



**International
Complement Society**

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the Experts!™*

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

ics@complement.org
www.complement.org

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**Focus on
Complement**

Issue #53

Editor

Trent Woodruff

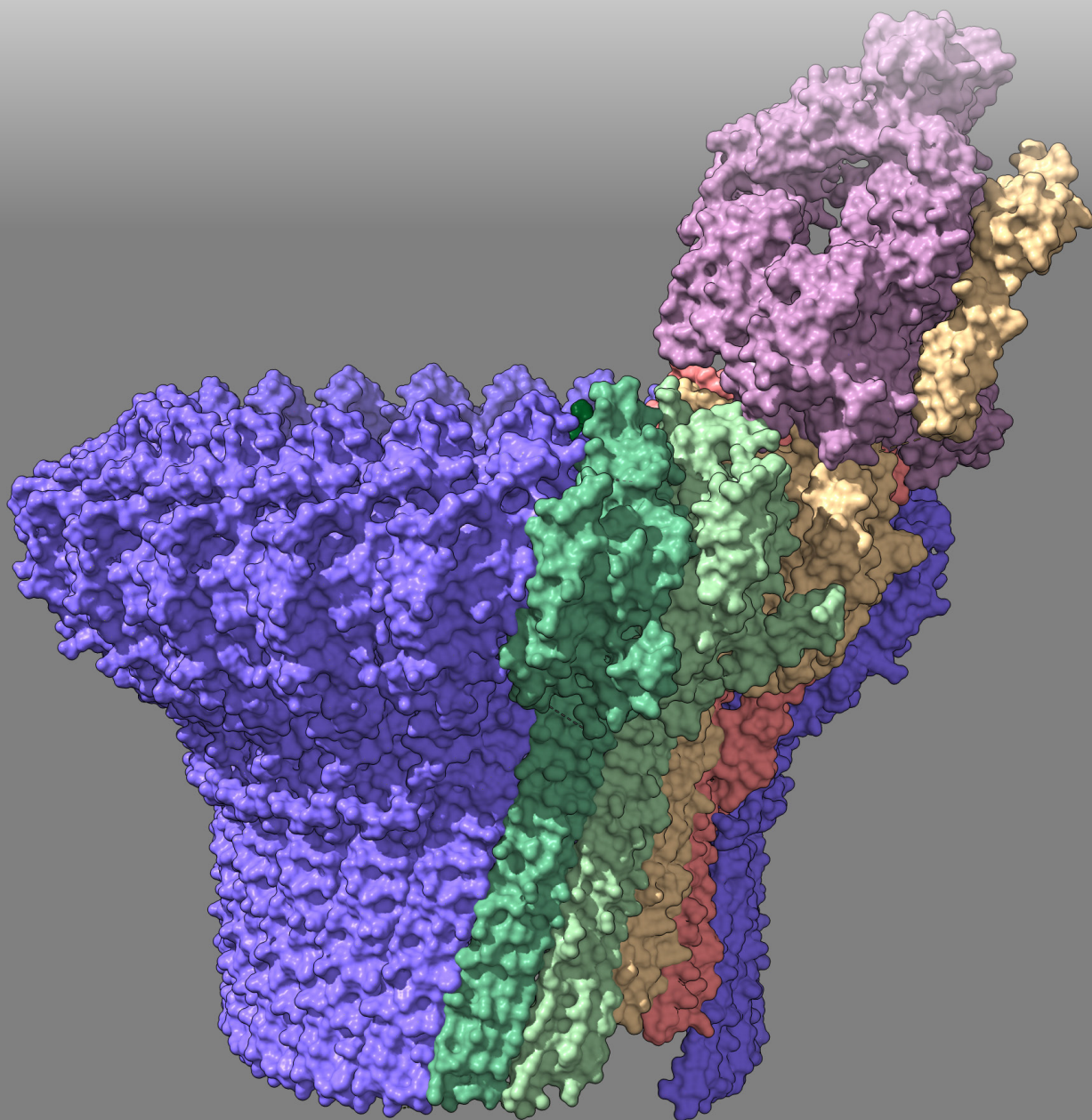
Issue Contributor

Nobutaka Wakamiya

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Dear Readers,

Welcome to the 53rd Issue of *Focus on Complement* – the official newsletter of the International Complement Society (ICS).

In this issue we highlight two research groups from Japan, Prof Norimitsu Inoue (Wakayama) and Prof Masashi Mizuno (Nagoya). Issue contributor Nobutaka Wakamiya reviews two research articles on eculizumab therapy in Guillain-Barré syndrome patients, and complement pathomechanisms in atypical hemolytic uremic syndrome. We also welcome our new ICS President Peter Garred, who provides a message to the ICS community.

We congratulate Anaïs Menny, who is the winner of the first FoC Young Investigator Cover Image Award for 2019. A description of Anaïs' research and cover image description can be found in the following pages.

