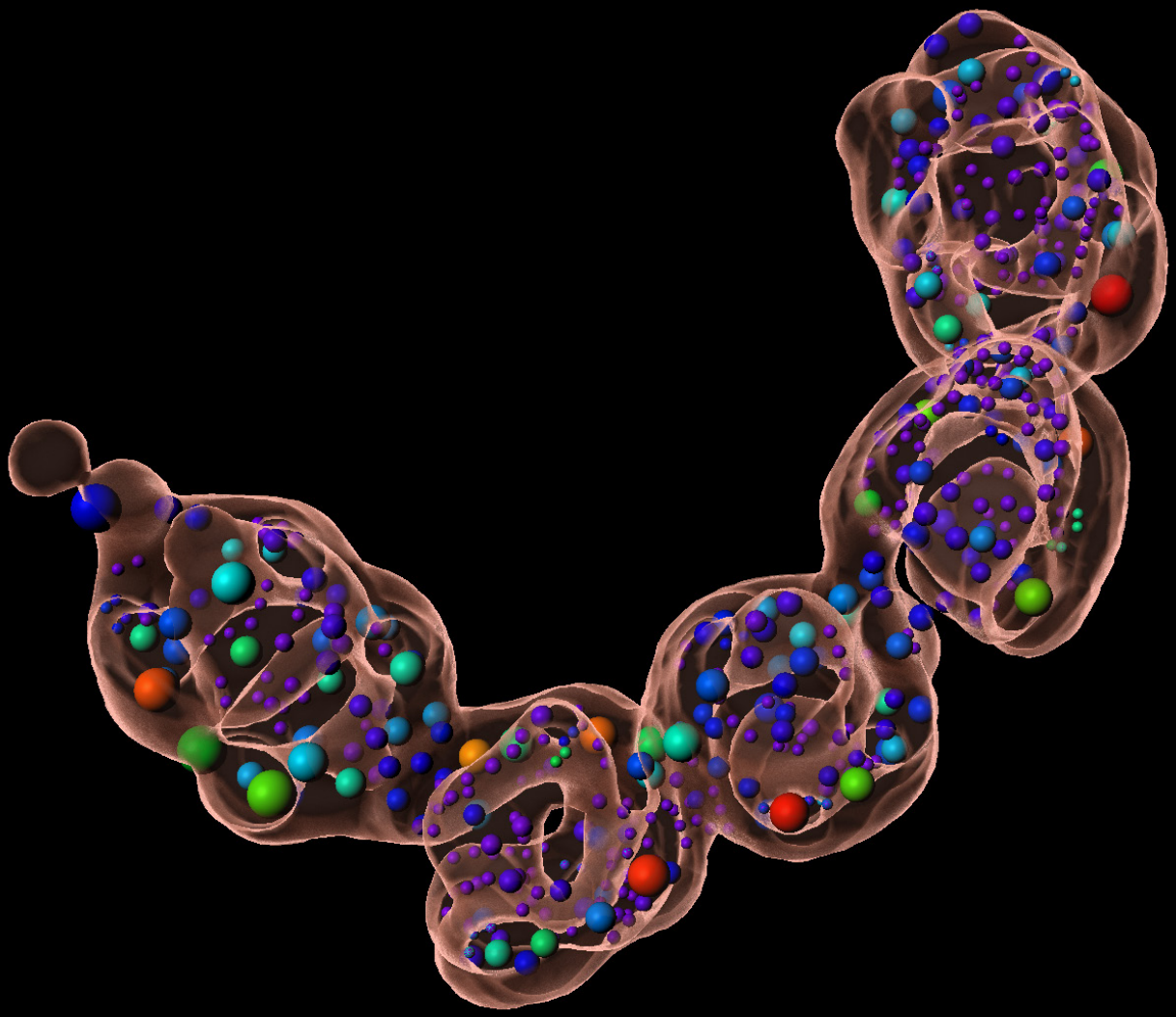
Focus on Complement

ISSUE #64 DECEMBER 2021



International Complement Society

"Complement...we are the Experts!™"

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Focus on Complement

Issue #64

Editor
Trent Woodruff

Issue Contributor
Viviana Ferreira

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From the Editor

Dear FoC Readership,

I welcome you all to final edition of *Focus on Complement* for 2021 – the official newsletter of the International Complement Society (ICS).

Next year I will be handing over the reigns of ICS Secretary to another ICS member. Therefore, this will be the final FoC issue with myself as Editor. FoC has now been running for over 15 years, with 63 published issues. We've highlighted 115 complement laboratories, and summarised >120 complement research articles. In 2018, we also introduced a new FoC format, and initiated a FoC Early Career Cover Image award, which I am delighted to say has presented 14 awards to ECRs to date - a summary panel of these images over the years is found on the following pages.

In this 64th issue of FoC, we now congratulate Dr. Cláudia Vilhena who is the next winner of the FoC Early Career Cover Image Award. A description of Cláudia's research and cover image can be found on the next page.

We feature research groups from Massachusetts, USA, and Pennsylvania, USA. Issue contributor Dr. Viviana Ferreira reviews two articles that summarise work describing complement biomarkers in renal cancer, and SARS-CoV-2 complement-kinin system interactions.

