

# Jenkins Group

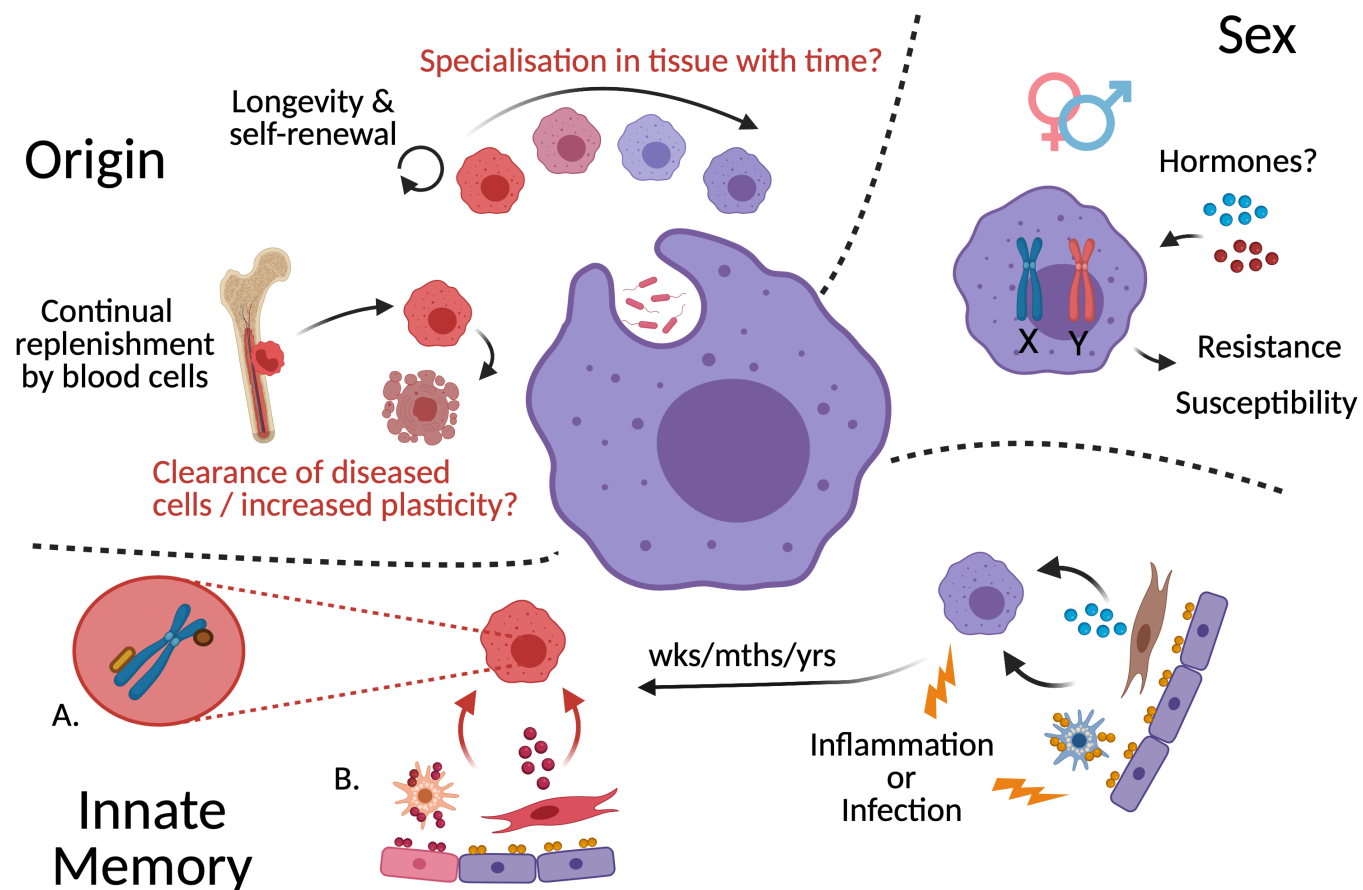
We study how macrophage function is regulated to identify pathways that promote resolution of disease.

- Where do macrophages come from and does their **origin** influence their success in combatting infection or initiating repair?
- How does a person's **sex** affect the function of their macrophages and how does this contribute to sex-differences in diseases?

A person's history of infection shapes how they respond to new and unrelated infections.

- Does altered macrophage function drive this **innate memory** and is this due to inherent changes in macrophages (A) or their tissue environment (B)?

## Control of macrophage function in health and disease



# Kendall Group

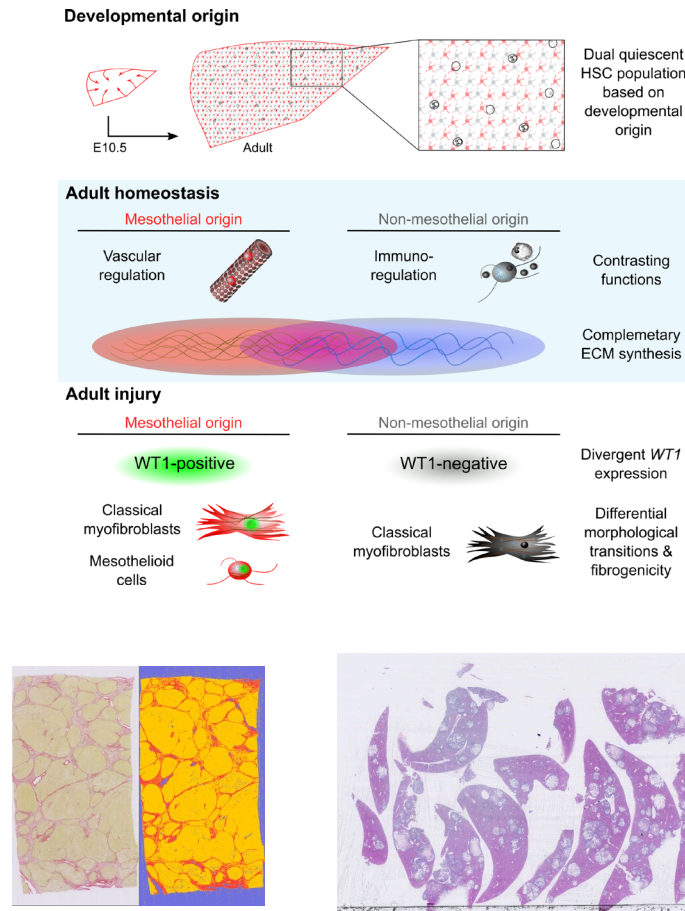
## Application of quantitative pathology to clinical and experimental chronic liver disease and cancer

### Pre-clinical models

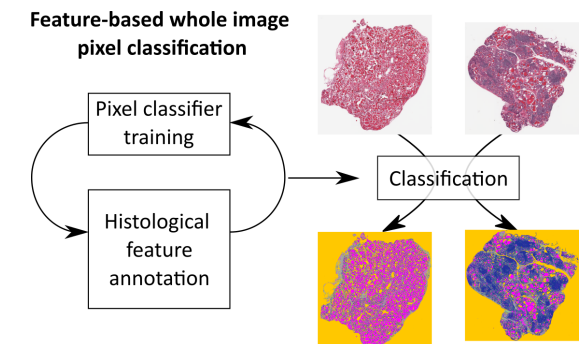
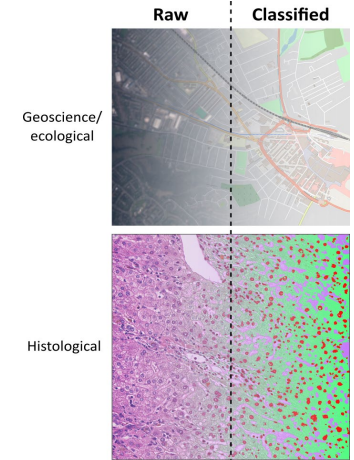
- Origins and heterogeneity of scar-orchestrating cells in liver fibrosis
- Comparative pathology of primary liver cancer (hepatocellular carcinoma and cholangiocarcinoma) models

### Quantitative pathology

- Quantitative histopathology allowing the accurate measurement of treatment response and identification of prognostic tissue biomarkers
- Development of a tissue- and disease-agnostic environmental science landscape approach to histological topography



Preclinical - Myofibroblast lineage heterogeneity & fibrogenesis. Primary liver cancer

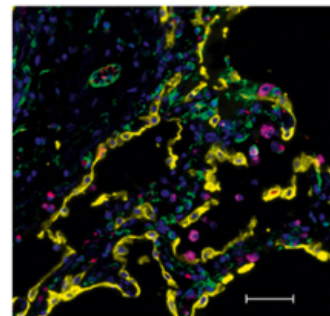
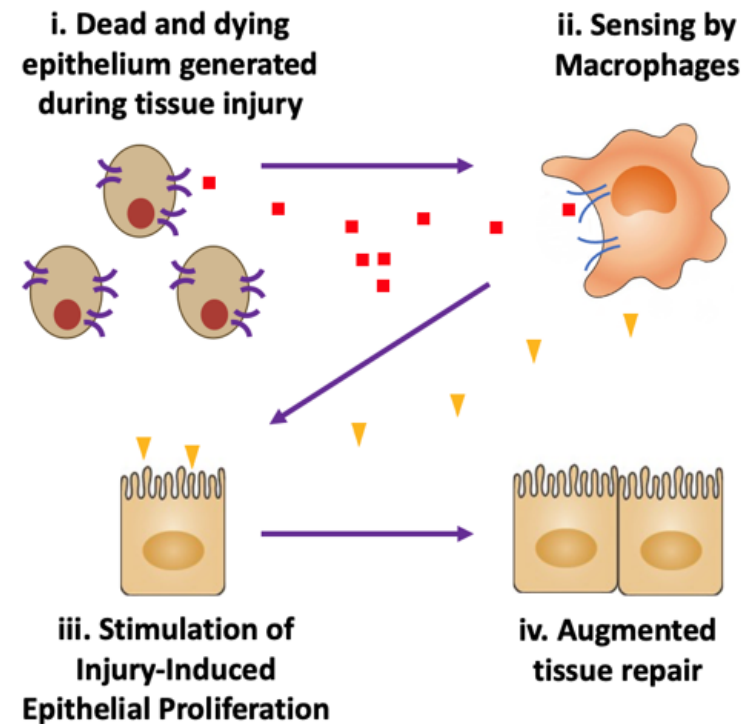


Quantitative pathology

# Lucas Group

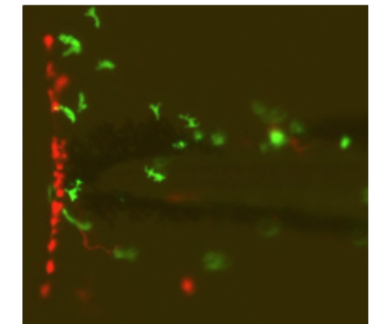
- Epithelial injury is a universal consequence of multiple organ insults; despite this no current treatments target homeostatic repair processes.
- The inflammatory response is pivotal for efficient repair but how immune cells sense injury and augment organ regeneration is poorly understood.
- During injury, macrophages recognize dead & dying cells to release factors that promote epithelial cell growth.
- By understanding how immune cells assist with organ regeneration we aim to develop new treatments that promote organ repair after serious infection or damage.

