

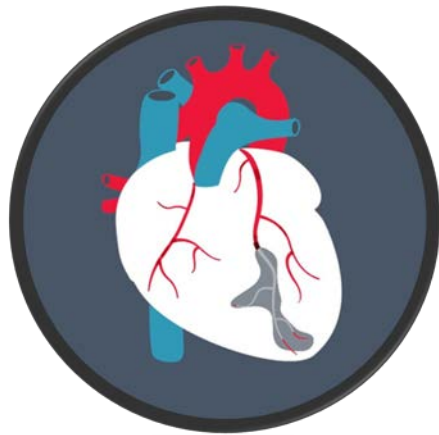
Functional Gene Analysis Reveals Cell Cycle Changes and Inflammation in Endothelial Cells Irradiated with a Single X-ray Dose

Bjorn Baselet

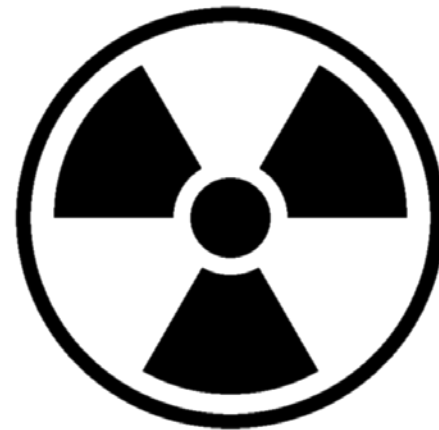


1. Introduction

Molecular characterization of endothelial cell response in the context of radiation-induced atherosclerosis