Finally, we present the second and final installment of summaries for each of the scientific sessions of the 27th International Complement Workshop, prepared by the Session Chairs.

I hope you all enjoy this first *Focus on Complement* for 2019.

Trent Woodruff, PhD.

Editor, FoC

Secretary, ICS

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 Peter Garred (Peter.Garred@regionh.dk).

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

 www.complement.org

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Prof Peter Garred, President, ICS

Dear Colleagues, I am very honored to have been elected to succeed Michael Holers as president of the ICS for the next 2 years. Michael's contribution as president has been invaluable. Fortunately, he continues as past president and as chairman of our Industry Relations Committee and I look forward to our further cooperation and his service for the Society. A big thank you also go to Denise Tambourgi and Bo Nilsson who have done an excellent job as councilors, but now leave the ICS board after the term of office and a big welcome to our two new council members Zoltan Prohaszka and Leendert Trouw as well as Claudia Kemper who is our new president elect. I also want to thank Andrea Tenner for her service to the ICS, and her lead role of organizing the XXVII Complement Workshop that took place in Santa Fe in September 2018. It was a terrific meeting, very well organized, which really showed that the complement field is expanding and more alive than ever. Another important person for our Society is our Executive Director Sheilah Jewart who has become the glue of our organization and that has brought many new ideas and important initiatives to our community. At the organizational level the new ICS Council recently held its first group conference call by video link to accomplish this task, which has become a very useful tool to easily and more frequently arrange councilor meetings, since our members are spread around the world. At the meeting, Santiago Rodríguez De Córdoba presented the details of the 17th European Meeting on Complement in Human Disease to be held in Madrid in September 2019 (<http://www.emchd2019.com>) as did Peter Zipfel who updated the council with the upcoming XXVIII Complement Workshop to be arranged in Berlin in September 2020 (<https://www.icw-conference.de>). Both conferences are something to look forward to. The call for bids for the 2022 Workshop is open and instructions on how to apply is described on our webpage (<https://www.complement.org>).

As a deeper understanding of the complement system in health and disease will continue, new

complement related therapies and diagnostic tools will be developed. Since many new complement drugs are in the pipeline, our young researchers, which are highly skilled and trained in complement, will become attractive candidates for the growing numbers of companies that have complement related drugs in their armament. This will hopefully accelerate the translation of basic complement knowledge into a clinically applicable setting. Thus, to strengthen the profile of ICS we have developed the slogan "Complement...We are the Experts™" as a trademark that we will use in future branding of ICS and our researchers.

A new initiative that recently has been launched is the scientific youth organization, Young Complement Investigators (YCI), that has been started as a collaboration between the International Complement Society and the European Complement Network (www.facebook.com/YoungComplement). The YCI will work to engage young researchers in the complement field. They will share information about science, job opportunities, fellowship-calls, as well as social activities and arrange gatherings and meetings to discuss complement related matters. The ICS will support and encourage the YCI, and I wish them the best success. I find it important that we support young researchers in their career path to become independent complement researchers and lay the foundation for new complement research groups around the world, and to strengthen the old ones.

New non-canonical roles of the complement proteins are being reported almost monthly in the literature, with surprising biological impact, that may lead us to rethink many old dogmas about the cascade and how the complement system interplays with other biological systems. I hope that during my tenure we can strengthen the society and our community both to spread the knowledge about complement, but also to stimulate the relationship between basic and clinical research and Industry to create the necessary ecosystem to turn complement research discoveries into clinical applications.



Anaïs Menny: Winner of the Focus on Complement Young Investigator Cover Image Award



Anaïs Menny is a post-doctoral researcher in Doryen Bubeck's group at Imperial College London. After defending her PhD on the conformational dynamics of ion channels at the Pasteur Institute in Paris, she joined the Bubeck lab to investigate how complement proteins interact with the lipid bilayer during assembly of the membrane attack complex (MAC). By integrating structural biology and biophysical experiments she has discovered that assembly precursors comprise an integral part of MAC's irregular β -barrel pore and play an important role in changing biophysical properties of MAC's membrane environment.

The membrane attack complex (MAC) is the direct killing arm of complement that acts by forming large pores in target cell membranes. Here, we use high resolution cryo electron microscopy to understand the structural flexibility of MAC and to derive the first atomic model for the complete pore. The structure shows differences in length and charge properties of MAC pore β -hairpins alter physical properties of the membrane to lyse cells and provides a general mechanism for how proteins cross lipid bilayers.