## Macrophage-epithelial communication drives tissue regeneration



Left: Macrophage (pink) epithelium (yellow) interactions in fatal lung injury in humans

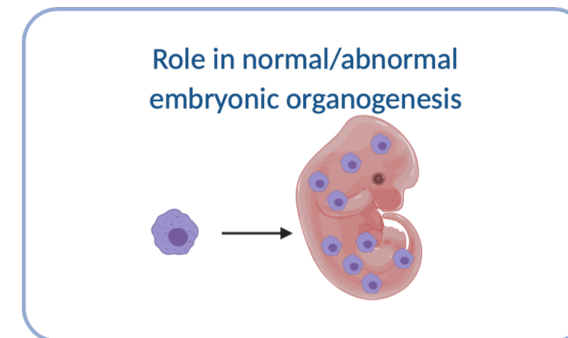
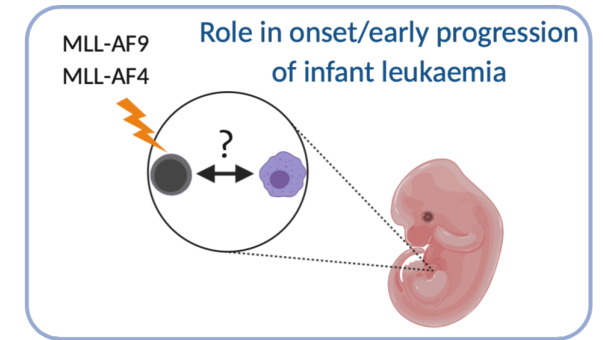
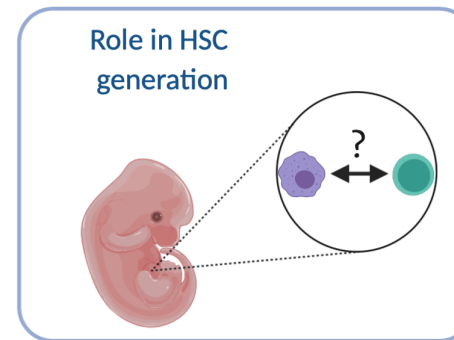
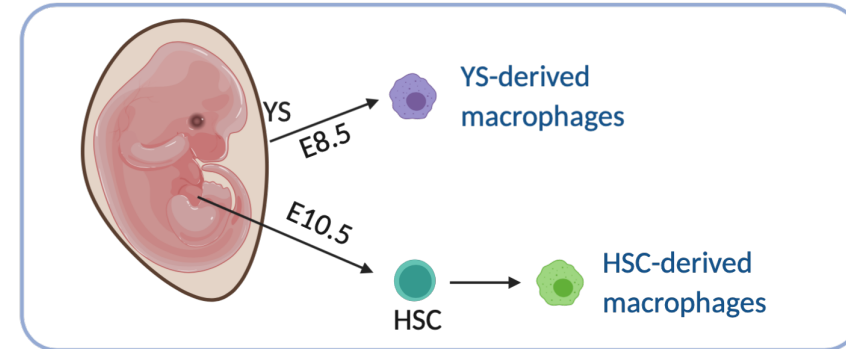
Right: Macrophage (red) and neutrophil (green) recruitment to epithelial injury in zebrafish



# Mariani Group

- Haematopoietic stem cells (HSCs) - the stem cells that give rise to all the blood cells – are first generated during embryonic development.
- **Macrophages have dual developmental origin** – some of them are derived from HSCs and others are generated in the yolk sac (YS) independently from HSCs.
- YS-derived macrophages become tissue-resident macrophages in several adult organs and contribute to their tissue homeostasis.
- However, **the role of YS-derived macrophages in the embryo itself is poorly understood.**

## Embryonic macrophages and their role in health & disease

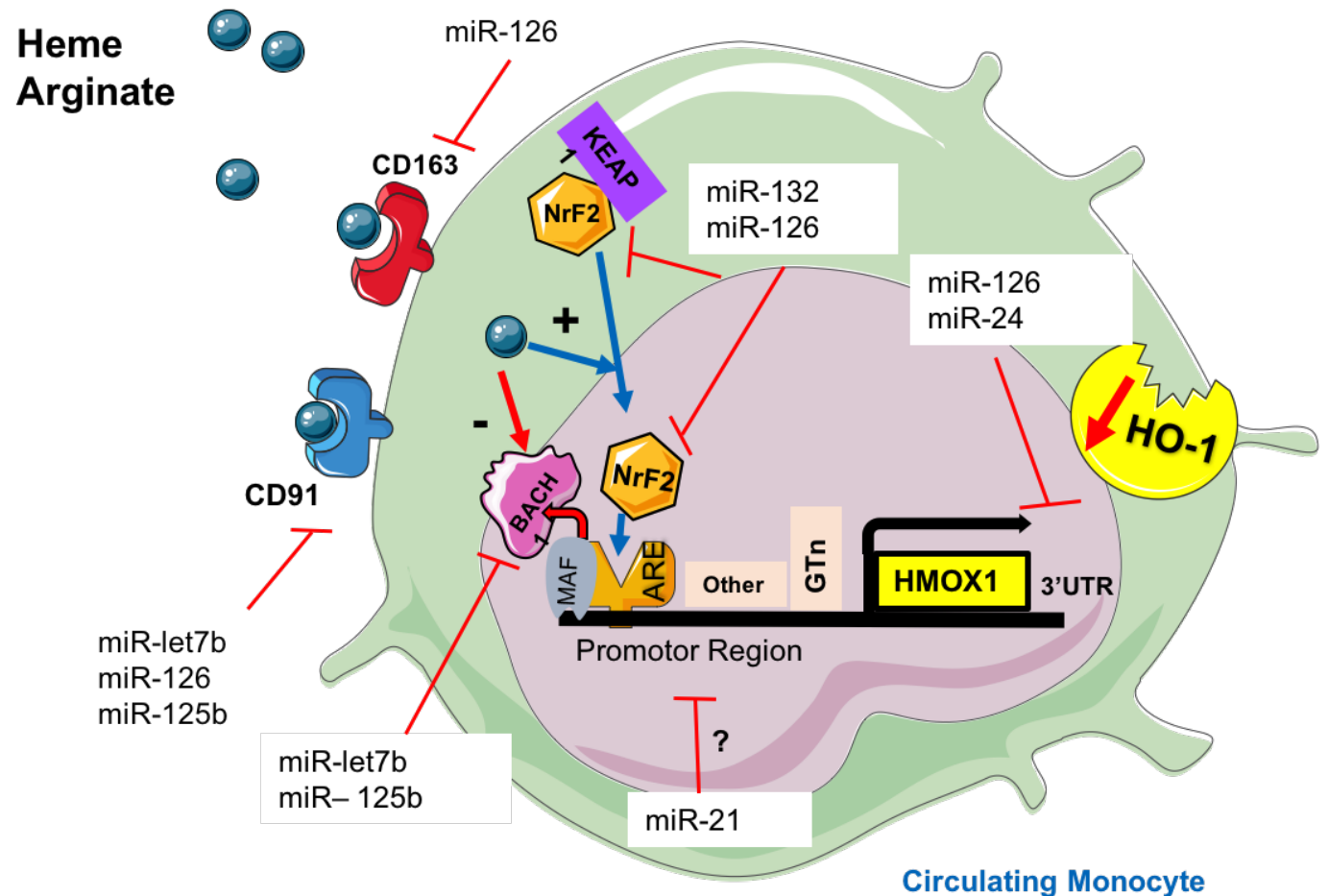


# Marson Group

- A kidney transplant is the most effective treatment for many patients with end stage renal failure
- Two significant clinical challenges remain: poor early kidney function, and long term development of fibrosis and loss of kidney function
- Heme oxygenase-1 (HO-1) is an endogenous stress response enzyme with anti-oxidant, anti-apoptotic effects
- Heme arginate (HA) upregulates HO-1 expression; we are currently leading a multicentre clinical trial aimed at determining its effect on early kidney transplant function
- MicroRNAs are small single strand non-coding RNAs that negatively regulate gene expression, gaining interest as biomarkers and therapeutic targets

MiR Work is undertaken in collaboration with Dr. Laura Denby, CVS

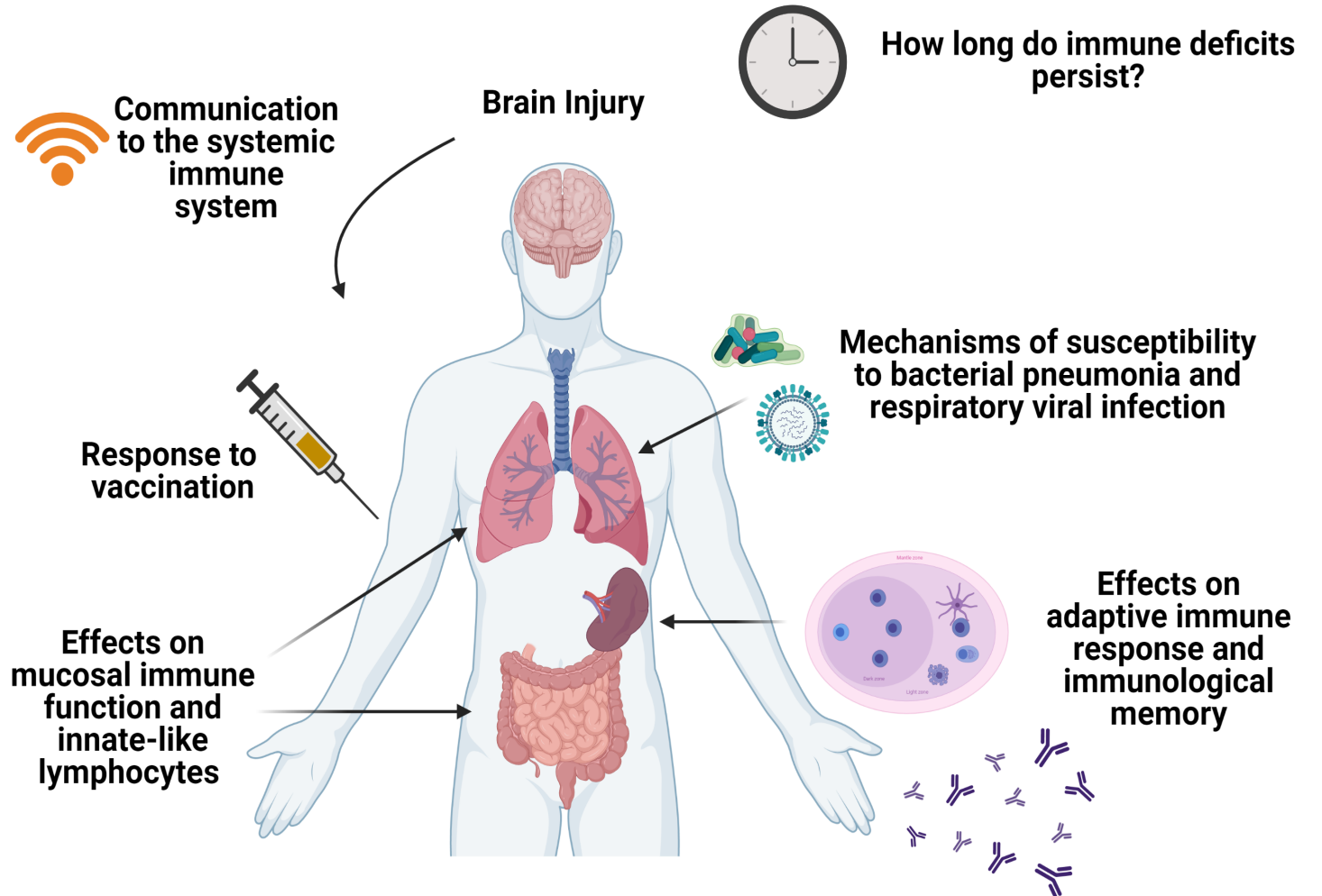
## MicroRNAs and Heme Oxygenase 1 in Kidney transplantation



# McCulloch Group

- **Brain injury**, such as stroke, has systemic effects on immune function that leave patients more susceptible to infection
- **Infection** increases mortality, disability and cost of patient care
- We have **no effective therapeutics** to prevent/ treat this
- We know little about the effects on the **adaptive immune system** and **immunological memory**
- **Neuroimmune communication** modulates these effects, however we are still learning about these signals in health and disease

## The effects of brain injury on systemic immune function

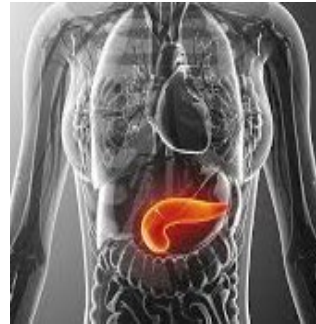


# Mole Group

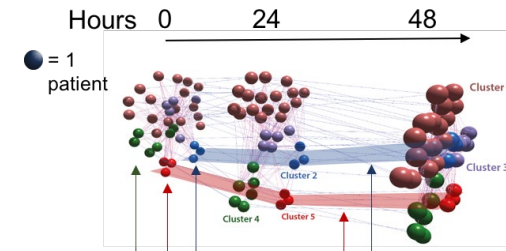
- Our research is driven by a vision to produce **innovative solutions** to difficult surgical problems and challenging diseases
- Our current challenge is **mechanism evaluation, precision medicine and drug discovery** for multiple organ dysfunction triggered by severe **acute pancreatitis**
- We work with molecules, cells, experimental animal models and human patients to discover new ways of tackling these challenges
- Our work on **KMO inhibitors** has been taken **from concept to clinical testing**, and is now expanding beyond acute pancreatitis into **cancer, immune control and endometriosis**
- Integrated **multiomics analysis** has identified **novel endotypes of acute pancreatitis** with potential therapeutic relevance.

