RUTGERS
BIOMEDICAL AND HEALTH SCIENCES

Canadian Nuclear Laboratories

Laboratoires Nucléaires Canadiens

Reflections on research accomplishments and a look to the future

Edouard Azzam

With support from the DOE Low Dose Radiation Research Program
1998 - 2011

Awards

- **DE-FG02–98ER62685 (PI: J.B. Little/ co-I: E.I. Azzam)**

  - Generated direct evidence for a role of junctional communication and oxidative metabolism in expression of bystander effects in human cell cultures exposed to low fluence α particles

- **DE-FG02-02ER63447 (PI: E.I. Azzam)**

  - Generated evidence for up-regulation of antioxidant defense in expression of adaptive responses in human cells exposed to low dose γ rays delivered at low dose rate.

  - Showed that gene expression and mitochondrial function are differentially regulated in human cells exposed to low dose vs. high dose γ rays

- **DE-FG02-05ER64050 (PI: D.R. Spitz/co-PI: E.I. Azzam)**

  i) Showed a prominent role for succinate dehydrogenase (mitochondrial respiratory complex II) in overall responses to low dose γ rays;

  ii) Showed that the metabolic enzyme 'aconitase' is a sensitive marker of the radiation response

- **DE-FG02-07ER64344 (PI: E.I. Azzam)**

  i) Discovered a new player (TCTP) in DNA repair (highly sensitive to low dose/low dose rate);

  ii) showed that protection against *in vivo* exposure to low dose γ rays is associated with decrease in mitochondrial function;

  iii) Showed that partial oxygen tension (pO_2) is an important regulator of cellular responses

Output: selected publications

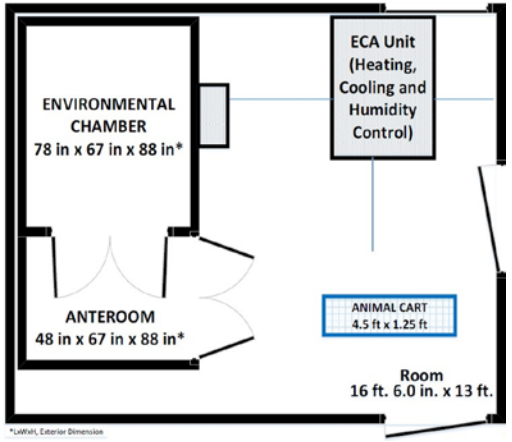
- Azzam EI *et al.* (2000) High and low fluences of α-particles induce a G_1 checkpoint in human diploid fibroblasts. *Cancer Res.*, **60**, 2623-2631.
- Azzam EI et al. (2001) Direct Evidence for the participation of gap-Junction mediated intercellular communication in the transmission of damage signals from α-particle irradiated to non-irradiated cells. *PNAS* **98**, 473-478.
- Azzam EI *et al*. (2002) Oxidative metabolism modulates signal transduction and micronucleus formation in bystander cells from α-particle-irradiated normal human fibroblast cultures. *Cancer Res.* **62**, 5436-5442.
- Azzam EI, de Toledo SM, Little JB (2003) Expression of *CONNEXIN43* is highly sensitive to ionizing radiation and other environmental stresses. *Cancer Res.* **63**, 7128-7135.
- Spitz DR *et al.* (2004) Metabolic oxidation/reduction reactions and cellular responses to ionizing radiation: a unifying concept in stress response biology. *Cancer & Metastasis Reviews* **23**, 311-322.
- Pandey BN *et al*. (2006) Normal human fibroblasts exposed to high or low dose ionizing radiation: differential effects on mitochondrial protein import and membrane potential. *Antioxidant & Redox Signaling*, **8**, 1253-1261
- de Toledo *et al*. (2006) Adaptive responses to low dose/low dose-rate γ-rays in normal human fibroblasts cultured in three-dimensional architecture: The role of oxidative metabolism. *Radiation Research.*, **166**, 849-857
- Venkatachalam *et al*. (2008) Regulation of Normal Cell Cycle Progression by Flavin-Containing Oxidases. *Oncogene,* **27**, 20-31.
- Azzam EI, Jay-Gerin J-P, Pain D (2012) Ionizing radiation-induced metabolic oxidative stress and prolonged cell injury. *Cancer Letters*, **327**(1-2):48-60.
- Zhang J *et al.* (2012) Role of the Translationally Controlled Tumor Protein in DNA Damage Sensing and Repair. *PNAS (Plus)* **109(16)**:E926-33.