Heart disease



Ionizing radiation

Cardiovascular system: structure and function

- Organ system that distributes blood to all parts of the body

- Transportation of

- Nutrients



- Oxygen

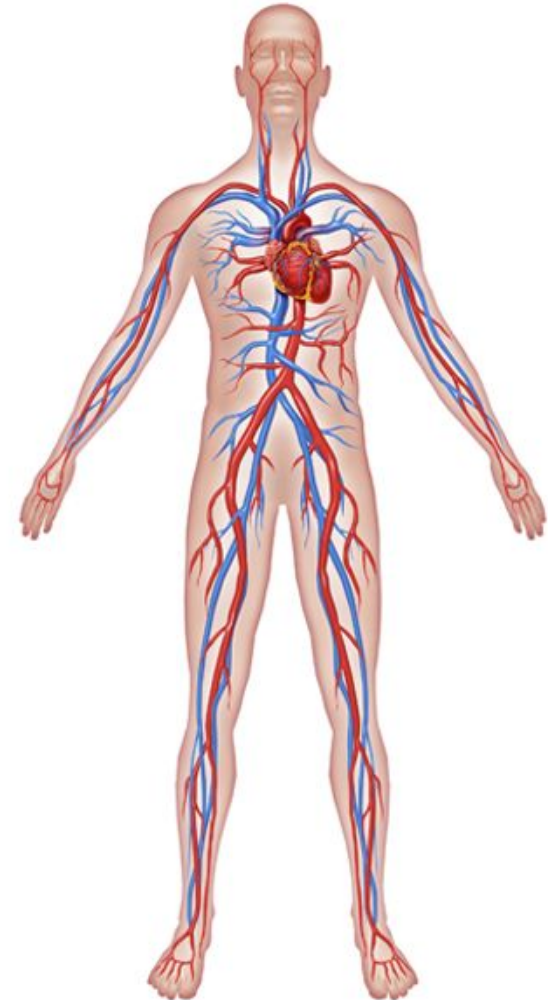
- Carbon dioxide



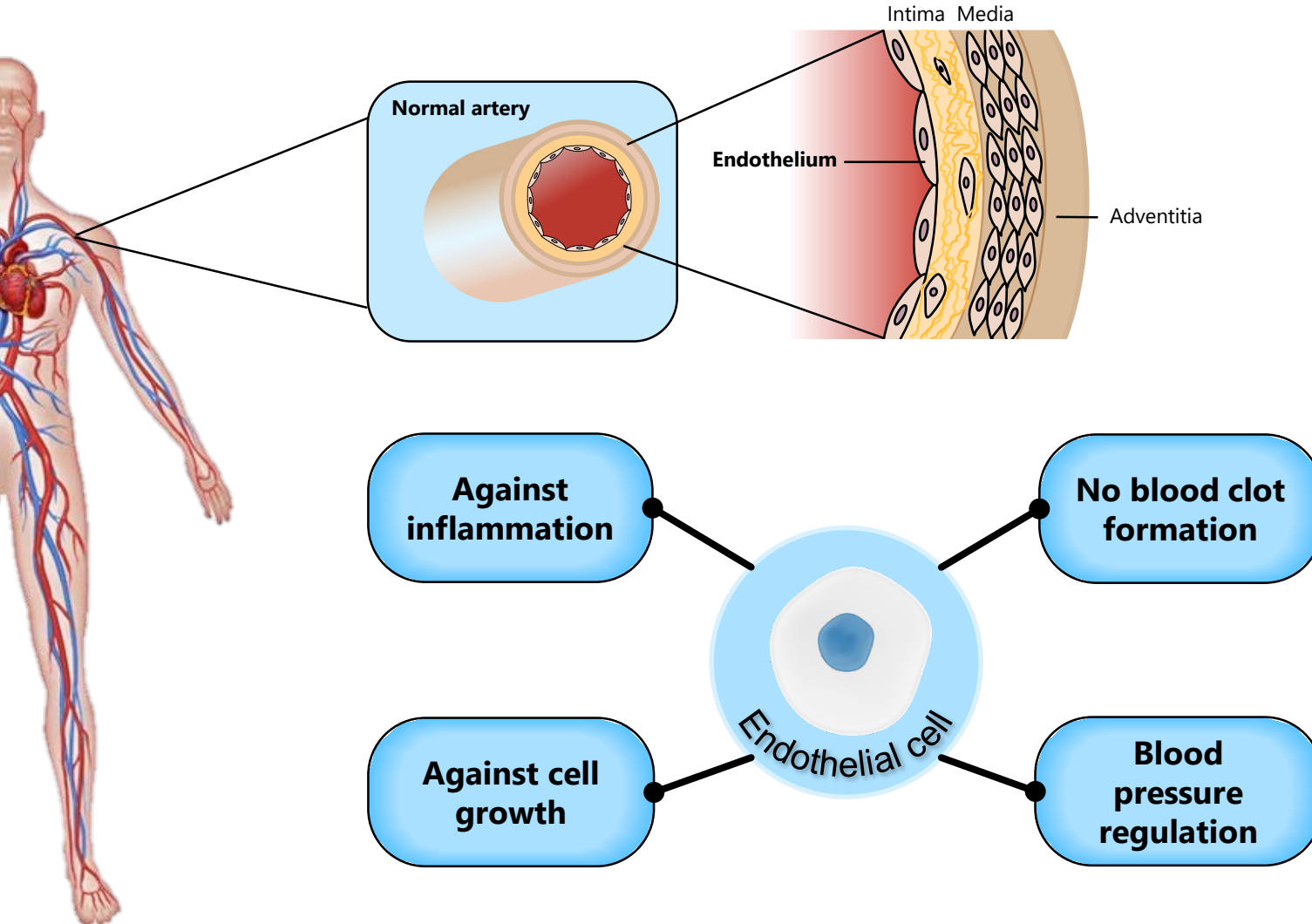
- Hormones

- Immune cells

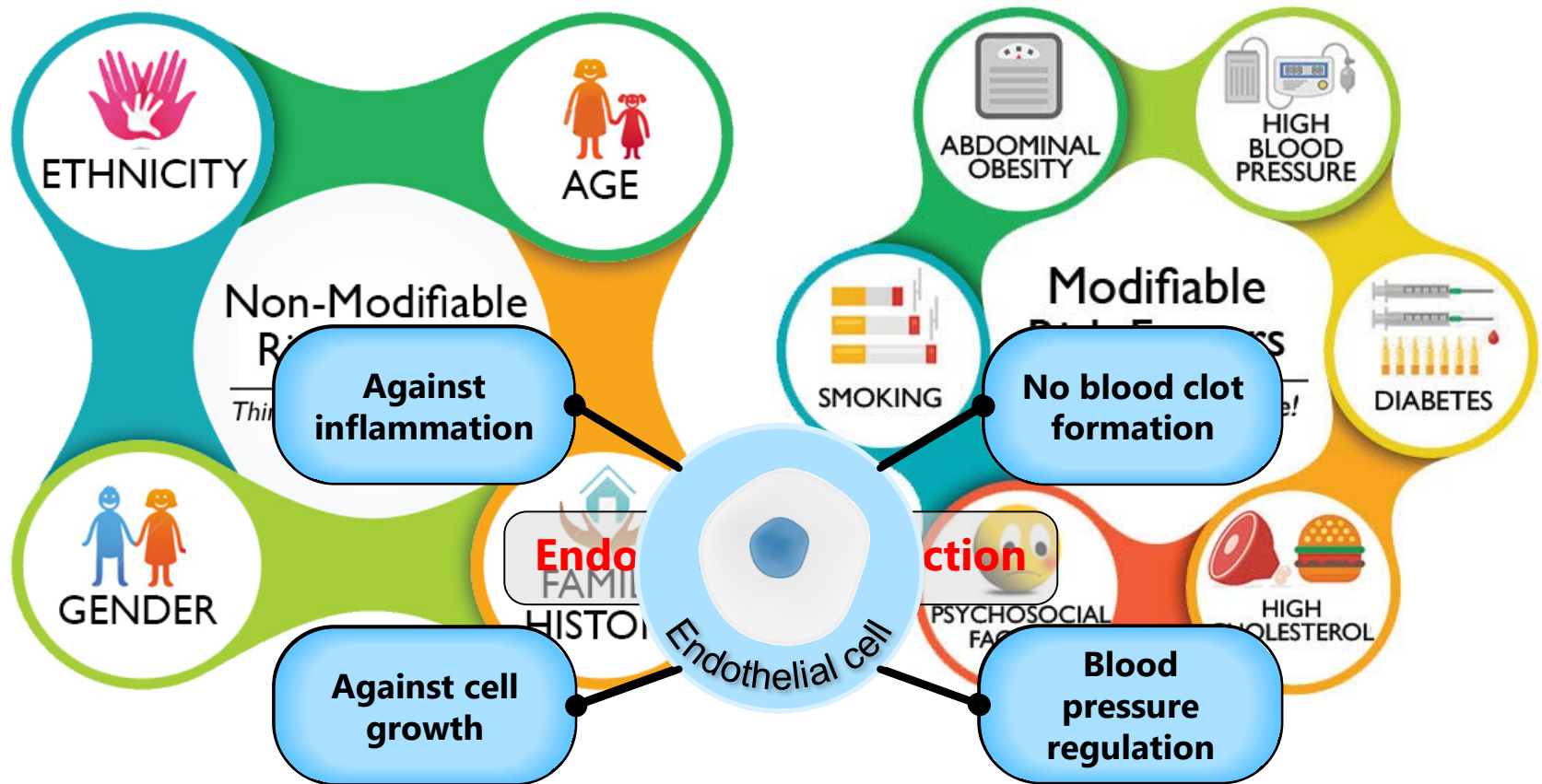
- ...



Normal endothelium and its functions

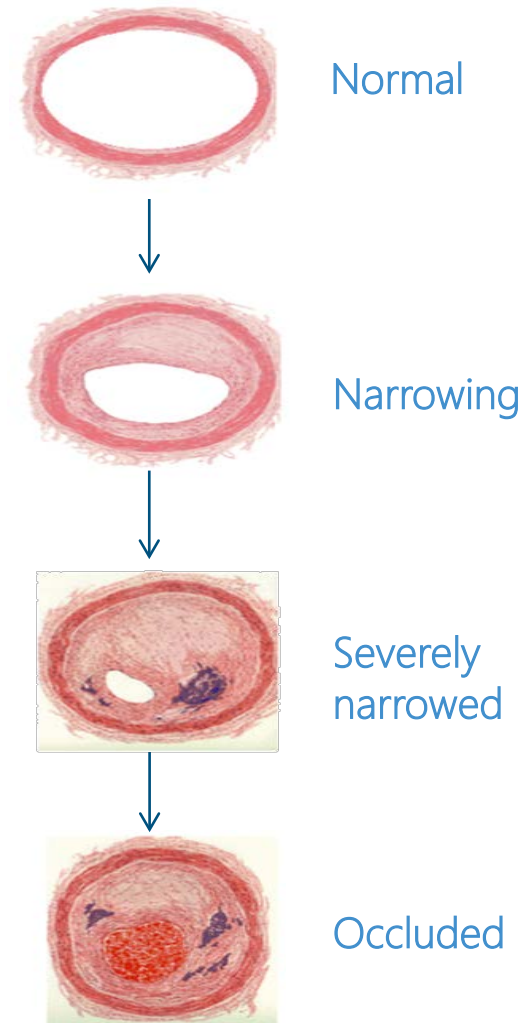


Risk factors and endothelial dysfunction

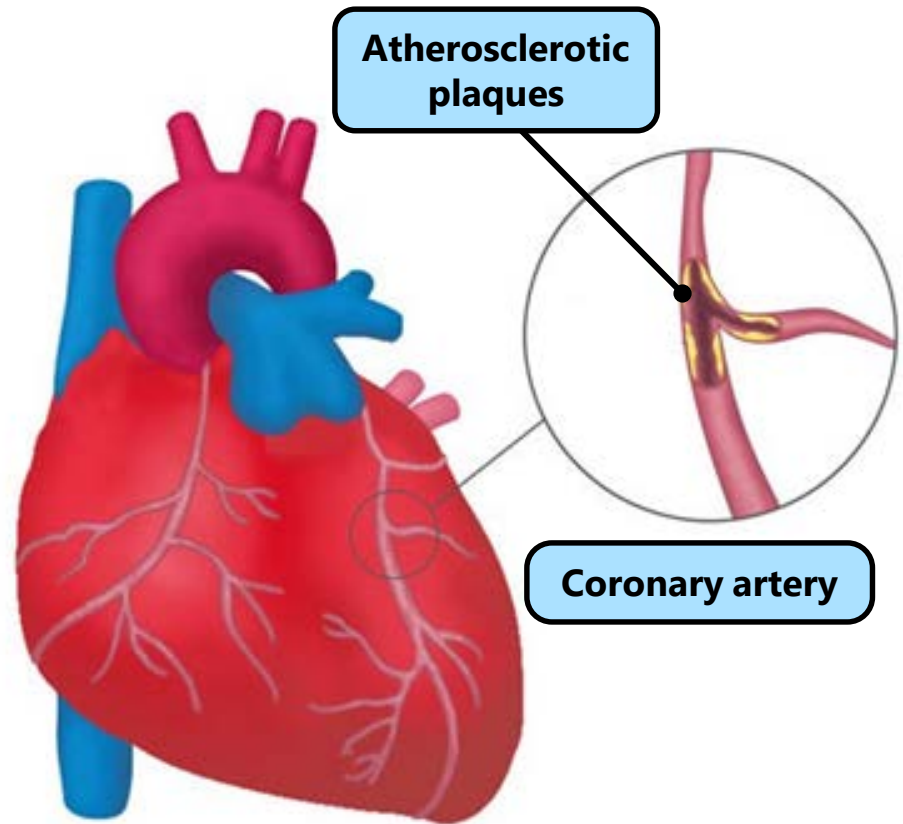


Endothelial dysfunction can result in atherosclerosis

- Atherosclerosis
 - Athere = Gruel/Paste
 - Skleros = Hard
- Plaques: deposit of fat, cholesterol, cells, calcium, etc. in the arterial wall
- Silent killer: only symptomatic when...
 - Limitation blood flow due to their size
 - Rupture of plaque and (partial) occlusion blood stream
 - Embolised thrombus

