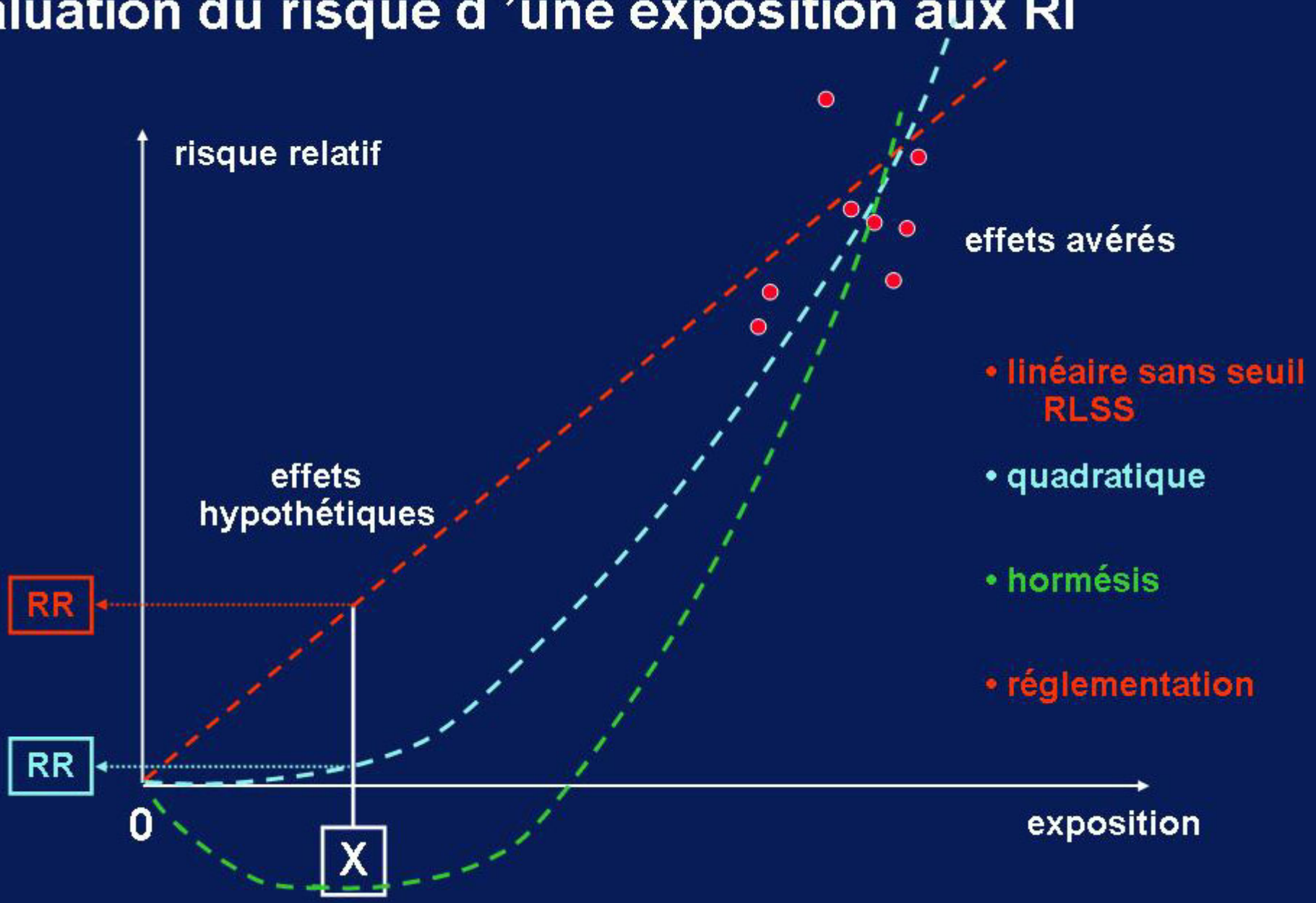
Méthodologies

Étude des effets faibles doses de rayonnement

évaluation du risque d 'une exposition aux RI



Contribuent à cette notion

- Le caractère aléatoire du dépôt d'énergie par les RI
- L'étude de la survie cellulaire et sa modélisation en $\alpha D + \beta D^2$
- Megamouse des Russell : pas de seuil pour les effets génétiques
- La notion de ''mutation somatique'' pour le cancer
- la découverte des oncogènes et des gènes suppresseurs
- L'apparente linéarité pour les cancers HN

Limites de l'épidémiologie

- Décrites en détail par CE Land 1980
- Si 10.000 patientes sont nécessaires pour établir un excès de cancers du sein à 0,1 Sv il faudra un effectif de 100 millions de patientes pour établir la réalité de ce risque dans la gamme de 0 à 0,1Sv

These difficulties are unlikely to be overcome by sample size expansion or by curve fitting, unless it can be established independently that the dose-response relationship is a particularly simple one. Research into the biological mechanisms of carcinogenesis would appear to be an essential part of the estimation process, by which plausible models can be derived. In the case of radiation carcinogenesis, radiobiological theory suggests that linear model analyses, confined to doses under a few hundred rads to low-LET radiation, may give credible upper limits of risk

Breckow 2006 Radiat Environ Biophys, 44, 257

‘’Recently, authors of some epidemiological studies tried to quantify—and some even claimed to having found evidence for—a significant increase of risk in the dose range of some 10 mSv.;...However, all cited estimates only hold under the precondition of LNT. Without this (or even any other) extrapolation model none of these studies would give evidence to any increased cancer rate ... ‘’

T Rockwell 15/11/06 ACNW

Policy makers advocate use of LNT because they argue it can do no harm to do so (ICRP-2005, ExecSummary). They claim one cannot prove lack of harm because it would require a test population of millions to get a statistically significant answer. But this is true only if LNT is true, so we have a silly syllogism: If LNT is true then we cannot prove LNT is true, so we must assume LNT is true.

Deux questions

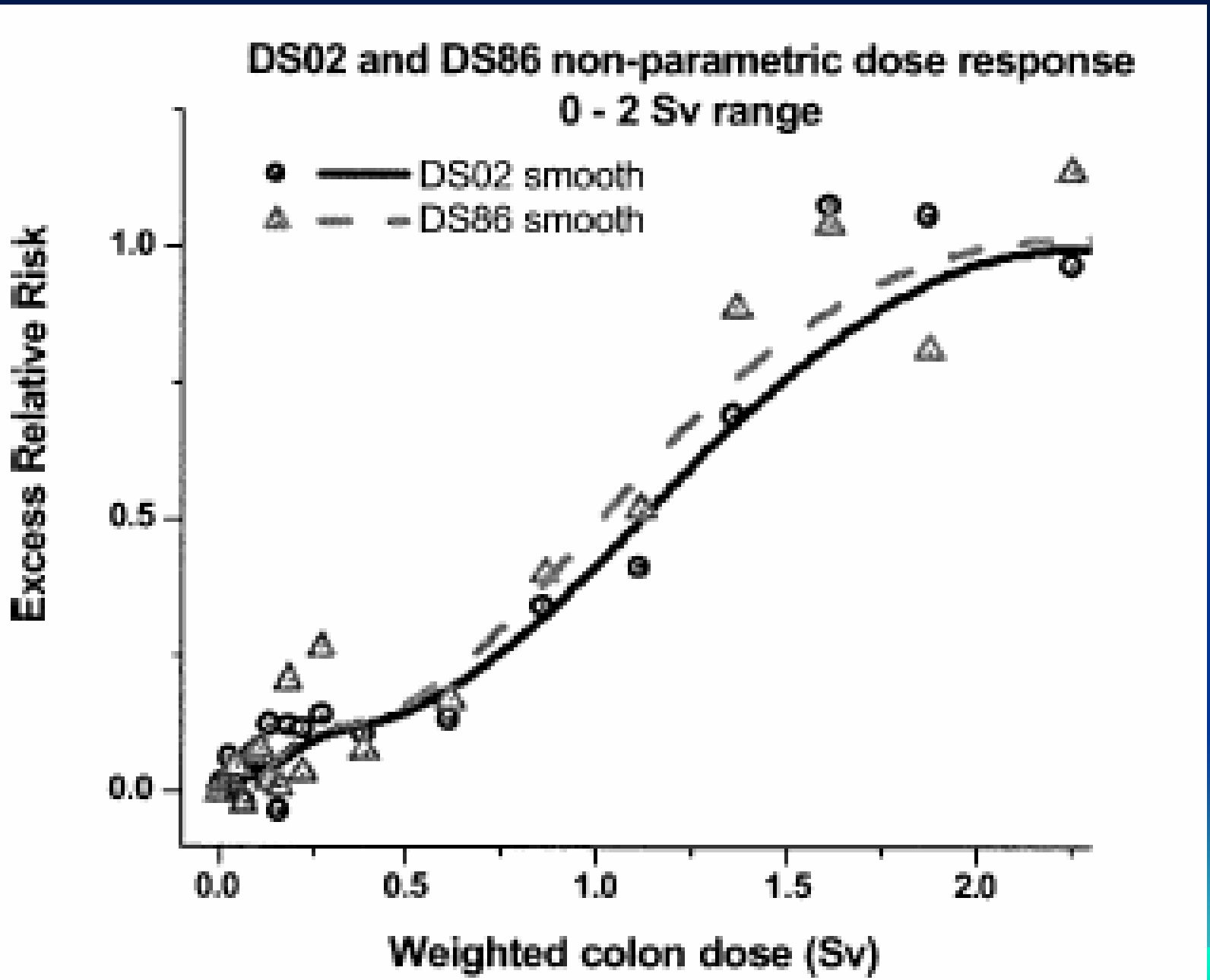
- 1 – Est-ce que l'hypothèse LNT assure vraiment une solution sûre au problème de gestion des doses?
- 2 - La LNT est ''non falsifiable'' et est impuissante à expliquer les multiples observations contraires à son principe, faut-il l'abandonner et quelles recherches seraient nécessaires?

