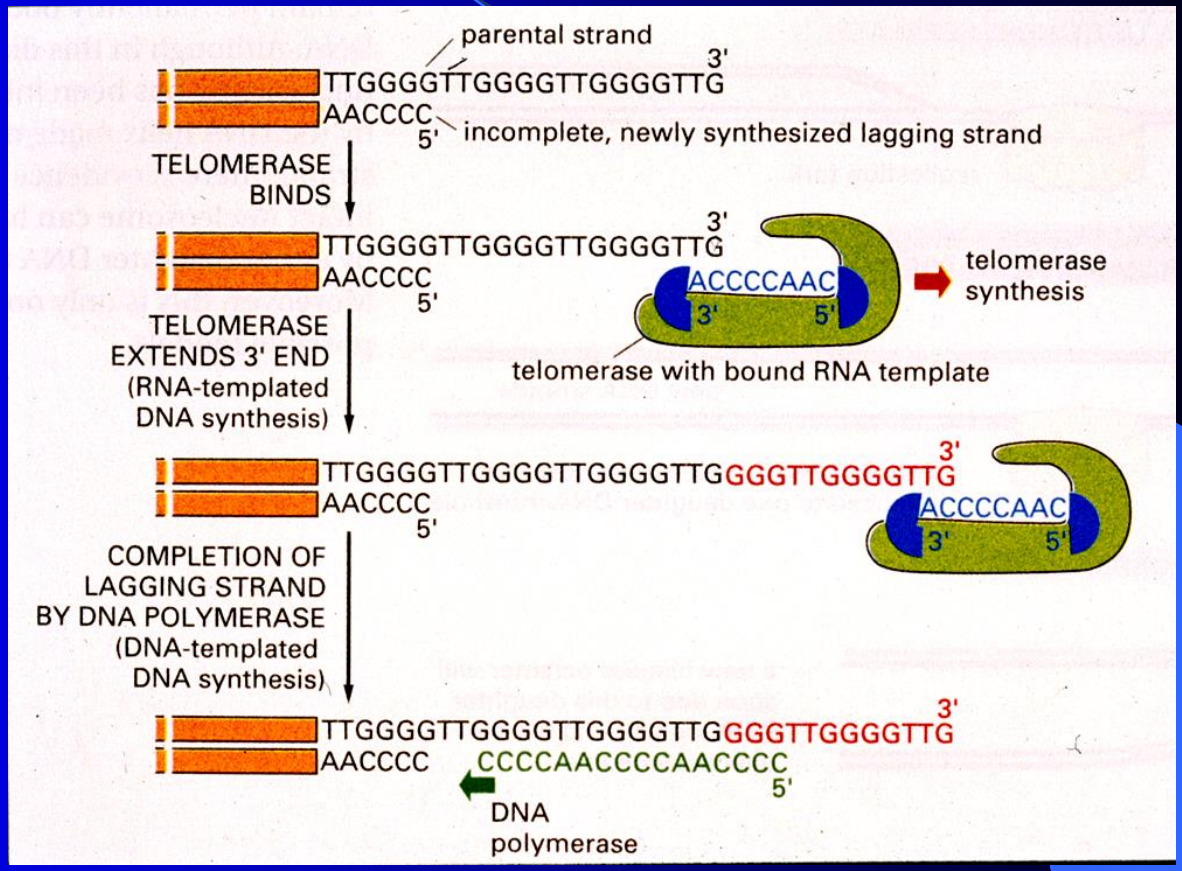
- Impaired nuclear localization of defective DNA helicases in Werner's syndrome (Nature Genetics 16: 335-336, 1997)
- The three faces of the WS helicase (Nature Genetics 19: 308-309, 1998)
- The premature ageing syndrome protein WRN, is a 3' -> 5' exonuclease (Nature genetics 20, 114-116, 1998)



The telomere theory: A feature shared by senescence cells in culture and in vivo is shorting of the telomeres.

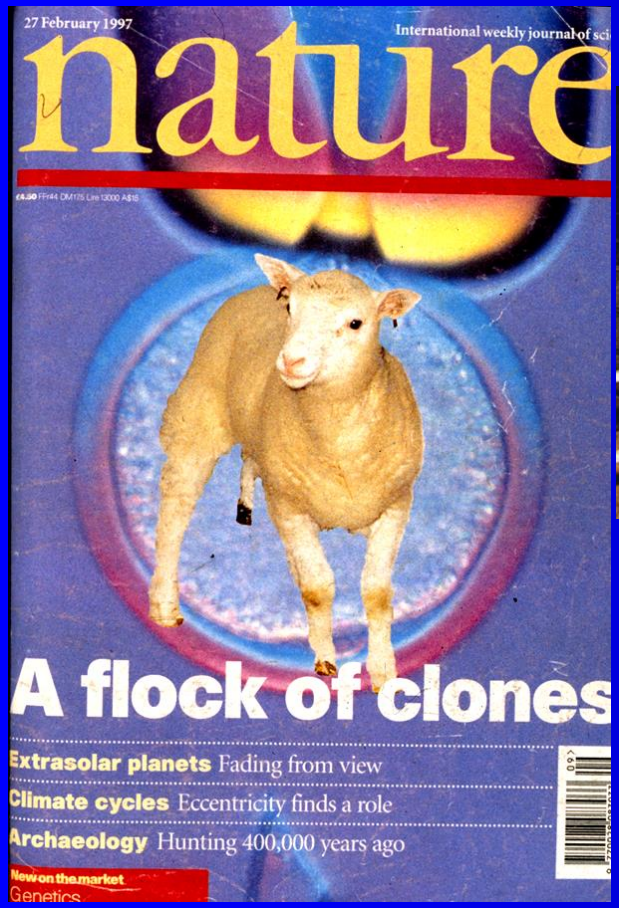
The length of the telomeres is reduced in older cells.



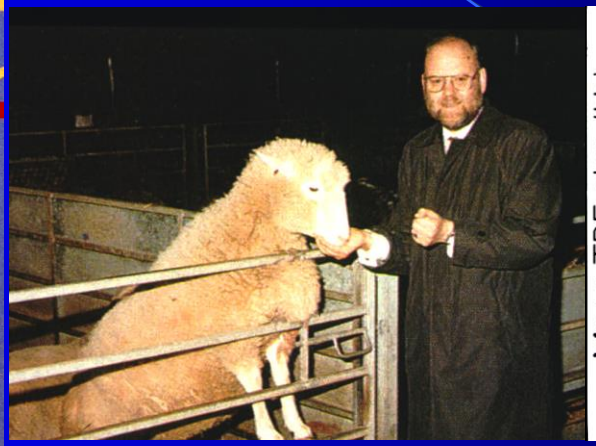


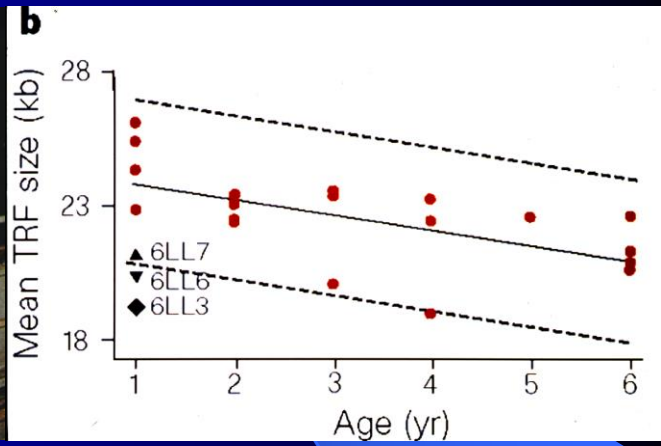
Telomerase: a reverse transcriptase that synthesizes telomeric repeats onto the ends of chromosomes (movie).

Analysis of telomere lengths in cloned sheep (Nature 399:316-317, 1999)



Cloned sheep Dolly
(Nature 385:810-813, 1997)





The length of terminal telemere fragment in Dolly is consistent with the age of her progenitor mammary tissue (6 years old).

