Focus on Complement

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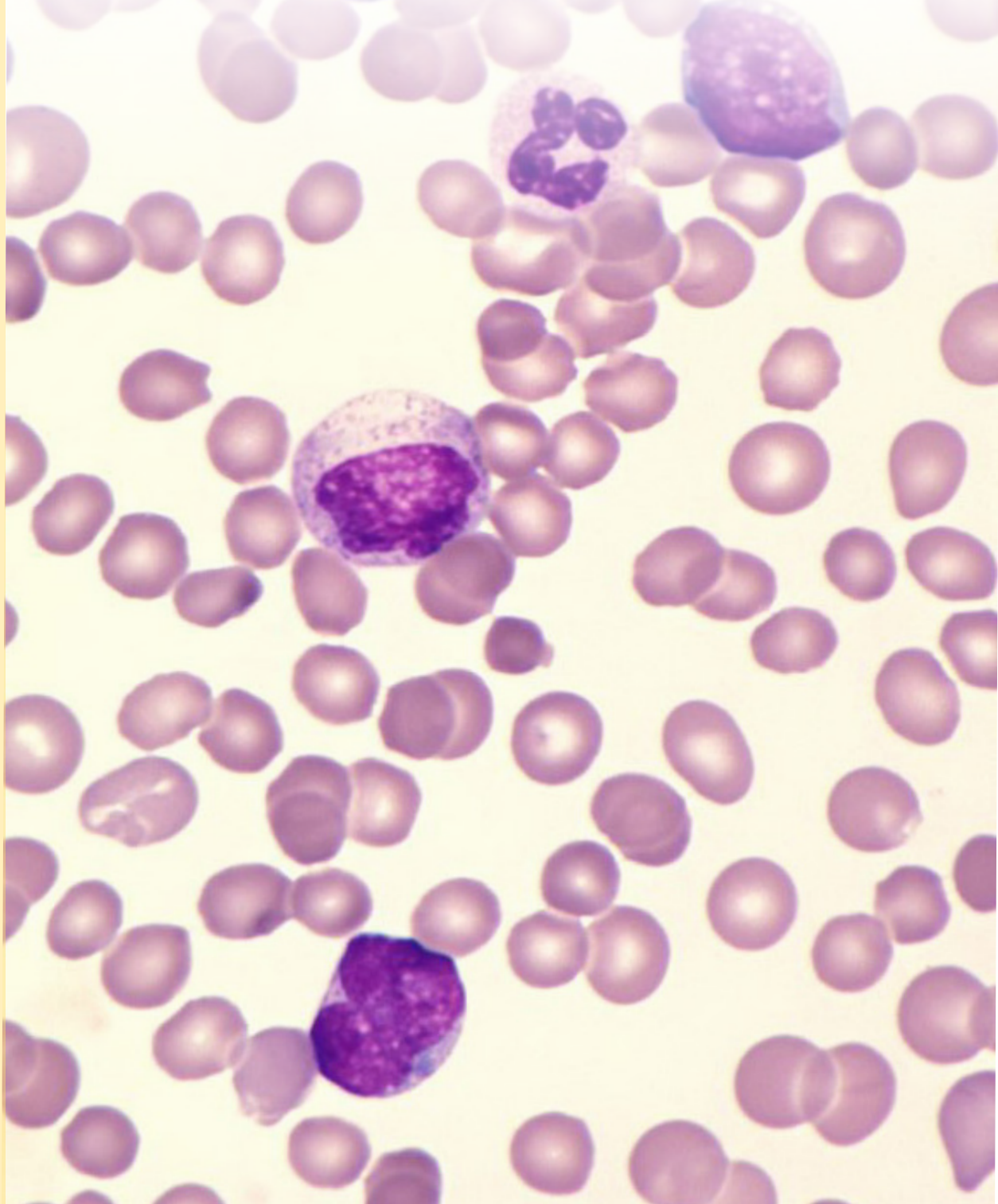

International Complement Society

9037 Ron Den Lane
Windermere
FL 34786-8328
T: 407-234-3274

ics@complement.org
www.complement.org

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Issue #50

Editor
Trent Woodruff

Issue Contributor
Michael Kirschfink

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In this 50th Issue of Focus on Complement:

From the Editor

Dear Readers,

Welcome to the new-look *Focus on Complement* – the official newsletter of the International Complement Society (ICS).

