New ICRP *Publication 131*: "Stem cell biology with respect to carcinogenesis aspects of radiological protection"

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This presentation has neither been approved nor endorsed by the Main Commission of ICRP

Background

- Protection guidelines are based on epidemiology of exposed human populations
- Radiation induced cancer is the main stochastic effect
- Dose-response models are supported mechanistically by damage to target cell populations
- Multistage carcinogenesis implicates long-lived cells as target cells, generally “stem cells” residing in “niches”
- Stem cell biology can provide scientific insight to the models used in protection guidelines for stochastic effects

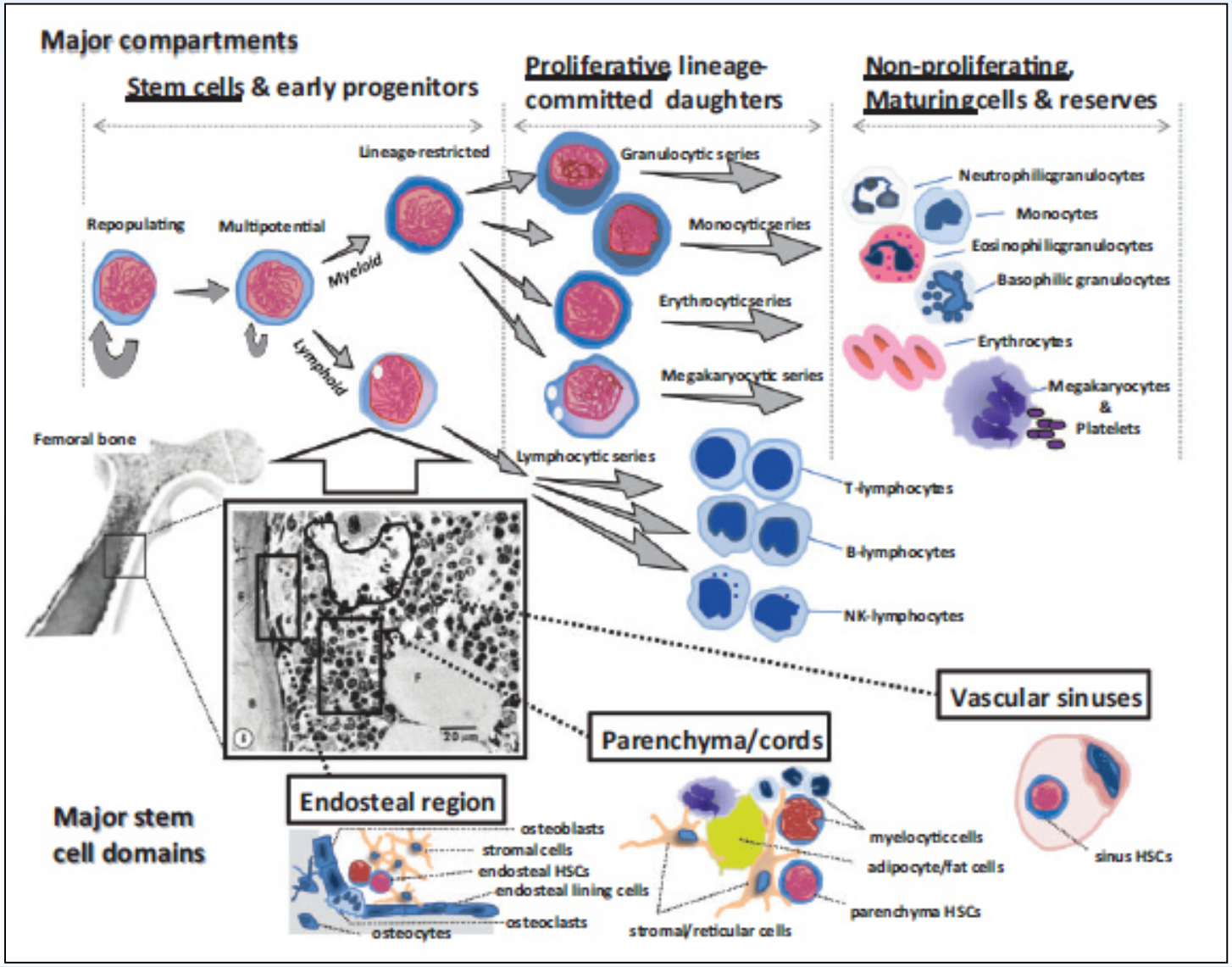
Stem cell biology with respect to carcinogenesis aspects of radiological protection

Ohtsura Niwa and Jolyon Hendry **- ICRP Committee 1**

Chapter 1: Introduction
Chapter 2: General features of tissue stem cells
Chapter 3: The role of tissue stem cells in radiation carcinogenesis

Annex A: Haematopoietic tissue	- TM Seed
Annex B: Mammary gland	- MH Barcellos-Hoff
Annex C: Thyroid	- K Suzuki, S Yamashita
Annex D: Digestive tract	- J Hendry
Annex E: Lung	- J Shay, M Story, P Jacob
Annex F: Skin	- M Martin
Annex G: Bone surface	- J Harrison, R Globus

