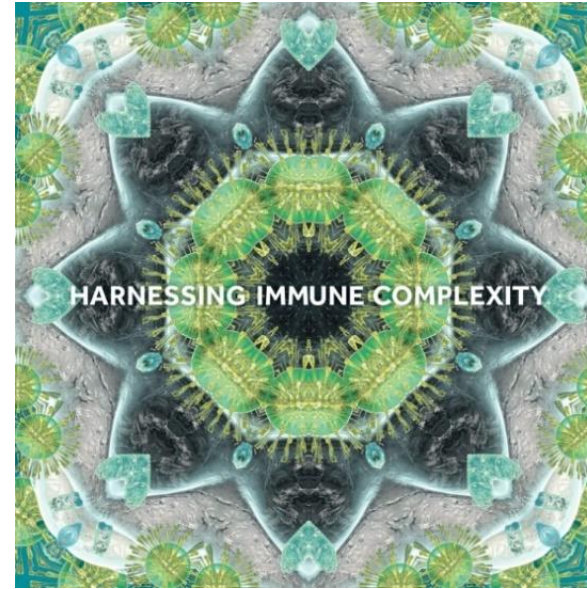


# The Lydia Becker Institute of Immunology and Inflammation



**Mark Travis**

**Head of Division for Immunology, Immunity to Infection,  
& Respiratory Medicine**

**CLARA-Shanghai-Manchester Joint Symposium**

**7th November 2024**

# Lydia Becker Institute of Immunology and Inflammation



Faculty of Biology Medicine  
and Health

Faculty of Science and  
Engineering

Faculty of Humanities

School of Biological  
Sciences

School of Medical  
Sciences

School of Health  
Sciences

Immunology,  
Immunity to  
Infection and  
Respiratory  
Medicine

Neuroscience

Cancer Sciences

Medical Education

Psychology and  
Mental Health

Population Health,  
Health Services  
Research and  
Primary Care

Musculoskeletal  
and Dermatological  
Sciences

Molecular and  
Cellular Function

Diabetes,  
Endocrinology and  
Gastroenterology

Developmental  
Biology and  
Medicine

Pharmacy and  
Optometry

Nursing, Midwifery  
and Social Work

Evolution, Infection  
and Genomics

Matrix Biology and  
Regenerative  
Medicine

Dentistry

Cardiovascular  
Sciences

Informatics,  
Imaging and Data  
Sciences

Psychology,  
Communication  
and Human  
Neuroscience

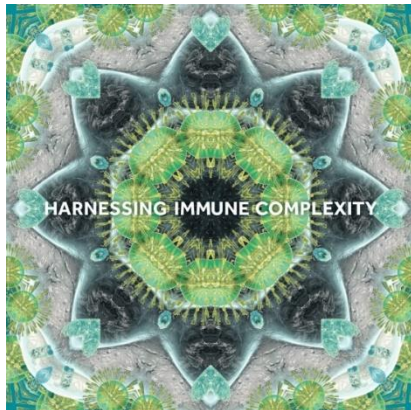
# The Lydia Becker Institute of Immunology and Inflammation



- ❖ Renowned botanist and astronomer from Manchester
- ❖ Major leader of women's suffragette movement



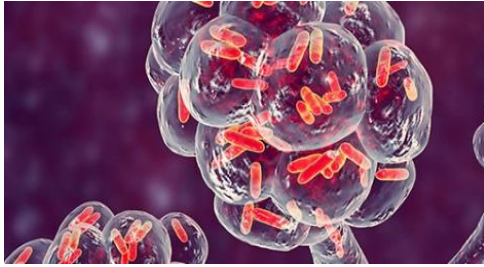
**Director:**  
Prof. Tracy Hussell



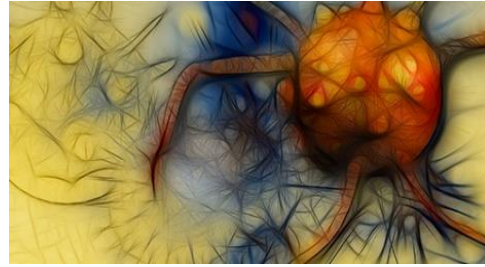
## **Harnessing immune complexity**

*“unite basic, translational, and clinical research to address the complex and ever-increasing role immunology plays in modern medicine”*

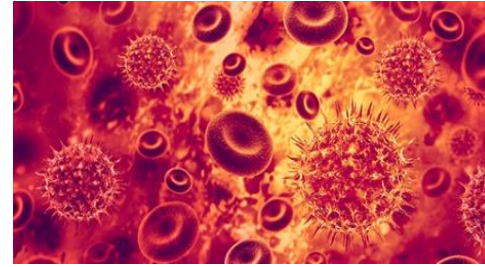
# The Lydia Becker Institute covers many areas of immunology



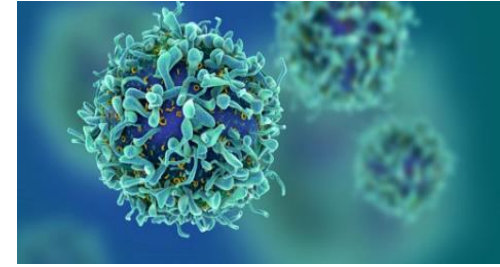
**Barrier Immunology**  
Joanne Konkel



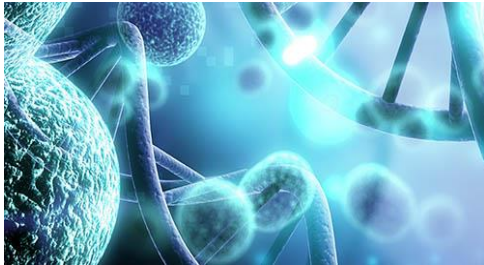
**Cancer Immunology**  
Santiago Zelenay



