DE LA RECHERCHE À L'INDUSTRIE

Quelles définitions pour La sensibilité individuelle?

Société Française de Radioprotection |

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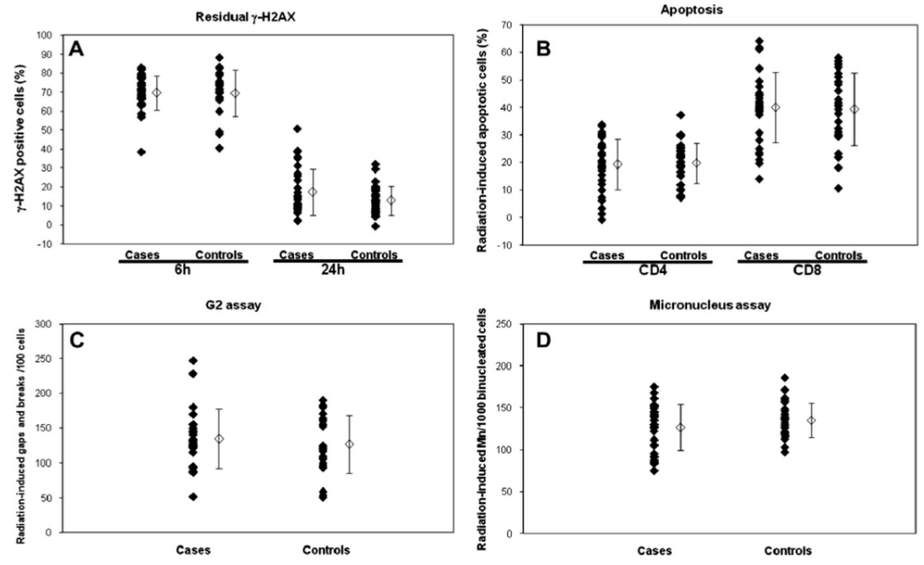
19 Mars 2013

La sensibilité individuelle reste sans test prédictif

Correlation of in vitro lymphocyte radiosensitivity and gene expression with late normal tissue reactions following curative radiotherapy for breast cancer

Paul Finnon et al.

Radiotherapy and Oncology 105 (2012) 329–336



Evaluation of Different Biomarkers to Predict Individual Radiosensitivity in an Inter-Laborato Comparison– Lessons for Future Studies

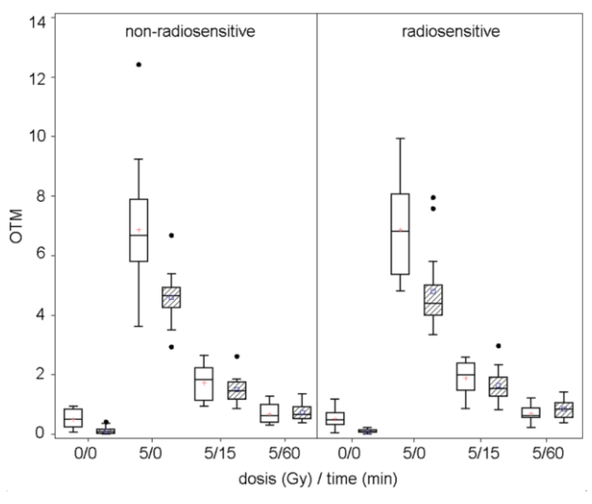
Burkhard Greve et al.

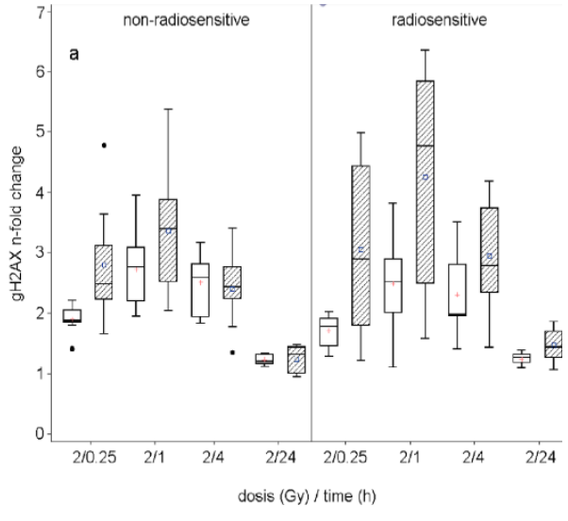
Plos one 2012, **7** :10 e47185

Table 3. Comparison between non-radiosensitive vs. radiosensitive patients for apoptosis and necrosis in each laboratory within the different dose rates.

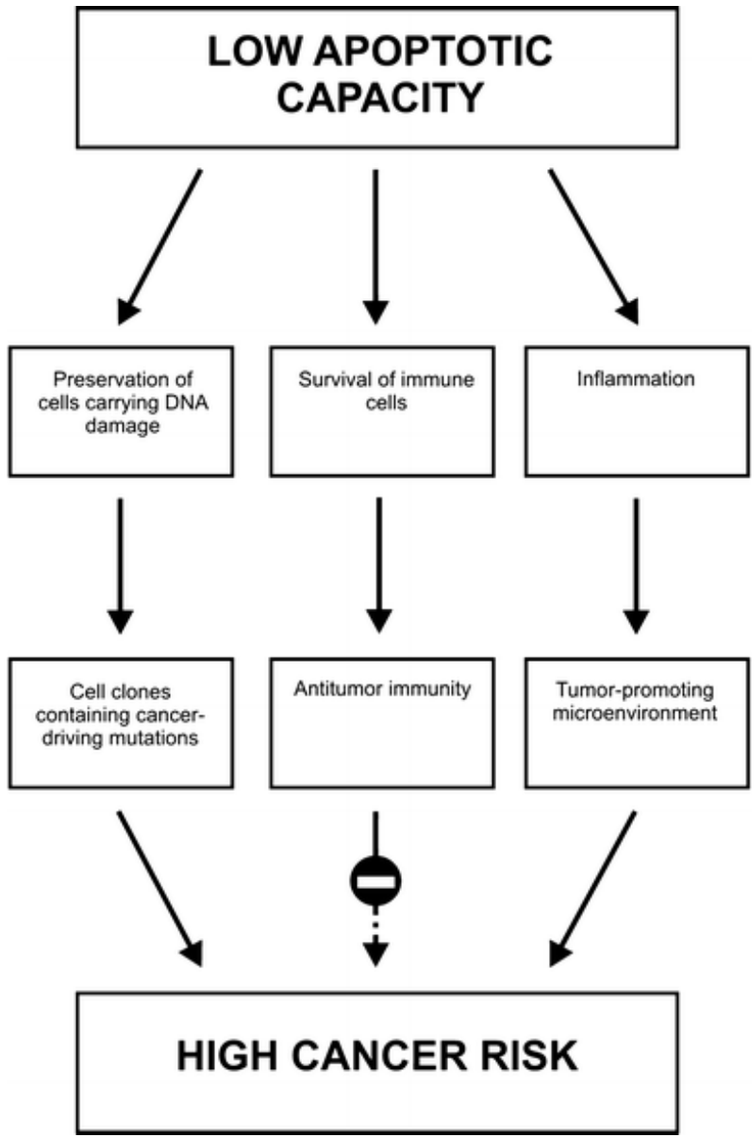
Apoptosis/ Necrosis	Non-radiosensitive vs. radiosensitive		
Dose (Gy)	**0.0**	**0.4**	**0.8**
Centre A	0.624	0.512	0.305
Centre B	0.830	0.645	0.798
Centre C	0.389	0.395	0.373

P values were determined by Mann-Whitney U test. The differences were statistically not relevant as indicated by the high p values >0.05.
doi:10.1371/journal.pone.0047185.t003





