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Dear Readers,

Welcome to the 52nd Issue of *Focus on Complement* – the official newsletter of the International Complement Society (ICS).

In this issue we highlight research groups from Cardiff, UK (Prof Paul Morgan) and Charlottesville, USA (Dr Ronald Taylor). Issue contributor Denise Tambourgi reviews two recent research articles on complement in the kidney and the bone, and ICS President Michael Holers presents an end-of-year message to the ICS community.

We also congratulate Weiju Wu, who is the winner of the second FoC Young Investigator Cover Image Award. A description of Weiju’s research and cover image description can be found in the following pages.

Finally, ICS past-president Prof Andrea Tenner presents an overview of the 27th International Complement Workshop, which was recently held in the lovely Santa Fe, New Mexico. This includes Part 1 of summaries for each of the scientific sessions, prepared by the Session Chairs.

I hope you all enjoy this final *Focus on Complement* for 2018.

Trent Woodruff, PhD.
Editor, FoC
Secretary, ICS

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**Connect with the ICS**

If you would like to contribute with an article to a future issue or have suggestions for a subject theme, please contact Trent Woodruff (t.woodruff@uq.edu.au) or Michael Holers (Michael.Holers@ucdenver.edu).

Plus visit our website and follow us on Twitter to keep updated with the latest ICS and complement news.

🌐 [www.complement.org](http://www.complement.org)  🌐 [@complementsoc](https://twitter.com/complementsoc)
Seasons Greetings to all of you, and hopes for a more sane New Year in all parts of the world!! For those who could attend the 27th International Complement Workshop in Santa Fe, New Mexico, Andrea Tenner and her Local Organizing Committee provided participants the best of many worlds, including science, southwest culture, artistic excellence and expansive landscapes in multiple hues. Many highly informative oral presentations and posters provided the basis for many collegial discussions. Three terrific plenary lectures and two newly introduced “Emerging Topics” sessions provided attendees with additional information and viewpoints to ponder. Travel Awards were presented to 28 trainees (16 oral and 12 poster presentations) to facilitate their participation, and no doubt we will watch some of them emerge as future leaders in the field. In other sections of this edition, Prof Tenner will provide additional information about the ICW Meeting, and summaries of the oral sessions are also presented.

As this calendar year ends, I look forward to handing off the role of ICW President to the very knowledgeable and more than capable hands of Peter Garred (Copenhagen, Denmark). In Santa Fe, the ICS membership also elevated a new President Elect, Claudia Kemper (Bethesda, Maryland), and voted to continue Dan Ricklin (Basel, Switzerland) and Trent Woodruff (Brisbane, Australia) in their current roles as Treasurer and Secretary, respectively. In addition, two new Councilors were elected to replace the members completing their terms. Those dedicated new Councilors are Leendert Trouw (Leiden, Netherlands) and Zoltan Prohaszka (Budapest, Hungary). The ICS leadership greatly appreciates their interest in working to guide our Society for the next 6 years in conjunction with our continuing Councilors Michael Kirschfink (Germany), Peter F. Zipfel (Germany), Nobutaka Wakamiya (Japan), Claire Harris, (UK), Josh Thurman (US) and Viviana Ferreira (US). This is a terrific group of individuals who will continue to provide our Society with an international perspective as well as keen insights into the challenges and opportunities for the complement community. All complement researchers should feel welcome to contact them with suggestions or concerns that the Society may be able to address effectively. Importantly, we owe our sincere gratitude to Bo Nilsson and Denise Tambourgi for bringing their experience, judgment and service to our Council for 6 full years each. Special thanks also goes to Andrea Tenner (US), who has been, since the ICS founding in 2000, continuously in the leadership of the organization, serving as Councilor, Secretary, President-Elect, President and Past President. Her knowledge, hard work, advice and intense interest in the wellbeing of the ICS and the complement research community will be sorely missed by the ICS leadership, but still called upon when needed. Lastly, we would not have made as much progress as we did over the past two years without Sheilah Jewart, our Executive Director who was hired in 2017 and also served as the meeting organizer in Santa Fe. She was everywhere, and in her informal, friendly and impactful manner made the ICW Meeting run amazingly well. In her role of Executive Director, Sheilah kept the ICS leadership on track through many changes and identified several new opportunities for expansion.

I thank all of these individuals for their contributions to ICS organization and to making my time as President so fulfilling.

Finally, we look ahead as the ICS is now soliciting bids to host the 29th Complement Workshop in 2022. If you are interested in hosting the ICW 2022 please submit your letter of intent to the ICS office by March 01, 2019. A full proposal must be submitted by Sept 01, 2019 in order for the ICS Council to select the site that month from applicants. Further information can be found at: https://www.complement.org/bids-loc.
Weiju Wu, Winner of the Focus on Complement Young Investigator Cover Image Award

Weiju is currently working in Prof. Claire Harris’s laboratory in Newcastle University, UK and investigating the roles of factor H related proteins in age-related macular degeneration. From 2014 to 2018, she worked in the laboratory of Prof. Wuding Zhou and Steven Sacks at King’s College London and studied the roles of complement, particularly C5a and collectin 11, in immune regulation and disease. She was focused on studying: 1) how C5a/C5aR1 signaling mediates the expression of carbohydrate ligands on renal tubules in acute pyelonephritis, 2) how collectin 11 increases acute kidney injury and promotes the development of renal fibrosis, and 3) how collectin 11 regulates the phagocytosis and cytokine production of retinal pigment epithelial cells.