The FoC was initiated in 2006 by past ICS councilor, secretary and president, Zvi Fishelson, who drove many of the familiar sections, including the News Flash, and Team Highlights. Over the following 12 years, there have been over 90 complement Teams highlighted, and almost as many complement research articles reviewed.

We have plans for future section additions to the FoC, so stay tuned, and as always, if you have any suggestions for improvements or newsletter additions, please contact myself, or our ICS president, Mike Holers.

I hope you all enjoy the new FoC format!

Trent Woodruff, PhD.
Editor, FoC
Secretary, ICS
t.woodruff@uq.edu.au

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 @complementsoc

The Focus on Complement Young Investigator **Cover Image Award**

Introducing a new initiative of Focus on Complement: 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 a 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).

Winners of the Award will additionally receive a signed certificate.

Complement Research in Lübeck at the Institute for Systemic Inflammation Research, Germany

The groups of Jörg Köhl, Christian M. Karsten, Yves Laumonnier, Admar Verschoor and Claudia Kemper

In 2008, Jörg Köhl moved from Cincinnati Children's Hospital (CCHMC; USA) to the University of Lübeck (UzL; Germany), where has was appointed the founding Director of the Institute for Systemic Inflammation Research (ISEF). During the past ten years, the ISEF became the nucleus for five different research groups focusing on different aspects of complement research.

During the past 30 years, the group of **Jörg Köhl** has been interested in the biology of the complement system. More specifically, the focus has been on the multiple functions of the small cleavage fragments of C3 and C5, i.e. C3a and C5a, in the networks of innate and adaptive immune responses. The lab has generated several floxed reporter mice to track and cell-specifically delete C3a receptor (Quell et al. J. Immunol. 2017), C5a receptor 1 (Karsten et al. J. Immunol. 2015) and C5a receptor 2 (Karsten et al. J. Immunol. 2017) and a unique C5aR1/C5aR2 inhibitor (Otto et al. J. Biol. Chem. 2004) that has been widely used in the complement community to target C5aR1/C5aR2 in experimental models of infections, autoimmunity, allergy and ischemia-reperfusion injury. In collaboration with the lab of his former Postdoc, Manoj. K. Pandey at CCHMC, Jörg Köhl recently uncovered that C5a controls cellular glucosylceramide metabolism as a critical mechanism for disease development in Gaucher disease (Pandey et al. Nature 2017). Currently, his lab is collaborating with basic scientists and clinicians all around the globe to further unravel the role of C3a and C5a in allergic diseases including allergic asthma and food allergy, autoimmune diseases with a particular focus on autoimmune bullous diseases (AIBD), several infectious diseases and cancer. Jörg Köhl has spearheaded the International Research Training Group (IRTG) 1911, a research program between the University of Lübeck and University of Cincinnati as well as Cincinnati Children's Hospital Medical Center (CCHMC). Funded by the German Research foundation (DFG), this program has been designed by him to achieve broad-based research cooperation between German and US institutions via exchange of doctoral candidate researchers between the two institutions. Since 2013, the program has been used to regularly invite and host colleagues from the complement field to Lübeck for talks and exchange, something that complement researchers in Lübeck experienced as extremely helpful and productive.

Christian. M. Karsten's team is interested in the anaphylatoxin C5a and its corresponding receptors C5aR1 and C5aR2. While the role of C5aR1 in inflammation and its downstream effector functions are relatively well described, the role of C5aR2 is still enigmatic. More specifically, his group aims to delineate the function of C5aR2 in the effector phase of experimental and clinical AIBDs, a group of autoimmune skin blistering diseases (Karsten et al. Nat. Med. 2012; Karsten et al. Front. Immunol. 2018). Recently, he uncovered in collaboration with the Köhl lab the exclusive expression of C5aR2 on NK and B cells (Karsten et al. J. Immunol. 2017). Following this observation, his lab aims to unravel