Apoptose, radiosensibilité et risque cancer



Gene polymorphisms, apoptotic capacity and cancer risk

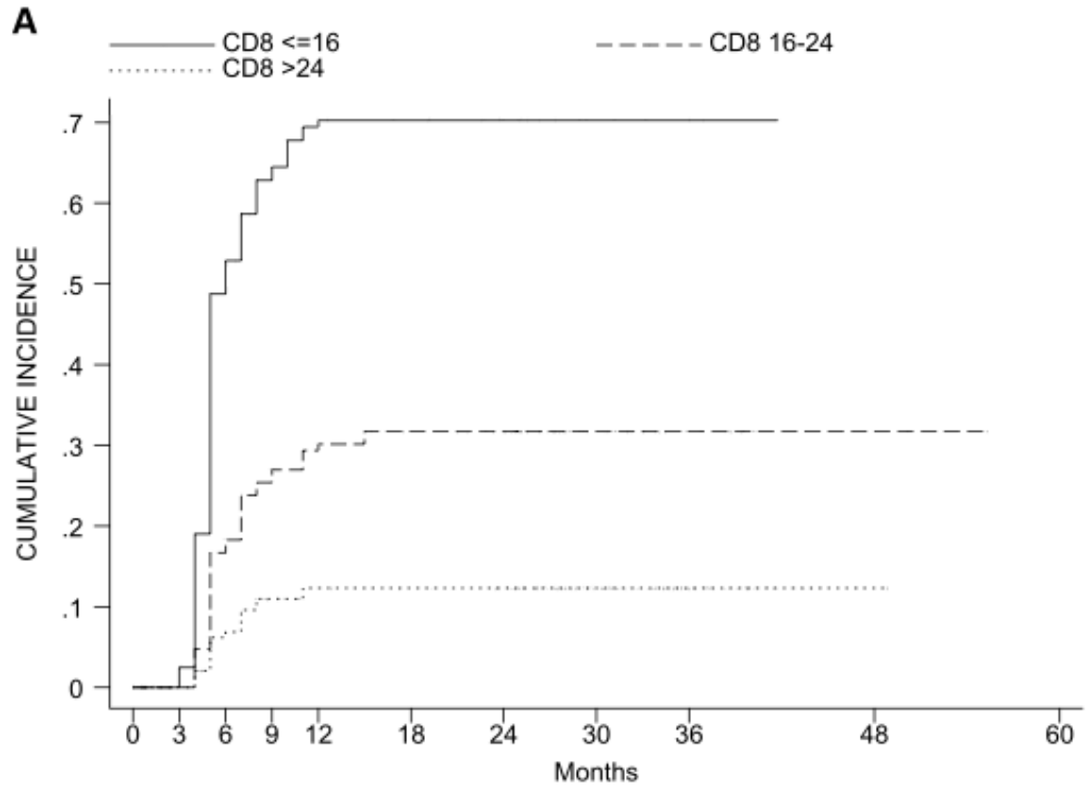
Evgeny N. Imyanitov
Hum Genet (2009) 125:239–246 DOI 10.1007/s00439-009-0636-7

Radiosensibilité clinique et apoptose

CD4 and CD8 T-Lymphocyte Apoptosis Can Predict Radiation- Induced Late Toxicity: A Prospective Study in 399 Patients

Mahmut Ozsahin etal.

Clin Cancer Res 2005;11(20)



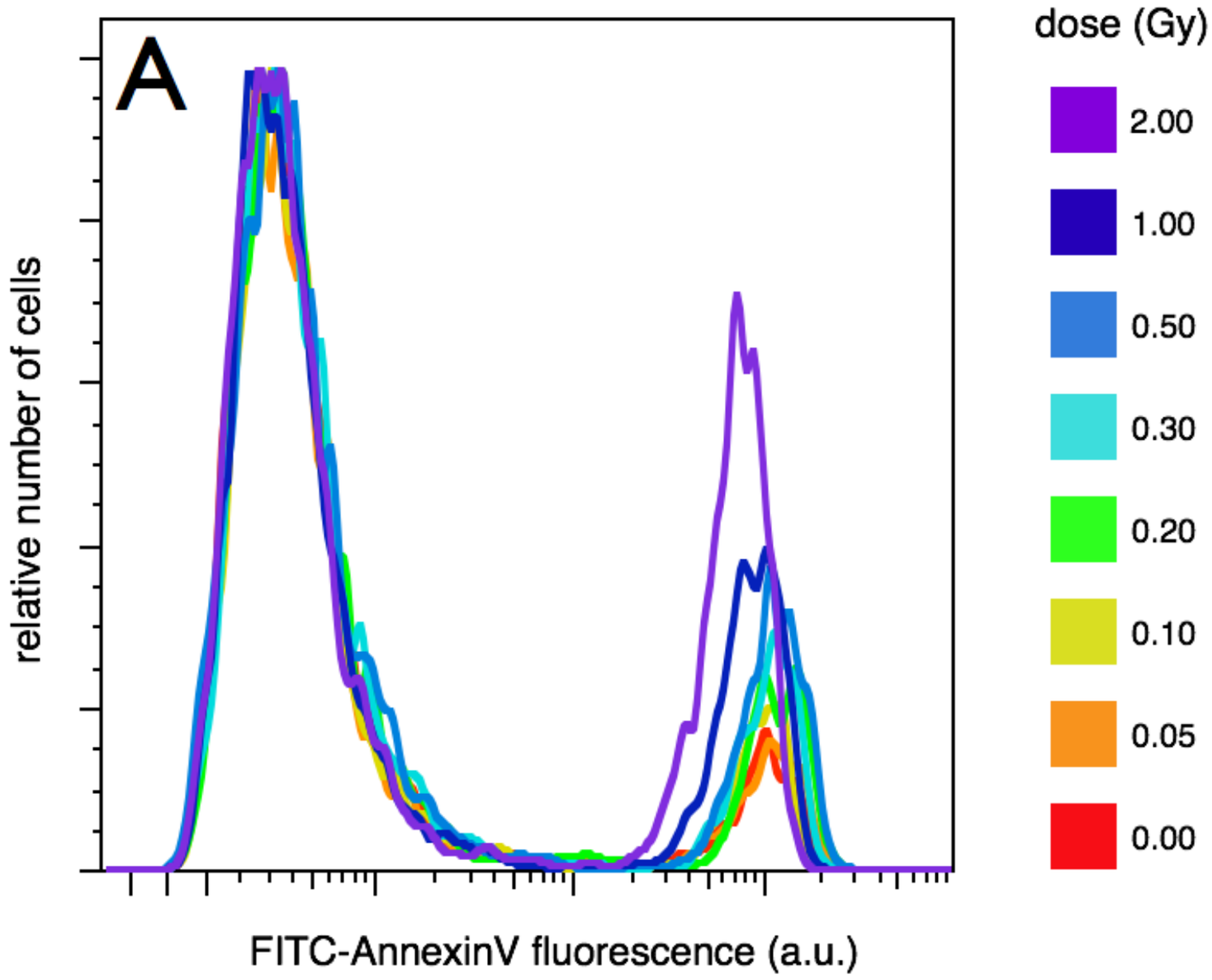
- 399 patients
- Test in vitro après 8Gy X-rays sur sang total
- apoptose sur T4 et T8 totaux 48h après IR

Radiation-Induced Lymphocyte Apoptosis to Predict Radiation Therapy Late Toxicity in Prostate Cancer Patients

Kara Schnarr et al.

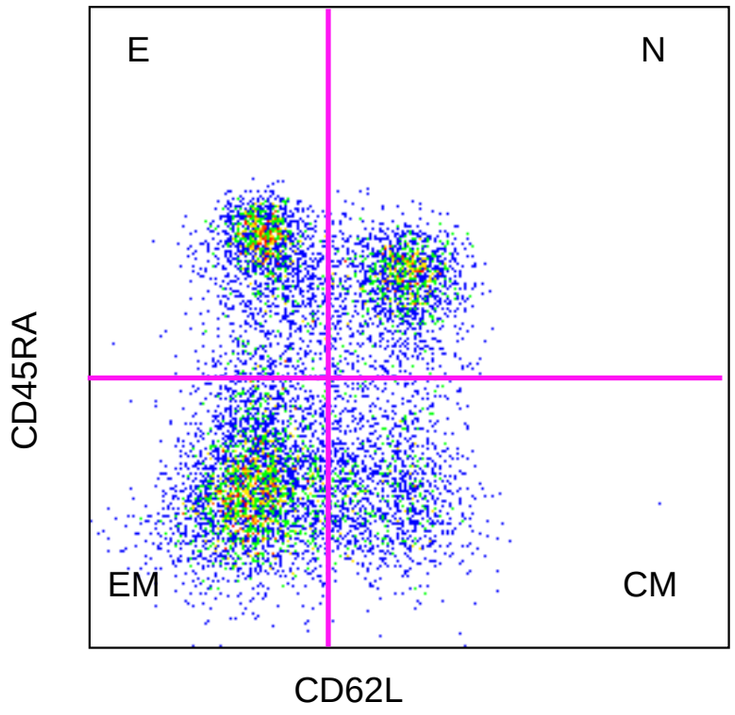
Int. J. of Radiat. Oncol. Biol. Phys 2009;74(5) 1424-1430

