Focus on Complement

March 1, 2017
Issue 45

International Complement Society

European Complement Network

Dear Readers,

Welcome to the March 2017 issue of 'Focus on Complement'. This 45th issue of FoC contains:

- **Letter from the new ICS President, V. Michael Holers**
- Bo Nilsson will review publications describing complement activation in AMD aqueous humor, and evidence for a pathogenic role for direct complement activation in intestinal epithelial cells during ischemia
- **The Complement research teams around the world** series featuring Dr Daniel Ricklin and his new laboratory in Switzerland, as well as Dr Christoph Schmidt, in Germany.
- Part II of the meeting report on the **XXVIth International Complement Workshop** that took place in Kanazawa, Japan, September 4 - 8th 2016
- **Work opportunities** in complement research
- Three upcoming **complement meeting announcements**

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).

Letter from the new ICS President: V. Michael Holers

To the International Complement Community,

It was with great pleasure that I assumed on January 1 2017 my current role as President of the International Complement Society (ICS). In the last issue, Andrea Tenner, now ICS Past President, thanked the many Councilors and other leaders whose terms have ended, and likewise I wish to add to that appreciation for the many jobs well done. I also want to thank Andrea for her outstanding tenure as President, and for her many years of service to this organization. Andrea was one of the first Councilors at the "birth" of the ICS over fifteen years ago, and has served in leadership roles ever since. We will miss her many active contributions to the ICS but wish her well and look forward to the ICW2018 that she is taking the lead in organizing! I certainly will continue to seek Andrea's superb guidance.

Another new addition to the ICS is Sheilah Jewart, for whom we are currently finalizing a role as part time Executive Director. Sheilah has extensive experience in a similar role for other professional organizations of the size of the ICS, and is bringing lots of new ideas and organizational skills to us. Hiring Sheilah is a clear example of the progress of the ICS, and we look forward to working with her to advance our field. Expect to see increased engagement and new member opportunities arise from our work with Sheilah.

As an organizational update, the new ICS Council recently held its first group conference call, using Skype to accomplish this task. Kudos especially to those Councilors at the extreme ends of the international time differences. It is unusual to have a call where both coffee and beer are appropriate accompaniments! During the call, the Council heard reports and updates from Daniel Ricklin, the new Treasurer, and Trent Woodruff, the new Secretary of the ICS. Andrea Tenner updated the group on plans for the ICW2018 in Santa Fe, including an outstanding group of potential invited speakers. Sheilah Jewart updated the group on new IRS reporting mandates and COI management approaches. New organizational funding ideas were discussed, which we hope to highlight in an upcoming FOCUS edition. It is also notable that the Council expects to have a number of proposals submitted for ICW2020; a reminder to those interested that a letter of intent is due to me by March 1 2017, and the formal proposal is due to me by September 1 2017 (please see the ICS website www.complement.org for instructions). In addition, the group heard an update from Peter Garred about the exciting upcoming European Meeting on Complement in Health and Disease in Copenhagen in September 2017, information from Andrea Tenner regarding the American Association of Immunology 2017 Complement Symposium supported by the ICS, and a progress report from Michael Kirschfink on the important Standardization Committee status and plans. As the call came to a close, the Council members began to discuss a strategic planning process, an opportunity in which we will seek broad input to help shape the future of our organization. Please feel free to email me directly at michael.holers@ucdenver.edu with ideas.

Finally, on a more personal note, I want to let our members know that recent policy changes in the United States adversely affecting travel and immigration have resulted in active work by many individuals and professional societies, including the many societies whose members thrive on scientific interchange, to re-inforce the traditional values of an American society open to international scientific and cultural exchange among individuals and institutions. It is certainly the intent of the ICS President and its leadership to follow those same values in its deliberations and actions.

NEWS FLASH (reported by Prof. Bo Nilsson, Sweden)

News Flash 1:

Local complement activation in aqueous humor in patients with age-related macular degeneration. *Schick T, Steinhauer M, Aslanidis A, Altay L, Karlstetter M, Langmann T, Kirschfink M, Fauser S.* ***Eye (Lond). 2017 Jan 27. doi: 10.1038/eye.2016.328.***

