

Immune Mediated Inflammatory Diseases



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Immune-mediated inflammatory diseases occur when the body has an inappropriate immune response, causing inflammation, leading to organ damage and morbidity. There are more than 80 autoimmune diseases, e.g. Type-1 diabetes, lupus, rheumatoid arthritis and Crohn's disease, which affect hundreds of thousands of individuals in the UK, placing a great burden on the healthcare system. Worryingly, these diseases are increasing in incidence, with current treatments alleviating symptoms but not curing the diseases (BSI Autoimmunity Policy briefing document).

The main goals of the IMID meeting were to present the grand challenges identified at the UK Autoimmunity workshop in May 2016, to the wider scientific community; to inform the community and funders of the current status and direction of research in IMIDs in the UK, to highlight the strengths in the field and identify any further challenges and opportunities for future research, to build strong, collaborative efforts and encourage more cohesive working to investigate IMIDs and drive the next step changes in the field.

The meeting was split into 5 sessions each addressing one of the 5 grand challenges, through presentations, an open discussion and breakout sessions. This report summarises the main discussion points from these sessions and identifies the next steps.

Introduction

Immune mediated inflammatory diseases (IMIDs) are a range of conditions that affect specific or multiple organs, and often share immunological and mechanistic features, but have different clinical manifestations. IMIDs include autoimmune conditions, which are characterised by a breakdown in tolerance due to self-reactive cells responding to auto-antigens, leading to specific immunological responses, and also include auto-inflammatory conditions, characterised by self-directed inflammation and activation of innate immune cells.

Recently there has been an increase in the prevalence of IMIDs in developed countries placing a severe burden on healthcare systems. Research into IMID conditions has previously been pursued in a disease-specific manner, according to clinical presentation, and often focussing on later stages of the disease. Consequently, some of the broader learnings around the early mechanisms of loss of immune tolerance or early instigators of inflammation have been overlooked. A better classification of IMIDs may aid in the early detection and therefore quicker therapeutic interventions.

The key grand challenges discussed at the meeting were:

- 1. Immunological tolerance**
- 2. Environmental impact on genetic predisposition**
- 3. Common mechanisms shared across IMIDs**
- 4. Toolkits, technologies and platforms**
- 5. Therapeutics: translational perspectives**

Session summaries

Session 1: Immunological Tolerance

When the immune system fails to respond to a signal, we call this “tolerance”. This is the normal system when the body sees a signal from our own body. But what happens when this self-tolerance mechanism is broken, and could this happen in a similar way in different IMID diseases or even cancer?

Different IMIDs may develop in a common way, and we heard in this session that evidence for this is that one individual may suffer from more than one autoimmune disease, or different members of the same family can display multiple diseases. One common way this could happen may be via altered function of the molecule CTLA-4, which is highly expressed on T regulatory cells (Tregs) and important for maintenance of tolerance. When this molecule is absent in mice, they quickly develop lethal autoimmunity and, humans with mutations in this molecule also display autoimmune features. Researchers may be able to learn about common pathways seen in IMID diseases by looking at other types of diseases, in particular cancer. In many cancer studies researchers have modified the signalling pathways that T cells use to recognise cancer cells and increase the chances of survival in cancer patients. Approaches designed to promote Treg cells may be useful in combating or overcoming autoimmunity.

We continued this discussion by focussing on specific examples of pathways to disease which are driven by changes in tolerance, and how to treat this. In type 1 diabetes (T1D), we heard about a new type of peptide (short protein chains) called hybrid insulin peptides, which may have broken the tolerance mechanism and be recognised by the body. We concluded the session by hearing how the IL-10 pathway, which is known to be an important immune-regulator, is being targeted to stop T cells being overstimulated, and that this may in future be exploited as a peptide based immunotherapy.

Session 2: Environmental Impact on genetic predisposition

Alongside genetics, there are a range of factors that trigger the development of IMIDs. What are these initiating factors and what is the role of the environment, the microbiome and infection in the development of IMIDs?

The gastrointestinal tract is home to many commensal bacteria (the gut microbiome) which may play an important role in nutrition and development of the immune system. We heard how diseases such as inflammatory bowel disease (IBD) can alter the microbiome and promote particular pathological processes. Interestingly we heard that there has been a large decline in major infections in the western world over the last 50 years, and a corresponding increase in the development of IMIDs, e.g. the incidence of T1D is doubling every 20 years. This difference may be attributed to differences in diets (and therefore the gut microbiota) between industrialised and less developed countries.

