Dear members of the immunology community,

This is the first issue of the 'Focus on Complement' in 2013 – which we hope will be a healthy and successful year for all of you. This 29th FoC issue contains:

- Announcement of Dr. Otto Götze's passing
- Welcome to the new ICS Board members
- Highlights from the XXIVth ICW 2012 in Crete. Special thanks to John Lambris, Daniel Ricklin and George Hajishengallis for organizing an exciting Workshop in Greece.
- Flash News discussing a publication suggesting that expression profiles of complement regulators may be used to detect infections and a paper that connects lack of C5aR/C3aR signaling on T cells with nTreg induction.
- Complement research teams around the world. This issue introduces two laboratories working in Australia: The team of Dr. Robert Pike located in Victoria, and the group of Trent Woodruff in Brisbane.
- Invitation to the 14th European Meeting on Complement in Human Disease, August 17th to 21st 2013 in Jena, Germany

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 Zvi Fishelson; Claudia.kemper@kcl.ac.uk; lifish@post.tau.ac.il

Thank you for your continuous sponsorship:
We sadly announce the demise of Dr. Otto Götze on February 4th 2013. The complement community will miss him.

An Obituary will be published in our next issue.

Changes in the ICS Board

During the XXIVth ICW in Crete, the elections for the new ICS President-Elect, the Treasurer and Council members took place. From January 1st 2013 on, Zvi Fishelson assumed his role as current President with Paul Morgan as Past President and Andrea Tenner as President-Elect.

Wenchao Song was elected to Treasurer (with Andrea Tenner as previous Treasurer) and Claudia Kemper is now taking the place of Berhane Ghebrehiwet as Secretary for the Society.

Denise Tambourgi, Bo Nilsson and Trent Woodruff were elected as new Council members. Council members who left the board because they served the six year term are Jörg Köhl, Anna Blom and Moh Daha.

We welcome all newly elected Board members and thank those that now ‘leave their post’ for the time and energy that they provided during their term.
The XXIV International Complement Workshop took place in Chania on the island of Crete, Greece, October 10th to 15th 2012. The following pages provide a summary of the highlights of the oral presentation sessions selected by the respective session chairs for those who were unable to participate and those who would like to be reminded of the good science, the beautiful setting and the lively atmosphere of the meeting.

Day 1, Thursday October 11th 2013

Session I: Structure and Function of Complement (Chairs: Susan Lea & Piet Gros). Recent studies suggest that C1q may have additional roles beside classic pathway activation and removal of apoptotic cells. The protocol described on the successful generation of recombinant human C1q by Isabelle Bally (Grenoble, France) will substantially facilitate future functional characterization of this molecule. Gregers S. Andersen (Arhus, Denmark) provided new insights into the structural basis of C4 activation by showing that MASP-2 and C1s recognize the C4 C345C region via exosites within their respective CCP regions. Finally, Joseph Caesar (Oxford, UK) presented in an elegant X-ray crystal structure that the oligomerization domain of the C4bp α-chain assembles as homoheptameric structure, suggesting that the α7 and α7β1 compositions among the many previously described are the likely physiological forms.

Session II: Complement in Host Pathogen Interaction (Chairs: Suzan Rooijakkers & Peter Zipfel). This session covered new aspects of the diverse complement system immune evasion strategies used by pathogenic microbes. Teresia Hallström (Jena, Germany) reported on the inhibition of the terminal complement pathway reactions by Borrelial burgdorferi-secreted protein CspA, providing an additional strategy how this pathogen controls the effector responses of its host. Julia Sharp (Virginia, USA) described the identification of SdrE, a new surface protein of Staphylococcus aureus that binds the complement regulator Factor H and that aids in degradation of C3b. David Ermert (Boston, USA, and Lund, Sweden, cooperation) presented a new animal model which allows to study the interactions between Streptococcus pyogenes and the rodent host complement system. In addition, two presentations by George Hajishengalis, (Philadelphia, USA) and Anna Reinicke (Lübeck, Germany) described important roles for the C5a receptor in mediating the immune response to inflammation.