## Inflammation and metabolism – drug discovery, precision medicine and prevention of long-term harm

Human disease



Precision medicine

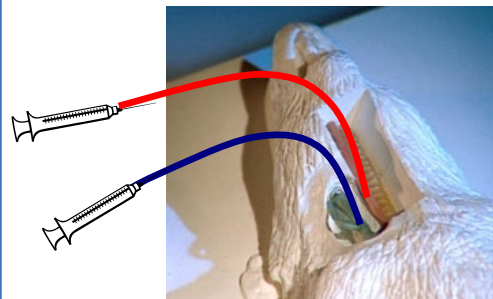


Cohorts + epidemiology

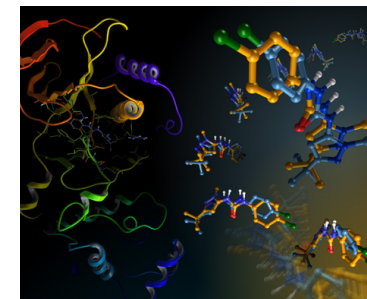


Regulating immune responses and inflammation – focus on KMO

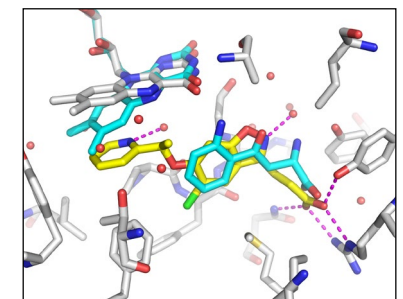
Experimental models



Molecular mechanisms



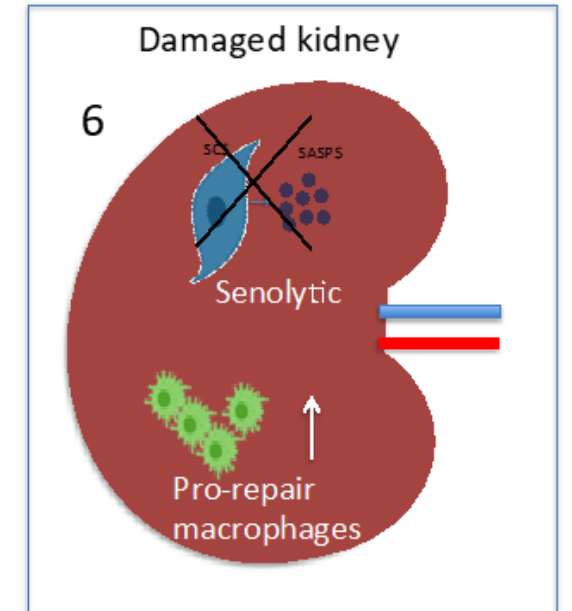
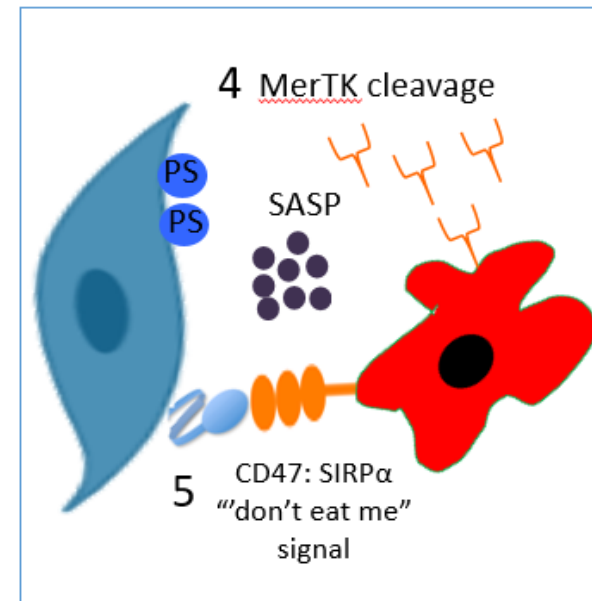
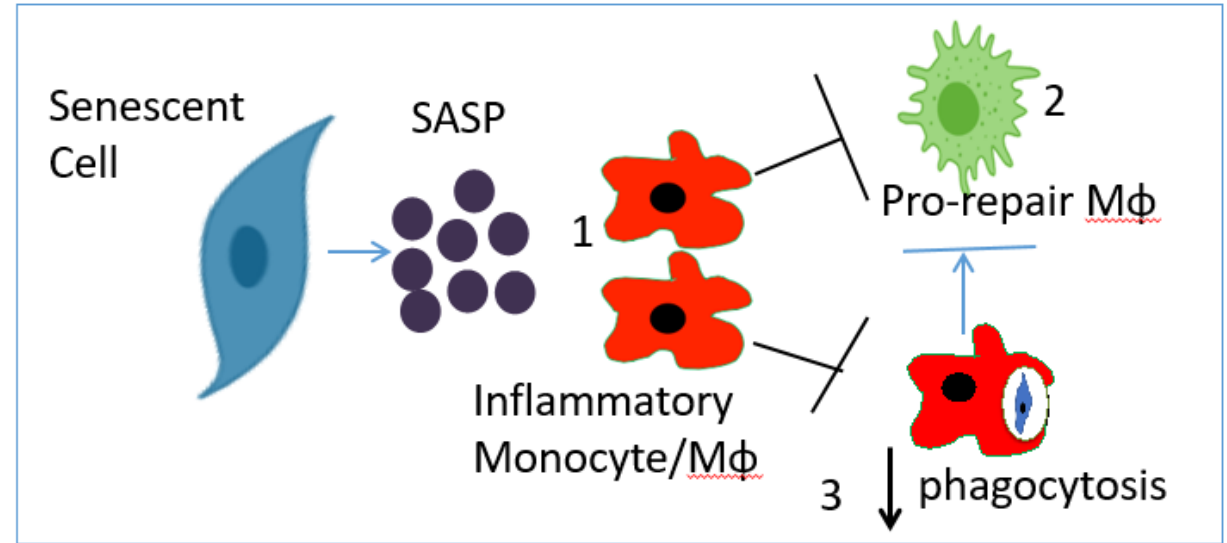
Drug discovery



# Mylonas Group

- Age-related accumulation of **senescent cells (SCs)** is associated with impaired tissue healing and regeneration. SCs are growth arrested yet metabolically active, promoting inflammation/fibrosis via release of senescence associated secretory phenotype (SASP) cytokines.
- **The senolytic (ABT-263)** eliminates SCs and improve kidney repair after injury.
- **Macrophages** are essential for tissue repair (switch to pro-repair) and for clearance of SCs e.g. phagocytic receptor MerTK interacts with PS, an “eat me” signal on SCs.
- We are investigating whether **SCs compromise macrophage-driven repair** after kidney injury, by **promoting inflammatory monocyte** recruitment (1), shifting macrophages **away from a repair phenotype** (2) and **avoiding immune clearance by phagocytosis** (3), which they may do by e.g. causing cleavage of MerTK on macrophages (4) and expressing CD47 that interacts with SIRPα on macrophages (5).
- **The aim is to drive kidney repair through modulation of SCs (using senolytics) and macrophages (drive pro-repair phenotype) (6).**

## Senescent cell interactions with monocytes/macrophages

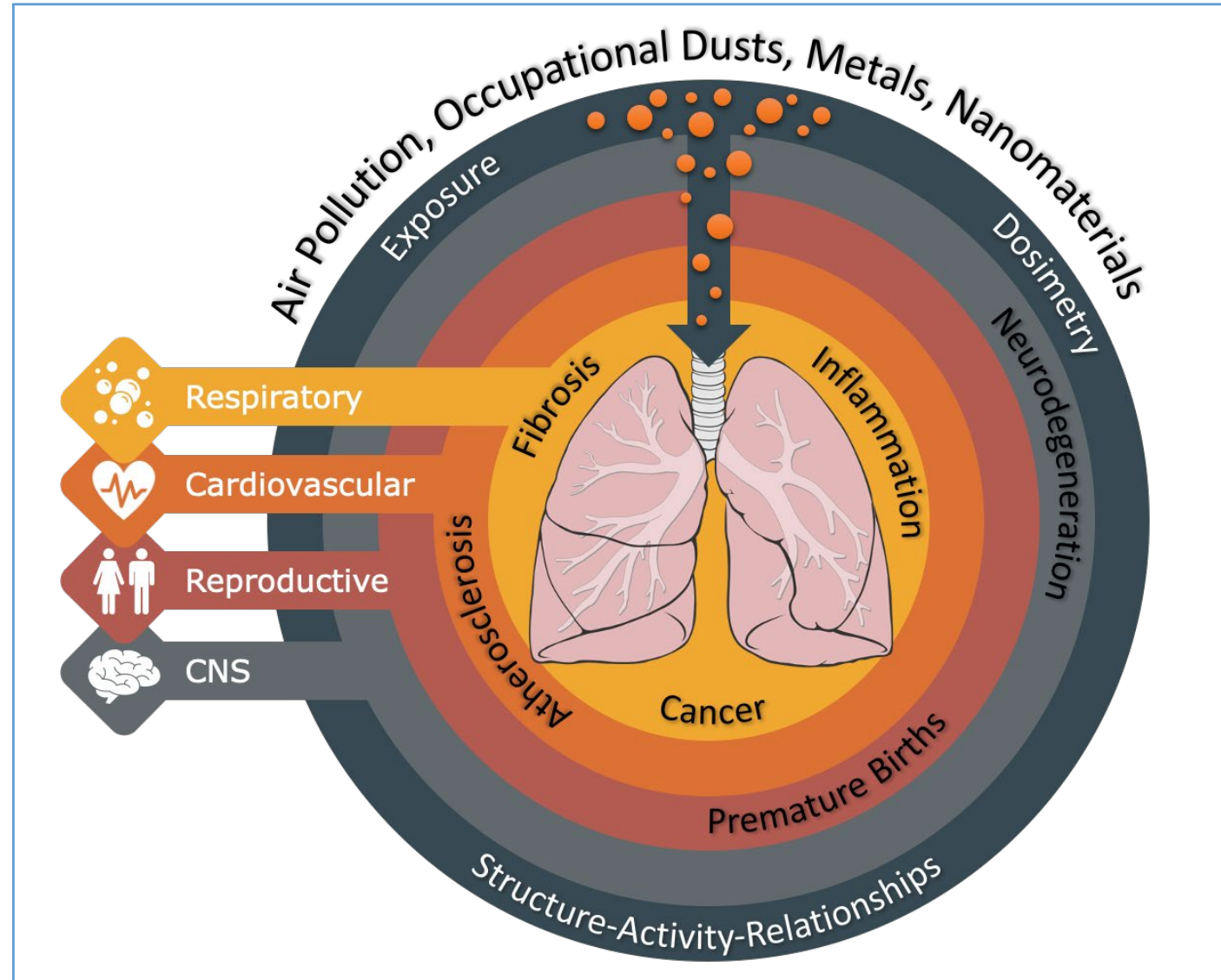




# Particle Research Group

- Particle inhalation is endemic, impacts on **every biological system**, is associated with a myriad of diseases and adversely effects the health of millions worldwide
- The relationships between particle properties and toxicity pathways (**structure-activity-relationships**) dictate disease – **these relationships are poorly understood**
- Whilst the exposures, tissues and effects are diverse, there are common mechanisms of which **inflammation** and **oxidative stress** are key
- Understanding these relationships between particle properties, inflammation and disease pathways is crucial to controlling risks and **preventing disease**