Telemere shortening in TR-/- embryos is associated with failure to close the neural tube. (EMBO J. 18:1172-1181,1999)

The EMBO Journal Vol.18 No.5 pp.1172–1181, 1999

Telomere shortening in mTR$^{-/-}$ embryos is associated with failure to close the neural tube

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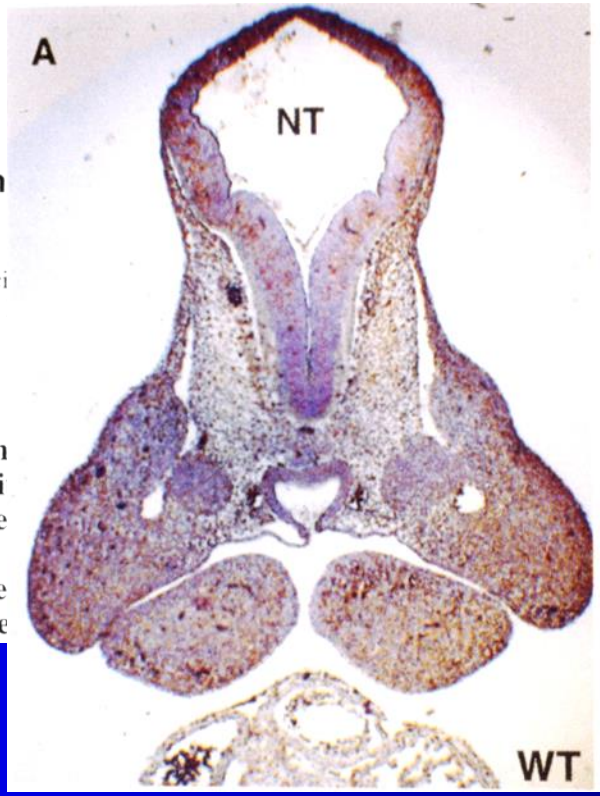
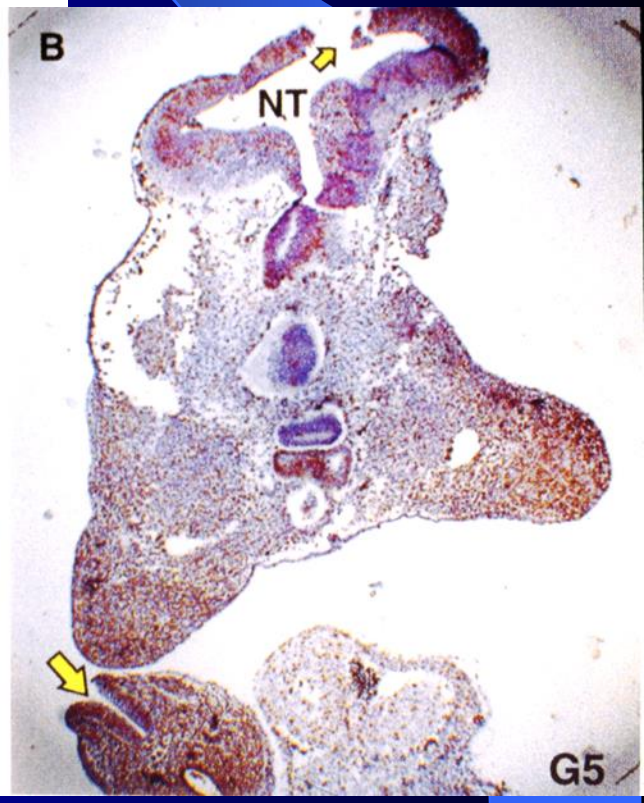
Mice genetically deficient for the telom
(mTR) can be propagated for only a limi
of generations. In particular, mTR$^{-/-}$ mice
C57BL6/129Sv genetic background are
the sixth generation and show serious he
defects. Here, we show that a percentage





Telomeres: Ageing hard or hardly ageing?
(Nature 398, 191-193, 1999)

Table 1. Ageing syndrome in mouse and man

Symptoms	*mTR$^{-/-}$ mice*	*Werner's syndrome*
Shortened division capacity	+	+
Accelerated cell senescence	–	+
Premature greying	+	+
Poor wound healing	+	+
Increased cancer incidence	+	+
Gut defects	+	?
Infertility	+	+
Shortened lifespan	+	+
Decreased adipose tissue	+	+
Hair loss	+	+
Brain changes	–	-
Osteoporosis	–	+
Diabetes	–	+
Atherosclerosis	–	+
Cataract	–	+

Klotho gene:

A new gene is involved in the suppression of several aging phenotypes. Mutation of the mouse *Klotho* gene leads to a syndrome resembling aging. (Nature 390:45-51,1997)

Mutation of the mouse *klotho* gene leads to a syndrome resembling ageing

Makoto Kuro-o*, Yutaka Matsumura*†, Hiroki Aizawa*†, Hiroshi Kawaguchi‡, Tatsuo Suga†, Toshihiro Utsugi†, Yoshio Ohyama†, Masahiko Kurabayashi†, Tadashi Kaname§, Eisuke Kume‖, Hitoshi Iwasaki‖, Akihiro Iida¶, Takako Shiraki-Iida*¶, Satoshi Nishikawa#, Ryozo Nagai†☆ & Yo-ichi Nabeshima*☆††

