Morgan BP, Kavanagh D.

[Introduction to complement in health and disease: novel aspects and insights.](#)

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Introduction.

With the realisation of the importance of complement as a driver to pathology in many and diverse diseases, and the advent of effective anti-complement therapies, the field has undergone an explosion in interest from clinical scientists and a tsunami of reviews and special issues addressing various aspects of complement biology. To separate this Special Issue from the pack, topics were carefully selected, relevant and erudite experts invited, and asked to go beyond a “standard” review format, expressing opinions and addressing controversies. The result is, as hoped, a little different and, we hope, a more interesting read. We hope that readers will find much to inform but also to contest and debate in future meetings and articles. Complement is no longer the rather static area of thirty years ago and there is much to discuss!

We have rather loosely divided this Issue into “Basic Biology” and “Disease” though the division is artificial – every article has something to say about basic biology and is relevant to understanding disease. We start with the building blocks – structural understanding has revolutionised the complement field over the last two decades providing a molecular picture of the contortions that these proteins undergo as they are activated, form complexes, bind regulators and receptors and are inactivated. This has involved the interlinking of multiple structural methods, including crystallography, NMR spectroscopy and, recently with great impact, cryo-electron microscopy. Santiago Rodrigues de Cordoba and colleagues describe how these methods have shone a spotlight on the beautiful intermolecular ballet of assembly and decay of complexes in the alternative pathway and assembly of the membrane attack complex. In particular, they highlight how structures have sometimes surprised us and changed our decades-old dogma of how complement works.

The positive feedback loop variously called the “alternative pathway”, “amplification loop” or “properdin pathway” is key for efficient activation of complement *in vivo*. Richard Harrison takes on the task of clarifying a rather confusing literature to arrive at a better understanding of this critical part of the complement system, confronting head-on the misconceptions that have stalked it since its first description in the 1950s. These clarifications are necessary to inform current attempts to regulate the amplification loop as a therapeutic approach.

One of the many surprises over the last twenty years was the demonstration that complement was not merely an innate immune effector but also played important roles in regulating adaptive immune responses. This finding catalysed a new area of complement research at this immune interface that has been both informative and controversial. Anne Astier and colleagues take on the challenge of making sense of these complex interactions. In particular, they focus on roles of complement in the regulation of antigen presenting cells, and activation of B and T lymphocytes. They describe the importance of locally produced complement proteins on this immunological cross-talk and touch on the recent proposition that complement proteins mediate some of these effects intracellularly. Finally, they put this in the context of disease.

In the first article in the “Disease” section, David Kavanagh and colleagues take on the monumental task of reviewing disease of complement dysregulation – sufficient for a journal issue in itself. They describe three prototypical complement dysregulation diseases, the haemolytic disorder paroxysmal nocturnal haemoglobinuria and the two renal diseases of complement dysregulation, atypical haemolytic uraemic syndrome and C3 glomerulonephropathy. They describe the common features of these diseases and the differences in where and how complement is dysregulated that lead to different pathologies.

Missing from the above is the fourth prototypical complement dysregulation disease, age-related macular degeneration (AMD), the commonest cause of blindness in the western world. Simon Clark and Paul Bishop discuss complement dysregulation in the eye, noting that, for anatomical reasons, the eye may be particularly at risk. They then discuss the how, when and where of complement activation in the retina in AMD and the complexities of effectively treating complement dysregulation at this difficult-to-access site.

The lectin pathway has emerged relatively recently as an important route to complement activation in homeostasis. Like every other part of the system, the lectin pathway can be dysregulated in disease and contribute to damage. Steven Sacks and colleagues describe the complex sets of lectin pathway activators, collectins, some of which are locally produced and tissue-specific. They provide a detailed description of the distributions and likely roles of the different collectins, describe pathologies in which collectins and the lectin pathway are implicated and discuss strategies for therapeutic targeting of this pathway in disease.

Complement is just one of a number of proteolytic cascades in blood and tissues, including the coagulation, contact activation and fibrinolytic systems. Bo Nilsson and colleagues describe these related pathways and the various checks and balances that limit cross-talk under homeostatic conditions. They then go on to describe the many situations in which this control is lost, leading to inter-pathway interactions, dysregulation and disease. Moving away from the complement-centric to a holistic picture of multi-pathway dysregulation will inform better therapies in future.

Pregnancy is a unique state where an organism must tolerate the presence of a large foreign body. The barriers to adaptive immune attack on the foetus are numerous and well-known, but defence against complement is less well studied. Guillermina Girardi describes the evidence from animal models and humans of the importance of complement regulation at the foeto-maternal interface. Complement dysregulation can contribute to multiple adverse pregnancy outcomes, including recurrent miscarriages, intrauterine growth restriction, preeclampsia and preterm birth. Tackling these with anti-complement drugs should now be considered, informed by a better understanding of the mechanism.

Alzheimer's disease is the commonest cause of dementia world-wide, a pandemic with no effective treatment. Once considered a degenerative disease, it is now broadly accepted that inflammation is an important driver, and a possible candidate for therapy. Paul Morgan summarises the growing multi-source evidence implicating complement as one of the drivers of inflammation in Alzheimer's disease. There remains a lack of clarity regarding when and where complement dysregulation occurs, and which complement effectors are responsible for damage. Efforts to bring clarity are underway and may make the case for targeting complement in some patients with early disease – if the problems of developing anti-complement agents suitable for treating a common and chronic disease can be overcome.

Almost every article in this issue refers to the possibility of therapeutic targeting of complement. It is thus fitting that we end with a contribution from Claire Harris discussing current and future approaches to anti-complement therapy. The article briefly reviews the past landscape and then focusses on the many challenges confronting the field and lessons learnt from past and present clinical studies. Novel approaches to overcome obstacles blocking success are explored with examples of the newest drugs in the pipeline that utilise these strategies.

We hope that you find lots to interest, inform and perhaps challenge you in this issue. Complement research has blossomed in the last decade and we are confident that the excitement will grow. The

importance of complement as a key component of the immune-inflammatory network in health and disease will be further clarified and anti-complement therapies will move beyond the ultra-rare disease niche and become commonplace in common diseases.