Musculoskeletal Disease Theme

NIHR Leeds Biomedical Research Centre

Rheumatology, Mechanical and Biological Engineering

Medicine for the Elderly, Podiatry

Professor Ann Morgan

NIHR Leeds BRC

Musculoskeletal Disease Background

- MSKD affect 1 in 4 people in the UK; commonest cause of chronic disability and one of the most expensive to treat, costing NHS England >£10B annually. Rare diseases affect 1:10 population – high unmet clinical need.

- MSKD are broadly divided into **immune-mediated inflammatory diseases** (IMIDs) and **osteoarthritis**.

- **IMIDs** have a strong **genetic** component, and many are inextricably linked to the **ageing immune system**, adverse **lifestyle** factors (obesity, smoking, poor diet and dental hygiene) and the social **inequalities** prevalent in our local population. IMIDs result in **multi-organ damage**, frailty and **reduced life expectancy**.

- 3% of the UK population >70 years of age are regularly taking oral **prednisolone** (dose dependent toxicity; £84.2M pa); major contributor to **multi-morbidity.** Currently accepted treatment for IMIDs that affect older age groups. Imperative we provide the **evidence base** to change clinical practice in the UK and beyond.

- **Overlapping disease mechanisms** - opportunities for prevention, molecular stratification and drug repurposing

- **Osteoarthritis** affects 250M people worldwide; prevalence is rapidly increasing with increased life expectancy and obesity; joint pain is central to multimorbidity.

- 250,000 **joint replacements** performed each year in UK, projected to increase to 400,000 by 2035, **Young, active, obese patients** place greater demands on implants; 15% rise in **revision surgery** over last 5 yrs.

Musculoskeletal Theme (7 Workstreams)

Our **vision** is to:

1. Identify people at risk of developing immune-mediated inflammatory diseases to **prevent** both the **onset** of inflammation (disease) and **complications**

2. Reduce **glucocorticoid toxicity burden, multi-morbidity** and frailty

3. Develop **individually-targeted**, cost-effective therapies for common/impactful MSKD

Enabled through strong **inter-disciplinary collaborations** (across MSKD, surgery, pathology, cardiometabolic, haematological and infectious disease and methodology BRC Themes)

Underpinned by accurate detection, early diagnosis and validation of novel therapeutic targets

Grand Challenges

- **WS1: rheumatoid arthritis (RA) prevention and stratified interventions** **(Paul Emery and Kulveer Mankia)**
Grand challenge: for those at risk of RA, provide validated stratification permitting preventative intervention.

- **WS2: prevention of psoriatic arthritis (PsA)** **(Helena Marzo-Ortega and Dennis McGonagle)**
Grand challenge: characterize the in-depth phenotype of psoriasis populations "at-risk" of developing PsA and identify innovative targets and remission induction strategies.

- **WS3: intervention in Connective Tissue and autoinflammatory diseases** **(Francesco DelGaldo and Ed Vital)**
Grand challenge: translate discoveries on prediction of onset and severity of autoimmune CTD into validated diagnostics and therapeutics.

- **WS4: early accurate diagnosis and precision prescribing in vasculitis** **(Ann Morgan and Mark Iles)**
Grand challenge: glucocorticoid-free treatment reducing long-term disease burden and treatment complications.

- **WS5: safer glucocorticoid therapy in polymyalgia rheumatica (PMR) reducing frailty** **(Sarah Mackie and Andy Clegg)**
Grand challenge: alleviate the "Cushingoid" phenotype in glucocorticoid-treated PMR, and retain therapeutic efficacy.

- **WS6: osteoarthritis stratification for targeted intervention** **(Philip Conaghan and Sarah Kingsbury)**
Grand challenge: reduce the burden of osteoarthritis pain for individuals with multimorbidities, leading to improved quality-of-life, and reduced NHS burden.

- **WS7: optimised joint replacement technologies** **(Ruth Wilcox and Tony Redmond)**
Grand challenge: deliver optimum treatment for every patient requiring joint replacement in a cost-effective way.

