Focus on Complement

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Issue 41

International Complement Society

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Dear Readers,

Welcome to the March 2016 issue of 'Focus on Complement'. This 41st issue of FoC contains:

- **Flash News** reporting on a new complement-targeted immune evasion strategy by *Borrelia burgdorferi* and on a novel role for C3a in leucocyte recruitment into the brain
- **The Complement research teams around the world** series featuring the teams of David Kavanagh, Kevin Marchbank and Neil Sheerin in Newcastle, UK, and of Sakari Jokiranta in Helsinki, Finland
- A **meeting report** on the meeting of the Complement Standardization Committee that took place in Budapest, Hungary, January 22-23, 2016.
- **XXVIth International Complement Workshop** announcement
- **Obituary:** Remembering Prof. Klaus Rother

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

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NEWS FLASH (reported by Prof. Denise Tambourgi, Brazil)

***Borrelia burgdorferi* BBK32 inhibits the classical pathway by blocking activation of the C1 complement complex.** *Brandon L. Garcia, Hui Zhi, Beau Wager, Magnus Höök, Jon T. Skare. PLoS Pathog. 2016 Jan 25; 12(1):e1005404. doi: 10.1371/journal.ppat.1005404.*

The etiologic agent of Lyme disease, *Borrelia burgdorferi* is transmitted to humans via the bite of infected ticks. During the ticks' blood meal, spirochetes enter the mammalian host and subsequently disseminate to tissues. *B. burgdorferi* spirochetes avoid Alternative Pathway (AP) complement-mediated killing by expressing a group of virulence factors (Csp proteins and OspE/F family). These proteins recruit human factor H, FHL-1 and factor H-related proteins to the bacterial surface, subverting the deleterious effects of AP activation. The spirochetes are also able to inhibit classical pathway activation (CP) by recruiting the host CP regulators, C4b-binding protein and C1 esterase inhibitor to their surface via interactions with specific borrelial lipoproteins. In this paper, Garcia and colleagues report an unprecedented mechanism of CP evasion, presented by *B. burgdorferi* spirochetes. They showed that BBK32, a fibronectin and glycosoaminoglycan-binding protein expressed on the surface of *B. burgdorferi,* is able to interact with C1. The interaction occurs via the C-terminal globular domain of BBK32, which binds in a non-covalently way to the C1r subunit of C1. The process occurs in a calcium-dependent manner and with high-affinity, resulting in the inhibition of C1r autoactivation and in the prevention of the enzymatic cleavage of C1s proenzyme. BBK32, thus, effectively renders C1 in the zymogen form, leading to the abrogation of CP activation. The discovery of this novel bacterial evasion mechanism may contribute to better understanding how *B. burgdorferi* survives in immune competent hosts and to new studies evaluating this mechanism of CP inhibition in other pathogenic bacteria.

Complement component C3a plays a critical role in endothelial activation and leukocyte recruitment into the brain. *Fengjiao Wu, Qiang Zou, Xiaodan Ding, Dongyan Shi, Xingxing Zhu, Weiguo Hu, Lixin Liu and Hong Zhou. J Neuroinflammation. 2016 Jan 28; 13(1):23. doi: 10.1186/s12974-016-0485-y.*

Neutrophils are key players in central nervous system (CNS) inflammation. Strategies able to block the recruitment of these cells are beneficial for the treatment of many types of CNS inflammation. Several studies have also suggested that the complement system plays a significant role in the CNS inflammatory response. In this paper, Fengjiao Wu and colleagues investigated the contributions of complement to leukocyte recruitment into the mice brain, in response to cerebral lipopolysaccharide (LPS) administration. Using complement-deficient mice, they showed that neutrophil infiltration into the brain cortex and hippocampus was significantly reduced in $C3^{-/-}$ mice and $C3aR^{-/-}$ mice, but not in $C6^{-/-}$ mice. C3 deficiency, but not C5 deficiency, also markedly attenuated leukocyte-endothelial interactions in brain postcapillary venules. Adhesion molecules, such as E-selectin and vascular cell adhesion molecule 1 (VCAM-1), showed reduced expression levels in the brains of $C3^{-/-}$ mice in response to LPS administration. These results suggest that C3a and C3aR, but not C5 and C5aR, are important for endothelial activation and subsequent leukocyte-endothelial interaction in the brain inflammation. The authors also observed that depletion of C3 from the circulation caused reduction of VCAM-1 and E-selectin, as well as leukocyte recruitment, suggesting that C3 in the circulation contributed to brain endothelial activation. *In vitro*, C3a directly stimulated cerebral endothelial activation. These interesting findings indicate that inhibition of complement activation may be a therapeutic approach for suppressing leukocyte recruitment and endothelial activation in brain inflammatory diseases.