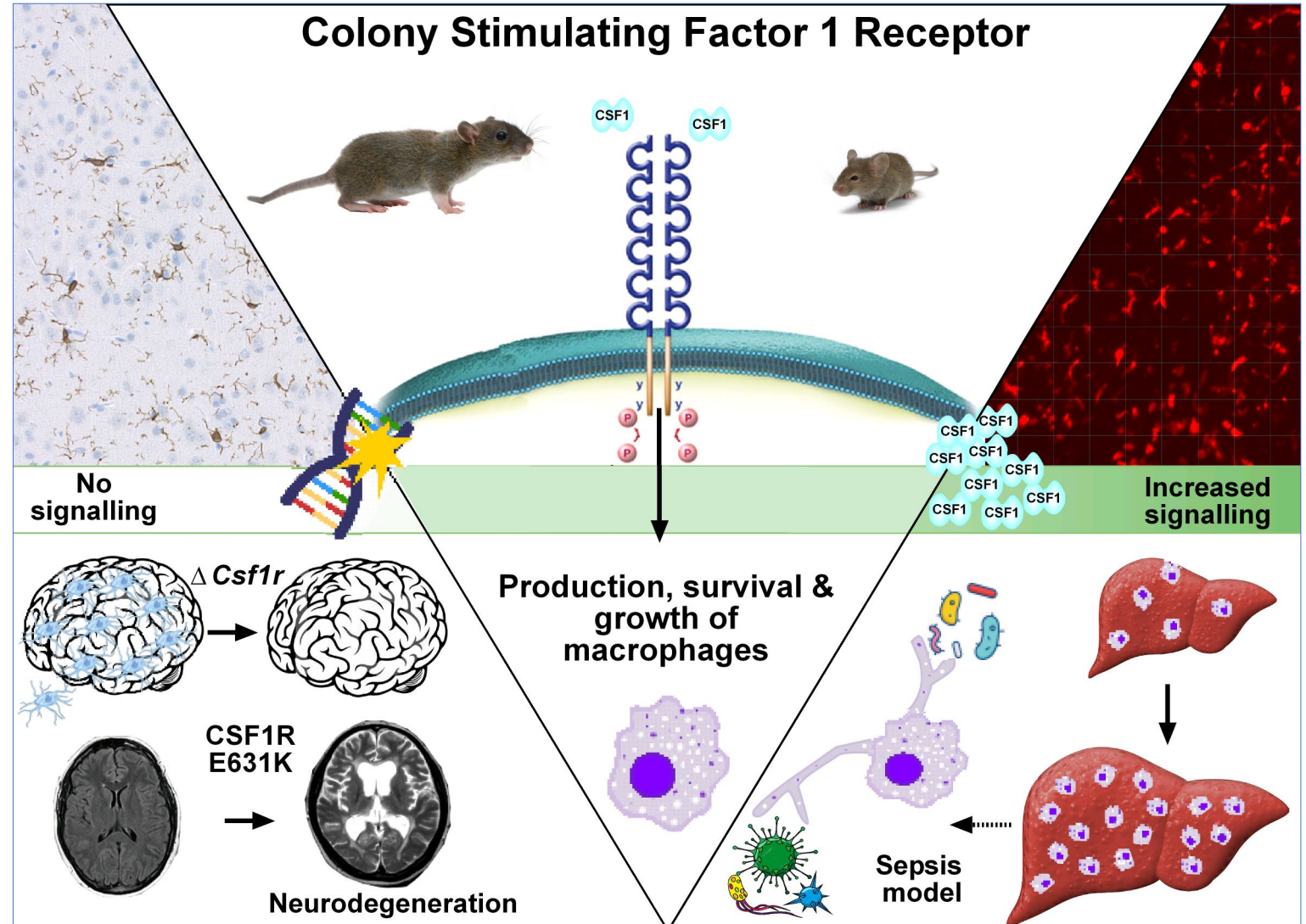
## Multi-system effects of [nano]particle inhalation in health & disease



# Pridans Group

- Signalling via the Colony Stimulating Factor 1 Receptor (CSF1R) is important for the development of macrophages.
- Macrophages are important for normal development of the body.
- CSF1R mutations in humans are associated with neurodegenerative disease.
- Transgenic mouse and rats models facilitate studies of the role of CSF1R during development and disease.
- Modifying CSF1R signalling has therapeutic potential.

## Regulation of macrophage development in rats and mice



# Prost Group

- Clinical biopsies contain spatial information critical for understanding diseases, including cell interactions, which pathologists utilise
- Identification of new markers can help interpreting biopsy for better diagnosis, prognosis & management of diseases

## What we do

- Work with clinicians & pathologists to identify relevant questions
- Gene expression analysis identifies markers
- In situ multiplex IF staining reintroduces the spatial information, allows identification of rare phenotypes and cell-cell interaction
- Correlation with clinical outcome & validation in patient cohorts feeds back to pathologists & clinicians

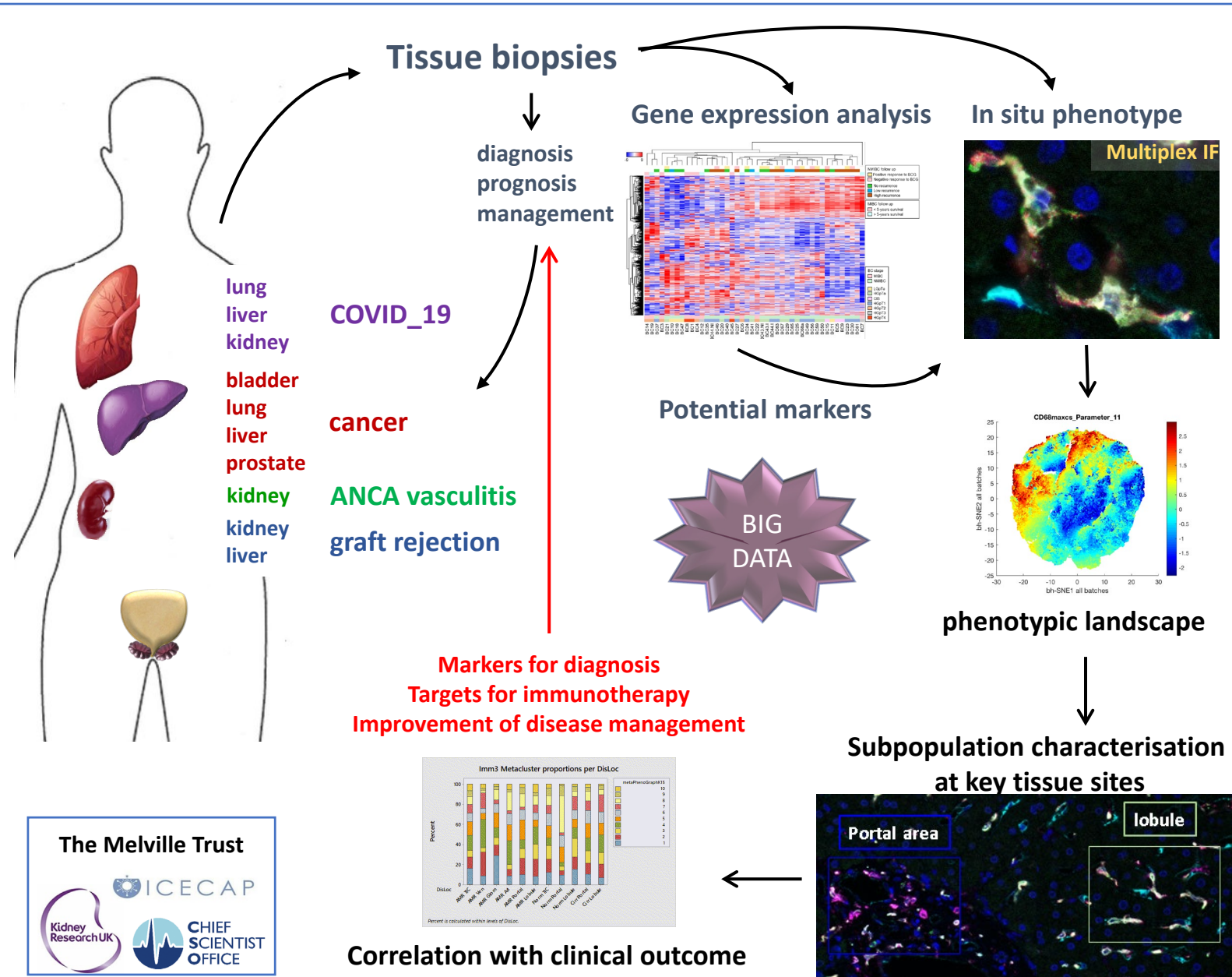
## What we study

- Immune environment, including macrophages' complex phenotypes
- Other relevant markers

## What diseases

- Inflammatory, auto & allo-immune conditions & cancers

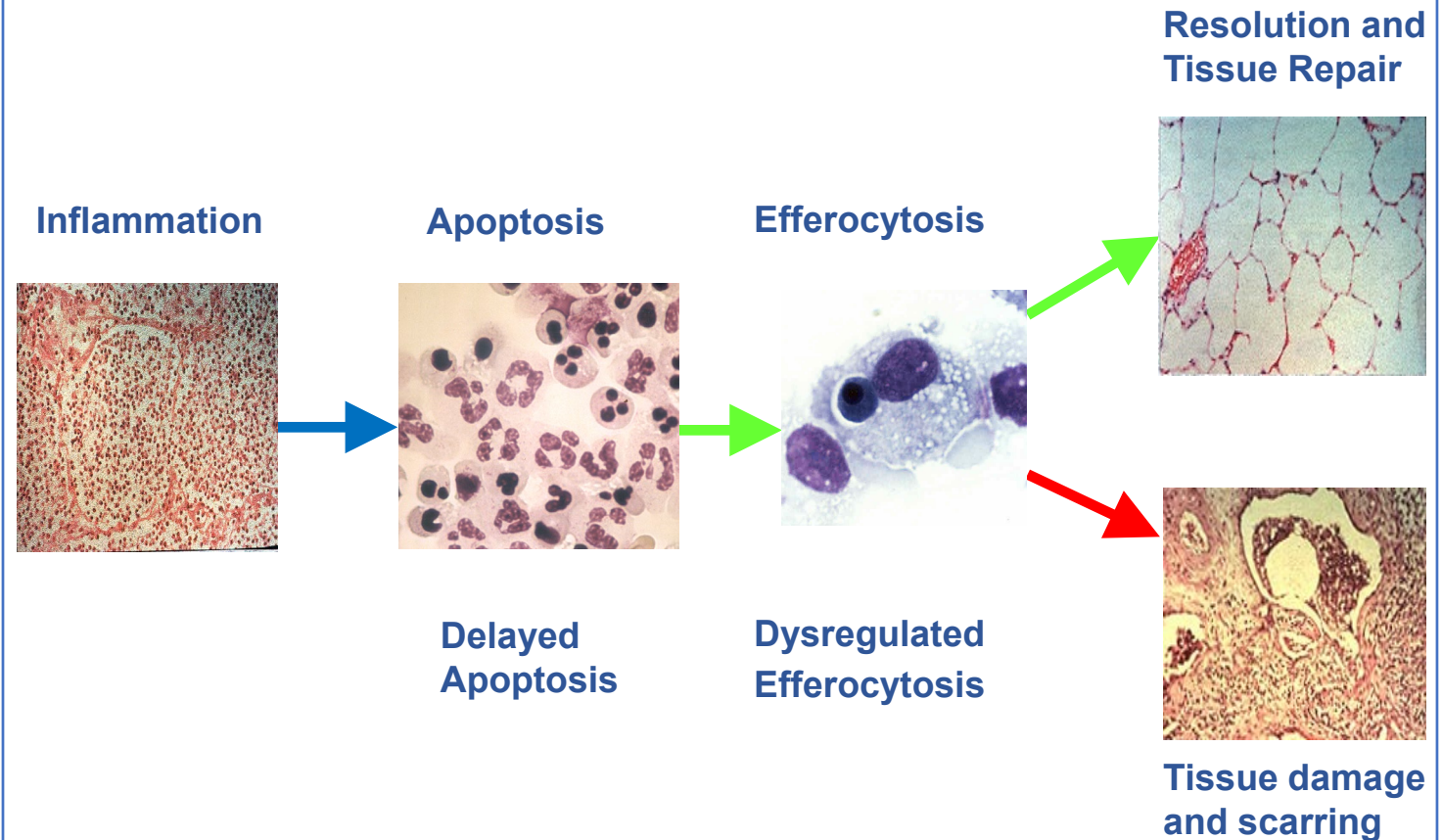
# Identification of markers for disease management



