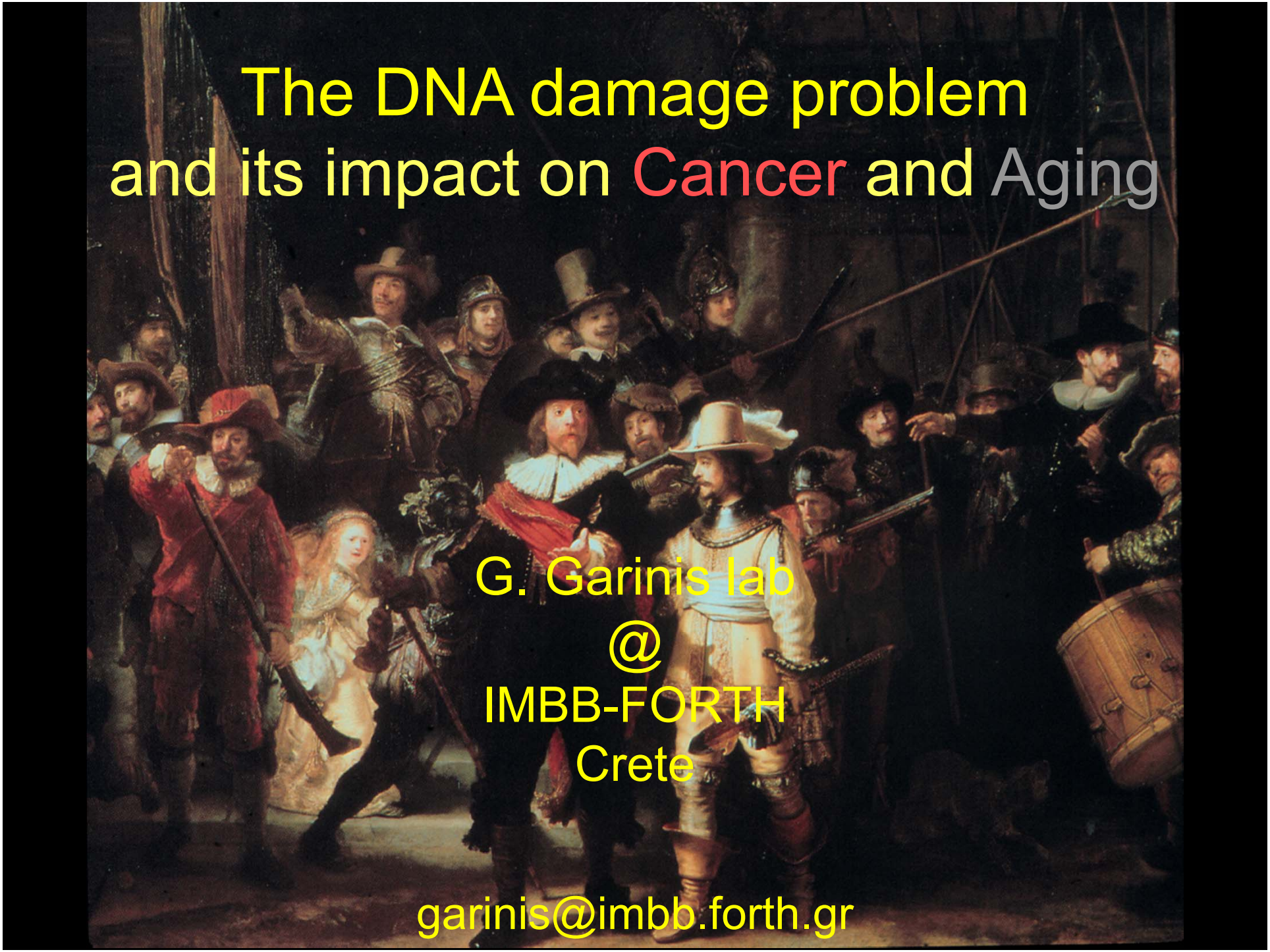

The DNA damage problem and its impact on Cancer and Aging

G. Garinis lab
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Crete

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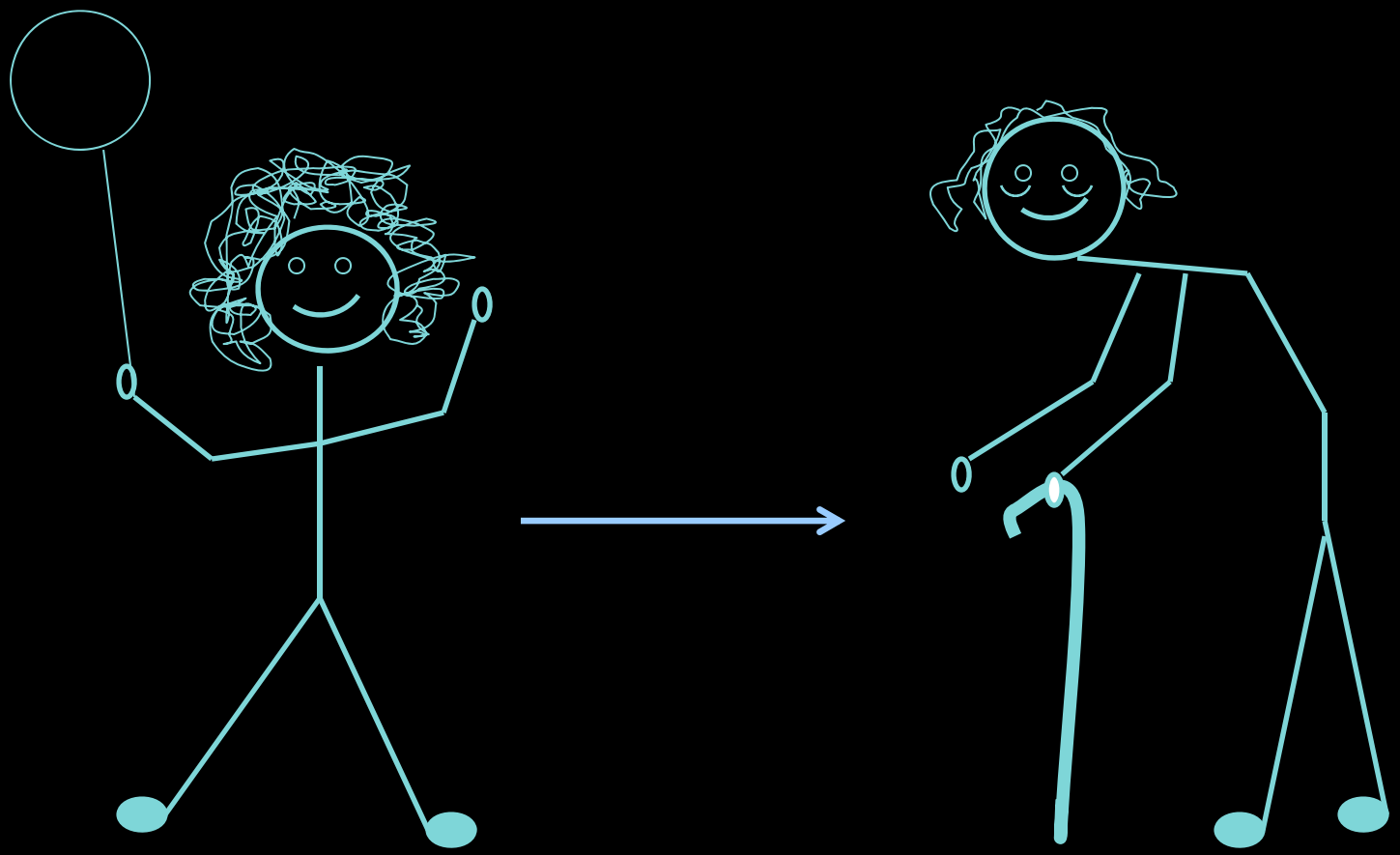


What IS Aging?

Aging is a PROCESS that converts a healthy, fit organism (for its environment) into one that is less healthy and fit

Aging is a biological process
Aging not disease, per se

AGING

Reduced tissue/physiological function

Increased susceptibility to disease (age-related diseases)

Decreased resistance to stress (physical and psychological)

Why does aging happen?

If we don't understand this, we can’t design rational interventions!

What can we do about it?

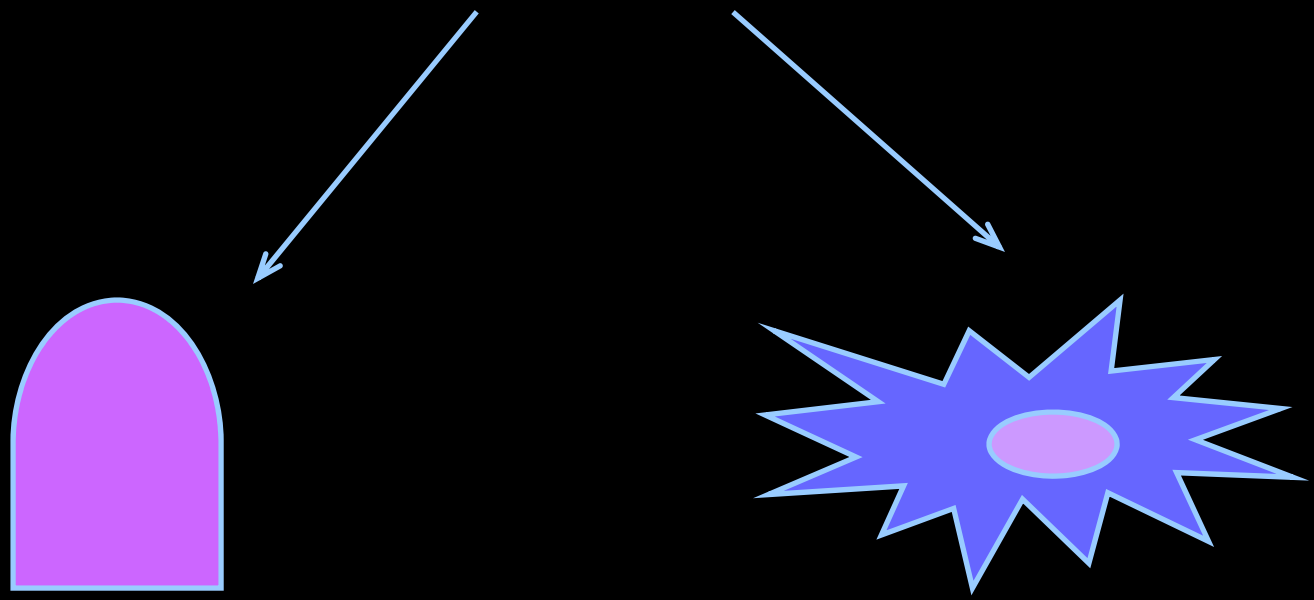
How can we postpone the effects of aging?

Aging occurs at multiple levels

- *molecules*
- *cells*
- *tissues*
- *organ systems*

Cells = molecules + response
-----> tissue, organ system effects

Cellular "aging" = response to damage or stress



Cell death
(apoptosis)

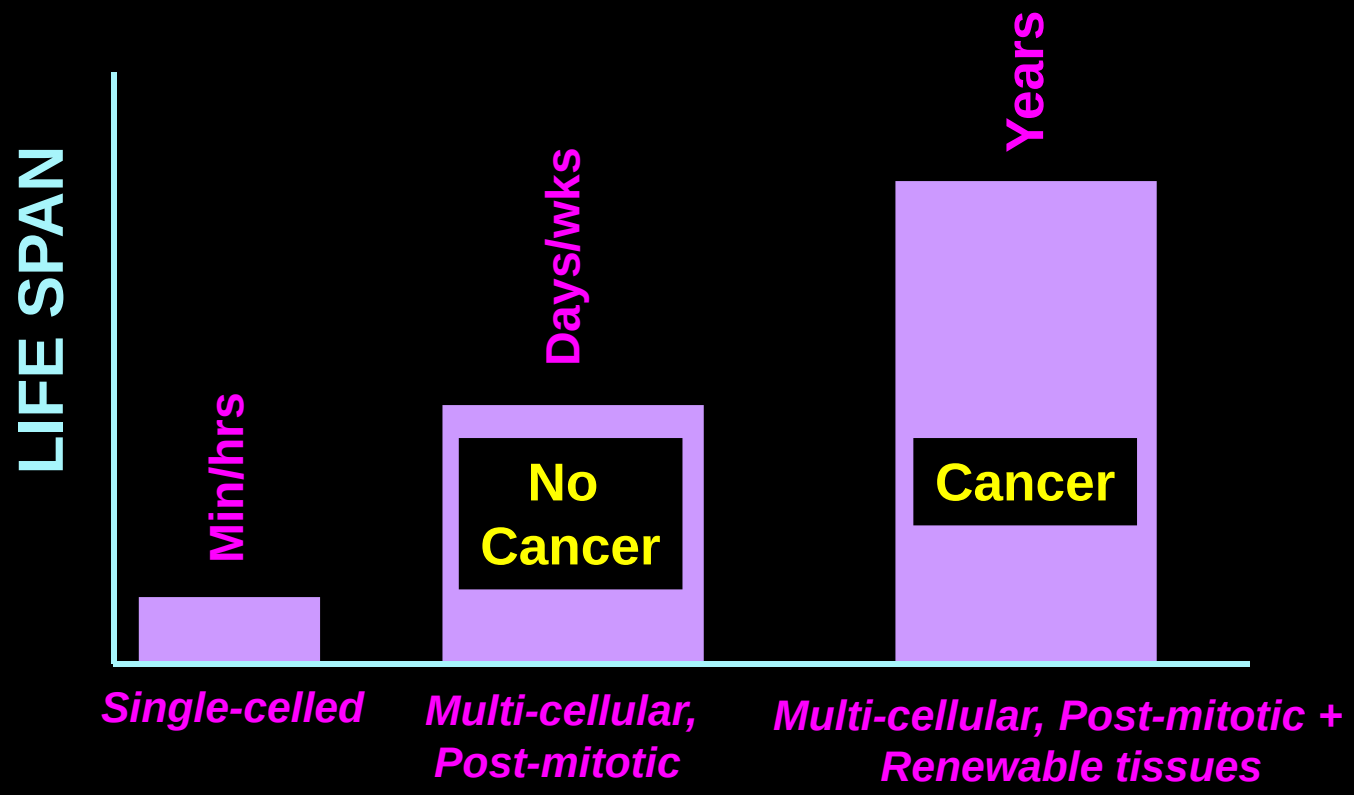
Arrested cell growth
(cell senescence)

Cellular "aging" responses:
YIN and YANG

Good news!
(prevents cancer)

Bad news!
(promotes aging)

Evolution of Long-Lived Organisms



CELL DIVISION IS RISKY!!

Cancer

The bad news!

Cancer risk rises exponentially with age

Fueled by (somatic) mutations

Mutations caused by DNA damage,
from endogenous and exogenous sources

Cancer

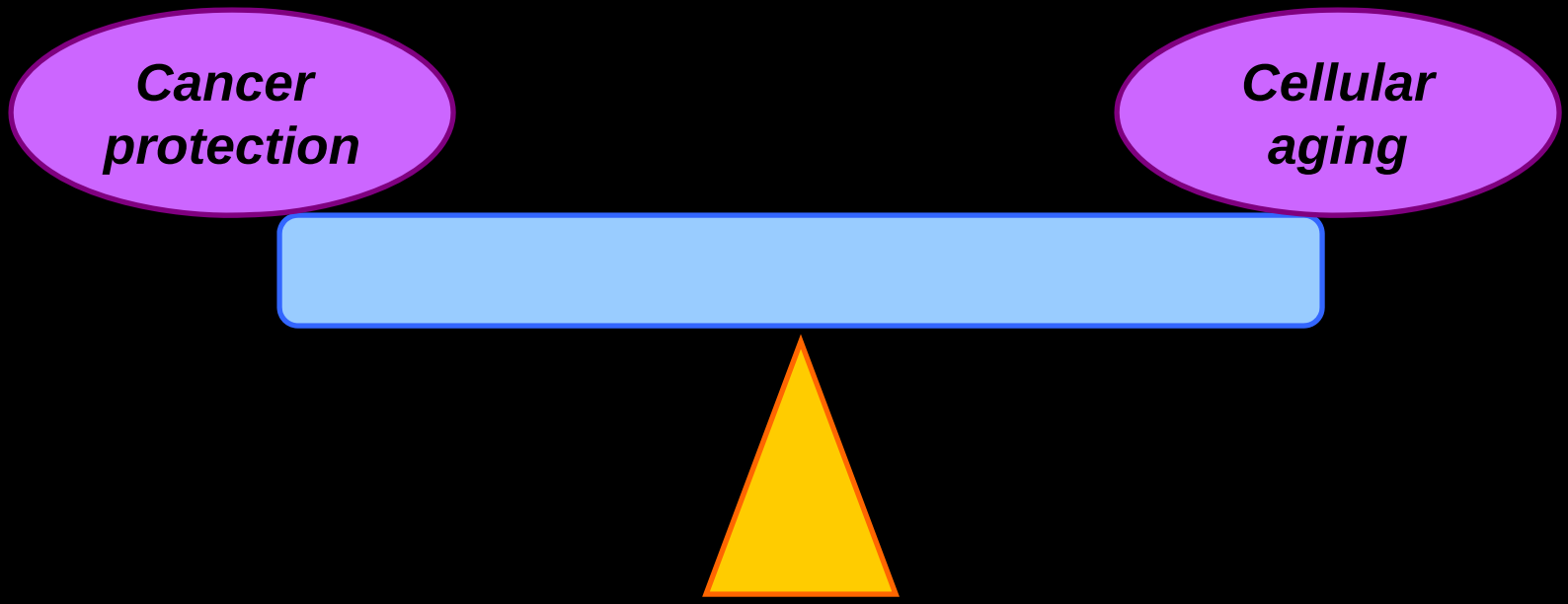
The good news!

Genes evolved to protect from cancer
(tumor suppressor genes)

Tumor suppressor genes cause damaged cells to die or arrest growth
(undergo apoptosis or senescence)

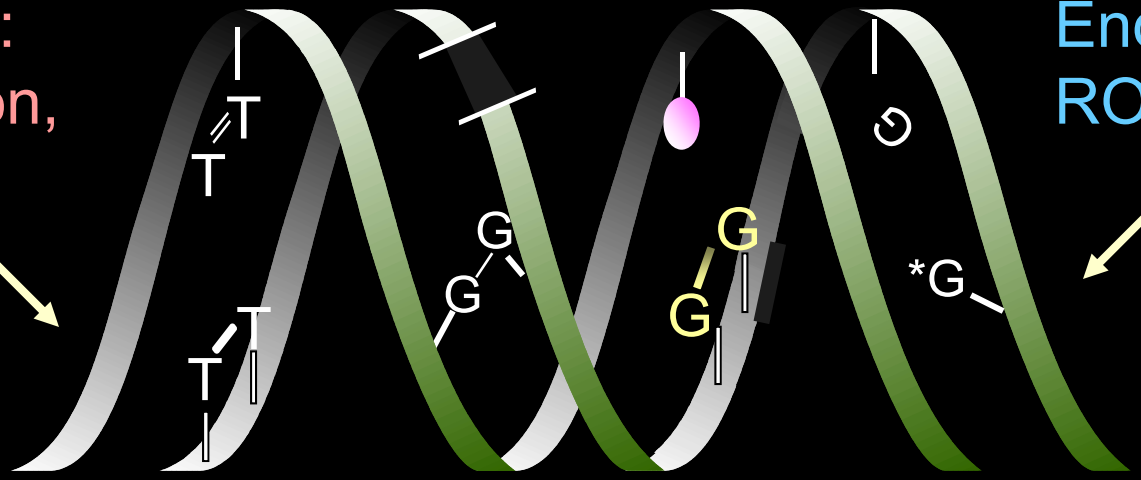
Apoptosis and senescence
= cellular 'aging' responses!

Tumor suppression and aging: An evolutionary balancing act!



Cellular consequences of DNA damage

Exogenous:
UV, radiation,
chemicals



Endogenous:
ROS, alkylation

Altered DNA metabolism

misreplication, aberrant
chromos. segregation

mutations
chromos. aberrations

DNA repair
systems

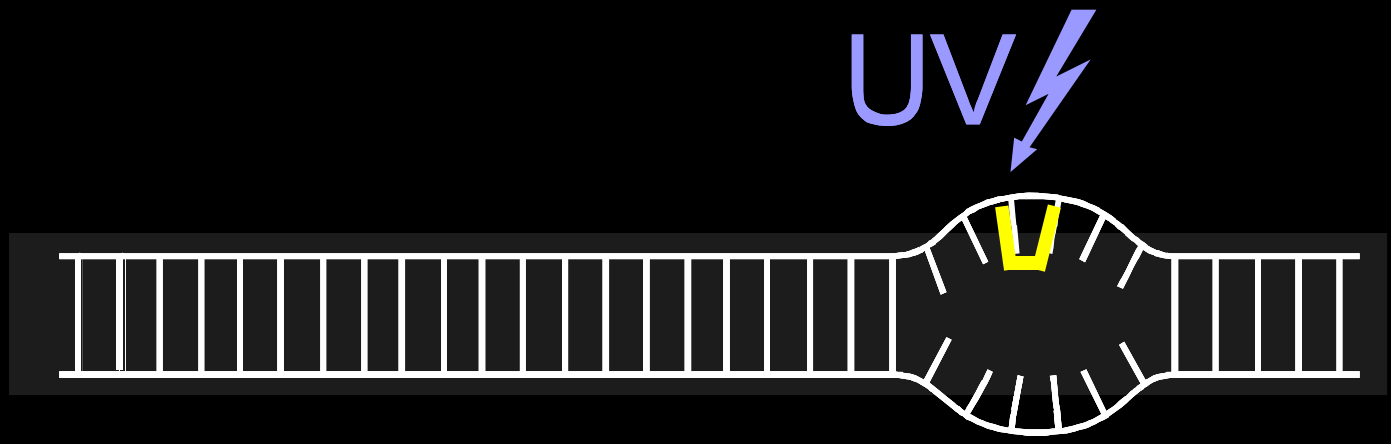
blocked transcription
blocked replication

cell cycle delay/arrest
cell death

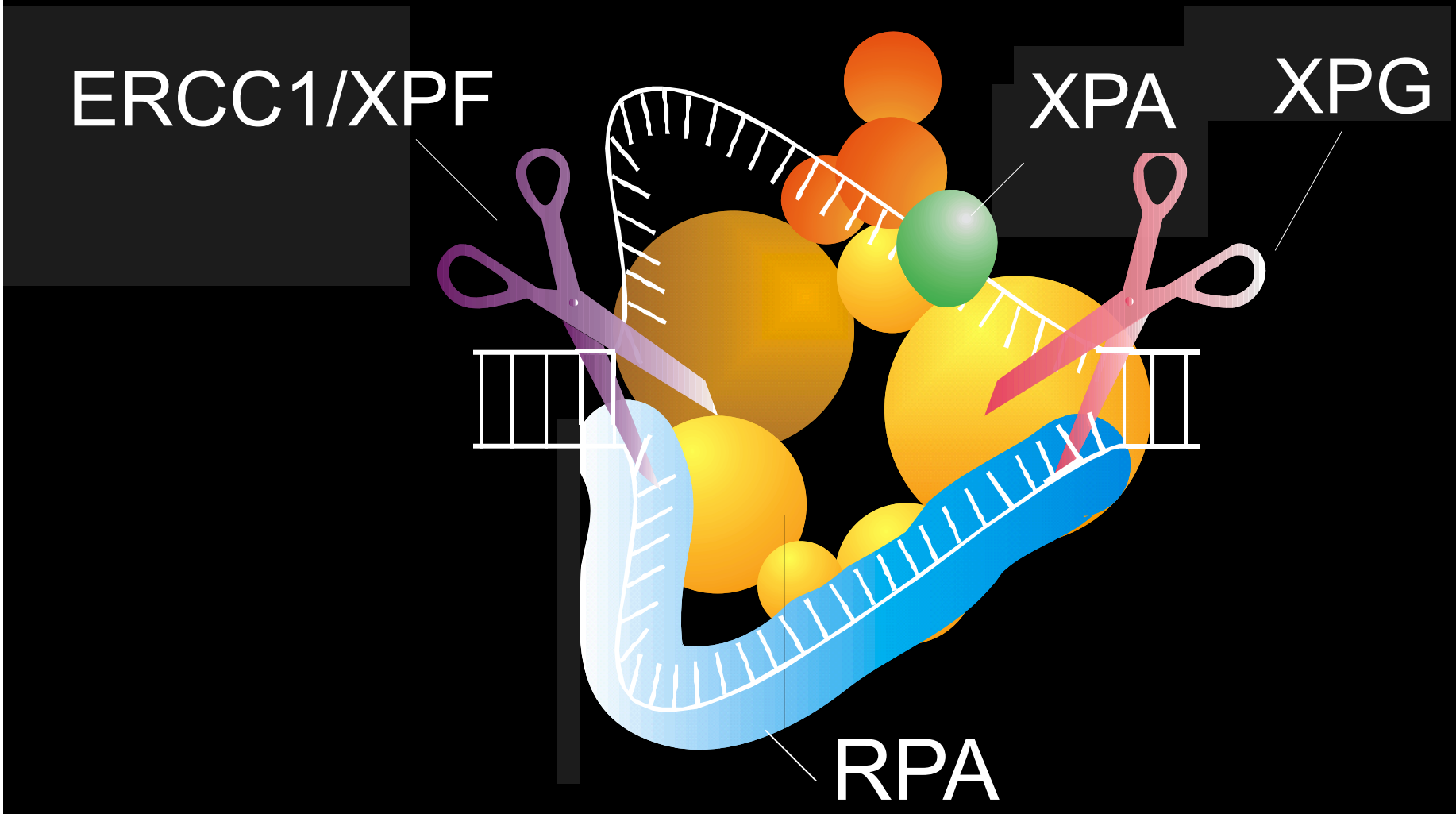
DNA repair systems in mammals

Pathway	DNA lesion
global genome NER	distorting, bulky
transc/tion-coupled NER	transcription-blocking
base excision repair (BER)	subtle base modification
homologous recombination	double strand break
endjoining	double strand break
cross-link repair	interstrand cross-links

