Jenkins Group

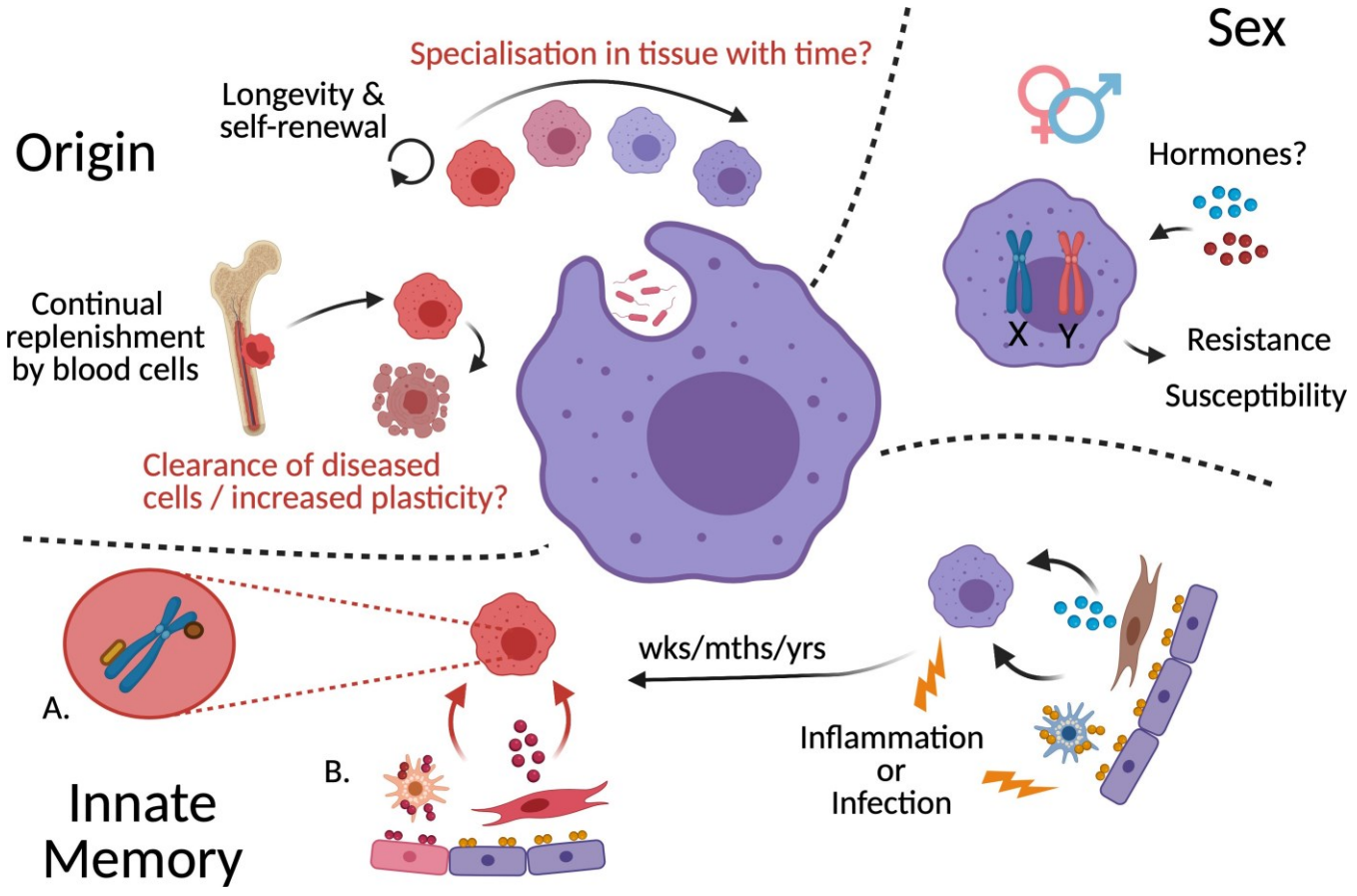
Control of macrophage function in health and disease

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 persons 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)?



Kendall Group

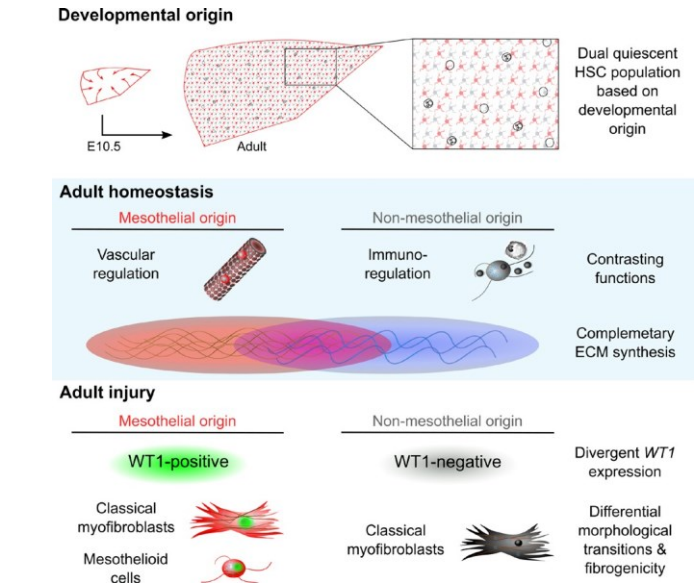
Application of quantitative pathology to clinical and experimental chronic liver disease and cancer

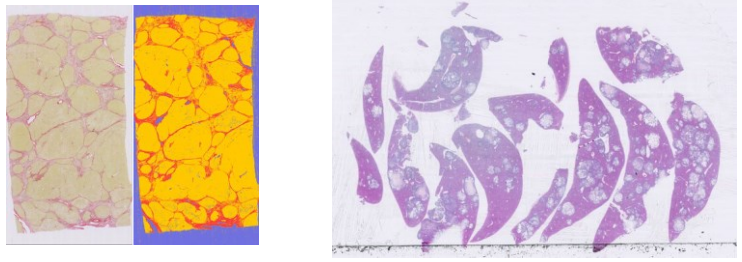
Pre-clinical models

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

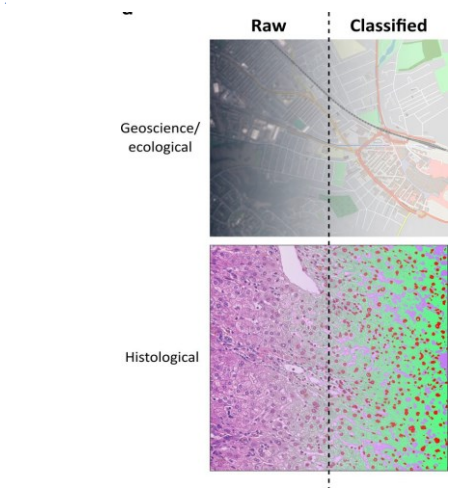
Quantitative pathology

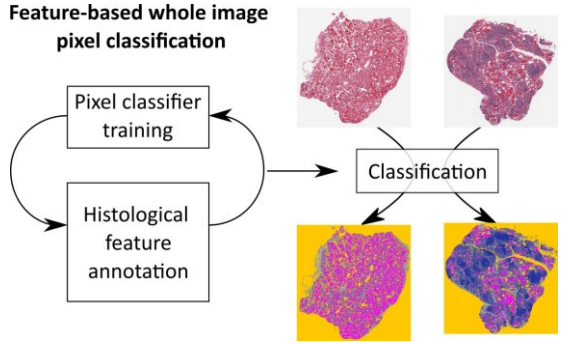
- Quantitative histopathology allowing the accurate measurement of treatment response and identification of prognostic tissue biomarkers
- Development of a tissue- and disease-agnostic environmental science landscape approach to histological topography





Preclinical - Myofibroblast lineage heterogeneity & fibrogenesis. Primary liver cancer



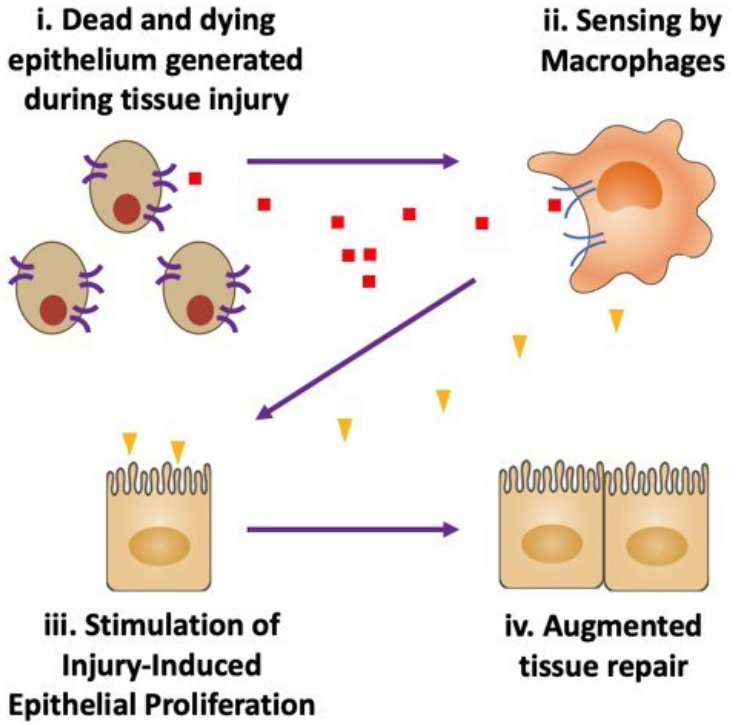


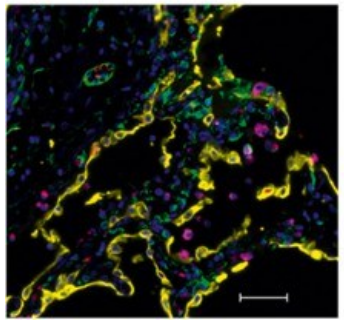
Quantitative pathology

Lucas Group

Macrophage-epithelial communication drives tissue regeneration

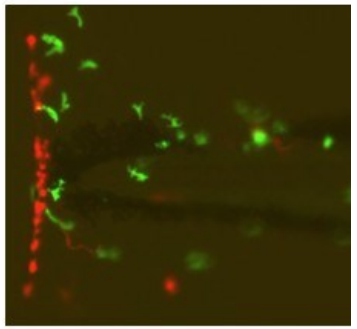
- Epithelial injury is a universal consequence of multiple organ insults; despite this no current treatments target homeostatic repair processes.
- The inflammatory response is pivotal for efficient repair but how immune cells sense injury and augment organ regeneration is poorly understood.
- During 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.