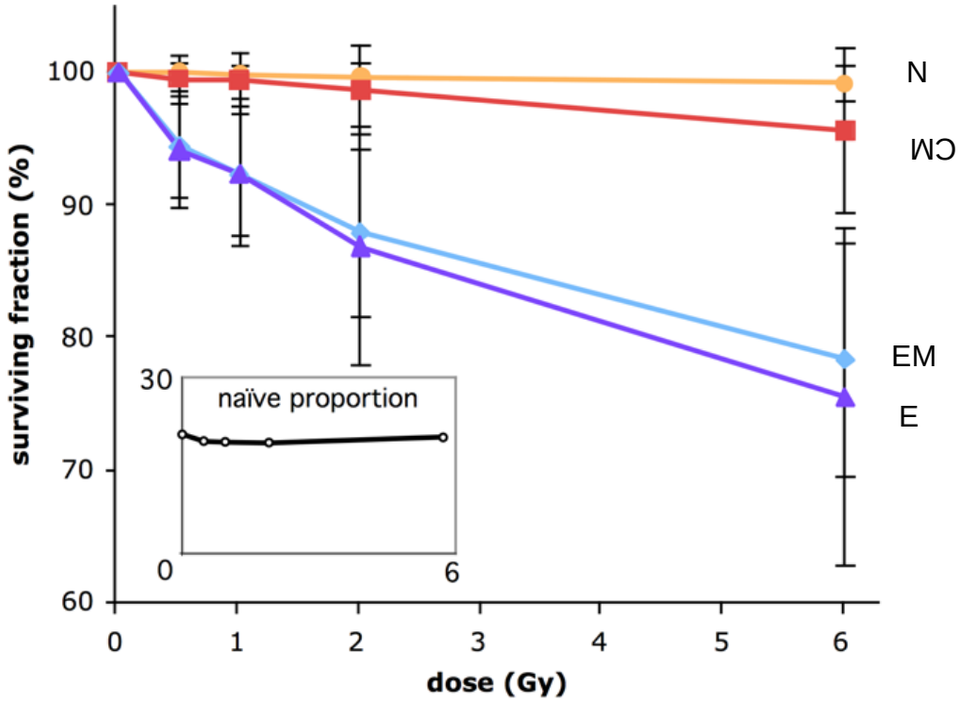
ex vivo ©radiation induced apoptosis in primary lymphocytes

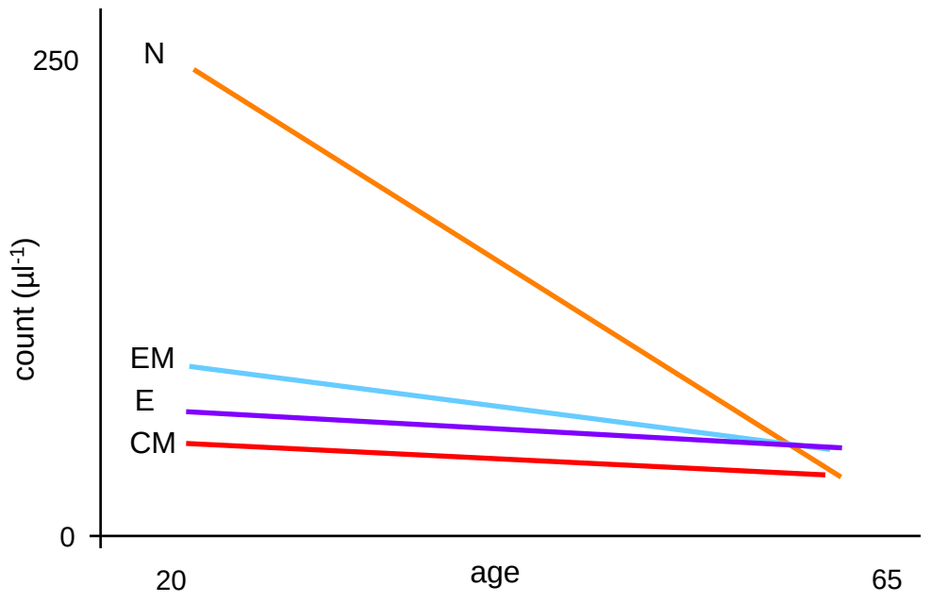


Radiosensitivity phenotyping...

- confounding quantitative traits
- relation to age







Individual lymphocyte homeostasis.

