Cellular Defenses Against Radiation-Induced Carcinogenesis:

- Cell Cycle Arrest
- DNA Repair
- Apoptosis

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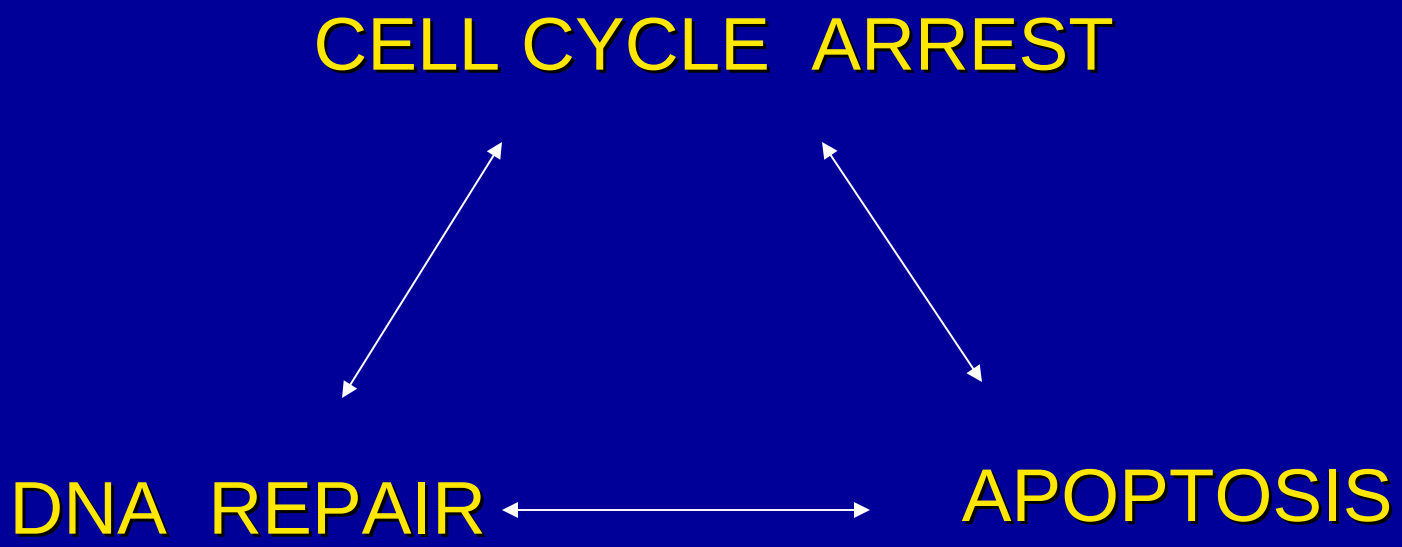

CELL CYCLE ARREST
DNA REPAIR
APOPTOSIS

GOALS:

- Provide an overall description of how these three processes work to inhibit transformation.
- Describe how they are mechanistically connected.
- Show how they interact with radiation damage.
- Discuss molecular epidemiology implications for gene-environment interaction studies.
- Review epidemiological biases and confounding issues.

DNA damage is thought to be the primary mechanism by which radiation transforms cells.

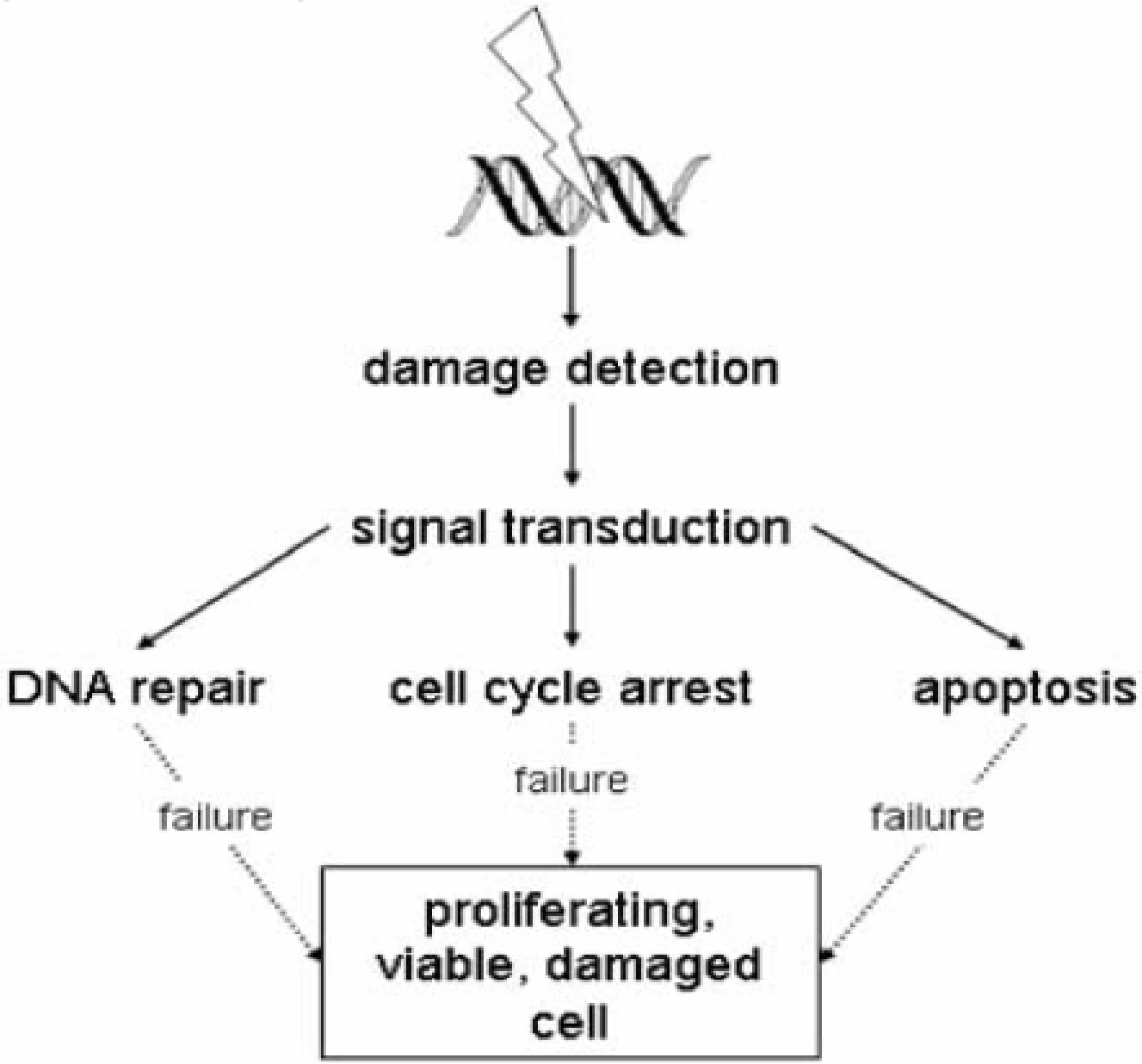
Yet, only a small number of cells are actually transformed.

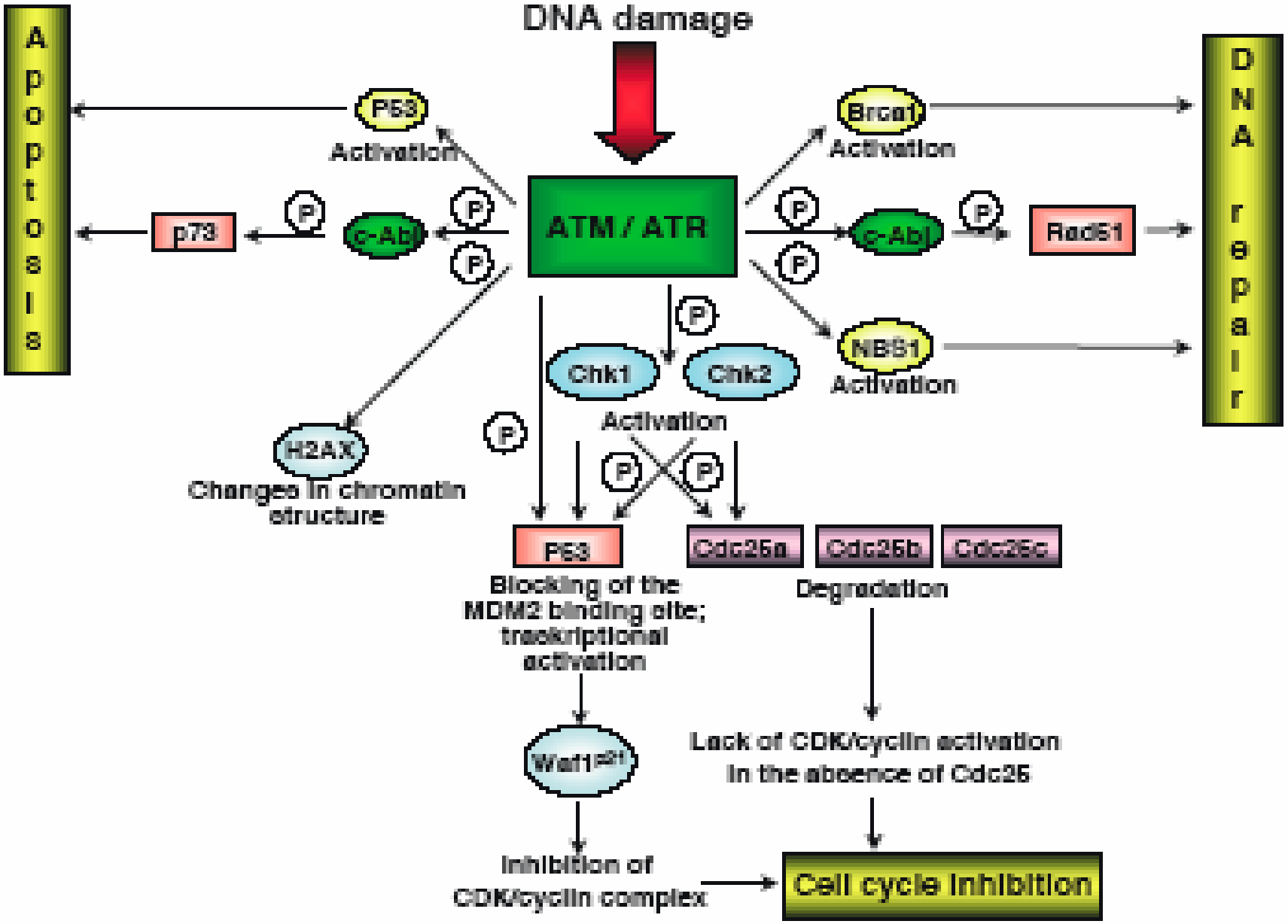
How are most cells protecting themselves from DNA damage-mediated transformation?

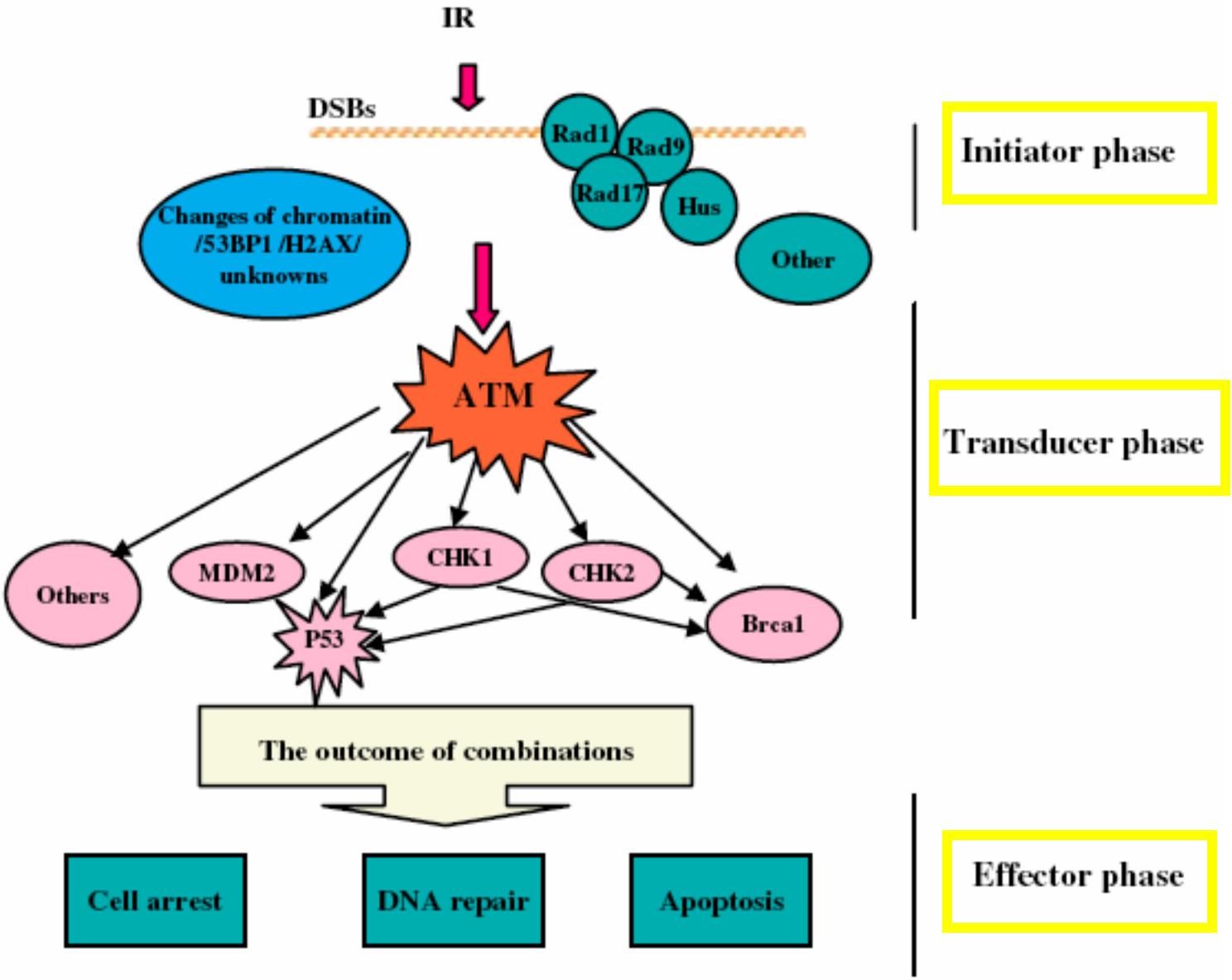
DNA damage and apoptosis

CJ Norbury and B Zhivotovsky

Oncogene (2004) 23, 2797–2808




DNA damage
Apoptosis
DNA repair
P53
Activation
Brca1
Activation
p73
c-Abl
ATM / ATR
c-Abl
Rad51
NBS1
Activation
Chk1
Chk2
Activation
H2AX
Changes in chromatin structure
P53
Cdc25a
Cdc25b
Cdc25c
Blocking of the MDM2 binding site; transkriptional activation
Degradation
Waf1p21
Lack of CDK/cyclin activation in the absence of Cdc25
Inhibition of CDK/cyclin complex
Cell cycle inhibition

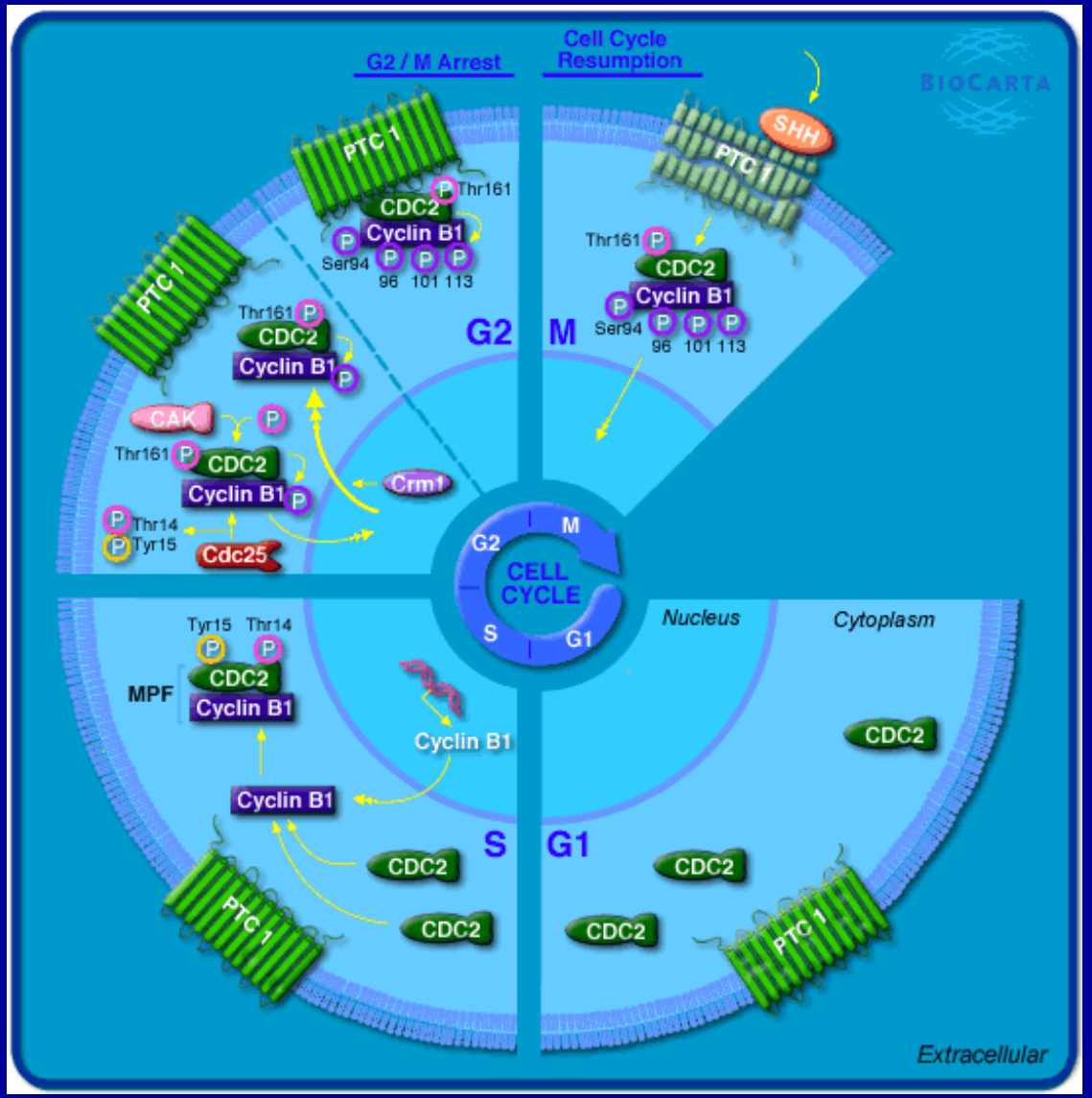


P53 and radiation responses

P Fei and WS El-Deiry

Oncogene (2003) 22, 5774–5783

CELL CYCLE ARREST



Cancer cells “evolve” into a highly unstable phenotype:

Loss of contact inhibition

Loss of anchorage dependence

Tumorogenesis

Metastasis

- The ability to undergo successive genetic change suggests that a loss of genetic stability is an early event in carcinogenesis.

- Cell cycle control via cell cycle checkpoints, is thought to be a major mechanism by which cells maintain genetic stability.

WHY CHECKPOINTS?

Fidelity of cell division is dependent upon faithful copying and segregation of genetic material, both spatially and temporally. That is, the ordered sequence of specific events is essential to proper execution of the task.

For this reason, cells have developed checkpoints that insure that the previous replication step is complete before the next step begins.

HOW DO CHECKPOINTS WORK?

- Checkpoints are governed by phosphorylation activity of a group of proteins called CDK (cyclin dependent kinases).
- The CDKs are active only in complexes that contain at least one other protein, called a “cyclin”.
- Changes in the cyclin and kinase components of the complexes are the “switches” that control and regulate progression through the cell cycle.
- In this model, a cohort of proteins required for progression of a particular phase are activated (or inactivated) by phosphorylation of the cyclin/CDK complexes.

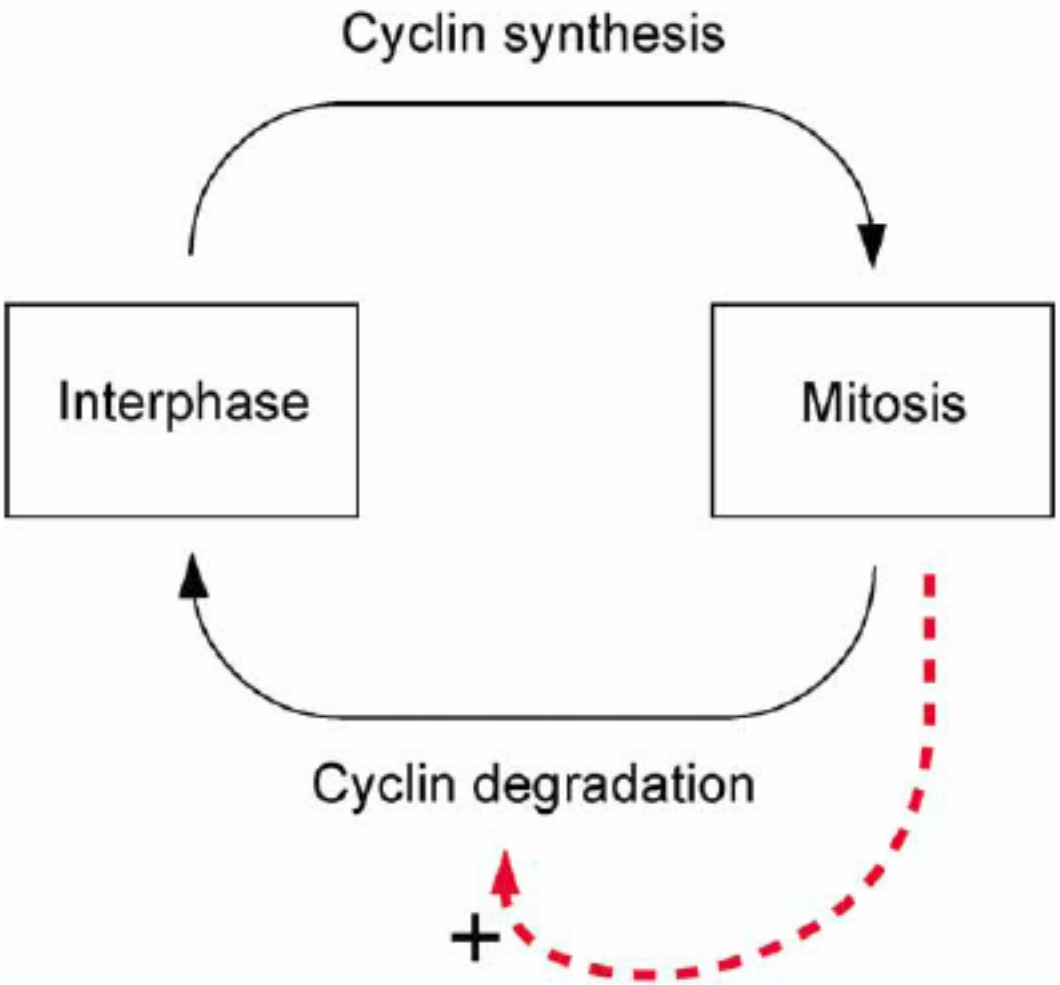


Figure 1. The Original Cyclin-Based Model for the Cell Cycle
The simplest possible model for the cell cycle based on the discovery of cyclin. See text for details.

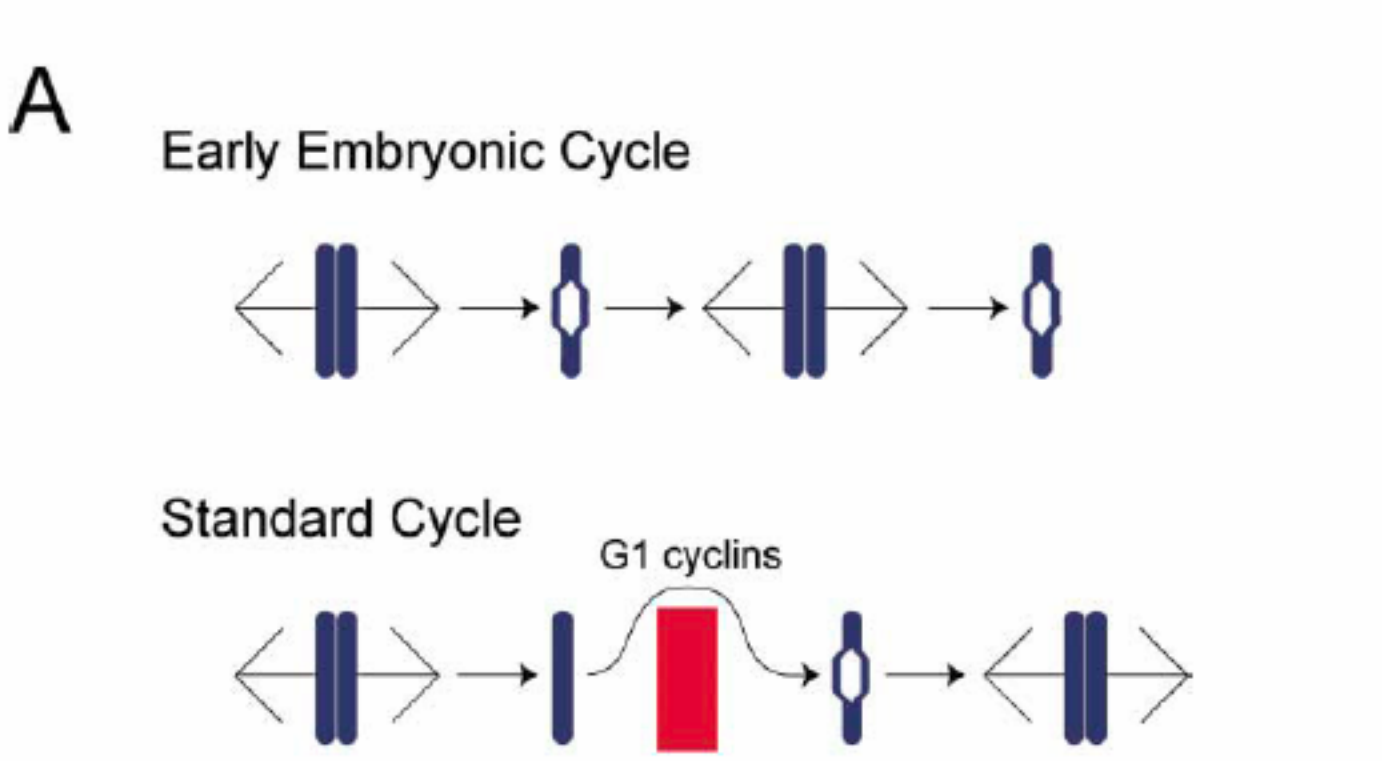
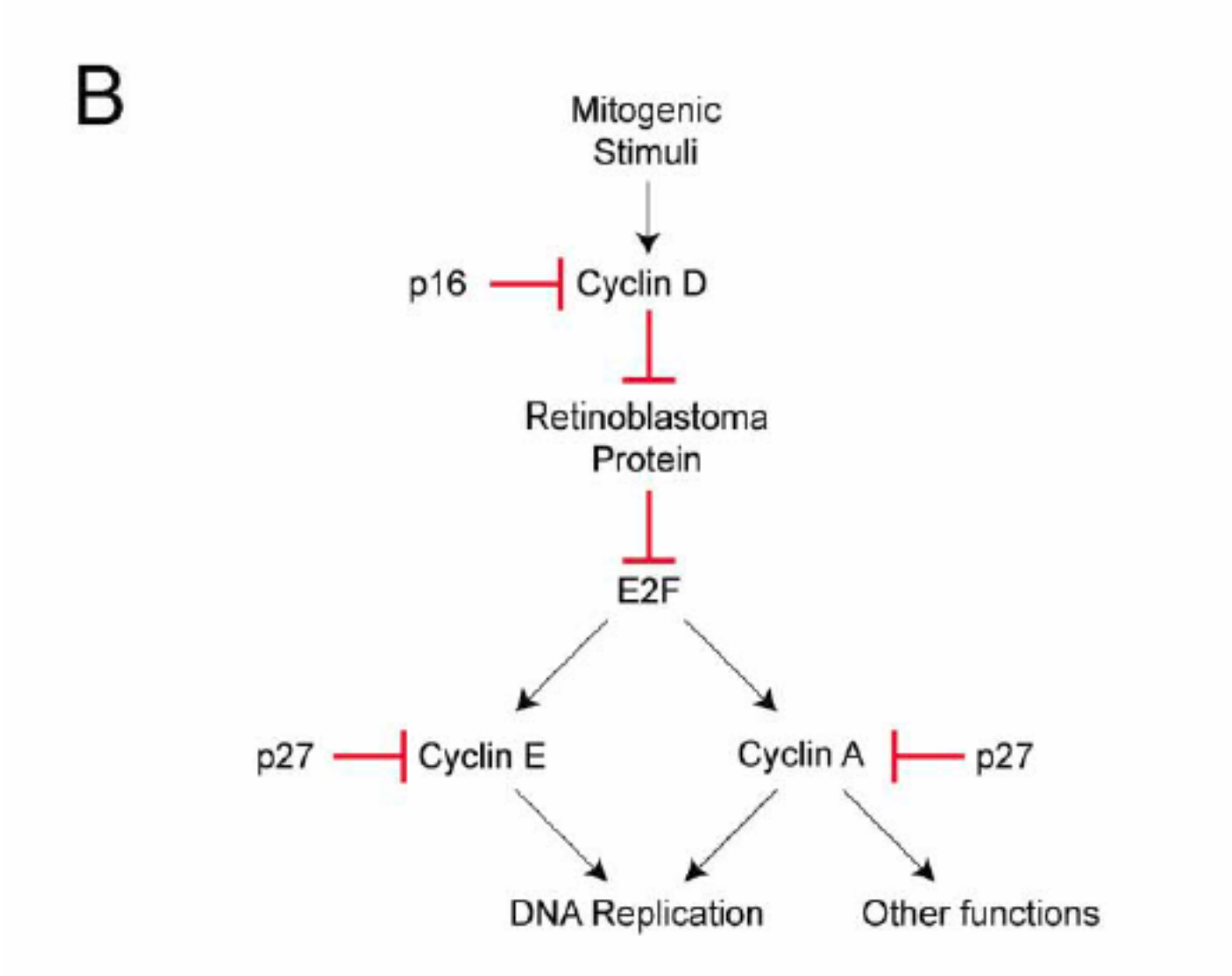


Figure 3. G1 Cyclins Overcome Inhibitors of Cell Cycle Progression

(A) In early embryonic cell cycles, DNA replication begins as soon as cells leave mitosis. In most cell cycles, however, the combination of anaphase promoting factor activity and Cdk inhibitors ensures that cells spend appreciable time in G1 and require the synthesis of G1 cyclins that overcome these inhibitory factors.



(B) The relationship between G1 (cyclin D) and S phase cyclins (A and E), growth factors, and Cdk inhibitors in animal cells. See text for details.

In yeast, only a single CDK is used by a sequence of different cyclins that are briefly transcribed and then quickly degraded at specific points in the cell cycle. The cyclin is, therefore, the important regulatory component determining the specificity of the CDK.

In mammalian cells, multiple CDKs appear to be involved:

	Cyclin
CDK4 functions early (in response to growth factors)	D
CDK2 is required to start DNA replication	E and/or A
CDC2 is essential for mitosis	A and B

Cyclin/CDK complexes seem to be regulated by a variety of feedback mechanism, both positive and negative, that include:

- Transcription of cyclin
- Degradation of cyclin
- Phosphorylation of CDKs

Negative feedback occurs during development, differentiation, and senescence. It probably acts to stop cell cycle progression when the integrity of the genome has been compromised for some reason.

WHAT EFFECT DOES DNA DAMAGE HAVE?

- A major challenge to genetic integrity is physical damage to DNA, and it appears that cells have developed strong negative feedbacks in response to DNA damage.