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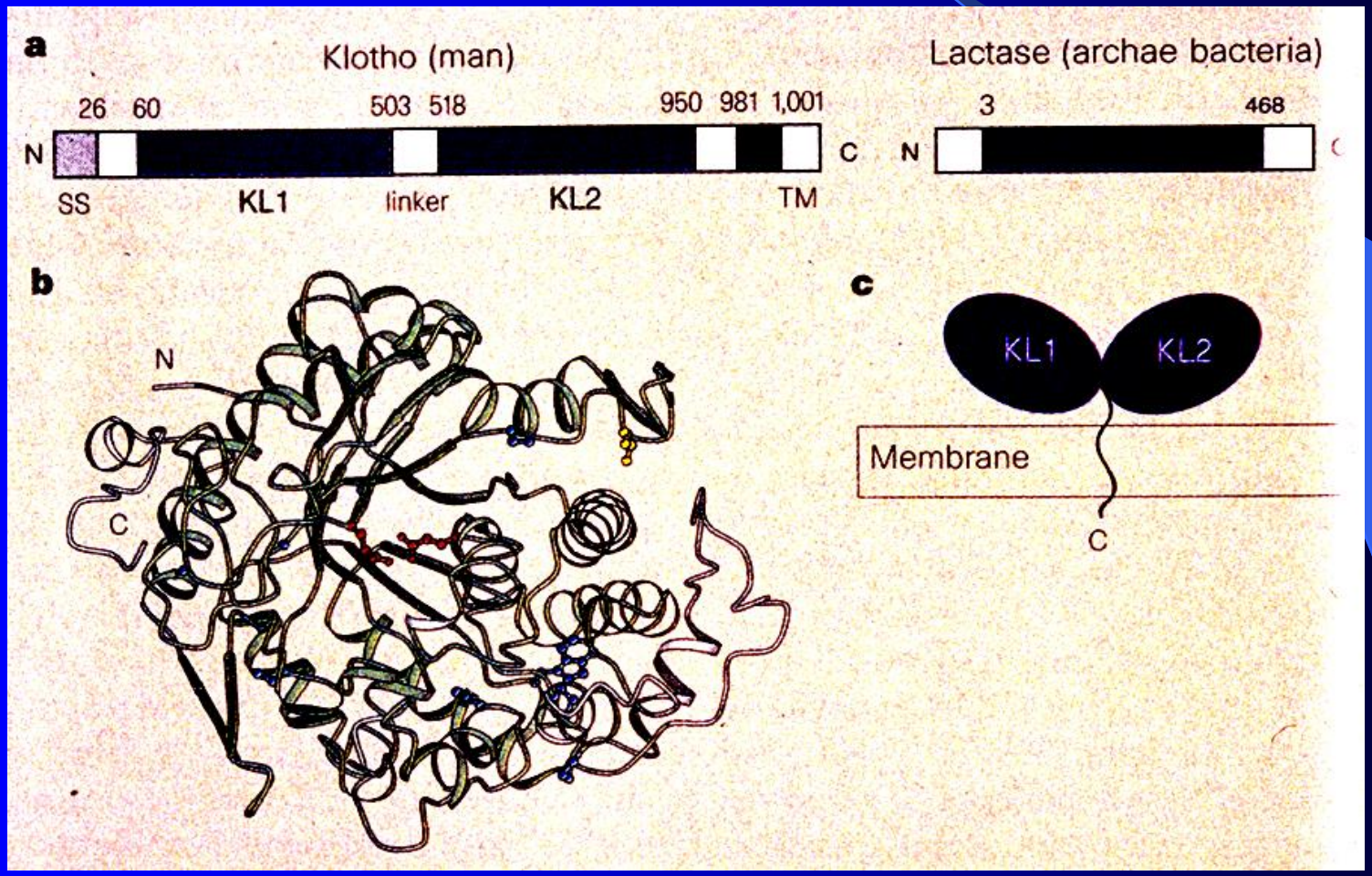
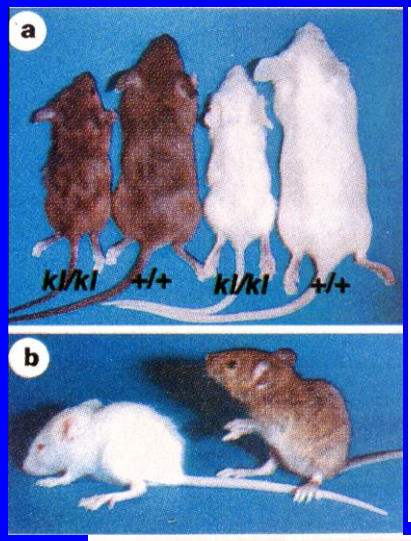
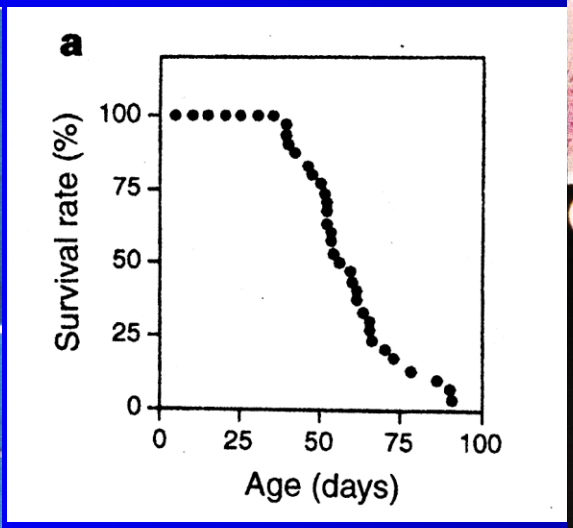
A new gene, termed *klotho*, has been identified that is involved in the suppression of several ageing phenotypes. A defect in *klotho* gene expression in the mouse results in a syndrome that resembles human ageing, including a short lifespan, infertility, arteriosclerosis, skin atrophy, osteoporosis and emphysema. The gene encodes a membrane protein that shares sequence similarity with the β-glucosidase enzymes. The *klotho* gene product may function as part of a signalling pathway that regulates ageing *in vivo* and morbidity in age-related diseases.

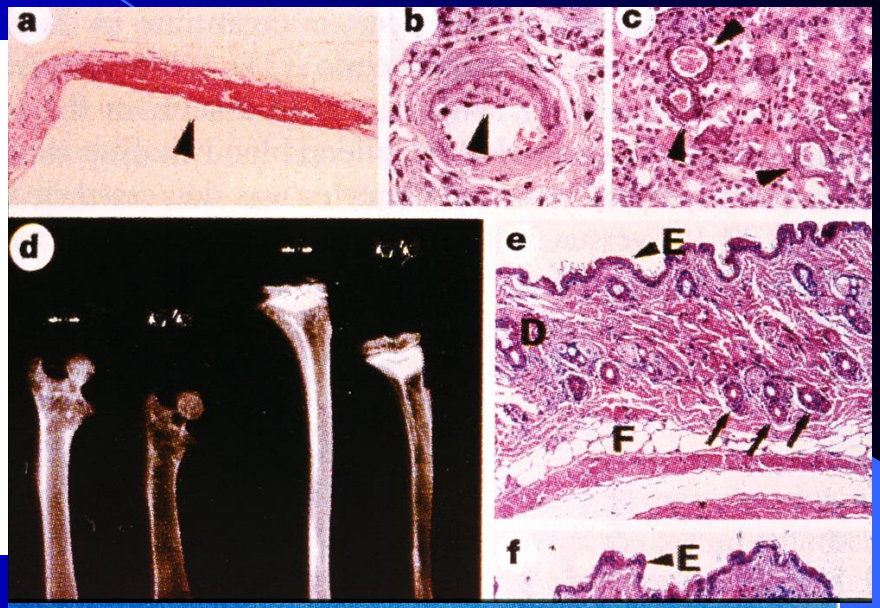
The *klotho* gene product (shares sequence similarity with glucosidase enzymes) may function as part of a signaling pathway that regulates aging *in vivo*.

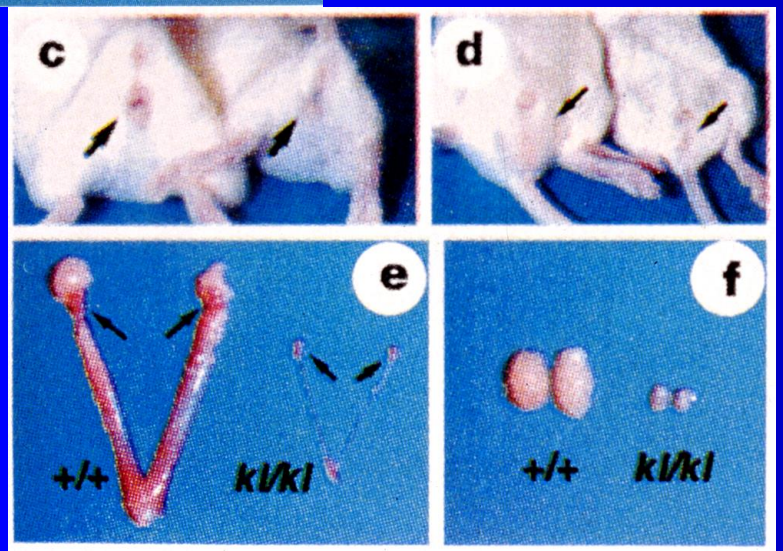


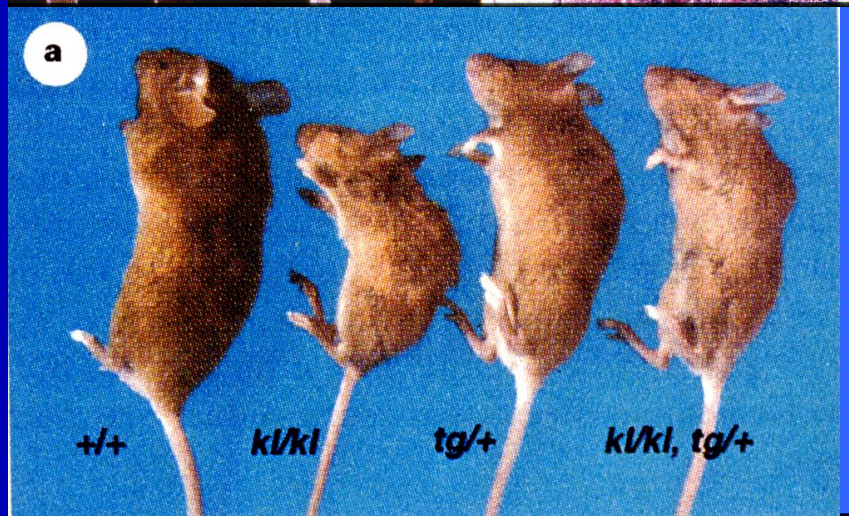
Mutation of the mouse *Klotho* gene leads to a syndrome resembling aging. Such as a short life span, infertility, arteriosclerosis, skin atrophy, and osteroporosis.