A strong association between the genotype and disease of patients with age-related macula degeneration (AMD) has been established. In this paper complement activation in aqueous humor and in plasma of patients with neovascular age-related macular degeneration (nAMD) was established for the first time. Aqueous humor and EDTA-plasma of 31 nAMD patients and 30 age-matched controls was collected. The levels of the complement 3 (C3), the regulators factor H (FH), and factor I (FI), and of the complement activation products Ba, C3a, and the terminal complement complex (sC5b-9) were measured. No significant differences were found between the nAMD group and the control group in plasma. But in aqueous humor, significantly increased levels of Ba (P=0.002), and C3a (P=0.002) indicate local complement activation in nAMD patients and a trend for a concomitant upregulation of the complement regulators FH (P=0.02) and FI (P=0.04). These findings provide strong direct evidence for a local complement dysregulation in nAMD patients in addition to the indirect evidence provided by the genotype and immunohistochemical findings. It also shows that the degree of activation can be determined in association with treatment (VEGF receptor antagonists) which suggest that complement analyses could be used for diagnosis and monitoring of the disease.

News Flash 2:

Intracellular Activation of Complement 3 Is Responsible for Intestinal Tissue Damage during Mesenteric Ischemia. *Satyam A, Kannan L, Matsumoto N, Geha M Lapchak PH, Bosse R, Shi GP, Dalle Lucca JJ, Tsokos MG, Tsokos GC.* ***J Immunol. 2017; 198:788-797.***

Ischemia/reperfusion injury is an important pathophysiological mechanism involved in a number of diseases and conditions. The extent to which ischemia contributes to ischemia/reperfusion injury has not been thoroughly studied. After careful evaluation of intestinal tissue following 30 min of ischemia, significant local mucosal injury in wild-type mice was observed. This injury was drastically reduced in C3-deficient mice, suggesting C3 involvement. Depletion of circulating complement with cobra venom factor eliminated, as expected, injury recorded at the end of the reperfusion phase but failed to eliminate injury that occurred during the ischemic phase. Immunohistochemical studies showed that tissue damage during ischemia was associated with increased expression of C3/C3 fragments primarily in the intestinal epithelial cells, suggesting local involvement of complement. In vitro studies using Caco2 intestinal epithelial cells showed that in the presence of LPS or exposure to hypoxic conditions the cells produced higher C3 mRNA as well as C3a fragment. Caco2 cells were also noted to produce cathepsins B and L, and inhibition of cathepsins suppressed the release of C3a. It was also found that mice treated with a cathepsin inhibitor and cathepsin B-deficient mice suffered limited intestinal injury during the ischemic phase. This demonstrates that significant intestinal injury occurs during ischemia prior to reperfusion and that this is due to activation of C3 within the intestinal epithelial cells in a cathepsin-dependent manner. Direct modulation of cathepsin activity may prevent injury of organs exposed to ischemia but also since cleavage of C3 by cathepsins can be regulated by intracellular phosphorylation, kinase inhibitors may also have an effect.

COMPLEMENT TEAMS AROUND THE WORLD

Two groups are newly established in Europe, both coming from Prof John Lambris' laboratory in Philadelphia. Their enthusiastic reports are presented below:

