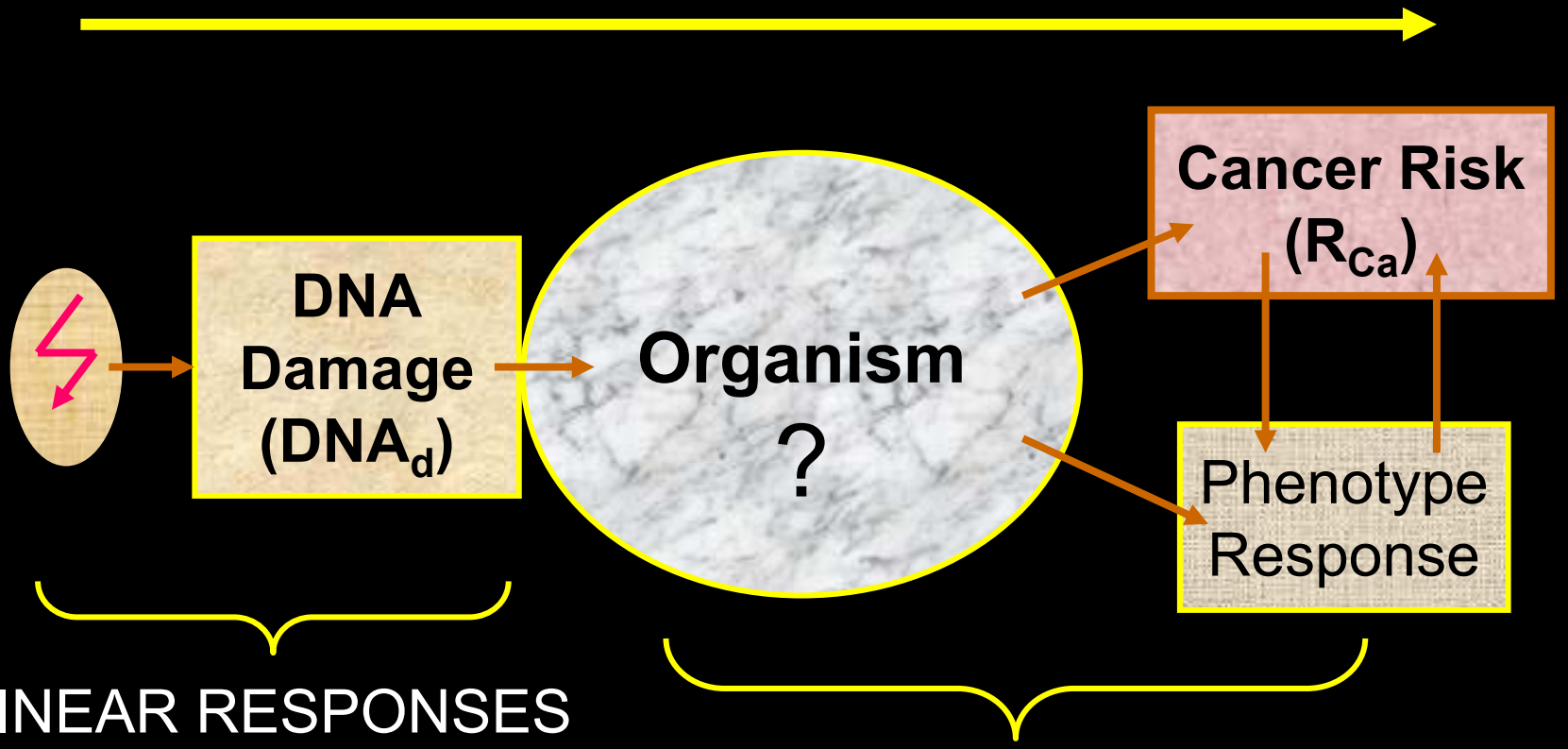
Three Barriers Block Damage after Low-Level Irradiation.

Ludwig E. Feinendegen
Myron Pollycove
Ronald D. Neumann

The 8th Annual International Conference: Dose-Response: Implications for Toxicology, Medicine, and Risk Assessment
University of Massachusetts, Amherst, April 28 - 29, 2009

From Physics to Biology

THERE ARE MULTIPLE DEFENSES AGAINST DAMAGE.

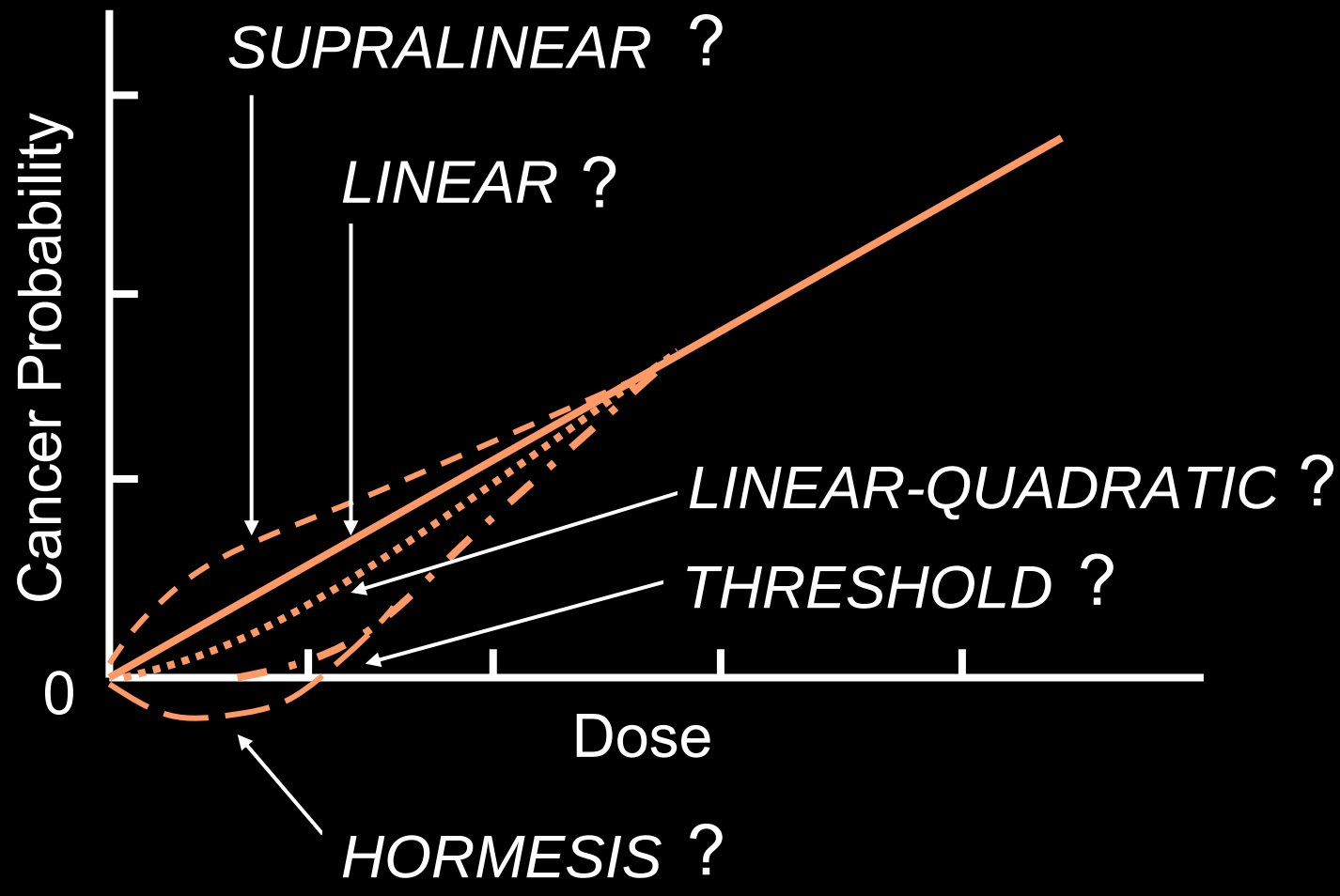


$DNA_d = \alpha_1 \bullet D$

$R_{Ca} \neq \alpha_2 \bullet DNA_d$

Five Possible Low-Dose Induced Cancer Risks

DECISIVE IS THE RATIO: DAMAGE / PROTECTION.



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1. Biological Systems and Dose Responses
2. Energy Deposition Events and Perturbations
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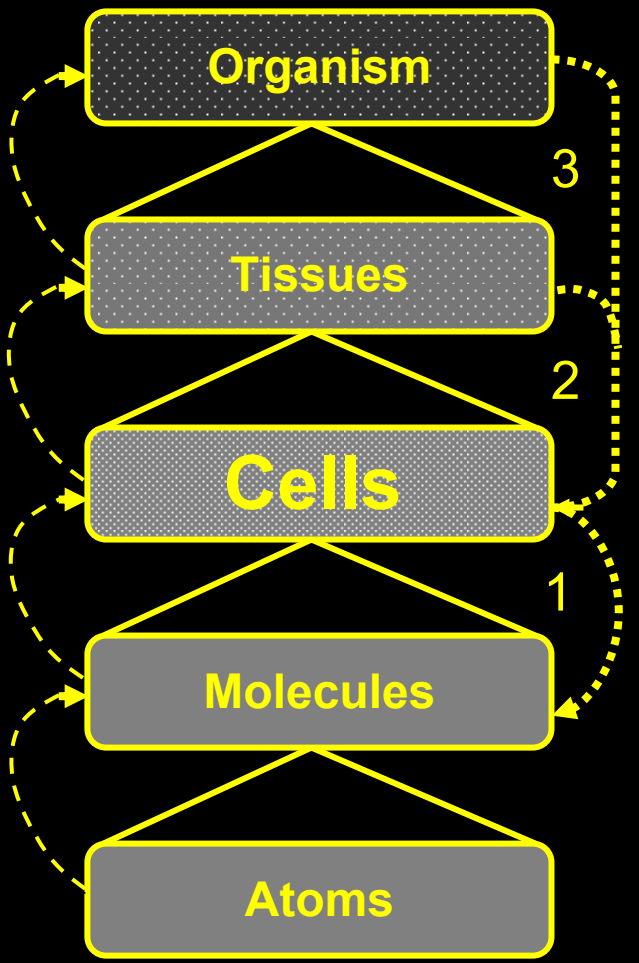
Hierarchy Levels of Biological Systems

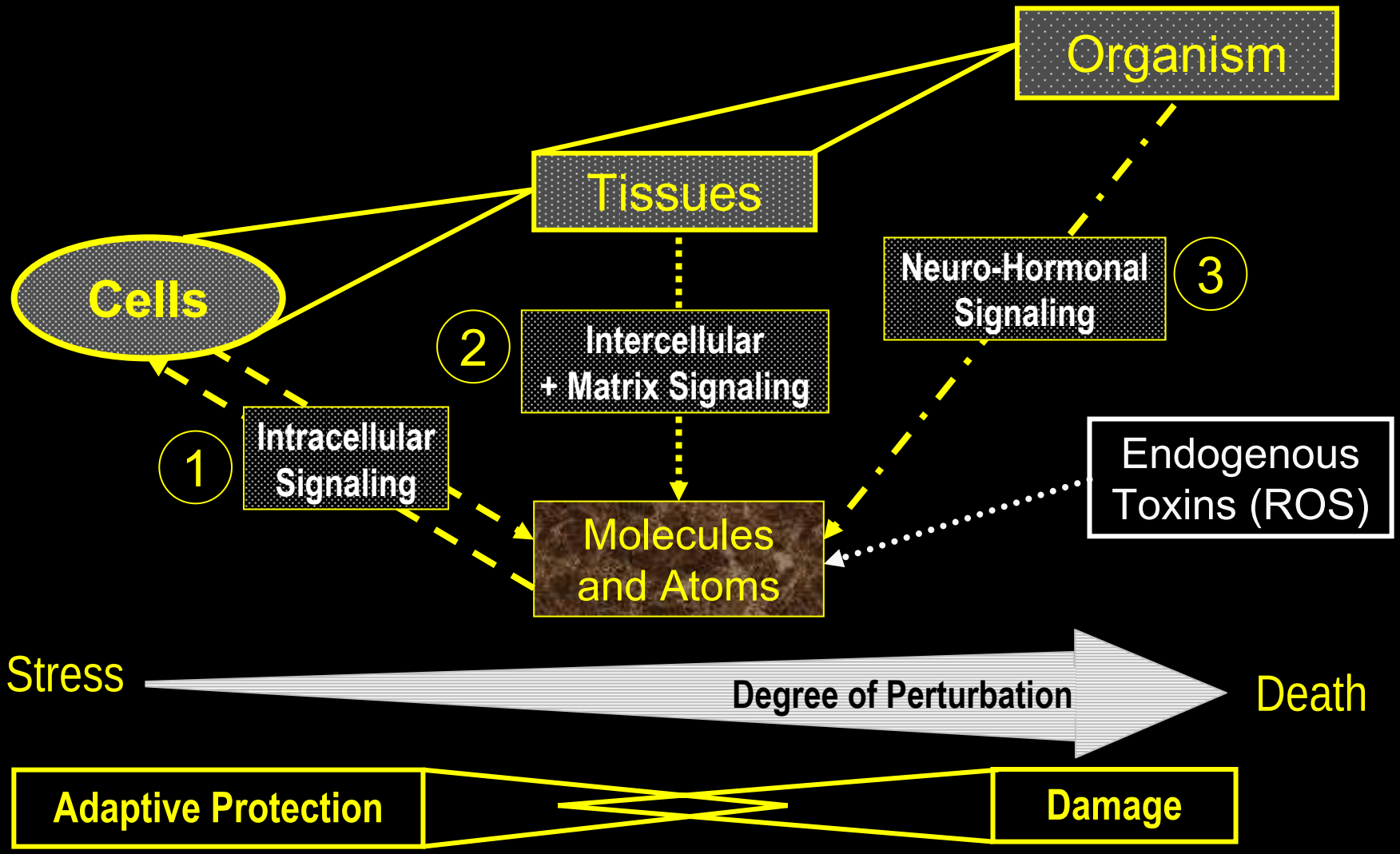
INCREASING ORGANIZATION AND COMPLEXITY.



SIGNALING LOOPS USE ELECTRONS AND MOLECULES IN AND BETWEEN CELLS

Biological Systems are Complex and Adapting

EACH LEVEL RESPONDS TO PERTURBATIONS.



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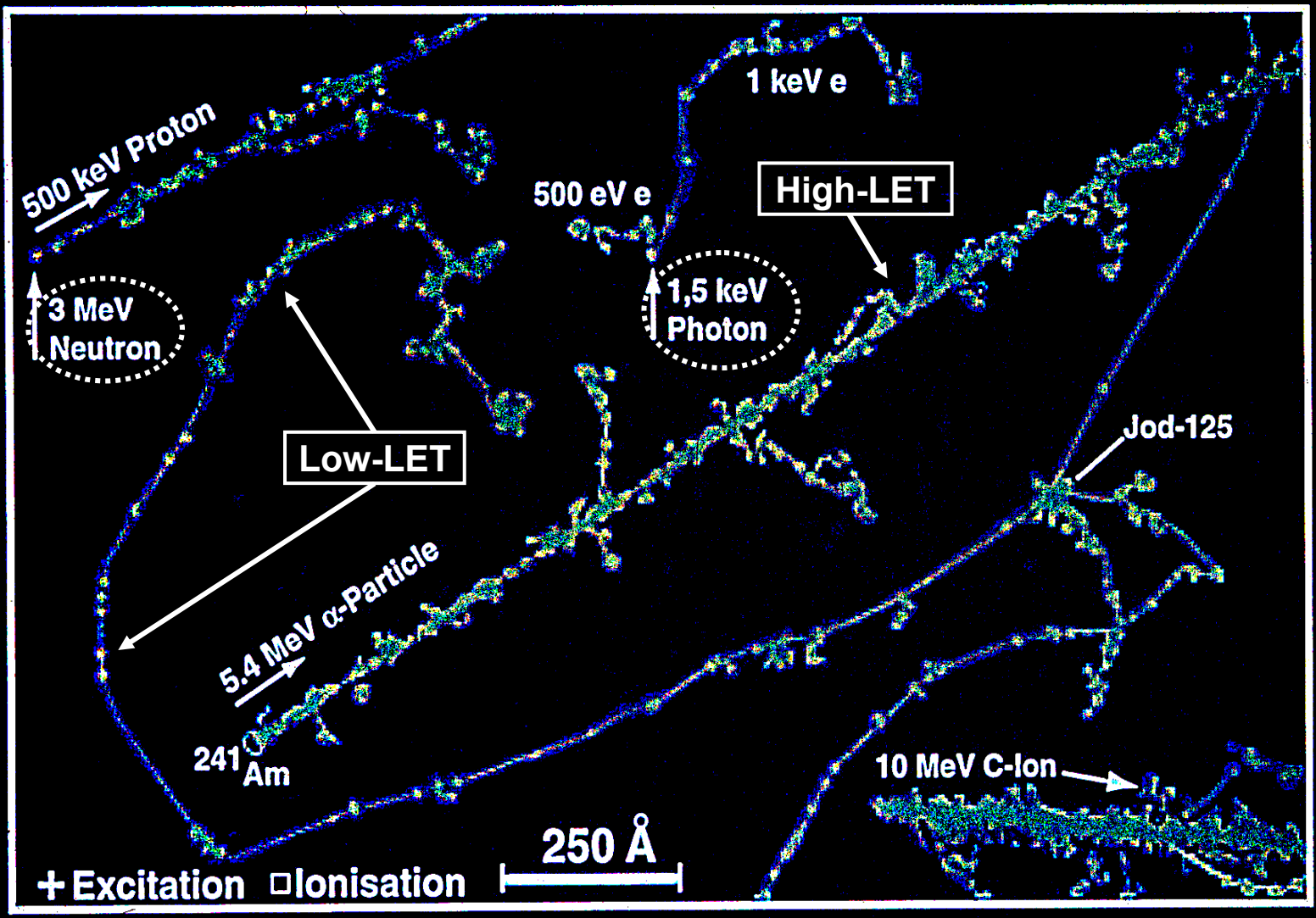
Individual Particle Tracks in Liquid Water at 10^{-15} Sec.

EXCITATIONS AND IONIZATIONS (◘) ALONG TRACKS.