Session III: Complement In innate & Adaptive Immunity I (Chairs: Wenchao Song & Claudia Kemper). Here, data were presented on the role of complement in B cell, T cell, NK cell and leukocyte biology. Continuing a major theme in recent complement research, the regulation of T cell immunity by complement, a presentation by Gaelle Le Friec (London, UK) identified Jagged1 as a novel physiological ligand for CD46. The investigators further observed that patients deficient in CD46 or Jagged1 are unable to mount T1 responses suggesting a role for the CD46/Jagged1 interaction in regulating T cell immunity. In two other presentations, one from the Köhl (Lübeck, Germany) and another from the Zhou (London UK) laboratory, novel roles of complement in B1 cell biology and NK cell biology were presented, with these effects of mediated by C5aR and CR3 signaling, respectively. The latter presentations are significant as they extend the regulatory function of complement from conventional T/ B cells to other cell types of the adaptive immune system.
Day 2, Friday October 12th 2013
Session IV: Complement activation & Regulation (Chairs: Peter Garred & Santiago Rodriguez de Cordoba). Søren Degn (Arhus, Denmark) and colleagues presented data showing that MASP-1 is necessary for activation of the lectin pathway: A patient harboring a nonsense mutation in the common part of the MASP1 gene, hence deficient in both MASP-1 and MASP-3 had normal alternative pathway activity in serum which was unaffected by reconstitution with MASP-1 and MASP-3. However, the patient had a nonfunctional lectin pathway, which could be restored by MASP-1, implying that this component is crucial for lectin pathway activation. Thus, different from a previous notion MASP-1 is necessary for MASP-2 activation in a physiological environment. Moreover, alternative pathway activation mechanisms may differ between mice and humans as in mice, MASP-1 and MASP-3 are both required for alternative pathway function. Søren Degn (Arhus, Denmark) and colleagues presented data showing that MASP-1 is necessary for MASP-2 activation in a physiological environment. Moreover, alternative pathway activation mechanisms may differ between mice and humans as in mice, MASP-1 and MASP-3 are both required for alternative pathway function.

Ying Jie Ma (Copenhagen, Denmark) presented data suggesting that collectin-11 functions as a novel recognition molecule for the lectin pathway. Their results clearly demonstrated that collectin-11 associates with all three MASPs, -1, -2 and -3 as well as the MASP-1 derived complement regulator MAP-1. Moreover, collectin-11 mediated deposition of C4b, C3b and the terminal complement complex on *Candida albicans* in a MASP dependent manner, implying that collectin-11 is the fifth recognition molecule in the lectin complement pathway.

Session V: Complement in Innate and Adaptive Immunity II (Chairs: Anna Blom & Andrea Tenner). Anna Erdei (Budapest, Hungary) showed that stimulated human T cells produce C3 activation fragments and that clustering of CR1 or MCP by such intrinsic C3b inhibits T cell proliferation. Conversely, high concentrations of IL-2 during ligation of CR1 and MCP by aggregated C3b enhanced proliferation and IL-10 production of activated T cells. Thus, CR1 engagement by T cell-intrinsic C3 activation fragments contributes to the down-regulation of T cell responses and induces Treg differentiation, similar to CD46. Martin Kolev (London, UK) on behalf of Kathy Liszewski (Saint Louis, USA) presented evidence for the intracellular generation of C3a and C3b by a convertase-independent mechanism involving cathepsin L in resting and activated T cells. TCR activation induces rapid movement of C3a and C3b stores onto the cell surface were these fragments support Th1 induction. Inhibition of cathepsin L-mediated C3b and C3a generation impaired Th1 induction; similarly, T cells from a C3-deficient patient could not assume a Th1 phenotype. These data suggest a novel pathway of intracellular complement activation required for human Th1 induction. Inken Schmudde (Lübeck, Germany) presented data showing that dendritic cell C5aR contributes to inflammation in the lung during the asthmatic response. Adoptive transfer of bone-marrow derived DCs from C5aR-/- animals resulted in a decreased asthmatic response relative to wild type DCs, including reduced IL-17 production and eosinophil infiltration, and better lung function. Further, C5a plays a role in directing DC polarization, which in turn impacts Th17 differentiation and survival in experimentally induced asthma.