Complement in Basel, Switzerland: Dr. Daniel Ricklin's Team

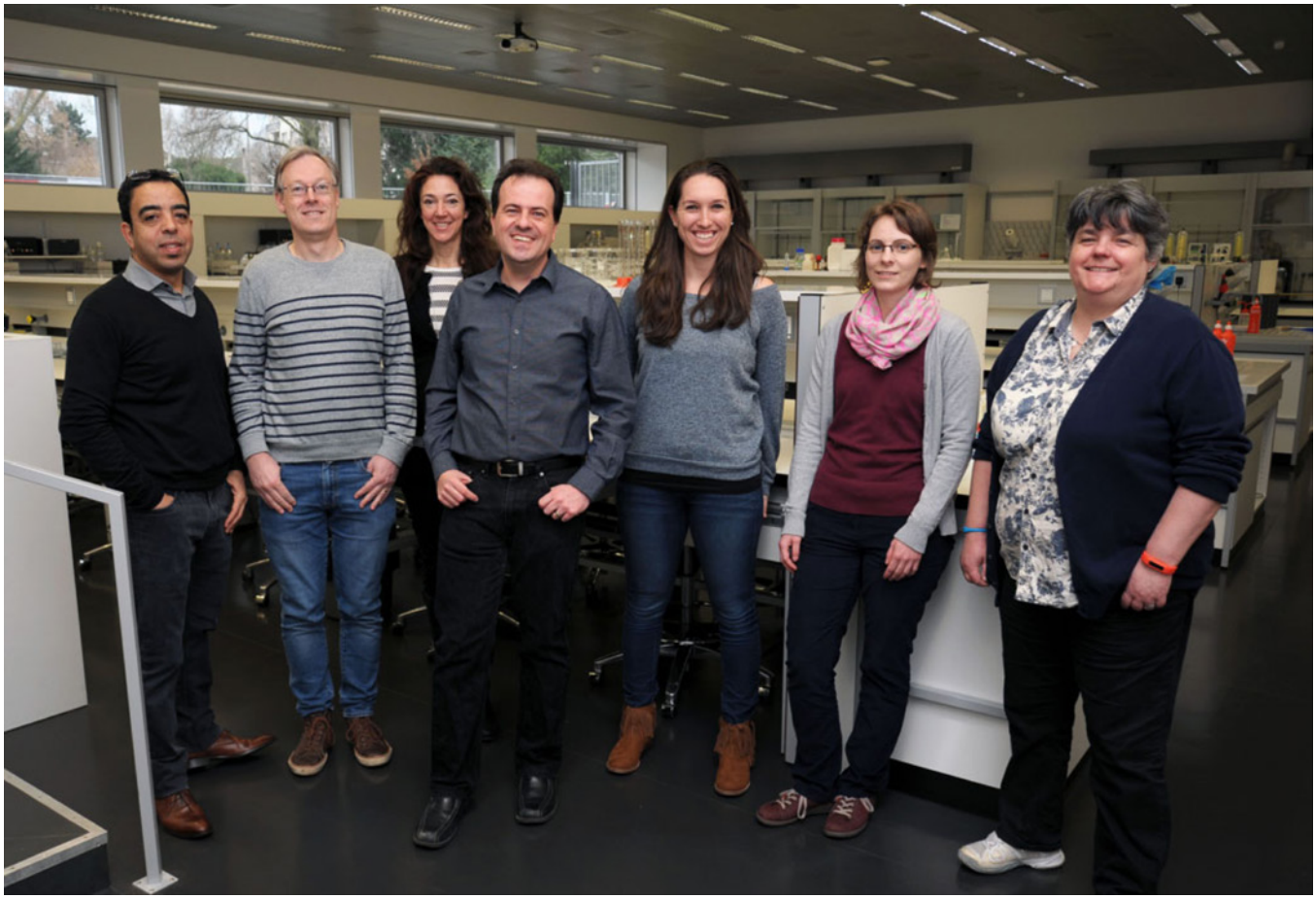
There likely are only few places that are as tightly associated with pharmaceutical innovation as the city of Basel. Located in Northern Switzerland, tucked in between Germany and France, it hosts the headquarters of several key players in Big Pharma such as Novartis, Roche and Actelion, as well as numerous regional subsidiaries, emerging Biotech and drug-related start-up companies. At the same time, Basel has a strong tradition in immunological research, featured by the former Basel Institute of Immunology and the current Friedrich Miescher Institute and the Biozentrum of the University of Basel. And of course, with laboratories as those headed by Dr. Jürg Schifferli and Dr. Marten Trendelenburg, the city also put an important mark on complement research, and hosted the XXII International Complement Workshop in 2008.

Establishing a research group focused on complement-targeted drug discovery in Basel therefore sounds like a perfect match. For me, this unique opportunity became real when the University of Basel offered a professorship in Molecular Pharmacy in the closing months of 2016. Being a pharmaceutical scientist with Swiss roots soothed the transition even if it meant to leave the great city of Philadelphia and a very fruitful research environment behind. When joining the laboratory of John Lambris at the University of Pennsylvania as a postdoctoral researcher in 2006, I immediately became fascinated by the scope and potential of complement research. While initially focusing on molecular mechanisms of C3 convertase activity and microbial complement evasion, complement-targeted drug discovery soon took center stage, especially during my activities as a Research Assistant and Associate Professor at UPenn. I very much enjoyed the chance working with John on the development and assessment of the peptidic complement inhibitor compstatin and additional therapeutic concepts that target the level of C3 activation such as the engineered regulator mini-FH and Factor H-binding peptides. Despite the ocean in between, the close and productive partnership of my group with John Lambris and the many wonderful colleagues in the USA will certainly continue.