COMPLEMENT TEAMS AROUND THE WORLD

Complement in Newcastle, United Kingdom:

The teams of David Kavanagh, Kevin Marchbank and Neil Sheerin

Complement research in Newcastle was born out of studies in the 1990's, which examined the genetics of familial atypical haemolytic uraemic syndrome (aHUS). At that time the pathogenesis of aHUS was unknown although there was evidence from previous studies of complement activation. However, it was not clear whether this was a primary event in the pathogenesis of the disease or a secondary epiphenomenon. Paul Warwicker´s seminal paper in Kidney International (Warwicker et al, Kidney Int 1998) clearly established linkage to the RCA cluster at 1q32 and described the first mutation in factor H. This provided overwhelming evidence that dysregulation of the alternative pathway was a primary factor in the pathogenesis of the disease. That not all families or patients with aHUS had a factor H mutation led us to look for and discover other inherited and acquired complement abnormalities in this disease. This work undertaken over two decades has led to the use of complement inhibition with eculizumab which has proved to be a profound step change in the management of the disease. Our interest in the role of complement in disease has led us to also examine age-related macular degeneration and C3 glomerulopathy. Our work has led to both a national complement genetic screening service and an expert centre for aHUS in Newcastle.

The KAVANAGH group' s main focus is the genetics of the complement mediated diseases: atypical haemolytic uraemic syndrome (aHUS); C3 glomerulopathies and age related macular degeneration (AMD). Over the past decade the group has been at the forefront of elucidating the genetic basis of aHUS, identifying mutations in complement regulators (JASN 2005, 2006) and more recently genomic re-arrangements resulting in hybrid genes (Blood 2012, JASN 2015). We have undertaken detailed functional analysis of rare genetic variants in the complement system (J Immunol, 2009, Hum Mol Genet, 2014) and key collaborations with the Barlow (Edinburgh, Nat Struct Mol Biol 2011) and Blaum (Tübingen, Nat Chem Biol) groups have allowed us to interpret these in the setting of co-crystal structures. The group is fully integrated with the English National aHUS complement therapeutics centre and, the UK National complement genetics screening laboratory, both based in Newcastle. This allows a bidirectional knowledge transfer improving interpretation of genetic screening results and speeding up our translational research. In addition to our core strengths the group has ongoing research programmes on secondary aHUS (NEJM, 2014), Retinal vasculopathy with cerebral leukodystrophy (Nat Genet 2007), C3 glomerulopathies (JASN, 2014) and with the Atkinson group (St Louis) on AMD (Nat Genet 2013, Hum Mol Genet, 2015).

Tim Goodship (2nd right), Kevin Marchbank (glasses center) and David Kavanagh (2nd from left) at the Institute of Genetic Medicine with the NHS genetics grouping and various group members.

The MARCHBANK group's focuses on autoimmunity driven by complement activation. We have investigated the prevalence and role of Factor H autoantibodies in association with kidney diseases (i.e. Moore et al, Blood, 2010) using Prof Goodship's large aHUS patient cohort. This work led to a number of follow up papers (including CJASN, 2012; Mol Biol, 2014) as well as an international assay standardization exercise (Immunobiology, 2014). We continue to examine the importance of anti-complement protein antibodies in numerous disease settings including C3 G via a highly productive collaboration with Dr Sally Johnson who has catalyzed the creation of a large UK wide C3 G/MPGN/DDD patient cohort. As a group, we have also become interested in using modified factor H proteins as therapeutics and recently demonstrated the *in vivo* potential of a mini-FH protein (KI, 2015) and we welcome a new postdoctoral researcher, Yi Yang, to this project. Long standing research interests into B cell signaling via CR2 now mix with the new via work on mutant murine C3 molecules with increased C3 activation potential. We hope to bring greater understanding to the importance of C activation/regulation in cell/tissue function (i.e. B/T cells in vaccine adjuvant development with Bath University or end stage renal failure in kidney disease models) using mouse models (such as *Cr2* KO, human CR2 transgenic and C3 KO).