The cover image was taken when Weiju worked at King’s College London. The C57 BL/6 wild mouse kidney section was stained with fluorescein-conjugated Lotus tetragonolobus lectin (LTL, green), C5a receptor 1 (C5aR1, red) and DAPI (blue). LTL specifically binds to L-fucose, which is richly expressed in the luminal and basolateral surfaces of proximal tubular epithelial cells. This picture shows that C5aR1 expression is located at the luminal surface of tubular epithelial cells and not associated with L-fucose, while another study shows that C5aR1 is co-localized with α-Mannose in the renal tubular epithelial cells.

The Young Investigator Cover Image Award. Each Issue the ICS board will select a scientific image to highlight on the front cover of FoC. The winning image will include a brief description of the image, and a profile of the winner within the newsletter.

Eligibility: graduate students, post-doctoral staff, and early career researchers (generally, but not exclusively under 40 years of age) are eligible to apply.

Interested applicants should email the FoC Editor (t.woodruff@uq.edu.au) at least 3 weeks prior to each issue release date (release dates: 1st March, 1st June, 1st September, 1st December), with one suggested image of their research. Images could include immunochemistry (tissues, cells etc), pathology, structures, or any other image of relevance to complement research. All images should not have any copyright that would be infringed if published in FoC (eg. work already published in a journal). Submissions should also include a brief profile of the researcher and a description of the image (~100 words each).

Winners of the Award will additionally receive a signed certificate from the ICS.
Complement Research in Cardiff, UK
The group of Prof Paul Morgan

Complement research in Cardiff is led by Prof Paul Morgan, ably supported by excellent students and fellows, independent PIs and clinical collaborators. Paul started the Complement Biology Group (CBG) on his return to Wales in 1986 after post-doc positions in the US. Over the years, the CBG has contributed to basic understanding of the complement system, particularly regarding terminal pathway and its regulation, and roles of complement in diseases, particularly neurological disorders.

We are embedded in the Medical School and University Hospital in Cardiff and take full advantage of the proximity and enthusiasm of research-friendly clinicians and the clinical samples and patients they provide.

Studies in the terminal pathway includes contributing to ever-higher resolution images of the membrane attack complex (MAC) that are altering understanding of how the MAC works, further dissecting how the MAC regulator CD59 impacts MAC assembly and function, and understanding how sublytic amounts of the MAC trigger multiple signalling pathways in nucleated cells, including activation of the inflammasome, likely key to explaining roles of MAC in driving inflammation. This last programme has involved collaborations with data scientists and development of bioinformatic methods to identify the critical signalling pathways for MAC effect on nucleated cells.

Lessons from eculizumab tell us that the terminal pathway is a great drug target, at least in the few rare diseases where eculizumab has so far been used. For common, chronic diseases, new approaches to inhibiting complement will be needed and we are seeking to identify suitable ways of inhibiting the terminal pathway – with a particular aim of developing agents that are suitable for treatment of brain diseases.

Brain disease, specifically dementia, has become a major focus of the work, fuelled by Programme funding from the UK Dementias Research Institute. Led by genetic discoveries that implicate complement in Alzheimer's disease, we are exploring the functional effects of the disease-associated complement hits in, for example, CR1 and clusterin, in order to explain HOW they are risk for dementia. Other work in the dementias programme includes in depth analyses of synaptic pruning in the brain and retina, and testing the impact of complement gene knockout or complement inhibition on disease in mouse models of Alzheimer's disease.

The Group collaborates widely – locally, across the UK and Internationally. Long-term productive collaborations include with Claire Harris in Newcastle, Simon Clark in Manchester, Santiago Rodriguez de Cordoba in Madrid, Masashi Mizuno in Nagoya, and too many more to list! We are always keen to develop new collaborations and very willing to share reagents and ideas. We also love to entertain complement visitors in our friendly city - so if you are in the UK come see us!
Team Highlights

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My initial interest in complement began during our investigations of the processing of antibody/dsDNA immune complexes (IC) in lupus. We focused on how these IC activate complement and capture C3b, thus promoting their binding to primate erythrocytes (E) via CR1, an example of Nelson’s immune adherence reaction.

Mike Frank at NIH was making important contributions in this field, based on purifying C3 and labeling it with radioactive tracers. Instead, we developed panels of mAbs specific for C3 and its fragments, in collaboration with UVA colleague William Sutherland. Several of the mAbs have particularly interesting properties (e.g., blocking either the alternative or classical pathway), and we have employed them, along with mAbs specific for CR1 (homemade as well as gifts from Mike Frank) to explore how complement impacts IC processing.

