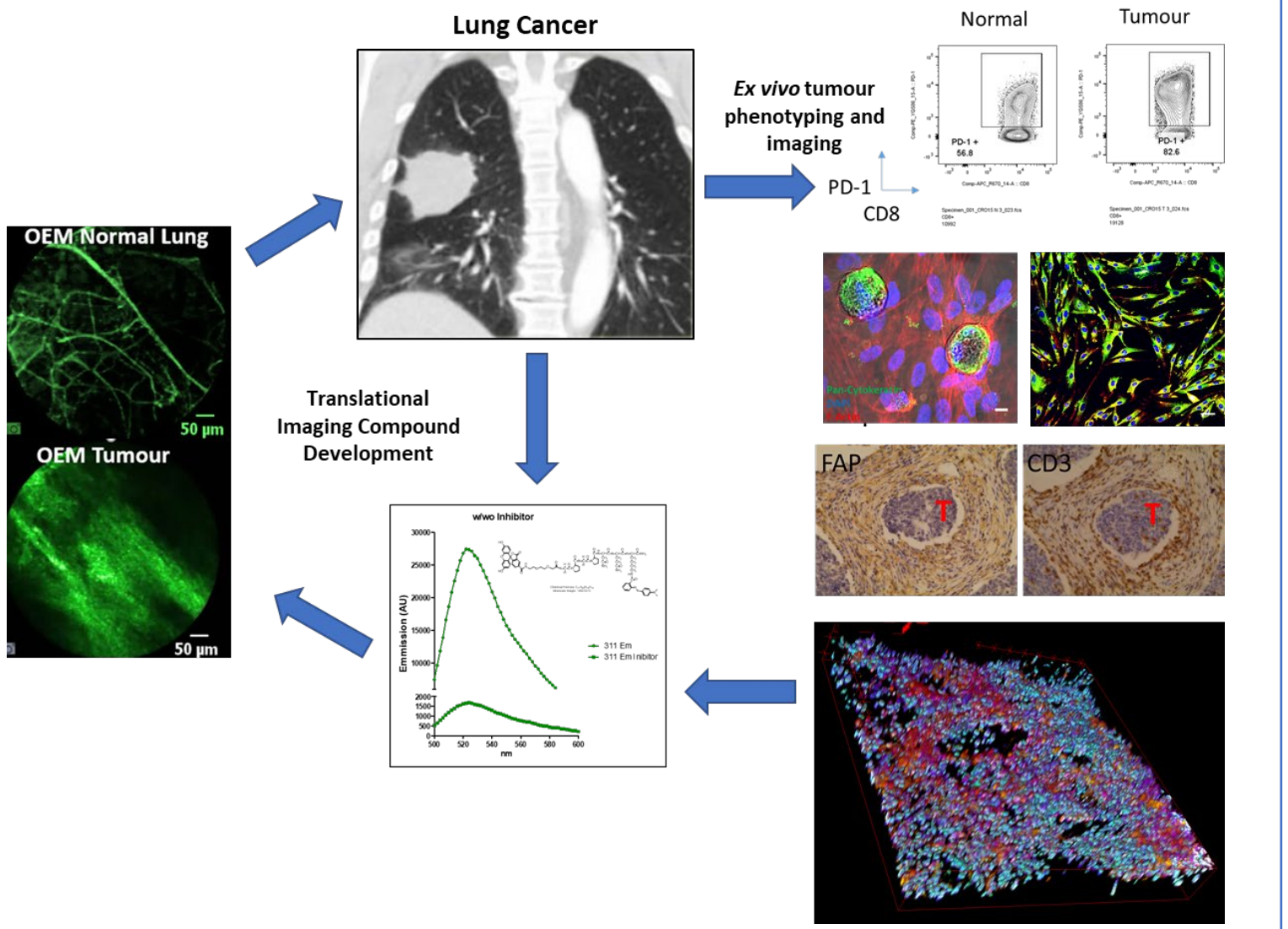
Akram Group

Lung Cancer Immunophenotyping and Imaging compounds for treatment stratification

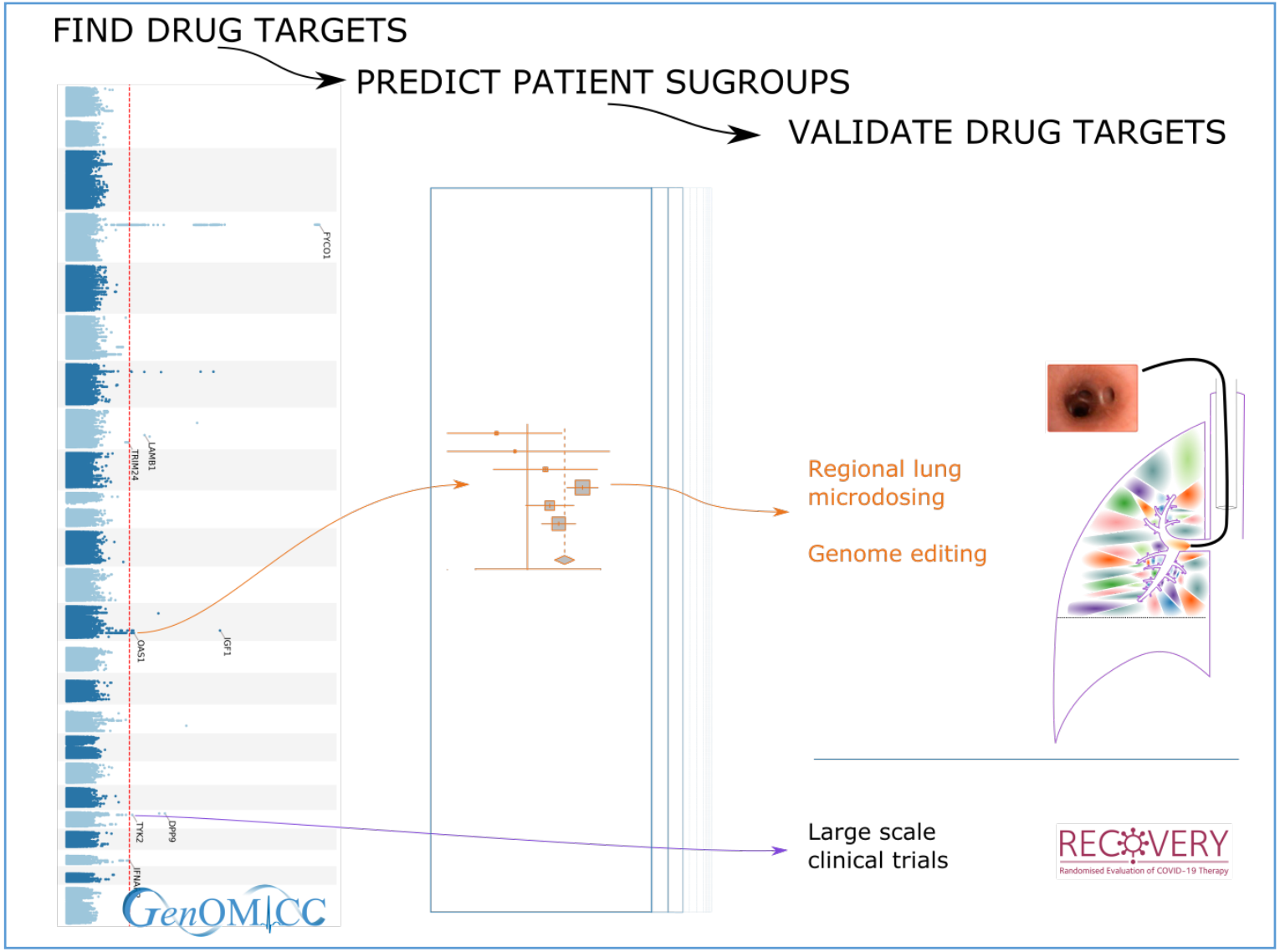
- Lung Cancer is a cancer of poor prognosis and unmet need
- Our work looks to understand the role of the tumour microenvironment in regulating response to therapy
- Assess this using *ex vivo* cancer specimens, translationally relevant model systems and *in vivo* imaging
- Developing imaging agents against key targets may allow treatment optimisation, informing treatment timing and efficacy
- Imaging modalities include high resolution optical imaging and whole body PET imaging



Baillie Group

Translational genomics in critical care

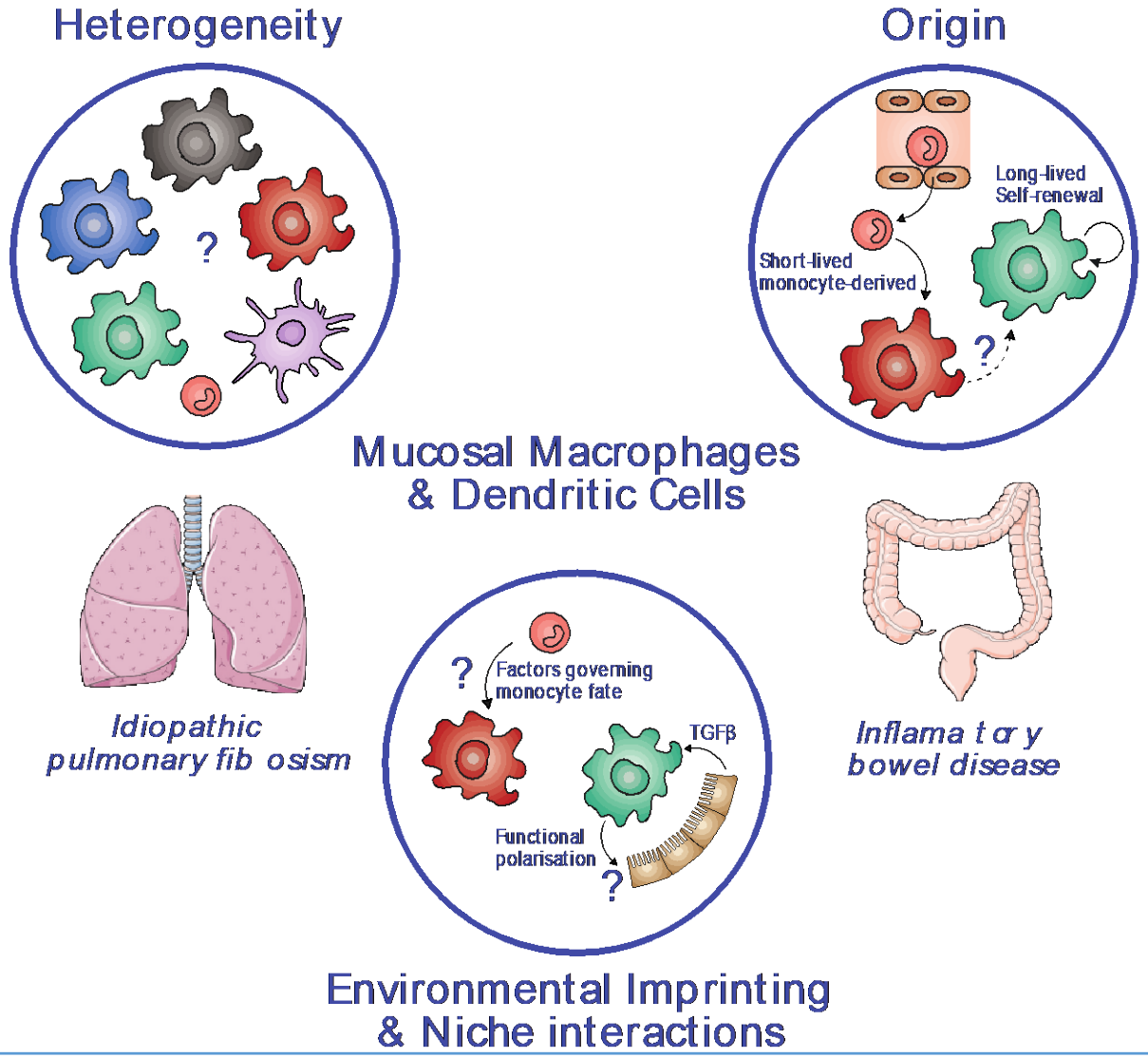
- Organ injury in critical illness is a mediated by the host immune system
- Genetic predisposition to susceptibility or mortality can identify therapeutic targets
- Computational methods prioritise targets
- Targets confirmed by
  - Genome editing
  - In vivo microdosing
  - Clinical trials