Global genome nucleotide excision repair (GG-NER)

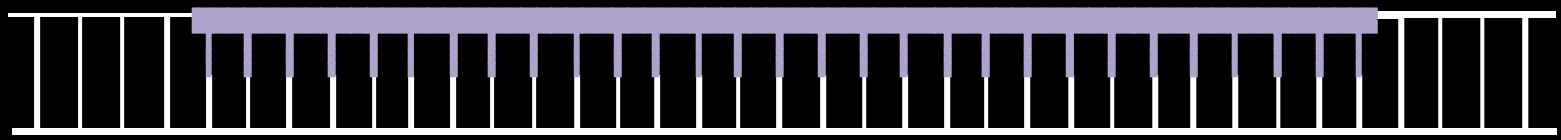


Global genome nucleotide excision repair (GG-NER)

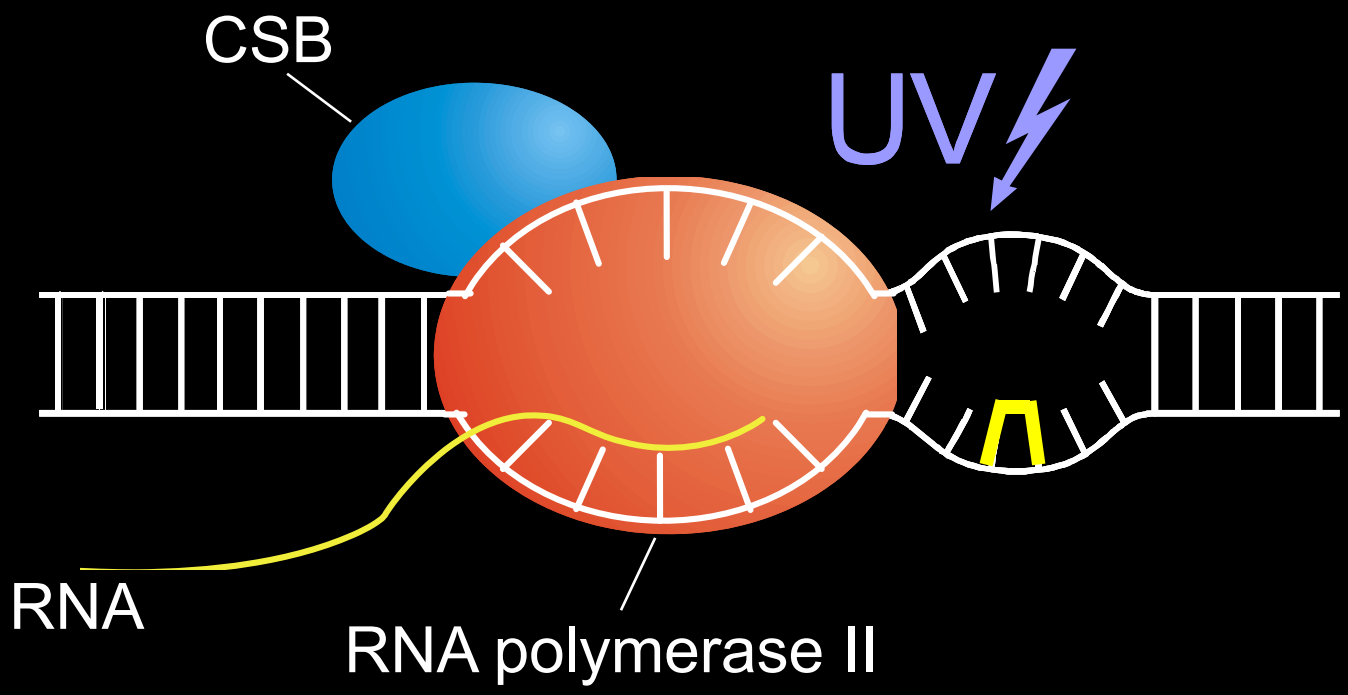


Global genome nucleotide excision repair (GG-NER)

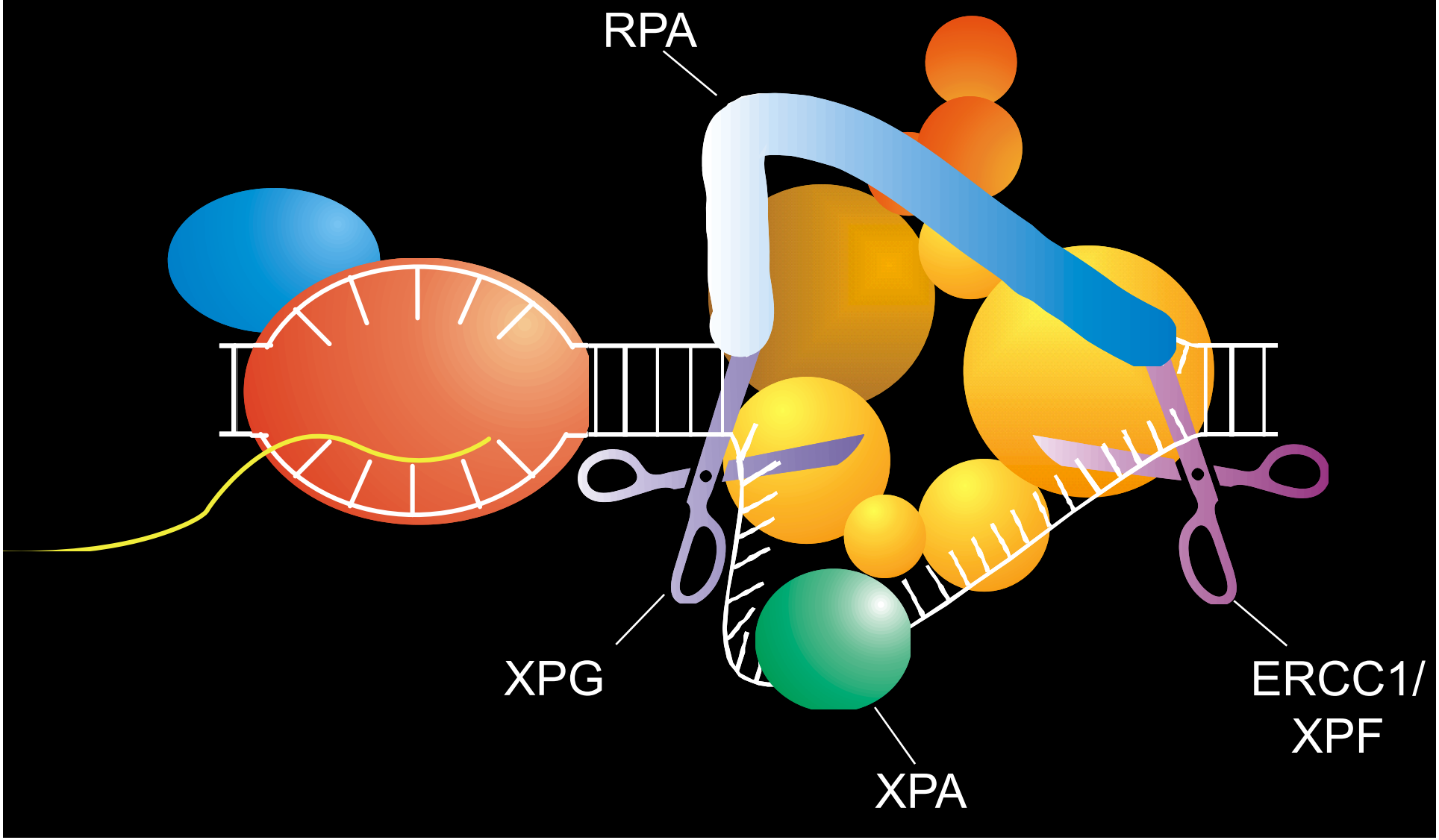
DNA polymerase δ/ε, RFC
PCNA and DNA ligase



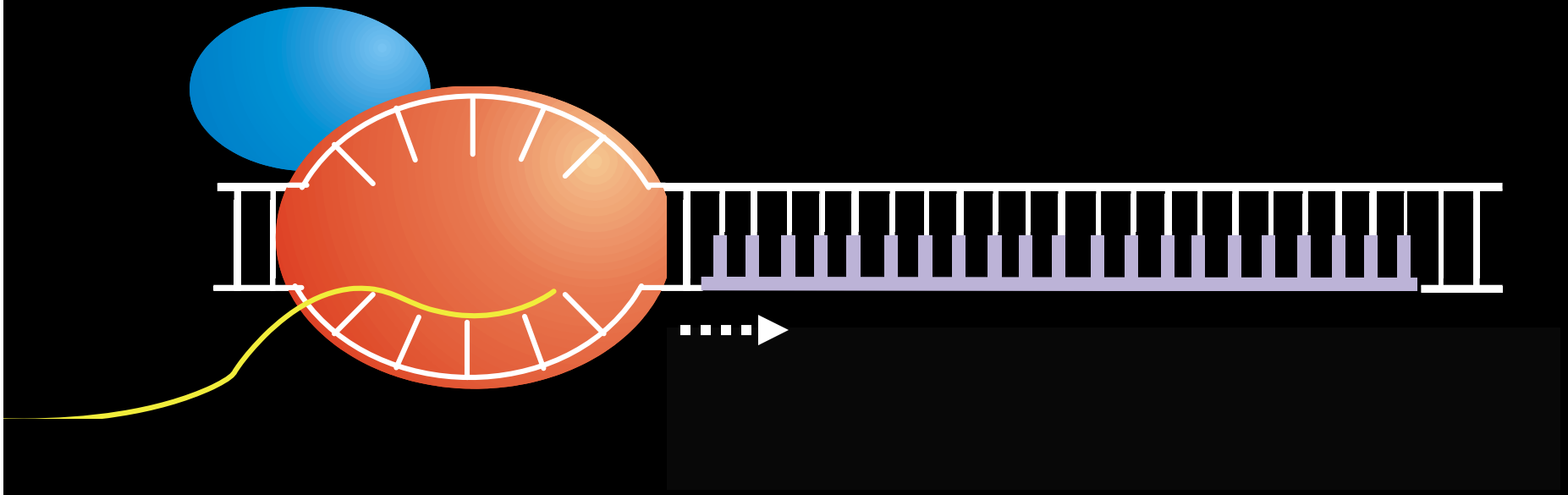
Transcription-coupled nucleotide excision repair (TC-NER)

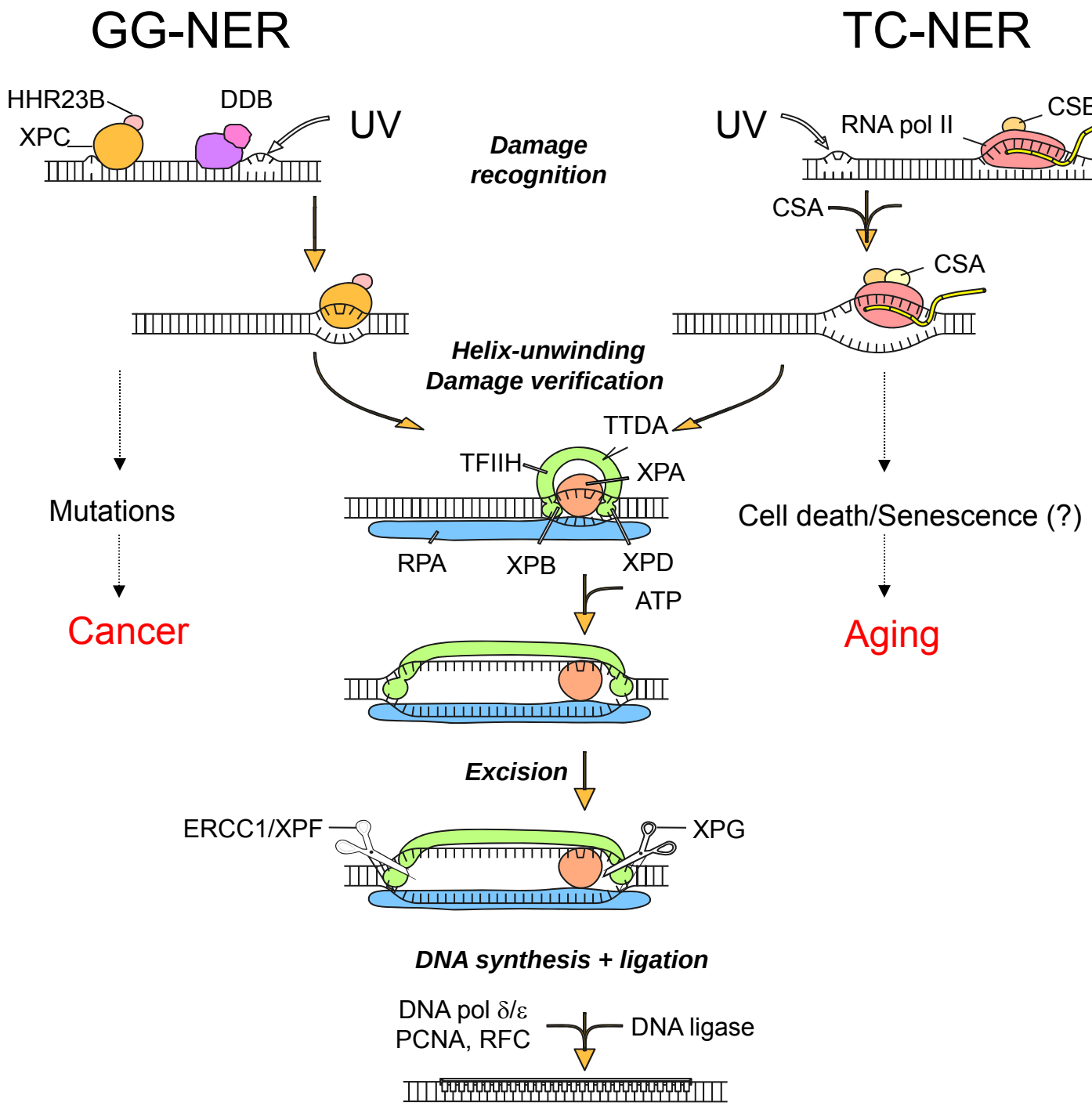


Transcription-coupled nucleotide excision repair (TC-NER)

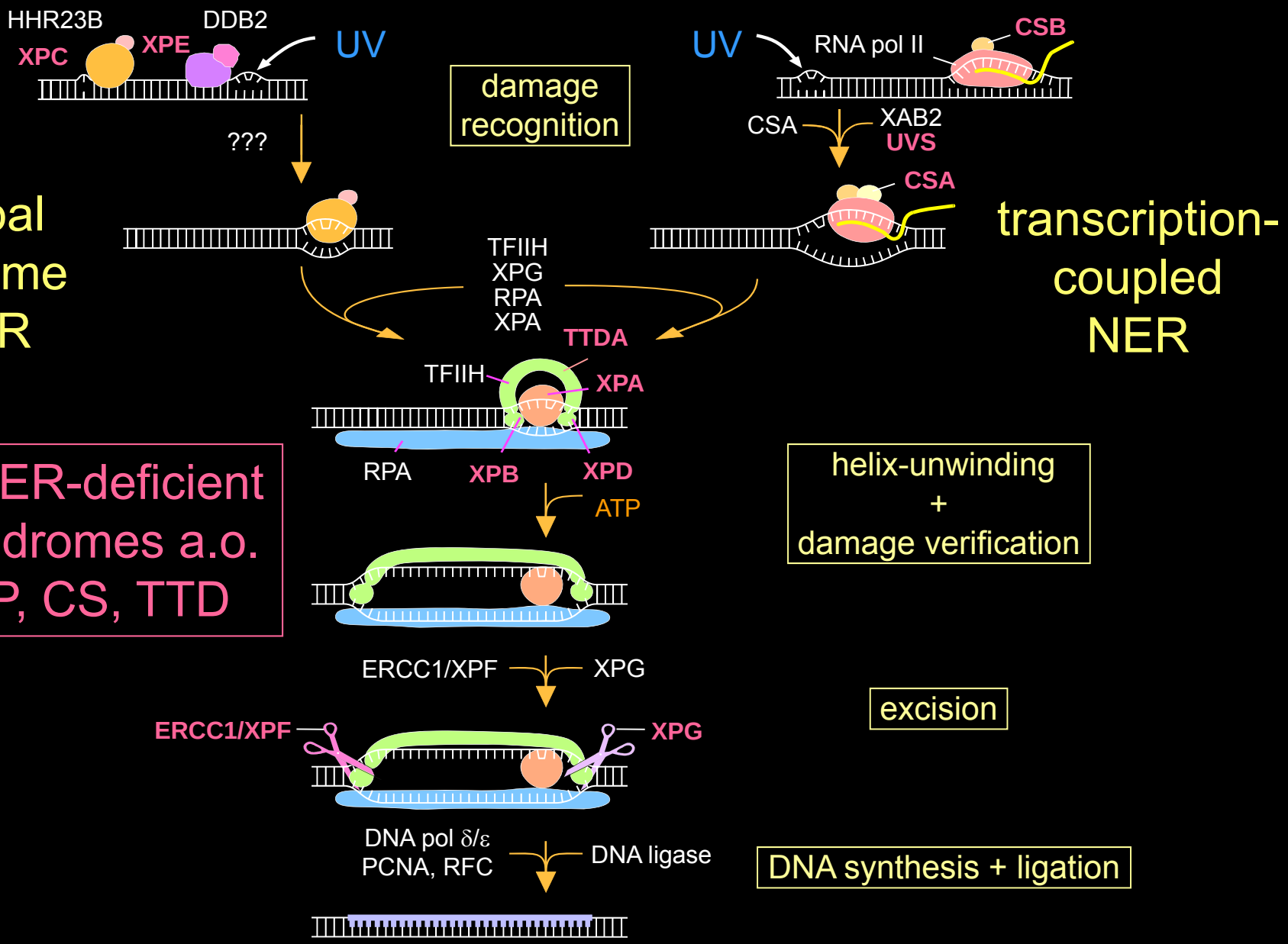


Transcription-coupled nucleotide excision repair (TC-NER)

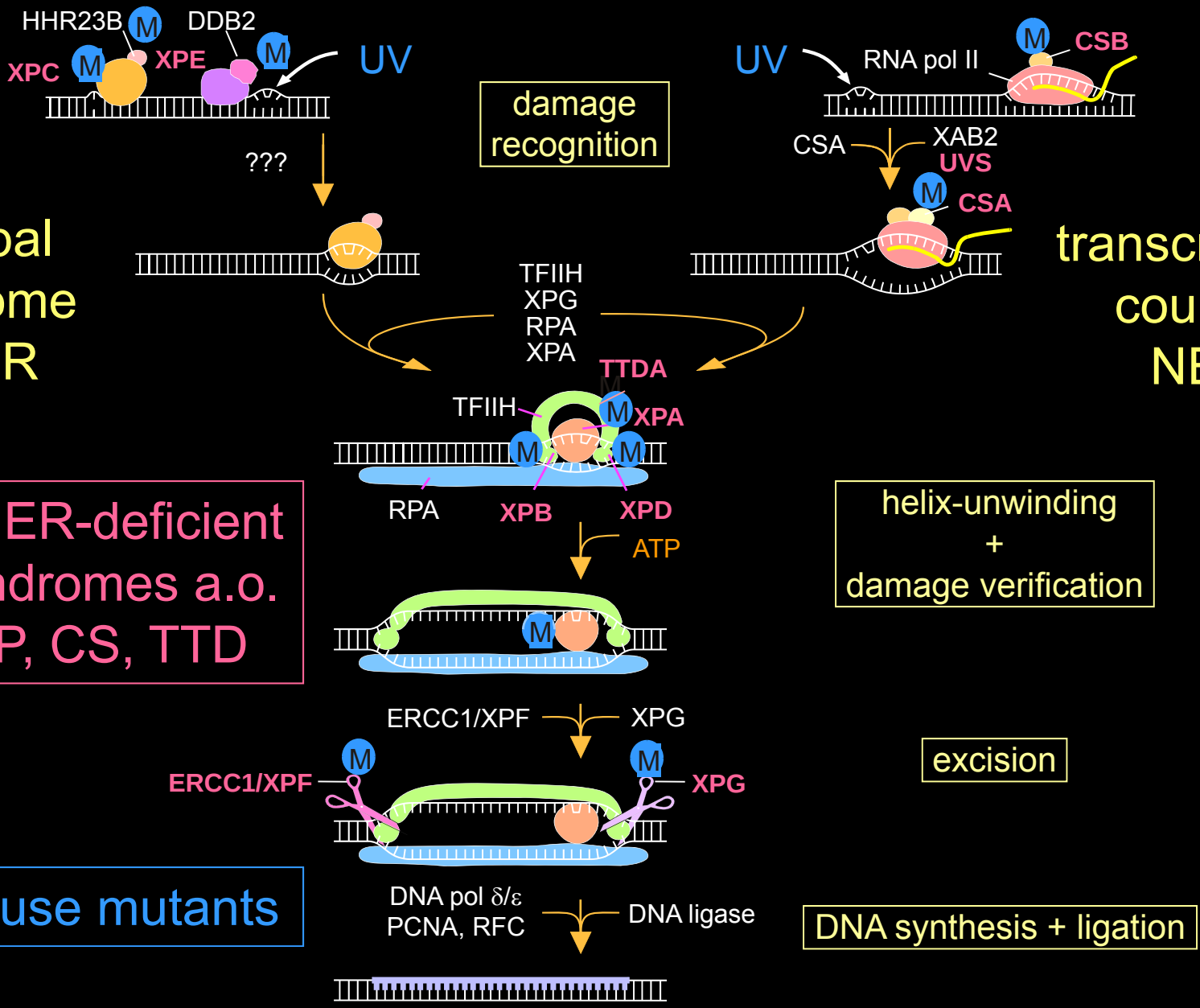



GG-NER
TC-NER
HHR23B
DDB
XPC
UV
Damage recognition
UV
RNA pol II
CSB
CSA
CSA
Helix-unwinding
Damage verification
TTDA
TFIIH
XPA
RPA
XPB
XPD
ATP
Mutations
Cell death/Senescence (?)
Cancer
Aging
Excision
ERCC1/XPF
XPG
DNA synthesis + ligation
DNA pol δ/ε
PCNA, RFC
DNA ligase