Absorbed Dose (D) is Energy (E) per unit Mass (M)

MICRODOSE:

$z_1 = E_1 / M_1$

N_E = Nr expos. M_1

N_H = Nr hits in Σ M_1

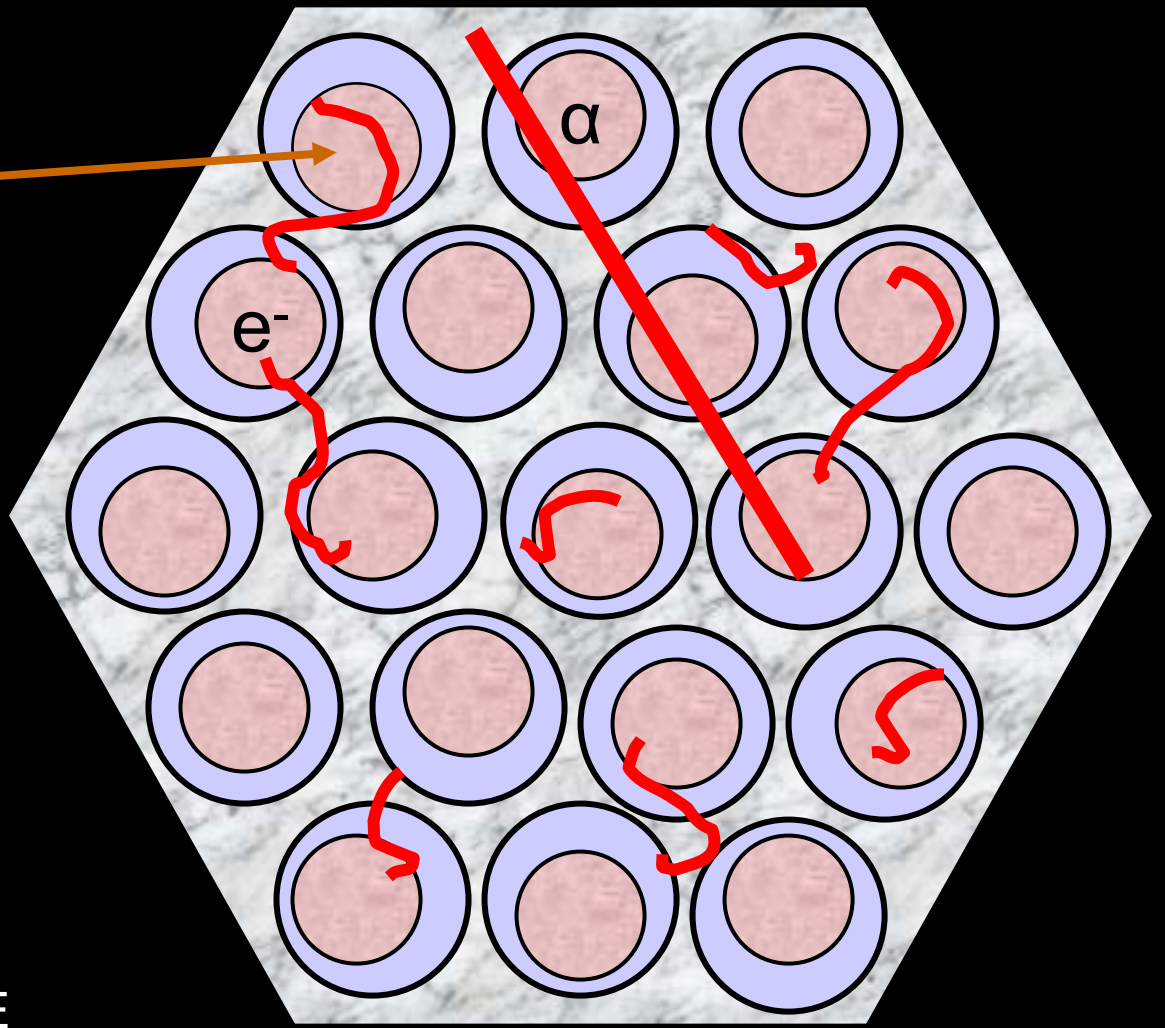
with M_1 = 1 ng

($\bar{x}$ mass of cell)

z_1 = CELL DOSE

TISSUE DOSE:

$\bar{D} = [\, \bar{z}_{F1} \bullet N_H \,] / N_E$

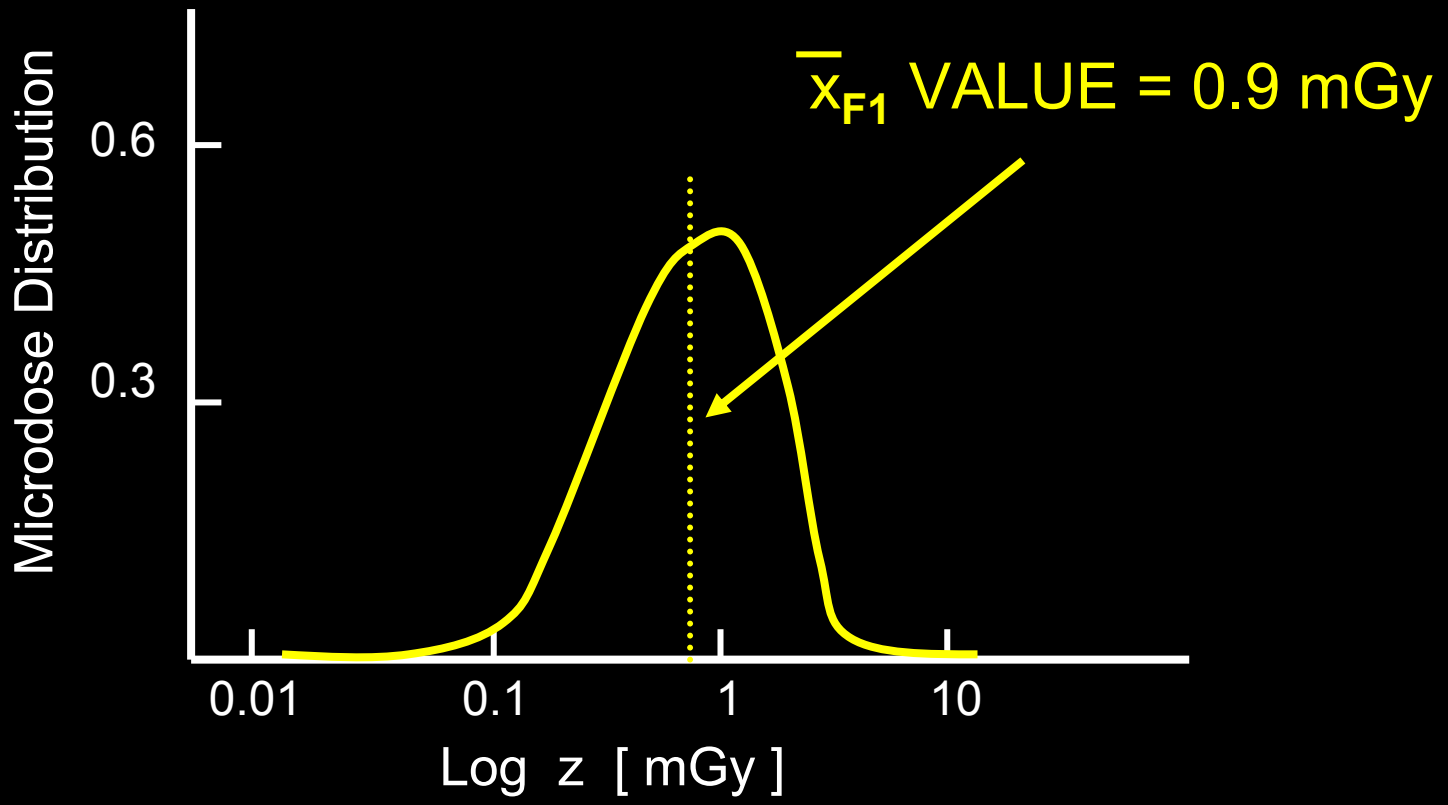


DOSE IS PROPORTIONAL TO NUMBER OF “HITS”

Distribution of z Values (1 ng Mass) in mGy

FOR 250 kVp X-RAYS IN WATER (TISSUE)

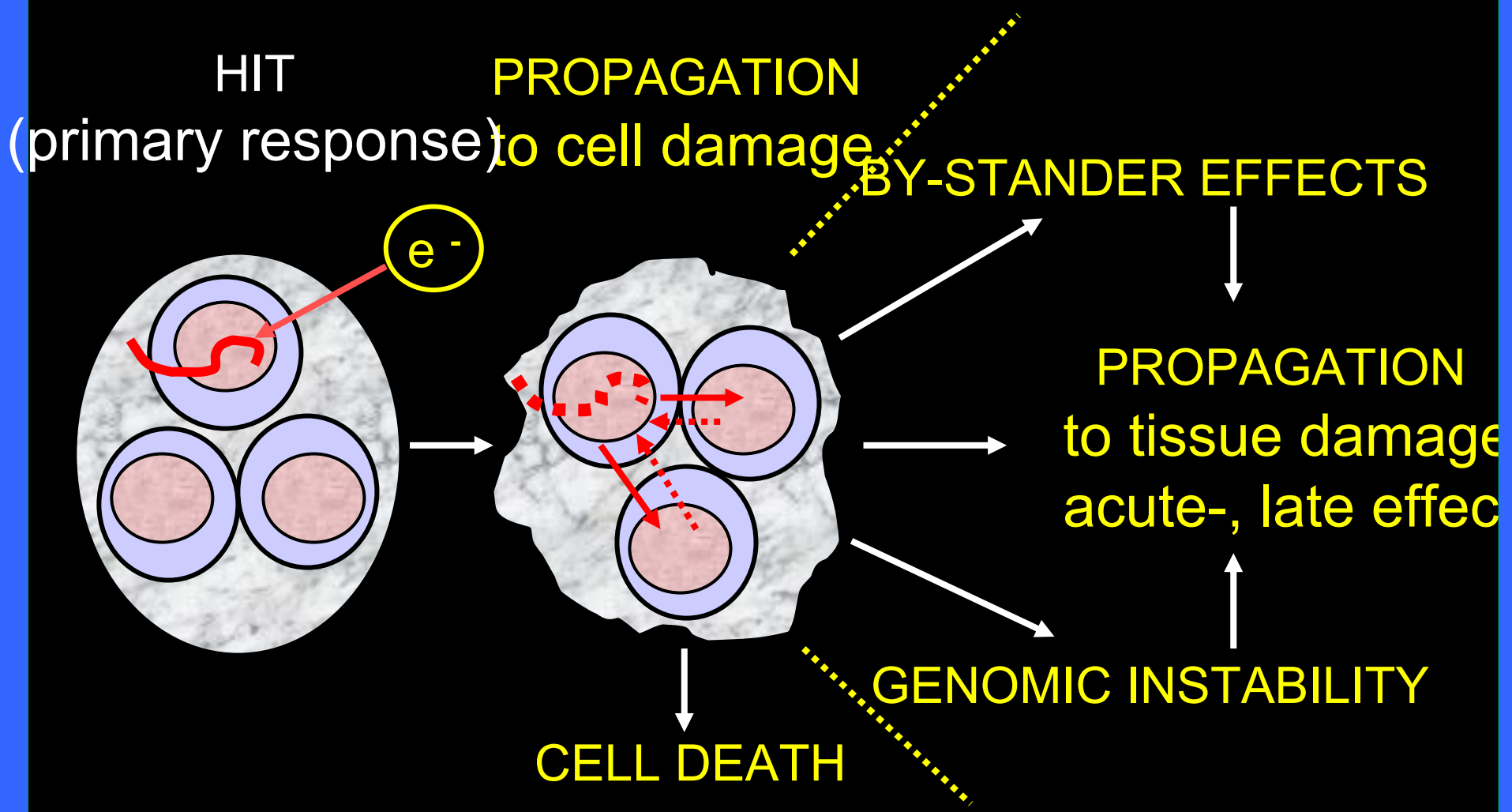
"HIT" SIZES VARY BY A FACTOR OF ~ 10^2



Adapted from: Booz J, pers. comm., 1986; ICRU Rep 36, 1983

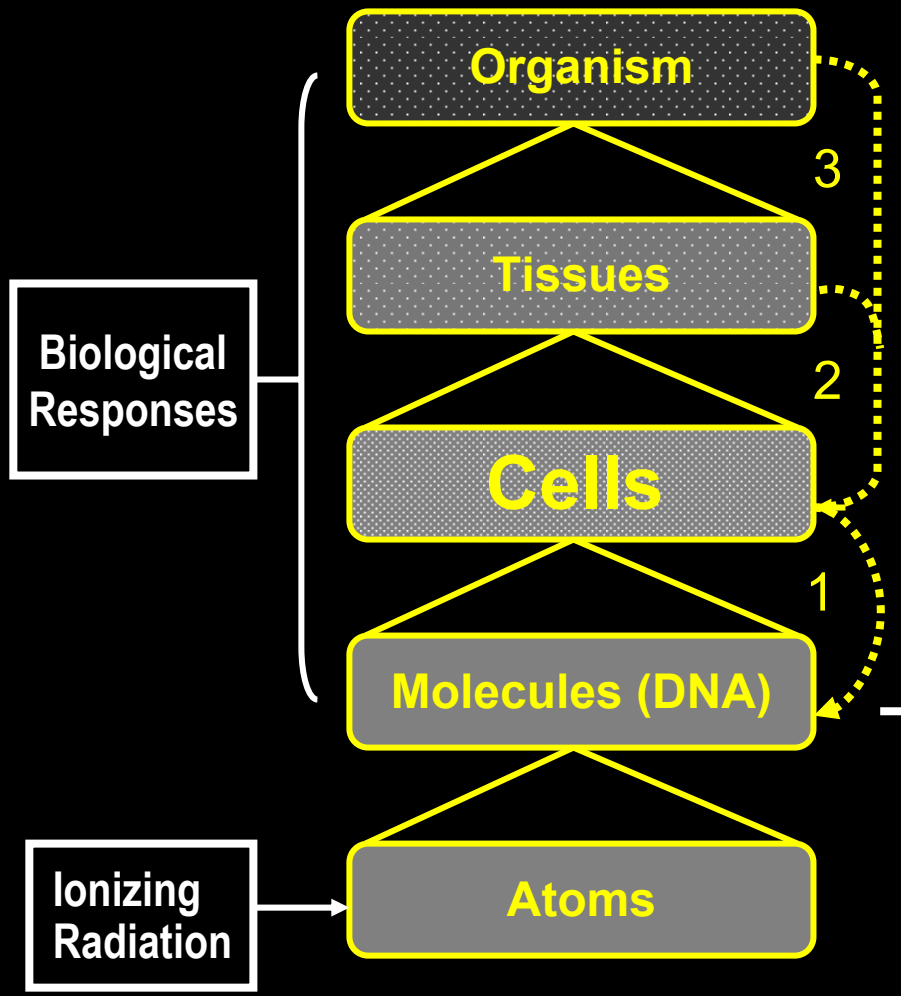
Cell Doses Trigger System Effects

PRIMARY RESPONSE IS AT MOLECULAR LEVEL, DNA

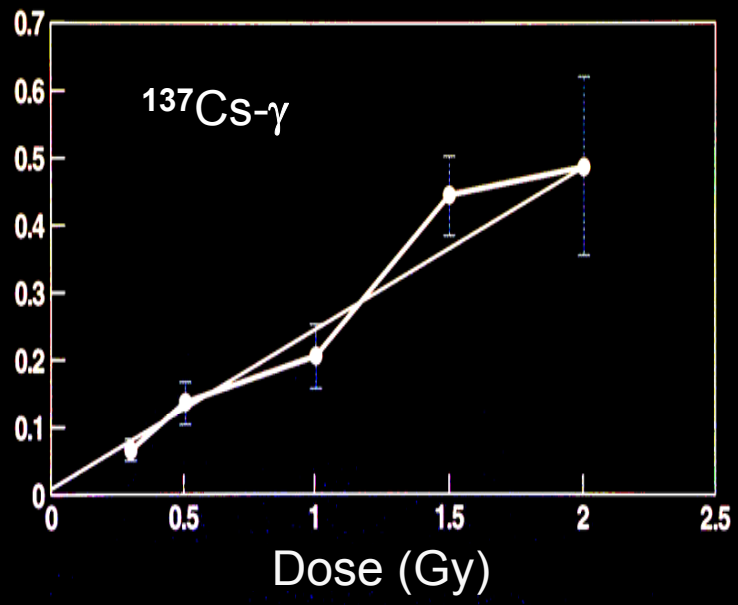


Dose-Risk Function is Linear for Instant DNA Damage

$$DNA_d = \alpha \bullet [\bar{z}_{F1} \bullet N_H] / N_E$$

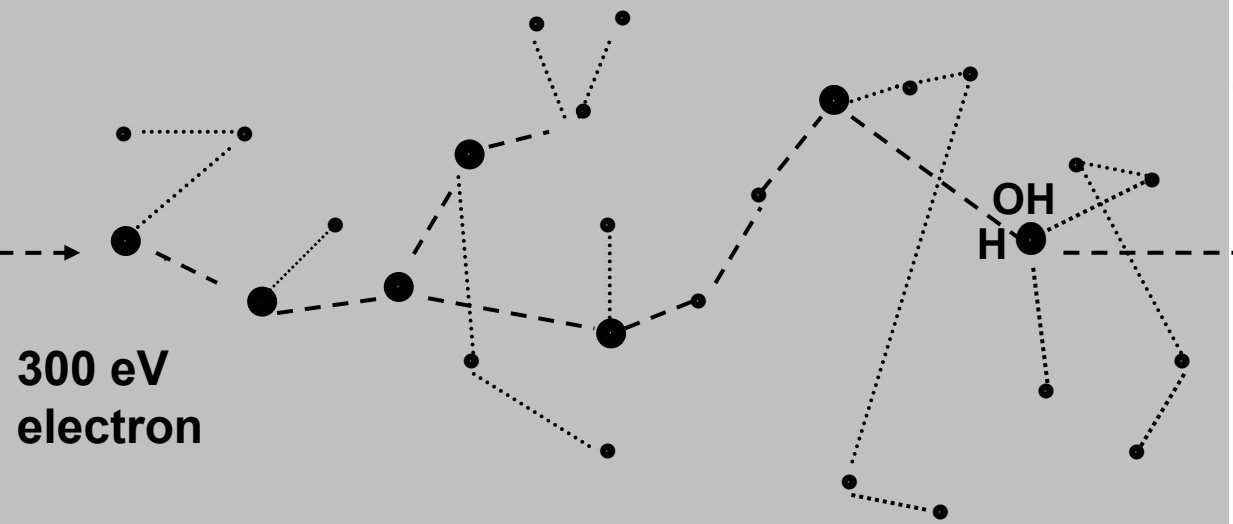


DNA DAMAGE
(here thymine-glycol
in T_1-Cells in Culture)



Machost D, Thesis, Aachen, 1995

~ 25 - 40 % OF DSB FROM X-RAYS HAVE COMPLEX STRUCTURE AND ARE < 1 % OF TOTAL DNA DAMAGE.



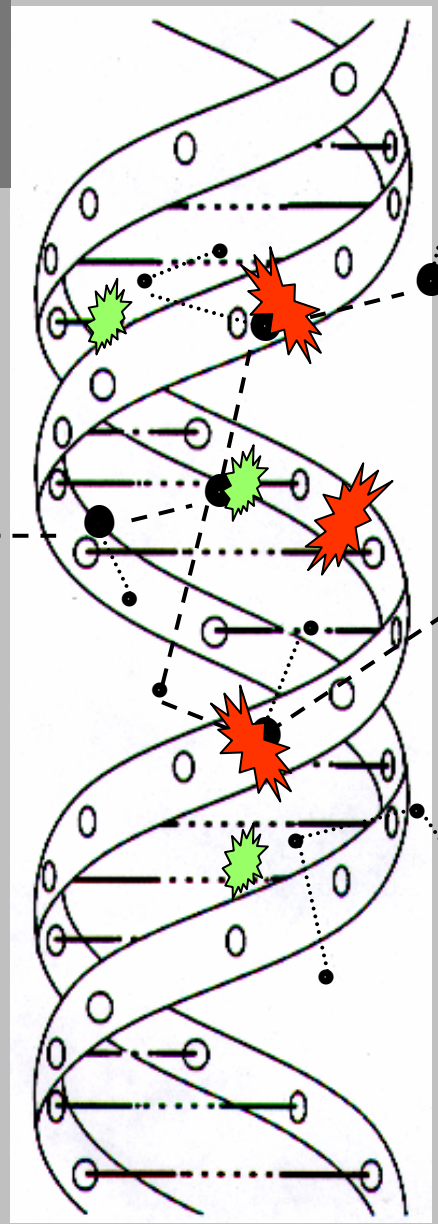
300 eV electron

One electron track

● = ionized molecule mainly H_2O

• = excited molecule

2 nm

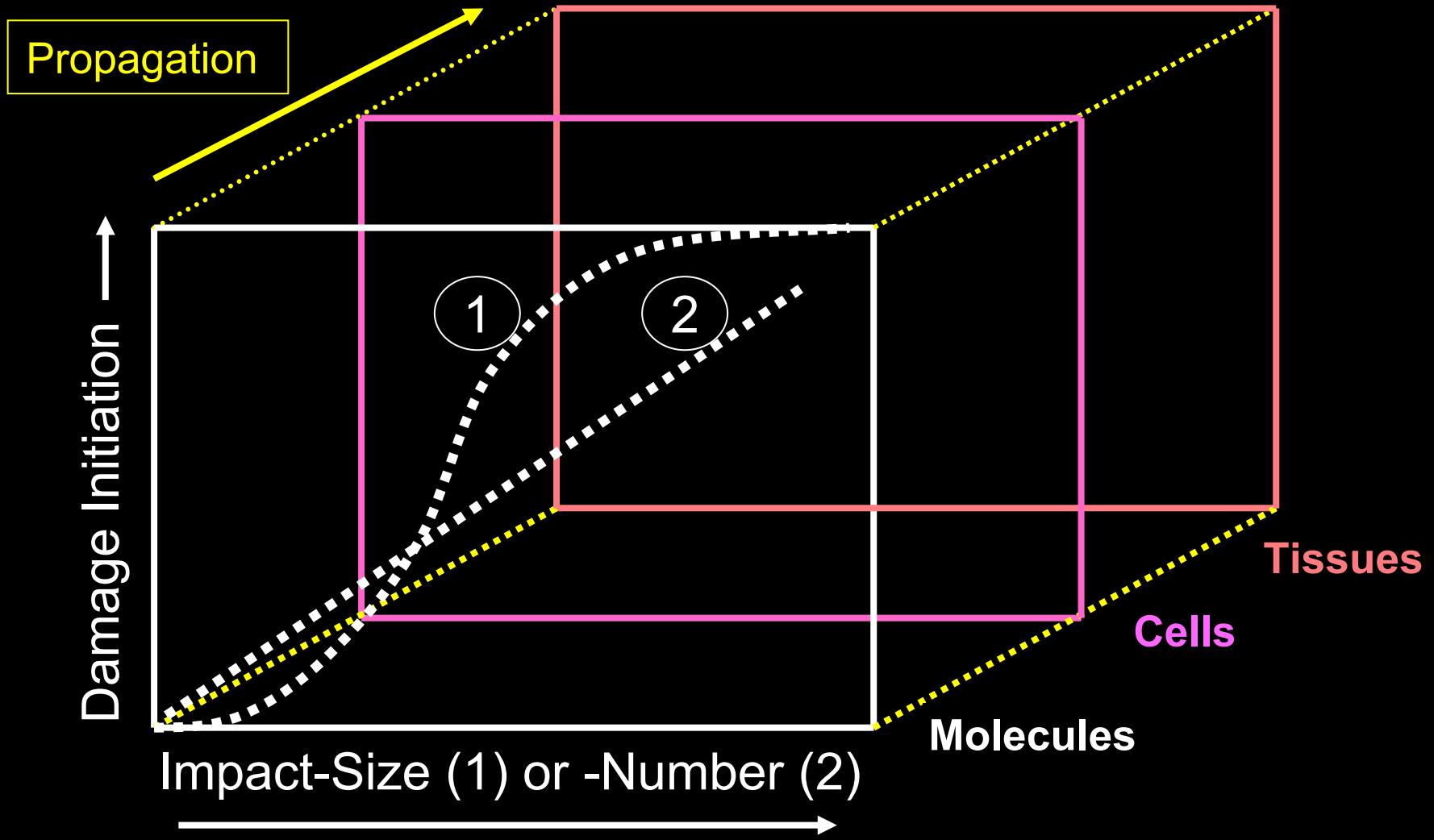


From: Goodhead D, pers. comm., 21. 08. 2003

DTG 21.8.03

The Dose-Risk Functions at Molecular Level (DNA)

THEY DEPEND ON TYPE AND SIZE OF IMPACT.



