Radiation-induced cardiovascular disease: Is it time for a new biology ?

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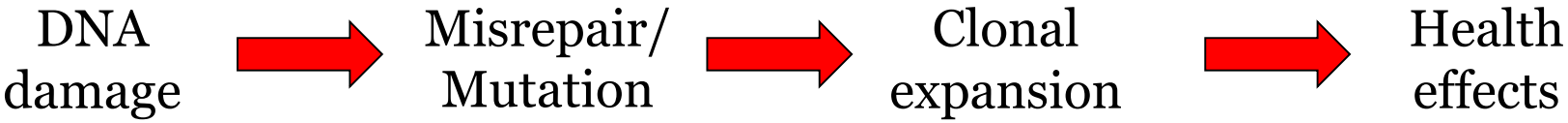
The radiobiology paradigm



Why (re)-consider the radiobiology paradigm ?

- We **know** that radiation causes DNA damage.
- We **know** that mutations cause late health effects.
- We **know** this follows an LNT dose response.

DNA damage → Misrepair/ Mutation → Clonal expansion → Health effects

The danger of a single story – Chimamanda Adichie

"If we only hear one story we risk simplification and a critical misunderstanding....."

https://www.ted.com/talks/chimamanda_adichie_the_danger_of_a_single_story

Things the “one story” paradigm can’t quite explain

- The lack of a fingerprint mutation in a driver gene.
- Probability of radiation actually hitting the driver gene.
- Diseases where mutation and clonal expansion do not exist.
- Non-targeted effects.
- Scarcity of solid cancers in DNA repair defect syndromes.
- „Radiation susceptibility“ cancer syndromes (e.g. Rb1, PTCH1)

“One story” doesn’t fit most radiation diseases

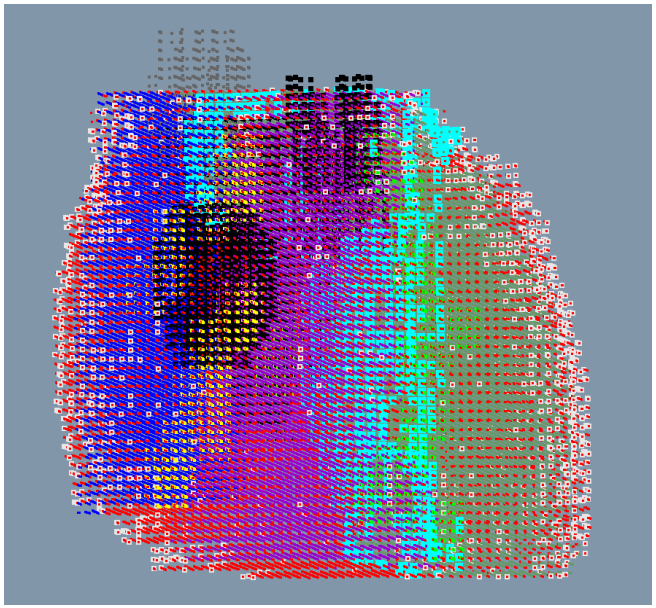
Cancer Cataract Inflammation CVD Cognition Metabolic

Pathology of radiation-induced heart disease

-coronary arteries: atherosclerosis
-myocardium: myocardial fibrosis; microvascular insufficiency and ischemia
-pericardium: acute / chronic pericarditis
-valves: valvular injury due to endocardial fibrosis
-conduction system: arrhythmias

CVD in childhood cancer survivors

- 212 cases (CVD) and controls from UK, France and Spain.
- Obtained outcomes, confouders, and irradiation plans.
- Retrospective dosimetry for 21 heart regions per patient.



3D representation of the voxels used for calculating heart sub- structures doses (17 year old male).

Preliminary report:
EOR/1Gy = 1.50 (95%CI: 0.21 to 33.27) for the risk of ischemic heart diseases or heart failure as a function of average dose to the left anterior descending artery.

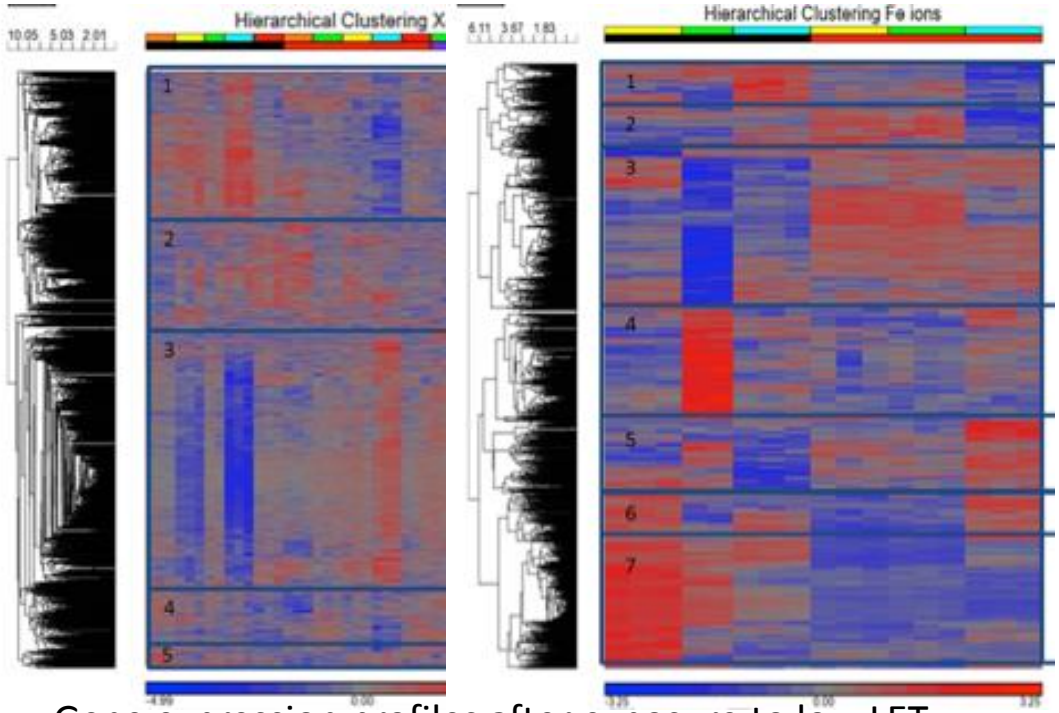
The cohort will be pooled with project PancareSurFup to give 900 cases/controls.