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

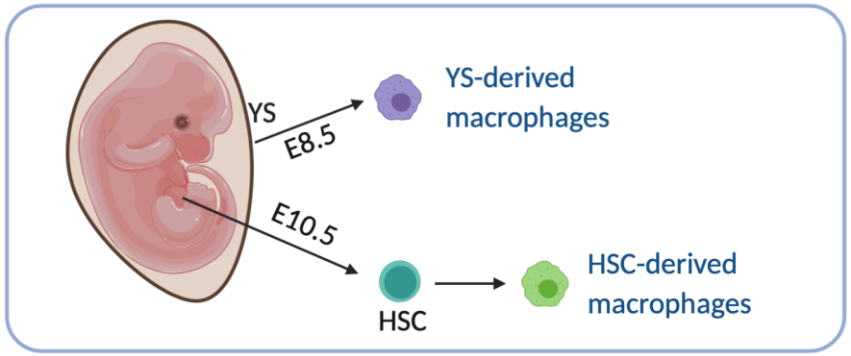
Right: Macrophage (red) and neutrophil (green) recruitment to epithelial injury in zebrafish

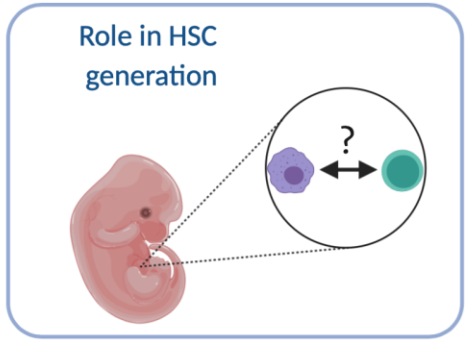


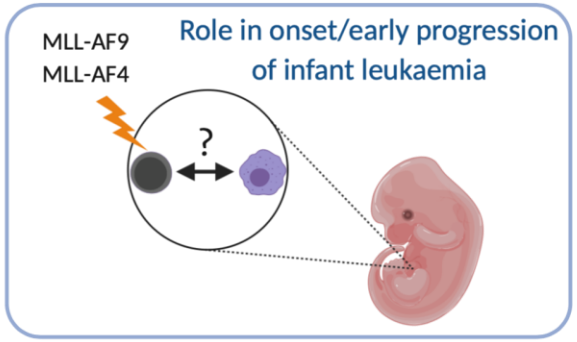
Mariani Group

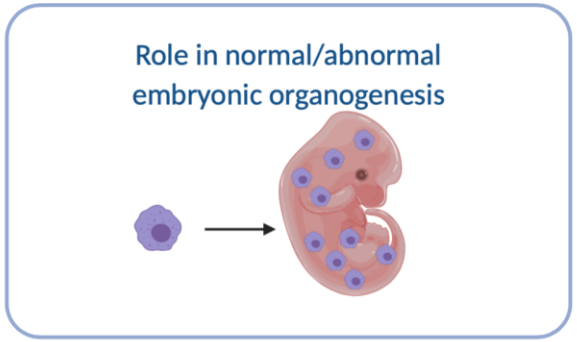
Embryonic macrophages and their role in health & disease

- 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.







