UNIVERSITY OF EASTERN FINLAND

Genomic instability and non-ionizing radiation

NSFS Conference 2019, Next level in radiation protection

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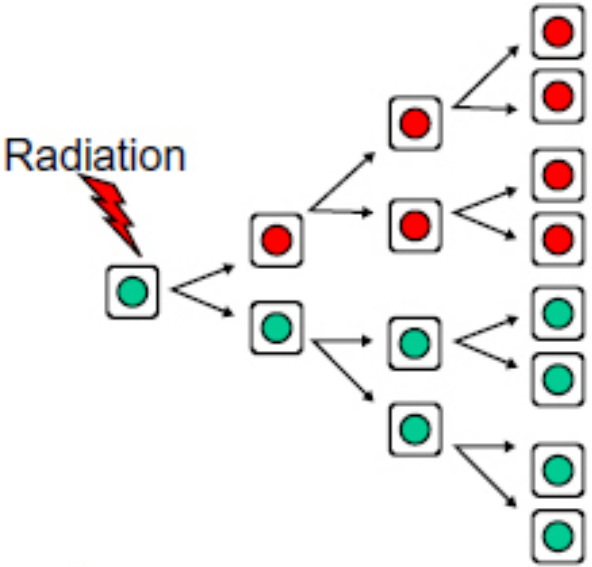
Induced genomic instability (IGI)

- *De novo* appearance of genetic damage in the progeny of exposed cells (or animals)
  - Basically delayed effects (e.g. mutations, apoptosis, chromosomal aberrations, micronuclei…)

- The cells (or organisms) inherit not only mutations but an **increased mutation frequency**

→ Highly relevant to cancer (development of cancer requires accumulation of multiple genetic changes)