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Multi-Disciplinary Collaboration

- NHS – across medical specialties and health care professionals

- University – methodology big data; biology target validation (inflammation)

- Disease specific groups/consortia: National and International

- Industry – biotech, pharma, device manufacturers

- NIHR BioResource

- NIHR-BRC PRS Initiative/ Our Future Health

- NIHR - Versus Arthritis MSK TRC

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NIHR BioResource – Leeds Recruitment
Sinisa Savic

18 BioResource Centres around England

- **The Leeds BioResource Centre recruitment programs (genome-wide SNP array)**
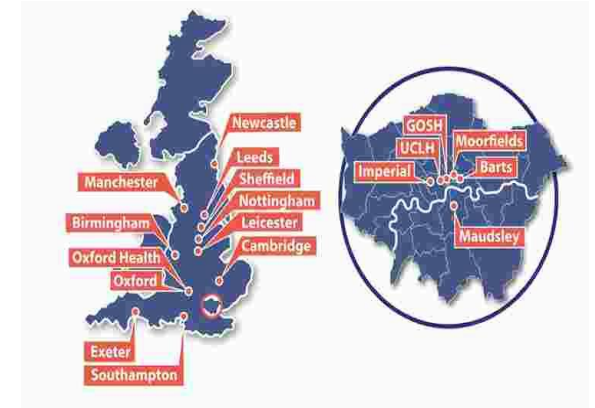 - 34/64 rare disease projects
  - IMID BioResource (Ed Vital)
  - IBD BioResource
  - Research tissue bank

- **We are also leading on 5 rare disease projects (whole exome sequencing – Genomics England)**
  - Systemic vasculitis (Ann Morgan)
  - Giant cell arteritis (Ann Morgan)
  - Systemic Sclerosis (Francesco del Galdo)
  - Systemic Autoinflammatory Disorder - AODs and uSAID (Sinisa Savic)

- **RNA Phenotyping Study (RNA Seq sorted cells, single cell RNA Seq, single cell ATAC Seq, proteomics)**
  - Vasculitis, GCA, Systemic Scleritis
  - Host satellite lab for RNA processing (Ann Morgan/ Jim Robinson: LIGHT): processing samples 3 days per week

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National Genomic Healthcare strategy

Vision create most advanced genomic healthcare system in the world

Genome UK

Our Future Health

Cross-BRC polygenic risk score (PRS) collaborative

1. **Glucocorticoid toxicity**
2. **IMID**
3. **Statistics methodology group**
   - Applying existing PRS to high-risk groups
   - Applying PRS to different ethnicities
   - Combining PRS with other risk factors/ multimorbidity

	Diagnosis and personalised medicine		Prevention	Research	
Key UK infrastructure	Genomics England and genomic testing in the NHS		ADD challenge	UK Biobank	NIHR BioResource
Unique capability	Delivering cutting-edge genomics services to the NHS. A pioneering research library powering academic and industry research	Clinical diagnostic testing for NHS patients embedding WGS into routine care for the first time	Long-term prospective cohort for early detection research at an unprecedented scale	World leading long-term prospective cohort research	Vast recruitment platform to support early translational research
Population	100,000 participants with rare diseases and cancer	Provision of genomic testing across the UK, including at least 500,000 whole genomes in England by 2024	5 million participants	500,000 participants healthy at the time of recruitment	200,000-400,000 participants with rare or common diseases or healthy at the time of recruitment
Genomic data	Whole genome sequencing	Whole genome sequencing and non-whole genome sequencing	Genotyping – PRS	Whole exome sequencing and whole genome sequencing	Whole genome sequencing or genotyping
Complementary data	Phenotypic and long-term clinical data collection	Phenotypic and long-term clinical data collection	Health-related data	Deep phenotyping and health-related data	Deep phenotyping, metabolomics, health-related data, medical records
Bio-sampling	✓	✓	✓	✓	✓
Clinical feedback	✓	✓	✓	x	✓
Recontact	✓	✓	✓	✓	✓
UK-wide	✓	✓	✓	✓	✓