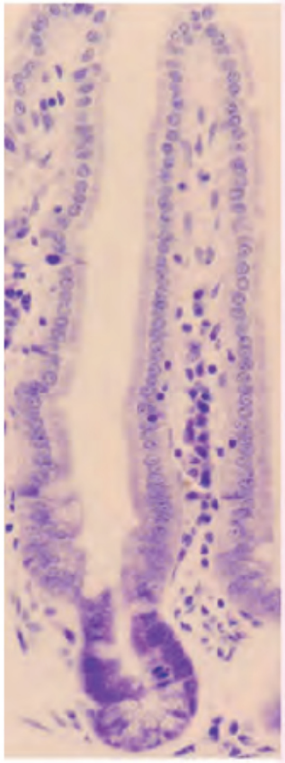
Bone marrow – haematopoiesis

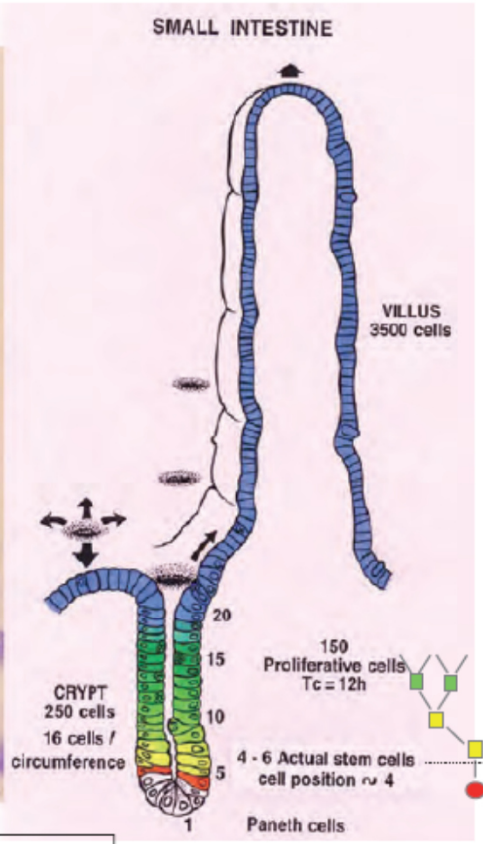


Courtesy of Tom Seed, Bethesda. Modified from an NIH online report (2008)

Intestinal crypts

Crypt stem cell lineage: steady and perturbed states



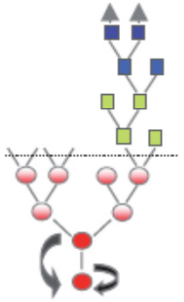


Takes into account many disparate observations. Similar stem cell hierarchy in the bone marrow.

Functional

Transit

Stem



Functional cells

Transit cells (amplification)

Potential clonogenic stem cells

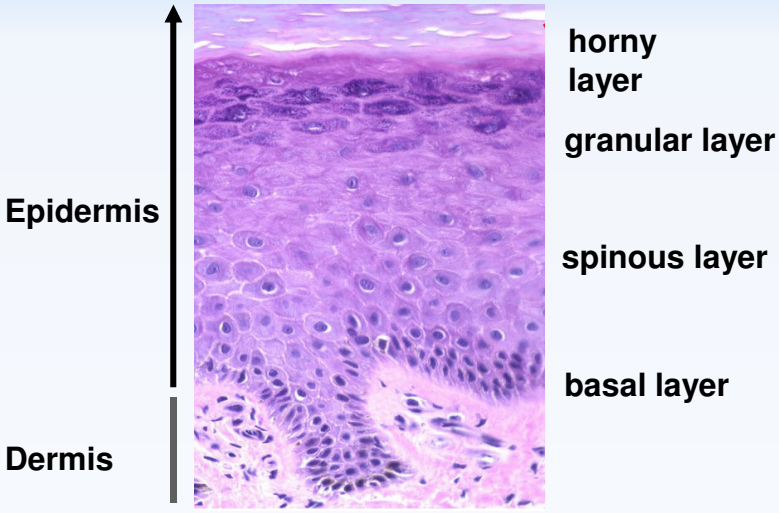
Self-maintaining stem cells

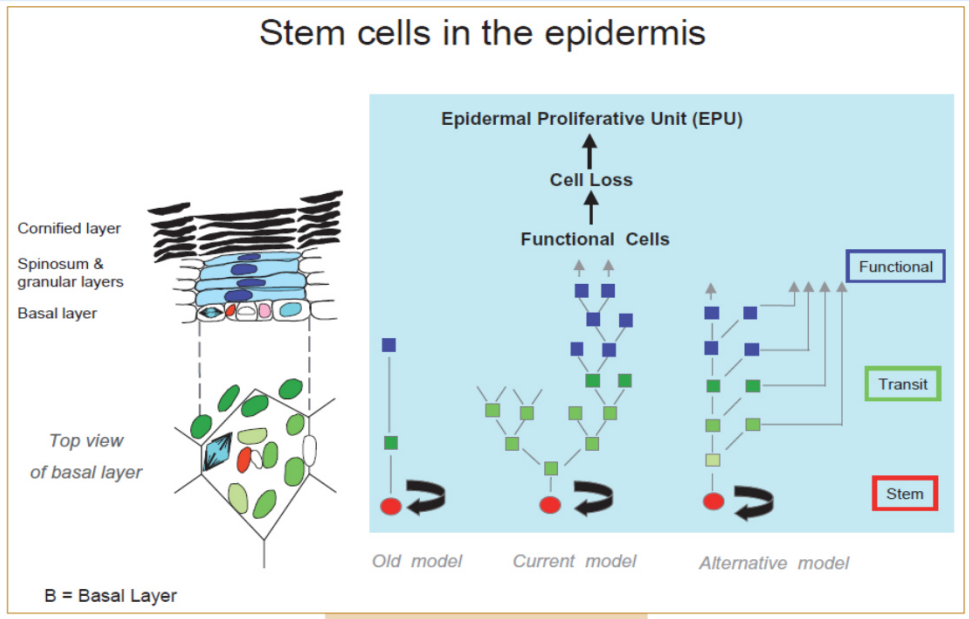
30-40 potential stem cells
4-6 actual stem cells