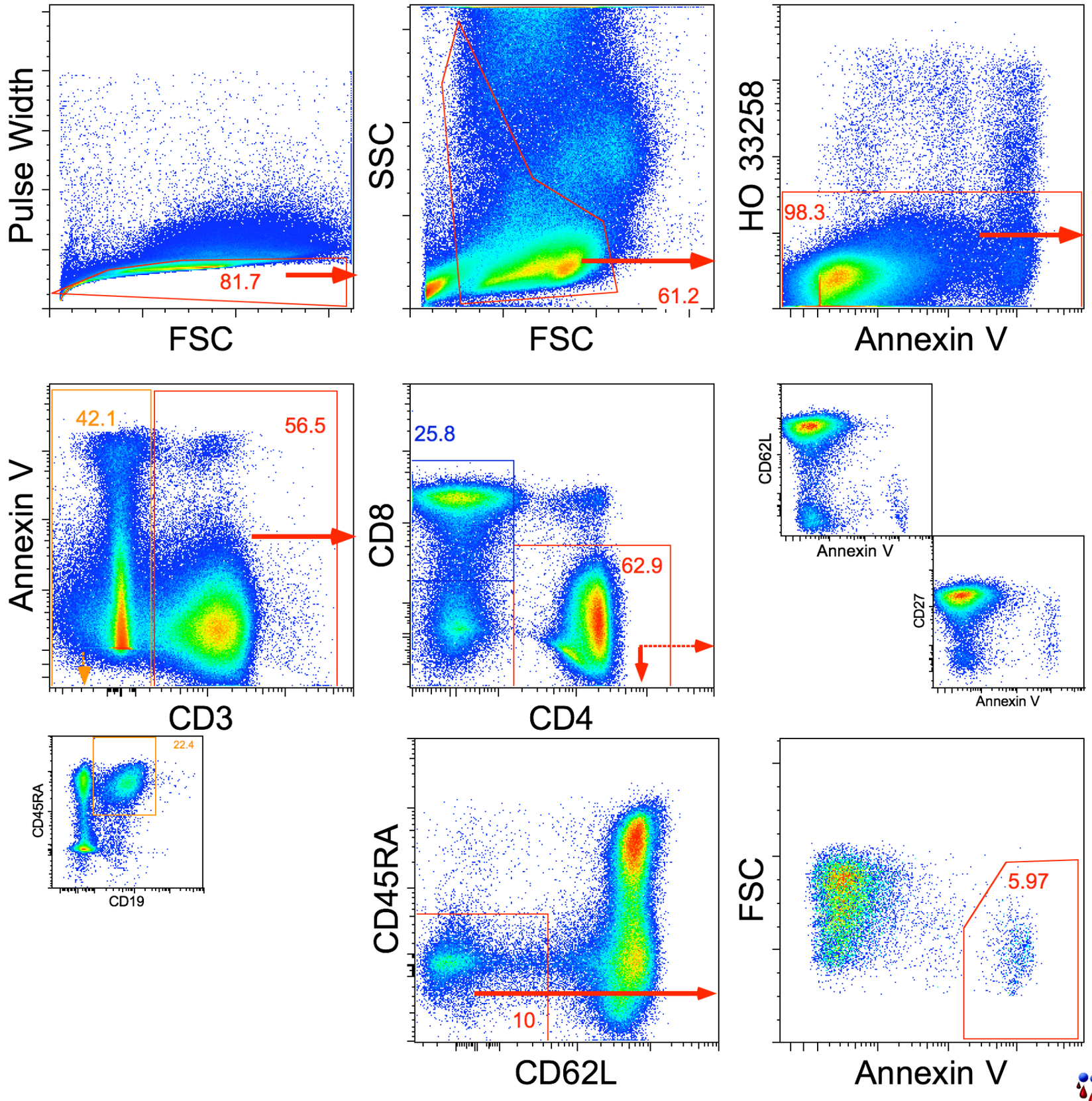
- effect of age sex and CMV serology

numbers of cells

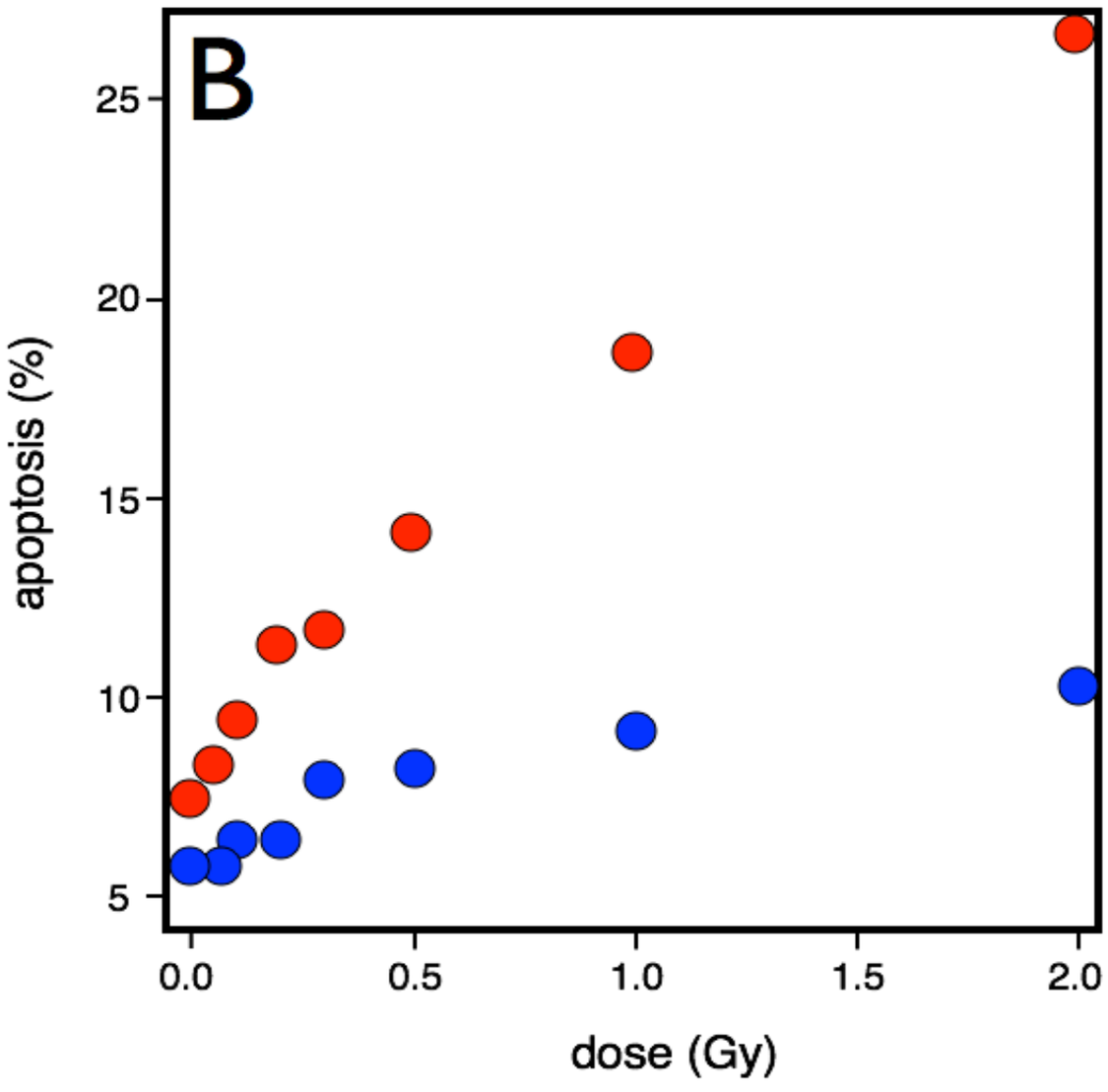
	Summary of Fit			REML variance	Summary of Fit			Restricted Maximum Likelihood (REML) variance component estimates			
Dependent Variable	R^2	R^2 adj.	F Ratio	Ind.	R^2	R^2 adj.	F Ratio	Ind	Age	Sex	CMV
				(%of total)					(%of total)		
Lymphs	0.83	0.79	8.1	63.7	0.83	0.79	8.1	63.7	.	.	.
T	0.83	0.78	7.8	62.5	0.83	0,79	8.0	61.0	4.9	.	.
TCRab	0.83	0.78	8.0	63.1	0.83	0.79	8.17	62.0	4.5	.	.
T4	0.83	0.78	8.1	65.4	0.83	0.79	8.5	62.9	.	6.8	.
T8	0.83	0.78	7.8	69.8	0.83	0.78	7.9	63.2	11.1	.	.
TCRgd	0.83	0.78	7.9	77.0	0.83	0.78	7.9	77.0	.	.	.
NK	0.80	0.75	6.5	72.7	0.80	0.75	6.5	72.7	.	.	.
B	0.85	0.81	8.9	72.0	0.85	0.81	8.9	72.0	.	.	.
T4/T8	0.86	0.82	10.1	79.3	0.86	0.82	10.1	62.4	13.5	7.5	.
T8Naive	**0.79**	**0.73**	**5.0**	**65.8**	**0.78**	**0.73**	**5.0**	**36.1**	**45.2**	**.**	**.**
T8 eff. Mem	0.79	0.73	4.8	67.2	0.77	0.71	4.7	67.2	.	.	.
T8 Mem.	0.80	0.73	5.3	72.8	0.80	0.73	5.3	72.8	.	.	.
T8 eff	0.85	0.80	7.3	73.6	0.84	0.80	7.4	55.5	2.6	.	22.1
T4Naive	**0.80**	**0.74**	**5.5**	**65.0**	**0.80**	**0.74**	**5.5**	**40.0**	**13.2**	**25.3**	**.**
T4 eff. Mem.	0.80	0.74	5.3	65.6	0.80	0.74	5.3	61.3	.	.	6.4
T4 Mem.	0.81	0.77	5.8	63.6	0.81	0.76	5.8	60.6	.	.	4.5
T4 eff.	0.69	0.59	2.9	41.7	0.69	0.59	2.9	41.7	.	.	.

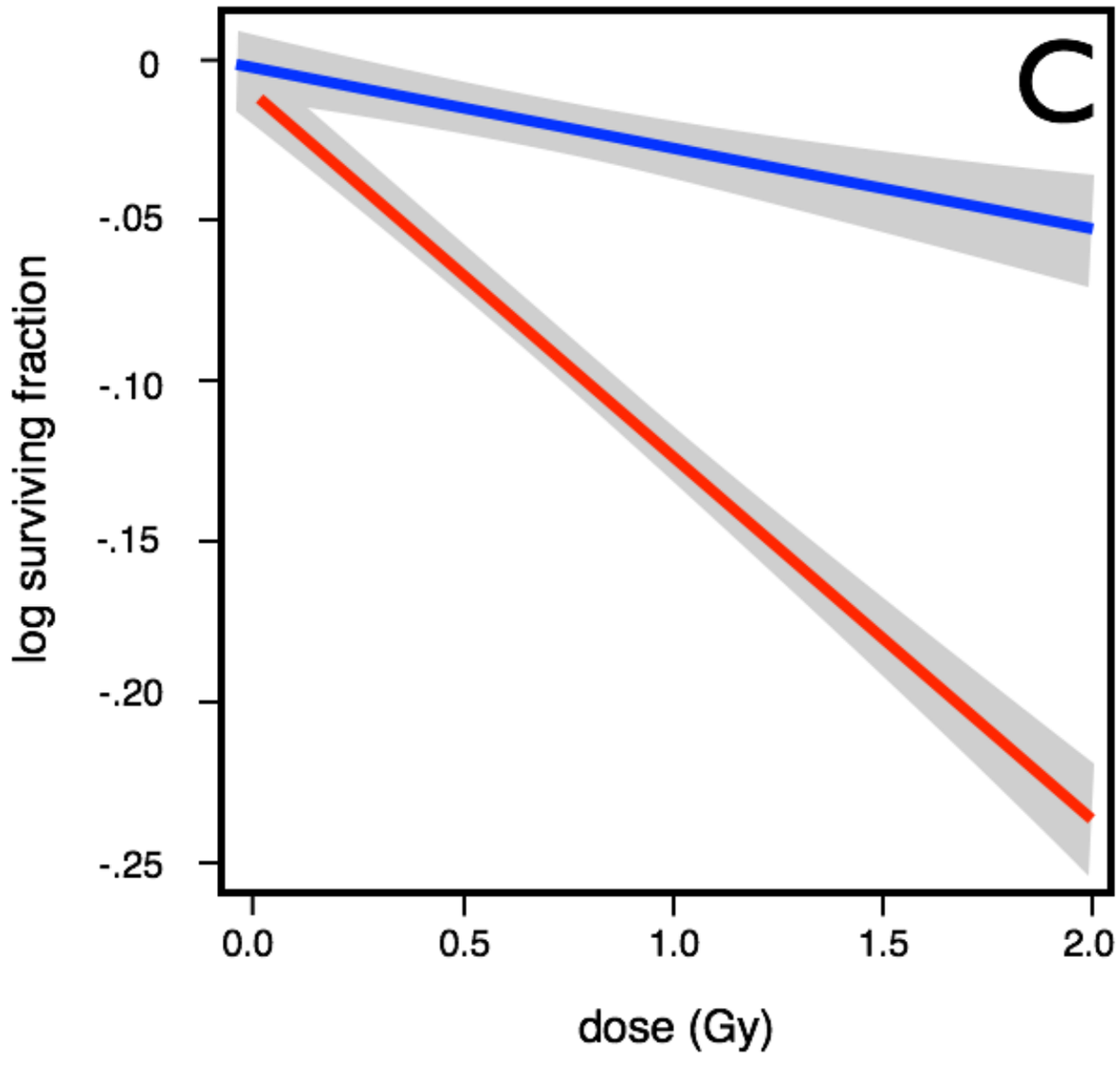
Peripheral Blood Lymphocyte :