The risk of developing an IMID is likely due to an imbalance in different immune cell (T cells) subsets. We heard that other specific immune cell subsets (neutrophils) are also involved, further mediating tissue inflammation. Several autoimmune diseases also exhibit autoantibodies (antibodies that recognise self) prior to clinical onset of the disease, providing a window for potential therapeutics. In addition, many IMIDs have a genetic association (HLA class II) that in combination with environmental factors can trigger the onset of disease. We heard from studies in the lung, that exposure to smoking, silica dust, textile dust or asbestos, can cause transition into the inflammatory disease rheumatoid arthritis.

Session 3: Common mechanisms shared across IMIDs

What genetic mechanisms are common in IMIDs and how have genome wide association studies (GWAS) helped in identifying common targets? Are there any common mechanisms that are shared between individuals with IMIDs?

It is important to study the whole family's genetics, as all IMIDs are heritable, have a gender bias, and often cluster in individuals or families. In particular there is a strong association of IMIDs with HLA and previous investments in genetic studies have identified many non-HLA associated single nucleotide polymorphisms (SNP) in autoimmune diseases associated with IMIDs. For example, 57 regions of the human genome identified, contribute to T1D risk. We heard that perhaps there are external drivers of some IMIDs, for example in coeliac disease; cereal gluten proteins cause harmful immune responses. In addition to conventional T cells which interact with peptides and lipids that are presented by HLA on their cell surface, we also heard that there may be a potential role for unconventional T cells in IMIDs. We finished the session with a focus on T1D, and a suggestion that the classical model of T1D does not fit anymore, and that a new model where autoimmune beta cell destruction and degeneration are combined.

Session 4: Toolkits, technologies and platforms

What are the relevant developments in technologies available for IMID investigation? How can we monitor conditions in a consistent way? What is the benefit and importance of good working relationships to drive further discovery and translation in IMIDs?

The session kicked off with two talks highlighting the importance of the development of new methods to research IMIDs e.g. mass cytometry and microscopy. Advances in technology are important to understand the complex interactions in IMIDs, provide optimal prevention, diagnosis and treatment, and offer considerable promise and greater insight into personalised therapies for IMIDs, without influencing the biological system under observation.

We then heard how the MRC have invested £60mil in 13 research networks in 32 academic institutions between 2010 and 2014, 7 of these are IMID related, to encourage engagement and good working relationships between academia and industry. By bringing together clinicians, academics and industry, the networks aim to increase the pace and scale of discovery and innovation in specific disease areas. RA-MAP, an example of such a network found that good project management, flexibility in the resources, clear lines of communication and decision making, led to good collaborative working between the different partners. Other MRC funded projects including RA-MAP, all share a central database (TRANSMART) to enable secure sharing and analysis of data.

Session 5: Therapeutics: translational perspectives

Why are some IMIDs organ-specific if they have similar pathways? What are the current industrial priorities for managing and curing IMIDs? This session aimed to share knowledge from industry regarding the challenges of working in the IMID field.

The session began looking at organ specificity, by discussing the role that tissue resident stromal cells play in chronic disease. These cells play a role in immune surveillance, and may alter the response of the inflammatory disease to therapies. Cohort studies are crucial to understanding this, and we saw how a cohort of early arthritis patients from Birmingham was used to demonstrate that the stroma can become pathogenic. The current availability of "omic" technologies means that huge data sets can be generated. The session continued by giving examples where these have been linked up with phenotype, or the visible characteristics, in both mice and humans. This has led to breakthroughs for understanding why patients with Autoimmune Polyglandular Syndrome Type 1 (APS-1) actually produce antibodies which can modify risk of other diseases, such as T1D.

We then moved to discussing therapeutics for IMIDs. Many IMIDs have different stages of disease and not all patients respond to treatment, it is important to ensure the right patient gets the right treatment at the right time. A variety of treatments were discussed, including a number of cell signalling inhibitors and nerve stimulation, as well as mining the gut microbiota for compounds that affect the immune system.