Sally Johnson (2nd from left) with the C3 G sub group in the Marchbank Lab.

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The SHEERIN group's focus is on understanding both the cellular and molecular events underpinning renal disease in order to identify potential therapeutic interventions. They have contributed to a greater understanding of the role of complement and immune modulators of renal disease. The group continues to work on the role of local complement synthesis in the development of acute and chronic renal injury as well as its effects on transplantation (Sheerin et al 2008). The team has identified the cells responsible for the synthesis of complement in the kidney and they are now developing new strategies to target local complement synthesis (Fearn et al 2011). Indeed, the group has used complement inhibition to reduce the severity of complement mediated renal injury (Atkinson et al 2012) leading to work investigating the role of lymphocytes in the development of renal injury. This has shown that CD4+ T lymphocytes play a key role in the development tubulointerstitial renal injury (Tapmeier et all 2008, Tapmeier et all 2010, Ingham et al 2009) and suggest that these lymphocytes appear to recognise antigens within the kidney, identifying a break in self-tolerance as an important factor in progressive renal disease (Ingham et al 2010).

So in just a short time complement research has grown exponentially in Newcastle and continues to grow from strength to strength. Indeed, we are happy to announce the recent recruitment of Prof Claire Harris to Newcastle University. Claire joins us in May after three years at GlaxoSmithKline R&D (Stevenage, UK); she brings expertise in therapeutics, structure/function analysis of complement proteins, complement-mediated disease mechanisms, and complement biomarkers in disease.

Please keep abreast of recent developments from our renal research teams by following us on Twitter at **@renalresearchUK**

Finally, as a group we are eternally grateful for the funding we have received for many of these projects from The Northern Counties Kidney Research Fund (NCKRF).

Above: Neil Sheerin (centre) and the Renal Fibrosis group

To the right: Prof. Claire Harris joining the Centre in May 2016

Complement in Helsinki, Finland: The team of Sakari Jokiranta

Complement has been studied in Helsinki for more than 30 years. The studies started from diagnostic complementology and the role of complement in kidney diseases and infections. Ever since these three lines have continued to be in the focus of research in Helsinki. Currently there are three senior medical doctors with their research groups working at least partially on complement, Prof. Seppo Meri, Adj. Prof. Sakari Jokiranta, and Adj. Prof. Hanna Jarva.

The group of Jokiranta has focused for the last ten years on the pathogenesis and diagnostics of atypical hemolytic uremic syndrome (aHUS) and the role of factor H (FH) in controlling the alternative pathway on self cells and on microbes. Lately subjects outside the complement field have gained more funding and therefore the focus has changed a bit but still the research line on aHUS and complement evasion of microbes is vital. The most important findings during the last years have been based on structure-function analyses of the interactions between FH and C3b or microbial proteins. Lately the research has included studies on the role of FH in coagulation and recognition of structures on self cells, such as malondialdehyde epitopes, glycosaminoglycans, or sialic acids. Although the recent studies have revealed the main questions of the molecular pathogenesis of complement-related aHUS, there is still burning need for studies on the pathogenesis of those aHUS cases with no known functional defects in complement proteins. This topic has lead Jokiranta research group to utilize novel tools in searching for mutations and cell surface defects in these patients. The researchers working on these topics include Satu Hyvärinen (MSc, MTech) and Aino Koskinen (MD).

Acquisition of host FH by a plethora of pathogenic microbes has been shown to be a key in complement evasion of variable organisms and the work of the Helsinki teams has contributed significantly to this progress. The next main question is whether this information can be utilized either in diagnostics, prevention, or therapy of certain clinically important infections. The microbial research of the Jokiranta group has lately focused on developing diagnostics, partially due to the new role of Dr. Jokiranta as the Medical Director of the largest private diagnostic laboratory in Finland (United Medix Laboratories Ltd). This role has led to initiation of clinical studies and more applied science strategy in research of both the main topics, aHUS and microbial infections. The group members working on microbes and diagnostics include Karita Haapasalo (PhD), Neeta Datta (PhD), Rigbe Weldatsadik (BSc), Hanne Amdahl (PhD), and Derek Ho (PhD).