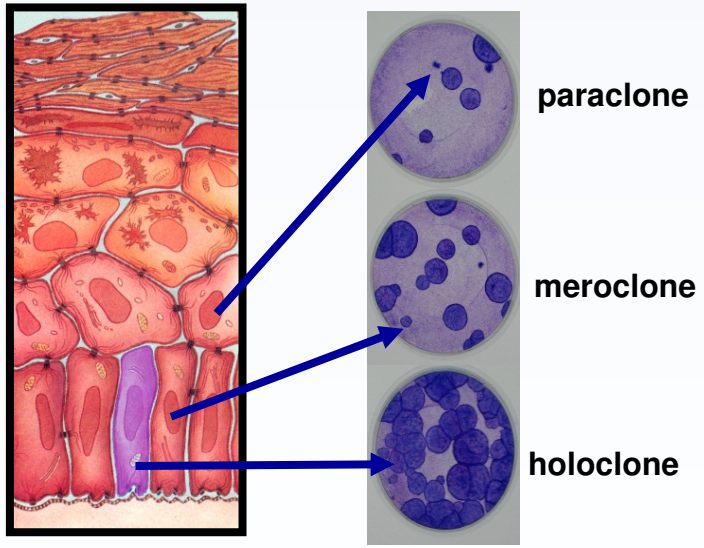
..... = differentiation event

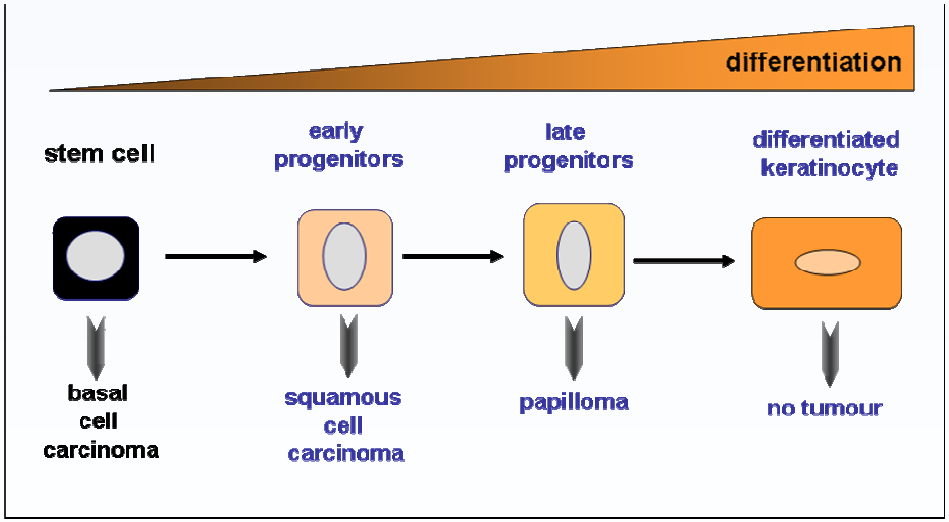
Wilson and Potten 2007

