



Stacking the odds towards a cure

Research Priority Workshop Report

Monday 9th April 2018

Medical Research Council, London

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A Forward from Stephen Simpson - Director of Research & Programmes

*“This report represents the summary of a workshop hosted by the charity to develop its second, and upcoming, insight-led challenge call for research that will **help improve the odds of finding a cure and more effective treatments for different forms of arthritis**. The ambition of the workshop was to harness insight and feedback from the research community and patients, represented largely by members of our strategic funding subcommittees, the charity’s College of Experts and guests. The workshop succeeded in giving opportunity for dynamic and open discussion, and for the charity to consider how to improve, strengthen and clarify its future research investment towards what we recognise as a difficult yet exciting goal. We are very grateful for the time and input of all our experts that joined us on the day and to those who led discussions and presented; we will continue to use the insight gained to develop and refine our approach”.*

Introduction and goals of the day

Dr Stephen Simpson

Dr Simpson explained that the charity had convened the workshop to review priorities and unmet need across the musculoskeletal diseases, in the context of the charity’s challenge call “Stacking the Odds towards a Cure”.

He explained that workshop brought together clinical and academic experts, as well as patients from several disease areas (from the Arthritis Research UK Patient Insight Partner Group), and representatives from other relevant UK funding organisations including the Medical Research Council, Innovate UK and Cancer Research UK (the latter, a partner through a shared investment in immunology).

The main goal of the workshop was to define the scope of the next call, which seeks to find a cure and more effective treatments for arthritis through discovery, translational and clinical research.

Session 1: The RheumaMap

Professor Iain McInnes

A central reference document for the workshop was the European League Against Rheumatism (EULAR)’s [RheumaMap](#), the first single global document describing unmet need in the rheumatic musculoskeletal diseases (RMD). Professor McInnes, as EULAR President Elect and chair of the RheumaMap taskforce, presented on the development of the document which aimed to highlight the breadth and scope of the RMD. He explained that the while RheumaMap presents a comprehensive overview of the RMD, it was written in part as a policy document to highlight the under-funding of RMD in member country Health Systems, relative to the burden of disability they cause; and as such it was focussed to two to three unmet needs in each group of conditions.

Iain noted that developing a comprehensive strategic document of this type was, in itself, a challenging undertaking and that the priorities set within it would require future review and

refresh. The presentation of RheumaMap, proved highly valuable as an introduction and was referenced throughout the discussions.

Session 2: The view in Osteoarthritis

Professor Ali Mobasher

Professor Mobasher spoke on behalf of the Osteoarthritis Research Society International (OARSI), and this most common form of arthritis. Osteoarthritis (OA) is also referenced with RheumaMap but a similar document concentrating only on this disease is in preparation by OARSI for submission as a white paper to the US Food and Drug Administration in 2018. The global incidence of osteoarthritis is on the increase, and it is currently the 11th highest contributor to world-wide disability. OARSI priorities towards a cure for this condition include; describing its sub-phenotypes, defining early disease (to open-up both treatment and prevention avenues), data harmonisation (for computer learning and artificial intelligence approaches to new research areas) and a meta-analysis of existing health data to explore the links between physical inactivity and OA.

Session 3: The patient perspective

Dr Natalie Carter, Dr Jane Taylor, Mr Colin Wilkinson, Mrs Lynn Laidlaw

Dr Natalie Carter began by describing market research that Arthritis Research UK has undertaken with people with arthritis^{1&2}, which sought amongst other topics, their views on the direction of the charity's investment in medical research. Almost half of those surveyed believed that research was key to managing their arthritis¹, and 68% believed that research into a cure would have the biggest relative impact on their quality of life². The ambition of the charity for a world where arthritis no longer exists, should be the ambition of the researchers applying to the 'Stacking the Odds towards a Cure' call, and ambition should be clearly articulated in their proposals. She emphasised the call should also be a sustainable initiative, given that the market research also indicated that less than 12% of those surveyed believe it will be possible to cure arthritis¹, and the length of the discovery research translation pathway.

Dr Jane Taylor, Chair of the Arthritis Research UK Patient Insight Partners (PIP) Group spoke about the outcomes of a positive and productive focus group discussion of the charity's growing patient insight partner group. She explained that the group directly tackled the key question from patients on the term 'cure' and what it means to patients and the expectations (from patients) of researchers in working to deliver towards such a goal. A number of points had arisen;

- There was no single universal description of 'cure'. It meant different things to different people, ranging from a better hip replacement to drug-free remission.
- It is very emotive for patients – in rare diseases it may be life-saving – and is viewed as something which transforms lives and ends disease.
- The PIP group members are realistic about the length of time it may take but want ambition, blue skies research, risk-taking, new approaches and new collaborations.