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 2 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 (for example 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 Wakayama, Japan *The group of Prof Norimitsu Inoue*

Our complement research was initiated in Osaka University when Dr. Inoue was a Ph. D. student and a research associate under the supervision of Prof. Taroh Kinoshita, who focused on the pathogenesis of paroxysmal nocturnal hemoglobinuria (PNH). In PNH patients, Red blood cells are deficient in two complement regulators, CD55 and CD59, which are linked to the cell surface membrane via glycosylphosphatidylinositol (GPI). We clarified that Phosphatidylinositol glycan-A (PIGA), whose somatic mutations cause GPI deficiency in PNH, is a subunit of enzyme complex involved in the first step that produces N-acetylglucosaminyl-phosphatidylinositol (GlcNAc-PI) in the GPI biosynthesis. Furthermore, we identified other genes involved in not only the reaction of GPI biosynthesis but also other steps. Then Dr. Inoue moved to Research Center, Osaka International Cancer Institute that is located in the middle of Osaka city, where we focused on the molecular mechanisms of clonal expansion of PNH cells. In PNH patients, some CD55- and CD59-deficient hematopoietic stem cells clonally expand and sometimes occupy almost all granulocytes and monocytes. We have identified genes involved in the clonal expansion.

The Japanese Association for Complement Research (JACR) was established in 1985 and it has been organizing meetings annually. From 2015, as a project of JACR, Prof. Wakamiya of

the JACR president and Dr. Inoue of the vice president began to develop comprehensive examination system for complement-related proteins and genes to elucidate the pathological mechanisms of complement-related diseases such as congenital complement deficiencies, atypical hemolytic uremic syndrome, secondary thrombotic angiopathy, C3 nephropathy, and hereditary angioedema. We collected blood and urine samples from patients with complement-related disease. For the protein analysis, we have established the examination system of 15 factors including C3, C4, CH50, sC5b-9, Ba, CFH, CFI, CFH-Ig, C1-inhibitor and C5. For the genetic analysis, we have examined 136 genes using a next-generation sequencer. Until now, we have analyzed more than 200 patients with various complement-related diseases. In future, we will establish several disease registries and biomaterial bank of patients with complement-related diseases in Japan.

Since January 2019, Dr. Inoue has just moved as a professor to Department of Molecular Genetics, Wakayama Medical University, which is located to the south of Osaka near Kansai International Airport. During the next 10 years, we would like to focus on the pathogenesis of diseases caused by abnormal complement-regulatory mechanisms and try to develop effective examination system to diagnose these diseases.



The members of Dr. Inoue's group in Osaka International Cancer Center



The members of Dr. Inoue's group in Department of Molecular Genetics, Wakayama Medical University

Contact information:

Dr. Norimitsu Inoue
Department of Molecular Genetics,
Wakayama Medical University
811-1 Kimiidera, Wakayama 641-8509, Japan
Tel: +81-73-441-0607
E-mail: inoue-no@wakayama-med.ac.jp



Complement Research in Nagoya University, Japan

The group of Prof Masashi Mizuno

Our complement (C) research work was originally started by Prof. Seiichi Matsuo in the 1980s' at Nagoya University. The initial studies primarily focused on roles of membrane C regulators (CRegs) in the kidney and also on their associations with the pathogenesis of renal diseases. Currently, the research targets at our laboratory have extended to the roles of CRegs and C activation in various tissues under pathological conditions through translational and/or clinical research work.

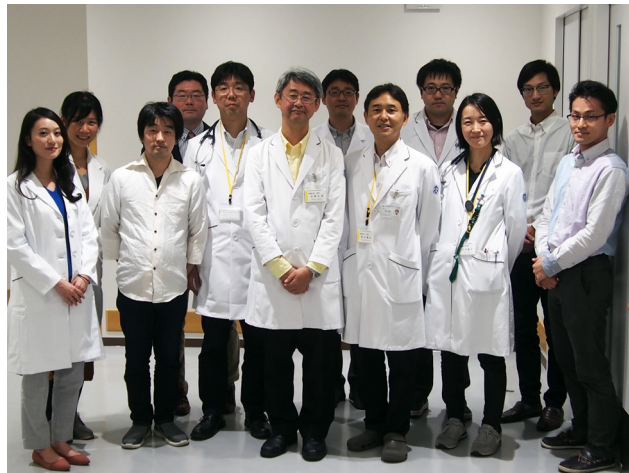
In recent decades, one of our main tasks is research to improve the prognosis of peritoneal dialysis (PD) therapy and to distribute PD, to enhance the clinical applications of PD, and education of physicians and other medical staff in Japan. To meet these objectives, unique C research focusing on roles of the C system in the field of PD is being conducted at our laboratory, as in the world. Briefly, we clarified important roles of CRegs in maintaining homeostasis

in the peritoneum. We are also continuously researching how each factor related to PD therapy will modify the C system in the host peritoneum. We have investigated whether or not progressive peritoneal injuries are related to modification of peritoneal CRegs. The goal is to clarify the development, progression and treatment of lethal encapsulating peritoneal sclerosis (EPS) due to peritoneal injuries in PD patients. We are investigating complement activation products in PD fluid to investigate adequate C-related biomarkers, with a focus on the development of anti-C therapy to prevent and improve peritoneal injuries, including EPS.

