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NHS The Leeds Teaching Hospitals NHS Trust

Haematology: aging and host biology drivers of clonal disorders

Darren Newton

Leeds Institute of Medical Research

University of Leeds

BRC 2022-27: Haematology

- Haematological malignancies are the 5th most common cancer grouping.
- Median diagnostic age >70, so therapeutic strategies for these diverse clonal conditions do not always result in beneficial effects and outcome determinants – treatment efficacy, resistance, and tolerance – are unclear.
- Part of this failure relates to host response biology (e.g. accelerated aging), coupled with distinct disease biology. Our inter-linked WSs will investigate drivers of treatment tolerance through mechanistic biology discovery, enabling development of personalised treatment strategies.
- Contemporary granular real-world data on clinically meaningful disease categories.

Theme Leads: Prof Gordon Cook & Prof Eve Roman

- Haemato-oncology is a fast-moving area in cancer research.
- Our research has improved diagnostic accuracy, enhanced trial designs, and changed clinical practice internationally through innovations in treatment and biomarker adoption leading to quantifiable improvements in costs of care.
- The lifetime grant success of the theme co-leads (Cook >£17M; Roman >£20M) evidences our extensive experience in delivering impactful science for patient benefit.
- The programme outlined solidifies existing links, extends our research portfolio, and enhances our ability to respond to real questions of concern to clinicians/patients.

Work Stream 1: Prof Gordon Cook

- Host Response Biology - Improving outcomes in blood cancer through personalising care
  - Immune profiling
  - Inflammation/vaccination efficiency (proteomics/transcriptomics)
  - Immunometabolic dysfunction (proteomics/radiomics)

Work Stream 2: Dr Darren Newton

- Immunity, inflammation & clonal haematopoiesis (CHP) - Defining mechanistic drivers of CHP & enhance treatments of complex multisystem disorders
  - Establishment of long-term bone marrow culture systems for primary material in CHP disorders
  - Identification of complementary CHP & inflammatory mechanisms in both clonal and inflammatory settings (sequencing/immunology)
  - Explore overlapping mechanisms of action (*in vitro*)

Work Stream 3: Prof Eve Roman & Prof David Westhead

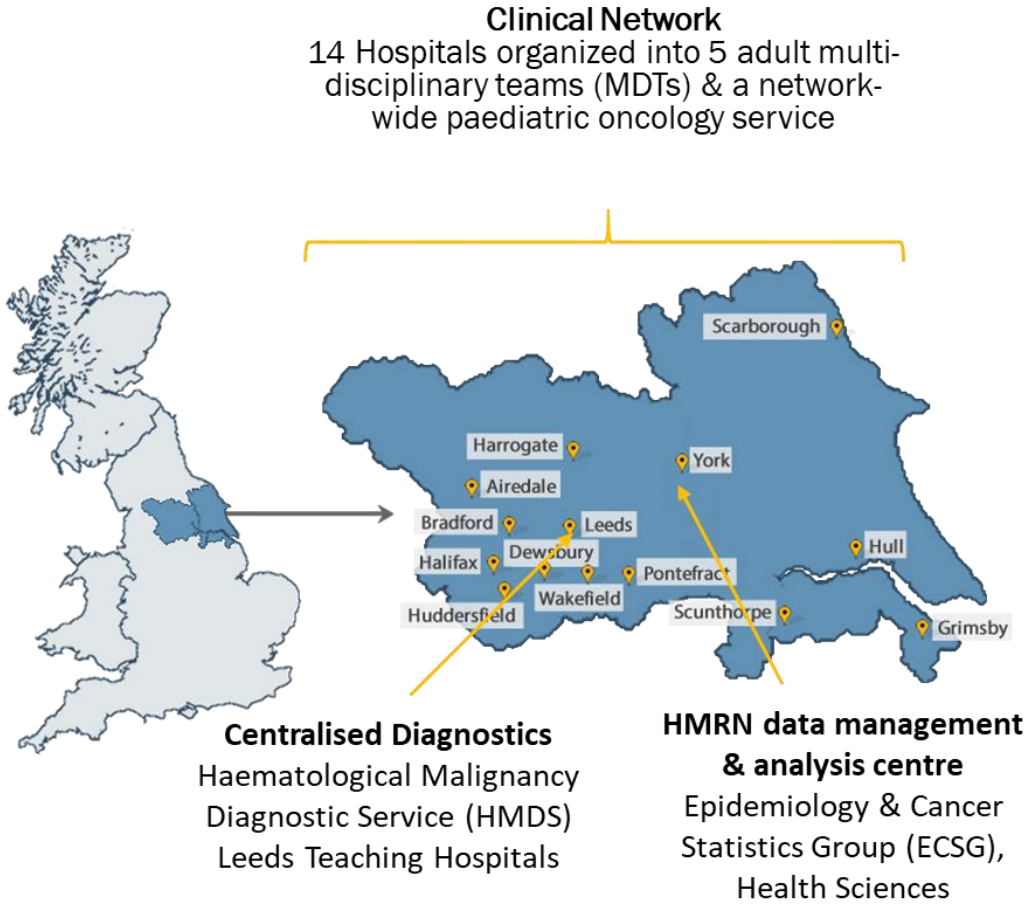
WS3

- Population-based epidemiology & data science - Integrating *real-world* patient & molecular data in biomarker discovery and validation
- Data augmentation and integration ('omics/digitized pathology/AI)
- Prognostic/predicative biomarker development
- Disease evolution; identification of early progressors/non-responders

Leeds & York Research Environment

- Leeds University internationally-leading research in: clinical trials; translational science in mature B-cell malignancies; immunity; clonal haematopoietic disorders; haematopathology; bioinformatics; real-world data. **LIMR**
- Leeds teaching hospitals trust has world-leading expertise and excellent access to bio-sampling; the Haematological Malignancy Diagnostic Service (HMDS) is the UK's model for delivery of complex diagnostic services.
- York University international-leading research in clonal haematopoietic disorders; haematopathology; bioinformatics; real-world data. **Centre for Blood Research**
- York Haematological Malignancy Research Network (HMRN) produces impact evidence of clinical trials in the patient population, and the tools to apply decision-making and patient-centred care.