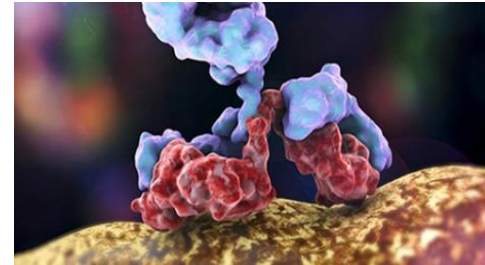
**Cardiovascular and multi - morbidity**  
Ashraf Kitmitto



**Cellular Immunology**  
Gloria Lopez-Castejon



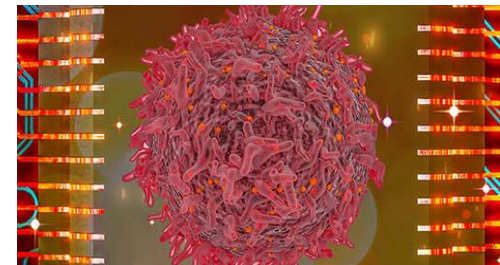
**Eco- and context-specific immunology**  
Kathryn Else



**Immune tolerance**  
Matthew Hepworth



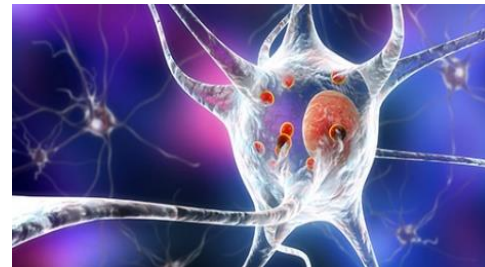
**Immunomatrix**  
Judi Allen



**Immunoinformatics**  
Andy Brass



**Life course Immunology**  
Peter Arkwright



**Neuro-immunology**  
Kevin Couper



**Pathogens, Parasites and Commensals**  
Richard Grencis

# Current immunology research priorities and strengths in Manchester

**Major overarching strength in tissue immunity**

**Pre-clinical models to understand basic mechanisms in health and disease**



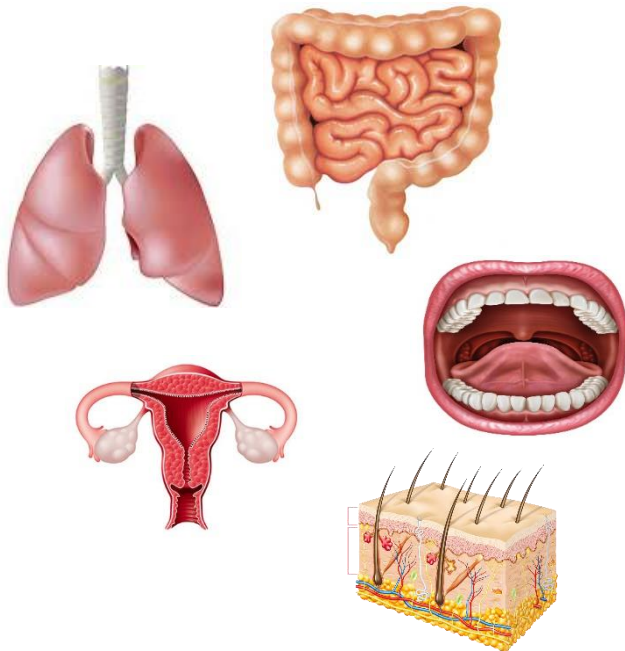
**Human patient samples to understand changes in immune system in disease**



# Current immunology research priorities and strengths in Manchester

## Three highlight themes

### Barrier Immunity



### Type 2 Immunity



### Neuroimmunology

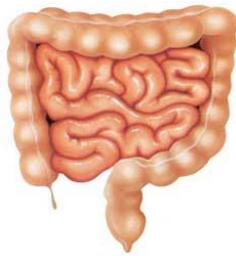


# Current immunology research priorities and strengths in Manchester

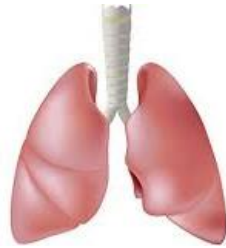
## Barrier Immunity



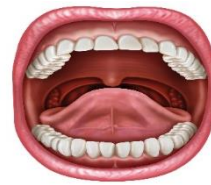
### Major strengths in understanding immune regulation in different barrier tissues in health and disease



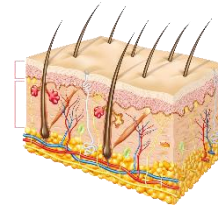
Mark Travis  
Richard Grecis  
Kathryn Else  
John Grainger  
Matthew Hepworth  
Dave Thornton  
Sheena Cruickshank  
Lizzie Mann  
↓  
Inflammatory bowel disease  
Intestinal infections



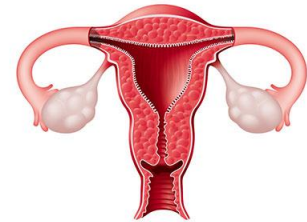
Madhvi Menon  
Sean Knight  
Judi Allen  
Tracy Hussell  
Dave Thornton  
Mark Travis  
Matt Hepworth  
Lizzie Mann  
↓  
COPD  
Lung cancer  
Lung infections



Joanne Konkell  
↓  
Periodontitis



Silvia Bulfone-Paus  
Joanne Pennock  
↓  
Allergy  
Atopic dermatitis



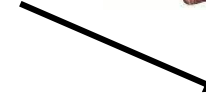
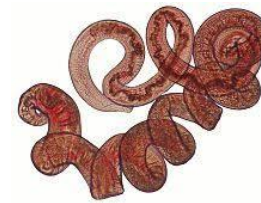
Lizzie Mann  
↓  
Infertility

# Current immunology research priorities and strengths in Manchester

## Type 2 immunity



Major strengths in immunity to helminth infections



### Intestinal infections

Richard Grencis

Kathryn Else

Sheena Cruickshank

Dave Thornton

### Lung and pleural cavity infections

Judi Allen

Also big clinical medicine interest in asthma



# Current immunology research priorities and strengths in Manchester



## Neuroimmunology

### Brain inflammation in stroke

Gloria Lopez-Castejon  
John Grainger  
Dave Brough  
Stuart Allan  
Matt Hepworth  
Craig Smith