We are also interested in mechanisms of the balance of C activation and regulation in acute/chronic kidney diseases, such as C3 nephropathy. To this end, we are conducting a nation-wide cohort study in Japan, as a complement research project of the Japanese Society for Complement Research and with the Japanese Society of Nephrology. In addition, we are interested in marine envenomation-related renal injuries and activation of the C system.

Since several decades, we have collaborated with other institutions both within and outside Japan. In particular, B. Paul Morgan (UK), Claire Harris (UK), and Prof. H Okada (Japan) have been important collaborators in resolving our research questions.

In the past, present and future, our aim has been and will continue to be contribution to C research work.



Contact information:

Prof. Masashi Mizuno

Renal Replacement Therapy, Nagoya University Graduate School of Medicine

65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan

E-mail Address: mmizu@med.nagoya-u.ac.jp; Tel: +81 (52)744-2205



Safety and efficacy of eculizumab in Guillain-Barré syndrome: a multicentre, double-blind, randomised phase 2 trial

Misawa, Kuwabara, Sato, Yamaguchi, Nagashima, Katayama, Sekiguchi, Iwai, Amino, Suichi, Yokota, Nishida, Kanouchi, Kohara, Kawamoto, Ishii, Kuwahara, Suzuki, Hirata, Kokubun, Masuda, Kaneko, Yabe, Sasaki, Kaida, Takazaki, Suzuki, Suzuki, Nodera, Matsui, Tsuji, Koike, Yamasaki, Kusunoki; Japanese Eculizumab Trial for GBS Group.

Lancet Neurol. 2018 Jun;17(6):519-529.

Guillain-Barré (GB) syndrome is an acute neuropathy that often occurs after infection. Most patients become severely disabled and unable to walk within a few days of onset, with 20–30% requiring assisted ventilation. Over 50% of patients with the need for artificial ventilation will recover independent ambulation within 6 months with only supportive therapy. However, in severe cases, despite receiving plasmapheresis and immunoglobulin treatment, many patients still have an incomplete recovery. Consistent evidence supports that GB syndrome is an autoimmune disease caused by an immune reaction against infectious agents which share antigens with nerves. In this article, Misawa and the Japanese Eculizumab Trial for GBS (JET-GBS) Study Group reported that the safety and efficacy of eculizumab, a humanized monoclonal antibody against C5, in patients with severe GB syndrome. This study was a 24 week, multicenter, double-blind, placebo-controlled, randomized phase 2 trial performed at 13 hospitals in Japan (Clinical Trials. gov, number, NCT02493725). Eligible patients with GB syndrome were aged 18 years or older and could not walk independently (GB syndrome functional grade 3-5). 34 patients were randomly assigned (2:1) to receive 4 weeks of intravenous immunoglobulin plus either eculizumab (900 mg) or placebo. At week 4, the proportion of the patients able to walk independently (primary endpoint) (functional grade ≤ 2) was 61% (90% CI 42-78; n=14) in the eculizumab group, and 45% (20-73; n=5) in the placebo group. At 24 weeks, the proportion of the patients able to run (secondary endpoint) (functional grade ≤ 1) was 74% (95% CI 52-90; n=17) in the eculizumab group, and 18% (2-52; n=2) in the placebo group. Adverse events occurred in all 34 patients. Three patients had serious adverse events, including anaphylaxis, and intracranial hemorrhage and abscess in the eculizumab group. The possibility that these serious adverse events were related to eculizumab could not be excluded. The primary outcome measure at 4 weeks did not reach the predefined response rate, but at 24 weeks, the secondary outcome showed a clear response. This report suggests that the complement inhibition by eculizumab might have the potential to suppress complement-mediated nerve damage and safely facilitate clinical recovery in patients with severe GB syndrome. It also suggests that the efficacy and safety of eculizumab could be investigated in larger, multinational, randomized controlled trials.



Hyperfunctional complement C3 promotes C5-dependent atypical hemolytic uremic syndrome in mice

Smith-Jackson K, Yang Y, Denton H, Pappworth IY, Cooke K, Barlow PN, Atkinson JP, Liszewski MK, Pickering MC, Kavanagh D, Cook HT, Marchbank KJ

