Focus on Complement

June 1, 2015
Issue 38

International Complement Society

European Complement Network

Dear Readers,

Welcome to the June 2015 issue of 'Focus on Complement'. This 38th issue of FoC contains:

- A report from the **Complement Standardization Committee**
- **News Flash** presenting two recent papers showing how the crosstalk between complement and pentraxins contribute to cancer and the distinct roles of C5a during the injury and repair phases in a spinal injury model.
- **The Complement research teams around the world** series featuring the teams of Marco Cicardi and Alberto Clivio in Italy and Steffen Thiel and Jens Jensenius in Denmark
- A **Meeting Report** on the first Theo Murphy International Meeting of the Royal Society titled 'Complement: Driver of inflammation and therapeutic target in diverse diseases' (Feb 2015)
- **15th European Meeting on Complement in Human Disease** announcement

If you would like to contribute with an article to a future issue or have suggestions for a subject theme, please contact Claudia Kemper or Andrea Tenner; Claudia.kemper@kcl.ac.uk; atenner@uci.edu

COMPLEMENT STANDARDIZATION COMMITTEE REPORT

The history of the Complement Standardization Committee:

Complement contributes to the pathophysiology of a large number of diseases, including nephropathies, autoimmune disorders and angioedema. 5-10% of all primary immunodeficiency disorders are due to complement deficiencies.

Complement analysis in the clinic is traditionally associated with C3 and C4 quantification, measurement of C1-inhibitor and, in some specialized laboratories, extended to functional complement screening tests, all parameters that have been available as routine diagnostic tests for decades. In recent years this field has tremendously grown with, novel techniques useful to define diseases such as atypical haemolytic uremic syndrome (aHUS), C3 glomerulopathies (C3G) and age-related macular degeneration (AMD). Another important application of traditional and novel complement diagnostic techniques is the assessment of the effects of emerging therapeutic drugs for complement-mediated diseases.

Clinical analysis of the proteins of the complement system varies widely between laboratories because, except for a few proteins such as C3 and C4, no well-characterized standard preparations are available on a wide scale. This is especially problematic for functional assays of the classical (CH50), the alternative (AH50) and the lectin pathway. An additional need exists for the standardization of the measurement of complement activation products (peptides and protein-protein complexes) that are valuable to determine whether clinically relevant complement activation has occurred *in vivo*. Finally, auto-antibodies to complement proteins (e.g. anti-C1q), C3 convertases (C3 nephritic factor) or antibodies to regulatory proteins (e.g. anti-C1inhibitor, anti-factor H) are of considerable importance in defining autoimmune processes and diseases based on complement dysregulation.

At the 2008 International Complement Workshop in Basel, Switzerland, a group of interested members of the International Complement Society (ICS) met to discuss the formation of a standardization committee and to define the major aims of this quality management initiative. Initiated by the late Prof. George Füst, Budapest, Hungary, a group of 18 complement scientists from 11 countries first met in Budapest in May 2009. At this meeting, Prof. Hans Reinauer of INSTAND e.V, Düsseldorf, Germany (a collaborating partner of WHO), a non-profit, interdisciplinary scientific medical society for the promotion of quality assurance in the medical laboratories and later his successor Prof. Michael Spannagl joined our initiative by taking over the distribution of the samples to the participating labs worldwide and by supporting technological development.

In 2010 the International Union of Immunological Societies (IUIS, http://www.iuisonline.org/) established the initiative officially as *Subcommittee for the Standardization of Complement Analysis.*

The subcommittee with its associated laboratories adopted the following goals:

1. **To initiate and organize measures (External Quality Assessment rounds) to improve the quality of complement analysis.**
2. **To make several standard materials available to the scientific and clinical laboratories which apply.**
3. **To define standardized methods of modern complement analysis.**
4. **To organize national and international workshops and training courses on modern complement analysis.**