Haddy N. et al Circulation 2016;133:31-38

HelmholtzZentrum münchen
German Research Center for Environmental Health

Is there evidence for an $RBE_{(CVD)}$?

- Endothelial and vascular smooth muscle cell models.
- Exposed to X-rays or Fe ions.
- End points: Electrophysiology, multiomics and cytokine profiling.



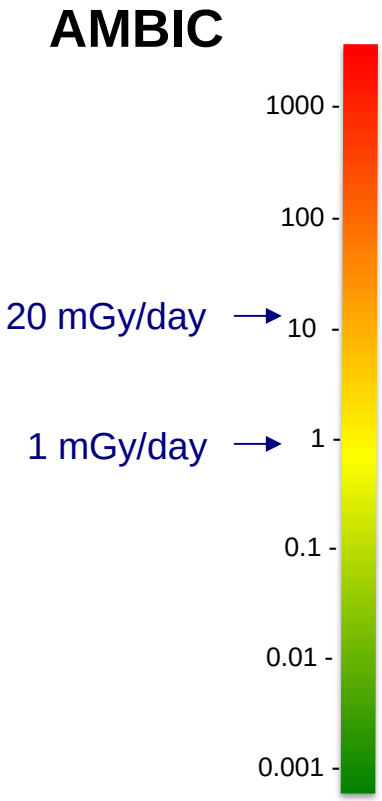
Gene expression profiles after exposure to low LET X-rays -left) versus high LET (Fe ions -right)

Evidence for an RBE_{CVD}, with an estimated value between 4 and 10 for HZE irradiation compared to photons.

SCK•CEN

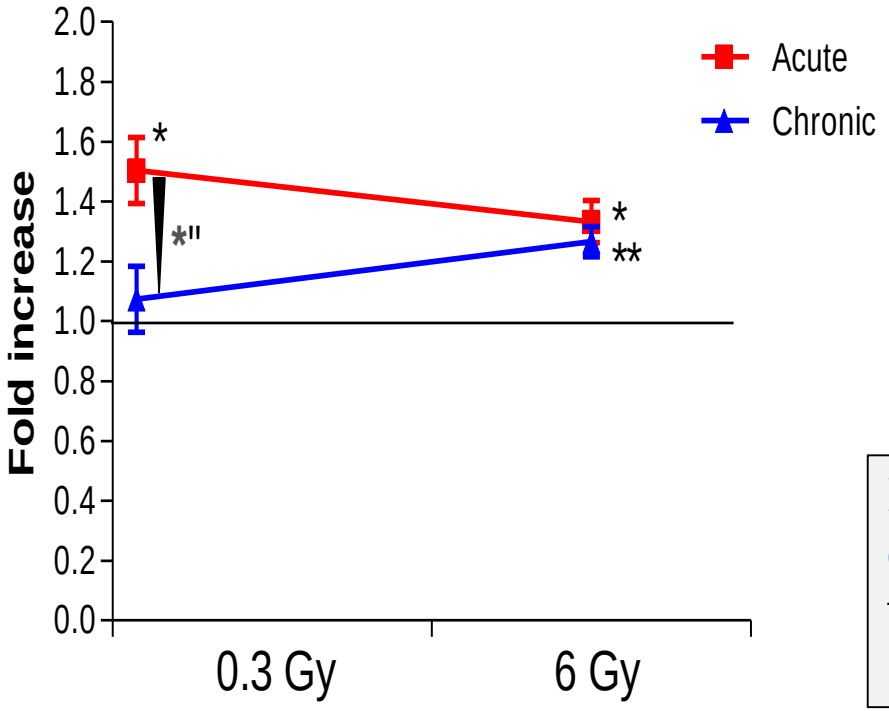
Is there evidence for an effect of dose rate ($DREF_{CVD}$)?