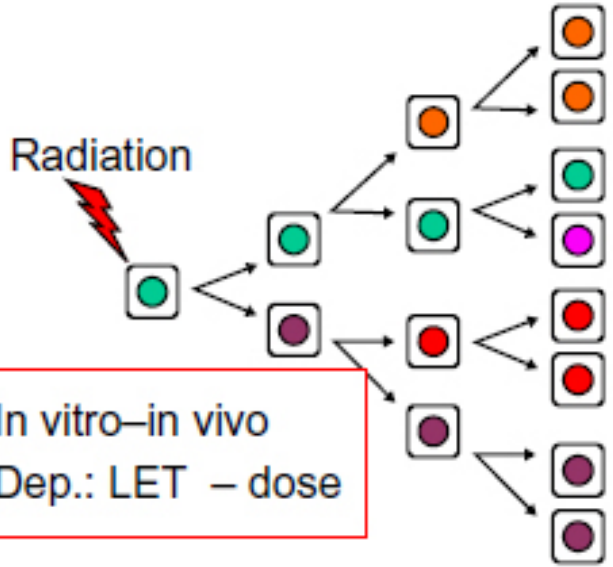
Directly induced mutation



"Targeted" effects

Direct effects on DNA sequence

Genomic instability

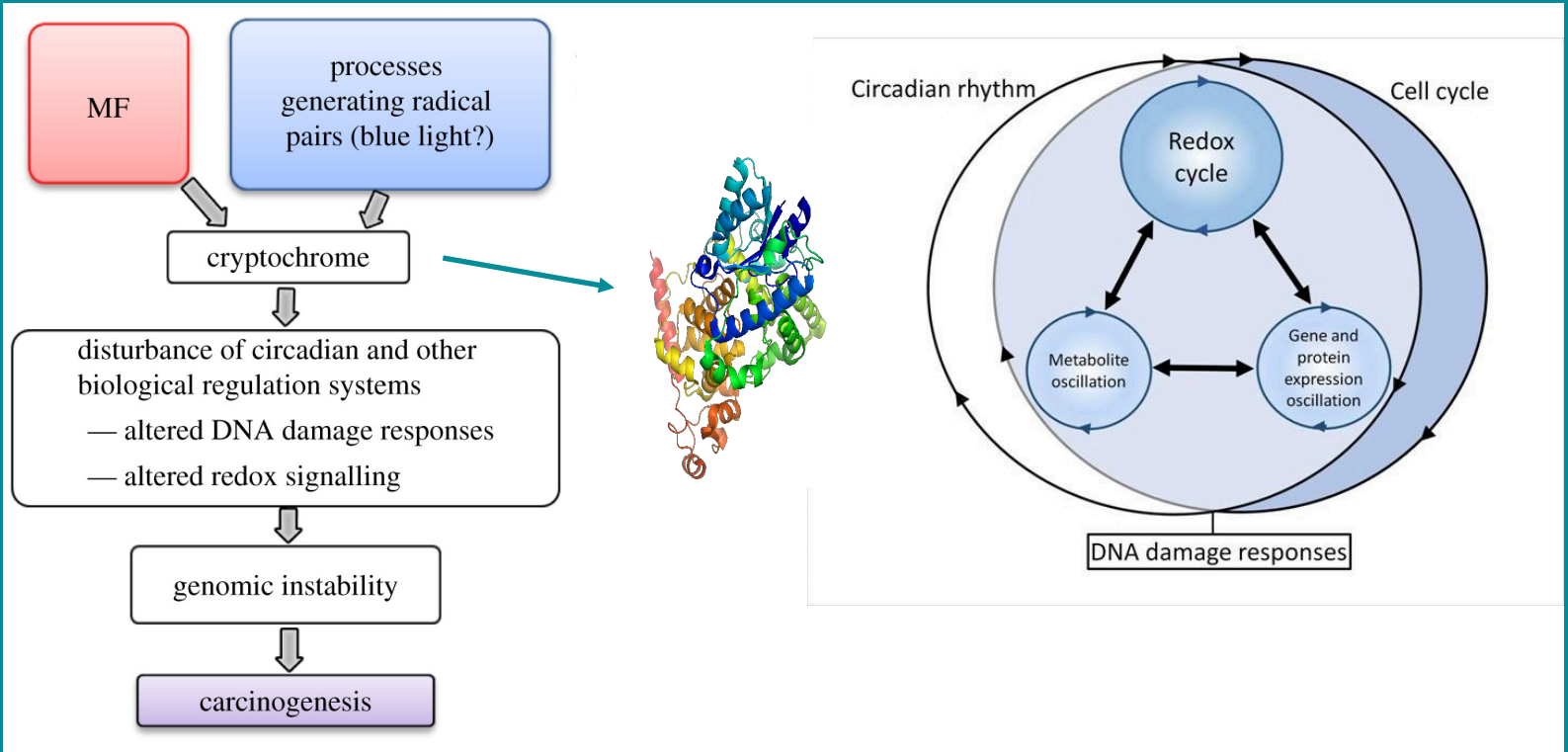


In vitro–in vivo
Dep.: LET – dose

"Nontargeted" effects

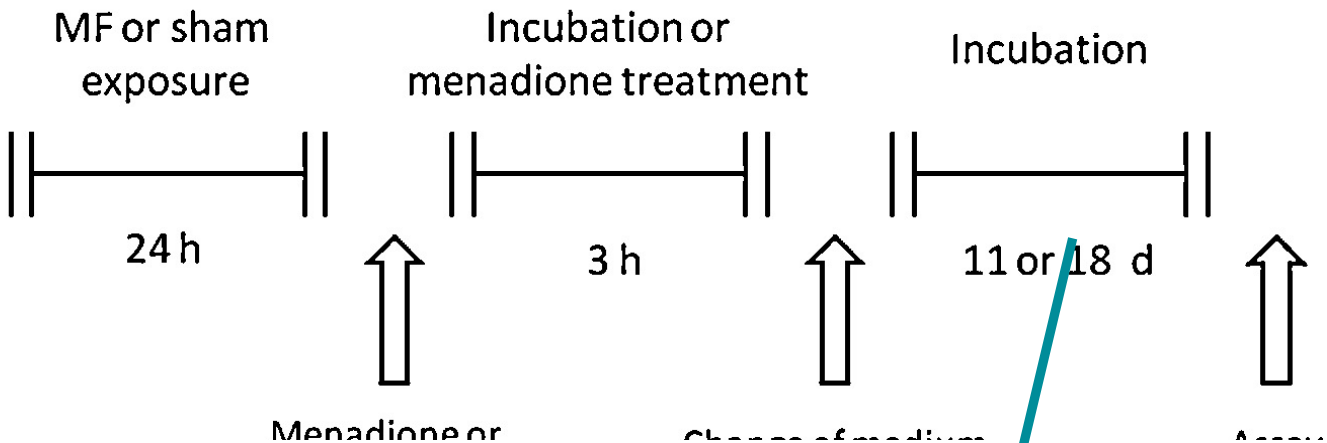
Epigenetic effects, e.g. DNA methylation, histone modifications, small RNAs…