Session VI: Complement in Disease: Ocular, I/R, Metabolic and Inflammatory (Chairs: Bärbel Rohrer & Stephen Sacks). Svetlana Hakobyan (Cardiff, UK) in collaboration with ophthalmologists from Southampton, presented data on incidences of age-related macular degeneration (AMD) in liver transplant patients. They conclusively demonstrated that recipient but not donor Y402H polymorphic status of complement regulator factor H (CFH) predicts risk of AMD, indicating that systemic administration of CFH is unlikely to be a useful treatment for AMD.
....continuing Session VI: Complement in Disease. To then determine which function of factor H was modified with the “risk” allele Y402H CFH, two mice were generated by Una Kelly and Catherine Bowes-Rickman (Duke University) on a cfh knockout background, one with the human Y<sup>flu</sup>CFH and the other with the H<sup>flu</sup>-CFH knock-in. They demonstrated that these animals will be viable tools to better understand the role of complement in the eye as the human CFH was functional with mouse complement components in vivo.

Day 3: Saturday, October 13<sup>th</sup> 2013:
Session VII: Complement Crosstalk with other Systems (Chairs: Maria Botto and Markus Huber-Lang). In this session, Christian Ehrntaller (Ulm, Germany) presented data clearly demonstrating that C5 and (although to a lesser extend) C3 are required for osteoclast formation and optimal bone fracture healing in a mouse fracture healing model. Two talks connected complement function and platelet biology: Lidia Barata (Philadelphia, USA) showed that in mice Crry/CD55 deficiency connects with abnormal platelet turn-over but also increased thrombopoiesis. Reinhard Sauter (Tübingen, Germany) demonstrated an unexpected role for C3a in platelet function as that C3aR-deficient mice presented with increased bleeding time in tail bleeding experiments as well as reduced infarct volume in an experimental stroke model.

Session VIII: Design and Application of Complement-Targeted Inhibitors (Chairs: Michael Holers & Trent Woodruff). Dr. Axel Vater (NOXXON Pharma AG, Germany) presented work on the development of an (l-)RNA oligonucleotide which selectively binds to human and murine C5a, thus blocking both C5aR and C5L2 activity, without affecting MAC formation. This compound showed a prolonged in vivo half-life and stability and significantly increased survival time when administered to cecal ligation-punctured mice. These novel compounds could represent a potential future drug class to inhibit C5a-mediated inflammation for human disease therapy. Two presentations from the Lambris Laboratory (Philadelphia, USA) updated participants regarding the development of novel complement therapeutics targeting the C3 convertase. The first described the ongoing work and improvements on the inhibitor designated compstatin, which has been in Phase 2 studies in patients with age-related macular degeneration. Described were improved molecules that demonstrated increased potency and longer in vivo half-lives as well as the creation of a molecule designated “mini-factor H”, which was constructed to contain only the amino-terminal and carboxy-terminal domains of factor H and interfere in a surface-targeted manner with the alternative pathway C3 convertase. The molecule demonstrated substantial ex vivo inhibitory activities.
**Day 4: Sunday October 14th 2013**