Bain Group

Mononuclear phagocyte biology at the mucosal barrier surfaces in health & disease

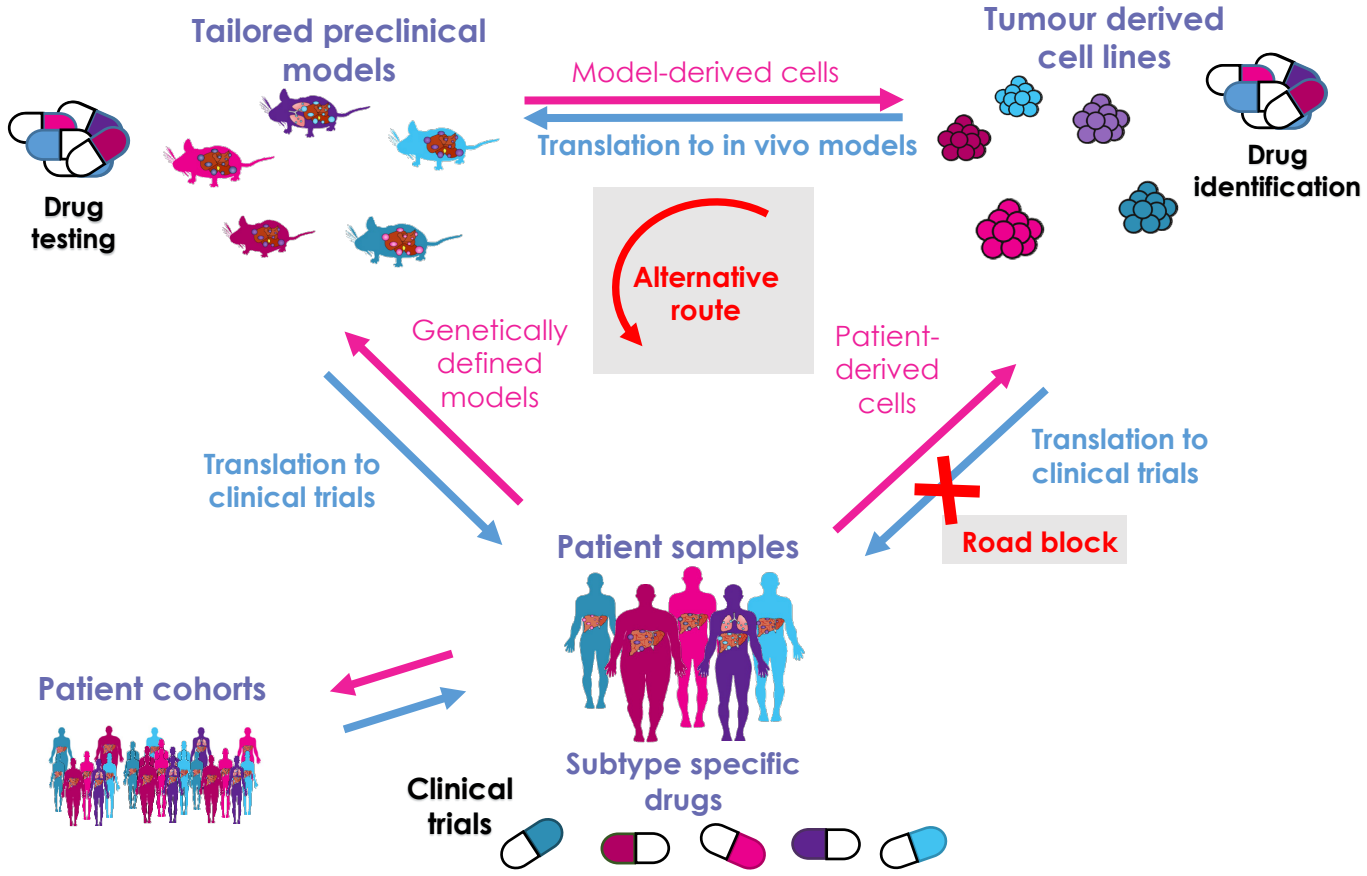
- Mononuclear phagocytes (**macrophages** & **dendritic cells**) are essential for **mucosal homeostasis** and **tissue repair** but also drive **chronic pathologies e.g. IPF & IBD**
- Tissue macrophages & dendritic cells are **highly heterogeneous** – distinct functions by discrete subsets?
- Macrophage subsets can arise from **distinct precursors** – developmentally-distinct macrophages behave differently in health and inflammation
- **Environmental signals** imprint the identity and function of macrophages & dendritic cells – **nature of these signals is poorly understood**



Bird Group

Translational research using preclinical models for precision medicine in liver cancer

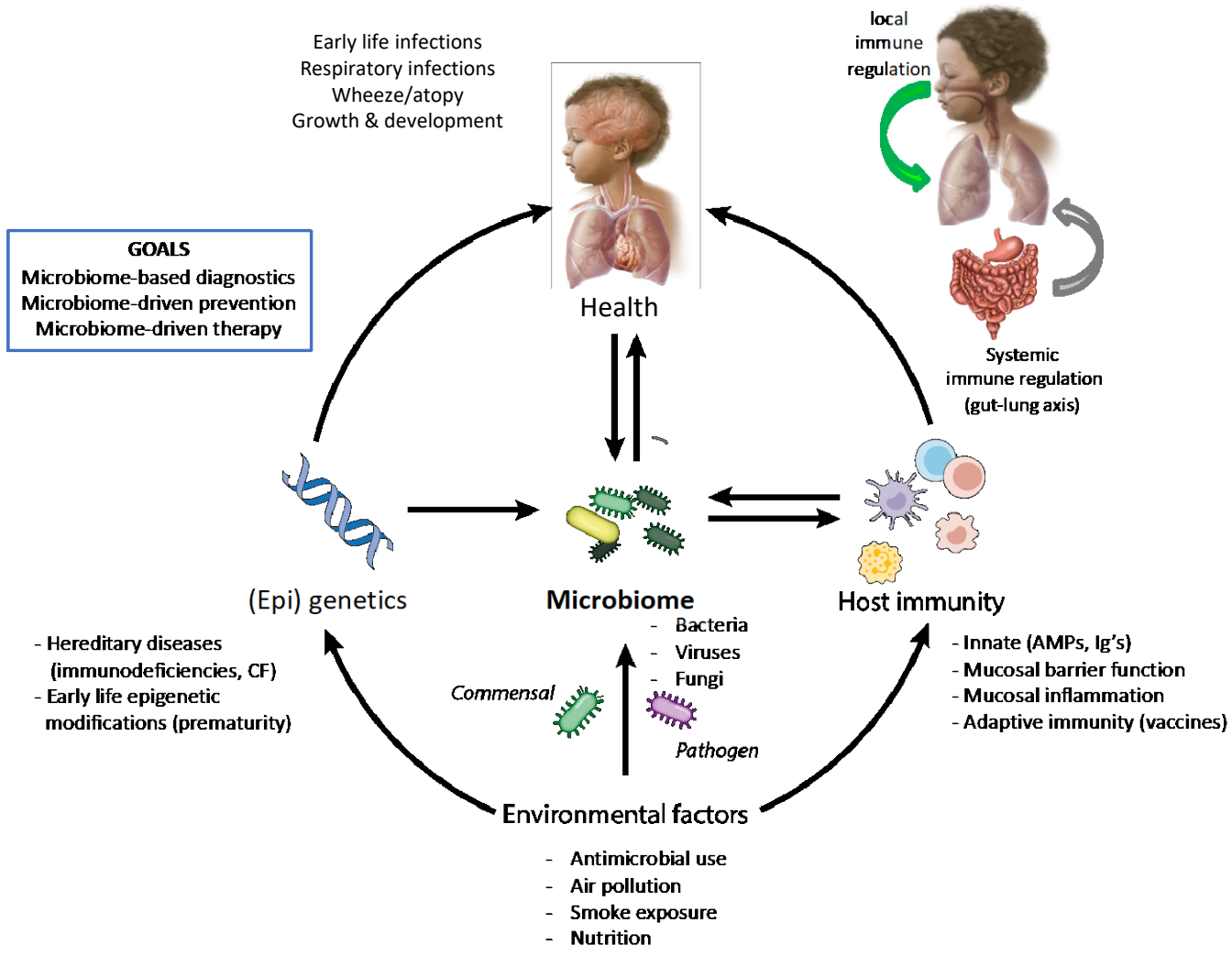
- Liver cancer is common and difficult to treat
- Cancer is a genetic disease and based on genomic profiling we have developed a suite of **subtype specific preclinical models of liver cancer** (hepatocellular carcinoma)
- With comparison to **human tissue and cell lines** we want to understand **unique therapeutic vulnerabilities of cancer subtypes**.
- The **tumour microenvironment** is variable between subtypes. **Treatment options** will be influenced by the understanding of these tumour: environment interactions.
- Tumours **evolve** during their development and in response to treatment. Insights into both may lead to **novel treatment targets**



Bogaert Group

Pathogenesis of common infections from an ecological perspective

- Infections commonly caused by potential pathogens (viral, bacterial, fungi) that are part of a diverse microbial ecosystem
- Microbial ecosystem important for:
  - pathogen resistance/containment
  -immune modulation
  -support of mucosal barrier function
- Microbiome seeded at birth, rapidly developing following (critical window)
- Certain microbial communities associated with protection against infections
- Beneficial microbes commonly Gram positive commensals
- Mechanisms of effect currently studied on host, microbial and environmental level

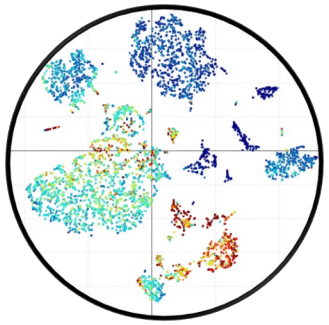


Cash Group

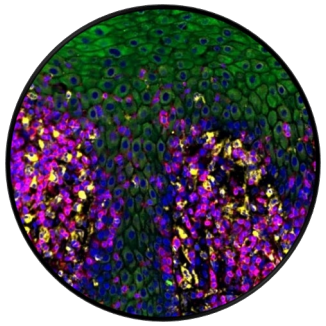
Understanding the mechanisms that govern skin repair versus repair failure

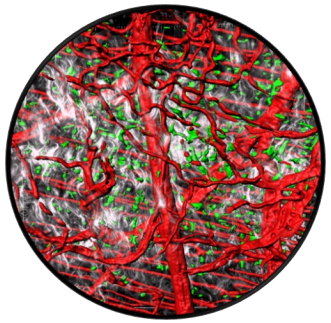
- Skin wounds typically repair by forming a **scar**. However, a growing proportion are developing into **chronic non-healing wounds.**
- Our work focusses on understanding how the healing process derails to identify novel **therapeutic targets** to reverse the process.
- We are exploring macrophage (**MΦ**) and granulocyte (**PMN) heterogeneity** and **function** in acute and chronic wounds, as these cells play both beneficial and detrimental roles in skin healing.
- We seek to understand how the **skin vascular niche** is impacted by the chronic wound microenvironment.
- We are investigating the use **of intelligent wound dressings** and novel **small molecule and biological therapies** to treat non-healing wounds.

