



The Immunomodulatory behaviour of Low Dose Radiation Therapy

Dr James McEvoy-May

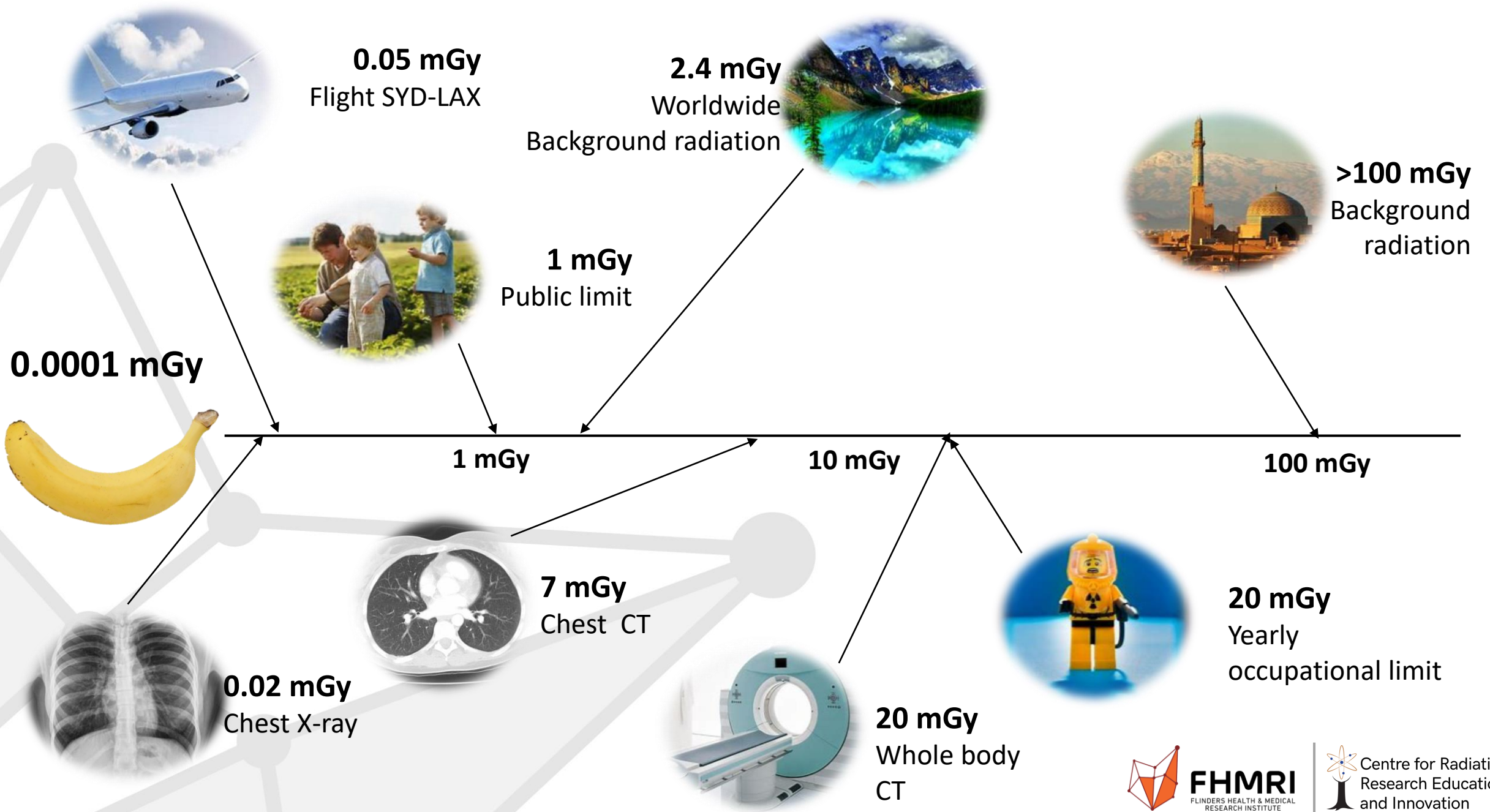
The Lung Lab



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Research Education
and Innovation