The first standard (pooled normal serum) for complement analytes was prepared by Bo Nilsson, and a second standard (a fully activated and stabilized serum to be analyzed for complement activation products) was produced by Tom Mollnes, allowing the first external quality assessment (EQA I) in June 2010, including 15 laboratories in 13 countries . Subsequently, further assessment rounds followed from 2011 every year with an extended list of now 18 parameters and an increasing number of participants now comprising 39 labs from 21 countries worldwide in 2015.
A major step forward was achieved by the replacement of fresh, frozen serum and plasma by lyophilized samples, overcoming all the disadvantages with respect to instability, at the same time allowing to significantly cut costs of transportation. Data management became more professional and structured when Zoltán Prohászka developed a comprehensive online data retrieval survey in 2014. At that year ICS, IUIS and INSTAND agreed to provide a certificate to document participation and the quality in complement analysis in the participating labs. This can not be overestimated as it meets for the first time the demands of national and international accreditation agencies to also provide a proof for the quality of diagnostic complement labs.

The next EQA meeting is scheduled for June 30th, 12:30, on the occasion of the upcoming European complement meeting in Uppsala to present the new results, and reports will be sent to all participating labs.

Current officers of the group are: ***Chairman Michael Kirschfink (Heidelberg, Germany), and Co-Chairs Zoltán Prohászka (Budapest, Hungary), Bosse Nilsson (Uppsala, Sweden) and Patricia C. Giclas (Denver, CO, USA).***

NEWS FLASH

NEWS FLASH 1: PTX3 is an extrinsic oncosuppressor regulating complement-dependent inflammation in cancer. *Bonavita E, Gentile S, Rubino M, Maina V, Papait R, Kunderfranco P, Greco C, Feruglio F, Molgora M, Laface I, Tartari S, Doni A, Pasqualini F, Barbati E, Basso G, Galdiero MR, Nebuloni M, Roncalli M, Colombo P, Laghi L, Lambris JD, Jaillon S, Garlanda C, Mantovani A. Cell. 2015 Feb 12;160(4):700-14.*

Tumor promoting inflammation is a hallmark of cancer development. The humoral arm of the innate immune system comprises diverse molecules including complement components, pentraxins, collectins, and ficolins. Pentraxins are highly conserved, present in the blood and body fluids, and involved in pathogen recognition and removal. The long pentraxin, PTX3, interacts with C1q, factor H, MBL and ficolins, improving microbial recognition and effector functions of the complement system. In this paper, Bonavita *et al.* demonstrate that PTX3 acts as an oncosuppressor in mice and humans by regulating complement-mediated tumor-promoting inflammation. PTX3 deficiency increases susceptibility to mesenchymal and epithelial carcinogenesis in mice, with elevated C5a production, macrophage infiltration, cytokine secretion, and angiogenesis. PTX3 KO mice also produce high levels of CCL2, which in turn recruits tumor-promoting M2 macrophages. Increased complement activation was observed in PTX3-deficient mice, as reflected by a higher C3 deposition at tumor sites. In line with a critical role for complement in this cancer pathogenesis, C3/PTX3 double deficient mice are less susceptible to carcinogenesis. Inhibition of Factor H binding to PTX3 increased C3 deposition on PTX3-producing cells. Tumors developed in a PTX3 deficient context had a higher frequency of *Trp53* mutations, increased DNA oxidative damage and higher expression of DNA-damage response (DDR) markers. To prove the clinical relevance of their findings obtained in mouse models, the authors extended their study to human cancers (sarcoma, colorectal and skin carcinoma) and found that the PTX3 promoter was hyper-methylated resulting in an inhibition of PTX3 expression. These results convincingly demonstrate that PTX3 is an important oncosuppressor, which regulates complement-mediated tumor-promoting inflammation.