MΦ and PMN heterogeneity

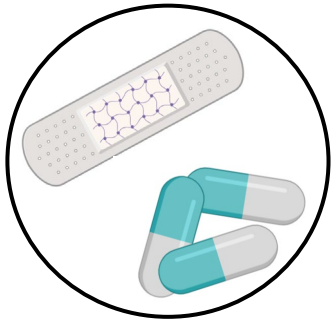


Function of distinct MΦ and PMN subsets





Skin vascular niche



Novel therapeutics

Cunningham Group

Mind the gap: Enabling early phase trials for Respiratory Disease in Children

- Respiratory disease is the most common illness in children
- There is a gap in knowledge for clinical phenotypes in young children and efficient clinical study designs.
- We create data to support and deliver clinical trials, including deep phenotyping, clinical outcome/biomarkers and protocol development for conditions including:
  - Bronchiolitis/Lower respiratory tract infection.
  - Cystic Fibrosis
  - Asthma
  - Rare Lung Disease

Cystic Fibrosis
- Modifier treatments in preschool children
- Registry effectiveness studies

Rare Lung Disease
- Phenotyping and biomarker studies
- Early phase novel therapeutics

RSV
- Epidemiology studies
- Early phase vaccine and antiviral studies
- Respiratory support during infection

Asthma
- Asthma Deaths
- Interventional clinical trials

Davidson Group

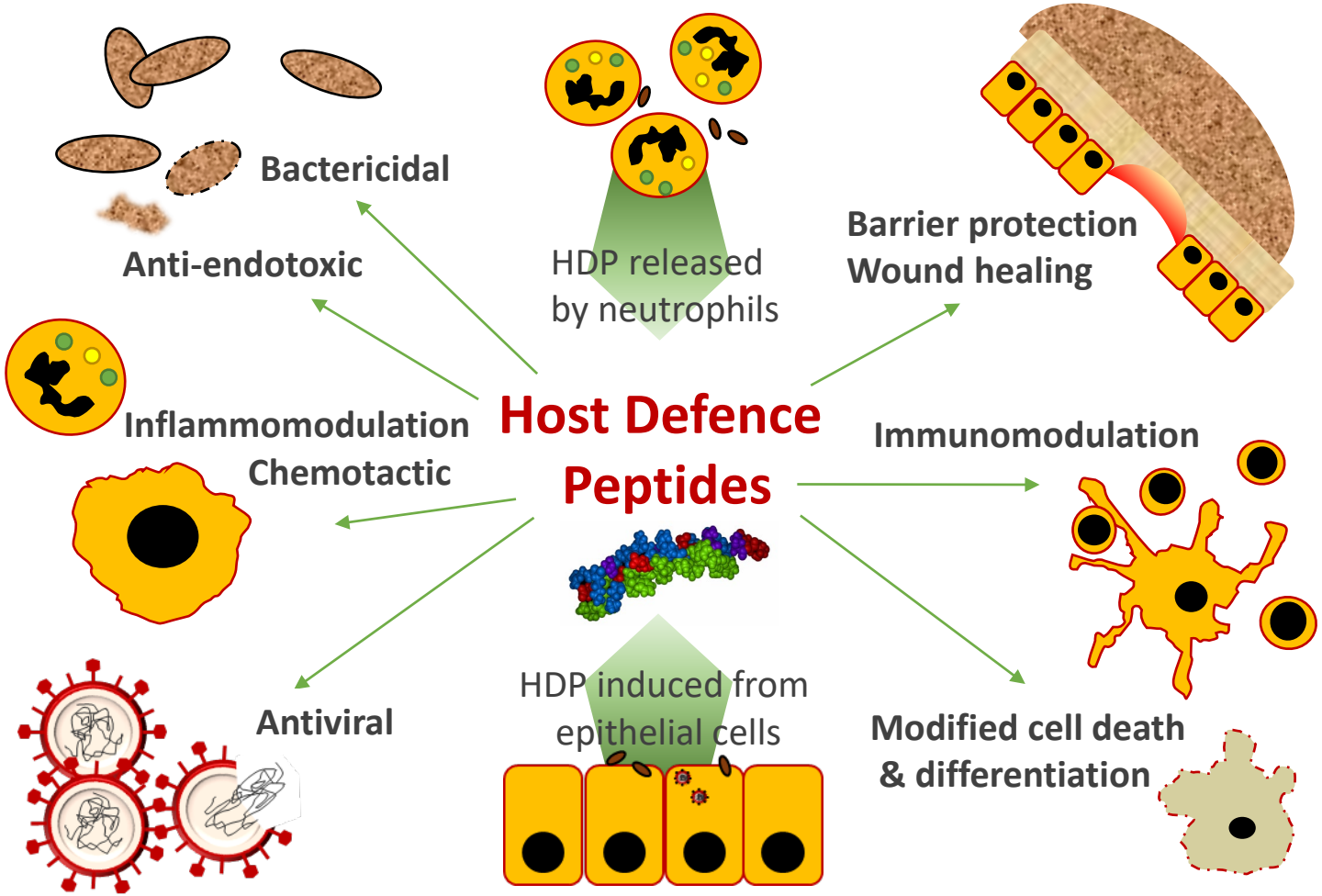
Host Defence Peptides as antimicrobial modulators of inflammation & immunity in infectious diseases

- **Viral lung infections (RSV, influenza) bacterial pneumonia eczema & cancer immunotherapy**
- Few treatments exist for viral infections
- Antimicrobial resistance is an increasing global threat
- **Host Defence Peptides** (HDP) are critical components of innate host defence

HDP properties:

- Antiviral / Antibacterial
- Anti-endotoxic
- Protective inflammation enhancing
- Wound healing promotion
- Cell differentiation modulation
- Immunomodulation
- Cell death modulation

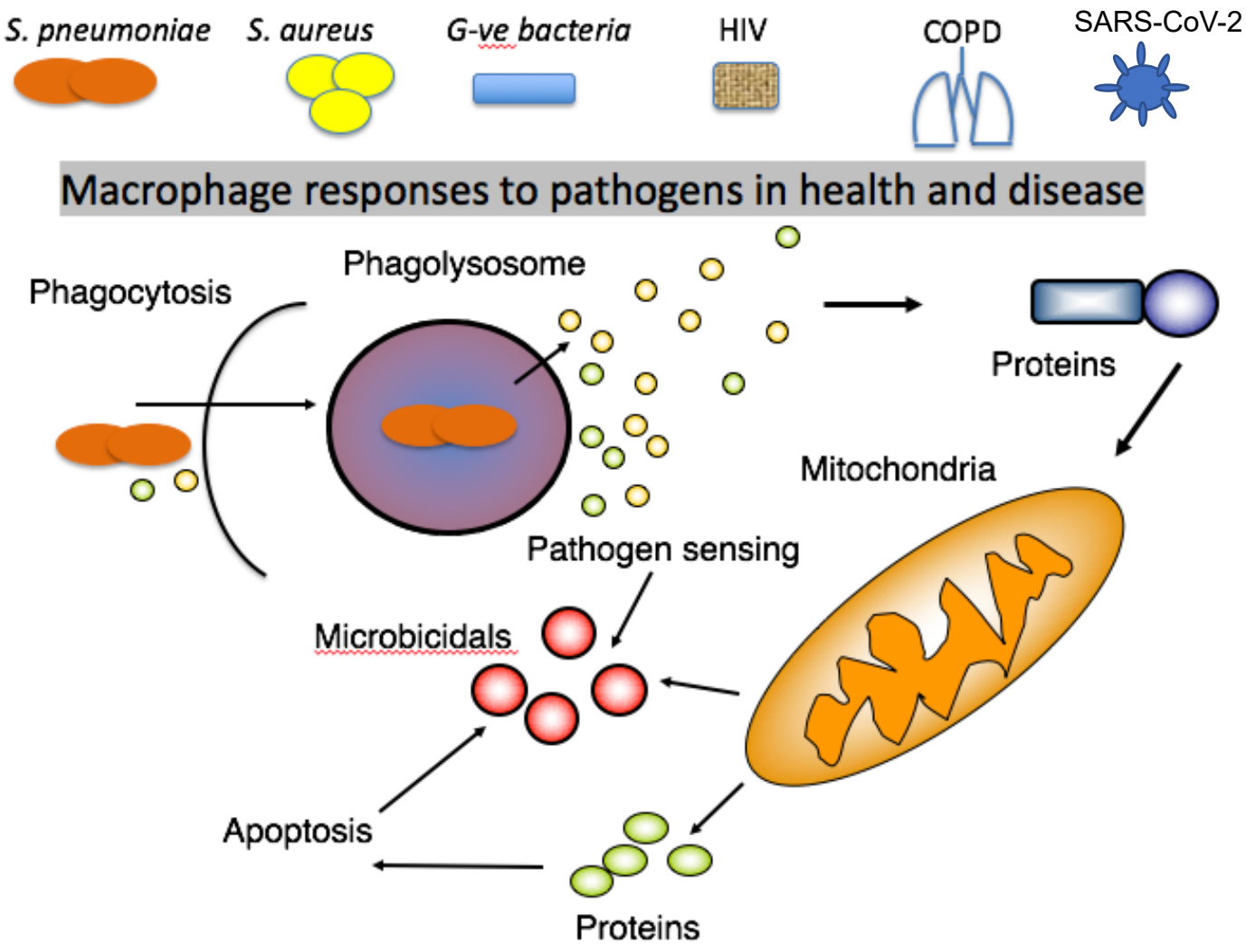
- HDP are translatable targets for novel interventions – by inducing endogenous expression or using peptide therapies



Dockrell Group

Macrophage roles in susceptibility to infection

- The basis of susceptibility and resilience to common infections is poorly understood.
- MACROPHAGES are the resident ALVEOLAR tissue phagocytes first responding to infections in the lung
- We study responses that influence infection outcome including:
  - Phagocytosis pathways
  - Microbicidal generation
  - Cell death paradigms
  - Pathogen sensing
  - Induction and regulation of inflammation
- Microbicidal responses are often the bottle-neck defining outcome
- We aim to recalibrate these host responses to develop host-based therapy to combat antimicrobial resistance.
- We also study how impaired host responses lead to aberrant inflammatory trajectories e.g. in Covid-19 utilizing CL3 facilities



Dorin Group

Host Defence peptides: roles in immune modulation & potential as therapeutics

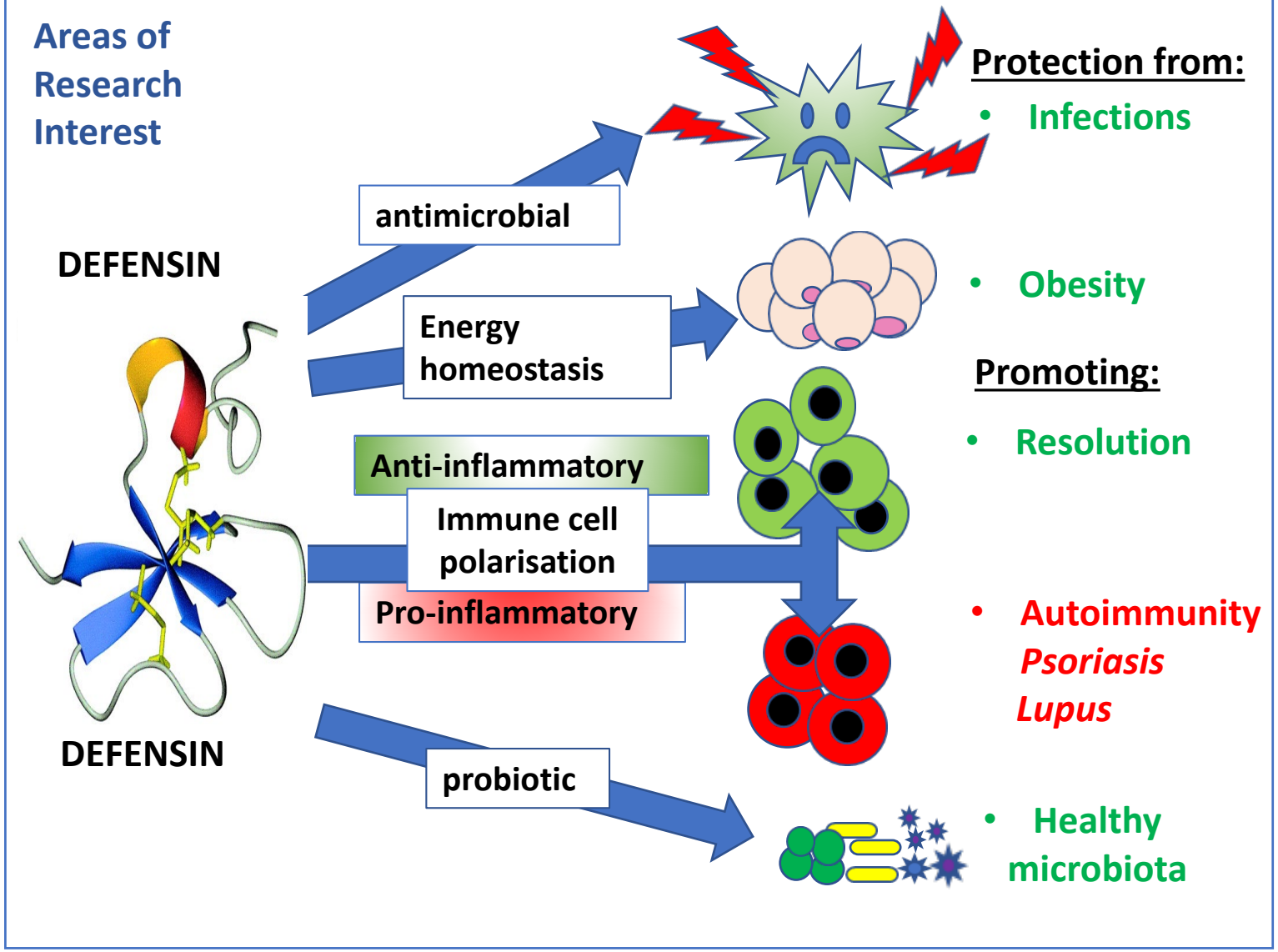
Host Defence Peptides

potent natural antimicrobials against:

- *Bacteria*
- *Viruses*
- *Fungi*
- *Including multi-drug resistant types*

AND modify immune responses:

- ***Increase*** *response to pathogen nucleic acids to increase type 1 interferon signature & bridge to adaptive immunity.*
- ***Decrease*** *response to LPS via TLR4*
- ***Increases*** *alternative activation of macrophages*
- ***Defensins*** *are* ***hyper copy number variable (CNV) in humans***
- ***Increased*** *CNV associated with psoriasis*
- ***reduced*** *CNV associated with increased adiposity*

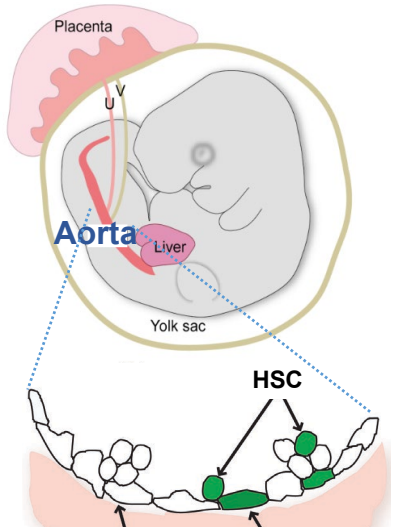


Dzierzak Group

Programming *in vivo* transplantable hematopoietic stem cells during development

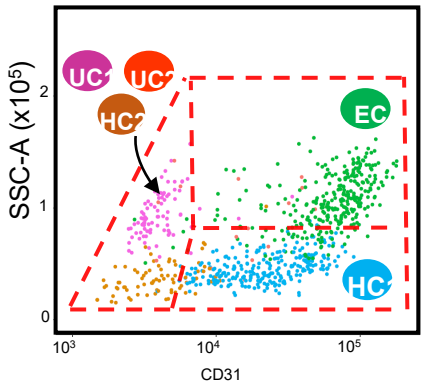
Haematopoietic stem cell (HSC) generation and expansion are key **challenges** facing clinical treatments for blood related-genetic disease and leukemia. We **aim** to uncover the molecular developmental program of HSC generation *in vivo* and harness this knowledge to generate, repair and expand these potent stem cells. We use mouse *in vivo* models, *in vitro* human and mouse pluripotent stem cells, genetic manipulations, vital imaging and single cell omics to examine:

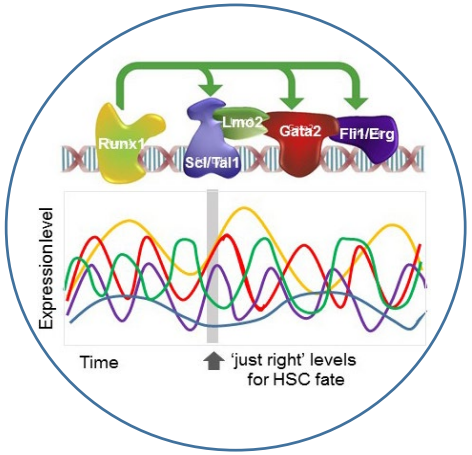
- Single cell omics associations with *in vivo* transplantable HSC function as cells transition from embryonic aortic endothelial cells.
- Stochasticity of dynamic transcription factor quantitative/combinatorial programming of hematopoietic fate development.
- GPR56 and GPR97 signaling pathways in the generation of healthy HSC and dysfunction in leukemic stem cells.



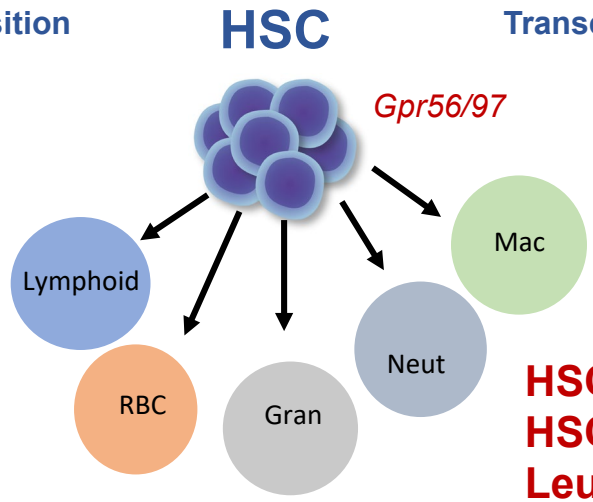
Endothelial-to-HSC transition

Single cell omics/function





Transcription factor dynamics



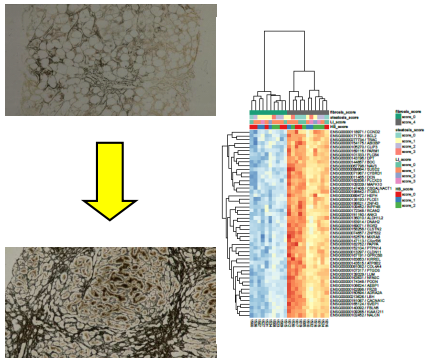
HSC generation
HSC lineage bias
Leukemia

Fallowfield Group

Developing new tests and treatments for people with chronic liver disease

- Translational liver research group with expertise in **disease models** and **drug discovery** in liver fibrosis/NASH
- Conduct **clinical trials** of new therapies (e.g. serelaxin, autologous macrophages) and tests (e.g. MRI, breathomics) in NASH/fibrosis/portal hypertension
- Use **clinical cohorts** (e.g. n=1000 *SteatoSITE* NAFLD Data Commons), bio-informatics, AI/ML for precision medicine
- Interest in disease **prevention** (e.g. coffee; minimum unit pricing of alcohol)
- Broad **Industry** engagement (e.g. GSK DPAc, Innovate UK collaborations; consultancy; scientific advisory boards)
- Strong focus on **public engagement**
- AASLD Portal Hypertension SIG Steering Committee, BAVENO VII Faculty, NICE MedTech Innovation Advisor, NIHR Leeds Diagnostic Evidence Co-operative (MIC)

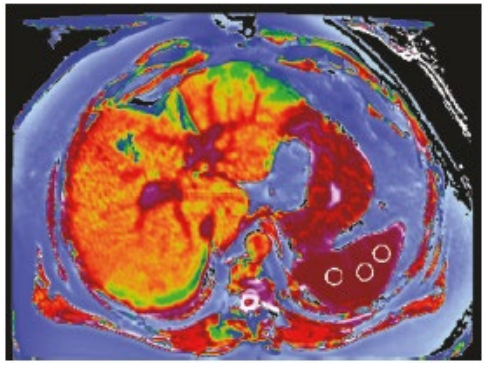
Unmet need = opportunities to impact on mortality



LIVER FIBROSIS PROGRESSION

(e.g. in NASH/high risk patients)

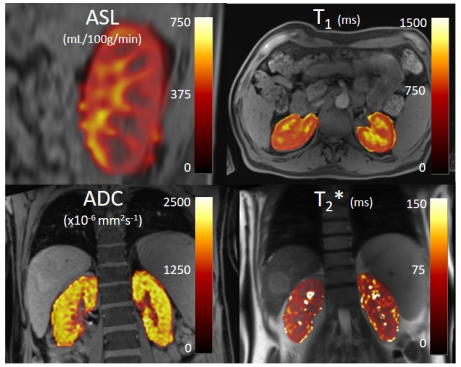
Need non-invasive biomarkers; NO licensed anti-fibrotic or anti-NASH drugs



PORTAL HYPERTENSION

Variceal bleeding occurs in 5-15% cirrhotics/year; Mortality still ~20%

Need non-invasive tests for portal pressure; Beta-blockers effective in only 30-60%; Adverse effects of acute drug therapies



ACUTE KIDNEY INJURY

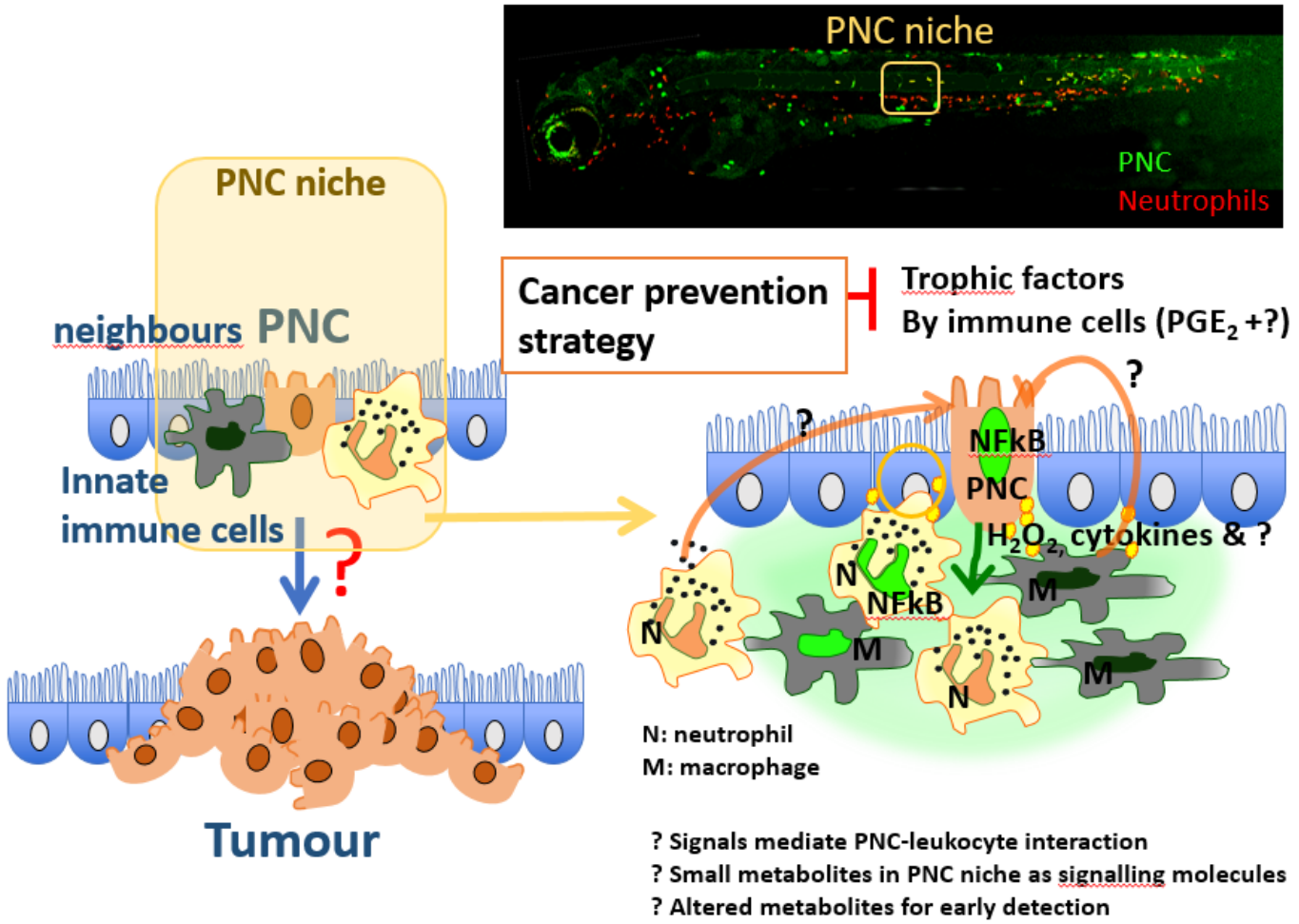
30-40% of hospitalized cirrhosis patients; Unacceptably high morbidity/mortality