Institute for Environmental Sciences (IES)
Rokkasho, Aomori, Japan

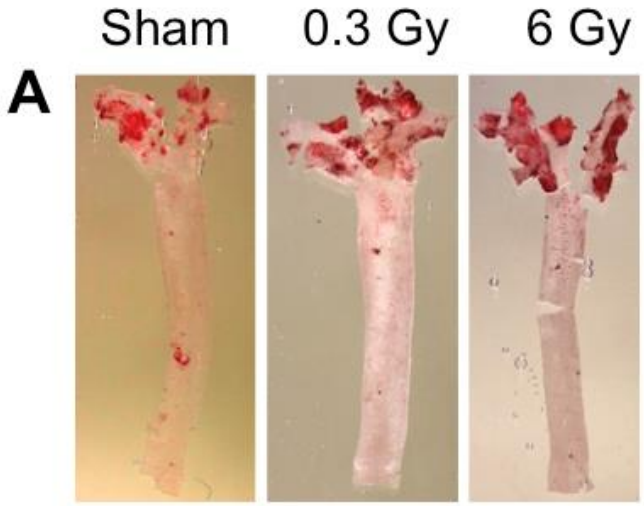


Mice are chronically irradiated with gamma-rays from a ^{137}Cs source under **SPF** conditions

Compare ApoE mice chronically irradiated at IES Japan or acutely irradiated at ENEA, Italy. Atherosclerotic lesions were measured for number, area and location.



Chronic 1mGy/d or 20mGy/d for 15 or 300 days

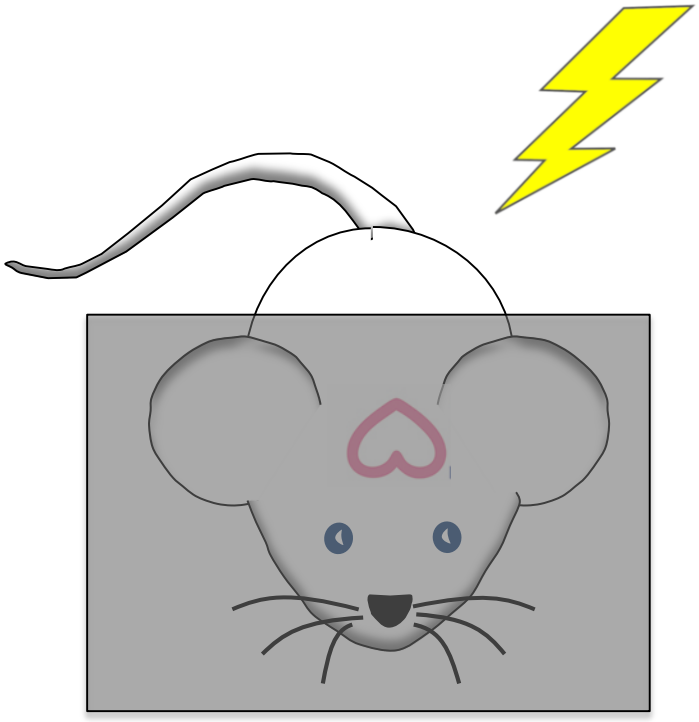


Effect seen at 300mGy acute. 300mGy chronic less damaging. This is evidence that a dose rate correction factor ($DREF_{CVD}$) is appropriate.

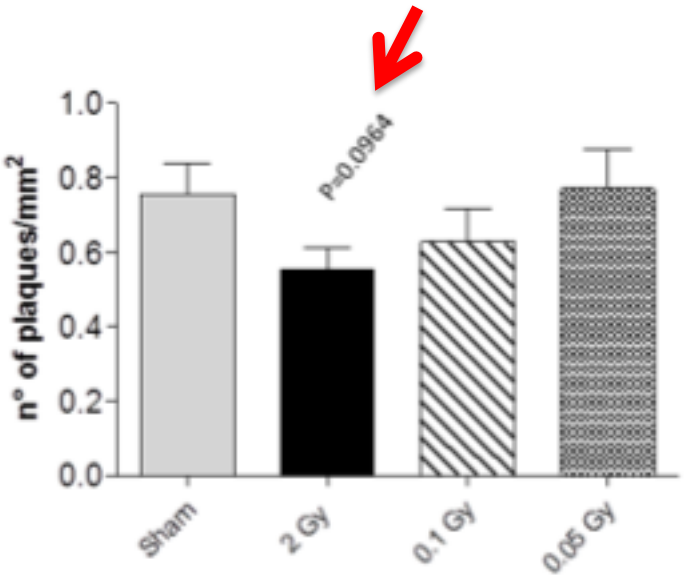
Mancuso et al Oncotarget. 2015 Oct 13;6(31):31263-71.

Systemic/local information exchange?

ApoE mice irradiated on hind quarters only. Atherosclerotic lesions quantified.