We also hear from outgoing President, Dr. Peter Garred, who provides an overview of ICS activities under his Presidency.

Before I sign off, I wanted to thank all the fantastic members from the ICS Council who contributed content to the issues over the years - without your efforts, this newsletter would not be possible.

Professor Trent Woodruff
Editor, FoC Secretary, ICS

Connect with the ICS

If you would like to contribute 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 @complementsoc

Dr. Cláudia Vilhena: Winner Focus on Complement Early Career Cover Image Award

Profile of Dr. Cláudia Vilhena: After completing my PhD in Microbiology at the University of Munich, Germany, I started my postdoctoral studies at the lab of Prof. Dr. Peter Zipfel from the Leibniz Institute for Natural Product Research and Infection Biology, Jena, Germany at the Department of Infection Biology. Both during my PhD and my postdoc, I focused on the interface between bacteria and the host, namely the cell-wall and how bacterial proteins interact specifically with the human complement system in order to promote immune system evasion. I perform super-resolution microscopy to address the dynamic organization of the cell wall and changes on the cell division cycle.

The attached image is entitled: "Streptococcus pneumoniae complement evasion protein PspA at the super-resolved level". The image was generated by myself within the Department of Infection Biology. The bioinformatics and systems biology evaluation was performed by the Department of Applied Systems Biology, both Leibniz Institute for Natural Product Research and Infection Biology, Jena, Germany.

The human pathogenic bacterium S. pneumoniae strategically and symmetrically positions the complement evasion protein PspA at the surface. S. pneumoniae was challenged with normal human serum and the position of the complement-evasion protein PspA was visualized using super-resolution 3D- Structured Illumination Microscopy (SIM). The original microscopic image was further evaluated by bioinformatics approach. The pneumococcal cell wall was reconstructed and is shown in transparent orange color. Each ball represents a PspA protein cluster. The color of each ball (rainbow pattern) reflects the fluorescence intensity of that cluster (the higher the intensity the warmer the color). The size of the balls correlates with the distance to the nearest neighbors. In consequence bigger balls are further separated from the next clusters; reversely, smaller balls are in closer proximity to neighboring clusters.

The ***Early Career 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.

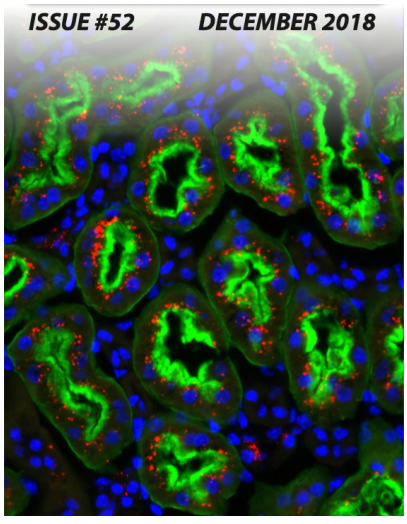
Eligibility: graduate students, post-doctoral staff, and early career researchers (generally, but not exclusively under 40 years of age) are eligible to apply.

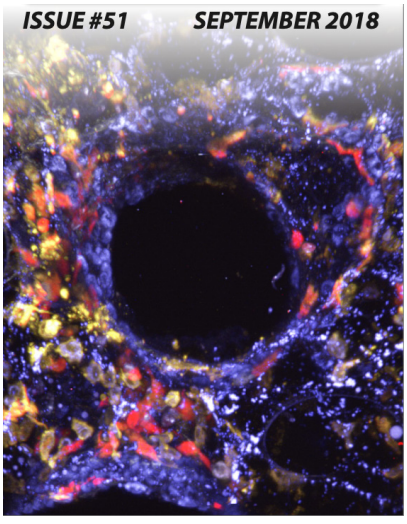
Interested applicants should email the FoC Editor (t.woodruff@uq.edu.au) at least 2 weeks prior to each issue production date (1st March, 1st June, 1st September, 1st December), with one suggested image of their research. Images could include immunochemistry (tissues, cells, etc.), pathology, structures, 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).

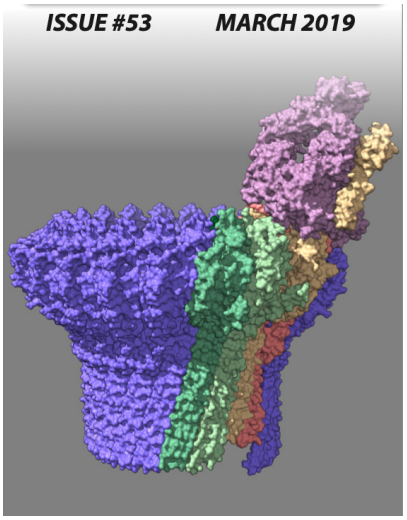
Winners of the Award will receive a $50 Amazon gift card, and a signed certificate from the ICS.