***Potentially* reversible; Current diagnostic tests inadequate, very limited treatment options**

Feng Group

Mechanisms that regulate tumour initiation, for early cancer detection and prevention

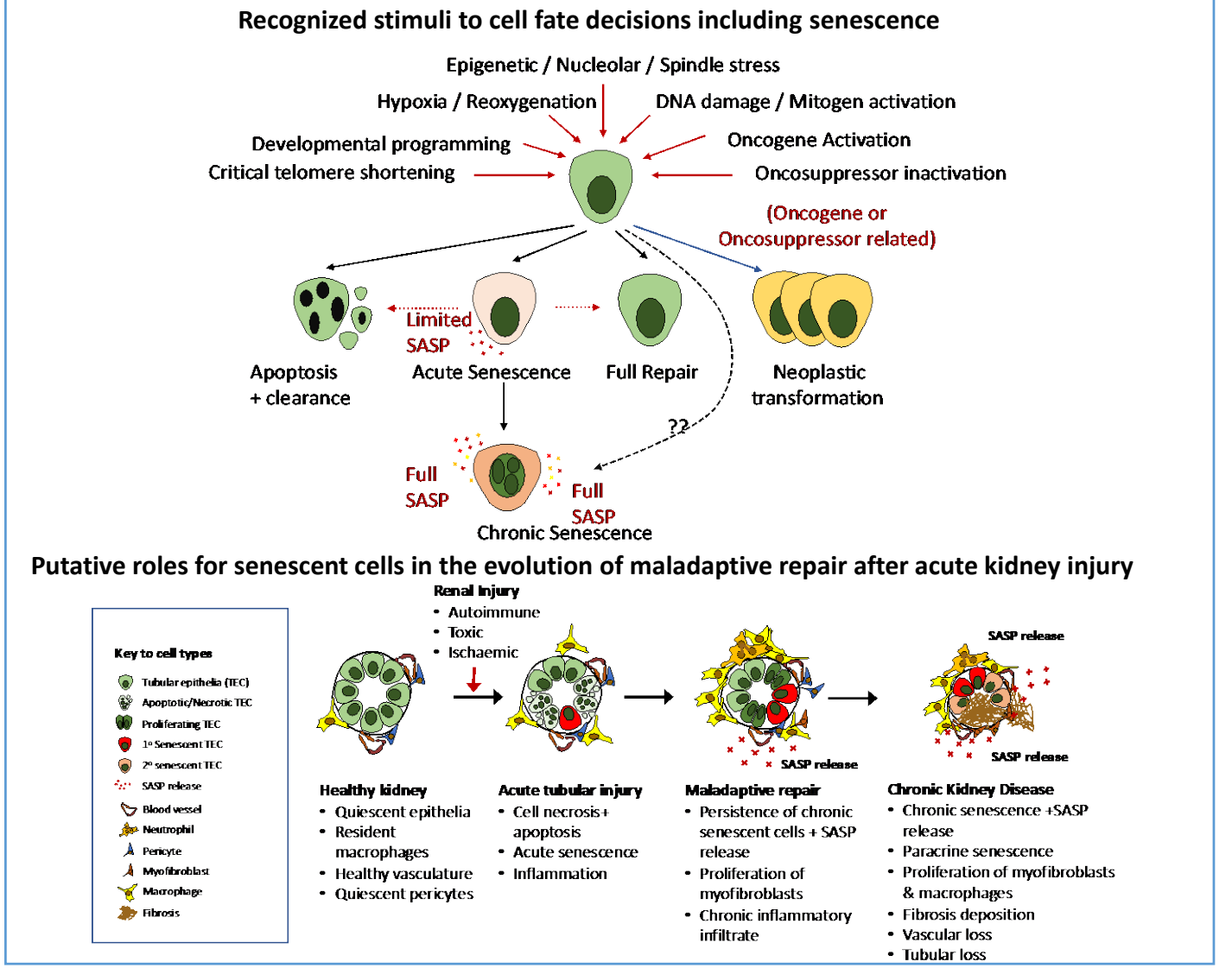
- In vivo live imaging of tumour initiation in zebrafish to investigate immune vs pre-neoplastic cell (PNC) interaction (mathematical modelling + scRNAseq+imaging)
- Mechanisms that regulate host innate immune cell function during tumour initiation (scRNAseq + zebrafish tissue specific CAS9 mediated gene KO)
- Combining Metabolomic, Imaging Mass Spectrometry and scRNAseq to characterization metabolic changes in PNC developing niche (early detection & prevention)
- Imaging based automated drug screening for cancer-preventing chemicals



Ferenbach Group

The influence of senescence on regeneration and fibrosis in the kidney

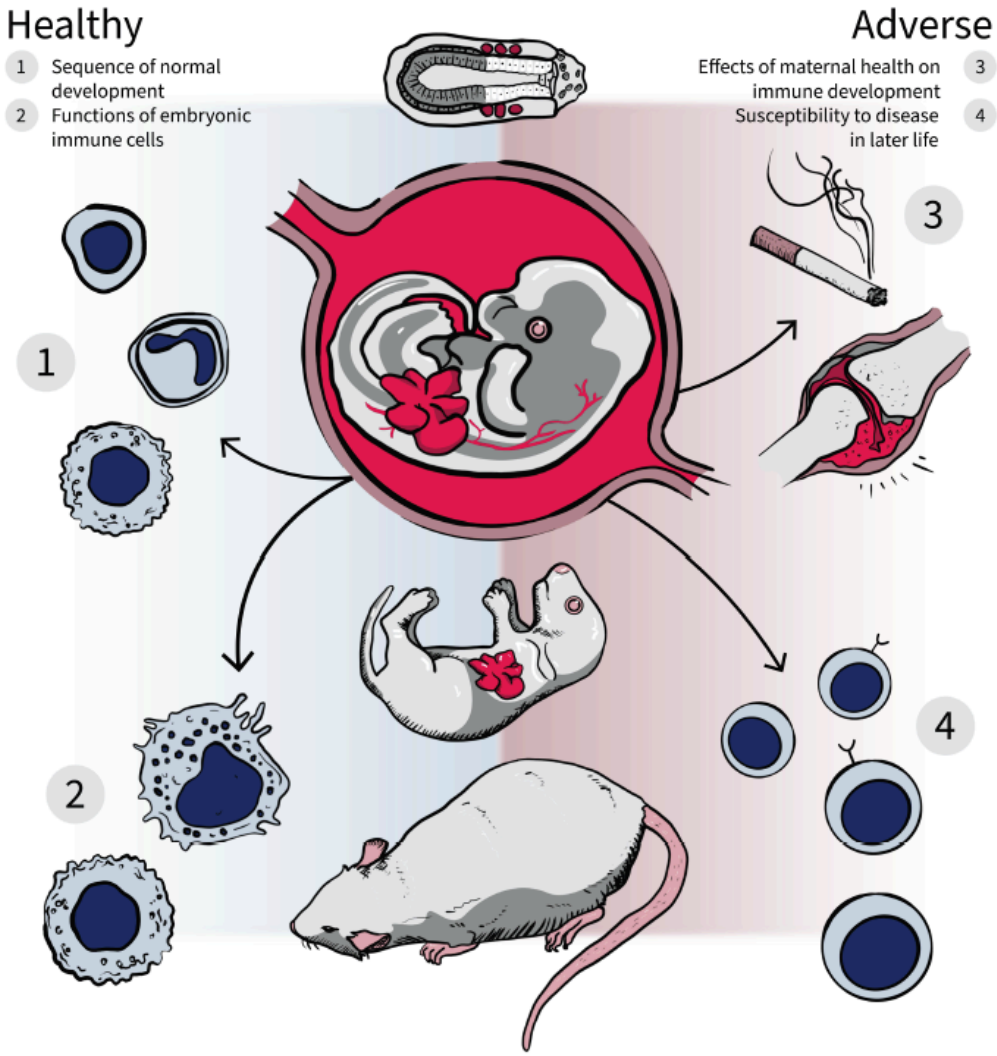
- **Senescent cells have undergone permanent growth arrest, adopt an altered secretory phenotype and accumulate in the kidney and other organs with ageing and injury.**
- **Recent murine studies have shown that depletion of chronically senescent cells extends healthy lifespan and delays age associated disease – implicating senescence and the senescence associated secretory phenotype as drivers of organ dysfunction.**
- **Our group studies the generation, function and clearance of senescent cells in the kidney, with the goal of developing novel therapies to prevent renal fibrosis and enhance renal regeneration.**



Gentek Group

Development, functions and programming of the “layered” immune system

- Immune cells first seed fetal tissues (1) – **key functions in development?** (2)
- At different life stages, “layered” immune cells (macrophages, mast cells, innate lymphocytes) derive from **distinct progenitors**
- Some fetal-derived immune cells **persist in adult tissues** – **they might be functionally distinct** (2)
- Adverse early life environments (3) predispose to many adult diseases, such as rheumatoid arthritis – **mediated by fetal immune cells** (4)?