¹Arthritis Research UK Arthritis as a compelling cause, November 2013; ²Unmet needs study June 2015.

Mr Colin Wilkinson (Vice Chair, PIP Group) spoke about a desire for creative innovation, adding:

- Researchers should not be limited to the tools currently available to this field and should consider new perspectives and new insights; for example, the learnings that can be had from other medical conditions such as cancer.
- He challenged that while RMD are diverse can there be research that links between them in a 'pan arthritis atlas'?

Mrs Lynn Laidlaw (PIP) talked about cure in the context of the rare MSK diseases identifying issues including:

- In the emerging era of personalised medicine, physicians are encouraged to treat the patient not the disease, however those with a rare disease have on average been misdiagnosed three times, increasing their morbidity and organ damage. Better knowledge of the diseases, and their earlier identification is vital.
- Taken as a group the rare MSK diseases are less amenable to cure, at least not until a cause is understood, and the immediate unmet need is for better diagnosis and access to care.
- While a definition of 'cure' of returning an individual to a disease and damage free state may not yet be possible, curing chronic symptoms of pain and fatigue was as important to patients for research to achieve.

Session 4: What does the term 'cure' mean for different rheumatic MSK diseases?

Breakout groups facilitated by Dr Stefan Siebert (group 1), Professor Christopher Denton (group 2), Dr Fiona Watt (group 3) & Professor Athimalaipet Ramanan (group 4)

Four breakout discussion groups were led in the following disease groupings by the Arthritis Research UK Research Advisory Group (RAG) Lead members;

1. **(Adult) Inflammatory Arthritis** (*including rheumatoid arthritis and spondyloarthropathies*)
2. **Autoimmune Rheumatic Disease** (*including lupus, scleroderma and rare MSK disease*)
3. **Musculoskeletal disorders** (*encompassing pain, musculoskeletal trauma, osteoarthritis and crystal diseases, and metabolic bone disease*)
4. **Paediatric rheumatology** (*including childhood and adolescent/ young adult arthritis*)

Each group took, as a starting point, the pre-existing priorities from the EULAR RheumaMap (and any other relevant research prioritisation exercises including James Lind Priority Setting Exercises, and Arthritis Research UK Clinical Study Group documents) and asked the following questions:

- *which of these priorities reflect the ambition of providing a cure?*
- *what's missing?*
- *where are the possibilities in discovery, pre-clinical and clinical research within the UK research landscape [to deliver a cure]?*

A summary of each group's discussion is presented in **Table 1** (see pages 7 & 8).

Session 5: Summary

Amongst the discussion highlights relating to the next “Stacking the Odds towards a Cure” Challenge were the following conclusions:

- Cure can be differentially interpreted. It could be a drug-free state of complete wellness (a definition used by RheumaMap) or in those diseases where that is not yet possible, secondary prevention [of symptom progression]. It could be therefore disease cure, symptom cure or potentially societal cure (by public health intervention).
- People with arthritis want the charity to tackle a cure. The charity wants to meet this challenge. The UK medical research community is prepared.
- The limitations, and different trajectories towards cure in different RMD are recognised, but nevertheless it is imperative, in ‘stacking the odds’, for researchers to aim for ambition, novelty and step-change.

The next Cure call

The next call for applications in the Stacking the Odds towards a Cure Challenge will launch on May 30 2018. Key points for applicants will include;

- The call has been broadened to include the full spectrum of discovery to clinical research (including clinical trials) and will be assessed by both Arthritis Research UK’s Disease and Treatment subcommittees accordingly.
- An encouragement to early career researchers will remain for proposals on the smaller end of the funding scale.
- Ambition and a clear articulation of the applicant’s concept of cure, how they have consulted with patients to decide upon it, and how this will be progressed towards, must be stated.

