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Cataract following low dose ionising radiation exposures: Mechanistic understanding and current research

Liz Ainsbury, PHE

CNSC/CRPA Webinar: Lens of the eye – 21st March 2018

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Human Lens

Diameter ~9-10 mm, thickness ~4.5 mm

Germinative zone of LEC

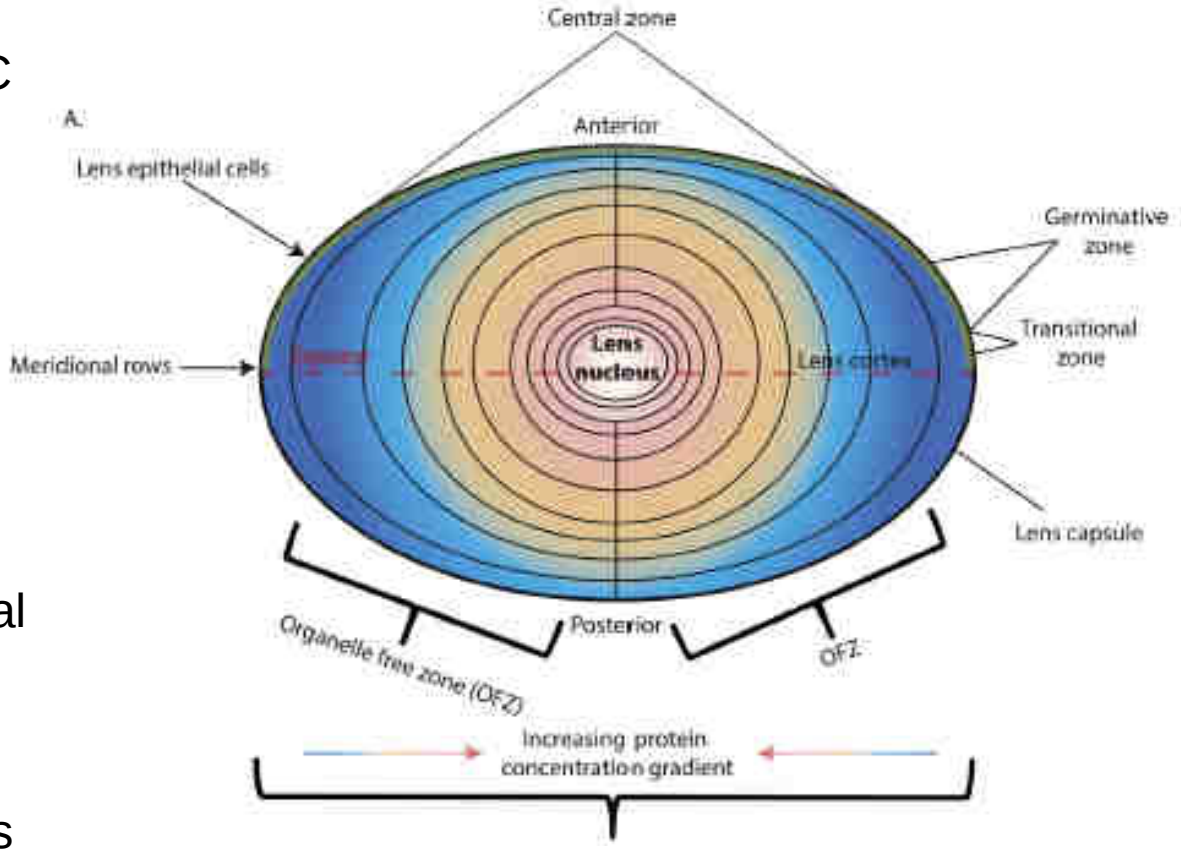
Growth factors

-> differentiation

-> lens fibres

Tight temporal and spatial organisation

Deregulation -> cataracts



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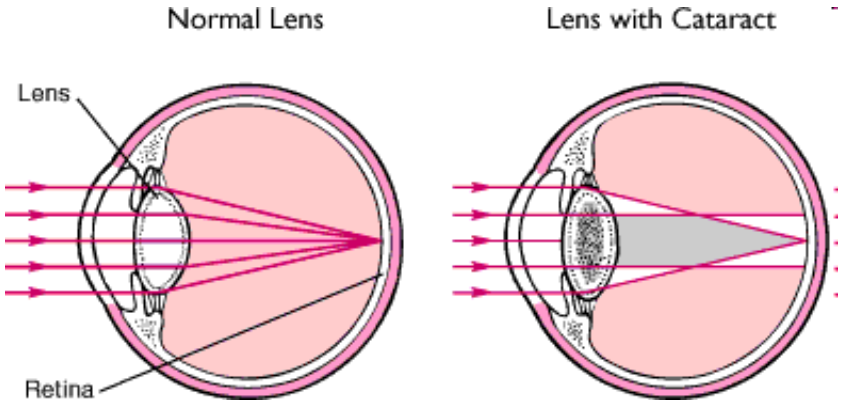
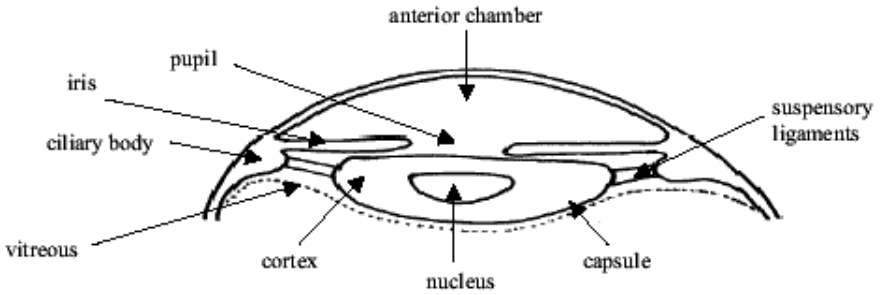
Radiation cataracts