**Session IX Therapeutic Intervention of Complement-Mediated Diseases.** (Chairs: Antonio Risitano & Greg Stahl). This session focused on complement therapeutics and started off with a talk by Mikkel-Ole Skjoedt (Copenhagen, Denmark) presenting that MAP-1 displaces MASPs with the MBL complex and inhibits MBL binding, resulting in decreased C3 deposition, preserved cardiac function and prevention of thrombogenesis in mouse models of disease. Antonio Risitano (Naples, Italy) demonstrated effective inhibition of hemolysis of PNH erythocytes with two novel C3 targeting peptides, mini-fH and Cp30, which may pave the way for prevention of not only intravascular hemolysis, but also extravascular hemolysis. Paolo Macor (Trieste, Italy) found that it is possible to direct the local synthesis of a recombinant minibody (MB12/22) in the affected knee joints of rats, which neutralizes C5, decreases inflammation and swelling, without detection of the minibody in the contralateral joint or other organs. This novel therapeutic strategy could possibly be used on a joint by joint basis, without compromising systemic host defense. Toshiharu Abe (Philadelphia, USA) introduced a mouse model of periodontitis and demonstrated an important role for the classic al pathway and the C5a receptor. This model will allow the study of complement therapeutics in treating periodontitis. Quian Chen (Jena, Germany) showed that patients with a novel mutation in CFHR2/CFHR5 gene caused membranoproliferative glomerulonephritis type II. Franca Orsini (Milan, Italy) explored the role of MBL in cerebral ischemia in mouse and rat stroke models and found that inhibition of MBL with a novel inhibitor, Polymy 2 or anti-MBL antibody protected against neurological deficits and ischemic stroke volume. This implies that that MBL inhibition may represent a novel stroke therapy. Finally, Andreas Barrat-Due (Oslo, Norway) showed that co-inhibition of complement C5 and LTB4 (with Ornithodoros moubata C Inhibitor) combined with anti-CD14 protected pigs from *E. coli* induced sepsis. Dual therapy was better than each alone and suggest that inhibition of C5 and CD14 prevents thrombogenesis, inflammation and hemodynamic abnormalities associated with gram negative sepsis.

**Session X: Complement in Disease: Kidney & Cancer** (Chairs: Tom Mollnes & Matthew Pickering). Factor H deficiency causes glomerulopathy and kidney failure, underscoring the important regulatory function of factor H. Properdin, the only positive regulator of complement, is regarded as an attractive target for manipulation of the system. Marieta Ruseva (London, UK) presented data that unexpectedly suggested that Properdin deficiency exacerbates C3 glomerulopathy in factor H-deficient mice. This ostensibly paradoxical finding was surprising. Moreover, in a related publication by Allison Lesher in the Wenchao Song group (Philadelphia, USA), properdin deficiency also exacerbated factor H-mediated C3 glomerulopathy (PMID:23204401; importantly, these authors demonstrate in Session IX that C5 inhibition prevents fatal C3 glomerulopathy). This suggests that inhibition of properdin could be detrimental in factor H-related kidney diseases. Selene Nunez-Cruz (Philadelphia, USA) showed that C5a supports ovarian cancer development and controls the expression of VEGF164/165 isoforms (PM:23184055). The role of complement in cancer is controversial as both complement activation and inhibition might enhance tumor growth. Here, the authors document an interesting link between complement activation and neovascularization, an essential factor for tumor growth. Development of ovarian tumors in genetic susceptible mice was dependent on complement, most likely through a C5a-dependent mechanism stimulating endothelial growth. Thus, tumor growth was restricted in complement deficient mice or mice treated with a complement inhibitor.
Flash News

Use of complement regulators, CD35, CD46, CD55, and CD59, on leukocytes as markers for diagnosis of viral and bacterial infections.

Over-use of antibiotics results in selection of antibiotic–resistant microorganisms and in the unnecessary disruption of normal human microbiome in oral, intestinal, vaginal, and other environments. The paper by Jari Nuutila et al. presents results that are interesting on two levels. First, they present evidence that the patterns of membrane-bound complement regulatory protein expression on blood cells may be used to rapidly (optimally, 1 hour) distinguish between bacterial and viral infections. Second, the differences in regulator expression indicate that there are differences in how the immune system handles complement during a viral infection versus how it responds during a bacterial infection. They performed quantitative analysis of membrane-bound complement regulators, CR1 (CD35), MCP (CD46), DAF (CD55), and MIRL (CD59), on peripheral blood neutrophils, monocytes, and lymphocytes from healthy controls (n=36) and febrile patients diagnosed with either bacterial (n=21) or viral (n=26) infections. Their results show that: a) increased CD35 and CD55 levels on neutrophils and monocytes present potent markers of bacterial infection, b) increased expression of CD46 on monocytes is an indicator of viral infection, and c) increased CD59 expression on neutrophils and monocytes is a general infection marker. They further developed two novel clinical flow cytometric markers (indices), specifically, clinical mononucleosis (CM)-INDEX (incorporating CD35, CD55, and CD59 expression on lymphocytes) and clinical bacterial infection (CBI)-INDEX (incorporating CD35 and CD55 expression on neutrophils and lymphocytes), for the effective detection of viral mononucleosis and bacterial infection, respectively. In summary, bacterial and viral infections induce different expression patterns of membrane-bound complement regulators in human leukocytes, which may be effectively exploited in clinical differential diagnosis.