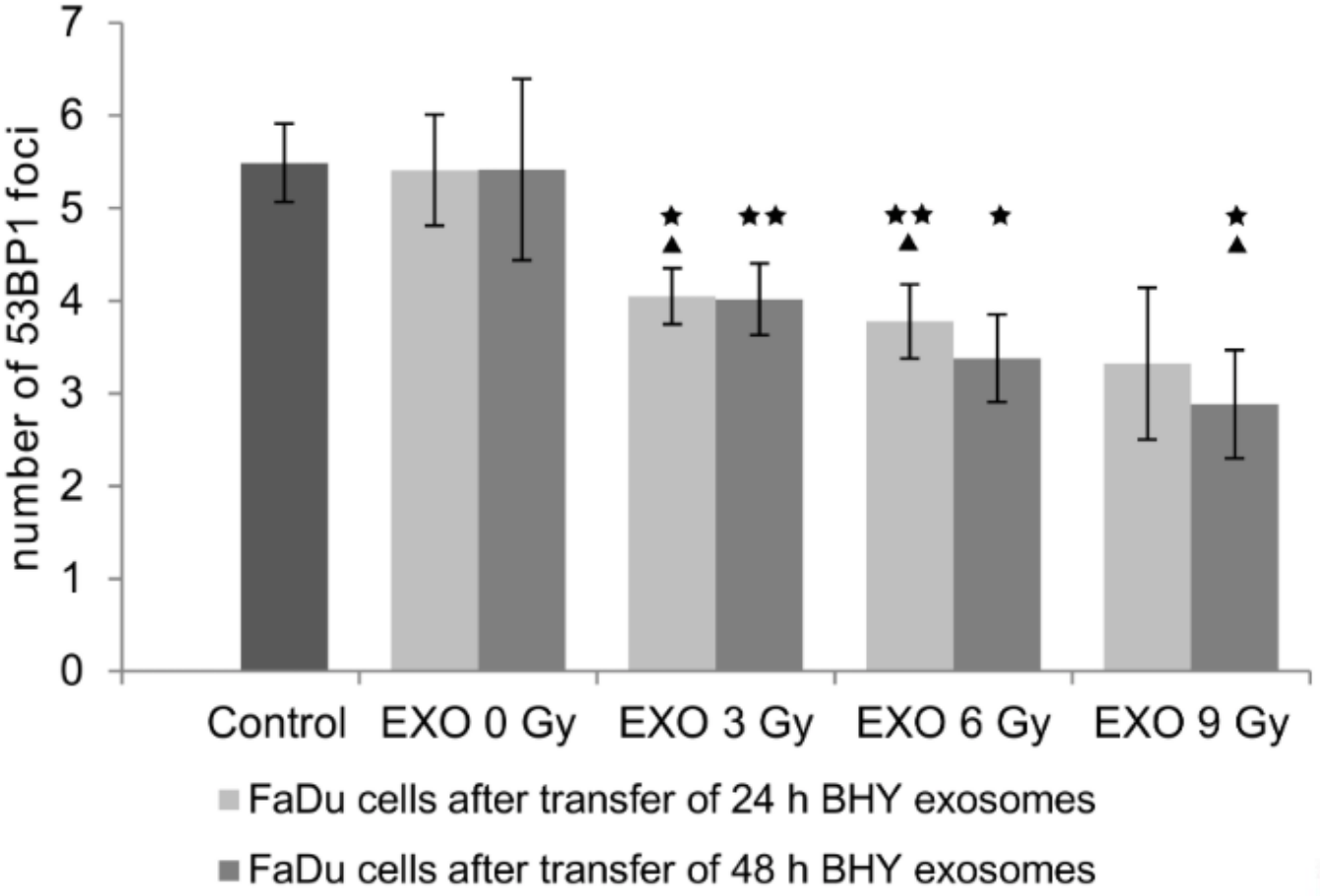


Lead shielding of heart



There is evidence for a dose-dependent **radio-protective** abscopal effect on atherosclerosis.

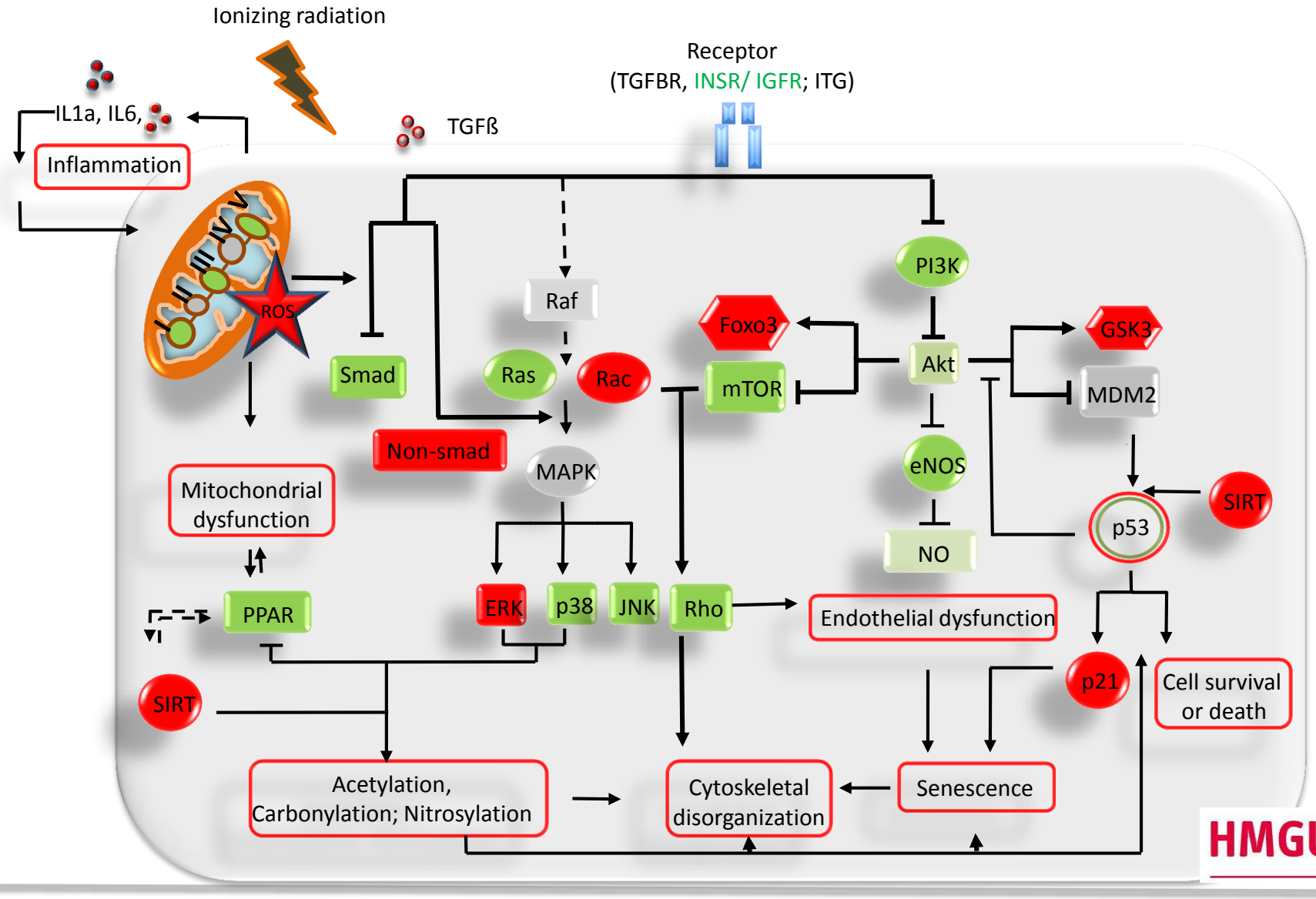
Exosomes from irradiated cells improve DNA repair in other irradiated cells