0.0001 mGy



0.05 mGy
Flight SYD-LAX



1 mGy
Public limit



2.4 mGy
Worldwide
Background radiation

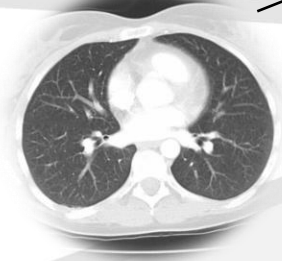


1 mGy

10 mGy

100 mGy

7 mGy
Chest CT



0.02 mGy
Chest X-ray



20 mGy
Whole body
CT

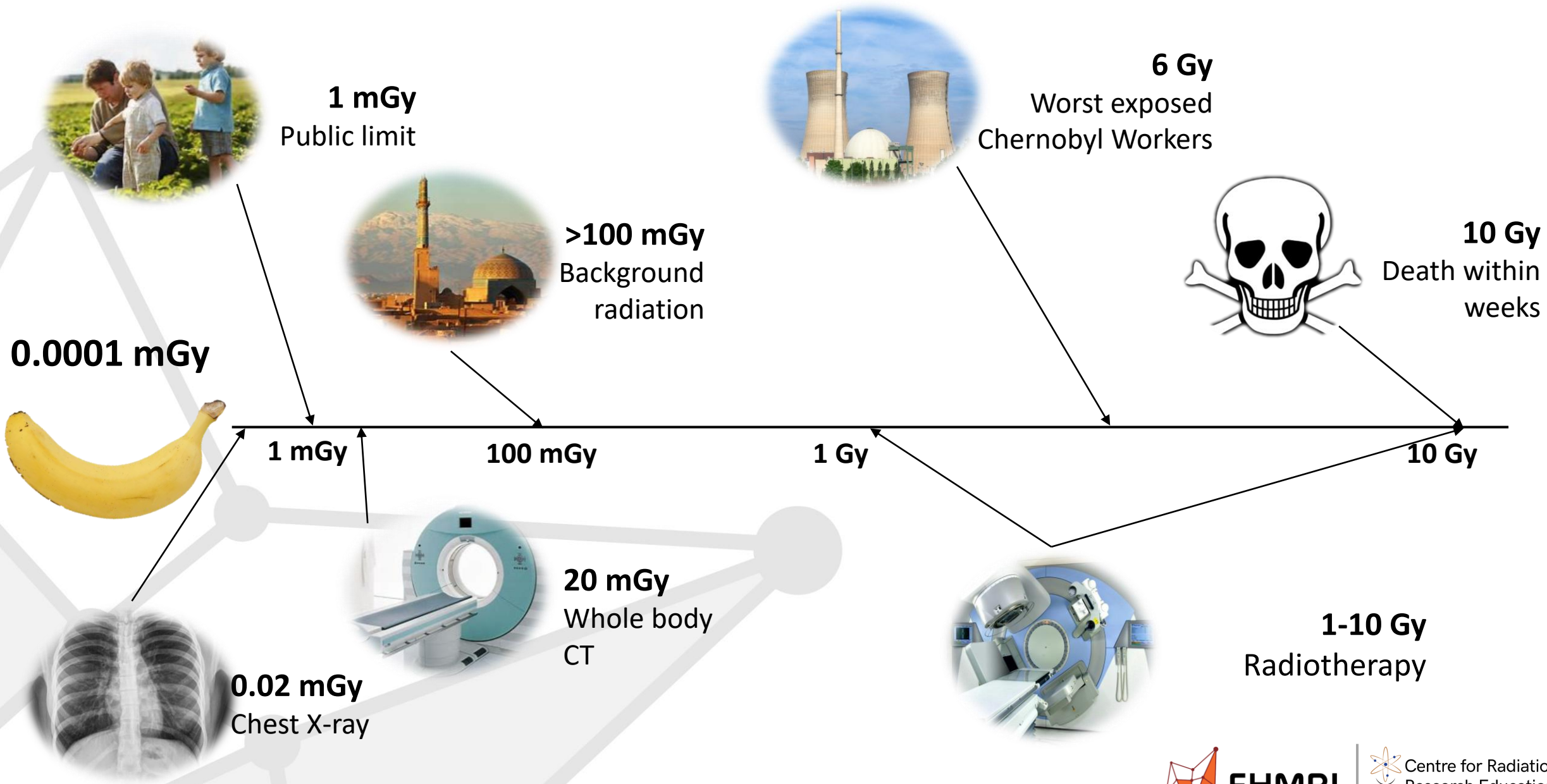


20 mGy
Yearly
occupational limit



>100 mGy
Background
radiation





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Low Dose Radiation Therapy - LDTR

100 mGy

1 Gy

Historic Low Dose Radiation Therapy

- Historically used to treat range of inflammatory diseases from turn of 20th century
 - gas gangrene, carbuncles, sinusitis, and arthritis
- In 1905, first trialled for respiratory inflammation
 - >1920 treatment for pneumonia and asthma

Table 1

X-ray therapy in the treatment of pneumonia.

Reference	Types of Pneumonia	Case Number	Cases Cured
Musser and Edsall [14]	Unresolved pneumonia	1	1
Edsall and Pemberton [37]	Unresolved pneumonia	2	2
Quimby and Quimby [15]	Unresolved pneumonia	12	11
Krost [20]	Unresolved pneumonia	12	11
Fried [72]	Post-operative pneumonia	40	32
Fried [73]	Post-operative pneumonia	57	N/A
Merritt and McPeak [22]	Unresolved pneumonia	7	6
Powell [3,28,33]	Lobar pneumonia and bronchopneumonia	231	215
Scott [24]	Lobar pneumonia	138	111
Solis-Cohen and Levine [25]	Lobar pneumonia	42	40
Settle [26]	Lobar pneumonia	34	32
Rousseau et al. [27]	Lobar pneumonia	104	98
Rousseau et al. [27]	Viral pneumonia	29	22
Correll and Cowan [34]	Acute atypical pneumonia (not pneumococcal)	23	22
Correll and Cowan, 1943	Unresolved pneumonia	9	7
Oppenheimer [32]	Interstitial pneumonia (children)	36	33
Oppenheimer [35]	Virus pneumonia	56	45
Torbett, 1936 (see Abstract of Discussion in Powell [3])	N/A	30	29
Total		863	717

Historic Low Dose Radiation Therapy

- Reduction in symptoms 12-24hrs
 - Fever
 - Painful/laboured breathing
 - Dyspnoea
 - General improvement
- Overall improvement by 48hrs

Table 1

X-ray therapy in the treatment of pneumonia.

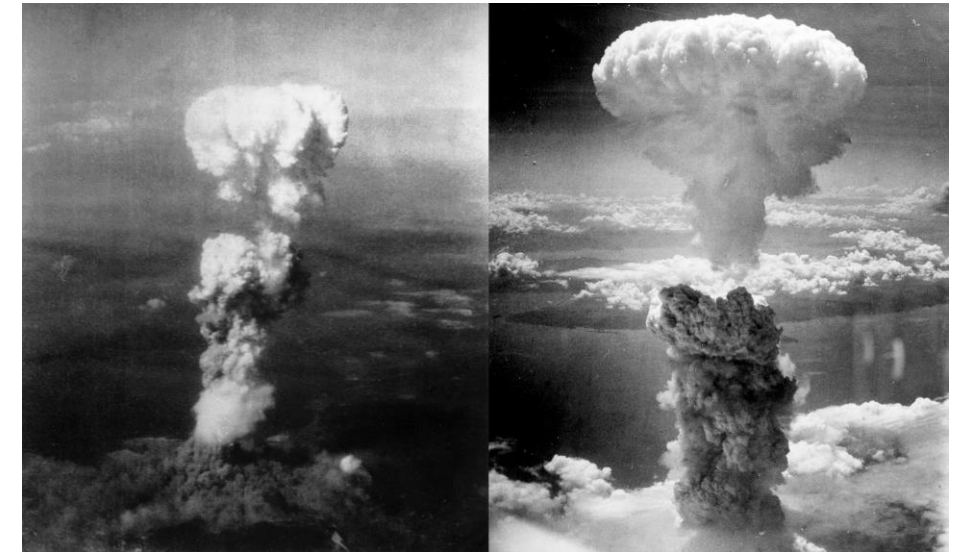
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Historic Low Dose Radiation Therapy

- Although not widely accepted, it was a common therapeutic option up to 1940's
- Rise in sulfonamides and other antibiotics (penicillin)
- Dropping of the atomic bomb in WWII



<https://www.news-medical.net/health/Penicillin-Developments.aspx>



https://en.wikipedia.org/wiki/Atomic_bombings_of_Hiroshima_and_Nagasaki#/media/File:Atomic_bombing_of_Japan.jpg

Calabrese and Dhawan, 2013, Yale J Biol Med; Musser and Edsall, 1905, Tr A Am Physicians; Rousseau et al, 1943, Radiology



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Current Low Dose Radiation Therapy