# Rossi Group

- Inflammation is key for host defence and tissue repair, however, dysregulated inflammation can lead to inflammatory diseases
- The inflammatory response involves many mediators and cell types that co-ordinate initiation, propagation and resolution of inflammation
- My group focuses on understanding mechanisms controlling the resolution of inflammation especially processes such as inflammatory cell apoptosis and clearance of apoptotic cells (efferocytosis).
- Manipulation of these processes can promote inflammation resolution leading to enhanced tissue repair and regeneration
- Thus, we believe that understanding promotion of inflammation resolution will lead to development of novel therapeutic strategies for treatment of inflammatory disease

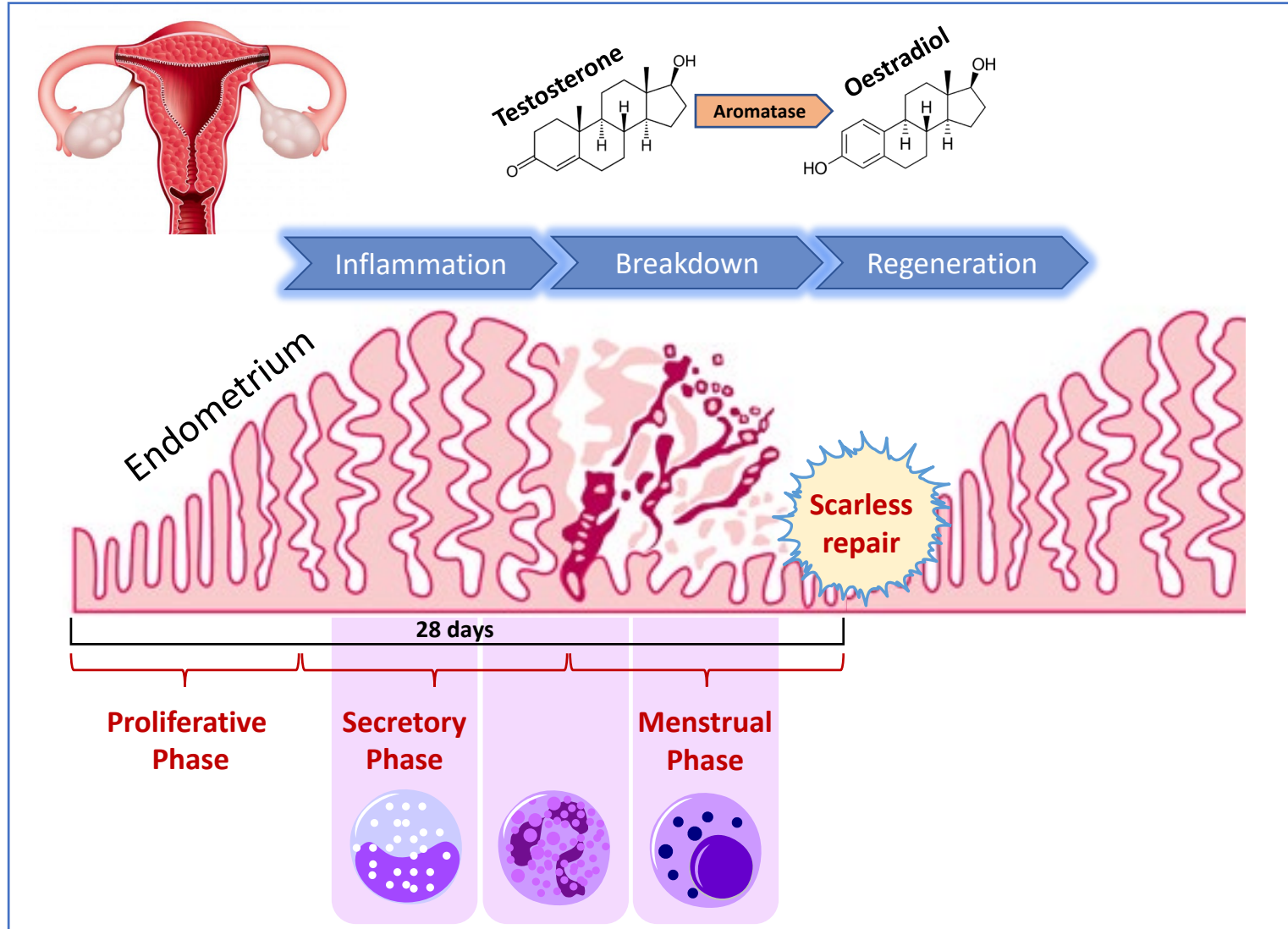
## Therapeutic Strategies to Enhance the Resolution of inflammation to Promote Tissue Repair and Regeneration



# Saunders Group

- Sex steroids are 'master regulators' of health and of disorders including cancer and endometriosis
- Sex steroid receptors function as ligand-activated transcription factors
- Fine-tuning of steroid hormone action is regulated by local (enzyme) metabolism within tissues (intracrinology)
- The endometrium is a sex-steroid dependent tissue that provides a model organ in which to study
  - Inflammatory processes/immune cell phenotypes
  - Differentiation and transdifferentiation of stem/progenitors (MET/EMT)
  - Mechanisms of scarless tissue repair
  - Drugs that target steroid receptors

## Impacts of steroid hormone ligands and receptors on reproductive (and general) health

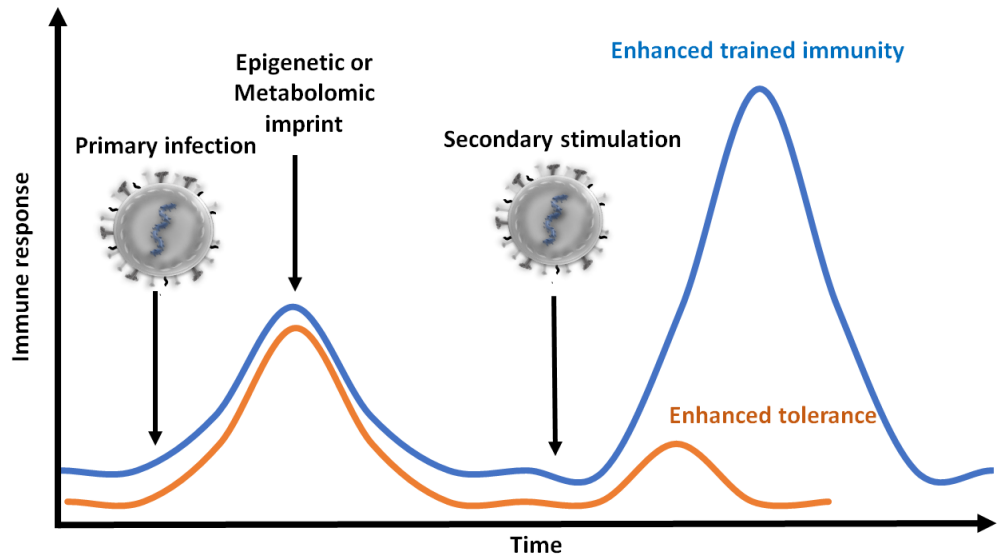


# Schwarze Group

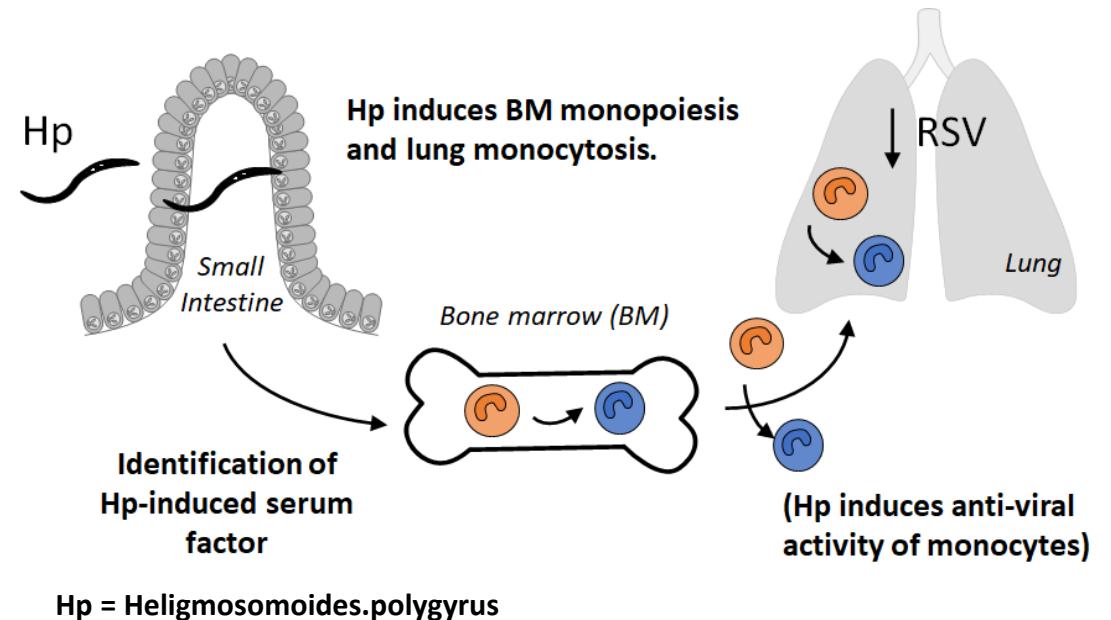
## Mechanisms and consequences of respiratory mucosal priming prior to and following respiratory syncytial virus infection

**Respiratory syncytial virus (RSV)** infection is the main cause of viral pneumonia in young children and bronchiolitis in infants and confers an increased risk of subsequent pre-school wheeze and childhood asthma.

Utilising in vivo models and air-liquid interface cultures, we investigate **long-term effects of RSV infection on airway epithelial cells** to determine if they undergo immune training.