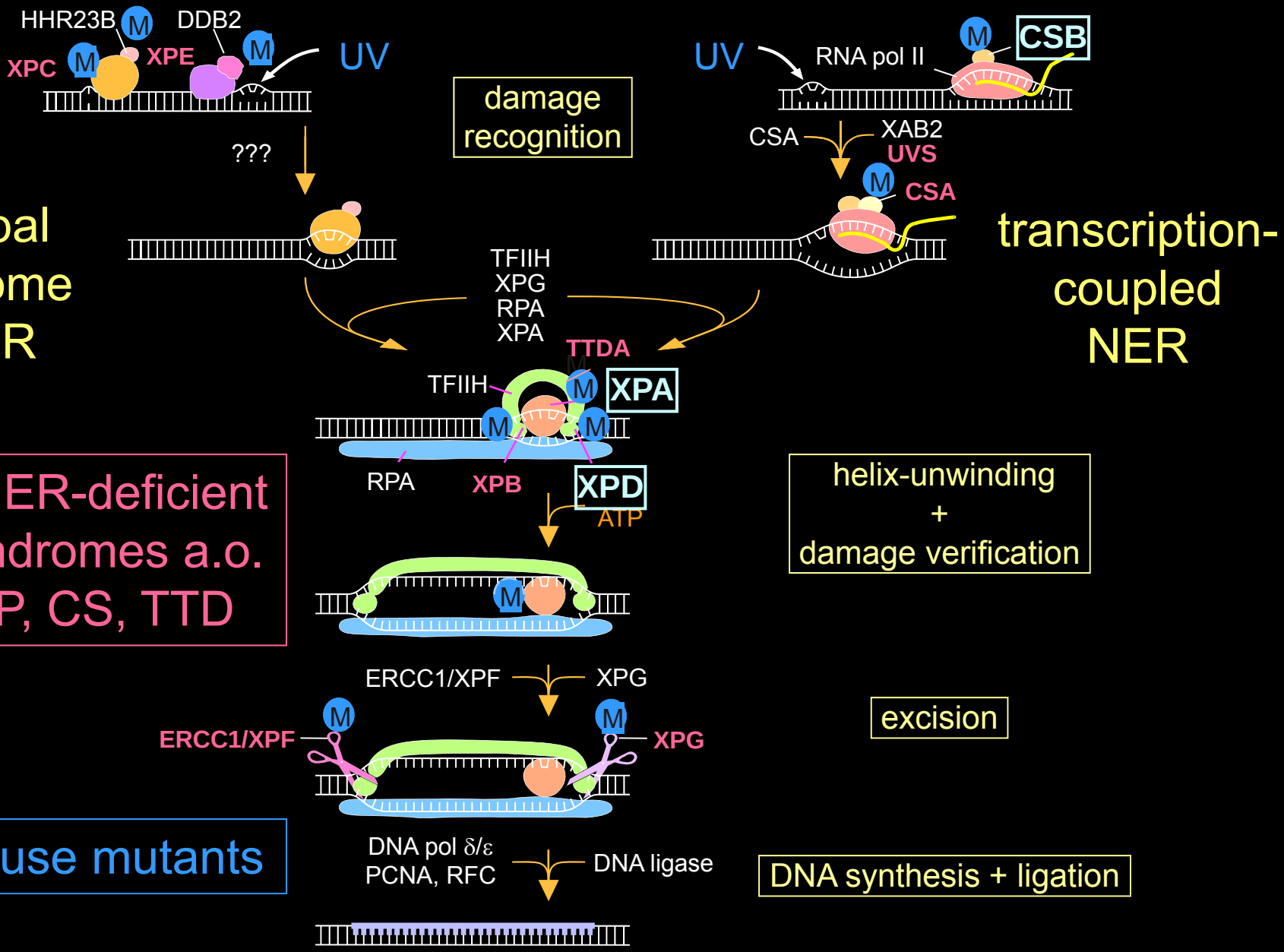
Nucleotide Excision Repair (NER) - Patients



Nucleotide Excision Repair (NER) - Mouse mutants



Nucleotide Excision Repair (NER) - Mouse mutants

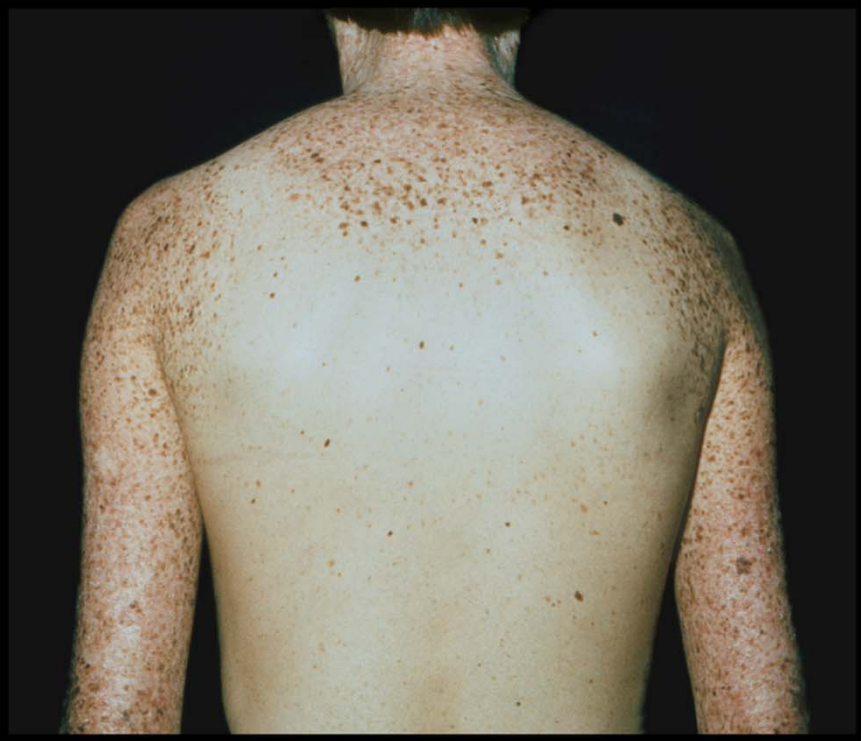


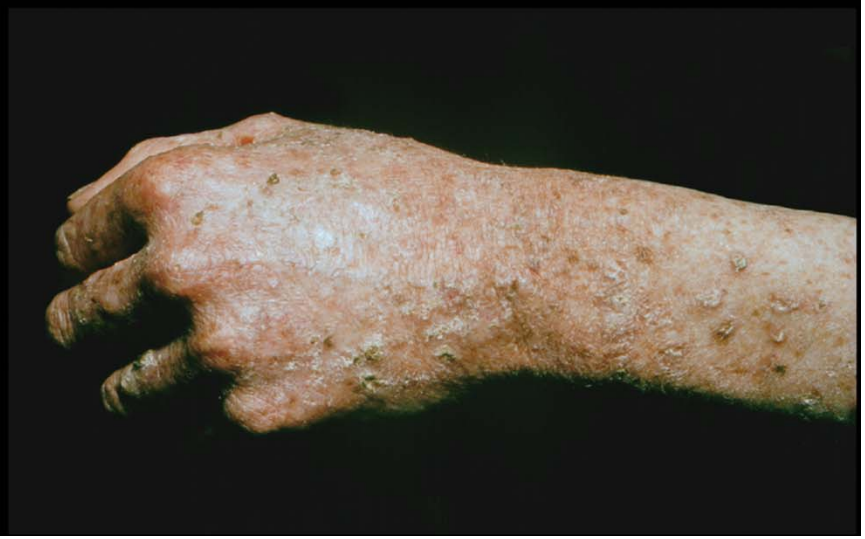
Xeroderma Pigmentosum (XP)

- Photo (UV) sensitivity
- Pigmentation abnormalities
- Atrophic skin
- Skin cancer (>2000x↑)
- Accelerated neurological degeneration

7 genes involved:

XPA - XPG





Skin tumors in xeroderma pigmentosum

Management of XP cancer

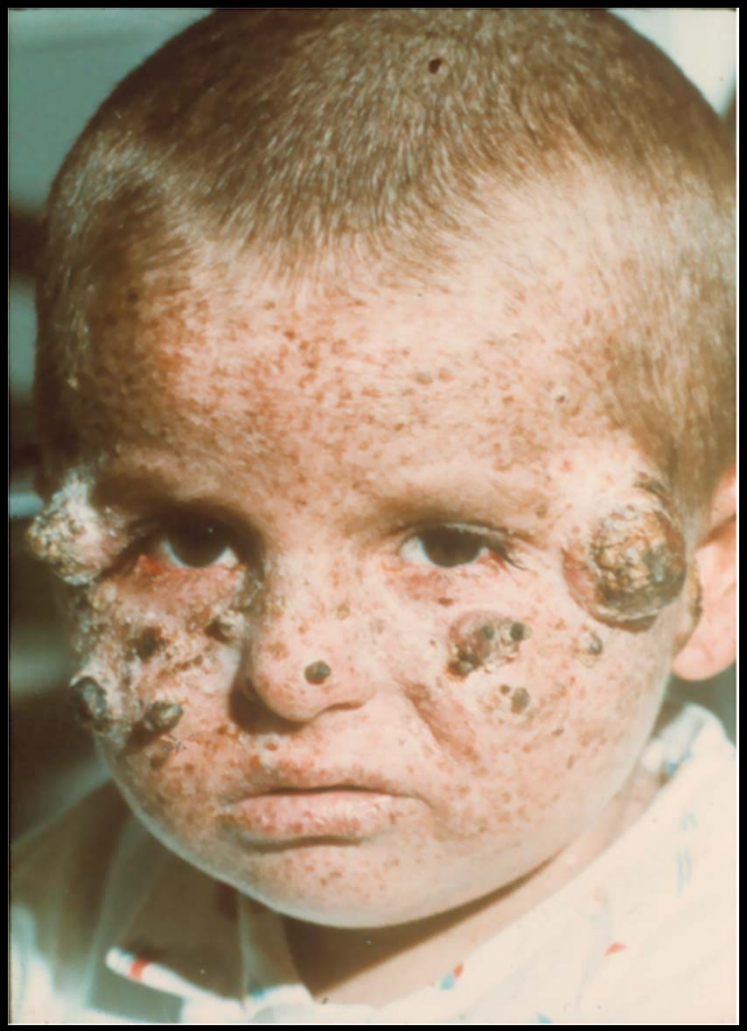
- very rigorous sun-light protection

- regular dermatologic intervention

- preventive oral retinoids (~50%)

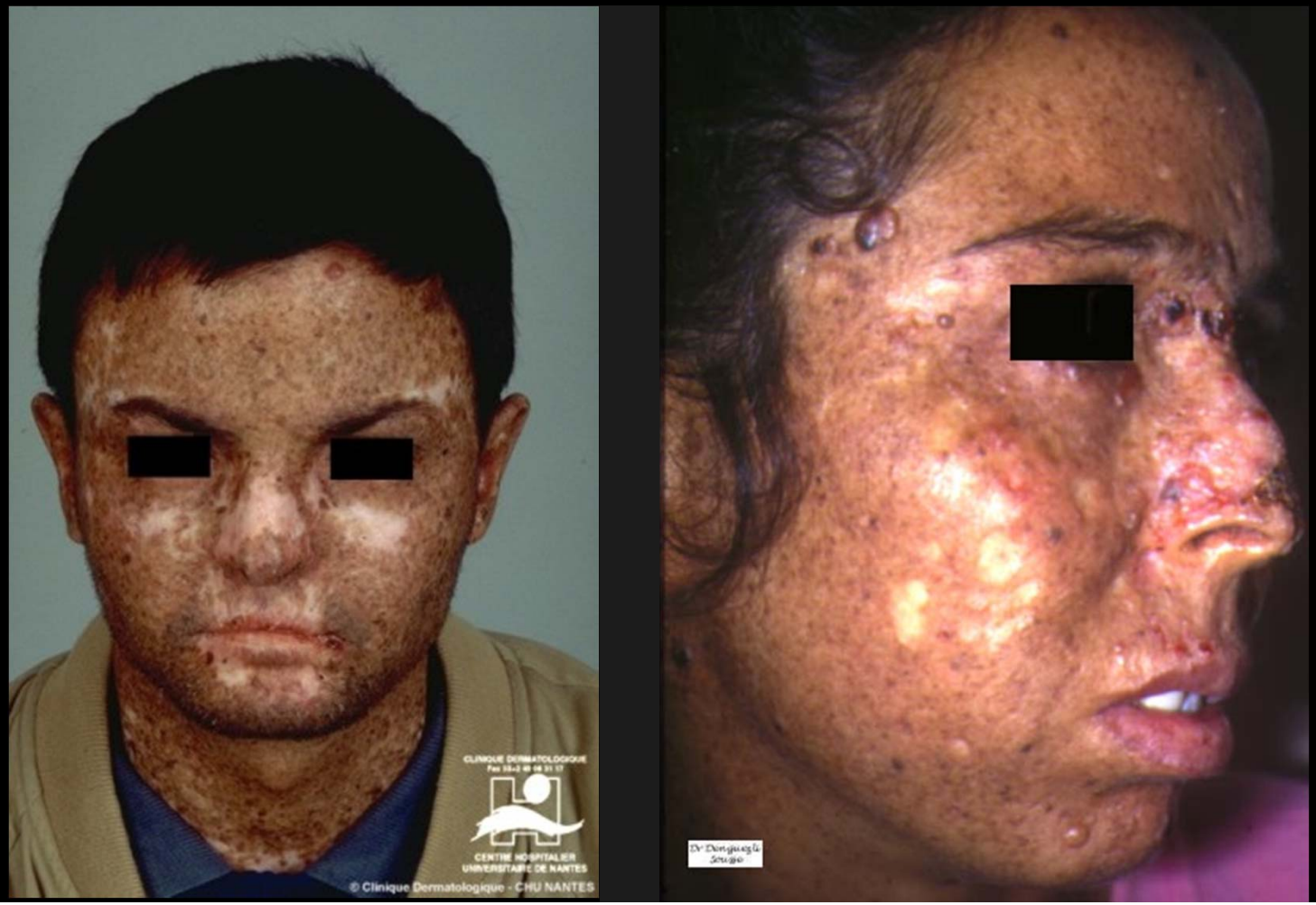
(Isotretinoid, Accutane®)

Neglect in patient XP20RO (XPC)



DNA repair deficiency with cancer predisposition

Xeroderma Pigmentosum



Cockayne Syndrome (CS)

- Photo (UV) sensitivity
- Growth failure
- Neurological abnormalities
- Retinal degeneration
- Cachexia
- Impaired sexual developm.

No skin cancer !

5 genes: *CSA,CSB*

combined with XP:

XPB, XPD, XPG

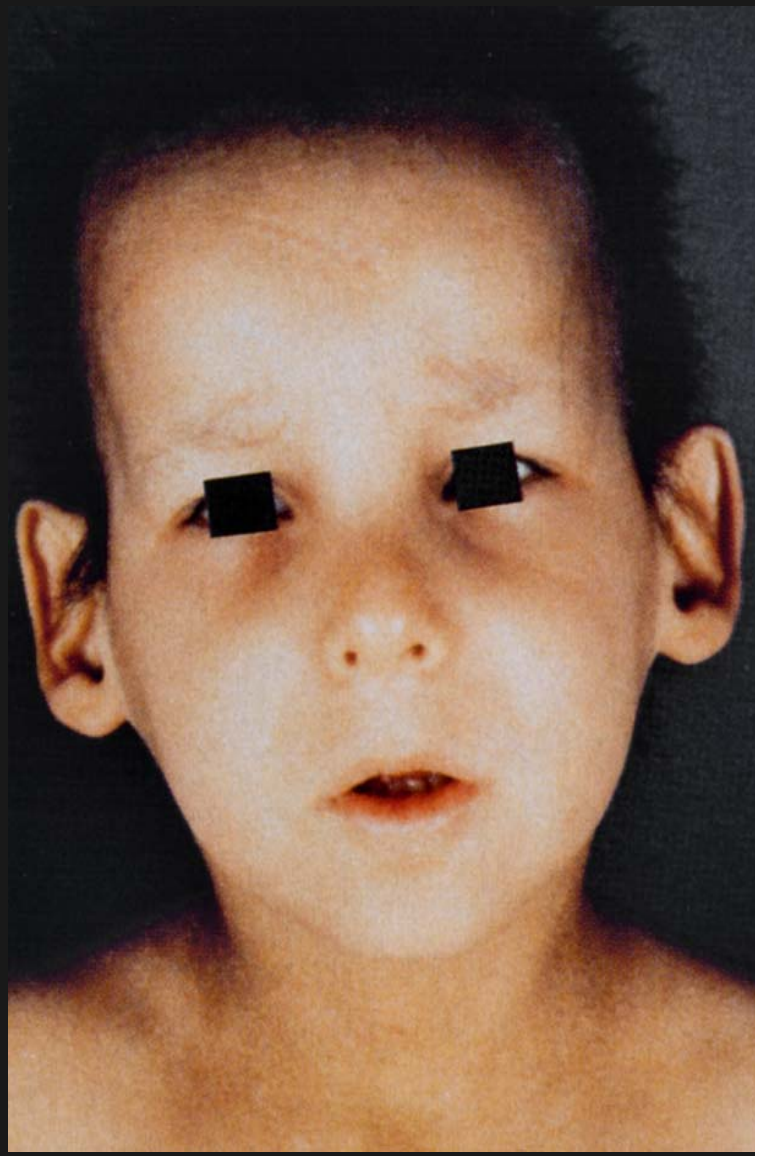
7 y

Trichothiodystrophy (TTD, PIBIDS)

- Photo (UV) sensitivity
- Ichthyosis
- Brittle hair/nails
- Impaired intelligence
  (dysmyelination of CNS)
- Decreased fertility
- Short stature

No skin cancer !

3 genes: *XPB*, *XPD*, *TTDA*



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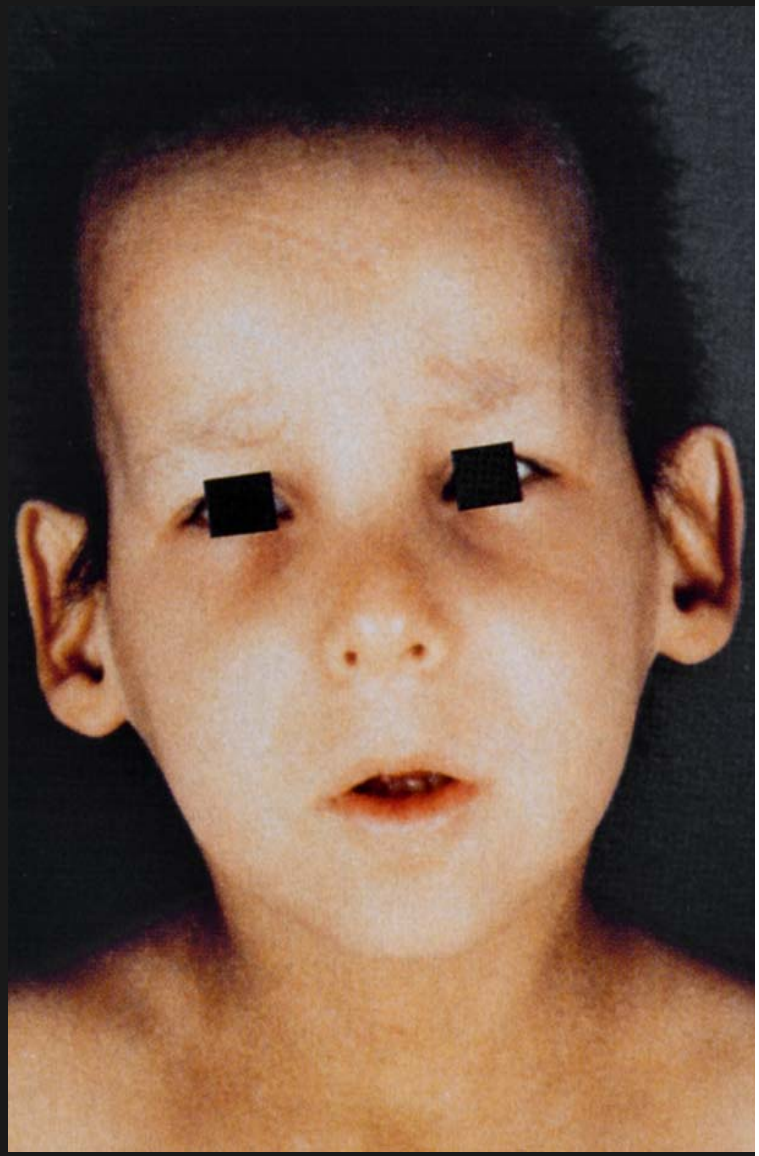
No skin cancer !