Reported by Michael Kirschfink, University of Heidelberg, Germany

NEWS FLASH 2: The Complement Receptor C5aR Controls Acute Inflammation and Astrogliosis following Spinal Cord Injury. *Brennan FH, Gordon R, Lao HW, Biggins PJ, Taylor SM, Franklin RJ, Woodruff TM, Ruitenberg MJ. J Neurosci. 2015 Apr 22;35(16):6517-31.*

The complement system plays a pivotal role in aggravation of tissue injury after spinal cord injury (SCI). However, recent reports indicate that complement may also exert neuroprotective effects with C5a as an important mediator. In this paper, Brennan et al. investigated the role of C5a in secondary injury following contusive SCI. Mice lacking C5aR showed improved signs of locomotor recovery and reduced inflammation during early phase of SCI. However, this effect was reversed during later stages of SCI, in which absence of C5aR leads to deterioration with larger lesion volumes, reduced myelin content and widespread inflammation. These findings indicate that C5a-C5aR signalling is injurious in the acute phase of SCI but plays a protective and/ or reparative role in the post-acute phase of SCI. To further support their observation, the authors performed bone marrow chimeric transplantations from which they conclude that the dual role of C5aR on SCI outcomes are mostly mediated through the expression of C5aR on resident CNS cells but not by circulating immune cells. The protective role of C5aR in a more chronic period of SCI was further defined by *in vitro* and *in vivo* experiments and it appears that C5aR signalling is required during the post-acute phase to regulate astrocyte proliferation, hyperplasia, hypertrophy, and glial scar formation. Brennan and colleagues thus provide evidence that C5a-C5aR signalling has both a destructive and a protective role in SCI emphasizing the importance of optimizing the timing of therapeutic interventions.

Reported by Michael Kirschfink, University of Heidelberg, Germany

COMPLEMENT TEAMS AROUND THE WORLD

Complement in Italy, Milan: Marco Cicardi's and Alberto Clivio's Teams

Angelo Agostoni, who had specific interest in the deficiency of C1 inhibitor and its related clinical condition hereditary angioedema, established the Milan complement study group 40 years ago. Luigi Bergamaschini and Marco Cicardi since the beginning, and later Massimo Cugno and Sonia Caccia, contributed to the understanding of the pathophysiology of C1 inhibitor deficiency and its interplay with the contact kinin system. Mainly due to the work of Bergamaschini, the group has provided original contributions on the role of complement and contact systems in neurologic diseases as Alzheimer and stroke. More recently, this group merged with the group of Alberto Clivio who had been working since long time on factor H and three current projects are more detailed here.

Angioedema

We assess samples from patients with different forms of non-allergic angioedema in the dedicated Laboratory of Complement and measure C1 inhibitor function, the only assay allowing secure diagnosis of angioedema due to inherited and non-inherited C1 inhibitor deficiency. We also measure C1 inhibitor, C4, C1q antigen and auto-antibodies against C1 inhibitor and C1q in serum.

A line of research of our group is focused on quantifying the activation of tsystems controlled by C1 inhibitor in patients with inherited C1 inhibitor deficiency. These studies provided important advances in the identification of the mediator responsible of the increase in vascular permeability. Recently, we measured cleaved high-molecular-weight kininogen (HK) in hereditary angioedema patients with C1 inhibitor deficiency as an indirect marker of contact activation and we demonstrated that the amount of cleaved HK correlates with the presence of angioedema and/or susceptibility to its development. Our aim now is to increase sensitivity and specificity of these methods and ultimately provide tools to be used in the clinical practice.

C1-Inhibitor

Our studies are prompt by the observation that despite C1-INH-HAE patients are normally heterozygous for C1-INH gene mutations (only few families with homozygous mutations are described), plasma levels of functional C1-INH protein are markedly below the half normal level that the wild-type allele should provide, suggesting a dominant-negative effect of the mutated allele over the wild-type one. We are looking for a mechanism of down-regulation of the normal allele both at pre and post-translational levels of C1-INH expression. In particular, we are focusing on the different conformational isoforms that C1-INH could adopt. C1-INH belongs to the serpin family, a class of proteins sharing the same mechanism of action and a highly similar tridimensional structure. Serpins give rise to a class of diseases called serpinopathies, where point mutations destabilize the native conformation, often leading to protein polymerization inside the cell of synthesis. Oligomers can be found also in the plasma of affected patients. Could mutant and wild-type C1-INH form mixed polymers and so exacerbate the dominant negative phenotype in the cases of polymerogenic variants? Since we know from C1-INH-HAE replacement therapy that plasma levels of normal C1−INH just above 50% maintain C1-INH-HAE patients symptom free, defining possible alterations in the functioning of the single normal C1-INH allele in C1-INH-HAE is essential.