After C3b-opsonized substrates bind to E CR1, they are transferred to fixed tissue macrophages, and an important question arises: how can this transfer be mediated without E destruction? Key clues include the observation that E CR1 levels are substantially reduced in lupus, as well as in other diseases associated with IC processing and complement activation. Our working hypothesis was that Fc receptors on acceptor cells are able to bind to, and mediate the removal and internalization of CR1 and associated IgG IC, in a process in which the E plasma membrane integrity is preserved. We selected IgG mAbs specific for CR1 as high affinity surrogates for C3b to investigate IC clearance. Suitable substrates were covalently bound to anti-CR1 mAbs (called heteropolymers, HP) and our studies, in vitro and in non-human primate (NHP) models, confirmed the hypothesized mechanism. Based on what we learned years later in our studies with rituximab, this transfer reaction is a form of trogocytosis. We also found that use of CR1-bound HP generated immune responses to the mouse IgG, but we did not pursue this question due to the lack of controls. However, Admar Verschoor’s group is now investigating whether immune adherence influences the immune response.

Successful immunologic paradigms (e.g., CR1 binding complement-opsonized IC) can be modified and/or replicated if there are good “evolutionary” reasons, and based on the classic papers of Humphrey and Fearon, we investigated the role of B cell CR2 in the immune response and in the processing of C3d-opsonized IC. Taroh Kinoshita, Mike Holers and Wolfgang Prodinger generously provided us with key mAb reagents specific for CR2, and we used these mAbs, both in vitro and in mouse and NHP models, as high-affinity surrogates for C3d to study transfer of these model IC from B cells to acceptor cells. We found that this transfer reaction occurs without loss of B cells (however CR2 is removed, due to trogocytosis), and we were also able to demonstrate that humoral immune responses were induced to antigens covalently cross-linked to anti-CR2 mAbs. In fact, we were able to break “tolerance” to mouse IgG, generating anti-idiotypic antibodies to mouse mAbs covalently bound to the rat anti-CR2 mAbs.

IC that fix complement certainly include cancer cells opsonized with mAbs, and we next investigated whether the C3b deposition reaction occurs when B cells are reacted with CD20-specific mAb rituximab. Our original motivation was to determine if C3 fragments could serve as neo-antigens for targeting cancer cells during mAb treatment. We successfully followed C3b deposition, both in vitro and in NHP models, and also analyzed B cells taken from the blood of patients with chronic lymphocytic
leukemia (CLL) after rituximab treatment. We demonstrated that C3 activation fragments are closely co-localized with cell-bound rituximab, and, in collaboration with our colleagues at Genmab, we have been able to extend this work to include next generation complement-fixing mAbs specific for CD20 (ofatumumab), CD38 (daratumumab), and CD37-specific mAbs bearing a hexamer-enhancing mutation (E430G).

In the course of these studies, we demonstrated that complement and other immune effector functions are exhausted when CLL patients with high tumor burdens are treated with rituximab or ofatumumab. Moreover, when patients receive the standard (high) doses of these mAbs, immune effector exhaustion is accompanied by loss of B cell CD20. Under these conditions, the mAb-CD20 IC on B cells are removed from the cells via trogocytosis, due to the action of Fc receptors on acceptor cells; however, the malignant B cells survive! This reaction also occurs during daratumumab treatment (loss of CD38) for multiple myeloma, and these observations may have profound implications for other mAb-based therapies. Our studies strongly support modification of standard dose paradigms to lower doses administered more frequently, and we continue to advocate for this approach.

Most recently we have examined the kinetics of CDC mediated by these mAbs in real time, based on four-color fluorescence microscopy movies. The molecular CDC sequence indeed follows the patterns described in textbooks. However, we found that, in the case of nucleated B cells (cell lines and primary CLL cells), they do not rapidly “burst”; rather it is the rapid influx of Ca2+ that mediates cell killing. Very soon after the MAC binds to the cell, it is flooded with Ca2+, the mitochondrial membrane is depolarized and then the cell dies, all in just 2-3 minutes. We also found, in collaboration with Paul Morgan, that even in C9-deficient serum, mAb-opsonized CLL cells are killed by complement; as reported by Piet Gros, pores produced by C5b-8 are adequate to allow influx of lethal amounts of Ca2+.

Our interest in IC processing has led us to many different and exciting paths. We are most grateful to our colleagues for their generous gifts of reagents and advice over many years. Although Peg Lindorfer and I are officially retired, we have provided our mAbs to a number of collaborators and we look forward to following their future progress in complement!

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Aliskiren Inhibits Renin-Mediated Complement Activation
Zivile D. Be´ka´ssy, Ann-Charlotte Kristoffersson, Johan Rebetz, Ramesh Tati, Anders I. Olin and Diana Karpman