Cataracts are most frequent cause of blindness worldwide

Multifactorial aetiology: Age related effect; Genetic component (congenital cataracts); Also: Sunlight, alcohol intake, nicotine consumption, diabetes, persistent use of corticosteroids, and *ionising radiation*…



www.uveitis.org/patient/glossary/a_f.html



www.ndrs.scot.nhs.uk/Train/Handbook/drh-27.htm

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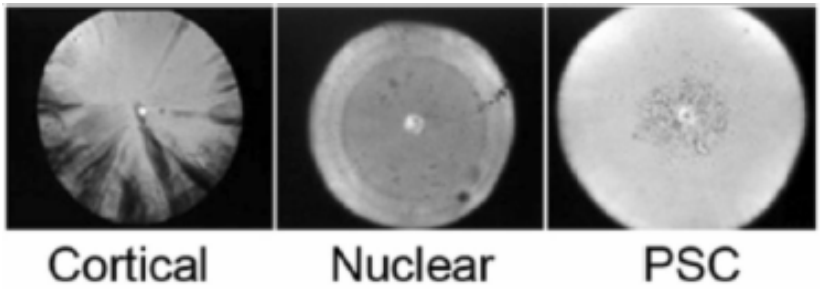
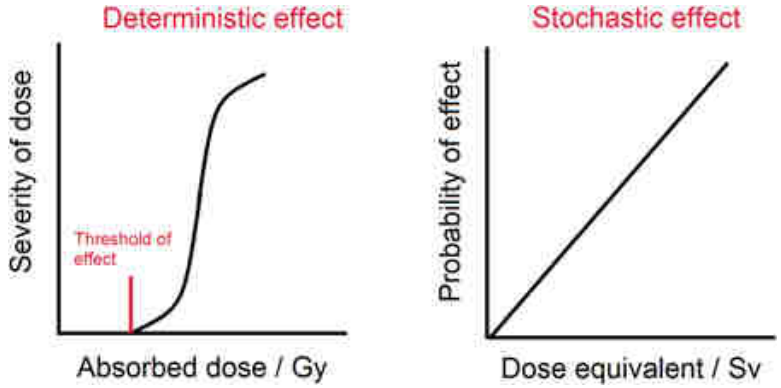
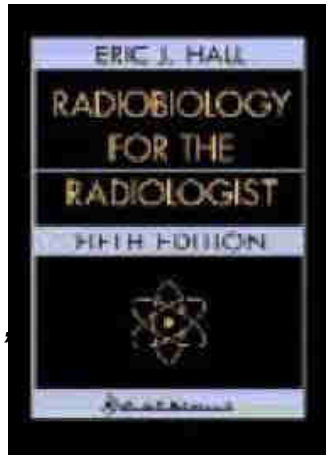
Radiation induced cataracts

Ionizing radiation is generally (but not exclusively) associated with posterior sub-capsular opacities



Adapted from Beebe , 2008





Well established paradigm: Radiation cataract is a deterministic, late, effect

ICRP, 1990 (and 2007), and others: Thresholds for radiation induced cataracts: 2 Gy acute; 4 Gy or higher fractionated/ chronic exposures

ICRP 2011: Threshold ~ 0.5 Gy…

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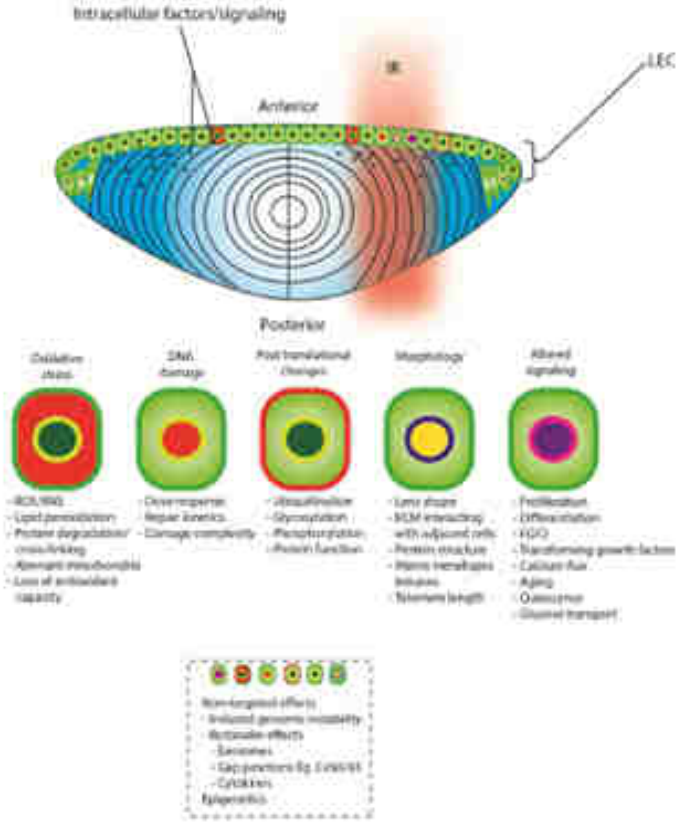
How does ionising radiation cause cataracts?