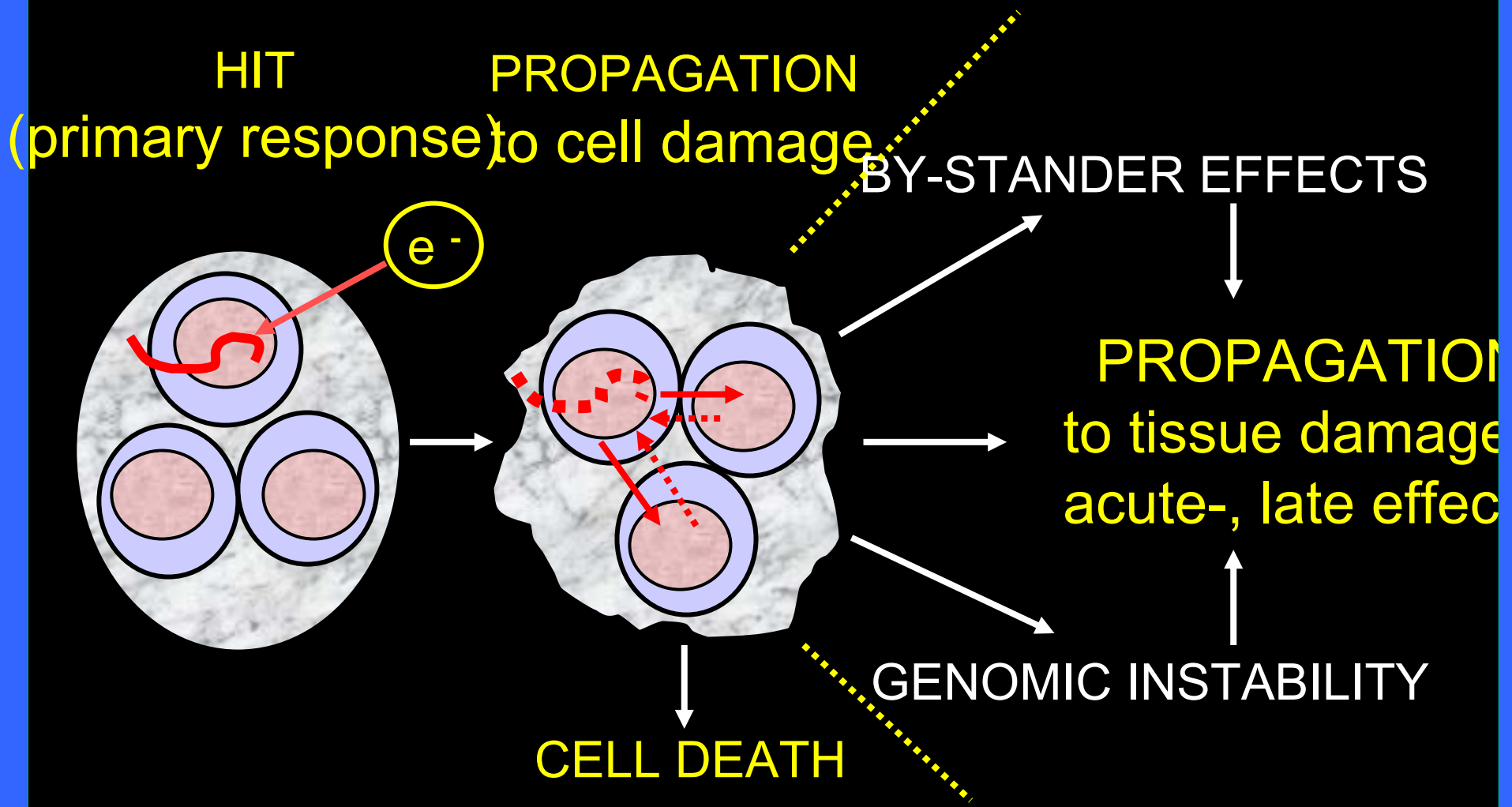
Responses to Impacts at the DNA Level

They are:

1. sigmoid with increasing concentrations to toxic agents (energy, heat, molecules, drugs); "Impact-Size-Effectiveness-Function" (ISEF). (Microdose presents impact-size).

2. linear with increasing numbers of tracks (microdoses with $\bar{z}_1$) from defined radiation; "Impact-Number-Effectiveness Function" (INEF). (Tissue dose presents impact-number.)

Microdoses (Cell Doses) Trigger System Effects



Contrary to instant DNA damage,

damages to DNA and cell from

by-stander effects and from genomic instability

both appear to have dose thresholds

and reach plateaus with increasing dose.

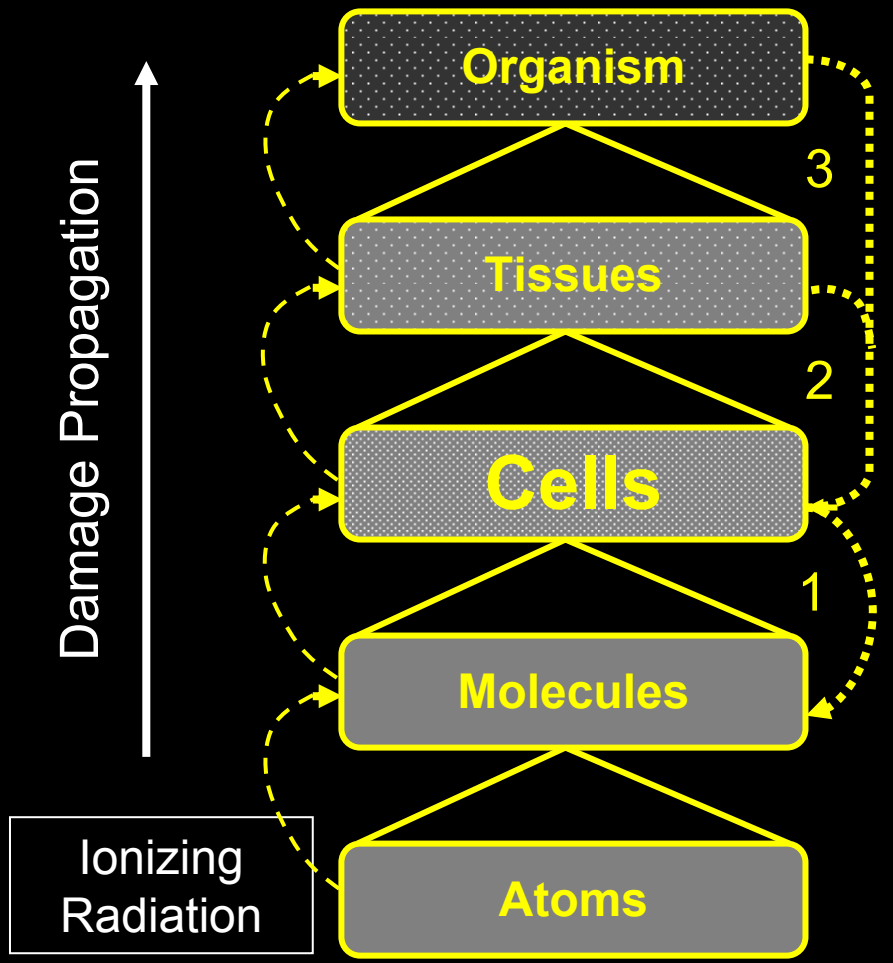
Instant plus secondary damages to DNA and cell

all confront the body's defenses

against damage and its propagation.

Damage and Its Propagation Confront Defenses

ORGANIMS HAVE THREE TYPES OF DEFENSES.



AT EACH LEVEL:

1. PHYSICAL-STATIC
2. METABOLIC “TYPE 1” IMMEDIATE
3. METABOLIC “TYPE 2” DELAYED

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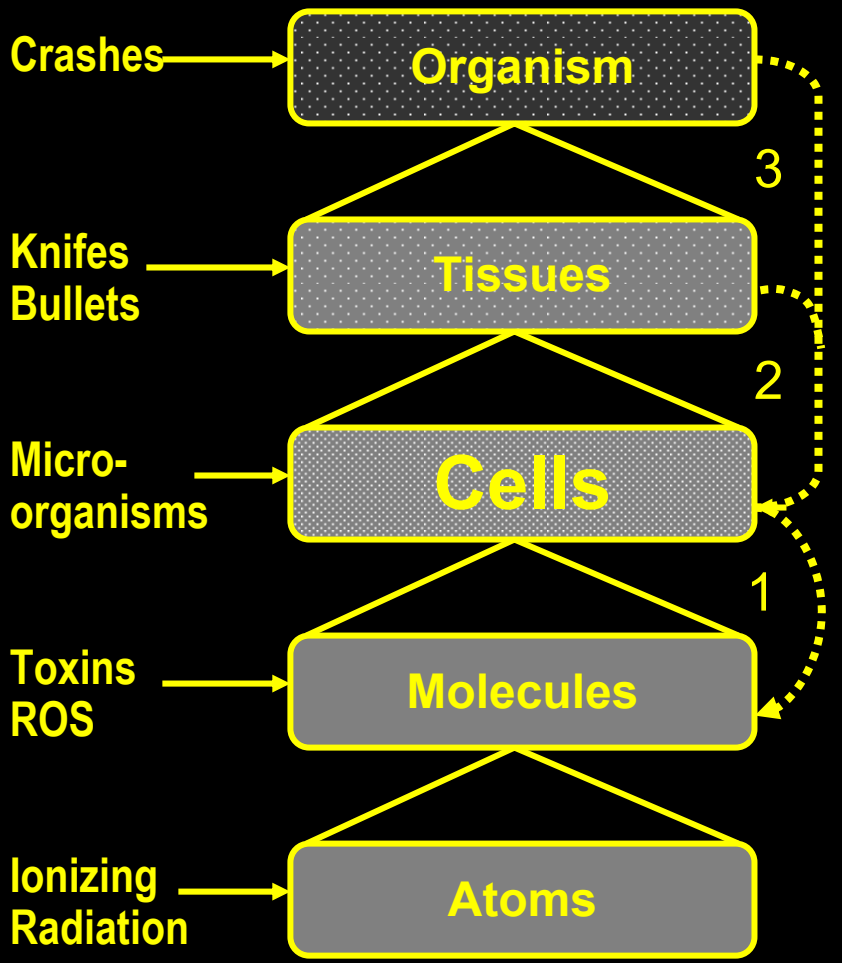
Physical-Static Defenses

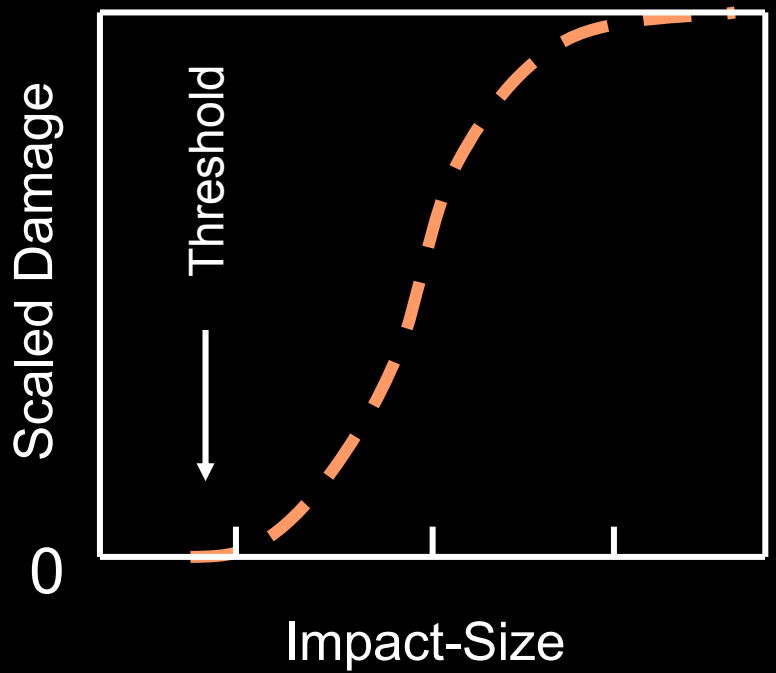
INERTNESS AND REDUNDANCY BLOCK DAMAGE.



AT EACH LEVEL:

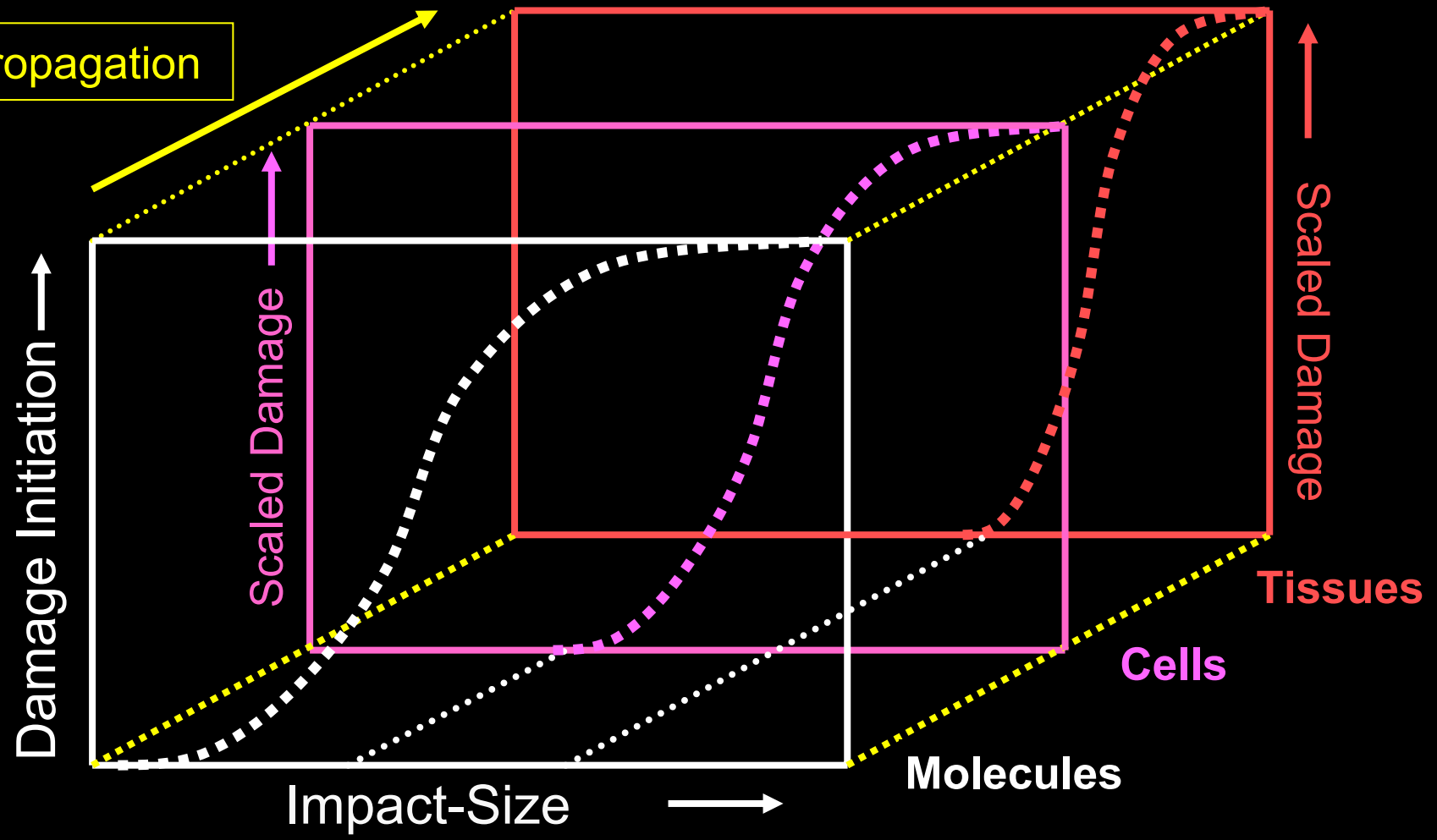
"Impact-Size-Effectiveness-Function"

ISEF



Physical-Static Defenses

EACH LEVEL BLOCKS DAMAGE AND PROPAGATION.



EACH HIERARCHICAL LEVEL HAS ITS ISEF.