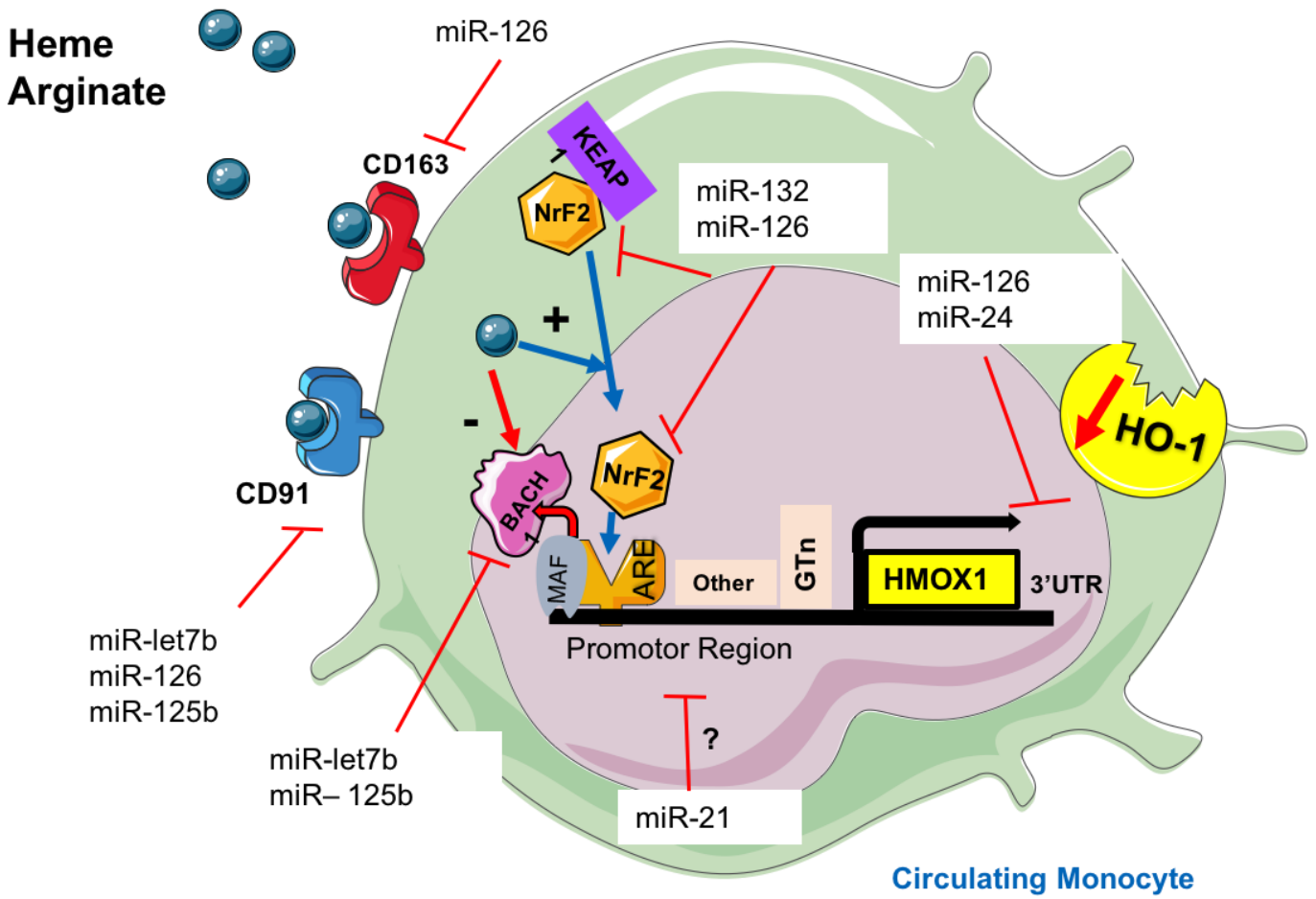


Marson Group

MicroRNAs and Heme Oxygenase 1 in Kidney transplantation

- 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

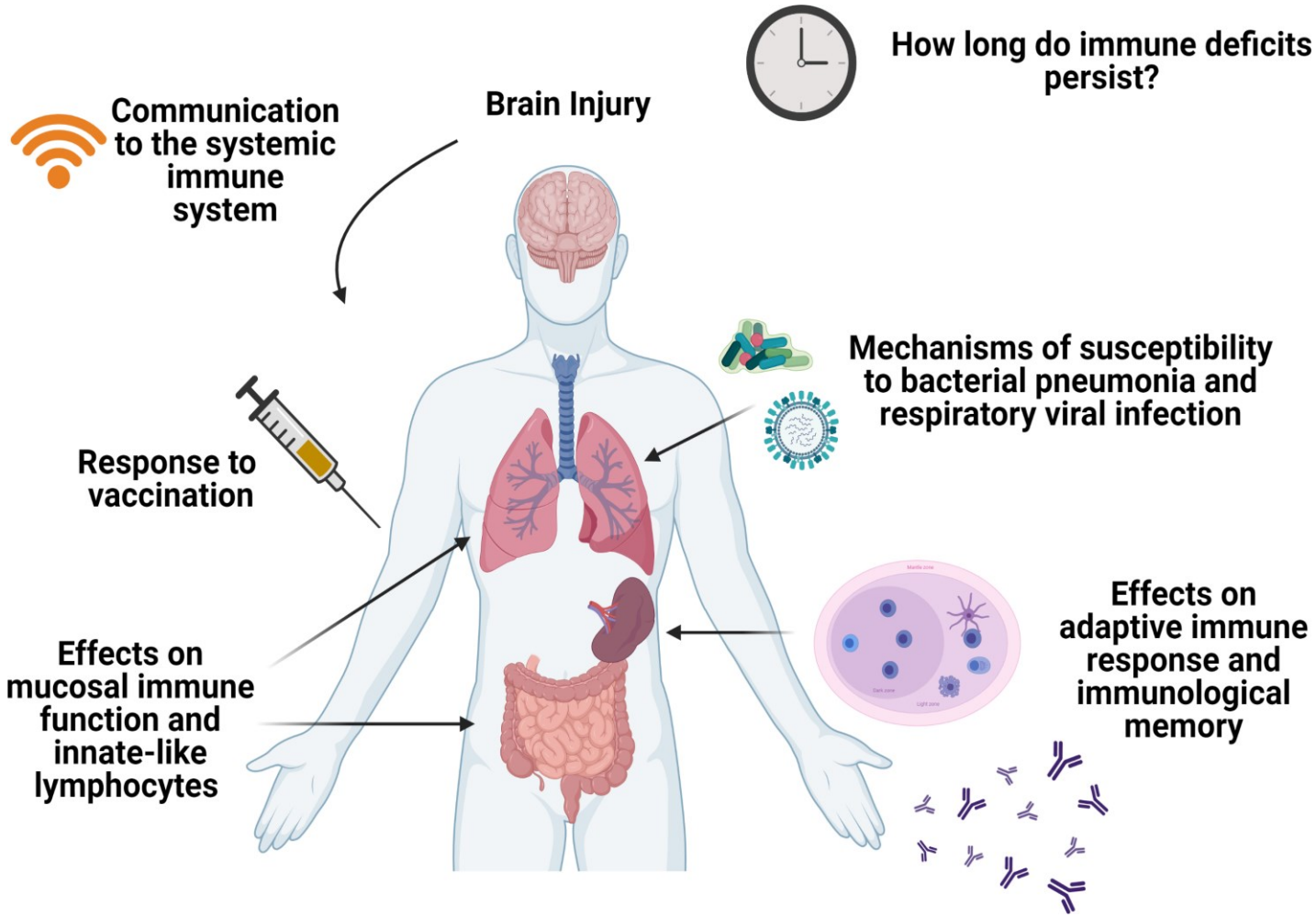
MiR Work is undertaken in collaboration with Dr. Laura Denby, CVS



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

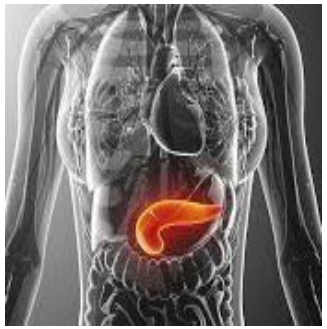


Mole Group

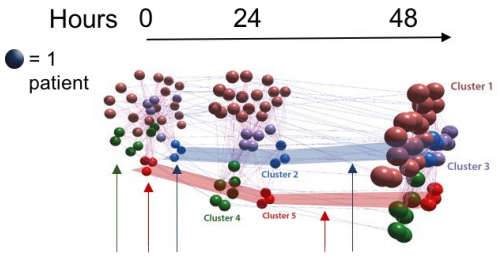
Inflammation and metabolism – drug discovery, precision medicine and prevention of long-term harm

- 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.