Cell, Vol. 62, 1073–1085, September 21, 1990. Copyright © 1990 by Cell Press

14

The *Wnt*-1 (*int*-1) Proto-Oncogene Is Required for Development of a Large Region of the Mouse Brain

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Roche Research Center
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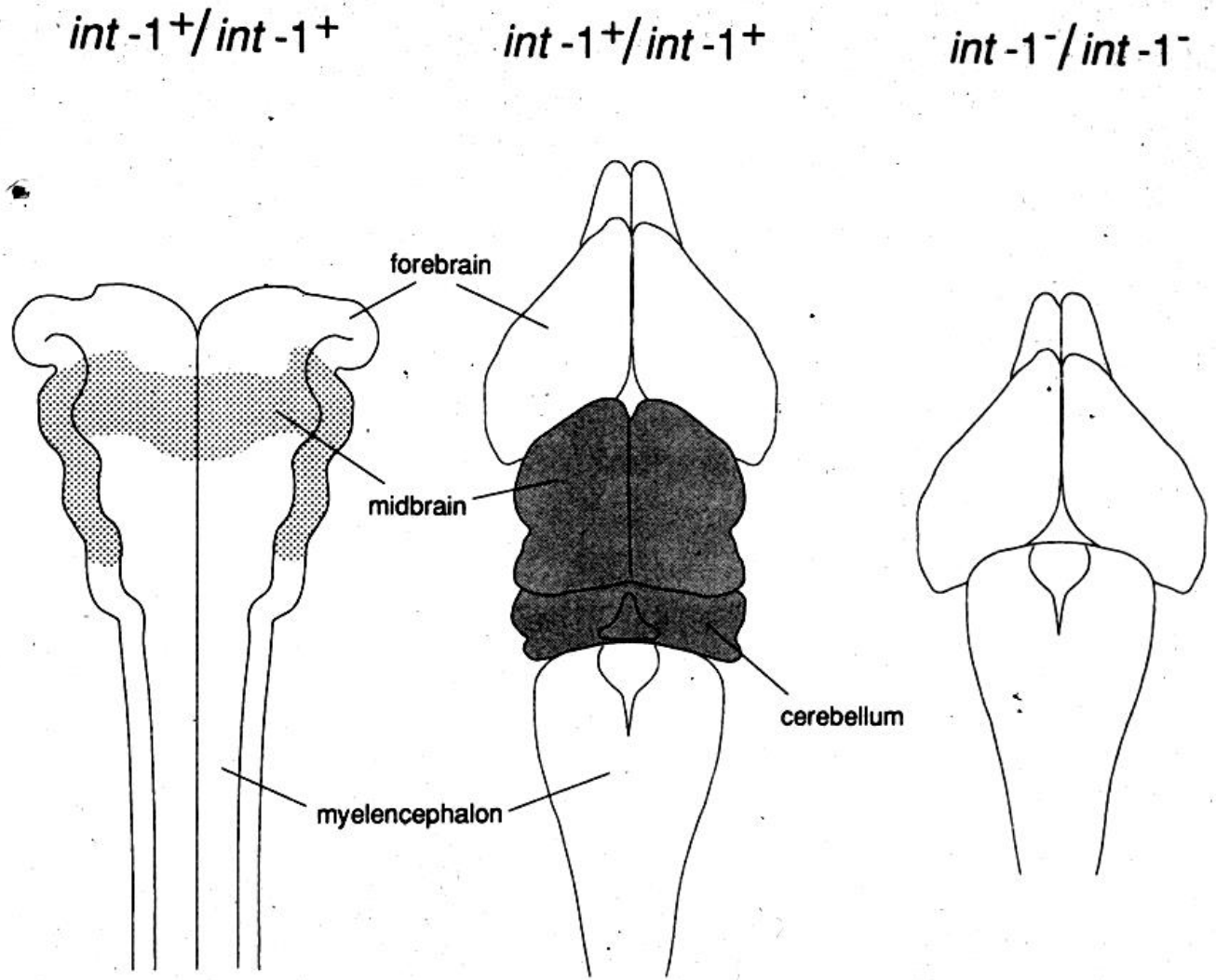
Houston, Texas 77030

Summary

**The *Wnt*-1 (*int*-1) proto-onco
putative signaling molecule, i
in the developing central ne
testes. To examine the role of
independent embryonic stem
tion of a *neo*^{R} gene by homol
activated a *Wnt*-1 allele. G**



N-myc KO: die during Organogenesis (E10.5 - E12.5)

(Genes & Development 6:2235-2247, 1992;
Genes & Development 6:2248-2257, 1992)

Embryonic lethality in mice homozygous for a targeted disruption of the N-*myc* gene

Jean Charron,[1,2] Barbara A. Malynn,[1,3] Peter Fisher,[1,4] Valerie Stewart,[1,3] Lucie Jeannotte,[2,5] Stephen P. Goff,[1] Elizabeth J. Robertson,[5] and Frederick W. Alt[1,3]

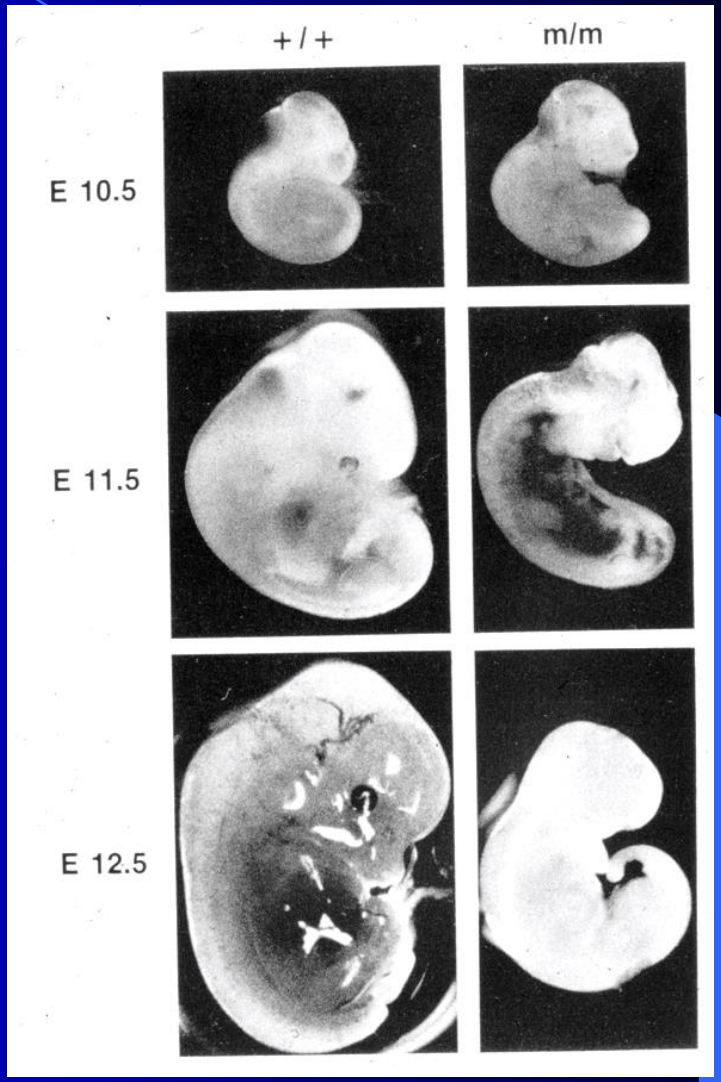
[1]The Howard Hughes Medical Institute and Departments of Biochemistry and Molecular Biophysics, and Microbiology, College of Physicians and Surgeons, Columbia University, New York, New York 10032 USA; [2]Centre de Recherche en cancerologie de L'Universite Laval, Hotel-Dieu de Quebec, Quebec, Canada, G1R 2J6; [3]The Howard Hughes Medical Institute, The Children's Hospital, Boston, Massachusetts 02115 USA; [4]Department of Pathology; [5]Department of Genetics and Development, College of Physicians and Surgeons, Columbia University, New York, New York 10032 USA