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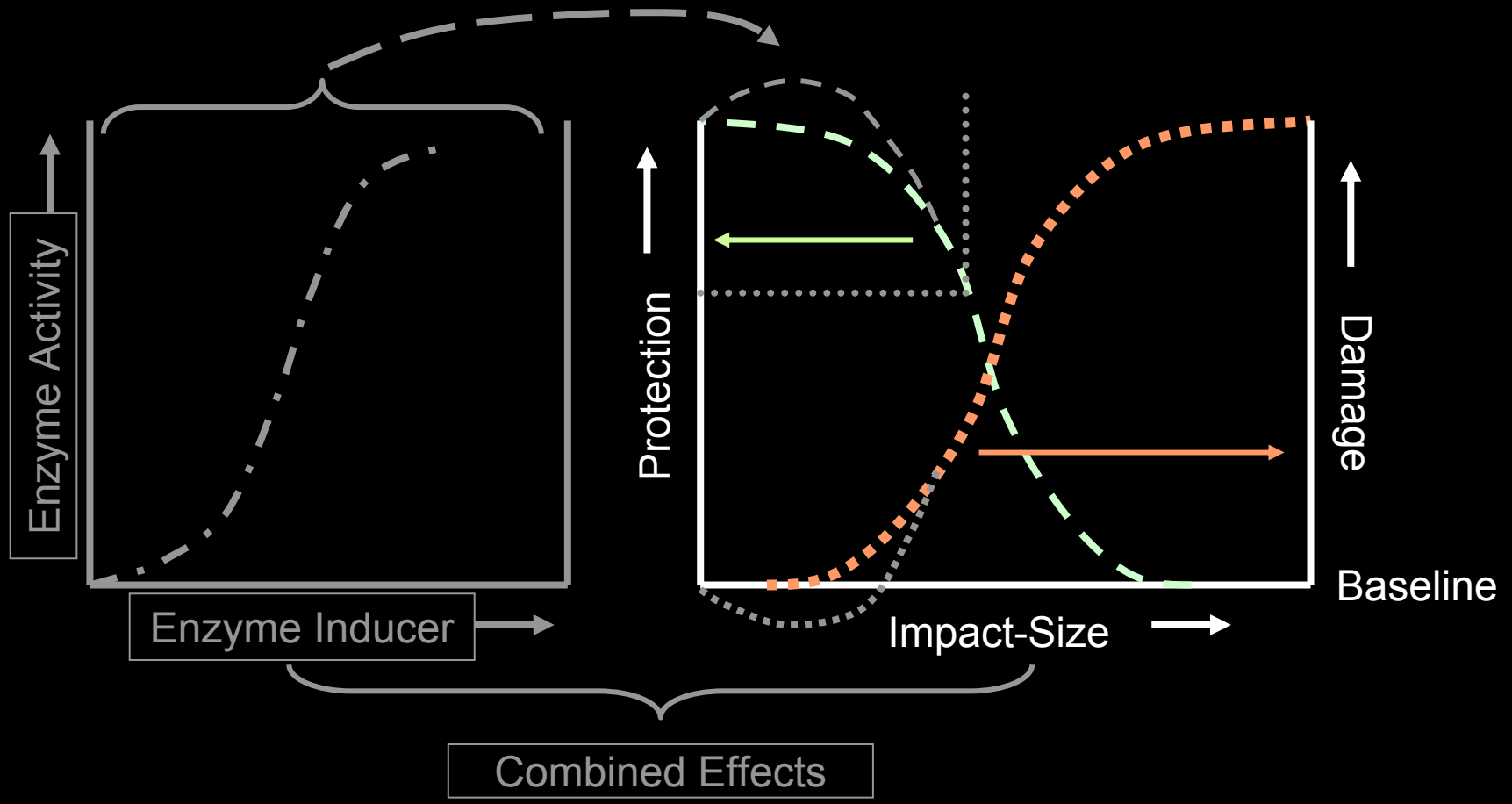
General Feature of Metabolic Defenses

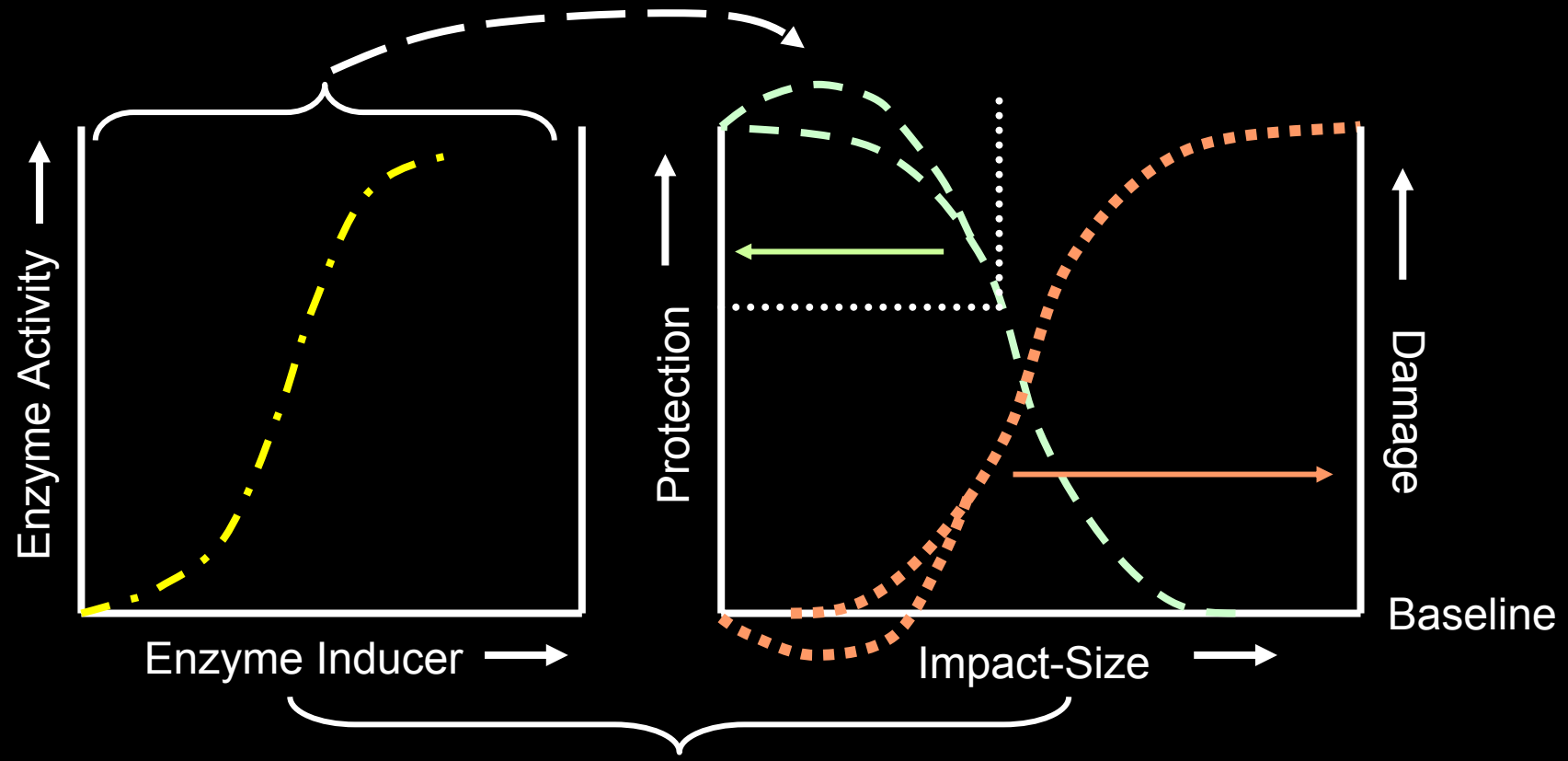
Impact-size also may induce enzyme for protection-repair.



Modified from Tubiana M et al., Radiology 2009

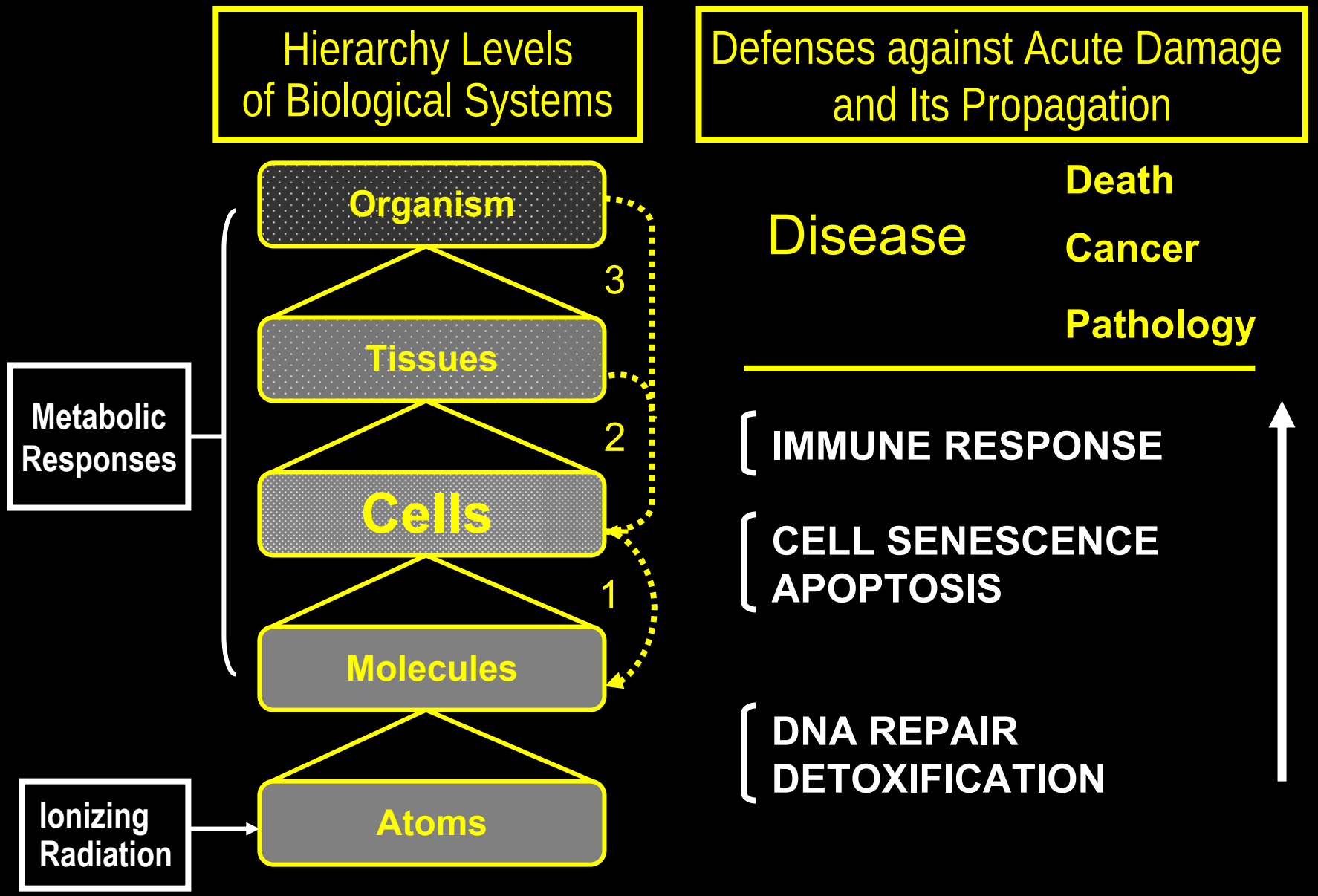
General Feature of Metabolic Defenses

IMPACT-SIZE MAY INDUCE ENZYMES DIRECTLY.



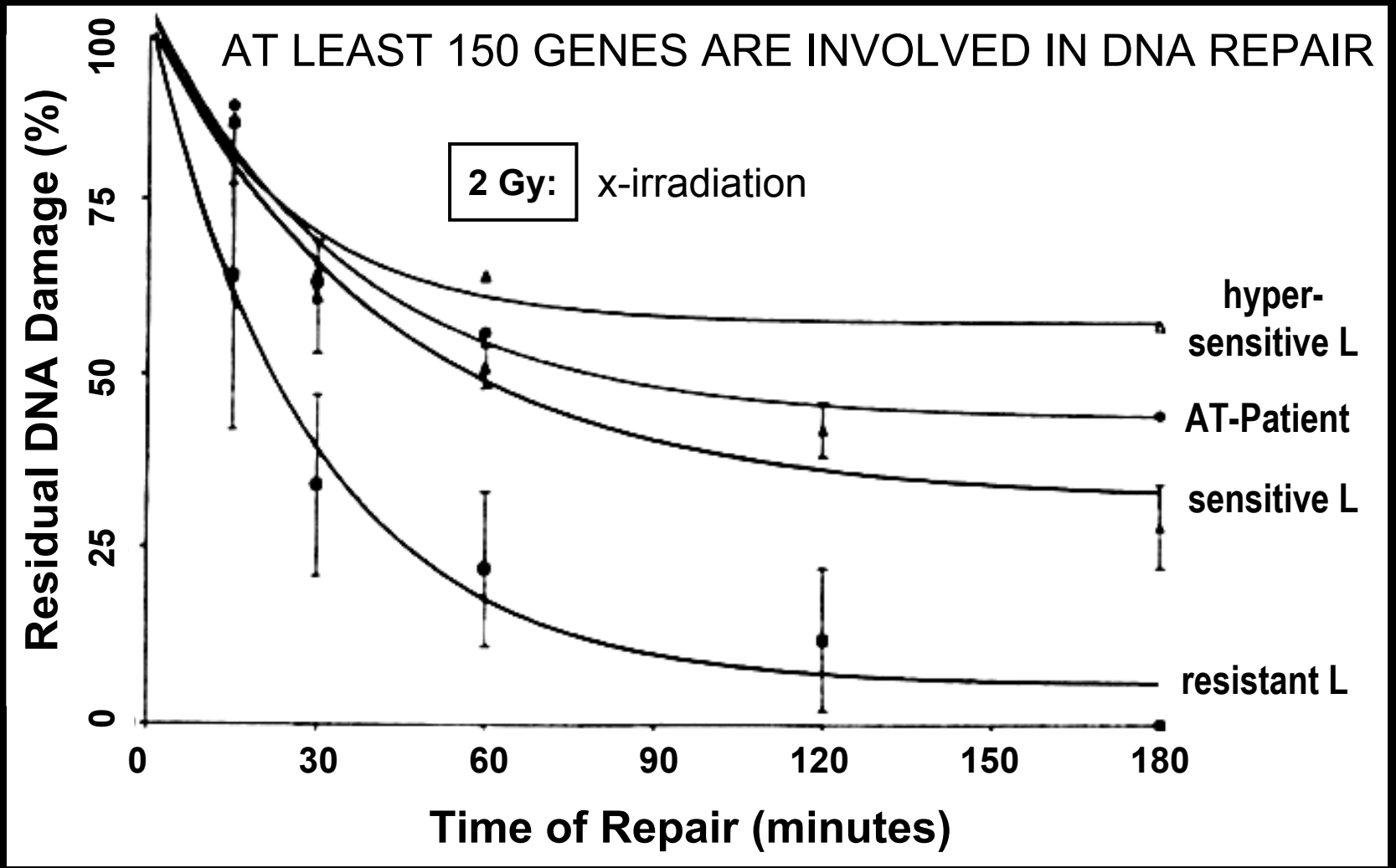
Modified from Tubiana M et al., Radiology 2009

Metabolic Defenses "Type 1" Operate Immediately



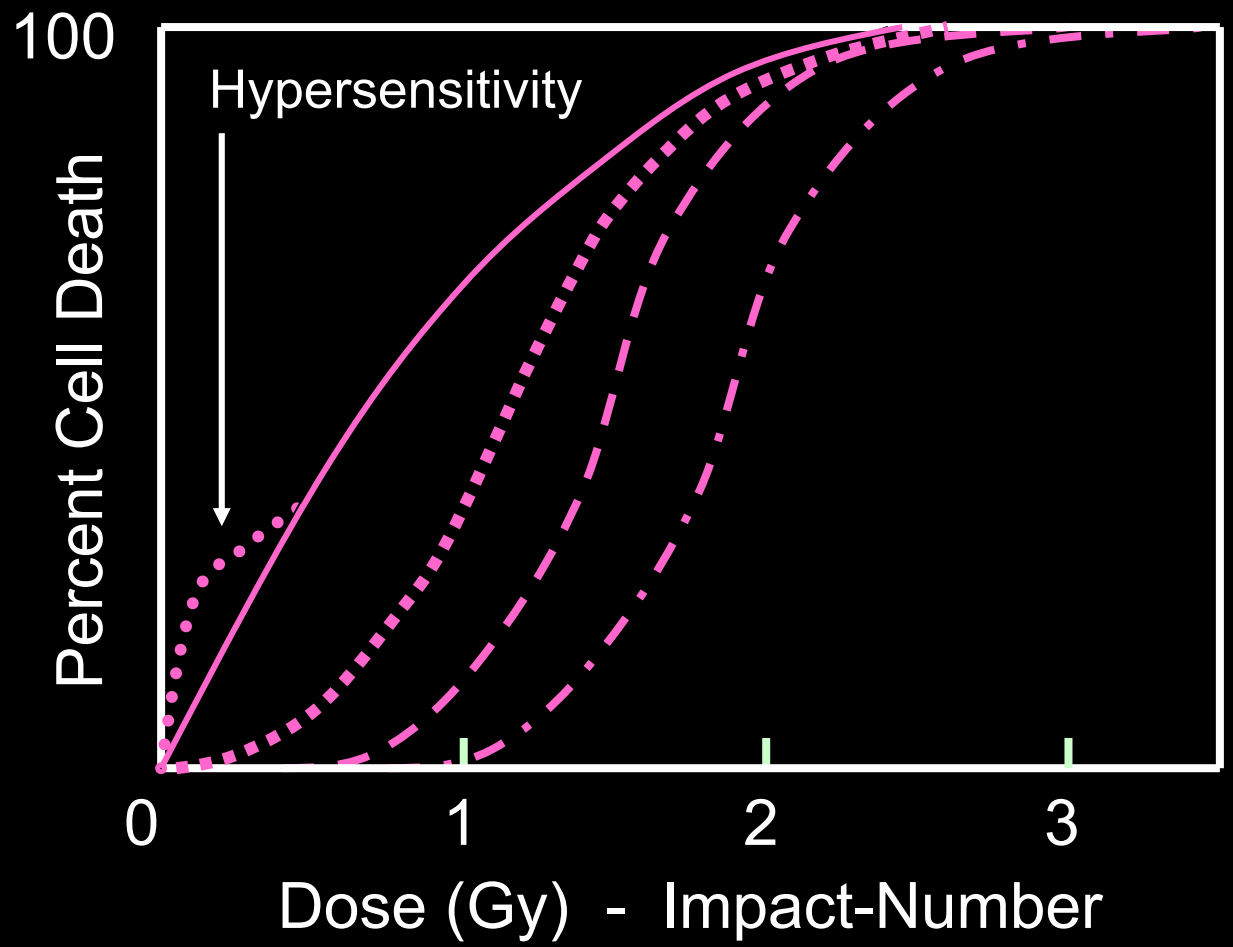
Repair of DNA-DSB from Different Patients

HUMAN LYMPHOCYTES (L) IN CULTURE.



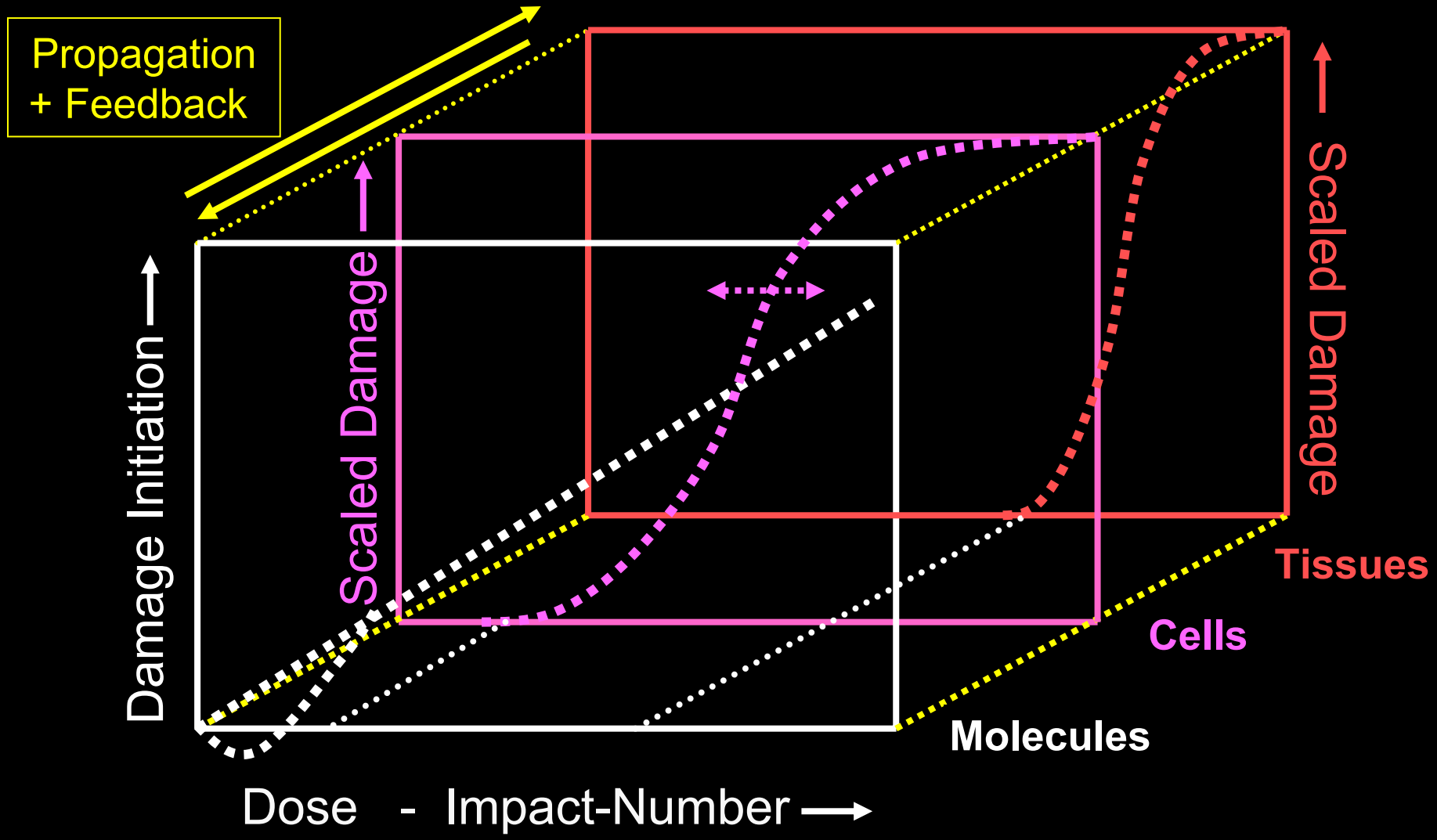
Müller WU et al., 2001

Cells Have Individual Sensitivities



Metabolic Defenses "Type 1" Respond Immediately

EACH LEVEL BLOCKS DAMAGE AND PROPAGATION.