Some renal diseases are associated with the activation of the Complement (C) alternative pathway, due to gene mutations in C-regulators or C-proteins and autoantibodies. These may result in dysregulation of the system, with deposition of components of the alternative pathway and terminal complement complex in the kidneys. Diseases as atypical hemolytic uremic syndrome and C3 glomerulopathies, such as dense deposit disease (DDD) and C3 glomerulonephritis, may lead to renal failure, although it is still not clear why the kidney is a target organ in these disorders. Renin is an aspartate-protease, produced only by cells of the renal juxtaglomerular apparatus that initiates the renin-angiotensin-aldosterone system by cleaving angiotensinogen into angiotensin I. In this article, Be´ka´ssy´ and collaborators, from Lund University, Sweden, identified C3 as a novel substrate of renin and showed that renin-mediated C3 cleavage is similar to that induced by the C3 convertase. The generation of C3 cleavage products, C3a and C3b, were detected, with the C3b renin cleavage product able to bind to FB. Functional assays showed mast cell chemotaxis in response to C3a and release of Ba when the cleavage product C3b was combined with FB and FD. In the presence of aliskiren, a nonpeptide renin inhibitor, the renin mediated C3 cleavage does not occur, and less C3 is deposited on renin-producing cells. The effect of aliskiren was evaluated in three patients with DDD. These patients exhibited a reduction in systemic and renal complement activation (decreased renal C3 and C5b-9 deposition and decreased of glomerular basement membrane thickness) over a follow-up period of four to seven years. Thus, this study demonstrates a novel kidney specific mechanism of complement activation by renin cleavage of C3 and its inhibition by the renin inhibitor aliskiren. It also shows a beneficial effect of aliskiren when used in DDD patients, which encourages further clinical studies.
Reduced Terminal Complement Complex Formation in Mice Manifests in Low Bone Mass and Impaired Fracture Healing

Yvonne Mödinger, Anna E. Rapp, Anna Vikman, Zhaozhou Ren, Verena Fischer, Stephanie Bergdolt, Melanie Haffner-Luntzer, Wen-Chao Song, John D. Lambris, Markus Huber-Lang, Cornelia Neidlinger-Wilke, Rolf Brenner and Anita Ignatius


The complement system affects the skeletal system both under homeostatic and inflammatory conditions. Terminal Complement Complex (TCC) seems to interfere on the bone architecture, since the absence of CD59 results in reduced cortical bone mineral density and increased osteoclastogenesis. Moreover, TCC may play a role in inflammatory diseases, affecting bone and the surrounding tissues, once increased TCC levels were found in the synovial fluids of patients with rheumatoid arthritis and osteoarthritis. In this context, Yvonne Mödinger and collaborators, from Ulm University Hospital, Germany, have analyzed the influence of TCC on bone turnover and repair, using C6 deficient (C6-def) or CD59 knockout (CD59-ko) mice. Thus, under homeostatic conditions, they showed that C6-def mice displayed a reduced bone mass, mainly because of increased osteoclast activity. After femur fracture, the inflammatory response was altered, and bone formation was disturbed, which negatively affected the healing outcome. By contrast, CD59-ko mice only displayed minor skeletal alterations, although the early inflammatory reaction to femur fracture was marginally enhanced. These results demonstrate that TCC-mediated effects regulate bone turnover and promote an adequate response to fracture, contributing to a normal healing outcome.
The **27th International Complement Workshop** was held in Santa Fe, New Mexico, September 16-20, 2018, with over 440 participants (27% students/postdocs) experiencing exciting new science and, for many, novel geographical and cultural experiences. Sixty-one talks were selected from 253 submitted abstracts, with the remainder of abstracts presented in lively poster sessions. All provided many different fascinating findings and the promise of future discoveries in the realm of complement biology. In addition, three plenary lectures (Drs. Huang, Diamond and Noris) and the Hans Muller-Eberhard Lecture (given by the first President of the International Complement Society, Dr. John Atkinson) provided broad vision on the evolution of past discoveries in complement and the beginnings of therapeutic applications, as well as recent novel discoveries in unexpected areas which promise even more applications in the clinical and diagnostic arena.

The **ICS Young Investigator Award** was presented to Lubka Roumenina of the INSERM Centre de Recherche des Cordeliers in Paris, France, and the **Lambris Complement Training Award** as awarded to Christoph Schmidt of Ulm University in Germany, each of whom presented exciting talks on their innovative work. Travel Awards were presented to 28 Trainees to recognize their excellence in oral and poster presentations and facilitate their participation in the conference. No doubt we will watch some of the emerge as future leaders in the field. A tremendous amount of appreciation goes to the 26 sponsors for their generous support, as well as the 15 exhibitors who informed us of their products designed to enhance our research productivity.

There were several “experiments” initiated at ICW2018 that were evaluated by an exit survey completed by 172 meeting participants (that reflected the makeup of the conference participants). 97% of those responding felt the meeting accomplished their goals, was of appropriate length, and updated them on current research in the complement field. New this year were two 50 min panels on “Emerging Topics” which the overwhelming majority considered highly favorable and encouraged future development.

Over 100 participated in the Teaching Day prior to the opening of the Workshop, with greater than 91% responding in the exit survey that it was well worth coming in an extra day. Thanks goes to the outstanding faculty delivering the program and to Josh Thurman for organizing it. Respondents liked the “all posters up the entire meeting” and especially liked the extended poster sessions (2 hours, 2 days) with “end of the day” refreshments. Clearly interactions with colleagues and new contributors to complement was one of the highlights of the meeting, in the scientific sessions, excursions and social programs (gala dance floor!).