### Immunity in traumatic brain injury and concussion

Andy Greenhalgh

### Immune response to brain infection

Kevin Couper

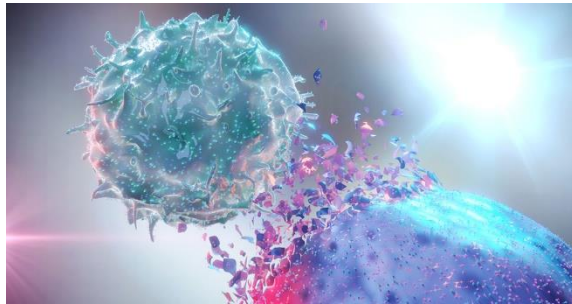
### Immunity in brain tumours/radiotherapy

Kevin Couper  
Doug Dyer

**Major links with the Geoffrey Jefferson Brain  
Research Centre**

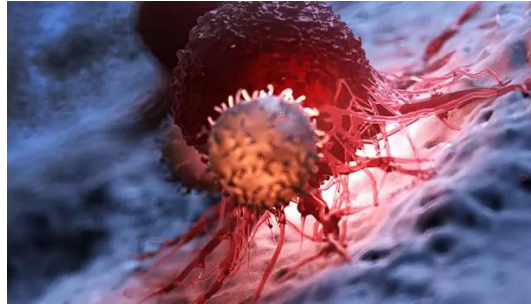


# Current immunology research priorities and strengths in Manchester



## Cancer immunology

Kevin Couper  
Adam Hurlstone  
Mark Travis  
Doug Dyer  
+ many more



## Immunomatrix

Doug Dyer  
Judi Allen  
Richard Grecnis  
Dave Thornton  
Mark Travis



## Environmental Immunology

Kathryn Else  
Sheena Cruickshank

# Current immunology research priorities and strengths in Manchester

Type 2 ↔ Barrier ↔ Neuroimmunology

**Broad interest in how microbiota  
interacts and regulates with all these  
systems**

Doug Dyer

Dave Thornton

Mark Travis

MANCHESTER  
1824



Lydia Becker  
Institute  
Immunology and  
Inflammation



CANCER  
RESEARCH  
UK

RADNET  
MANCHESTER

# Immune Regulation of Intestinal Toxicity Following Radiotherapy

Mark Travis



@TravislabUoM

CLARA-Manchester-Shanghai Symposium

7<sup>th</sup> November 2024



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UK

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MANCHESTER



**Urszula Cytlak-  
Chaudhuri Nabina Pun**



**Tim Illidge**



**Doug Dyer**



**Kaye Williams**

# Radiotherapy in cancer treatment



- Radiotherapy: most effective non-surgical cancer treatment
  - >50% of cancer patients receive radiotherapy
  - >40% of those cured receive RT as part of their treatment