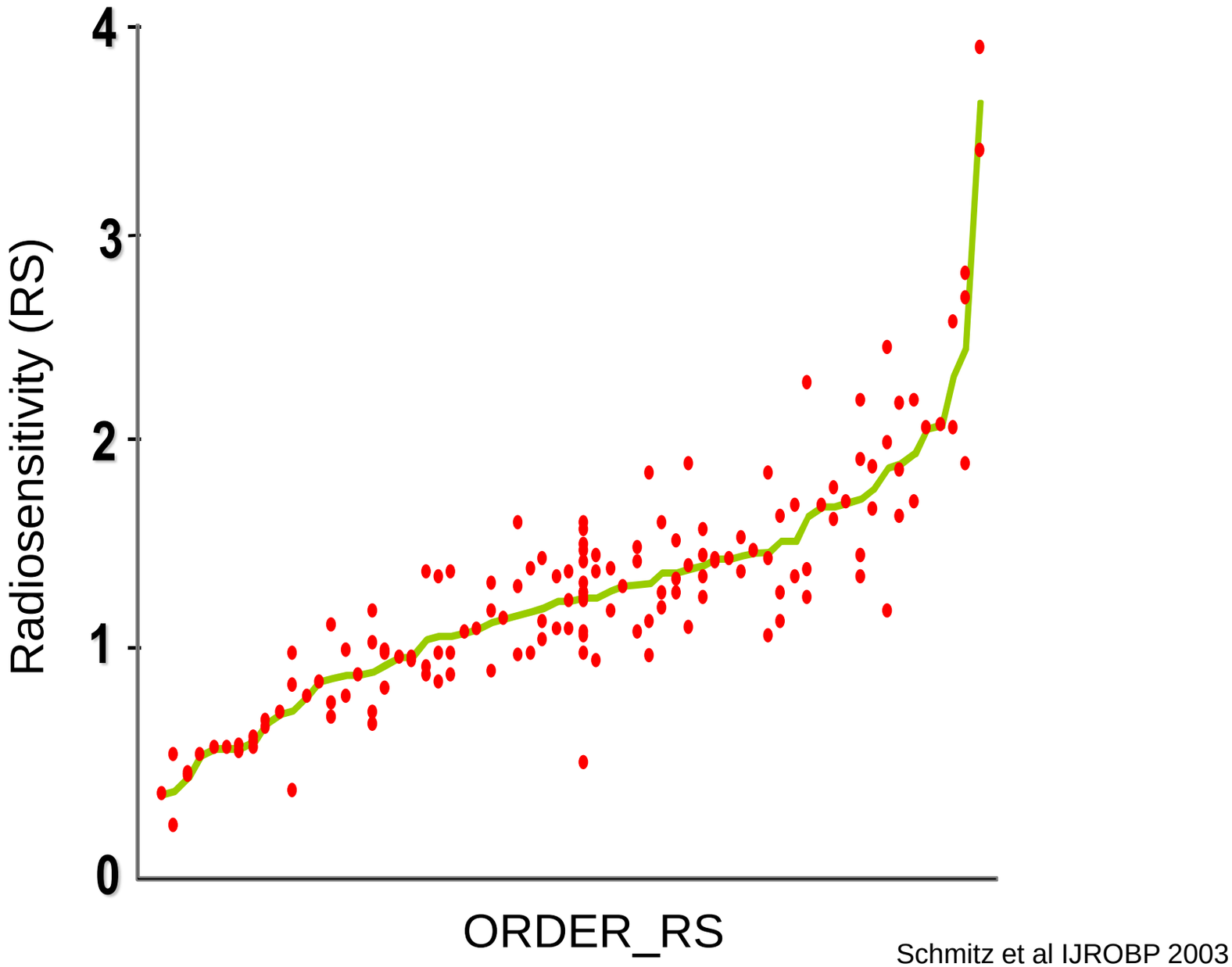
9 Color immunophenotyping and apoptosis quantification by flow cytometry