As has been done in the past, all exit survey comments have been forwarded to the organizers of the future complement meetings to facilitate constant improvements and evolution of our gathering to promote and accelerate progress in our field; so many thanks to all who contributed your time to respond. I also want to thank the other members of the Local Organizing Committee, John Atkinson, Nirmal Banda, Ashley Fraser-Abel, Josh Thurman and Rick Wetsel and our ICS president, Michael Holers, for a tremendous amount of thoughtful evaluation, planning and organization in the two years working toward the meeting and dedication at the meeting itself. A special thanks goes to our “amazing” meeting coordinator, Sheilah Jewart, for so much effort and skill in ensuring this meeting was enjoyable and memorable for all. Finally, many thanks to each and every ICW2018 participant, as you made the meeting impactful and significant.
SESSION I – New Technologies Shed Light on Long Held Questions

Chairs: Nicole Thielens (Grenoble, France) and Daniel Ricklin (Basel, Switzerland)

Breakthrough technologies in structural biology, genetics and other areas are increasingly employed in complement research and help to answer lingering or controversial questions. Four abstracts in the opening session of the ICW nicely showcased the potential of introducing novel technologies to study complement. The first talk of the series, given by Piet Gros from Utrecht University, shed light into classical pathway (CP) activation. Using cryo-electron tomography and antigen-coated liposomal surfaces, the study described the IgM-induced assembly of the initiating complex of the CP in unprecedented molecular detail. Surprisingly, the study not only confirmed a homogeneous binding of C1q to the dome-shaped penta- or hexameric IgM structures via its globular heads but also that C4/C4b directly assembles with the initiation complex. Finally, the cryo-ET structure provided additional insight about the arrangement of the C1r and C1s units, the elucidation of which had long remained elusive. The second talk given by Divyansh Agarwal from Nancy Wang’s laboratory (University of Pennsylvania, USA) reported mapping of complement expression using the single-cell RNA-sequencing technique in retinal cells from healthy mice. Retinal cells could be classified into eleven major cell types and “hotspots” of complement expression determined in the spatial context of retina. A differential distribution was observed on a functional basis and transcription of complement genes was found to be “out-of-phase”, specifically in retina, by comparison with mice and human liver. The third talk given by Per Nilsson from Tom Mollnes’ laboratory (University of Oslo, Norway) described a novel whole blood model optimized to study cross-talk between the coagulation and complement systems. This model uses a peptide anticoagulant (GPRP) that targets coagulation at the level of fibrin polymerization and the thrombin inhibitor lepirudin was used for comparison. It was concluded that thrombin cannot cleave native C5, but cleavage may occur in pathophysiological conditions such as mild acidosis associated with thromboinflammation. The fourth talk given by Christine Pham (Washington University School of Medicine, USA) reported that serum transfer in the K/BnX serum model of RA triggers activation of the alternative complement pathway that is detected on circulating neutrophils and upregulates adhesion molecules. Use of a RA model with subcutaneous administration of arthrogenic K/BxN serum and in vivo two-photon microscopy revealed that complement activation is indeed critical for neutrophil adhesion and extravasation at the site of inflammation. Generation of C5a stimulates the release of neutrophil-associated proteases, mediating VE-cadherin degradation and promoting endothelial barrier dysfunction, which could be suppressed by C5aR antagonism.
SESSION II – Complement in the Nervous System

Chairs: Paul Morgan (Cardiff University, UK) and Anna Blom (Lund University, Sweden)

The subject of this session, Roles of Complement in the Nervous System, is a novel subject with many outstanding answers. Jessy Presumey (Harvard, USA) talked about C4A, its genetic association with schizophrenia, and roles in synaptic pruning for which the classical pathway is important. She used mice overexpressing human C4A or C4B alleles to show that in such a system, enhanced synaptic pruning was dependent on C4A, but not C4B, which may be explained by increased binding to synaptosomes. SRPX2 is a recently identified protein expressed in CNS, which has been implicated in synaptic pruning. Qifei Cong (University of Texas Health Science Center, USA) identified SRPX2 as a potential complement inhibitor binding C1q. Andrea Tenner (University of California, Irvine, USA) showed in turn that absence of C5a-C5aR1 signaling resulted in a decrease of CR3 in microglia, correlating with protection from cognitive loss in Alzheimer’s prone Arctic mice. Trent Woodruff (University of Queensland, Australia) continued the C5a-in-brain theme, showing that C5aR1 on microglia was critical in driving inflammasome activation in response to fibrillar α-synuclein, a key player in Parkinson’s disease. Katja Pilti (University of California, Irvine, USA) used a rat spinal cord injury model to explore the impact of C1q on stem cell infiltration into and resolution of the injured area. Infusion of a C1q-blocking antibody into the lesion reduced astrogliosis and scar formation with resultant reduction or delay in recovery from the injury; the precise mechanism of this effect remains to be discovered. The final presentation of the session described a gene targeting approach to inhibit neurodegeneration in the retina in a glaucoma model. Alejandra Bosco (University of Utah, USA) used a viral vector to deliver the hybrid C3 convertase inhibitor to the eye in glaucoma-prone mice. CR2-sCrry-treated animals showed reduced C3d deposition, slowed optic nerve degeneration and increased retinal ganglion cell survival through 8 months of follow-up.
SESSION III – Lectin and Alternative Pathway: Deep Connections?