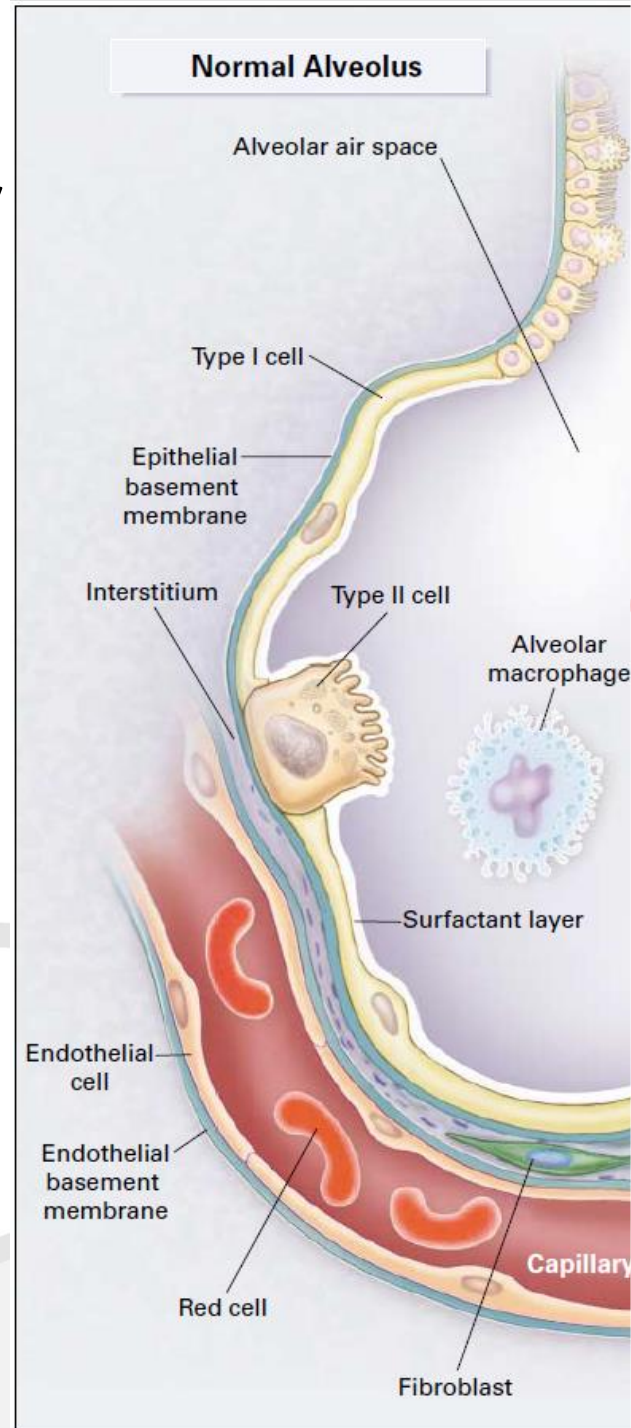
- Current use is limited
 - Primarily used in Germany for degenerative or chronic inflammatory disorders
 - Tendonitis, eczema, arthritis etc.
- Dormant treatment option for respiratory inflammation, until now

Royo et al, 2020, Rep Pract Onco Radiother

Trial details	Patients, No.	Age, y	Requiring O ₂ supplementation?	Whole-lung radiation dose	Outcome metric
RESCUE 1-19 (Emory)	10	≥18	Yes	150 cGy	Safety Clinical recovery
Imam Hossein Hospital (Iran)	5	>60	Yes	50 cGy (+ optional 50 cGy)	SaO ₂ Length of hospital/ICU stay
COLOR-19 (Italy)	30	≥50	Yes	70 cGy	Length of hospital stay Clinical recovery
VENTED (Ohio State University)	24	≥18	Yes (ventilated)	80 cGy	30-d mortality
All India Institute trial	10	≥18	No (but NEWS ≥ 5)	70 cGy	Symptom improvement (NEWS), 30-d ICU admission rate and mortality
Hospital La Milagrosa (Spain)	15	>18	Yes	80 Cgy	Oxygen therapy deescalation SaO ₂

^aCOVID-19 = coronavirus disease-2019; ICU = intensive care unit; LDRT = low-dose radiation therapy; NEWS = National Early Warning Score; SaO₂ = oxygen saturation.