Radiosensitivity phenotype

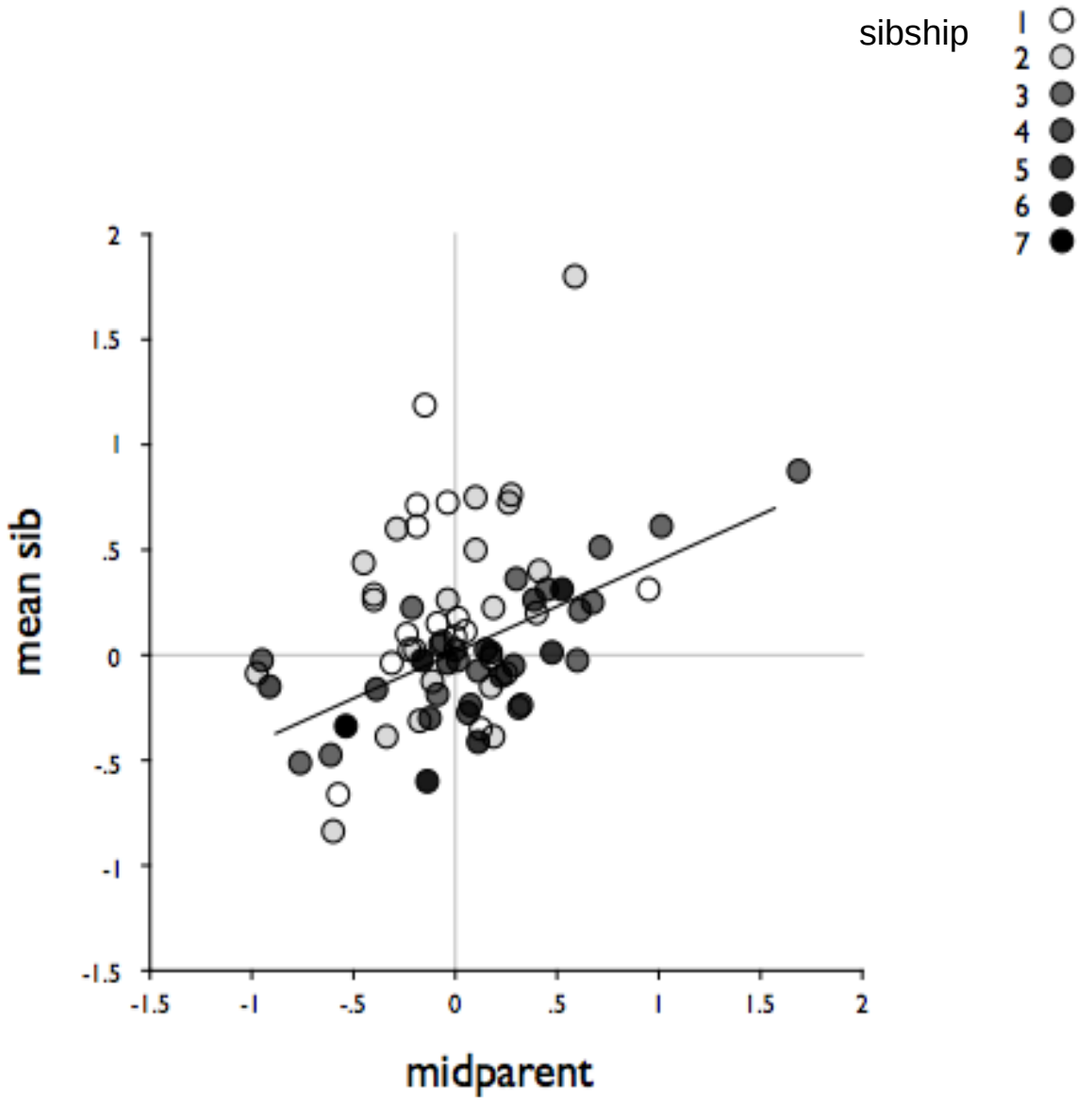






Schmitz et al IJROBP 2003

Correlations of radiosensitivity among first degree relatives



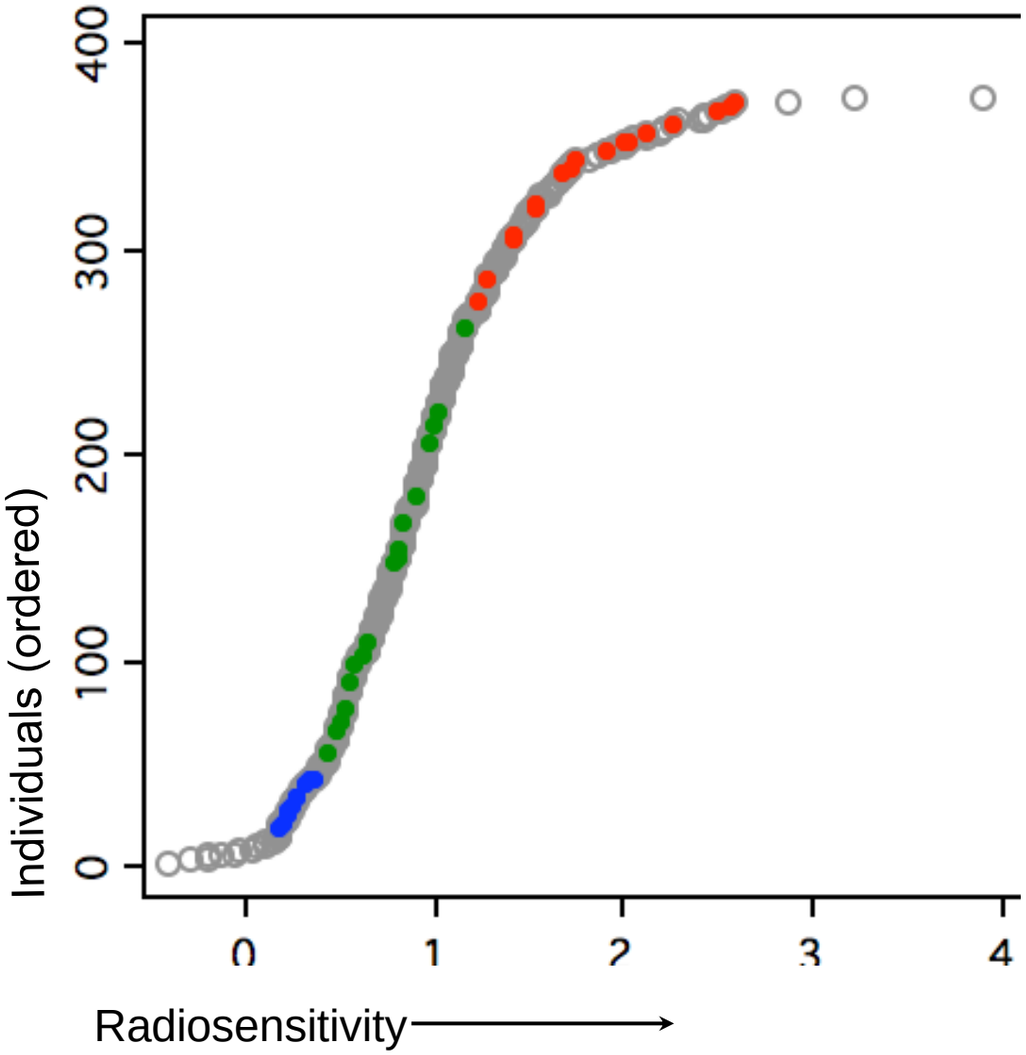
	Parent-offspring	Sibling	Spouse
T4	0.13 (0.07)	0.33 (0.09)	0.10 (0.11)
T4-EM	0.26 (0.06)	0.21 (0.08)	−0.003 (0.12)
T8	0.08 (0.06)	0.08 (0.07)	0.02 (0.11)
T8-EM	0.16 (0.05)	0.09 (0.07)	0.02 (0.11)
B	0.40 (0.06)	0.29 (0.08)	0.32 (0.10)

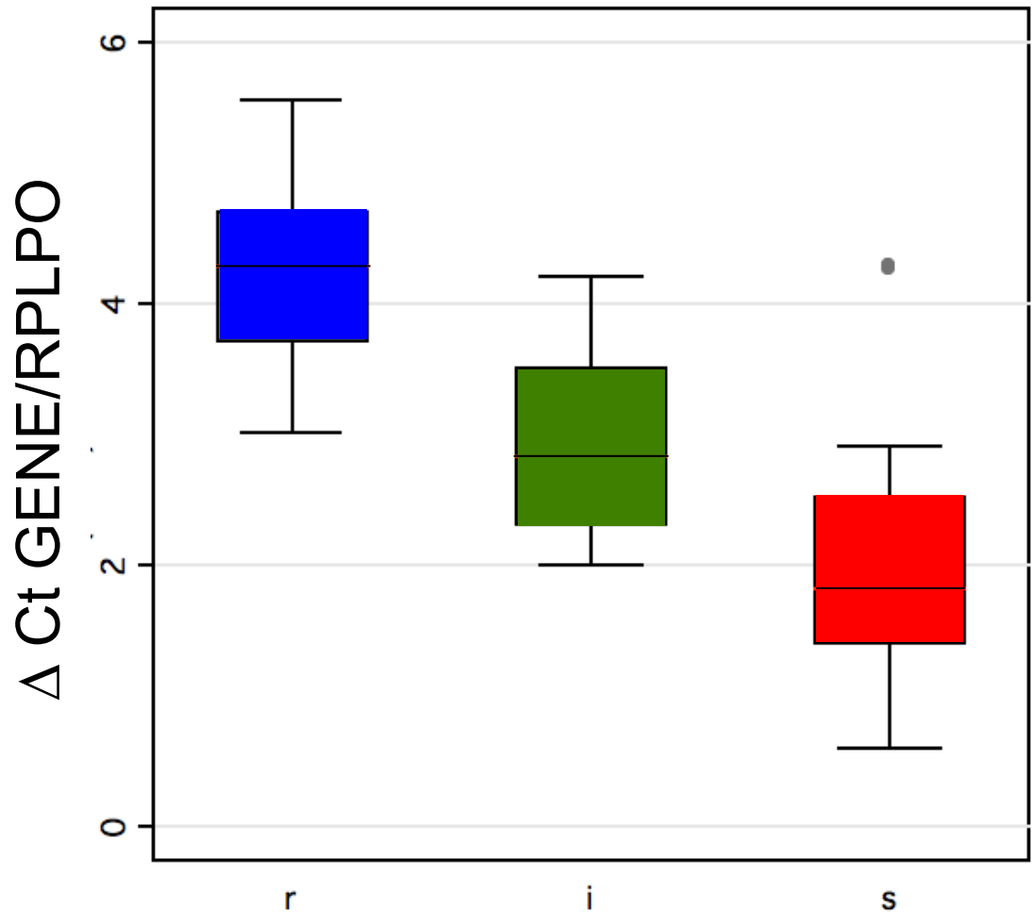
correlations (standard errors adjusted for non independance of relative pairs) by FCOR in SAGE-package