Target cells: Germinative Zone on lens epithelium (?)

Potential mechanisms might include:

- Oxidative stress
- DNA Damage/Repair/Mis-repair
- Intracellular signalling
- Gene expression
- Cellular proliferation / mobility / migration
- Damage to proteins/ECM/lipids
- Post translational modifications
- Senescence
- Systemic/Non-targeted effects …



Modifying factors: Dose, Dose rate, Age at exposure, Genetic background …

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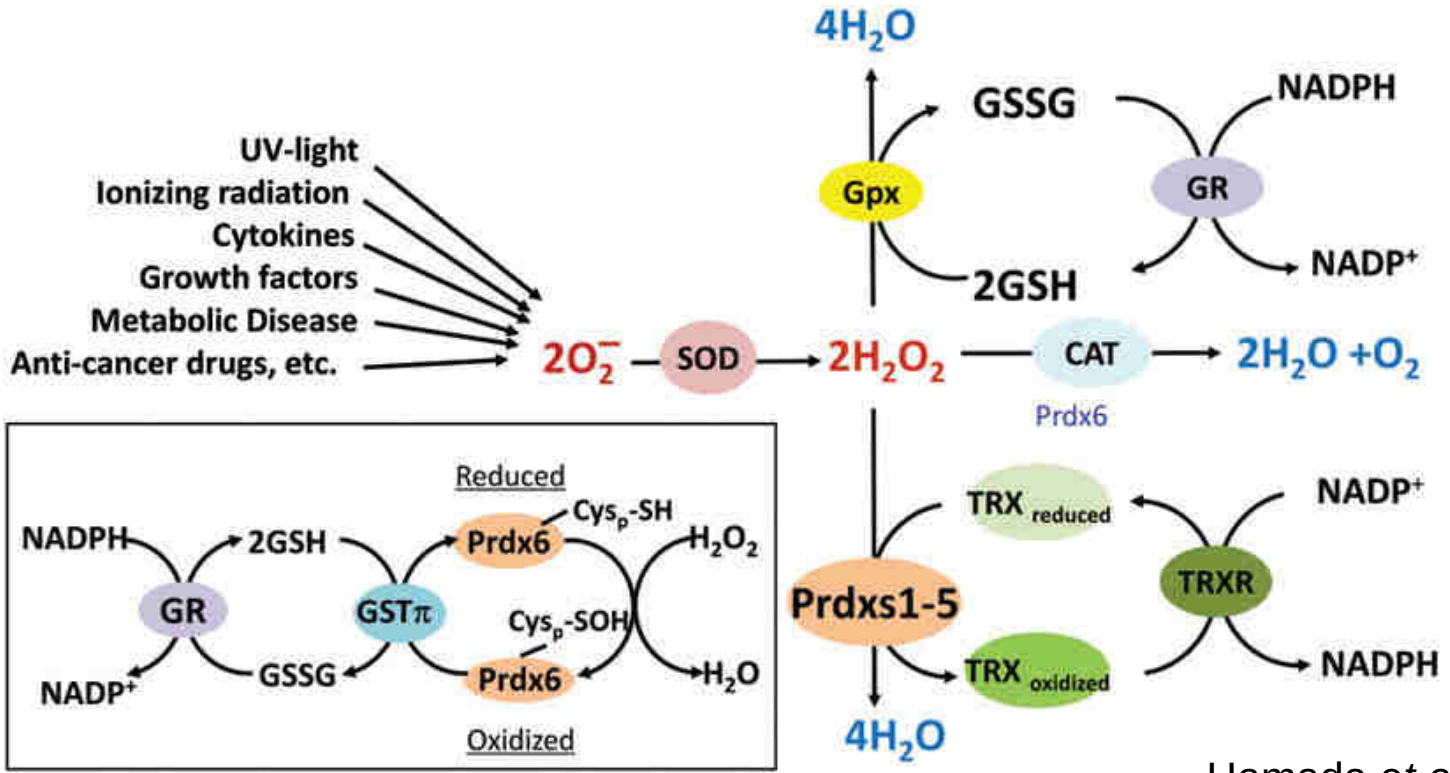
What do we know about oxidation?