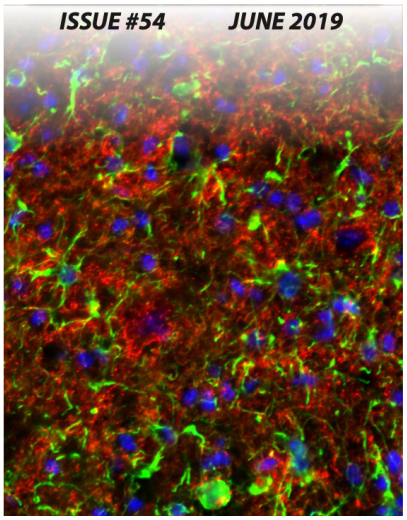
Cover Image Award

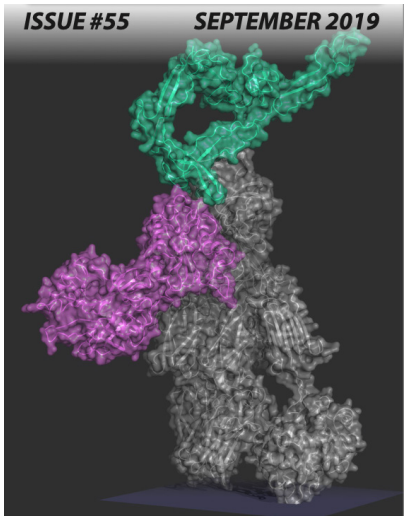
A collection of FoC Issue ECR Winning Covers over the years