Table 1: Summary points and themes emerging from the Advisory Group-led discussions

<p>Advisory Group Areas</p> <p>Question:</p>	<p>Adult inflammatory</p>	<p>Autoimmune rheumatic</p>	<p>MSK Disorders (<i>Osteoarthritis, pain, orthopaedics, metabolic bone, crystal diseases</i>)</p>	<p>Paediatric rheumatology</p>
<p><i>Which of the pre-existing priorities reflect ambition of the cure?</i></p>	<p>All the priorities identified across the RheumaMap and the previous CSG priorities for inflammatory arthritis.</p> <p>Stratification, precision medicine and outcome measures</p>	<p>Not all have been identified, but RheumaMap priorities are pertinent. Particularly, those with focus on: Early diagnosis/ prevention/ prevention of progression. Preclinical models – to underpin biology of a cure. Human immunology in rare disease – “in-depth human” immunology (at a cellular level). Seeking causal disease mechanism(s).</p>	<p>Existing priority-setting exercises have identified many patient and clinical priorities that are relevant to the Cure Challenge. But may not include all priorities pertinent to the call. Applicants should not feel restricted but highlight additional source material including (new) priority setting exercises or other evidence of high unmet need when answering the call.</p>	<p>All the priorities identified previously by CSG for paediatric (and adolescent) arthritis.</p> <p>Outcome measures particularly needed.</p> <p>Linkage to adult disease (life course approach).</p>
<p><i>What’s missing (from existing priorities)?</i></p>	<p>Outcome measures related to cure, not explicitly described/ asked for in last Challenge Call.</p> <p>Encouraged collaboration</p>	<p>Consideration of disease burden and frequency.</p> <p>Need for collaboration for a cure – shared networks, and systems for data collection at scale (Impact of) Barriers to accessing therapy.</p>	<p>Epidemiology and development of biomarkers for stratification as tools for answering research questions.</p>	<p>Tolerating current medication (sickness with methotrexate).</p> <p>Commonalities with other autoimmune diseases.</p> <p>Links to industry.</p>
<p><i>Where are possibilities in the current research landscape to address these?</i></p>	<p>Challenge can be met by UK research community but need to demonstrate ambition and justify as a Cure</p>	<p>Science which links to clinical trials/ studies.</p> <p>Will need; interaction with industry, rigorous collection of patient-centric information, genomic approaches, underpinning basic science.</p>	<p>Broad scope of conditions in MSK Disorders grouping; in some cases, aiming for drug-free remission would be appropriate (e.g. gout, early surgical intervention)</p>	<p>Challenge can be met by UK research community but needs encouragement for more joined-up work (including adult rheumatology field). Also, for linkage with pharma.</p>

<p><i>Definition of Cure</i></p>	<p>Means different things to different people and depends on context, e.g. can be dependent upon length and severity of condition. Newly diagnosed patient will view cure as a complete removal/cessation of the condition. But, a patient with a condition for a prolonged period of time (20 years) could view a cure as change in their condition that makes it easier to manage and live with.</p>	<p>Cure is a metaphor for meaningful clinical impact. Cure requires sharing learning from more common diseases (e.g. RA) to rare diseases (e.g. vasculitis). Sharing knowledge across units and across nations. Gaining access to pre-existing drugs without a prior indication for rare MSK disease.</p> <p>Greater need for underpinning studies as well as more aspirational research; where less progress, in particular diseases, has been made to-date.</p>	<p>A cure can be defined as secondary prevention, stopping or reducing progression or stopping or reducing persistence of MSK conditions.</p> <p>A cure is achieving a 'patient acceptable state' i.e. a substantial and persisting clinical improvement in their condition.</p>	<p>A definition of 'Drug-free wellness' - remission without medication is difficult.</p> <p>A situation of control on treatment - without pain or fatigue - could be considered 'cure'. However, many medications give children side effects.</p> <p>Perception of cure can be different between parents' and children's or young adult patient's ideal.</p>
<p><i>Other points to consider</i></p>	<p>Health services is a key area for "cure" if talking about management, but this area is not covered by the Disease and Treatment Subcommittees.</p> <p>Phase III studies may be too expensive without an industrial or other partner.</p>	<p>Health service delivery – using disease management to “cure” (catered for in concurrent call)</p> <p>Fatigue and “cure” – unmet need in diseases like Sjögren's Syndrome.</p> <p>Organ-level cure could substantially reduce morbidity/mortality.</p>	<p>Proposals in painful conditions should focus on pain in relation to disease progression or persistence, and/or disease mechanism.</p> <p>Pain as a surrogate outcome measure for disease would be appropriate but research with focus on symptomatic treatment of pain shouldn't be included (concurrent call)</p>	<p>Non-pharmaceutical disease management.</p> <p>Antibiotic-use/ microbiome, influence on disease onset.</p> <p>Paediatric-accessible formulations of drugs (liquid, capsules)</p>

Appendix 1: Programme

**ARTHRITIS RESEARCH UK
STRATEGIC WORKSHOP: STACKING THE ODDS TOWARDS A CURE**

10:30am to 15:30pm on 09 April 2018
Room L13-06, MRC, 1 Kemble Street, London

PURPOSE: to define the scope of the next ambitious research challenge call, which seeks to find a cure and more effective treatments for arthritis through discovery, translational and clinical research.