Yet the move to Basel also opens opportunities and shapes the directions of my new group's scientific activities. Complement therapeutics will continue to be a defining element in the research program, which is termed "Therapeutic Modulation of Host Defense Pathways" and planned to extend into areas such as innate immune and coagulation crosstalk. Alongside rational drug design and screening efforts, the translation of microbial immune evasion strategies into therapeutic concepts will mark an area of interest. Taking over the Molecular Pharmacy group at the Department of Pharmaceutical Sciences in January 2017 from Prof. Beat Ernst, a specialist in the field of glycomimetic drugs and selectin antagonists, provided invaluable resources concerning personnel and infrastructure. The core team of my group accumulates decades of experience in medicinal chemistry, expression/purification of lectins and other targets, and instrumental analytics (SPR, ITC, LC-MS, NMR) that can be directly translated to the new research topic and facilitate molecular approaches reaching from small molecules and peptides to engineered proteins. In addition to chemistry and biology labs and infrastructure, our group also maintains cell culture and S2 lab facilities. Importantly, the extensive expertise in glycobiology and chemistry may also pave the way to projects exploring and/or exploiting the many protein-carbohydrate interactions that define complement activity in health and disease. The location of the group in the Pharmacenter of the university offers great potential for collaboration with specialists covering key areas such as molecular modeling,

natural product screening, drug transport and pharmacokinetics, drug delivery and formulation, pharmacology, toxicology and clinical development. And having the University Hospital of Basel, the Swiss Tropical Institute, the Biomaterials Science Center and many academic and industrial partners available at an arm's length may certainly shape translational aspects.

Initial efforts, though, will of course focus on establishing projects, models, technologies and key assays, especially with respect to complement and host defense pathway activity/inhibition. With a great core team set and ready to go, the group and its projects will continue to expand in the coming months. We are therefore very much looking forward to discussing ideas and opportunities with collaborators and students/postdocs interested in joining us on these new endeavors.



From left to right: Dr. Said Rabbani (Biology), Dr. Oliver Schwardt (Synthesis), Claudia Huber (Administration), Prof. Daniel Ricklin (Head of Group), Dr. Rachel Hevey (Synthesis), Dr. Brigitte Fiege (Bioanalytics), and Bea Wagner (Synthesis, Technical Support). Not on the picture: Kevin Widmer (PhD candidate, Biology).

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Complement in Ulm, Germany: Dr. Christoph Schmidt's Team

The group of Dr Christoph Schmidt is based at the Ulm University Medical Center in Germany. One of the group's primary goals is to understand the structure-function relationships that govern the regulatory activity of several natural complement control proteins. The focus lies on regulators controlling the initiation and amplification processes of the complement convertases at the centre of the complement cascade. While originally mainly focused on the alternative pathway regulator Factor H (FH), the group recently started investigating the common features shared between basically all convertase-directed complement regulators. Aspects of this project entail how these "catalytic-like" regulators, which maintain a high regulatory turnover rate without getting consumed, target to C3-activation fragments to control complement convertases. The insights gained with this project have been directed towards the rational, modular engineering of artificial complement control proteins that surpass natural regulators in controlling the complement cascade (e.g. miniFH vs. FH).

Another long-standing interest, pursued through a close collaboration with Waihong Tham's lab in Australia, lies in unravelling the interplay between the complement system and malaria parasites. Recently, a collaborative study led by Dr Schmidt has unravelled that C5 inhibition by different clinically developed inhibitors is overridden by strong complement activation.

The group continues to be fascinated by the interface between basic and applied science. Understanding the functioning of natural complement regulators and effectors and their potential future exploitation will remain a core interest to the group.

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ICW 2016 Meeting Report

Below is PART II of the summaries of the Scientific Sessions and Lunchtime Seminars of the 26th ICW in Kanazawa, Japan (September 4th to 8th 2016), each composed by the respective chair persons.

SCIENTIFIC SESSIONS

SESSION VII: Receptors

Chairs: Rick Wetsel (Houston, USA) and Marina Botto (London, UK)