Hypothesis



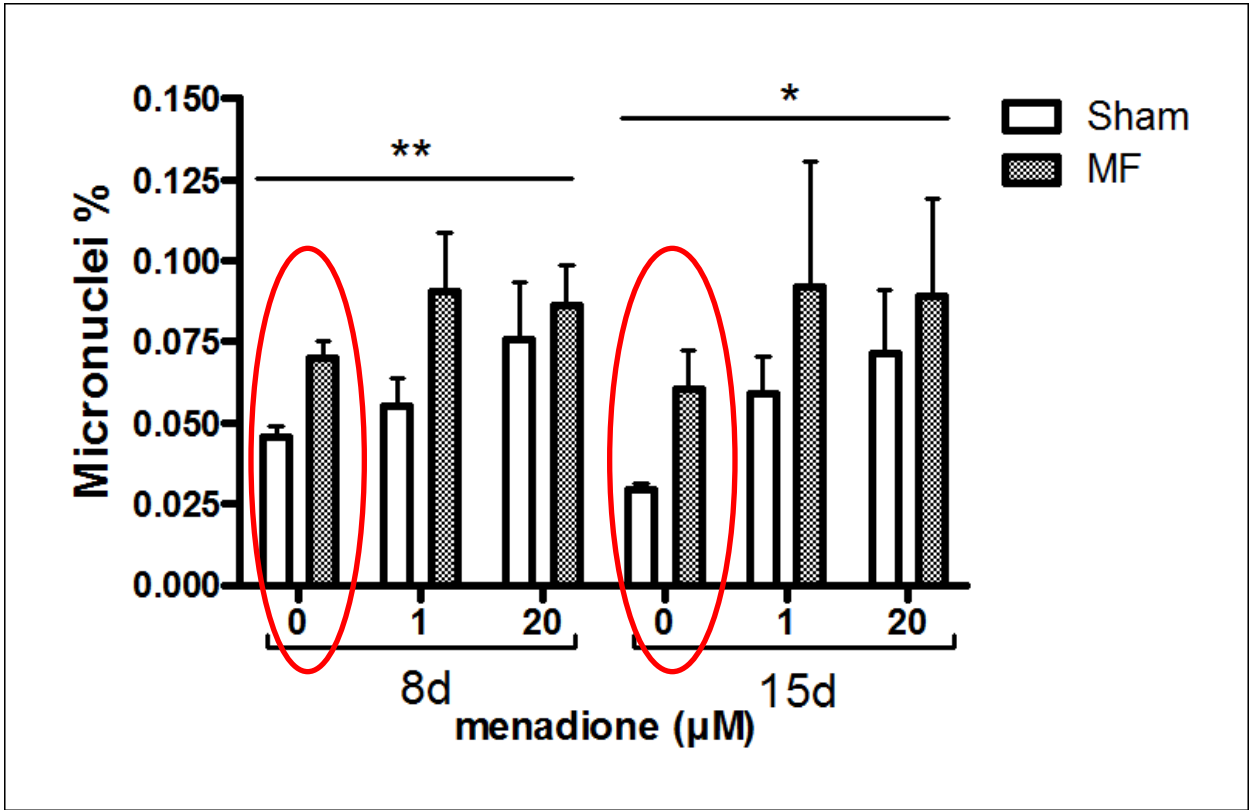
Proc Biol Sci. 2018 May 30; 285(1879): 20180590.