1 - Académie des sciences Académie de médecine 2005

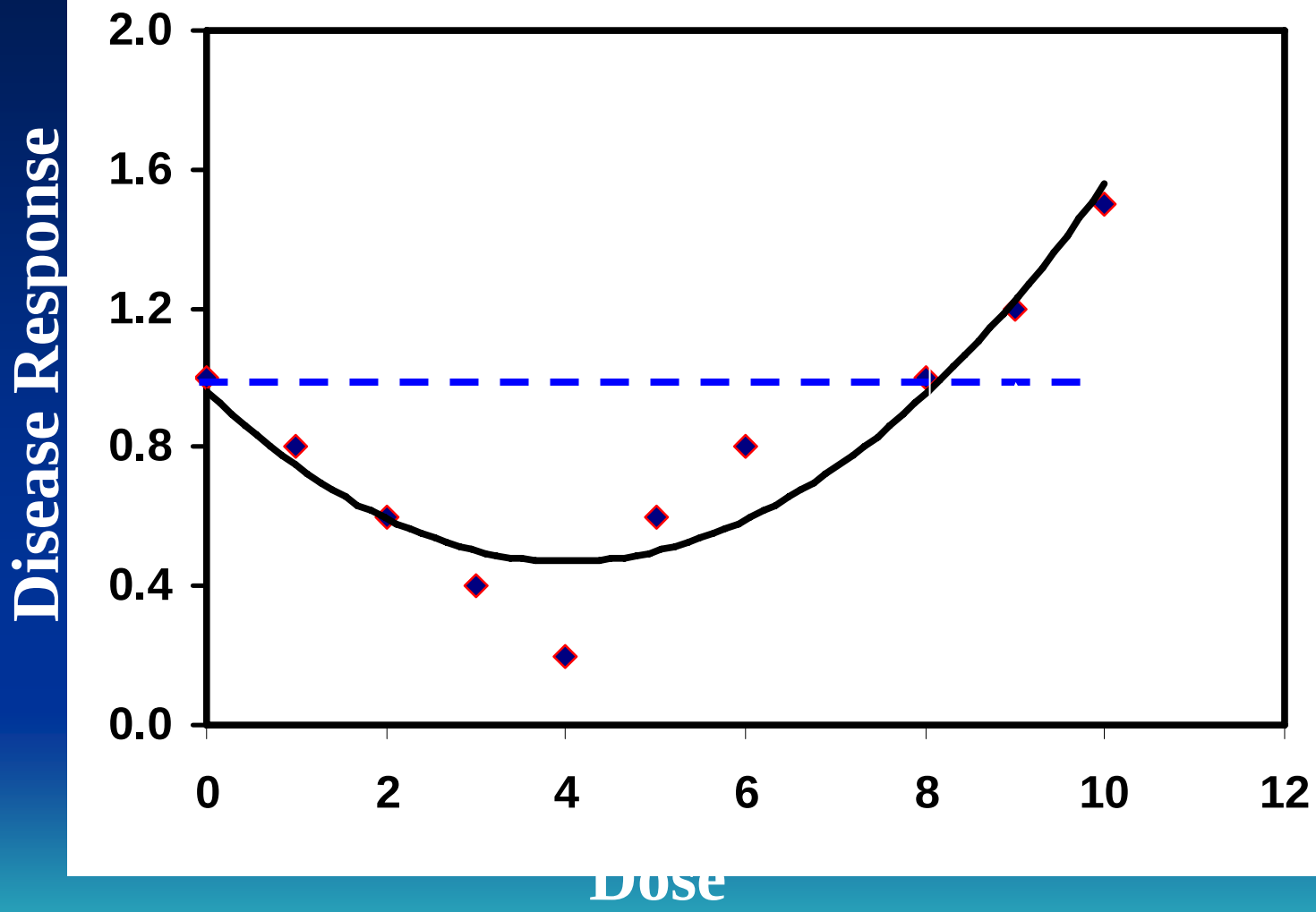
- Une mauvaise appréciation du risque a un coût sanitaire important
  - En faisant obstacle à des examens médicaux utiles au diagnostic
  - En créant une situation d'anxiété dans des populations exposées
  - En dévoyant l'utilisation de ressources limitées

2-Les points critiques

- Linéarité, signatures?
- Quelle signification biologique a la dose?
- Signalisation et débit de dose
- Adaptation vs amplification
- Accepter la complexité
- Modéliser?


DS02 and DS86 non-parametric dose response
0 - 2 Sv range
DS02 smooth
DS86 smooth
Excess Relative Risk
1.0
0.5
0.0
0.0
0.5
1.0
1.5
2.0
Weighted colon dose (Sv)

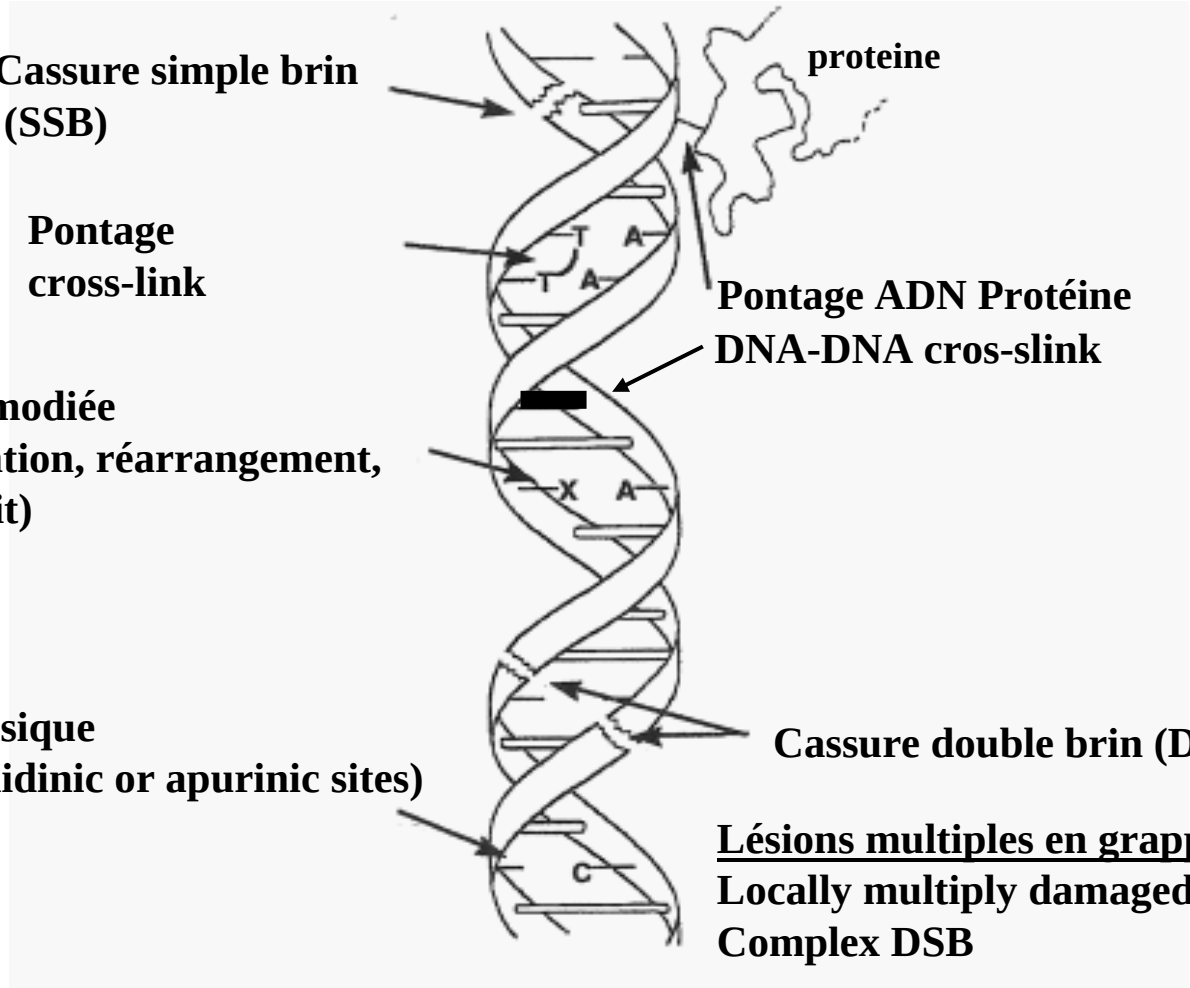
U-Shaped Dose-response Relationship



Signatures?