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Many reports since 1979 attest that

low-doses can cause late up-regulation

of physiological defenses

that may last for more than a year,

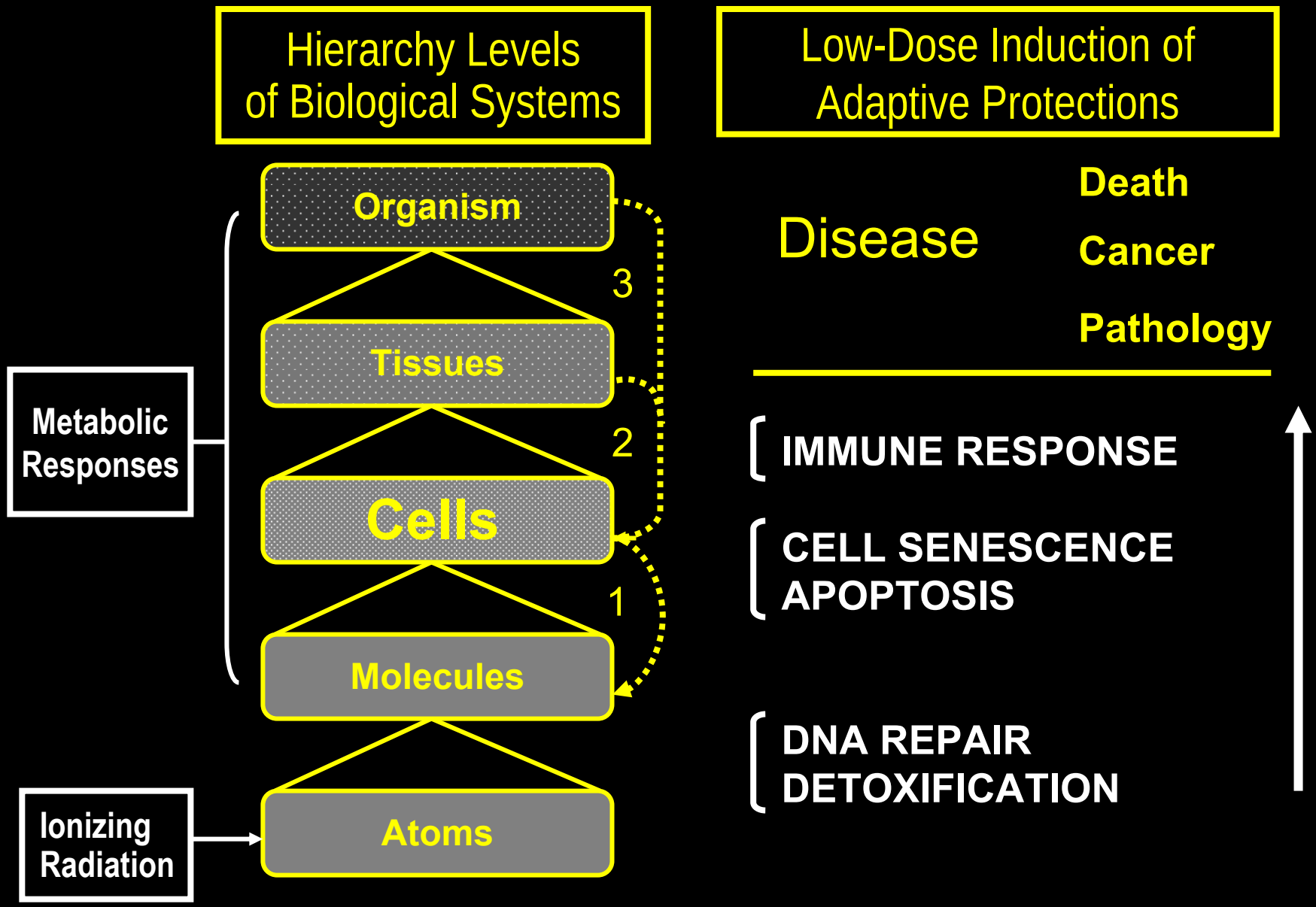
i.e., cause adaptive responses

in terms of adaptive protections.

These adaptive protections may be called

metabolic protections “type 2”.

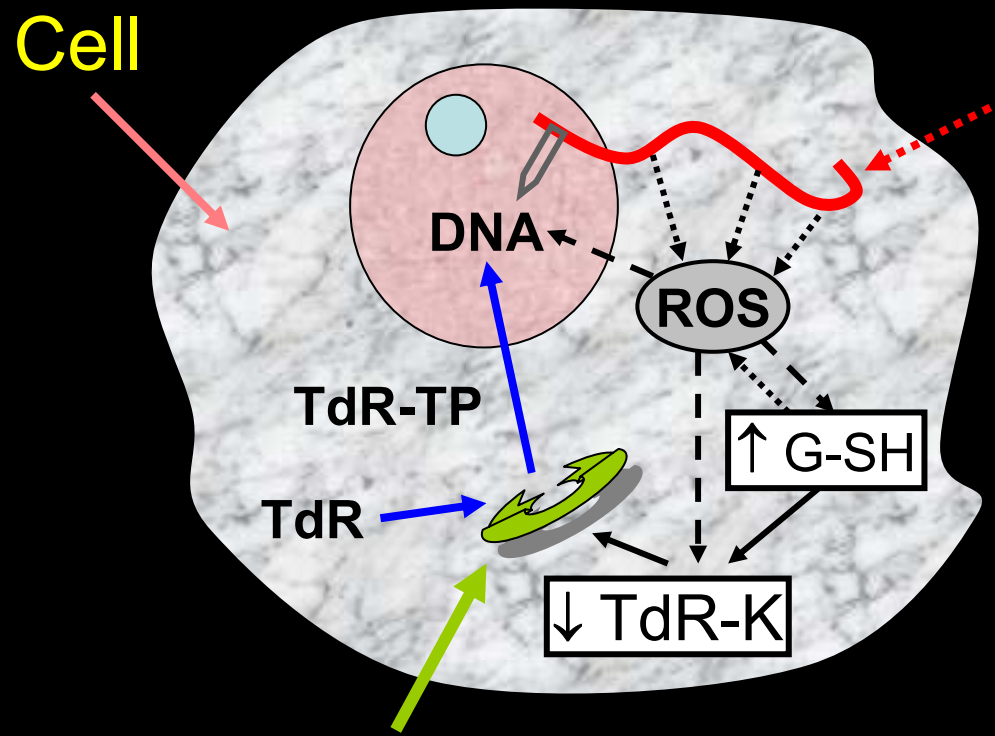
Metabolic Defenses "Type 2" Respond Delayed



Low Dose Changes Signaling for Delayed Effects

WB MOUSE γ-IRRAD. < 10 mGy → 4 HRS BM TESTING

FOR THYMIDINE-KINASE (TdR-K); GLUTATHIONE (G-SH)



TdR-K phosphorylates thymidine (TdR)
to thymidine-triphosphate (TdR-TP)
for incorporation into DNA

SIGNALING CASCADE
in mouse bone marrow:

↑ ROS →

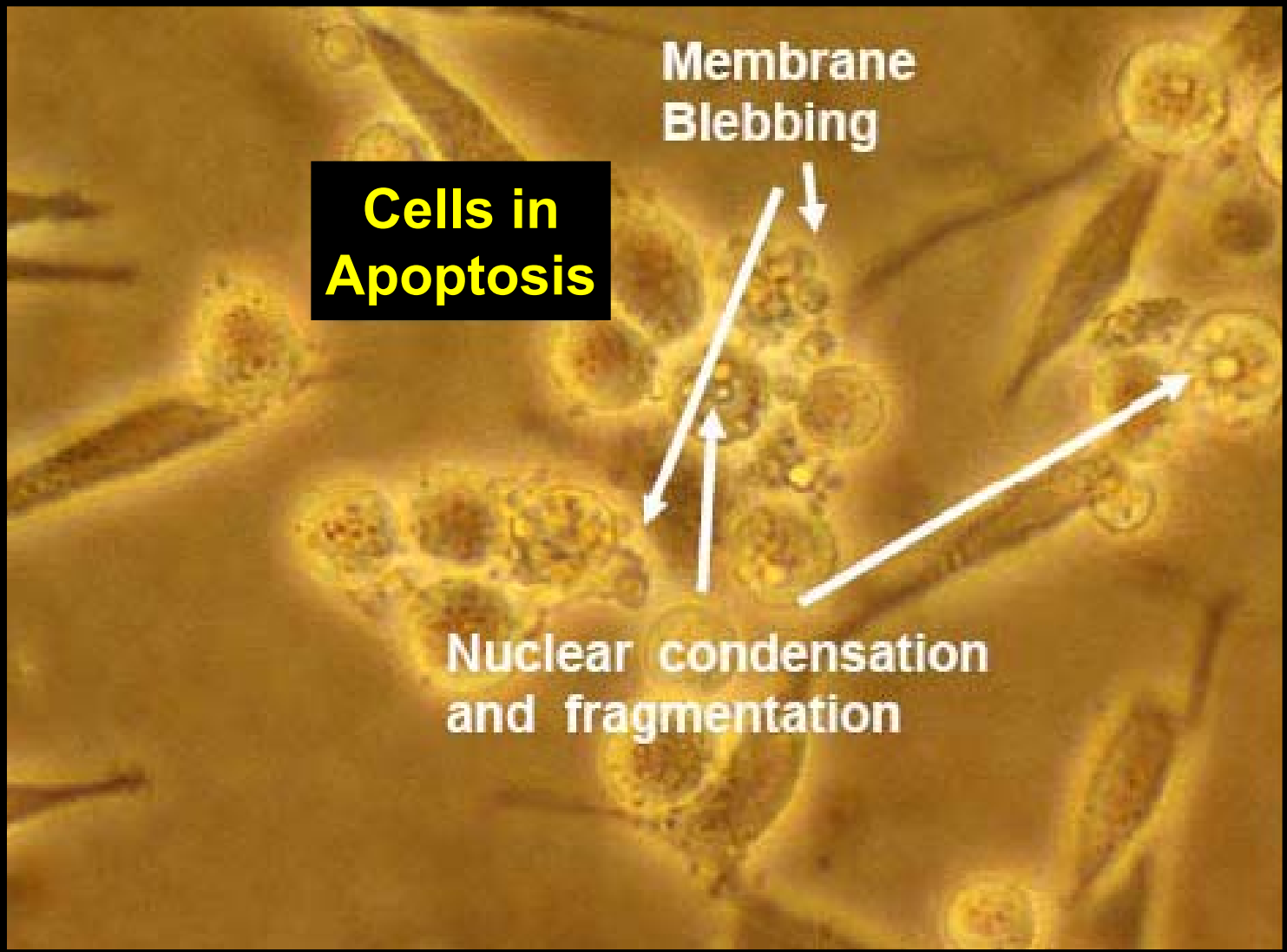
↑ G-SH →

↓ TdR-K

for up to ~ 12 hours

Zamboglou N et al., 1981
Feinendegen LE et al., 1982 -1987
Hohn-El-Karim et al, 1990

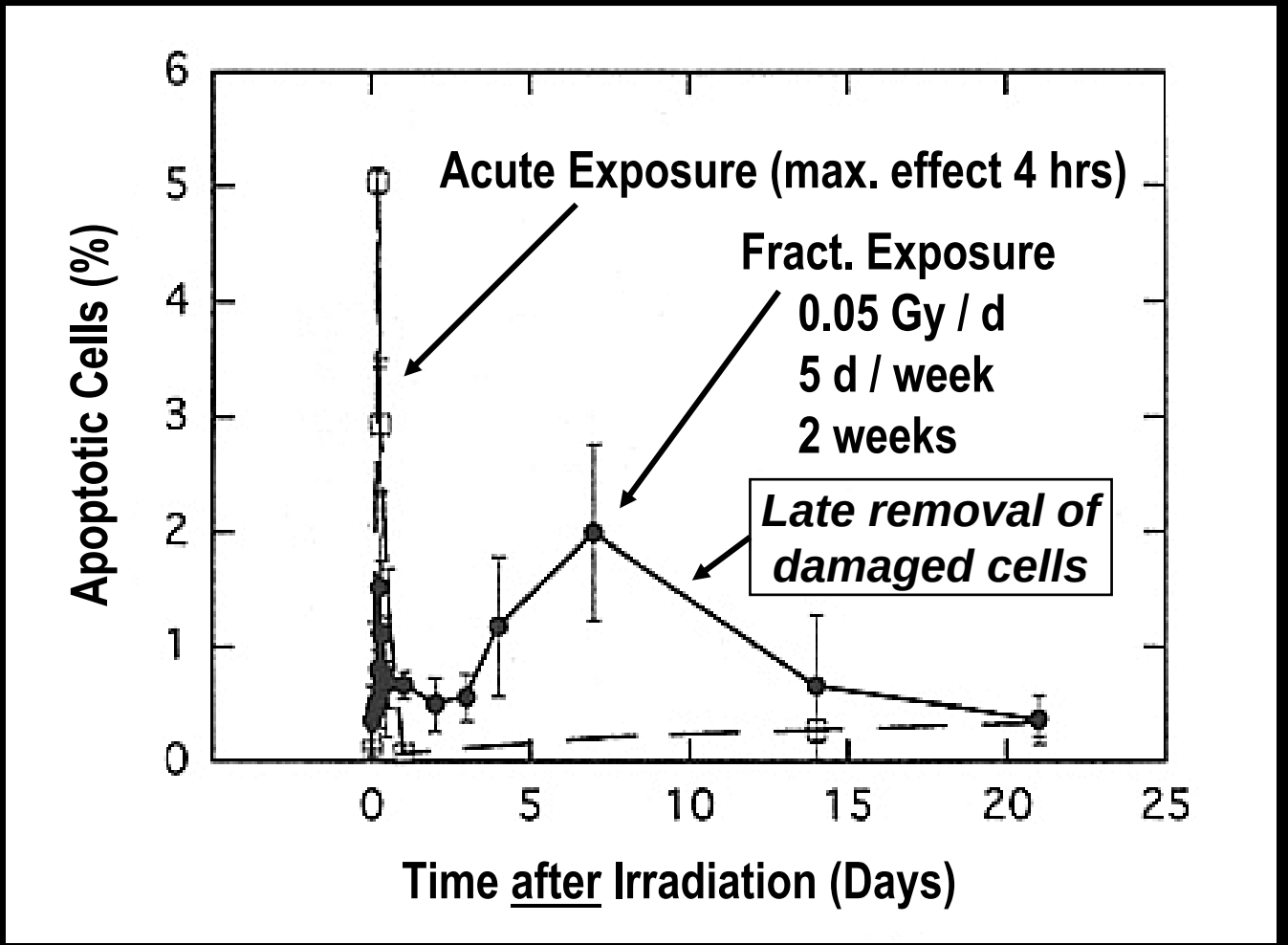
Apoptosis = Signal-Induced Cellular Suicide



Bauer G, University Freiburg, Germany, pers com, 2007

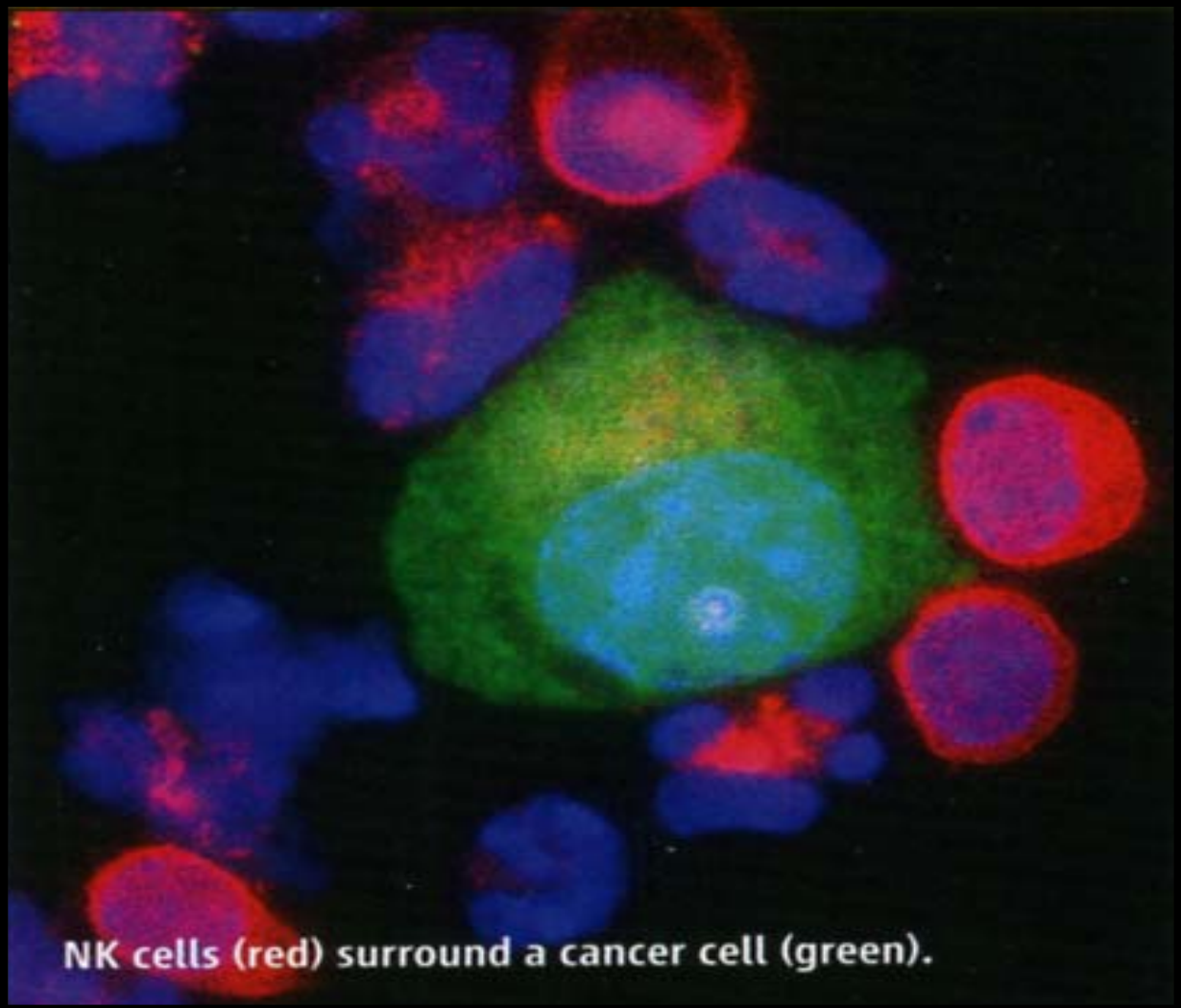
Low-Dose Induces Late Apoptosis of Damaged Cells