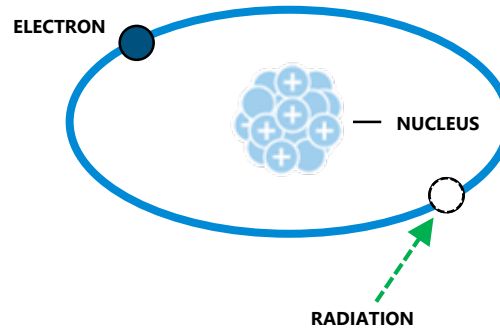


Atherosclerosis at coronary arteries: heart attack



Ionizing radiation: definition

Ionization



Radiation is everywhere



Food



Dwellings



Soil



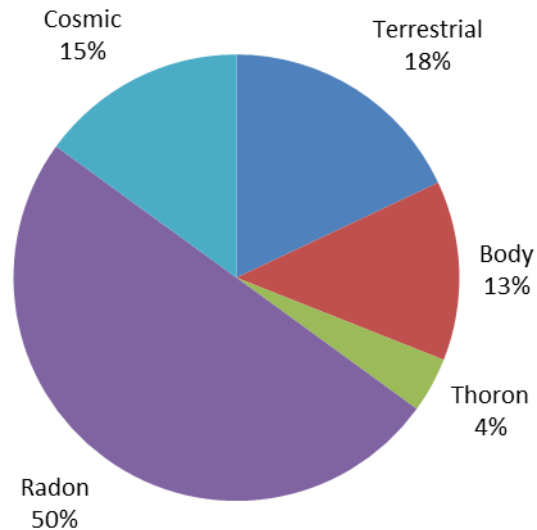
Plants



Human body

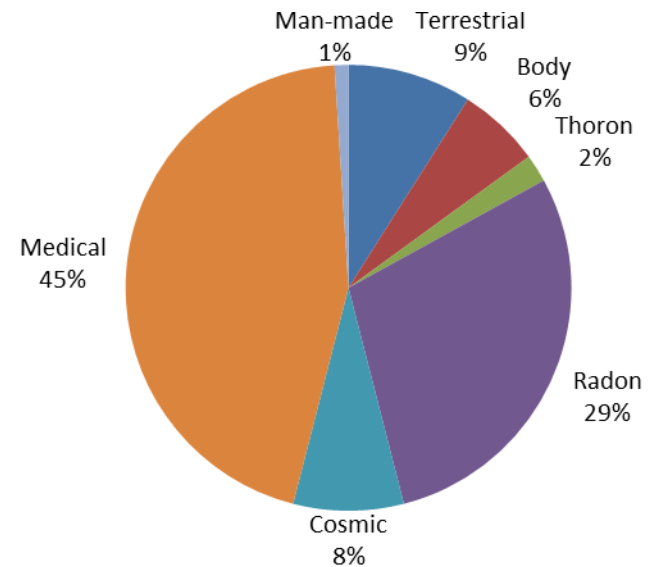
Increasing exposure to ionizing radiation

Average effective dose (Belgium, 1895)



2.3 mSv/year

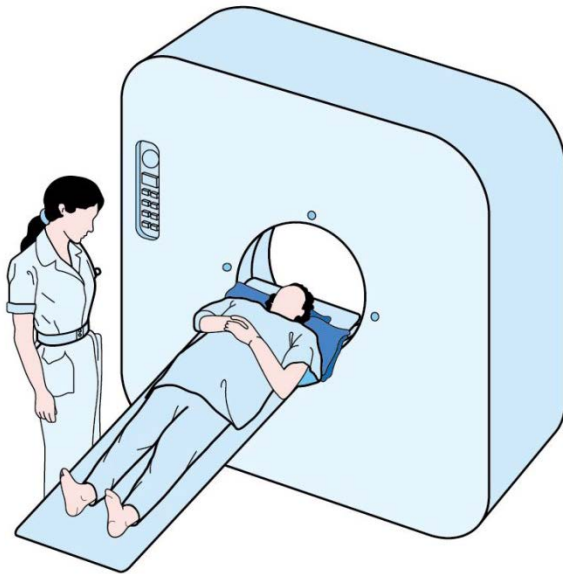
Average effective dose (Belgium, 2006)



4.6 mSv/year

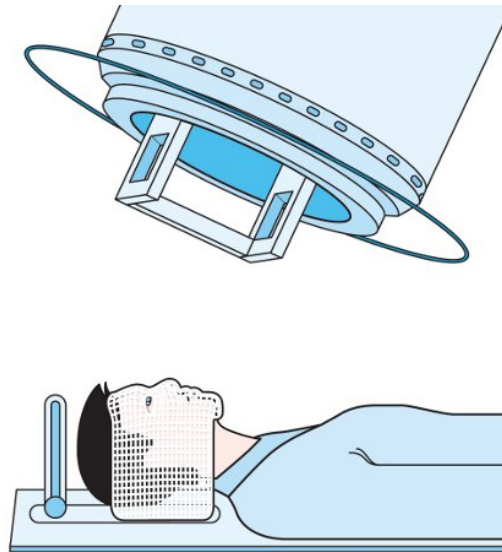
Ionizing radiation for diagnostic and therapeutic use

Diagnostics



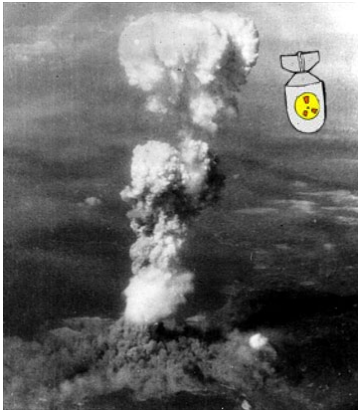
Acute low dose

Therapeutics



Fractionated dose
Low – Medium – High

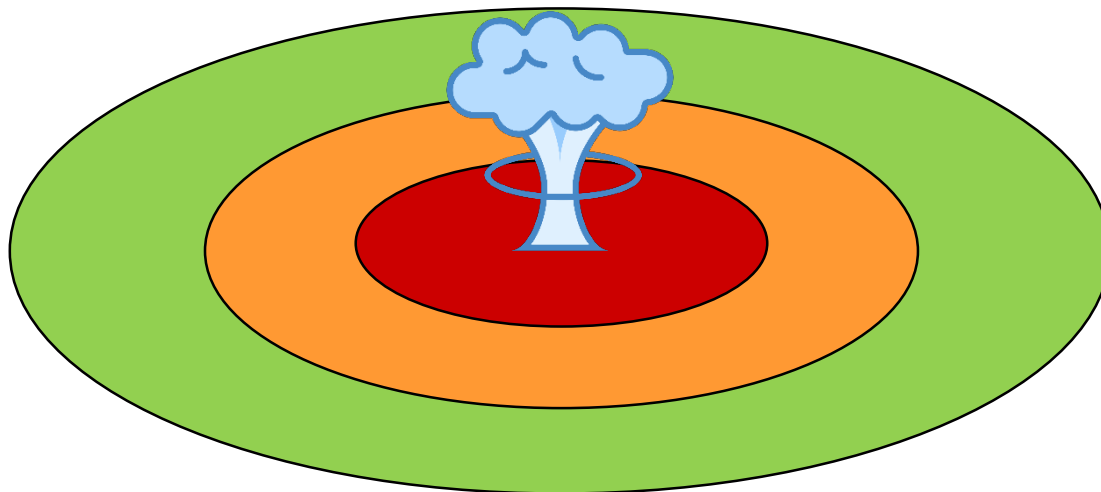
Ionizing radiation: cardiovascular disease risk factor