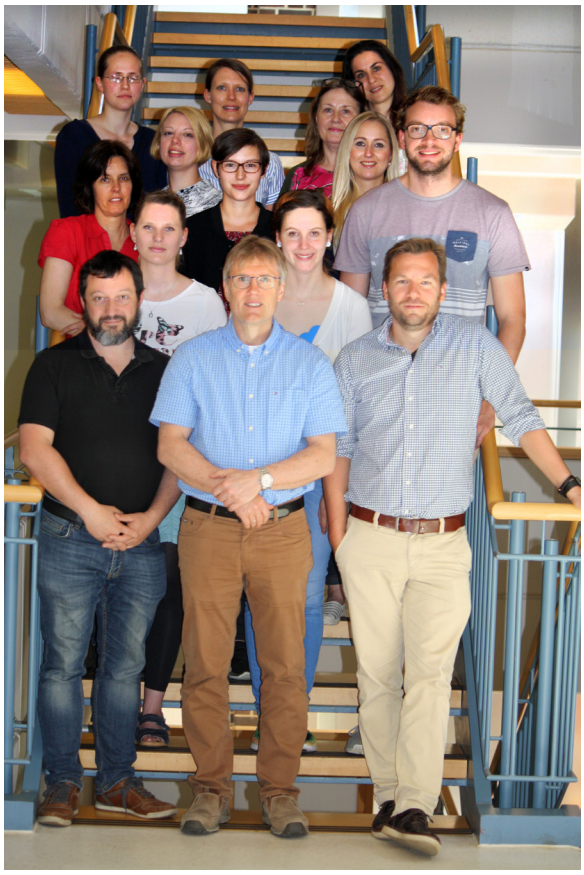
the relevance of C5aR2 in the regulation of C5aR1–C5aR2+ NK cells in a model of Toxoplasma gondii infection. Further, NK cells are also important for placental angiogenesis and development during the first trimester of pregnancy. Therefore, his team became interested in determining the role of C5aR2 in controlling the uterine NK cell compartment and its role in pregnancy. Finally, his team focuses on the role of the C5a/C5aR1/C5aR2 axes in the regulation of the B-1 cell compartment with a particular emphasis on B-1 cell dynamics during steady state in the peritoneal cavity, spleen and bone marrow and natural IgM antibody production (Bröker et al. Front. Immunol 2018). Another focus is on the inflammation-driven egress of B-1 cells from the peritoneum into the spleen. The Karsten lab enjoys intense collaborations with national and international research groups. For example, in AIBD research, his group collaborates with several clinicians in the context of the RTG 1727 and CRU 303; regarding NK cells, his lab interacts with the Hoebe lab at CCHMC (IRTG 1911).

The focus of **Yves Laumonnier's** group is on the pleiotropic functions of the anaphylatoxins and their cognate receptor in experimental allergic asthma. Pro-allergic and pro-inflammatory functions have been reported for C3aR. In contrast, C5aR1 functions are more complex. Several studies demonstrated a pro-inflammatory role during the effector phase of allergic asthma. However, targeting C5aR1 during allergen sensitization results in aggravation of the allergic asthma phenotype, suggesting a dual role for C5aR1 in allergic asthma. In addition to C5aR1, also C5aR2 seems to drive the allergic phenotype during the allergic effector phase. Using a wide range of allergic asthma models together with C3aR, C5aR1 and C5aR2-deficient and reporter mice, his team aims at understanding the functions of C3aR, C5aR1, and C5aR2 in different cell subsets involved in the development and severity of allergic asthma (Laumonnier et al. Mol Immunol. 2017). One major focus is to delineate the functions of C3aR that is induced in alveolar macrophages exclusively upon allergic inflammation. This project is conducted within the IRTG 1911 in collaboration with Ian Lewkowich (CCHMC). In collaboration with the Köhl lab, the Laumonnier lab recently identified a highly vacuolated eosinophil subpopulation in the lung of allergic mice. In the next steps they aim to understand the functions of the anaphylatoxin receptors in this cell population with a particular emphasis on T cell proliferation and differentiation under allergic asthma conditions.

The group around **Admar Verschoor** focuses on the role of complement in instructing immune and hemostatic processes that take place during the clearance of pathogens from the circulation. He started in the complement field during his PhD studies with Mike Carroll in Boston, studying the role of C3-derived opsonins in instructing B cell immunity and directing the handling of pathogen associated antigens. With his own group at the Technical University in Munich, he began to explore how processes of gradual opsonization direct the handling and targeting of pathogens from the bloodstream to distinct phagocyte populations across diverse organs. His team showed how complement cross-connects with receptors and cells that are traditionally associated with hemostasis, in particular GP1b and platelets, and how this interaction promotes the induction of protective adaptive immunity (Verschoor et al, Nat Imm 2011). In 2015, he took the opportunity to join forces