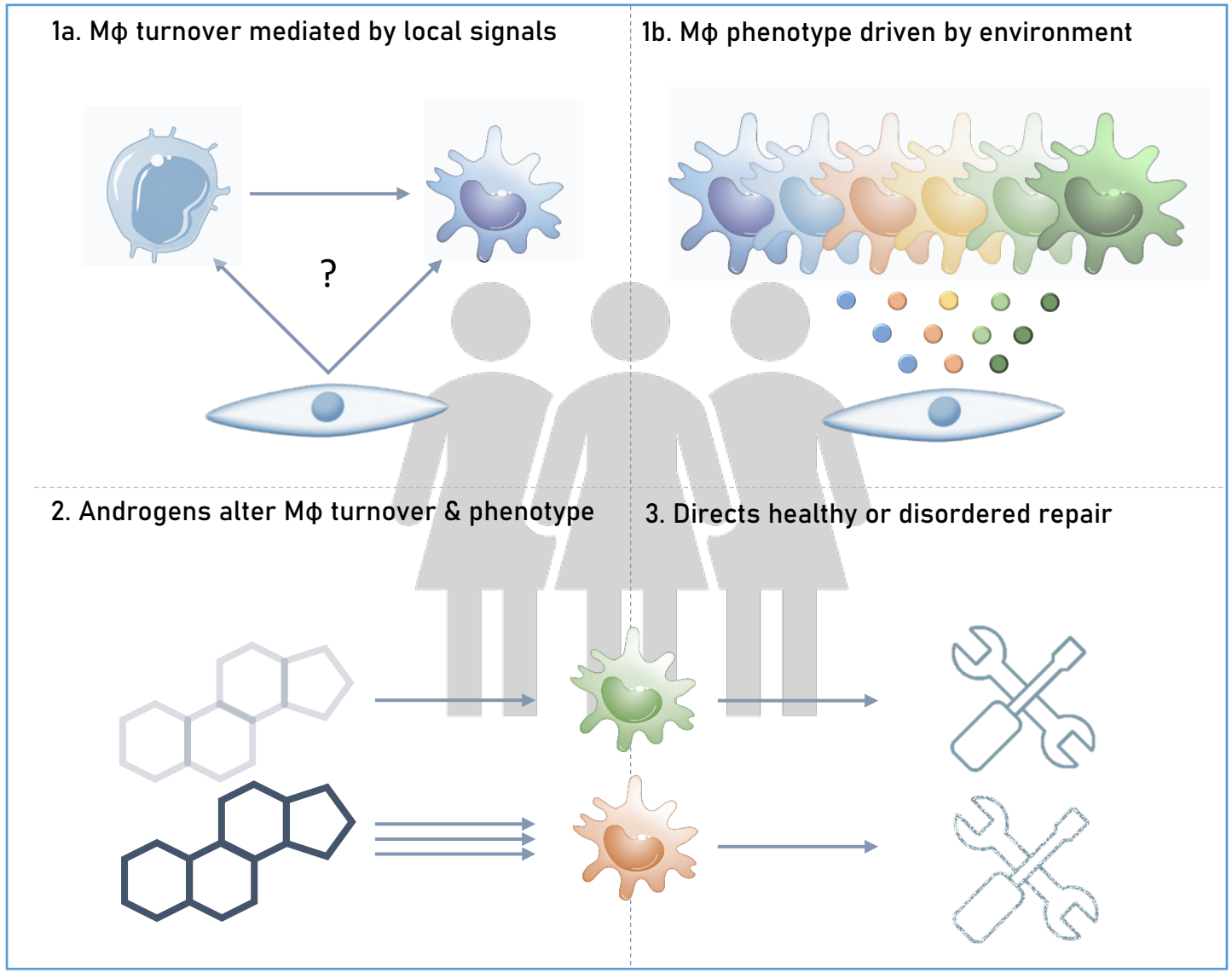
Gibson Group

Hormones | Inflammation | Repair

- **Endometrial repair** is essential for reproductive health and ongoing fertility.
- Deficits in **endometrial repair** are associated with reproductive health disorders that affect millions of women (1 in 3 in the UK).
- **Hormones** are unbalanced in reproductive health disorders which can disrupt tissue repair.
- **Macrophages** are essential mediators of tissue repair but our knowledge of how they are regulated in the endometrium is limited.
- Our research focuses on understanding how **hormones** (focussing on androgens) can control **macrophage** function during endometrial repair.

We aim to understand:

1. how macrophages are regulated in endometrial repair,
2. how their function may be altered in response to hormones (androgens), and
3. how this can impact on women's reproductive health.

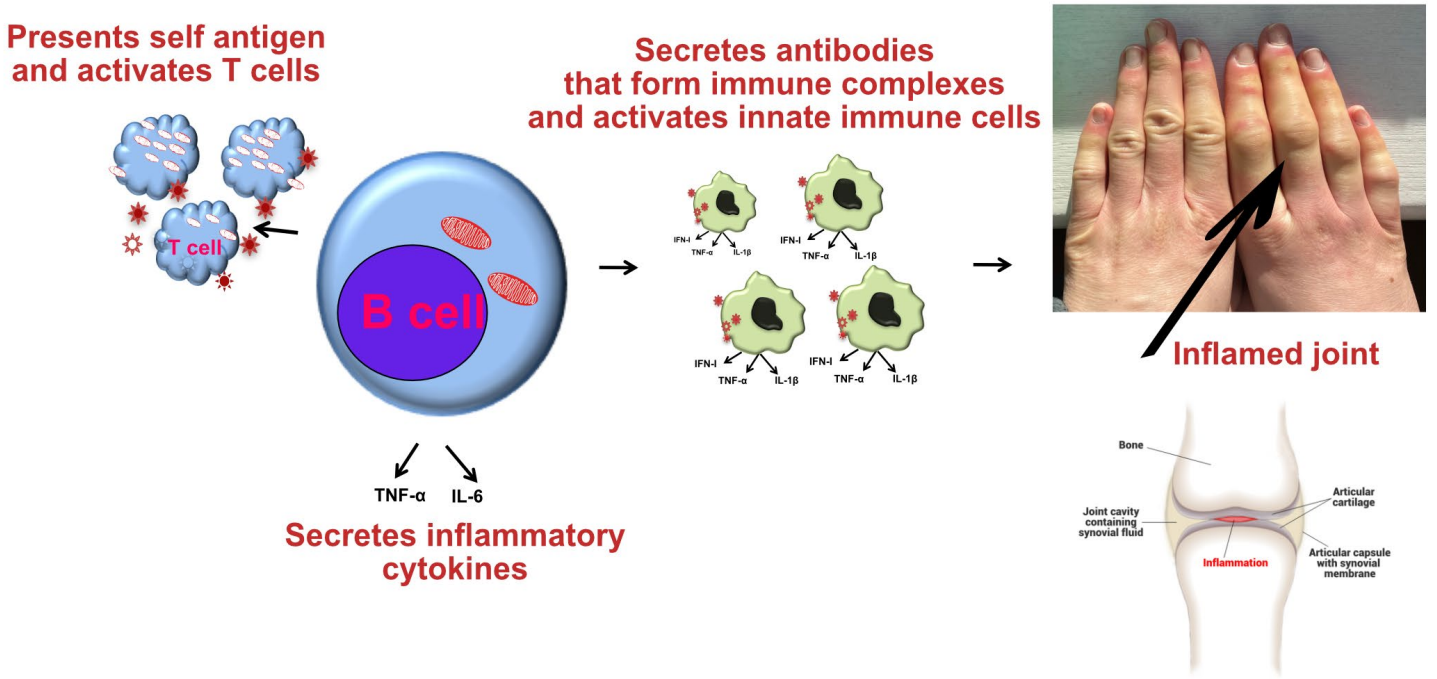


M. Gray Group

Pinpointing Pathogenic B cells in Autoimmunity

- Autoimmune diseases are reaching epidemic proportions and cost billions of pounds each year to treat
- Biologic therapy targets downstream inflammatory pathways and is ineffective in up to 50% of patients
- We hypothesize that chronic autoimmune inflammation is driven by pathogenic B cells
- To identify these B cells in human autoimmune diseases we are using advanced methods of immune system analysis, bioinformatics and data science.

B cells drive chronic autoimmune inflammation

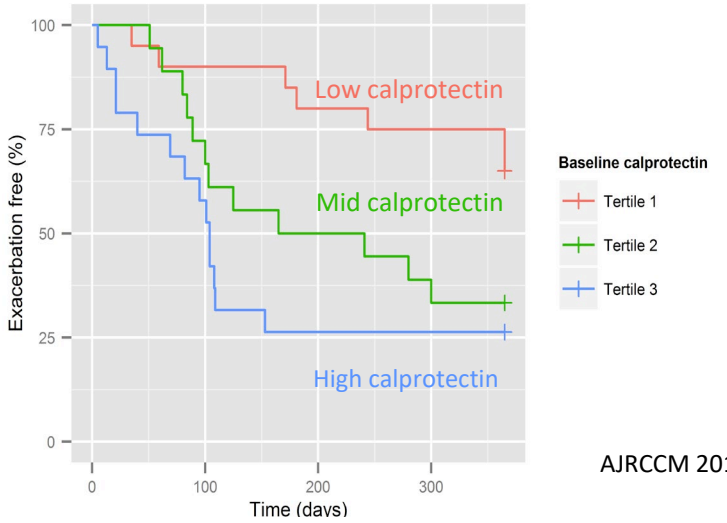


R. Gray Group

Inflammation, Resolution and Repair in Cystic Fibrosis

What's the problem?

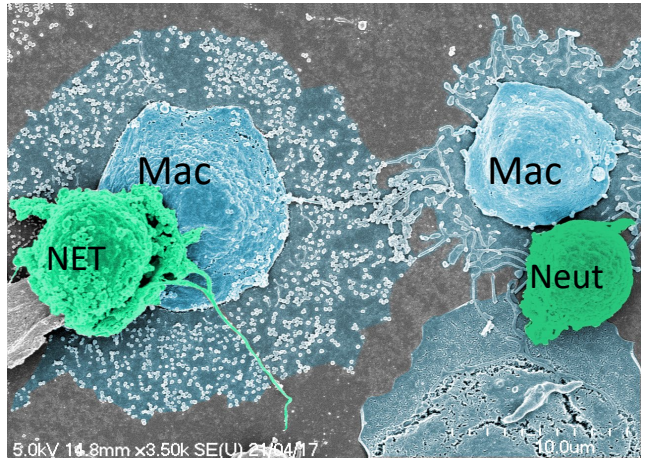
- **Inflammation** damages lungs in CF
- We described calprotectin as a major biomarker of inflammation in CF
- We discovered that CF neutrophils live longer and release more NETs which contain calprotectin
- We have demonstrated that NETs and calprotectin stimulate macrophages and drive inflammation
- We have pioneered the measurement of calprotectin in people with CF and higher levels mean worse outcomes



AJRCCM 2015

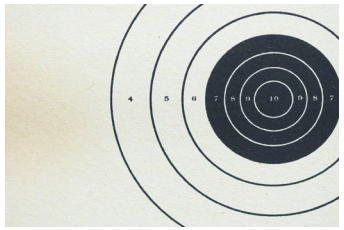
How do we investigate this ?

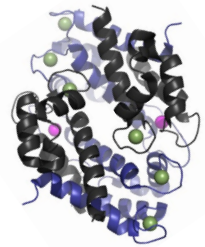
Immune cell co-culture



Drug discovery

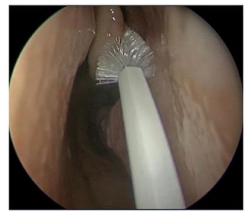
Can we target calprotectin to stop bad neutrophil macrophage interactions and drive **resolution**?



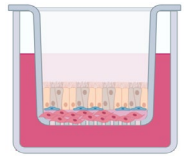


Pioneering 2D and 3D cultures of epithelial and immune cells for lung repair research