Example of exposure scheme



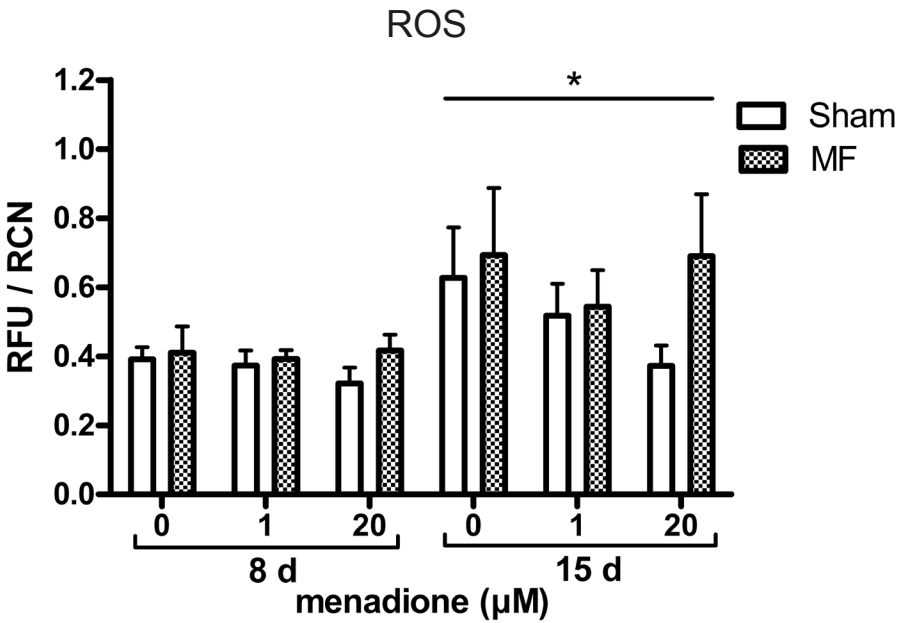
About 8 or 15 cell generations in secondary human Neuroblastoma cells

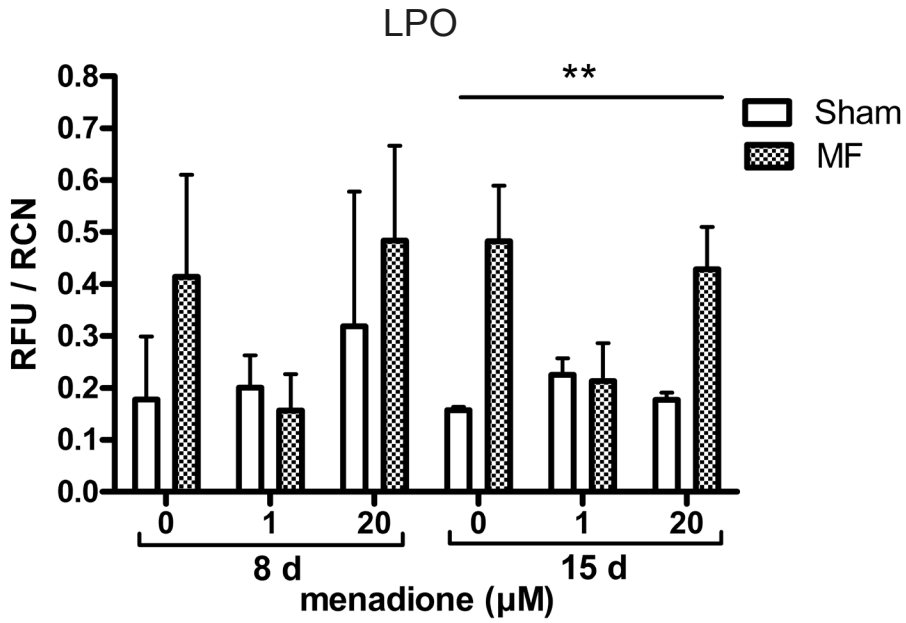
Persistently increased micronucleus frequency 8 and 15 days after exposure in cells exposed to ELF MF (50 Hz, 100 μT, 24 h) and menadione