Skin epidermis



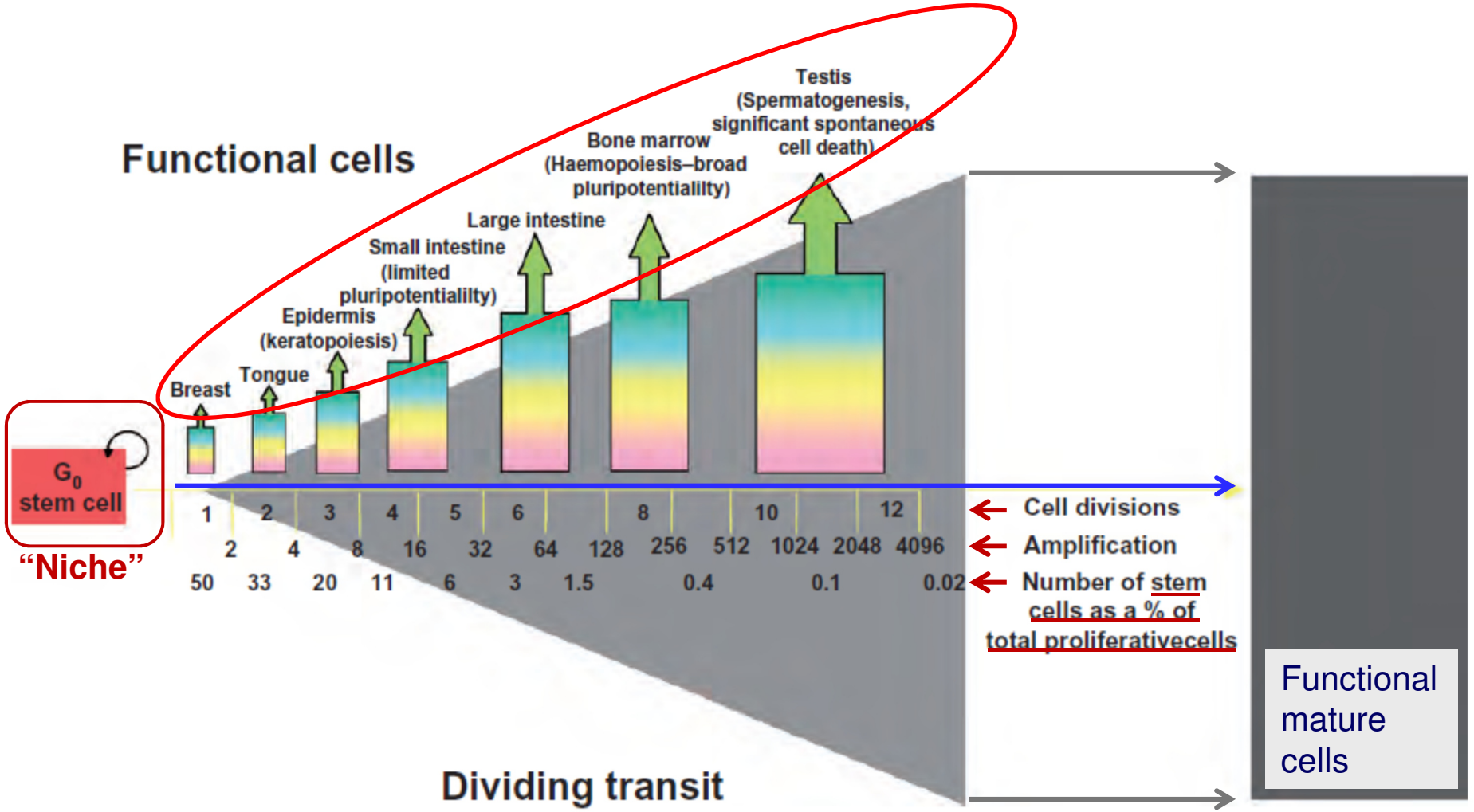






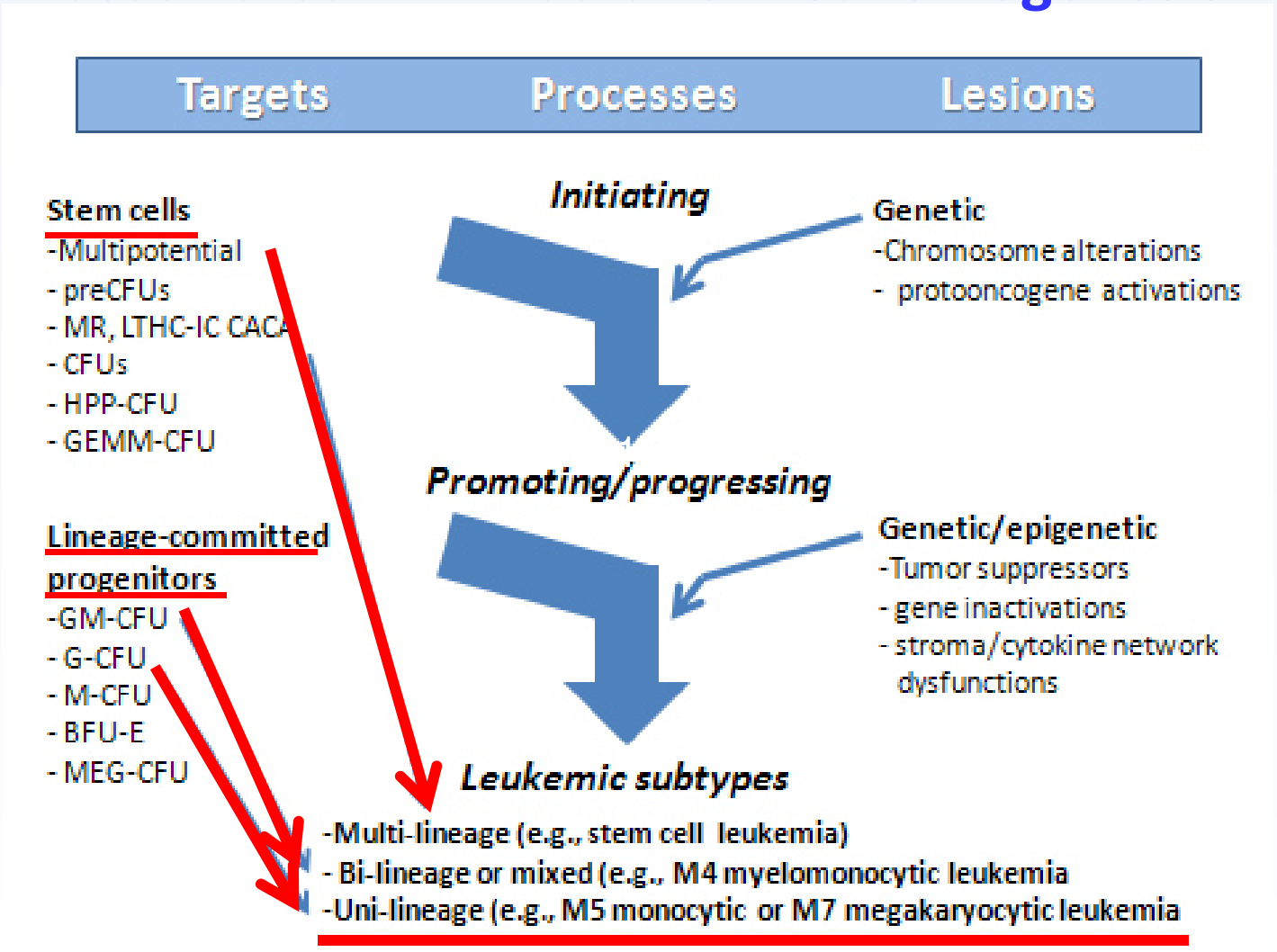
Sell 2004; Potten and Wilson 2007; Martin 2015