Factor H

Large sets of genetic sequences are now available on variants of the FH gene in different pathologies such as atypical Hemolytic Uremic Syndrome (aHUS), Age-related Macular degeneration (AMD and Membranous Glomerulonephritis (MGN). We developed a micro-affinity method for the rapid assessment of the different functional activities of human FH, making use of a homemade monoclonal antibodies that recognize only FH and are unreactive with FH-Like and FH-related proteins. This allows for the assessment of the functional features of all the FH variants - so far defined only based on DNA sequence - and will provide valuable information on the functional consequences of specific mutations. These reagents will also allow confirming which and to which extent mutations cause impairment of FH function.

Additionally, we have produced full-length FH cDNA as well as three fragments of FH spanning SCR domains 1-5, 8-14 and 15-20 to be expresses both in prokaryotic and in eukaryotic hosts, in order to assess the role of glycosylation on the function of FH. As far as the FHL-1 protein is concerned, we are interested in investigating in further detail its role in the development of AMD. With this in mind, we are currently investigating in the identification/generation of antibodies capable of discriminating FH-Like protein 1 from FH, two different proteins derived from alternative splicing of the same FH gene transcript, with only a small difference at the *C*-terminal end.

Contact: Profs. Marco Cicardi and Alberto Clivio, Dipartimento di Scienze Cliniche "Luigi Sacco", Università di Milano, Milan, Italy. E-mails: **marco.cicardi**@unimi.it; **alberto.clivio**@unimi.it

Complement in Denmark: Steffen Thiel's and Jens Jensenius' Teams

The group of Steffen Thiel and Jens Christian Jensenius has been studying the lectin pathway (LP) of complement activation since 1990. We have thus participated in unravelling the mysteries of the LP through identifying the mannan-binding lectin (MBL) associated proteins, MASP-2, MAp19 (sMAP), MASP-3 and MAp44 (MAP1); and have described the role of MASP-2 in activating C4 and C2; and determined the role of MASP-1 in activating MASP-2. Recently we have suggested an inter-complex-activating mode for getting the pathway running, i.e., that tetrameric MBL comprises only one MASP dimer, and that MBL/MASP-1 activates MASP-2 on adjacent MBL/MASP-2 complexes. The complexes, studied by small angle X-ray scattering and electron microscopy, revealed a structure quite different from the canonical structure of the C1 complex with the non-activated MASP dimer in a rod-like shape, ready to be activated by another MASP and then activate C4 and C2. We have developed time-resolved fluorescence immune assays for MBL, collectin LK (CL-LK), the three ficolins, and the five associated proteins, and employed these assays on clinical cohorts for determining possible associations with diseases and biologically meaningful functions. To list some results: development of nephropathies in type I diabetes is less pronounced in MBL deficient patients; high M-ficolin levels are associated with poor prognosis in rheumatoid arthritis; low MBL associated with infections in cancer patients undergoing chemotherapy; inhibition of viral infections; possible association of ficolin deficiency with the development of necrotizing enterocolitis in preterm babies. Importantly, screening of serum/plasma samples has identified individuals lacking some of the LP proteins, and such samples have been invaluable for the studies of the function of the proteins. We are also involved in trying to bring our research to clinical use: Together with Statens Serum Institut in Copenhagen we devised a GMP procedure for the purification of MBL from plasma. Such a preparation was in 1998 used for reconstitution therapy in a trial in Iceland in collaboration with Helgi Waldimarsson. We established a company, Natimmune ApS, for the GMP production of recombinant MBL.

After a successful Phase I trial, the project was moved by Enzon Pharmaceutical in NJ into a Phase II trial. Unfortunately, the project was put on hold for financial reasons. During our work we have enjoyed immensely the collaboration and friendship with colleagues around the world. We believe that insight in the description of inflammatory processes, in normal situations and in clinical situations will lead to new avenues for treatment of diseases.