J Clin Invest. 2019 Feb 4. pii: 99296. doi: 10.1172/JCI99296

Atypical hemolytic uremic syndrome (aHUS) is a renal disease that encompasses the clinical triad features of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. Dysregulation of the alternative pathway of the complement system at the cell or extracellular matrix surface is a major factor in susceptibility to aHUS. Approximately 60% of individuals with aHUS have mutations, which occur either in the genes encoding complement-regulating proteins such as factor H (FH), factor I (FI), and membrane cofactor protein (MCP) or in genes encoding complement-activation proteins (C3 and factor B). aHUS is frequently associated in humans with loss-of-function mutations in complement-regulating proteins or gain-of-function mutations in complement-activating proteins. However, there remains a need for better model of complement-mediated diseases to trial drugs and dissect the molecular pathways that are common among complement-associated diseases. In this paper, Kate Smith-Jackson et al. tried to perform the transfer of human C3 gain-of-function aHUS-associated mutations to murine C3. Following in vitro characterization of these murine C3 mutants, they introduced a point mutation in murine C3 (p.D1115N) in conditional knockin mice. Homozygous C3 p.D1115N (C3KI) mice developed spontaneous chronic thrombotic microangiopathy with hematuria, thrombocytopenia, elevated creatinine, and evidence of hemolysis. Mice with active disease had reduced plasma C3 with C3 fragment and C9 deposition within the kidney. Therapeutic blockade or genetic deletion of C5, a protein downstream of C3 in the complement cascade, protected homozygous C3KI mice from thrombotic microangiopathy and aHUS. Thus, their results provide in vivo modeling evidence that gain-of-function changes in C3 drive aHUS. They also show that long-term C5 deficiency is not accompanied by development of other renal complications (such as C3 glomerulopathy) despite sustained dysregulation of C3. Thus, this study indicates that this preclinical model will allow testing of novel complement inhibitors with the aim of developing precisely targeted therapeutics that could have application in many complement-mediated diseases.

Young Complement Investigators



As a brand-new initiative, the scientific youth organisation, Young Complement Investigators (YCI), has been established with endorsements from the International Complement Society and the European Complement Network.

The purpose of the YCI is to provide a platform where young researchers in the complement field are in focus. The YCI is run by a committee (see below), and currently provides information about leading science in the field, job opportunities, fellowship-calls, as well as social activities. Follow the weekly updates on social media, and participate in shaping the complement society via Twitter: @YoungComplement and Facebook: www.facebook.com/YoungComplement. For general enquiries about YCI, please contact Martin (details below).

CONTRIBUTE your science: Recently published a paper relevant to the complement field? Submit your work for “Paper of the week”, and have a shot at being nominated as “Scientist of the month!” For ideas and contributions on social media, please contact Nikolaj or Inkeri.

JOIN US: At our annual YCI meetings and events where we bring young scientists together to discuss developments in the field, share protocols, socialise and build new collaborations.

- 7-9th of June, 2019: YCI annual meeting in Luxembourg!
- 14-17th of September 2019: Join us at the EMCHD meeting in Madrid.
- 13-17th of September 2020: Participate in our event at the International Complement Workshop in Berlin.

Keep an eye on Facebook or follow the link below for details:

https://docs.google.com/document/d/e/2PACX-1vRzC_fkaGOp_QSYeWhhtZy1JH98QQDL-pIJgxn_N3uswwjo0rE9Sr5UPuWhqU-FPyR3H5Xi2ZbRn-00/pub

For further information about meetings and events, please contact Nicole.

The current committee:

Chair: Dr. Martin P. Reichhardt, Oxford, United Kingdom: martin.reichhardt@path.ox.ac.uk
 Ms. Nicole Schäfer, Regensburg, Germany: nicole.schaefer@ukr.de
 Mr. Nikolaj Kirketerp-Møller, Copenhagen, Denmark: nikolaj.kirketerp-moeller@regionh.dk
 Dr. A. Inkeri Lokki, Helsinki, Finland: inkeri.lokki@helsinki.fi





27th International Complement Workshop (Session Summaries Part 2)

SESSION VII – Genetic and Protein Variances in Human Disease

Chairs: Santiago de Cordoba (Madrid, Spain) and Joshua Thurman (Colorado, USA)

Talks in this session presented several novel findings linking variants in complement genes with disease. Agustin Tortajada described a C3 genetic variant, R735W that has been identified in both aHUS and C3G patients. The variant is in the C3a region of the protein and results in hyperactivation of C3. The authors are examining whether the variant also affects the C3a-mediated response to infection. Dr. Fremeaux-Bacchi reviewed the results of complement gene analysis in patients with HUS. The authors found no differences in the frequency of rare variants among controls, patients with Stx positive-HUS, and patients with secondary HUS. In patients with Hypertensive Emergency-associated HUS, however, the rate of rare genetic variants (51%) was similar to that found in patients with aHUS (67%), suggesting that complement may mediate injury in hypertension-associated disease. A. Inkeri Lokki presented a study looking at complement variants in women from two Finnish cohorts who developed preeclampsia. They found 21 variants, 10 of which were in the genes for factor H or factor H-related proteins. The factor H variants were associated with early onset or severe disease. Laura Lucientes Continente studied the role of complement in ANCA-associated vasculitis (AAV). The authors identified the FB-R32 polymorphism as a novel AAV risk factor. Their data also suggested a role for the terminal pathway in the disease pathogenesis and that plasma FHR-1 levels may provide a marker of renal function recovery. In the last presentation of the session, Ewelina Golec presented data showing that CD59 is expressed intracellularly by pancreatic islet cells and is necessary for insulin secretion. Experiments demonstrated that different regions of CD59 mediate MAC inhibition and insulin secretion. A non-GPI anchored form of CD59 remained in the cell cytosol, and trafficking to this compartment was dependent on N-glycosylation of the protein.