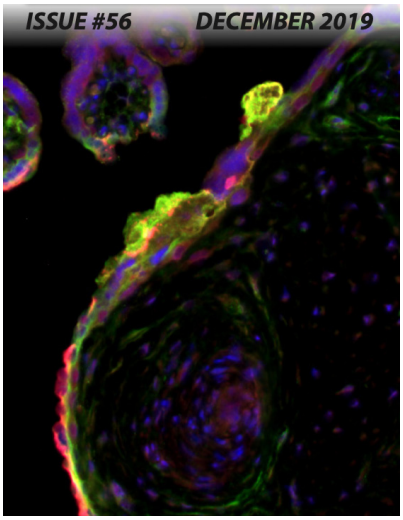


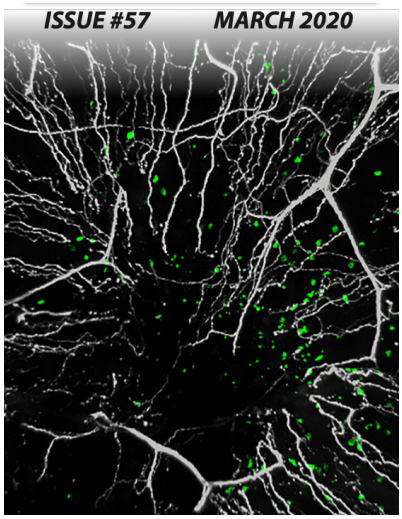


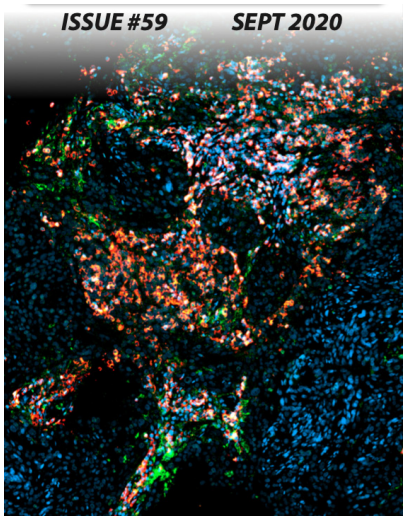


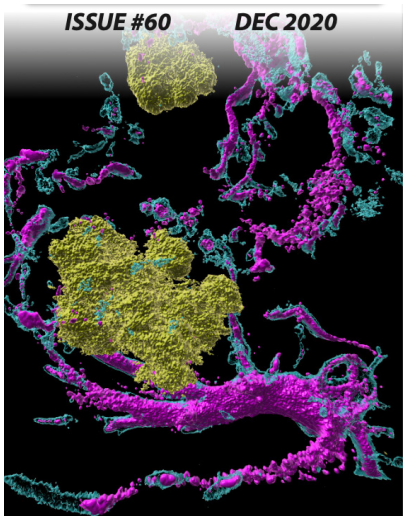


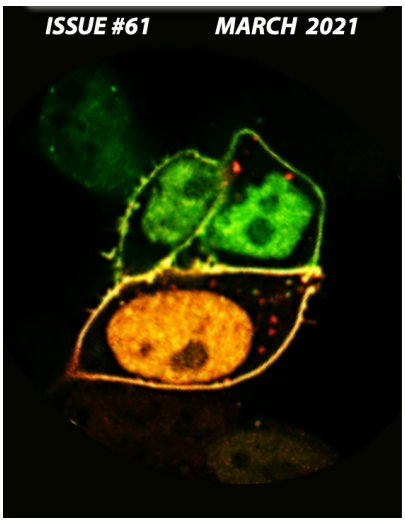


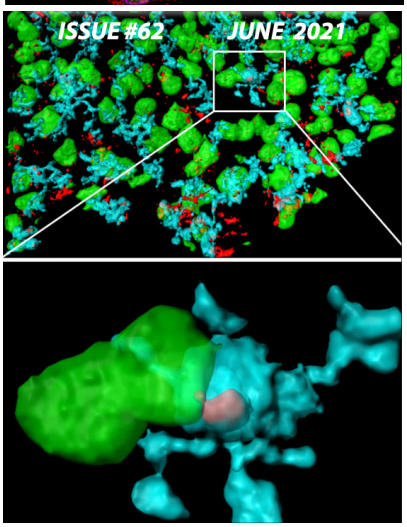












Message from the ICS President

The President's Swan Song - Dear Colleagues – it is with mixed emotions that the end of my tenure as President comes to an end. It has been a pleasure to serve you during these last three years together with the Council, and last but not least, with Sheilah Jewart, our administrator. Sheilah will be retiring at the end of the year and I am most grateful for her outstanding contribution to our Society. I am also thankful to past-President Mike Holers for making the transition into my tenure as smooth as possible, and for his never-ending attention to the Society. Dan Ricklin as Treasurer has ensured that our economy is in good shape, and Trent Woodruff has kept the pieces together as Secretary and been a fantastic editor for FoC. The incoming President Claudia Kemper has been exceedingly helpful, so I am sure I can pass the torch safely to her hands.

Below is a reflection of some of the items the ICS Council has worked with recently to ensure the field of complement stays at the forefront of our research and discussions.

Pandemic shuts down the World – ICW – it was challenging for the ICS Council to make decisions with the COVID landscape changing daily, causing us to cancel, postpone and finally determine not to let another year go by without meeting, and to embrace new technology and turn the ICW into a virtual workshop to be held this December. I am very confident that this will be a success despite the difficulties, and I congratulate Christine Skerka, Peter Zipfel and the LOC for their hard work to get this meeting on its feet, which has not been easy.

ICS Symposium: C3: Complement Clotting and COVID – after 6 months of lockdown and new COVID research being announced daily, the Council felt it was essential to address complement's role in this Pandemic to the members. The virtual symposium was held in October 2020 with an excellent lineup of speakers, with over 600 people attending.

ICS Symposium: Complement and Inflammation – was another project that the Council undertook in July 2021 to continue to connect with the complement community and members. A special thank you to the organizers chairing the symposium with more than 500 people attending.

Nomenclature – thank you Seppo Meri, Claudia Kemper and Andrea Tenner, for taking care of the different aspects of the nomenclature issues that have been intensively discussed and will now be formally handed over to IUIS.

Pioneering Women of Complement – This initiative aims to showcase female complementologists as role models for early career female scientists in the field, and honor the female members of the complement community for their impactful research contributions. It was our intention to highlight the ICS Pioneer Women and invite them to attend the ICW 2020 in Berlin. Although it will be virtual, these pioneers in complement will finally be formally honored at the ICS Virtual Workshop in December. Please join us to celebrate their accomplishments.

Message from the ICS President (*continued*)

AAI and FOCIS Symposiums – Thanks to Josh Thurman and Viviana Ferreira, who had to make adjustments from in-person to virtual formats for these meetings. They both were well attended and continue to complement the agenda and discussion at those conferences.

In 2021 Frontiers in Immunology and ICS - joined together for a complement and COVID-19 special research topic organized and edited by Zoltan Prohaszka and Nicolas Stephane Merle.

ICW 2023 Newcastle – the LOC has also been busy moving the dates from 2022 to 2023 and all that was involved in those details. Thank you, Claire Harris, and your colleagues, for all you have done to make that transition smooth. I want to encourage everyone to mark your calendar now to attend the ICW 2023 where we hopefully can all finally be together in person for our workshop.

Early-Career Complementologists (ECCO) – is a new initiative chaired by Nicole Schäfer from ICS and the European Complement Network (ECN) together. This effort is welcomed by the ICS. They have been very active on Twitter and have created a forum for sharing information about great science (eg. paper of the week, clinical highlight of the month, scientist of the month), job opportunities, fellowship calls, and social activities. In this frame, an ICS sponsored ECCO PhD Journal Article Award has been established.

New ICS administrator – I am happy to announce that we have found a successor for Sheilah, after a successful formal interview. Her name is Karen Gottlieb. Sheilah has worked with Karen for many years with societies including Neurochemistry (ASN) Neurotrauma (NNS), Reproductive Immunology (ASRI), Biochemistry Educators (ABE) and several other scientific associations, and has the background and skills needed to support ICS into the future. Karen is also working with The Meeting Planners on the upcoming ICS Virtual Workshop, taking care of the speakers and recordings and helping to run the show during the virtual conference.

ICS PCO – ICS has now established a formal collaboration with a professional congress organizer (PCO) - The Meeting Planners, a Copenhagen-based company specializing in organizing and managing congresses, conferences, seminars, and similar events. The Meeting Planners already know the complement societies from the 2017 EMCHD Copenhagen Meeting and the Bern Meeting next year, and have been instrumental in organizing the upcoming virtual ICW during a difficult time when another PCO did not live up to expectations.

Several new ICS initiatives will be disclosed in the next period, which will open new opportunities for the members of our Society.