Loss of N-*myc* function results in embryonic lethality and failure of the epithelial component of the embryo to develop

Brian R. Stanton, Archibald S. Perkins[1], Lino Tessarollo, David A. Sassoon,[2] and Luis F. Parada[3]

Molecular Embryology and [1]Molecular Genetics of Oncogenesis Sections, ABL–Basic Research Program, National Cancer Institute—Frederick Cancer Research and Development Center, Frederick, Maryland 21702-1201 USA

myc **genes are thought to function in the processes of cellular proliferation and differentiation. To gain insight into the role of the N-*myc* gene during embryogenesis, we examined its expression in embryos during postimplantation development using RNA in situ hybridization. Tissue- and cell-specific patterns of expression unique to N-*myc* as compared with the related c-*myc* gene were observed. N-*myc* transcripts become progressively restricted to specific cell types, primarily to epithelial tissues including those of the developing nervous system and those in developing organs characterized by epithelio-mesenchymal interaction. In contrast, c-*myc* transcripts were confined to the mesenchymal compartments. These data suggest that c-*myc* and N-*myc* proteins may interact with different substrates in performing their function during embryogenesis and suggest further that there are linked regulatory mechanisms for normal expression in the embryo. We have mutated the N-*myc* locus via homologous recombination in embryonic stem (ES) cells and introduced the mutated allele into the mouse germ line. Live-born heterozygotes are under-represented but appear normal. Homozygous mutant embryos die prenatally at ~11.5 days of gestation. Histologic**



Rb KO: defects in neurogenesis and haematopoiesis (Nature 359: 288-294, 1992; Nature 359:295-300, 1992).

ARTICLES

Mice deficient for Rb are nonviable and show defects in neurogenesis and haematopoiesis

Eva Y.-H. P. Lee*†, Chi-Yao Chang*, Nanpin Hu*, Yi-Chun J. Wang*, Chen-Ching Lai*‡, Karl Herrup§, Wen-Hwa Lee* & Allan Bradley‖

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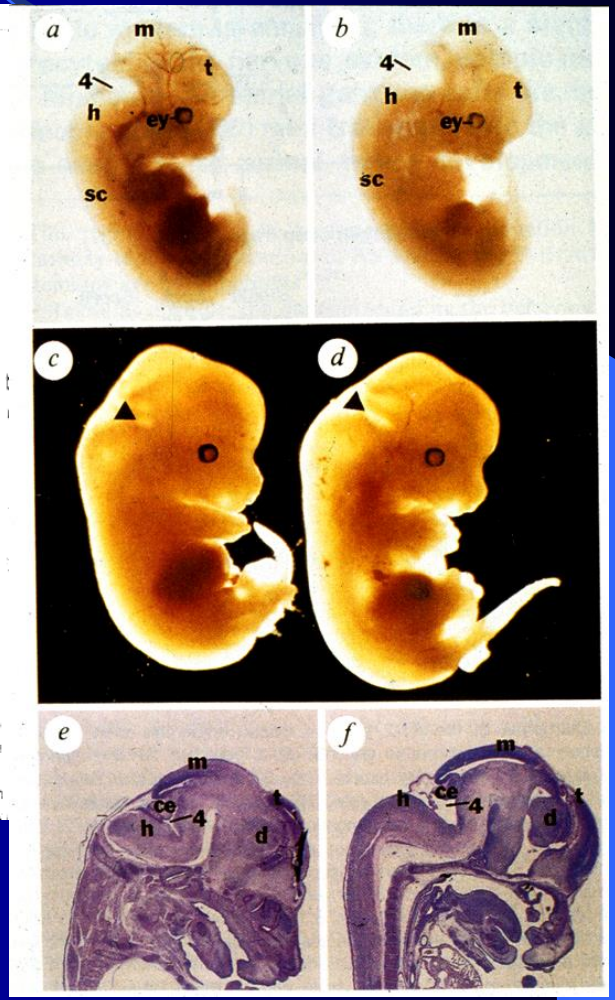
§ Alzheimer Research Lab, Case Western Reserve Medical School, Cleveland, Ohio 44106, USA
‖ Institute for Molecular Genetics, Baylor College of Medicine, Houston, Texas 77030, USA

The retinoblastoma gene, a prototypic tumour-suppressor gene, encodes a nuclear phosphopr (Rb). To understand better the role of Rb in development and in tumorigenesis, mice with an insert mutation in exon 20 of the *Rb-1* locus were generated. Homozygous mutants die before the embryonic day with multiple defects. The haematopoietic system is abnormal; there is a signif increase in the number of immature nucleated erythrocytes. In the nervous system, ectopic mit and massive cell death are found, particularly in the hindbrain. All spinal ganglion cells die, bu neural retina is unaffected. Transfer of the human retinoblastoma (*RB*) mini-transgene into the mu mice corrects the developmental defects. Thus, Rb is essential for normal mouse development.

RETINOBLASTOMA, an ocular childhood tumour, has been a model for studies of the role of tumour suppressor genes in cancer predisposition[1,2]. The hereditary form of the disease is an autosomal dominant trait[3]. But a recessive nature of the mutant gene was proposed in Knudson's 'two-hit' hypothesis[4], and later substantiated[5–9]. Although the eye is usually the first site of tumour formation, patients with hereditary retinoblas-

This region seems to be important for Rb function b carboxy-terminal truncations of Rb deleting the T/E1A-b domains are nonfunctional[16,38].

Taken as a whole, the data surrounding the behaviour present something of a paradox. Its ubiquitous expressio seeming involvement in cell-cycle regulation suggest that it a central role in essential cellular activity. But by con



p53 KO: developmentally normal but susceptible to spontaneous tumors (Nature 356:215-221, 1992)

Mice deficient for p53 are developmentally normal but susceptible to spontaneous tumours