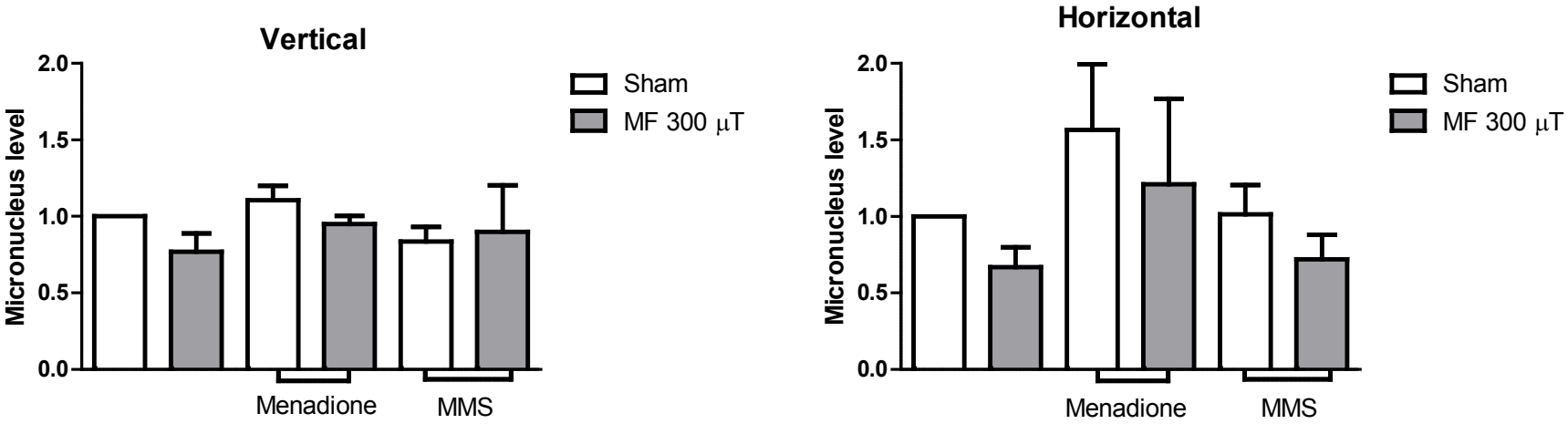
Luukkonen et al., Mutat Res 760:33– 41 (2014)

ROS production and lipid peroxidation in Human SH-SY5Y neuroblastoma cells 8 or 15 d after exposure to a 50 Hz, 100 µT ELF MF for 24 h





IGI is not induced by 7.5 kHz intermediate frequency fields (IFs) after 36 days after exposure

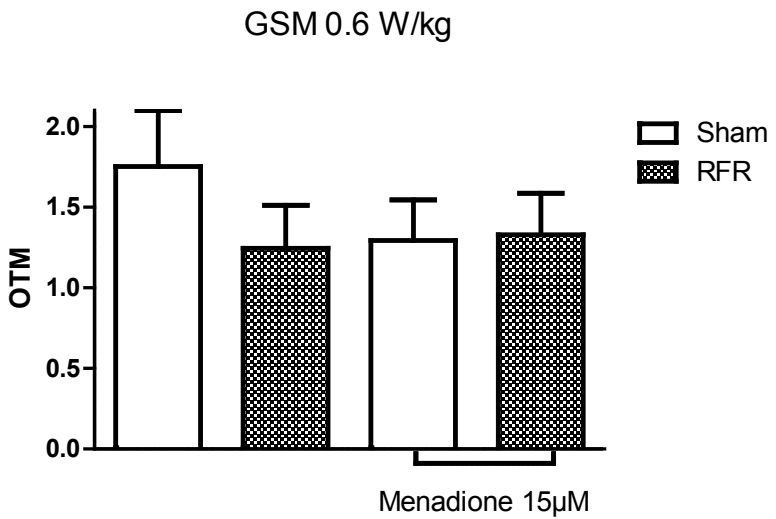


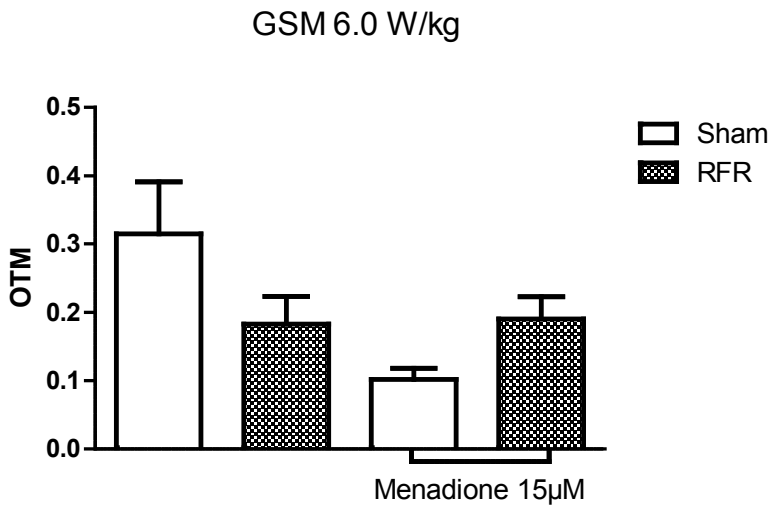
Some evidence of *decreased* genomic instability when above data are combined.