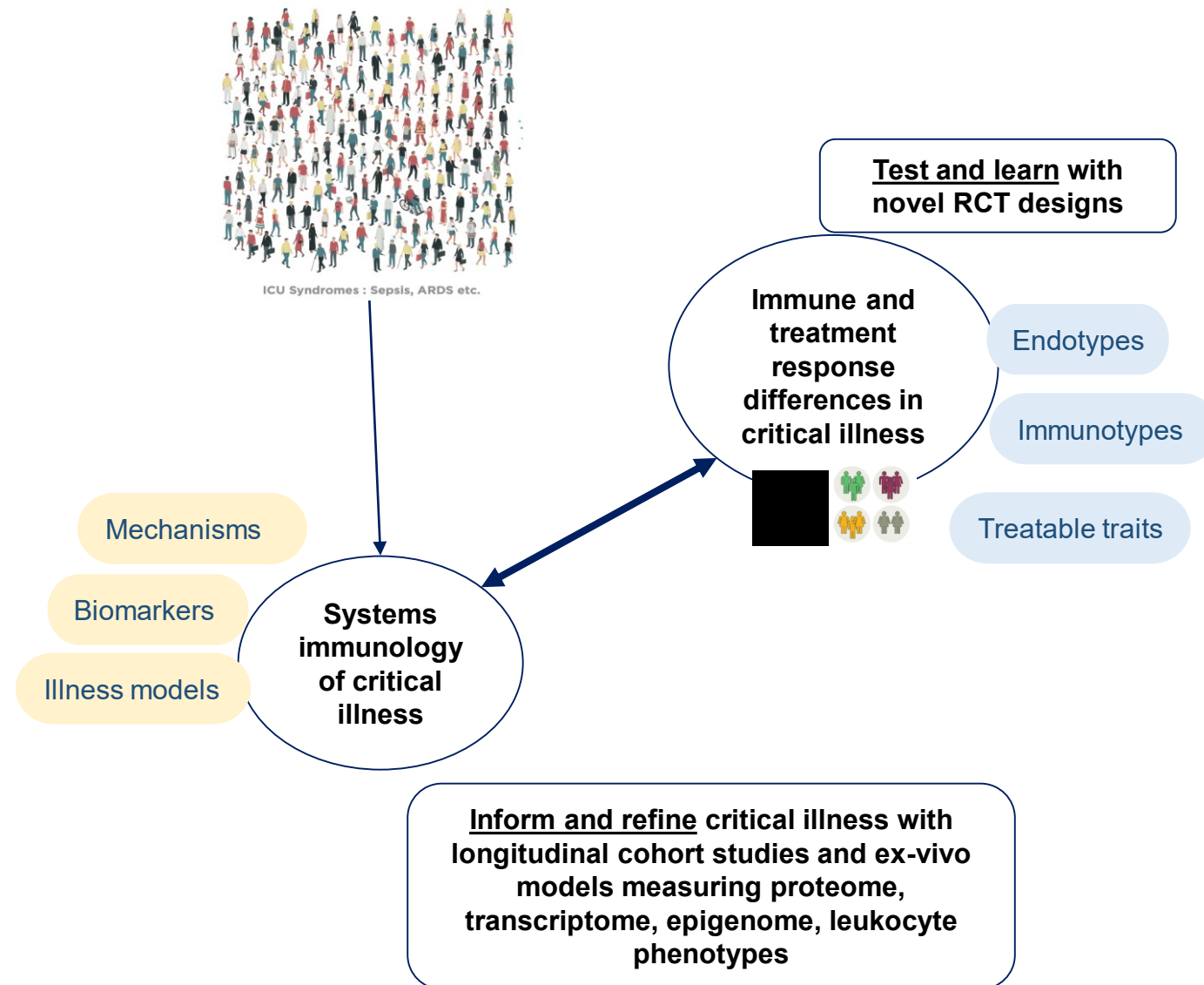
**Concurrent infections** can modulate the immune system and RSV immunity. In mice, a **gut helminth infection** (*H. polygyrus*) greatly **reduces viral load in subsequent RSV infection** in a type-I interferon and microbiome dependent manner. We investigate the mechanisms of this anti-viral effect, in particular the role of helminth-induced monocytes and their recruitment to the lung.



# Shankar-Hari Group

- Our human translational research program
  - Focus is on the two common critical illnesses without effective pharmacologic treatments - sepsis and ARDS.
  - We pursue the hypothesis that critical illnesses are determined by changes within cells and altered intercellular networks ( $\therefore$  organs) caused by dysregulated immune responses.
- We use
  - Systems immunology approaches to refine models of critical illness, to identify treatable traits, biomarkers, & therapeutic targets.
  - Novel trial designs to enable precision immunomodulation for critical illnesses

## Translational immunology of critical illness

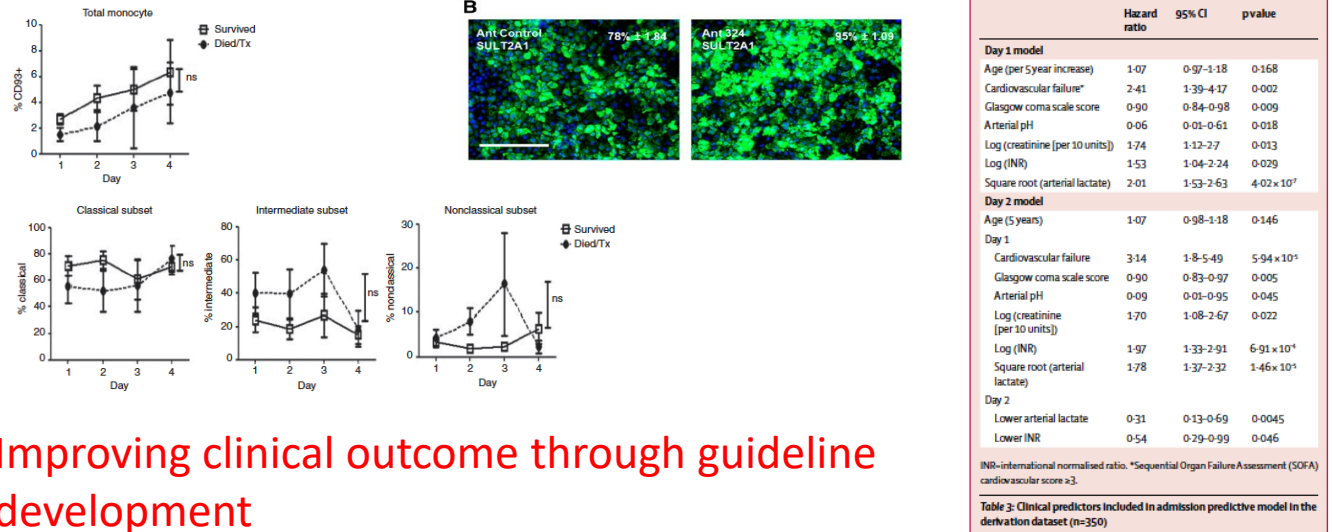


# K. Simpson Group

- **Acute liver failure** is a rare and devastating disease, with a high (approximately 40%) short term mortality.
- **Acute on chronic liver failure** is much more common and occurs in patients with liver cirrhosis, but is also associated with high short-term mortality.
- The pathogenic mechanisms underlying these liver diseases are **poorly understood**.
- A potential unifying mechanism involves an uncontrolled systemic inflammatory response to tissue injury, driving multi-organ failure and death.

# Improving understanding and clinical care of acute and acute on chronic liver failure

## Improving understanding of pathogenesis and biomarkers of outcome



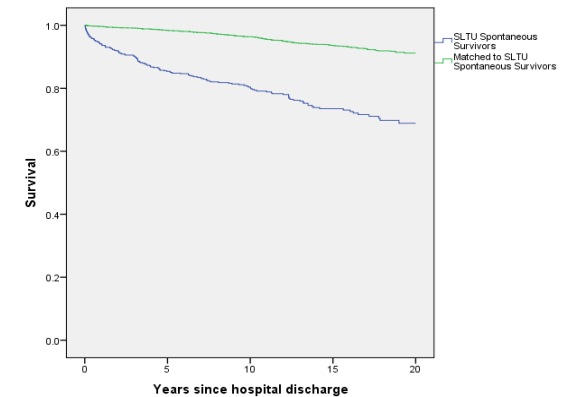
## Improving clinical outcome through guideline development

Clinical Practice Guidelines  

### EASL Clinical Practical Guidelines on the management of acute (fulminant) liver failure<sup>☆</sup>

European Association for the Study of the Liver\*

## Improving understanding of long-term consequences

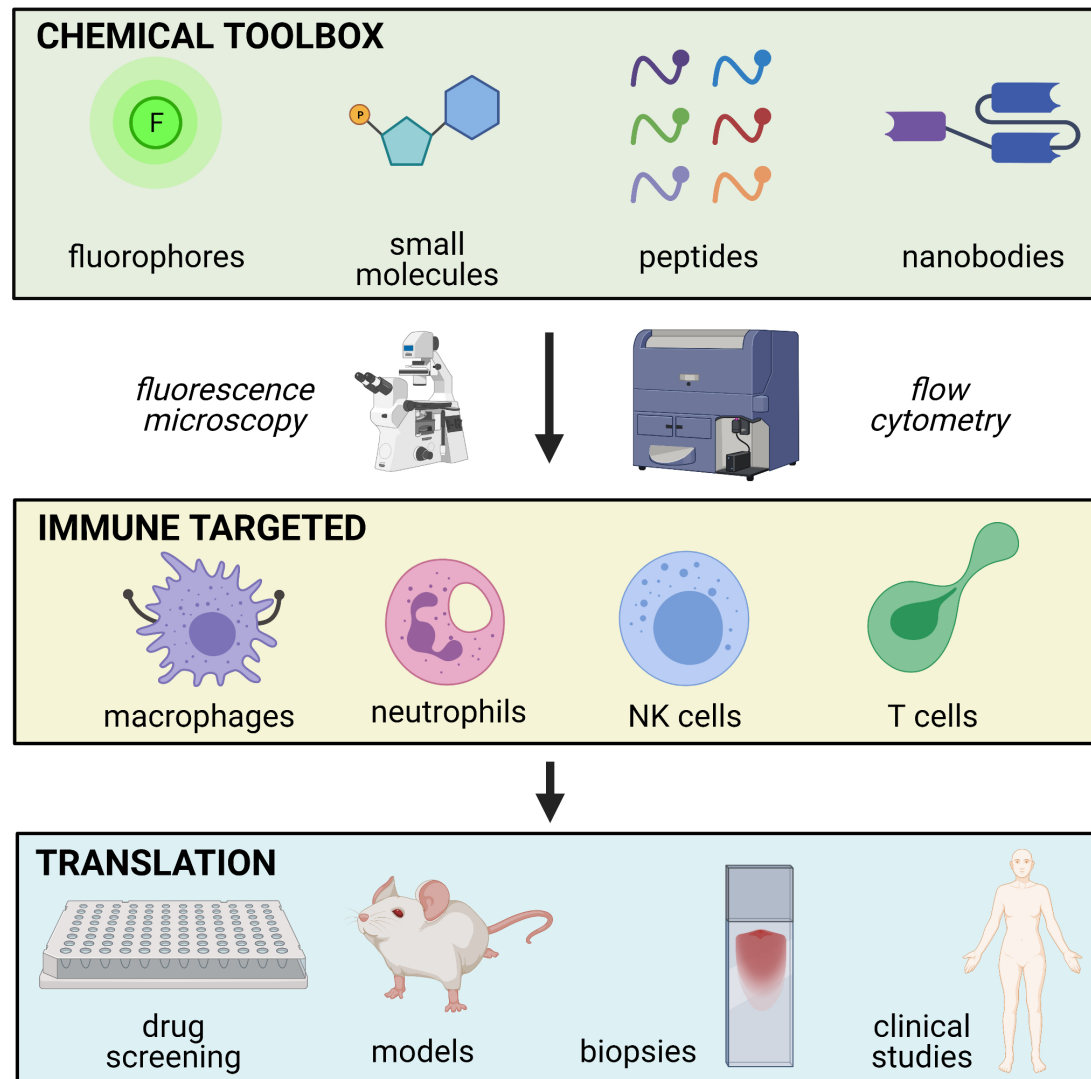




# Vendrell Group

- Chemical probes to study immune cell function:
  - enzyme activity
  - metabolite uptake
  - protein expression
  - intracellular levels of ions
- Focussed on the roles of macrophages, neutrophils and T cells in cancer and inflammation
- Probes compatible with:
  - in vitro platforms (flow, microscopy, high-throughput screenings)
  - disease models (zebrafish, mouse, rat)
  - clinical studies (biopsies and in humans)
- GMP Chemistry Lab & Sterile Fill units to manufacture materials for in-human clinical studies (with HTAF)