- Suppression of cell cycle works in concert with DNA repair to:
    1. Allow time for DNA repair
    2. To stimulate DNA repair activity

- Feedback mechanisms are mediated via intermediate proteins that detect or respond to either the damaging agent or the damage itself and act on the cyclin/CDK complexes to suppress their ability to promote progression to the next stage of the cell cycle. There are probably many checkpoints throughout the cell and only the major ones are known.

- At least two checkpoints are responsive to DNA damage:
    1. G1-S transition
    2. G2-M transition

- In mammalian cells the G1-S checkpoint is best understood.

G1-S checkpoint:

An early response to DNA damage is induction of p53 by a post-translational mechanism.

P53 then transcriptionally activates a set of p53 dependent genes:

- Gadd45 is a growth arrest DNA damage dependent gene
- p21 inhibits the kinase activity of multiple cyclin/CDK complexes.

The major consequence of p53 induction is either arrest in G1 or apoptosis.

DO DEFECTIVE CHECKPOINTS CAUSE CANCER?

Evidence suggests that the loss of the G1-S checkpoint can result in cancer:

1. p53 is commonly mutated in a wide variety of cancers.
2. p53 mutant cells are typically highly aneuploid and have gene amplifications.
3. Some cancer viruses express proteins that bind to p53.
4. Cells from A-T patients (cancer prone) have abnormal induction of p53.

Evidence for the role of the G2-M checkpoint in cancer is weaker:

1. Cells from A-T patients undergo reduced G2-M arrest in response to DNA damage.
2. Cancer cell lines often have reduced G2-M arrest.
3. Some cancer cells have altered expression of cyclins A, B, and CDC2.

Radiation-Induced G2 delay in lymphoblasts may be a good biomarker for lung cancer

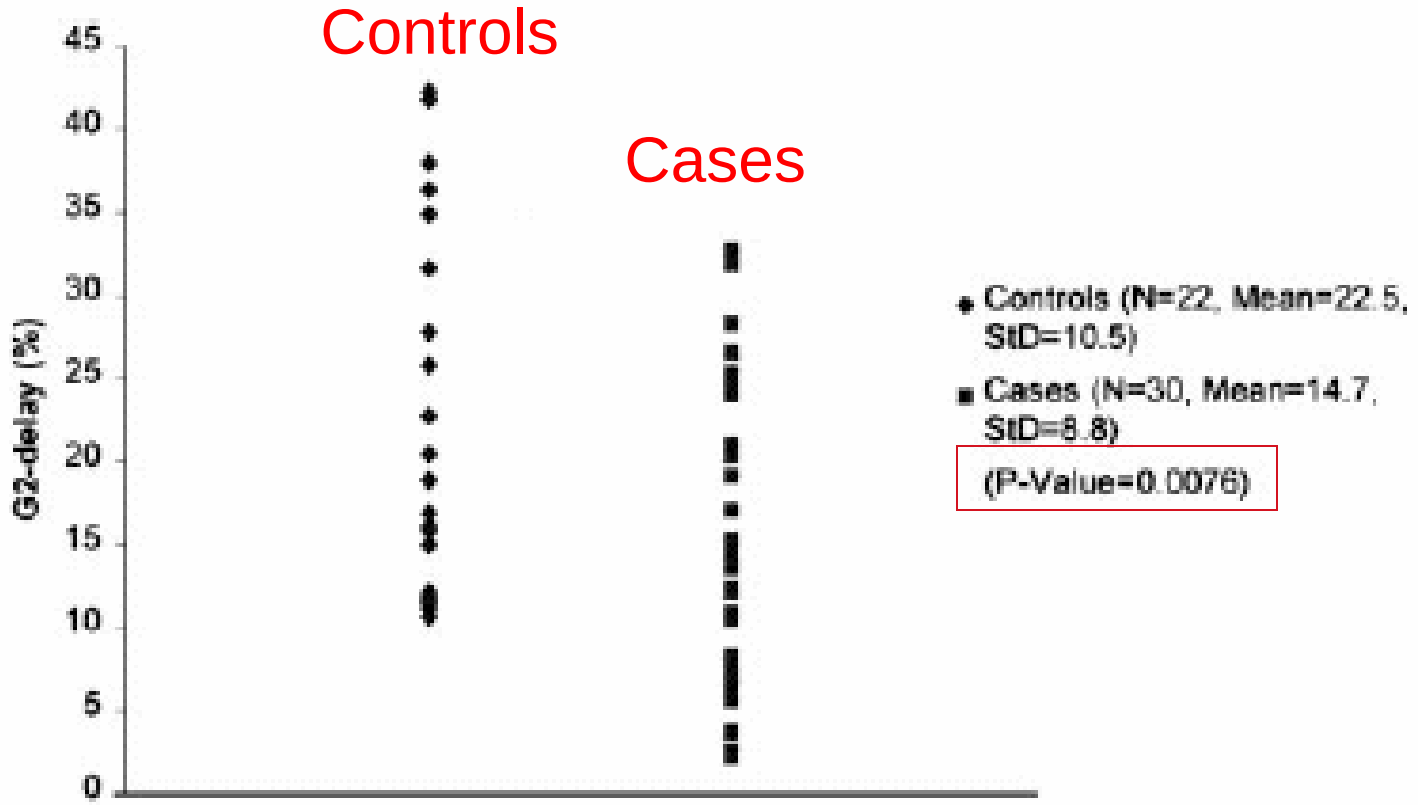


Fig. 3. Distribution of G_2 delay in lymphoblastoid cells of lung cancer cases and controls. Cell lines from 22 normal healthy donors and 30 lung cancer patients were exposed to 2.5 Gy of γ-radiation for 10 h. The values shown are the mean values from three separate experiments.

Zhou et al. *Cancer Res*. 61:7819, 2001

APOPTOSIS

R. Mirakian et al. / Journal of Immunological Methods 265 (2002) 161–175

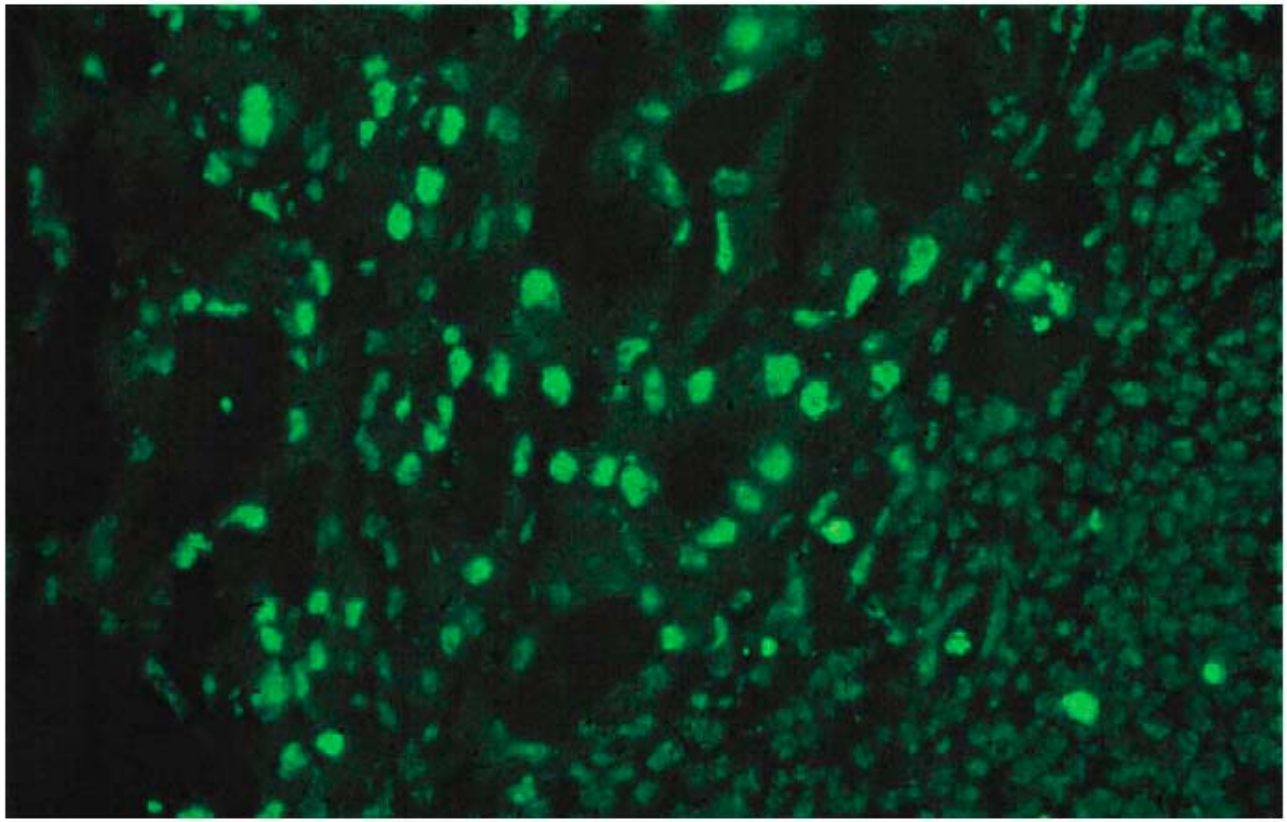
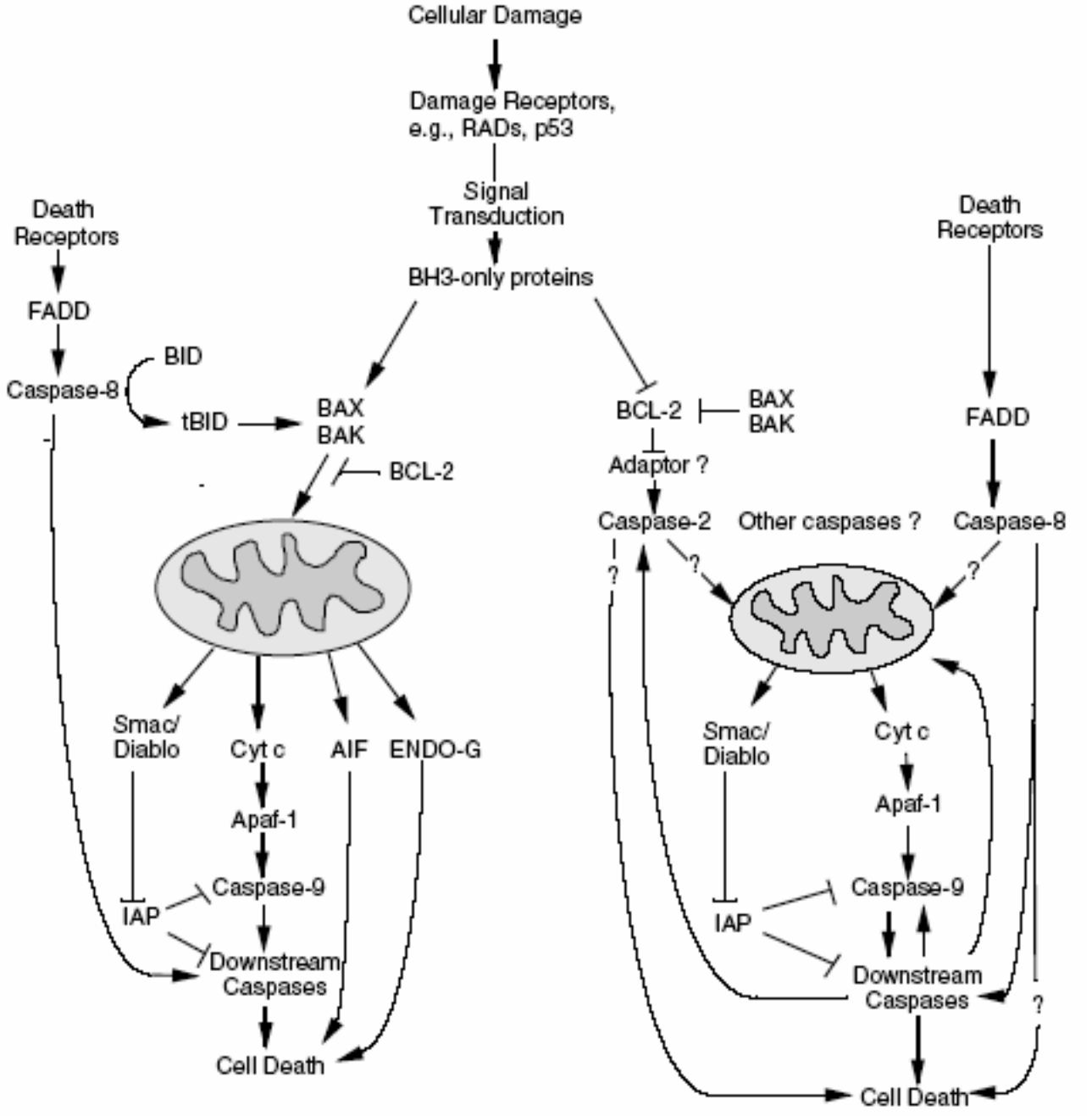


Fig. 1. In situ fluorescence staining of apoptotic cells using the TUNEL technique. Positive staining in nuclei of disrupted follicles in a Hashimoto's thyroiditis gland (magnification $\times 250$).

Apoptosis and anticancer drug resistance

SH Kaufmann and DL Vaux

Oncogene (2003) 22, 7414–7430



APOPTOSIS

Science 285:898, 1999

Fas Ligand: A Sensor for DNA Damage Critical in Skin Cancer Etiology

Laurie L. Hill, Allal Ouhtit, Susan M. Loughlin, Margaret L. Kripke, Honnavara N. Ananthaswamy, Laurie B. Owen-Schaub*

DNA-damaged cells can either repair the DNA or be eliminated through a homeostatic control mechanism termed "cellular proofreading." Elimination of DNA-damaged cells after ultraviolet radiation (UVR) through sunburn cell (apoptotic keratinocyte) formation is thought to be pivotal for the removal of precancerous skin cells. Sunburn cell formation was found to be dependent on Fas ligand (FasL), a pro-apoptotic protein induced by DNA damage. Chronic exposure to UVR caused 14 of 20 (70 percent) FasL-deficient mice and 1 of 20 (5 percent) wild-type mice to accumulate p53 mutations in the epidermis. Thus, FasL-mediated apoptosis is important for skin homeostasis, suggesting that the dysregulation of Fas-FasL interactions may be central to the development of skin cancer.

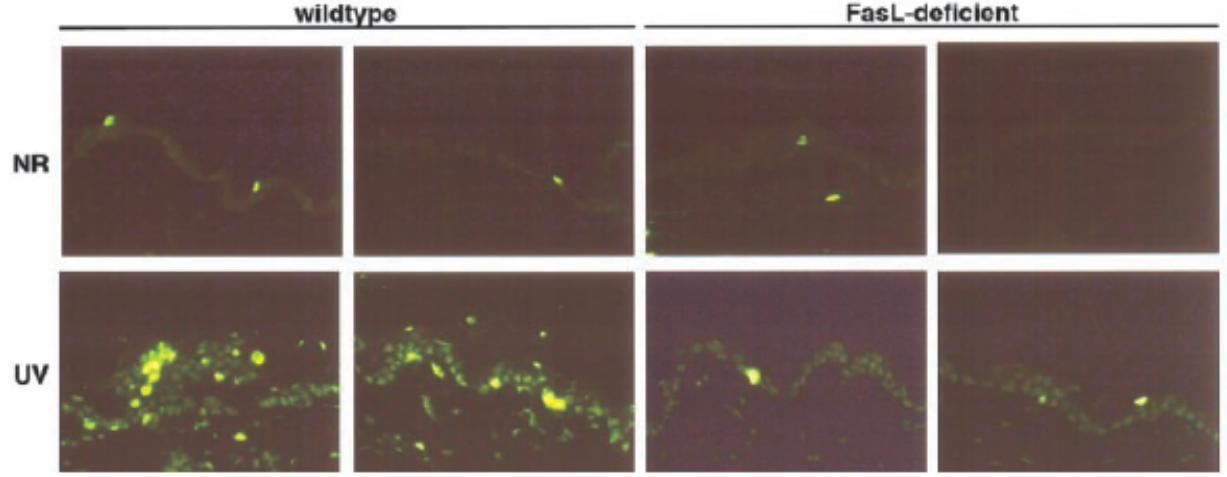
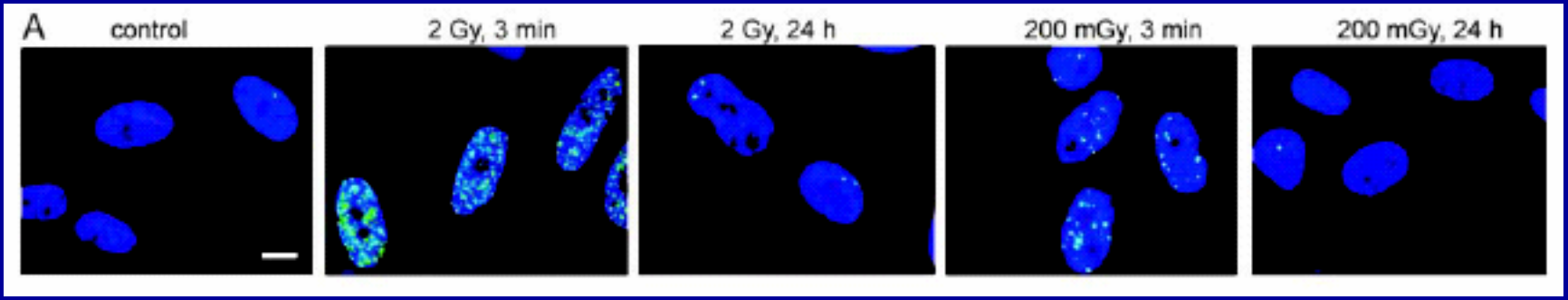
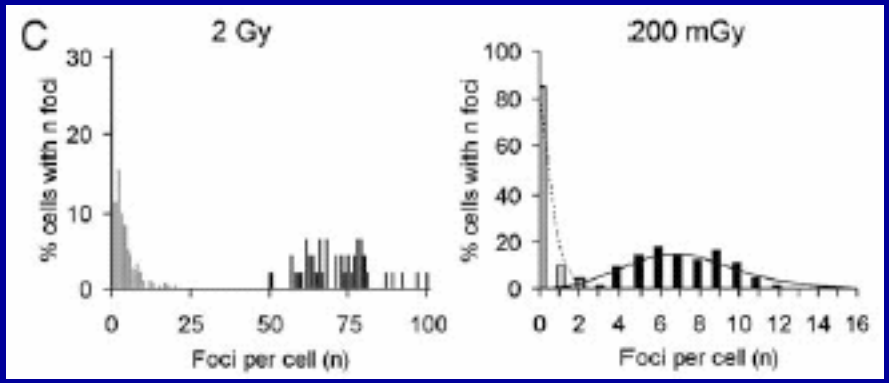
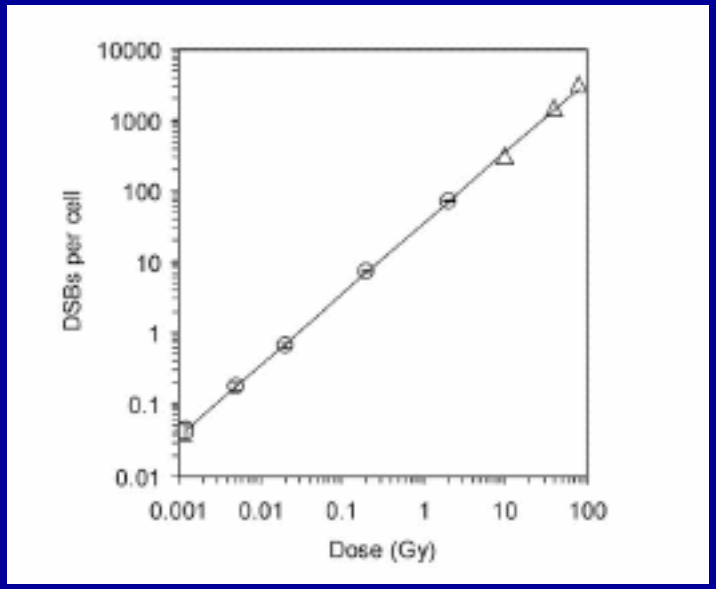


Fig. 2. Sunburn cell induction in wild-type and FasL-deficient (*gld/gld*) mice after UVR. Mice were acutely exposed to UV-B light (5 kJ/m^2), and skin sections were harvested for TUNEL analysis at 0 (NR) and 24 (UV) hours (*15*). A minimum of four mice (nonirradiated and irradiated) were examined; sections from two individual mice are shown. NR, nonirradiated. Magnification, ×10.







Rothkamm and Lobrick, PNAS, 2003

DNA REPAIR

Somatic Mutation and Cancer

Environmental carcinogens

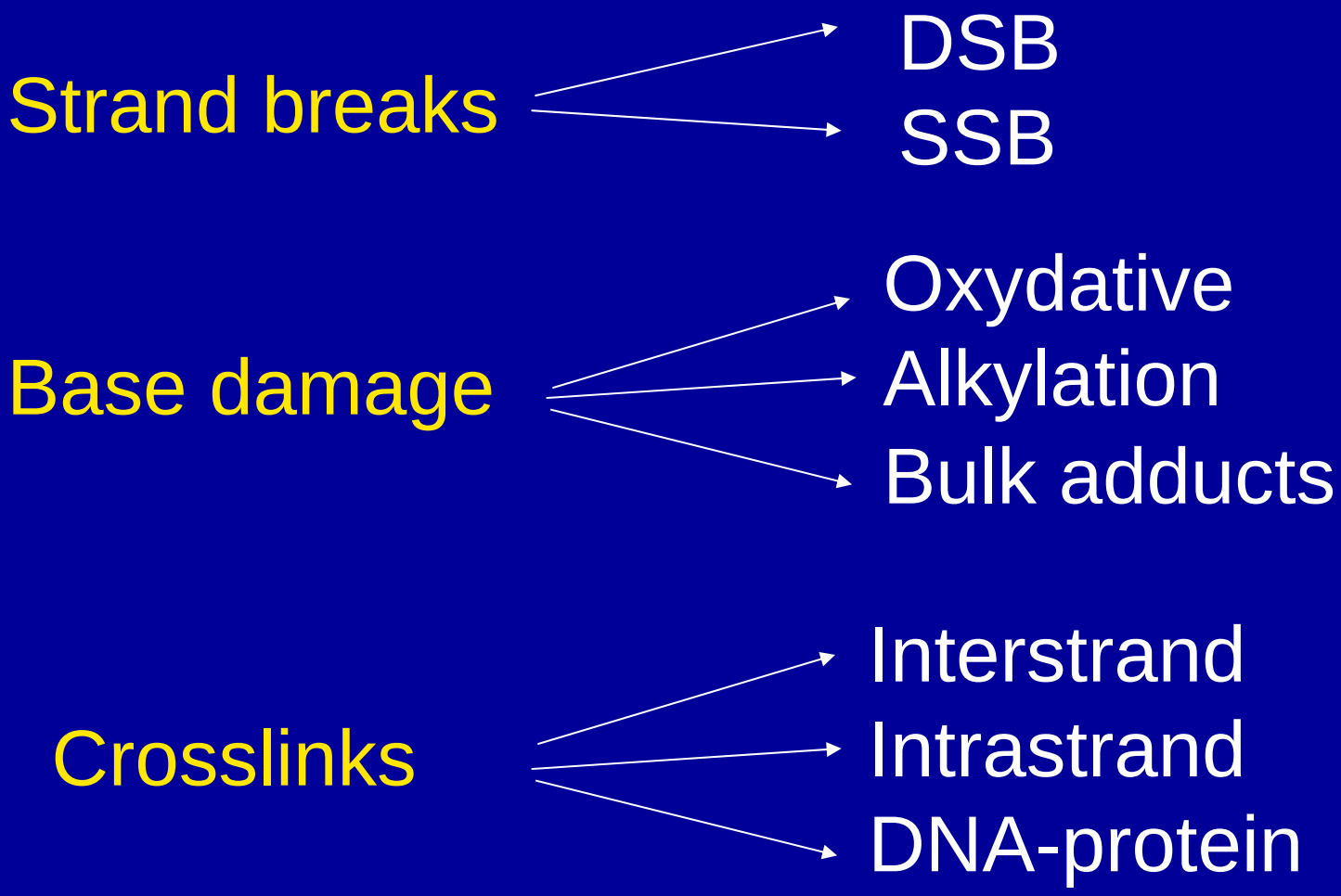
DNA Damage

DNA Repair

Mutatagenesis

Carcinogenesis

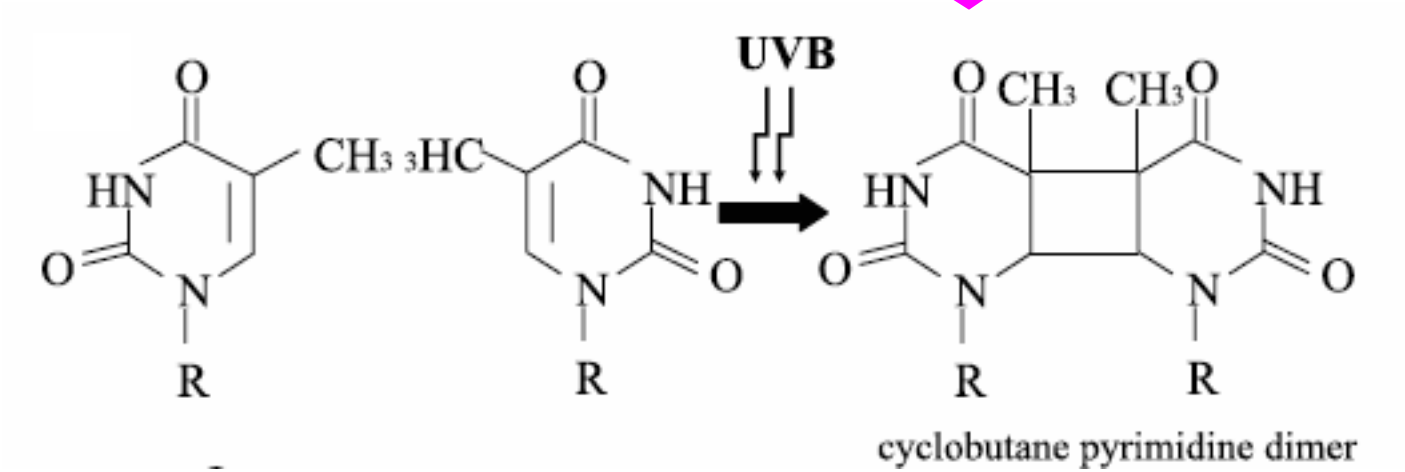
Major classes of DNA damage:



Major DNA repair pathways:

- Non-homologous end joining (NHEJ)
- Base Excision Repair (BER)
- Nucleotide Excision Repair (NER)
- Homologous Recombination Repair
- Illegitimate Recombination Repair
- Mismatch Repair (MMR)

254 nm



>320 nm

Proc. Natl. Acad. Sci. USA
Vol. 74, No. 12, pp. 5574–5578, December 1977
Cell Biology

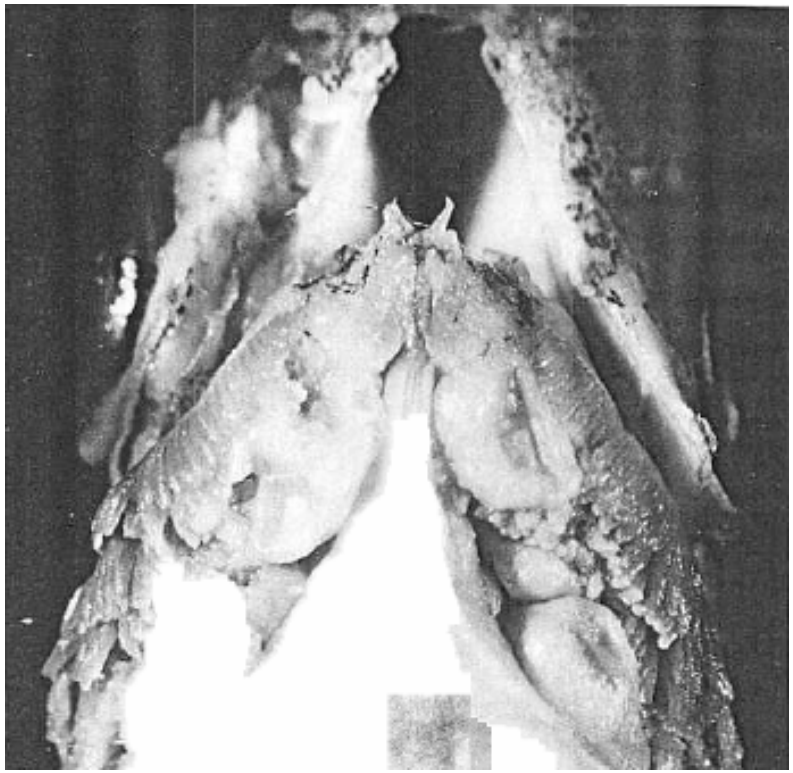
Evidence that pyrimidine dimers in DNA can give rise to tumors

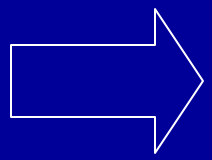
(UV irradiation/photoreactivation/fish/thyroid)

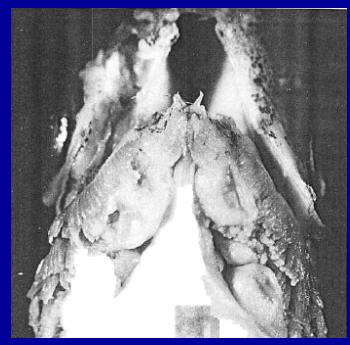
R. W. HART*, R. B. SETLOW, AND A. D. WOODHEAD

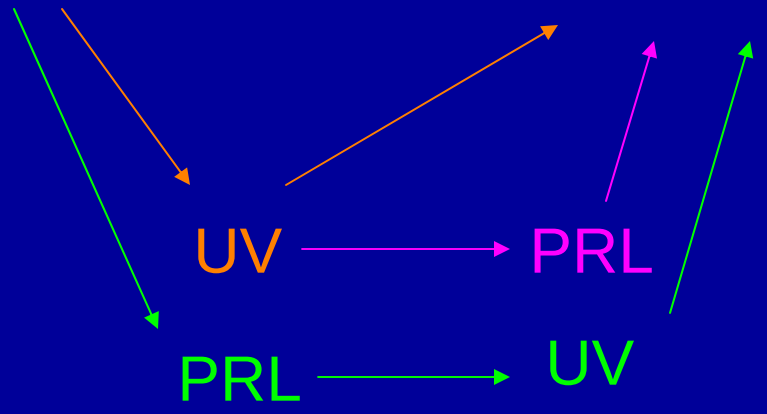
Biology Department, Brookhaven National Laboratory, Upton, New York 11973

Contributed by R. B. Setlow, September 12, 1977









Fish with thyroid tumors

	Number	Percent
UV (24 J/m2)	40/40	100%
UV + PRL	0/22	0%
PRL + UV	38/40	95%
untreated	0/22	0%

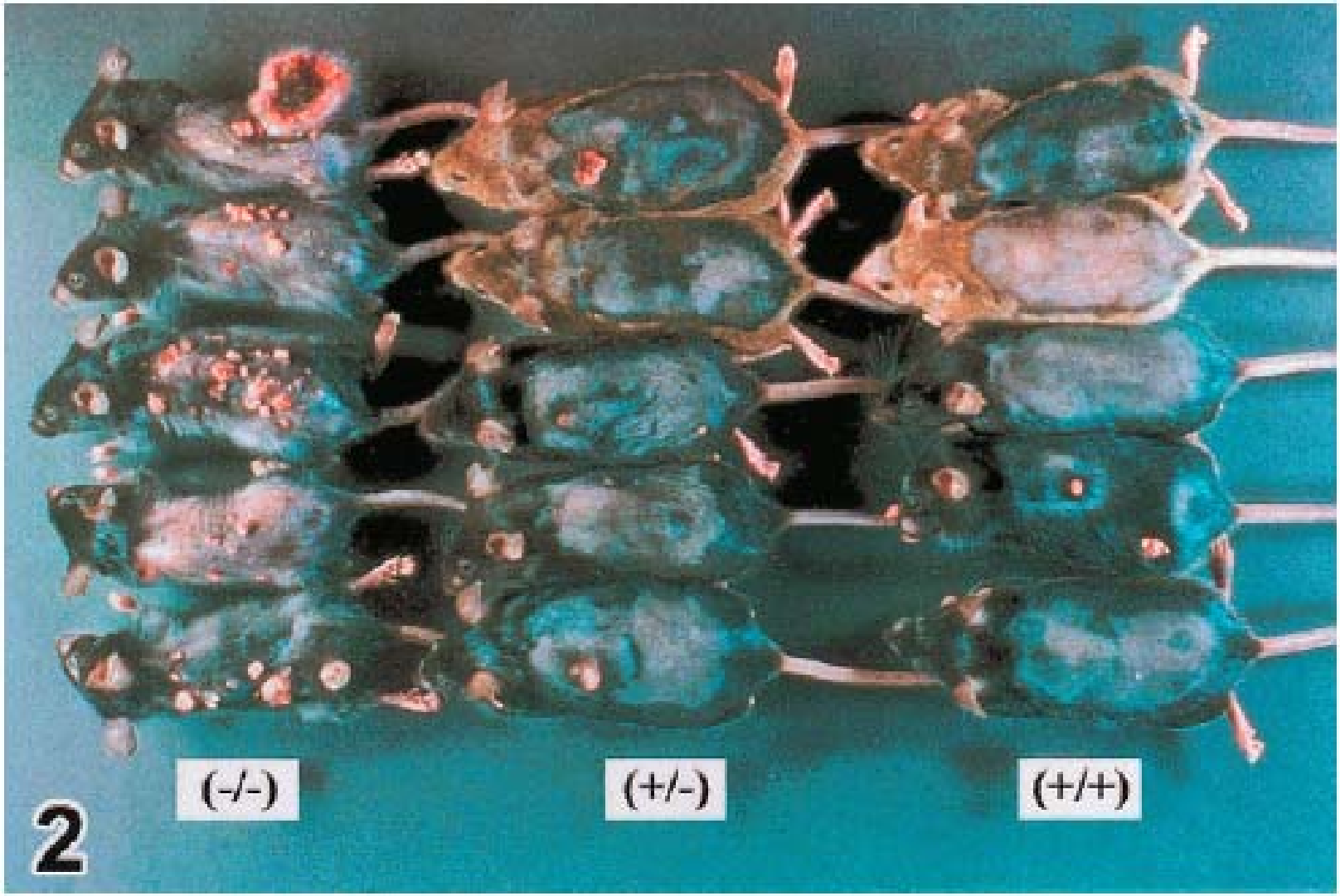


Fig. 2. DMBA-induced skin tumors in *XPA*-deficient (left), heterozygous (middle) and wild-type (right) mice. Tumors are more frequent in *XPA*-deficient mice.