Human disease



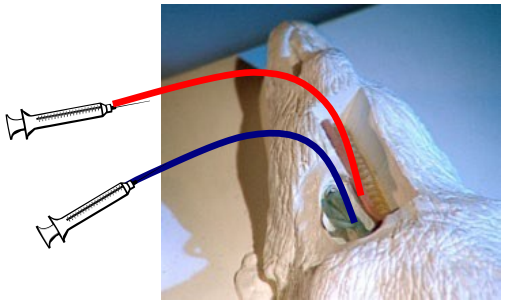
Precision medicine



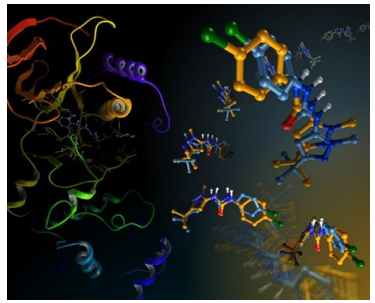
Cohorts + epidemiology

Regulating immune responses and inflammation – focus on KMO

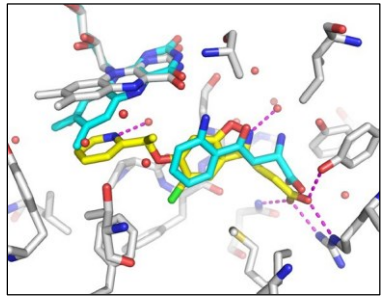
Experimental models



Molecular mechanisms



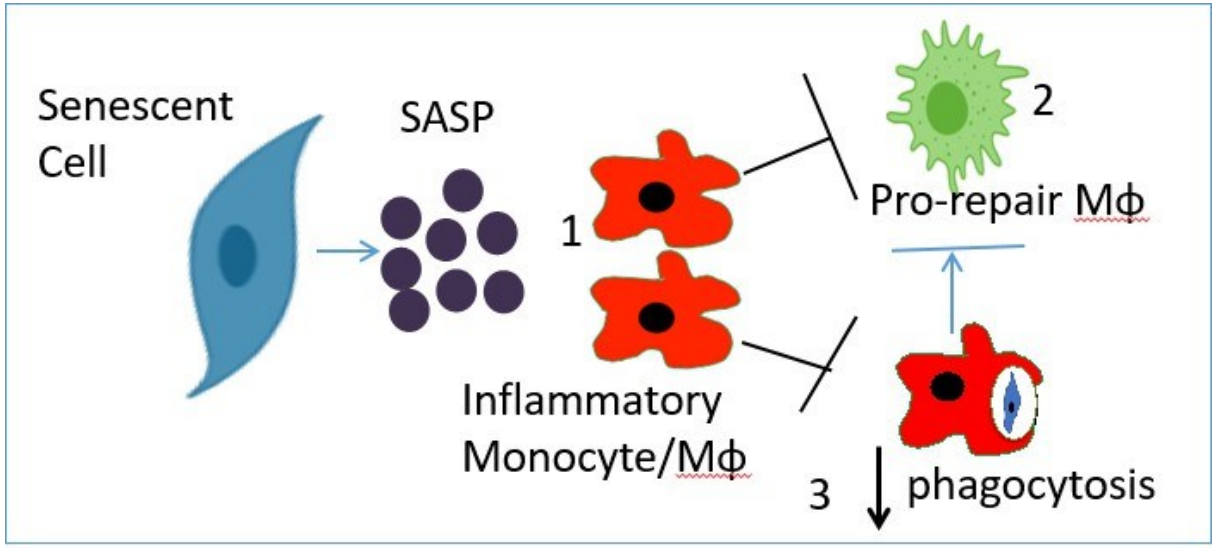
Drug discovery

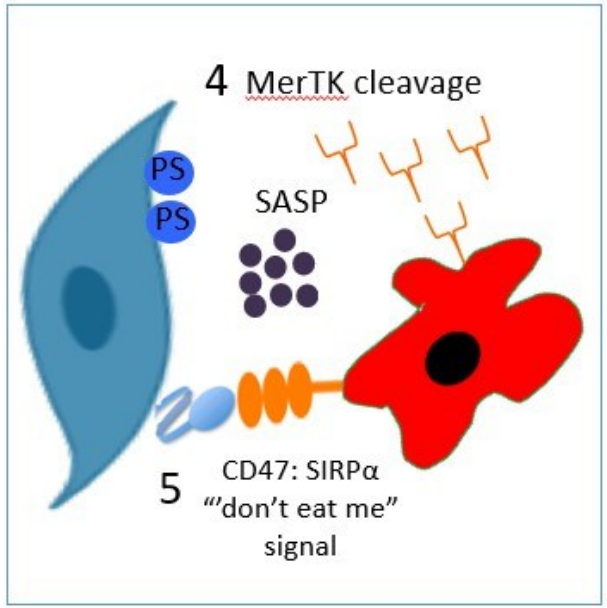


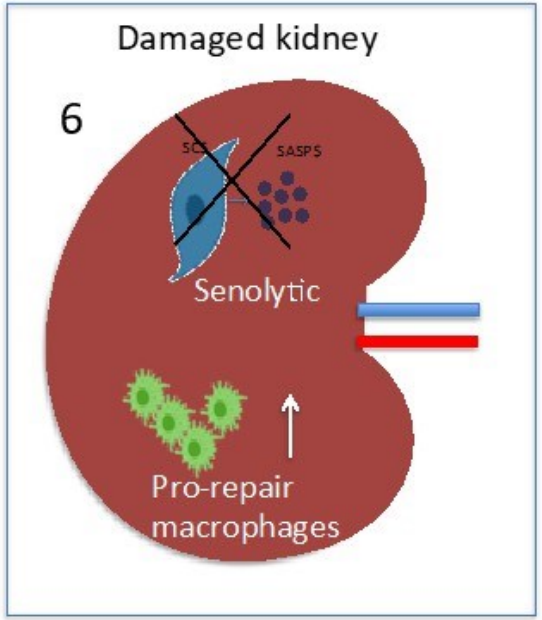
Mylonas Group

- 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



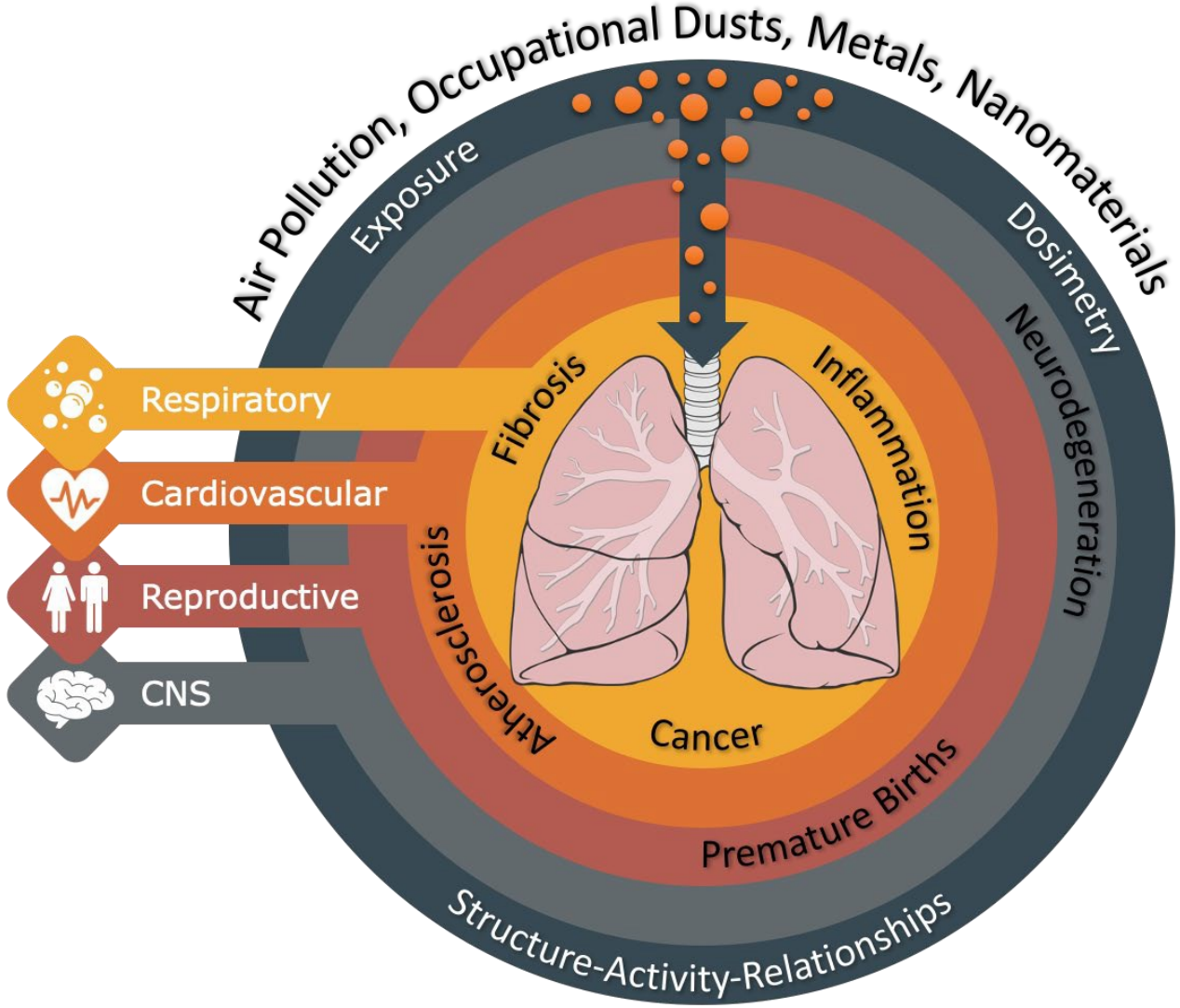




Particle Research Group

- 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**

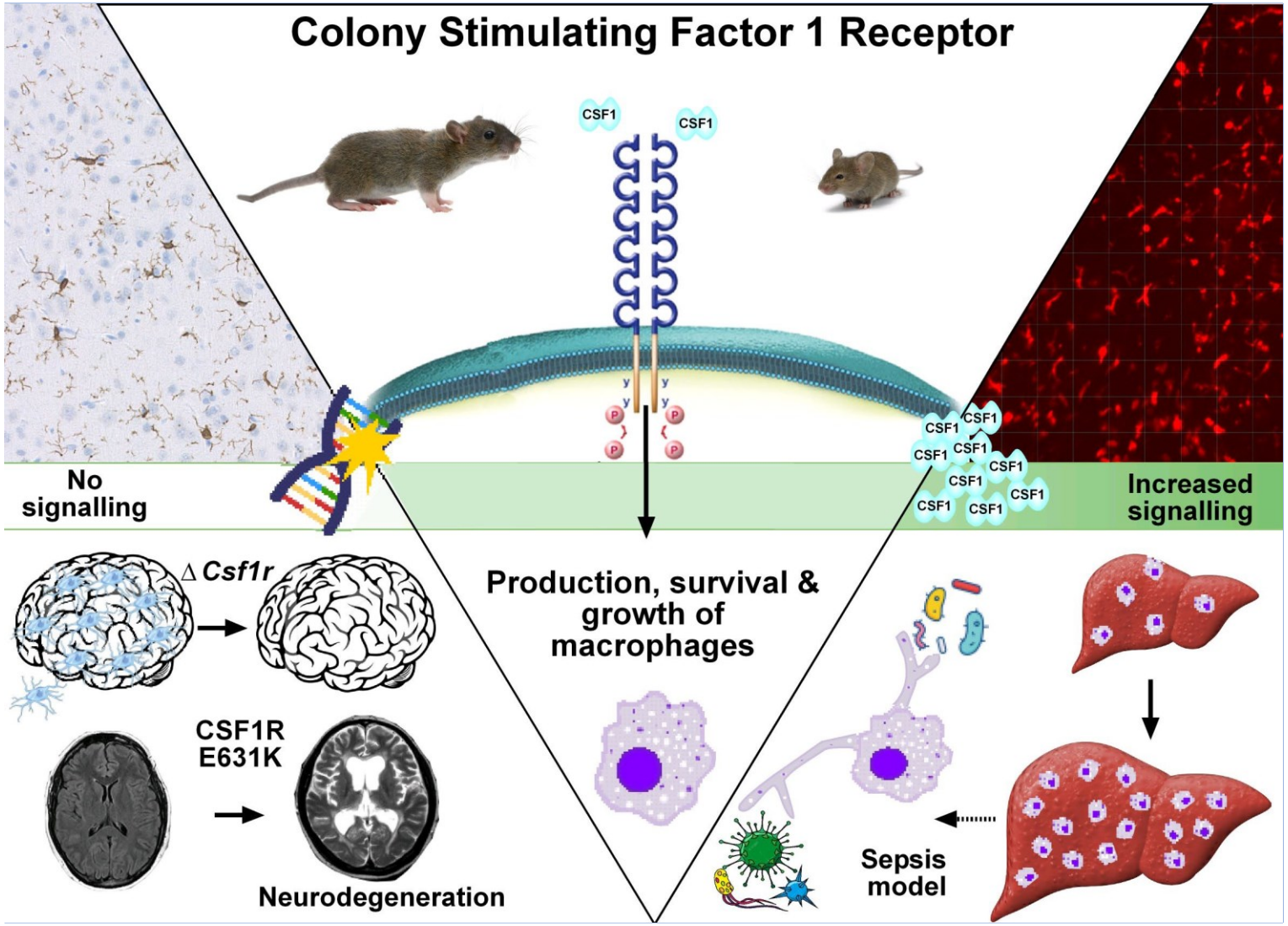
Multi-system effects of [nano]particle inhalation in health & disease



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

Identification of markers for disease management

- 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

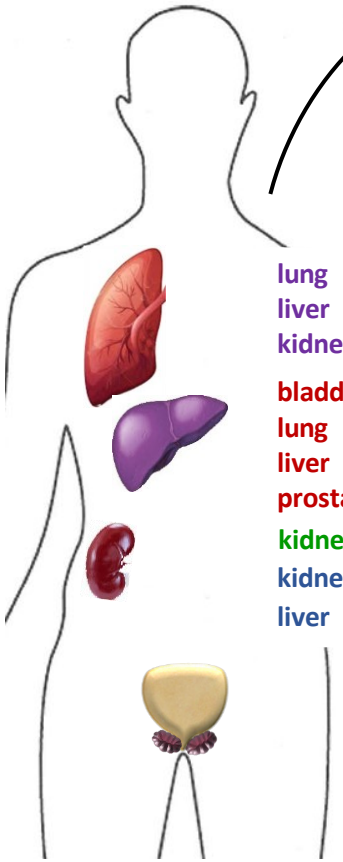
- Work with clinicians & pathologists to identify relevant questions
- Gene expression analysis identifies markers
- In situ multiplex IF staining reintroduces the spatial information, allows identification of rare phenotypes and cell-cell interaction
- Correlation with clinical outcome & validation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



Tissue biopsies

diagnosis
prognosis
management

lung
liver
kidney

COVID_19

bladder
lung
liver
prostate

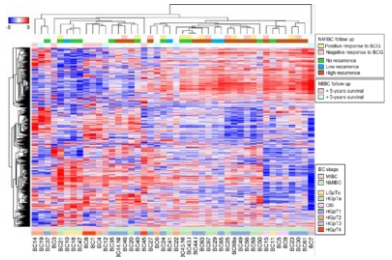
cancer

kidney
kidney
liver

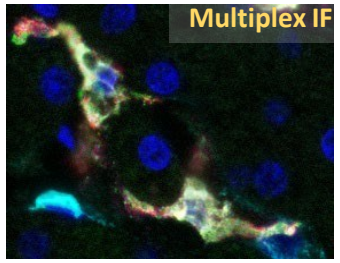
ANCA vasculitis

graft rejection

Gene expression analysis

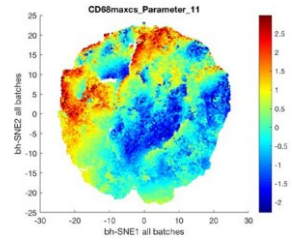


In situ phenotype



Potential markers

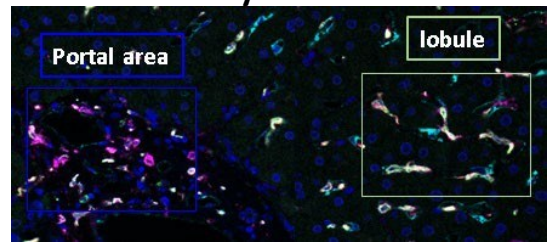
BIG DATA

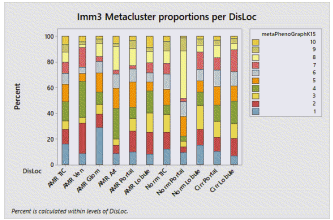


phenotypic landscape

Markers for diagnosis
Targets for immunotherapy
Improvement of disease management