Chairs: Peter Garred (Copenhagen, Denmark) and Péter Gál (Budapest, Hungary)

This session focused on the latest results regarding the cross-talk between the lectin and the alternative pathways. The first presentation given by Péter Gál (Budapest, Hungary) reported an unexpected role of MASP-1 in the alternative pathway activation. Inhibition of MASP-1 attenuated the alternative pathway activity on LPS-coated surface and also on the surface of Gram-negative bacteria. To clarify the individual roles of MASP-1 and MASP-3, Manabu Hayashi and colleagues (Fukushima, Japan) generated mice lacking MASP-1 or MASP-3. The MASP-1-deficient mouse serum showed no lectin pathway activity and had active FD. The MASP-3-deficient mice showed full lectin pathway activity, while the alternative pathway was absent since the pro-FD was not activated. József Dobó and colleagues (Budapest, Hungary) studied the activation mechanism of MASP-3 in “resting blood” where neither coagulation nor complement activation occurs. They concluded that a protease is present in the “resting blood” that cleaves and activates MASP-3 and the N-terminal domains facilitate this activation. Using specific inhibitors, they excluded MASP-1 and MASP-2 as potential MASP-3 activating proteases. Nirmal Banda and colleagues (Denver, Colorado, USA) studied the effect of RNAi targeted liver expression of MASP1 and MASP2 in the collagen antibody induced arthritis (CAIA) mouse model. No significant effect of MASP-1 silencing was seen on CAIA disease activity. MASP-2 silencing decreased CAIA, suggesting that MASP-2 might be more important than MASP-1 in the pathophysiology of the disease. Cui Quang and colleagues (London, UK) studied whether collectin-11 might have a role in dendritic cells (DCs) maturation. They showed that murine bone marrow derived DCs synthesized CL-11 and that CL-11 could bind to DCs. They also studied DCs derived from WT and CL-11−/− mice, providing evidence for a regulatory role of CL-11 in DC maturation and activation. Jie Zhang and colleagues (Copenhagen, Denmark) studied the interaction between soluble collectin-12 deposited on Aspergillus fumigatus and Neisseria meningitides and its involvement in alternative pathway activation. They demonstrated that pre-opsonization of sCL-12 recruits properdin in serum without initial C3 activation. In this way properdin may specifically direct the alternative pathway activation via recognition of endogenous sensor molecules like sCL-12.
SESSION IV - Extracellular Complement Influences Acquired Immunity

Chairs: Rick Wetsel (Texas, USA) and Claudia Kemper (NIH, USA)

This session gave an overview on new developments on the ever expanding roles of the complement system in directing adaptive immunity. Deborah Fraser (California State University, USA) presented data that further solidified C1/C1q’s non-canonical roles as a direct modulator of cell activity. Her data demonstrated that recombinant variants of human C1q unable to bind C1r/C1s, still induce strong phagocytosis with concurrent suppression of pro-inflammatory cytokine secretion in phagocytes. This suggests that the phagocytosis-mediating active site in C1q is independent of the C1r/C1s binding site. Michael Carroll (Harvard University, USA) showed the human complement C4 locus (C4A and C4B) varies in copy number and isoforms, and C4A deficiency is associated with an increased risk for SLE. Mice only express a single, non-polymorphic C4 gene. The Carroll lab generated mouse strains that express human C4A or human C4B, respectively and demonstrated that mice expressing human C4A were protected relative to mice expressing human C4B in a lupus model – and they now are dissecting the exact molecular mechanism behind this finding. Luke Halder (Leibniz Institute, Jena, Germany) presented data that suggest that human monocytes release distinct populations of extracellular microvesicles containing TGFβ-1 in response to C. albicans infection in a CR3-dependent manner. TGFβ-1+ microvesicles dampened LPS inflammatory responses in human M1 macrophages by activating the SMAD2/3/7 pathway, which may create a microenvironment more conducive to infection propagation. Konstantina Antoniou (University of Luebeck, Germany) presented new insights into the protective role of C5a/C5aR1 signaling in the initial sensitization phase of allergic asthma in an OVA model. She found that that C5aR1− but not C5aR1+ cDCs induced strong proliferation of OVA-transgenic Th cells in response to in vitro allergen exposure. Impaired T cell proliferation induced by the C5aR1+ cDCs was partially rescued by blocking of C5aR1 signaling, which was associated with increased CD40 and MHC-II expression, indicating that allergen-induced paracrine C5/C5a generation by pulmonary CD11b+ cDCs controls tolerance towards aero-allergens via C5aR1 signaling. The session was closed by a presentation from Erin E. West (NIH, USA). Her work lent further substance to the understanding that the intracellular complement system (the complosome) is a master mediator of required nutrient influx and metabolic reprogramming in activated human CD4+ T cells. Complosome-regulated expression of Arginase-1 in T cells controls arginine consumption which in turn is a rheostat for the initiation of the Th1 shutdown program. In consequence, patients with ARG1 deficiency have the propensity to shorten their Th1 cell effector phase and hasten into the shutdown phase and have altered T cell memory pools.
SESSION V - Complement vs Pathogens