Table 3
Mouse models with inactivated DNA repair genes

Repair system	Type of DNA damage	Inherited human disease	Cancer risk	Transgenic mouse model
Direct repair	Alkyl adducts	?	?	*Mgmt*
BER	Single-base	?	?	*Aag*, *Ogg*, *Udg*, etc.
NER	Bulky adducts	XP	+	*Xpa*, *Xpb*, *Xpc*, *Xpg*
		CS	−	*Csa*, *Csb*
		XP-CS	+	*Xpb*, *Xpd*, *Xpg*
		TTD	−	*Xpd-Ttd*
MMR	Base pair mismatch	HNPCC	+	*Msh2*, *Msh3*, *Msh5*, *Msh6*, *Mlh1*, *Pms1*, *Pms2*
Homologous recombination	Strand breaks, cross-links	?	?	*Rad52*, *Rad54*, *Rad54B*
End joining	Strand breaks, cross-links	?	?	*Ku70*, *Ku80*, *DNA-PK$_{CS}$*

BER: base excision repair; NER: nucleotide excision repair; MMR: mismatch repair. - = not present (existing patients do not have a cancer phenotype); ? = no patients existing or known.

652 NATURE. VOL. 218. MAY 18. 1968

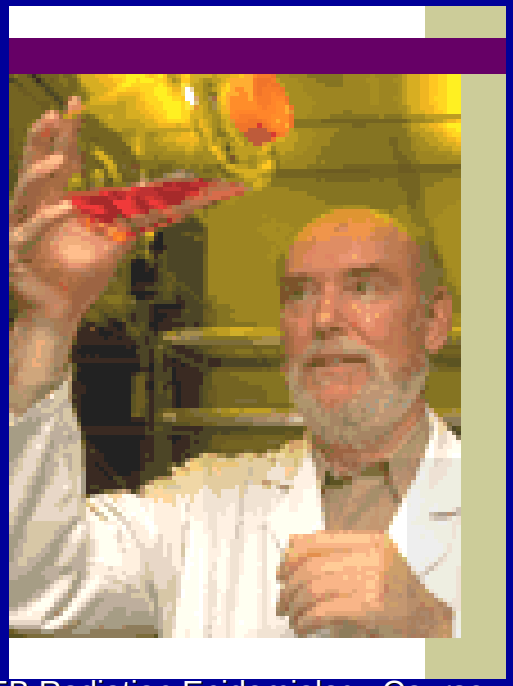
Defective Repair Replication of DNA in Xeroderma Pigmentosum

by

J. E. CLEAVER

Laboratory of Radiobiology,
University of California Medical Center,
San Francisco, California

Normal skin fibroblasts can repair ultraviolet radiation damage to DNA by inserting new bases into DNA in the form of small patches. Cells from patients with the hereditary disease xeroderma pigmentosum carry a mutation such that repair replication of DNA is either absent or much reduced in comparison to normal fibroblasts. Patients with xeroderma pigmentosum develop fatal skin cancers when exposed to sunlight, and so the failure of DNA repair in the skin must be related to carcinogenesis.



"… the failure of DNA repair in the skin *must* be related to carcinogenesis."
-- James E. Cleaver

Nucleotide Excision Repair (NER)

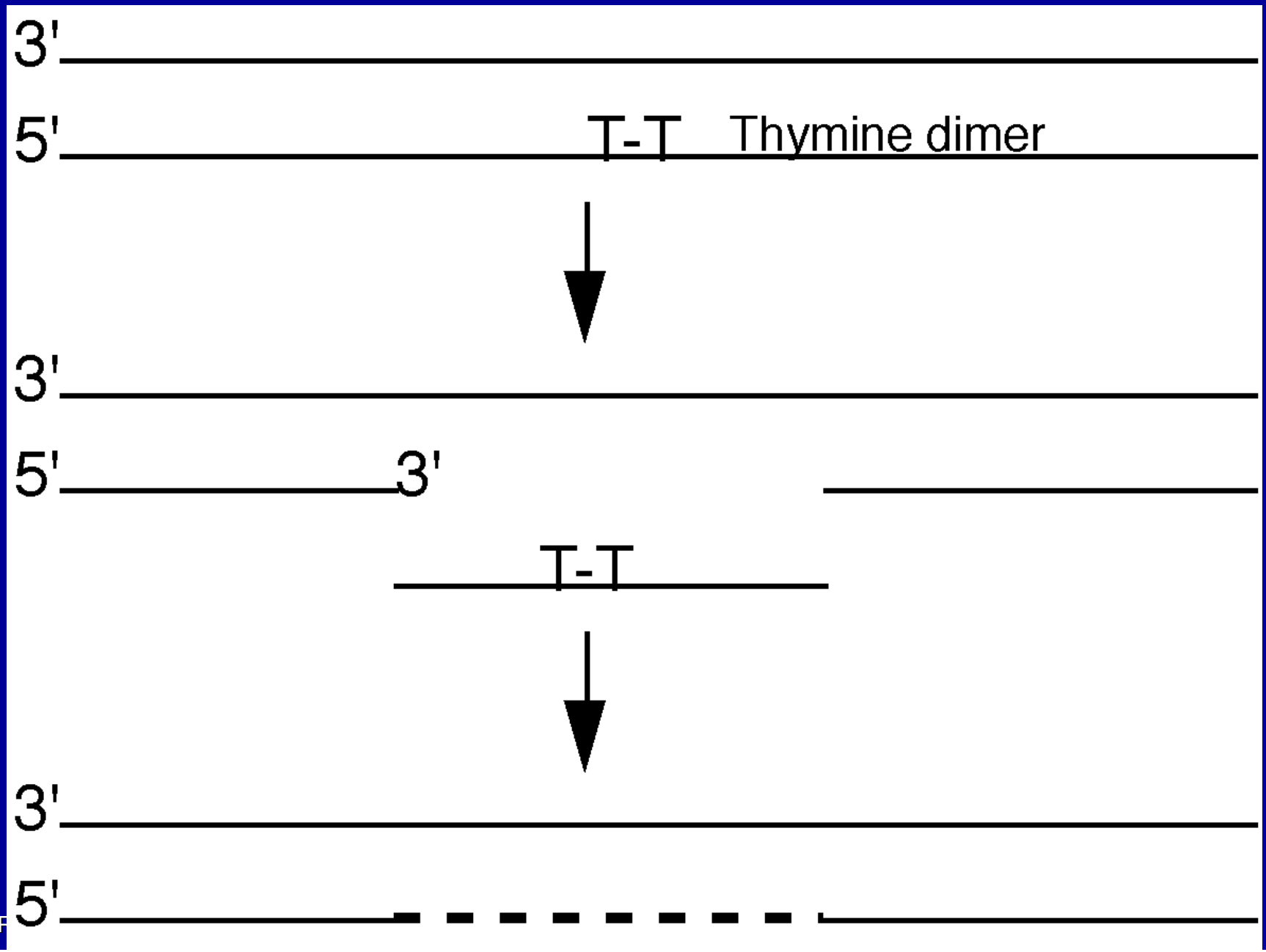
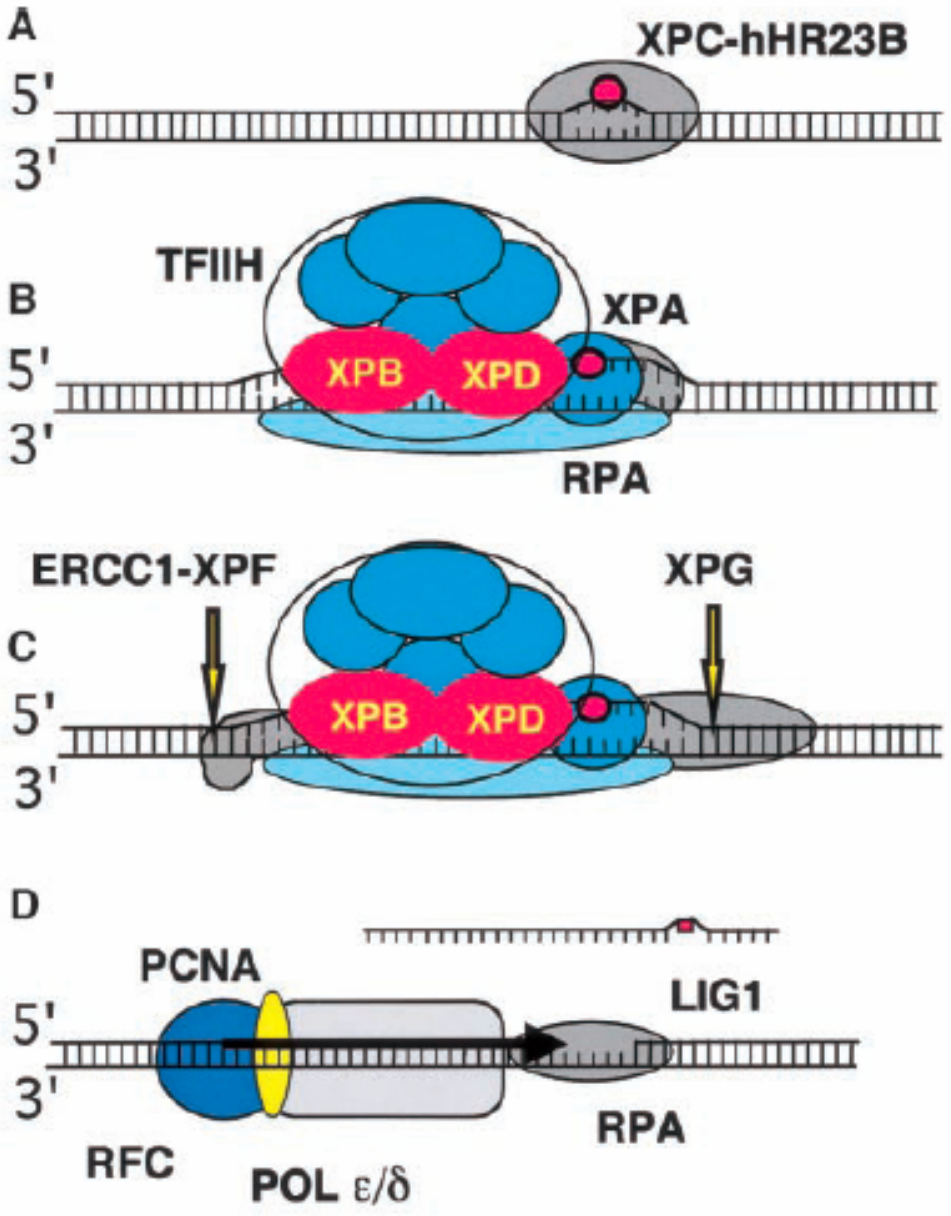
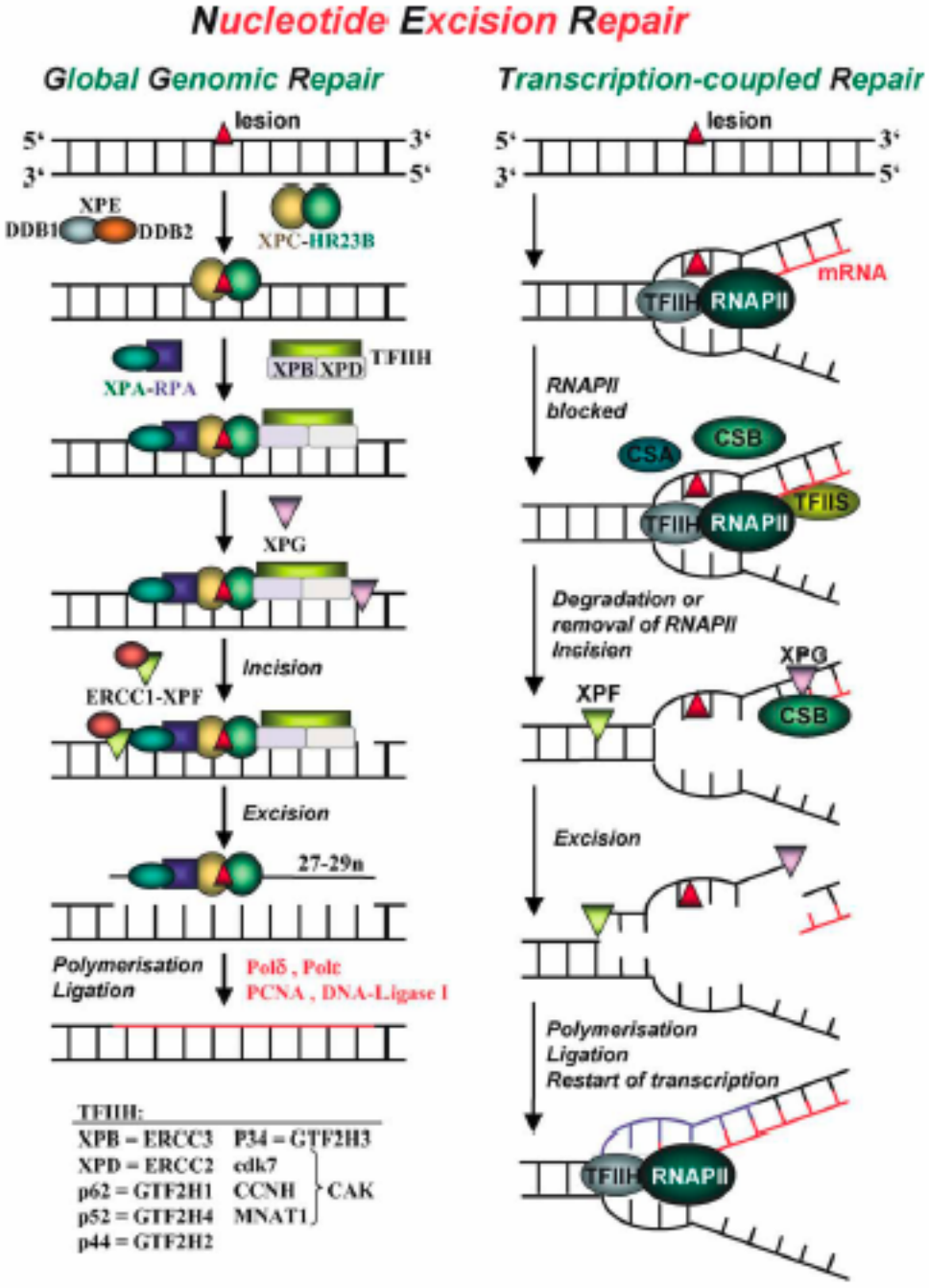


Fig. 3. Nucleotide excision repair in nontranscribed regions (the bulk of DNA). Initially, a distortion is recognized, probably by the XPC-hHR23B protein (**A**). An open bubble structure is then formed around a lesion in a reaction that uses the ATP-dependent helicase activities of XPB and XPD (two of the subunits of TFIIH) and also involves XPA and RPA (**B**). Formation of this open complex creates specific sites for cutting on the 3′ side by the XPG nuclease and then on the 5′ side by the ERCC1-XPF nuclease (**C**). After a 24- to 32-residue oligonucleotide is released, the gap is filled in by PCNA-dependent POL ε or δ and sealed by a DNA ligase, presumably LIG1 (**D**).



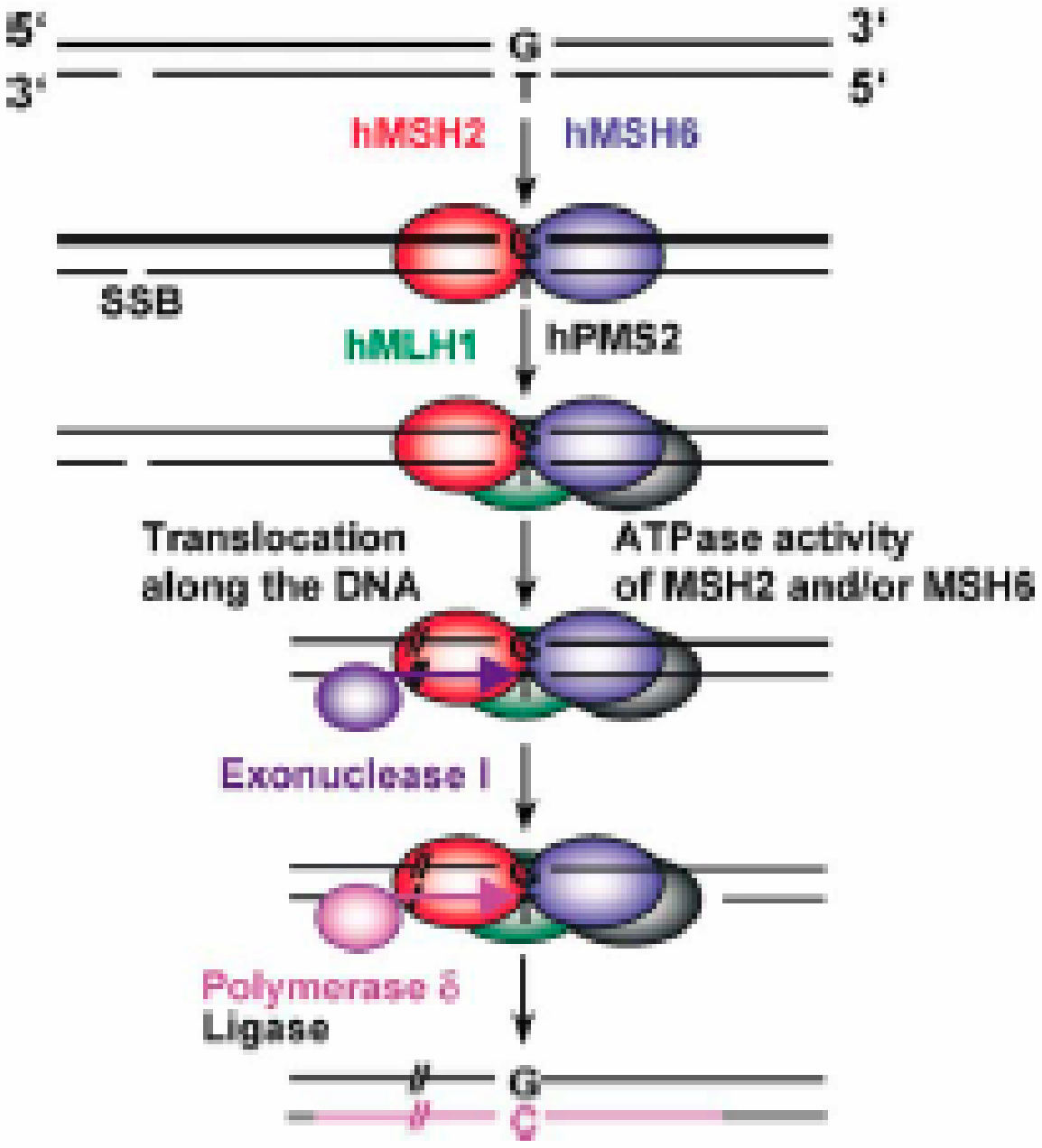
T. Lindahl and R.D. Wood, *Science* 286, 1897, 1999


Nucleotide Excision Repair
Global Genomic Repair
Transcription-coupled Repair
lesion
5'
3'
XPE
DDB1
DDB2
XPC-HR23B
XPA-RPA
XPB XPD
TFIIH
XPG
ERCC1-XPF
Incision
Excision
27-29n
Polymerisation
Ligation
Polδ , Polε
PCNA , DNA-Ligase I
TFIIH:
XPB = ERCC3
XPD = ERCC2
p62 = GTF2H1
p52 = GTF2H4
p44 = GTF2H2
P34 = GTF2H3
cdk7
CCNH
MNAT1
CAK
mRNA
TFIIH
RNAPII
RNAPII blocked
CSA
CSB
TFIIS
Degradation or removal of RNAPII
Incision
XPF
Excision
Polymerisation
Ligation
Restart of transcription

NER PATHWAY GENES

GENE	ALIASES	DESCRIPTION
CCNH		cyclin H
CDK7		cyclin-dependent kinase 7
CETN2	CALT CEN2	caltractin isoform 1 (Centrin 2)
CKN1	**CSA**	Cockayne syndrome 1 (classical)
DDB1		damage-specific DNA binding protein 1
DDB2		damage-specific DNA binding protein 2
ERCC1	UV20	excision repair cross-complementing group 1
ERCC2	**XPD**	excision repair cross-complementing group 2
ERCC3	**XPB** BTF2 GTF2H RAD25 TFIIH	excision repair cross-complementing group 3
ERCC4	**XPF** RAD1	excision repair cross-complementing group 4
ERCC5	**XPG** UVDR XPGC ERCM2	excision repair cross-complementing group 5
ERCC6	**CSB** CKN2 COFS RAD26	excision repair cross-complementing group 6
GTF2H1		general transcription factor IIH, polypeptide 1
GTF2H2		general transcription factor IIH, polypeptide 2
GTF2H3		general transcription factor IIH, polypeptide 3
GTF2H4		general transcription factor IIH, polypeptide 4
LIG1		ligase I, DNA, ATP-dependent
MNAT1		menage a trois 1 (CAK assembly factor)
RAD23A	HHR23A	RAD23 homolog A
RAD23B	HHR23B P58 HR23B	RAD23 homolog B
RPA1		replication protein A1
RPA2		replication protein A2
RPA3		replication protein A3
XAB2	HCNP	HCNP protein; XPA-binding protein 2
XPA	XP1 XPAC	XP complementation group A

Mismatch Repair



Mismatch repair associated tumors in mouse models

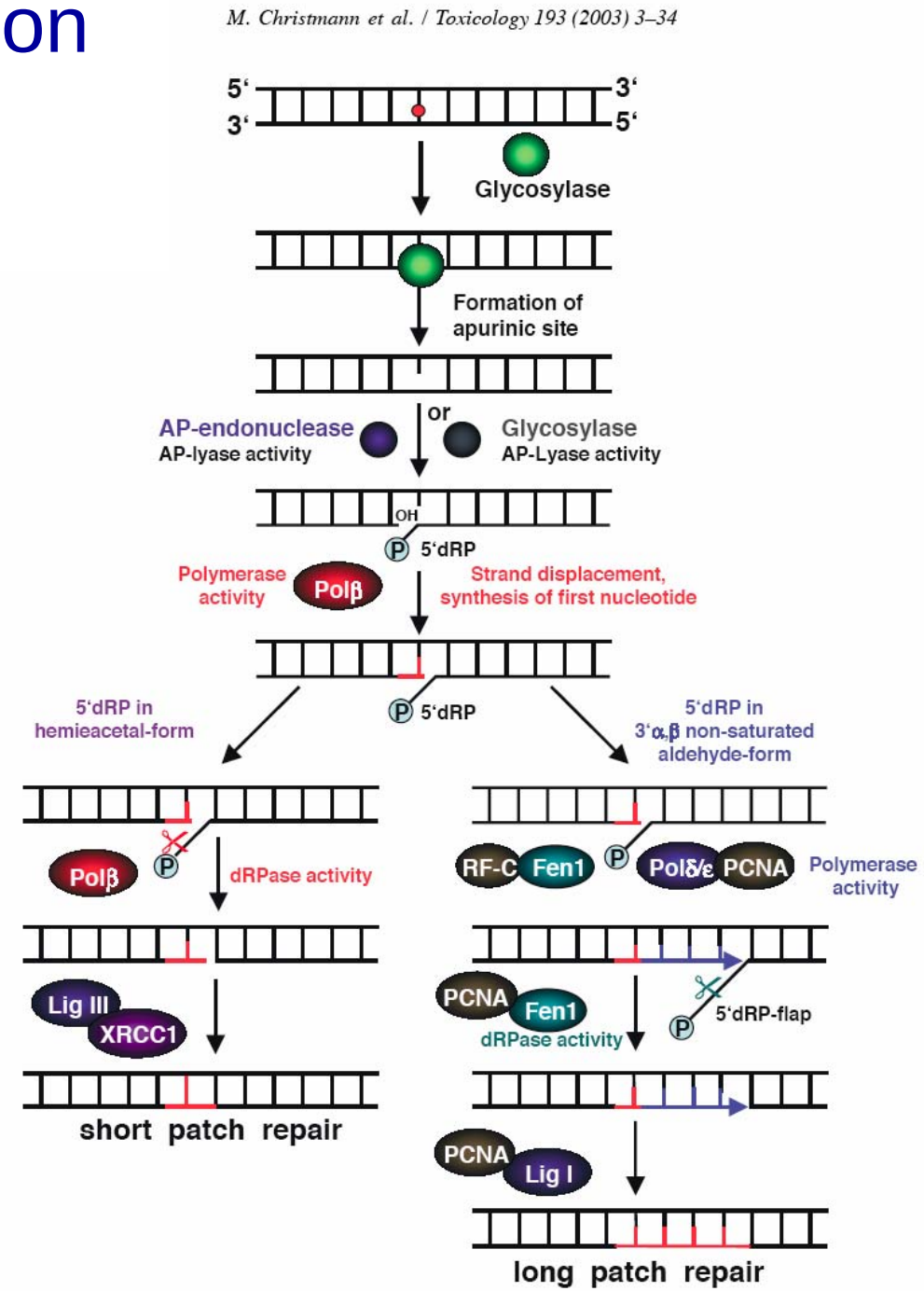
Table 3
Phenotypes of MMR gene knockout mice[a]

Mouse	Median survival	Tumor spectrum	Other abnormalities	References
Msh2$^{-/-}$	5–6 months	Lymphoma (T-cell) Gastrointestinal and skin cancers in animals that do not succumb to lymphoma	Hyperrecombination	[14,43,44]
Mlh1$^{-/-}$	6 months	Intestinal adenocarcinomas Lymphoma	Males and females are infertile (reduced levels of chiasmata)	[45,46]
Msh6$^{-/-}$	10 months	Lymphoma (B- and T-cell) Gastrointestinal tumors Uterine tumors	–	[47,48]
Msh3$^{-/-}$	Normal life span	No tumors until late age (gastrointestinal tumors)	–	[34,48]
Msh6$^{-/-}$; *Msh3*$^{-/-}$	6 months	Gastrointestinal tumors Non-Hodgkin lymphomas	–	[34,48]
Pms2$^{-/-}$	6–9 months	Lymphomas and sarcomas	Males are infertile (abnormal chromosome synapsis in meiosis)	[46,49]
Pms1$^{-/-}$	Normal life span	No increased tumor development	–	[46,49]

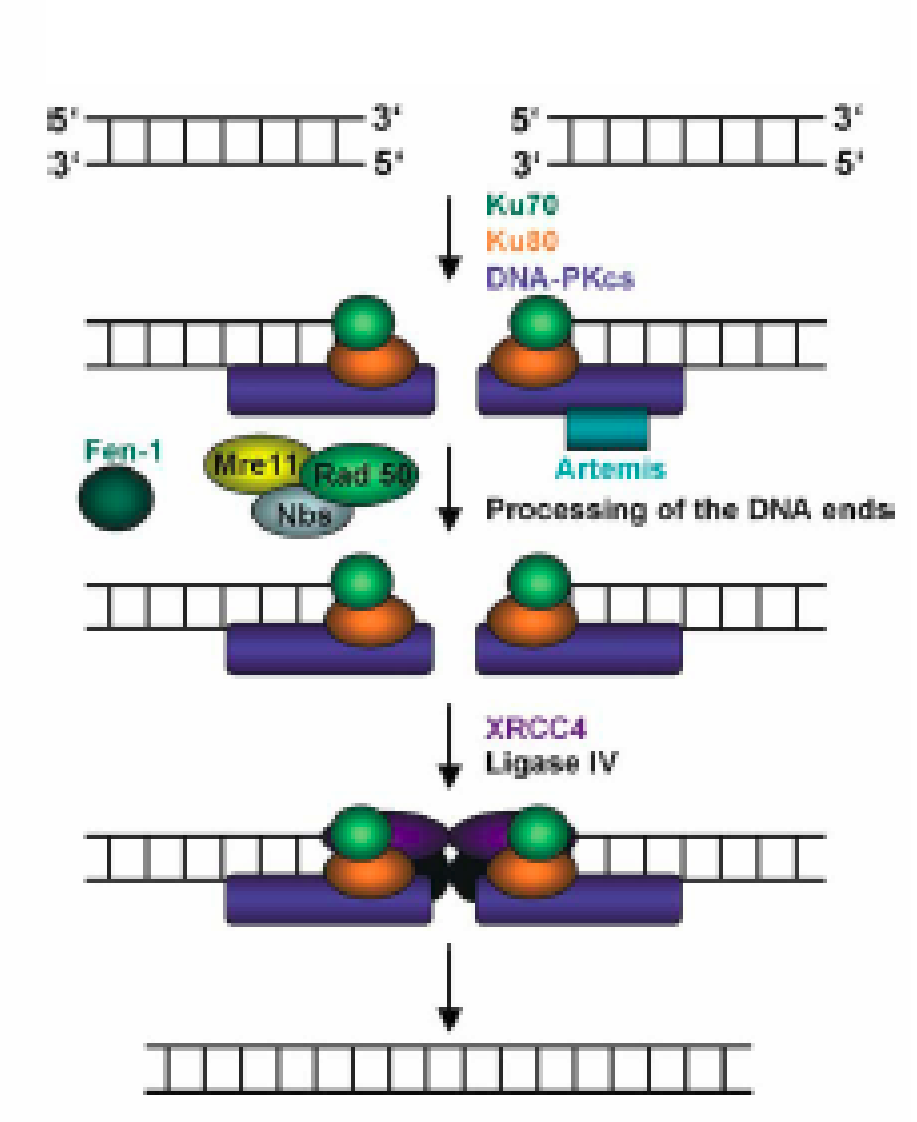
[a] Mice heterozygous for the mutations do not show increased tumor formation.