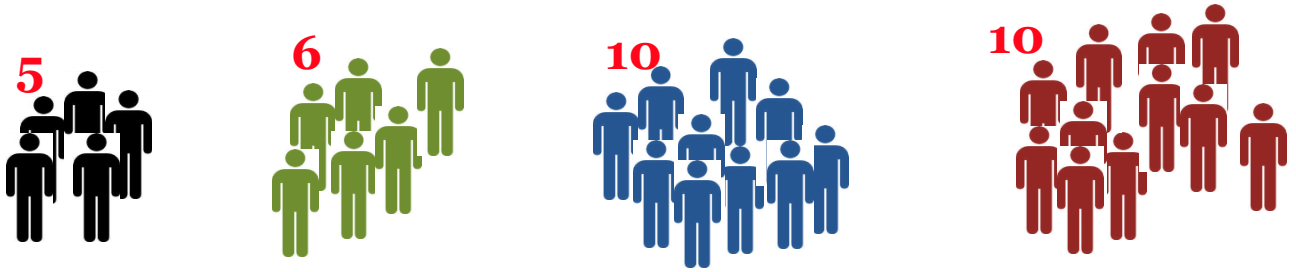
Mutschelknaus et al PLoS One. 2016 Mar 23;11(3):e0152213

HMGU

What are the effects on the heart?



Fresh-frozen samples: label free proteomics



Control	Low dose < 100 mGy	Moderate dose 100- 500 mGy	High dose > 500 mGy

Protein extraction (left ventricle, mix FFPE / frozen)

↓

FASP (clean up)