**Healthy tissue damage is a major health problem for patients receiving radiotherapy**



**Severely limits the dose of radiation that can be given**



**Understanding what drives these side-effects may identify therapeutic targets to reduce them**



**Reduce side-effects = increase dose of radiation that can be given  
= increase chance of eliminating tumour**

# **Our focus is on immune-mediated mechanism of bowel damage following radiotherapy**

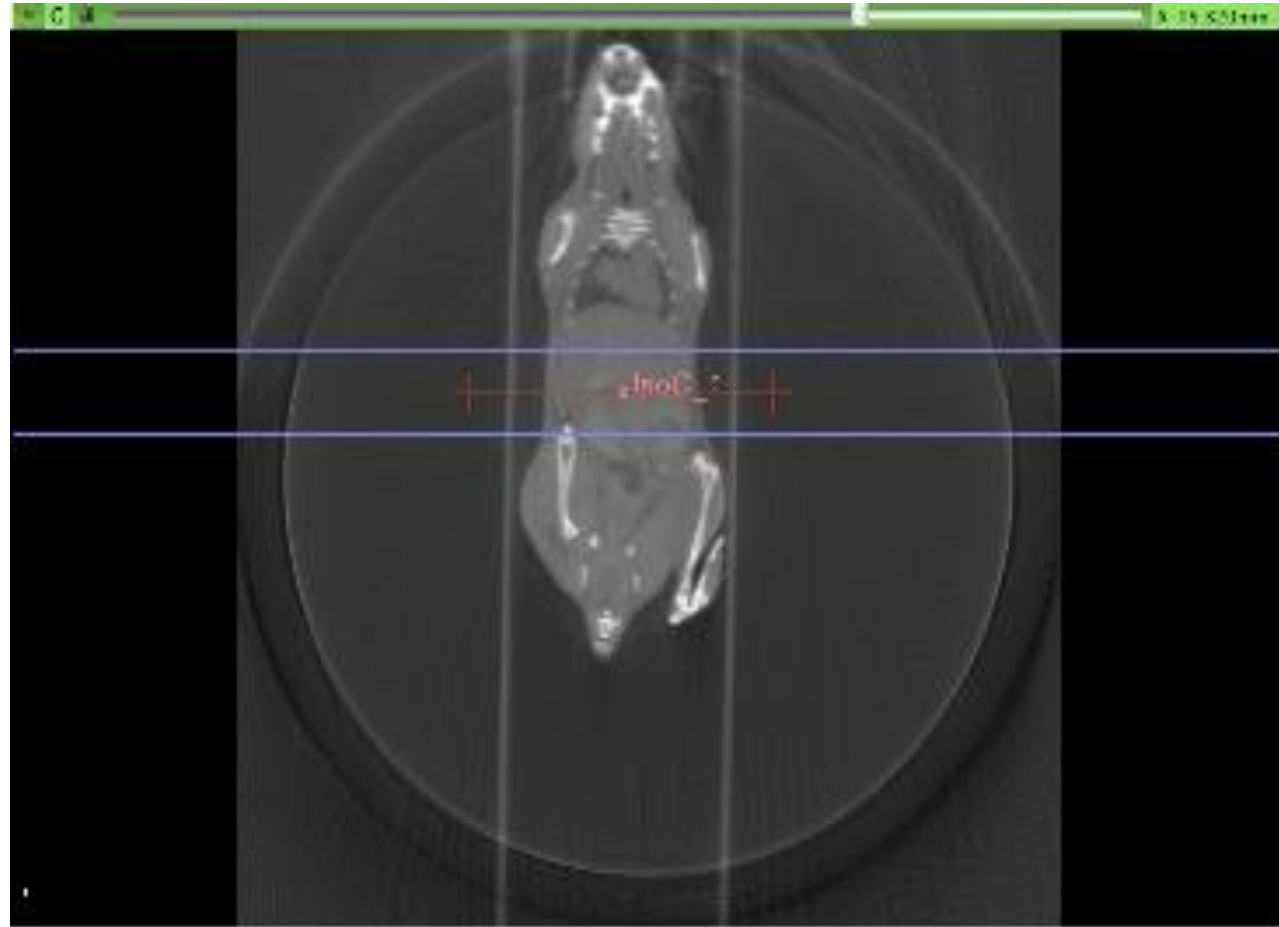
- Pain and discomfort



# Mouse model of radiotherapy-induced damage to the healthy intestine



Small animal radiation  
research platform  
(SARRP)



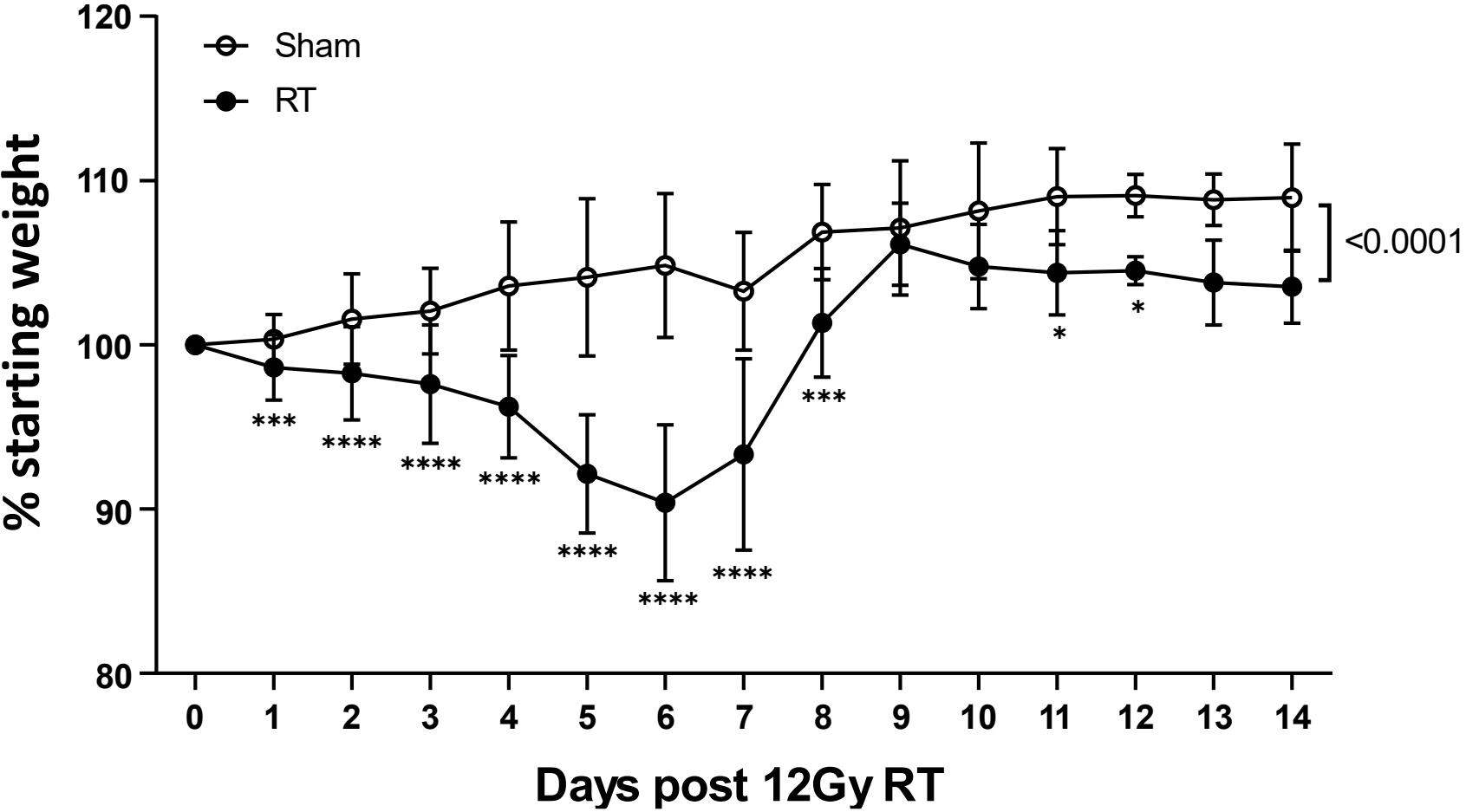
**Used single large radiation dose  
= models Stereotactic Ablative Body  
Radiotherapy (SABR) in clinic**



**Induces DNA damage in the small  
intestine and proximal (not distal) colon**

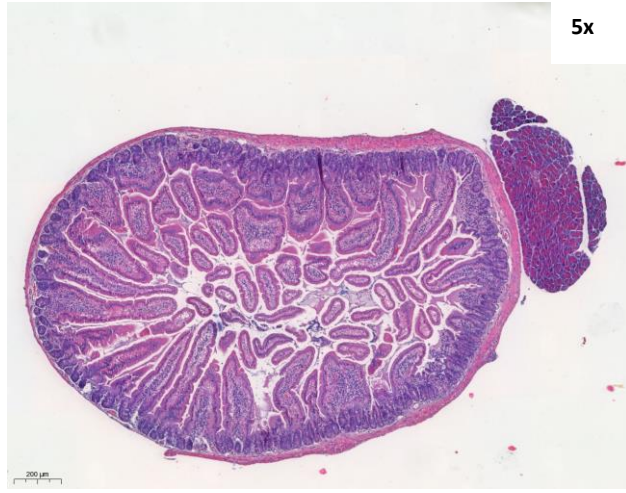
**Does the model induce clinical features of bowel toxicity?**