Analysis by Lynn Goldin NCI-NIH
Schmitz et al IJROBP 2007

Gene Expression correlation with radiosensitivity

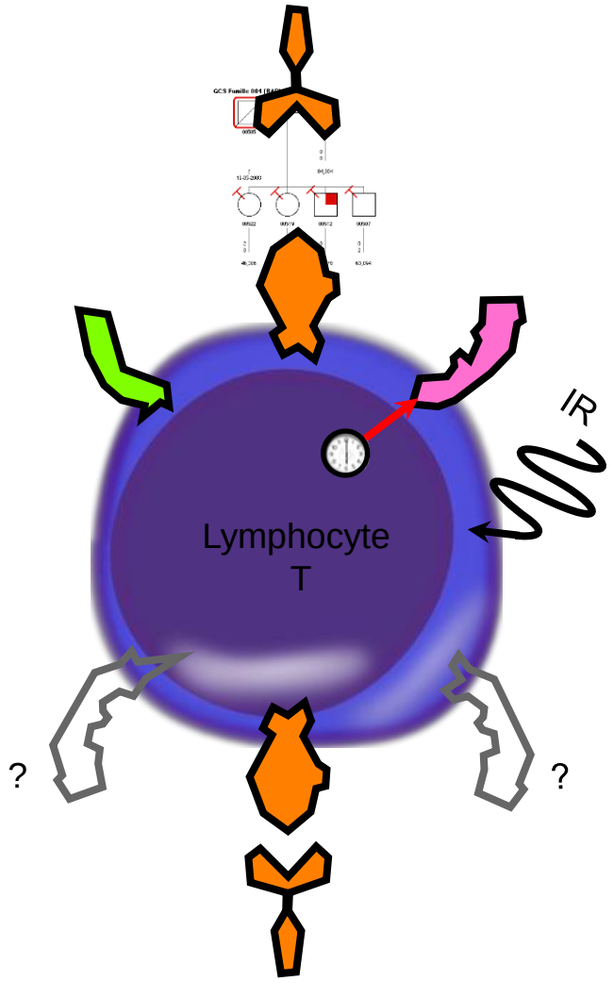
- validation on extended set of individuals for 1 candidate gene
- Taqman real time QPCR preceded by single step RT and multiplex-preamplification on 300 sorted live T4EM lymphocytes from cryopreserved PBL of GCS samples

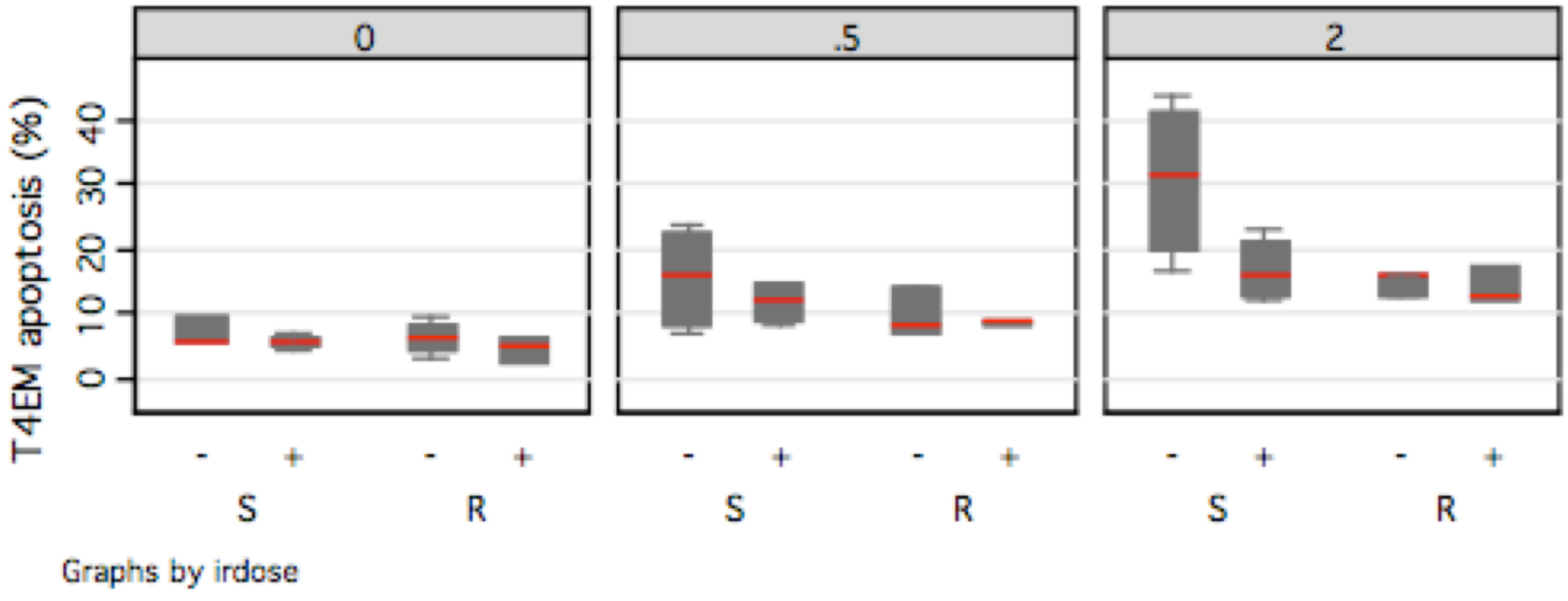




Schmitz et al, publication en cours

Radiation induced apoptosis capacity modulation





Schmitz et al, publication en cours

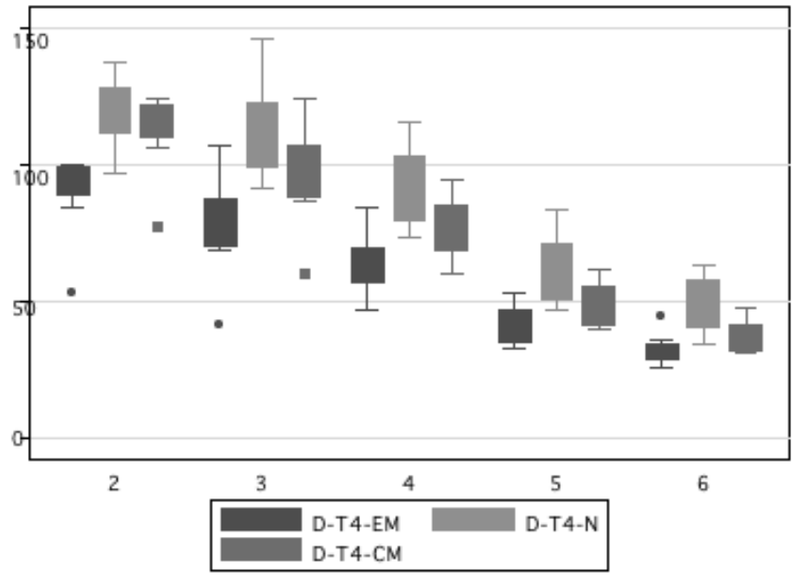
Domage à l'ADN / Apoptose

- Lymphocytes quiescent (G0/G1)
- Immunophenotypage et ©H2AX par CMF

- Parmi les sous populations T4

  T4 effecteur (susceptibles à l'apoptose)

  cinétique de résolution ©H2AX rapide

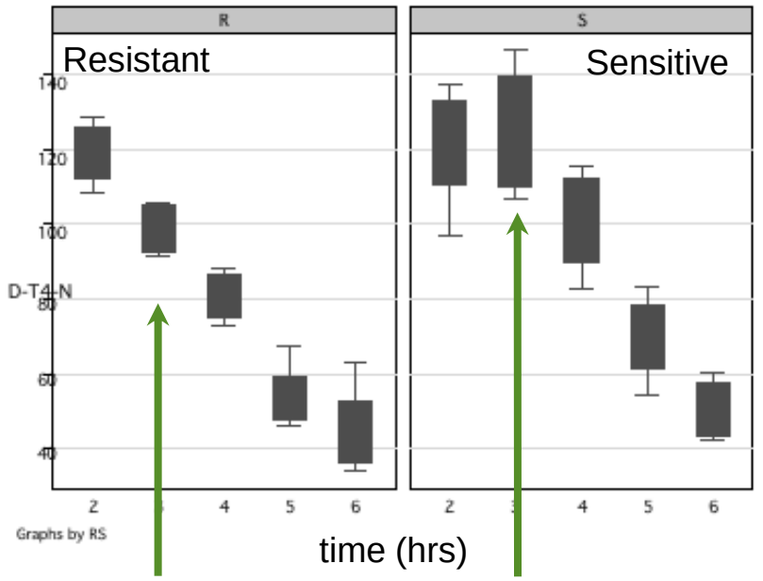


ex vivo irradiation of cryopreserved PBL at 2Gy (1Gy/min); N=10

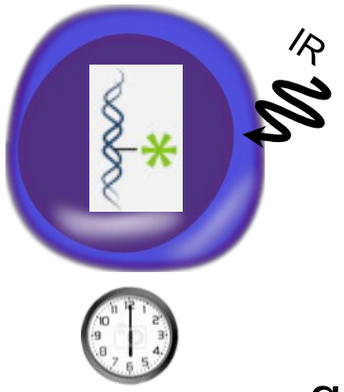
- Parmi les individus phenotypés pour la susceptibility a l'apoptose radio-induite

  Les lymphocytes T4 N des individus resistants

  cinétique de résolution ©H2AX rapide



Schmitz et al, unpublished data



somatique

germinal

apoptose
réparation fidèle
réparation infidèle
instabilité...