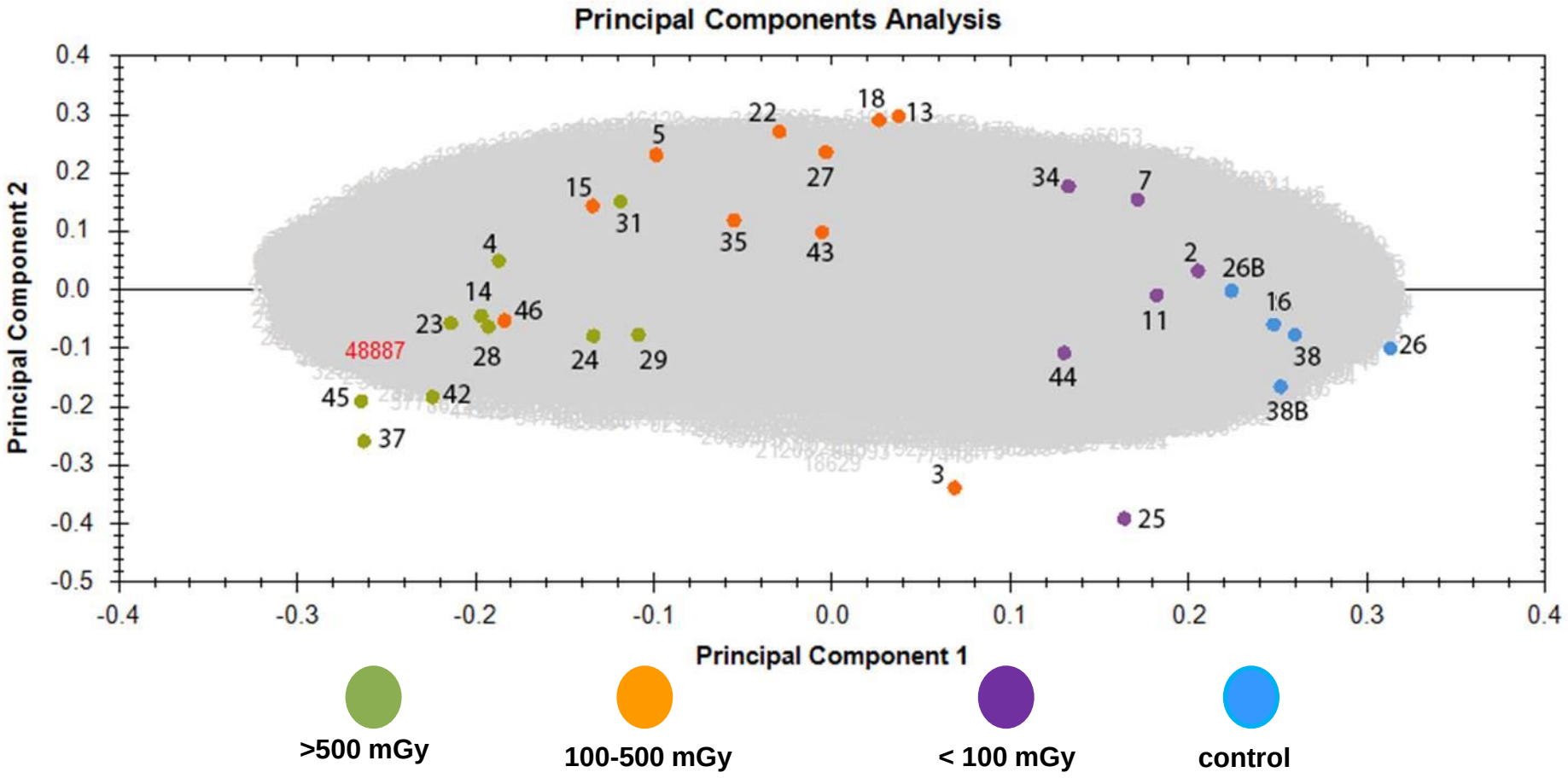
↓

MS/MS

↓

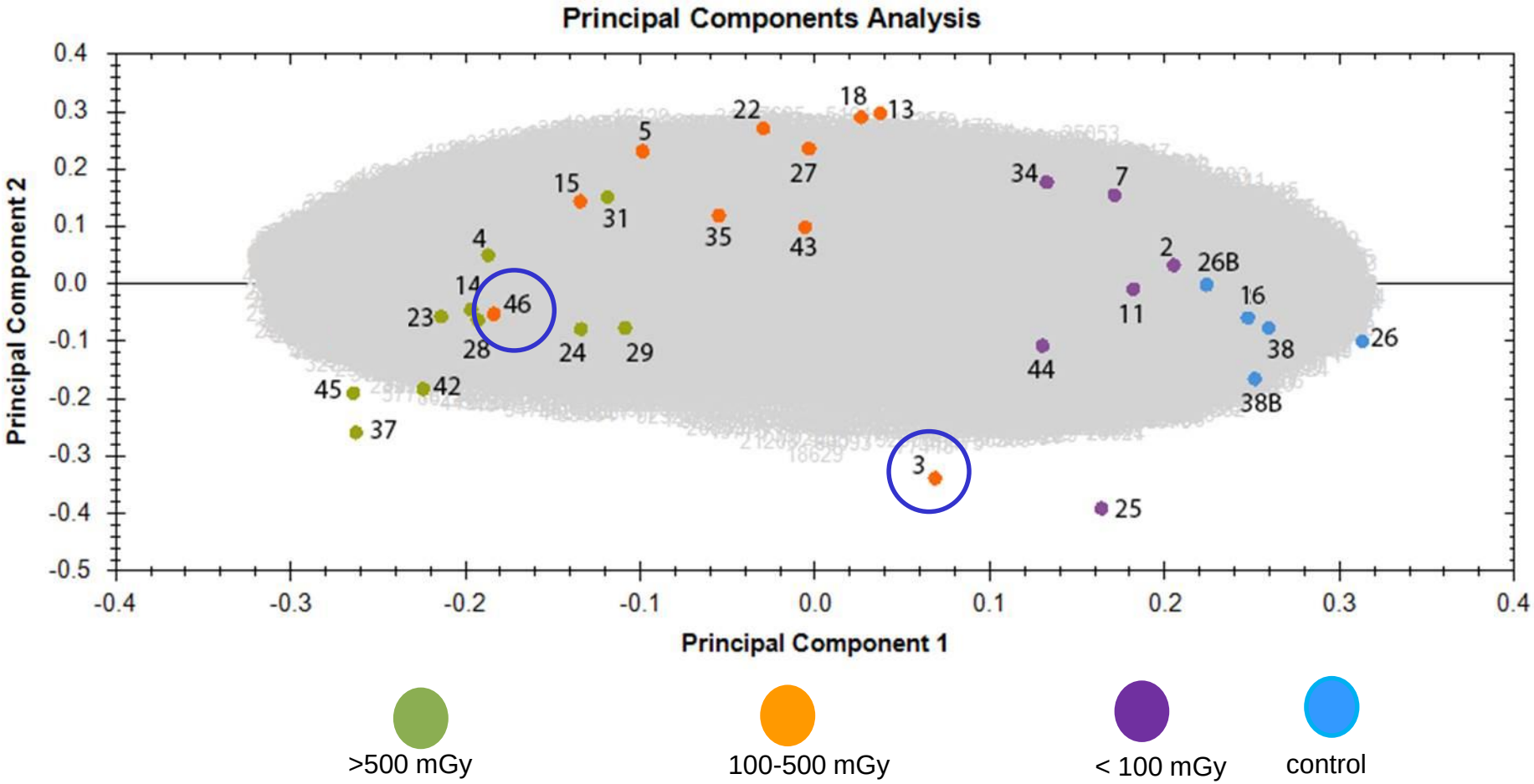
Protein quantification

Principal component analysis of heart proteomes

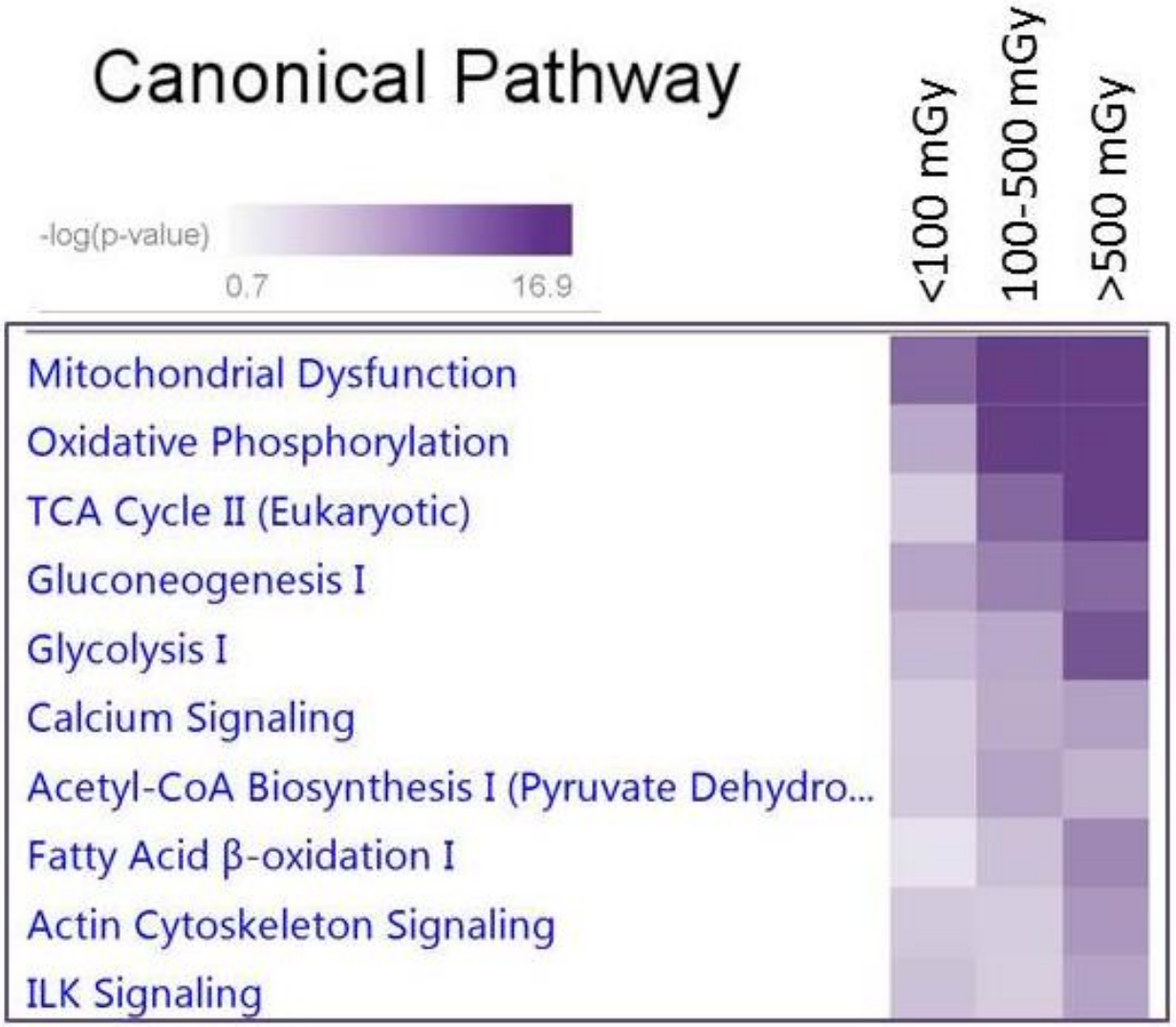


Azimzadeh et al Oncotarget. 2016 Jul 6. doi: 10.18632

Principal component analysis of heart proteomes



Proteomic changes in the hearts of Mayak workers fit our network model in a dose-dependent manner