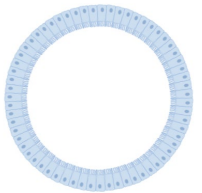
Patient Samples



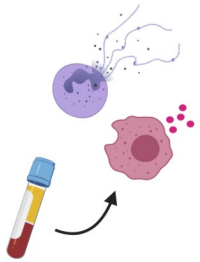
Airway Cells



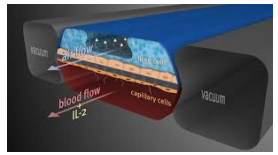
Airway Cultures



Organoids

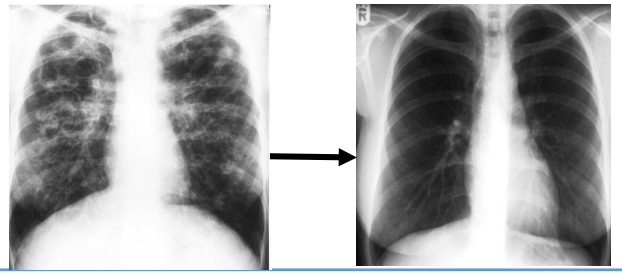


Immune Cells



Lung Chip

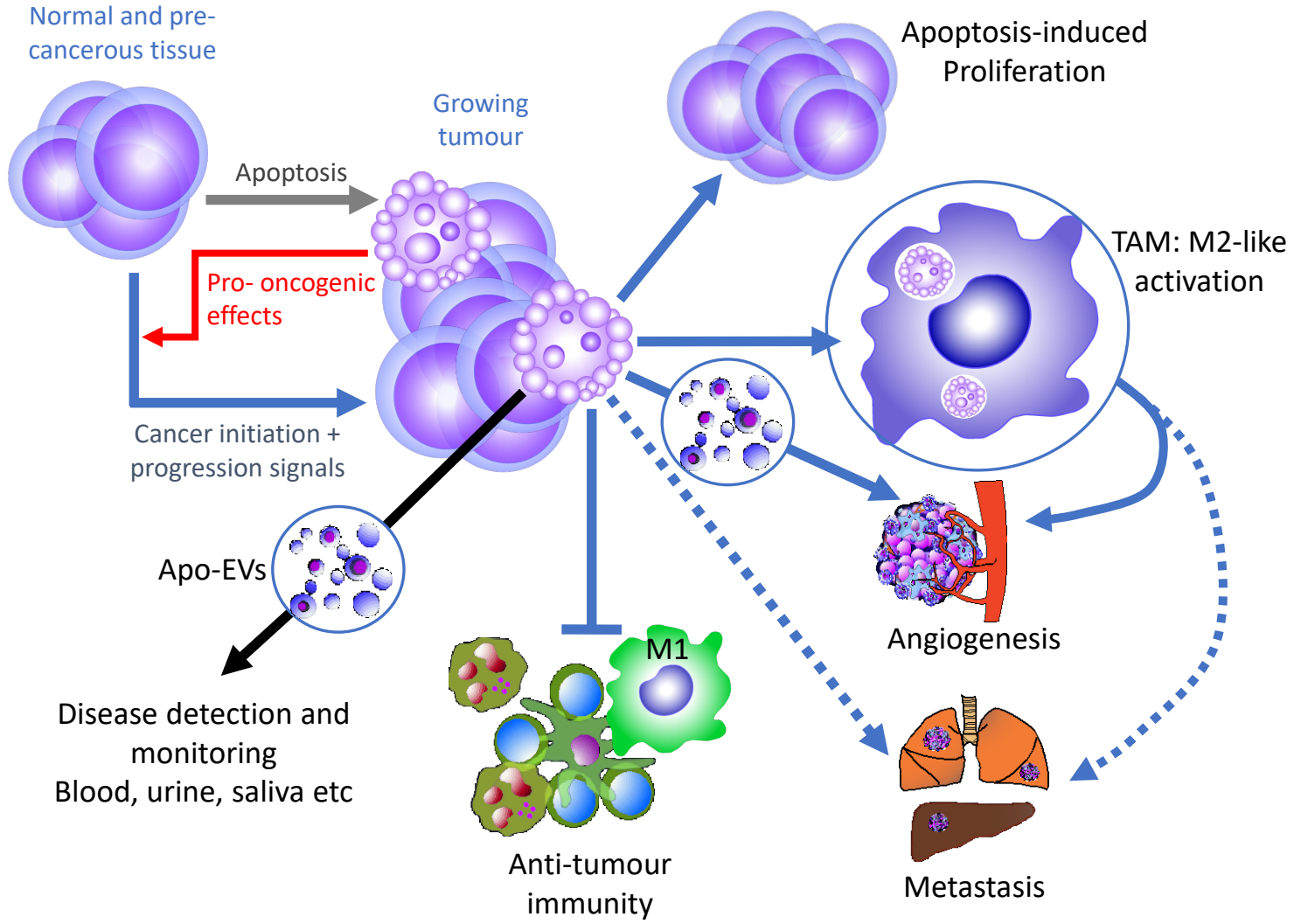
By resolving inflammation can we help CF lungs to **repair** themselves?



Gregory Group

Tissue repair and regeneration responses driven by cell death in the tumour microenvironment

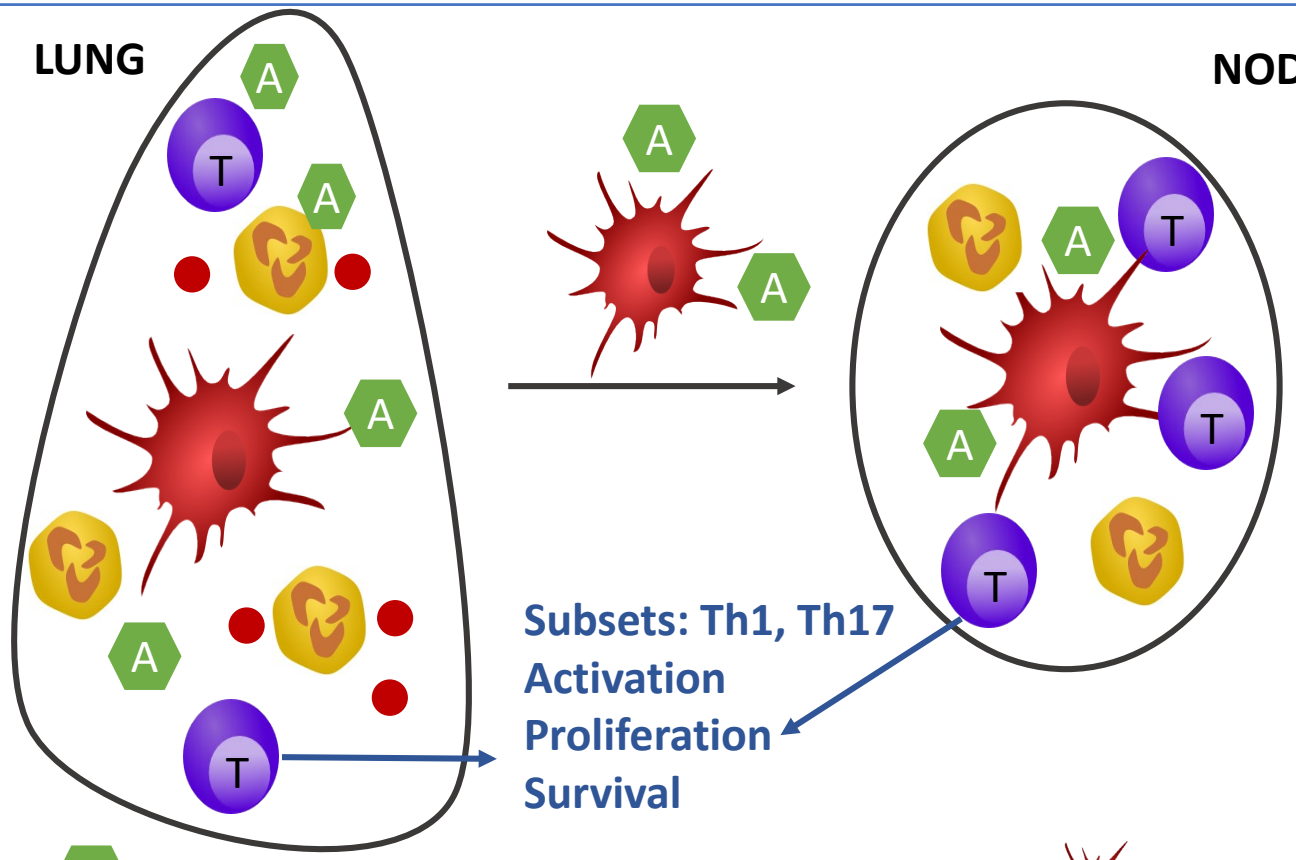
- Cancers grow when the rate of proliferation of tumour cells **outpaces** their rate of cell death
- Remarkably, cell death by **apoptosis** is most common in the most aggressive tumours
- Dying tumour cells can generate **pro-oncogenic**, “reparatory” signals
- Apoptosis can:
  - promote **proliferation**
  - **activate** tumour-associated macrophages (**TAM**) M1-> M2-like
  - stimulate **angiogenesis**
  - promote **metastasis**
  - **suppress** anti-tumour immunity
- **Extracellular vesicles** produced by apoptotic tumour cells (**Apo-EVs**) have oncogenic properties
- Apoptotic tumour cells and Apo-EVs are rich sources of **biomarkers**
- Readily detectable in **liquid biopsies**
- Uses in **early cancer detection**, staging and disease monitoring



Gwyer Findlay Group

- Focus 1: how neutrophil death, de-granulation and NETosis affect T cell differentiation and activation
  - In the lymph node
  - In the intestine during inflammatory disease
  - In the spinal cord during MS
- Focus 2: how anti-microbial peptides produced by neutrophils, microglia and intestinal epithelial cells impact on T cell development and activation

How do neutrophils affect T cell function?

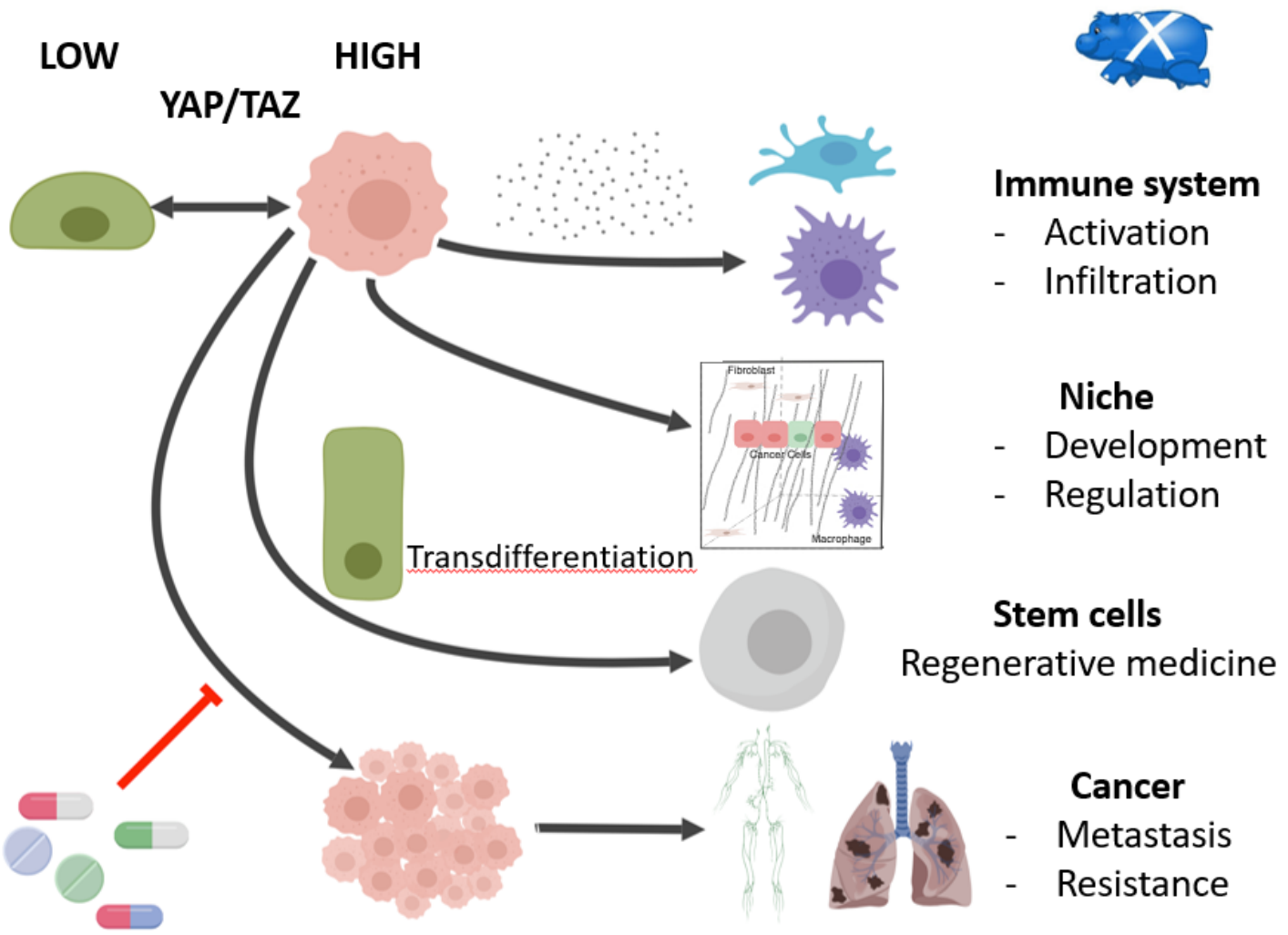


Antigen A released in tissues is collected by dendritic cells and primes T cells T in lymph nodes and *in situ*. Neutrophils, some of which release anti-microbial peptides ●, are also present. Their impact on T cell behaviour in disease is scarcely known and what we focus on.