27th International Complement Workshop (Session Summaries Part 2)

SESSION VIII – C3G and aHUS

Chairs: Michael Holers (Colorado, USA) and Viviana Ferreira (Ohio, USA)

The presentations in the scientific session entitled “C3G and aHUS” focused on emerging data relevant to the complement-mediated diseases C3 Glomerulopathy (C3G) and atypical Hemolytic Uremic Syndrome (aHUS). The session started with a presentation by Anuja Java from Washington University in St. Louis on the role of Factor I (FI) variants identified in patients with aHUS. Using functional assays, she was able to sub-divide the FI molecular changes as likely pathogenic or benign, providing further understanding of genotype-phenotype relationships in this disease. Hongsu Kim from the University of Pennsylvania then presented an analysis of the relative roles of the membrane attack complex (MAC) as compared to the anaphylatoxin C5a on the development of renal injury and macrovascular thrombosis in a murine model of aHUS. Unique effects were demonstrated for each effector pathway. In the third presentation, Jin Chen from the University of Toledo described a key role for properdin in the development of hemolysis in an ex vivo model of paroxysmal nocturnal hemoglobinuria (PNH) and in vitro model of aHUS, and also showed that inhibition of properdin exhibited a lower IC₅₀ than inhibitors of Factor B, C3 or C5. The next presentation by Marina Noris from the Mario Negri Institute described a microplate/western blot assay that specifically quantifies C3bBb and the C3 proconvertase C3bB for investigating the mechanisms by which C3NeFs carry out their effects in patients with primary immune complex-MPGN and C3G. The data showed different mechanisms of complement dysregulation. In the fifth presentation, Kishor Devalaraja-Narashimha from Regeneron Pharmaceuticals described therapeutic effects of C5 and C5 inhibitory antibodies in two novel genetic models of C3G, one which leads to dysregulated complement activation by replacing mouse C3 gene with human C3 (C3hu/hu) in mice, while the other model is a FH deficient rat. In the final presentation, Damodar Gullipalli from the University of Pennsylvania described the generation and evaluation of AAV-based gene transfer to deliver an engineered mouse FH construct in a murine model of lethal C3G. The data show that AAV-based gene transfer of engineered FH may be a feasible approach for treating complement-mediated diseases such as C3G.



27th International Complement Workshop (Session Summaries Part 2)

SESSION IX – Pros and Cons of Factor H and FHR Proteins

Chairs: Peter F. Zipfel (Jena, Germany) and Veronique Fremeaux-Bacchi (Paris, France)

Nikolina Papac-Milicevic from Vienna in Austria reported on a new genome wide association study which identified the two FHR proteins, FHR1 and FHRE3 as competitors for Factor H binding to pro-inflammatory MDA adducts. This new genomic study substantiates the role of Factor H as a ligand for modified lipids and provides a very clear explanation of why FHR1-FHR3 deficiency is protective in the retinal disorder age related macular degeneration. In the second talk Sarah Irmscher from the Leibniz Institute in Jena, Germany identified a new role of the FHR1 protein as an inducer of sterile inflammation. FHR1 upon binding to necrotic cells triggers the inflammasome and this link is relevant in human diseases, in particular in ANCA vasculitis. In the third talk Nicole Schäfer from the University Hospital in Regensburg Germany showed an activating effect of FHR3 in the activation of the complosome in retinal pigment epithelia cells. She demonstrated that FHR3 when internalized influences transcription and expression of central complement and immune components both in terms of induction and in inhibition. These three reports highlight the role of FHR proteins in several human disorders. The presentation by Delu Song from the University of Pennsylvania in Philadelphia, USA showed a study with transgenic mice that express a Factor H variant with Arg1206 in retinal thrombosis and ischemic retinopathy. The investigators crossed these mice with C5a receptor deficient or C6 deficient animals which allowed the dissection of which effector branch of activated complement contributes to pathological features. Jennifer Laskowski from the University of Colorado, Denver, Co, USA showed relevant data on the new role of Factor H in the hepatic inflammation cancer axis. Absence of Factor H triggers inflammation and spontaneous hepatic carcinogenesis. Thus Factor H being an established complement inhibitor shows new functions which are related to disease.