# Abdominal RT induces transient weight loss in mice

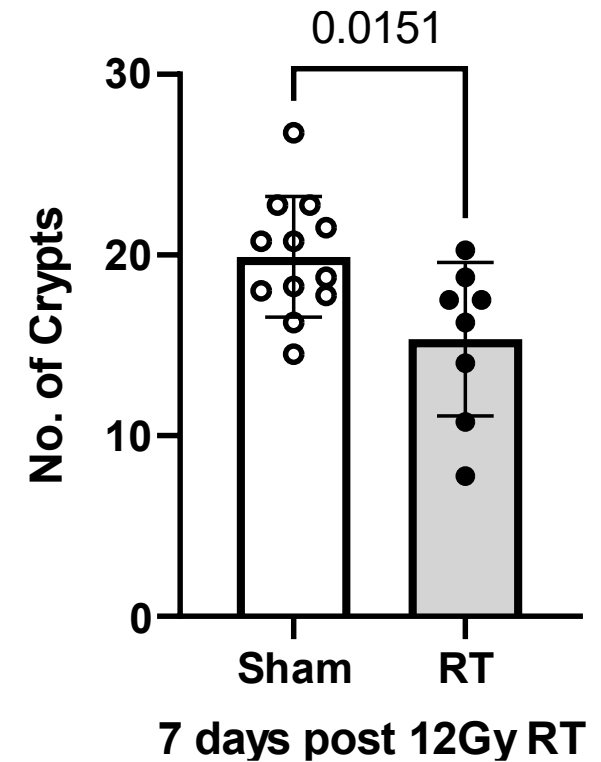
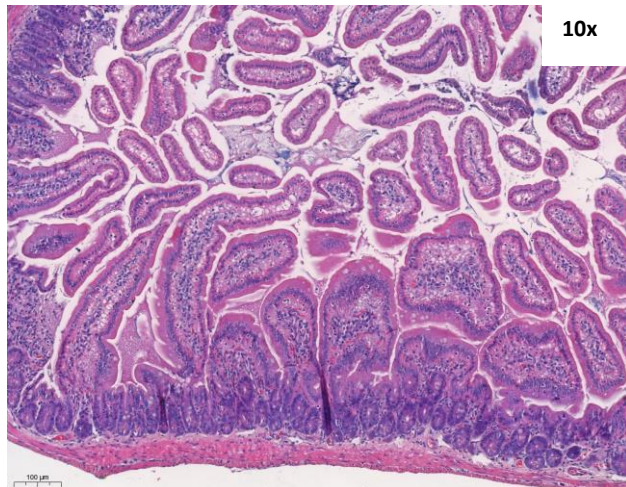


# Abdominal RT induces transient intestinal damage

Sham



RT



# Abdominal RT induces transient intestinal leakiness

**What happens to the immune system  
after abdominal RT?**

# Abdominal RT induces a transient innate immune response in the small intestine

Neutrophils

Eosinophils

**What is driving the innate immune response?**



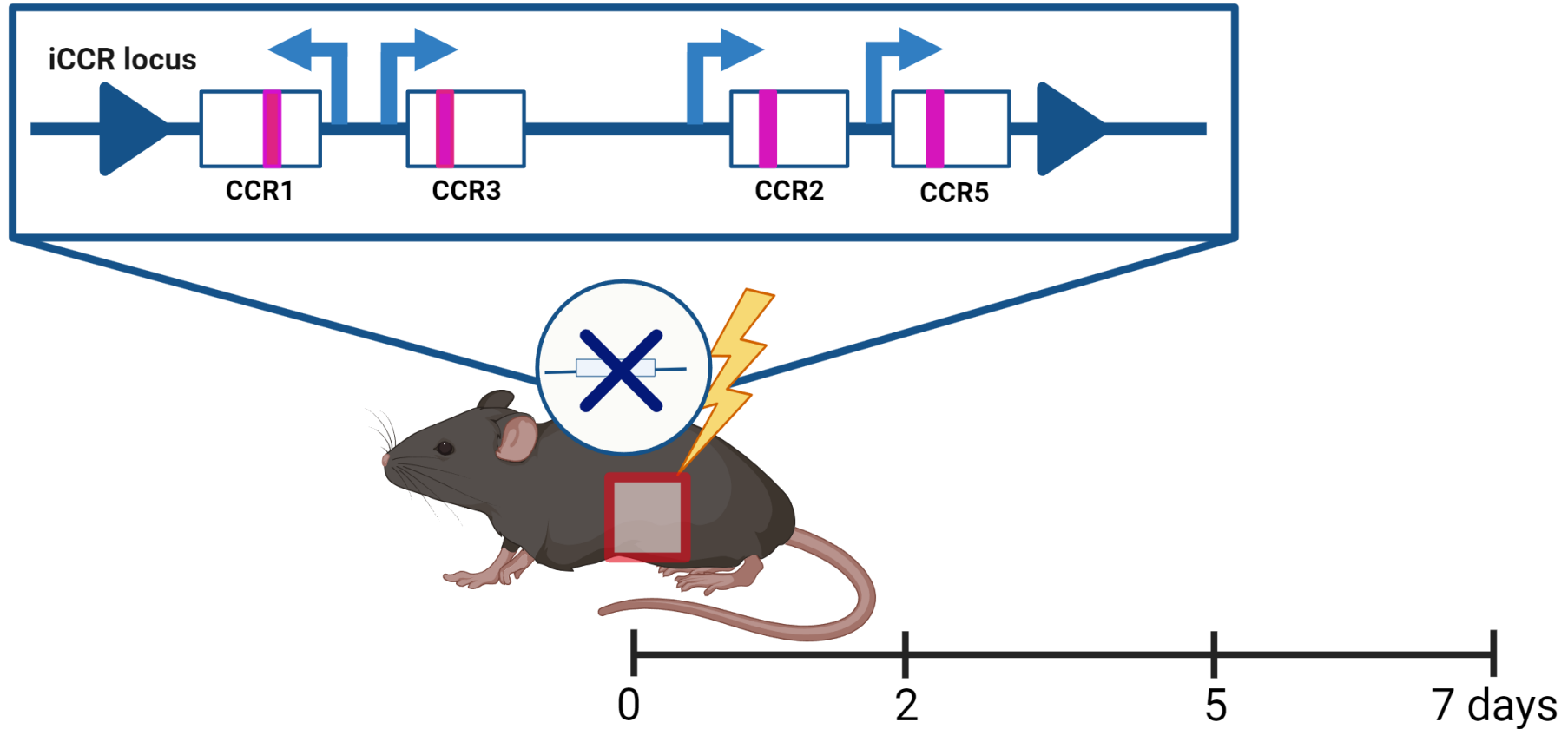
**Upregulation of inflammatory chemokine receptors  
(CCR1, 2, 3, 5)**