Reporter: Michael Pangburn

Absence of signaling into CD4+ cells via C3aR and C5aR enables autoinductive TGF-β1 signaling and induction of Foxp3+ regulatory T cells.

Liver-derived serum complement C3 and C5 are indisputably required for the detection and removal of pathogens. However, an emerging paradigm suggests that immune cell-derived and intrinsically operating complement activation fragments are key in driving and modulating adaptive immunity. For example, C3b and the anaphylatoxins C3a and C5a are generated during T cell activation by both APCs and CD4+ T cells and engage their respective receptors on these latter cell populations. Further, this complement-driven autocrine signaling is needed for successful induction T17 and T17 responses in humans and in mice. In this exciting new study, Strainic et al. deliver new evidence that links the absence of C3aR and/or C5aR engagement on T cells during tolerogenic APC/T cell interactions with a default-pathway leading to Foxp3+ regulatory cell induction in naïve CD4+ T cells. The authors show that CD4+ T cells isolated from C3aR/C5aR−/− mice produce substantially less IL-6 and IFN-γ upon activation but at the same time secrete elevated amounts of IL-10 and TGF-β and express increased Foxp3. This intrinsic TGF-β induction initiates a positive feed-back loop further stabilizing this anti-inflammatory cytokine programme. In vitro activated T cells from C3aR/C5aR−/− animals assume a stable phenotype and are suppressive in vitro and in vivo as they ameliorate established disease in a mouse model of EAE. Mechanistically, the lack of C3aR and/or C5aR-mediated intracellular signals during T cell activation prevents AKT phosphorylation and subsequent mTOR activation – events required for effector T cell induction and driven by C3aR/C5aR engagement. Importantly, pharmacological inhibition of C3aR/C5aR signaling in human CD4+ T cells also induces Foxp3+ T cells with regulative capacity. This suggests that targeting of anaphylatoxin receptors during T cell activation may be of therapeutic value in autoimmune or transplant settings.

Reporter: Claudia Kemper
Research into the proteases that activate the classical and lectin pathways of the complement system has been carried out in Prof. Rob Pike’s laboratory in the Department of Biochemistry & Molecular Biology at Monash University since the early 2000’s. Rob is highly experienced in the protease field, having actively researched these enzymes since his early postgraduate studies in the 1980’s. He has previously researched the proteases of pathogenic organisms during post-doctoral fellowships at the University of Georgia in the USA and back at his alma mater, the University of Natal in South Africa. During his third post-doctoral fellowship at the University of Cambridge in the UK, Rob became very interested in the proteases and inhibitors of the coagulation system, especially the serpin, antithrombin. This later evolved to his present interest in the similar molecules of the complement system after he moved to Monash University in 1997. Complement research now dominates the research activities of his laboratory, although he maintains an interest and collaborations into research on periodontal disease and proteases of a number of pathogens.

Rob’s research group has made a number of contributions to knowledge of the serine proteases and serine protease inhibitors affecting complement. Initially, work of his PhD students, Grace O’Brien and Felicity Kerr, was strongly focused on the specificity of the proteases, MASP-2 and C1s. More recently, his PhD student, Renee Duncan, and senior post-doctoral fellow, Lakshmi Wijeyewickrema, worked together to identify a so-called exosite on the C1s protease of the C1 complex that regulates the interaction of this enzyme with its substrate, C4. This work gelled very nicely with subsequently published structural work that demonstrated a similar exosite on the MASP-2, the enzyme with similar function to C1s in the lectin pathway. His group is actively pursuing new knowledge on each of the 5 proteases of the initiating complexes of the classical and lectin pathways, with a particular focus on their interaction with substrates and inhibitors.