This was a very interesting session focusing on novel insights into the cellular-specific expression and biological role(s) of the anaphylatoxin receptors: C3aR and C5aRs. The session started with a novel study presented by Jörg Köhl in collaboration with Anna Czabanska, which examined the impact of C3a and C5a on central and peripheral circadian rhythms (abstract 141). Their findings showed that double KO mice ($C3aR^{-/-}/C5aR1^{-/-}$) as well as fibroblasts from these mice exhibited an extended circadian cycle, suggesting that C3a/C5a modulate both the suprachiasmatic nucleus driven central clock as well as functions of the peripheral clock. In addition, this group showed that the C5a/C5aR1 axis controls the circadian fluctuation of macrophages and $CD11b^{+}$ cDC levels in the lung. From this presentation, it is clear that continued studies in the area of complement and circadian rhythms should prove very interesting. Yves Laumonnier then presented a study that used a novel Td-Tomato-C3aR reporter knockin mouse to examine and compare C3aR expression in myeloid versus lymphoid cells (abstract 109). Their findings showed that in contrast to C5aR1 expression, C3aR is more restricted in expression within the myeloid lineage and appears strongest in $siglecF^{-}$ tissue macrophages. This new knock-in mouse should prove useful (along with other knock-in mice from this group as well as others) to clarify and further delineate the cells that express C3aR in healthy and diseased tissues. In keeping with the novel data of this session, Anna Valeska Wiese presented her work examining the impact of a previously unrecognized vacuolated eosinophil cell (vEOS) population during allergic pulmonary disease in the context of the C5a/C5aR1 axis (abstract 153). Her findings made a strong case for vEOS in driving many of the pro-inflammatory properties during allergic lung disease and that C5a/C5aR1 signaling was important in homing of vEOS from the lung to mLN for activation of T-cells. From these data, a case was made for targeting C5aR1 on vEOS as a therapy for the treatment of the effector phase of asthma. The next study presented by Sayaka Sato (abstract 129) illustrated the usefulness of deleting the C5ar1 gene in a cellular-specific manner to investigate the role(s) of this key molecule in models of lung injuries. The study also highlighted the lack of C5aR1 expression in mouse T cells (CD4 and CD8), a topic that remains controversial. The session ended with a very interesting presentation by Patrick Biggins (abstract 43) describing the neuroprotective effects of C5aR2/C5L2 in a model of spinal cord injury. The study complemented previous work from the same group (Dr Marc Ruitenberg) showing the injurious role of C5aR1 during the acute phase of injury.

SESSION VIII: Complement and Disease II
Chairs: Matthew Pickering (London, UK) and Santiago Rodriguez de Cordoba (Madrid, Spain)

Work on two mouse models of atypical hemolytic uremic syndrome (aHUS) were presented and discussed. Kate Smith-Jackson (Newcastle, UK, abstract 13) reported the initial characterization of novel knock-in mouse model in which a gain of function aHUS-associated human C3 mutation was introduced in mice. Interestingly, whilst homozygote mice recapitulated a very severe form of the disease with C3 consumption and documented renal impairment and glomerular TMA, heterozygote mice are completely normal. This is an interesting model to study aHUS triggering factors and therapeutic approaches upstream of C5. Yoshiyasu Ueda (Pennsylvania, USA, abstract 128) presented new data on their aHUS mice model, carrying a prototypical FH C-terminal mutation, to show the beneficial aspects of knocking down properdin in this model. Of interest, their data illustrate the two faces of properdin in complement-related disorders and how these opposite roles relate to the site of complement activation. Héctor Martín Merinero (Madrid, Spain, abstract 152) reported the development of an analytical strategy for the routine analysis of *CFH* gene variants, which they apply to the analysis of 28 previously uncharacterized *CFH* gene variants from the aHUS and C3G Spanish registry. Their data revealed both the existence of functionally relevant variants outside the conventional FH functional regions. They also illustrate the potential pitfalls of the prediction algorithms when gene variants are located within these FH regions. Finally, Ying Jie Ma (Copenhagen, Denmark, abstract 195) presented interesting new data suggesting that collectin-12 confers protection against *N meningitides* by interacting with PTX3, which promotes properdin deposition on the bacterial surface and AP complement activation.

SESSION IX: Host-Pathogen Interaction
Chairs: Anna Blom (Lund, Sweden) and Sanjay Ram (Boston, USA)

Rick Wetsel (abstract 95) showed that C3a and C5a, acting via their respective receptors, suppress type I interferon production in response to *Listeria monocytogenes* infection and its secondary messenger molecule, c-di-AMP. IFN suppression was dependent on Bruton's Tyrosine Kinase, p38 MAPK and TANK-binding kinase 1. The next presentation, by Christian Karsten and colleagues (abstract 87) then shared a novel role for the C5a-C5aR axis in controlling *Toxoplasma gondii* infection. IL-12 and IFN-γ levels were markedly decreased in C5aR1 and C5aR2 deficient-mice infected with *T. gondii*, which was associated with increased parasite burden in the brain and a higher mortality. Interestingly, dendritic cells from C5aR1 KO mice released similar levels of IL-12 as DCs from wild-type mice when stimulated with *T. gondii*, suggesting that C5a probably affected migration of effector cells to the brain or the interaction of DCs with IFN-γ producing NK or T cells was impaired. Complement evasion by malarial parasites was discussed by Alexander Kennedy (abstract 56), who showed that *Plasmodium falciparum* merzoites recruited FH and FHL-1 through a surface protein called Pf92 to evade complement. *P. falciparum* merozoites also bound C1 INH via *Pf*MSP3.1 to block C1s function and classical pathway activation. Ya-Ping Ko and colleagues (abstract 32) then furthered our understanding of complement evasion by *Staphylococcus aureus*. The cell wall-anchored *S. aureus* proteins Bbp and SdrE selectively blocked the AP by binding to C3b in the C3 pro-convertase (C3bB) complex and prevented FD from cleaving B to Bb and to generate functionally active convertase. Nicole Thielens (abstract 66) described an interaction between human ficolin-1 and sialylated moieties of the mucin domain of Ebola surface glycoprotein. Intriguingly, ficolin-1 enhanced infection of Vero cells and human monocyte-derived macrophages by wild-type Ebola virus, pointing to a novel virulence mechanism. The session was then closed by a presentation from Insu Hwang (abstract 190) who showed that binding of collectin kidney 1 (CL-K1) to *Streptococcus pneumoniae* enhanced C3 deposition in bacteria. CL-K1 knockout mice did not effectively clear *S. pneumoniae* from their lungs and suffered more severe pulmonary inflammation and greater mortality compared to wild-type mice indicating an important role for this lectin in host defenses against this pathogen.

