

The Immune Modulating Effects of Low Dose Ionizing Radiation and Its Applicability for Cancer Therapy

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## Disclosure of Affiliations, Financial and In-Kind Support:

#### **Acknowledgement Statement:**

 This program has received financial support from "NOSM René Guilbeault Research Award" and "Northern Cancer Foundation Grant".

#### The following steps have been taken to mitigate bias:

- All speakers have been provided with a speaker letter outlining the certification/accreditation requirements for their presentation.
- The SPC or designate has reviewed the presentation(s) prior to their delivery.
- If a breach is detected the SPC will approach the speaker to discuss the concern and update the presentation as required.



## **Ionizing Radiation**

- Radiation Therapy uses high doses of radiation to kill cancer cells
- The amount of energy deposited in human tissue by radiation is measured in Gray (Gy)





[1] Radiation units. (2018.). Environmental Health and Safety.





## **The Immune System**



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Antitumor Immunity: The immune responses which lead to tumor control



#### Natural Killer (NK) Cells

- Large granular lymphocytes derived from lymphoblasts
- Comprise 10-15% of circulating lymphocytes and tissues
- Cytotoxic = contain granzymes that cause apoptosis in abnormal cells
- 2 main receptors: activating and inhibitory
- Not antigen specific = recognize cells without MHC Class I antigens





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### **Three Major Pathways of NK Cytotoxicity**

**1** Perforin/granzyme pathway

#### 2 Fas/FasL & TRAIL pathway

**3**Cytokine/Chemokine pathway

[3] Peppa, D. (2019). EBioMedicine, 44, 26–27.



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# MAIN GOALS:

- Explore the impacts of LDR on NK cell cytotoxicity in-vitro.
- Identify the mechanisms of LDR stimulated NK cell cytotoxicity.

## **HYPOTHESIS:**

• Radiation exposures below 500 mGy will increase cytotoxicity of NK cells through the three major pathways of NK cell killing.



## **Cell Lines Used**

#### 1) NK-92 - Natural Killer Cell Line

- Human immortalized cell line isolated from a patient with NK cell lymphoma
- Share similar characteristics as circulating NK cells
- Requires recombinant IL-2 to maintain proliferation





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### 2) K-562 - Tumorigenic Cell Line

- Human leukemia cell line
- Target of NK cell lytic activity because lack of MHC class I molecule expression





## **Objectives:**

To assess the effects of LDR on...





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# Aim 1 Results Growth Curve



## **Doubling Time - Radiated NK-92s**

#### Main findings:

- Significant increase of doubling time at higher radiation doses (5-10 Gy) = suppressed growth
- No observable changes at lower doses (0.01-1 Gy)





# Aim 2 Results Cytotoxicity Assay



## NK-92 Cytotoxicity Assay

- Co-culturing of irradiated NK-92 (effector cell) and K-562 (target cell)
- Compare percent K-562 killing after 4-hour co-culture



### NK-92 Cytotoxicity Assay Preliminary Results (n=2)

3:1 E:T Ratio





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# Aim 3 Results Mechanistic Assay/ qPCR



### **Perforin/Granzyme Pathway**

**Preliminary Results (n=2)** 





### **FasL and TRAIL Pathway**

**Preliminary Results (n=2)** 





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## **Cytokine/Chemokine Pathway**

**Preliminary Results (n=2)** 





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## **Next Steps**

Further explore which mechanisms are involved in NK cytotoxicity.



## **Acknowledgements-NFRF Project Team**

#### **Supervisors:**

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# Thank you!



## Cancer



[1] Canadian Cancer Stats (2018.). Canadian Cancer Society

#### Effects of LDR on the Immune System Previous Studies

	Immune system	Modification following LDR regimen	Role of immune system in LDR response
	Cellular component		
	Innate immunity		
	NK ADCC Macrophage Dendritic cell	Increase in functionality Increase Increase in functionality Activated	Lysis of tumor cells Lysis of tumor cells Phagocytosis and antigenic presentation Increase in T-cell proliferation and antigenic presentation
	Adaptive immunity		
	CD8+(CTL) CD4+ Th1 Th2 T-regulatory	Increase in cytolysis Enhanced responsiveness Increase No change Decrease	Lysis of the tumor cells Helping other immune cells Anti-tumor activity Proinflammatory response Breaking of tumor tolerance during carcinogenesis and induction of anti-tumor immunity
	Secretary component		
	Cytokines		
	IL-2 IL-12 IFN-γ TGF-β IL-10 TNF-α	↑ ↑ ↓ ↓ ↑	T-cell proliferation Proinflammatory response Phagocytosis and antigenic presentation Maturation and proliferation of T and B cells Immunactivation Proinflammatory response
	ADCC: Antibody-dependent cell-mediat	ed cytotoxicity; CTL: Cytotoxic T lymphocy	te; LDR: Low-dose radiation; NK: Natural killer.

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[3] Farooque, A. et al, (2011). *Expert Review of Anticancer Therapy*, 11(5), 791–802.

## **Doubling Time - Radiated K-562s**

#### Main findings:

- Significant increase of doubling time at higher radiation doses (5-10 Gy) = suppressed growth
- No observable changes at lower doses (0.01-1 Gy)





#### Previous results??



## **Next Steps**





### **Effects of LDR on the Immune System**