Unified Cell Lineage Organization



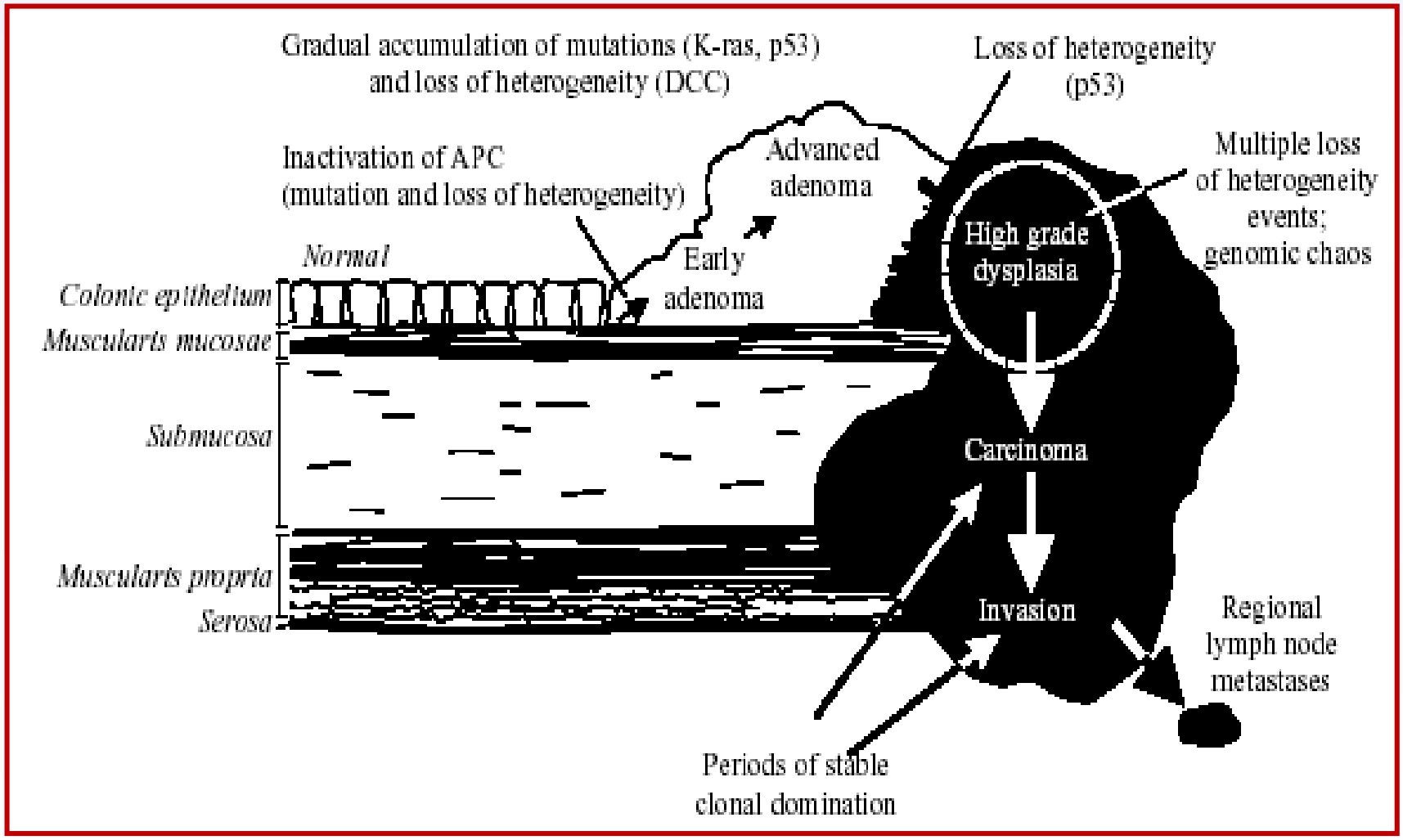
Wilson and Potten 2007

Potential cell targets, processes and lesions associated with radiation leukemogenesis