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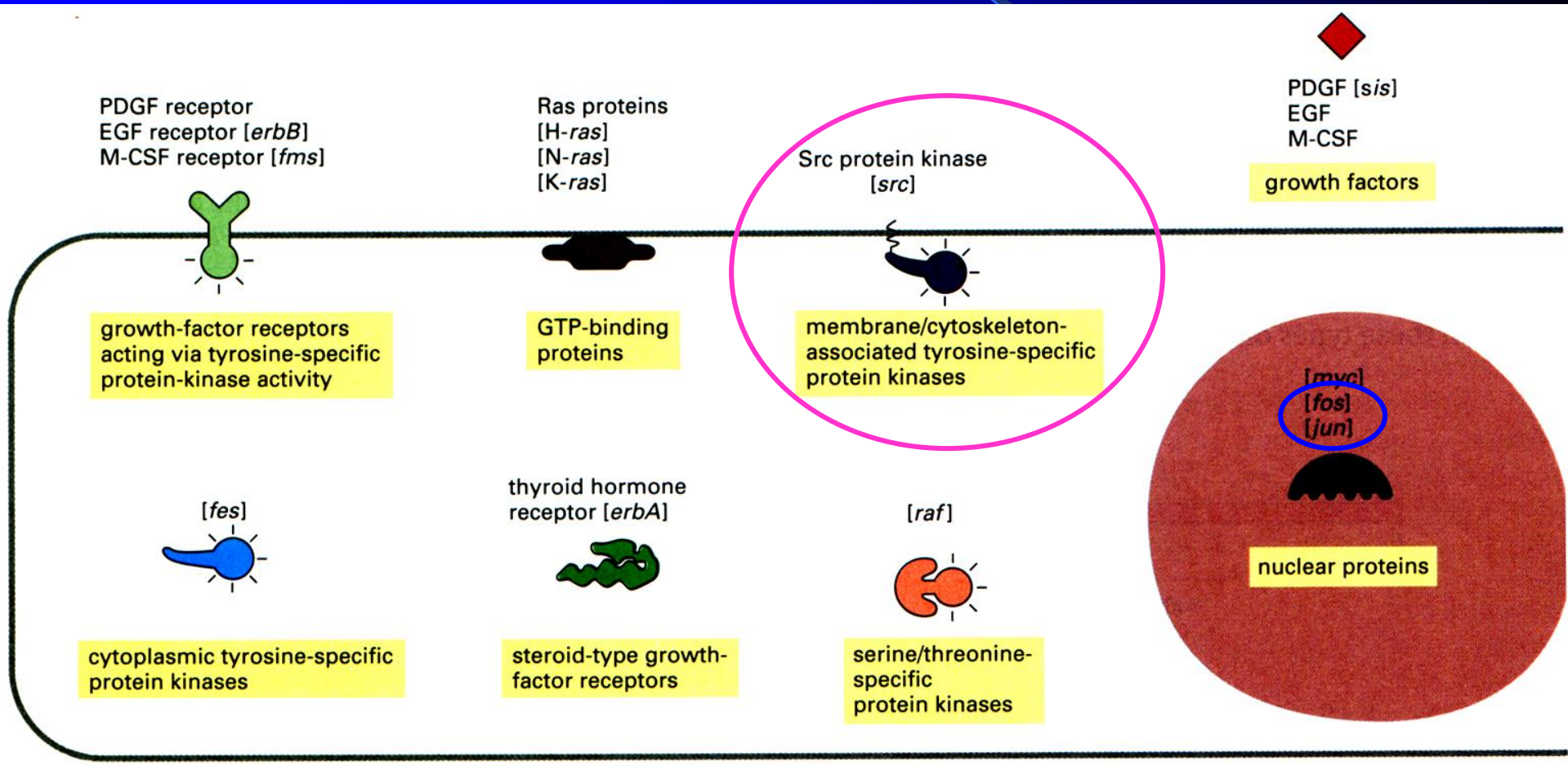
Mutations in the p53 tumour-suppressor gene are the most frequently observed genetic lesions in human cancers. To investigate the role of the p53 gene in mammalian development and tumorigenesis, a null mutation was introduced into the gene by homologous recombination in murine embryonic stem cells. Mice homozygous for the null allele appear normal but are prone to the spontaneous development of a variety of neoplasms by 6 months of age. These observations indicate that a normal p53 gene is dispensable for embryonic development, that its absence predisposes the animal to neoplastic disease, and that an oncogenic mutant form of p53 is not obligatory

c-fos KO: defects in bone formation and haematopoiesis (Cell 71:577-586, 1992; Nature 360:741-745, 1992).

c-src KO: osteopetrosis (impaired osteoclast function) (Cell 64:693-702., 1991)



***MyoD* KO**: normal in muscle development, yet leads to up-regulation of the myogenic gene *Myf*-5 (Cell 71:383-390, 1992)

***Myf*-5 KO:** abnormal rib development and perinatal death (Cell 71: 369-382, 1992)

Table 2. Identification of MyoD1 and some MyoD1 homologs

MyoD1 homolog	Animal	Homology
MyoD1	Mouse	MyoD1
Myf-3	Human	MyoD1
XMyoD	Frog (*X. laevis*)	MyoD1
CMD1	Chicken	MyoD1
qmf1	Quail	MyoD1
CeMyoD	Worm (*C. elegans*)	MyoD1
nau	Fly (*D. melanogaster*)	MyoD1
Myogenin	Rat/mouse	myogenin
Myf-4	Human	myogenin
qmf2	Quail	myogenin
myf-5	Human	myf-5
qmf3	Quail	myf-5
MRF-4	Rat	MRF-4
Herculin	Human	MRF-4

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Inactivation of *MyoD* in Mice Leads to Up-Regulation of the Myogenic HLH Gene *Myf*-5 and Results in Apparently Normal Muscle Development

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the skeletal myocyte lineage (Olson, 1990; Weintraub et al., 1991; Buckingham, 1992).

In vertebrates, skeletal muscle originates from a sma pool of progenitor cells that arise in the early somite (re viewed by Buckingham, 1992; Miller, 1991, 1992). Thes premyoblast stem cells become the dermamyotomal con partment of the maturing somite, from which myoblas expand into the developing embryo. In mice, skeletal mu cle development occurs in several phases. First, to diffe entiate in the fetus at 8.5 days of gestation, the myotom fiber precursors give rise to small spindle-like myotom fibers displaying the earliest expression of muscle-specif

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Targeted Inactivation of the Muscle Regulatory Gene *Myf-5* Results in Abnormal Rib Development and Perinatal Death

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Summary

The *Myf-5* gene, a member of the myogenic basic HLH factor family, has been inactivated in mice after homologous recombination in ES cells. Mice lacking *Myf-5* were unable to breathe and died immediately after

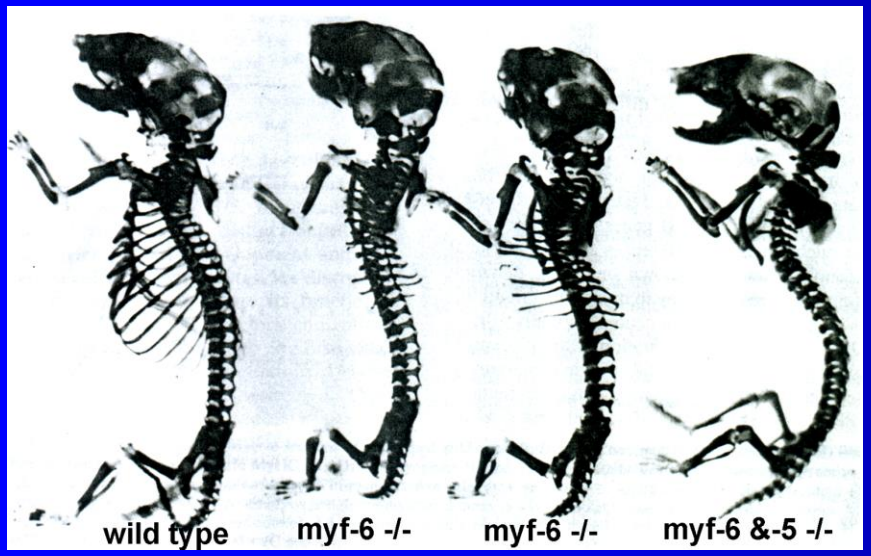
CANNTG. Detailed mutational analysis of MyoD (Davis et al., 1990), myogenin (Brennan et al., 1991), and Myf-5 (Winter et al., 1992) has demonstrated that the conserved basic and HLH domains are responsible for sequence-specific DNA binding and heterodimerization with the ubiquitously expressed HLH products of the E2A gene, respectively. Transcriptional activation is dependent on a transactivator domain located in the NH_2–terminus of MyoD (Weintraub et al., 1991b), and on two regions located upstream and downstream of the conserved HLH domain in myogenin and Myf-5 (Schwartz et al., 1992; Braun et al., 1990b; Winter et al., 1992).

