IMMUNE HOMEOSTASIS

FUNDED PROJECTS FROM THE INNOVATION WORKSHOP

18-20 JULY 2017

CANCER RESEARCH UK

ARTHRITIS RESEARCH UK

AIMS

The immune system continues to intrigue and test us: as we get closer to finding ways of harnessing or modulating immune responses, new and unexpected consequences and challenges present themselves, often testing even our most fundamental understanding. Cancer Research UK and Arthritis Research UK came together to engage the research community to tackle the specific challenge of understanding how the immune system regulates itself under normal physiological conditions (immune homeostasis), how it is dysregulated in different diseases and how we can stimulate the immune response to prevent or treat disease (immunotherapy).

We brought together researchers and clinicians in the fields of inflammatory disease, cancer, theoretical physics, computational medicine and other areas, whose expertise could be applied to the key questions concerning immune homeostasis. This workshop encouraged participants from a diverse range of backgrounds to melt barriers, develop a common language to promote collaboration, and suggest new ways to harness the immune system to treat disease.

Director

The role of the Director was to work with the facilitators to lead the event and guide the process from a scientific content perspective. The Director worked closely with the Subject Guides, guiding them as they interacted with the participants, and also played a key role in the funding decisions.

Subject Guides

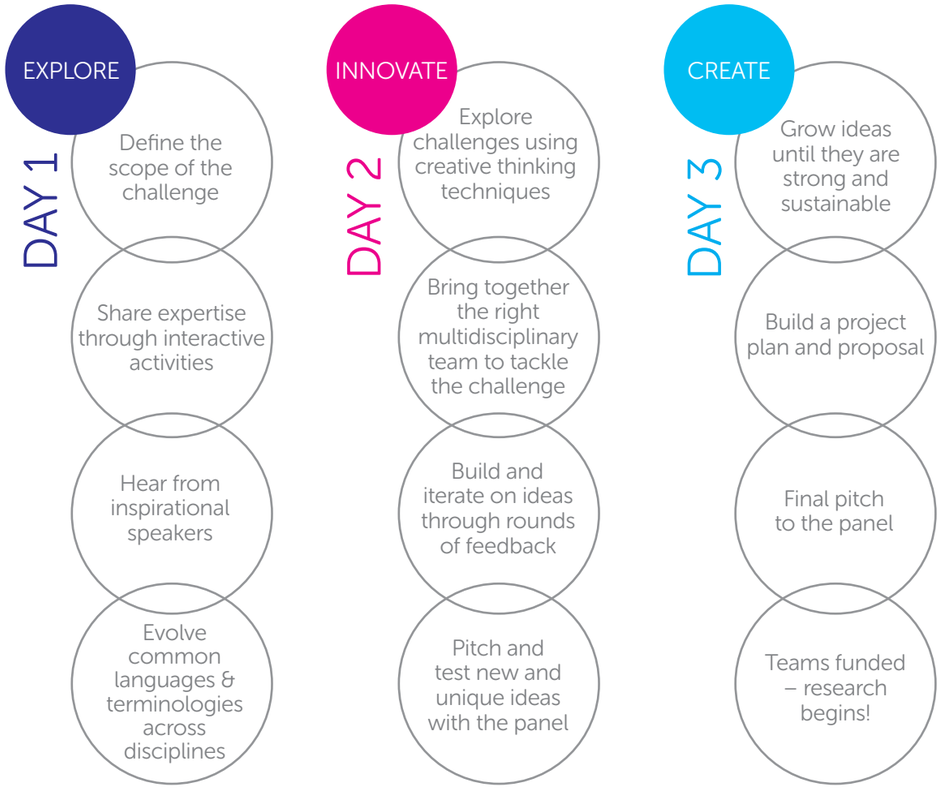
The Subject Guides were experts from complementary research areas and worked with the Director to help guide the scientific agenda of the event. At the start of the event, their job was to encourage new ideas by asking questions, highlighting potentially exciting ideas, and by making connections between participants and to the wider body of knowledge. However, towards the end of the event, the role of the Subject Guides changed; they adopted a more critical perspective and assisted with making the funding decisions.

Theme Champion

The Theme Champion attended the final day of the workshop to observe the pitches and feed into the funding decisions. As the Theme Champion only attended the final pitches, their role was to bring a fresh pair of eyes to the proposed projects and offer further insight when making the funding decisions.