- Il n’y a pas de signature dans les cancers radio induits (p53, RET..)
- Prédisposition?
- Les mutations radio induites ont un spectre différent des mutations spontanées, y compris à faible dose
- Les avancées de ‘’l’omique’’ peuvent révéler des voies spécifiques?

Lésions à l'ADN



DNA

institutCurie

Dommages endogènes et radio-induits de l ’ADN

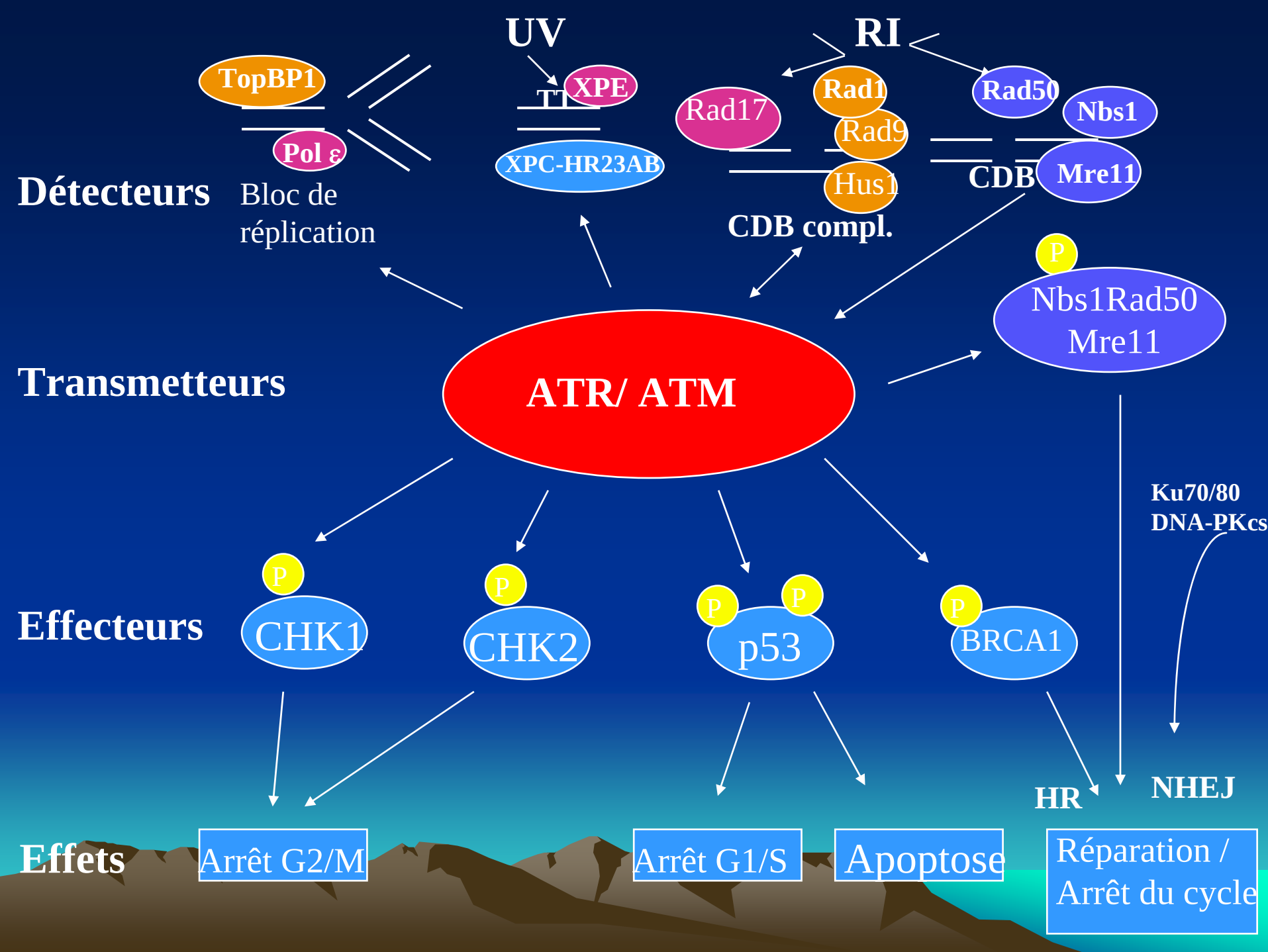
Dommages	Endogènes / cellule / jour	Radio-induits / Gy
Cassures simple brin	10 000 à 55 000	1 000
Pertes de bases	12 600	?
Dommages de base	3 200	2 000
Cassures double brin	8	40
Pontages ADN-ADN	8	30
Pontages ADN protéine	Quelques-uns	150
(LMDS)	?	Quelques-unes

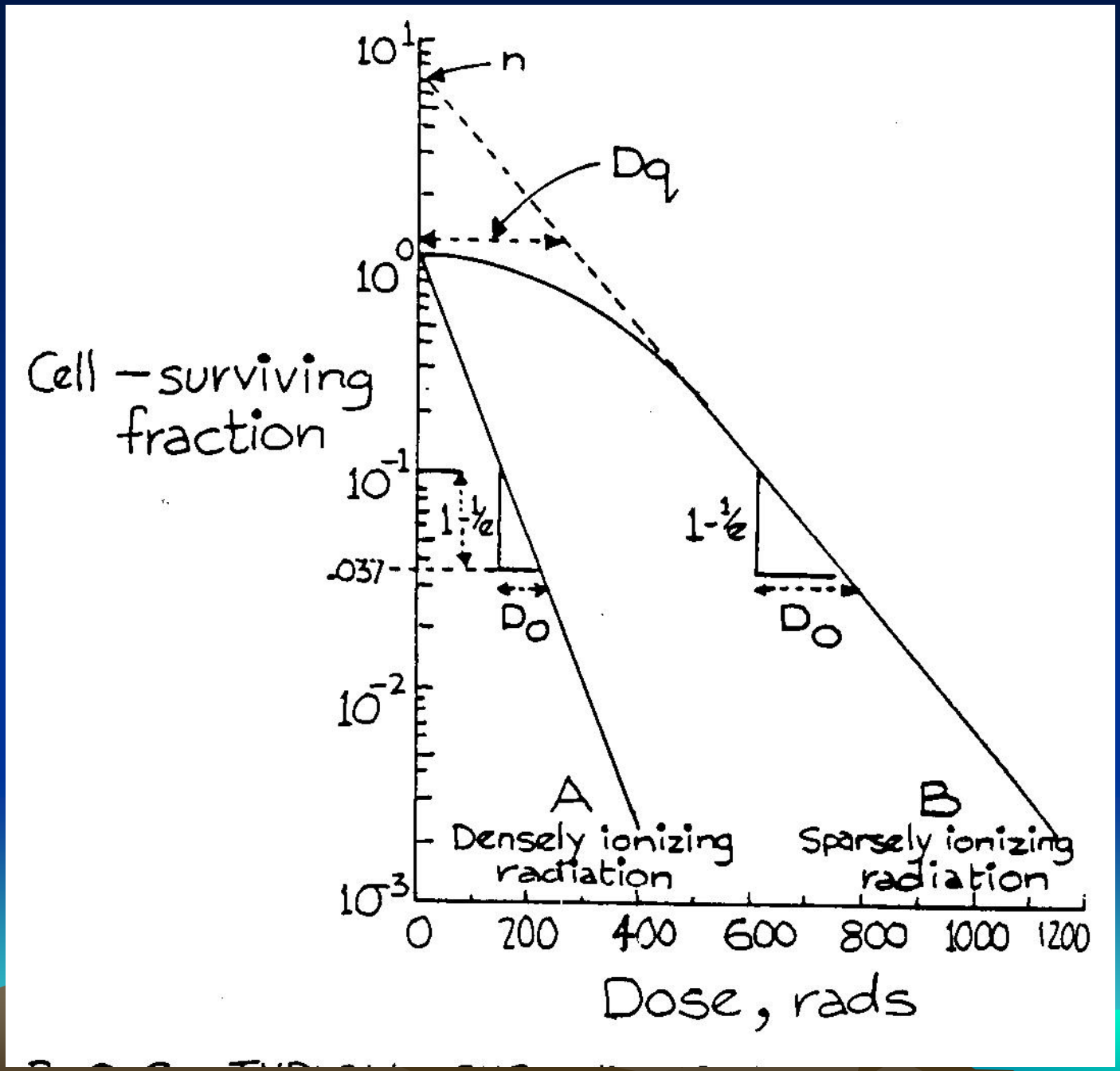
(selon Burkart W et al. CR Acad Sci III 1999; 322:89-101; Ward JF Prog Nucl Acdids Res Mol Biol. 1988; 35: 95-125)

