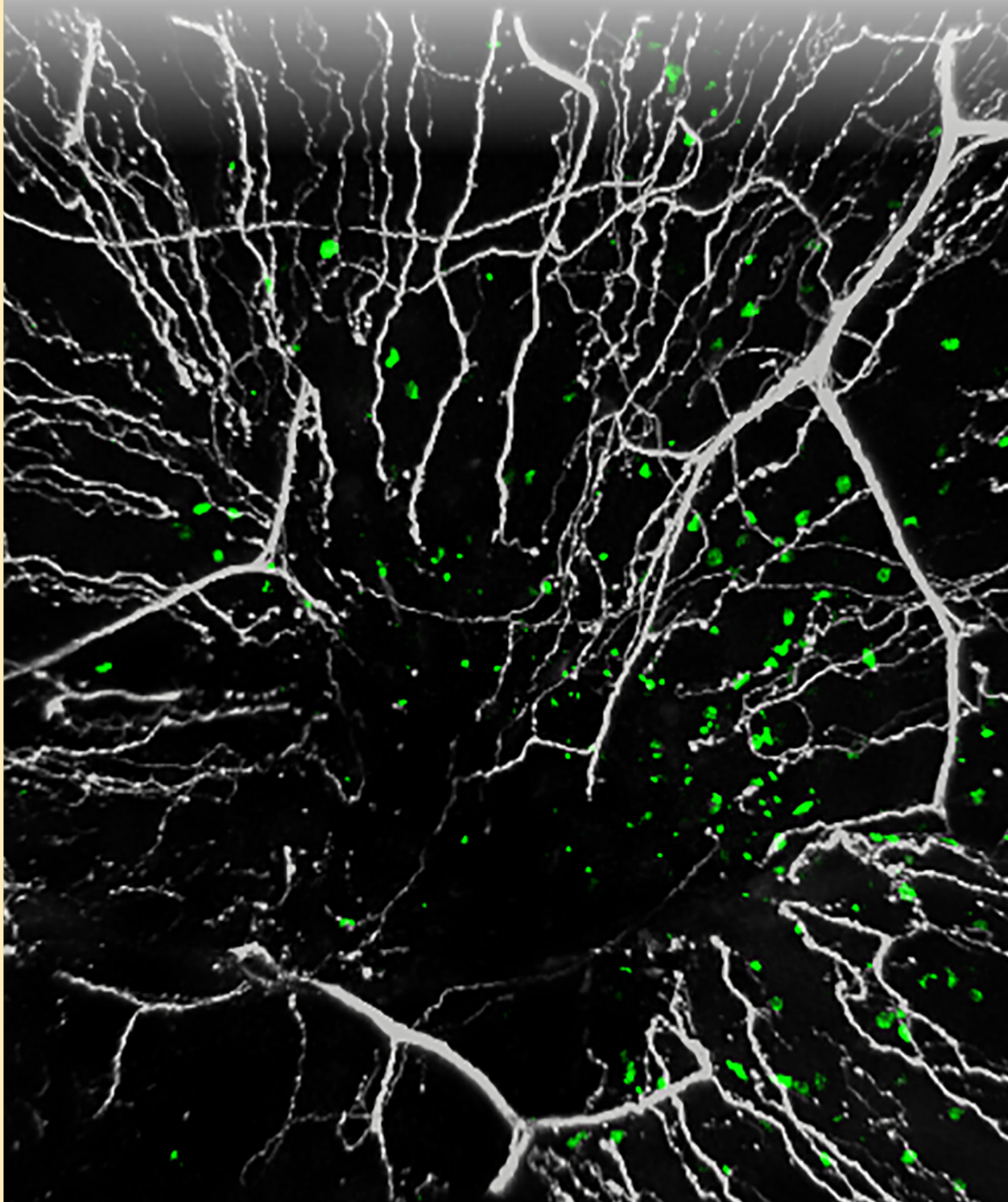
Focus on Complement

ISSUE #57 MARCH 2020



International Complement Society

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Focus on Complement

Issue #57

Editor
Trent Woodruff

Issue Contributor
Viviana Ferreira

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In this 57th Issue of Focus on Complement:

From the Editor

Dear Readers,

Welcome to the 57th Issue of *Focus on Complement* – the official newsletter of the International Complement Society (ICS).