Contact: Profs. Steffen Thiel and Jens Christian Jensenius, Aarhus University, Department of Biomedicine, Denmark. E-mails: **st@biomed.au.dk**; **j.c.jensenius@immunology.au.dk**

ANNOUNCEMENTS

The **15th European Meeting on Complement in Human Disease (EMCHD)** is coming up soon and will take place in Uppsala, Sweden, the 27th to 30th of June 2015. Abstract submission is closed as is early bird registration.
For further information, please go to the meeting web page:

https://akkonferens.slu.se/emchd2015/

ALEXION PHARMACEUTICALS

Title: **Research Scientist III, Protein Sciences**
Location: **Cheshire, CT, USA**

Position Summary:
Provides leadership in identifying and prosecuting discovery research programs, specifically in the field of complement biology, and also in other disease pathways as needed; participates in proposing, identifying, evaluating new targets/programs for the research portfolio; provides leadership in designing screening cascades in aid of lead identification, in developing cellular and PK/PD assays in support of the discovery projects; participates in performing diligence activities in support of Business Development initiatives and in performing competitive intelligence analyses; establishes and manages external collaborations as needed.

Qualifications:

- Ph.D. in biochemistry/cell biology /molecular biology /pharmacology/structural-biology with 5-6 years of relevant industrial/academic research experience
- Extensive knowledge in complement biology, structure-function relationships, disease areas related to complement dysregulation
- A sound understanding of the theory governing macromolecular behavior
- Experience in research programs towards identifying therapeutic lead molecules is a plus
- Experience in collaborating/managing/directing within a matrix research organization desirable
- Ability to effectively allocate efforts amongst multiple projects and drive to aggressive timelines
- Good oral and written communications skills

MEETING REPORT – ROYAL SOCIETY MEETING 2015

THEO MURPHY INTERNATIONAL SCIENTIFIC MEETING REPORT
THE ROYAL SOCIETY, CHICHELEY, BUCKINGHAMSHIRE, ENGLAND

contributed by Prof. Girish J. Kotwal
(University of Massachusetts, MA, and President InFlaMed Inc., Louisville, KY)

The first of the Theo Murphy International Scientific Meetings 'Complement: driver of inflammation and therapeutic target in diverse diseases', took place on February 23/24 2015 at Chicheley Hall, the country home of The Royal Society. The meeting was organized by Professor Paul Morgan, Cardiff University and Professor Sir Peter Lachmann, University of Cambridge, UK, on behalf of The Royal Society. Amongst the 16 invited speakers and almost 80 participating complement enthusiasts from academia and the pharmaceutical industries, were complement researchers Sir Keith Peters, Senior consultant in Research and Development for GlaxoSmithKline and Sir Mark Walport, Chief Scientific Adviser to HM Government and Head of the Government Office for Science. The Royal Society host at Chicheley Hall during the meeting was Sir Peter Knight, British physicist, Professor of Quantum Optics and Senior Research Investigator Imperial College London, and Principal of the Kavli Royal Society International Centre. A group picture of the participants can be found at the end of this meeting report.

The goal of the meeting was to share recent advances in complement biology and discuss novel diagnostic and therapeutic applications for inflammatory diseases mediated by the dysregulation of complement. The meeting was organized in 4 scientific sessions with 4 speakers in each session with the exception of the final session which was followed by a summary of discussions and closing remarks chaired by Professor Sir Peter Lachmann. The unique feature of the meeting was a 15 minute discussion period following the talk of each of the speakers, providing space for lively debate. The highlights of each session (that can be shared publically) have been summarized below.
As an overall assessment though: This lively meeting demonstrated the current excitement in the field and the growing sense that collaboration between academia and pharma is now delivering on the long-held promise of effective drugs for diseases of complement dysregulation.