**Chairs: Denise V. Tambourgi (São Paulo, Brazil) and Nobutaka Wakamiya (Hokkaido, Japan)**

In the first presentation, David Ermert (Lund University, Sweden) reported a novel complement evasion strategy whereby human IgG enhances C4BP binding to Group A Streptococcus pyogenes, accentuating the virulence of this gram positive bacteria, able to cause invasive life-threatening infections. Sunita Gulati (University of Massachusetts, USA) summarized novel data on the use of a humanized mAb, derivative from the murine mAb 2C7, capable to recognize Neisseria gonorrhoeae lipooligosaccharide. By using Hexabody technology, which enhances IgG hexamerization and complement activation, the group showed an increased ability of this chimeric human antibody derivative, in attenuating gonococcal vaginal colonization in mice. Mueller-Ortiz (University of Texas Medical School at Houston, USA) presented interesting data on the role of the second C5a anaphylatoxin receptor, C5aR2, in host immune response to Listeria monocytogenes systemic infection. The authors showed, by using C3a and/or C5a receptors deficient mice, that C5aR1 and C3aR signaling protect the host during L. monocytogenes infection, by suppressing type I interferon expression, while C5aR2 impairs the host response to this infection, possibly by inhibiting IFN expression. The fourth talk, by Kay Ole Johshwich (University of Wuerzburg, Germany), showed distinct roles of the anaphylatoxin receptors C5aR1, C5aR2 and C3aR during experimental invasive meningococcal diseases (IMD). Generally, complement plays a defense role on IMD caused by Neisseria meningitidis, using the membrane attack complex. With C3a and/or C5a receptors deficient mice, the authors showed that these receptors are involved in severe damage and inflammation, while the C3a/C3aR axis is beneficial during IMD. Nuntaya Pornmun (Mahidol University, Thailand), presented a novel Dengue virus (DENV) strategy to escape host immune surveillance and disseminate infection. They showed that DENV and immune complexes composed by DENV and anti-DENV antibodies, formed during the acute disease phase, activate the complement system and bind to CR1 on red blood cells (RBCs). RBCs carrying complement deposited DENV or DENV/anti-DENV immune complexes can transfer infectious virus to replicate in susceptible target cells, including hepatocytes, monocytes and macrophages in liver and spleen, resulting in a productive infection. The last speaker, Jutamas Shaughnessy (University of Massachusetts, USA), demonstrated the therapeutic potential of two chimeric molecules, composed by FH domains 6 and 7 fused to human IgG1 Fc fragment (FH6,7/Fc) or by FH domains18-20 (with a D to G mutation at position 119) fused to Fc (FHD119G/Fc). These molecules, which target distinct N. gonorrhoea ligands, are capable of activating complement on various gonococcal strains in vitro, and, in vivo, they can protect mice against multidrug resistant gonoccoci, when administered as topical intravaginal preparation.
SESSION VI – Intracellular Complement System

Chairs: John P. Atkinson (Washington University, USA), Jörg Köhl (Lübeck, Germany)

Dennis Hourcade (Washington University, USA) employed mass cytometry (Cytof) technology to perform a comprehensive exploration of the human T-cell complement system. A 36-Ab conjugate panel including 18 complement biomarkers was used to examine CD4+ circulating T-cells from normal individuals and patients with early systemic sclerosis. In these rheumatic disease populations, they identified an aberrant T cell complement signature indicative of a hyperactive phenotype, illustrating the potential of this methodology for identifying and following patient populations with autoimmunity. In two presentations from Anna Blom’s laboratory (Lund University, Sweden), investigators explored a role for human C3 in B lymphocytes and in islet cells from patients with Type II diabetes mellitus (T2D). They showed that, while C3 expression is very low in human B cells, a combination of extracellular complement activation and uptake by the cells of C3, FD and FH led to local complement effects. Following uptake, C3 (and C3a) became bound to nuclear DNA and thereby was able to regulate gene transcription. The second presentation reported that C3 is produced by beta-cells in human pancreatic islets. The magnitude of C3 expression correlated with T2D donor status, proinflammatory signals and levels of glycated hemoglobin. Further, C3 upregulation protected against pancreatic beta-cell dysfunction via modulating autophagy. This connection was further substantiated utilizing a knockout of C3 in a clonal beta-cell population. Claudia Kemper (NIH, USA) showed data, including those from a novel tdTomato C3- reporter-mouse, suggesting that CD4+T cells upregulate C3 transcription in response to ICAM-1-mediated LFA-1 (CD11a/CD18) integrin activation after they exit the circulation to migrate into tissues. Enhanced C3 production together with T cell receptor stimulation then drives Th1 differentiation. This finding is of clinical relevance, as LFA-1 deficient patients failed to upregulate C3 transcription and generate Th1 responses in vitro. However, Th1 responses could be restored upon adenovirus-delivery of C3 to cells. Hrishikesh Kulkarni (Washington University, USA) provided novel insights into the protective role of intracellular C3 in human airway epithelial cells (AEC) in response to oxidative-stress induced cell death. AECs produce endogenous C3 and can take up exogenous C3(H2O) to mitigate H2O2-induced cell death through reduction of intracellular reactive oxygen species. Proinflammatory cytokines increased AEC C3 production and short-term cell protection from oxidant-induced cell damage. Finally, Parul Singh (NIH, USA) provided new insights into the role of CD46 in basic cell physiology and an explanation for mechanisms underlying the failure of CD46-deficient patients to mount a Th1 immune response. Chip-seq data identified transcription factor binding motifs of the CD46 cytoplasmic tail -1 regulating chromatin packaging/accessibility critical for nucleosome regulation and cell metabolism.
Meeting Notices

Please plan to attend:

Link: https://www.immunology2019.org/scientific-program/scientific-program-by-session-type/

Many events are programmed that will be of great interest to the complement community:

**Distinguished Lecture:**

*Complement: primitive yet powerful – new discoveries in immunity and the nervous system*

Andrea J. Tenner, Ph.D.
Past-President International Complement Society
Univ. of California, Irvine

**International Complement Society Guest Symposium:**

*Newly Defined Essential Roles of Complement*

Chairs:
- Ron Taylor, Univ. of Virginia
- Sanjay Ram, Univ. of Massachusetts Med. Sch.