NIHR/ Versus Arthritis Translational Research Collaborative
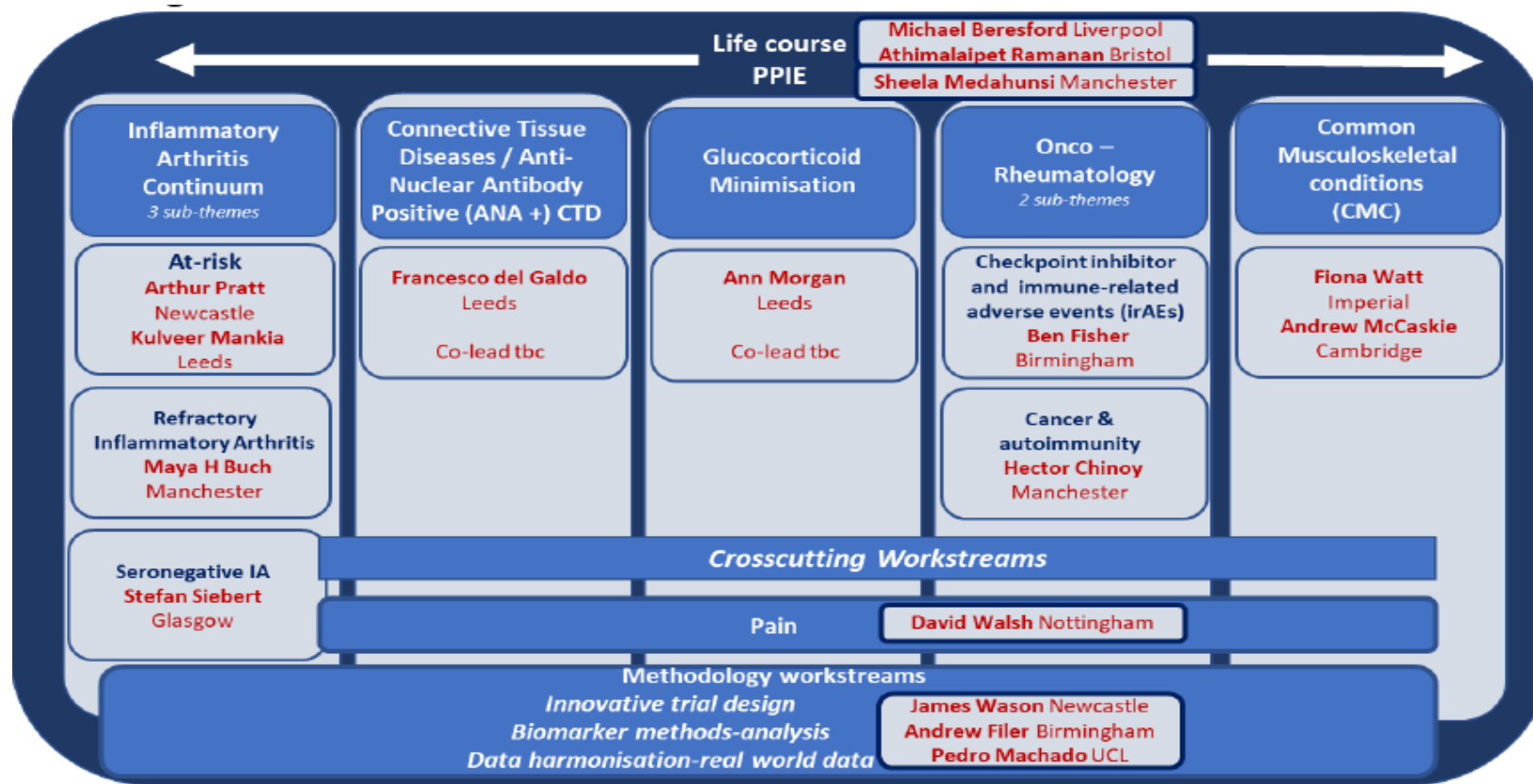
Revised Strategy Approved 2023

Questions?