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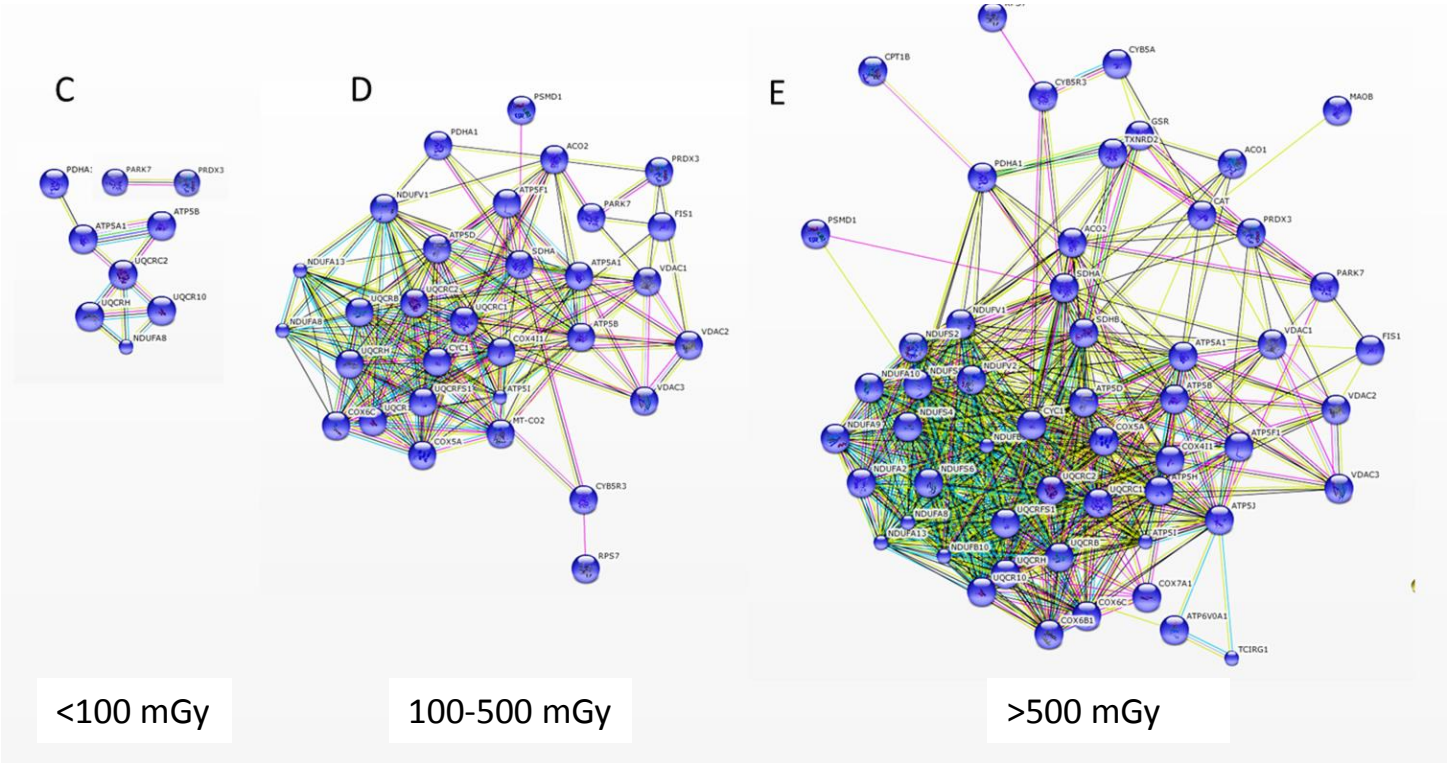
Dose-dependent increase in down-regulated mitochondrial proteins



Azimzadeh et al. *Oncotarget. 2016*

So what do we still not know ?

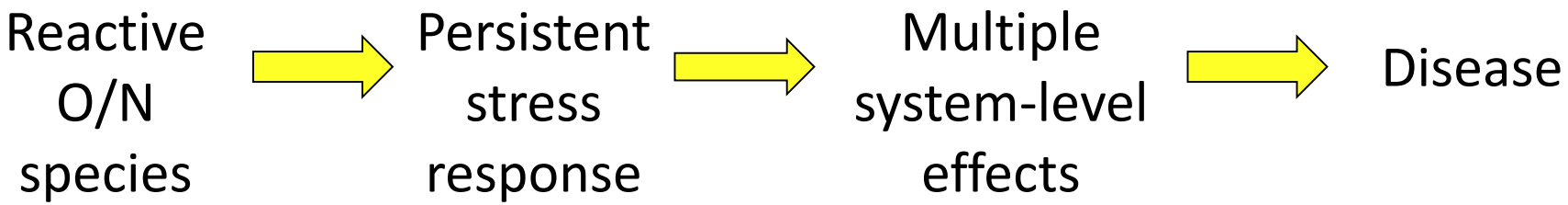
Biology

- RBEs for all radiation qualities and all endpoints.
- Does the $DREF_{CVD}$ apply to all end points ?
- Shape of the dose response in vivo.
- Are biological effects model dependent, can we find a better model ?
- Which cells cause the damage, what are cell autonomous effects?

Epidemiology/Biomarkers

- Results of completed case-control study ?
- Long-term predictive value of proteomics /EVs.
- Biomarkers of metabolism / mitochondrial function.
- Long-term follow up of CVD biomarkers in radiation cases.
- Contribution of individual variation.

Hypothesis: progressive stress damage leading to CVD



Thank you to the ProCardio team

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