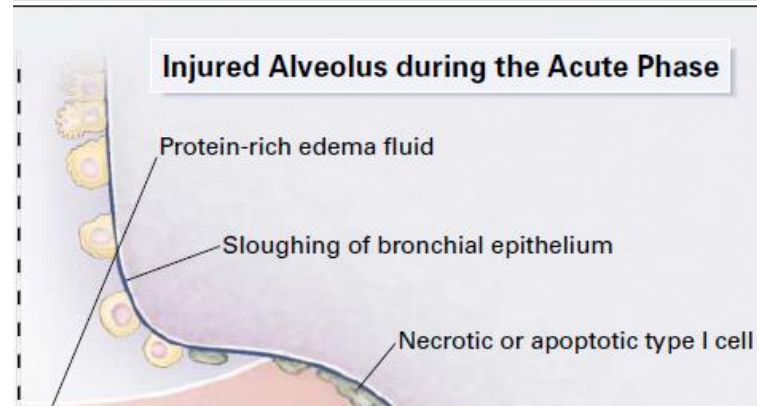
Pathology



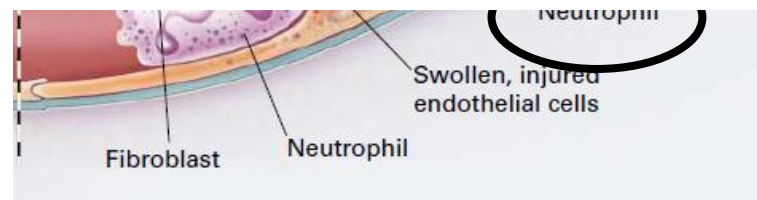
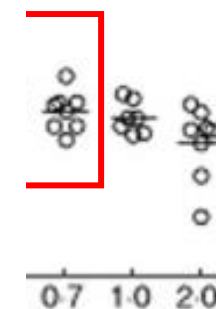
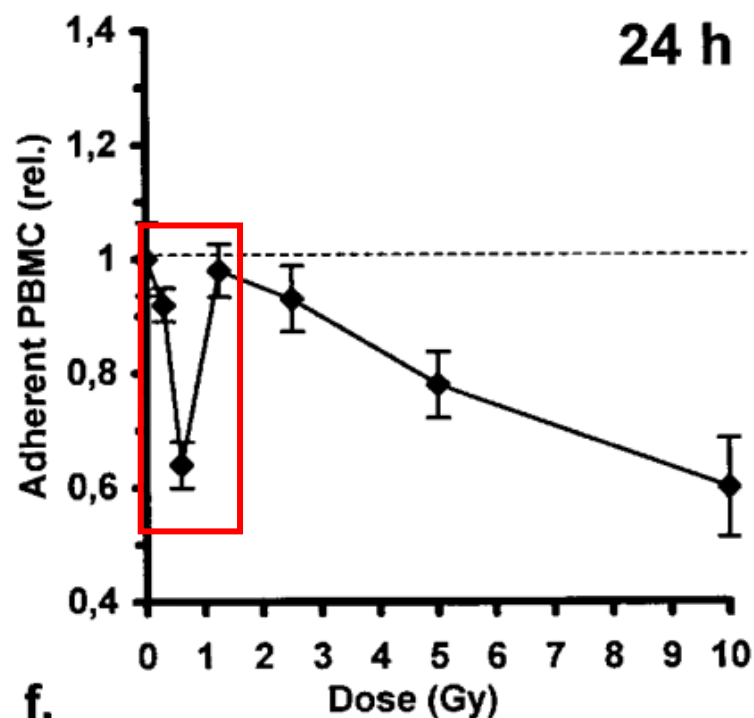
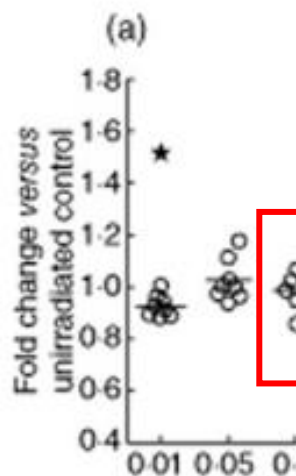
Ware and Matthay, 2000,
N Eng J Med

Response to LDRT

- In both *in vitro* and *in vivo* models
- Change from M1 > M2
 - ↓ IL-1b, TNF- α
 - ↑ IL-6, IL-10, TGF- β
- Downregulation of adh molecules
 - ↓ P-selectin, L-selectin
 - ↓ leukocyte migration
- Leads to overall reduced inflammation and improved respiratory function



Ware and Matthay, 2000, *N Eng J Med*; Frischholz et al, 2013, *AutoImm*; Wunderlich et al, 2015, *Clin Exp Immunol*; Kern et al, 2000, *Radiother Oncol*; Hilderbrant et al, 2002, *Int J Radiat Biol*; Roedel et al, 2002, *Int J Radiot Biol*; Rodel et al, 2004 *Strahlentherapie und onkol*; 2008, *Radiother Oncol*; Rodel et al, 2006, *Int Biol Phys*.



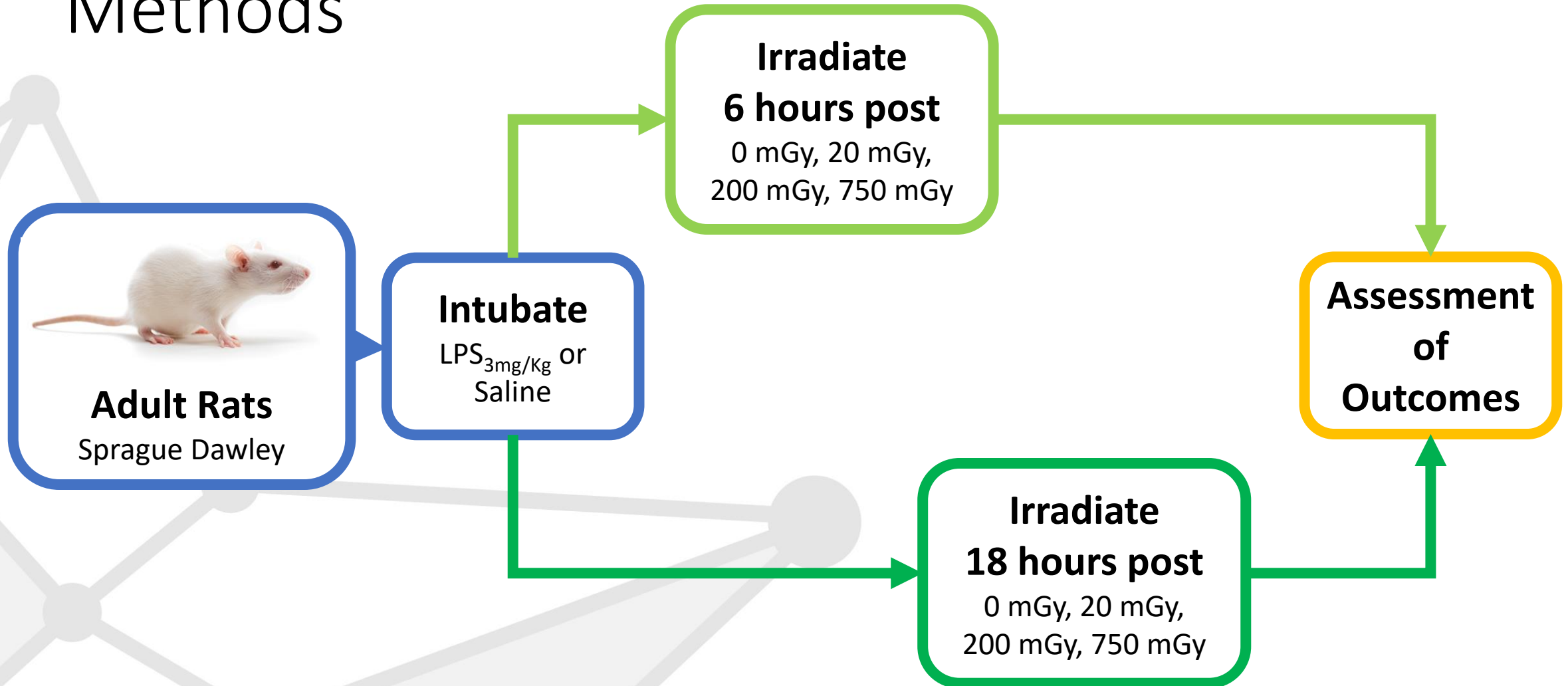
Aim:

To investigate the efficacy of a single dose of low-moderate X-irradiation in immunomodulating the effects of acute respiratory inflammation at 6 and 18-hours post LPS-insult

Hypothesis:

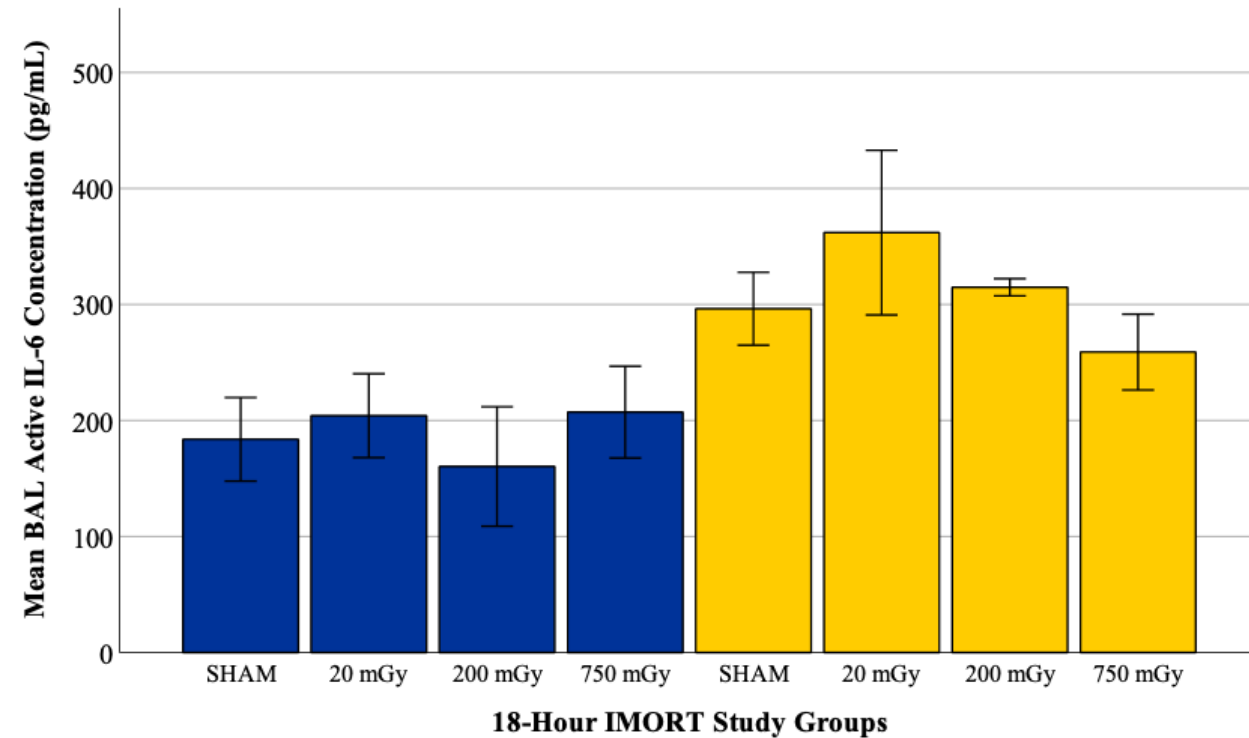
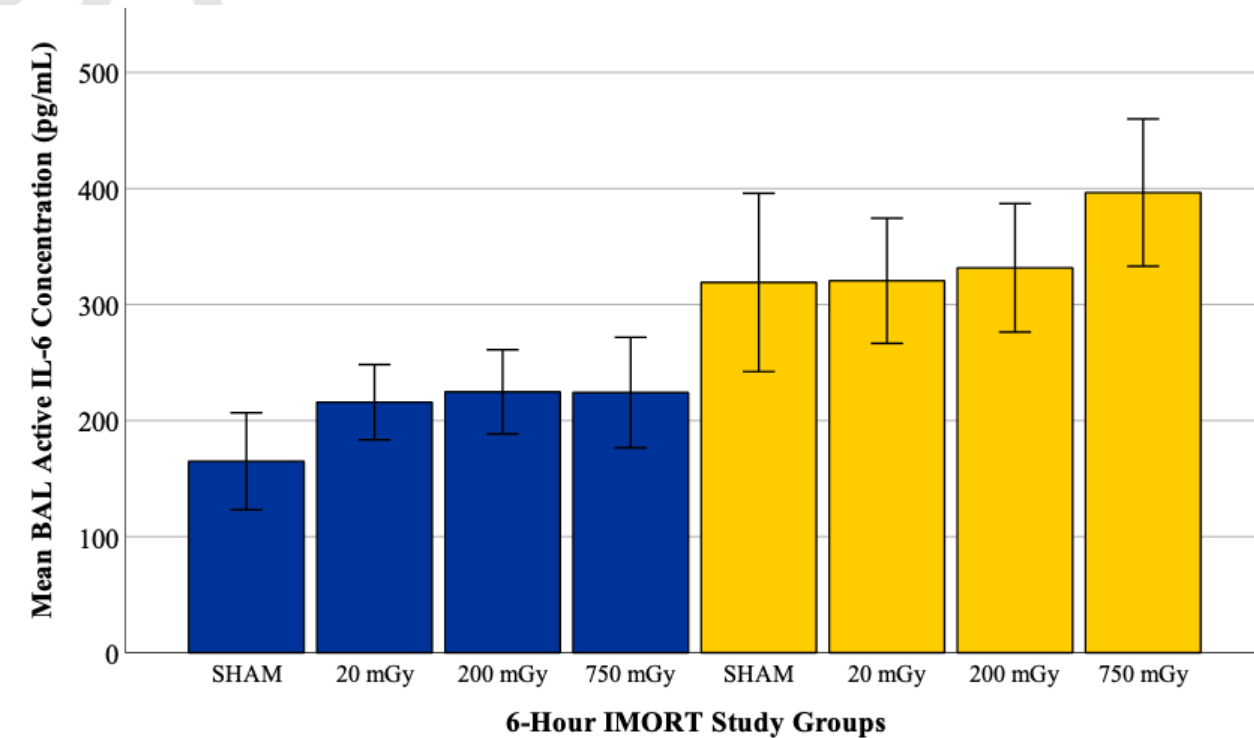
A single dose of X-irradiation will have a dose-dependent immunomodulatory effect on LPS-induced acute respiratory inflammation.