SESSION 1:Pathways to inflammation, Chair: Professor Sir Keith Peters, GSK, UK
Professor Sir Peter Lachmann discussed the C3 amplification loop or the C3b feedback cycle as a major driver of inflammation and central to all three pathways of complement activation. Factor I and Factor D greatly influences the extent of the amplification by generating a key mediator iC3b, the breakdown fragment of C3. The interaction of iC3b with complement receptor 3 on neutrophils is a prerequisite for all inflammation mediated by complement. The primary mediators of complement-mediated recruitment and activation of neutrophils are therefore iC3b and C5a and the down-regulation of these mediators would therefore result in significantly diminished inflammation.
Professor Hans-Wilhelm Schwaeble, University of Leicester, UK then explained in detail the relevance of the lectin-activation pathway in health and disease. Pattern recognition surface molecules are sensors for the lectin pathway whose interactions contribute to the activation of 3 different effector enzymes. Genetic deficiencies in the lectin pathway components could result in abnormalities during embryogenesis while predisposition to certain infectious diseases could be an additional 'defect'. Inflammatory conditions, ischaemia/reperfusion injury, haemolytic disease and collagen-induced arthritis could be attributed to the defects in the effector arms of this pathway and could signpost a therapeutic route to treatment of these diseases.
Professor Paul Morgan, Cardiff University, Wales, UK defined the membrane attack complex (MAC) as a major pro-inflammatory trigger implicating specific signaling pathways and inflammasome involvement in a range of cells and argued that targeting the adverse inflammatory effects of MAC formation while allowing the clearance of foreign microbes would be a truly unique way of developing novel therapeutics.

Professor Marina Botto, Imperial College, UK drew lessons from rodents on the role of complement in driving autoimmune diseases like systemic lupus erythematosus (SLE) and others. Although the deficiencies of the C1 subunits (C1q, C1s and C1r) and C4 are associated with autoimmune diseases, especially SLE, she suggested that neither of the current hypotheses to explain complement-mediated autoimmunity (the waste-disposal or the tolerance hypothesis) provide a fully satisfactory explanation for the disease. Professor Botto then argued that work from her and other laboratories point to a novel role for intracellular C3 activation fragments in the regulation of intracellular protein trafficking and control of lysosomal fusion of apoptotic cell cargo.

SESSION2: Complement dysregulation drives inflammation, Chair: Sir Peter Lachmann, University of Cambridge, UK

Professor Santiago Rodriguez de Cordoba, CSIC, Spain, presented a summary of extensive work on genetic deficiencies of complement components and regulatory molecules contributing to inflammatory diseases due to complement dysregulation. The focus of his group is the analysis of the characteristic genotype-phenotype correlation by gaining insights into the distinct functional consequences that can be attributed to specific gene defect.

Professor Mathew Pickering, Imperial College, London, UK, discussed C3 glomerulopathy as a consequence of complement dysregulation. C3 glomerulopathy can result in red cell lysis similar to that seen in paroxysmal nocturnal haemoglobinuria, glomerular thrombosis as seen in atypical haemolytic uraemic syndrome, and glomerular inflammation. The current approaches to management of C3 glomerulopathy were discussed at the meeting and have been recently reviewed elsewhere.

Professor Steven Sacks, University College London, UK, focused his presentation on two new pathways of complement-mediated injury of donor kidneys following kidney transplantation and ways in which these can be targeted with a novel class of protein implants that inhibit the activation of C3. Professor Sacks also reported the recent detection of collectin 11 expressed in kidney epithelial cells and its ability to trigger the lectin pathway. He suggested though that it will be challenging to design inhibitors that will specifically block collectin 11from interacting with ligands as the collectin 11/ligand interaction is of very high affinity.

Professor V. Michael Holers, University of Colarado, Denver, USA presented an overview on the emerging concept that natural antibodies are pro-inflammatory and that amplification of complement-mediated injury is influenced by effector-pathway-catalyzed amplification processes and components of the lectin pathway. An imaging strategy reviewed by Professor Holers to measure precisely the levels of local complement C3 activation and fixation of activation products in tissues will be a powerful tool to evaluate the efficiency of therapeutic mechanisms targeting complement activation at tissue sites.

SESSION 3: Strategies for inhibition, Chair: Professor Paul Morgan, Cardiff University, Wales

Prof. Susan Lea, University of Oxford, UK presented her work on structure-guided design of drugs that regulate complement, demonstrating the value of high quality structural information for drug design.