Subpopulation characterisation at key tissue sites





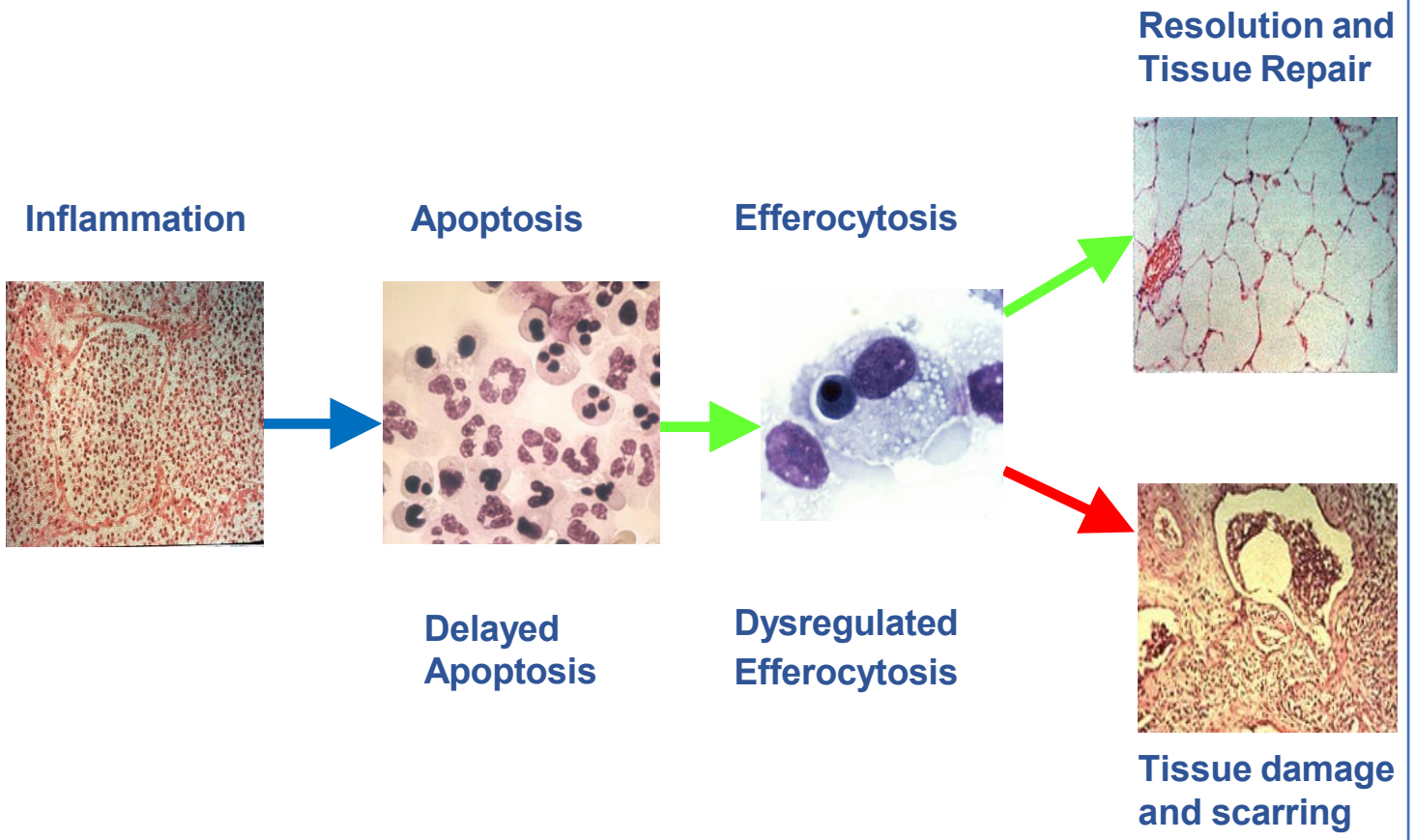
Correlation with clinical outcome

The Melville Trust
ICECAP
Kidney Research UK
CHIEF SCIENTIST OFFICE

Rossi Group

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

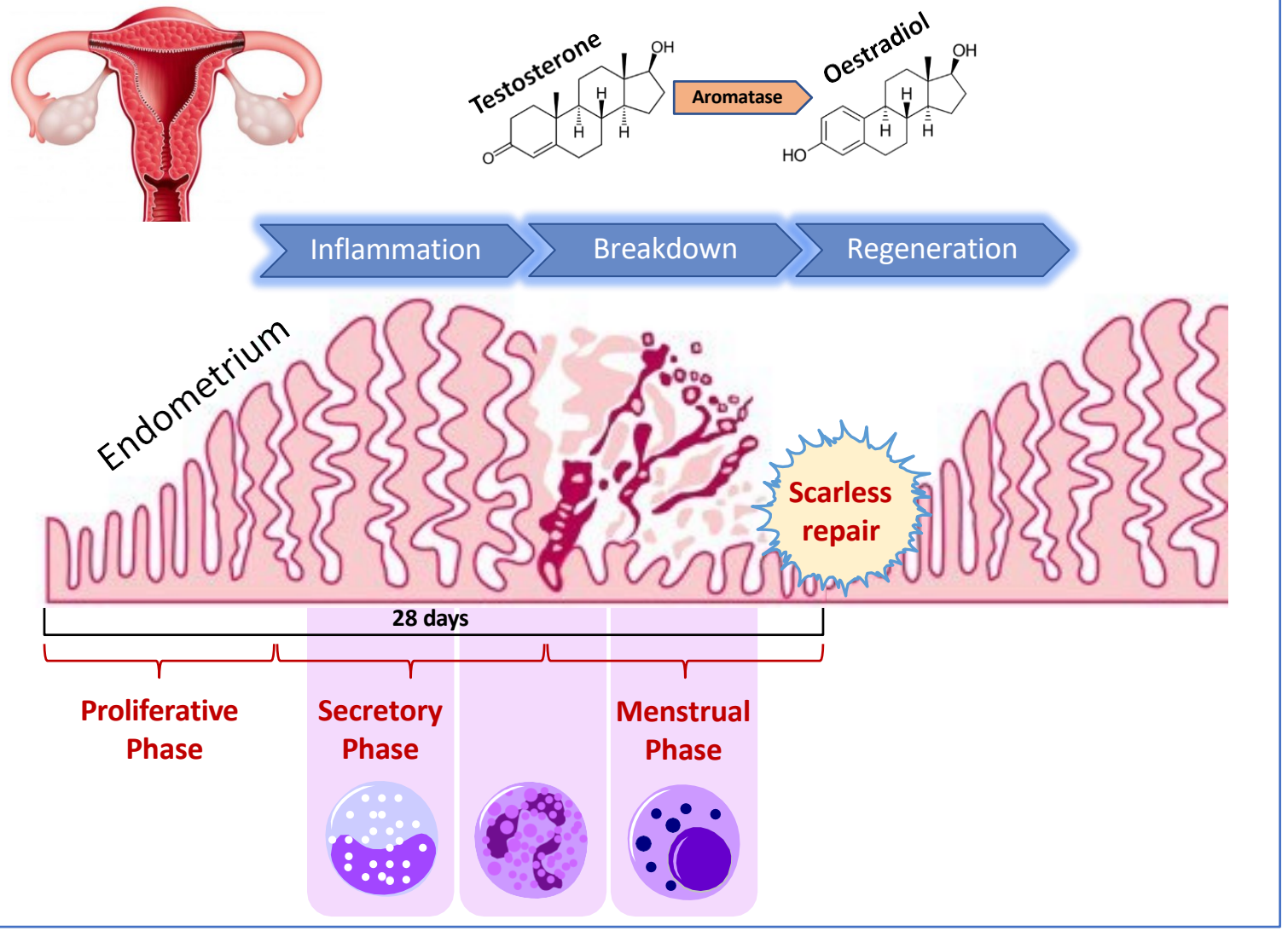
- Inflammation is key for host defence and tissue repair, however, dysregulated inflammation can lead to inflammatory diseases
- The inflammatory response involves many mediators and cell types that co-ordinate initiation, propagation and resolution of inflammation
- My group focuses on understanding 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