Speakers:
- Maciej Markiewski, Texas Tech Univ. Health Sci. Cent., *Complement as an emerging target for cancer immunotherapy*
- Claire Harris, Newcastle Univ., United Kingdom, *Complement and disease: the changing landscape of treatment and therapy*
- Anna Blom, Lund Univ., Sweden, *Regulation of autophagy by complement component C3*
- Viviana Ferreira, Univ. of Toledo Col. of Med., *Properdin and Factor H: Mechanisms of complement dysregulation in disease*

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**Major Symposium:**

*Acute and Chronic Inflammation*

Chairs:
- Claudia Kemper, NHLBI, NIH
- Michael C. Carroll, Boston Children’s Hosp.

Speakers:
- Claudia Kemper, NIH, *Non-canonical roles for intracellular complement in normal cell physiology and in inflammatory disease*
- Michael C. Carroll, Boston Children’s Hosp., *Functional importance of allelic differences in human complement C4A and C4B and inflammatory disease*
- Jörg Köhl, Univ. of Lübeck, Germany, *Non-canonical functions of complement in inflammatory diseases*
- Clare E. Bryant, Univ. of Cambridge, England, *Pattern recognition receptor signalling in response to bacterial infection*
- Grace Y. Chen, Univ. of Michigan, *Regulation of intestinal inflammation by NLRs and the gut microbiota*
- Susan Carpenter, Univ. of California, Santa Cruz, *The how and why of IncRNA function during inflammation*

**Back to School: A Review of Four Fast-Moving Fields**

Sponsored by the AAI Program Committee

Speakers:
- Joshua Thurman, Univ. of Colorado, *The complement system – new tricks for an old dog*
- Dennis Burton, Scripps Res. Inst., *Super Antibodies: the fourth generation*
- Alex Shalek, Massachusetts Inst. of Technol., *Cellular heterogeneity in the immune system: turning a bug into a feature with single-cell genomics*
- Catherine Hedrick, La Jolla Inst. for Immunology
We are pleased to announce and to invite you to the “17th European Meeting on Complement in Human Disease” (EMCHD 2019), to be held in Madrid, Spain, from September 14th to 17th, 2019.

This EMCHD 2019 meeting represents a new edition of a very successful series of congresses in which the expanding role of complement in human disease and the excitement of novel diagnostic and therapeutic developments will be updated. It will be a fruitful and stimulating encounter for professionals in the complement field from all over the world and an opportunity to share and discuss cutting-edge topics in this continuously evolving area. Our scientific program will include several top-notch keynote speakers, selected presentations from the best abstracts submitted, and poster viewing sessions. A satellite meeting will address specific questions on complement-related kidney diseases. Commercial stands, placed in a large hall shared with refreshment break meeting points, and industry-fostered luncheon seminars will round up the program.

We very much hope you will join us and enjoy Madrid, a modern, cosmopolitan and fun city, along with the warmth of its people and the taste of its food and wines.

We look forward to welcoming you in Madrid!

Prof. Santiago Rodríguez de Córdoba
Chairman of EMCHD 2019

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Meeting Topics:
Complement structure and function
Complement crosstalk
Complement genetics
Infection and autoimmunity
Complement-related diseases
Animal models
Complement therapies

Our website is already available at: http://emchd2019.com

If you would like to be automatically updated on news and other useful information regarding EMCHD-2019, then please

CLICK HERE
12th International Conference on Complement Therapeutics

The field of complement-targeted drug discovery has experienced an profound transformation during the past decade. With the first complement-specific drugs on the market, clinical experience is gained and novel indications are being explored. At the same time, efforts in both academic and pharmaceutical research have produced new innovative therapeutic concept that interfere at different levels of the complement cascade; many of these candidates are currently undergoing clinical evaluation. Finally, genetic and molecular studies continue to reveal contributions of complement in both orphan and highly prevalent diseases. Apart from offering new hope for patients suffering from such diseases, the study of complement pathways, mutations, and deficiencies also teaches us important lessons about the role of complement in health and disease and allows us to refine our models and tools for applied and basic research. This conference aims to bring together academic and industry scientists and clinical development experts who are focused on contemporary and emerging aspects of complement-mediated disease pathogenesis and the development of therapeutics that modulate this system in a beneficial manner.

Topics discussed during the conference include: Molecular mechanisms and targets in complement-related diseases; Novel inhibitors & pipeline compounds; Hematological disorders; Organ & cell transplantation, I/R injury and chronic rejection; Kidney diseases; Neurological & ocular diseases; Acute and chronic inflammatory disorders; Infectious diseases & sepsis; Cancer; Informative complement biomarkers in therapeutic development; Novel and unexpected indications.

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