Message from the ICS President (*continued*)

The President's Swan Song

In my message at the beginning of my tenure as President, I said that I hoped that during my term 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. In doing so, this would create the necessary ecosystem that will make the wheel turn in a way that the findings in the complement research laboratories can find their way into a clinical applicable setting. The Pandemic presented unexpected challenges, and I am proud of the Council members working hard on behalf of the ICS to get the Society through the worst of times. We will, in the future, expand our relationships with Industry. Indeed, several of our distinguished researchers have left academia to pursue a career in Industry to develop new complement therapeutics and diagnostics. If we as a Society can also embrace this development, I think we will have moved our field forward for the better.

The incoming President, Claudia Kemper, will bring the strengths needed for this next phase. Next year, the Council will have several new members, and I am confident that they will continue the good work that is progressing in complement. I will remain as past-President for the next two years, and look forward to continuing my association with the ICS.

Thank you, it has been a pleasure. Enjoy the upcoming virtual ICS Workshop.

Peter Garred
ICS President

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Department of Clinical Immunology, Section 7631
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e-mail: peter.garred@regionh.dk

Complement Research in Pittsburgh, USA

Dr Janet S. Lee's Research Group

The West Wing Lung Injury Suite headed by Dr. Janet S. Lee at the University of Pittsburgh in the United States of America studies pulmonary host defense and the molecular pathogenesis of acute lung injury. We utilize a wide variety of relevant murine models of injury, molecular genetic approaches, in vitro biochemical assays, and human bio-samples to examine host defense in the lung. We are particularly interested in studying host-pathogen interactions, of which the complement cascade is of crucial importance. Studies currently focused on how alternative complement pathway function may provide host protection during acute respiratory failure are headed by Dr. William Bain. Using hemolytic assays with serum from critically-ill patients, we have shown that alternative, but not classical, pathway function is associated with improved survival during critical illness. We are currently investigating the role of Factor B and Factor H levels and function during acute respiratory distress syndrome, or ARDS, utilizing bio-banked human samples from two multi-center randomized controlled trials. Dr. Nouraie is an accomplished bio-statistician who provides epidemiological and statistical modeling expertise to support our lab's translational complement work. Another line of inquiry focuses on myeloid cell and platelet regulation of alternative pathway function at both tissue and molecular-cellular levels. We are grateful to be highlighted in this issue and look forward to learning more complement biology from the tremendous science being conducted by members of the International Complement Society.

First row (left to right): Dr. Janet S. Lee, Tolani Olonisakin, Dr. Hernan Penaloza, Ria Hosuru, Shekina Gonzalez-Ferrer, and Dr. Xiaojing An.
Second row (left to right): Dr. William Bain, Dr. Tomeka Suber, Rick van der Geest, Dr. S. Mehdi Nouraie, Dr. Zeyu Xiong, and Dr. Reza Tabary.
Contact: Dr. Janet S. Lee (leejs3@upmc.edu) and Dr. William Bain (bainwg@upmc.edu)