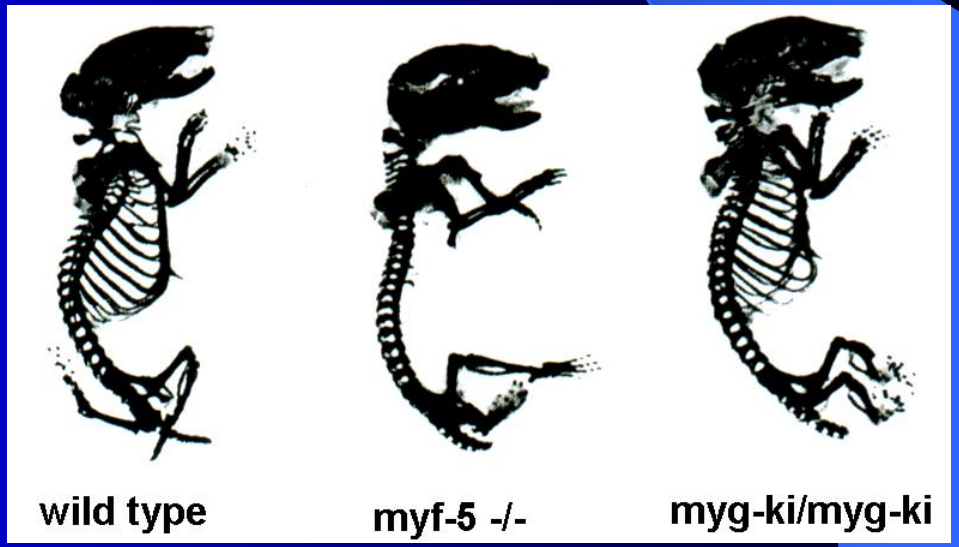
Despite suggestive evidence obtained from tissue culture experiments, the individual or collective role of myogenic factors during muscle development in vivo has not been determined to date. It has been difficult to ascribe specific functions to the individual myogenic HLH proteins, because each factor can influence its own expression as well as that of the other factors in most cell lines (Thayer

Myogenin KO: Muscle deficiency and neonatal death (Nature 364:501-506, 1993)

Myf-5 and Myf-6 double KO: alterations in skeletal muscle development (EMBO J. 14: 1176-1186, 1995)

Myogenin knock-in in myf-5 KO mice: Functional reduundancy of the muscle-specific transcription factors Myf5 and myogenin (Nature 379: 823-825, 1996)





Regulation of skeletal muscle mass in mice by a new TGF-β superfamily member

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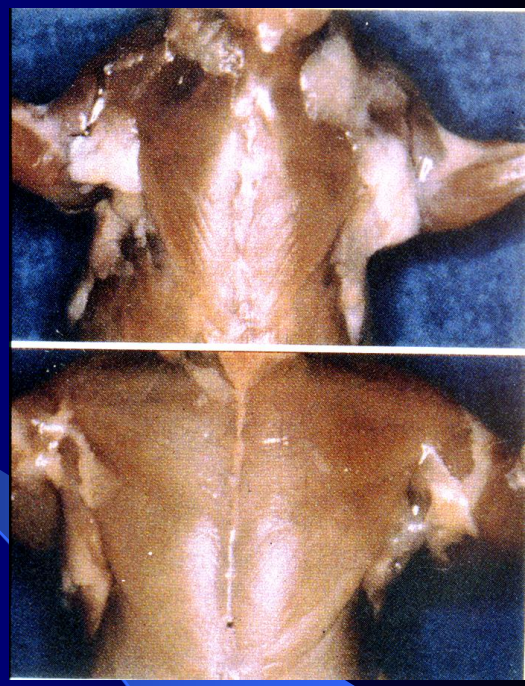
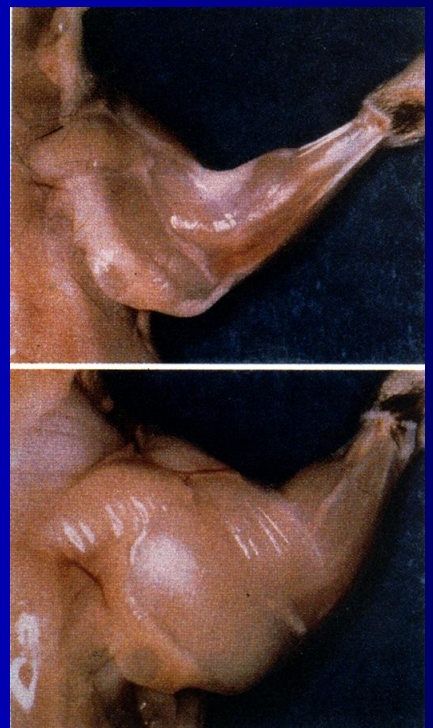
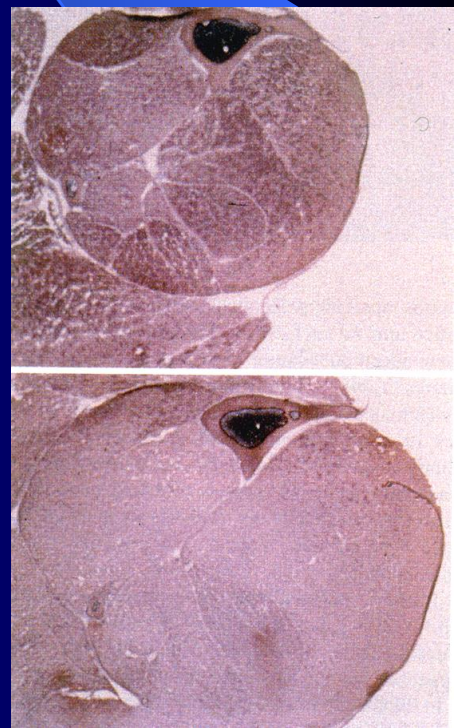
The transforming growth factor-β (TGF-β) superfamily encom passes a large group of growth and differentiation factors playin important roles in regulating embryonic development and i maintaining tissue homeostasis in adult animals[1]. Using deger erate polymerase chain reaction, we have identified a new murin TGF-β family member, growth/differentiation factor-8 (GDF-8 which is expressed specifically in developing and adult skelet muscle. During early stages of embryogenesis, GDF-8 expressio is restricted to the myotome compartment of developing somite At later stages and in adult animals, GDF-8 is expressed in mar different muscles throughout the body. To determine the biol gical function of GDF-8, we disrupted the GDF-8 gene by ge targeting in mice. GDF-8 null animals are significantly larger tha wild-type animals and show a large and widespread increase skeletal muscle mass. Individual muscles of mutant animals wei 2–3 times more than those of wild-type animals, and the increase mass appears to result from a combination of muscle cell hype plasia and hypertrophy. These results suggest that GDF-8 fun tions specifically as a negative regulator of skeletal muscle growt

To identify new members of the TGF-β superfamily, we design degenerate oligonucleotides corresponding to conserved regio among the known family members and used these oligonucleotid as primers for polymerase chain reaction (PCR) on mouse genom

Myostatin gene KO (Nature 387:83-90, 1997)