0.5 GY WB γ-IRRADIATION MICE, THYMUS, *IN VIVO*



Fujita et al., in Apoptosis, Business Ctr. Acad. Soc. Japan, 1998

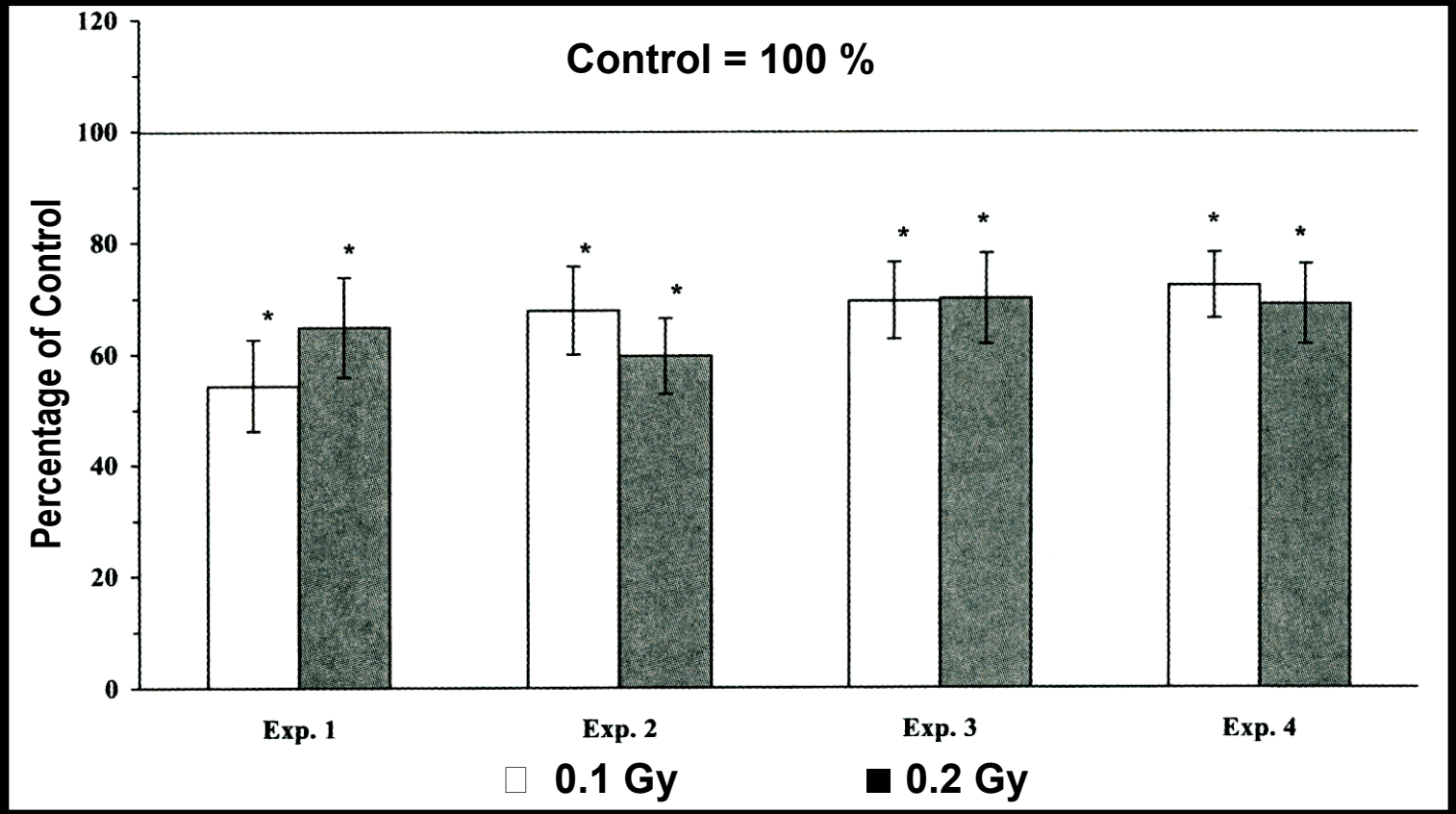
Lymphocytes (red) on Cancer Cell (green)
IN SR/CR STRAIN OF MICE



Hicks et al., PNAS 103: 10.1073 (2006)

Low-Dose Induced ↓ of Lung Metastasis, BALB Mice

WB X-IRRADIATION → 2 HRS: SARCOMA TRANSPLANT → 2 WKS: LUNG METASTASIS COUNT

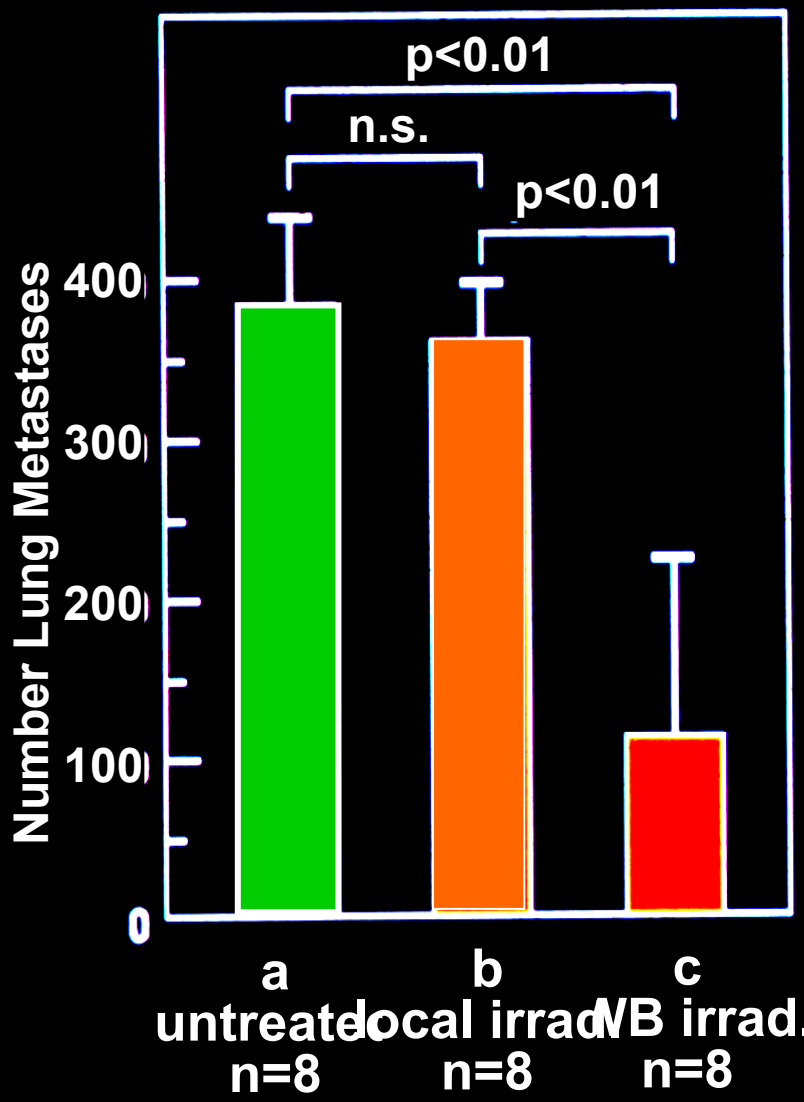


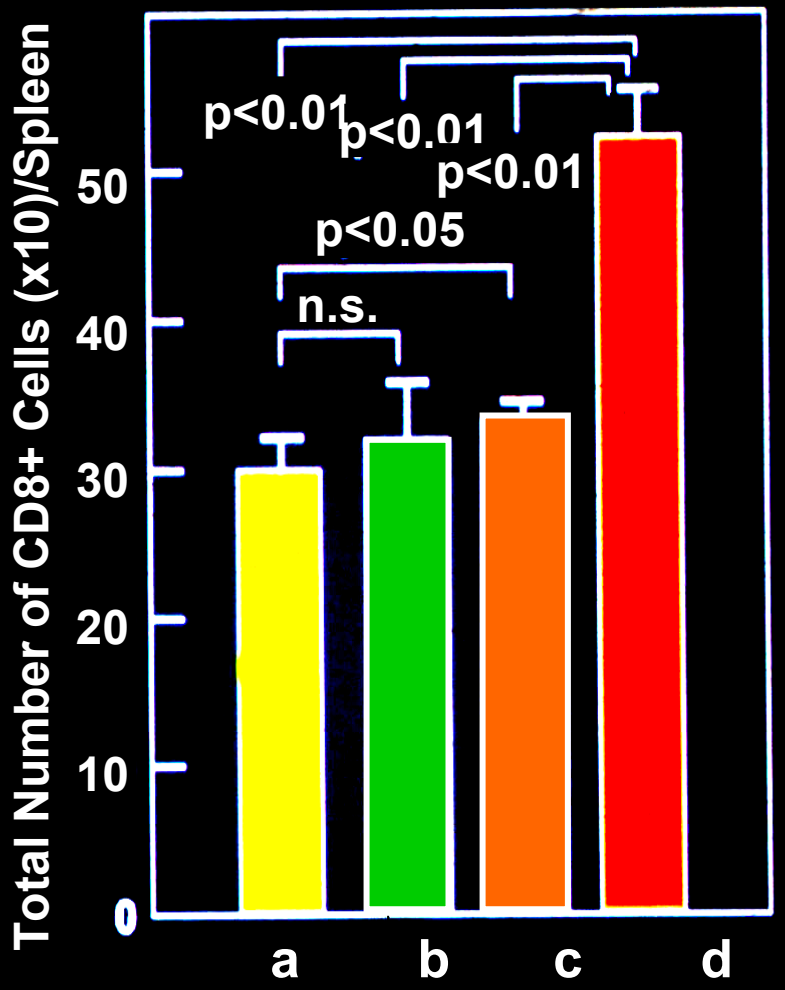
L 1 sarcoma cells are nonimmunogenic for BALB/c mice (each experimental group had 12 mice)

Cheda A et al., Radiat Res, 2004

Low-Dose Induced ↑ of Immune Response Rats

HEPATOMA IMPL. → 2 WKS: 0.2 Gy γ-IR. → 4 WKS: CTS.





a): normal rat; b) tu: not treated;
c): tu: local irrad.; d) WB irrad.

Hashimoto S et al., Radiat. Res., 1999

A single dose of ^{60}Co γ-rays (300 mGy)

delivered at low dose-rate (300 mGy / hr),

may induce responses in tissue culture cells

to last for more than a year,

by releasing of a factor into culture medium,

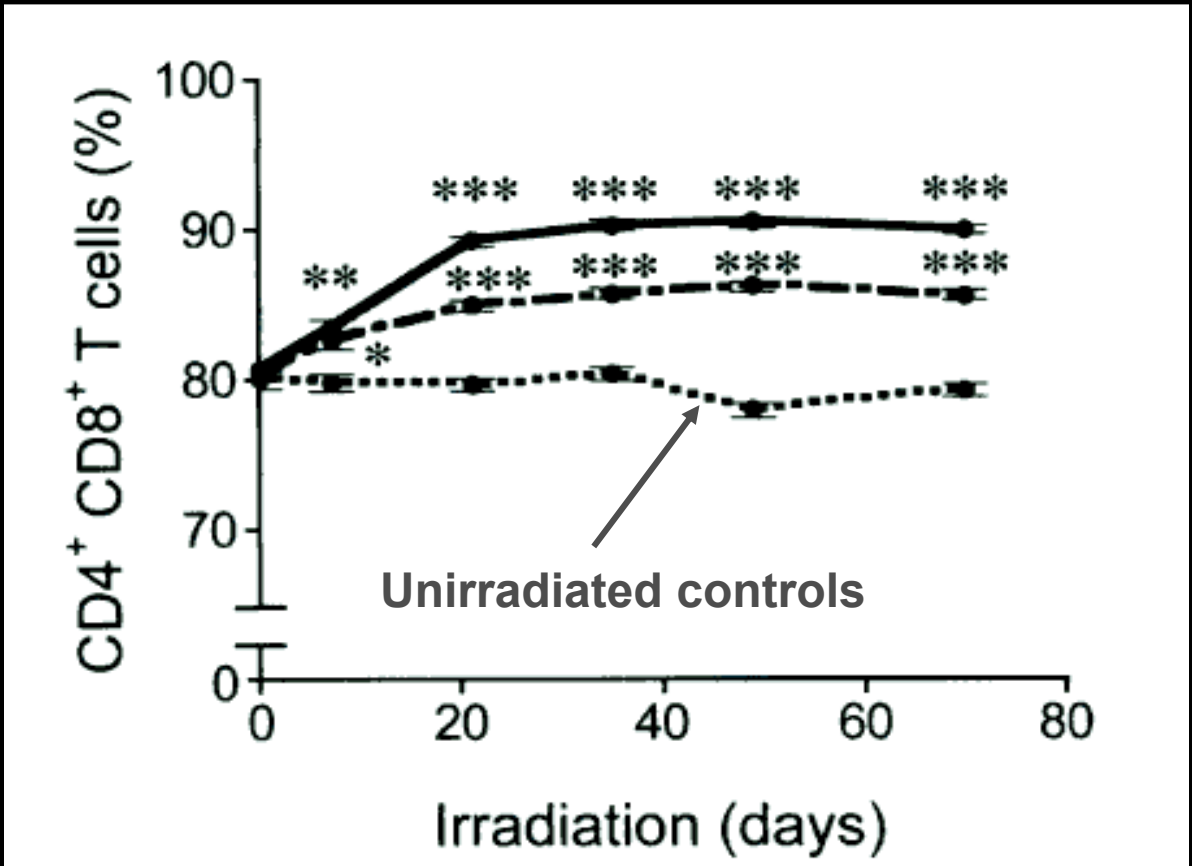
that abolishes radiation hypersensitivity

in non-irradiated cells.

Edin NJ et al., Radiat Res, 2009

Chronic Low γ-Dose Rate Induced ↑ of Immune Cells

MICE WITH DEFECT IN APOPTOSIS-REGULATING *FAS* GENE



• = p < 0.01

** = p < 0.001

*** = p < 0.0001

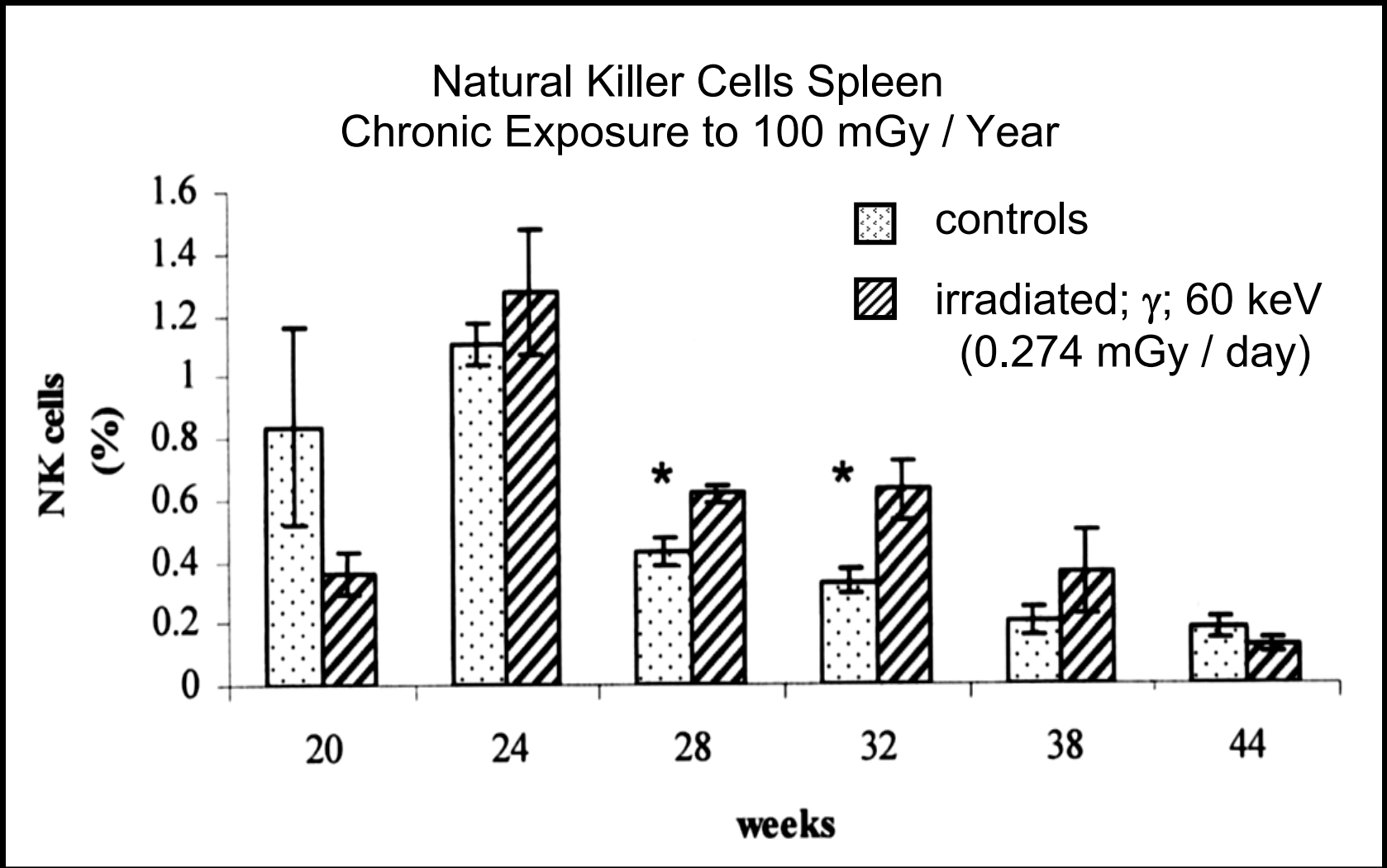
Middle curve: Life time irradiation. 0.35 mGy/hr

Upper curve: dto 1.2 mGy/hr

Ina Y, Radiat Res, 2005

Chronic Low γ-Dose Rate Induced ↑ of Immune Cells

MICE GENETICALLY PRONE TO B-CELL LYMPHOMA

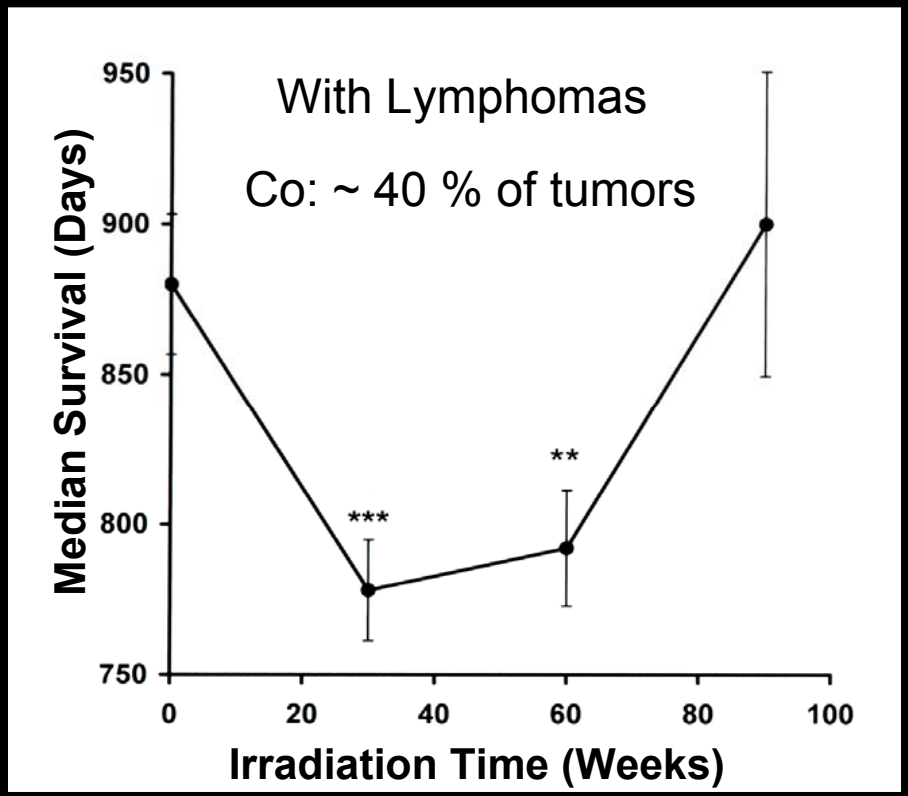


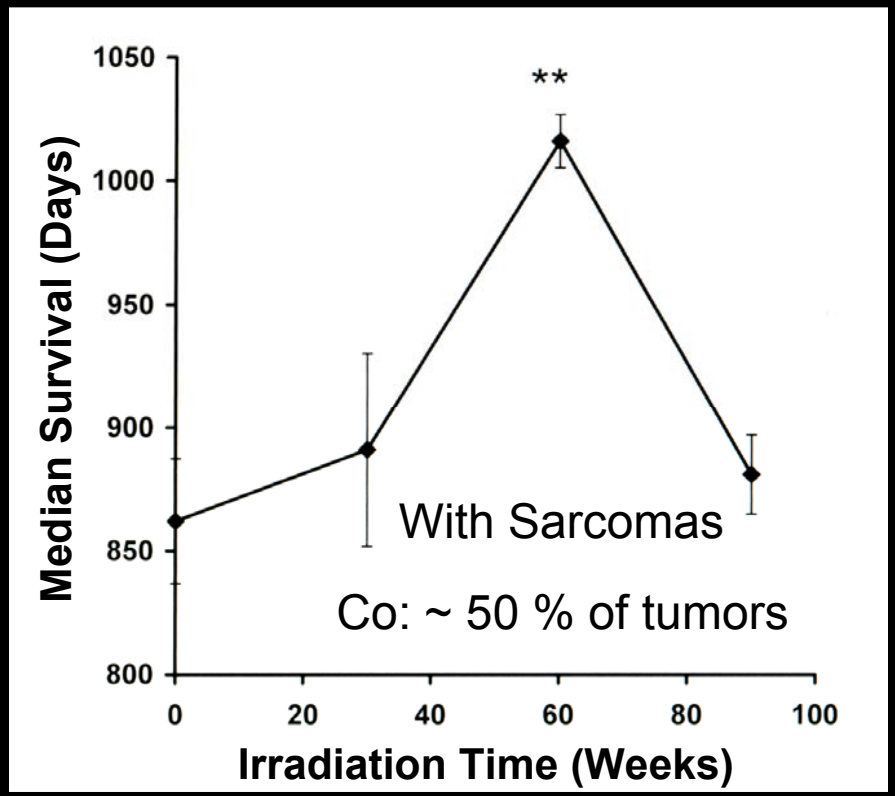
Lacoste-Collin L et al., Radiat Res, 2007

Repetitive Low-Dose WB γ-Irradiation and Tumors

NORMAL MICE 6 WEEKS OLD: 0.33 mGy/d, 5 x / wk.