Haematological Malignancy Research Network (HMRN)



- Established in 2004, HMRN is a collaboration between NHS clinicians & university academics
- Population ~4 million: similar socio-demographic structure to UK
- Around 2,500 patients are newly diagnosed by HMDS each year. All are registered into HMRN – no exclusions.
- Legal framework permits routinely compiled NHS health data to be collected on all registered patients, without explicit consent
- The patient cohort currently contains >45,000 patients

Work Stream 1: Early Goals

- Establish *in vitro* model systems to interrogate tumour- immune interactions. Establish efficient sample pipeline from clinical trial and real-world datasets for transferral to research laboratories. Establish imaging and liquid biopsy biomarker variations in non-cancer population
- Recruit and embed new staff members responsible for establishing accrual and disseminating to linked research groups; establish *in vitro* model systems and assays for biomarker studies.
- Establish appropriate governance procedures for all sample tracking and usage.

Work Stream 1: Early Progress

- Internationally leading work on frailty drivers in myeloma
- 2 abstracts at international meeting ASH from Myeloma XIV
- 2 Grants pending outcome (MRC CARP & NIHR RFpB)
- Translational program for delivering CRUK clinical trial bid (£5M industry funding to support the trial)
- Pending NIHR ACF competition

Work Stream: 2 Early Goals

- Identify patients who either develop bone marrow failure after presenting with an inflammatory syndrome, or develop an inflammatory syndrome after presenting with BMF.
- Establish effective lines of tissue sample collection through the ethically approved PNH Research Tissue Bank. Implement wide- ranging assessment of inflammatory markers in all patient subgroups. Further develop long-term *in vitro* bone marrow culture system.
- Recruit and embed staff members contributing to implementing research objectives including sample collection process and dissemination.
- Establish collection of samples from PNH, and identification and enrolment of patients showing signs of systemic inflammation or bone marrow failure in the opposite context. Access samples from the PNH National Service, HMDS diagnostic reference centre and immunology clinics.
- Establish processes for sample dissemination to research team members with governance and monitoring.

Work Stream 2: Early Progress

- Centre for Blood Research launched in York on 11 July - >100 attendees, links HMRN with experimental and clinical biology in York, Catherine Cargo spoke at event.
- Anjum Khan (Leeds) was awarded an MRC Clinical academic research partnership (CARP) to work with Bill Grey and David Kent (York)
- Alyssa Cull (PDRA, Kent lab) was awarded an NIHR BRC Short Term Internship to prepare her Fellowship applications on the back of a recently accepted *Nature Medicine* paper.
- *Cell* paper (Hitchcock Lab).
- £1million grant in review with MRC (Kent/Savic) following joint publication
- Industry-funded PNH Clinical Research Fellow looking at breakthrough.

Work Scheme 3: Early Goals

- Develop infrastructure and capability necessary to conduct the research; integrate and augment existing datasets 'omics data and images. Establish efficient dataset linkage, security and governance procedures for integrated data analysis, alongside efficient processes for extracting, analysing, and scanning samples of selected archival material and new cohorts for dataset enrichment.
- Recruit two staff members; one (Leeds-based) with expertise in research software engineering who will collaborate with existing staff to create a trusted research environment (TRE) for the theme in the AI Core Laboratory; one (York-based) with expertise in data science to work alongside colleagues in Leeds to ensure linkage between York and Leeds is robust and effective.

Work Scheme 3 – Early Progress

- Provide integrated datasets from NHS sources, HMRN, and the clinical trials units in the TRE. This will include, as appropriate, currently available patient clinical, treatment and outcome data, and any molecular 'omic data, digital images of molecular pathology and radiology imaging.
- Establish appropriate data governance procedures for applications to use this data.
- Collaboration for digital pathology with HMDS and commercial spin off

Next steps

- Using the pipelines that we've established to begin *in* vitro and expand these to primary tissue studies to interrogate tumour/immune system interactions.
- Define an integrated assessment of immunological senescence, inflammation and frailty. Use single cell sequencing to define aberrant inflammation and clonal expansion. Deploy immunological senescence and body composition/frailty biomarkers in clinical trials.
- Address questions related to identification of early progressors/ non-responders in actively treated and watch and wait patient cohorts. Link disease-specific features with physiological impact of aging and wider host biology to define potential interventions that target disease mechanisms adapted to patient physiology and frailty

Core groups

- **Theme Leads**
  - Prof Gordon Cook
  - Prof Eve Roman
- **Work Stream 1**
  - Prof David Cairns
  - Dr Frances Seymour (EL)
  - Dr Gina Doody
  - Prof Ulf Klein
  - Prof Andy Scarsbrook
  - Prof Reuben Tooze
- **Work Stream 2**
  - Dr Darren Newton
  - Prof David Kent
  - Prof Ian Hitchcock
  - Prof Sinisa Savic
  - Dr Jillian Barlow
  - Dr Richard Kelly (EL)
- **Work Stream 3**
  - Prof David Westhead
  - Prof Alex Smith (EL)

Questions?