THE SANDPIT PROCESS CAN BE BROKEN DOWN INTO SEVERAL STAGES:

- Defining the scope of the challenge
- Sharing understanding of the challenge and expertise brought to the sandpit by participants
- Evolving common languages and terminologies amongst people from a diverse range of backgrounds and disciplines
- Breaking down preconceptions of researchers and stakeholders
- Taking part in break-out sessions focussed on challenges, using creative thinking techniques
- Capturing outputs in the form of highly innovative feasibility study proposals
- A funding decision on those proposals at the sandpit, using “real time” peer-review.



WORKSHOP DIRECTOR

PROFESSOR ADRIAN HAYDAY

Kay Glendinning Professor and Chair in the Department of Immunobiology at King's College London and group leader at the Francis Crick Institute

WORKSHOP SUBJECT GUIDES

DR RAB PRINJHA

Vice President, Head of Epinova Epigenetics DPU at GlaxoSmithKline

PROFESSOR LUCY WALKER

Professor of Immune Regulation at University College London

PROFESSOR ALLAN BRADLEY

Senior group leader and Director Emeritus at the Wellcome Trust Sanger Institute

PROFESSOR JAMES SPICER

Professor of Experimental Cancer Medicine at King's College London, and Consultant in Medical Oncology at Guy's and St. Thomas' Hospitals London

THEME CHAMPION

PROFESSOR JOHN ISAACS

Director of the Institute of Cellular Medicine at Newcastle University and Consultant Rheumatologist at the Freeman Hospital

WORKSHOP SPEAKERS

The role of the speakers was to encourage provocative thinking among the participants.

PROFESSOR GERARD EVAN

Sir William Dunn Professor of Biochemistry at the University of Cambridge

Gerard discussed the role of the transcription factor Myc, which stimulates cell proliferation but also regulates cell death, competition and differentiation. Elevated activity of Myc is a hallmark of tumour formation (tumorigenesis). Gerard challenged the participants to consider the parallels between tumour formation and the processes which occur in tissues of wounds that fail to heal properly.

ADRIENNE MORGAN AND COLIN WILKINSON

Patient advocates

Adrienne (Cancer Research UK) and Colin (Arthritis Research UK) spoke of the challenges they faced as patients affected by each disease area. Their talks and engagement with participants throughout the workshop encouraged the researchers to consider the bigger picture and broader impact of their ideas.

On the final day of the workshop, each group presented their research idea. The Funding Panel, comprised of Adrian Hayday, John Isaacs, the Subject Guides, and the Patient Advocates, awarded funding to the best proposals, to support the subsequent pilot and feasibility studies.

3 PROJECTS WERE FUNDED

COMMENCING **JANUARY 2018** FOR 12 MONTHS

PROJECT 1

IPADS (IMMUNE PATHWAYS FOR DRUG SIDE EFFECTS)

This project focussed on trying to better understand the biological pathways involved in autoimmunity in both rheumatoid arthritis and cancer patients. The researchers felt that this was necessary to help predict the patient response and side effects from a treatment, and ultimately, enable a more personalised treatment plan to be developed for each individual patient.

Regulatory molecules in the immune system, called immune checkpoints, can increase or decrease immune system activity. They play an important role in ensuring the immune system remains stable and does not attack the body's own tissues, known as immune tolerance. These immune checkpoints can be manipulated to treat both cancer and rheumatoid arthritis. In cancer, proteins which decrease the activity of the immune system can be inhibited with 'checkpoint inhibitors' to increase the immune response. However, these treatments can cause serious adverse autoimmune reactions in some patients and there is no way to predict which patients this will happen to. Conversely, patients with rheumatoid arthritis can be treated with abatacept to decrease the immune response, reducing the autoimmunity. However, not everyone responds to abatacept and there is currently no way to predict who will respond.

To determine the pathway critical for regulating autoimmunity, the team proposed to use a number of techniques to study immune cells from patients treated with checkpoint inhibitors, in this case CTLA4, who did or did not develop autoimmunity, as well as immune cells from patients treated with abatacept, a CTLA4-Fc fusion protein, who either responded to therapy or not. By studying these immune cells, they hope to identify candidate pathways which explain these differences in response to treatment, which would then be validated in mouse and computer models of each disease.