3 genes: *XPB*, *XPD*, *TTDA*

CS component in TTD



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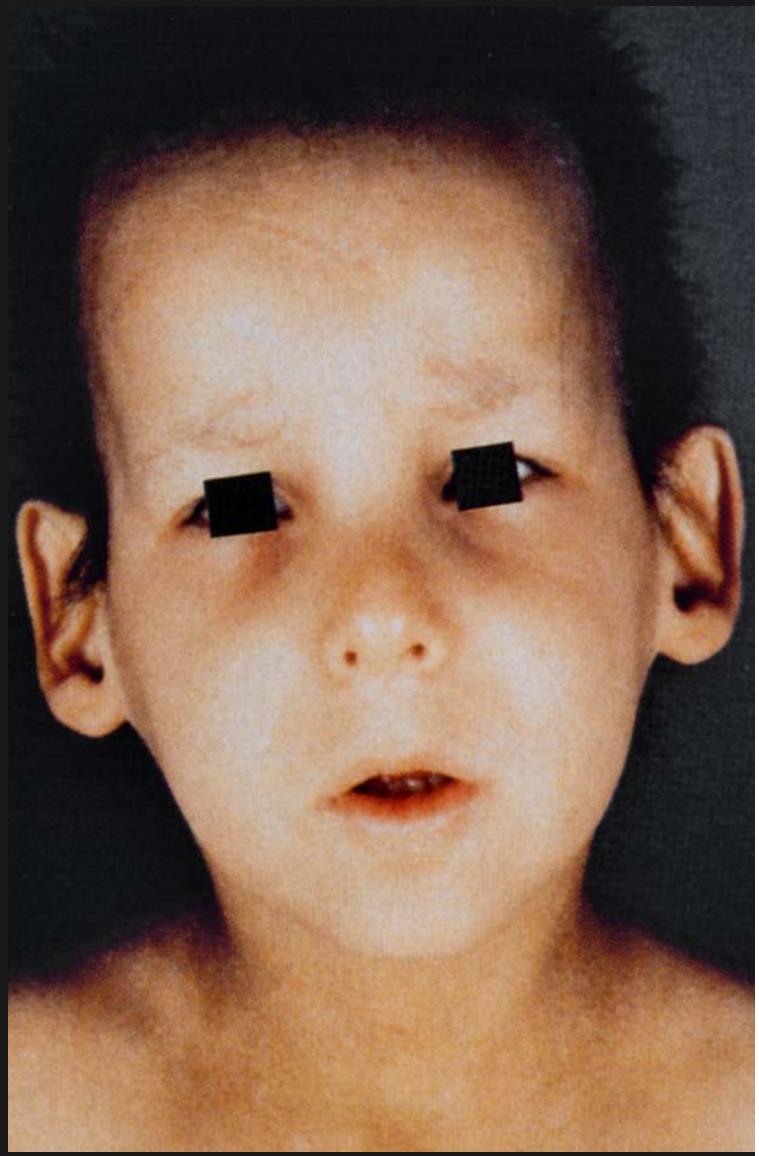
3 genes: *XPB*, *XPD*, *TTDA*

Specific to TTD



Questions from UV-sens. NER syndromes

1. Xeroderma pigmentosum (XP):
   - extremely cancer-prone
2. Cockayne syndrome (CS), trichothiodystrophy (TTD)
   - seem protected from cancer
   - clinical picture instead is dominated by accelerated aging

However,

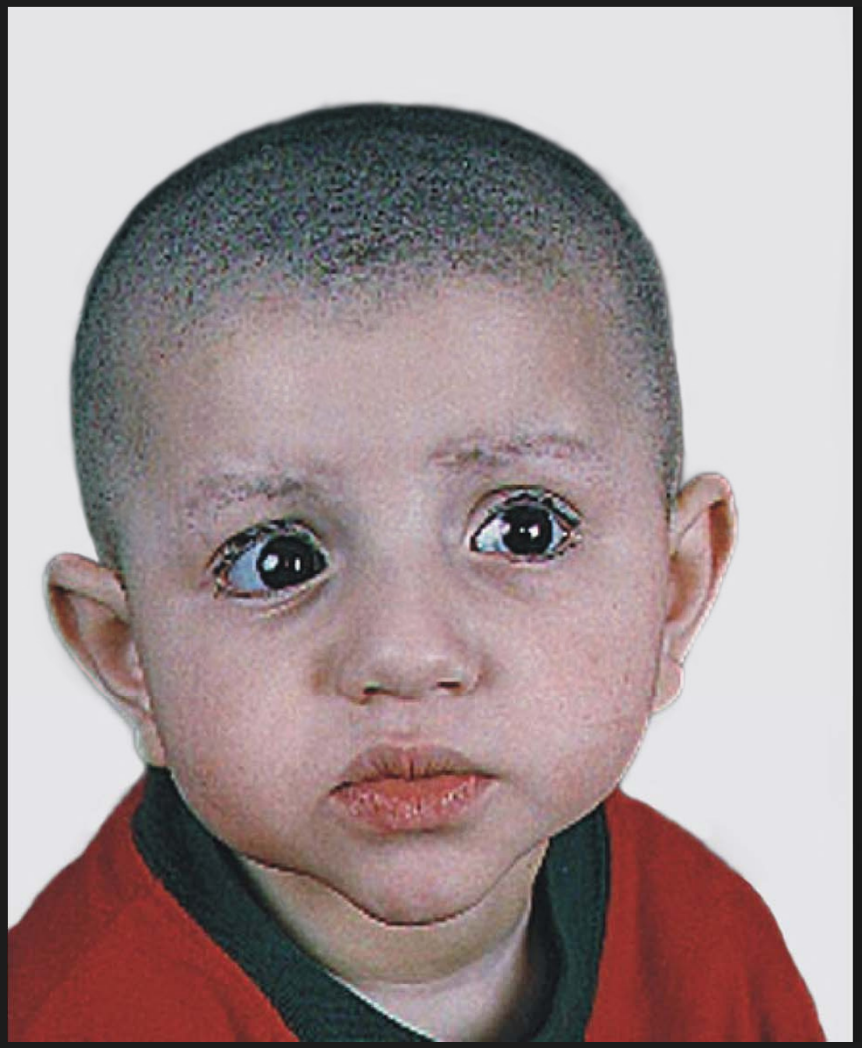
- all are deficient in the same repair system and
- even can be due to mutations in the same gene (notably XPB and D subunits of TFIIH)

Can mouse models mimic the patients?

Phenotype TTD mice

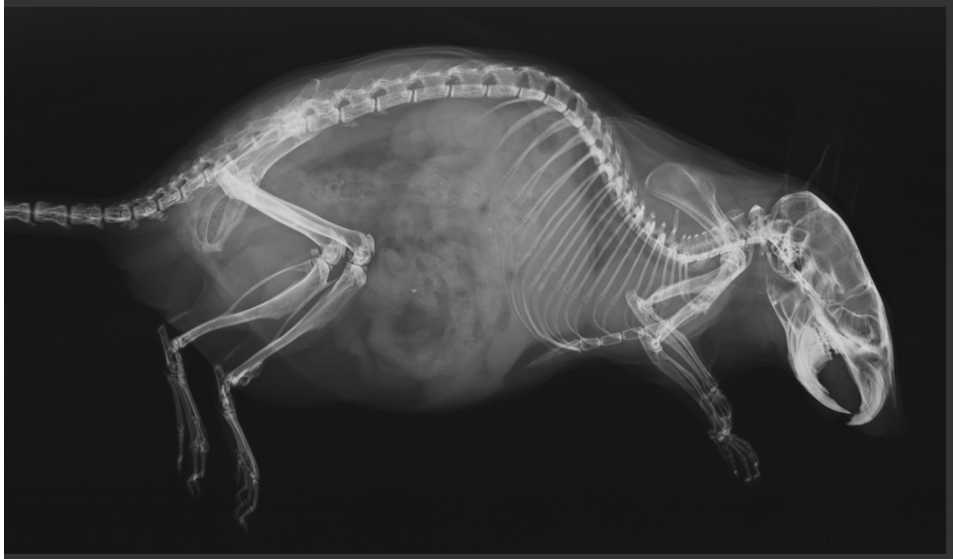
TTD mouse,
4-5 weeks

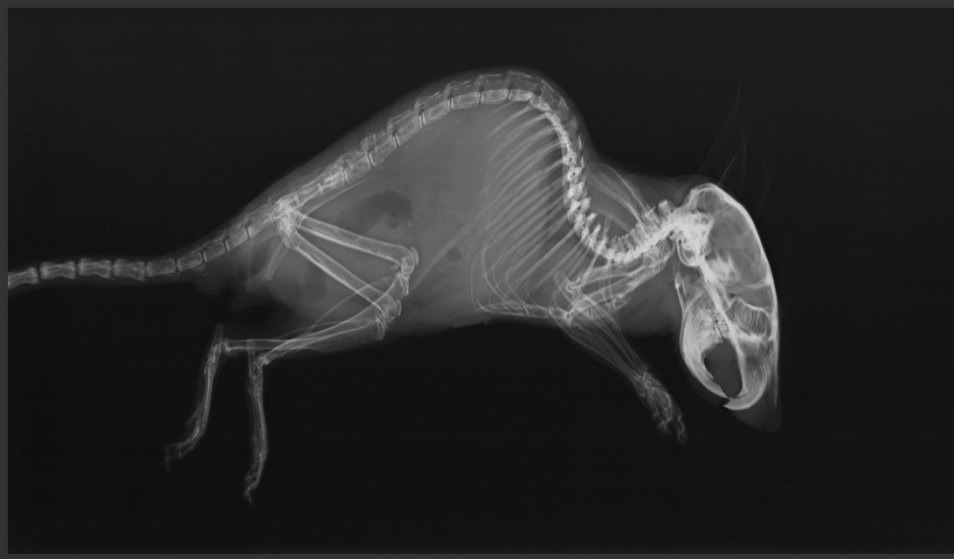
Striking parallels between TTD patient/mouse



Early greying in TTD mice

Skeletal abnormalities in aging TTD mice





wt

TTD

Kyphosis and demineralisation of the skeleton, sclerosis of the skull

Premature aging symptoms in TTD

Mice (cohort study)	patients
- reduced life span (93 vs 103 wks)	- reduced life span (<5 yrs)
- cachexia, sarcopenia	- cachexia
- early infertility (females)	- sexual developm. arrest
- cutaneous symptoms Hair depigmentation, sebaceous gland hyperplasia,	- aged-like appearance
- skeletal abnormalities kyphosis, osteoporosis, osteosclerosis	- skeletal abnormalities osteoporosis
- progr. neurological abnorm.	- progr. neurol. abnorm.

Striking parallels between TTD patient/mouse

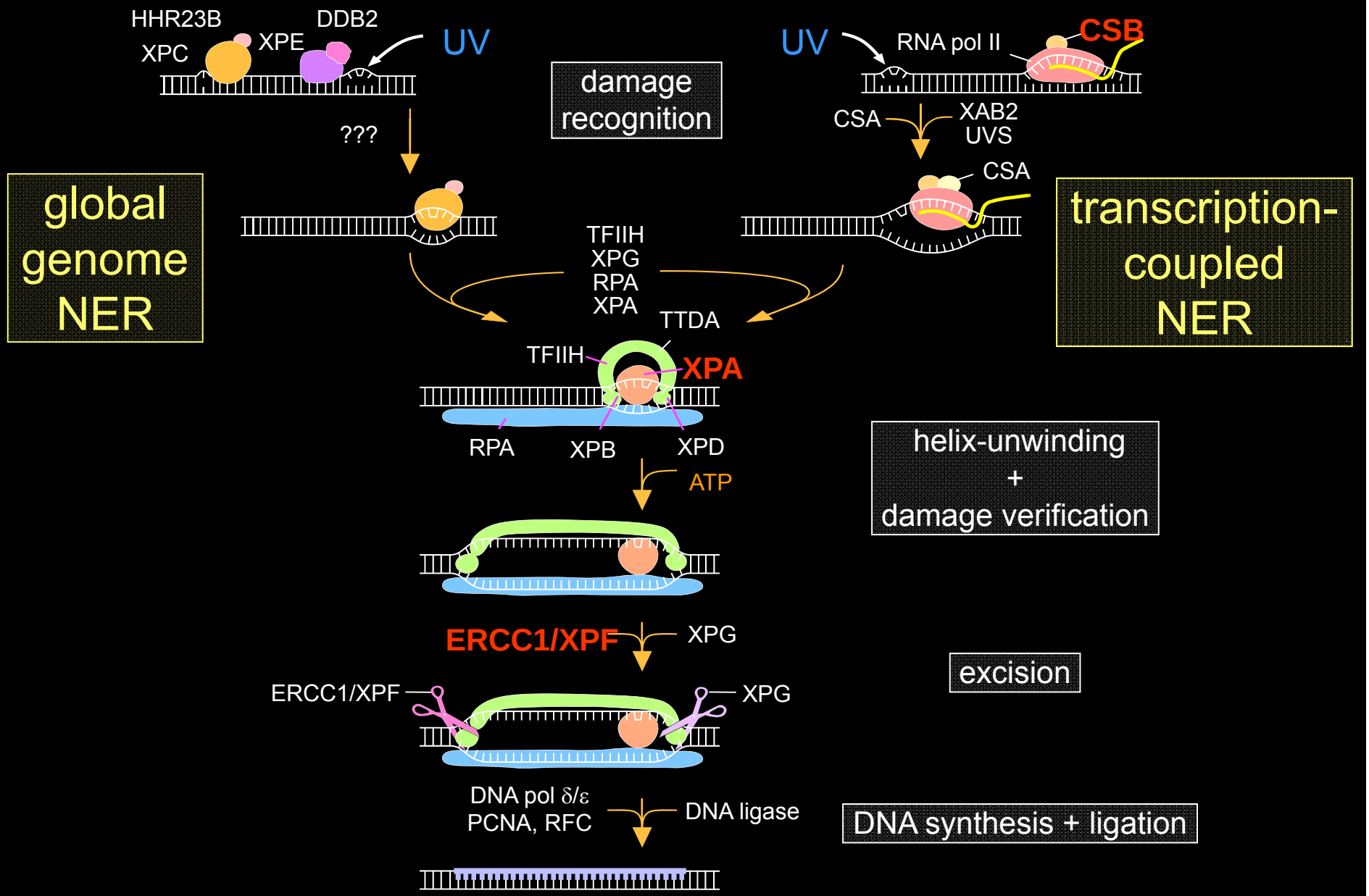
What about cancer predisposition?

Reduced spontaneous cancer in the aging XPD^{TTD} cohort

	C57Bl/6 (n=40)	XPD^{TTD} (n=35)
Neoplasm (cause of death)	35%	20%
Number of tumor-bearing mice	75%	54%
Total number of tumors	42	22
Mean number of tumor/mouse	1.1	0.6
Significantly reduced tumors:		
lymphoma	10	3
pituitary adenoma	20	3

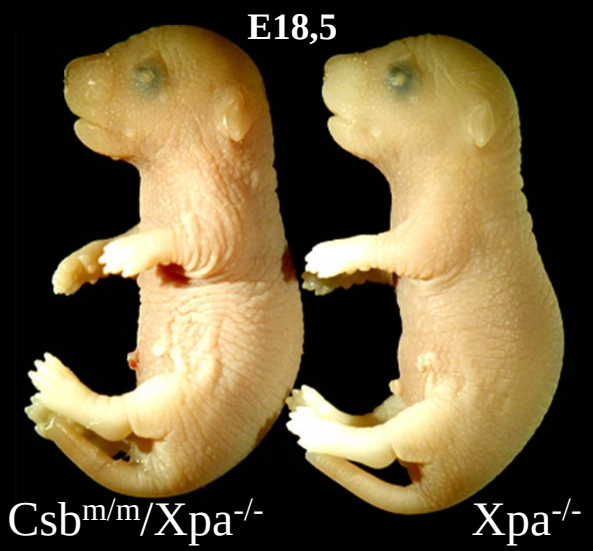
Connecting longevity to tumor prevention

Nucleotide Excision Repair (NER)



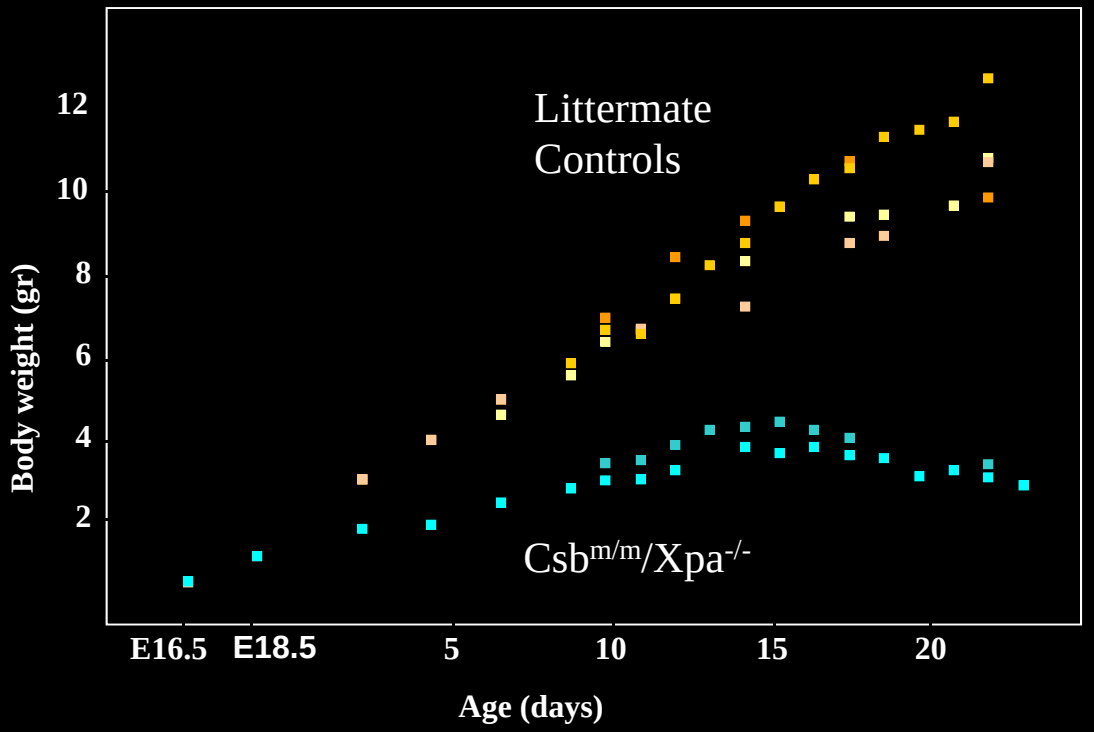
$Csb^{m/m}/Xpa^{-/-}$ mice: Normal at birth but don't gain weight

A.



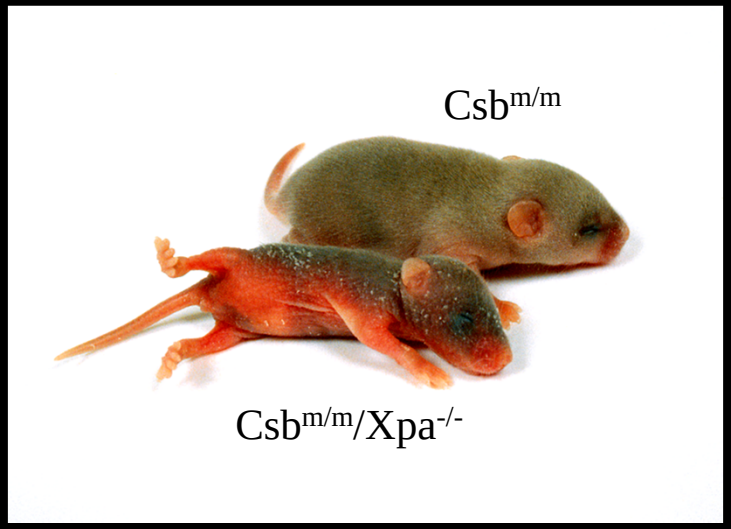
Pure C57Bl/6 background

B.



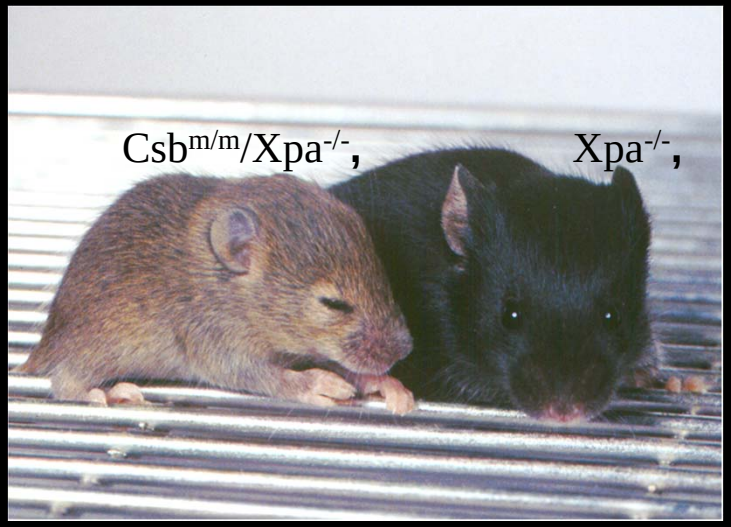
$Csb^{m/m}/Xpa^{-/-}$ mice are runted, fail to thrive and die prematurely

A



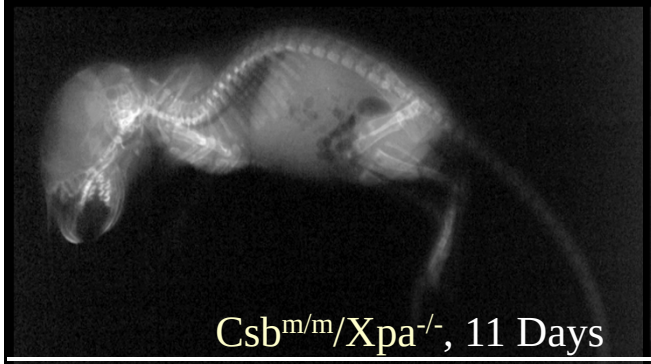
Day 8

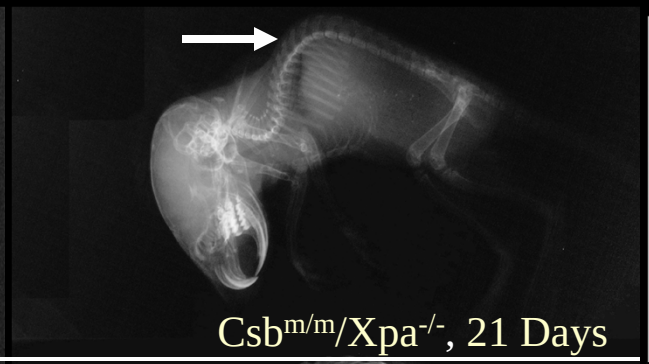
B

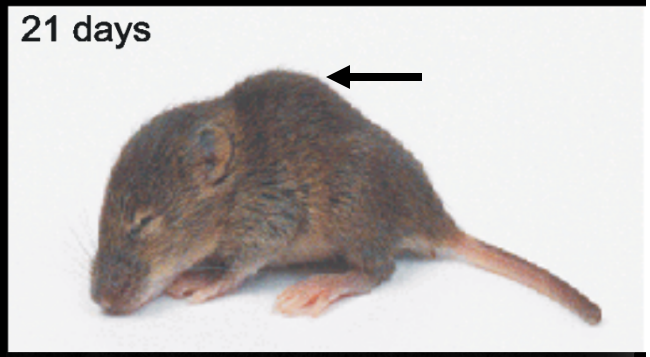


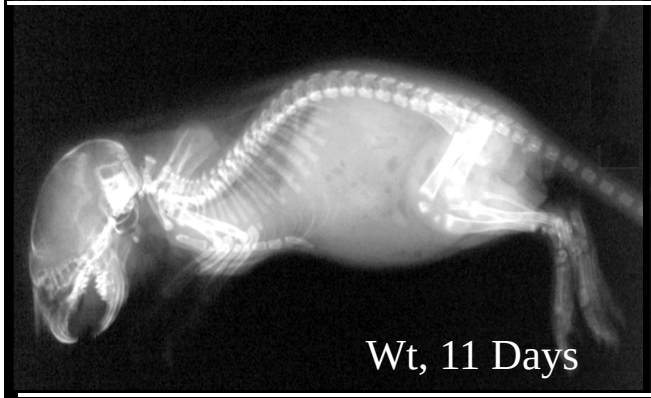
Day 21

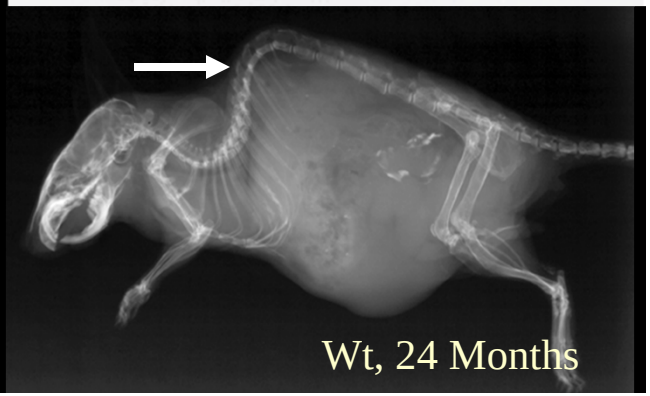
$Csb^{m/m}/Xpa^{-/-}$ mice develop kyphosis