27th International Complement Workshop (Session Summaries Part 2)

SESSION X - Complement Therapeutics

Chairs: Michael Kirschfink (Heidelberg, Germany) and Claire Harris (Newcastle, UK)

To overcome complement resistance to the attack of complement Ron Taylor (Charlottesville) found a significant enhancement of the CLL killing potency of antibodies against CD37 and CD20 upon IgG hexamerization, allowing optimal C1q binding. He also pointed to the important role of Ca^{2+} for CDC. Shanawaz Ghouse (Texas Tech University Health Sciences Center) presented a novel promising approach to interfere with early angiogenesis, which contributes to the premetastatic niche. In a mouse breast cancer model, inhibition of the C5aR1, which regulates premetastatic angiogenesis through the recruitment of pro-angiogenic myeloid-derived suppressor cells (MDSC) synergized with anti-angiogenic vaccines leading to reduced metastasis and improved anti-tumor immunity. Tamar Grossman (Ionis Pharmaceuticals) presented preclinical data which illustrated the ability of factor B antisense (ASO) to knock-down factor B in mice and monkeys and to ameliorate a mouse model of Lupus Nephritis. The agent targets the liver and reduces levels of circulating factor B, raising possibilities for systemic therapy in man which may overcome the challenge associated with high target concentrations associated with blocking complement at the protein level. In the following talk, Michael McCaleb, also from Ionis, illustrated the progression to man and presented phase 1 clinical data of factor B ASO. The data from the multiple ascending dose study confirmed that factor B ASO could substantially reduce circulating levels of protein and indicated that treatment was safe. Multiple subcutaneous dosing of 20mg reduced levels of circulating factor B by 72% and decreased alternative pathway activity (ex vivo hemolysis). Moving from treatment of a common disease to rare diseases, Dror Mevorach from Hadassah-Hebrew University (Jerusalem) discussed the use of eculizumab in treating syndromes caused by complete deficiency of CD59 or CD55. While the precise mechanism leading to the accompanying syndromes (GBS & PLE) are not fully elucidated, it is clear that blockade of C5 has a profound therapeutic effect in these patients pointing to a role of C5a and/or MAC in pathogenesis. The final talk of the session was given by Ali Alawieh from Medical University of South Carolina, who showed the dramatic therapeutic effect achieved by 'homing' complement control proteins to damaged tissue, in this case, to a post-ischemic marker in a mouse model of stroke. While previous data from this group have highlighted the therapeutic potential of such drugs in a multitude of models, the data presented dramatically illustrated that the homing therapy had potential to modulate chronic inflammation for many weeks after the initial insult, thus providing a brake to chronic as well as acute inflammation.



27th International Complement Workshop (Session Summaries Part 2)

SESSION XI - C3a/C5a Mediating and Modulating Inflammatory Responses

Chairs: Trent Woodruff (Brisbane, Australia) and Bo Nilsson (Uppsala, Sweden)

In the first presentation, Ning Ma (Xi'an, China) presented evidence that the C3a receptor mediates protection from the development of atherosclerosis in the ApoE^{-/-} mouse model. C3aR deficiency in ApoE^{-/-} mice led to more severe atherosclerosis phenotypes and systemic and aortic inflammatory responses, furthering the evidence for anti-inflammatory roles of C3a in vivo. The next talk by Johanna Neeb (Luebeck, Germany), examined functional roles for C5aR2 in natural killer (NK) cells. Uterine NK expressed C5aR2, and surprisingly, C5aR2 deficiency caused increased uterine IFN-gamma, and increased fetal resorptions during pregnancy. Ranjit Sahu (Charlottesville, USA) then presented evidence that C5aR1 contributes to kidney fibrosis. Using Foxd1-cre mice crossed with C5aR1GFPfl/fl mice, it was shown that conditional deletion of C5aR1 from Foxd1 stromal cells reduces pathology in a kidney fibrosis model, correlating with reduced inflammatory responses of kidney pericytes. The next very interesting presentation was presented by Marlies Bode (Hamburg University, Germany). It concerned the damages that are associated with hypertension and that those are not only a result of hemodynamic injury but also damage caused by the innate immune system. The same group has previously shown that KO of the C5aR1 protects against renal injury in murine hypertensive models. Now they demonstrate that KO of C5aR2 instead increases the injury indicating that this receptor has a protective role in two different hypertensive models. Riccardo Sfriso (Bern, Switzerland) presented data on complement-mediated rejection in pig-to-baboon cardiac xenotransplantation. In a model using pigs with combined KO of the Gal antigen and hyperexpression of human CD46 and thrombomodulin together with an optimized immunosuppression protocol, it was demonstrated that both complement and coagulation activation was significantly inhibited as reflected by low immunoglobulin, C4b/c, C3b/c and fibrin deposition. These findings were correlated with a much prolonged survival. The final presentation by E Farris Langley (Charleston, USA) concerned traumatic brain injury (TBI). The same group has previously shown, using injury-site targeted inhibitors (CR2-Crry, CR2-fH, CR2-CD59), that inhibition of C3 activation ameliorated neuronal loss in a murine model. In this study using the same model, it is demonstrated that complement activation continues for more than 3 months and that if CR2-Crry is given 30 days after the injury combined with rehabilitation therapy an improvement in motor and cognitive tasks occurs. This indicates that C3 activation is associated with chronic neuroinflammation after TBI, and if inhibited can improve cognitive functions.