with other complement-oriented researchers at ISEF, when he was appointed as Professor of Systemic Complement Research and moved his lab with Steven Broadley, Julia Ritter and Hanna Ulrich from Munich to Lübeck. Together with the imaging expert Peter König from the Department of Anatomy and Christin Lehmann his team continues to shed light on intravascular pathogen clearance and the role of complement and its receptors in these processes (Broadley et al Cell Host Microbe 2016). Building on this, Martina Buscaiova from Christine Mannhalter´s group in Vienna currently spends a year in his group to detail platelet-pathogen interactions. He also pursues other aspects of his work in collaboration, for instance with Menno van Lookeren-Campagne (San Francisco) and Edith Janssen (CCHMC; IRTG 1911).

Claudia Kemper joined the ISEF in 2017, when she was appointed Adjunct Professor of Translational Complement Research (20%; *she spends her remaining time at NHLBI/NIH*). Her team has recently discovered that complement can be – surprisingly – activated within cells, where it serves critical non-canonical roles in the regulation of basic cell metabolic pathways (West et al. Annu. Rev. Immunol. 2018) Specifically, the temporal regulation of intra- and extracellular signalling through the anaphylatoxin receptors C3aR, C5aR1 and C5aR2 and CD46 via C3 and C5 activation fragments generated by CD4+ T cells in an intracellular/autocrine fashion are critical checkpoints in human T cell lineage commitment and control initiation and resolution of inflammatory Th1 responses (Arbore et al. Science 2016). Mechanistically, the signalling pathways induced by these receptors engage the NLRP3 inflammasome and drive glycolysis, oxidative phosphorylation and oxygen metabolism – thus connecting complement unexpectedly with the regulation of basic processes of the cell. Importantly, her group found that these complosome-driven pathways are also operative in other (immune) cells and suggest that they are of broad physiological relevance. In collaboration with the other complement groups at the ISEF and the UzL, she now focuses on defining these new, non-canonical roles of intracellular complement (the Complosome) in the control of normal (immune) cell physiology in health and disease with an eye on three core questions: **1.** What is the composition of the Complosome? **2.** What are the functions of the Complosome? and **3.** How is the Complosome regulated?



Complement Research in Jena, at the Leibniz Institute for Natural Product Research and Infection Biology, Germany

The groups of Professor Peter Zipfel and Professor Christine Skerka

The Department of Infection Biology headed by Professor Peter Zipfel and the Research Group Immunoregulation headed by Professor Christine Skerka are both located at the Leibniz Institute for Natural Product Research and Infection Biology and are members of the Friedrich Schiller University in Jena, Germany.

There is a strong interaction between the groups and they join forces to understand complement regulation in basic science with the aim to understand complement activation and regulation in human diseases, focusing on the role of soluble complement regulators. During the last two decades the two groups examined the regulatory role and the immune modulatory profile of Factor H and their second major interest: to define the functional roles of factor H related proteins. Following the initial identification of the factor H-related (FHR) proteins in the early 1990s, both groups have remained rooted in this field and have contributed much to the enlightenment of the CFHR genes and FHR proteins, like identifying the association of CFHR3/CFHR1 deficiency with the presence of Factor H autoantibodies in autoimmune HUS patients.

Interested to understand the role of all five FHR protein in immune homeostasis, the two groups characterize gene variations in the CFHR gene cluster in patients, like the described deletion in the CFHR gene cluster in familial DDD patients who express a FHR2-FHR5 hybrid protein. This work again linked FHR proteins with human kidney diseases and also identified FHR5 as new surface complement activator, and anchor for properdin.

The Department of Infection Biology in Jena

In conjunction with national collaborators, the group of Immunoregulation also characterized the functional activity of a new human complement activator ARMS2 (age-related macular susceptibility protein 2), which plays a major role in age-related macular degeneration. By knowing about pathogenic microbes that evade the immune system by recruiting human complement regulators, both groups are engaged in microbial work to learn more about the activities of immune regulators like Factor H and FHR proteins.

The two research groups are integrated into national collaborative research programs funded by the Deutsche Forschungsgemeinschaft (DFG) like CRC FungiNet and CRC1192 Immune-Mediated Glomerular Diseases. Close and fruitful collaborations with complement researchers in Germany, Europe and other countries allow the groups in Jena to define new aspects in their field of complement research, but also to extend the knowledge in clinical settings ultimately for the benefit of patients and their families.