Apoptose
Comet
G2 assay
Micronoyaux
Cytogénétique
©H2AX
TCR
Glycophorine A
Expression
Genotypage

agrégation familiales
pathologies radiosensibles

syndromes autosomiques rescessifs

intégrité de l'ADN
génétique des tumeurs
gènes
indicateurs
signatures

Type cellulaire
cellules souches
Lignées
ARN
ADN

dose
qualité
débit

variants génétiques communs

sensibilité individuelle

facteurs de risque

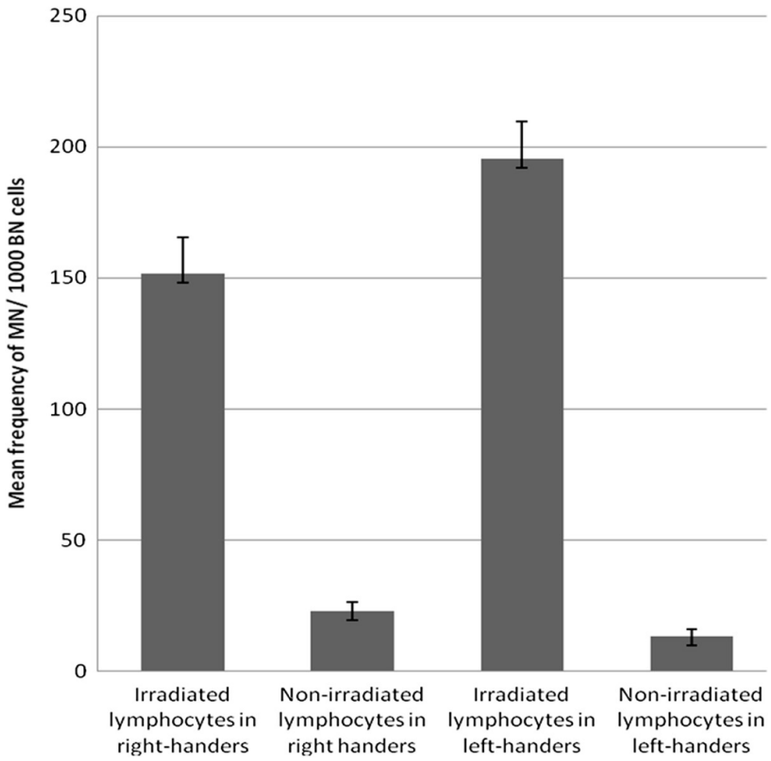
La question reste difficile a formuler

The study of radiosensitivity in left handed compared to right handed healthy women

Meysam Khosravifarsani[1] et al.

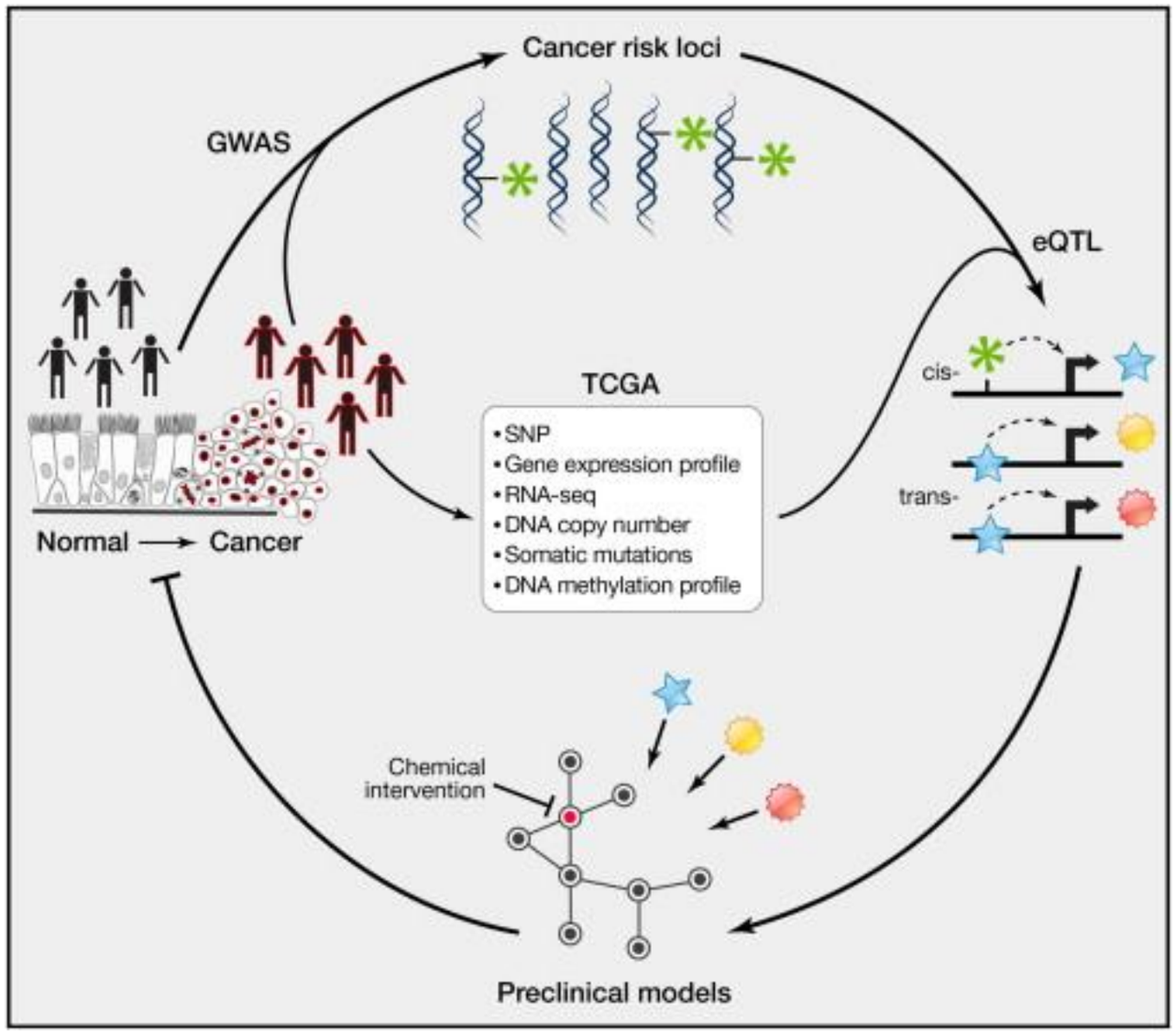
BMC Medical Physics 2012, **12**:3 doi:10.1186/1756-6649-12-3

- 100 femmes en bonne santé (40-60)
- micronoyaux (2 Gy)



La plupart des cancers radioinduits surviendront dans un contexte de prédisposition

Identification de lien causal entre facteur de risque / gène /radio-protection



Stratégie de protection pour la prévention de radiopathologies

biomarqueurs fonctionels et prédictifs pour une radioprotection personalisée

Figure 1. Bridging the Gap between Detection of Cancer Risk Loci and Development of Disease Prevention Strategies. High-resolution annotation of molecular correlates in tumor samples can be dovetailed with GWAS to elaborate causal relationships between risk loci and target genes. These target genes serve as both functional and predictive biomarkers for personalized medicine. This, in turn, can lead to testable mechanistic hypotheses and nomination of early detection and prevention strategies.

GWAS Meets TCGA to Illuminate Mechanisms of Cancer Predisposition
Cell Volume 152, Issue 3 2013 387 - 389
Hyun Seok Kim , John D. Minna , Michael A. White