ROS: Degradation, cross-linking, aggregation of lens proteins, DNA damage



Hamada *et al.*, 2014

-> Aberrant lens epithelial cell division, cell migration, differentiation…

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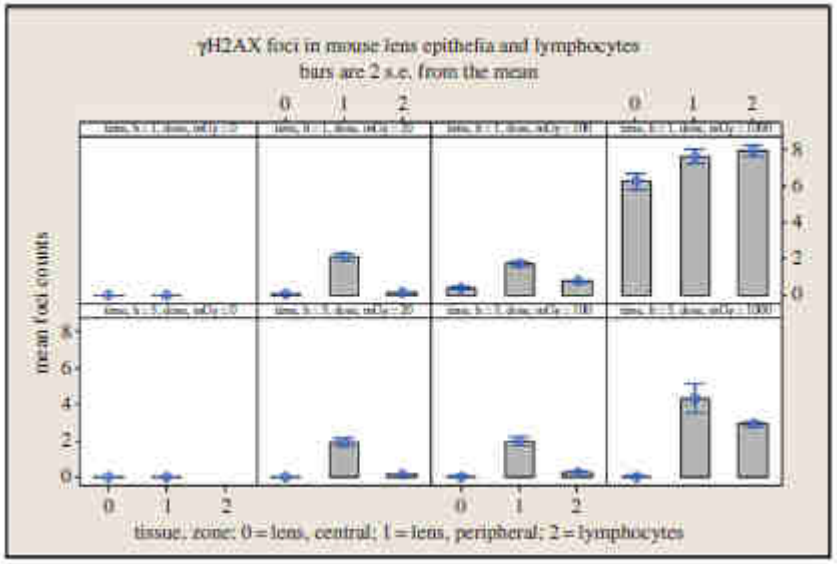
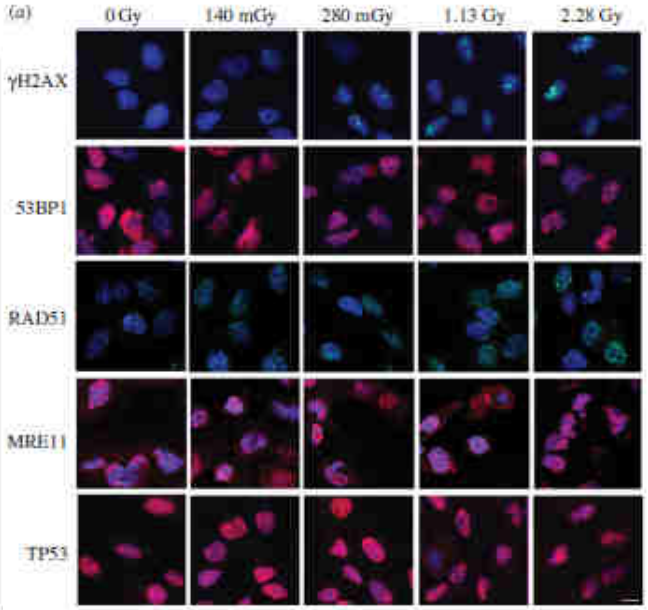
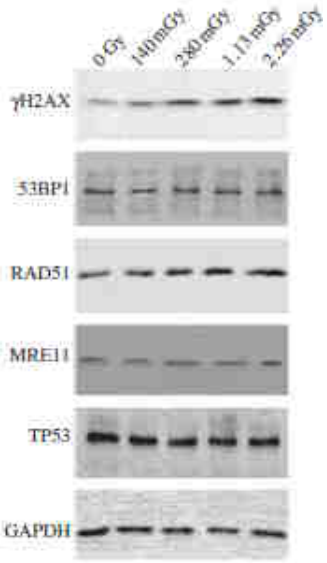
Evidence from a study looking at DNA damage and repair

Markiewicz *et al.*, 2015:

- Low dose, dose-response for DNA damage response in the lens
- Lens (peripheral region) is more sensitive than circulating lymphocytes







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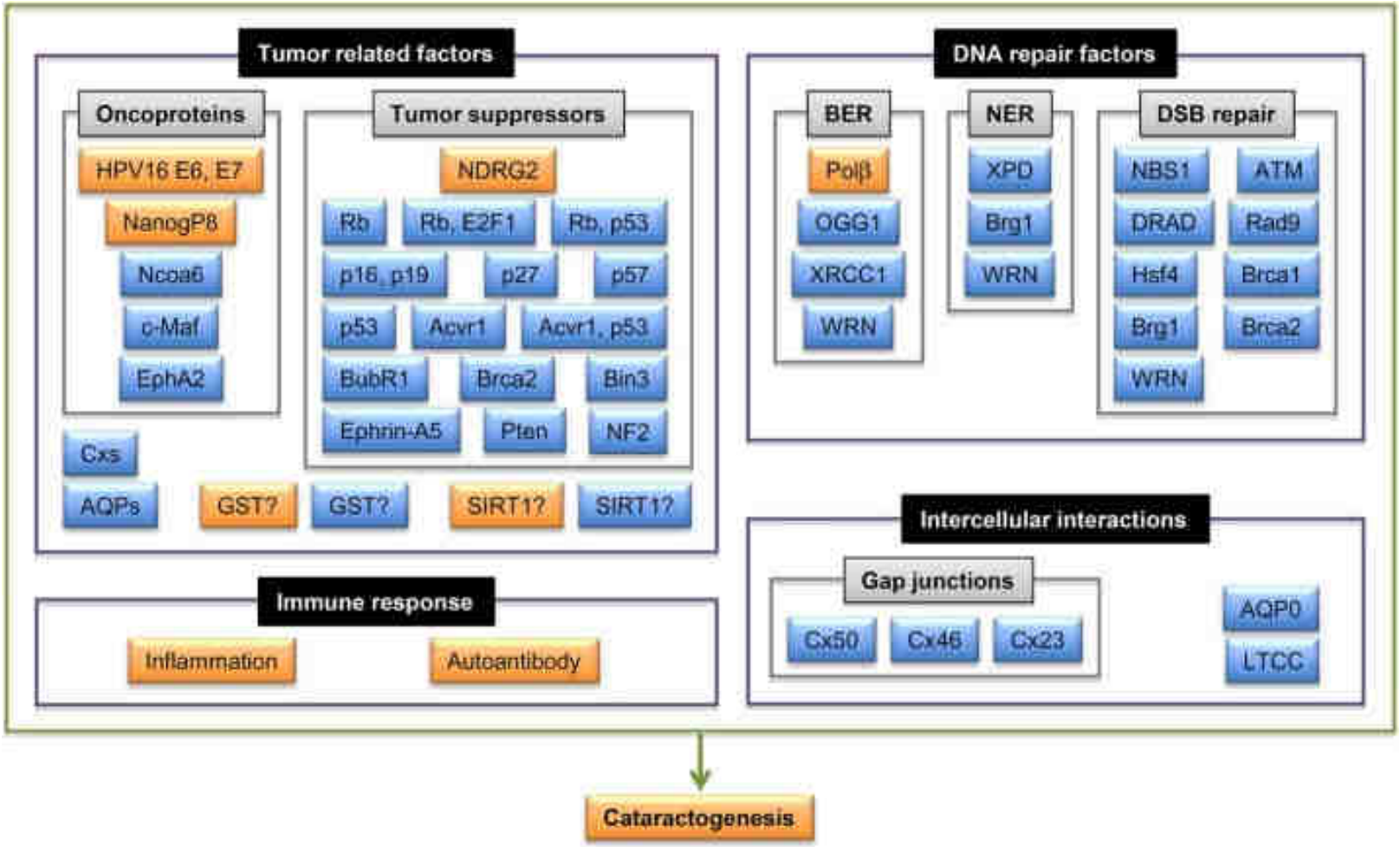
Signalling: Tumour related factors