Saunders Group

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

- 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

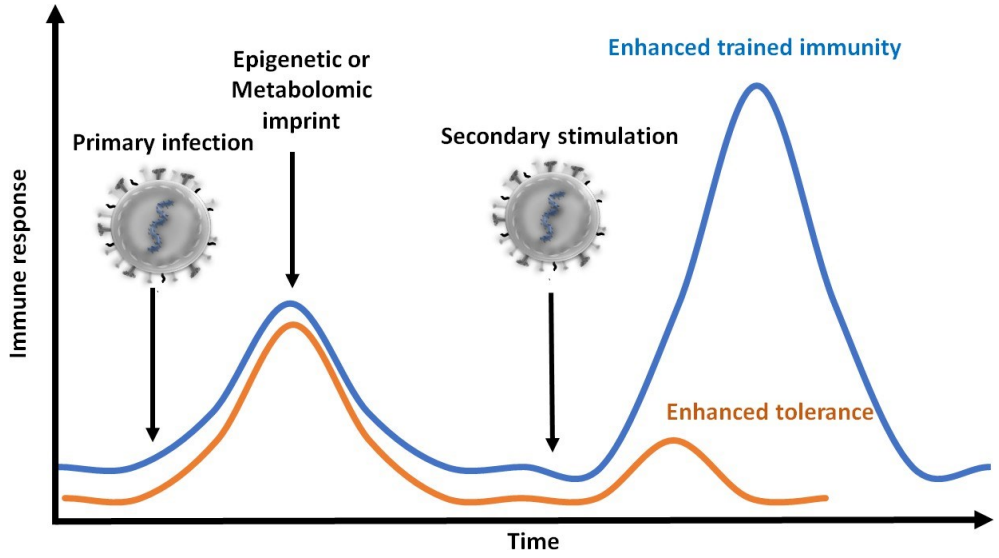


Schwarze Group

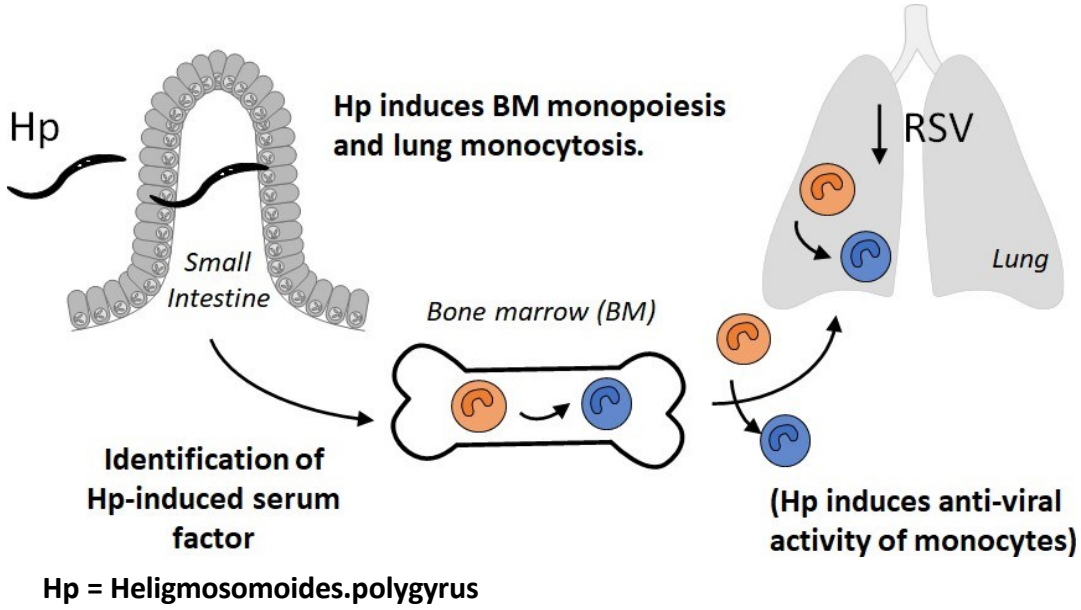
Mechanisms and consequences of respiratory mucosal priming prior to and following respiratory syncytial virus infection

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 monocytosis and their recruitment to the lung.



Hp = Heligmosomoides.polygyrus

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 (∴ 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

Test and learn with novel RCT designs

Immune and treatment response differences in critical illness

Endotypes

Immunotypes

Treatable traits

Mechanisms

Biomarkers

Illness models

Systems immunology of critical illness

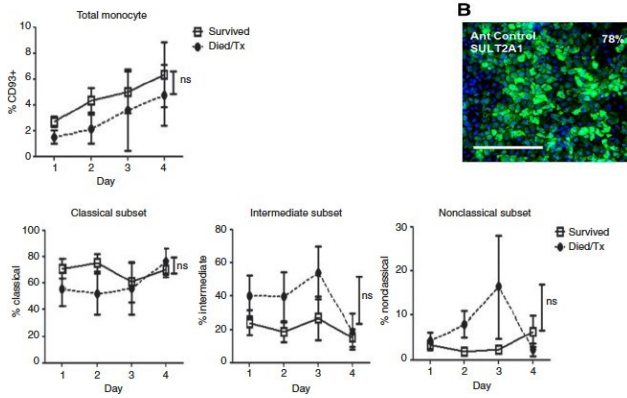
Inform and refine critical illness with longitudinal cohort studies and ex-vivo models measuring proteome, transcriptome, epigenome, leukocyte phenotypes

K. Simpson Group

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

- 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 of pathogenesis and biomarkers of outcome



	Hazard ratio	95% CI	pvalue
Day 1 model			
Age (per 5 year increase)	1·07	0·97–1·18	0·168
Cardiovascular failure*	2·41	1·39–4·17	0·002
Glasgow coma scale score	0·90	0·84–0·98	0·009
Arterial pH	0·06	0·01–0·61	0·018
Log (creatinine [per 10 units])	1·74	1·12–2·7	0·013
Log (INR)	1·53	1·04–2·24	0·029
Square root (arterial lactate)	2·01	1·53–2·63	$4·02 \times 10^{-7}$
Day 2 model			
Age (5 years)	1·07	0·98–1·18	0·146
Day 1			
Cardiovascular failure	3·14	1·8–5·49	$5·94 \times 10^{-5}$
Glasgow coma scale score	0·90	0·83–0·97	0·005
Arterial pH	0·09	0·01–0·95	0·045
Log (creatinine [per 10 units])	1·70	1·08–2·67	0·022
Log (INR)	1·97	1·33–2·91	$6·91 \times 10^{-4}$
Square root (arterial lactate)	1·78	1·37–2·32	$1·46 \times 10^{-5}$
Day 2			
Lower arterial lactate	0·31	0·13–0·69	0·0045
Lower INR	0·54	0·29–0·99	0·046

INR=international normalised ratio. *Sequential Organ Failure Assessment (SOFA) cardiovascular score ≥3.

Table 3: **Clinical predictors included in admission predictive model in the derivation dataset (n=350)**

Improving clinical outcome through guideline development

Clinical Practice Guidelines

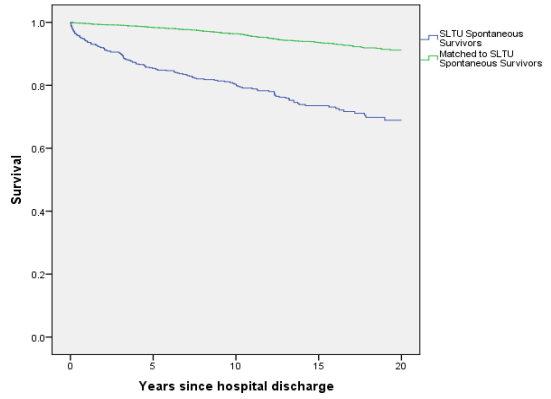
CrossMark

EASL JOURNAL OF HEPATOLOGY

EASL Clinical Practical Guidelines on the management of acute (fulminant) liver failure☆

European Association for the Study of the Liver*

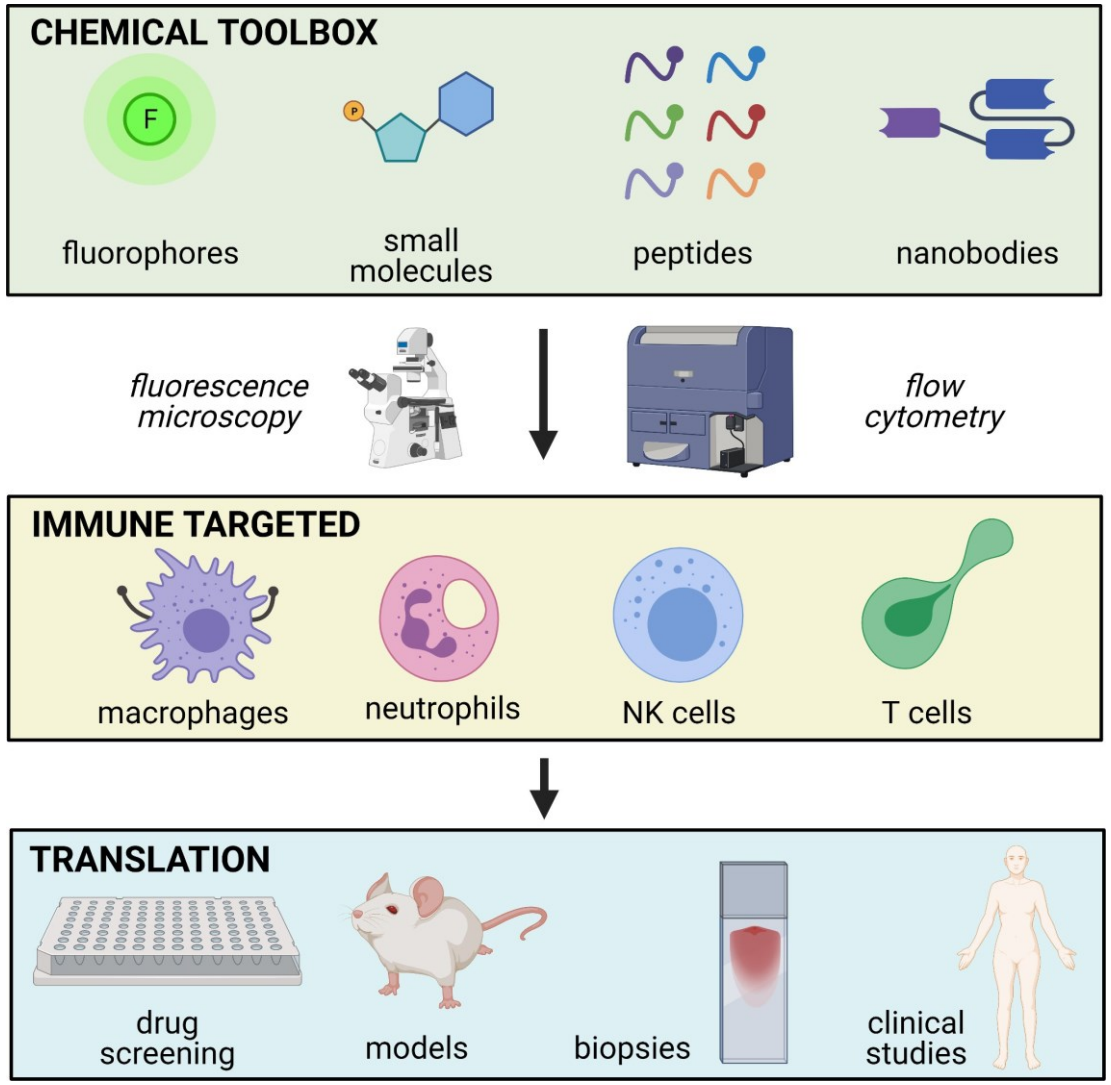
Improving understanding of long-term consequences