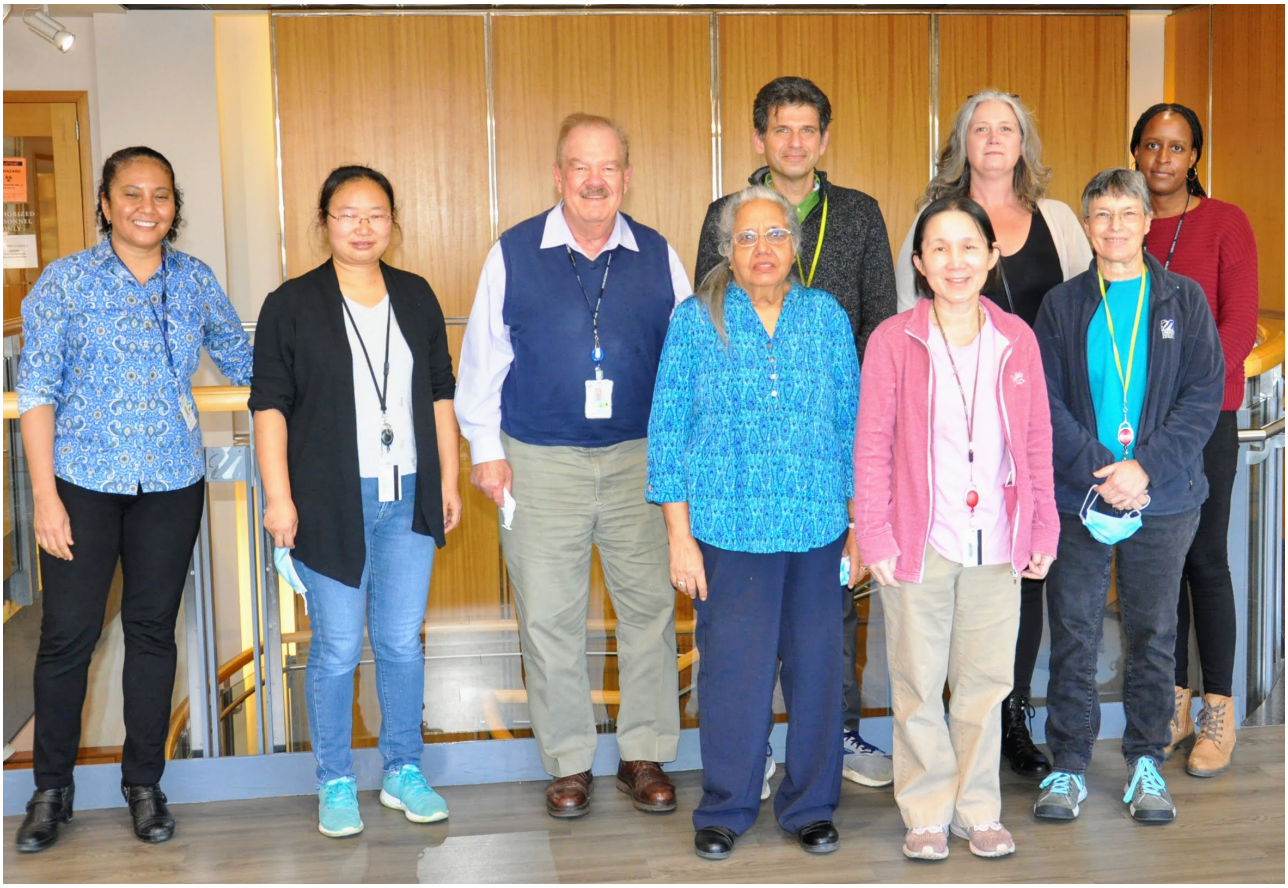
Complement research in Worcester, USA

The UMass Chan Medical School Neisseria/Complement group

The Neisseria/Complement group at UMass Chan Medical School has had a long-standing interest in elucidating complement interactions with Neisseriae. The two pathogenic Neisseria species include Neisseria gonorrhoeae, the second most common bacterial sexually transmitted infection globally, and N. meningitidis, an important cause of acute bacterial meningitis and sepsis. Complement is critical for host defenses against Neisserial infections. Both gonococci and meningococci have evolved elegant ways to evade killing by the complement system and our group has uncovered several such mechanisms. We have characterized how these bacteria scavenge complement inhibitors such as factor H (FH) and C4b-binding protein (C4BP) to dampen complement activation on their surfaces, a strategy used by several pathogens. Interestingly, the pathogenic Neisseriae colonize only humans and accordingly, also evade complement in a human-specific manner. We have examined the evolutionary aspects of species-specific complement evasion. One of the meningococcal FH-binding proteins is a key component of both licensed group B meningococcal vaccines. Another area of considerable interest is how sialic acid – configured in various linkages – on Neisserial surfaces subvert complement and other arms of innate immunity, including cationic antimicrobial peptides (CAMPs).

Over the years, gonococci have developed resistance to almost every conventional antibiotic, thus severely limiting treatment options. A major thrust of our research is to utilize our knowledge of complement interactions with these bacteria to design novel immunotherapeutics and vaccines. As an example, FH/Fc fusion proteins are being developed as 'anti-pathogen immunoadhesins', and have shown efficacy in in vivo against *N. gonorrhoeae*, *N. meningitidis*, group A streptococci and non-typeable Haemophilus influenzae. Another strategy is to 'trick' gonococci into displaying analogs of sialic acid on their lipooligosaccharide (LOS); these sialic acid analogs do not protect them against host complement and CAMPs. A monoclonal antibody that targets LOS and eliminates gonococci in vivo in a complement-dependent manner is also being optimized for maximal function. Finally, a peptide vaccine that mimics an LOS epitope elicits antibodies whose efficacy in the mouse vaginal colonization model also depends on complement activation, and is being developed for a clinical trial.

Faculty members in our group include Sunita Gulati, Jutamas Shaughnessy, Lisa Lewis, Peter Rice and Sanjay Ram. We have enjoyed several fruitful collaborations with our complement colleagues for over two decades and welcome the opportunity to continue our work with more complement groups.



The UMass Chan Medical School Neisseria/Complement group. *From L to R*: Rosane DeOliveira, Bo Zheng, Peter Rice, Sunita Gulati, Sanjay Ram, Jutamas Shaughnessy, Lisa Lewis, Nancy Nowak and Aleyo Chabeda

Complement C1s and C4d as Prognostic Biomarkers in Renal Cancer: Emergence of Noncanonical Functions of C1s

Daugan MV, Revel M, et al., Russick J, Dragon-Durey MA, Gaboriaud C, Robe-Rybkine T, Poillerat V, Grunenwald A, Lacroix G, Bougouin, Meylan M, Verkarre V, Oudard SM, Mejean A, Vano YA, Perkins G, Validire P, Cathelineau X, Sanchez-Salas R, Damotte D, Fremeaux-Bacchi V, Cremer I, Sautès-Fridman C, Fridman WH, Roumenina, LT

Cancer Immunol Res; 2021 Aug; 9(8):891-908.