## Translational chemistry and biomedical imaging



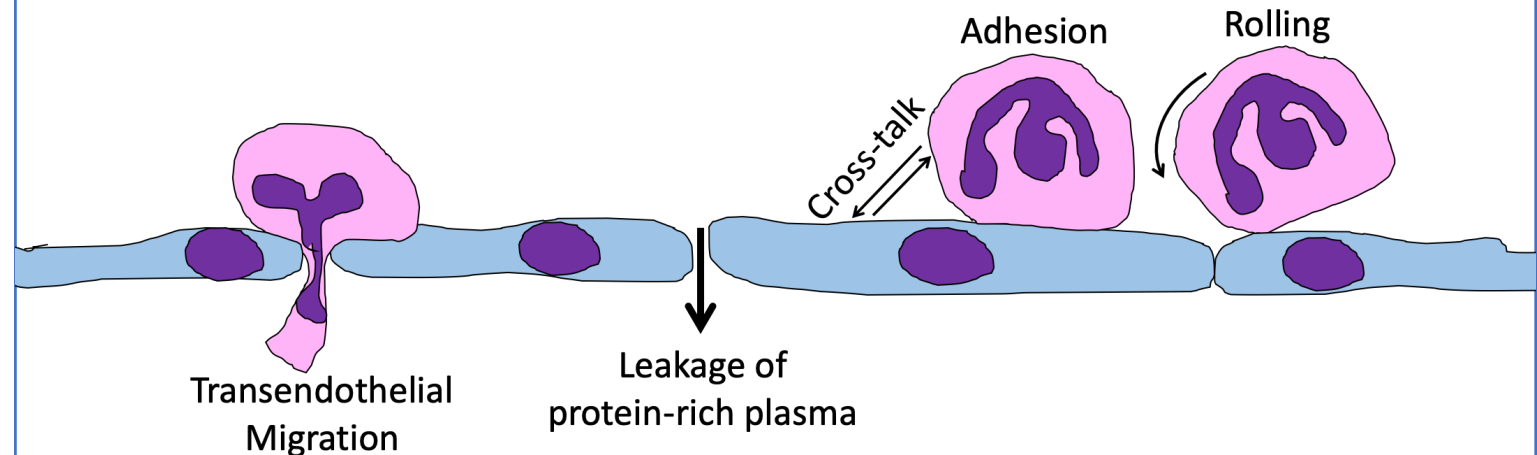
# Vermeren Group

- Neutrophils cross-talk with immune and non-immune cells to coordinate the inflammatory response
- One focus of our work involves cross-talk with endothelial cells, where we analyse cellular signalling that regulates endothelial permeability as well as neutrophil adhesion and extravasation.
- We also analyse receptor signaling which regulates neutrophils in inflammation

## Signalling in inflammation

Vasoactive compounds and neutrophil interactions trigger vascular leakage during the inflammatory response.

Vascular leakage caused by complications of serious pre-existing conditions represents a leading cause of mortality in ICUs.



# Walmsley Group

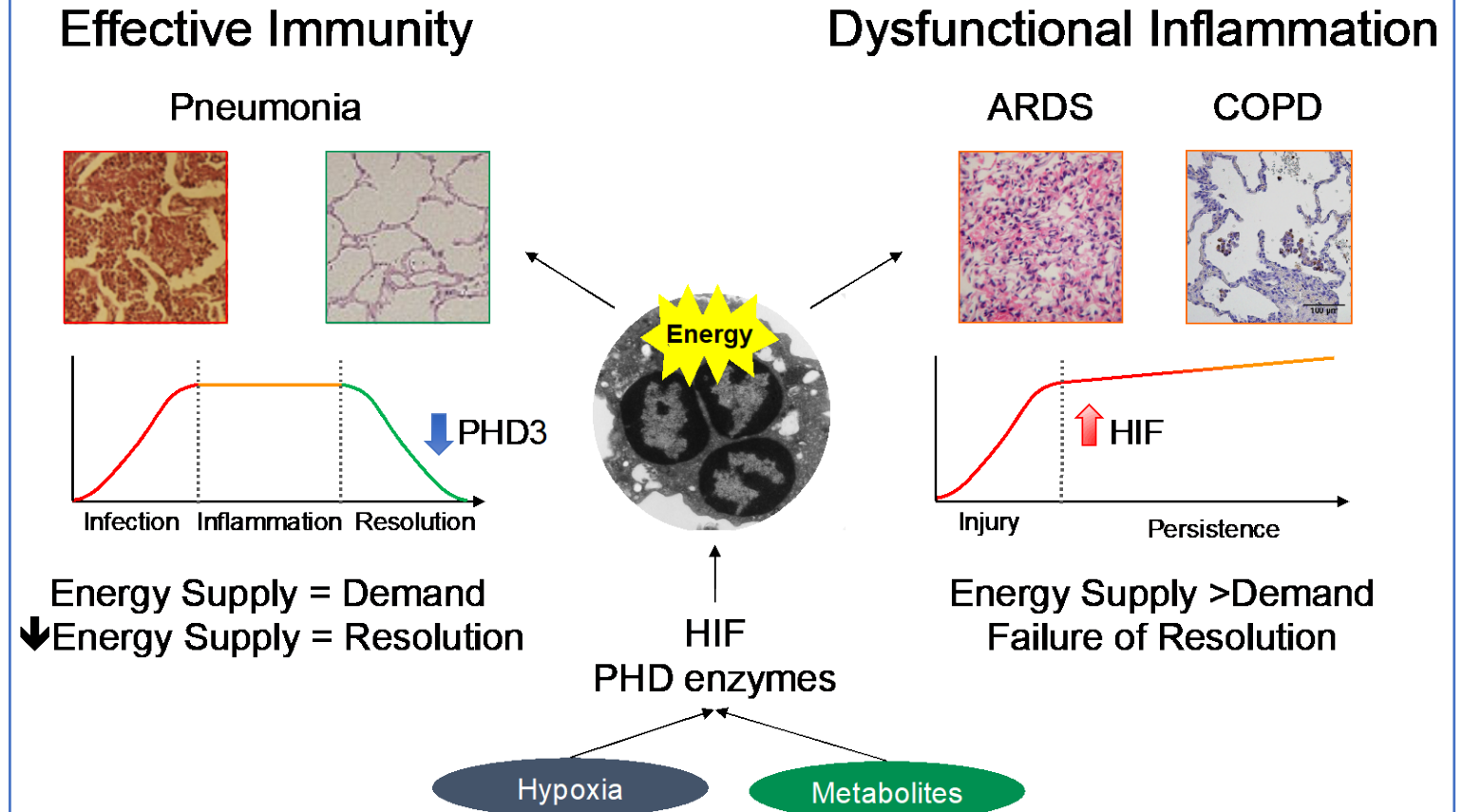
## Research goal

Identify tissue-specific factors that can be targeted to limit detrimental inflammation whilst preserving systemic immunity

## Specific Aims:

- Characterise neutrophil adaptation to oxygen and metabolite availability
- Determine how hypoxia (HIF/PHD pathway) reprograms neutrophil energy production
- Define how neutrophil access to internal energy stores determines inflammation outcomes
- Delineate mechanisms of long-term reprogramming of neutrophil function

# Regulation of neutrophilic inflammation by oxygen and metabolite sensing pathways

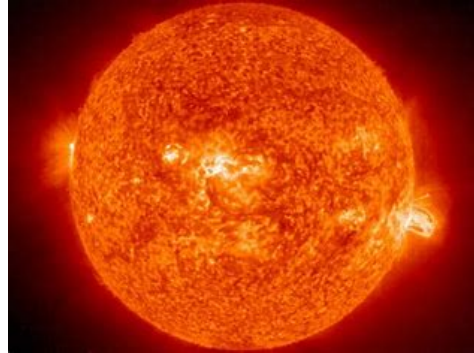


# Weller Group

## Ultraviolet Radiation and Systemic Health

### *Epidemiology*

All cause mortality  
Cardiovascular disease  
COVID



### *Mechanism*

UV and Nitric Oxide mobilisation from skin  
Action spectrum and dose dependency  
Immunological effects  
Cardiovascular effects

### *Intervention studies*

Phototherapy and Blood Pressure

## Ultraviolet Radiation and Systemic Health / Eczema

### Eczema

#### *Immunology*

PGE2-IL22 pathway in eczema  
Fillagrin deficiency and antigen presentation

#### *Barrier*

Anti protease actions of HBD2 in maintaining skin barrier function

#### *Clinical*

Translational studies and registry studies linking the clinical eczema service with laboratory science

# Wigmore Group

## Drivers and diagnostics for primary liver cancers, functional liver imaging and organ preconditioning

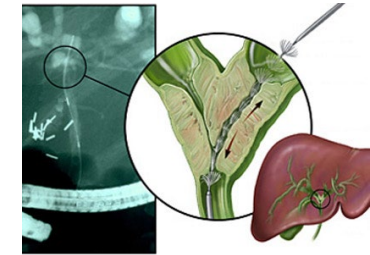
- Inflammation drives formation of liver and bile duct cancers
- Identification of cell-free DNA signatures using exosome or epigenetic analysis may facilitate detection and improve treatment of liver cancers
- Functional imaging makes liver surgery safer
- Harnessing natural cell protection pathways eg Heme oxygenase-1 can provide a therapeutic target for preconditioning organs for transplant
- Major UK RCT in renal transplant
- MicroRNA profiling may predict response: stratified medicine
- Funding MRC, KRUK, NIHR, CRUK, Lothian Endowments, RCSEd

Inflammation as a driver for bile duct cancer formation in primary sclerosing cholangitis

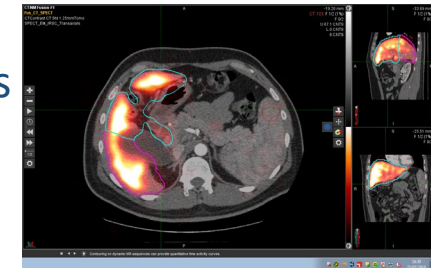
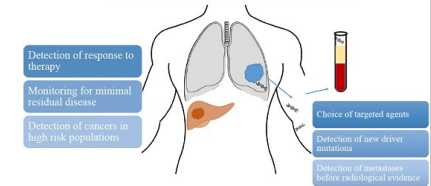
Liquid biopsy, epigenetics and genomic Analysis of patients with primary liver cancer

Functional liver imaging and novel techniques for imaging primary liver cancer

Novel therapeutic interventions to precondition organs for transplantation



Clinical Applications of Liquid Biopsy



**HOT2**  
**Study Meeting**

The **HOT2** Trial is due to open to recruitment this summer. For those unable to attend the Edinburgh Site Initiation Visit last month, you have a second chance to hear about this exciting trial on:

**Monday 13th August 2018**  
3.30pm-5.30pm  
Transplant Seminar Room  
(outside ward 206, R1E)

For further details contact Chief Investigator, Prof Lorna Marson (Lorna.Marson@ed.ac.uk) or the HOT2 Trial team (hot2@ed.ac.uk)

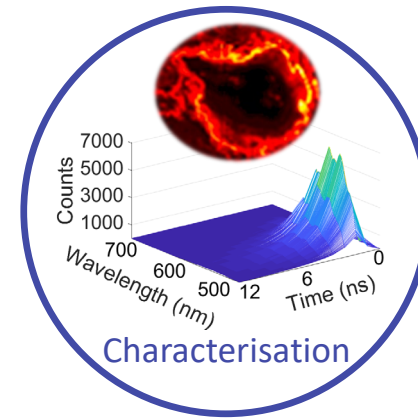
ALL WELCOME. REFRESHMENTS WILL BE PROVIDED