Hamada and Fujimichi, 2015

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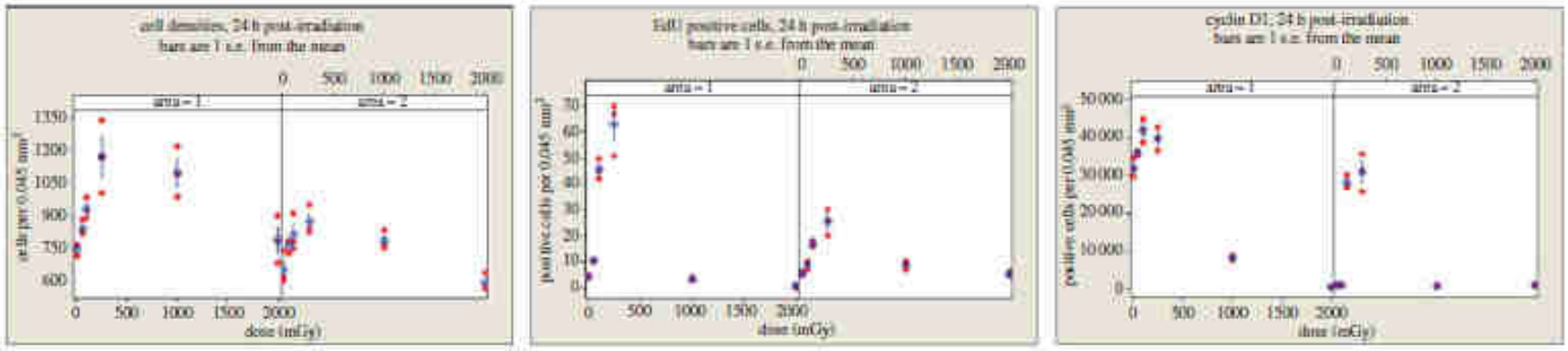
Data on stimulation of proliferation

Fujimichi and Hamada, 2015: “IR not only inactivates clonogenic potential but also stimulates proliferation of surviving unactivated clonogenic HLE cells”

IR -> abnormal activity

Historical data: Irradiation induces excessive proliferation of rabbit lens epithelial cells; suppression of lens epithelial cell divisions inhibits radiation cataractogenesis in frogs and rats

Markiewicz *et al.* 2014:



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Some publications on lens protein modifications

Abnormal lens protein accumulation -> Aggregation, lens scatters light instead of focusing on the retina

Bloemendal *et al*, 2004: Lens crystallins: α-,β- and γ-, form the refractive medium of the lens; proteins e.g. αA- or αB- protect from aggregation

Muranov *et al*., 2010: Protein changes in irradiated lenses similar to those seen in old age

Wiley *et al*., 2011: Role of abnormal cellular proliferation, e.g. p53 effect?