SESSION X: Complement and Disease III
Chairs: Bo Nilsson (Uppsala, Sweden) and Reinhard Würzner (Insbruck, Austria)

In the first presentation, Ronald Taylor (abstract 3) described a novel technique to improve complement activation by IgG antibodies, which is based on specific point mutations in the Fc domain that enhance IgG hexamerization. He showed that these antibodies result in efficient CDC under complement component-limiting conditions thereby demonstrating a strategy for improved complement-mediated immunotherapy. The second presentation focused on mechanisms underlying the pathogenesis of age-related macular degeneration (AMD), which is associated with an overactive complement system. One of the main ocular target cells for complement activation is the retinal pigment epithelial (RPE) cells. Bärbel Rohrer (abstract 177) showed that anaphylatoxins can signal directly via their respective receptors in RPE cells and that C5aR engagement dominates/reverses C3a-receptor-mediated responses thereby possibly controlling the magnitude of the RPE injury responses. David Ermert (abstract 126) then presented data from a collaboration between Malmö and Worcester on a Factor H-IgG fusion protein as a novel therapeutic against group A streptococcus (GAS) infections. This fusion protein comprises domains 6 and 7 and 18 through 20 of Factor H, fused to a human IgG1 Fc backbone. They could show that the Factor H-IgG fusion protein prevents host Factor H binding to GAS, but also activates complement, leading to enhanced bacterial cell killing. In the final presentation of the session, Per Nilsson (abstract 162) from a Norwegian-Swedish collaboration investigated the question whether properdin binding is primary or dependent on initial C3 activation. Their data challenge the view of properdin as a 'danger' recognition molecule by showing data, which rather support the role of properdin as a stabilizer of the C3bBb convertase on endothelial cells or bacteria – as a trimer.

Lunchtime seminar II: Marco Cicardi (University of Milan, Italy)
Angioedeme due to C1 inhibitor deficiency: from research on complement to treatments tailored to patients. ***Chair: Michael Kirschfink (University of Heidelberg, Germany)***

In his excellent 'lunch talk' Marco Cicardi, currently the leading expert in the field of angioedema, presented a comprehensive overview, elegantly bridging the first discoveries of C1 inhibitor (C1-INH) to our current knowledge on the potentially life-threatening hereditary angioedema (HAE). It was between 1957 and 1961 when Lepow and coworkers, in the lab of Louis Pillemer at Western Reserve University in Cleveland, identified the enzymatic nature of the C1 complex and its regulatory protein C1-INH. Virginia Donaldson, in the same lab, later discovered that the deficiency of this protein segregates with angioedema symptoms in families affected by HAE, a genetically transmitted disease already described by William Osler in 1888. Starting from these seminal discoveries it became clear that C1-INH regulates proteases also outside of the complement system. For example, it has also a pivotal role in maintaining the homeostasis of the contact system where it inhibits the enzymatic activities of plasma kallikrein (PK) and active factor XII (FXIIa) and via this preventing cleavage of high molecular weight kininogen (HK) and release of bradykinin. Episodic local activation of the contact system on endothelial cells overlaying cutaneous and mucosal vessels results in angioedema symptoms. Patients with hereditary C1-INH deficiency are particularly exposed to local contact system activation and angioedema mediated by bradykinin. This nonapeptide binds specific receptors (bradykinin B2 receptor, B2R) that activate the intracellular nitric oxide pathway with phosphorylation of intracellular actin, retraction of inter-endothelial cell junctions (tight and adherence junctions), increase in permeability and edema formation. This sequence of events accounts for angioedema symptoms with attending mortality, for laryngeal edema, and morbidity for inability accompanying cutaneous and gastrointestinal recurrent edema. HAE patients may suffer from rare to weekly episodes of angioedema (average 1-2 per month), each lasting from two to five days.