P. Peltomäki / Mutation Research 488 (2001) 77–85

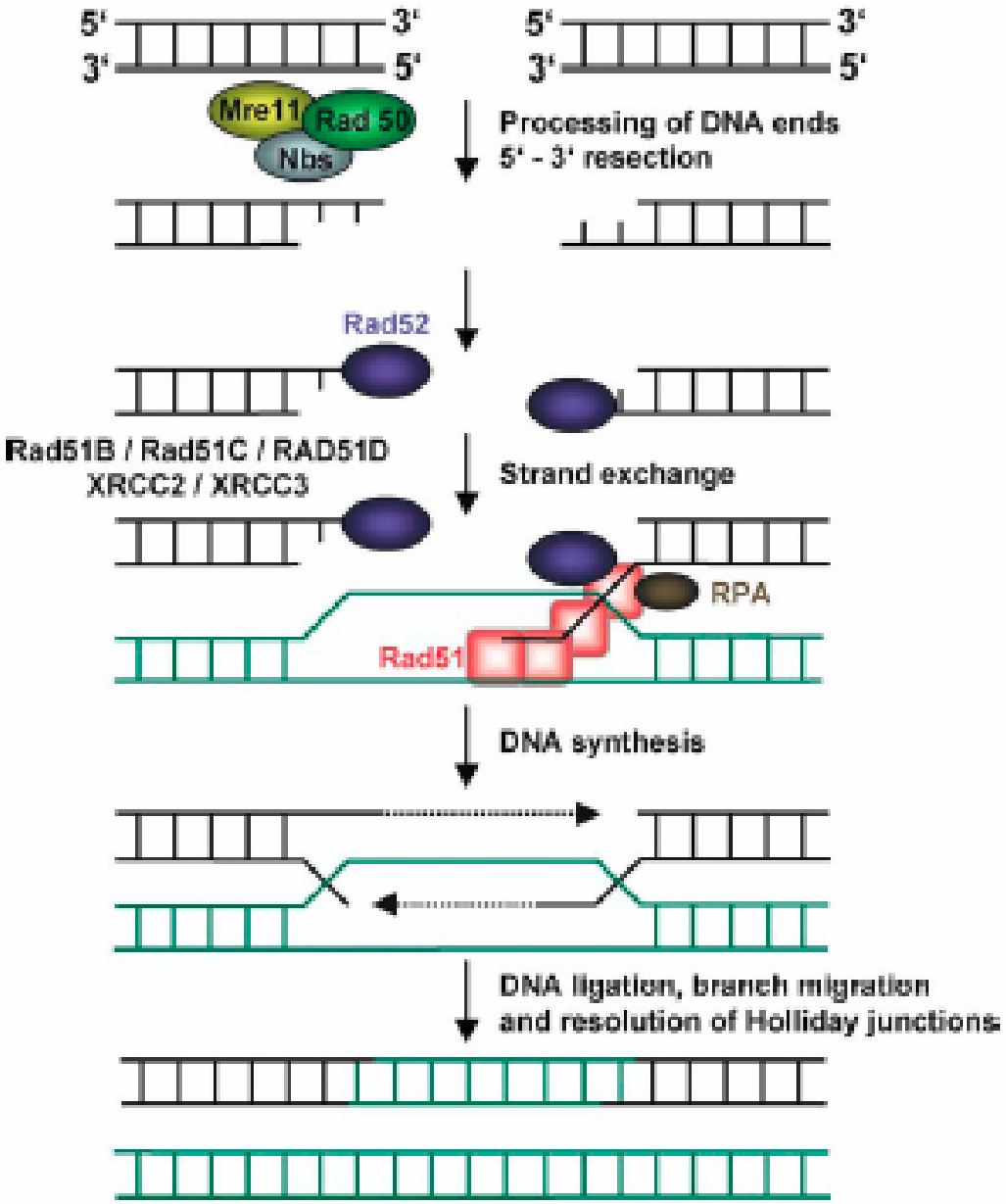
Base Excision Repair



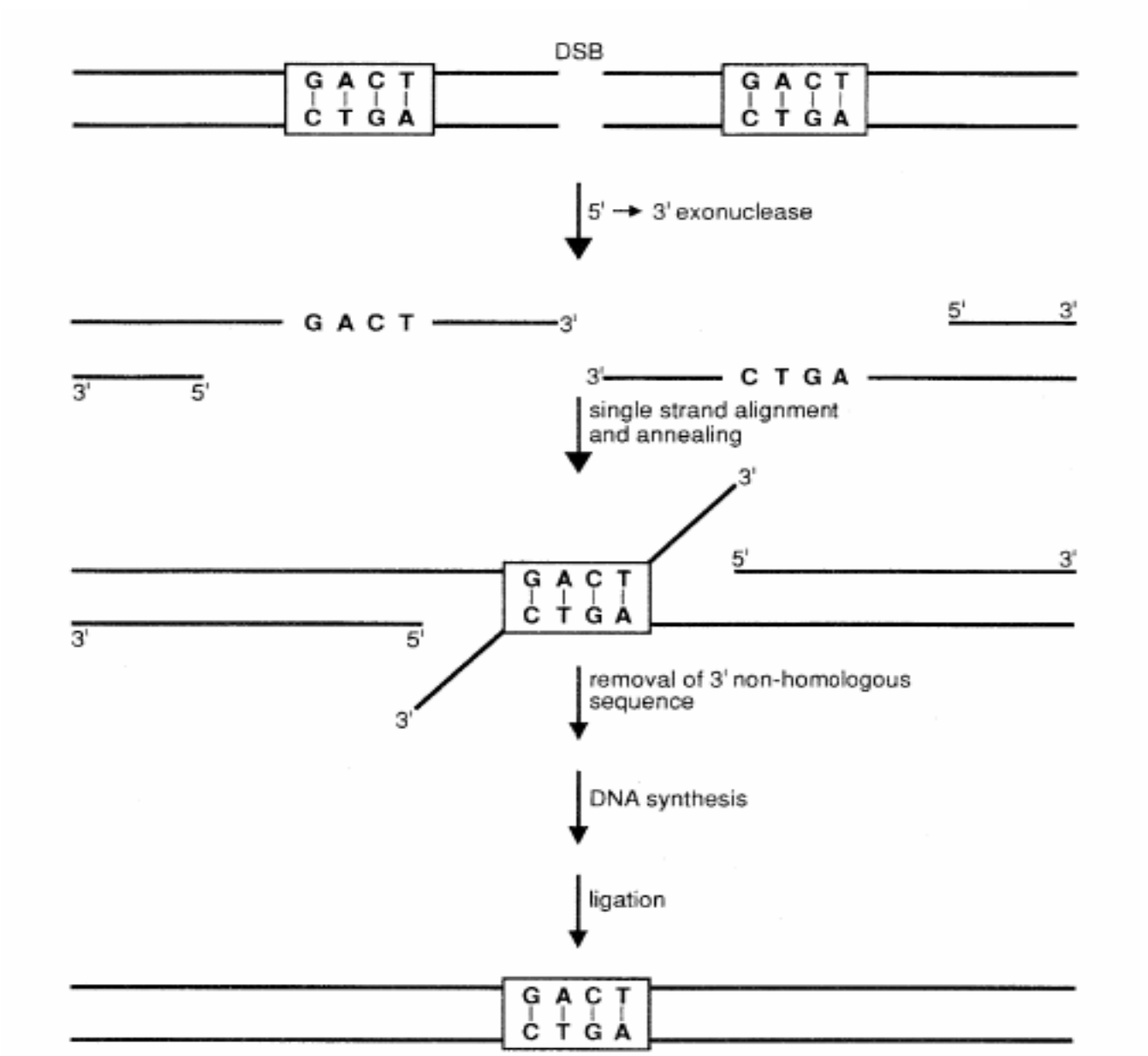
Non-Homologous End Joining (NHEJ)



Homologous Recombination



Illegitimate Recombination

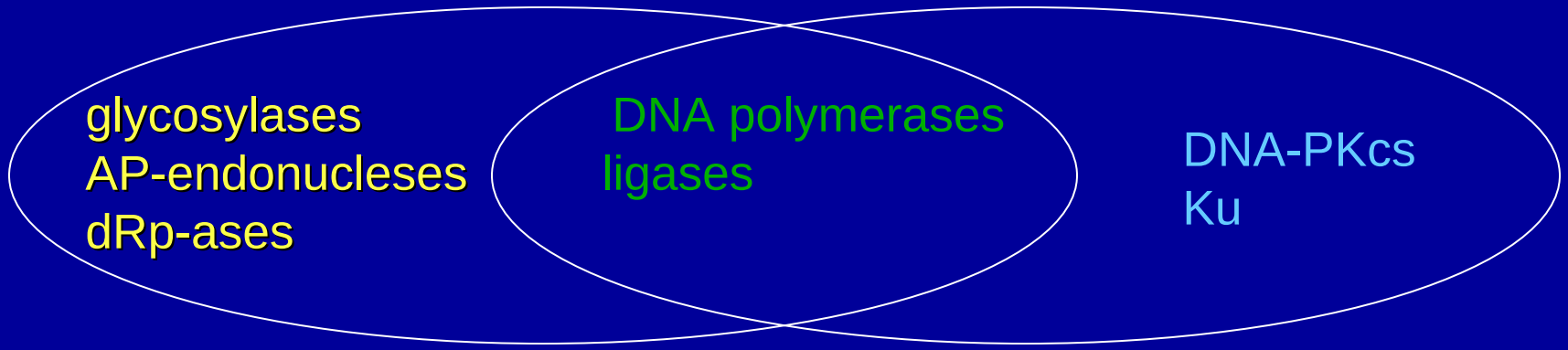


Mutation Research 384 (1997) 169–179

DNA REPAIR PATHWAYS

ERROR-FREE PATHWAYS
base excision repair
nucleotide excision repair
mismatch repair

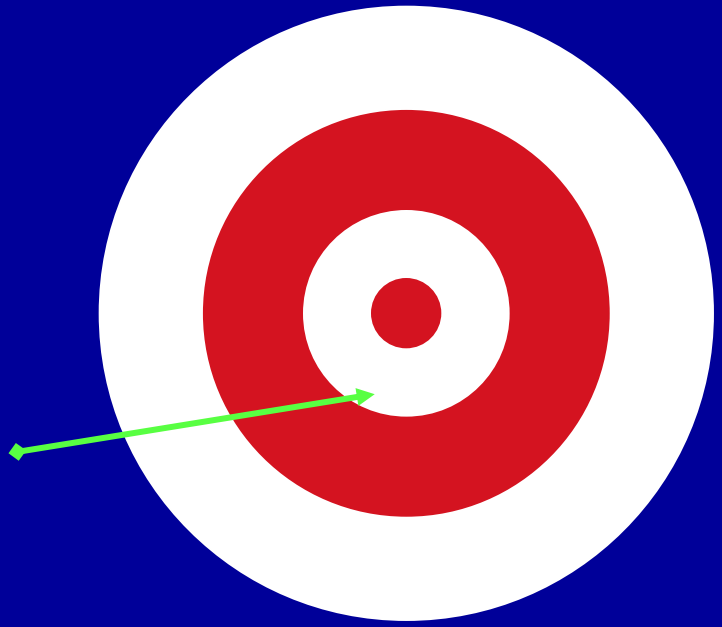
ERROR-PRONE PATHWAYS
NHEJ
illegitimate recombination



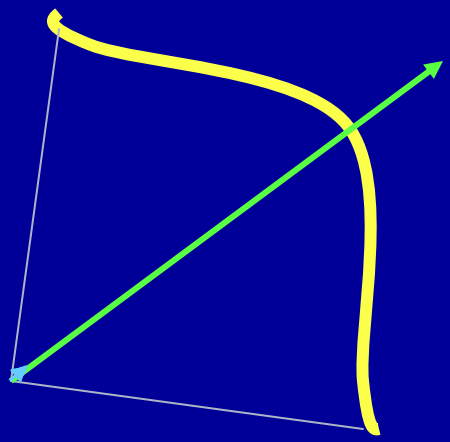
TARGET THEORY

NORMAL CELL

CANCER

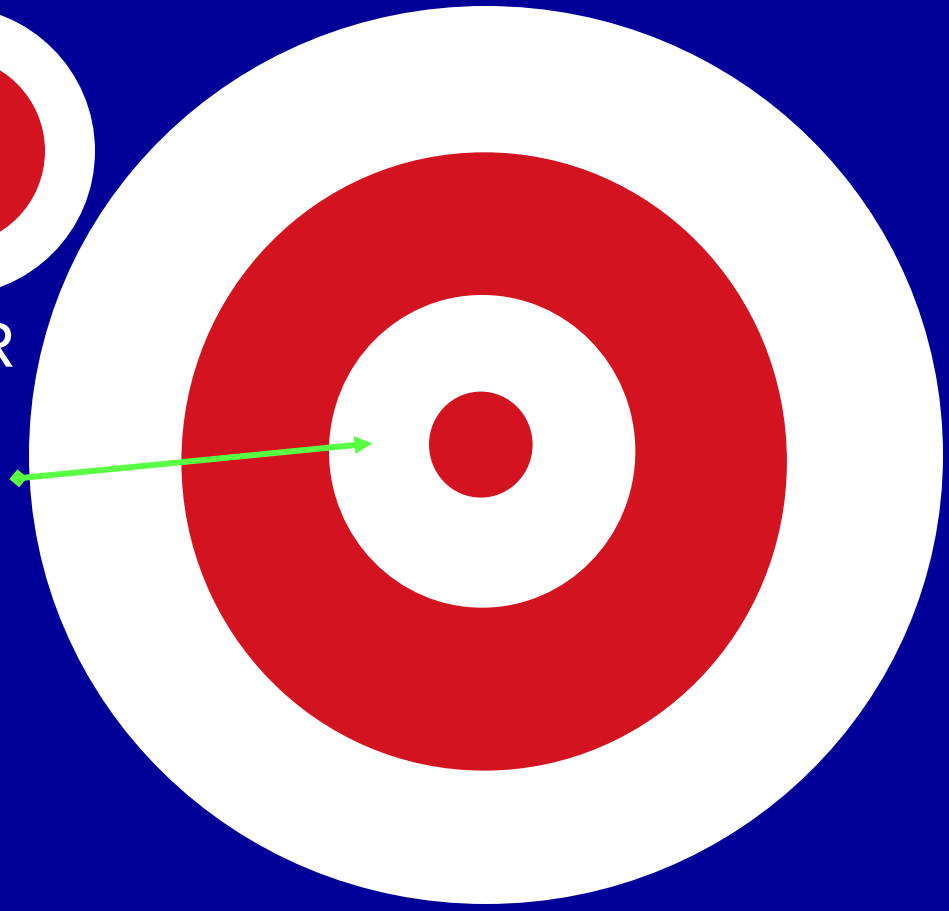


CELL DEATH

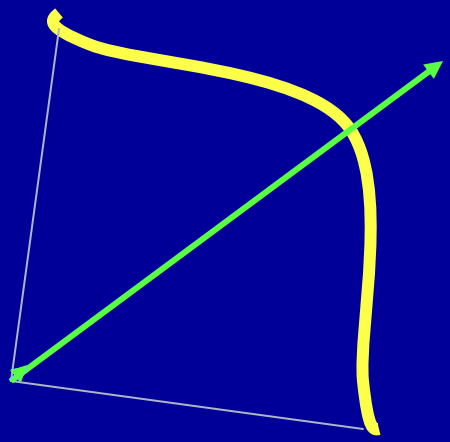


A-T CELL

CANCER

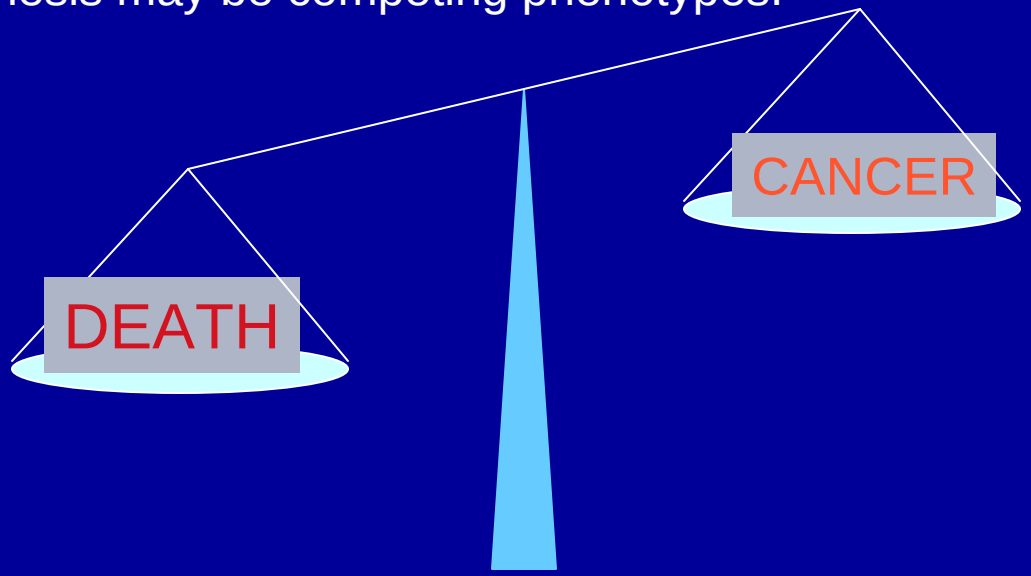


CELL DEATH



Are radiation sensitivity genes and radiation carcinogenesis genes the same?

- Several radiation sensitivity genes are known (e.g. ATM), but generally these genes confer sensitivity specifically to radiation-induced *killing*.
- Cellular radiosensitivity genes are potential radiation carcinogenesis genes, but association with increased cancer risk has not been established.
- The problem may be that sensitivity to radiation lethality and radiation carcinogenesis may be competing phenotypes.



OTHER TARGET QUESTIONS:

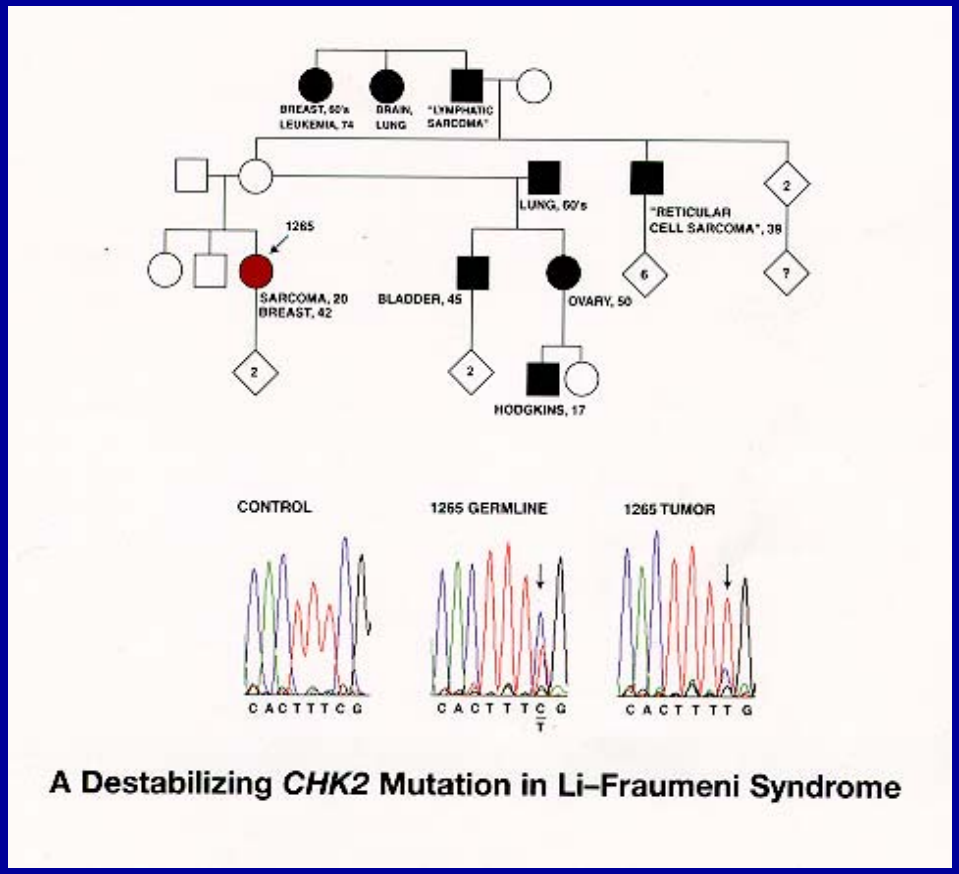
- If DNA repair deficiency predisposes to radiation induced cancer, then what are the mutated target genes that cause cellular transformation?

- What is the mechanism of transformation?

Li-Fraumeni Syndrome

- Caused by a germline mutation in p53 gene (TP53)
- Characterized by the occurrence of early onset:
  - sarcomas
  - breast cancer
  - brain tumours
  - leukemia
  - adrenocortical tumors

Mutations in Chk2 produce the Li-Fraumeni phenotype



Family pedigree with proband (1265, *arrow*) diagnosed with both breast cancer and sarcoma. A heterozygous germline mutation in *CHK2* is accompanied by loss of the wild type *CHK2* allele in breast cancer of the proband. The mutant R145W allele encodes and unstable protein. (S.B. Lee et al. Cancer Res. 61: 8062, 2001)

With all of these well-defined pathways and well-characterized genes that are known to be involved in resisting radiation damage to cells, it is tempting to speculate that different forms of the genes from these pathways might alter individual risk of radiation-induced cancer.

We know this to be true in the special case of individuals with genetic diseases that have functional mutations in both alleles. But is it true for heterozygotes of mutated genes, or normal individuals with polymorphic forms of these genes?

How do we go about answering this fundamental question?

CASE STUDY:

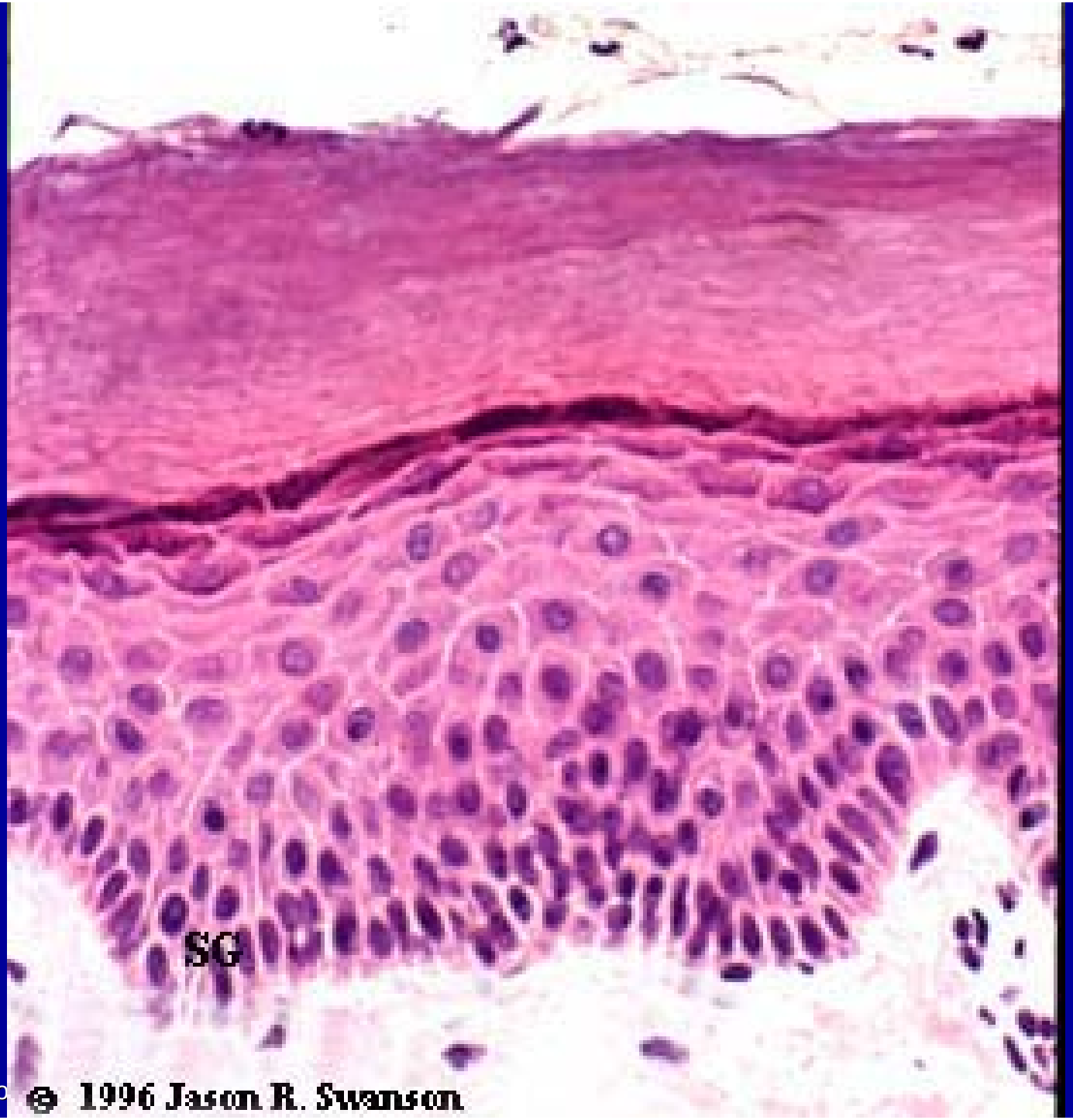
Finding Molecular Targets for Radiation-Induced Basal Cell Carcinoma

Gene-Environmental Interactions in Cancer

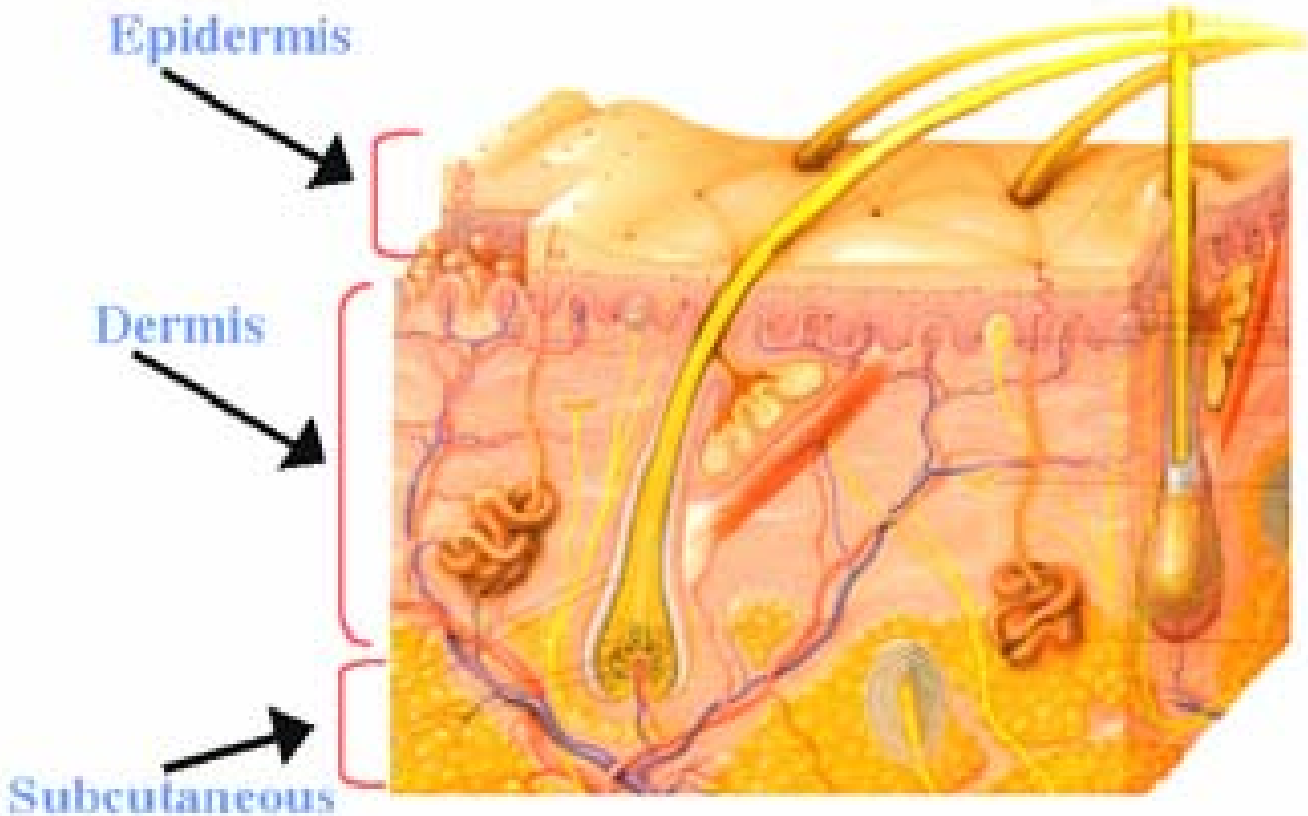
Which environmental carcinogens?

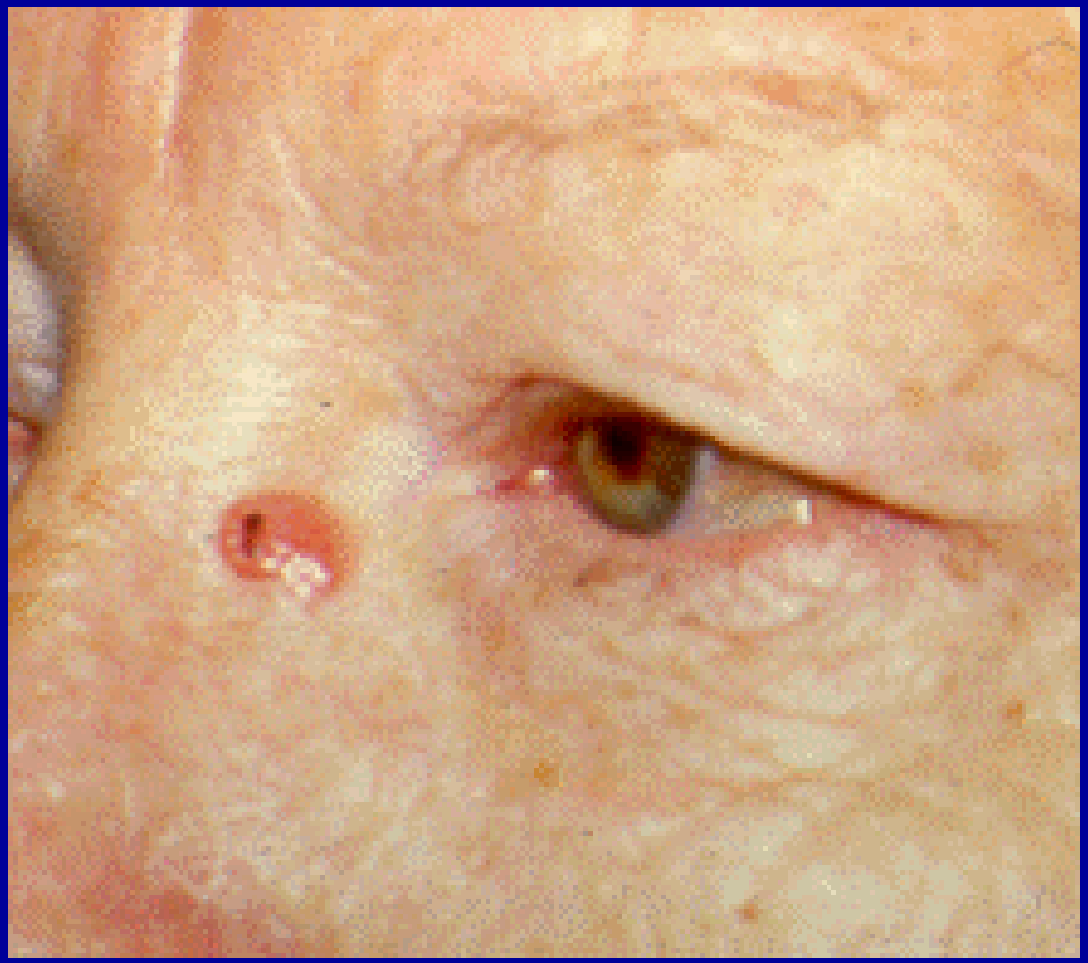
Which cancers?