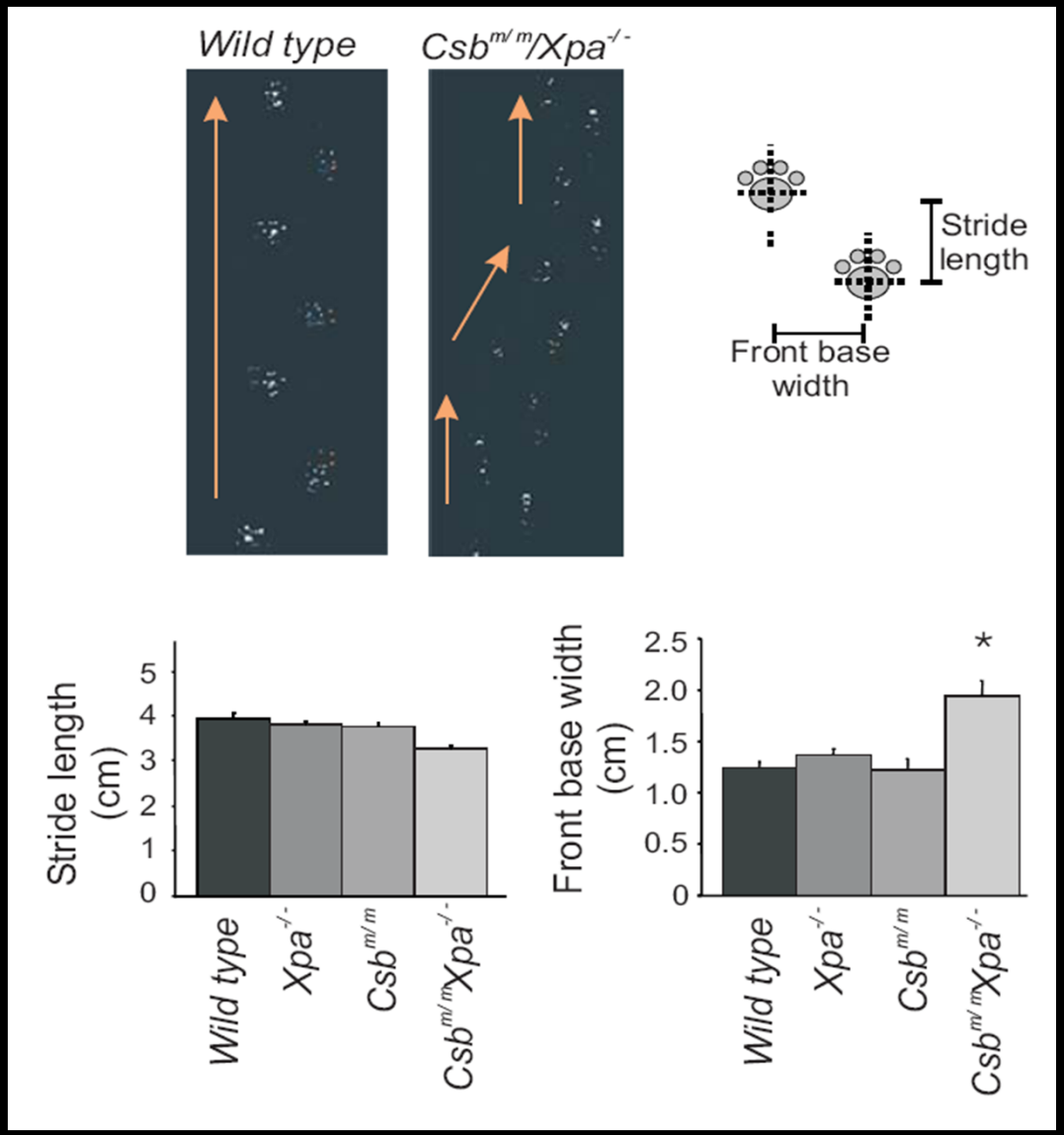
Retarded growth (as in CS patients)
Relatively large skull and extremities

Kyphosis (consistent with accelerated aging)

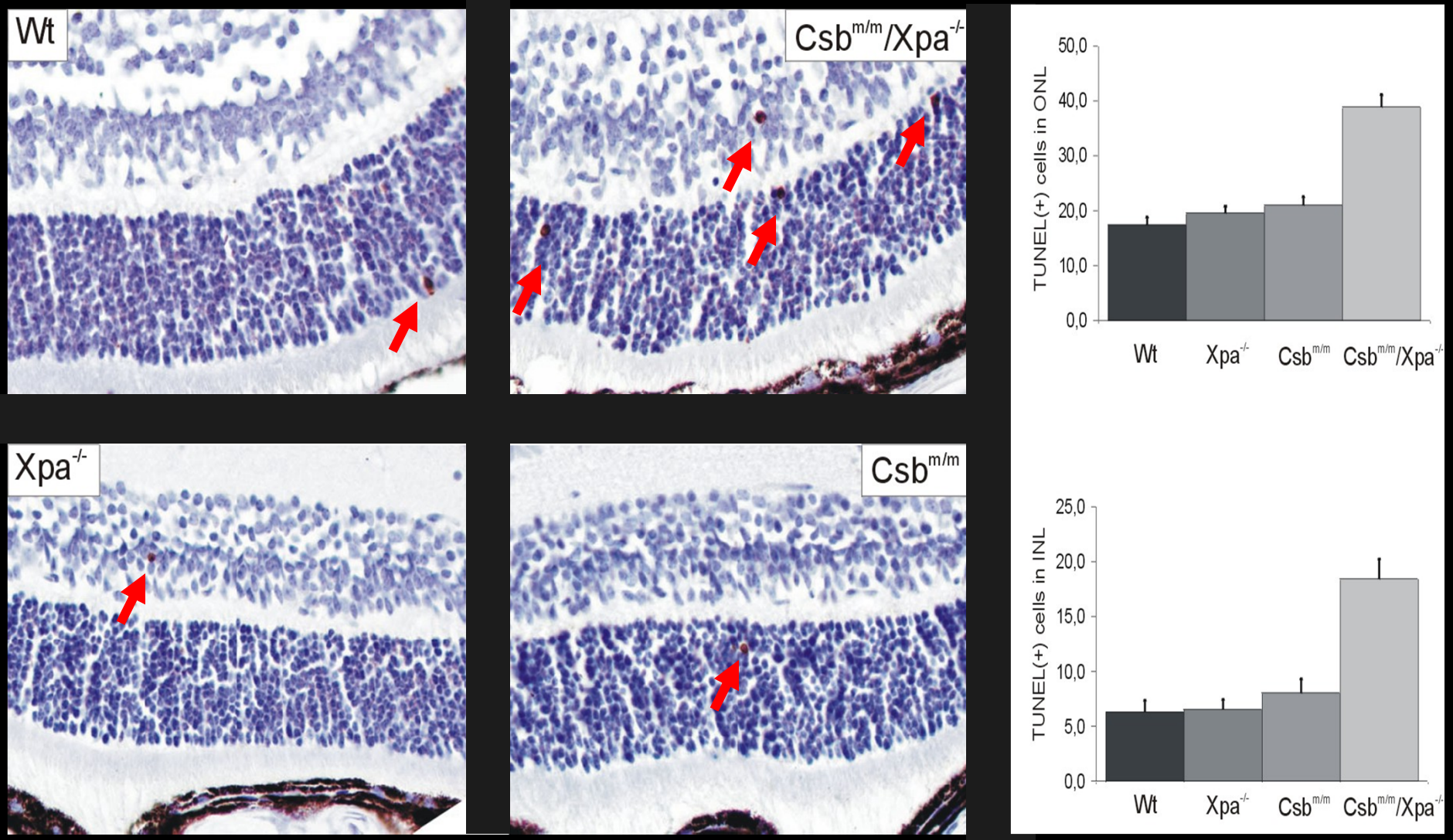
Csb$^{m/m}$/*Xpa*$^{-/-}$ pups show progressive ataxia

Ataxia is in line with Purkinje cell loss (apoptosis)

Murai et al., PNAS 2001



Enhanced retinal degeneration in *Csb$^{m/m}$/Xpa$^{-/-}$* mice



Photoreceptor loss by apoptosis (assayed by TUNEL)

Summary phenotype *Csb$^{m/m}$/Xpa$^{-/-}$* mutant mice

- Normal embryonic development
- Born at submendelian frequency (likely due to birth stress)
- Runted, growth retarded, cachexia
- Purkinje cell loss cerebellum
- Ataxia
- Kyphosis
- Osteoporosis?
- Enhanced retinal cell loss
- Premature death (around weaning)
- Absence of apoptosis or proliferative defects in the liver

Day 21

How to explain the *Csb*$^{m/m}$/*Xpa*$^{-/-}$ mouse phenotype ?

Are short-lived *Csb*$^{m/m}$/*Xpa*$^{-/-}$ mice aging prematurely ?

Reservations exist with respect to the importance of short-lived mouse models in delineating the aging process

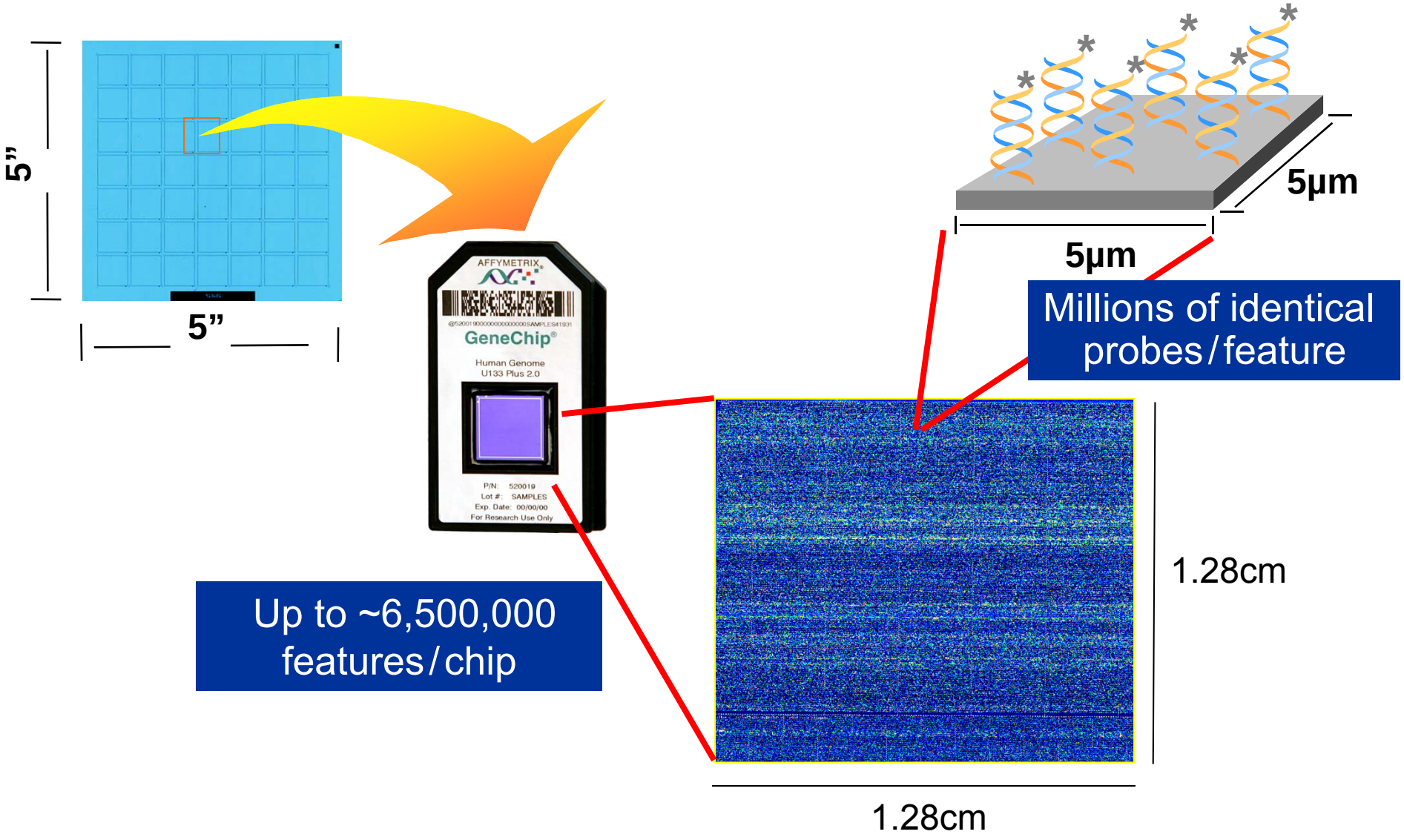
How does the mouse phenotype relate to human CS ?

Affymetrix 430 V2.0 mouse arrays (covering full genome)

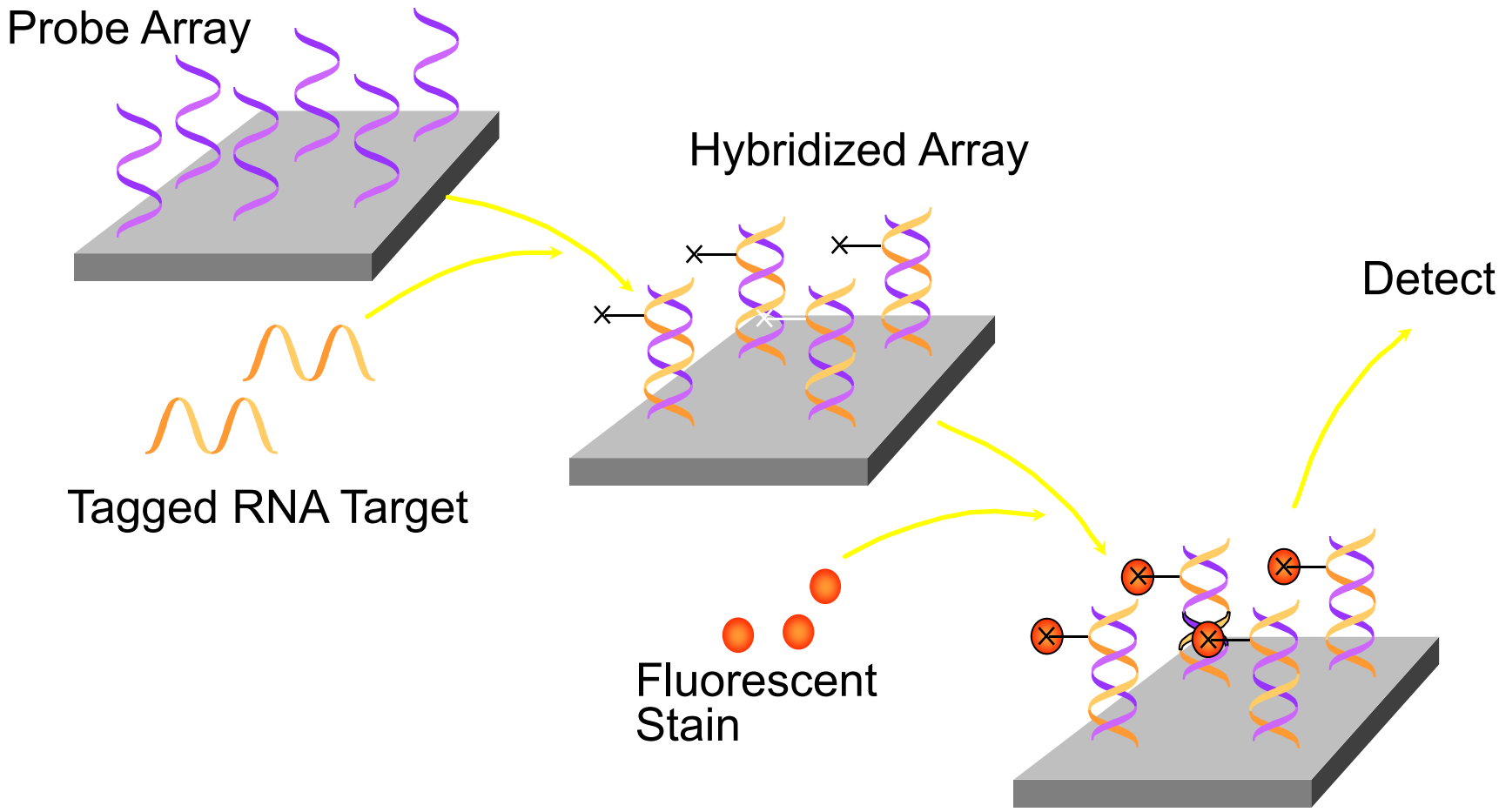
Liver	
Csb$^{m/m}$/*Xpa*$^{-/-}$	2 wk
wt	2 wk
Xpa$^{-/-}$	2 wk
Csb$^{m/m}$	2 wk
all C57BL6/J	n = 4

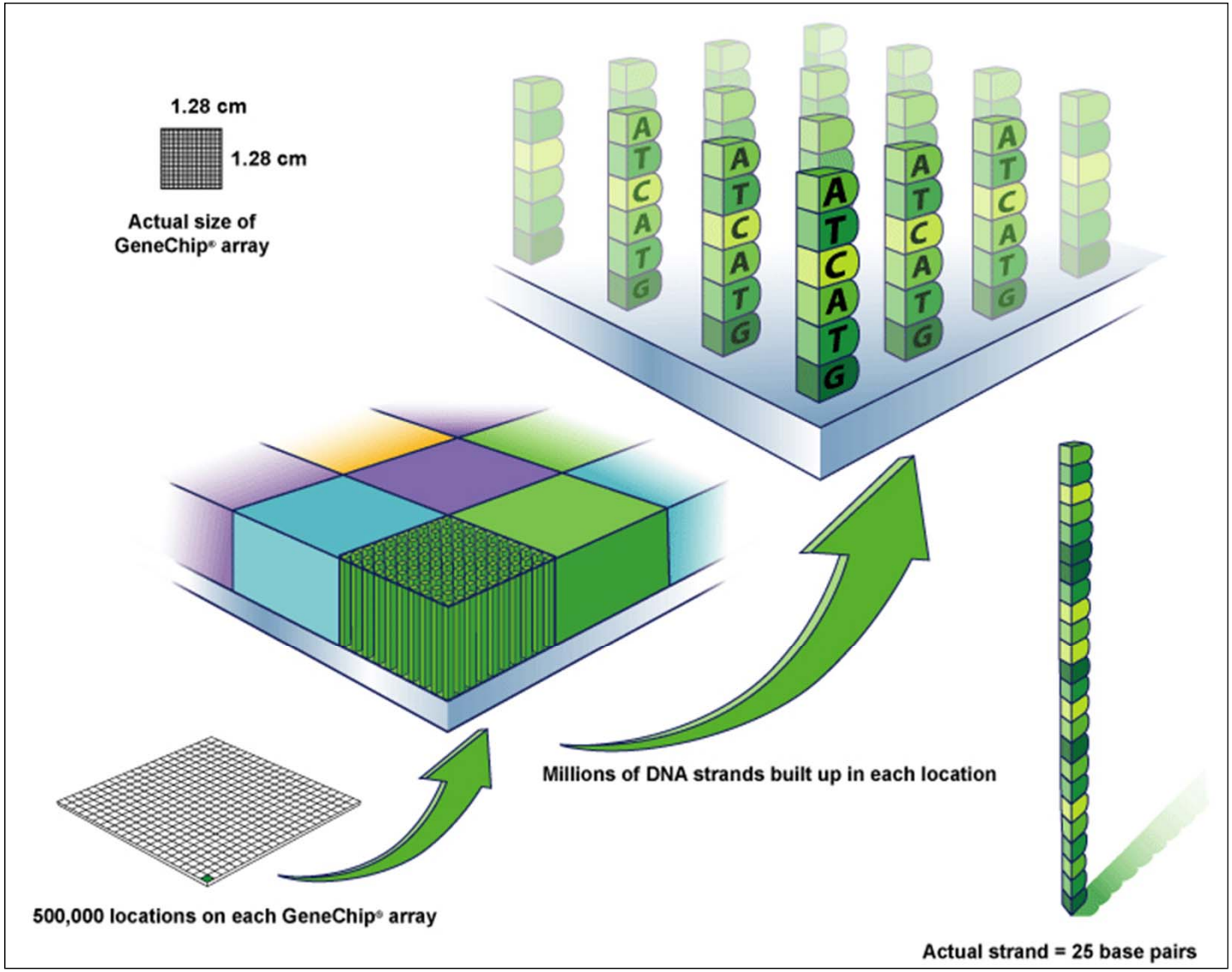
Liver	
wt	8 wk
wt	16 wk
wt	96 wk
wt	130 wk
all C57BL6/J	n = 4