Unraveling the pathogenetic mechanisms leading to bradykinin release allowed the development of tailored therapies for this condition. HAE patients can now use therapies to revert or prevent angioedema symptoms. Plasma derived and recombinant C1-INHs are available as intravenous treatment of acute attacks. The B2R antagonist icatibant and the recombinant plasma kallikrein inhibitor ecallantide are registered as subcutaneous treatments of attacks. These treatments are highly effective and reduce the length of an angioedema attack from an average of forty hours to about ten hours. Prophylaxis of angioedema attacks relies on oral alkylated androgens used since 1975. They are effective, but need careful monitoring due to side effects and potential liver toxicity. In 2009, one plasma-derived C1-INH preparation was registered for long-term prophylaxis, given intravenously twice per week. This treatment is highly effective with the main limitation related to venous access. Specific therapeutic approaches based on individual needs should be designed to optimize cost/benefit ratio.

The future of HAE already sees new upcoming approaches for symptoms prophylaxis. A subcutaneous formulation of plasma derived C1-INH just completed a large 'phase 3 study'. As an alternative to C1-INH replacement therapy, drugs targeted to block plasma kallikrein have been produced using different technologies. Most advanced in development is a fully humanized monoclonal antibody against plasma kallikrein, now in phase 3. A small molecule that binds the reactive site of plasma kallikrein is currently tested in a dose-ranging study to evaluate the efficacy, safety, tolerability, pharmacokinetics, and pharmacodynamics. Other products are completing preclinical phases.

In conclusion, starting in the fifties complement research allowed understanding the mechanisms underlying angioedema symptoms due to C1-INH deficiency and opened the route for developing therapeutic approaches that drastically improved the lives of patients.

SESSION XI: Adaptive Immunity
Chairs: John P. Atkinson (Saint Louis, USA) and Seppo Meri (Helsinki, Finland)

The session on adaptive immunity discussed cellular responses to complement anaphylatoxins, integrins and mRNAs. Mariann Kremlitzka (Budapest, Hungary, abstract 18) showed that stimulation of human B-cells with a TLR9 receptor agonist leads to increased transcription and intracellular production of C3aR. Treatment with C3a (or C3a desArg) increased proliferative responses but inhibited MAPK activation and cytokine production thus, assumingly, suppressing inflammation. Inhibition of the uptake of CpG oligonucleotides by C3a was suggested as a potential mechanism. This was followed by a presentation from Pooja Shivshankar (Houston, USA, abstract 202), who used co-culture and vascular trans-well culture systems to demonstrate that C3a/C3aR1 and C5a/C5aR1 signaling affects human vascular endothelial cell integrity and migration. Human B-cells further enhanced the transmigration. In co-culture, B-cells became activated and attached to C3a-activated endothelial cells, whereas T-cells differentiated into Th1-type cells. Anaphylatoxin-activated endothelial cells can thus activate B-cells and polarize T-cells. Christian Karsten (Lübeck, Germany, abstract 388) employed $C5aR^{-/-}$ mice to describe the role of C5a/C5aR in homing of natural IgM antibody producing B1 cells from spleen into peritoneum. C5 was produced by peritoneal macrophages and cleaved to produce C5a. C5a promoted synthesis of CXCL13 to mediate homing of B1 cells. In $C5aR^{-/-}$ mice, this process was interrupted as B1 cells remained in the spleen and differentiated into nIgM- producing plasma cells. Martin Kolev (London, UK, abstract 143, and the 'Complement Trainee Award' winner) reported that the LFA-1 integrin interaction with endothelial ICAM-1 induced intracellular C3 expression in human T cells upon direct contact or during migration through an endothelial cell layer. LFA-1 acted like a co-stimulatory ligand during TCR activation leading to increased IFN-γ production. It was speculated that the LFA-1/ICAM-1 interaction during extravasation could 'license' immune cells for effector functions via intracellular C3a generation. Finally, Yaron Hillman (Tel Aviv, Israel, abstract 112) reported differential expression of miRNAs in complement-resistant versus -sensitive human cancer cell lines. In particular, miR-150 mediated resistance to complement-killing by the MAC, whereas miR-328 and miR-616 made cells more susceptible to CDC. It remains to be shown what the targets are for these miRNAs. However, the primary outcome appears to be that of increasing the resistance to damage by complement.