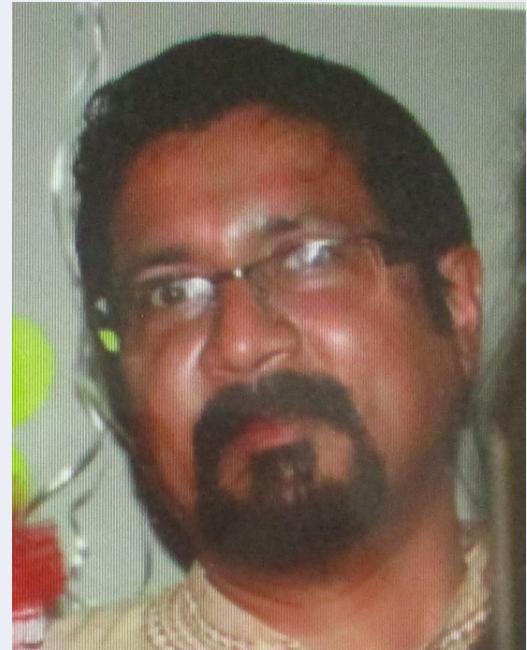


Obituary

Dr. Purushottam Jha

It is with great sadness that we announce the passing of Dr. Jha earlier this year. Dr. Purushottam Jha was born in the state of Bihar in India and received his Ph.D. from the Department of Microbiology and Immunology, University of Louisville School of Medicine in the early part of this century. He co-authored 4 Pubmed listed publications with his graduate school research mentor Prof. Girish J. Kotwal. Other co-authors included Professor William G. Cheadle and the late Professor David E. Justus of Louisville and Dr. Scott A. Smith, currently a faculty at Vanderbilt University, Nashville, TN. He did post doctoral research at the Kentucky Lions Eye Center of the Department of Ophthalmology in Louisville with Dr. Nalini Bora and moved with her group to Arkansas as Research Assistant Professor. Purushottam co-authored 22 Pubmed listed publications with Drs Bora and Bora. Overall, he made a significant contribution to the understanding of the role of complement in human diseases such as arthritis, macular degeneration and uveitis. Until his passing away in late 2018, he was a Research Associate at Harvard Medical School. He was recently diagnosed with hypertension. The cause of death was believed to be a cardiac arrest. His body was cremated in Boston, MA and his ashes will have been immersed in the Ganges from the banks in Haridwar, India. He is survived by his mother and his wife Bharati Mata and daughters Vaishali and Vanshika. He was in his mid 40s and his passing away has been shocking to his many friends and family. He was a very special one of a kind energetic and friendly person.

Contributed by Prof Girish Kotwal



Dr Purushottam Jha



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 lncRNA 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



17TH EUROPEAN MEETING ON
COMPLEMENT IN HUMAN DISEASE
EMCHD 2019
MADRID, SEPTEMBER 14 – 17, 2019



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

Local Organizing Committee:

Santiago Rodríguez De Córdoba (Chair)

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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

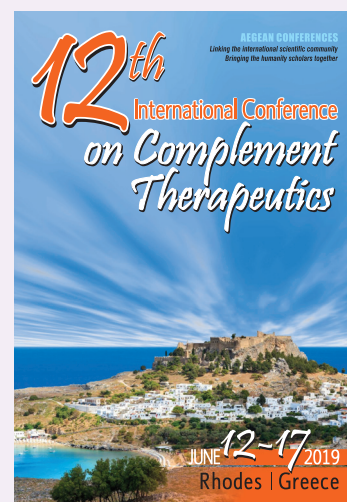
[CLICK HERE](#)



12th International Conference on Complement Therapeutics

The field of complement-targeted drug discovery has experienced a 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.



Organizing Committee:

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**12th - 17th June 2019
Sheraton Rhodes Hotel**

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





CompTech

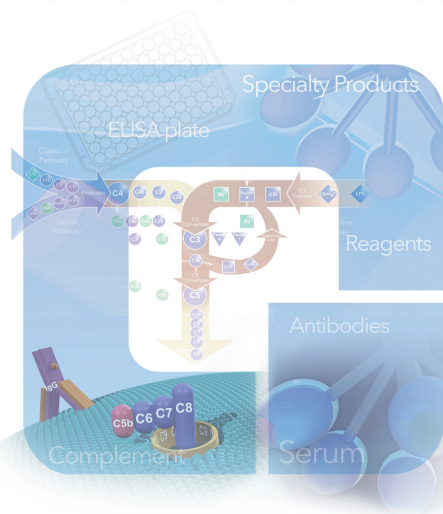
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