Vendrell Group

Translational chemistry and biomedical imaging

- 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)



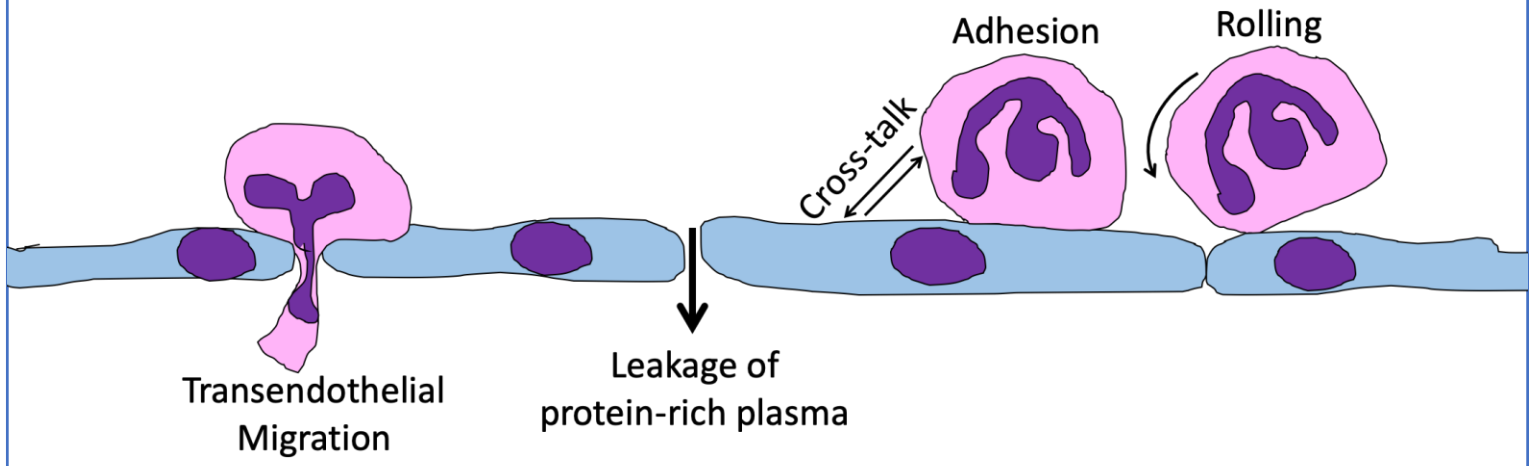
Vermeren Group

Signalling in inflammation

- 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

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

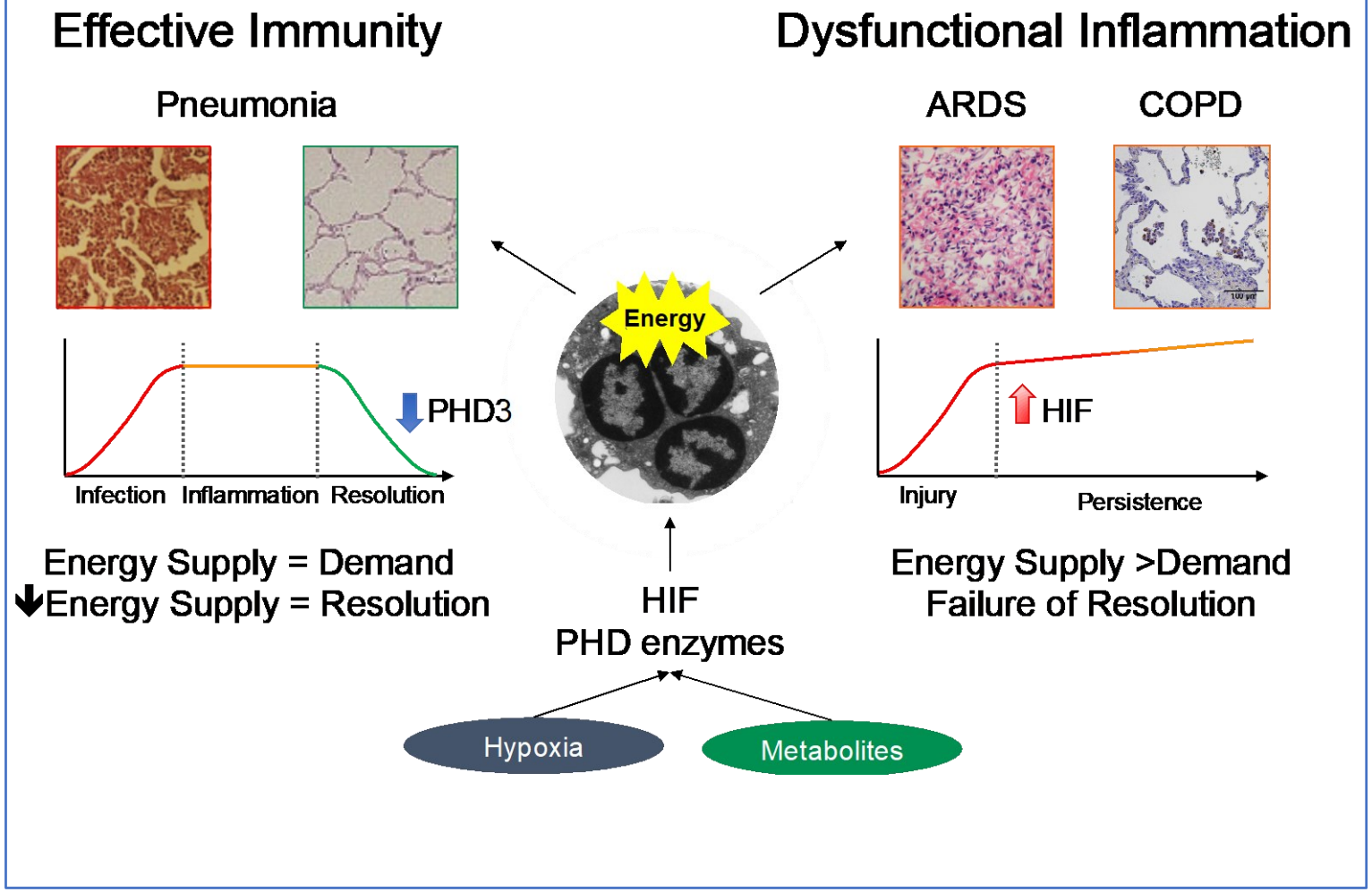
Regulation of neutrophilic inflammation by oxygen and metabolite sensing pathways

Research goal

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

Specific Aims:

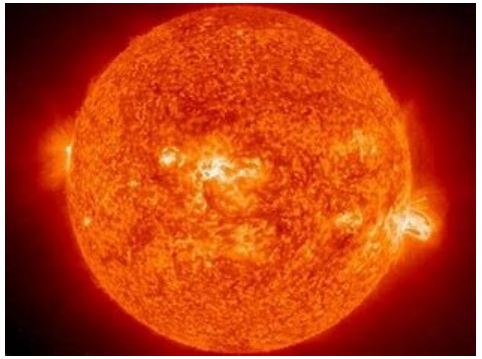
- Characterise neutrophil adaptation to oxygen and metabolite availability
- Determine how hypoxia (HIF/PHD pathway) reprograms neutrophil energy production
- Define how neutrophil access to internal energy stores determines inflammation outcomes
- Delineate mechanisms of long-term reprogramming of neutrophil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



Weller Group

Ultraviolet Radiation and Systemic Health / Eczema

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

Eczema

Immunology
PGE2-IL22 pathway in eczema
Fillagrin deficiency and antigen presentation

Barrier
Anti protease actions of HBD2 in maintaining skin barrier function

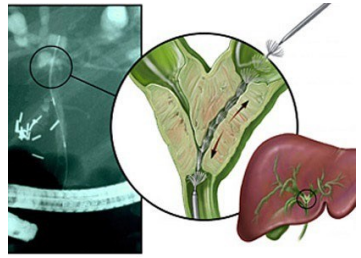
Clinical
Translational studies and registry studies linking the clinical eczema service with laboratory science

Wigmore Group

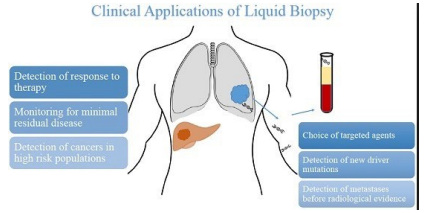
Drivers and diagnostics for primary liver cancers, functional liver imaging and organ preconditioning

- 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

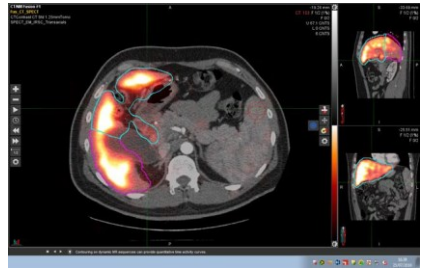
Inflammation as a driver for bile duct cancer formation in primary sclerosing cholangitis