SESSION XII: Complement-Mediated Inhibitors: Therapeutic Intervention
Chairs: Michael Holers (Denver, USA) and Wenchao Song (Philadelphia, USA)

There were 5 presentations in the last scientific session of the Workshop entitled "Complement-mediated inhibitors: therapeutic intervention". The session started with a presentation by Sandip Panicker from True North Therapeutics on its clinical stage anti-C1s mAb, TNT009, for the treatment of primary cold agglutinin disease (CAD) (abstract 89). Efficacy data were presented from a phase I trial involving 5 CAD patients, with results supporting further clinical development of TNT009. Paul Tamburini from Alexion then presented data on the design and preclinical characterization of ALXN1210, an engineered and improved version of the humanized anti-C5 mAb Eculizumab (abstract 63). Site-directed mutagenesis of the CDRs and Fc region of Eculizumab was utilized to increase the efficiency of endosomal and FcRn-mediated recycling. ALXN1210 was shown to have >3 times longer half-life than the parent mAb, making it possible to be used at monthly instead of bi-weekly frequencies for PNH and aHUS patients. Damodar Gullipalli from the Song laboratory at the University of Pennsylvania presented data showing the efficacy of anti-properdin mAbs in preventing alternative pathway complement-mediated intravascular and extravascular hemolysis (abstract 176). Data were presented on transgenic mouse models and from ex vivo hemolytic assays of paroxysmal nocturnal hemoglobinuria (PNH) erythrocytes, providing proof of concept for anti-properdin mAbs as a potentially improved therapy over Eculizumab for PNH, given that the latter does not prevent extravascular hemolysis. In the fourth talk, Richard Pouw from the University of Amsterdam (abstract 59) described an interesting anti-FH mAb that enhances FH binding to C3b, thereby potentiating FH activity on host cells. This mAb was able to rescue impaired activity of mutant FH of aHUS patients and appeared to be as effective as Eculizumab in a hemolytic assay. The session concluded with a presentation from the session co-chair Michael Holers of the University of Colorado (abstract 179) on a novel mAb that blocks C3d:CR2 interaction and its therapeutic efficacy in a murine model of lupus. The mAb, directed to the C3d ligand rather than CR2, was shown to effectively ameliorate proteinuria and autoantibody production in MRL/lpr mice and holds promise as a potential new therapeutic approach in patients with systemic lupus erythematosus (SLE) and other autoantigen-driven diseases.

ANNOUNCEMENTS

ALEXION PHARMACEUTICALS

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

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

Qualifications:

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

COPENHAGEN 2017
16th European Meeting on
COMPLEMENT
IN HUMAN DISEASE

On behalf of the organizing committee, Professor Peter Garred invites members of the complement community and beyond to the 17th European Meeting on Complement in Human Disease. The meeting will take place in Copenhagen, Denmark from September 8th to 12th 2017.

For opening dates for abstract submission, the preliminary program, accommodation and travel information, please see ***http://emchd2017.dk***

Introducing the Program for the AAI ICS Symposium:
"**21st Century Complement: Beyond the Textbooks"**

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http://www.immunology2017.org/scientific-program/

Speakers:

Jörg Köhl, M.D., University of Lubeck, Germany and Cincinnati Children's Hospital
Complement as a potential clinical driver and therapeutic target in Gaucher's Disease.

Baerbel (Barb) Rohrer, Ph.D., Medical University of South Carolina
Complement and Age Related Macular Degeneration – anaphylatoxins and RPE signaling

Rick A. Wetsel, Ph.D, Institute of Molecular Medicine, University of Texas Medical School, Houston,
Complement Response to Listeria monocytogenes: Modulation of an Intracellular Beta-Interferon Response Pathway

Suzan H. M. Rooijakkers, Ph.D., Medical Microbiology University Medical Center Utrecht, Nl.
Complement Activation as a target for combating infections.

Dear colleagues,

Please find the final program of the *6th International meeting* on "**HUS & related disorders**" held in Innsbruck-Igls, June 11-13, 2017 at: http://www.hus-online.at/de/Conference3_en.html where you can register and submit an abstract for a short oral presentation or a poster.

Abstract deadline: April, 15, 2017.
Further details in the program.
Fees: Reception, lunches and Tyrolean dinner are included in the registration fee!

Best regards,
Reinhard Würzner, MD, PhD
Congress President HUS Meeting 2017

COMPLEMENT REAGENT RESOURCES