Multiple studies indicate that complement activation contributes to tumor progression in several cancer types. This work identifies complement component C1s and C4d as new markers of prognosis in clear cell renal cell carcinoma (ccRCC). While the direct origin of plasma C4d remains unknown in these patients that lack hypocomplementemia, plasma C4d was significantly increased in the plasma of patients with ccRCC and conferred a poor prognosis. The role of C1s in tumor progression was identified as being driven partly by the canonical role of C1s that involves triggering complement activation and partly by novel non-canonical roles of C1s that affect cell transcriptional activity, proliferation, viability, and cross-talk with T cells, modulating the tumor microenvironment. Silencing of the C1s gene altered the transcriptional program of ccRCC cells and reduced cell proliferation and viability. The extracellular activity of C1s did not play a detectable role under the reported experimental conditions and does not explain the observed phenotype. The data suggests a bidirectional cross-talk in tumors that express high levels of C1s and that are infiltrated by high numbers of T cells, whereby (a) the infiltrating T cells stimulate C1s via IFNγ and (b) C1s-high expressing tumor cells prevent T-cell activation and may promote exhaustion. The authors conclude that overexpression of C1s by tumor cells could be a new escape mechanism to promote tumor progression.

SARS-CoV-2 Exacerbates COVID-19 Pathology Through Activation of the Complement and Kinin Systems

Savitt AG, Manimala S, White T, Fandaros M, Yin W, Duan H, Xu X, Geisbrecht B, Rubenstein D, Kaplan AP, Peerschke EI, Ghebrehiwet B

Front Immunol; 2021 Nov 5; 12:767347.

Although complement plays a role in triggering and maintaining an inflammatory state, the specific molecular mechanisms of complement in COVID-19 pathology are still being elucidated. Given the rate of coronavirus mutation that leads to new infectious strains, complete understanding of the molecules and the mutations that trigger and/or exacerbate the diseases caused by SARS-CoV-2 may help identify novel pharmacological targets for helping to control and/or prevent future pandemics. It has been previously reported that infection with SARS-CoV-2 triggers the alternative and lectin pathways of complement, as well as the kallikrein-kinin system (KKS), generating in the process potent vasoactive peptides that contribute to severe acute respiratory syndrome (SARS) and multi-organ failure. This study shows for the first time that all 4 of the major structural proteins [i.e. spike (S) protein, nucleocapsid (N) protein, membrane (M) protein, and the envelope (E) protein] are able to activate the classical complement pathway [i.e. by binding to the globular heads of C1q (gC1q)] and kinin systems [i.e. by binding FXII and high molecular weight kininogen (HK), and activating the KKS to generate bradykinin]. Moreover, these proteins bind to the receptor for the globular heads of C1q (gC1qR), which has the ability to activate both the complement system and the KKS, possibly modulating the crosstalk between the complement and coagulation pathways through fibrin formation, immune injury and/or inflammation during COVID-19 pathology. In addition, given the cell surface and intracellular location of gC1qR, further studies to explore additional novel roles for gC1qR during SARS-CoV-2 infection, such as serving as an alternate receptor for cellular entry and/or intercellular communication, are warranted.

28th International Complement Workshop ICW 2021 Virtual Meeting

December 6 – 10, 2021

Abstract submission closed
Registration open

http://www.icw2021berlin.de/loc.html

EMCHD 2022

18th European Meeting
on Complement in Human Disease
Bern Switzerland • 25.-29.08.2022

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on Molecular and Cellular Biology

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April 3-6, 2022 • Snowbird Resort • Snowbird, UT, USA

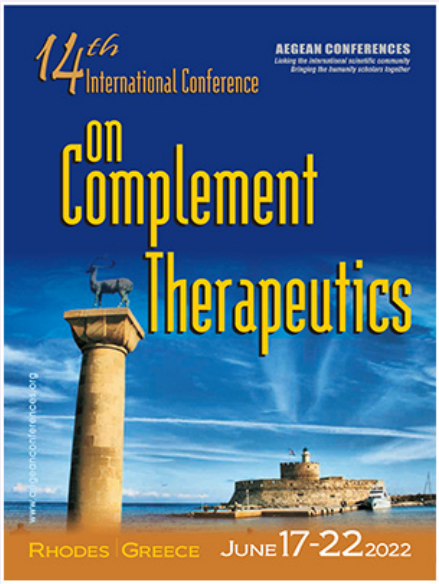
Scientific Organizers: Claudia Kemper, Christoph J. Binder and Feng Shao

Supported by the Directors' Fund

Global Health Travel Award Deadline: March 14, 2022 / Scholarship Deadline: December 6, 2021 / Abstract Deadline: December 14, 2021 / Discounted Registration Deadline: February 2, 2022

14th International Conference on Complement Therapeutics

The field of complement drug discovery has never been riper with opportunities for therapeutic intervention in diverse clinical indications. 14 years after the clinical approval of the first complement-specific drug, eculizumab, the complement drug space has garnered renewed interest owing to a series of game-changing clinical developments. The recent clinical approval of the first compstatin-based C3-targeted therapeutic for treating PNH and the approval of a small-molecule C5aR1 antagonist for severe ANCA-associated vasculitis have expanded the clinical arsenal of complement therapeutics bringing tailored complement intervention closer to fruition and bolstering confidence in the broader therapeutic scope of complement inhibitors.