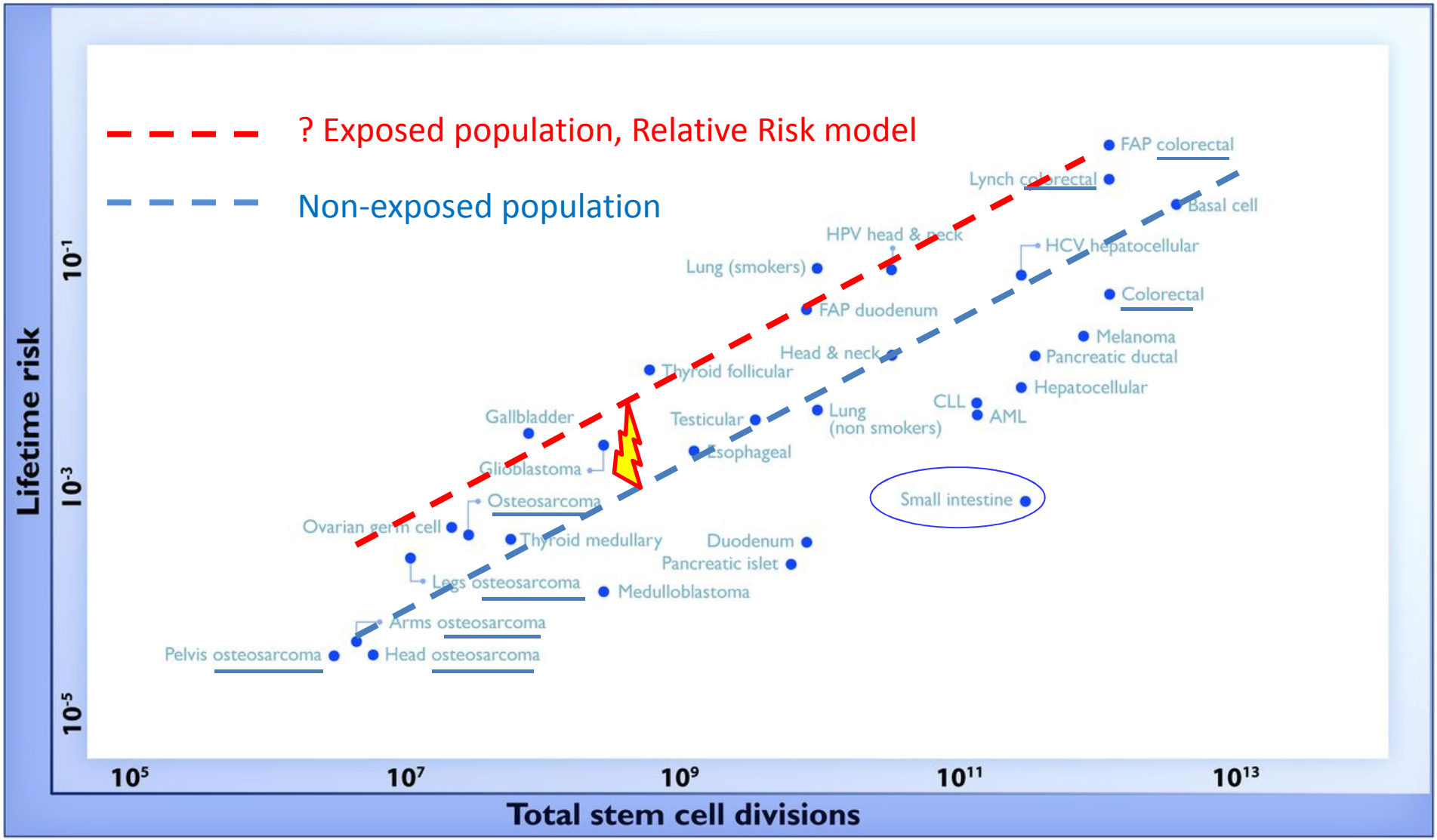
NCRP-150, 2005

A model of the sequence of genetic events in neoplastic development in the human colon



Boland, 1995; UNSCEAR, 2000

Lifetime spontaneous cancer risk versus lifetime stem cell divisions



FAP = Familial Adenomatous Polyposis ◇ HCV = Hepatitis C virus ◇ HPV = Human papillomavirus ◇ CLL = Chronic lymphocytic leukemia ◇ AML = Acute myeloid leukemia

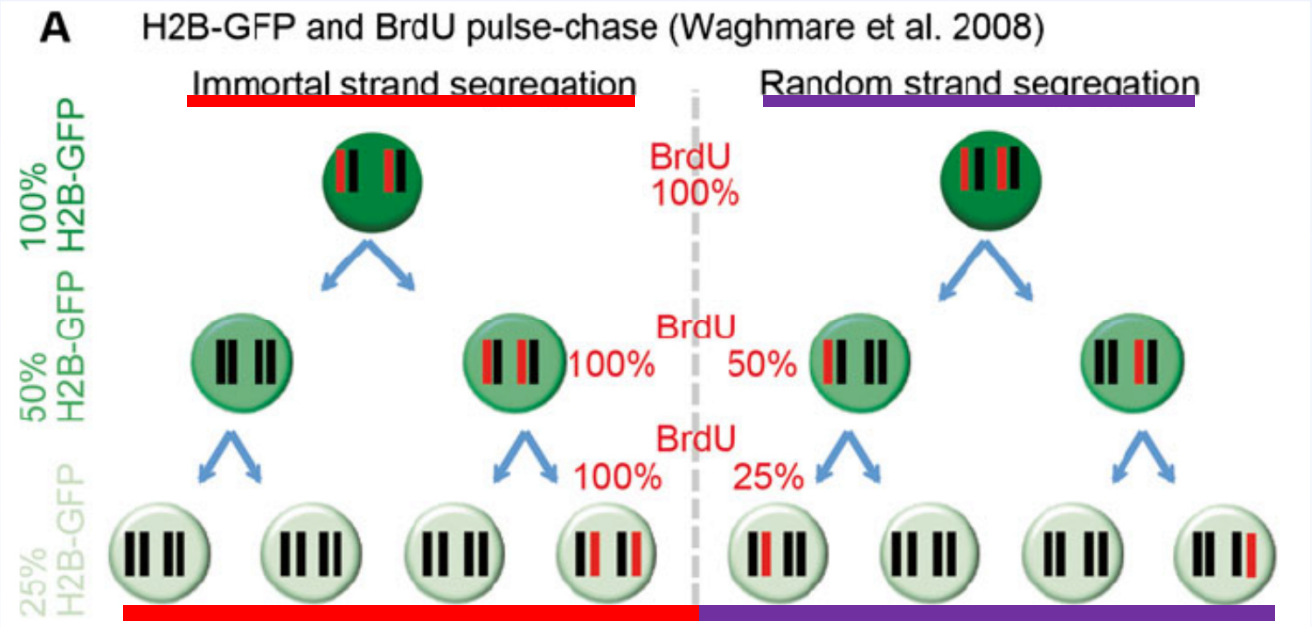
US SEER cancer incidence database; Tomasetti & Vogelstein, 2015