# Williams Group

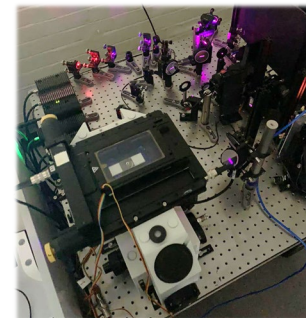
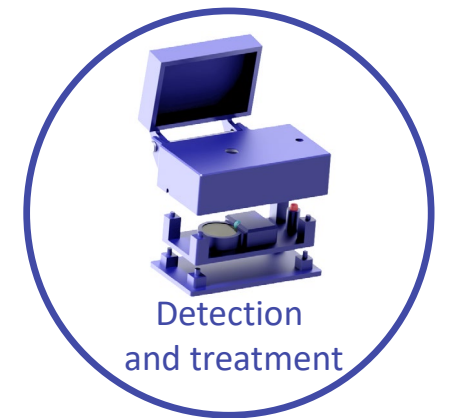
- Optical fingerprinting ( inc. **fluorescence**, **fluorescence lifetime** & **Raman**) enables **rapid** and **minimally invasive** possibilities for characterising tissue and disease
- **Ex-vivo** characterisation of disease drives learning for **in-vivo**, **bedside**, technology development to investigate **poorly understood disease pathways**
- **Multiplexed** imaging and sensing – **intrinsic** molecular signals enhanced by **extrinsic** chemical probes to **track disease**
- **Frugal innovation** pathways to enable global access to optical technologies for disease **detection** and **treatment** via photodynamic therapies

## Translational photonic technologies for probing and treating disease

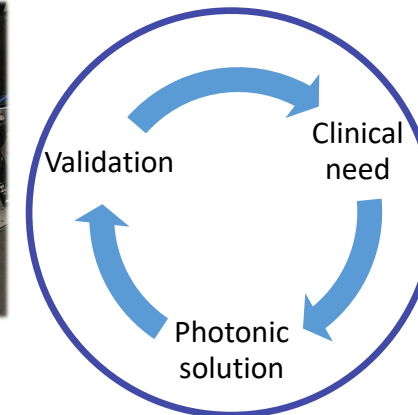
### Optical Fingerprinting



### Frugal Innovation



*Ex-vivo*



Clinical Translation

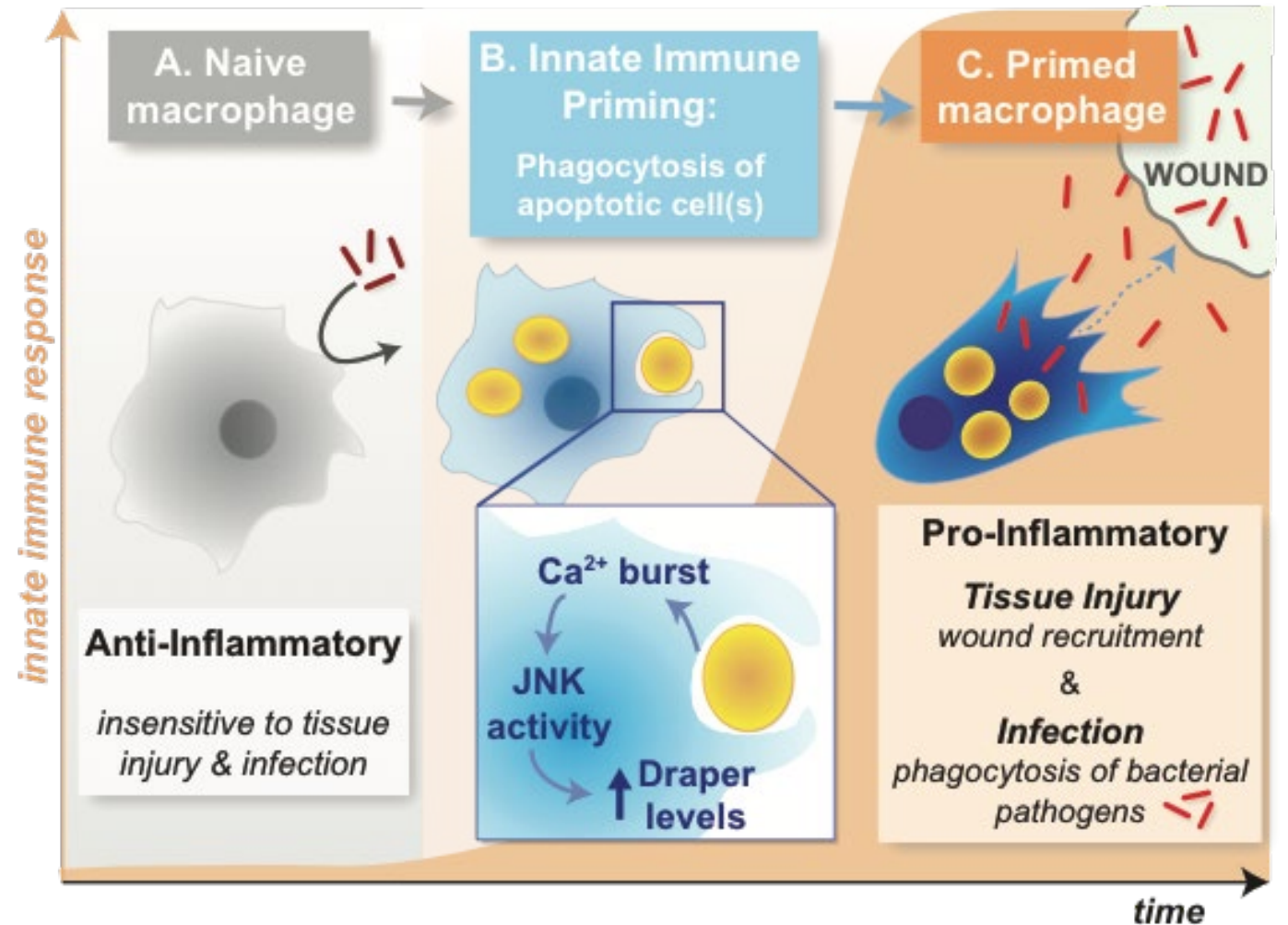


*In-vivo*

# Wood Group

- *Drosophila* (fruitflies) are a powerful genetic model for studying immune cell biology in vivo
- We use timelapse confocal imaging to live image the recruitment of inflammatory cells to wounds and sites of infection in vivo.
- We want to understand how immune cells integrate different signals that may be telling them to do very different things
- One key question is how exposure to one signal (i.e infection, a wound or an apoptotic corpse) can alter the ability of an immune cell to respond to a subsequent cue.
- We are trying to understand the molecular machinery that underlies this 'innate immune memory'

## Using *Drosophila* to Understand Inflammatory Cell Migration and Signal Integration



# Yao Group

## Bioactive lipid mediators and mucosal inflammation

### Our aim:

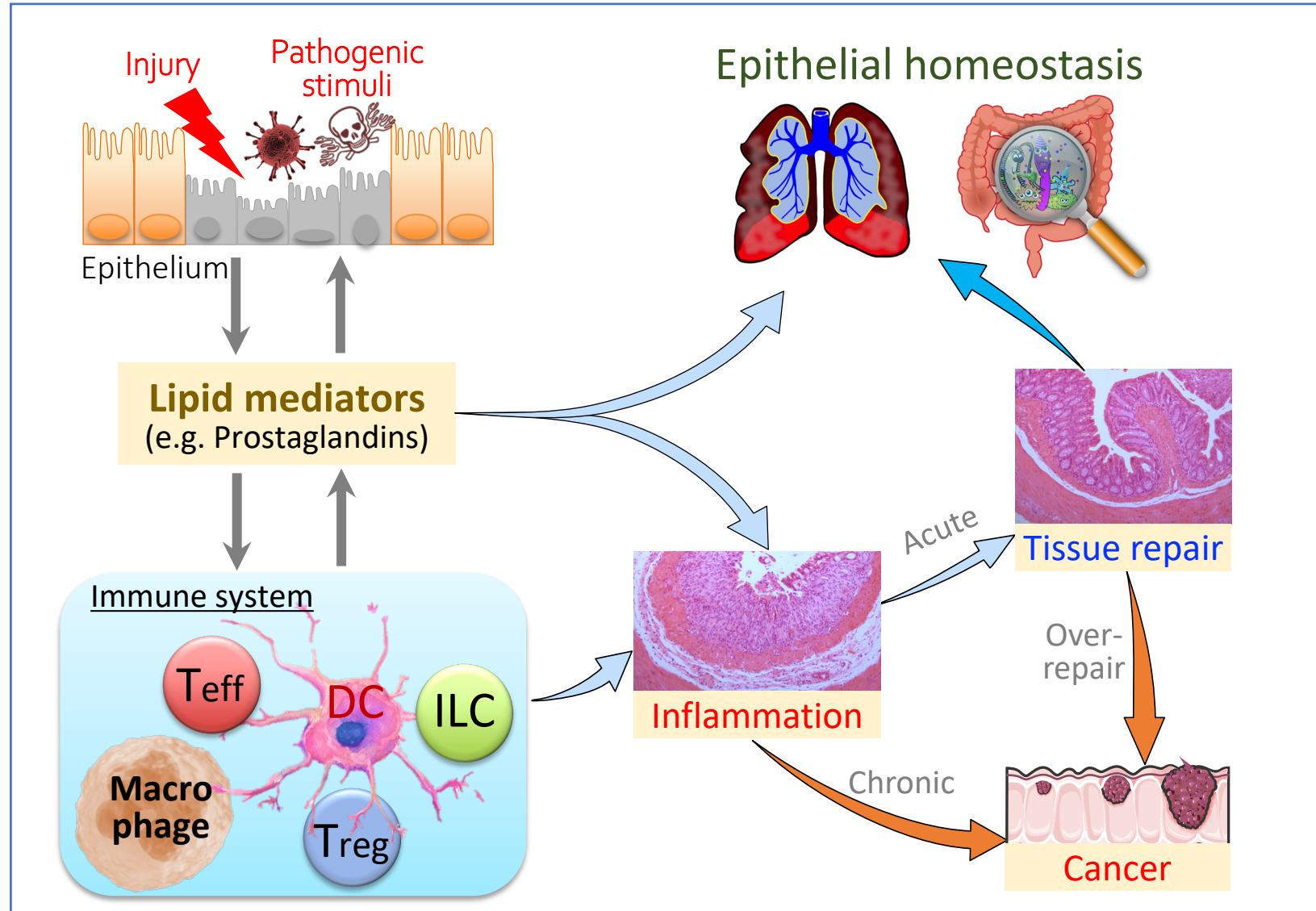
To understand how bioactive lipid mediators modulate mucosal immune responses and control epithelial homeostasis, inflammation, repair, and tumorigenesis.

### Our approaches:

- Immunological, pharmacological, and genetic tools.
- Models of immune-related diseases including cancer.
- Systems biology analyses.

### Our ultimate goal:

To develop new treatments for immune inflammation-associated mucosal diseases.





# Yule Group / Surgical Sabermetrics

- Surgical teams lack multidimensional quantitative feedback in order to **improve performance and enhance patient safety**.
- Unlike athletics data science, **technical and non-technical skills** assessment tools for the operating theatre are subject to bias, collect limited continuous data, and lack scalability.
- We are using **sensors to objectively measure** significant concepts (cognitive load, kinematics, situation awareness) **augmented with video** in surgery and spaceflight.
- Our innovative AI-enabled sabermetrics platform will assess human performance in extreme environments, add to knowledge, and **democratise performance feedback**.

## Applying athletics data science to enhance performance in surgery and spaceflight