The Jokiranta Research group goes bowling and keeps rolling (from left to right: Derek Ho, Satu Hyvärinen, Hanne Amdahl, Rigbe Weldatsadik, Karita Haapasalo-Tuomainen, Aino Koskinen, Neeta Datta, and Sakari Jokiranta).

Contact: Prof. Sakari Jokiranta (sakari.jokiranta@helsinki.fi and sakari.jokiranta@medix.fi). http://research.med.helsinki.fi/immuno/en/default.html

ANNOUNCEMENTS

On behalf of the organizing committee, Dr. Teizo Fujita (Chair) and Dr. Nobutaka Wakamiya (President of the Japanese Association for Complement Research, JACR) invite members of the complement community and beyond to the 26th International Complement Workshop in Japan. The meeting will take place in the historical city of Kanazawa from September 4th to 8th 2016.

For further information, please see ***www.icwkanazawa2016.com***

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 – Complement Standardization Committee

2nd Meeting of the standardization group on diagnostic complement measurements

Laboratory services act as a cornerstone for public health programs by supporting diagnosis, monitoring, screening, and surveillance to control and manage diseases.

Diagnostic analysis of the complement system is challenging, especially since quality control and external proficiency testing needs to be considered. There are only a few analytes with commercial and external proficiency testing available.
Upon the initiative of George Füst (Budapest, Hungary) a first meeting dedicated to complement standardization was held in Budapest in 2009 which resulted in formation of the IUIS and ICS Sub-Committee for the standardization and quality assessment of complement measurements now led by Michael Kirschfink (Heidelberg University, Germany), Zoltán Prohászka (Semmelsweis University, Budapest, Hungary) and Bo Nilsson (Uppsala University, Sweden). Since 2010, an external quality assessment (EQA) program has been established, supported by INSTAND (Society for Promoting Quality Assurance in Medical Laboratories e.V.).
The goal of the program is to provide reliable information to allow laboratories to assess and monitor the quality status of internal procedures and processes, suitability of diagnostic systems, accountability and competence of the staff, along with the uncertainty measurement definitions inherent to laboratory results. In 2015, at its 5th round, 34 laboratories from 21 different countries participated.
Organized by Zoltán Prohászka and Michael Kirschfink the group met in Budapest for its 2nd strategy workshop on January 22-23, 2016 with 31 participants (see picture below) representing 21 complement laboratories worldwide to review the accomplishments of the first 5 years of the program and discuss further developments. The participants critically assessed the current situation of routine complement analysis and discussed consequences for its further improvement focusing on key elements such as assay selection, calibration, presentation and interpretation of results. Five section groups were established to develop guidelines for measurements of functional complement activity, complement proteins, regulators, autoantibodies, and activation products.
An ICS/ECN/IUIS-linked cloud-based homepage will be established for the group to foster a continuous communication in their joint efforts to further improve diagnostic complement testing.
The next meeting of the standardization group will take place during the 26th International Complement Workshop (Kanazawa, Japan in 2016), and the 6th External Quality Assessment is planned for autumn 2016.

OBITURY

Remembering Professor Klaus Rother (1926 – 2016)

On January 16th 2016, shortly before his 90th birthday, Prof. Dr. med Klaus Rother passed away. Klaus Rother was a highly appreciated member of the scientific community who, together with his wife and long-term collaborator Ursula, contributed to field of complement in its early days.
Klaus Rother was Professor emeritus of the University of Heidelberg, where he served for more than 20 years as director of the Institute of Immunology and Serology, as well as in numerous positions within the academic administration.

Klaus Rother studied medicine in Mainz and in Freiburg. He started his clinical and scientific career with his doctoral thesis under the supervision of the famous Freiburger nephrologist Hans Sarre. The topic of the thesis, mechanism of glomerulonephritis, sparked his life-long interest in the link between the immune response and inflammatory diseases. Though nowadays, there is no question about the intricate relationship between the two entities, at that time (1957/58) the idea was novel. Hence, the German research council (Deutsche Forschungsgemeinschaft, DFG) funded a research grant for a 2-year fellowship at Case Western University, Cleveland, Ohio (1957/58). There, by Myron Leon, Klaus Rother was introduced to immunological science. From thereon, his future work and research area was dedicated to investigating the immunologic basis of inflammatory disease, particularly with regard to the reactivity of the complement system.