Fujii *et al*., 2001: Role of post translational modifications? May reduce solubility to alter transparency

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Some genetics data

Mouse models: ATM, RAD9, BRAC1 genes control signalling for DNA damage response signalling; Heterozygosity of these genes known to leads to increased risk of cancers

Worgul *et al.*, 2002:

- Cataracts earliest in homozygotes for Atm, then heterozygotes, then wildtype
- Severity and latency proportional to number of damaged cells attempting differentiation
- Atm homozygotes/heterozygotes – genetic predisposition to cataracts

Kleiman *et al*., 2007: Cataracts develop earlier and in greater numbers in Atm/Rad9 double heterozygotes

Smilenov *et al.*, 2008: Atm/Rad9/Brca1 double heterozygotes showed increased resistance to apoptosis and increased radiation sensitivity

Humans: e.g. Cataractogenic mutations in human crystallin genes

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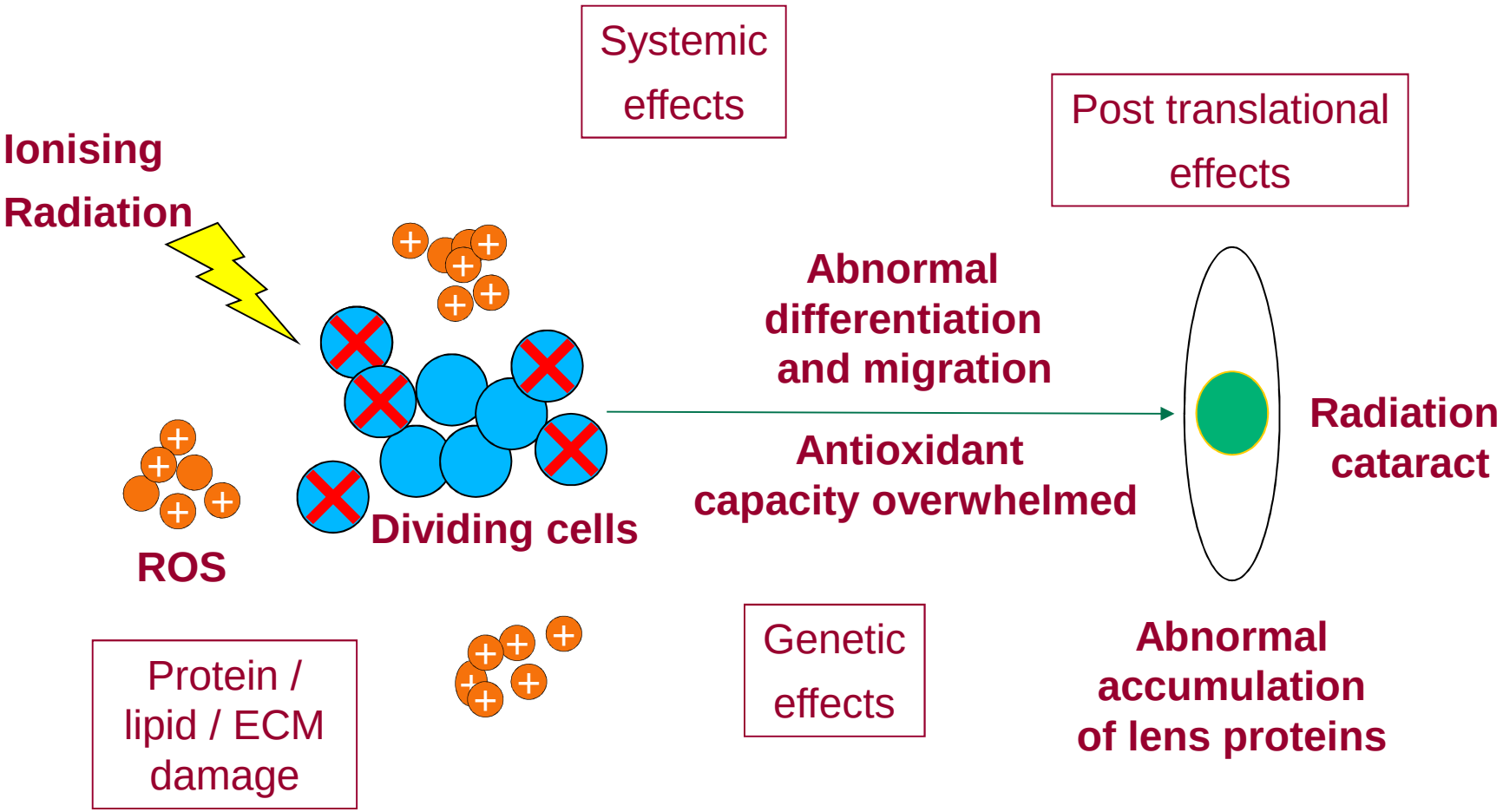
(Very basic) summary of current (incomplete) mechanistic hypothesis



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What do we know?

Understanding of lens biology (structure, physiology, process of fibre cell formation)