Which genes?


SG
© 1996 Jason R. Swanson

Skin Anatomy





Problems for Epidemiology of BCC

BCC and SCC are not in most cancer registries because:

- Large numbers to follow
- Multiple lesions per individual
- Multiple lesions diagnosed simultaneously
- High cure rate

Nevertheless, it is estimated that the combined incidence of BCC and SCC is nearly equal to the incidence of all other cancers combined.

Environmental Causes of BCC

- UV radiation
- Ionizing radiation
- Arsenic

Bazex-Dupre-Christol Syndrome

- Skin disorder with high incidence of BCC on face and hands
- BCC onset from 15-25 years of age
- X-linked transmission
- Gene unknown

Rombo Syndrome

- Similar to Bazex, but with male to male transmission
- Gene unknown

Xeroderma Pigmentosum

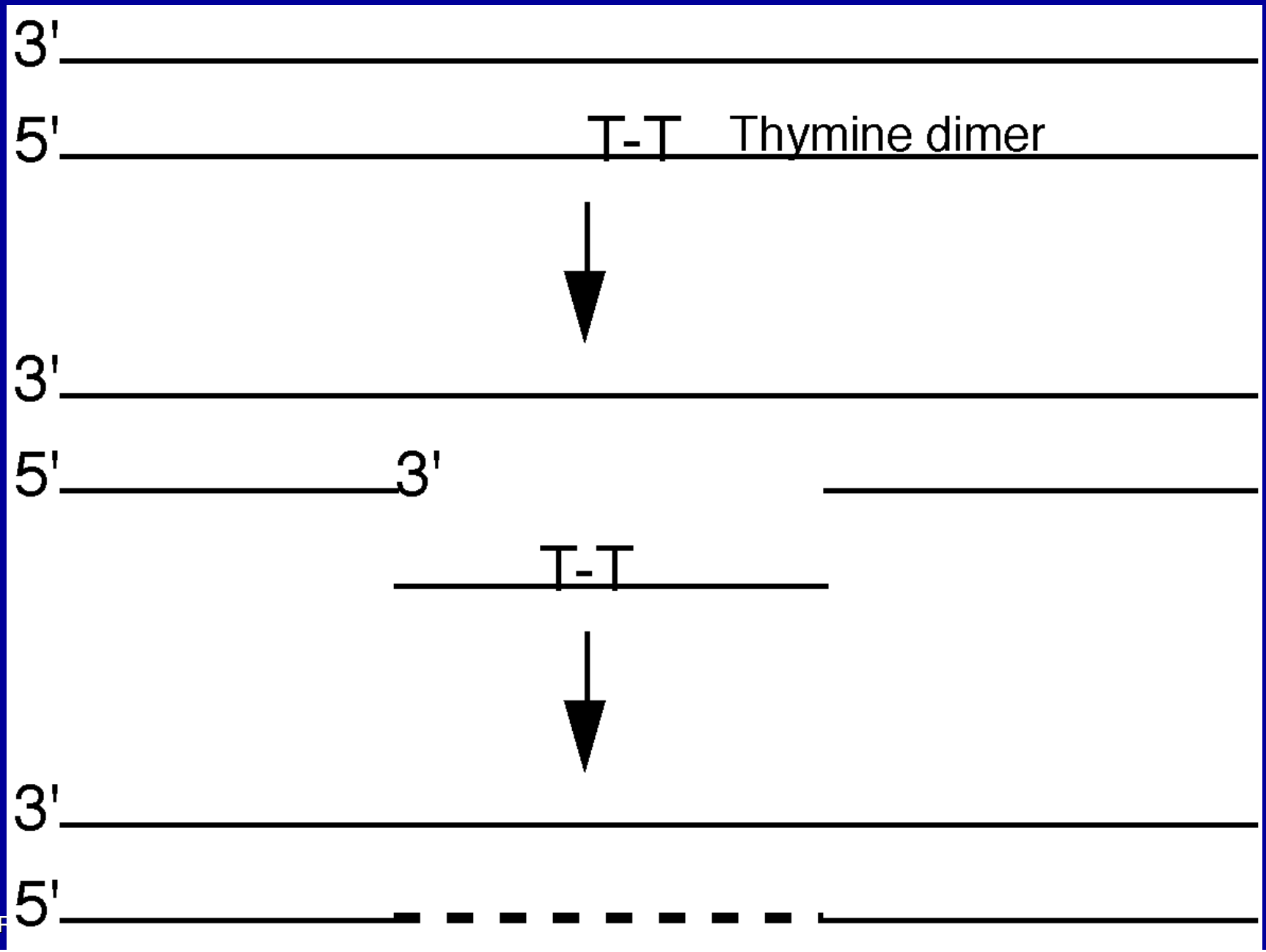
- High incidence in BCC, SCC, and melanoma
- Mean age of cancer onset is 8 years
- Defect in one of 7 nucleotide excision repair genes

Gorlin Syndrome

- Nevoid basal cell carcinoma syndrome (NBCC)
- 90% of patients have at least one BCC by age 40
- Germline mutation in the PTCH gene

UV DAMAGE TO DNA

Nucleotide Excision Repair (NER)



NER PATHWAY GENES

GENE	ALIASES	DESCRIPTION
CCNH		cyclin H
CDK7		cyclin-dependent kinase 7
CETN2	CALT CEN2	caltractin isoform 1 (Centrin 2)
CKN1	**CSA**	Cockayne syndrome 1 (classical)
DDB1		damage-specific DNA binding protein 1
DDB2		damage-specific DNA binding protein 2
ERCC1	UV20	excision repair cross-complementing group 1
ERCC2	**XPD**	excision repair cross-complementing group 2
ERCC3	**XPB** BTF2 GTF2H RAD25 TFIIH	excision repair cross-complementing group 3
ERCC4	**XPF** RAD1	excision repair cross-complementing group 4
ERCC5	**XPG** UVDR XPGC ERCM2	excision repair cross-complementing group 5
ERCC6	**CSB** CKN2 COFS RAD26	excision repair cross-complementing group 6
GTF2H1		general transcription factor IIH, polypeptide 1
GTF2H2		general transcription factor IIH, polypeptide 2
GTF2H3		general transcription factor IIH, polypeptide 3
GTF2H4		general transcription factor IIH, polypeptide 4
LIG1		ligase I, DNA, ATP-dependent
MNAT1		menage a trois 1 (CAK assembly factor)
RAD23A	HHR23A	RAD23 homolog A
RAD23B	HHR23B P58 HR23B	RAD23 homolog B
RPA1		replication protein A1
RPA2		replication protein A2
RPA3		replication protein A3
XAB2	HCNP	HCNP protein; XPA-binding protein 2
XPA	XP1 XPAC	XP complementation group A

QUESTIONS:

- If NER repair deficiency predisposes to radiation induced BCC, then what are the mutated target genes that cause cellular transformation?

- What is the mechanism of transformation?

Skin cancers have unique p53 mutations:

Table 1. Mutations in the p53 gene in invasive squamous cell carcinoma of the skin

Tumor	Age, yr	Sex	Site	Codon	Sequence	Base change	Amino acid change
NI 6	86	♀	Preauricular	7	tCt	C → G	Asp → His
NI 9	77	♀	Chest	56	tcttCa	C → A	Glu → stop
SI 2	82	♂	Preauricular	104/105	gcct	ΔC	Gly → Ala . . . stop
SI 20	82	♂	Temple	104/105	gcct	ΔC	Gly → Ala . . . stop
SI 16	69	♀	Scalp	151	cCccc	C → A	Pro → His
SI 15	69	♀	Hand	152	cccCc	C → T	Pro → Ser
NI 4	76	♂	Front scalp	179	acCa	C → A	His → Asn
NI 3	68	♂	Cheek	245	gcCg	C → A	Gly → Cys
NI 9	77	♀	Chest	245	gCCg	CC → TT	Gly → Asn
SI 13	80	♀	Nose	247–248	aCC*g	CC → TT	Asn-Arg → Asn-Trp
SCC 13	56	♀	Side of face	258	ttCc	C → T	Glu → Lys
NI 11	76	♂	Cheek	278	tCct	C → T	Pro → Ser
SI 1	85	♂	Face	285–286	tCCt	CC → TT	Glu-Glu → Glu-Lys
NI 5	89	♂	Forehead	286	tCct	C → T	Glu → Lys
NI 8	75	♂	Postauricular	317	cccCa	C → T	Gln → stop

The sequence is written 5′ → 3′ for the strand containing the pyrimidine. A wild-type allele was observed in all cases except SI 1, SI 15, and SCC 13. Sample NI 9 contained two point mutations. For SI 2, 13, 15, 16, and 20 and NI 4 and 11, an inherited mutation at the site could be excluded based on the presence of a normal sequence in a section of normal tissue or in a second tumor. For SI 13 and 16 and NI 3, 6, and 9, the mutant band was present at less than a 1:1 ratio to the wild-type band; these samples were also those that contained <70% neoplastic cells. SI, Sweden; NI, New York; uppercase letter of sequence, base mutated; ΔC, deletion of a C; C*, cytosine known to be methylated at this site.

DE Brash et al. *PNAS* 88:10124, 1991

Mutation spectrum matched UV mutagenesis and differs from mutations in internal tumors:

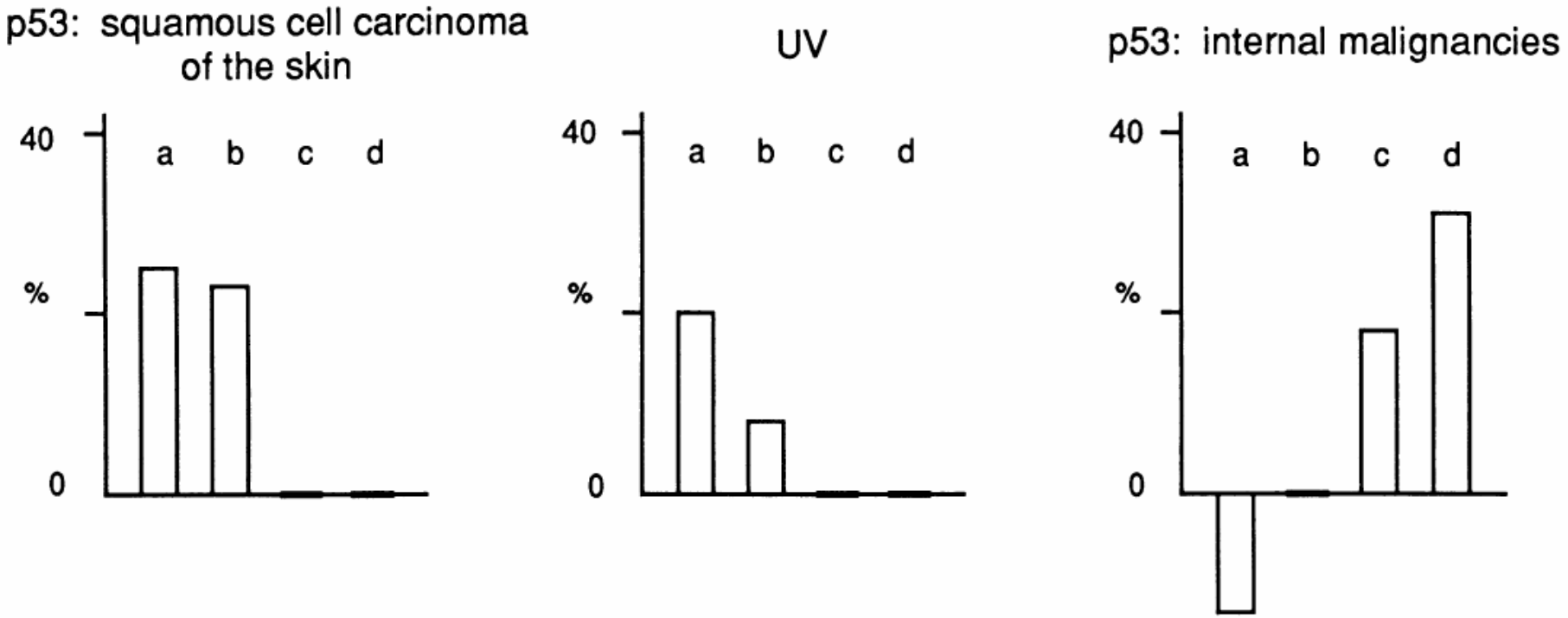


FIG. 2. Diagnostic types of base substitutions in p53 in 13 squamous cell carcinomas of the skin compared with p53 mutations reported in 97 internal malignancies (refs. 25, 27–31, and references therein) and compared with 66 UV mutations studied in endogenous genes in mammalian cells (10, 12). The comparisons are limited to endogenous genes because CG frequencies are underrepresented in mammalian DNA. The vertical axis indicates percentage of total skin squamous cell carcinoma p53 mutations, UV mutations, or internal malignancy p53 mutations that are of mutation type a, b, c, or d. Histograms: a, mutation located at a dipyrimidine site (in excess of the 75% expected randomly); b, CC → TT double-base substitution; c, C → T substitution not at a dipyrimidine site; d, C → T substitution at a CG dinucleotide.

DE Brash et al. *PNAS* 88:10124, 1991

For BCC, PTCH may be even a bigger target than p53

p53

PTCH

Table 1
Demographic data and genetic alterations of sporadic BCCs in Koreans

Case number	Age (Sex)	Location	Histologic type[a]	*p53*					*PTCH*			
				Exon(Codon)	Nucleotide Change[b]	Predictive Effect	DNA Strand[c]	LOH[d]	Exon (Codon)	Nucleotide Change[b]	Predictive Effect	DNA Strand[c]	LOH[d,e]
1	66(M)	Scalp	S.					–	21(1195), 21(1214)	aCa3572aTa, aCg3629aTg	Thr→Ile, Thr→Met		
2	60(M)	Face	S.	8(282)	CCg→cTg	Arg→Trp	NT	–	8(362), 9(439), 16(903)	aCc1073aTc, gTc1304gCc, 2694complex	Thr→Ile, Val→Ala, Frameshift	NT, NT	–
3	57(M)	Face	S.	8(281–282)	CC→TT[f]	Asp–Arg→Asp–Trp	NT	–					+[g]
4	64(F)	Face	S.	5(179)	cCa→cTa	His→Tyr	NT	–	6(252), 9(410)	Cc742Tc, aGt1217aAt	Pro→Ser, Ser→Asn	NT, T	+[g]
5	83(F)	Face	K.	5(152)	cCc→cTc	Pro→Ser	NT	–					+[g]
6	87(F)	Face	A.					–					+[g]
7	66(F)	Face	A.					–					+[g]
8	64(F)	Face	K.					–					–
9	69(F)	Face	S.					–					+[g]
10	57(M)	Face	S.					–	10(469), 13(691)	1394ins13, Cc2060Tc	Frameshift, Thr→Ile	NT	+
11	69(M)	Face	S.					–					–
12	67(F)	Face	S.					–	10(478)	gCa1421gTa	Ala→Val		–
13	86(F)	Face	S.					–					–
14	78(M)	Face	S.					–					–
15	63(F)	Face	S.	5(140)	aCc→aTc	Thr→Ile	NT	–	13(678)	Cc2021Tc	Thr→Ile	NT	–

[a] S., solid; K., keratotic; A., adenoid.
[b] The mutations are indicated in capitals on the coding strand, written 5′–3′, as described by Hahn et al.; amino acids are numbered as described by Johnson et al.; complex, insertion and deletion; ins, insertion.
[c] The column entitled DNA strand gives the location of Py–Py lesion on the transcribed DNA strand (T) or nontranscribed DNA strand (NT) of the *p53* and *PTCH* gene.
[d] '–' Retention of heterozygosity or not informative, '+' loss of heterozygosity.
[e] LOH of any of the five markers (D9S197, D9S196, D9S280, D9S287, D9S180), constitutes LOH.
[f] Tandem mutation was taken as one event.
[g] Tumor showed LOH at microsatellite marker D9S287, located closet to the *PTCH* gene.

M.-Y. Kim et al. / Journal of Dermatological Science 29 (2002) 1–9

J Dermatol Sci 29:1, 2002

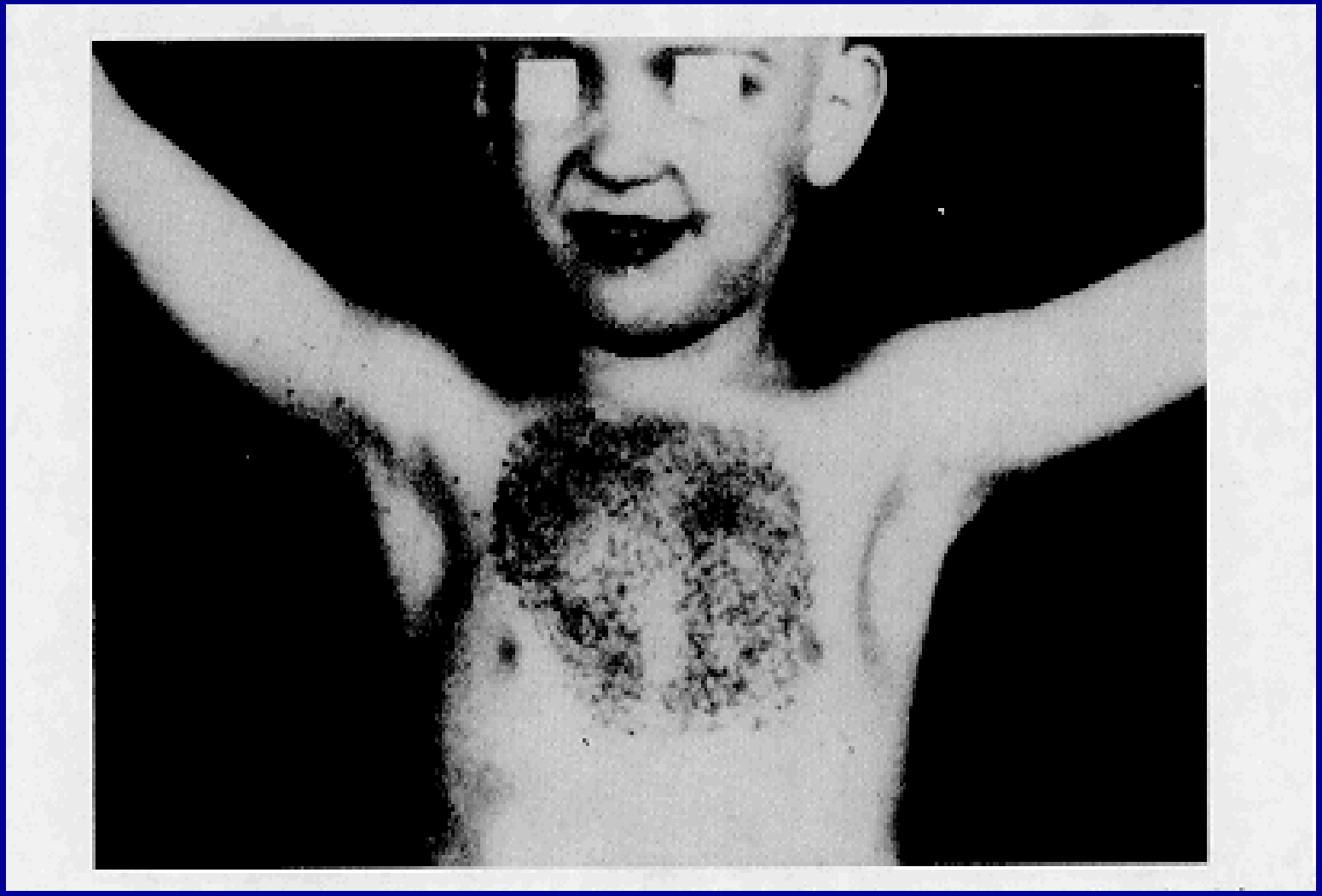
p53

PTCH

p53						*PTCH*			
Exon(Codon)	Nucleotide Change[b]	Predictive Effect	DNA Strand[c]	LOH[d]	Exon (Codon)	Nucleotide Change[b]	Predictive Effect	DNA Strand[c]	LOH[d,e]
				–	21(1195), 21(1214)	aCa3572aTa, aCg3629aTg	Thr → Ile, Thr → Met		
8(282)	CCg → cTg	Arg → Trp	NT	–	8(362), 9(439), 16(903)	aCc1073aTc, gTc1304gCc, 2694complex	Thr → Ile, Val → Ala, Frameshift	NT, NT	–
8(281–282)	CC → TT[f]	Asp–Arg → Asp –Trp	NT	–					+[g]
5(179)	cCa → cTa	His → Tyr	NT	–	6(252), 9(410)	Cc742Tc, aGt1217aAt	Pro → Ser, Ser → Asn	NT, T	+[g]
5(152)	cCc → cTc	Pro → Ser	NT	–					+[g]
				–					+[g]
				–					+[g]
				–					–
				–					+[g]
				–	10(469), 13(691)	1394ins13, Cc2060Tc	Frameshift, Thr → Ile	NT	+
				–					–
				–	10(478)	gCa1421gTa	Ala → Val		–
				–					–
				–					–
5(140)	aCc → aTc	Thr → Ile	NT	–	13(678)	Cc2021Tc	Thr → Ile	NT	–

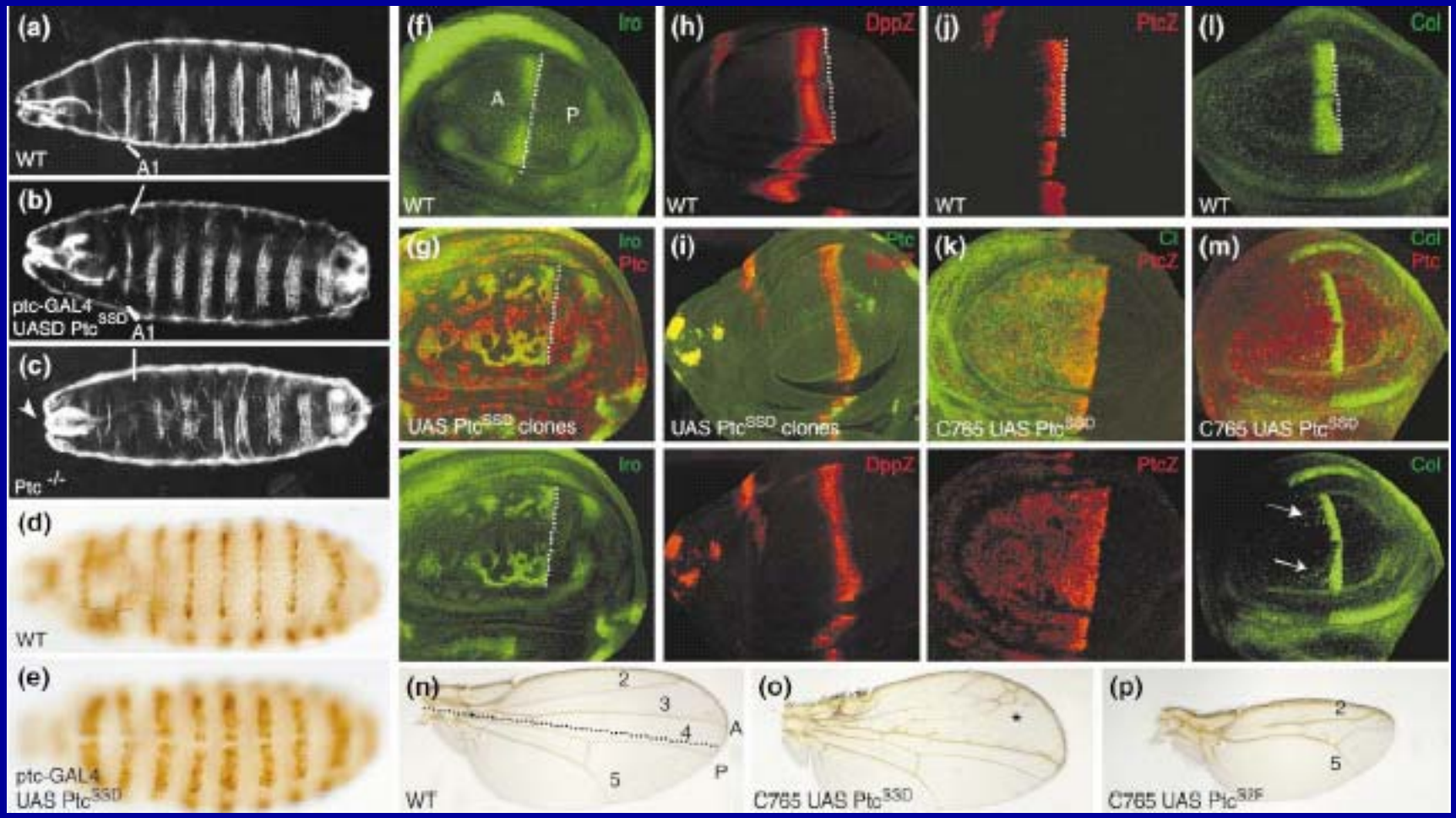
Gorlin Syndrome

- Nevoid basal cell carcinoma syndrome (NBCCS)
- Autosomal dominant disease with high penetrance
- Accounts for ~0.5% of all BCC cases (probably much higher percentage of early onset BCC)
- 20% of the patients also develop medulloblastoma and other cancers.
- Patients treated with radiotherapy develop large numbers of basal cell carcinomas in the radiation field.
- Gene responsible is the human homolog of the “Patched” gene (PTCH) in Drosophila, and may be a tumor suppressor in mammalian cells.
- Patched is a transmembrane signal transduction protein upstream of sonic hedgehog, Smoothened, and the proto-oncogene Gli1.
- PTCH heterozygote mice have enhanced sensitivity to radiation-induced teratogenesis.

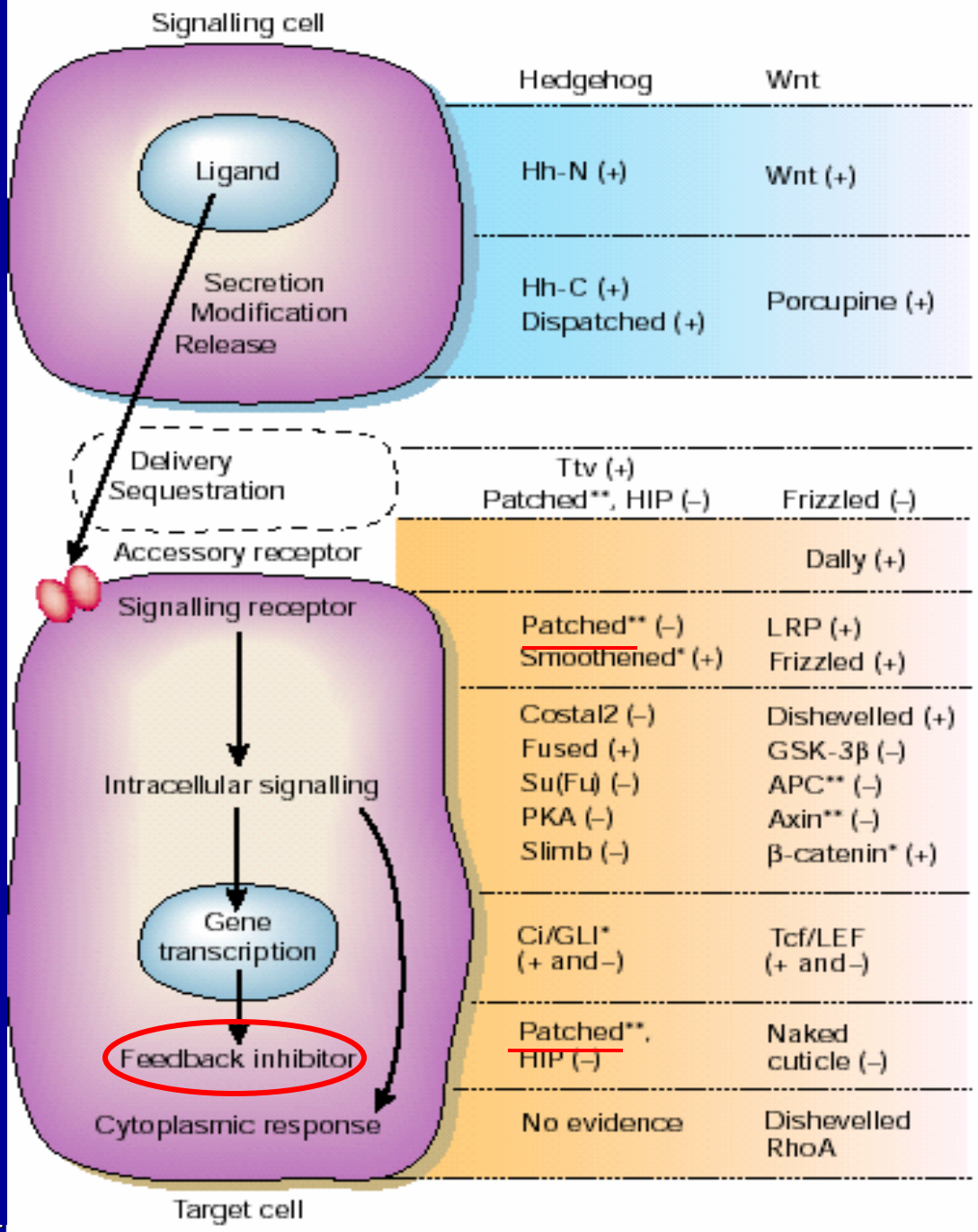


- Very early onset
- Many primary tumors

ICRP Publication 79, 1998



Verónica Martín, Graciela Carrillo, Carlos Torroja and Isabel Guerrero. The sterol-sensing domain of Patched protein seems to control Smoothened activity through Patched vesicular trafficking, *Curr. Biol*. 11: 601-607 (2001).