- Open for Abstract Submission until: 15/03/2022
- Open for Travel Award Application until: 15/03/2022
- Early Registrations Fee until: 15/03/2022

Embracing these important developments, we are delighted to announce the 14th International Conference on Complement Therapeutics which will bring together leading experts from academia, the biopharma industry and drug regulatory agencies to discuss the latest developments in complement therapeutics, clinical trials and new aspects of complement-driven pathophysiology in emerging indications. Topics will 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 & COVID-19; complement targeting in cancer immunotherapy; complement biomarkers in disease diagnosis and therapy; Novel and unexpected indications.

Organizing Committee: John Lambris, PhD; Dimitrios Mastellos, PhD; Lubka Roumenina, MD

17th - 22nd June 2022, Rhodes, Greece

QUIDEL®

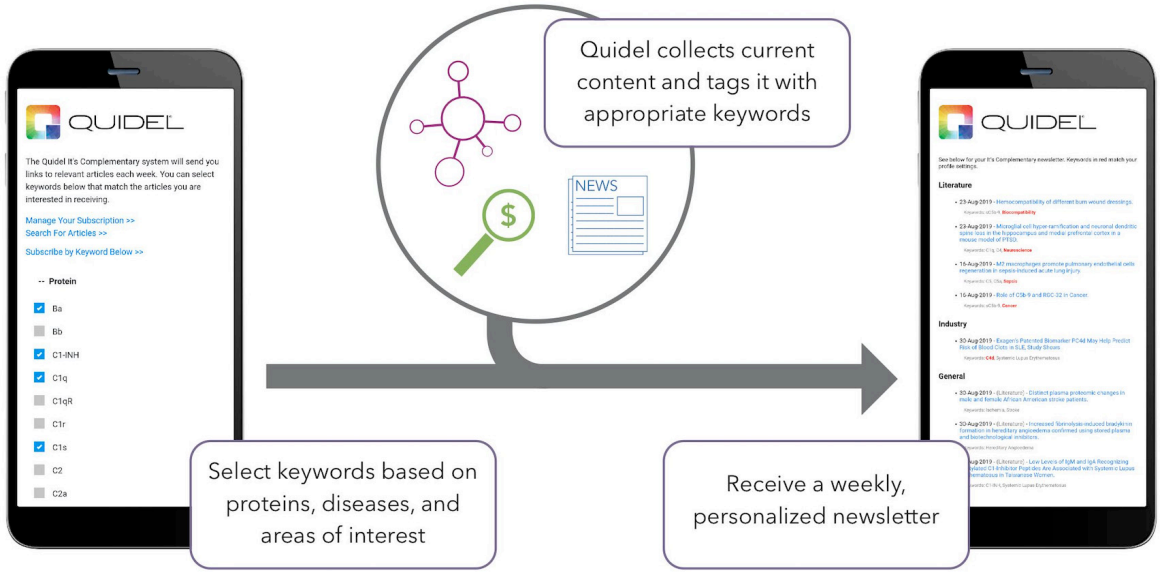
It's Complementary

A Personalized Complement System Newsletter

As complement system research expands, keeping up to date on the latest literature, news, and funding is difficult. Quidel Specialty Products Group (SPG) has leveraged the information it tracks to create a new tool for complement scientists: It's Complementary – a personalized newsletter that highlights the interest of each individual researcher.

How It's Complementary works:

- Build Your Profile: Select keywords for complement proteins and Diseases/Areas of Interest that match your research interests.
- Subscribe: Submit your contact information and confirm your subscription via email.
- Relax and Enjoy: Every Tuesday (8am PST) the It's Complementary newsletter arrives with new complement information collected over the last week, with the content such as literature, news, and funding categorized to match your profile.



Each week SPG personnel collect complement system information and tag it with the appropriate keywords. The system matches content and subscribers, building a personalized newsletter that gives researchers the information they need. In addition, use the "Search For Articles" to browse the extensive database.

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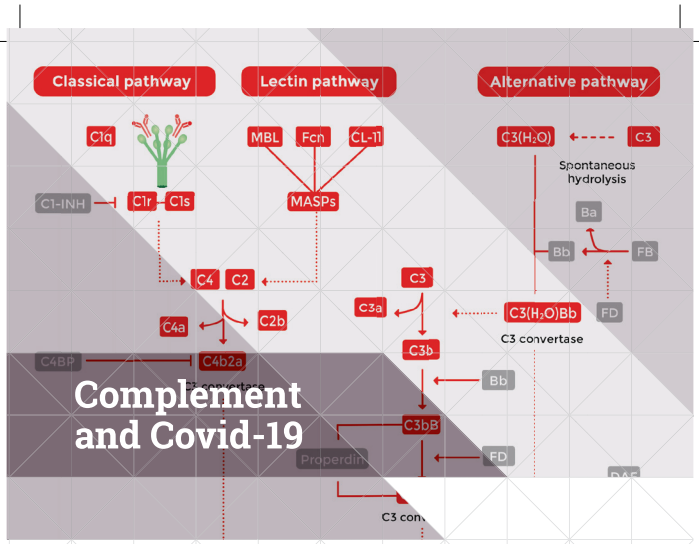

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