Correlation (?) of radiation cancer risk among tissues with their estimated lifetime number of stem-cell divisions

Independent variable and model	Log cancer risk % per Sv per unit variable (95% CI)	P value
log[Japan, ICRP mixed ERR/EAR model] vs log[cumulative number of stem-cell divisions]	0.082 (-0.113, 0.277)	0.34
log[Japan, BEIR mixed ERR/EAR model] vs log[cumulative number of stem-cell divisions]	0.051 (-0.151, 0.253)	0.56

Calculated using 10 of the 31 cancer types/sites used by Tomasetti and Vogelstein (2015), where radiation risk values are available (Little, Hendry, Pushkin, submitted for publication)

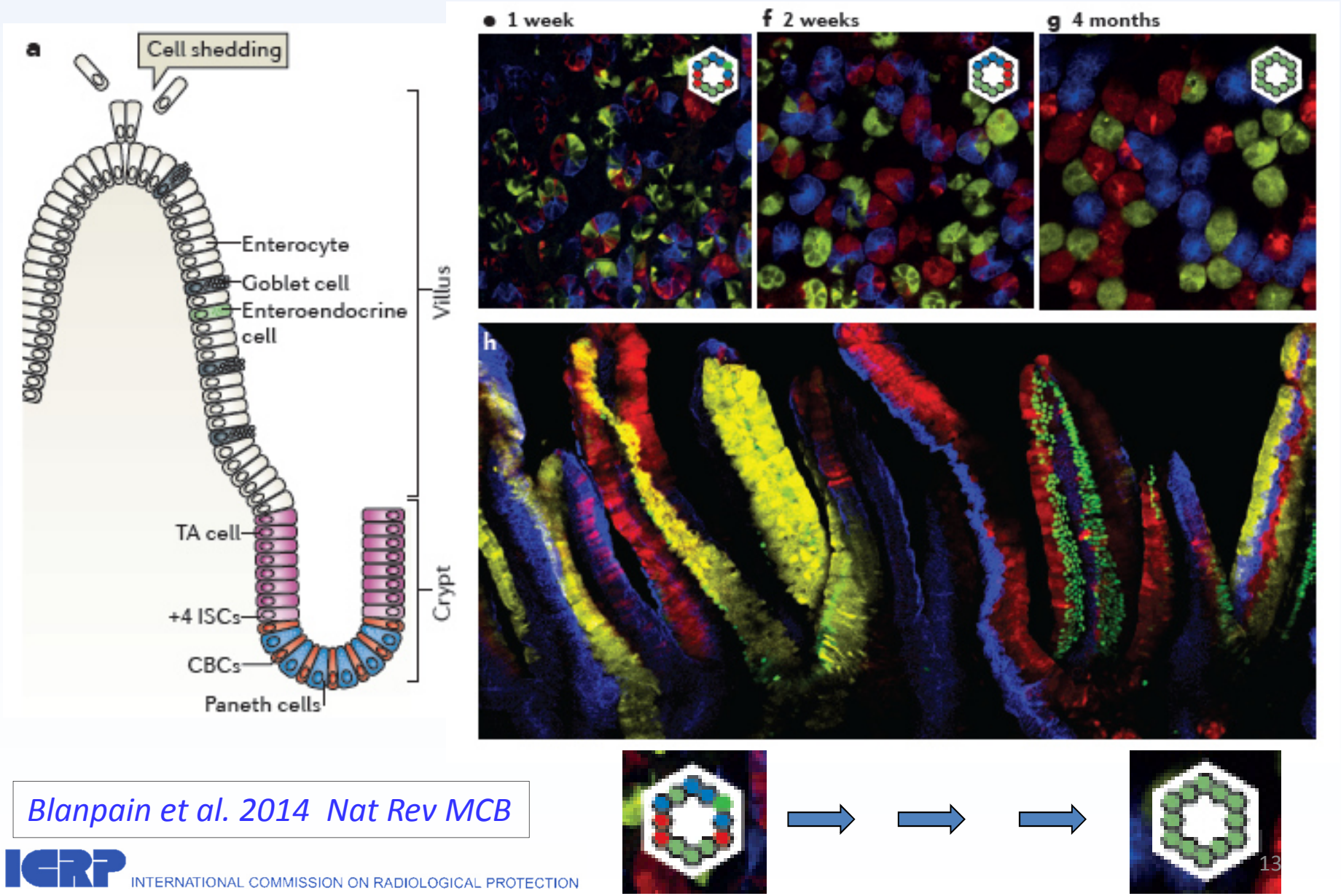
The ‘immortal strand’ hypothesis: – parental DNA template retention