Implications of termination of DOE low dose program

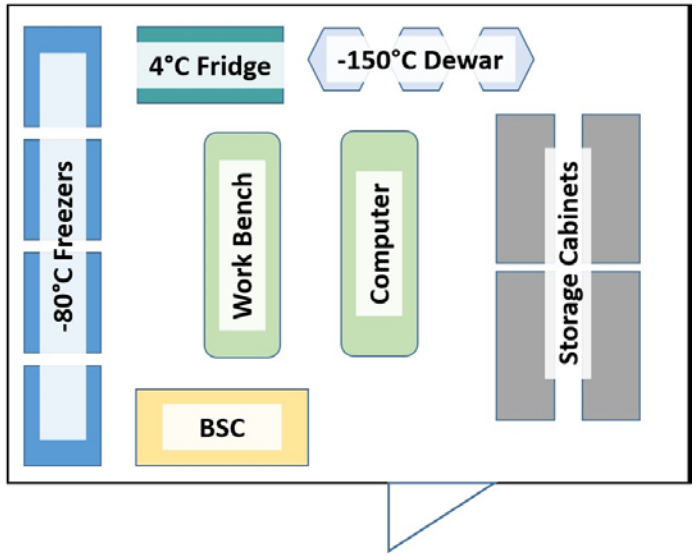
- Work on low doses/low dose rates of sparsely ionizing radiation could not continue
- Training of medical students and radiology residents in projects involving low doses of radiation such as encountered in diagnostic procedures significantly curtailed
- Research program in the laboratory continued with support from
  - NASA to characterize mechanisms underlying the effects of protons and high atomic number (Z) and high energy (E) HZE particles
  - NCI to examine induction of non-targeted effects of radiation following exposure to therapeutic doses.
- Work on low fluence α particles such as from radon gas continued

2021: resumed work on low dose/low dose rate ionizing radiation at Canadian Nuclear Laboratories

- **30 m long 'Gamma Hall' located in SPF Animal Facility**
- Cs-137: 605 µGy/h to 5.4 Gy/h
- Co-60: 76.4 µGy/h to 65.7 mGy/h
- Allows for acute & chronic exposures of live cell cultures and small animals (https://www.cnl.ca/facilities/biological-research-facility/)



Radon Inhalation Chamber



Tissue Biobank:

- Securely store tissues and cultures derived from radiobiological studies
- Engage both national and international collaborations

The future: re-launch of 'low dose radiation research program' in the USA

- Contribute not only in reducing the uncertainty of predicting adverse health risk, but also whether low dose radiation can potentiate efficacy of disease treatments: immune modulation, regenerative medicine …
- Training of high quality personnel in occupational and educational settings
- Eminent factors (*e.g.*, ↑ in nuclear power generation) are pressing for <u>greater understanding</u> of health outcomes of exposure to low dose ionizing radiation, and the <u>communication</u> of potential risk. To this end, an <u>integrated research plan</u> that addresses several variables is essential:

P = G + E

Genetic Susceptibilities
Males & females
Cells, animals, human organoids

Pathological outcomes
Omics/Bioinformatics/<u>data sharing</u>

Age at exposure, time after exposure, life style (diet, microbiome, …), co-stressors, dose, dose-rate, LET

Identification of key pathways that impact health risk assessment & contribute, together with <u>human epidemiology</u> surveys, to generation of predictive <u>dose response risk models</u>