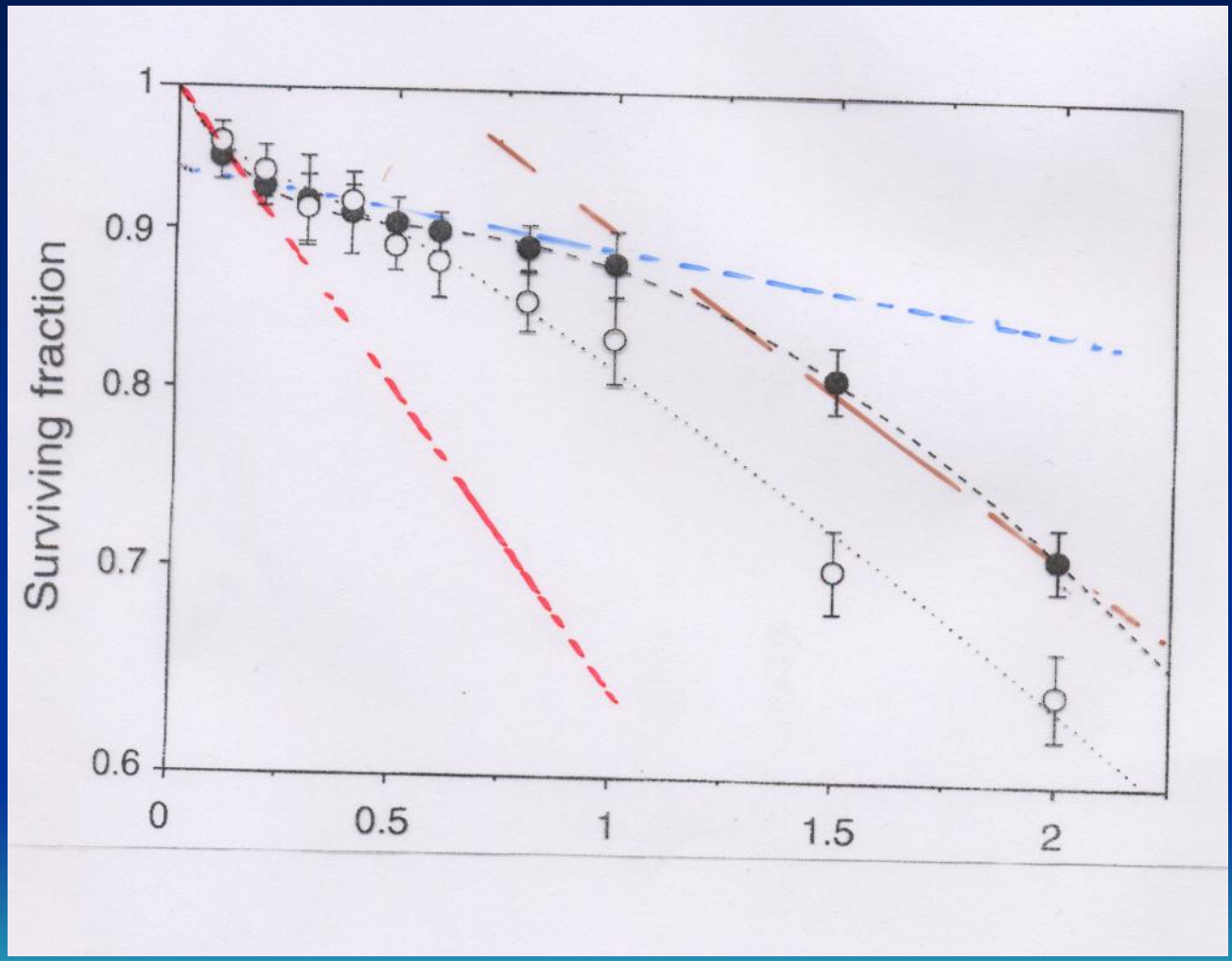
institutCurie

Les LMDS sont elles importantes pour la RP (Averbeck 2006)?

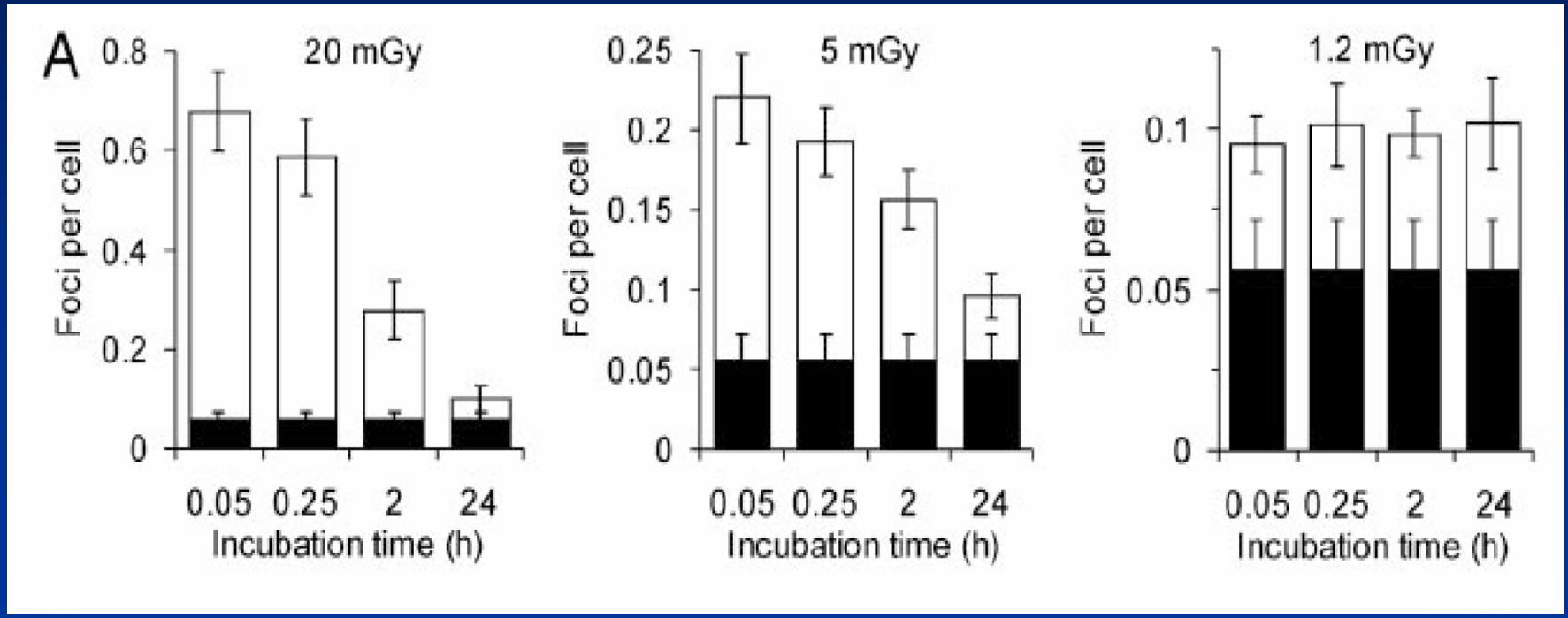
- Signature des RI, difficilement réparables et induites par de fort TEL (Beir 7) ?
- En réalité essentiellement un artefact dû à l'oxydation pendant l'extraction de l'ADN
- Peuvent induites artificiellement par H2O2
- Non dose dépendantes, contrairement aux DSB
- Essentiellement létales


UV
RI
TopBP1
Pol ε
XPE
XPC-HR23AB
Rad17
Rad1
Rad9
Hus1
Rad50
Nbs1
Mre11
CDB
CDB compl.
Détecteurs
Bloc de réplication
Transmetteurs
ATR/ ATM
P
Nbs1Rad50 Mre11
Ku70/80
DNA-PKcs
Effecteurs
CHK1
CHK2
p53
BRCA1
HR
NHEJ
Effets
Arrêt G2/M
Arrêt G1/S
Apoptose
Réparation / Arrêt du cycle


Cell – surviving fraction
10^1
10^0
10^{-1}
10^{-2}
10^{-3}
n
Dq
1-1/e
.037
Do
1-1/e
Do
A
Densely ionizing radiation
B
Sparsely ionizing radiation
0
200
400
600
800
1000
1200
Dose, rads