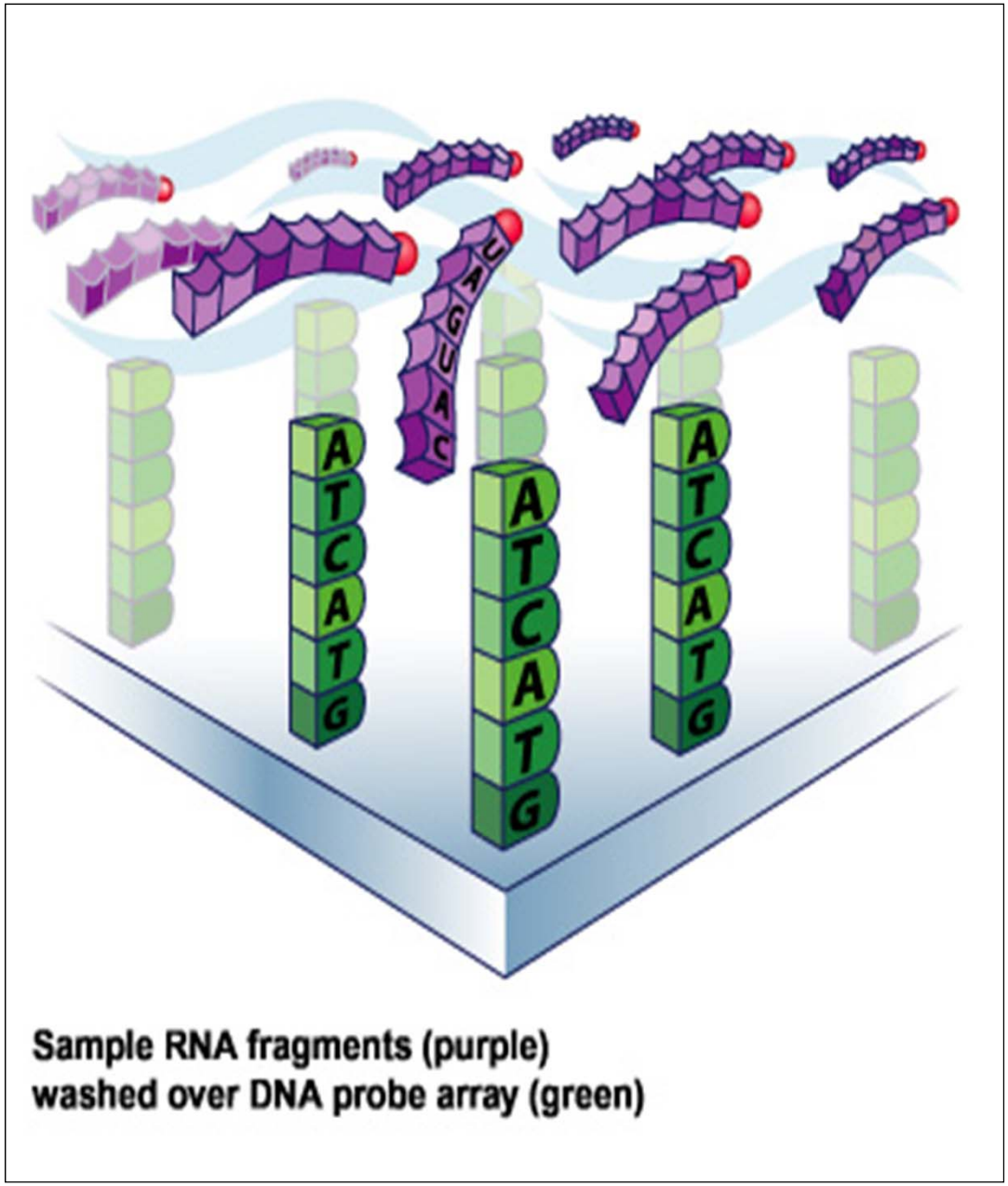
The Dimensions of a GeneChip



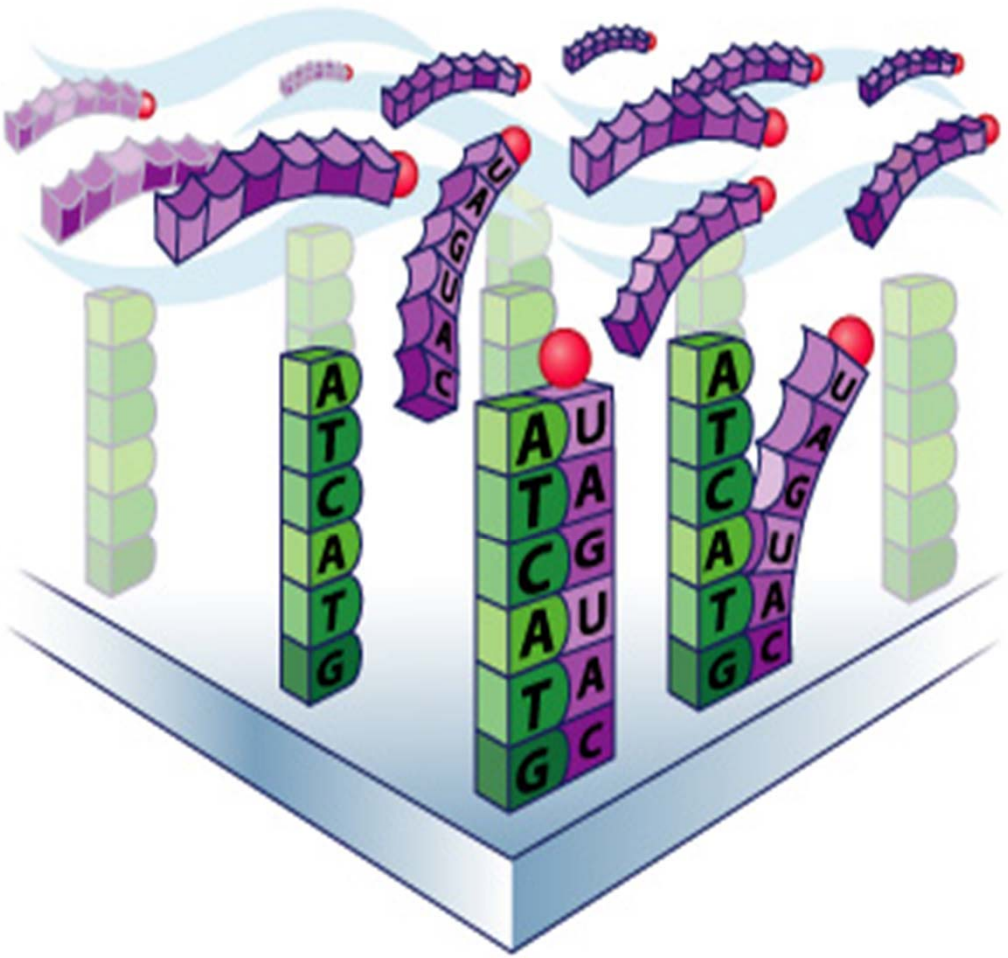
Hybridization



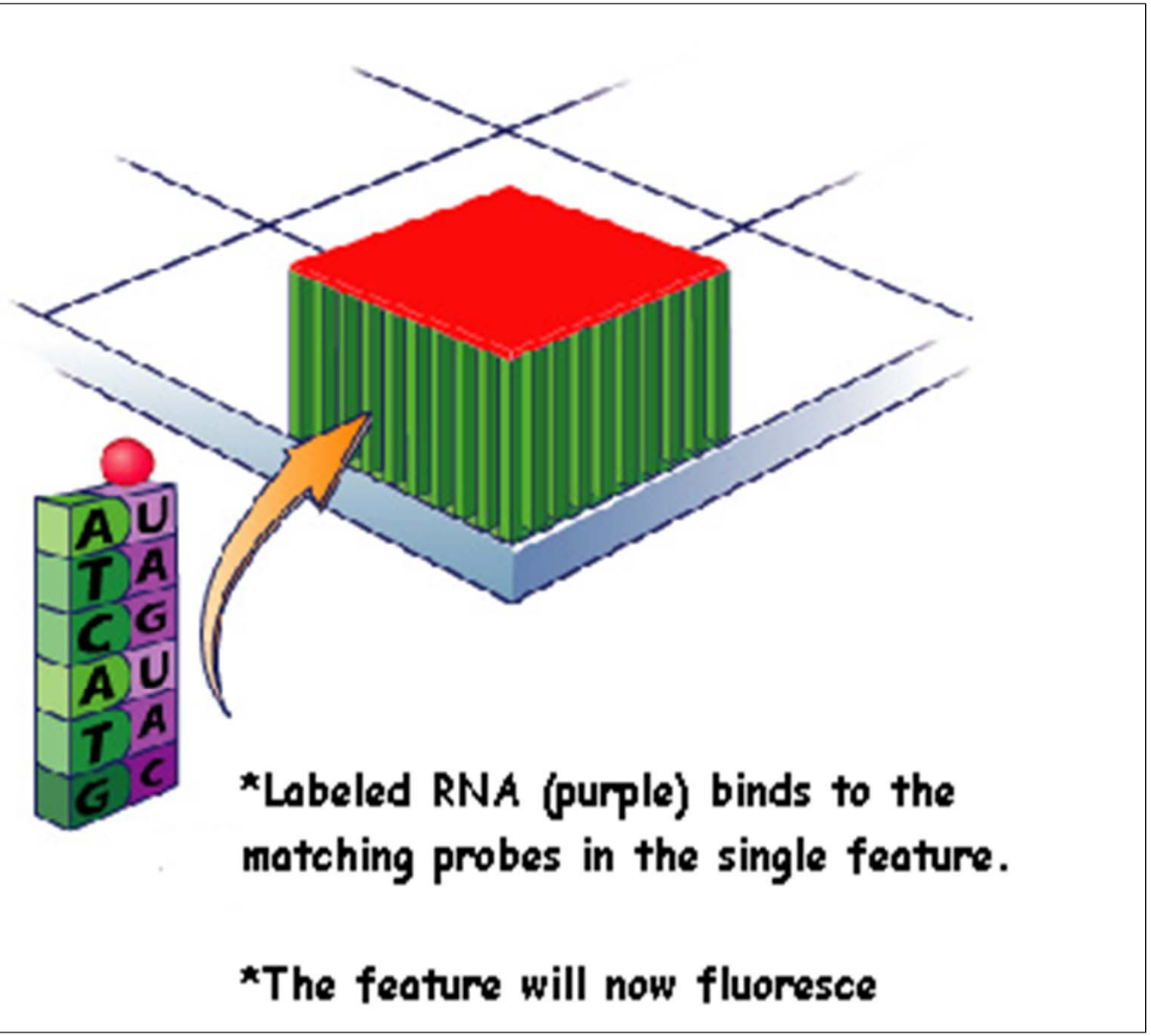

1.28 cm
1.28 cm
Actual size of GeneChip® array
Millions of DNA strands built up in each location
500,000 locations on each GeneChip® array
Actual strand = 25 base pairs

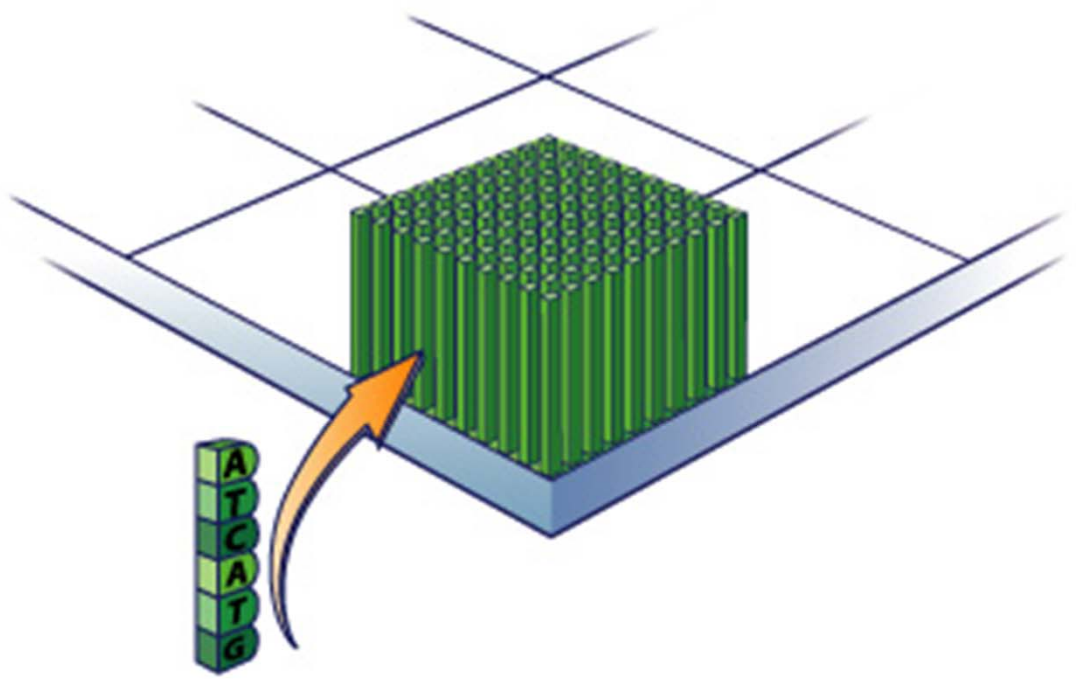


Sample RNA fragments (purple)
washed over DNA probe array (green)



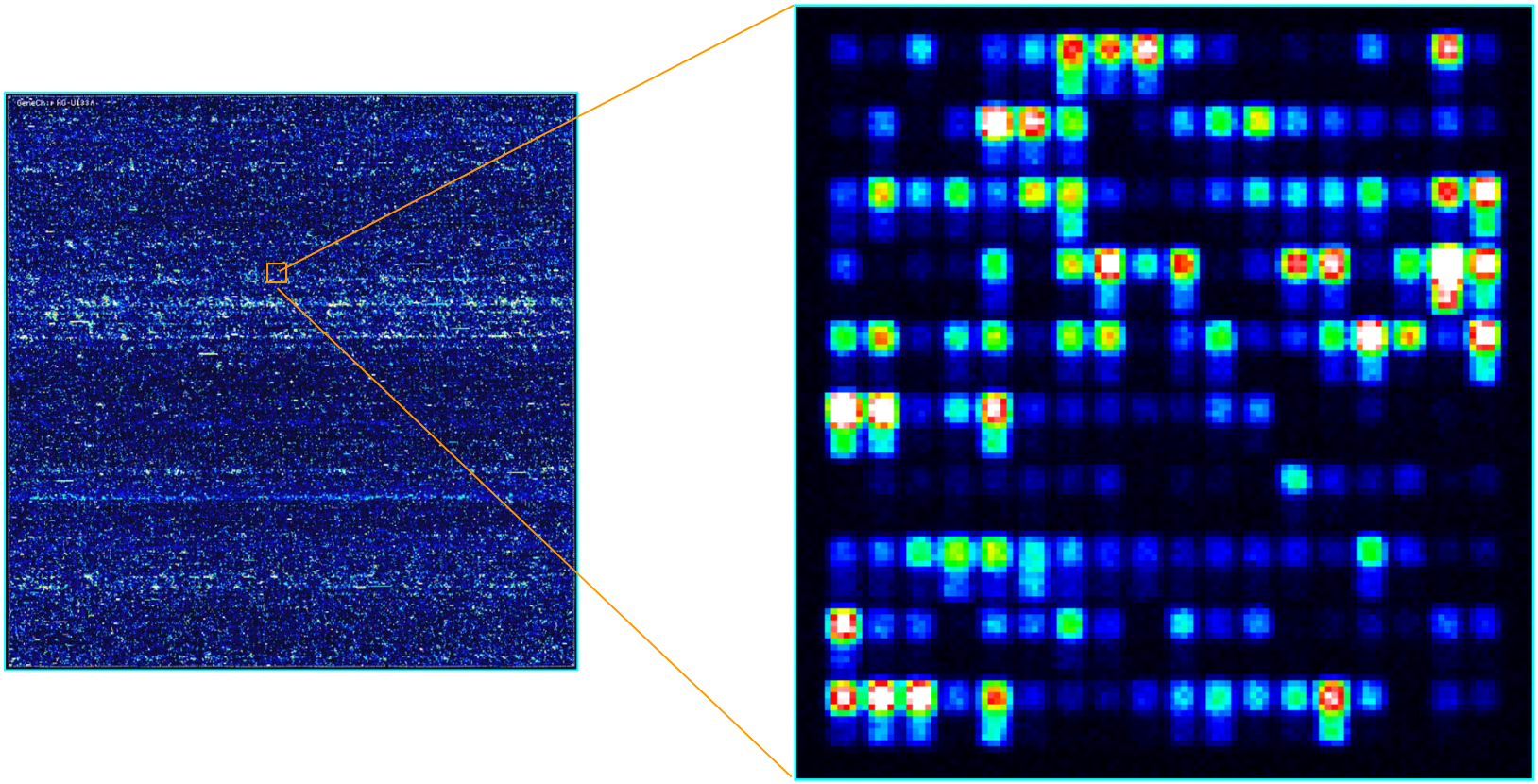
Sample RNA fragments (purple)
hybridized to DNA probe array (green)


A U
T A
C G
A U
T A
G C
*Labeled RNA (purple) binds to the matching probes in the single feature.
*The feature will now fluoresce



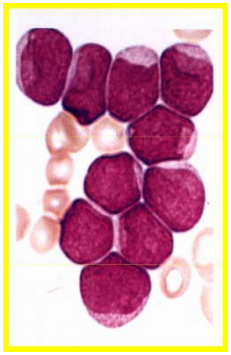
We know there was no match because
there is no fluorescent RNA bound to the probe.

Affymetrix GeneChip® Array



Diagnosis → Classification → Prognosis → Therapeutic Choice

Is it benign?



Which class of cancer?

What are my chances?

Which treatment?

How to explain the *Csb*$^{m/m}$/*Xpa*$^{-/-}$ mouse phenotype ?

Are short-lived *Csb*$^{m/m}$/*Xpa*$^{-/-}$ mice aging prematurely ?

Reservations exist with respect to the importance of short-lived mouse models in delineating the aging process

How does the mouse phenotype relate to human CS ?

Affymetrix 430 V2.0 mouse arrays (covering full genome)

Liver	
Csb$^{m/m}$/*Xpa*$^{-/-}$	2 wk
wt	2 wk
Xpa$^{-/-}$	2 wk
Csb$^{m/m}$	2 wk
all C57BL6/J	n = 4

Liver	
wt	8 wk
wt	16 wk
wt	96 wk
wt	130 wk
all C57BL6/J	n = 4

Down regulation of the IGF-1/GH axis

Code	Gene description	Gene Symbol	$Csb^{m/m}Xpa^{-/-}$/Wt	P-Value
The IGF-1/GH growth axis				
1434413_at	insulin-like growth factor 1	Igf1	-1.74	0.00
1419519_at	insulin-like growth factor 1	Igf1	-2.13	0.00
1452014_a_at	insulin-like growth factor 1	Igf1	-1.98	0.00
1437401_at	insulin-like growth factor 1	Igf1	-1.37	0.00
1422826_at	insulin-like growth factor binding protein, ac.lab. subunit	Igfals	-2.35	0.00
1421991_a_at	insulin-like growth factor binding protein 4	Igfbp4	-1.73	0.00
1421992_a_at	insulin-like growth factor binding protein 4	Igfbp4	-1.36	0.00
1458268_s_at	insulin-like growth factor binding protein 3	Igfbp3	-1.44	0.00
1423062_at	insulin-like growth factor binding protein 3	Igfbp3	-1.37	0.00
1451501_a_at	growth hormone receptor	Ghr	-1.51	0.00
1417962_s_at	growth hormone receptor	Ghr	-1.50	0.00
1430164_a_at	growth factor receptor bound protein 10	Grb10	1.68	0.00
1425458_a_at	growth factor receptor bound protein 10	Grb10	1.86	0.00
1451844_at	prolactin receptor	Prlr	-1.45	0.01
1425853_s_at	prolactin receptor	Prlr	-1.87	0.00
1448556_at	prolactin receptor	Prlr	-2.04	0.00
1450226_at	prolactin receptor	Prlr	-1.76	0.00
1421382_at	prolactin receptor	Prlr	-1.96	0.00
1452661_at	transferrin receptor	Trfr	-2.30	0.01
1427777_x_at	fibroblast growth factor receptor 4	Fgfr4	-1.33	0.01
1421841_at	fibroblast growth factor receptor 3	Fgfr3	-1.43	0.00
1450869_at	fibroblast growth factor 1	Fgf1	-1.37	0.00
1435663_at	estrogen receptor 1 (alpha)	Esr1	-1.90	0.00
1460591_at	estrogen receptor 1 (alpha)	Esr1	-1.58	0.00
1417991_at	deiodinase, iodothyronine, type I	Dio1	-2.12	0.00

Down regulation of oxidative metabolism

Code	Gene description	Gene Symbol	$Csb^{m/m}Xpa^{-/-}/Wt$	P-Value
NADPH-dependent Oxidative metabolism				
1422904_at	flavin containing monooxygenase 2	Fmo2	-4.50	0.01
1422905_s_at	flavin containing monooxygenase 2	Fmo2	-3.23	0.00
1453435_a_at	flavin containing monooxygenase 2	Fmo2	-2.46	0.00
1417429_at	flavin containing monooxygenase 1	Fmo1	-1.38	0.00
1435459_at	flavin containing monooxygenase 2	Fmo2	-2.80	0.00
1449525_at	flavin containing monooxygenase 3	Fmo3	-13.76	0.00
P450 Oxidative metabolism				
1417070_at	cytochrome P450, family 4, subfamily v, polypeptide 3	Cyp4v3	-1.41	0.00
1418821_at	cytochrome P450, family 2, subfamily a, polypeptide 12	Cyp2a12	-1.50	0.00
1419590_at	cytochrome P450, family 2, subfamily b, polypeptide 9	Cyp2b9	-1.55	0.00
1417651_at	cytochrome P450, family 2, subfamily c, polypeptide 29	Cyp2c29	-1.55	0.01
1424273_at	cytochrome P450, family 2, subfamily c, polypeptide 70	Cyp2c70	-1.59	0.00
1418767_at	cytochrome P450, family 4, subfamily f, polypeptide 13	Cyp4f13	-1.67	0.01
1449479_at	cytochrome P450, family 2, subfamily b, polypeptide 13	Cyp2b13	-2.24	0.00
1438743_at	cytochrome P450, family 7, subfamily a, polypeptide 1	Cyp7a1	-2.27	0.00
1448792_a_at	cytochrome P450, family 2, subfamily f, polypeptide 2	Cyp2f2	-2.37	0.00
1422100_at	cytochrome P450, family 7, subfamily a, polypeptide 1	Cyp7a1	-2.37	0.01
1417531_at	cytochrome P450, family 2, subfamily j, polypeptide 5	Cyp2j5	-2.50	0.00
1440327_at	cytochrome P450, family 2, subfamily c, polypeptide 70	Cyp2c70	-2.52	0.00
1422257_s_at	cytochrome P450, family 2, subfamily b, polypeptide 10	Cyp2b10	-2.81	0.00
1425645_s_at	cytochrome P450, family 2, subfamily b, polypeptide 20	Cyp2b20	-2.90	0.00
1417532_at	cytochrome P450, family 2, subfamily j, polypeptide 5	Cyp2j5	-3.08	0.00
1419559_at	cytochrome P450, family 4, subfamily f, polypeptide 14	Cyp4f14	-3.57	0.00

Up regulation of anti-oxidant responses

Code	Gene description	Gene Symbol	$Csb^{m/m}Xpa^{-/-}$/Wt	P-Value
Antioxidant and detoxification response				
1451124_at	superoxide dismutase 1	Sod1	1.23	0.00
1452592_at	microsomal glutathione S-transferase 2	Mgst2	2.96	0.00
1417883_at	glutathione S-transferase, theta 2	Gstt2	2.75	0.00
1421041_s_at	glutathione S-transferase, alpha 2 (Yc2)	Gsta2	1.88	0.00
1448300_at	microsomal glutathione S-transferase 3	Mgst3	1.49	0.00
1449575_a_at	glutathione S-transferase, pi 2	Gstp2	1.37	0.00
1416842_at	glutathione S-transferase, mu 5	Gstm5	1.28	0.00
1421817_at	glutathione reductase 1	Gsr	1.18	0.01
1448239_at	heme oxygenase (decycling) 1	Hmox1	2.43	0.00
1422438_at	epoxide hydrolase 1, microsomal	Ephx1	2.11	0.00

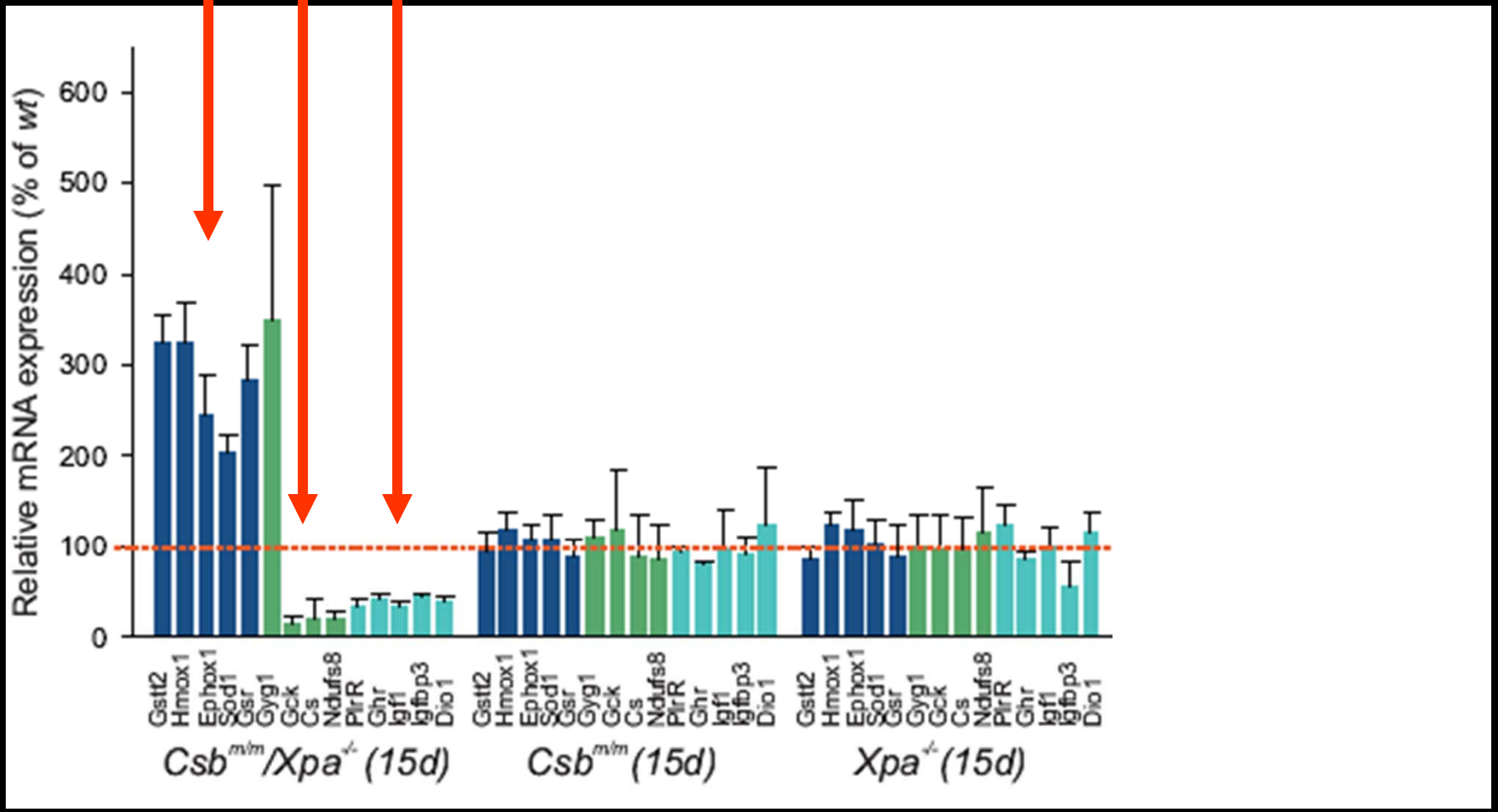
Code	Gene description	Gene Symbol	$Csb^{m/m}Xpa^{-/-}$/Wt	P-Value
Glycogen metabolism				
1459522_s_at	glycogenin 1	Gyg1	1.26	0.01
1424815_at	glycogen synthase 2	Gys2	1.80	0.00
1425303_at	glucokinase	Gck	-4.79	0.00
1419146_a_at	glucokinase	Gck	-6.69	0.00
1417741_at	liver glycogen phosphorylase	Pygl	-1.35	0.00

Transcriptome analysis/Q-RT-PCR confirmation reveals

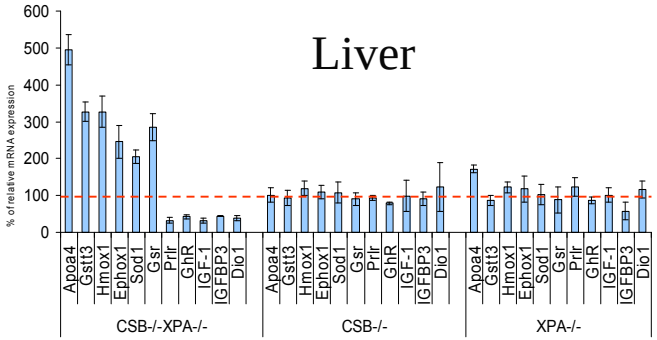
up-regulation anti-oxidant defense

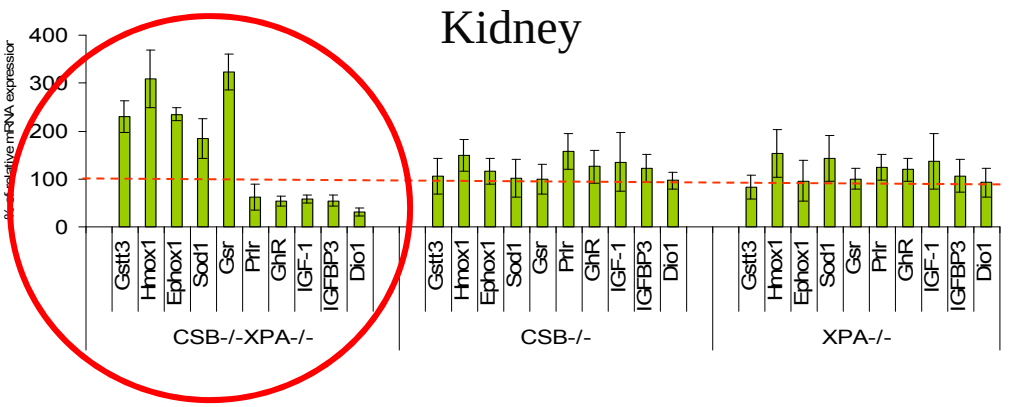
down-regulation catabolic metabolism (glycolysis, Krebs, ox.phos.)