**=**

**Are inflammatory chemokine receptors driving the  
innate immune response after RT?**



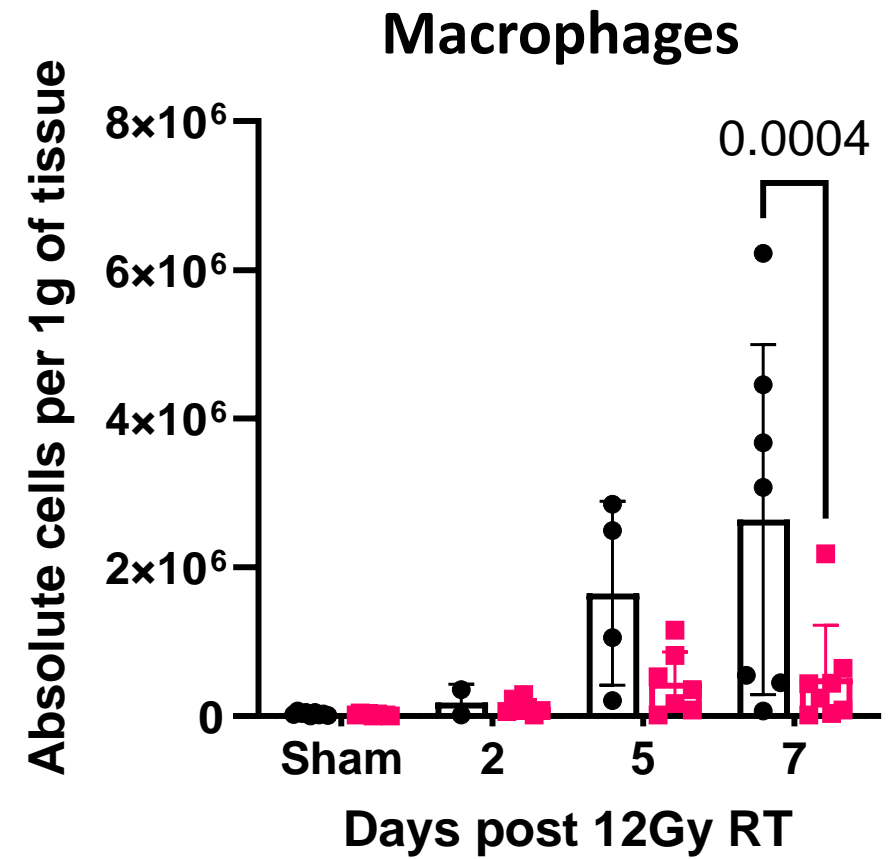
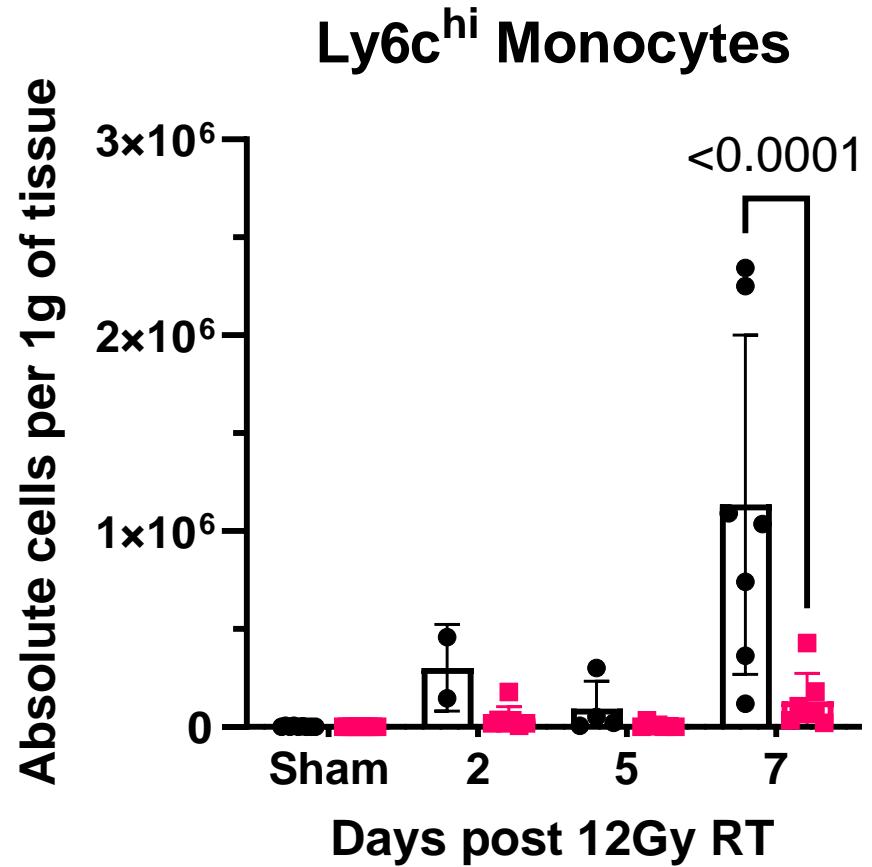
# Determining the role for inflammatory chemokine receptors in the small intestine after RT