Methods



Cytokine Concentration

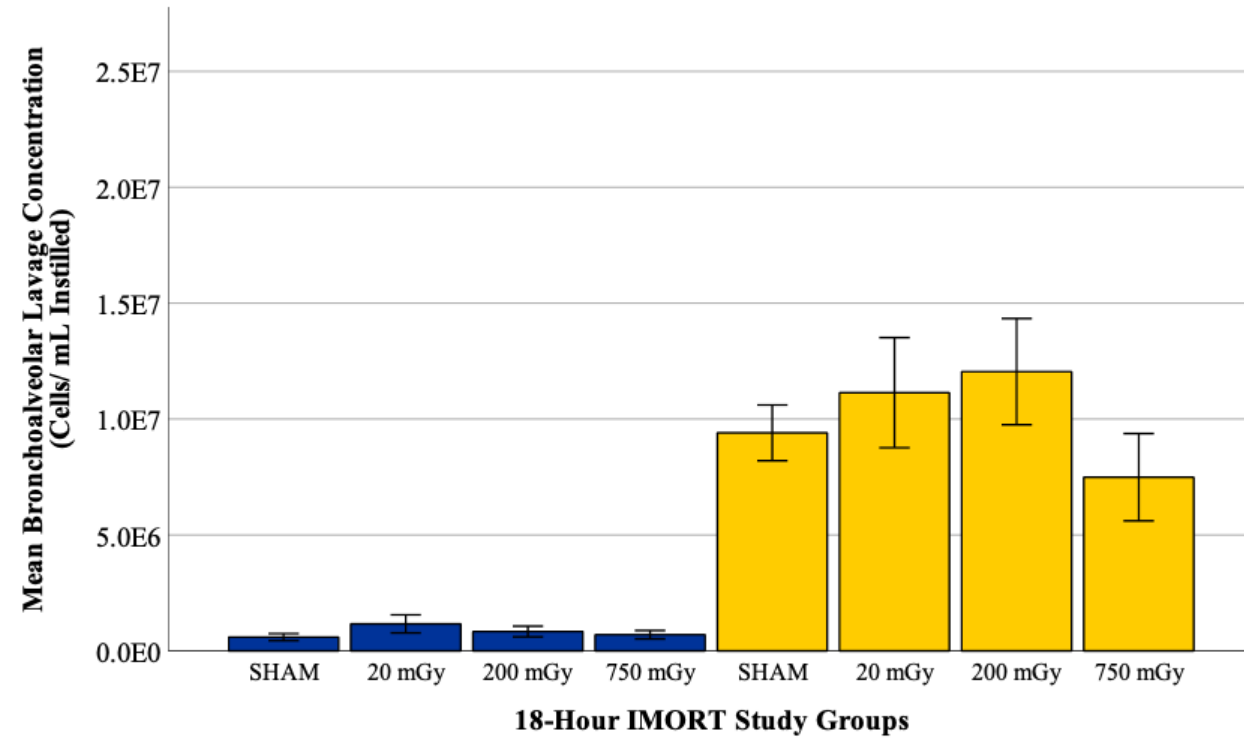
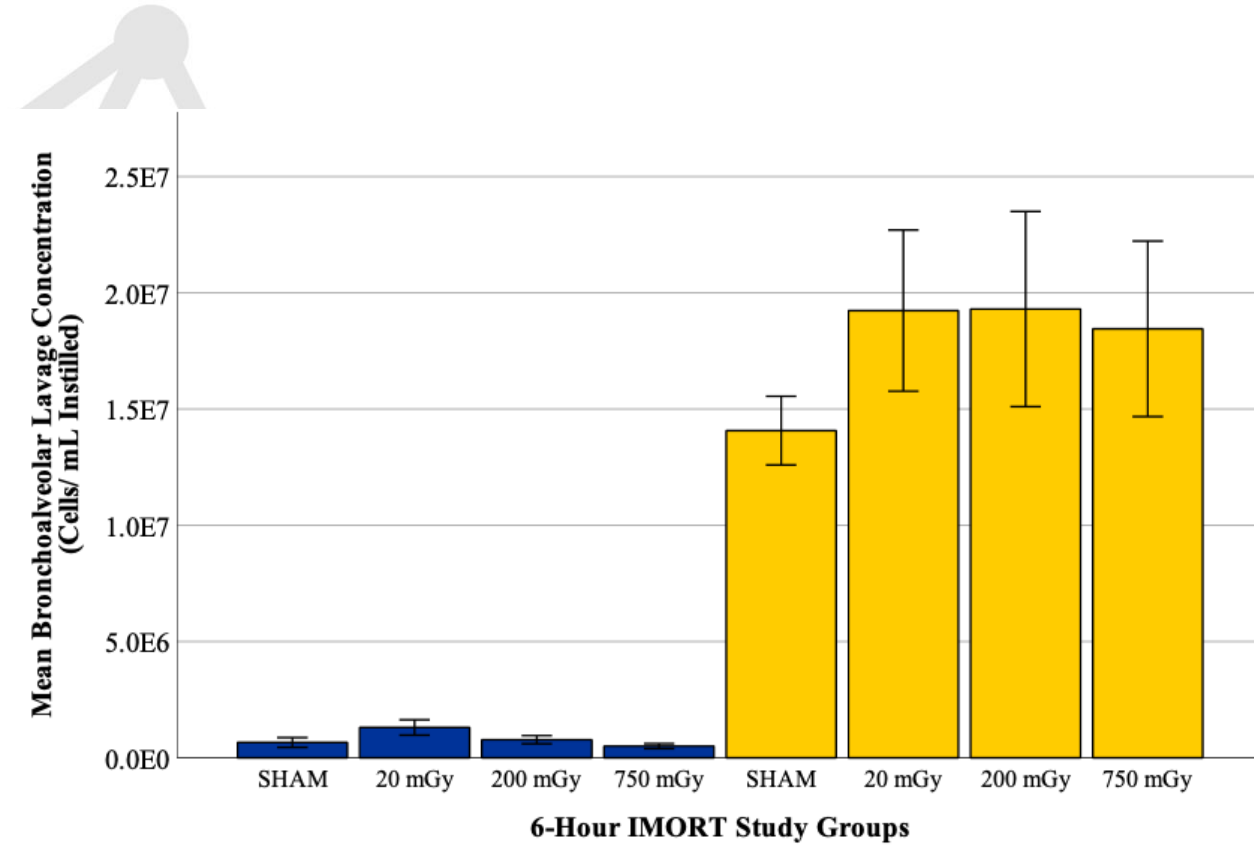
Stimuli
LPS
Saline



Data represented as mean \pm 1SE (n=4-6)