Haematopoietic stem cells	- No
Intestinal stem cells	- Yes and No
Skin stem cells	- Yes
Hair follicle stem cells	- No
Tongue epidermal stem cells	- Possibly
Mammary epithelium	- Yes
Stem cells in colon, blood, head & neck tissues (mutation accumulation)	- No

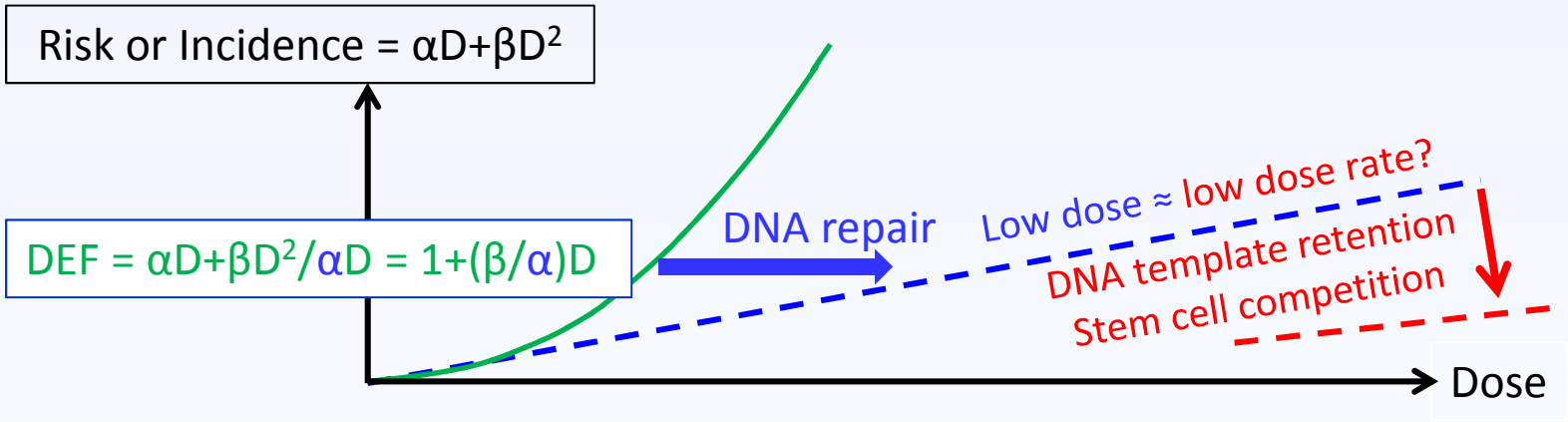
?

Stem cell "competition" in intestine



Blanpain et al. 2014 Nat Rev MCB

DEF – Dose Effectiveness Factor
DREF – Dose Rate Effectiveness Factor



- The DEF and DREF are based on the Linear Quadratic model.
- The LQ model is good for description of chromosome aberrations.
- The LQ model assumes **β** is dose-rate sensitive while α is insensitive.
- The DDREF predicts the same risk value at low dose and low dose rate, but there are various examples of a dose-rate-dependent decrease of the α term.
- Selective elimination of 'unfit' stem cells by 'DNA template retention' and/or 'stem cell competition' may result in a lowering of the α term.

Age dependency

1. Age-dependent sensitivities to radiation carcinogenesis: embryo and fetal stages - low to moderate sensitivity; children – higher sensitivity; adults, lower sensitivity declining with age.
2. High rates of cell proliferation in children considered not the sole and simple reason. More symmetrical stem cell divisions, associated with growth, might allow more replication errors.
3. Less competition of fit versus unfit stem cells for residence in more niches might increase sensitivity.
4. Animal/human developmental stage differences make interpretations uncertain.

Summary & Conclusions

1. Hierarchical lineage type of cell renewal and stem cell 'niche' in all tissues with radiation risk factors.
2. Stem cells and some progenitors are the target of carcinogenesis.
3. Lack of correlation of stem cell number/replications and radiation risk.
4. LQ model supported; DEF and DREF are different factors.
5. Use of the Relative Risk model implies that health promoting actions to reduce baseline risk might also reduce radiation risk.
6. Evidence for the immortal-strand hypothesis (might reduce risk) in some but not all tissues.
7. Stem cell 'competition' (fit versus unfit cells) might reduce risk, but speculative.
8. Age dependency also explainable by stem cell competition, but lack of evidence.

Future research

1. Further investigate stem cell systems in chronic irradiation conditions.
2. Clarification of importance of DNA template retention – some evidence in intestine, mammary, skin, but not found in bone marrow.
3. Does fit versus unfit stem-cell competition occur at low radiation doses and dose-rates, and in which tissues?
4. Resolve DDREF issues – DEF, DREF, animal values versus various human epidemiology studies.
5. Resolve animal/human differences in fetal/neonatal risks, and elucidate childhood sensitivities.
6. How to manage/integrate any consensus regarding **individual sensitivity, genomic instability**, **non-targeted effects** and **adaptation** within the framework of protection principles – **systems biology** approaches?

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