After his return to Freiburg, Germany, Klaus Rother continued his clinical career in Internal Medicine, and also his scientific work. During that time he and Ursula described complement-deficient rabbits, and eventually pinpointed the defect to a genetic defect of complement C6. For lack of appropriate working conditions in research, particularly in Immunology, which was practically not-existing in Germany at that time, Klaus and Ursula Rother decided to emigrate to the USA and moved to New York University. Numerous publications from that time reflect the inspiring spirit of the emerging field of immunology in general and in complement research in particular. Collaborative research projects brought them twice to Hans Müller-Eberhard's lab at the Scripps Research Institute in La Jolla, California.

Eventually, while having advanced to Professor of Pathology at NYU, Klaus Rother decided to return to Freiburg, where he then established a research group at the Max Planck Institute of Immunobiology in 1968.

Only 3 years later, he moved to the University of Heidelberg with the assignment to convert the then-existing Institute for “Serology” and Blood Banking” to a modern Institute of Immunology at the Medical School. The new institute began its early days in a converted basement of the “Old Serology”, but moved in 1974 to the new Campus “Im Neuenheimer Feld”, to a state-of-the art, well-equipped Institute and building. In the following 22 years with an exceptional vision, sound judgment and great integrative skills Klaus Rother established the largest University Institute for Immunology in Germany. With his ‘translationally oriented’ institute and strict focus on the human immune system he became an important partner of Heidelberger clinics and research institutes. Among his key missions was the goal to train aspiring clinicians/scientist, with many of those acquiring important leading positions later on.

With the establishment of the DFG Collaborative Research Centre 136*,Cancer Research'*, where he served as spokesman from 1974 until 1979, Klaus Rother built an important bridge between the Medical Faculty and the German Cancer Research Center.

Also internationally, Klaus Rother was well recognized; guest professorships took him to Adelaide, Australia, Wuhan, China and Sao Paulo, Brazil, which further promoted the already lively exchange of scholars. His versatile scientific and organizational experience qualified him to serve as president of the German Society of Immunology for two consecutive periods of office (1976-1982), as a member of various scientific committees, organizer of congresses, editor of scientific journals as well as a national and international consultant.

His deep commitment to the University and to the University Hospital reflect positions as Vice-Dean of the Medical Faculty (1971-1979), as Vice-Rector of the University (1980-1982) and as a member of the Hospital Management Board (1986-1989).

Klaus Rother significantly contributed to the reconstruction of Immunology in Germany in the post-war times and for his life work Klaus Rother received the Federal Merit Cross of the Federal Republic of Germany (Bundesverdienstkreuz am Bande) in 1986.

In 1996, after a quarter century of successful work, Klaus Rother retired and handed over a scientifically active and internationally renowned institute to his successor, Stefan Meuer.

With Klaus Rother, the scientific community loses an internationally esteemed scientist, a physician who was instrumental in the reconstruction of immunology in Germany, but also a wonderful friend and colleague.

This obituary was written by Professors Maria Hänsch and Michael Kirschfink, University of Heidelberg

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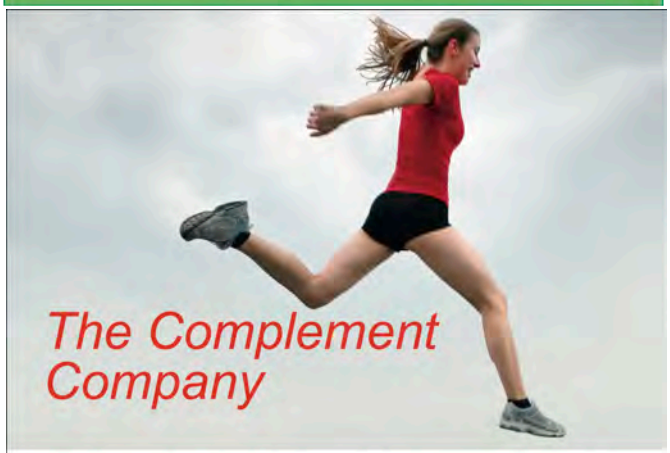

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