# Inflammatory chemokine receptors drive the innate immune response in the small intestine after RT

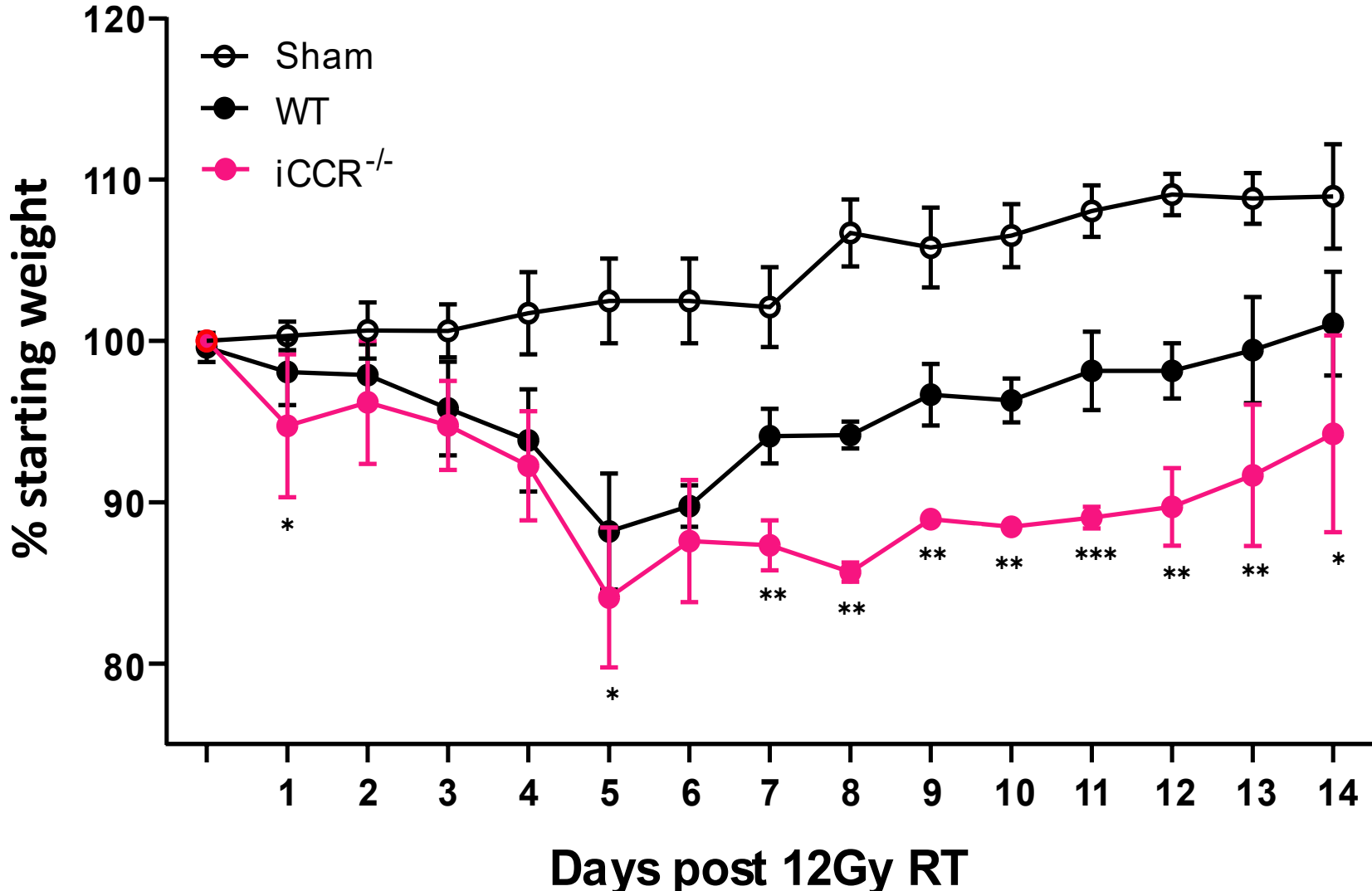
● WT  
■ *iCCR*<sup>-/-</sup>



**Is the inflammatory chemokine-driven  
innate immune response after RT  
important functionally?**

**= Looked at intestinal  
toxicity in iCCR KO mice**

# Inflammatory chemokine receptors are crucial in protecting from intestinal toxicity after RT



# Inflammatory chemokine receptors are crucial in protecting from intestinal toxicity after RT

**Inflammatory chemokine receptor-  
driven innate immune response is  
important in protecting from RT-  
mediated acute bowel toxicity**

0 5 10 15  
Sham WT iCCR<sup>-/-</sup>  
7 days post 12Gy RT

0 5 10 15  
Days post 12Gy RT

**Inflammatory chemokine receptors are crucial in protecting from**

**Which innate immune cell is important in driving protection?**

**How is protection being driven?**



**Focussed on potential role of monocytes/macrophages**

**7 days post 12Gy RT**

**Days post 12Gy RT**

# Model to study the role of monocytes/macrophages in RT-mediated bowel toxicity

**CCR2 KO mice**



**Lack monocytes in  
blood and reduced  
macrophages in  
intestine**

**CCR2 KO mice have reduced monocytes/macrophages in the small intestine after RT but normal eosinophil and neutrophil numbers**

**Does lack of monocytes/macrophages alter RT-mediated bowel toxicity?**

Normalised cells

7 days post 12Gy

7 days post 12Gy

7 days post 12Gy

7 days post 12Gy

**CCR2 KO mice show enhanced weight loss and gut**

**leakiness following abdominal RT**

**Can transferring monocytes into KO mice rescue the enhanced toxicity observed after RT?**



**Transferring monocytes into iCCR KO mice (which lack eosinophil as well as monocyte recruitment) rescues enhanced toxicity observed after RT**