Surviving fraction
1
0.9
0.8
0.7
0.6
0
0.5
1
1.5
2

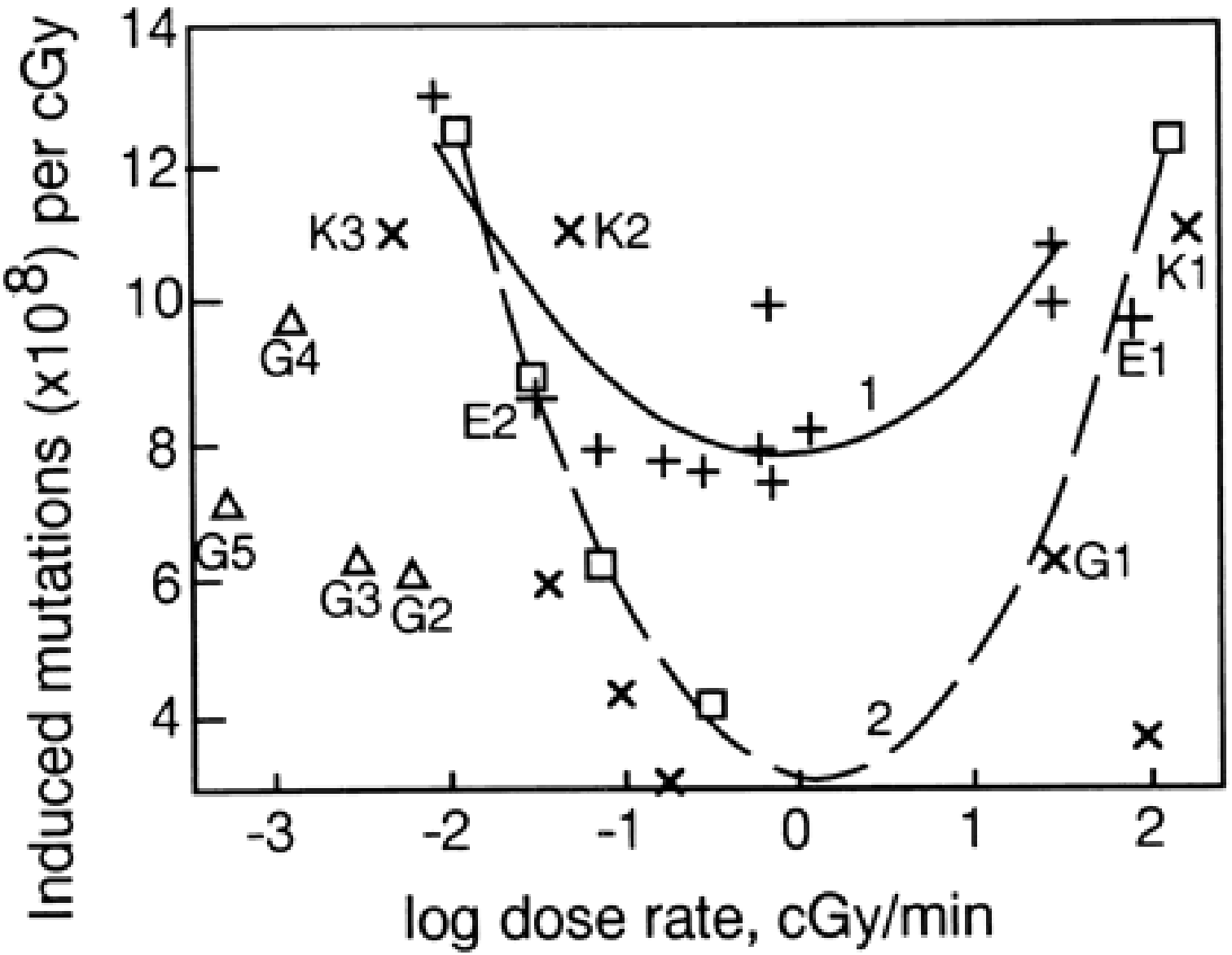
Induction et réparation de CDB après de faibles doses de rayons X



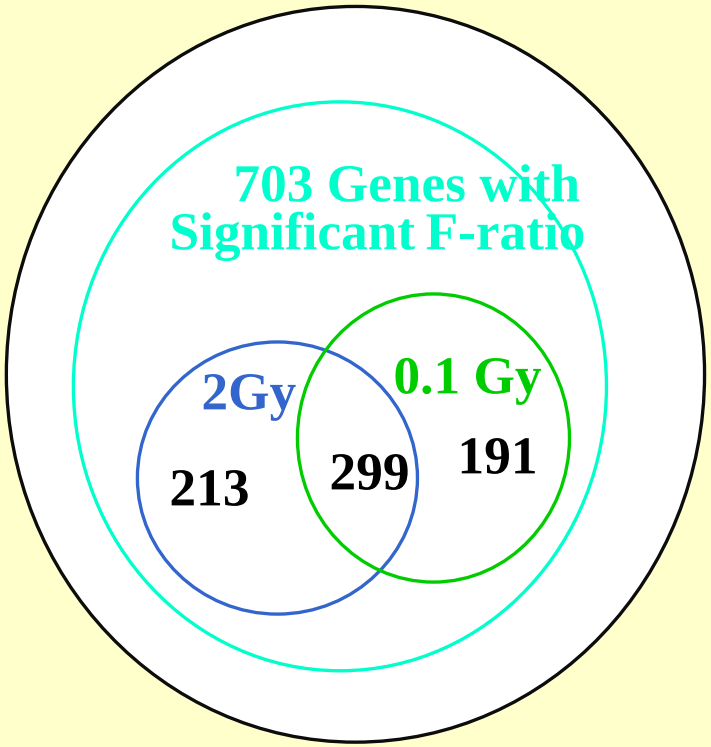
Absence de réparation à très faible dose (1,2 mGy)

(Rothkamm et Löbrich, PNAS 2003;100:5057-5062)

institutCurie


Induced mutations (x10^8) per cGy
14
12
10
8
6
4
-3
-2
-1
0
1
2
log dose rate, cGy/min
K3
K2
K1
G4
G5
G3
G2
G1
E2
E1
1
2

DIFFERENCES IN TRANSCRIPTION PROFILES BETWEEN LOW AND HIGH DOSE IRRADIATION IN MURINE BRAIN CELLS



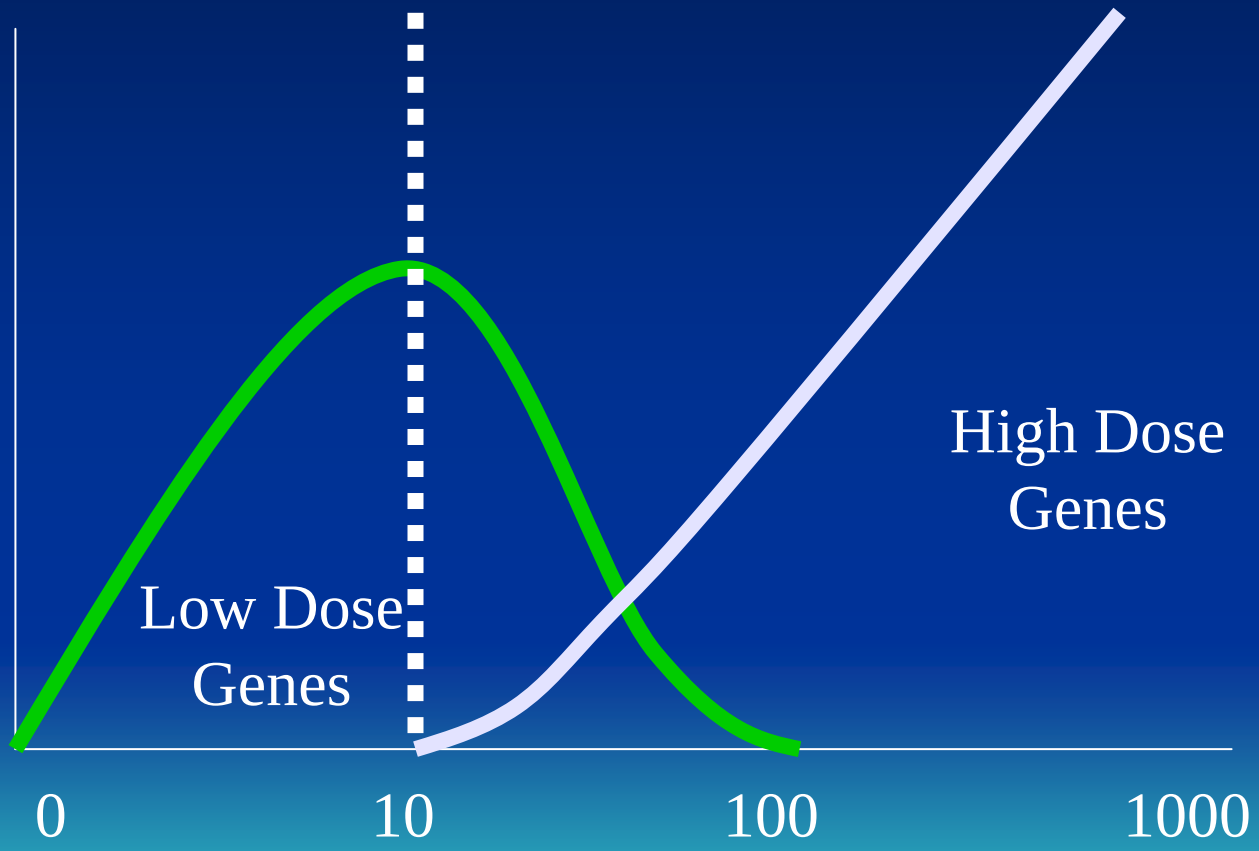
Total gene set contains nearly 10,000 genes

Numbers of Genes Differentially Regulated in HLB Cells 4 hr after IR

Up-regulated at 2Gy	245
Down-regulated at 2Gy	135
Up-regulated at 0.1Gy	182
Down-regulated at 0.1Gy	187