AGENDA

<u>Time</u>	<u>Agenda Item</u>	<u>Lead</u>
10am	Refreshments	
10:30	Welcome	Stephen Simpson
10:40	Aiming for a cure – priorities for MSK research Perspectives from EULAR (RheumaMap strategy) and OARSI	Iain McInnes Ali Mobasher
11:20	Patient insight – what does cure look like & what does it mean for people with musculoskeletal conditions? Summary of patient insight, including findings from the Patient Insight day.	Natalie Carter Patient Insight Partners
11:30	Introduction and framing the afternoon discussions Building on Stacking the Odds towards a Cure challenge and previous clinical priorities.	Stephen Simpson
12:00	Lunch	
12:45	Breakout Sessions <i>Group discussions to test unmet needs and research priorities previously identified</i>	

	<ul style="list-style-type: none"> • <i>which of these priorities reflect the ambition of providing a cure?</i> • <i>what's missing?</i> • <i>where are the possibilities in discovery, pre-clinical and clinical research within the UK research landscape?</i> <p><u>Sessions chaired by Research Advisory Group Leads</u> Group 1: Inflammatory arthritis Group 2: Autoimmune Rheumatic Disease Group 3: Musculoskeletal Disorders Group 4: Paediatric Rheumatology</p>	<p>Stefan Siebert Christopher Denton Fiona Watt Athimalaipet Ramanan</p>
14:45	Final Discussion	Stephen Simpson
15:30	Close	

Appendix 2: Attendees

Attendees:

Dr Martin Broadstock, Medical Research Council
Professor Maya Buch, Arthritis Research UK Treatment SC
Mrs Susan Burn, Arthritis Research UK Disease SC
Mr David Chandler, Arthritis Research UK Disease SC
Professor Philip Conaghan, University of Leeds
Dr Maurice Darding, Cancer Research UK
Professor Cosimo De Bari, University of Aberdeen
Professor Christopher Denton, Arthritis Research UK RAG
Miss Oonagh Diamond, Arthritis Research UK PIP
Dr Alessandra Gaeta, Catapult
Dr Mohini Gray, Arthritis Research UK Disease SC
Mr Michael Green, Arthritis Research UK Treatment SC
Dr Maureen Grossman, Arthritis Research UK Disease SC
Professor Elaine Hay, Arthritis Research UK Treatment SC
Professor Christian Hedrich, University of Liverpool
Dr John Ioannou, Arthritis Research UK Treatment SC
Professor John Isaacs, Arthritis Research UK Disease SC
Dr David Jayne, Arthritis Research UK Treatment SC
Professor Simon Jones, Arthritis Research UK Disease SC
Mrs Lynn Laidlaw, Arthritis Research UK PIP
Professor Dave Leon, Arthritis Research UK Disease SC
Dr Rose Maciewicz, AstraZenica

Professor Claudia Mauri, University College London
Professor Iain McInnes, University of Glasgow
Dr Stephen Meader, Medical Research Council
Professor Kim Midwood, Arthritis Research UK Disease SC
Professor Ali Mobasher, Arthritis Research UK Disease SC
Dr Clare Pain, Alder Hey Children's Hospital
Professor Costantino Pitzalis, QMUL
Professor Athimalaipet Ramanan, Arthritis Research UK CSG
Mr Alan Reynolds, Arthritis Research UK Treatment SC
Professor Brigitte Scammell, University of Nottingham
Professor Linda Sharples, Arthritis Research UK Treatment SC
Dr Stefan Siebert, Arthritis Research UK RAG
Professor Ken Smith, University of Nottingham
Mr Simon Stones, Arthritis Research UK PIP
Dr Jane Taylor, Arthritis Research UK PIP
Dr Kristina Tubby, Cancer Research UK
Dr Isolde Victory, Arthritis Research UK Treatment SC
Dr Fiona Watt, Arthritis Research UK RAG
Professor Lucy Wedderburn, Arthritis Research UK Disease SC
Mr Colin Wilkinson, Arthritis Research UK Disease SC
Professor Jane Worthington, Arthritis Research UK Disease SC

In attendance from Arthritis Research UK:

Dr Elizabeth Waterman
Dr Stephen Simpson
Dr Caroline Aylott
Dr Keith Pugh
Ms Jane Hirst

Dr Sarah Rudkin
Dr Clare Farmer
Dr Anna Durrans
Dr Natalie Carter