Herrala et al., Environ Res 173:112-116 (2019)

IGI is not induced by 872 MHz radiofrequency fields (RFs) after 36 days after exposure

DNA damage measured by Comet assay





Herrala et al., Int J Radiat Biol 94:883-889 (2018)

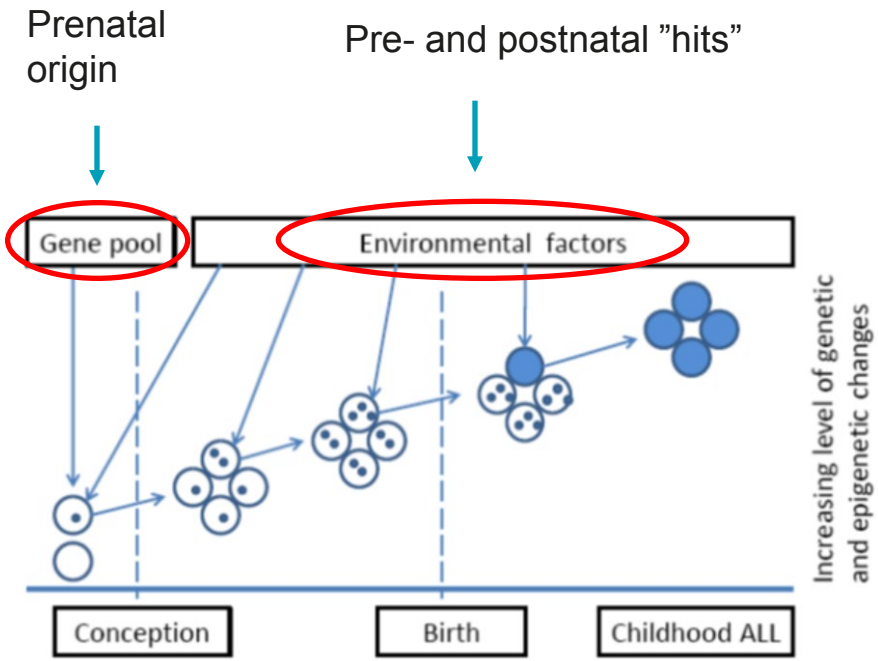
Is IGI important factor in non-ionizing radiation biology?

Yes, sure, but seems to be so only for ELF MF exposure

Only basic science oriented interest or is there also a disease based rationale?

Induced genomic instability as a basis for childhood leukaemia

- There is increasing evidence that induced genomic instability plays a role in environmentally induced cancer
- Epidemiological studies have consistently reported an association between childhood leukaemia and extremely low frequency (ELF) magnetic fields (MFs)
  - the risk of leukaemia increases for time-average magnetic flux densities above about 0.3-0.4 μT



Ongoing now or in the near future…

- As predicted by the radical pair mechanism, the exposure–response relationship should be biphasic
  - Different magnetic flux densities and frequencies should be tested
  - Different cell lines (primary, secondary, neuronal based, myelopoietic progenitors, stem cell derived cells…)
- CRY should respond to ELF magnetic fields, and magnetic field effects should depend on the presence of functional CRY in the exposed cells or organisms.
  - CRY gene and protein expression, and also other circadian genes plus DNA damage response genes; silencing of CRY

In the near future…

- To reveal causal relationships, temporal order of biological changes should be studied
  - Fluorescent live cell imaging (LCI) by microscopy or IncuCyte S3 LCI platform. The measurements will include CRY protein expression, gene expression of CRY and associated genes, mitochondrial and cytosolic ROS, and responses to induced DNA damage
- To determine whether MF exposure can enhance genomic instability in haematopoietic organs *in vivo*
  - Short-term animal study to determine whether MF exposure can enhance genomic instability in haematopoietic organs

Challenges in genomic instability research in general

- To reveal, how the instability is signalled from cell to cell, from cell generation to cell generation, and transgenerationally
  - Bystander effect, epigenetic signalling, microvesicles...
  - System biological approach will be needed to understand the big picture
- Genomic instability vs. cellular instability?
  - Dynamical state of a cell
- How the instable state is maintained in cells?
  - What is the memory for instability?

Thank you very much!

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GERoNiMO
Generalized EMF research using novel methods
An integrated approach: from research to risk assessment and support to risk management

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