**Men and Women working on Complement in ‘Down Under’**

**Professor Robert Pike’s Team**

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Dr. Trent Woodruff’s Team

Complement research began in Brisbane 20 years ago when Prof Stephen Taylor returned to Australia in 1993 at the University of Queensland. Prof Taylor had previously worked at The Scripps Research Institute, with Dr Tony Hugli who introduced him to the inflammatory complement factor C5a. In Brisbane, Prof Taylor’s group focused on developing peptide ligands of the C5a receptor, based on the C-terminus of C5a. With the help of Prof David Fairlie, this eventually led, in 1998, to the development of the first orally active cyclic peptide C5aR antagonist, AcF-[OPdChaWR], now known as PMX53.

In 2000, Trent Woodruff began a PhD in Prof Taylor’s laboratory first taking the newly developed C5aR antagonists into animal models of disease. He demonstrated the efficacy of this drug in models of arthritis, ischemia-reperfusion injuries, and inflammatory bowel disease. Following his PhD, Dr Woodruff worked for Promics Ltd, where he helped progress PMX53 to three Phase I/IIa clinical trials, where he stayed until Promics’ sale in 2006. Since then, Dr Woodruff has continued his research into complement C5a, with a focus on neurodegenerative diseases. He was the first to demonstrate a pathogenic role for C5a in models of amyotrophic lateral sclerosis and Huntington’s disease by using a newly developed lipophilic derivative of PMX53, called PMX205.

In 2010, Dr Woodruff took up an academic position and began his own laboratory at the University of Queensland as a Senior lecturer in Pharmacology, and has since attracted competitive national research funding, and expanded his group. His team now focuses on the functions of complement in the brain. Specifically their current research is examining roles for C3a and C5a in Parkinson’s disease, Huntington’s disease, amyotrophic lateral sclerosis, and ischemia-reperfusion injuries, using both cellular and animal models, as well as in patients in the clinical setting. His group is also now revealing novel roles for complement in early embryogenesis and brain development, and with Prof Taylor, has recently shown an interaction of C5a signaling in the developing murine neural tube after maternal folate deficiency. The latter studies have shown a novel and unexpected role for C5a in preventing neural tube defects in folate-stressed embryos.

He also retains an active interest in developing new drugs to target both C3a and C5a receptors to aid in the clinical translation of their work. It is the belief of the group, that complement activation, whilst essential for aspects of embryonic neural development, is also a driver of numerous degenerative brain diseases. His group aims to bring complement-mediated neuromodulation to the forefront of research into these diseases, and ultimately to trial novel targeted complement therapeutics in these conditions. Dr Woodruff’s team invites anyone interested in visiting or collaborating "down-under" to contact his group.

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Dear Colleagues,

It is a pleasure to invite you to the 14th European Meeting on Complement in Human Disease from August 17–21, 2013, which will take place in Jena, a charming university city in the state of Thuringia, located right in the heart of Germany. The European Complement Meeting is a biannual event that is being organised by active researchers in the field of complement and being held in different cities and countries all over Europe. Therefore it is both our honor and pleasure to invite researchers in the field of complement to Jena, to attend this 14th European Complement Meeting and to allow an active exchange on the timely topics in the field of complement and beyond. Jena is Germany’s “City of Science” and is home to the internationally renowned Friedrich Schiller University and several excellent research institutes.

For the 14th European Complement Meeting we are now extending this scientific spirit to provide a thrilling environment that allows scientific discussions in combination with an active university life in a historical German city. We hope that in addition to an exchange of excellent scientific ideas and new concepts you will find the time and opportunity to visit historical places in Jena as well as in the nearby located historical town Weimar, which was the European Capital of Culture in 1999.

The local scientific organising committee, Prof. Peter F. Zipfel, Prof. Gunter Wolf, Docent Christine Skerka and Dr. Teresia Hallström with the help of Conventus Congress Management, invites you to save the date and come to Jena for a fantastic meeting.

Professor Peter F. Zipfel
(for the local organizing committee)
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