Yin 2003

Radiation-induced changes in gene expression

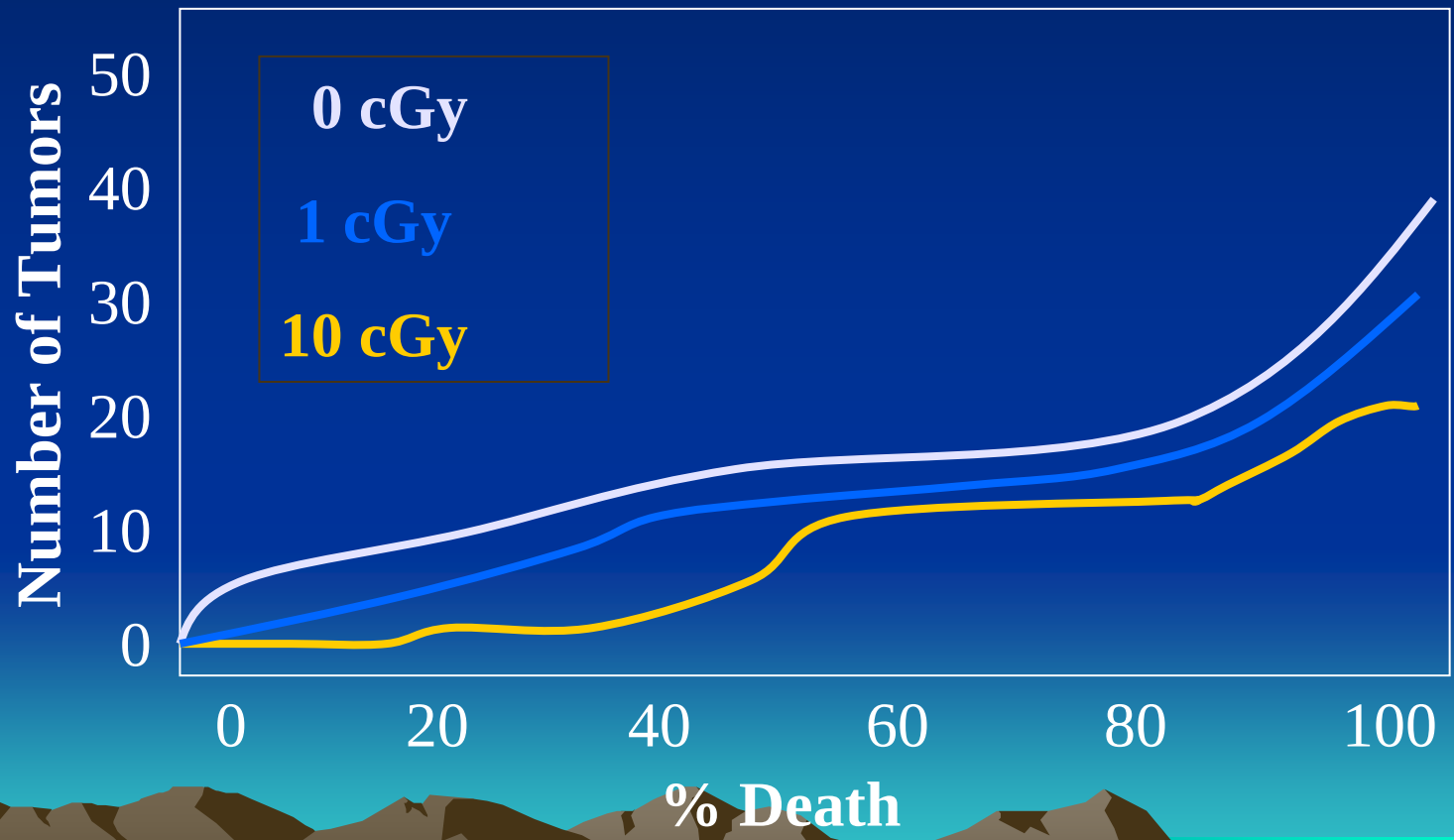


Wyrobek

Adaptation à faible dose

Traitement in vitro de lymphocytes humains	Pertes dans 200 chromosomes analysés
Lymphocytes témoins	2
0,01 Gy	2
1,5 Gy	74
0,01Gy +1,5 Gy	39**
0,01 Gy + CHM 6h + 1,5 Gy	75

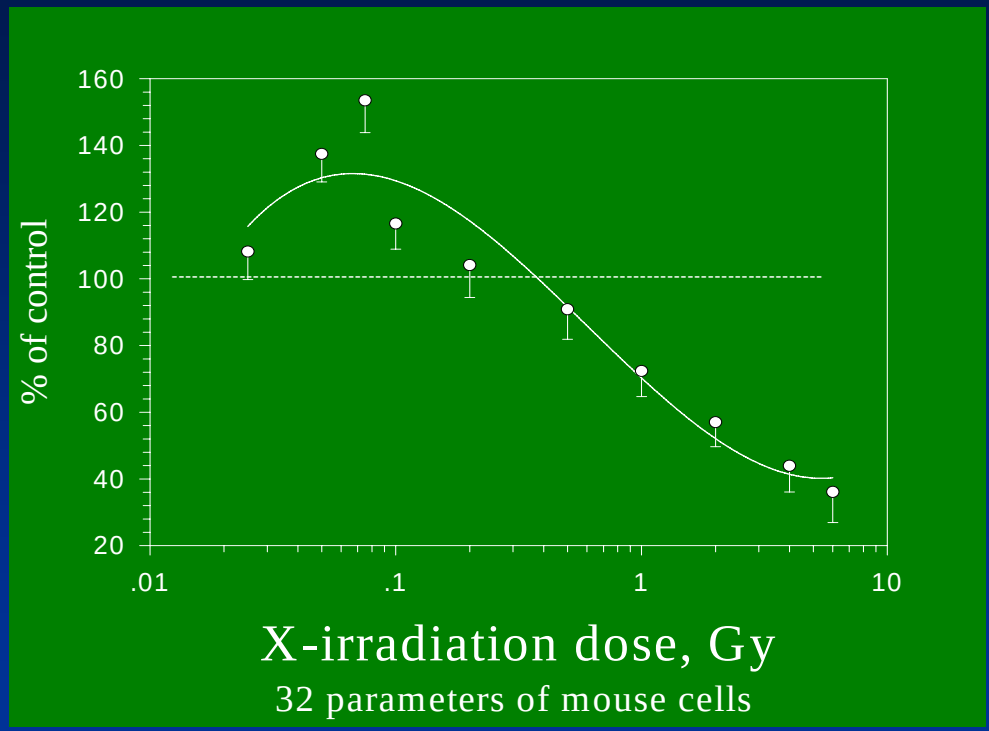
Lymph Tumors in Mice



Lymphomas in Trp53+/- Mice

Mitchel et al. 2003

Inverted J-shaped dose-effect curve constructed from 32 parameters



These parameters include:

1) Cell number, such as

Thymocyte count

Splenocyte count

Peripheral blood WBC count

2) Cell acitivity, such as

Spontaneous ^{3}H-TdR incorporation into thymocytes

Proliferative reaction of splenocytes to Con A and LPS

PFC reaction of spleen

NK and ADCC activity of splenocytes

3) Cytokine secretion, such as: IL-2, IFN-gamma secretion

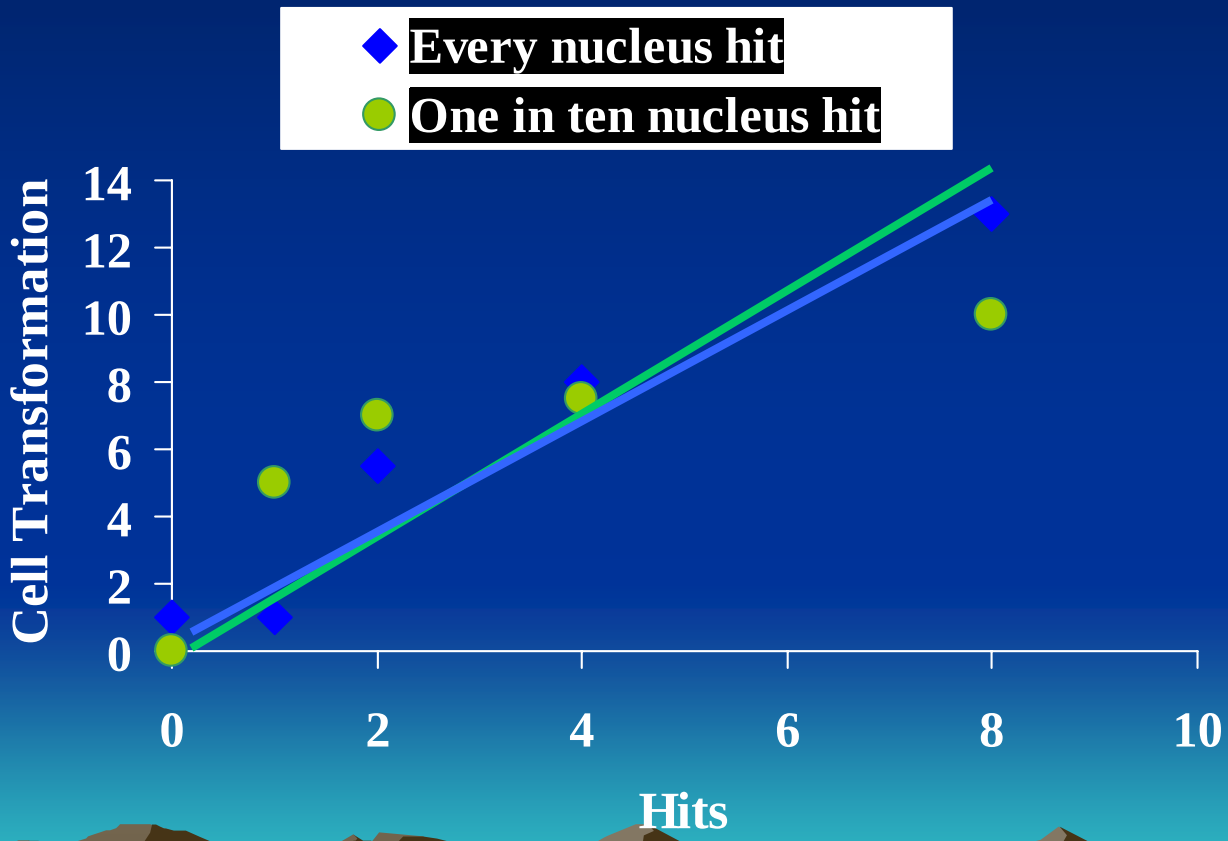
4) Surface molecule expression, such as: IL-2R, TfR, CD28, CD2, CD48