Radiation causes posterior subcapsular cataracts

High dose responses; impact of RBE, LET, DR

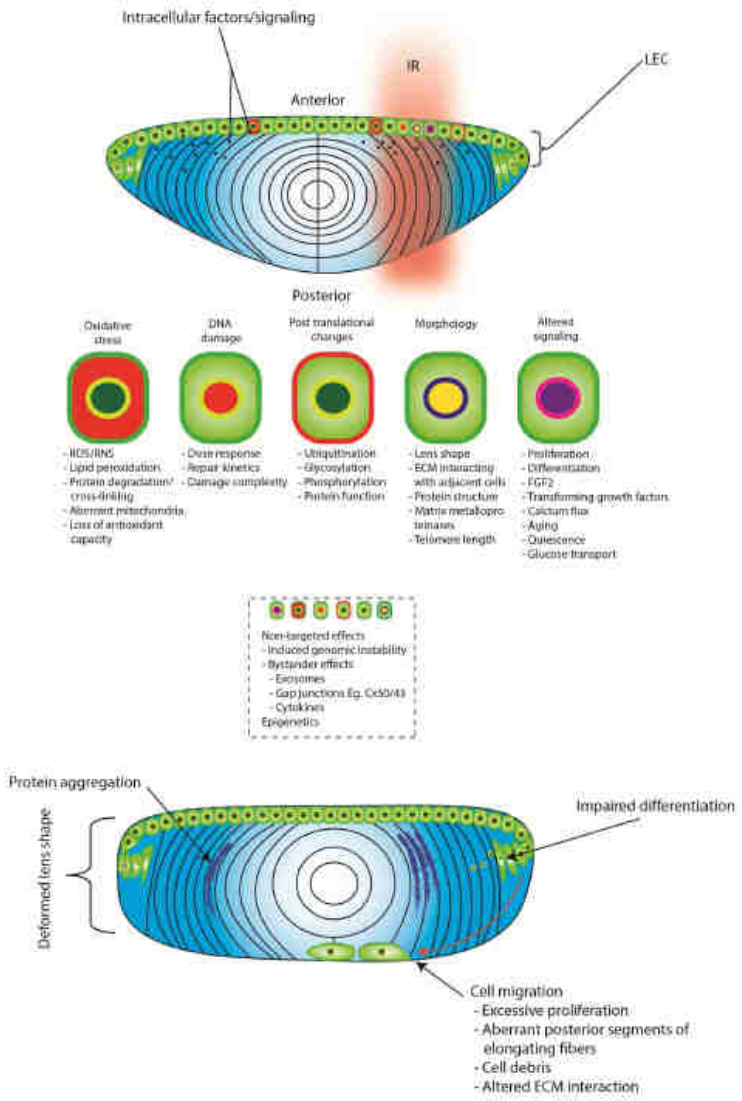
Number of potential competing/parallel mechanisms from wider cataract studies

Cellular and tissue level studies *ex vivo* or *in vitro* support the paradigm of genomic damage of lens epithelial cells as key mechanisms of cataractogenesis

Genetic background (e.g. heterozygosity for *Atm* or *Ptch1*), gene expression

Age dependence, impact of normal aging

Cataract detection/assessment



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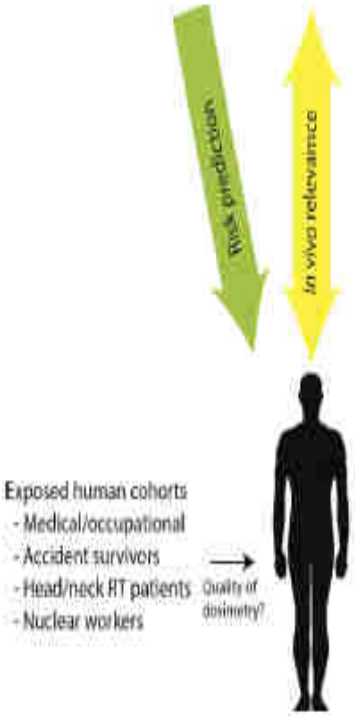
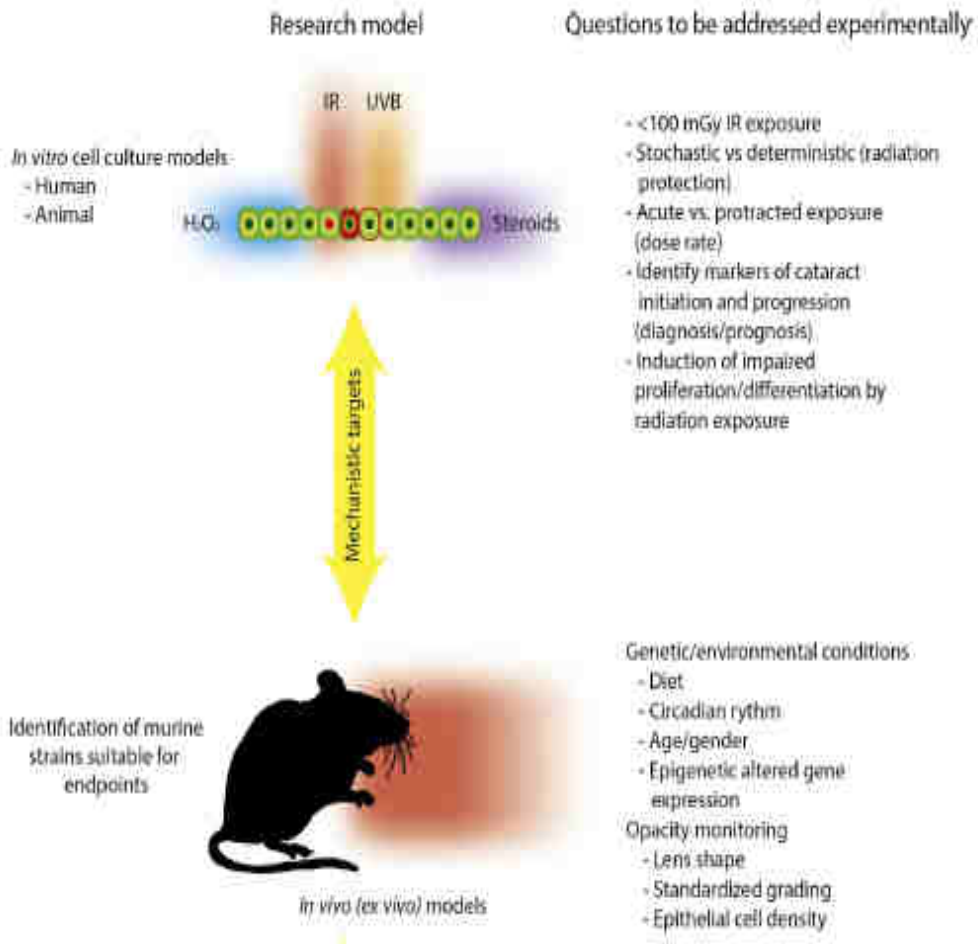
What don't we know?