Hiroshima
06/08/1945



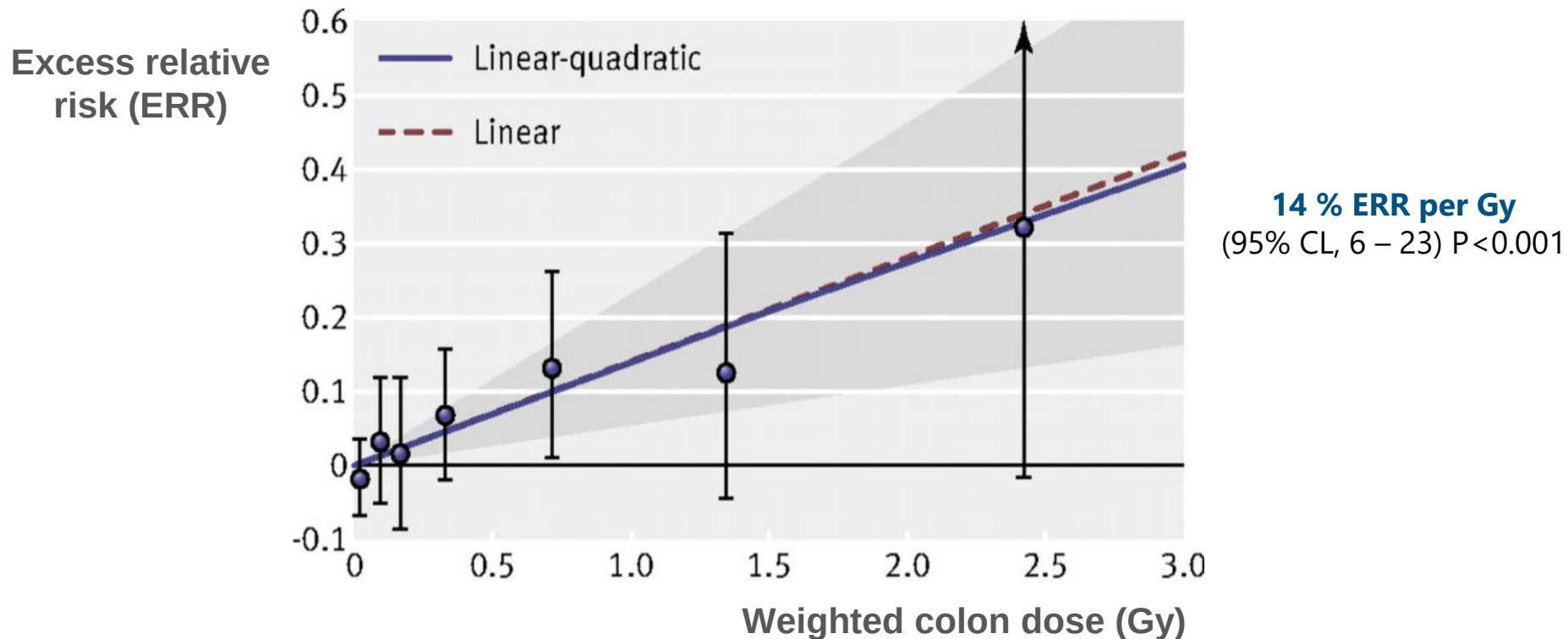
Nagasaki
09/08/1945



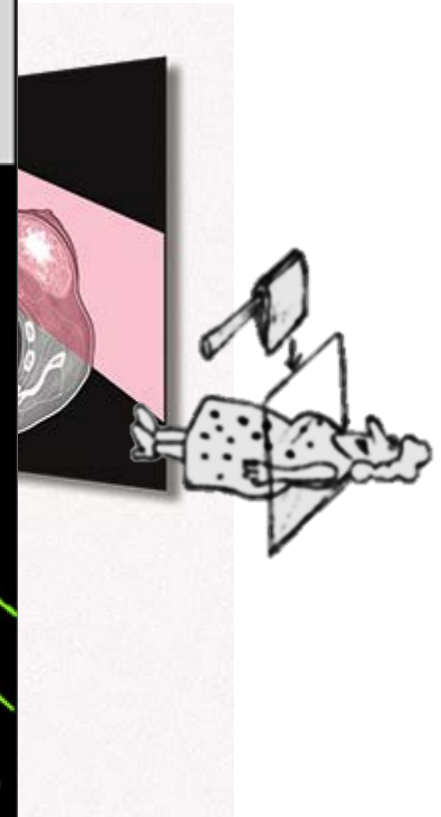
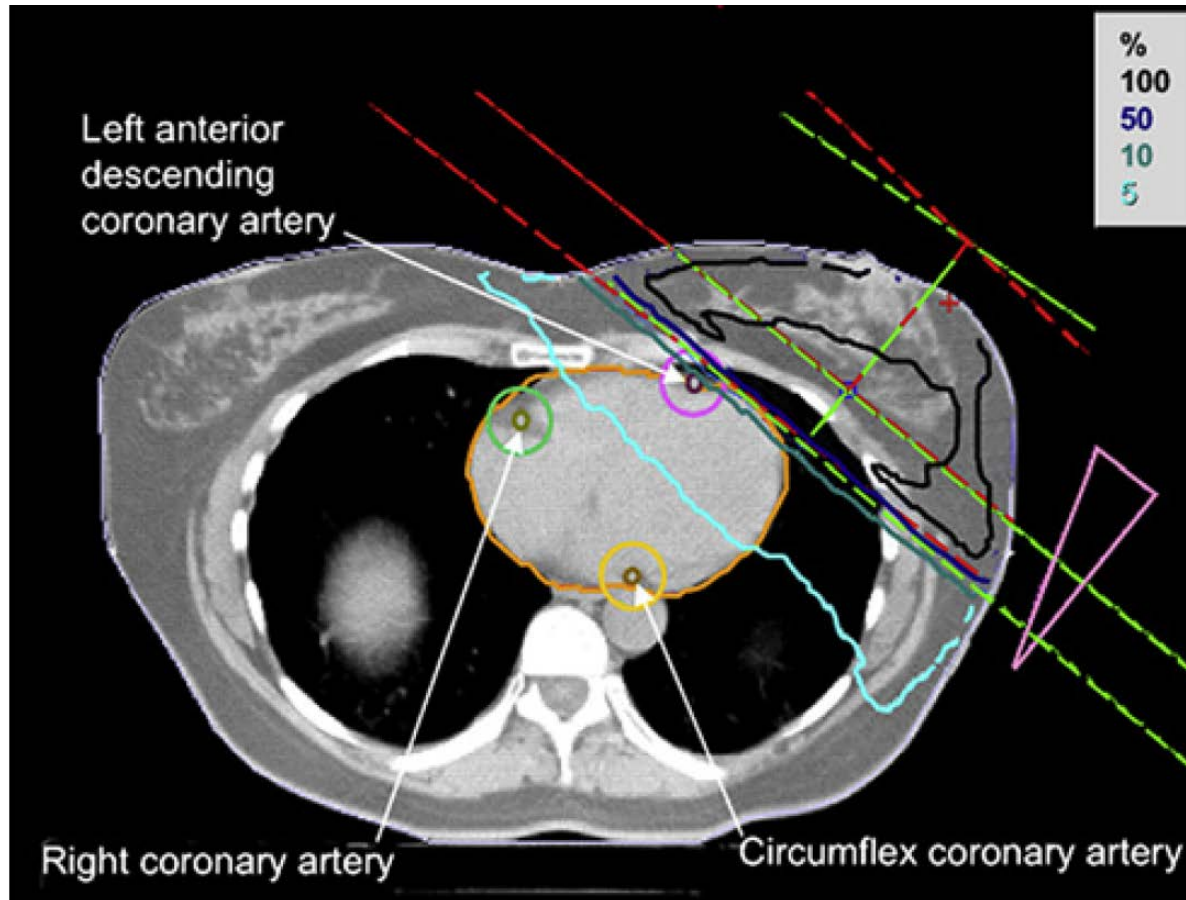
	0 – 1.8 km, >100 mSv	HIGH – MEDIUM
	1,8 km – 2,7 km, 5-100 mSv	LOW
	>2700m, <5 mSv	UNEXPOSED