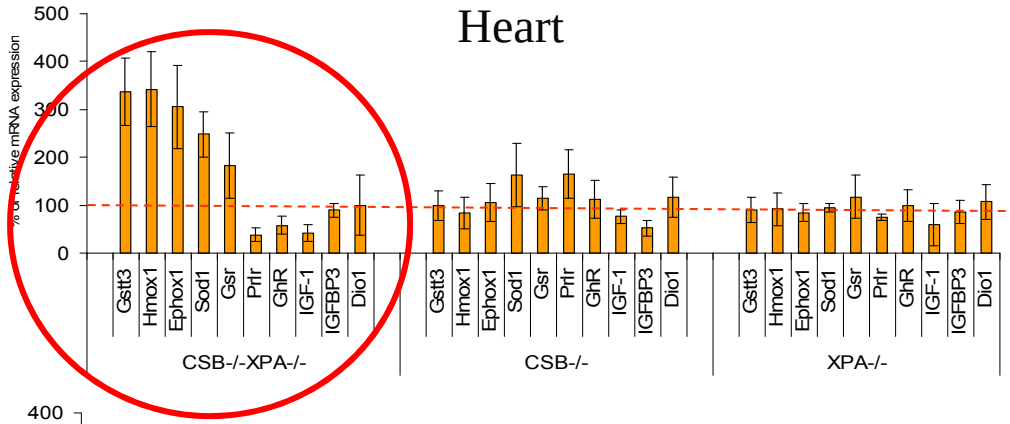
down-regulation GH/IGF1 growth axis

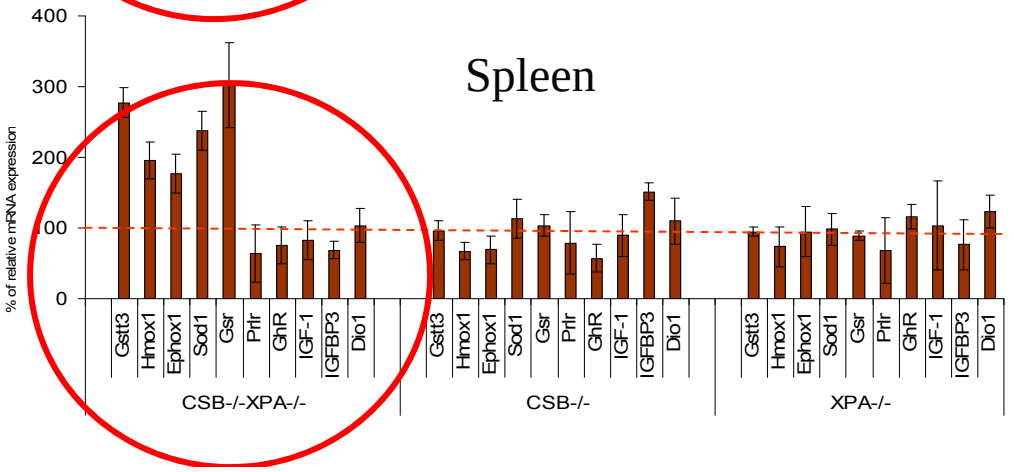


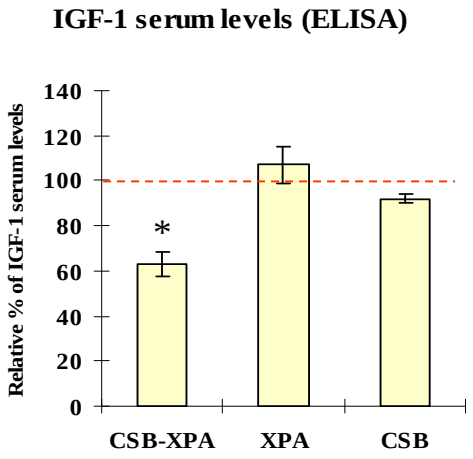
This response is systemic:



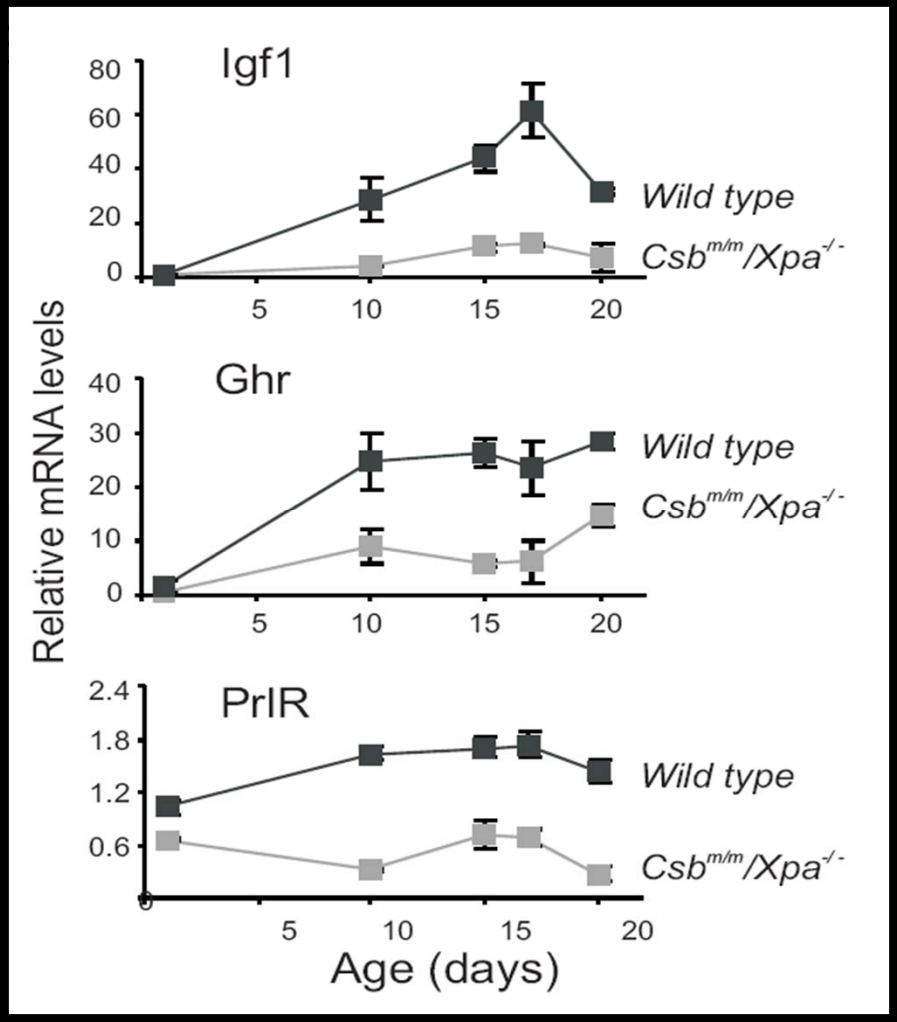




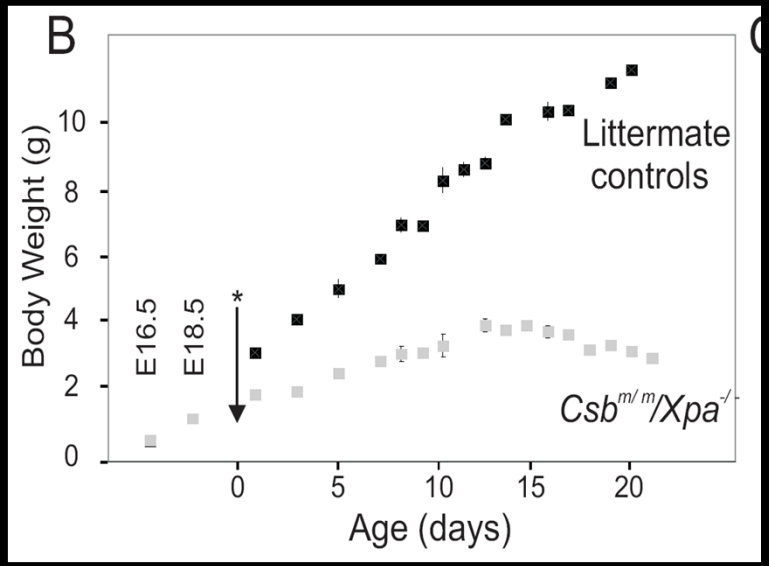




Kinetics of the GH/IGF1 decline

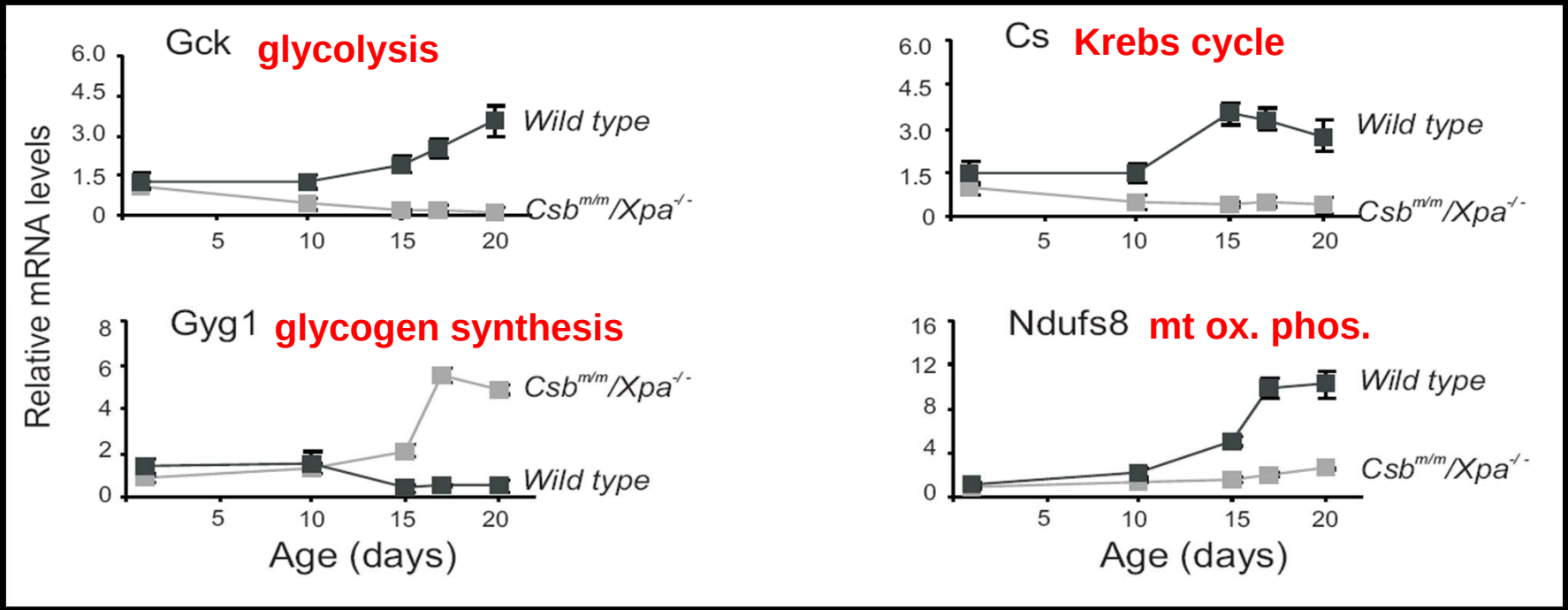


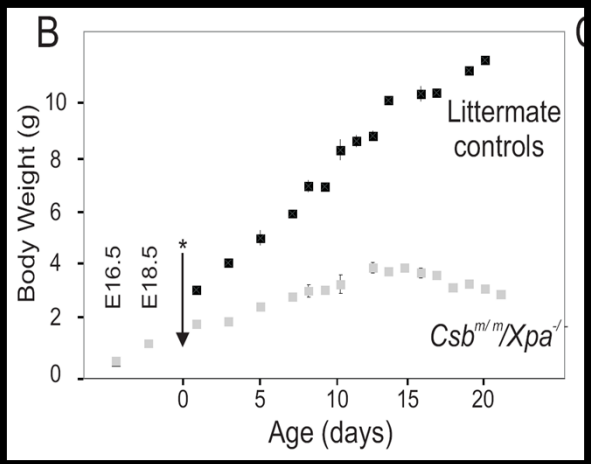
Q-RT-PCR

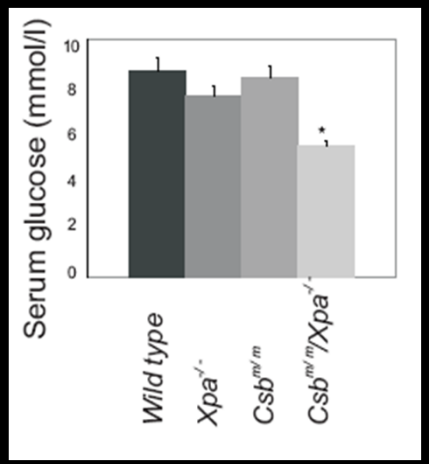


Postnatal attenuation of the GH/IGF1 axis well explains growth defect

Kinetics of the catabolic changes



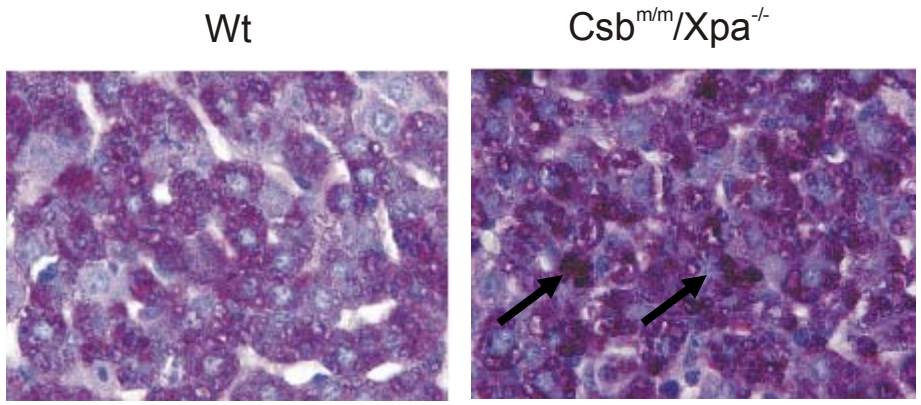




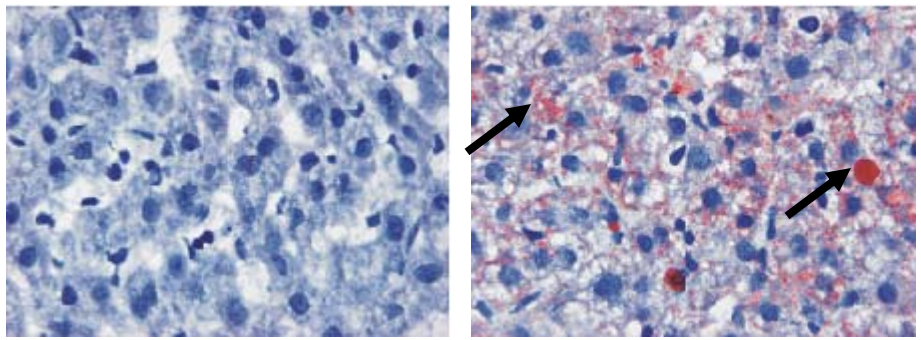
Inability to up-regulate catabolism coincides with onset of weight loss

Animals store, rather than utilize glucose
(visceral glycogen, fatty acids)

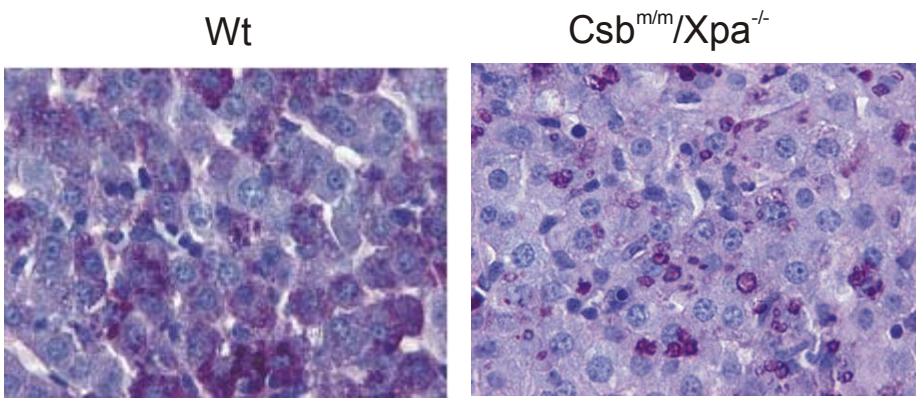
$Csb^{m/m}/Xpa^{-/-}$ appear to store glycogen and fat



Glycogen



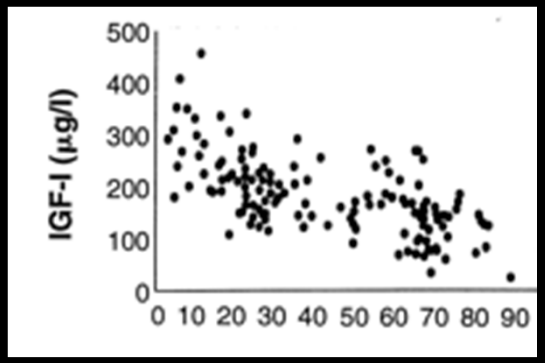
Triglycerides



Glycogen (upon fasting)

Comparison with human ageing

1. Both GH and IGF-1 decline with advancing age:



Lamberts et al 1997

somatopause:

- Reduced muscle mass
- Increased visceral fat mass
- Attenuated bone mineral density
- Cardiovascular changes
- Reduced elasticity of the skin
- Cognitive performance

(van Dam et al 2000)

2. The anti-oxidant defense is upregulated with advancing age.

Overlap between short-lived mutants and 2.5-years old mice

Code	Title	Gene	*Csb* $^{m/m}$ *Xpa* $^{-/-}$		2.5-years old	
			fc	p	fc	p
The IGF-1/GH growth axis						
1419519_at	insulin-like growth factor 1	Igf1	-2.13	0.000	-1.48	0.005
1434413_at	Insulin-like growth factor 1	Igf1	-1.82	0.000	-1.36	0.003
1437401_at	Insulin-like growth factor 1	Igf1	-1.43	0.001	-1.37	0.000
1452014_a_at	insulin-like growth factor 1	Igf1	-2.02	0.000	-1.30	0.021
1417962_s_at	Growth hormone receptor	Ghr	-1.53	0.000	-1.51	0.071
1451501_a_at	Growth hormone receptor	Ghr	-1.51	0.001	-1.50	0.097
1451871_a_at	Growth hormone receptor	Ghr	-2.21	0.012	-2.37	0.001
1458832_at	Growth hormone receptor	Ghr	-1.53	0.038	-1.88	0.012
1459948_at	Growth hormone receptor	Ghr	-1.08	0.642	-3.98	0.035
1425853_s_at	prolactin receptor	Prlr	-1.87	0.004	-1.20	0.232
1448556_at	prolactin receptor	Prlr	-2.03	0.000	-1.13	0.403
1450226_at	prolactin receptor	Prlr	-1.76	0.001	-1.17	0.271
1421841_at	fibroblast growth factor receptor 3	Fgfr3	-1.43	0.001	-2.66	0.016
1427777_x_at	fibroblast growth factor receptor 4	Fgfr4	-1.32	0.009	-1.97	0.044
1450869_at	fibroblast growth factor 1	Fgf1	-1.38	0.003	-2.42	0.001
1417991_at	deiodinase, iodothyronine, type I	Dio1	-2.12	0.000	-1.69	0.043
1435663_at	estrogen receptor 1 (alpha)	Esr1	-1.91	0.001	-1.36	0.090
1460591_at	estrogen receptor 1 (alpha)	Esr1	-1.59	0.000	-1.07	0.384
1421991_a_at	insulin-like growth factor binding protein	Igfbp4	-1.74	0.000	-1.40	0.118
1421992_a_at	insulin-like growth factor binding protein	Igfbp4	-1.43	0.000	-1.16	0.231

GH/IGF1 mouse models live very long…

1. Gh-r KO mice - profound decrease of hepatic IGF-1 (GH-resistant)
   - reduced somatic growth within 2 to 4 weeks after birth
   - decreased body size
   - live longer
   - increased antioxidant defense mechanisms (Bartke et al 2003)

2. Hypopituitary Ames/dwarf mice (deficient in GH, PRL and TSH)
   - exhibit 40-65% extension of their lifespan
   - reduced body size
   - increased anti-oxid. defense mechanisms (Brown-Borg et al. 1996).

3. Ghrh mutant mice and heterozygous IGF-1R KO mice
   - live longer
   - reduced body size (Flurkey et al 2001, Holzenberger et al 2003 (resp.)