Accelerated aging
- Nuclear/cortical
- Latency period length

Monte Carlo modeling of dose deposition

Confounding factors
- Smoking
- Alcohol consumption
- Background IR exposure
- UV exposure
- Obesity
- Diabetes
- Hypertension
- Eye injury/inflammation
- Asthma
- Steroids
- COPD



- <100 mGy IR exposure
- Stochastic vs deterministic (radiation protection)
- Acute vs. protracted exposure (dose rate)
- Identify markers of cataract initiation and progression (diagnosis/prognosis)
- Induction of impaired proliferation/differentiation by radiation exposure

Genetic/environmental conditions
- Diet
- Circadian rythm
- Age/gender
- Epigenetic altered gene expression

Opacity monitoring
- Lens shape
- Standardized grading
- Epithelial cell density

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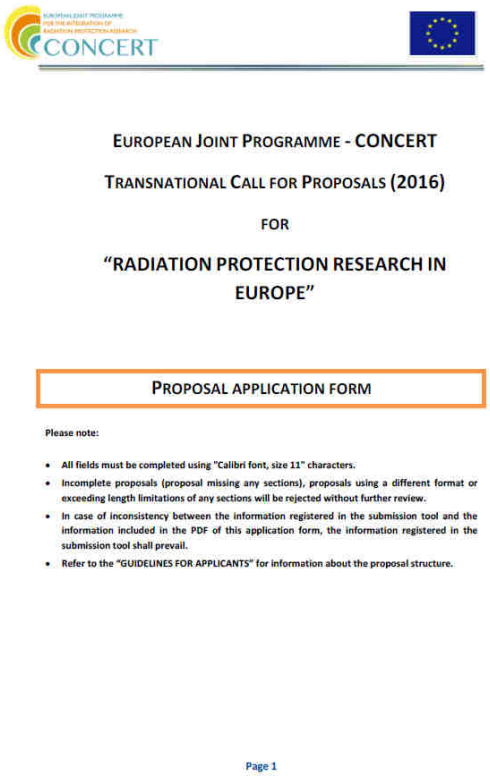
LDLensRad Project

EJP CONCERT LDLensRad: Towards a full mechanistic understanding of low dose radiation induced cataracts

Objective:

"*To advance knowledge to solve the question of how radiation causes and/or promotes cataracts.*

This will be achieved by providing concrete evidence of the ability of radiation exposure <= 500 mGy to cause cataracts, the impact of dose protraction on the dose response and the biological mechanisms behind cataractogenesis."



CONCERT

EUROPEAN JOINT PROGRAMME - CONCERT

TRANSNATIONAL CALL FOR PROPOSALS (2016)

FOR

"RADIATION PROTECTION RESEARCH IN EUROPE"

PROPOSAL APPLICATION FORM

Please note:

- All fields must be completed using "Calibri font, size 11" characters.
- Incomplete proposals (proposal missing any sections), proposals using a different format or exceeding length limitations of any sections will be rejected without further review.
- In case of inconsistency between the information registered in the submission tool and the information included in the PDF of this application form, the information registered in the submission tool shall prevail.
- Refer to the "GUIDELINES FOR APPLICANTS" for information about the proposal structure.

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Specific research questions

- Is there a low dose dose-response in radiation cataractogenesis?
- What is the impact of dose rate?
- What is the impact of genetic background?
- What is the impact/involvement with the ‘normal’ aging process?
- How are oxidative stress and intracellular communication, DNA damage, translational, proteomic and lipidomic responses, proliferation and lens morphology impacted by radiation?
- Can the lens be viewed as an indicator of global radiosensitivity?
- Are radiation cataracts most appropriately viewed as a deterministic/tissue reaction or a stochastic effect?

LDLensRad will contribute to answering some of these questions but:

Further collaborative research is needed!

Project collaborators and Advisory Board members

LDLensRad: Towards a full mechanistic understanding of low dose radiation induced cataracts

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Ionizing radiation induced cataracts: Recent biological and mechanistic developments and perspectives for future research

Elizabeth A. Ainsbury[a,*], Stephen Barnard[a], Scott Bright[b], Claudia Dalke[d], Miguel Jarrin[e], Sarah Kunze[d], Rick Tanner[a,1], Joseph R. Dynlacht[c,1], Roy A. Quinlan[e,1], Jochen Graw[d,1], Munira Kadhim[b,1], Nobuyuki Hamada[f,**]

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Thank you for listening!

Questions/Comments/Suggestions?

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