Dr. Tamar Grossman, ISIS Pharmaceuticals, USA presented the identification and characterization of antisense oligonucleotides (ASOs) targeting C5, Factors B and D and described the use of these potential therapeutics in murine models of renal diseases, including lupus nephritis. Efficacy of the three ASOs was tested by systemic administration to MRL/lpr mice. A lowered expression of the target genes was observed with decrease in plasma levels of the target protein along with improved renal outcome as demonstrated by diminished protein in urine, better preservation of renal structure and reduced accumulation of C3 fragments in the kidneys.

Dr. Daniel Ricklin, University of Pennsylvania, USA presented a comprehensive overview of all the contemporary therapeutic strategies surrounding the inhibition of C3 by targeting levels or its functionality primarily in preclinical studies but also in few cases in human clinical trials. Most of the ensuing discussion focused on peptides such as Compstatin, a circular C3-binding peptide and its derivatives POT-4, AL-78898A and Cp40 that have been studied in several conditions including AMD but have yet to be effectively taken to the bedside. Other proteins mentioned were sCR1, CDX-1135, Mirococept, APT070, TT30, rFactor H, Mini Factor H and AMY-201 and vaccinia virus control protein (VCP), which binds both C3 and C4 and blocks C3 convertase formation and accelerates its decay.

Professor Markus Huber–Lang, University Hospital Ulm, Germany presented his work on targeting the C5a/C5aR interaction and neutrophil activation either individually or simultaneously by inhibiting the complement system at C5 level with C5 inhibitor coversin and toll-like receptors at the CD14 level with anti-CD14 Ab biG 53. In an experimental sepsis model, he observed that blocking the C5a/C5aR interaction resulted in significant protection from sepsis even after 12 hours of administration. Neutrophil functions such as chemotaxis, phagocytosis, oxidative burst were altered when CD14 levels were blocked. A double-blockade was found to be more effective than single treatment.

SESSION 4:Clinical Trials of Complement inhibition, chair: Sir Mark Walport, Government Office for Science, UK

Dr. Richard Smith, King's College London, UK presented his view on the 'trials and tribulations' of clinical trials using membrane-targeting complement inhibitors, referred to as cytotopic agents, biopharmaceuticals that bind to cell surfaces. Candidate therapeutic protein and peptide inhibitors are engineered with synthetic-membrane-interactive peptides to enable them to attach to membranes, ensuring that the systemic exposure is minimized. The candidate focus of the Smith group has been sCR1-derived-Mirococept and the envisioned application has been in ischaemia-reperfusion associated with renal transplantation. Phase II studies (called EMPIRIKAL) have been designed following demonstration of efficacy, safety and the lack of antibodies elicited against the candidate agent in pre-clinical studies, followed by Phase I study in healthy volunteers and an ongoing Phase II pilot study.

Professor Tim Goodship, Newcastle University, UK presented his work on the use of Soliris (eculizumab, E-mab) to treat a cohort of 79 British patients with atypical Hemolytic-uremic syndrome (aHUS), who have excessive activation of the alternative pathway due to an inherited or acquired abnormality of complement. National Health Service (NHS) England funds E-mab and has commissioned a policy for both new aHUS patients as well as those undergoing transplantation. Professor Goodship concluded that the cohort provides unique resource for treatment and patient stratification and he did not anticipate that the monopoly of E-mab will be replaced with alternative therapies any time soon.

Dr. Menno van Lockeren Campagne, Genentech Inc, CA, USA presented his work on modulating the rate-limiting enzyme of the alternative pathway, Factor D (CFD) in geographic atrophy (GA), the late stage of age-related macular degeneration. In a phase II clinical study (MAHALO), the Genentech candidate monoclonal antibody fragment (lampalizumab), an inhibitor of CFD, showed a 44% reduction in GA region progression at 18 months in patients with the complement I risk allele. This result suggests that genetic variation in AMD could be utilized to identify precise pathways for GA progression and select patients for appropriate therapy.

COMPLEMENT REAGENT RESOURCES