Ionizing radiation: cardiovascular disease risk factor

A-bomb survivors



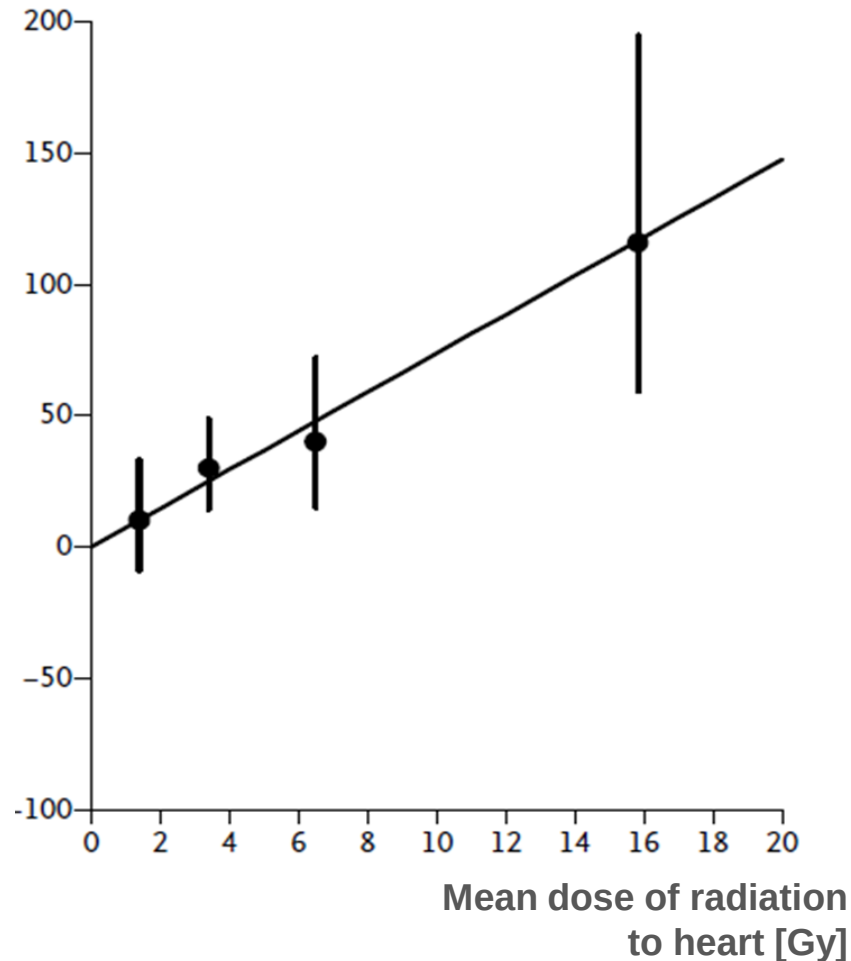
Ionizing radiation: cardiovascular disease risk factor



Ionizing radiation: cardiovascular disease risk factor

Breast cancer radiotherapy

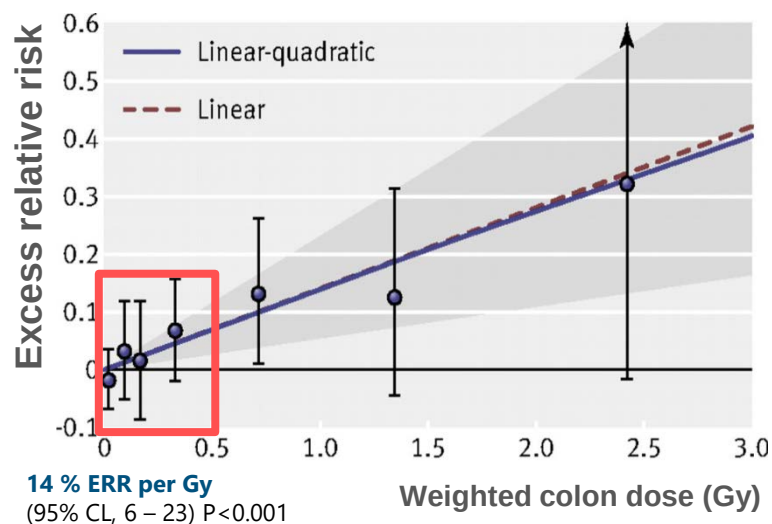
Percent increase in rate of major coronary events



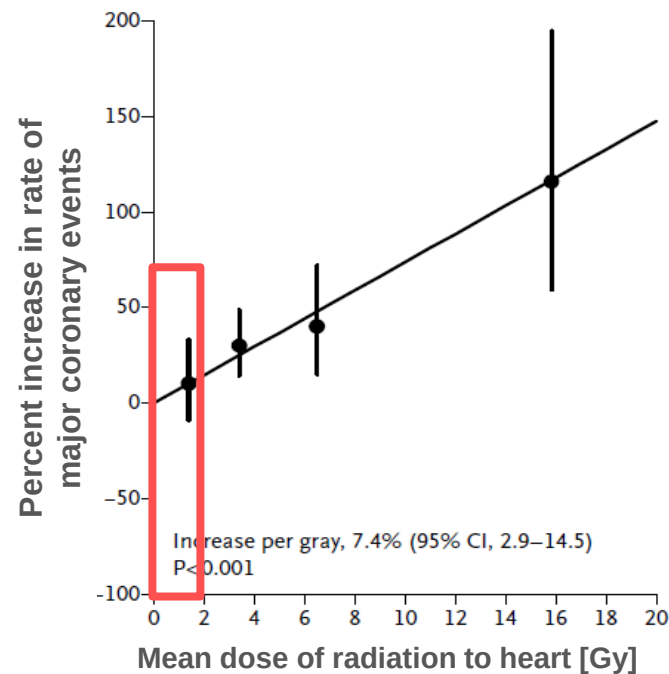
7,4 % increase per Gy
(95% CL, 2,9 – 14,5) $P < 0.001$

Ionizing radiation: cardiovascular disease risk factor

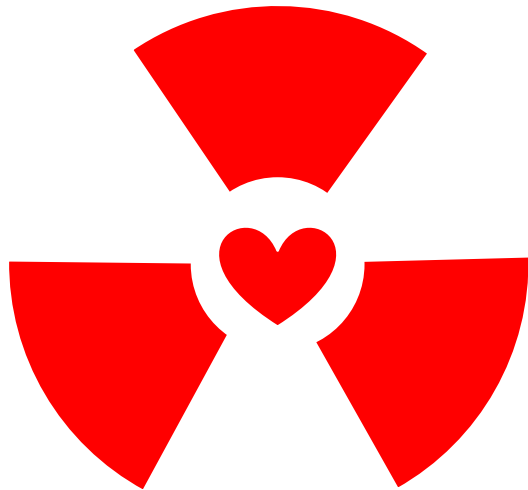
A-bomb survivors



Breast cancer radiotherapy

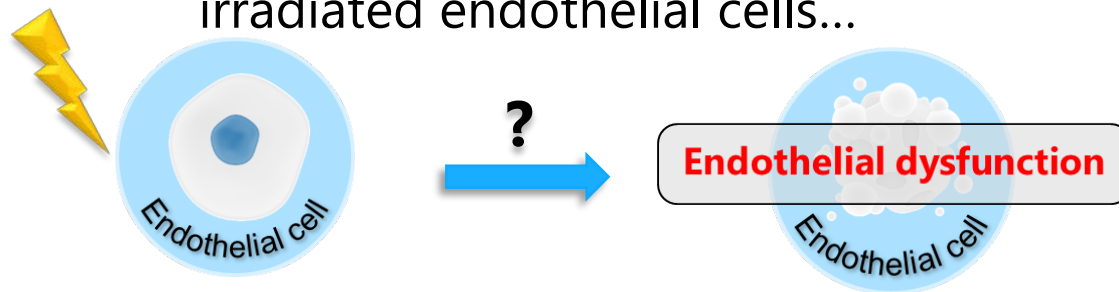


What happens at low doses of ionizing radiation? What are the mechanisms?

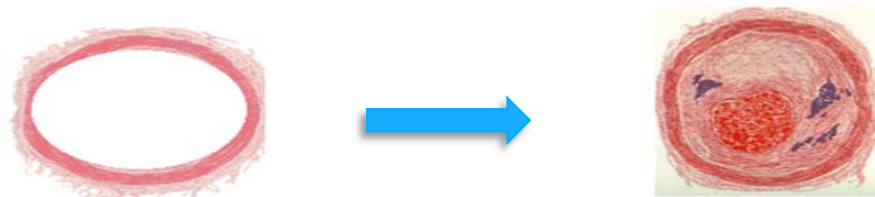


2. General aim

To identify **molecular mechanisms** accounting for **dysfunction** of irradiated endothelial cells...