Hh and Wnt Pathways

Taipale J and Beachy PA

Nature 411:349-54 (2001)

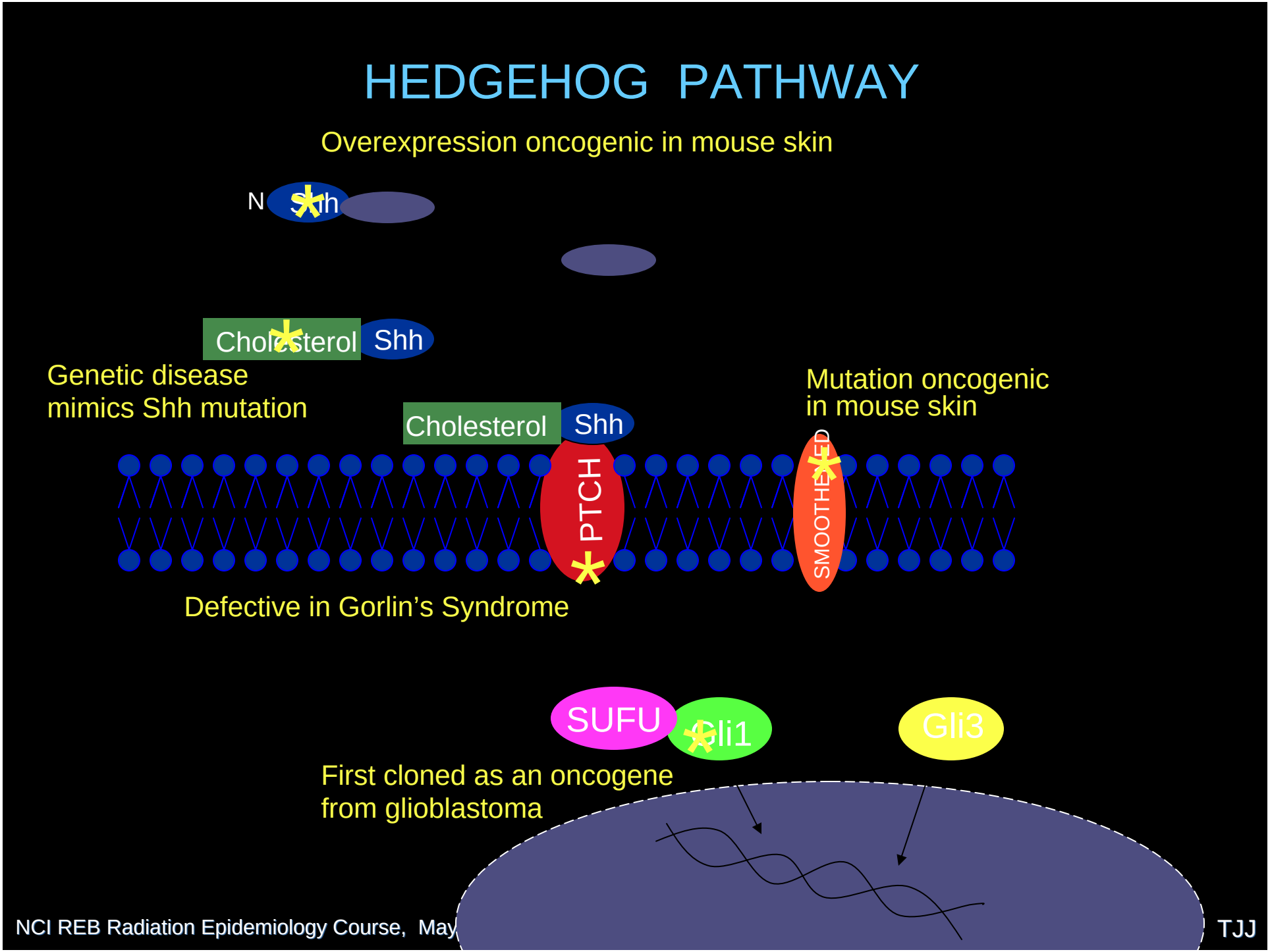
Table 1 Wnt and Hedgehog pathways in cancer

Pathway	Tumour type	Occurrence of mutations in sporadic cases	Familial syndrome, tumour incidence
Hedgehog	Basal cell carcinoma	~50%	BCNS, ~100%
	Medulloblastoma	~25%	BCNS, 1–3%
	Fibrosarcoma	ND	BCNS, low
	Rhabdomyosarcoma	ND	BCNS, very low
Wnt	Colorectal cancer	85%	FAP, very high in untreated cases
	Desmoid tumour	74%	FAP, 10%
	Hepatoblastoma	67%	FAP, <1%

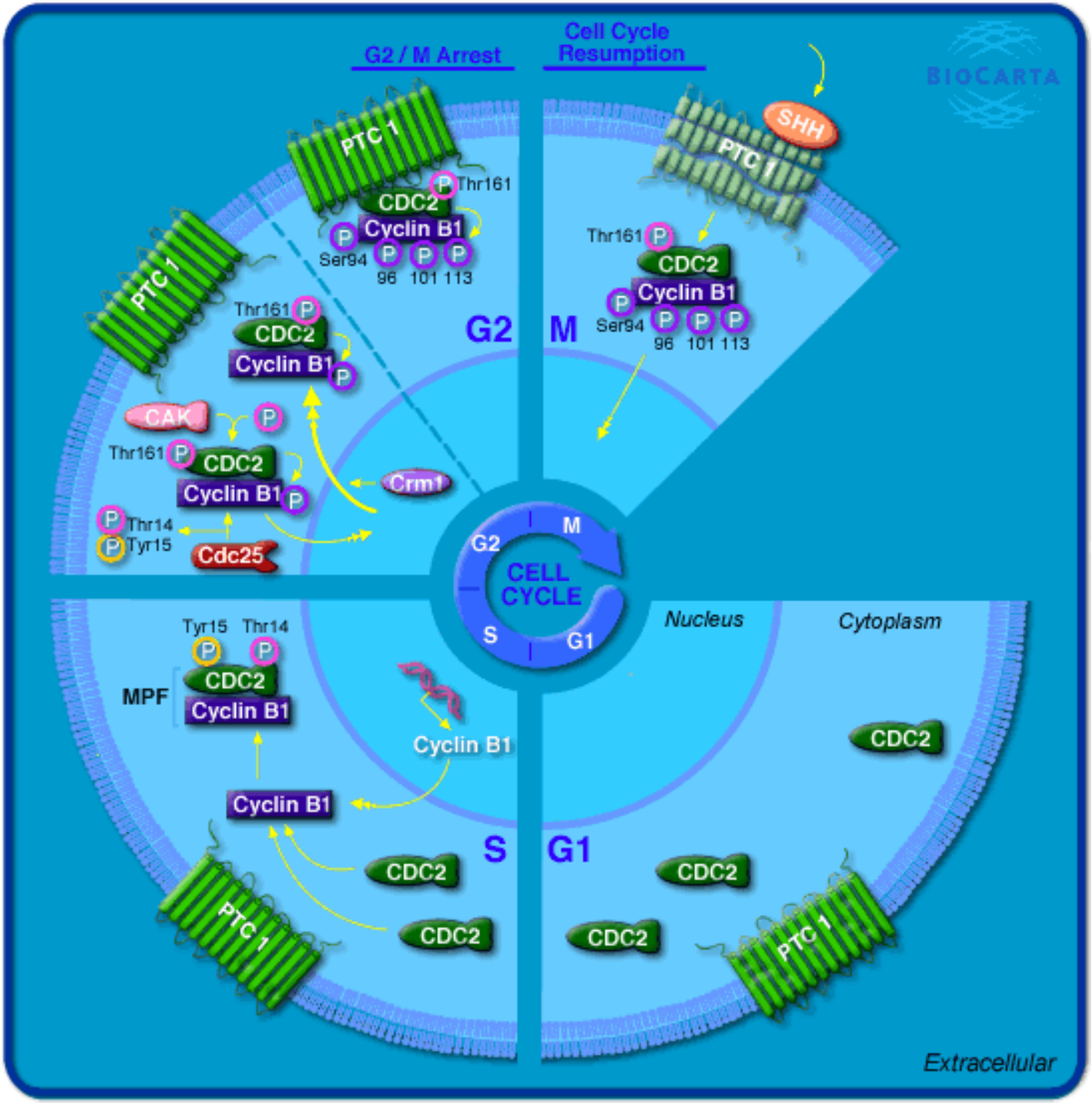
The list presented is not comprehensive and underestimates the prevalence of mutations, as neither all components of a given pathway nor transcriptional targets indicative of pathway activation have generally been examined. Included are cases where clear genetic evidence links increased cancer risk in humans or mice to a germline loss of function of a single copy of a tumour suppressor (*PTCH* in Hh, *APC* in Wnt). ND, no data; BCNS, basal cell nevus syndrome; FAP, familial adenomatous polyposis. (Source: OMIM (http://www.ncbi.nlm.nih.gov/omim/) and refs 2, 32, 33, 35, 47, 68–70.)

Taipale J and Beachy PA *Nature* 411:349-54 (2001)

HEDGEHOG PATHWAY



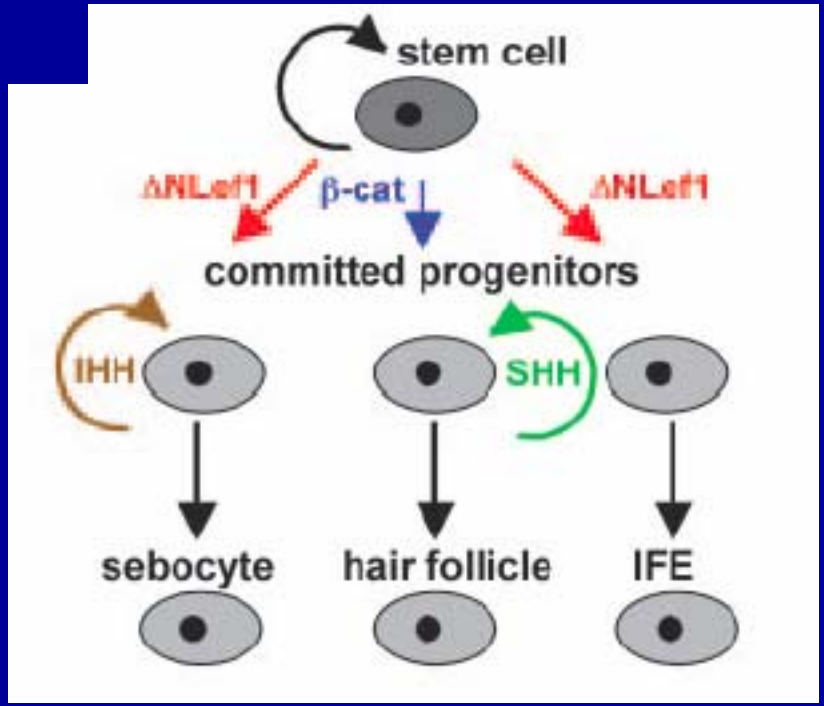
PTCH may play a role in cell cycle regulation



EMBO J. 20:2214, 2001

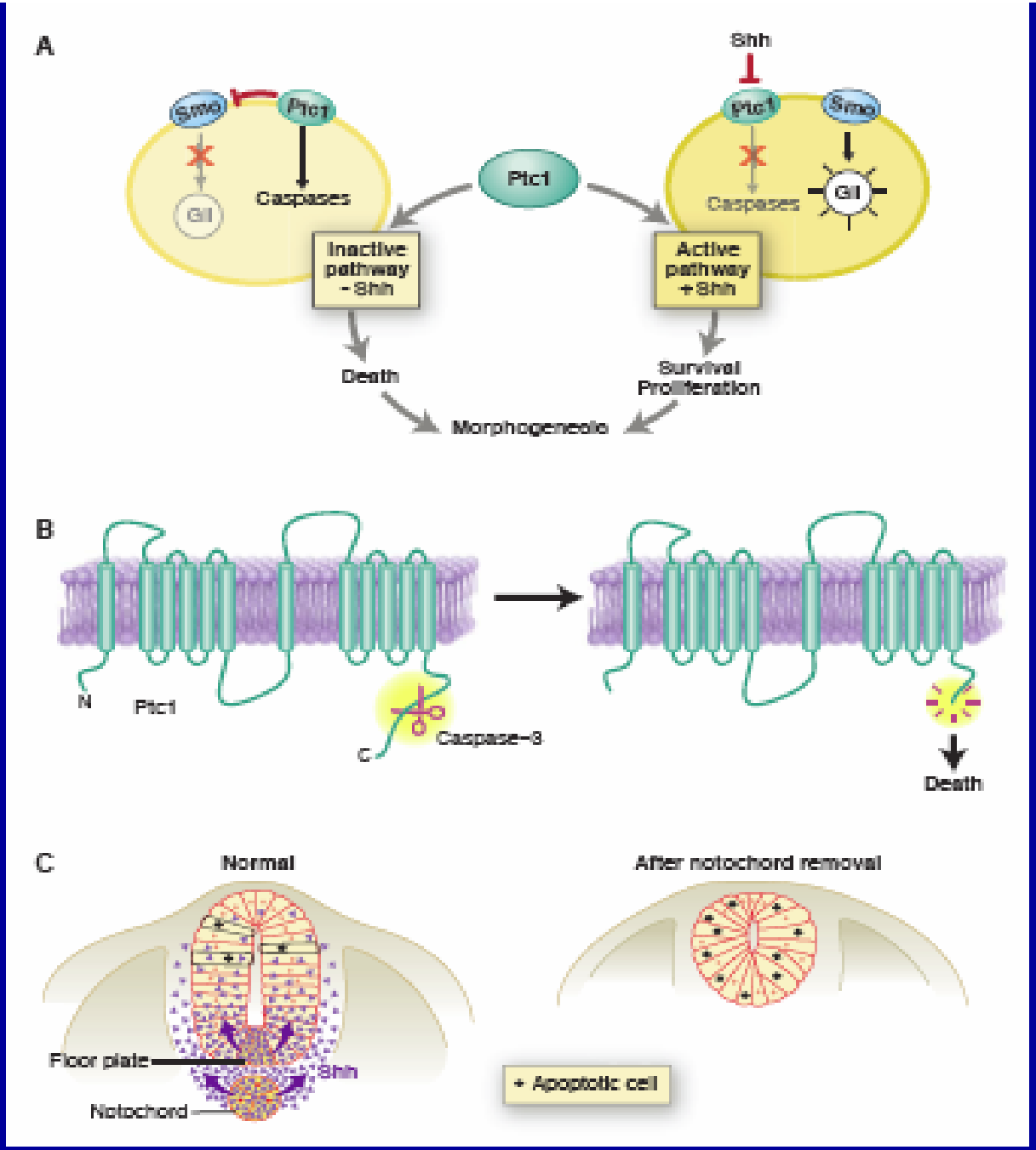
F.M. Watt's Model for Skin Cell Differentiation

- **Beta-Catenin levels determine commitment to differentiation pathway.**
- **Sonic Hedgehog drives hair follicle lineage.**
- **BCC tumors are believed to derive from this lineage.**

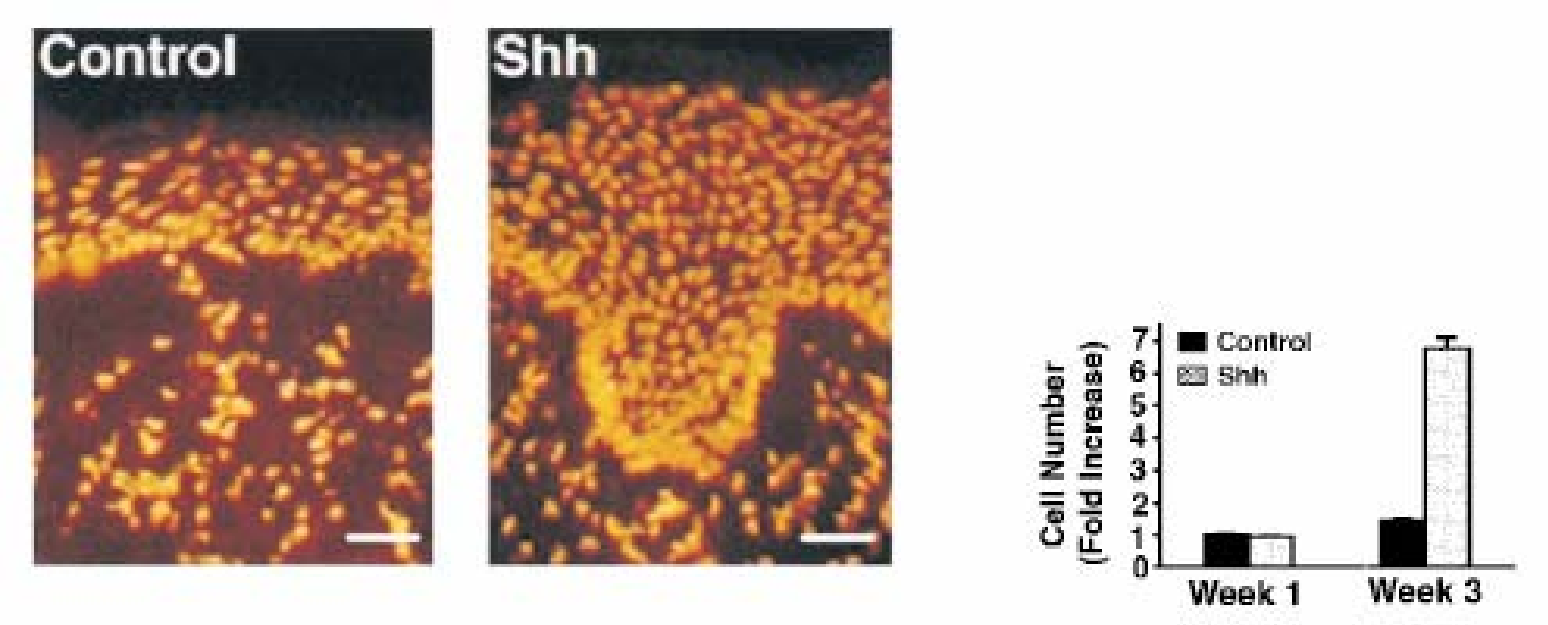


Tumor types: sebaceous tumors BCC SCC

adapted from Niemann et al. *PNAS* 100:11873, 2003



Guerrero et al., *Science* 301:774, 2003



Fan et al. *J. Cell Biol*, 147:71, 1999

Table 1 Skin tumor incidence size

	No treatment			Ultraviolet radiation			Cesium[a]		X-ray	
	Ptch$^{+/-}$ 3–8 months old	Ptch$^{+/-}$ > 9 months old	wild-type	Ptch$^{+/-}$ 3–8 months old	Ptch$^{+/-}$ > 9 months old	wild-type	Ptch$^{+/-}$	wild-type	Ptch$^{+/-}$	wild-type
Mice biopsied (*n*)	37	54	33	13	13	19	10	5	8	3
% with BCC	3%	40%	0%	100%	100%	0%	100%	0	100%	0
Average BCC number	1	0.5	0	7	9	0	12	0	17	0
Average BCC area (mm^2)	0.003	0.004	—	0.002	0.232	—	0.17	—	0.07	—
% with SCCs[b]	0%	0%	0%	0%	89% (8/9)	25%(4/16)	(%)	(%)	(%)	(%)

Aszterbaum et al. *Nature Med.* 5:1285, 1999

Dahmane et al. *Nature* 389: 876, 1997

Table 1 Gene expression in human skin tumours

Case	type	location	Gli1 ab	HNF-3β Ab	Gli1-as	Gli1-s	Gli3-as	Gli3-s	Shh-as	Shh-s	Ptc-as	H&E
1	BCC	auricular	+									+
2	BCC	nasolabial fold	+	–								+
3	BCC	temple	+	–								+
4	BCC	forehead	+									+
5	BCC	post-auricular			++							+
6	BCC	inner canthus	+	–	++							+
7	BCC	post-auricular	+	–	++	–						+
8	BCC	nasolabial fold			++							+
9	BCC	post-auricular			++							+
10	BCC	canthus			+/–	–	+/–					+
11	BCC	canthus			+	–	+					+
12	BCC	back			++	–	++	–				+
13	BCC	nasal rim			++	–		–				+
14	BCC	nasal rim			++	–	–	–				+
17	BCC	nasal rim			+/–	–	–	–				+
18	BCC	nasal rim			++	–	–	–				+
24	BCC	nose			+		–		+			+
26	BCC	periareolar			++		+		++	–		+
27	BCC	eyelid			+		–		–	–		+
28	BCC	nose			+		+/–	–	–			+
29	BCC	temple			+		+		+	–		+
30	BCC	midback			++		+		+	–		+
32	BCC	lat. forehead			+		–		–			+
33	BCC	eyebrow			+		+		+			+
34	BCC	nosetip			+		+		–			+
37	BCC	lat. upper cheek			+/–		+/–		+/–			+
39	BCC	upper lip			+		+		+/–			+
41	BCC	malar ocular			++		++		+/–			+
42	BCC	malar ocular			++		+		–			+
43	BCC	temple			++		+		–			+
44	BCC	nose			+		+		–			+
45	BCC	cheek			++		+		+			+
46	BCC	nostril			++		++		–			+
47	BCC	zygoma			++		+		–			+
48	BCC	upper eyelid			+		++		+			+
51	BCC	glabella			++		+		+			+
52	BCC	nose			+		++		–			+
53	BCC	nose			+		+/–		–			+
54	BCC	ear			++		+/–		+/–			+
57	BCC	clavicle			+		–		–			+
59	BCC	nose			++				+	–	++	+
61	BCC	nose			++				++	–	+	+
63	BCC	nose			+						++	+
64	BCC	forehead			+/–				–	–	++	+
66	BCC	temple			+				–	–	+	+
67	BCC	forehead			+				+	–	++	+
69	BCC	forehead			++				–	–	++	+
70	BCC	scalp			++				–	–	++	+
71	BCC	eye			+				–	–	+	+
72	BCC	nose			++				–	–	++	+
74	BCC	temple			+				–	–	+	+
15	SCC	upper back			–	–	–	–				+
23	SCC	preauricular			–		–		–	–		+
25	SCC	eyelid			–		–		–	–		+
31	SCC	elbow			–		–		–			+
35	SCC	cheek			–		–		–			+
40	SCC	cheek			–		–		–			+
49	SCC	cheek			–		–		–	–		+
55	SCC	hand			–		+/–		–	–		+
56	SCC	neck			–		–		–	–		+
58	SCC	bridge nose			–		–		–	–		+

The case number, type of tumour (BCC or SCC *in situ*) and location of the tumour is given on the left. The presence (+) or absence (–) of gene expression is indicated, with strong expression indicated by ++. A section of each excision was also stained with haematoxylin and eosin (H&E) for histological examination and confirmation of the presence of tumour. Case no. 10 was ambiguous and was counted as negative for *Gli1* expression. Abbreviations: as, antisense RNA probe; s, sense RNA probe; Ab, antibody; lat., lateral.

Shh, PTCH, and SUFU mutations produce developmental defects, suggesting gene dosage effects.

Table 1. Diseases associated with mutations in the Sonic hedgehog (Shh) pathway

Gene	Condition	Clinical characteristics	References
Sonic hedgehog	Holoprosencephaly	Incomplete separation of cerebral hemispheres, craniofacial anomalies (e.g. cyclopia)	24,25
	Tumors	Basal cell carcinoma	41
		Medulloblastoma	41
		Breast carcinoma	41
Patched	Nevoid basal cell carcinoma syndrome (Gorlin syndrome)	Basal cell carcinomas, dyskeratotic palmar/plantar pits, jaw cysts, skeletal anomalies	8,33,34
	Tumors	Sporadic basal cell carcinoma	35
		Medulloblastoma	36
		Trichoepithelioma	39
		Breast carcinoma	37
		Meningioma	37
		Esophageal carcinoma	38
Smoothened	Tumor	Basal cell carcinoma	43
GLI3	Greig cephalopolysyndactyly	Polydactyly, syndactyly, hypertelorism	20,46
	Pallister–Hall syndrome	Hypothalamic hamartoma, polydactyly, anal anomalies	47
	Postaxial polydactyly type A	Postaxial polydactyly	48

Holoprosencephaly

J.E. Ming et al. *Mol. Med. Today* 4:343, 1998

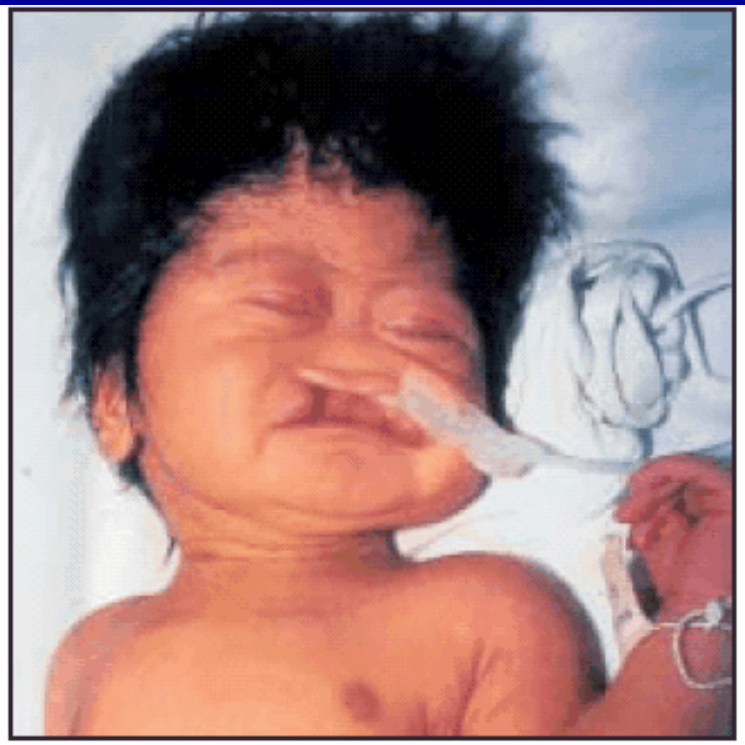


Figure 1: Showing midline cleft lip and palate, hypotelorism, flattened nose with a single nostril

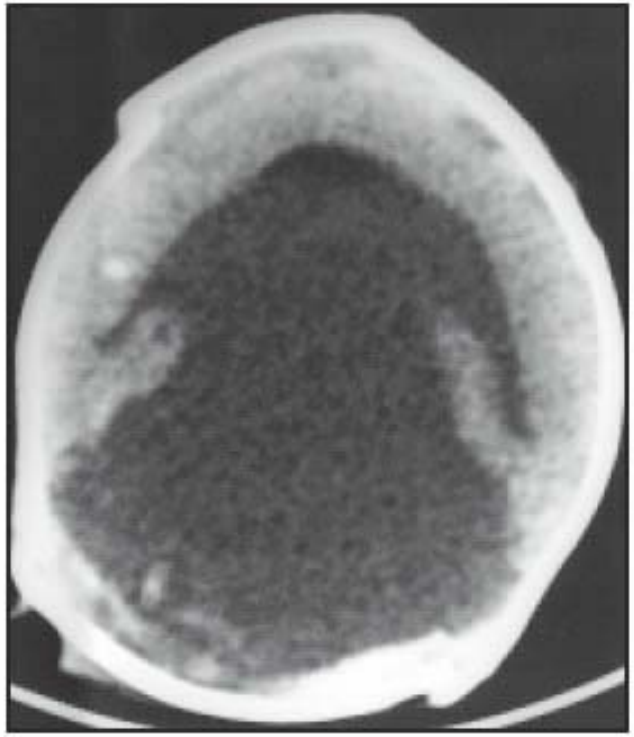


Figure 2: CT scan brain showing absence of midline structures, a single ventricle with thinned out cortex

Thomas et al., *J. Postgrad Med.* 49:173, 2003

PTCH

Nucleotide substitutions (missense / nonsense)

In association with

Accession Number	Codon	Nucleotide	Amino acid	Phenotype
CM014378	93	TACa-TAA	Tyr-Term	Nevoid basal cell carcinoma syndrome
CM971257	135	aCGA-TGA	Arg-Term	Nevoid basal cell carcinoma syndrome
CM004009	241	TTA-TGA	Leu-Term	Nevoid basal cell carcinoma syndrome
CM961209	365	cCAG-TAG	Gln-Term	Nevoid basal cell carcinoma syndrome
CM981663	376	TTC-TCC	Phe-Ser	Nevoid basal cell carcinoma syndrome
CM961210	387	TGG-TAG	Trp-Term	Nevoid basal cell carcinoma syndrome
CM020750	393	gGCA-ACA	Ala-Thr	Holoprosencephaly
CM971258	460	TGGg-TGA	Trp-Term	Nevoid basal cell carcinoma syndrome
CM962578	509	tGGT-CGT	Gly-Arg	Nevoid basal cell carcinoma syndrome
CM971259	513	gGAT-TAT	Asp-Tyr	Nevoid basal cell carcinoma syndrome
CM971260	529	tAAA-TAA	Lys-Term	Nevoid basal cell carcinoma syndrome
CM971261	663	cCAG-TAG	Gln-Term	Nevoid basal cell carcinoma syndrome
CM971262	688	gCAG-TAG	Gln-Term	Nevoid basal cell carcinoma syndrome
CM971263	694	aCAG-TAG	Gln-Term	Nevoid basal cell carcinoma syndrome
CM020751	728	ACG-ATG	Thr-Met	Holoprosencephaly
CM020752	827	cAGT-GGT	Ser-Gly	Holoprosencephaly
CM981664	926	TGGg-TGA	Trp-Term	Nevoid basal cell carcinoma syndrome
CM971264	945	cCGA-TGA	Arg-Term	Nevoid basal cell carcinoma syndrome
CM971265	1009	TACc-TAA	Tyr-Term	Nevoid basal cell carcinoma syndrome
CM020753	1052	ACG-ATG	Thr-Met	Holoprosencephaly
CM971266	1069	cGGC-CGC	Gly-Arg	Nevoid basal cell carcinoma syndrome
CM011474	1132	gTCC-CCC	Ser-Pro	Nevoid basal cell carcinoma syndrome
CM962579	1132	TCC-TAC	Ser-Tyr	Nevoid basal cell carcinoma syndrome
CM971267	1438	GAGg-GAT	Glu-Asp	Nevoid basal cell carcinoma syndrome

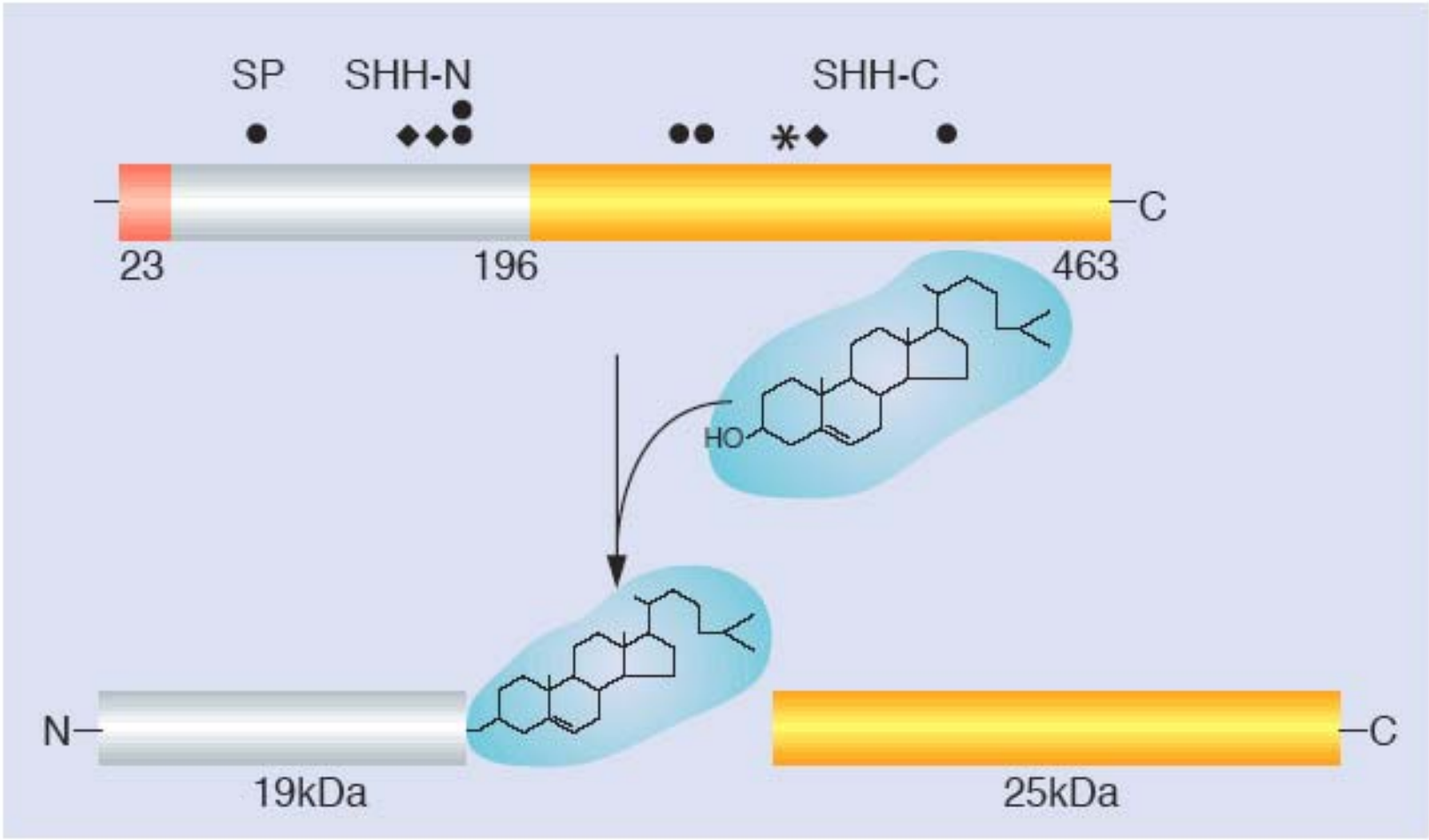


Figure 1. The Sonic hedgehog protein (SHH). Following translation, the signal peptide [SP, amino acids (aa) 1–23] is removed. Autocatalytic cleavage yields an N-terminal portion (SHH-N, aa 24–196) and a C-terminal portion (SHH-C, aa 197–463). A cholesterol transferase domain, located in SHH-C, directs the addition of cholesterol to the C-terminus of SHH-N. *SHH* mutations associated with holoprosencephaly (HPE) are distributed throughout the gene (filled diamond, nonsense mutation; filled circle, missense mutation; asterisk, 21 bp deletion).