5) DNA repair:, such as UDS, ribonucleotide reductase, DNA polymerase

6) Signal molecules, such as: free calcium ion concentration, cGMP content, p38MAPK

Up-regulation of these parameters in the immune organs would lead to activation of immunity. They are up-regulated after low dose radiation.

Cell Transformation

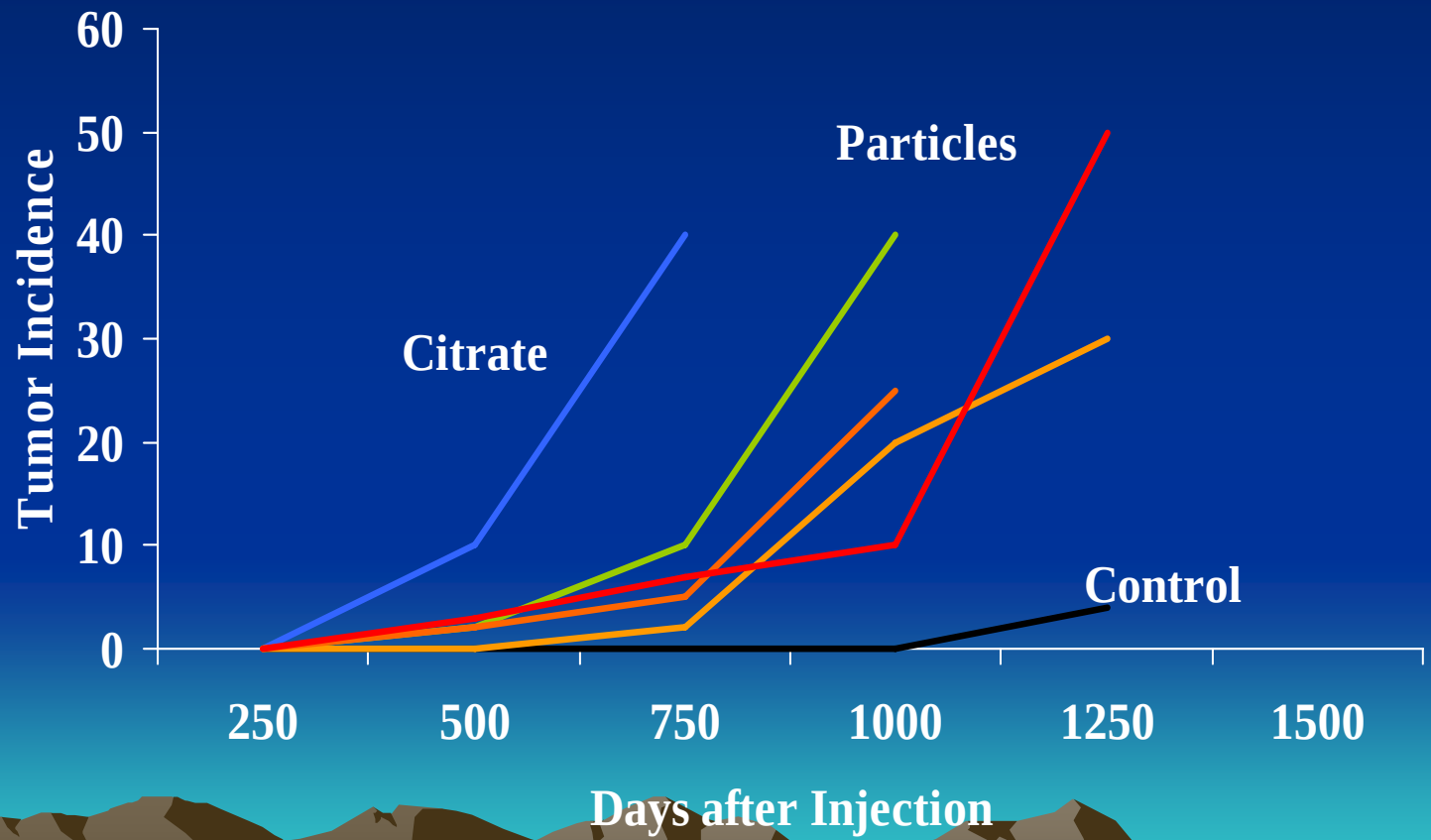


Sawant et al.2000

The Influence of ^{239}Pu Dose-Distribution on Chromosome Aberration Frequency

Brooks et al

Cumulative Liver Tumor Incidence After $^{239}PuO_2$ or ^{239}Pu Citrate Exposure