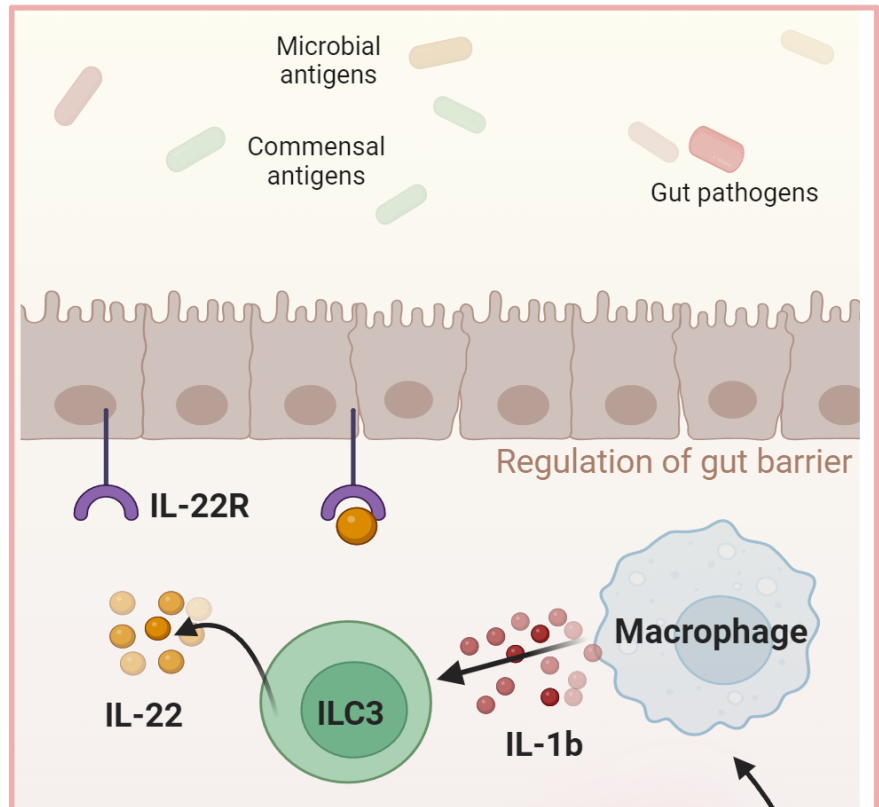
## Transfer of monocytes to CCR2 KO mice rescues enhanced

**What are the mechanisms driving monocyte-driven protection from bowel toxicity after RT?**

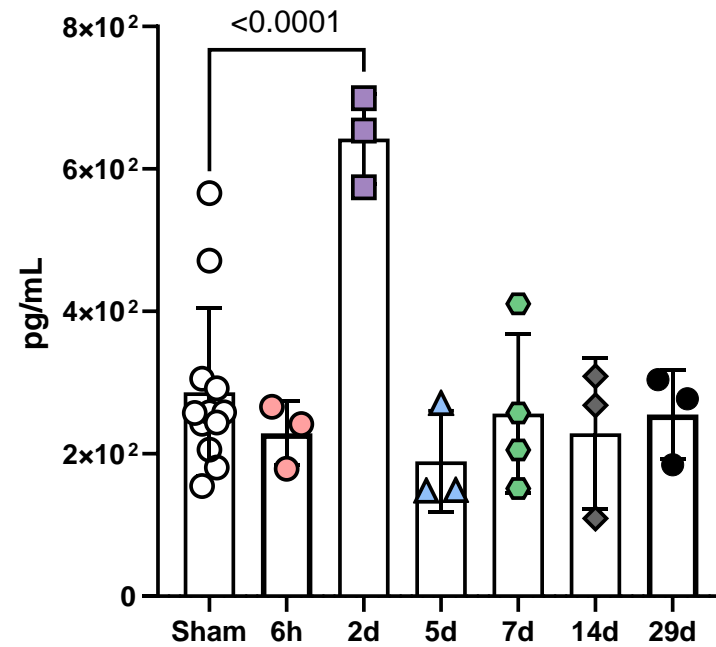
6

7 days post 12Gy RT

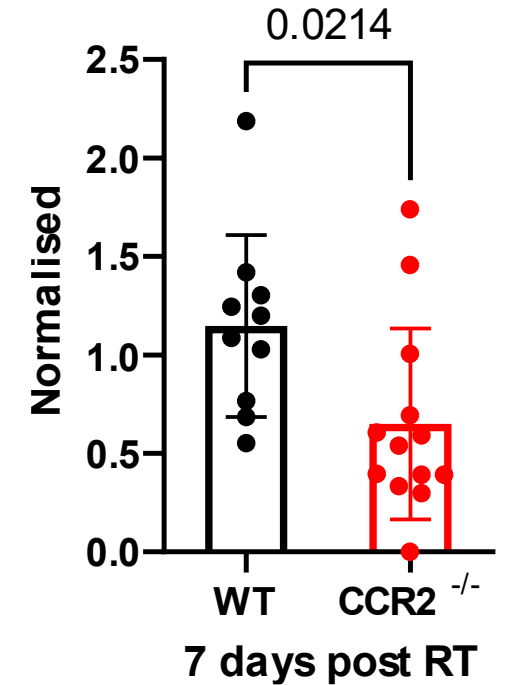
# Potential macrophage-ILC3 axis promoting protection from RT-mediated bowel toxicity?



## Enhanced levels of IL-1β early after RT.....



## .... And decrease in IL22+ ILC3s



# Potential clinical relevance?

Early Phase clinical trials in pancreatic cancer  
investigating CCR2 inhibitors



Increase in Grade 3 or higher adverse events,  
including diarrhoea, leading to cessation of  
therapy

## **Current experiments:**

- Are there similar effects mediated by fractionated radiotherapy?**
- What happens when a tumour is present?**
  - Are there effects of abdominal radiotherapy on other organs of the body?**



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UK

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**Urszula Cytlak-  
Chaudhuri**    **Nabina Pun**



**Tim Illidge**



**Doug Dyer**



**Kaye Williams**

**Duncan Forster  
Matt Hepworth  
Dave Lee  
Rita Domingues  
Ellie Cheadle**

**Gerry Graham (Glasgow)**