Dose-rate: 0.7 mGy / hr (^{60}Co γ-rays) – *n= 188 - 232*



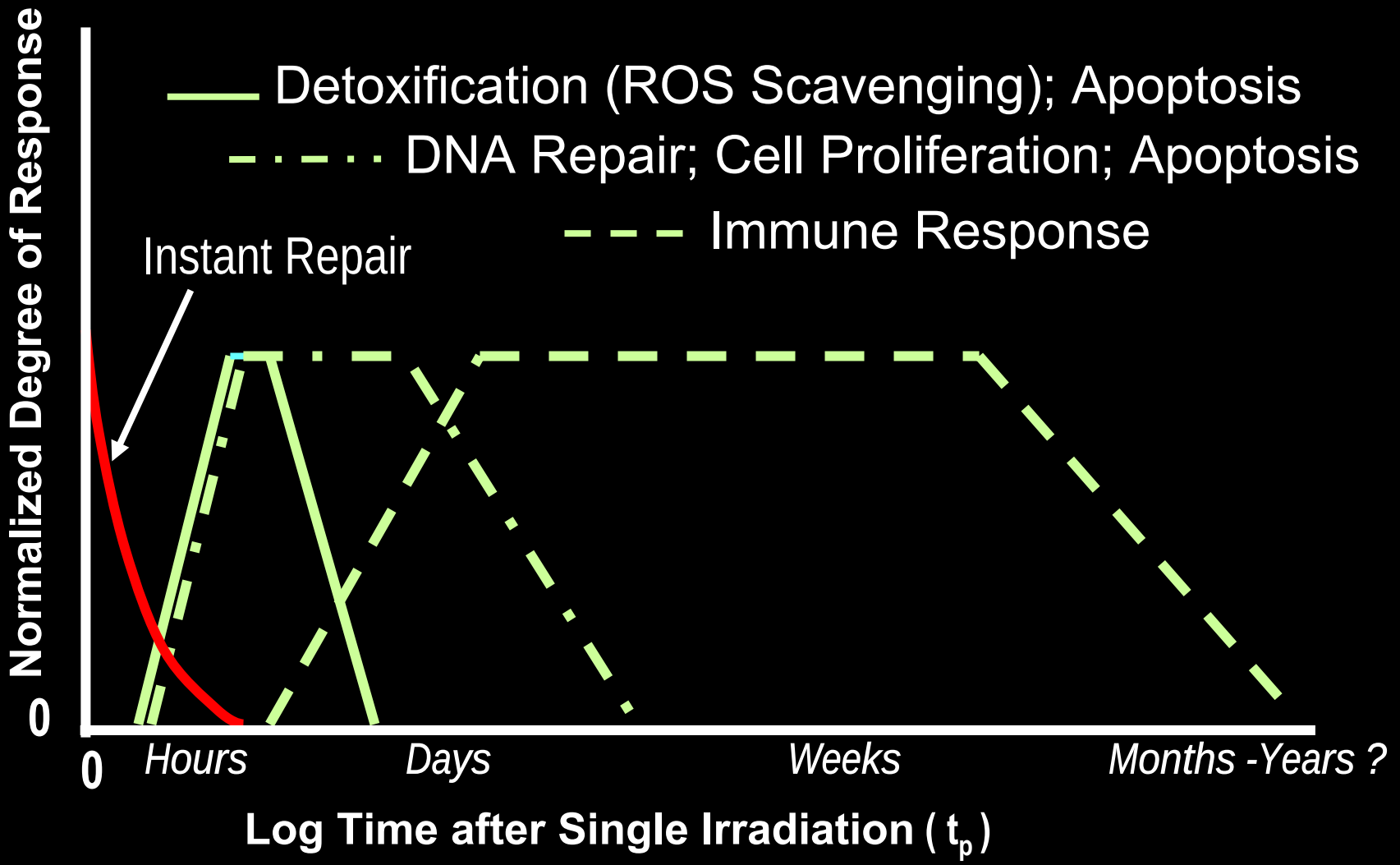


Note: 44 % of mice get tumors; different tissues respond individually.

Mitchel REJ et al., Radiat Res, 2008

Adaptive Protections May Last Beyond a Year

SCHEME: DURATIONS OF PROTECTIONS (t_p).



Feinendegen LE, Brit J Radiol, 2005

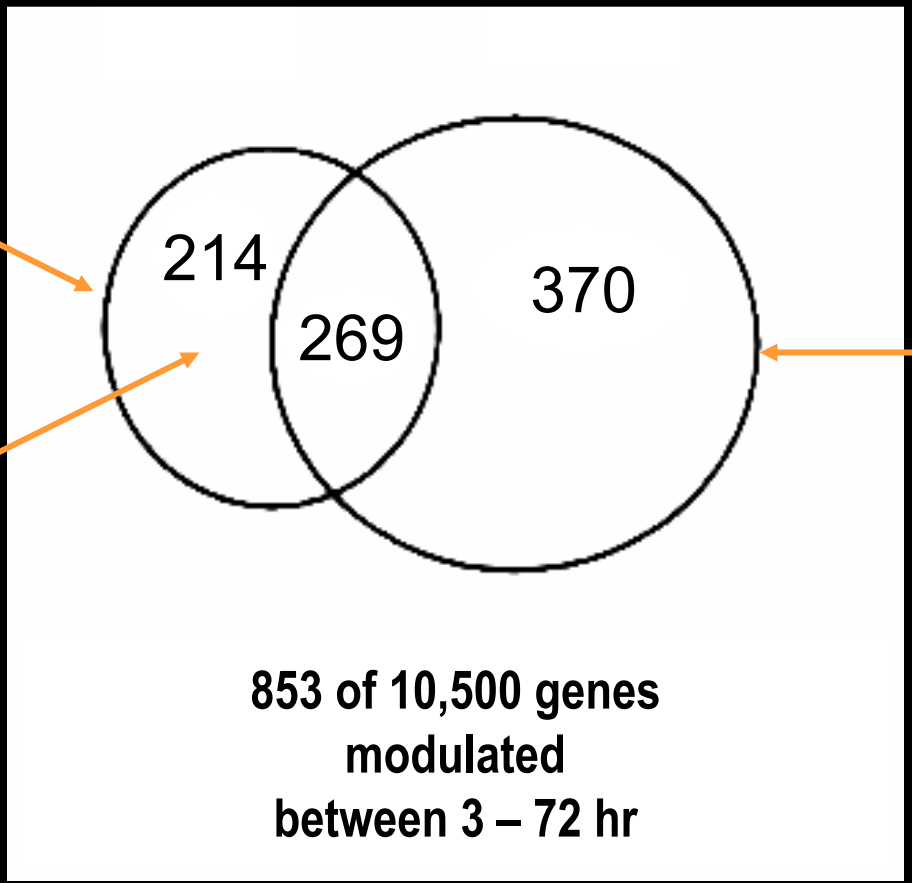
Late Modulation of Specific Genes by Low Dose

HUMAN KERATINOCYTES IN CULTURE

3 – 72 HRS AFTER γ-IRRADIATION.

10 mGy

STRESS RESPONSE GENES MAINLY

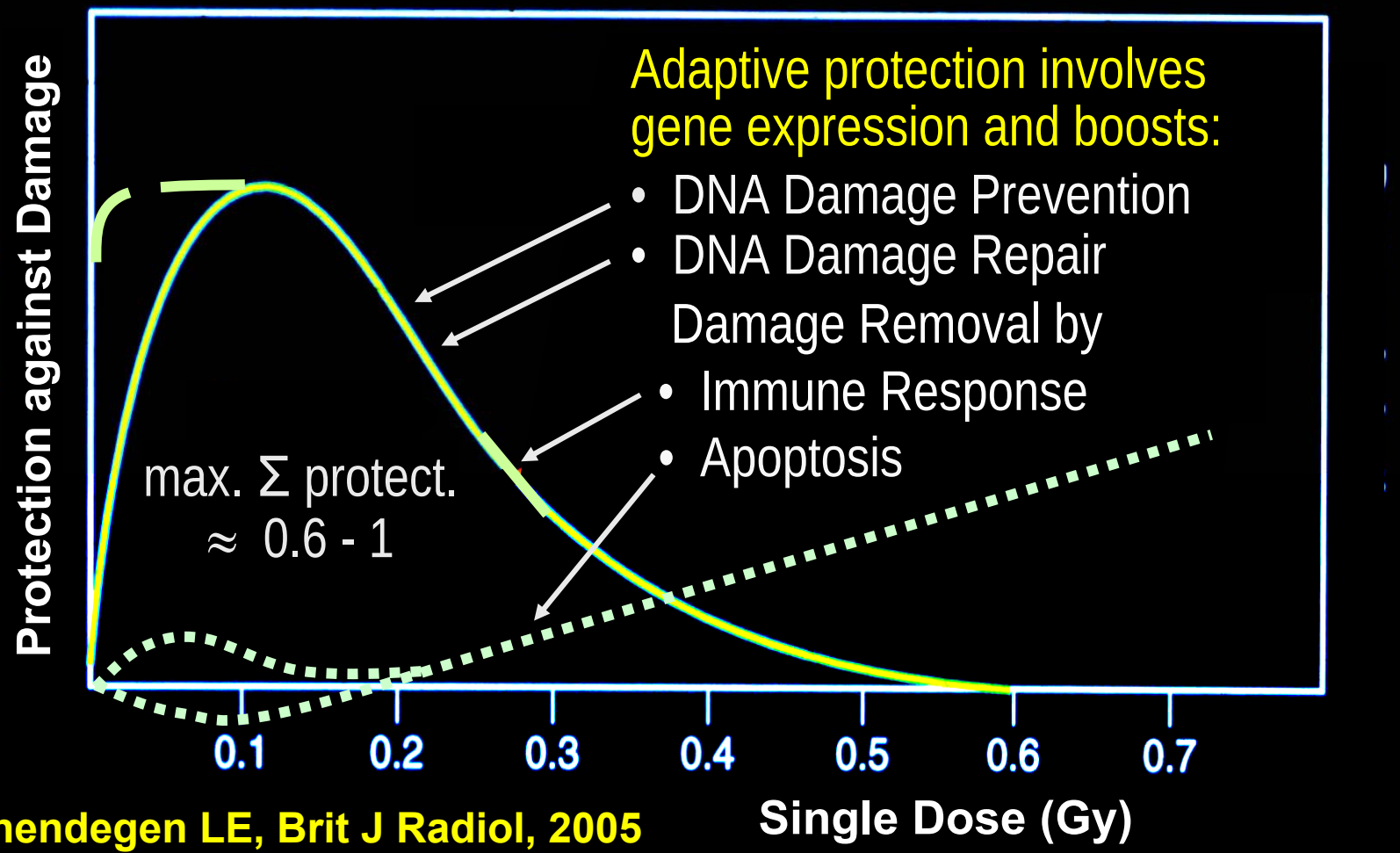


2 Gy

Franco N et al., Radiat Res, 2005

Dose Responses for Adaptive Protections

MOST ADAPTIVE PROTECTIONS (AP) ARE NOT PROPORTIONAL TO DOSE.



Feinendegen LE, Brit J Radiol, 2005

Major late damage following irradiation is cancer.

The LNT model predicts
cancer incidence to rise
also following low-dose irradiation.
This prediction is scientifically invalid.

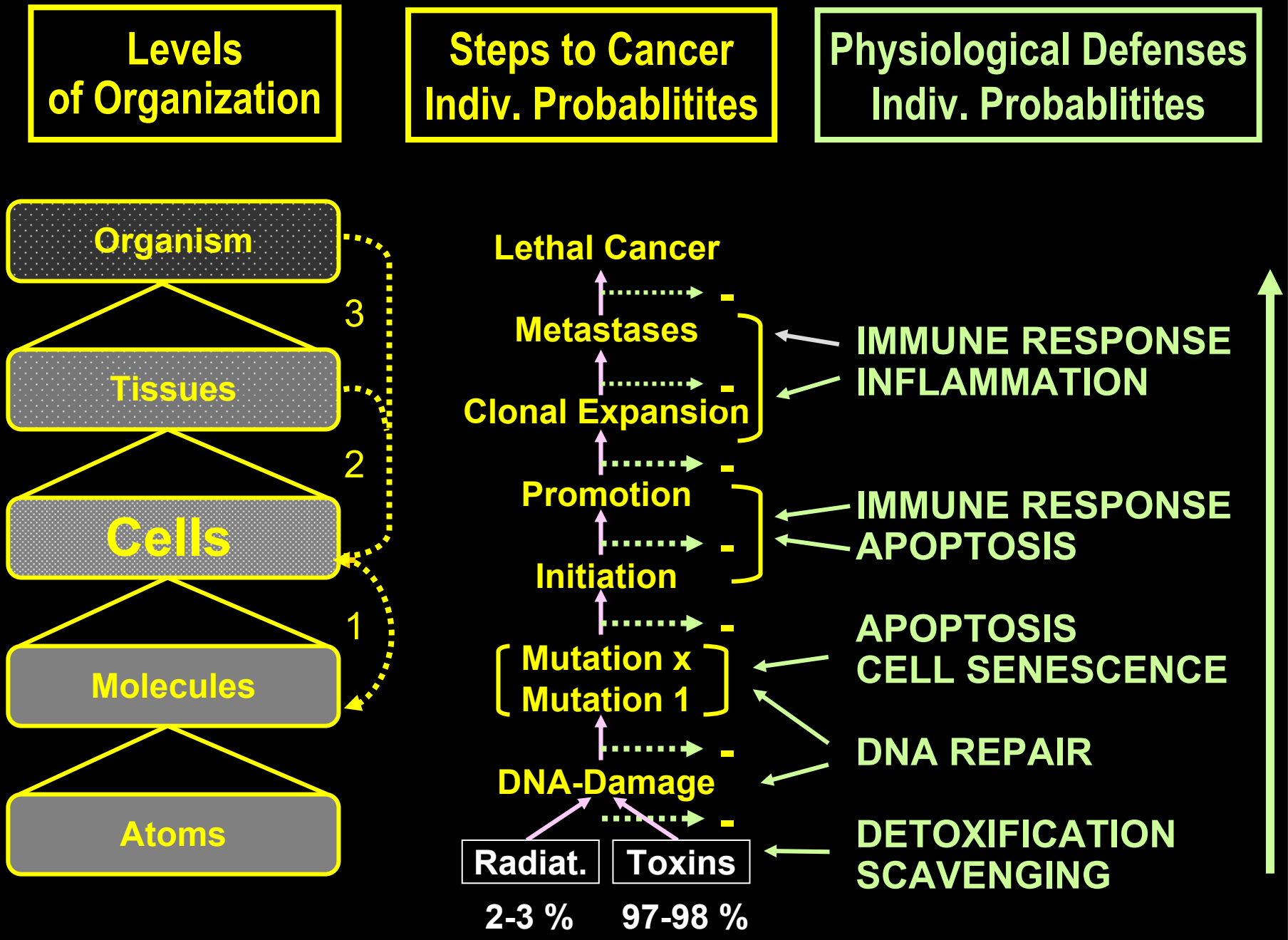
Cancer May Appear Years after Irradiation

1. Malignant cells show multiple genome alterations changing core-pathways and signaling, - tumor-type specific.

   (Jones S, et al, 2008; Parson et al., 2008)

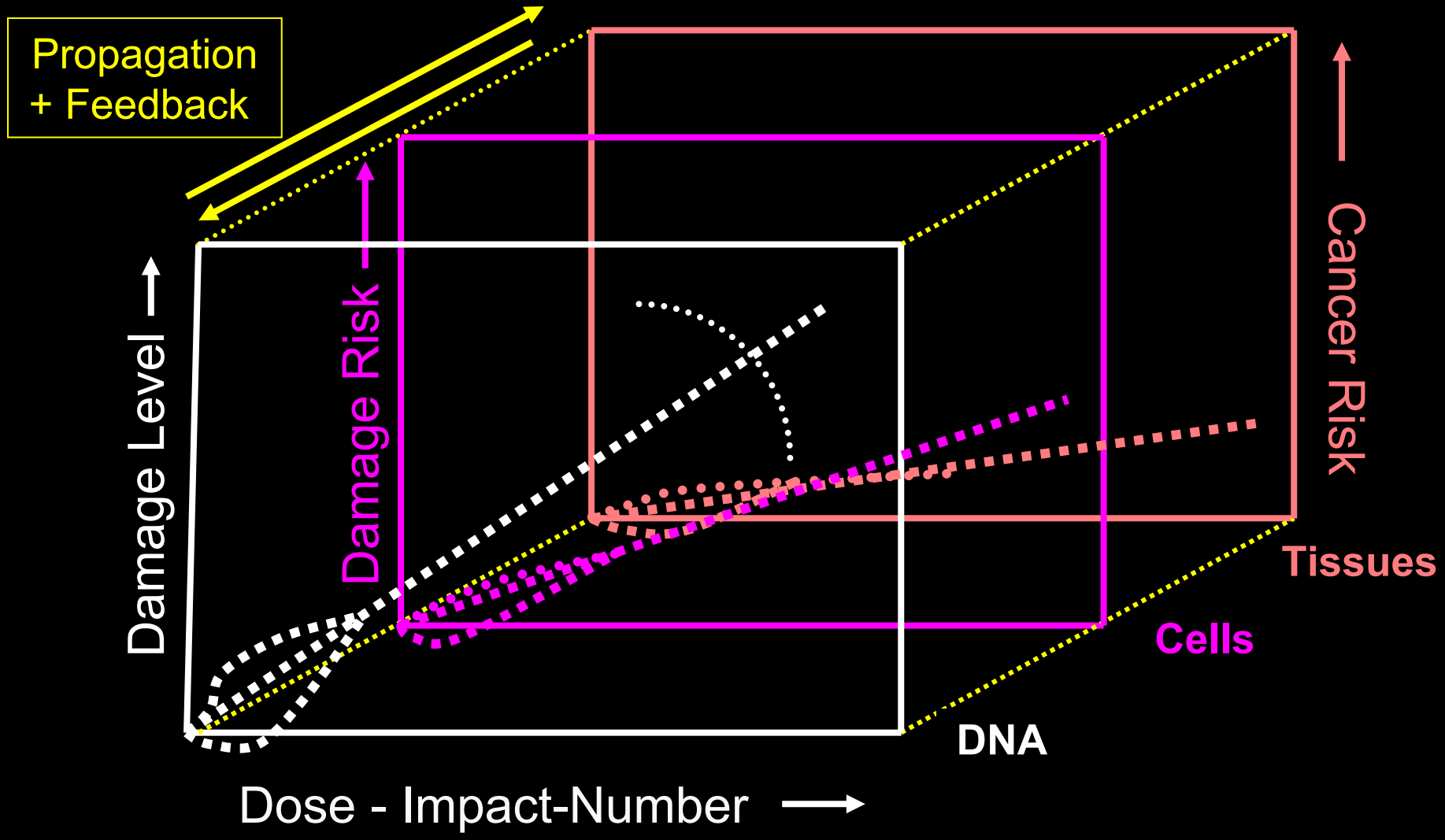
2. A single low dose exposure hardly causes multiple genome alterations at once.

3. Low-doses may change one or few genes and advance but not singly cause malignancy.


Levels of Organization
Steps to Cancer Indiv. Probablitites
Physiological Defenses Indiv. Probablitites
Organism
Tissues
Cells
Molecules
Atoms
3
2
1
Lethal Cancer
Metastases
Clonal Expansion
Promotion
Initiation
Mutation x
Mutation 1
DNA-Damage
Radiat.
Toxins
2-3 %
97-98 %
IMMUNE RESPONSE
INFLAMMATION
IMMUNE RESPONSE
APOPTOSIS
APOPTOSIS
CELL SENESCENCE
DNA REPAIR
DETOXIFICATION
SCAVENGING

Very Few Cancer Cells Escape Defenses

ASSUME: CONSTANT ESCAPE PROBALITY / UNIT DOSE.