Gram Hansen Group

The Tumour and Regenerative Niches: Cellular Regulation of and by the Hippo Pathway

- High YAP/TAZ transcriptional activity of the Hippo pathway drives
  - Regenerative processes
  - …but also cancer
- We focus on YAP/TAZ as drivers in
  - Prostate cancer and mesothelioma
  - Regeneration
- We provide fundamental insights into the pathway via
  - The activity in and the interplay with the immune system
  - Mechanotransduction
- We are developing small molecule modulators of the Hippo pathway
- This allows us to explore precision medicine-based approaches

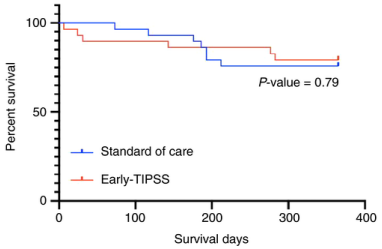


Hayes/Plevris Group

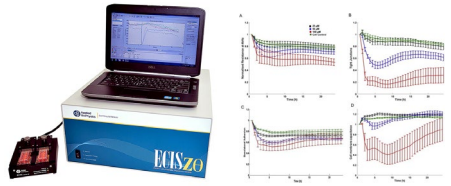
Understanding metabolic stress in the context of Non-alcoholic Fatty Liver and drug toxicity testing

- Optimise drug therapy for NAFLD and liver cirrhosis (carvedilol, coffee)
- Understand liver toxicity(paracetamol, chlorpromazine)
- Develop diagnostics (breathomics)
- Refine Treatments (Calibre, Early TIPSS trial)

RCTs eg Calibre, Early TIPSS



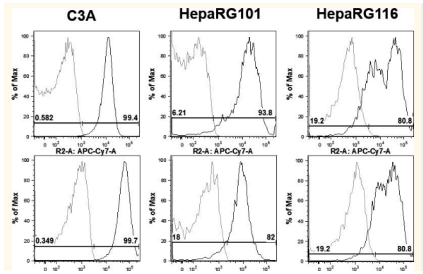
ECIS Cellular impedance assays

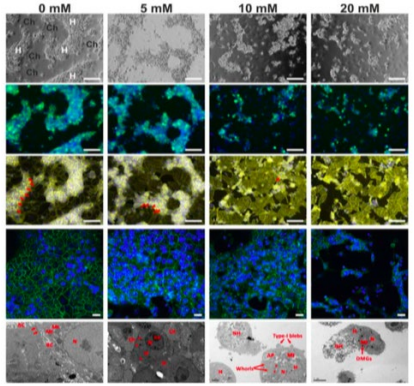


Using innovative techniques to explore the mechanisms of drug toxicity *in vitro* and clinical trials

Breathomics

In vitro

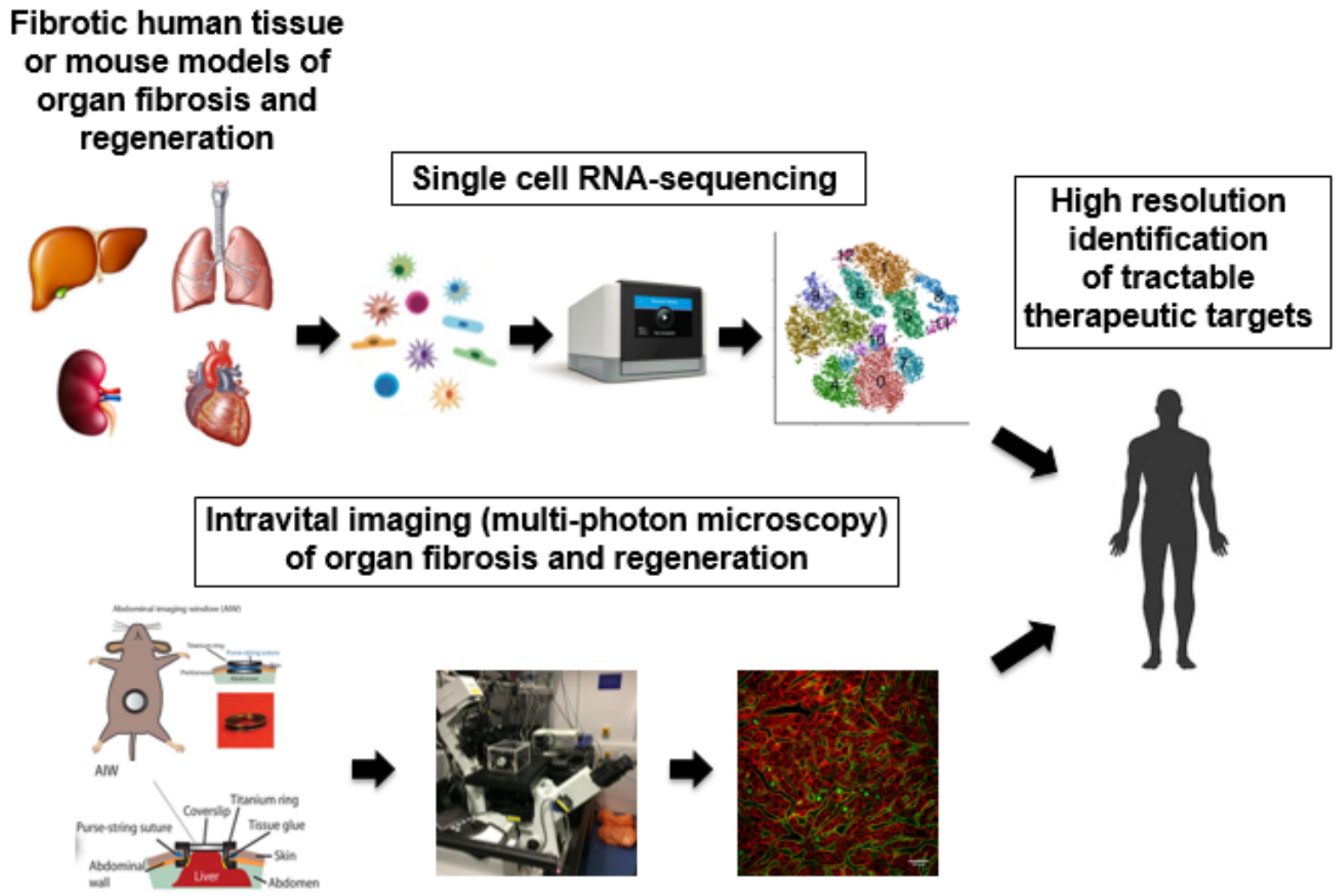




Henderson Group

Combining single cell RNA-sequencing and intravital imaging to identify therapeutic targets to drive tissue regeneration and repair

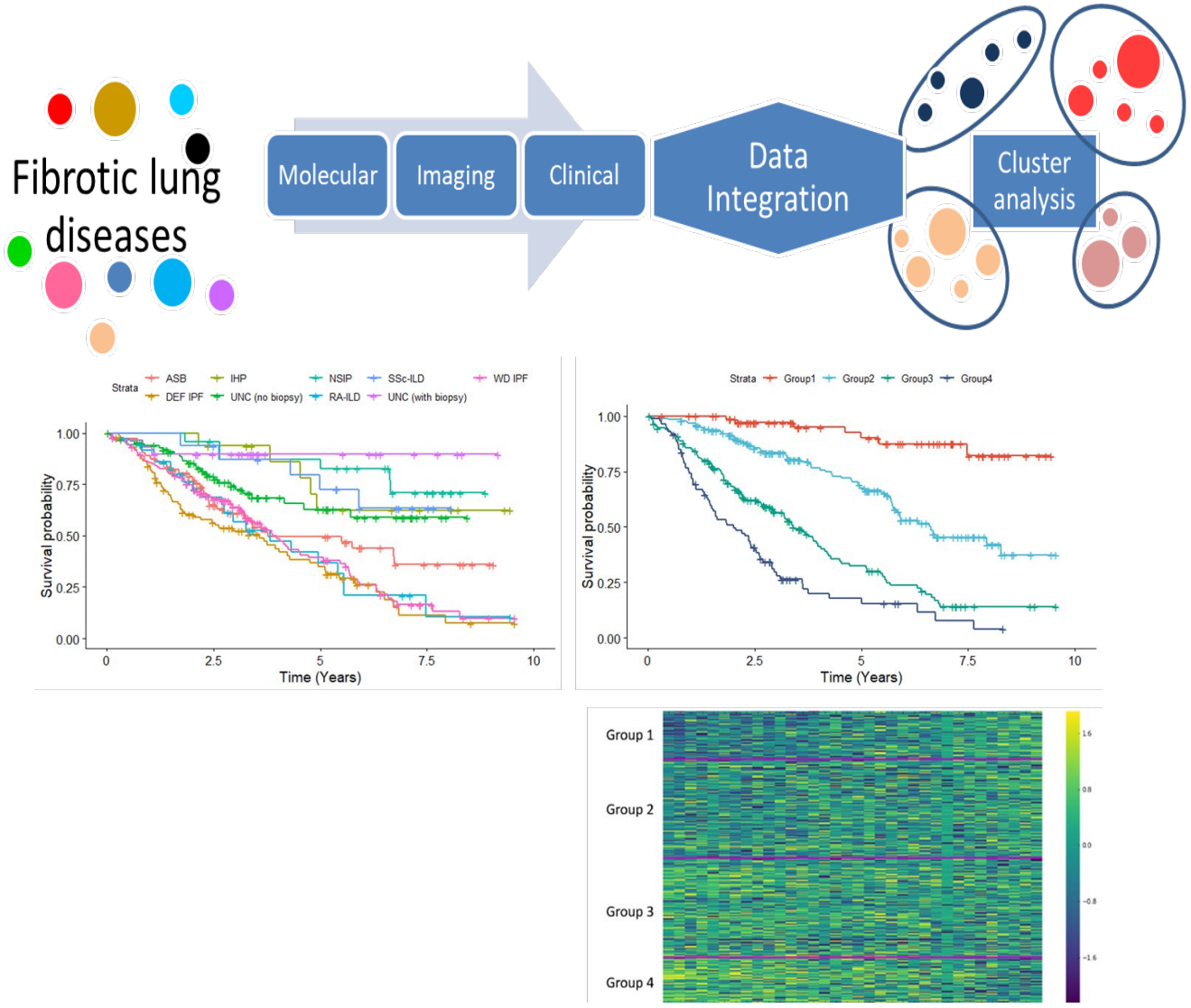
- Tissue fibrosis (scarring) accounts for nearly 45% of deaths in the developed world
- Iterative tissue damage results in progressive fibrosis, disrupted organ architecture and function, and aberrant regeneration
- Single cell RNA sequencing is transforming the way we think about disease pathogenesis, allowing the interrogation of individual pathogenic cell populations with unprecedented resolution
- We combine cutting-edge single cell RNA sequencing approaches with real-time intravital imaging of organ fibrosis and regeneration, to **identify therapeutic targets to drive tissue regeneration and repair**



Hirani Group

Understanding fibrotic lung disease through proof of concept clinical trials, cohort studies and biobanks

- Endotyping fibrotic lung disease to reveal novel therapeutic targets, refine prognostication and The Edinburgh Lung Fibrosis Molecular Endotyping (ELFMEN) project houses >10000 biosamples (BAL, blood, genomic) from >2500 subjects with allied clinical data
- Early phase clinical trials particularly aimed at determining target engagement within the lung
- Conventional and novel techniques to sample the alveolar compartment, specifically to explore the role of alveolar macrophages and exosomes in lung fibrosis



Ho Group

Mitochondria in Inflammation & Immunity

- Mitochondria are intracellular organelles that provide energy to our cells.
- Mitochondria are important in controlling inflammation, anti-viral and anti-bacterial immune responses.
- Mitochondria also control how a cell dies and are sources of major ‘danger signals’ that can promote inflammation.
- **The Ho lab has a bench to bedside program to understand mitochondria-mediated inflammation in human diseases.**
- Our main focus is on Inflammatory Bowel Diseases (IBD) with several basic science programmes to on-going Phase 2 clinical trials in mitochondria-based treatments in IBD