The Research Group Immunoregulation

The Renaissance of Complement Therapeutics

Ricklin D, Mastellos DC, Reis ES, Lambris JD.

Nature Reviews Nephrology. 2018 Jan; 14:26–47.

In this comprehensive review the authors present current therapeutic concepts, targets and candidate drugs to interfere with an overactivated complement system causative for numerous diseases. They summarize insights from clinical trials, and reflect on existing challenges for the development of complement therapeutics for kidney diseases and beyond. The increasing number of clinical conditions that involve a pathological contribution from the complement system — many of which affect the kidneys — has spurred a regained interest in therapeutic options to modulate this host defence pathway. Molecular insight, technological advances, and the first decade of clinical experience with the complement-specific drug eculizumab, have contributed to a growing confidence in therapeutic complement inhibition. More than 20 candidate drugs that target various stages of the complement cascade are currently being evaluated in clinical trials, and additional agents are in preclinical development. Such diversity is clearly needed in view of the complex and distinct involvement of complement in a wide range of clinical conditions, including rare kidney disorders, transplant rejection and haemodialysis-induced inflammation. The existing drugs cannot be applied to all complement-driven diseases, and each indication has to be assessed individually. Alongside considerations concerning optimal points of intervention and economic factors, patient stratification will become essential to identify the best complement-specific therapy for each individual patient.

Extracellular Vesicles: Packages Sent With Complement

Karasu E, Eisenhardt SU, Harant J, Huber-Lang M.

Frontiers in Immunology. 2018 Apr; 9:721.

Throughout evolution, communication via extracellular cargo carriers appears to be a highly conserved method. Cells communicate with other cells in their microenvironment by transferring lipids, peptides, RNA, and sugars in extracellular vesicles (EVs), thereby also influencing recipient cell functions. In a comprehensive overview, Karasu et al. summarize the limited current knowledge on the crosstalk between complement and EVs. Current studies are presented which indicate complex interactions of the complement system with EVs, with a dramatic influence on local and systemic inflammation. During inflammatory conditions with highly activated complement, including after severe tissue trauma and during sepsis, elevated numbers of EVs were found in the circulation of patients. There is increasing evidence that these shed vesicles contain key complement factors as well as complement regulators on their surface, affecting inflammation and the course of disease. These data provide compelling evidence that the interaction of EVs regulates complement activity and contributes to the pro- and anti-inflammatory immune balance. However, the molecular mechanisms behind this interaction remain elusive and require further investigation. A further intersting aspect discussed by the authors is the clinical relevance of EVs with an emphasis on their capacity as potential therapeutic vehicles in the field of translational medicine.

You are invited to attend the 27th International Complement Society meeting being held in historic Santa Fe, New Mexico…UNESCO World Heritage City of Crafts. Santa Fe is a magical city with legendary history and culture that will fascinate and inspire you. The art galleries and diverse visual arts span ancient traditional art to the most contemporary, making Santa Fe one of the largest and most important art markets in the country.

The meeting will be held at the Santa Fe Convention Center, located in the historic center and one block from the hotels and the cities best galleries, museums, and handicraft stores. Fly into either Santa Fe Airport (SAN) or for more flight choices Albuquerque Airport (ABQ), and take a scenic 50-minute shuttle to Santa Fe.

The Program Committee is developing a program which will include an exciting mix of formal presentations and panel discussions on diverse topics of scientific and educational interest to the Complement community. We look forward to seeing in historic Santa Fe!

Local Organizing Committee:

Andrea Tenner, PhD (Chair)
John Atkinson, MD
Nirmal Banda, PhD
Ashley Frazer-Abel, PhD
Joshua Thurman, MD
Rick Wetsel, PhD

Plenary Speakers:

Michael Diamond, MD, PhD
Washington Univ School of Medicine, St Louis, MO

Eric Huang, MD, PhD
Univ of California School of Medicine, San Francisco, CA

Marina Noris, PhD
Mario Negril Institute for Pharmacological Research, Bergamo, Italy

If you would like to promote your Complement-focused meeting in FoC, please contact Trent Woodruff (t.woodruff@uq.edu.au) or Michael Holers (Michael.Holers@ucdenver.edu).

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