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



Functional liver imaging and novel techniques for imaging primary liver cancer



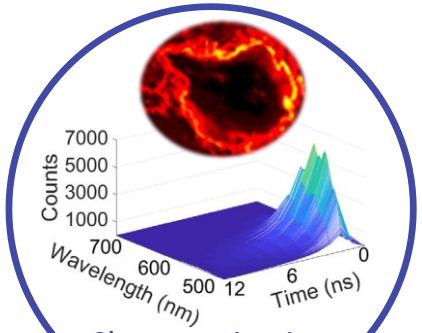
Novel therapeutic interventions to precondition organs for transplantation

Williams Group

Translational photonic technologies for probing and treating disease

- 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

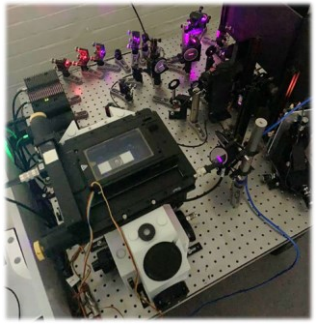
Optical Fingerprinting



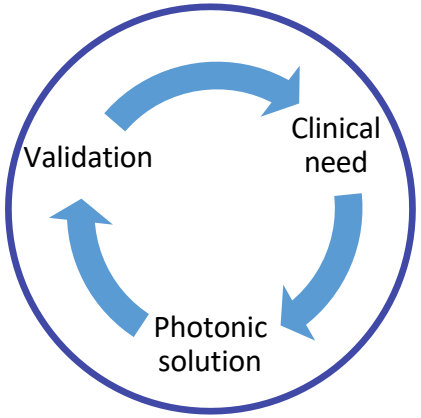
Characterisation

Frugal Innovation

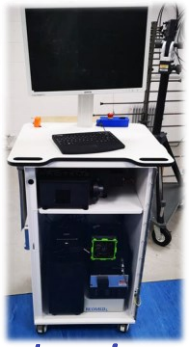
Detection and treatment



Ex-vivo



Clinical Translation

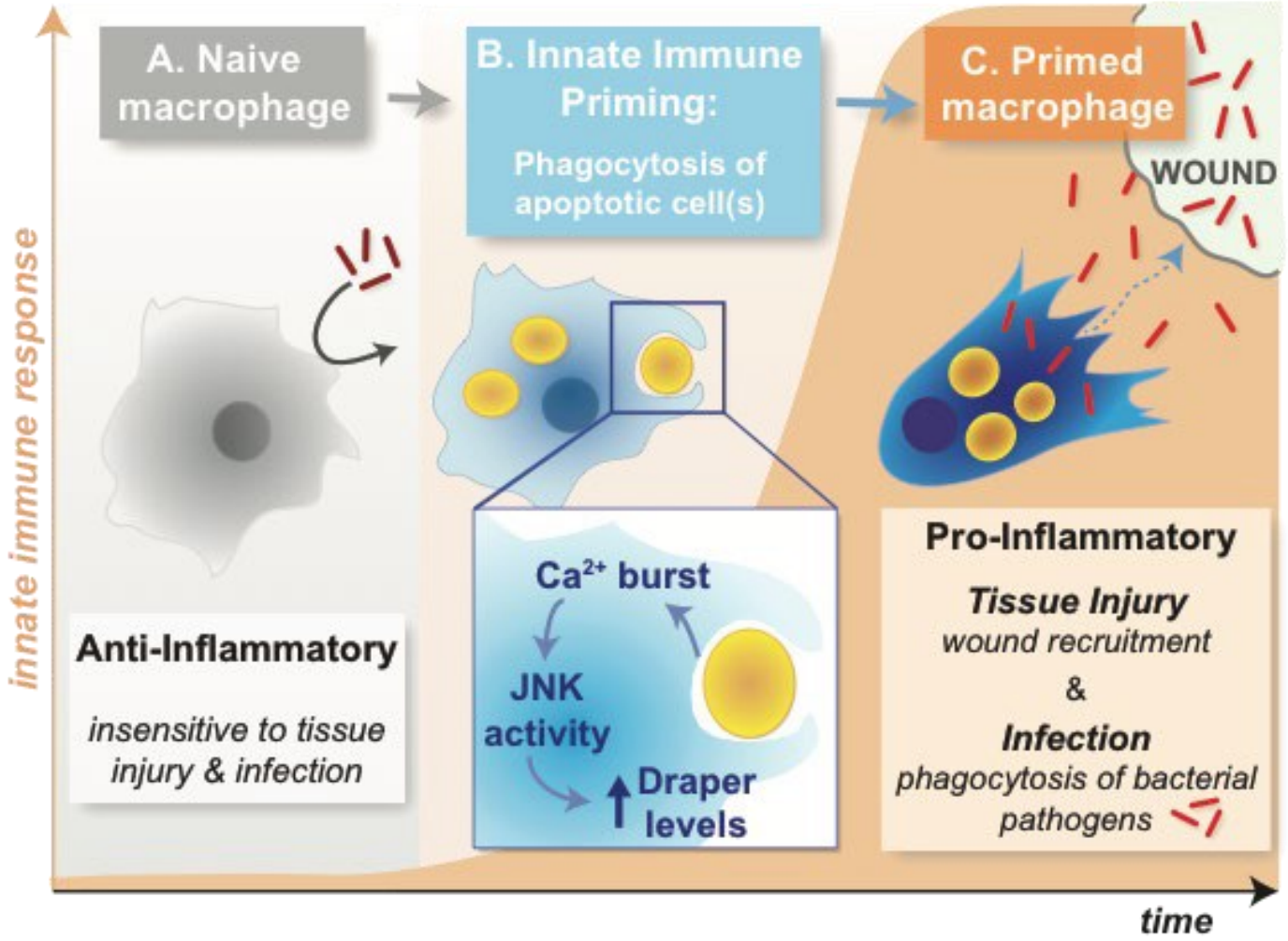


In-vivo

Wood Group

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

- *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'



Yao Group

Bioactive lipid mediators and mucosal inflammation

Our aim:

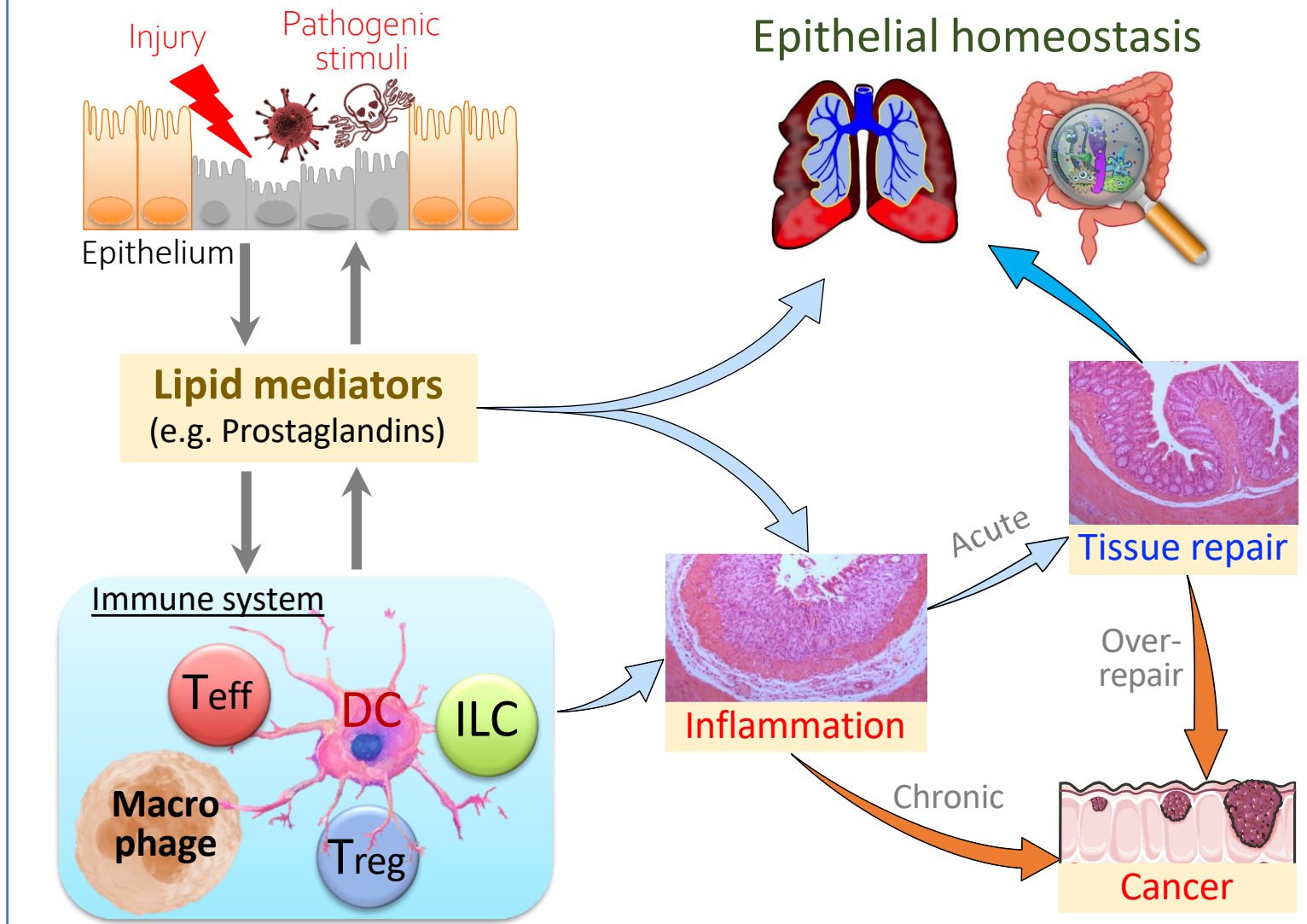
To understand how bioactive lipid mediators modulate mucosal immune responses and control epithelial homeostasis, inflammation, repair, and tumorigenesis.

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

Applying athletics data science to enhance performance in surgery and spaceflight

- 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**.