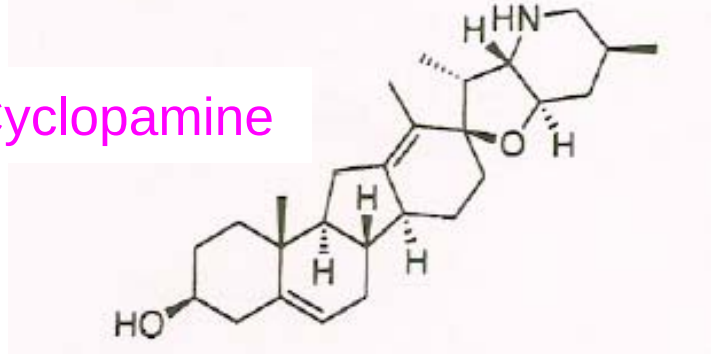
J.E. Ming et al. *Mol. Med. Today* 4:343, 1998

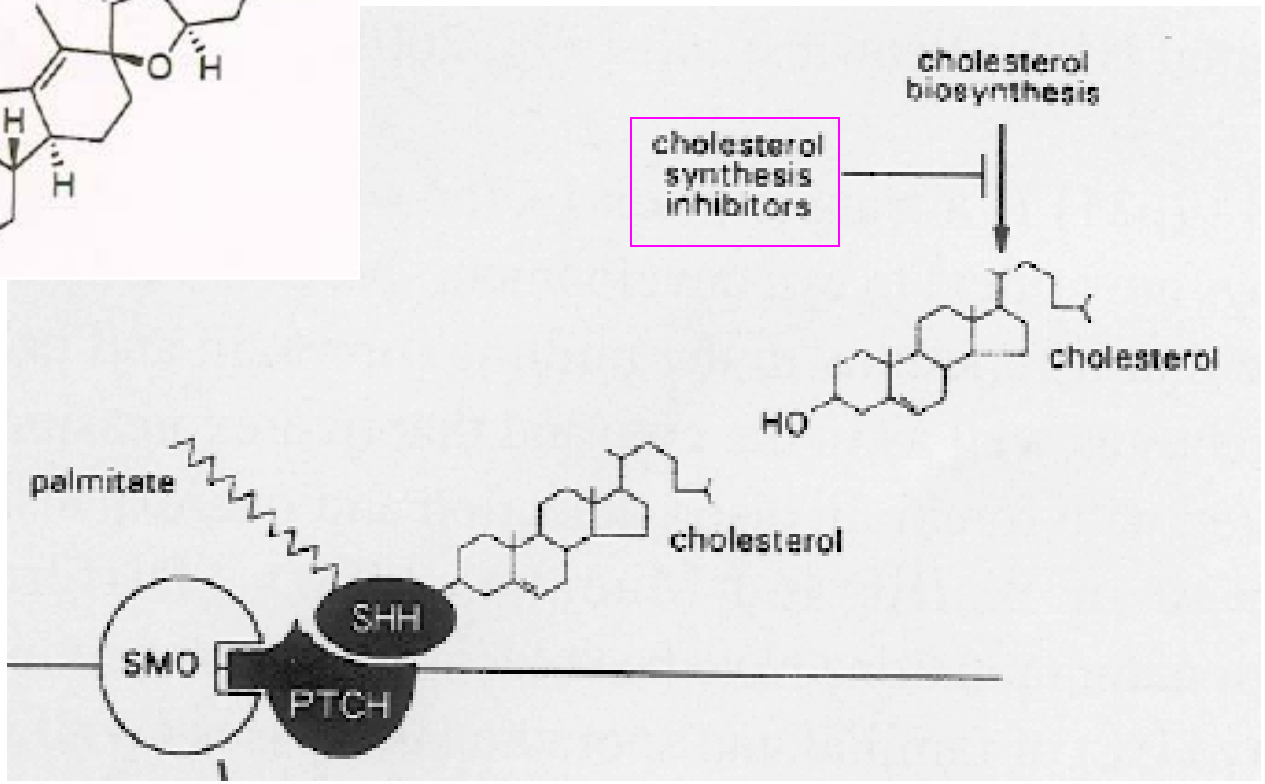
Cyclopamine

Veratrum californicum
(corn lily)

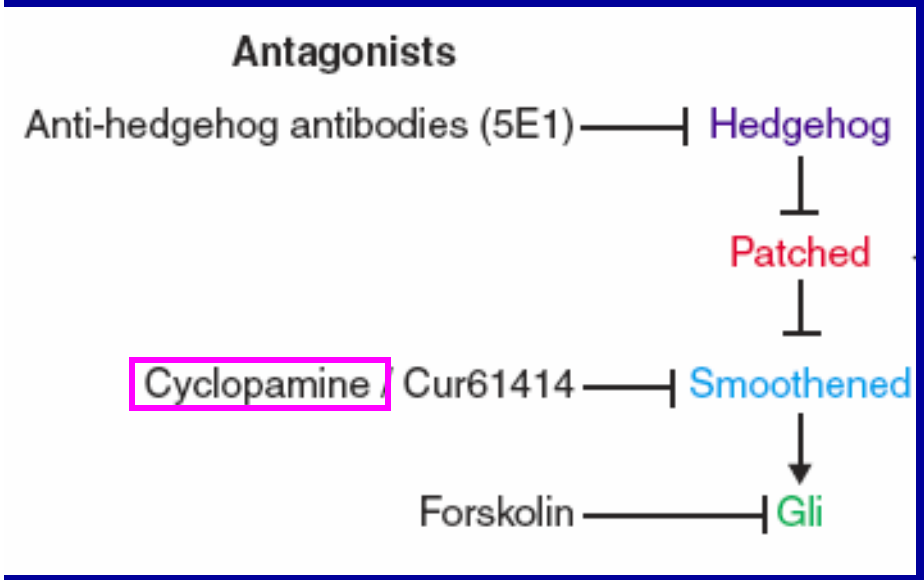
Cholesterol

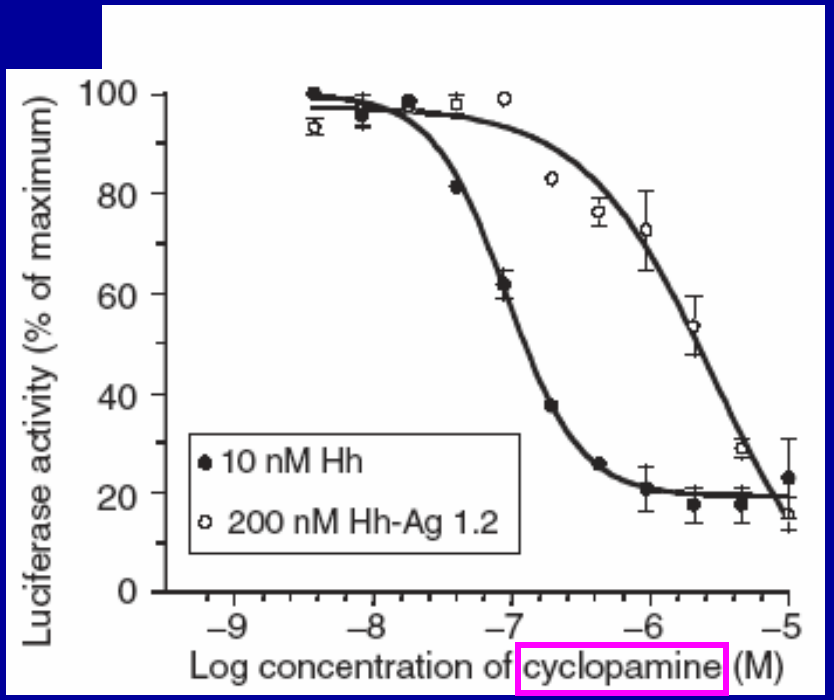
Cyclopamine





Edison and Muenke *Congenital Abnormalities* 43:1, 2003





Frank-Kamenetsky et al. J. Biol. 1:10, 2002

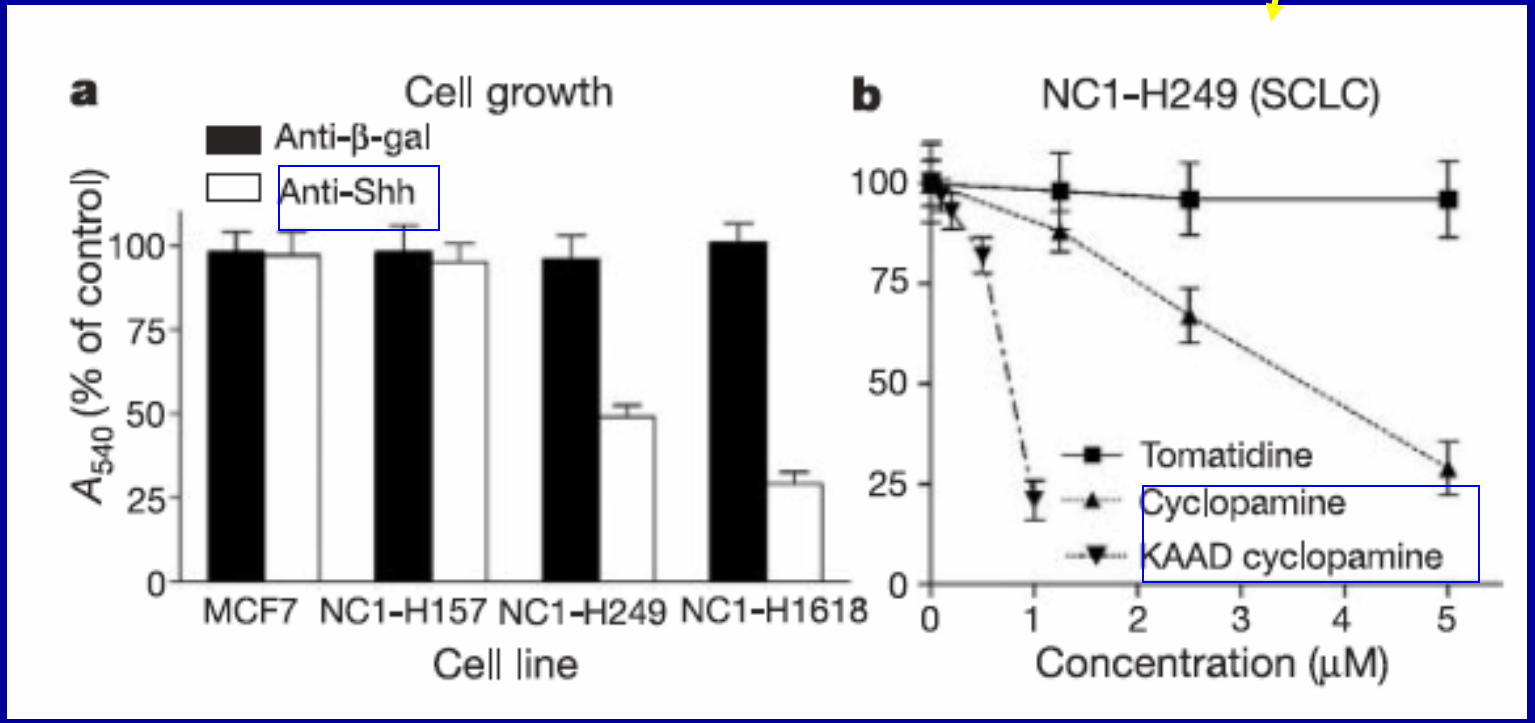
Hedgehog signalling within airway epithelial progenitors and in small-cell lung cancer

D. Neil Watkins*, David M. Berman†‡, Scott G. Burkholder*, Baolin Wang‡, Philip A. Beachy‡ & Stephen B. Baylin*

** Sidney Kimmel Comprehensive Cancer Center, † Department of Pathology, ‡ Department of Molecular Biology and Genetics, and Howard Hughes Medical Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland 21231, USA*

Nature 422:313, 2003

Cyclopamine inhibits growth of tumors with activated hedgehog pathways.



CONFOUNDERS:

AGE

SKIN COLOR

DOSE

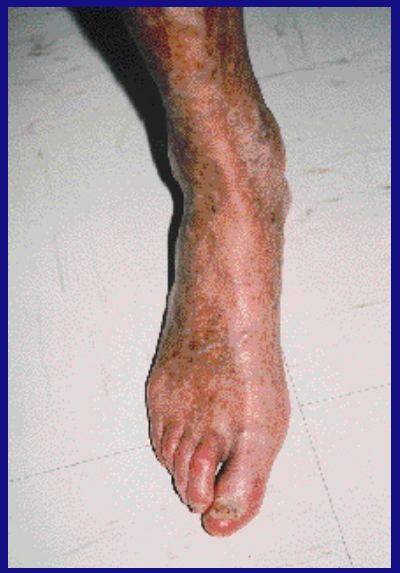
AGE

The Bare Facts of Aging
Photograph by Sarah Leen

National Geographic Magazine, November 2002

WERNER SYNDROME

- A disease of accelerated aging.
- Gene (WRN) encodes a helicase (RecQ) involved in DNA repair and DNA replication.
- Normal aging may involve decrease in DNA repair.
- Scleroderma-like skin changes.
- Increased incidence of malignancy: GI tract, lung, kidney, ovary, breast.



Age and DNA Repair Capacity (DRC) in BCC

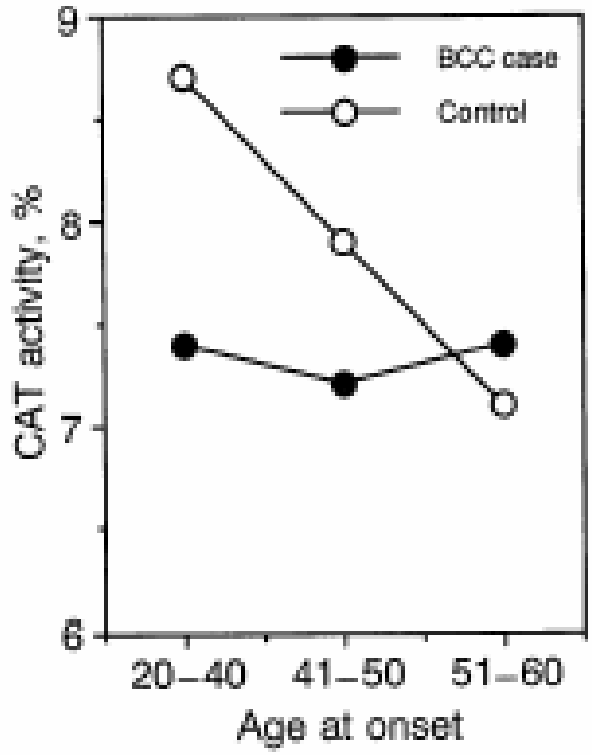


FIG. 1. Relationship between age at first BCC and DRC. The age-related decline in DRC among controls in comparison with that of age-matched cases is displayed. The linear-regression modeling and statistical tests of these data are presented in Table 5.

Wei et al. *PNAS* 90:1614, 1993

Age-Dependent Reactive Oxygen Species (ROS)

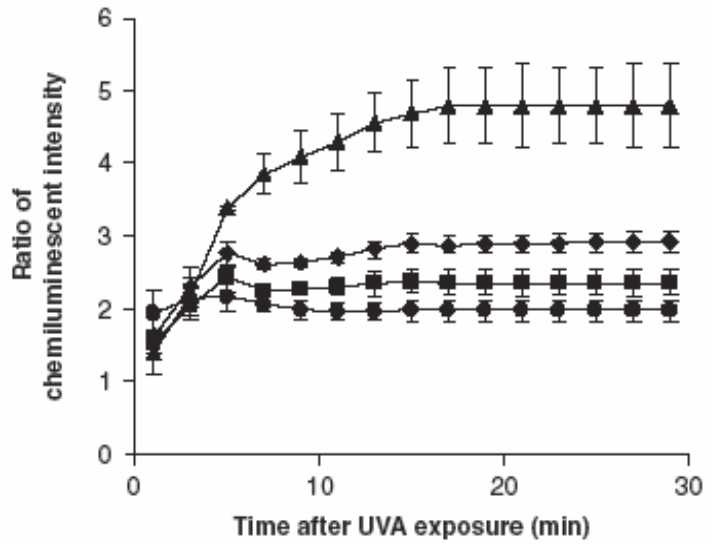
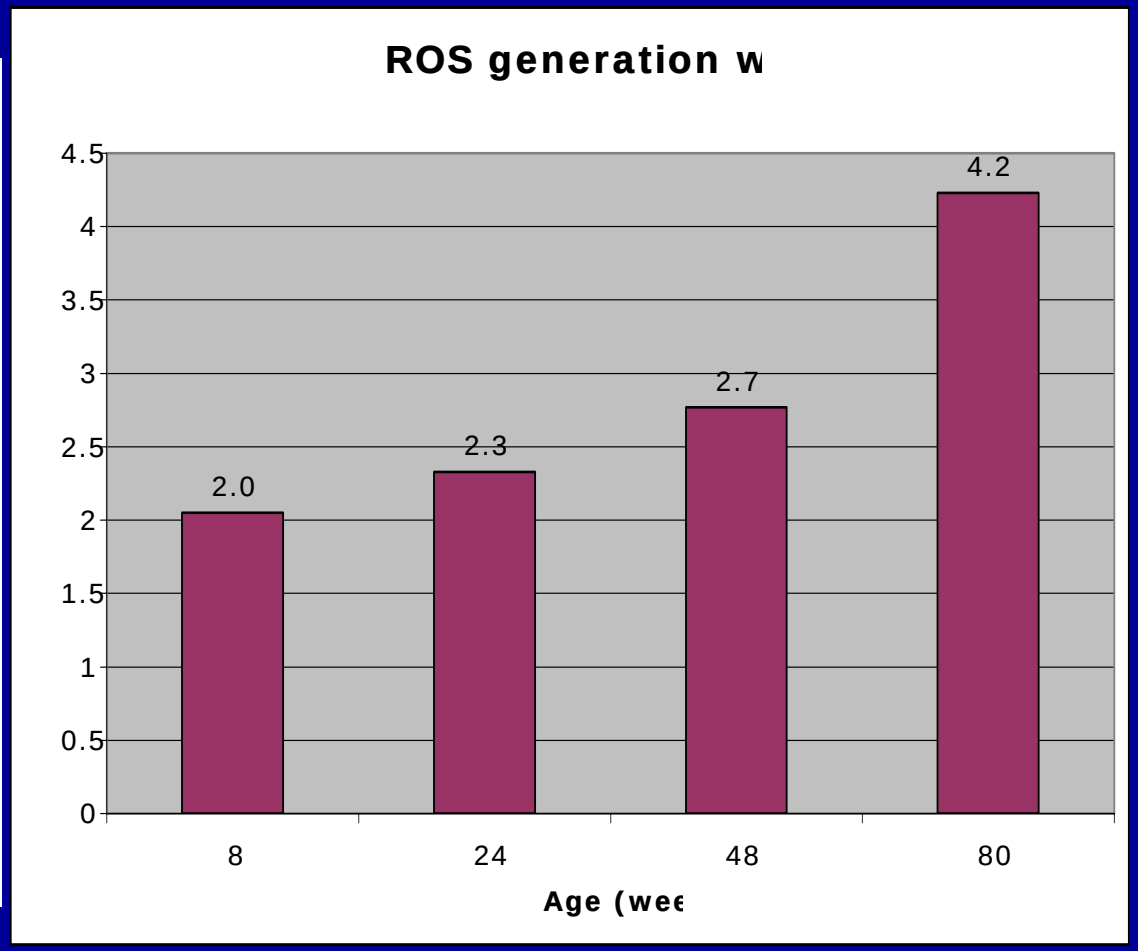
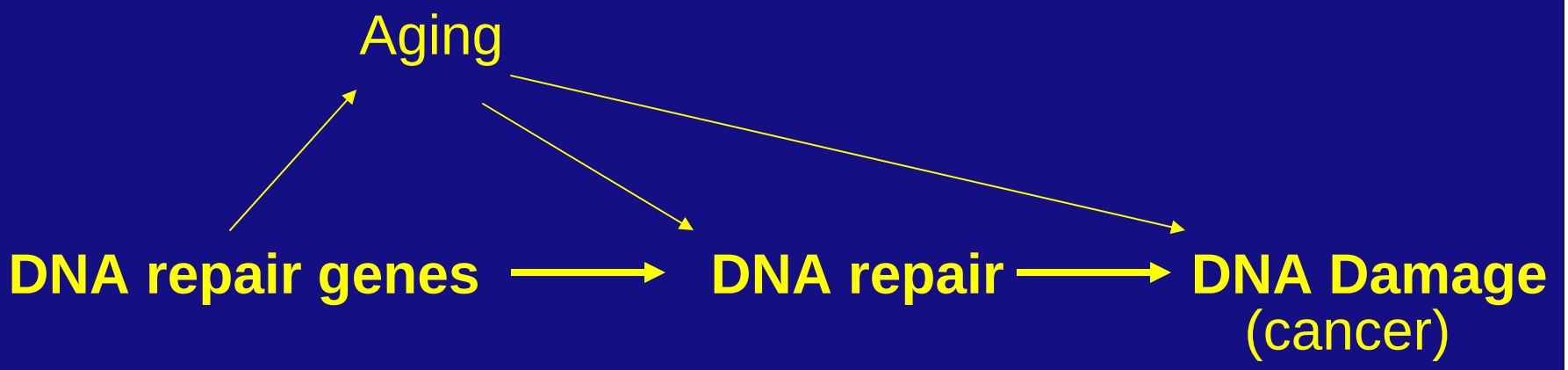


Figure 3. Age-dependent enhancement of the ratio of chemiluminescent intensities due to the ROS generation in UVA-exposed skin to those in the untreated skin of hairless rats aged 8 (●), 24 (■), 48 (◆), and 80 (▲) weeks. Data are expressed as the means ± standard deviations of six rats in each experiment.

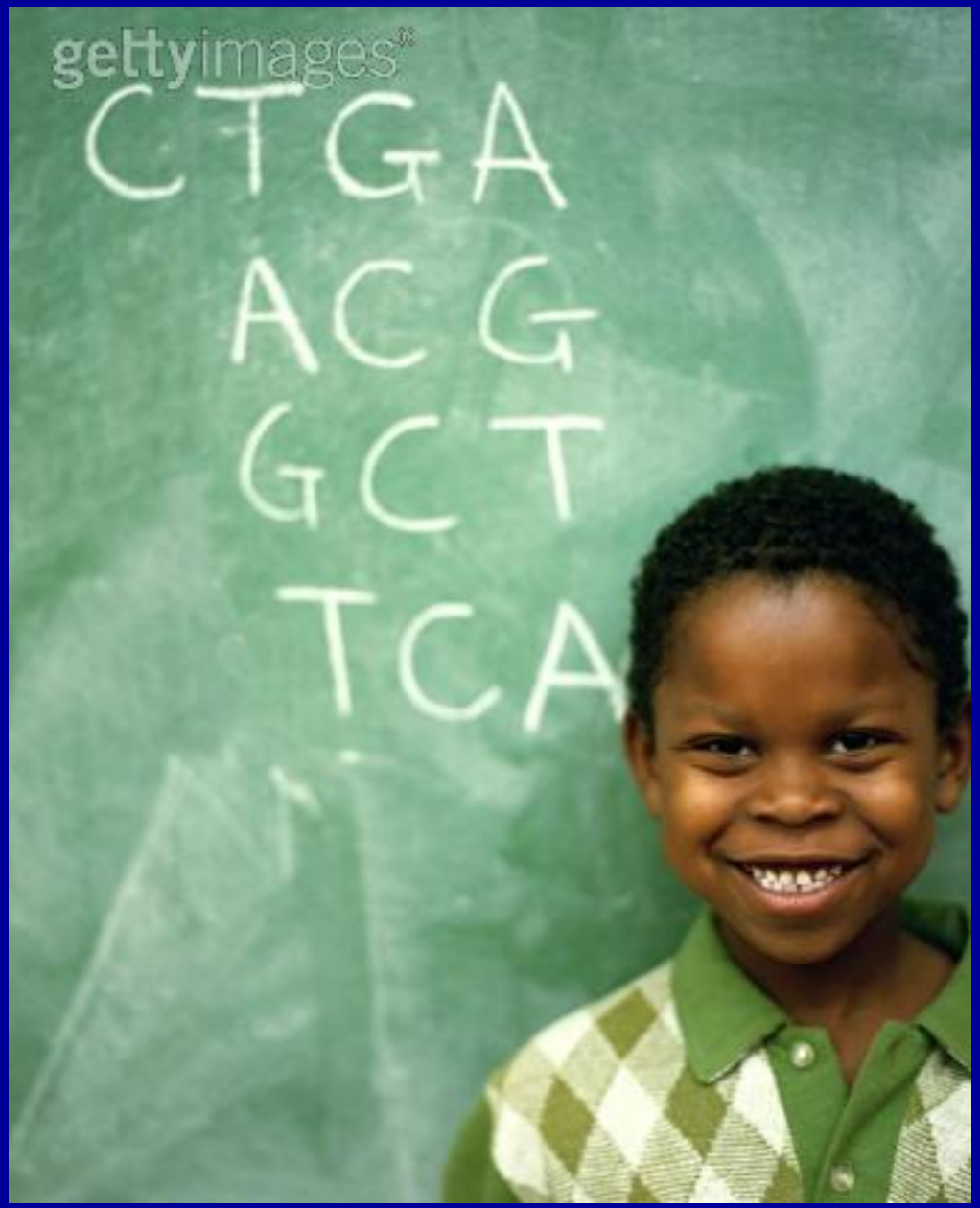


Exp Dematology 12:655, 2003



The multiple pathways through which aging can interact in the gene to cancer pathway, makes aging an important confounder that needs to be carefully adjusted for.

Epidemiological limitation is that we can only adjust for chronological age and not biological age.



SKIN COLOR GENETICS

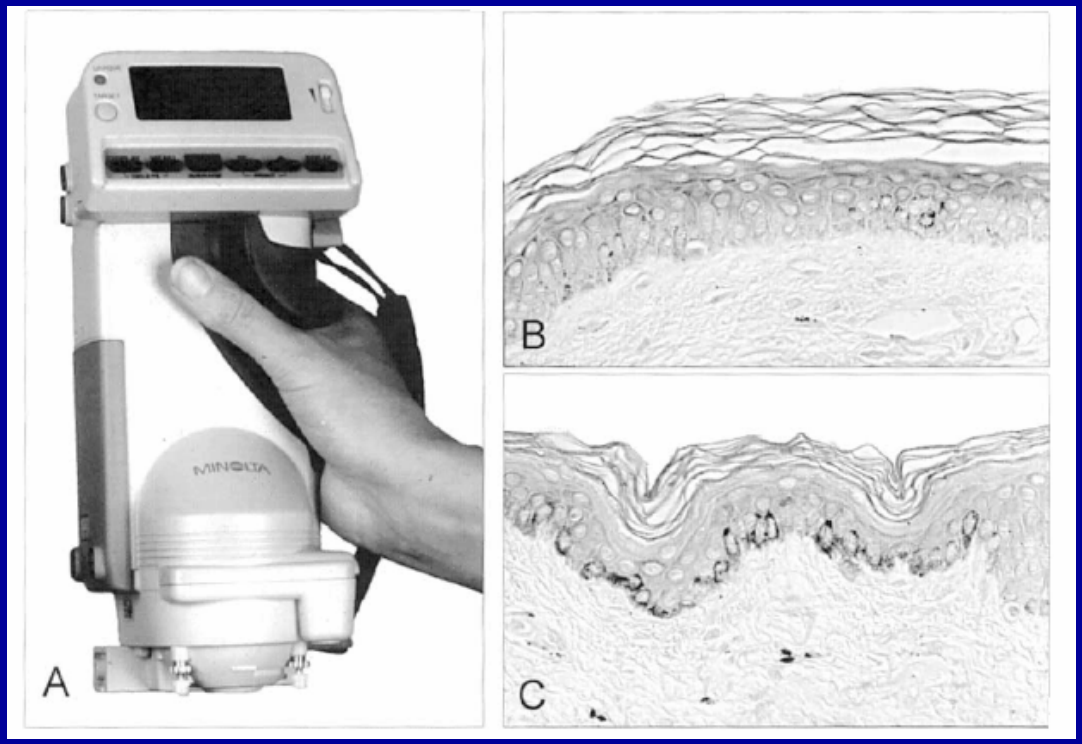
Skin color is a powerful risk modifier:

Whites have ~100-fold higher BCC incidence than blacks.

Whites have ~10-fold higher SCC incidence than blacks.

Am J Epidemiol 155: 614, 2002

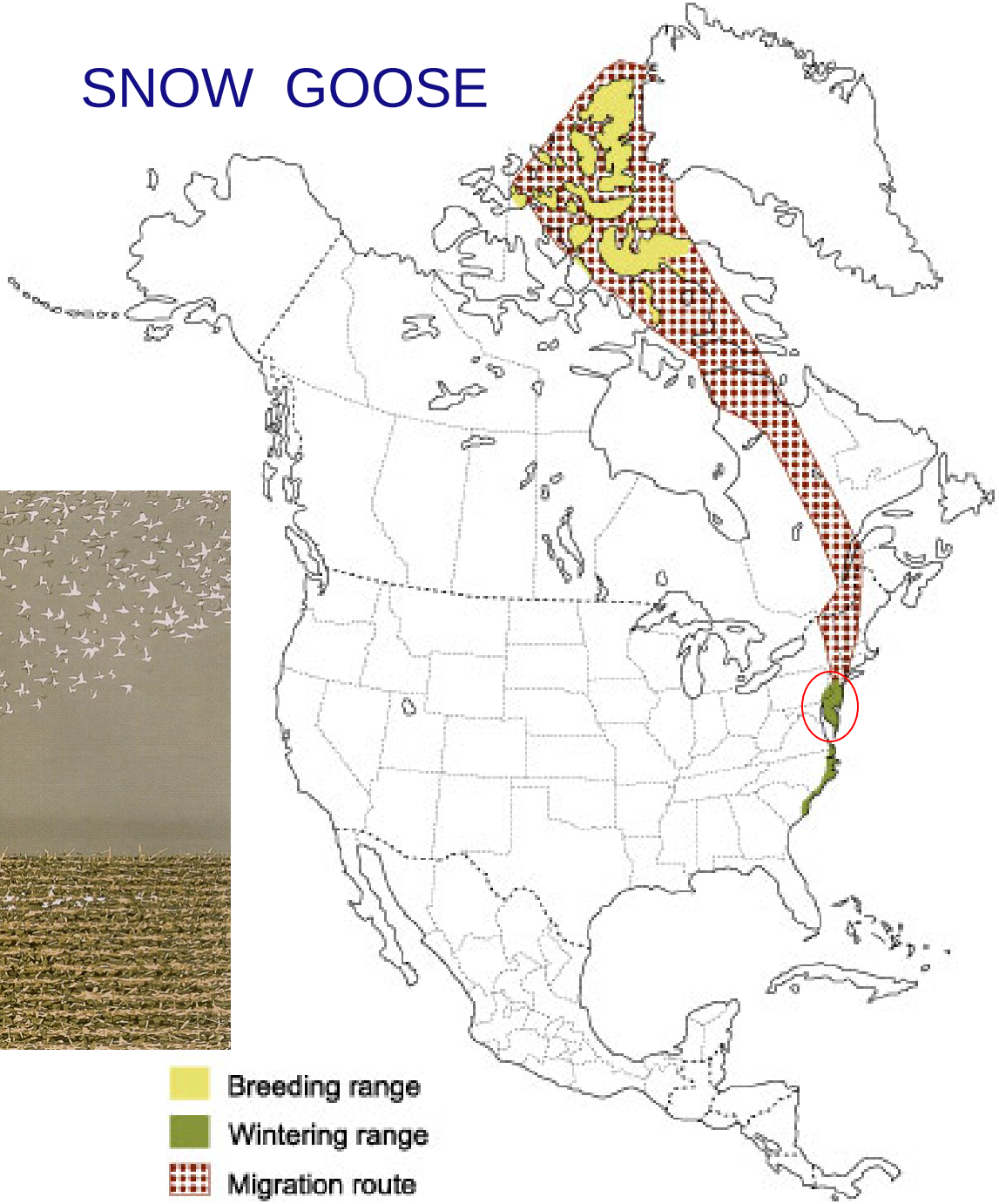
Melanin density is inversely related to skin cancer risk.