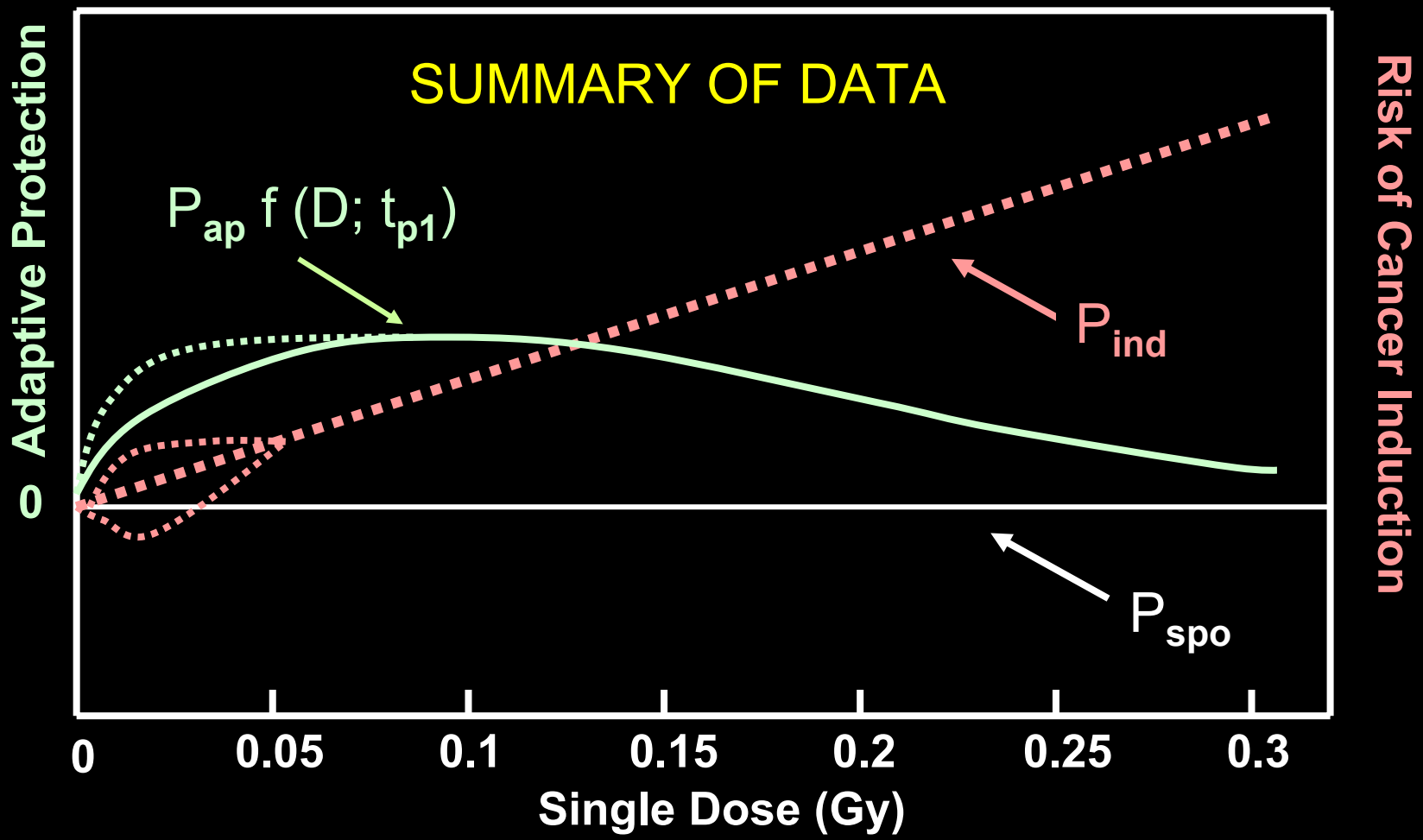
Agenda

1. Biological Systems, Complexity and Defenses
2. Energy Deposition Events and Perturbations
3. Physical-Static Defenses
4. Metabolic Defenses against Initial Damage
5. Metabolic Defenses against Late Damage
6. Model of Low-Dose Cancer Risk

Dual Responses after Single Low-Doses

Up-regulation of defenses

Cancer at constant defenses



Adapted from Feinendegen LE, et al., Exp Hematol, 2007

There are ~1000 times more DNA-DSB per $\bar{x}$ cell / d by metabolic toxins than by background radiation.

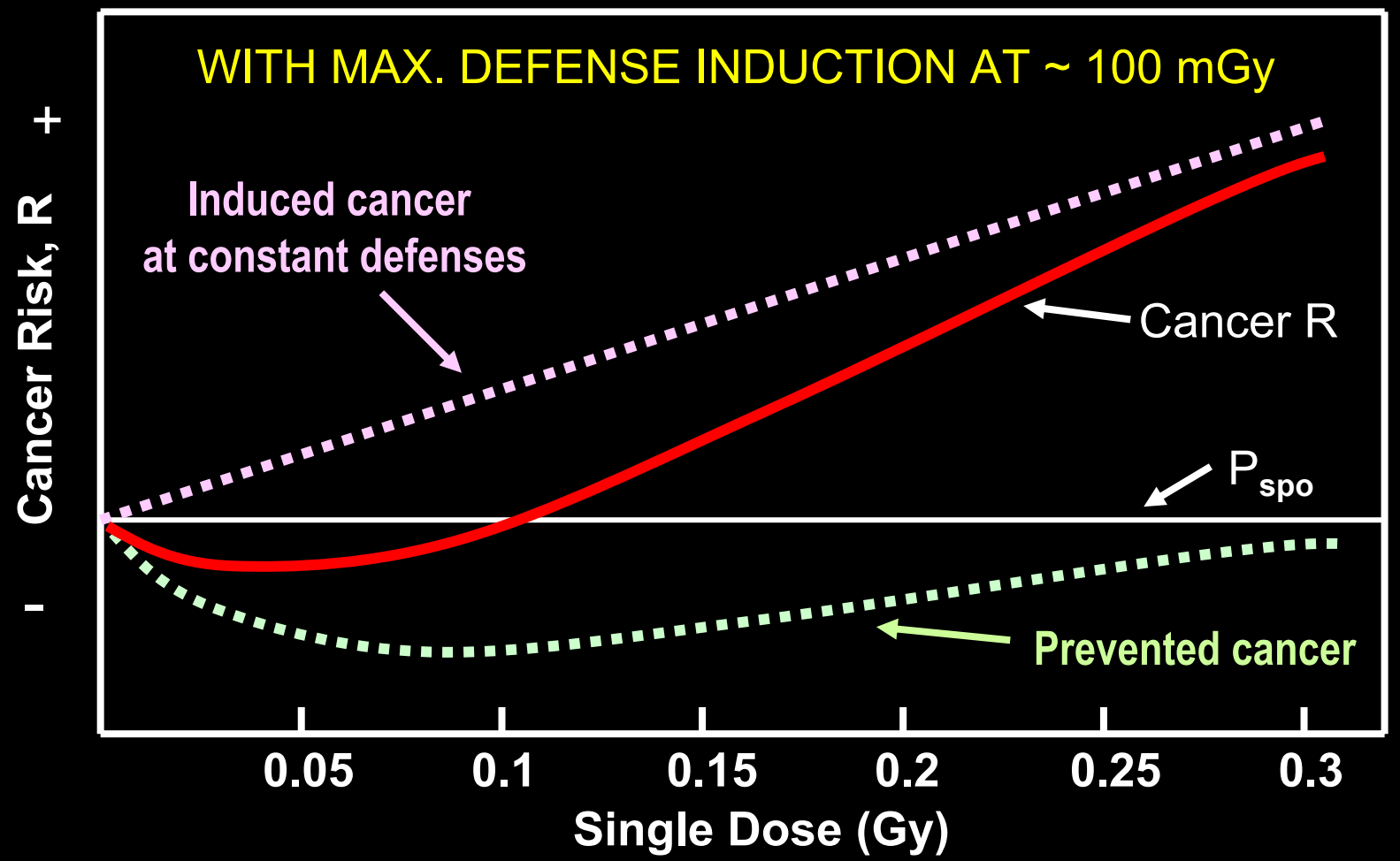
The incidence of non-radiogenic cancer in the West is more than ~ 30 to 50 times higher than that of cancer from background radiation.

Adaptive protection operates also against non-radiogenic DNA damage and its propagation.

Feinendegen LE et al., 1995; Azzam EI et al., 1996; Pollycove M, Feinendegen LE, 2003; Mitchel REJ et al., 2003, 2008

Dose-Risk Function for Single Exposure to Dose D

$$R_x = P_{ind} D_x - P_{ap} f(D_x; t_{p1}) (P_{spo} + P_{ind} D_x)$$



Adapted from Feinendegen LE et al., Exp Hematol, 2007

The model can explain

epidemiological data

on cancer incidence

following single exposures.

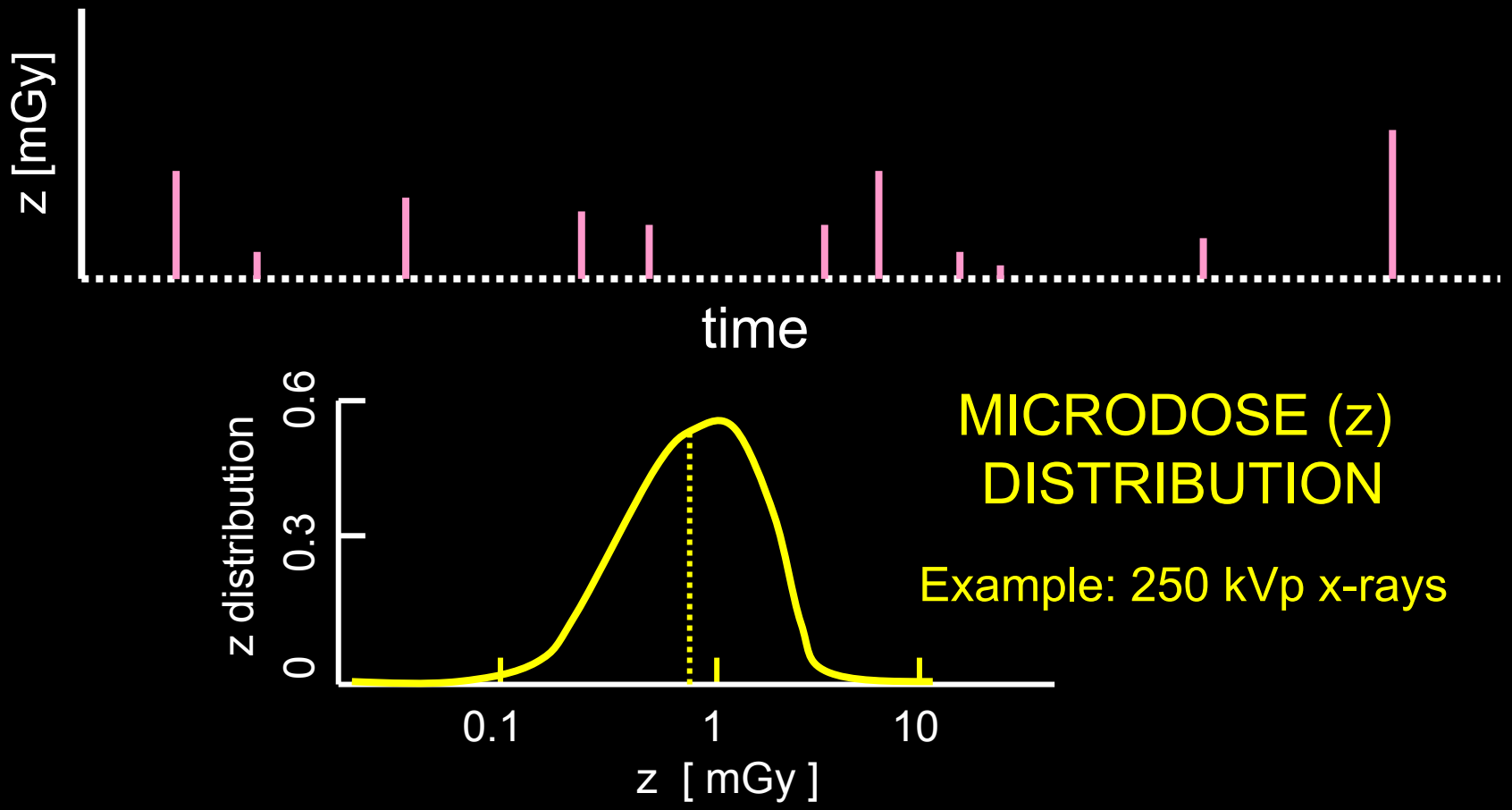
The model is applicable also to

chronic, or repetitive low dose irradiation.

Feinendegen LE, Grässle D, Brit Institute Radiol, 2002

Dose Distribution from Background Radiation

MICRODOSE EVENTS PER MICROMASS OVER TIME.



Adapted from: Booz J, pers. comm., 1986; ICRU Rep 36, 1983

Biological Responses to Dose Rate Exposure

They are cell and tissue specific and depend on both

- the values of microdose z_1

  z_1 defines P_{ind} and P_{ap},

  and on

- the mean time interval t_x between events of z_1

  t_x defines cell response time t_p.

Open Questions on Dose-Rate Cancer Risk

What are the values of

- $\bar{z}_1$ for inducing metabolic defenses (type 1) upon repetitive cell irradiation, at given t_x

- $\bar{z}_1$ for inducing adaptive protections upon repetitive cell irradiation, at given t_x

- t_x for changing above responses to $\bar{z}_1$.

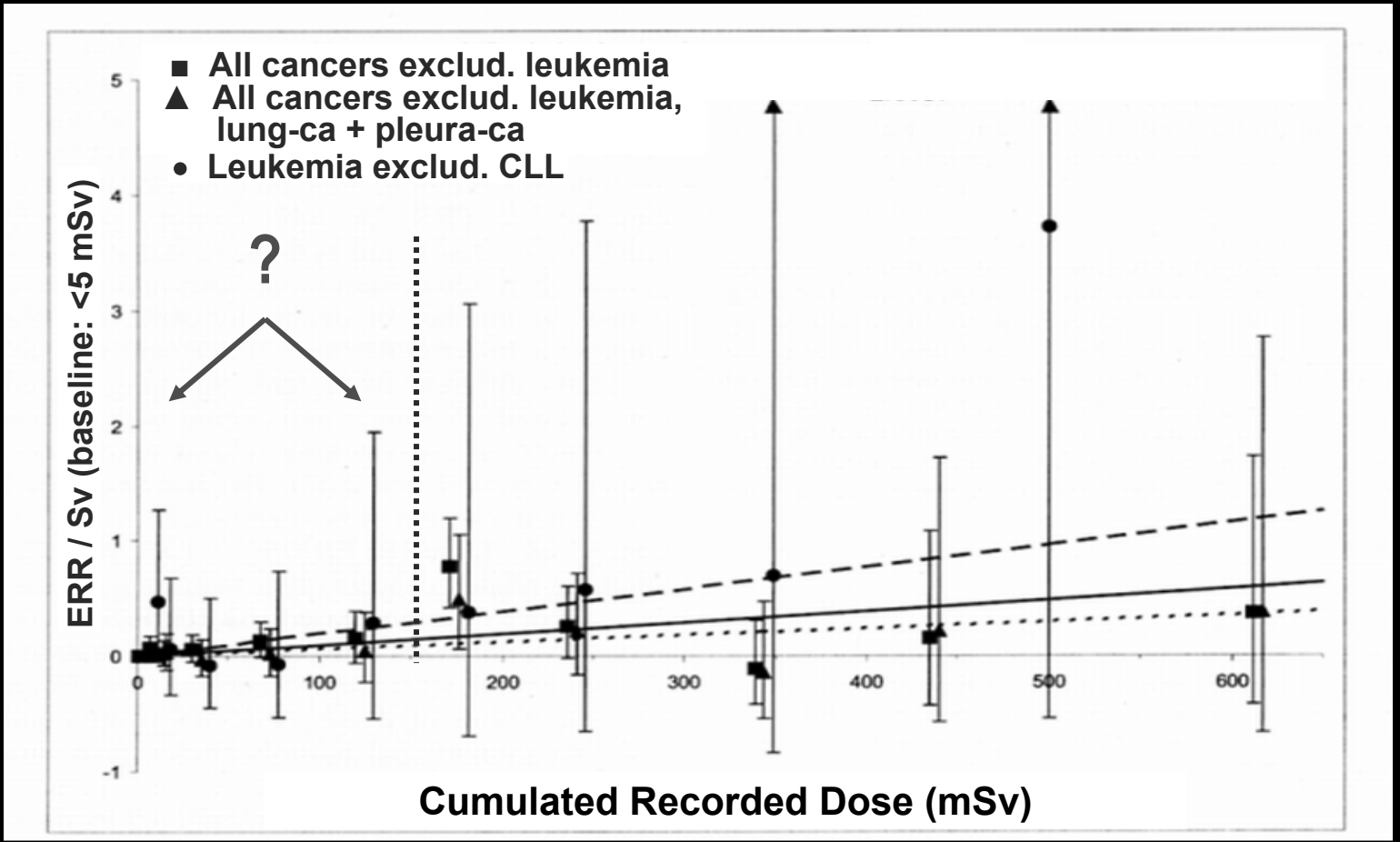
The model can explain

various experimental and epidemiological data

on DNA damage and cancer incidence

after chronic, or repetitive low-dose irradiation.

Cancer Risk, in 407,391 Nuclear Workers (15 Countries)



Excess relative risk by dose category (relative to <5 mSv category) and 90% CI: for all cancers excluding leukemia: all cancers excluding leukemia, lung and pleural cancers; leukemia excluding CLL.

Cardis E et al., Radiat Res, 2007

Cancer in Kerala - Hindu Times, January 2009

Monazite sand does not cause excess cancer incidence

by K.S. Parthasarathy
Prev. Secretary AERB.

Now it is official. In the January 2009 issue of the *Health Physics Journal*, researchers from the Regional Cancer Centre (RCC), Thiruvananthapuram, and their collaborators have shown that there is no excess cancer risk to people living in the area of high natural background radiation in Kerala from exposure to terrestrial gamma radiation.

The Journal highlighted the importance of the paper by carrying a photo of the beaches in its cover page.

CANCER RISK: *The study found that there is no excess cancer risk to people living in the area of high natural background radiation in Kerala.* – PHOTO: C. SURESH KUMAR

Gamma radiation

The coastal belt of Karunagappally, Kerala, is known for high background radiation (HBR) from thorium-containing monazite sand.

In the coastal panchayats, the median outdoor gamma radiation levels are more than 4 mGy y^{-1} and in certain locations, the levels are as high as 70mGy y^{-1}.(Gy is a unit of radiation dose; mGy is one thousandth of a Gy; the an-

received indoors and outdoors and taking into account how long and where they stayed during the period.

By the end of 2005, they identified 1379 cases of cancer including 30 cases of leukaemia.

chayats (Chavara, Neendakara, Panmana and Alappad) which had HBR and two control areas (Oachira and Thevalakkara) which have relatively low natural radiation levels.

They estimated the excess

stantial contribution of airborne radon and thoron daughters to the individual radiation dose. This may not affect the main conclusion that there is no excess cancer in areas of high natural background radiation.

Background Radiation and Solid Cancer

KARUNAGAPPALLY COHORT, Kerala, India, 173,067 people.

Dose rate: (0.7 x indoor) + (0.3 x outdoor) - 71,674 houses

Dose Rate mGy y^{-1}	Relative Risk (RR) at Age (yrs)			
	30 – 49 yrs	50 – 69 yrs	70 + yrs	Total
0 - 0.9	1	1	1	1
1 - 1.9	0.91	0.91	0.95	0.92
2 - 4.9	0.87	0.91	0.88	0.89
5 - 9.9	0.83	0.92	0.84	0.88
10 +	0.88	1.02	0.74	0.91
P Value for trend	*> 0.5*	*> 0.5*	*0.212*	*0.307*

from Nair RRK et al., Health Physics, 2009

Conclusion 1

Epidemiology cannot confirm the LNT-model at low doses.

The LNT model is inconsistent with experiments.

These rather show hormetic responses.

Conclusion 2

- Low doses can induce acute and delayed defenses at all organizational levels of the body.
- The late defenses operate mainly against endogenous damage and its consequences.
- Low-dose induced cancer prevention can be equal to or larger than cancer induction.

Conclusion 3

- Quality and extent of cell and tissue defenses are under genetic control.

- Effects of low-dose irradiation are expected to vary among individuals and may become predictable also for clinical use by individual gene-expression profiles.

A final Quotation

"While scientific disciplines are self correcting,
regulatory 'science' fails
to display the same self-correcting mechanism
despite contradictory data."

Calabrese EJ, Arch Toxicol, 2009

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