Cellular Infiltration

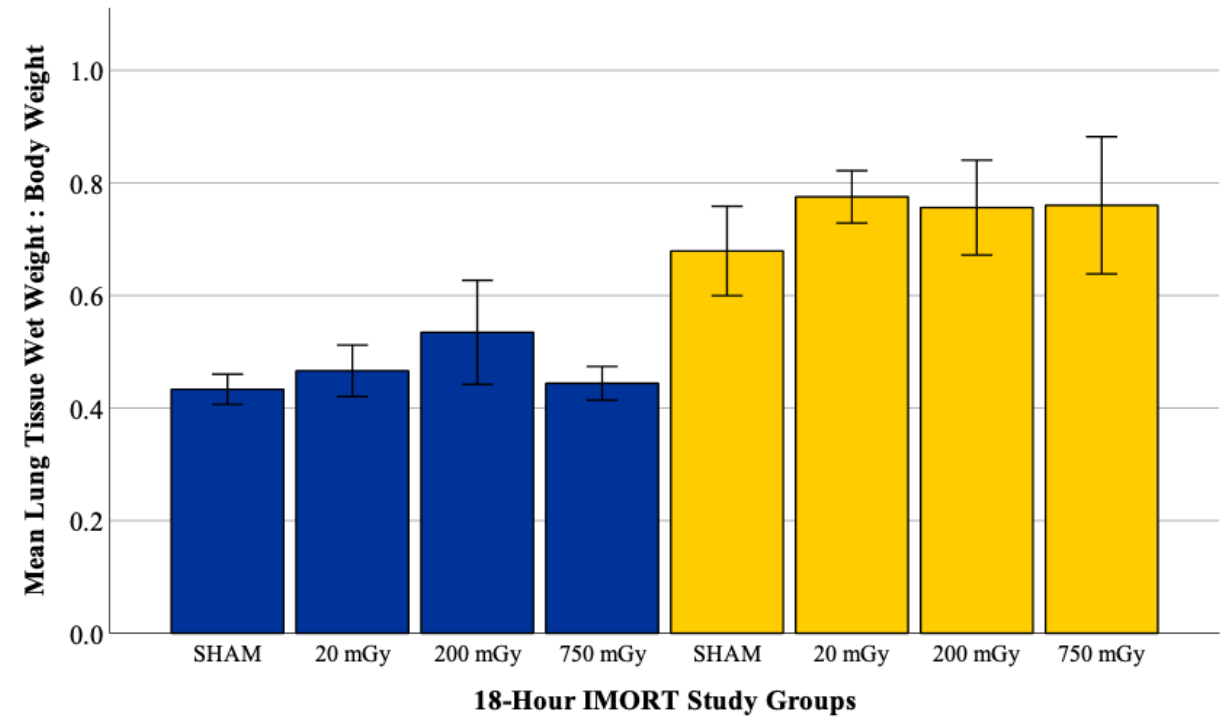
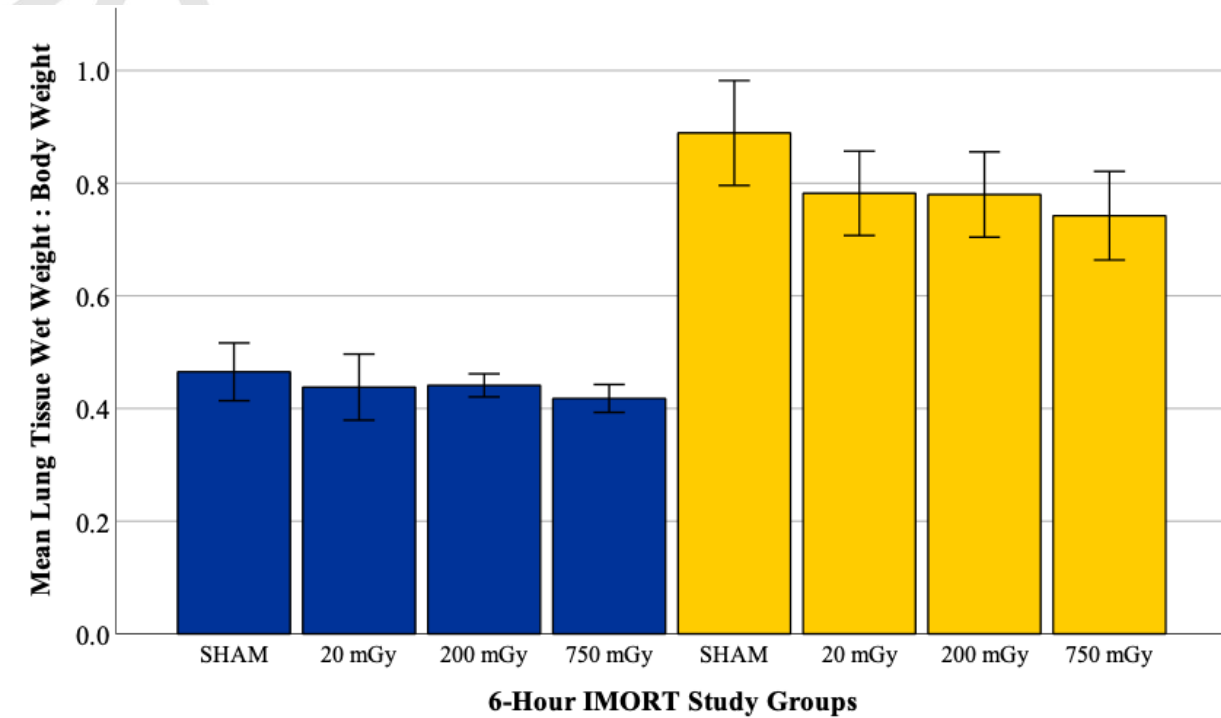
Stimuli
LPS
Saline



Data represented as mean \pm 1SE (n=4-6)

Pulmonary Oedema

Stimuli
LPS
Saline



Data represented as mean \pm 1SE (n=4-6)