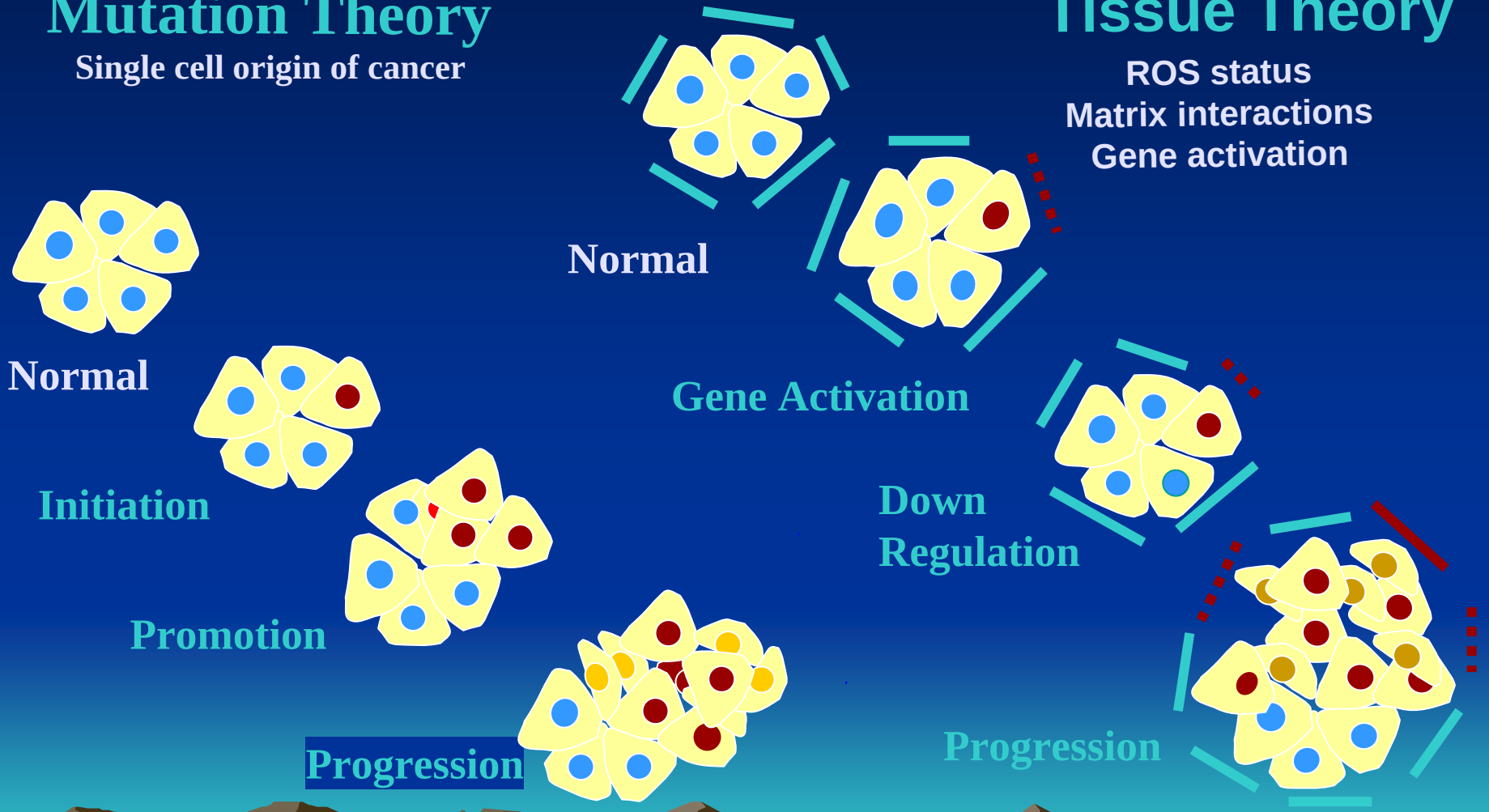
Gene Mutation and Expression in Cancer

Mutation Theory

Single cell origin of cancer

Tissue Theory

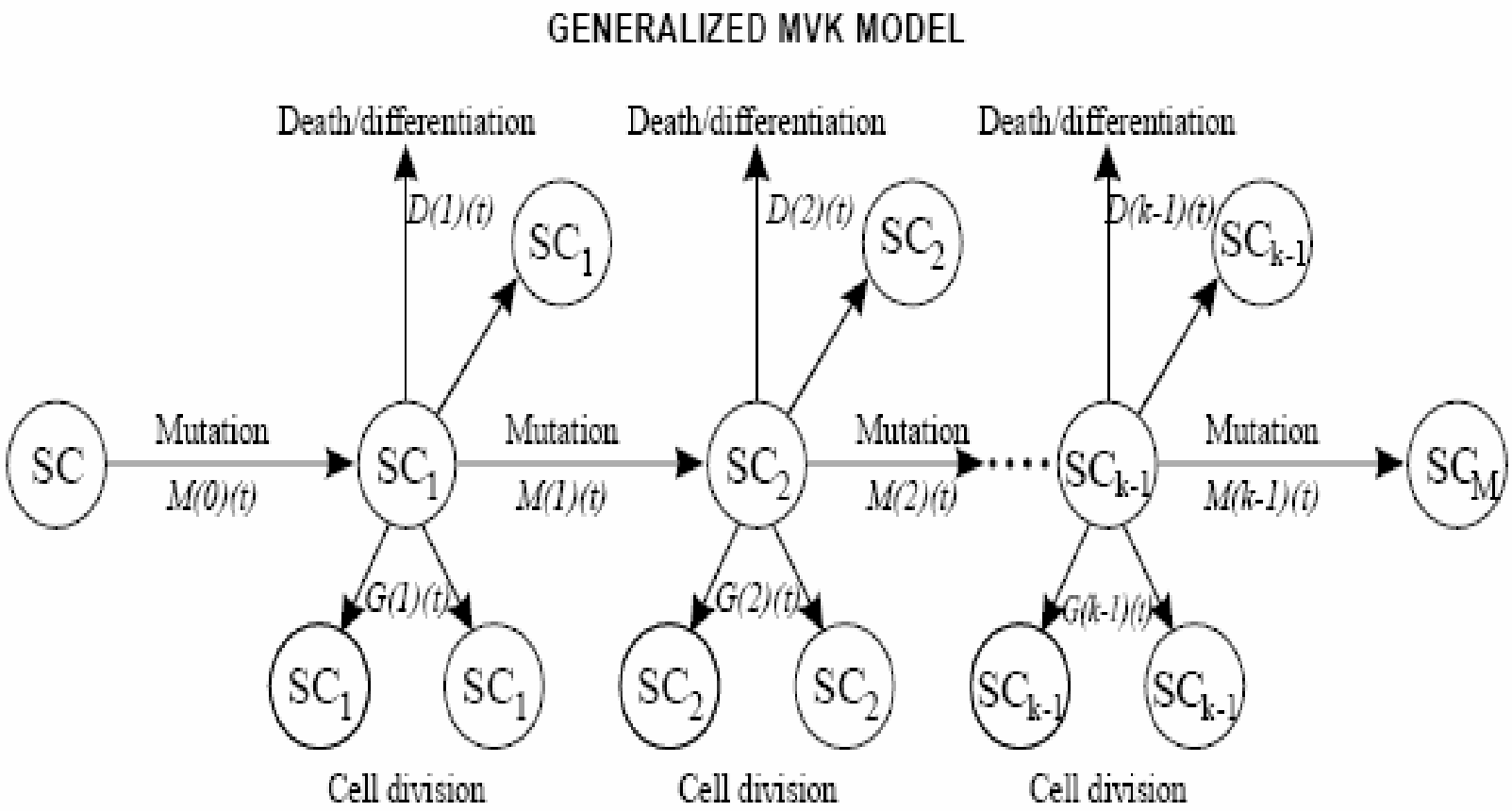
ROS status
Matrix interactions
Gene activation



Gene Mutation- a rare event

Tissue response- a frequent event

UNSCEAR 2000

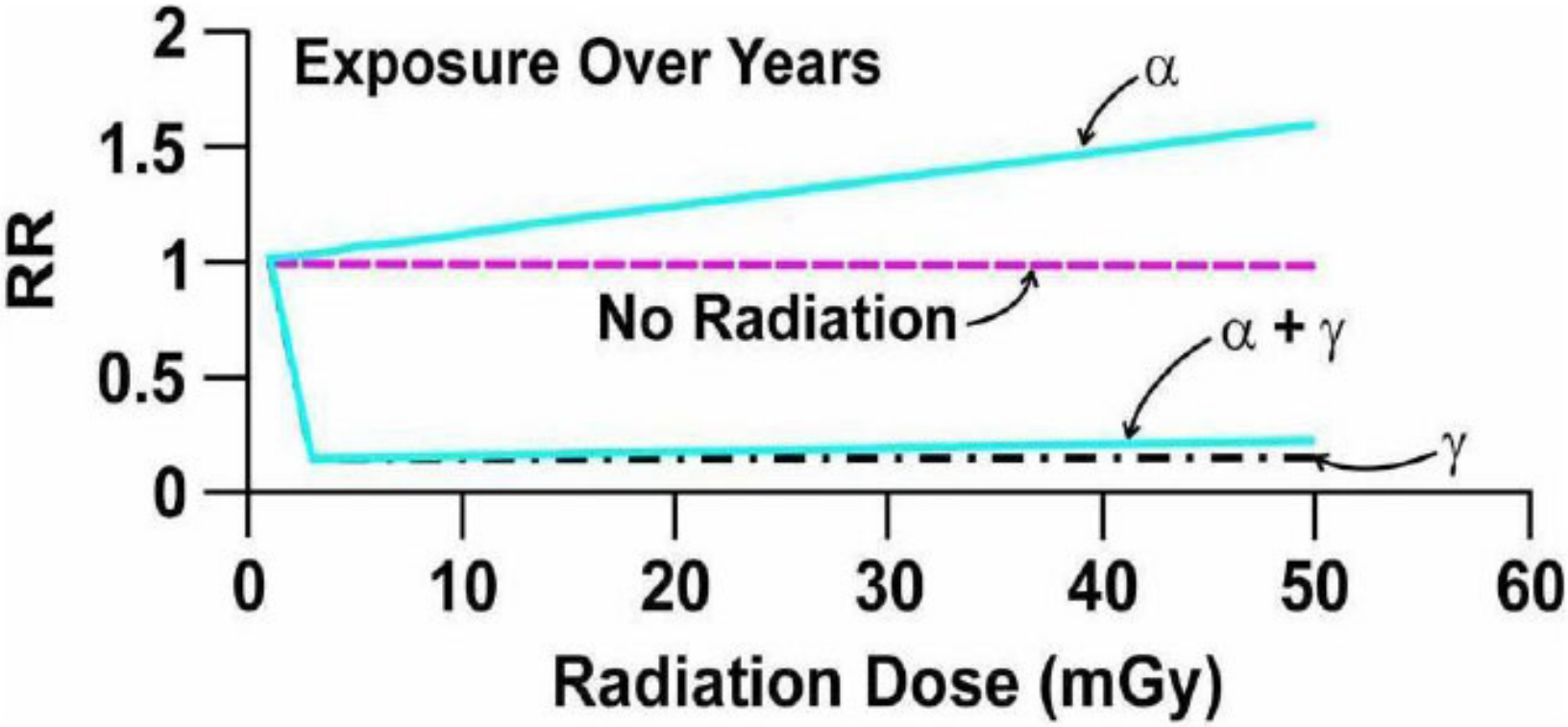


NEOTRANS$_3$ Model for Low-Dose Radiation-Induced Stochastic Effects

- Includes protective bystander effects.
- Applies to low doses and dose rates.
- Models mutation or neoplastic transformation frequency.
- Relative risk equations for transformation adapted for cancer induction (allows for immune-system stimulation).

Scott BR. Mut. Res. 568:129-143, 2004.
Scott BR. Nonlinearity (in press), 2006a,b.

Lung Cancer Relative Risk: Mayak Workers



Hormetic dose-response curves were obtained for chronic γ and α + γ irradiation but not for chronic α irradiation only; ***PROFAC = 0.86 (Scott 2006a)***.

Conclusion

- Il est désormais possible d'explorer directement les effets biologiques de doses de l'ordre du mGy
- Les observations faites sont convergentes
- Elles ne soutiennent pas la linéarité, elles doivent être consolidées
- Elles ont des implications pour l'évaluation de risque et la thérapie