4. GH transgenic mice (carrying a bovine GH gene)
   - renal lesions
   - hepatic alterations
   - drastic reduction in lifespan (Carter et al 2002)

5. CR extends lifespan and down regulates both GH and IGF-1

Rationale of the GH/IGF1 response in normal aging

Early in life, development to adulthood is priority:

- resources are used for growing and to generate progeny
- GH/IGF-1 and metabolism are high,
- however, at the expense of more DNA damage

When this goal is reached, priorities shift:
"now it is important to switch to maintenance"

- remaining resources are used to extend life span
- GH/IGF-1 and rate of metabolism are turned down
- will reduce the DNA damage load

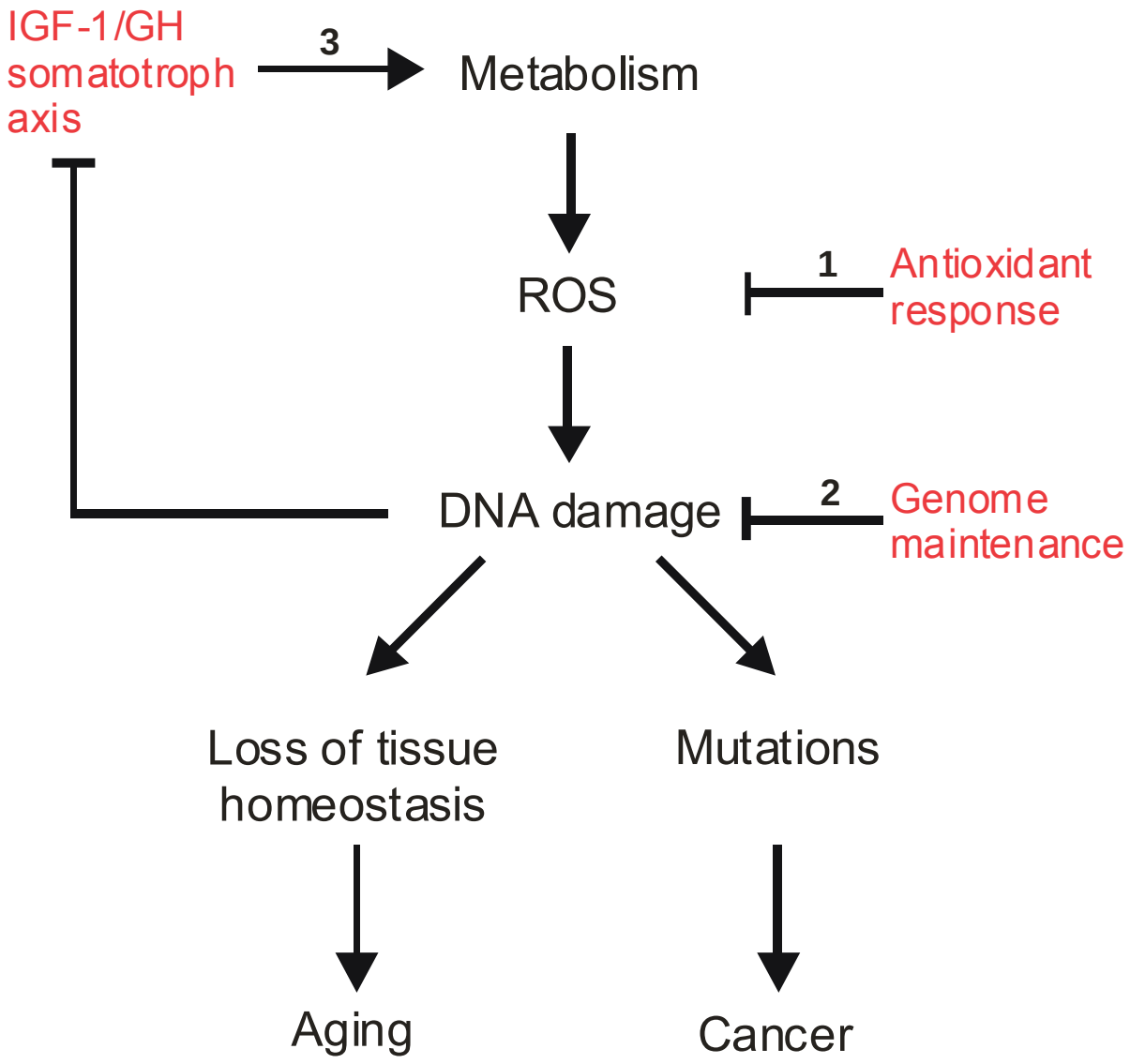
Rationale of the GH/IGF1 response in *Csb$^{m/m}$/Xpa$^{-/-}$*

Why do *Csb$^{m/m}$/Xpa$^{-/-}$* mice display a caloric restricted-like response associated with long life span, whereas they live extremely short?

We interpret this reaction as a (desperate) attempt to extend life span in face of a very high DNA damage load

This implies that reducing metabolism and thus extending life span are intended strategies driven by the DNA damage problem

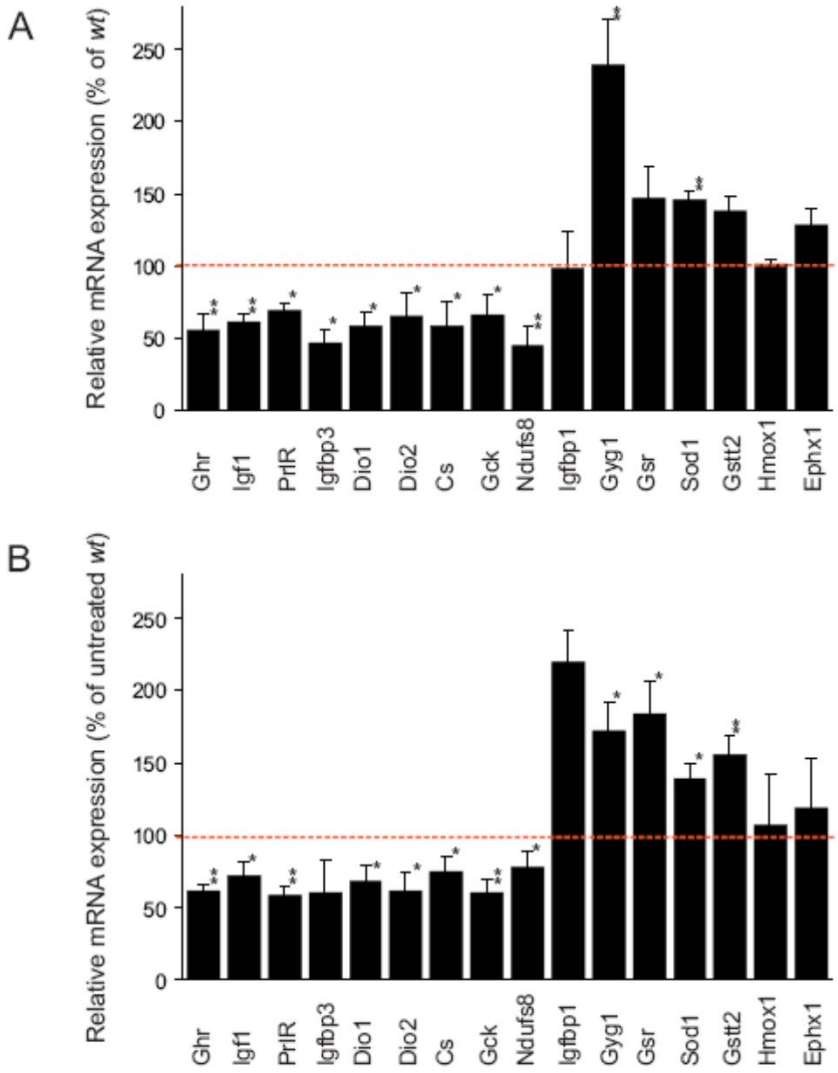
Scenario for *Csb*$^{m/m}$-*Xpa*$^{-/-}$ progeria and natural aging



PLoS Biology 2007

A. 13-week old *Csb*$^{m/m}$ mice

B. Wt mice chronically (4 weeks) exposed to a low dose (1500ppm) of pro-oxidant DEHP



Is there a similar response in Ercc1$^{-/-}$ mice?

Growth delay
Kyphosis
Progressive ataxia
Infertility
Cachexia
Sarcopenia
Polyploidization in liver/kidney
Premature death at 3 weeks

In Cockayne syndrome and other DNA repair deficient patients?

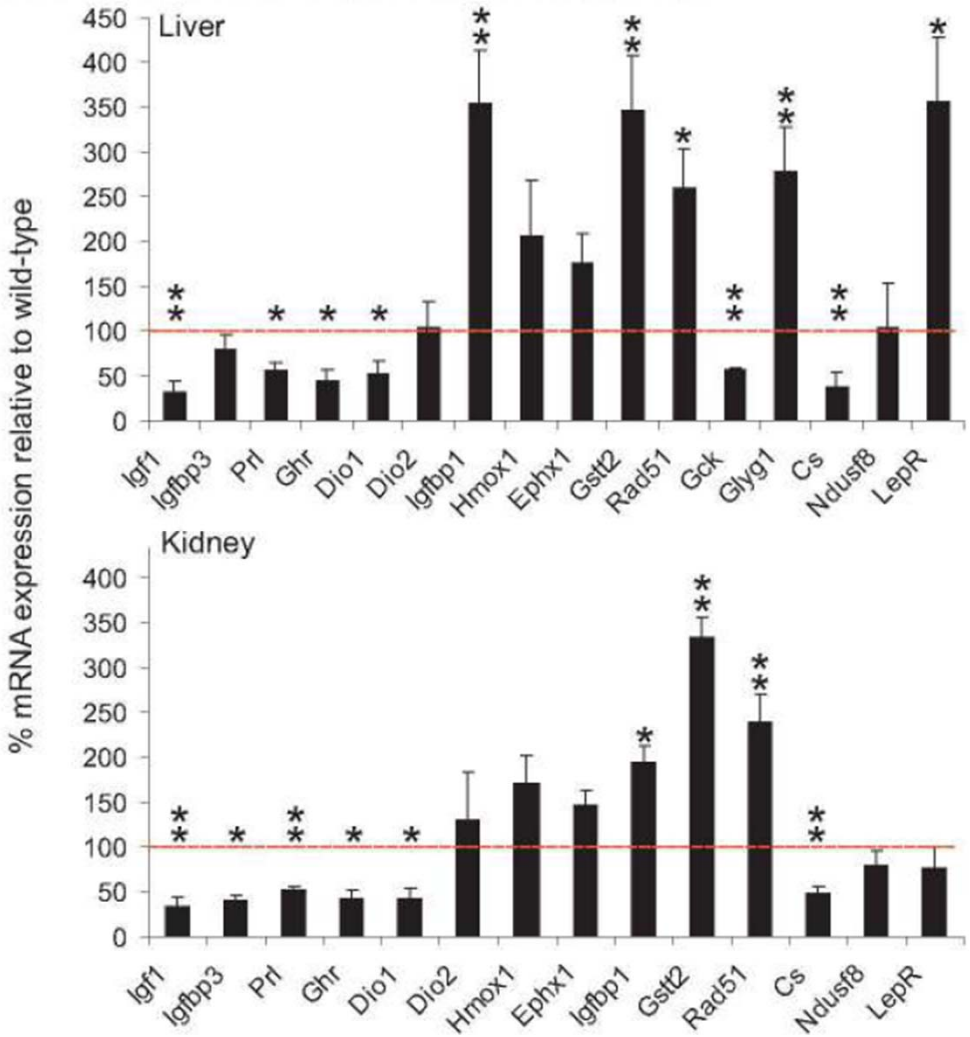
Nature 2007

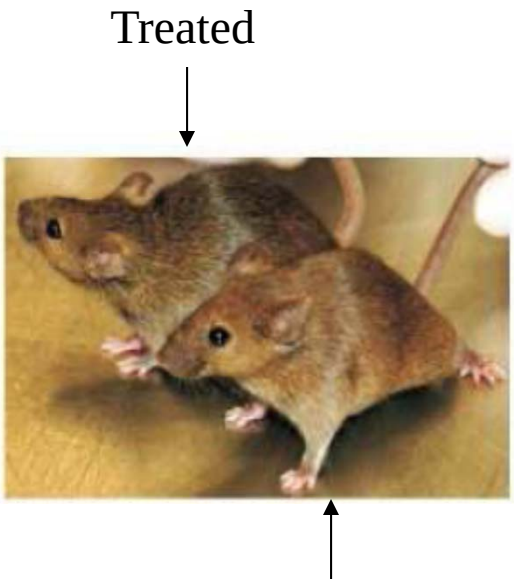
Code	Title	Xpa$^{-/-}$/Csb$^{m/m}$	Ercc1$^{-/-}$	Significant in:
Insulin-like ligands				
1437401_at	insulin-like growth factor 1	-1.37	-1.57	ercc1 ; csb-xpa
1419519_at	insulin-like growth factor 1	-2.13	-1.50	ercc1 ; csb-xpa
1434413_at	insulin-like growth factor 1	-1.74	-1.34	csb-xpa
1452014_a_at	insulin-like growth factor 1	-1.98	-1.71	ercc1 ; csb-xpa
1458268_s_at	insulin-like growth factor binding protein 3	-1.44	-1.17	csb-xpa
1423062_at	insulin-like growth factor binding protein 3	-1.37	-1.41	ercc1 ; csb-xpa
1421991_a_at	insulin-like growth factor binding protein 4	-1.73	1.01	csb-xpa
1421992_a_at	insulin-like growth factor binding protein 4	-1.36	-1.16	ercc1 ; csb-xpa
1422826_at	insulin-like growth factor binding protein, acid labi	-2.35	-1.68	ercc1 ; csb-xpa
Growth hormone receptor				
1451501_a_at	growth hormone receptor	-1.51	-1.18	csb-xpa
1417962_s_at	growth hormone receptor	-1.50	-1.25	csb-xpa
Prolactin receptor				
1451844_at	prolactin receptor	-1.45	-1.35	csb-xpa
1425853_s_at	prolactin receptor	-1.87	-1.62	ercc1 ; csb-xpa
1450226_at	prolactin receptor	-1.76	-1.58	ercc1 ; csb-xpa
1448556_at	prolactin receptor	-2.04	-1.86	ercc1 ; csb-xpa
1421382_at	prolactin receptor	-1.96	-1.57	ercc1 ; csb-xpa
1452661_at	transferrin receptor	-1.05	-1.78	ercc1
Growth factor receptor bound protein 10				
1430164_a_at	growth factor receptor bound protein 10	1.68	1.34	csb-xpa
1425458_a_at	growth factor receptor bound protein 10	1.86	1.37	ercc1 ; csb-xpa
Serotonin receptor				
1422288_at	5-hydroxytryptamine (serotonin) receptor 1B	-1.47	-1.68	ercc1
Thyroid hormone				
1417991_at	deiodinase, iodothyronine, type I	-2.12	-2.35	ercc1 ; csb-xpa
1418938_at	deiodinase, iodothyronine, type II	-1.31	-1.27	ercc1
Estrogen receptor 1 (alpha)				
1435663_at	estrogen receptor 1 (alpha)	-1.90	-1.26	csb-xpa
1460591_at	estrogen receptor 1 (alpha)	-1.58	-1.24	csb-xpa
1460591_at	estrogen receptor 1 (alpha)	-1.58	-1.24	csb-xpa
1435663_at	estrogen receptor 1 (alpha)	-1.90	-1.26	csb-xpa
Fibroblast growth factor 1				
1423136_at	fibroblast growth factor 1	-1.16	-1.51	ercc1
1450869_at	fibroblast growth factor 1	-1.37	-1.51	ercc1 ; csb-xpa
1421841_at	fibroblast growth factor receptor 3	-1.43	-2.02	ercc1 ; csb-xpa
1427777_x_at	fibroblast growth factor receptor 4	-1.33	-1.15	csb-xpa

Code	Title	Xpa$^{-/-}$/Csb$^{m/m}$	Ercc1$^{-/-}$	Significant in:
P450 Oxidative metabolism				
1450095_a_at	acylphosphatase 1, erythrocyte (common) type	-1.02	-1.32	ercc1
1421022_x_at	acylphosphatase 1, erythrocyte (common) type	-1.11	-1.44	ercc1
1444138_at	cytochrome P450, family 2, subfamily r, polypeptide 1	-1.28	-1.52	ercc1
1417590_at	cytochrome P450, family 27, subfamily a, polypeptide 1	-1.32	-1.29	ercc1
1418780_at	cytochrome P450, family 39, subfamily a, polypeptide 1	-1.37	-1.56	ercc1
1417070_at	cytochrome P450, family 4, subfamily v, polypeptide 3	-1.41	-1.28	ercc1 ; csb-xpa
1417017_at	cytochrome P450, family 17, subfamily a, polypeptide 1	-1.42	-2.03	ercc1
1450715_at	cytochrome P450, family 1, subfamily a, polypeptide 2	-1.50	-2.16	ercc1
1418821_at	cytochrome P450, family 2, subfamily a, polypeptide 12	-1.50	-1.25	ercc1 ; csb-xpa
1419590_at	cytochrome P450, family 2, subfamily b, polypeptide 9	-1.55	-1.22	ercc1 ; csb-xpa
1417651_at	cytochrome P450, family 2, subfamily c, polypeptide 29	-1.55	-1.06	csb-xpa
1424273_at	cytochrome P450, family 2, subfamily c, polypeptide 70	-1.59	-1.41	ercc1 ; csb-xpa
1422230_s_at	cytochrome P450, family 2, subfamily a, polypeptide 5	-1.59	-2.25	ercc1
1418767_at	cytochrome P450, family 4, subfamily f, polypeptide 13	-1.67	-1.37	csb-xpa
1449479_at	cytochrome P450, family 2, subfamily b, polypeptide 13	-2.24	1.06	csb-xpa
1438743_at	cytochrome P450, family 7, subfamily a, polypeptide 1	-2.27	-1.43	csb-xpa
1448792_a_at	cytochrome P450, family 2, subfamily f, polypeptide 2	-2.37	-2.28	ercc1 ; csb-xpa
1422100_at	cytochrome P450, family 7, subfamily a, polypeptide 1	-2.37	-1.37	csb-xpa
1417531_at	cytochrome P450, family 2, subfamily j, polypeptide 5	-2.50	-2.63	ercc1 ; csb-xpa
1440327_at	cytochrome P450, family 2, subfamily c, polypeptide 70	-2.52	-1.95	ercc1 ; csb-xpa
1422257_s_at	cytochrome P450, family 2, subfamily b, polypeptide 10	-2.81	-1.56	csb-xpa
1425645_s_at	cytochrome P450, family 2, subfamily b, polypeptide 20	-2.90	-1.69	csb-xpa
1417532_at	cytochrome P450, family 2, subfamily j, polypeptide 5	-3.08	-2.40	ercc1 ; csb-xpa
1419559_at	cytochrome P450, family 4, subfamily f, polypeptide 14	-3.57	-2.91	ercc1 ; csb-xpa
NADPH Oxidative metabolism				
1417429_at	flavin containing monooxygenase 1	-1.38	-1.14	csb-xpa
1453435_a_at	flavin containing monooxygenase 2	-2.46	-1.32	csb-xpa
1435459_at	flavin containing monooxygenase 2	-2.80	-1.38	csb-xpa
1422905_s_at	flavin containing monooxygenase 2	-3.23	-1.37	csb-xpa
1422904_at	flavin containing monooxygenase 2	-4.50	-1.45	csb-xpa
1449525_at	flavin containing monooxygenase 3	-13.76	-2.55	csb-xpa
Oxidative phosphorylation				
1456015_x_at	NADH dehydrogenase (ubiquinone) flavoprotein 1	-1.22	-1.25	ercc1
1434213_x_at	NADH dehydrogenase (ubiquinone) Fe-S protein 8	-1.16	-1.24	ercc1
1423908_at	NADH dehydrogenase (ubiquinone) Fe-S protein 8	-1.23	-1.19	csb-xpa
1434212_at	NADH dehydrogenase (ubiquinone) Fe-S protein 8	-1.56	-1.35	ercc1 ; csb-xpa

Code	Title	Xpa$^{-/-}$/Csb$^{m/m}$	Ercc1$^{-/-}$	Significant in:
Antioxidant and detoxification response				
1452592_at	microsomal glutathione S-transferase 2	2.96	3.75	**ercc1 ; csb-xpa**
1417883_at	glutathione S-transferase, theta 2	2.75	4.12	**ercc1 ; csb-xpa**
1421041_s_at	glutathione S-transferase, alpha 2 (Yc2)	1.88	3.27	**ercc1 ; csb-xpa**
1421040_a_at	glutathione S-transferase, alpha 2 (Yc2)	1.73	3.41	**ercc1**
1448300_at	microsomal glutathione S-transferase 3	1.49	1.49	**ercc1 ; csb-xpa**
1449575_a_at	glutathione S-transferase, pi 2	1.37	1.20	**csb-xpa**
1416842_at	glutathione S-transferase, mu 5	1.28	1.38	**ercc1 ; csb-xpa**
1421817_at	glutathione reductase 1	1.18	1.11	**csb-xpa**
1448239_at	heme oxygenase (decycling) 1	2.43	1.51	**csb-xpa**
1422438_at	epoxide hydrolase 1, microsomal	2.11	2.91	**ercc1 ; csb-xpa**
1430979_a_at	peroxiredoxin 2	1.60	1.50	**csb-xpa**
1415996_at	thioredoxin interacting protein	2.11	1.91	**ercc1 ; csb-xpa**
1435304_at	superoxide dismutase 1, soluble	1.21	1.06	**csb-xpa**

Wt mice chronically exposed to the crosslinking agent mitomycin C





In conclusion:

ERCC1$^{-/-}$

Csb$^{m/m}$/Xpa$^{-/-}$

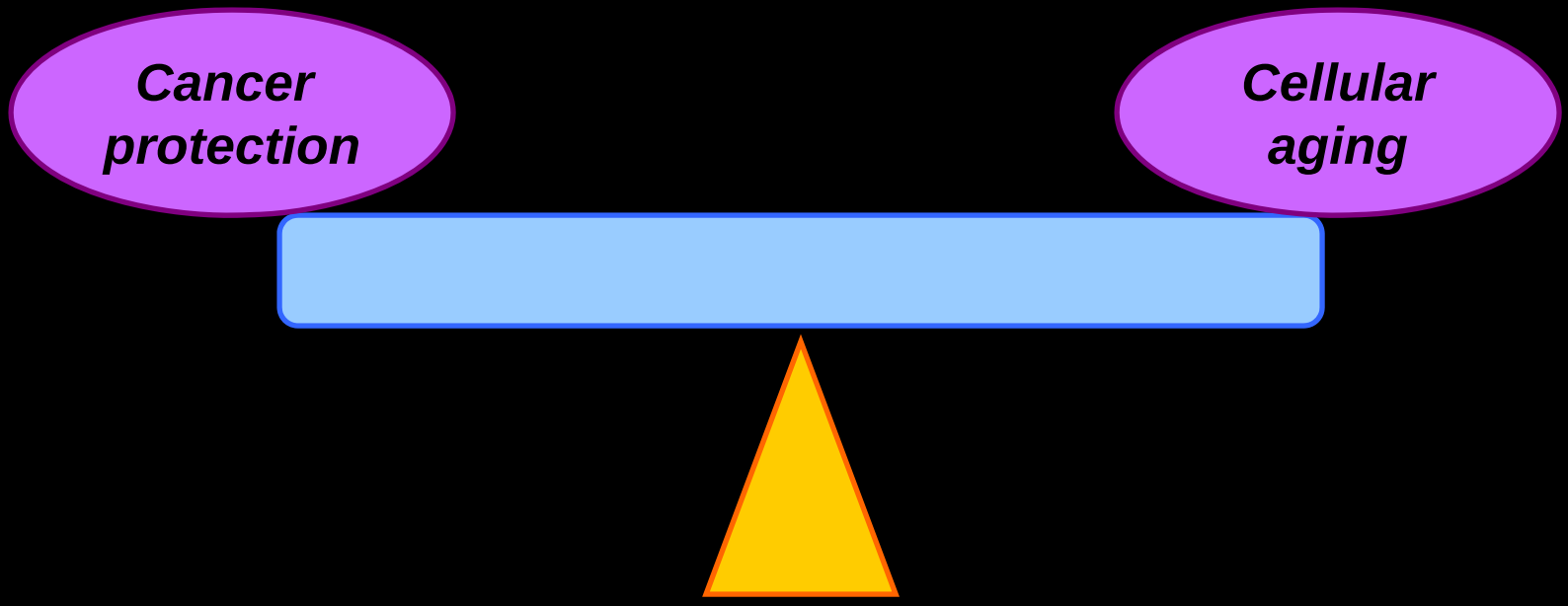
The full mouse transcriptome in the liver of 15-day old *Csb$^{m/m}$/Xpa$^{-/-}$* and *Ercc1$^{-/-}$* mice recapitulates the hormonal shift and anti-oxidant defense response that occurs in normal aging

Short-lived NER mutants display a dramatically accelerated form of natural aging.

The DNA repair defect triggers the aging-related hormonal response

Endogenous persisting DNA damage is the cause of the hormonal shift and responsible for the acceleration of the aging process

Tumor suppression and aging: An evolutionary balancing act!



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