... potentially leading to **cardiovascular disease**,





3. Results

Functional gene analysis reveals cell cycle changes and inflammation in endothelial cells irradiated with a single X-ray dose

Baselet B, et al. **Front. Pharmacol.** 2017; 8:213

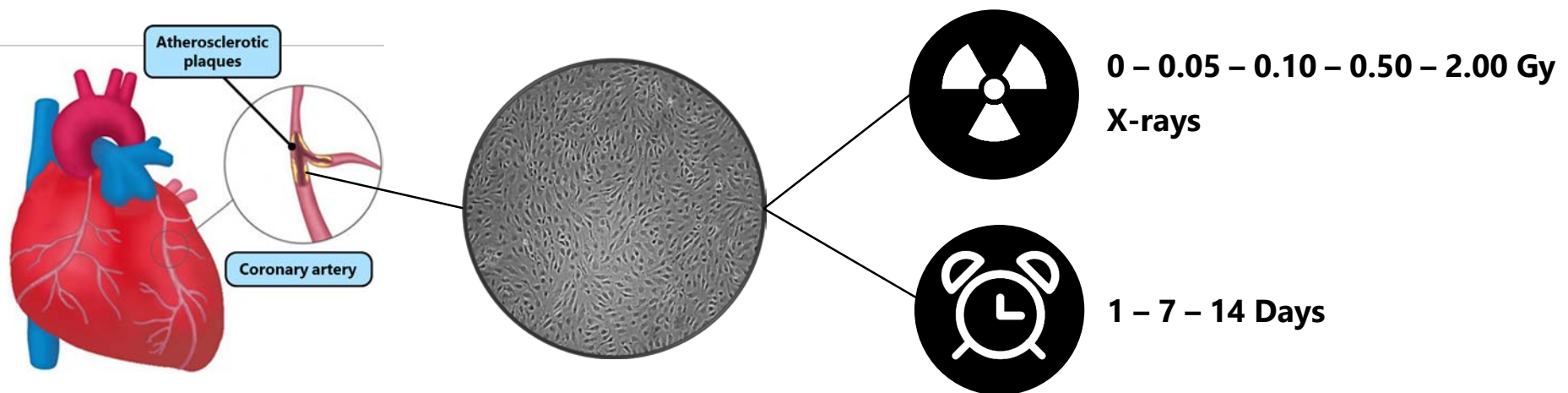


#1

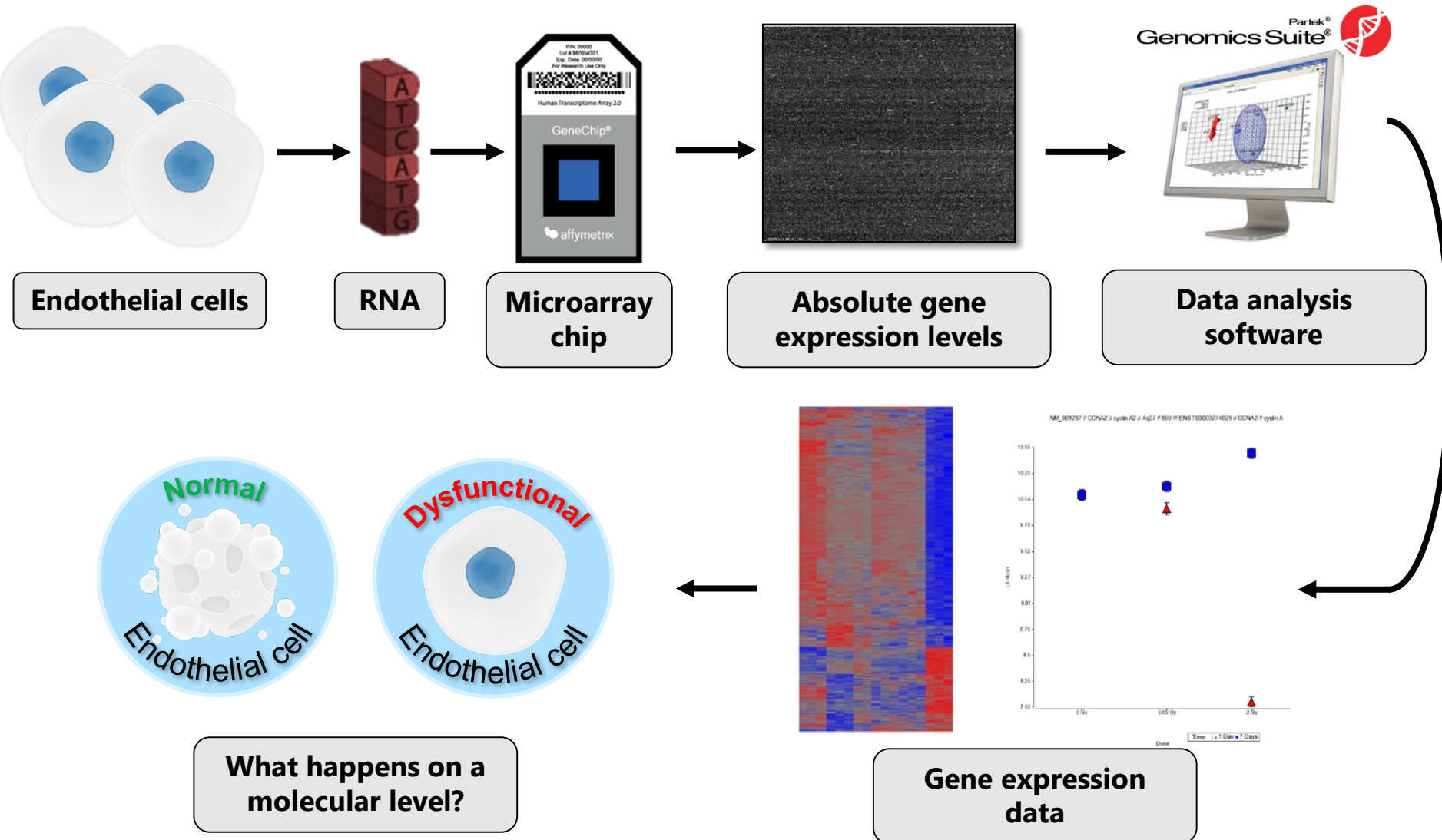
Aims and experimental set-up

- Epidemiological evidence has shown that radiation exposure (> 0.5 Gy) accelerates **age-related atherosclerosis** leading to coronary artery disease
- **Endothelial dysfunction** is a risk factor for the development of atherosclerosis

AIM: to provide molecular insights into the endothelial phenotype after exposure to different radiation doses

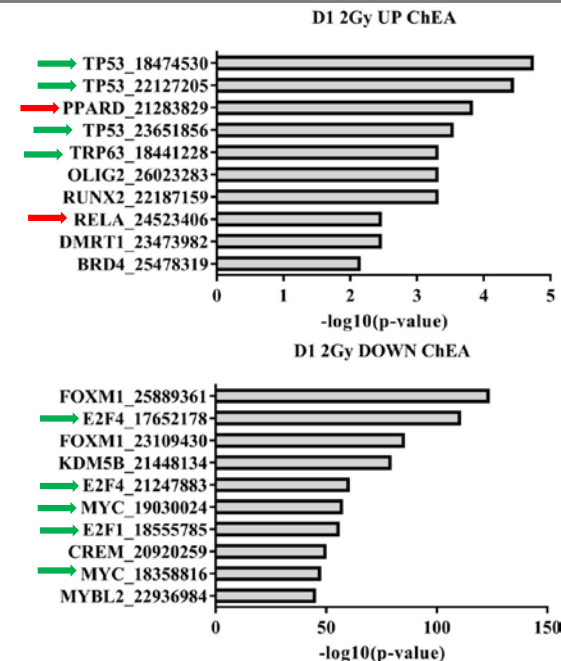
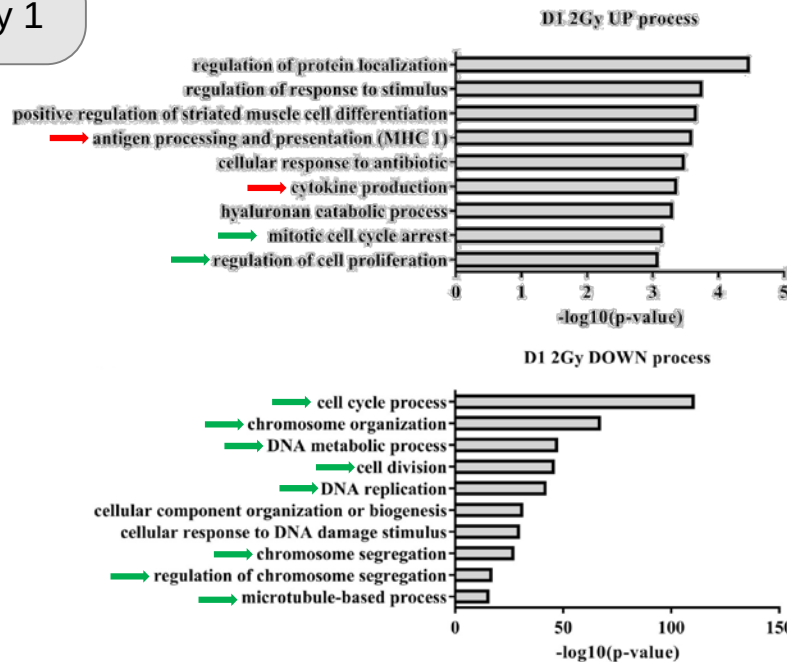