Belgian Blue Mutation at the myostatin gene

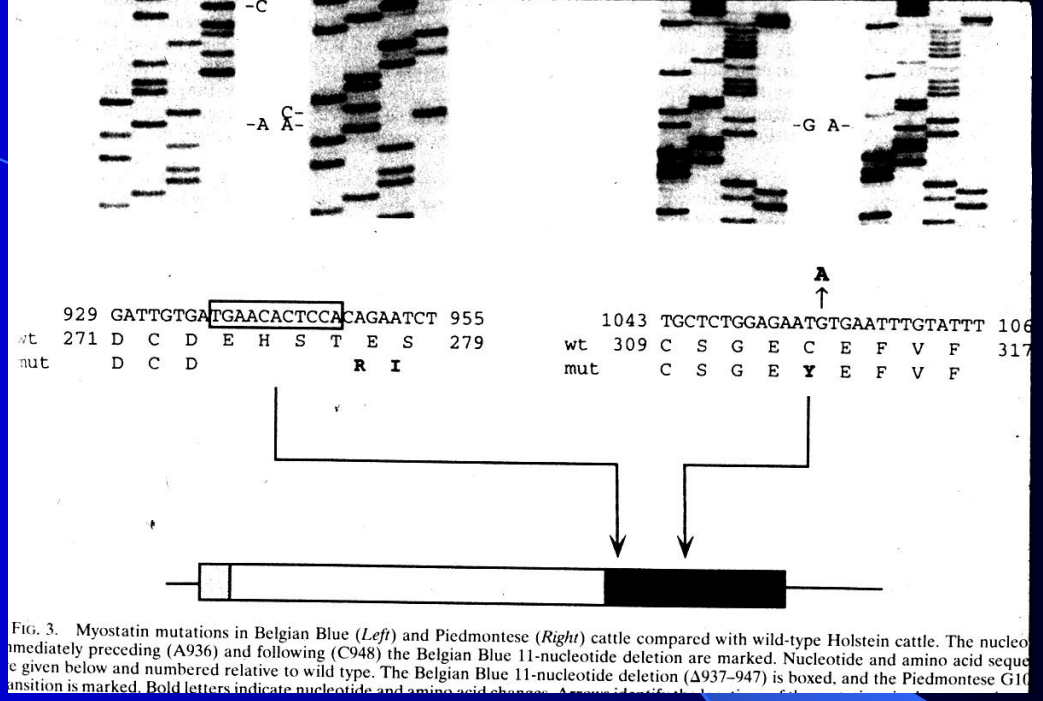
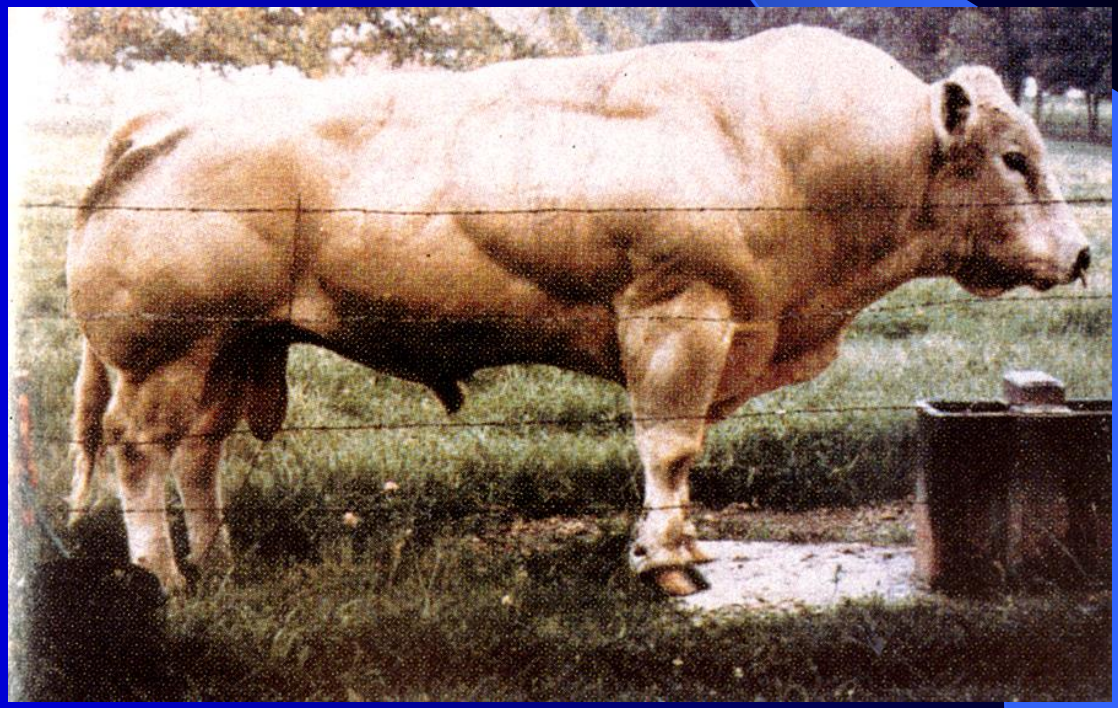


FIG. 3. Myostatin mutations in Belgian Blue (*Left*) and Piedmontese (*Right*) cattle compared with wild-type Holstein cattle. The nucleo
mediately preceding (A936) and following (C948) the Belgian Blue 11-nucleotide deletion are marked. Nucleotide and amino acid seque
e given below and numbered relative to wild type. The Belgian Blue 11-nucleotide deletion (Δ937–947) is boxed, and the Piedmontese G1
ansition is marked. Bold letters indicate nucleotide and amino acid changes.

Nature KO mutants: in the Belgian Blue



QUESTION 1:
Can genes be truly redundant?

• Superfluous, nonfunctional expression of proteins in the development or even in the adult. (Erickson, 1993, J.Cell Biol. 120:1079-1081) e.g. NGF in salivary gland

• Highly expression of c-src , a tyrosine kinase in platelets, in neurons, and in testis, surprisingly, these tissues appeared completely normal in c-src KO mice.

Data from immunocytochemistry (or Western) and *in situ* hybridization (or Northern)

→*Please do not jump to the conclusion too fast. Especially, if you want to address the function of your favor gene products (mRNA or proteins).*

QUESTION 2:
"No phenotype" means nothing wrong? How about "positive" effect?

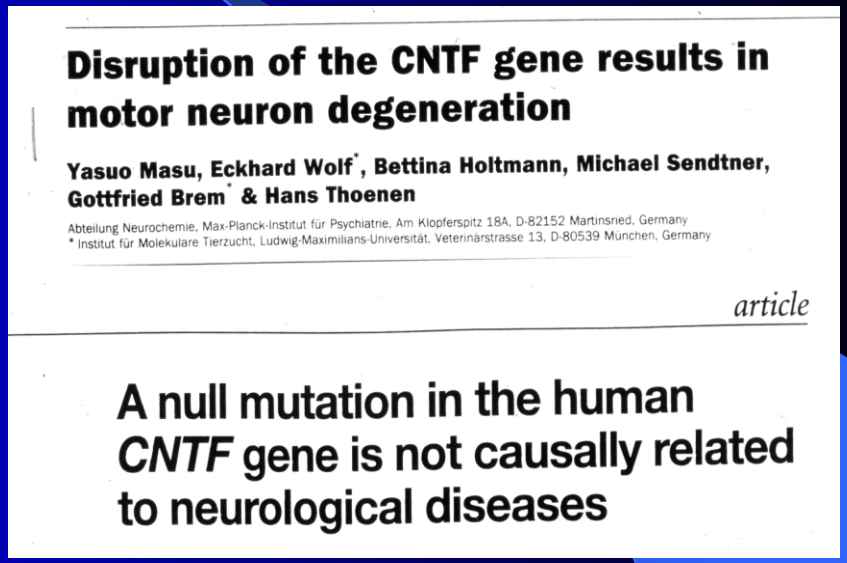
vimentin KO: No phenotype (Cell 79:679-694, 1994)
GFAP KO: No phenotype (EMBO J. 14:1590-1598, 1995)

It depends on the viewpoint from gross function.
It also depends on the physiological or pathological view.
e.g. p53 KO→ Abnormal centrosome amplification
(Science 271: 1744 -1747, 1996)

Knockout the Negative factor:
Regulation of skeletal muscle mass in mass by a new TGF-β superfamily member (myostatin KO)
→ "Super" mouse!! (Nature 387: 83-90, 1997)

QUESTION 3:
A knockout mouse model is a really good animal model for studying human genetic disease?

- CNTF (ciliary neurotrophic factor) KO mice: motor neuron degeneration (Nature 365:27-32, 1993)
- A null mutation in the human CNTF gene is not causally related to neurological diseases. (Nature Genetics 7:79-84, 1994).



Disruption of the CNTF gene results in motor neuron degeneration

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article

A null mutation in the human *CNTF* gene is not causally related to neurological diseases

- CNTFR KO mice: die perinatally and display severe motor neuron deficits. (Cell 83:313-322, 1995)