Breakout session summary / next steps

We held breakout sessions towards the close of the meeting to allow the community to discuss issues raised during the meeting and stimulate discussions on future endeavours. The main points raised are summarised below:

Immunological Tolerance

In this breakout session, a “back to basics” approach was adopted after a discussion focussing on our gaps in knowledge of immunological tolerance. The gaps identified included how B cell tolerance works and the role of memory T cells.

The group identified a strategy to go forwards; to better understand when tolerance is broken and how deep clinical phenotyping in patients with IMIDs at different stages would provide fundamental information about tolerance.

Environmental impact on genetic predisposition

Discussion focused on the different types of environmental factors that trigger IMIDs, and that certain diseases have good cohorts to study this (e.g. T1D and RA).

The group identified there are multiple differences in populations, and therefore good epidemiological studies were needed, alongside a multidisciplinary approach to investigating IMIDs. These studies will generate a large amount of data, and so it will be important to have the right expertise to analyse it, e.g. bioinformaticians.

Common mechanisms shared across IMIDs

Discussion focused on why there has been so little progress on IMIDs and it was suggested that this may be due to the structural problem in the way specialities are set up in hospitals, specific departments and a division between paediatrics and adult medicine, and primary and secondary care.

It was suggested that there had to be some consistency and reproducibility in big data sets and cohorts, and it was important to bring together the areas of genetics, response to treatments

and mechanisms of IMIDs so that common mechanisms can be found and investigated.

Toolkits, technologies and platforms

In this breakout session, the discussion focussed on the relationships between different partners and how there is a synergy between different diseases.

Going forwards, it is important to have good working relationships with industry to deliver on goals, and milestones to assess progress. It was also suggested that there should be multiple and faster readouts in trial designs with the uptake of adaptive design.

Therapeutics: translational perspectives

The key points in this discussion were covering how to get faster readouts from clinical patients, and plans for the future involved strategies for better engagement with industry and de-risking the process of industry and academia forming partnerships.

There was discussion on training highly skilled individuals (statisticians, bioinformaticians, etc.) and providing them a career structure to retain them and also developing centres of excellence in the area of IMIDs or a UK IMID platform with input from industry.

Conclusions

This meeting generated energy and enthusiasm for research into immune mediated inflammatory disorders collectively. There was very clear agreement that understanding where similar mechanisms in IMIDs could be targeted had the potential to bring about real change for people living with these conditions.

A post-meeting survey revealed that 62% of participants believed that this meeting would lead to new collaborations for them with examples of this given being invitations to speak at other institutes and preparation of collaborative grant applications.

Since the meeting, JDRF and Arthritis Research UK have been working together to form a joint funding call, and the MRC and Wellcome have received applications in the area of IMID research.

Acknowledgements

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Glossary

Cohorts – a group of people with common defining characteristic(s).

CTLA-4 – Cytotoxic T lymphocyte associated protein 4. A protein receptor expressed on T regulatory cells that functions as an immune checkpoint and downregulates immune responses.

Foxp3 – Forkhead box protein P3. Master regulator involved in the development and function of regulatory T cells

GWAS – Genome-wide association study. An examination of a genome-wide set of genetic variants in different individuals to see if a variant is associated with a trait.

HLA – gene complex encoding cell surface proteins that help the immune system to distinguish foreign proteins from the body's own proteins (self).

IBD – Inflammatory bowel disease. A group of inflammatory conditions that affect the colon and small intestine, these include Crohn's disease and ulcerative colitis.

IL-10 – Interleukin 10. An anti-inflammatory cytokine and key immune regulator during infection, limiting the immune response and reducing pathology.

IMIDs – Immune mediated inflammatory disorders. A group of different diseases where the body has an inappropriate immune response causing inflammation.

Omic technologies – a collection of technologies which study the role of molecules in the body, for example genomics, metabolomics, transcriptomics.

RA – Rheumatoid Arthritis. A chronic condition that causes painful stiffness and swelling in the joints.

Tregs – Regulatory T cells. A sub population of immune cells which maintains tolerance of "self" markers.

T1D – Type 1 Diabetes. A disease where the bodies insulin producing cells are inappropriately targeted by the immune system.

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**Wellcome Trust, 215 Euston Road,
London NW1 2BE, UK
T +44 (0)20 7611 8888, F +44 (0)20 7611 8545,
E contact@wellcome.ac.uk, wellcome.ac.uk**

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