Microarray experiments to study gene expression

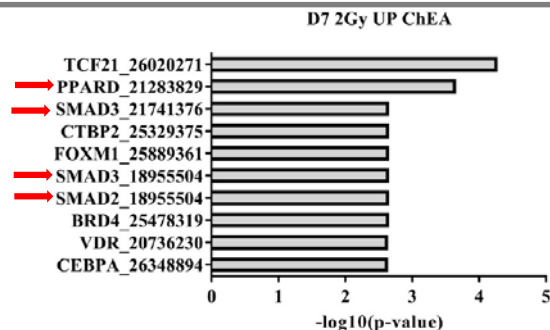
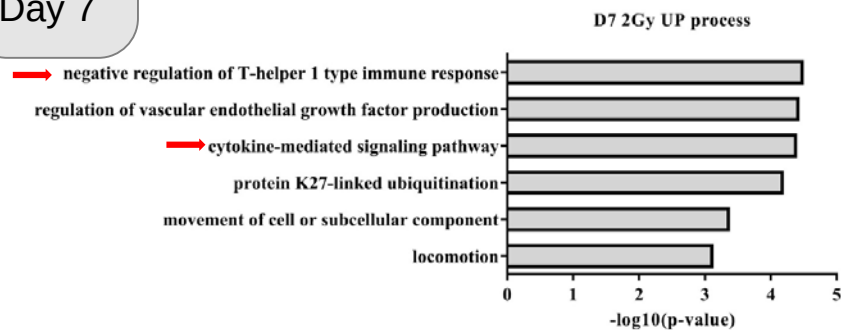


2 (and 0.5) Gy of X-rays repress the expression of genes involved in *cell cycling* and induce genes involved in *inflammation*