This research has the potential to lead to the development of an accurate model of immune response, enabling us to better understand how a patient may respond to treatment and the side effects they could experience.

> WE AIM TO IDENTIFY IMPORTANT PATHWAYS INVOLVED IN THE DEVELOPMENT AND RESOLUTION OF AUTOIMMUNITY IN BOTH RHEUMATOID ARTHRITIS AND CANCER PATIENTS.

Dr Yin Wu
University College London

Prof Carmen Molina-Paris
University of Leeds

Dr Mohini Gray
University of Edinburgh

Dr Sebastien Viatte
University of Manchester

Dr Miguel Pineda
University of Glasgow

PROJECT 2

SYNOVIAL HYPERPLASIA IN RHEUMATOID ARTHRITIS AND CANCER (SHARC)

Rheumatoid arthritis is an autoimmune disease, meaning the body's immune system attacks its own tissues, resulting in joint inflammation and bone erosion. People with rheumatoid arthritis have an increased number of cells within the lining of the joint, or synovium. However, it is unknown whether this increase is a cause or consequence of the disease. Unlike in cancer, where unregulated cell growth is common, in arthritis this does not lead to a tumour within the joint.

A characteristic feature of rheumatoid arthritis is the thickening of the synovium due to the proliferation of synovial fibroblasts and an influx of inflammatory immune cells. This dysregulated proliferation of synovial fibroblasts seen in arthritic joints resembles the unchecked proliferation of tumour cells, but rarely develops into a tumour itself.

Overall, this team had two main objectives:

1. To determine if cell growth within the joint was an early trigger for inflammatory arthritis
2. To understand why this growth does not develop into cancer, by using specially designed experimental models and human data sets to identify differences in cell cycle regulation in rheumatoid arthritis and cancer.

In the future, results from this study could lead to new preventative treatments for arthritis, which could be given at the first sign of cell changes within the joint, as well as shedding new light on the drivers and regulators of cancer development.

Dr Megan MacLeod
University of Glasgow

Dr Luca Pellegrinet
University of Cambridge

Prof Leonie Taams
Kings College London

Dr Henrique de Paula Lemos
Newcastle University

> A NOVEL ANGLE TO UNDERSTAND WHY CANCER DEVELOPS IS TO ADDRESS WHY IT DOES NOT PROGRESS IN THE RHEUMATOID JOINT.

PROJECT 3

DOES DEFECTIVE WOUND HEALING CONTRIBUTE TO IMMUNE DYSREGULATION IN BOTH CANCER AND ARTHRITIS?

Abnormal wound healing is associated with autoimmune diseases, such as rheumatoid arthritis, and the development of tumours. Correct immune functioning is vital for the wound healing response. In response to damage and injury, immune cells mediate key roles in the coordination and resolution of wound repair. Failure of a wound to heal appropriately leads to continued and aberrant immune activity at the damaged site, promoting loss of immune homeostasis.

This team aimed to assess whether early defects in wound healing contribute to the initiation and progression of rheumatoid arthritis and cancer. The central hypothesis of this team was that aberrant wound healing was a contributing factor to the loss of immune homeostasis in both rheumatoid arthritis and cancer, as failure of immune homeostasis had been shown in both diseases. Therefore, in this project the team aimed to:

1. Understand whether wound-healing pathways were altered in rheumatoid arthritis and cancer using existing data sets
2. Evaluate the potential of specialised molecules, which promoted healing, to limit both rheumatoid arthritis and cancer onset, progression and/or severity.

If proven to be true, this hypothesis could support a step-change in our understanding of these different disease states. The outcome of this preliminary study could establish whether rheumatoid arthritis and cancer share an underlying cause – defective wound healing. The results could provide information on the pathways involved in wound healing in both rheumatoid arthritis and cancer, and may also identify molecular mechanisms shared by these seemingly different diseases.

> WE SEEK TO ASSESS WHETHER EARLY DEFECTS IN WOUND HEALING CONTRIBUTE TO THE PATHOGENESIS OF RHEUMATOID ARTHRITIS AND CANCER.

Dr Carolina Arancibia
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For more information about funded projects from the Innovation Workshop, contact

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