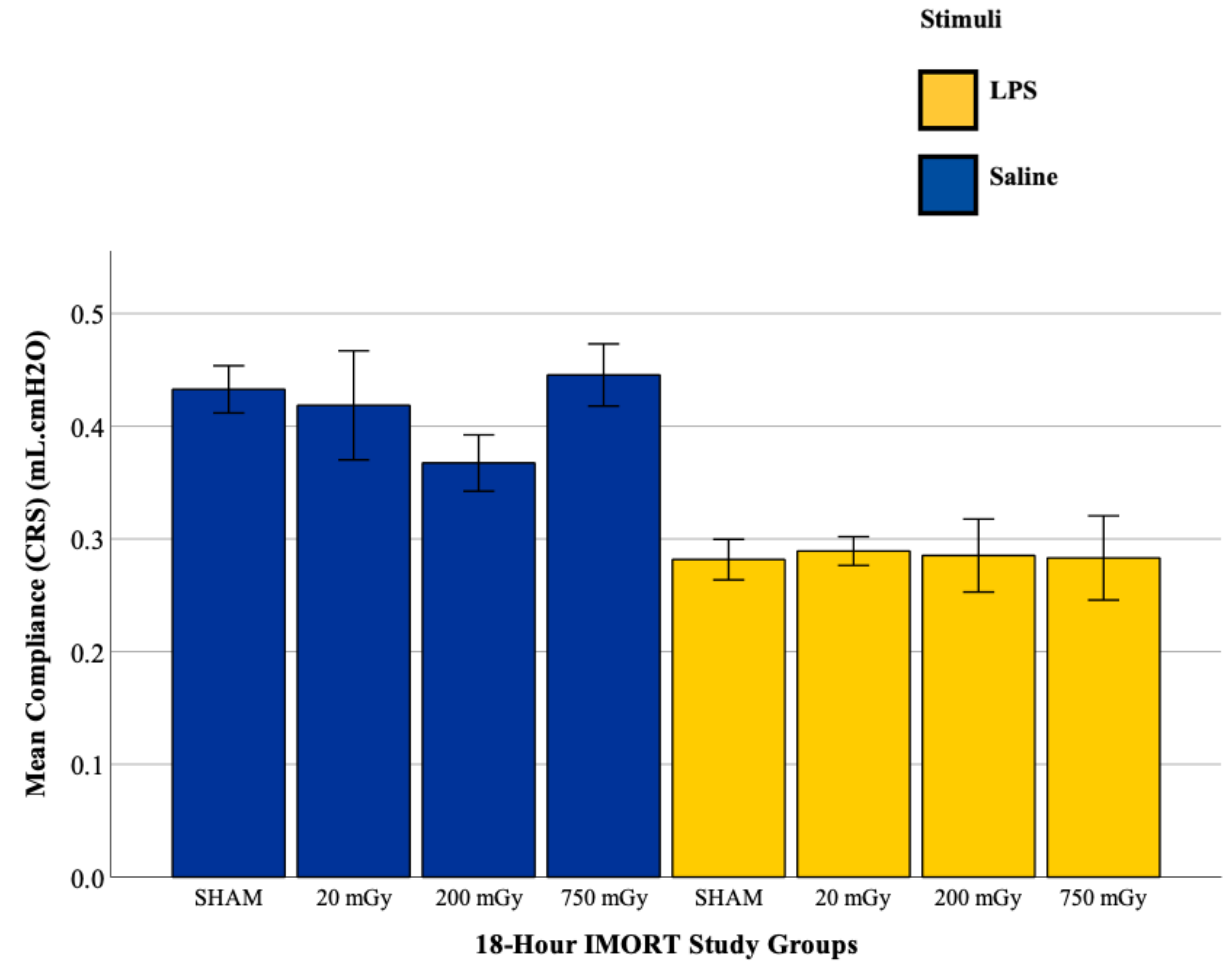
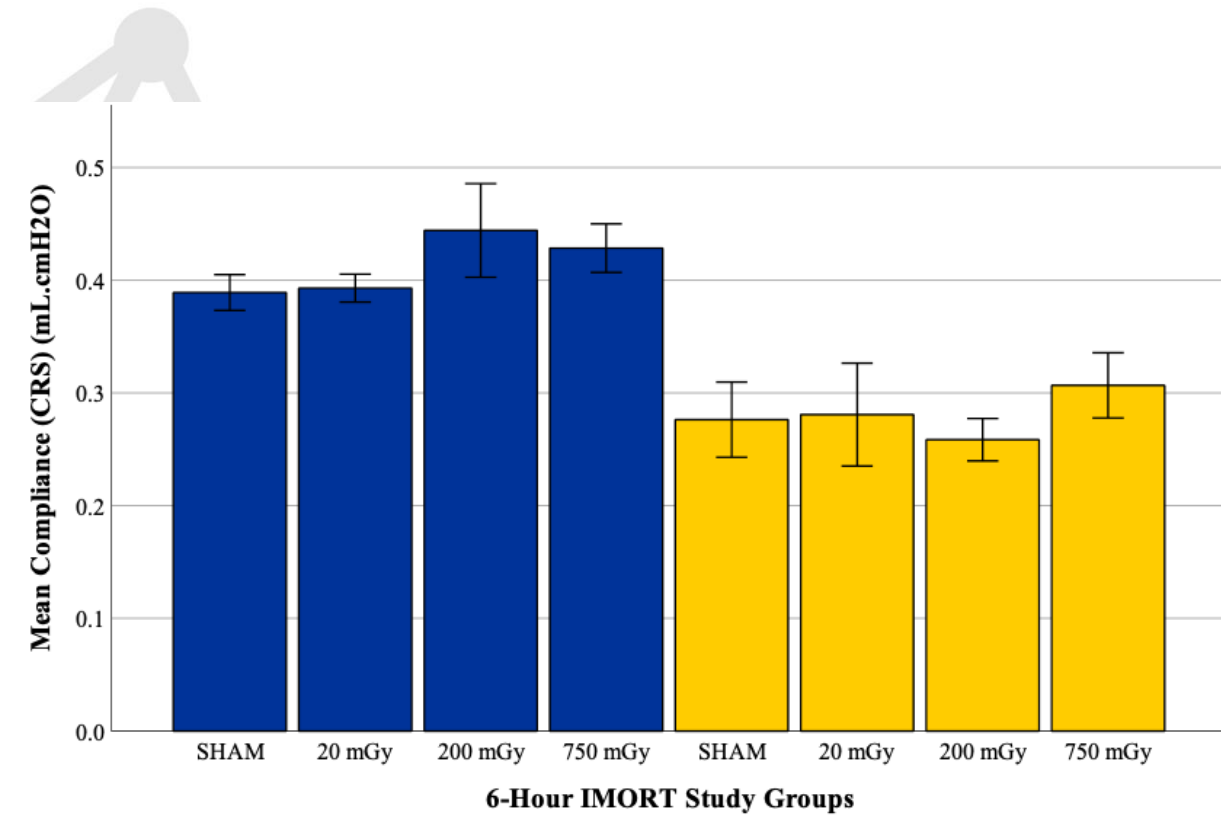


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Respiratory Function



Data represented as mean \pm 1SE (n=4-6)

Conclusion

- Rat Model of LPS induced Acute Lung injury was successful but Model of immunomodulation was unsuccessful
- Limitations
 - Non-replicating infection model
 - Single dose of ionising radiation at a single timepoint

Acknowledgements

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CRREI

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