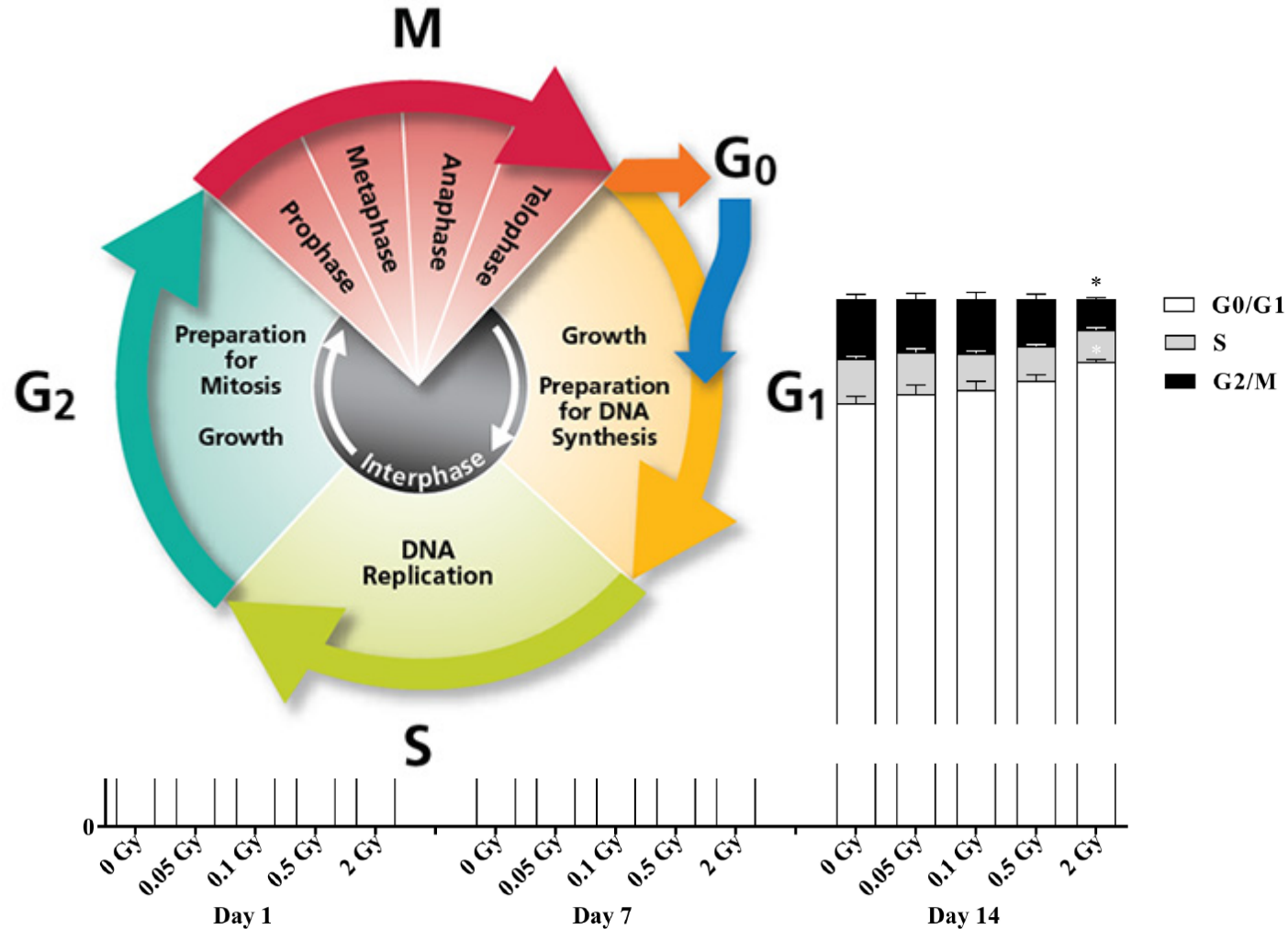
Day 1



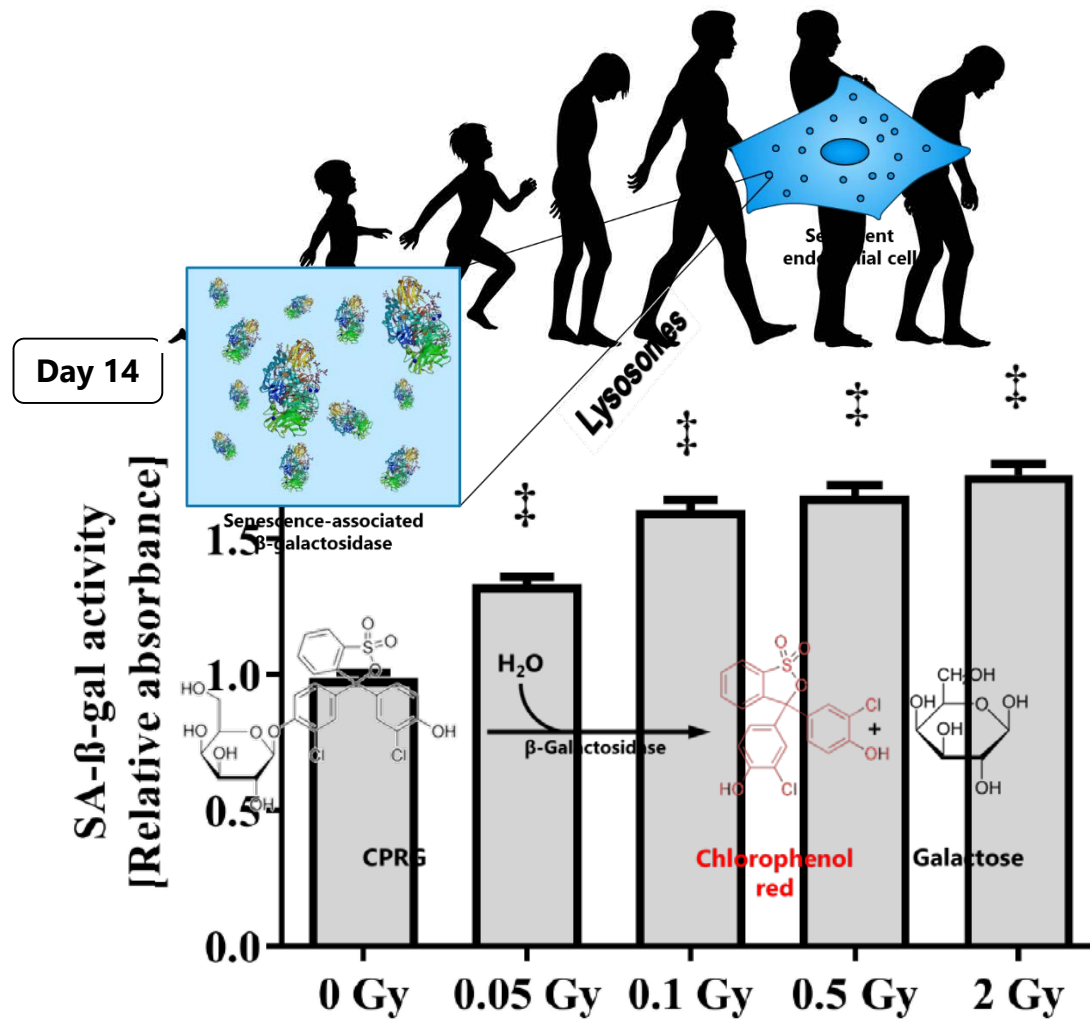
Day 7



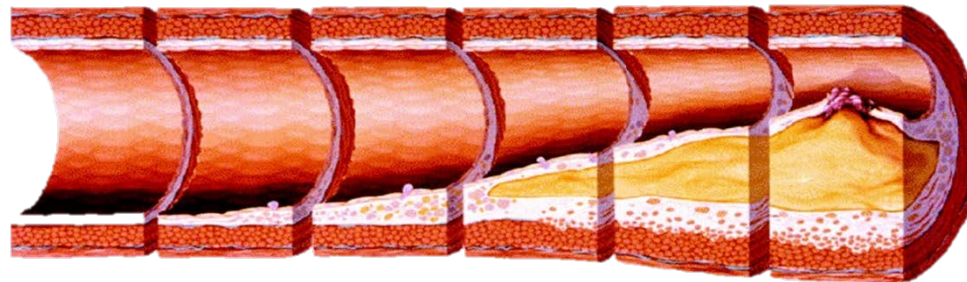
0.5 and 2 Gy of X-rays induce an *acute G1 cell cycle arrest*



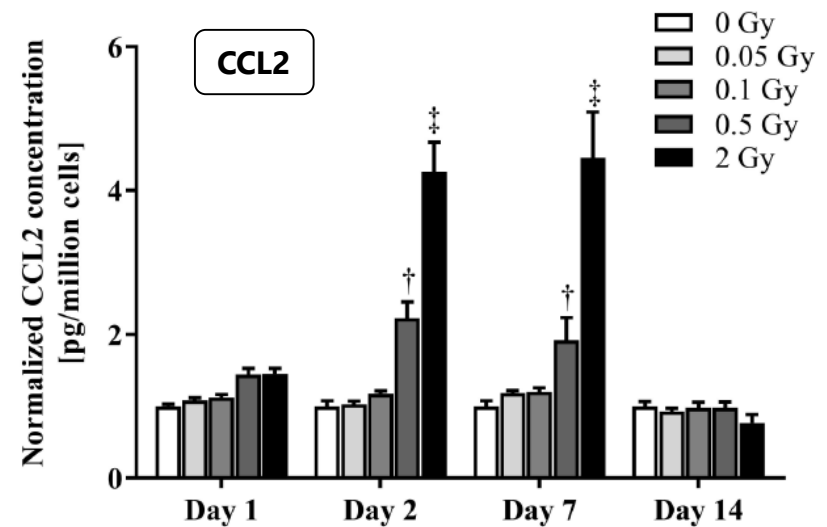
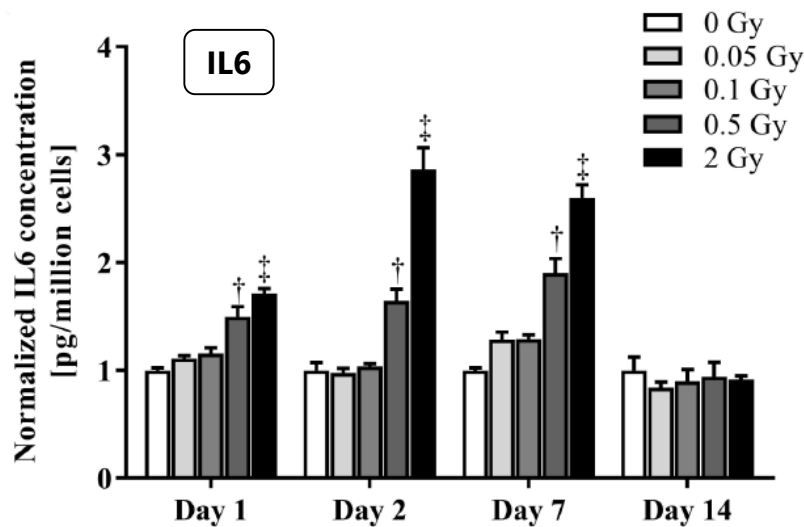
All X-ray doses induce *premature endothelial senescence*



0.5 and 2 Gy of X-rays induce the *secretion of pro-inflammatory cytokines*



Inflammation messengers	Cellular adhesion molecules	Plaque destabilization	Plaque rupture
IL-1 TNF- α IL-6 IL-18 CCL2	ICAM VCAM Selectins	IL-18 oxLDL GPX-1 MMP CCL2 MPO	PAPP-A sCD40L

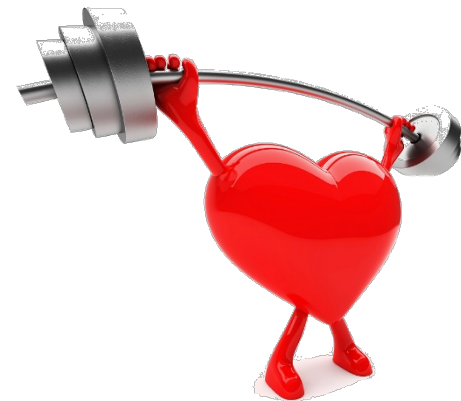


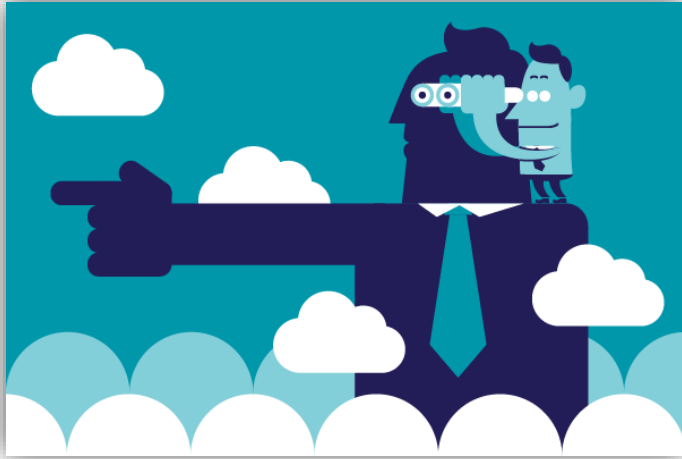


4. Concluding remarks

- No effect of 0.05 and 0.1 Gy on gene expression after endothelial irradiation
- In endothelial cells, a single X-ray dose of 0.5 or 2 Gy induces
 - G1 cell cycle arrest (24 h + 14 days)
 - Senescence (14 days)
 - Pro-inflammatory cytokine secretion (1 – 2 – 7 days)
- All X-ray doses increase endothelial senescence-associated β -galactosidase activity

- **Validation** in more complex *in vitro* and *in vivo* models
- Foundation to build **further scientific knowledge**: How does ionizing radiation induce cardiovascular disease?
- With follow-up studies
 - **Ameliorate** current radiation protection system
 - Cardiovascular **risk-reducing** strategies
 - Pharmaceutical agents
 - Detection methods (e.g. biomarkers)
 - **Alleviating** radiation-induced cardiovascular disease in exposed people
 - Strive to a **better life quality** of ionizing radiation exposed people





*If I have seen further,
it is by standing on the shoulders of giants.*

— Isaac Newton

5. Acknowledgements

Thanks to all my collaborators

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