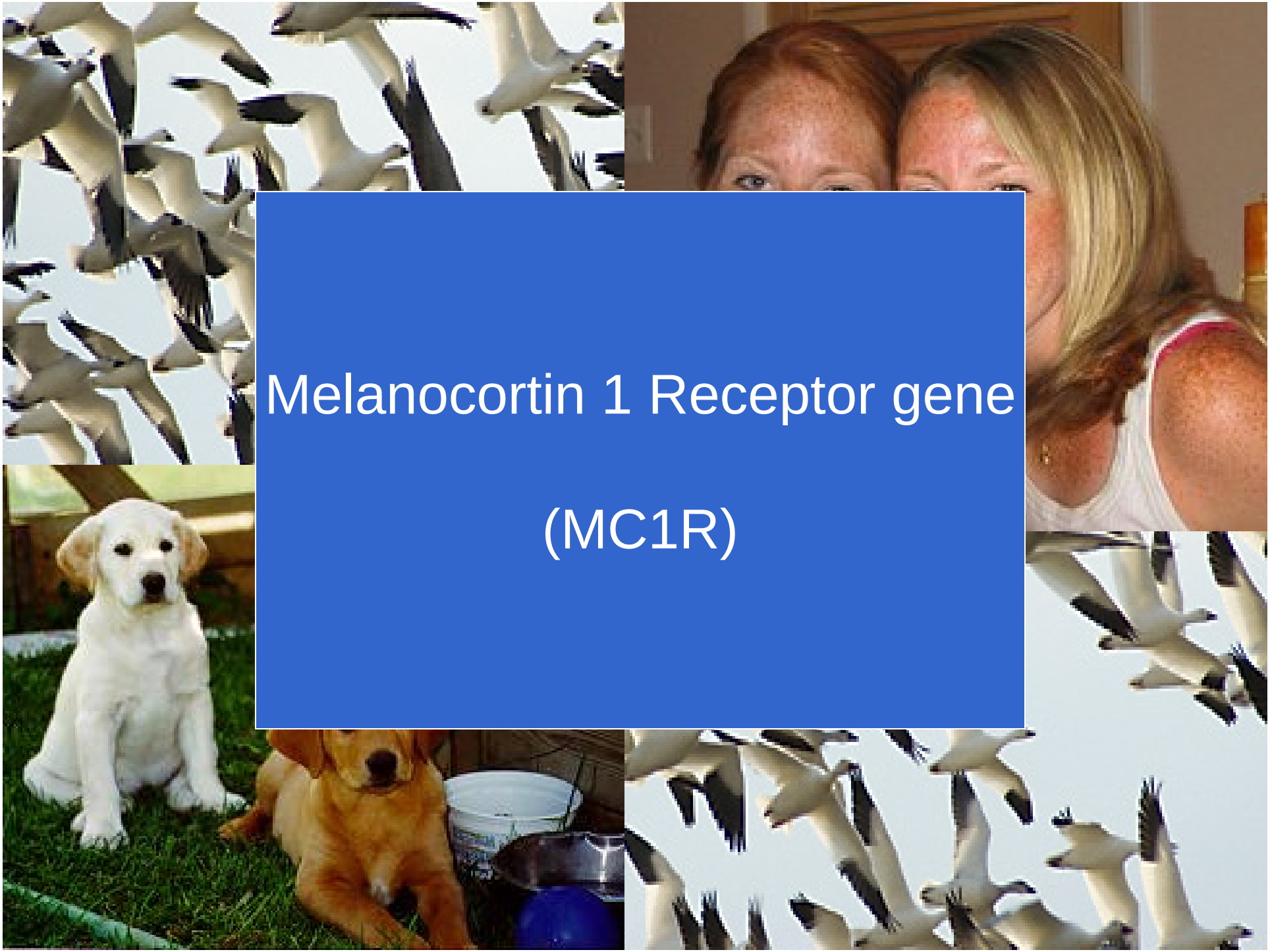


Arm melanin (%)	No. of controls	CMM*			BCC*			SCC*		
		No. of subjects	OR*	95% CI*	No. of subjects	OR	95% CI	No. of subjects	OR	95% CI
Adjusted for age										
≥3.00	44	6	1.0		8	1.0		8	1.0	
2.00–2.99	75	22	2.2	0.8, 5.8	19	1.4	0.6, 3.5	28	2.1	0.9, 5.2
1.00–1.99	75	41	4.1	1.6, 10.4	40	2.9	1.3, 6.8	36	2.6	1.1, 6.1
<1.00	38	31	6.2	2.3, 16.6	41	6.3	2.6, 15.1	25	4.2	1.7, 10.8
Linear trend				$p < 0.01$			$p < 0.01$			$p < 0.01$

SNOW GOOSE

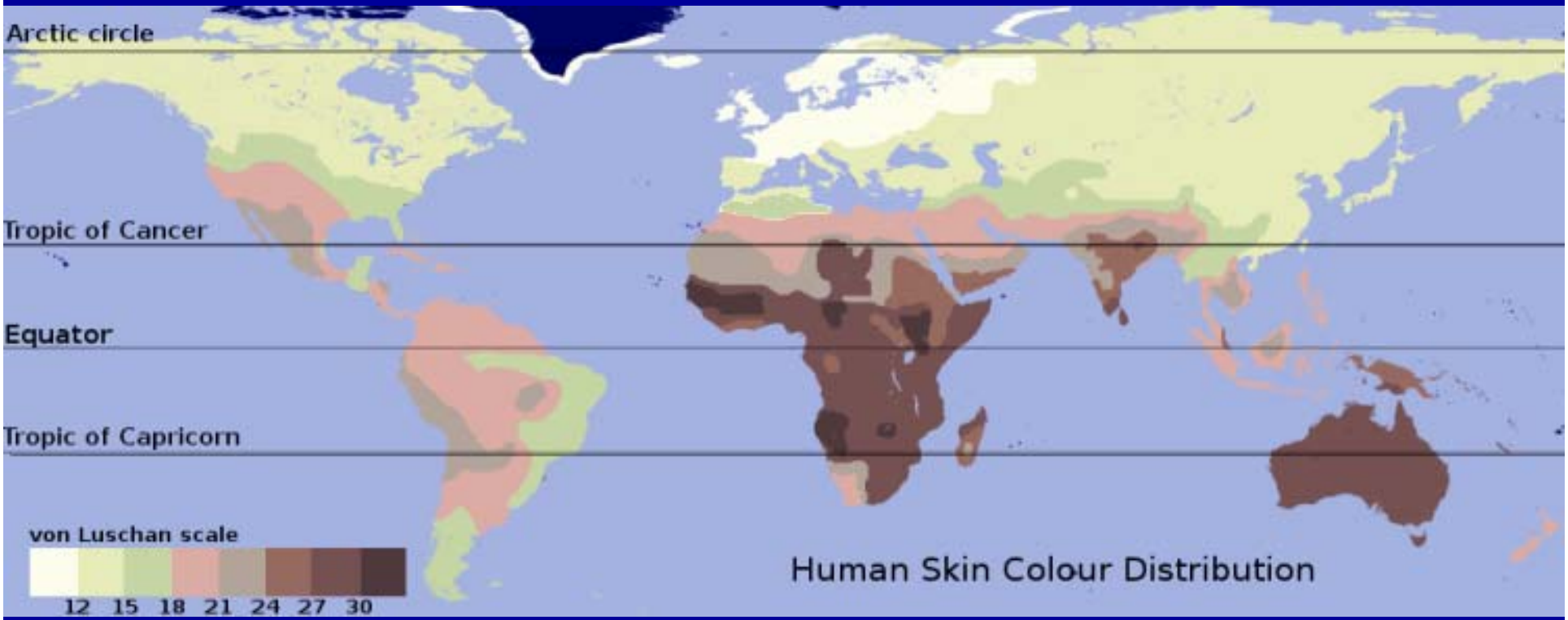

NATIONAL GEOGRAPHIC
Find more wallpapers at www.nationalgeographic.com
Photograph courtesy U.S. Fish & Wildlife Service/Dave Menke


Breeding range
Wintering range
Migration route



Melanocortin 1 Receptor gene

(MC1R)


Arctic circle
Tropic of Cancer
Equator
Tropic of Capricorn
von Luschan scale
12 15 18 21 24 27 30
Human Skin Colour Distribution

SKIN COLOR GEOGRAPHY

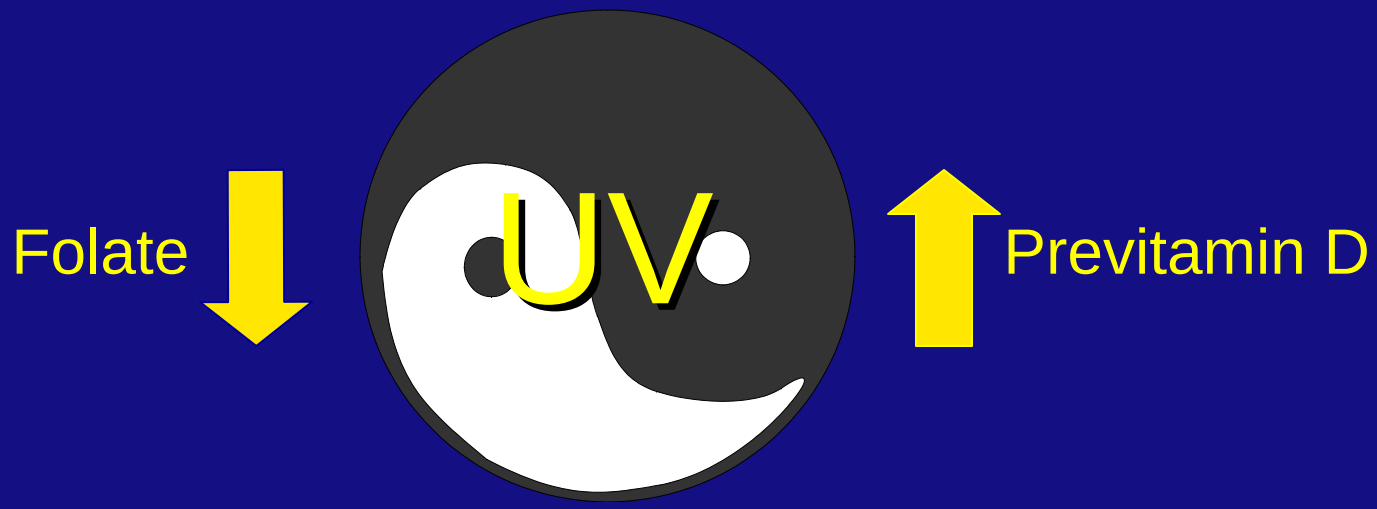
Photograph by Sarah Leen;
map created by George Chaplin

Australian Aborigine Glenys Martin holds a map of human skin colors based on global ultraviolet radiation intensity and precipitation levels.

National Geographic Magazine, November 2002

PROBLEM:
Sun burn and skin cancer are not thought to affect reproductive success. So what is the evolutionary pressure selecting for skin color correlation with UV exposure?

Competing Nutrient Hypothesis of Skin Color



Jablonski and Chaplin, *J Human Evolution* 39:57, 2000


DOSE

Altered Epidemiologic Paradigm:

Radiation Dose is NOT the Exposure

Genotype = Exposure

Dose = **Effect Modifier** or **Confounder**

National Geographic Magazine
April 2007

HEALTH

UNPATTERNED FINGERPRINTS

NORMAL FINGERPRINTS

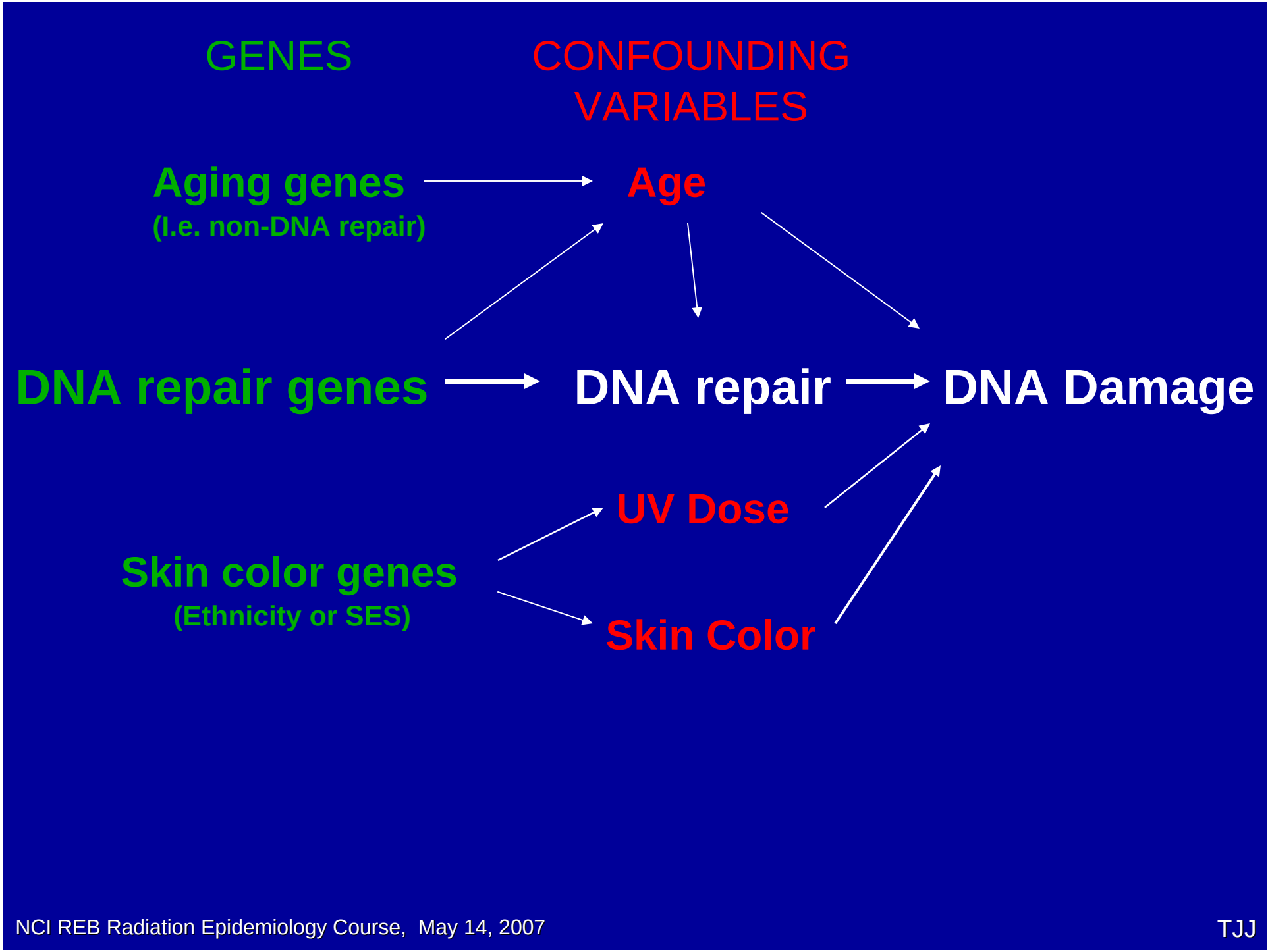
Case of the Missing Prints Cheryl Maynard (below) was born with a trait that old-time gangsters would have killed for—fingers that leave no prints. Along with an impaired ability to sweat and a lacy brown pigmentation over her body, the lack of a unique patterning on her fingers and palms comes from an exceedingly rare condition called dermatopathia pigmentosa reticularis—passed on for at least five generations in her mother's family. Like her relatives, Maynard has learned to live with it. Turning slick magazine pages requires her to lick her fingers for traction on the paper. Her hands slide right off the sides when she tries to carry a cardboard box.

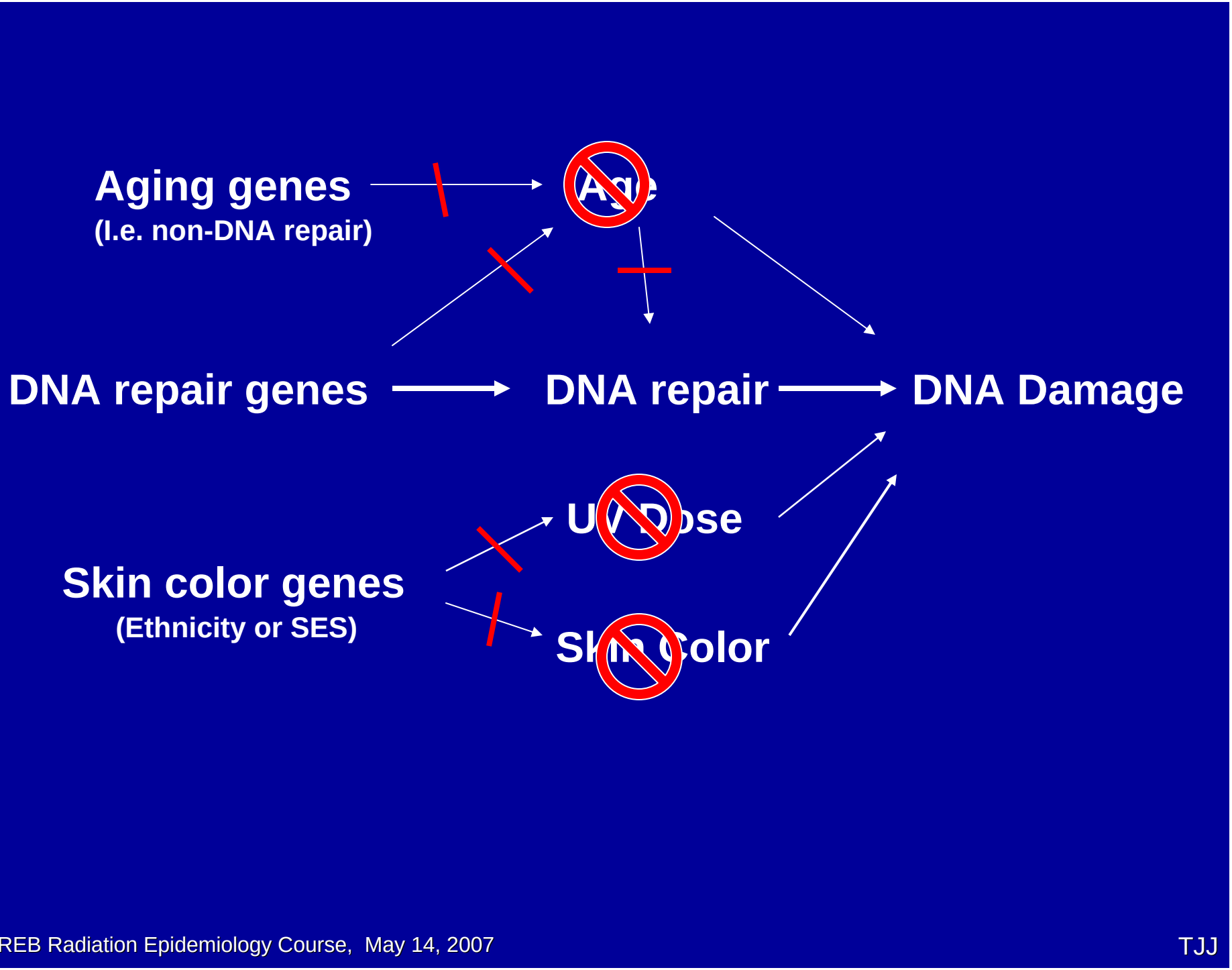
Scientists recently found the root of Maynard's disorder: a genetic defect in a protein that also keeps cells from dying prematurely. Learning how that protein works may improve understanding of why skin cancer cells are hard to kill. Though there is no cure, Maynard still finds humor in situations such as security checks. Puzzled by her lack of prints, an official once asked, "Can't they just give you some?" No, she shot back, "but if I could have anybody's, I'd want Al Capone's." —*A. R. Williams*

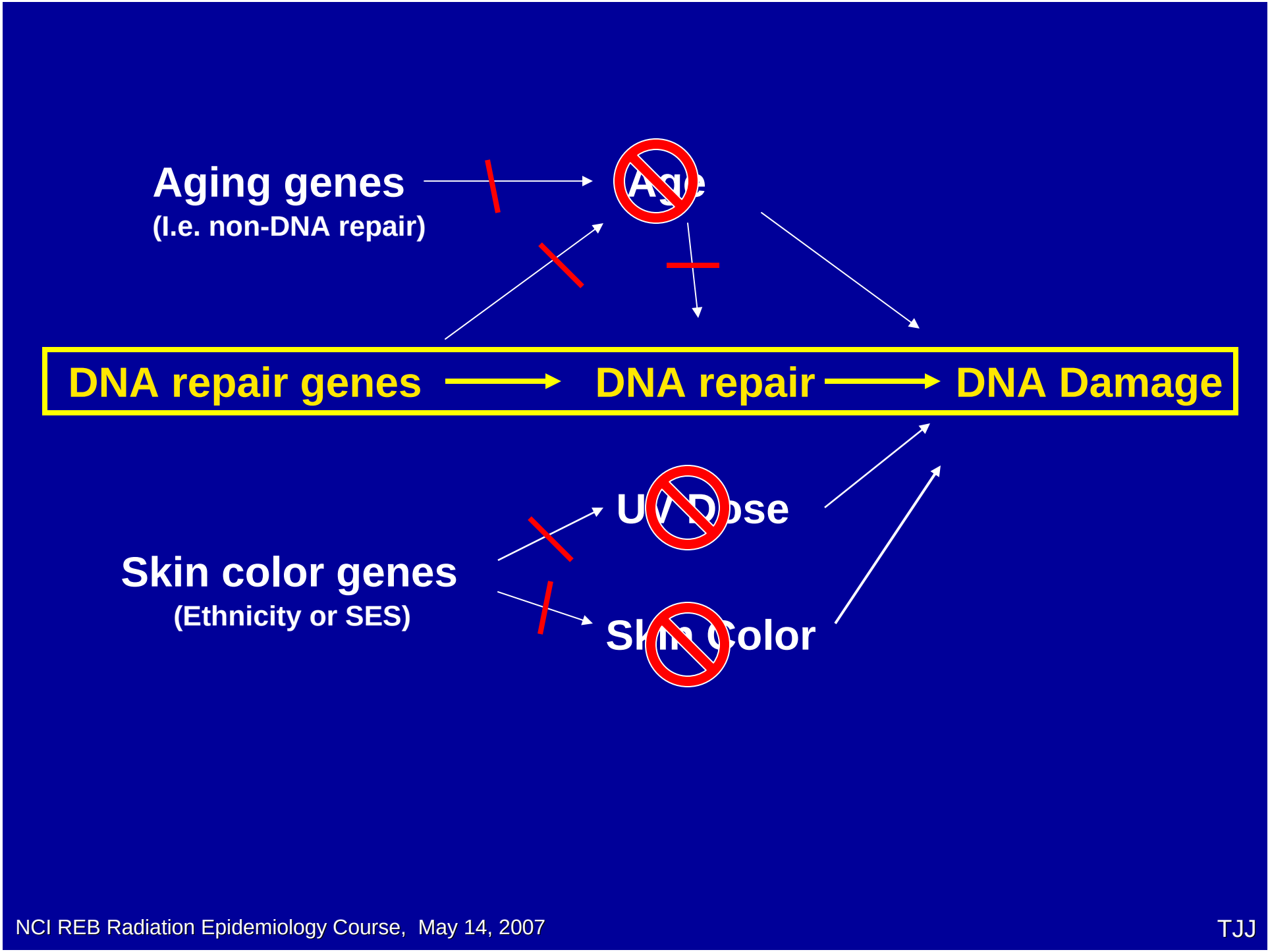
Overexpressed in BCC

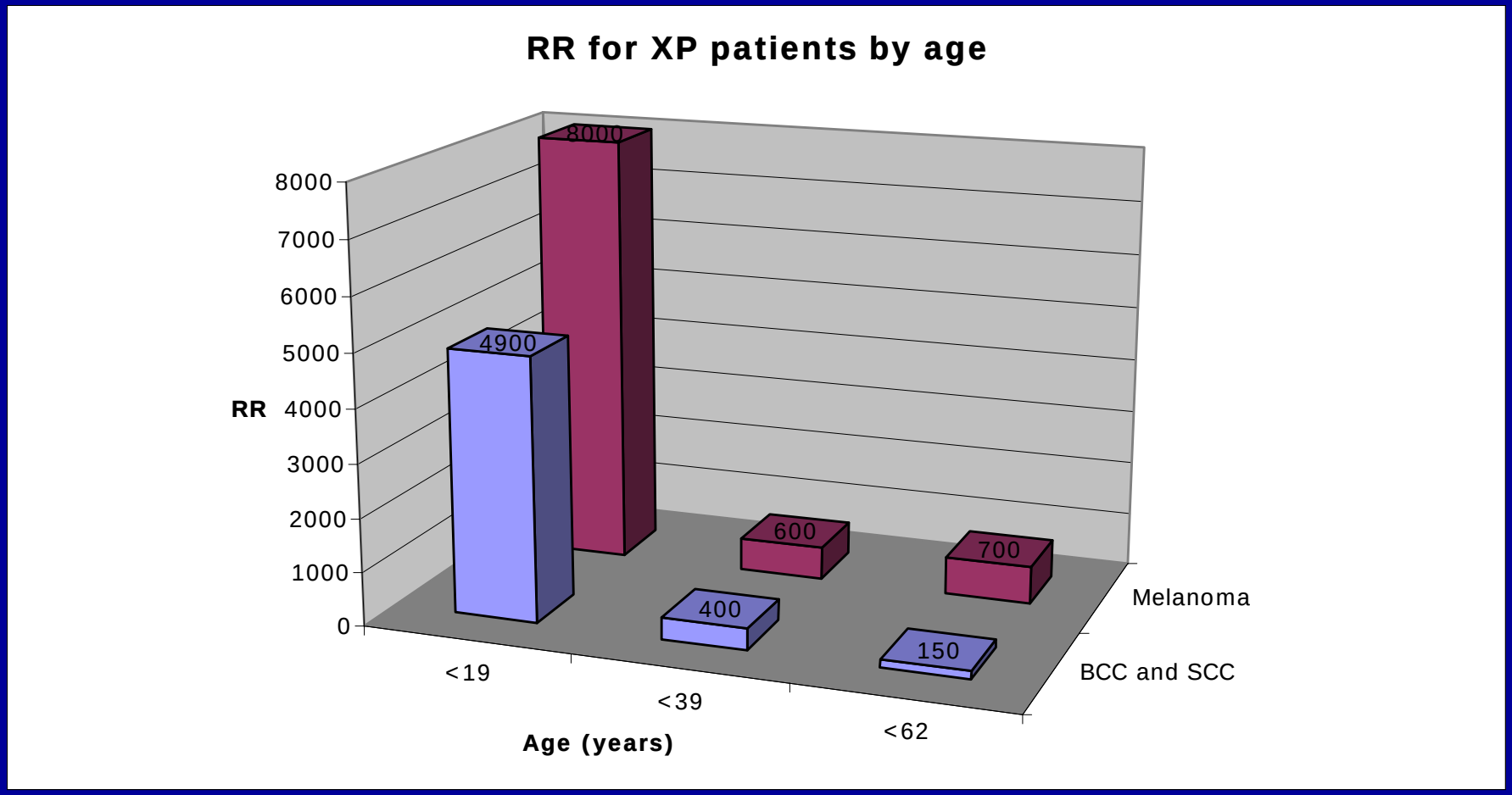
Protein Keratin 14 (KTR14 gene)

PHOTO: DANA ROMANOFF


GENES
CONFOUNDING VARIABLES
Aging genes
(I.e. non-DNA repair)
Age
DNA repair genes
DNA repair
DNA Damage
UV Dose
Skin color genes
(Ethnicity or SES)
Skin Color


Aging genes
(I.e. non-DNA repair)
DNA repair genes
DNA repair
DNA Damage
Skin color genes
(Ethnicity or SES)


Aging genes
(I.e. non-DNA repair)
Age
DNA repair genes
DNA repair
DNA Damage
UV Dose
Skin color genes
(Ethnicity or SES)
Skin Color



If age dependence of RR in XP holds true for "normal" variants, then a strong negative multiplicative interaction may be involved.

adapted from Kraemer et al. *Arch Dematol* 130:1018, 1994

BCC itself is a risk factor for other cancers

Association of Nonmelanoma Skin Cancer with Second Malignancy

The Women's Health Initiative Observational Study

Prevalence and Odds of History of Other Malignancies by Nonmelanoma Skin Cancer History Status at Enrollment

	Reported ever having NMSC						
	No (n = 85,170)		Yes (n = 7665)				
Other history of malignancy	No.	%[a]	No.	%[a]	OR	95% Wald confidence limits	P value
Any other cancer (excluding NMSC)	9927	11.66	1878	24.86	2.30	2.18–2.44	< 0.0001
Breast	4444	5.22	831	10.91	2.09	1.93–2.26	< 0.0001
Ovary	540	0.63	98	1.29	2.01	1.61–2.50	< 0.0001
Endometrium	1302	1.53	264	3.47	2.00	1.74–2.29	< 0.0001
Colon, rectum, bowel, or intestine	727	0.85	124	1.63	1.68	1.38–2.04	< 0.0001
Thyroid	401	0.47	94	1.24	2.60	2.07–3.28	< 0.0001
Cervix	1030	1.21	165	2.17	1.92	1.62–2.28	< 0.0001
Melanoma	885	1.04	299	3.93	3.29	2.87–3.76	< 0.0001
Liver	25	0.03	10	0.13	5.96	2.71–13.11	< 0.0001
Lung	162	0.19	56	0.74	3.43	2.51–4.69	< 0.0001
Brain	43	0.05	9	0.12	2.12	1.02–4.39	0.0429
Bone	51	0.06	13	0.17	2.90	1.55–5.44	0.0009
Stomach	47	0.06	12	0.16	3.17	1.63–6.18	0.0007
Blood (leukemia)	64	0.08	24	0.32	3.58	2.21–5.80	< 0.0001
Bladder	168	0.20	23	0.30	1.26	0.81–1.95	0.3114
Lymphoma	163	0.19	42	0.55	2.73	1.92–3.86	< 0.0001
Hodgkin disease	37	0.04	17	0.22	5.69	3.12–10.39	< 0.0001
Other	979	1.17	209	2.89	2.26	1.94–2.64	< 0.0001

NMSC: nonmelanoma skin cancer; OR: odds ratio.

[a] Percentages were based on women with a nonmissing response for the cancer in question who reported no history of nonmelanoma skin cancer (NMSC) and reported a history of NMSC, respectively.

Radiation as a Model Carcinogen:

- Known to be a human carcinogen for almost 100 years.
- Strong epidemiological evidence shows clear dose response.
- High dose risks known with reasonable precision/accuracy.
- Low dose risks are highly uncertain and model dependent.
- All tissues believed to be at risk.
- Some risk incurred at all dose levels (i.e. no threshold).
- Dosimetry is very good. (What is a “pack-year” anyway?!)
- All individuals in a population are exposed to some degree.
- Range of exposures within a population can be quite broad.
- Direct interaction with the target of carcinogenesis, and confines the problem to downstream of DNA damage.
- Major cellular protective molecular mechanisms known in some degree of detail (e.g. DNA repair and cell cycle arrest).
- Radiation is a relatively weak carcinogen (room for genetic enhancement).

TAKE-HOME MESSAGE

- Radiation has many advantages as a model carcinogen for studying gene-environment (G-E) interactions in cancer.
- BCC has many advantages as a cancer model for G-E interactions.
- DNA repair genes in the NER pathway are prime candidates for G-E interaction in BCC.
- Genes in Hedgehog pathway may also be very important to BCC etiology.
- Cell cycle, apoptosis, and other pathways may play a role in BCC, but the evidence is weaker.
- Care must be taken to avoid confounding genes, such aging and skin color related genes.
- Dose should be viewed as a powerful affect modifier and potential confounder.
- There is probably a strong multiplicative interaction between age of onset and BCC RR, that needs to be adjusted for.
- Genes involved in BCC are probably important for other cancers as well.