In this issue we feature the research groups of Dr. Jessy Alexander from Buffalo, USA, and Dr. Carl Atkinson from South Carolina, USA. Issue contributor Viviana Ferreira reviews two articles on complement in forgetting and in multiple sclerosis, and we highlight upcoming Complement conferences.

We also congratulate Dr. Derek Royer, who is the winner of the FoC Early Career Cover Image Award. A description of Derek's research and cover image can be found in the following pages.

I hope you all enjoy the first issue of *Focus on Complement* for 2020, and wish you all the best for the year ahead!

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 @complementsoc

Derek J. Royer: Winner of the Focus on Complement Early Career Cover Image Award

Derek J. Royer, PhD is a senior research associate at Duke University's Center for Ocular Immunology led by Victor L. Perez, MD. Derek's research on ocular surface disease has kindled his interest in complement-mediated corneal inflammation and pathology. His recently published work (https://elifesciences.org/articles/48378) shows that local complement activation and $CD4^+$ T cells coordinate sensory nerve damage in mouse models of herpes keratitis and ocular graft-versus-host disease (GVHD). He plans to continue investigating the mechanistic basis of complement-mediated ocular surface pathology, with the hope of identifying suitable targets for topical ophthalmic drug development.

Cover Image Description: The cornea contains the body's highest density of sensory nerve fibers which are exquisitely sensitive to damage following ocular surface inflammation. The confocal image featured on the cover shows βIII $tubulin^+$ nerves (white) and infiltrating $CD3^+$ T cells (green) in the cornea of a mouse with GVHD following ophthalmic treatment with cobra venom factor. While rudimentary, topical cobra venom factor treatment prevented corneal nerve destruction and completely preserved sensory function. This approach provides proof of concept that topical complement inhibitors may help mitigate the signs and symptoms of inflammatory ocular surface diseases.

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 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 at Buffalo-Niagara, USA

The group of Dr. Jessy Alexander

Jessy Alexander, PhD is a Research Professor in the Department of Medicine at the University of Buffalo. With standing support from the NIH, she established her own lab during her time with the 'Quigg group'. Her complement journey began by identifying platelet complement Factor H as the immune adherence receptor in rodents similar to that of CR1 in humans. The focus of the lab is to understand the role of complement proteins in the 'filtering units', namely the kidney and the brain in immune complex (IC)-mediated diseases such as serum sickness and systemic lupus erythematosus. The lab is located within the Clinical and Translational Research Center which allows for close interactions with the clinics and Roswell Park, and fosters collaborations with investigators of several disciplines housed in the same building.

Studies from the lab thus far indicate that complement activation plays a crucial role in IC-mediated glomerulonephritis. Further, inhibition of C5a/C5aR signaling was protective in this setting, indicating the viability of downstream complement proteins for therapeutic manipulation in IC diseases. At the cellular level, macrophages were seen to play a critical role in this model and so the lab is currently studying the mechanism/s and pathways that can be manipulated in macrophages to prevent the observed pathology.

Another scope of work which the lab has taken on is to determine the role of complement in the lupus brain. The studies using the MRL/lpr mouse model show that complement inhibition by overexpression of Crry or deletion of Factor B alleviated the disease pathology in CNS lupus, and acted through anaphylatoxin/receptor signaling. The pathological changes in CNS lupus include: loss of blood-brain barrier (BBB) integrity, reduced hippocampal volume and significant behavioral changes. The BBB is lined with endothelial cells that form the line of demarcation between the organ microenvironment and systemic circulation. The lab has done a comprehensive study surrounding the role of complement in both mouse and human brain endothelial cells and the signaling pathways involved, and has demonstrated the beneficial effect of C5aR antagonist on maintaining BBB integrity in lupus.

Most recently, Dr. Alexander has begun to further investigate the idea that environment plays a vital role in a wide spectrum of diseases. As a recipient of the prestigious Fulbright fellowship, she has begun an international collaboration with Dr. John Mathew at Christian Medical College in Vellore, India and is currently studying the role of the microbiome in lupus patients.

Contact: Dr. Jessy Alexander,
Department of Medicine, University of Buffalo
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Seen in the photo are L to R: Michelle Sudyn (PhD student), Lauren Peralta (undergraduate), Lee Chaves (Research Asst Professor) and Jessy Alexander. Not seen are Kazuki Okamura (Masters student) and Nivetha Pushpanathan (undergraduate).

Complement Research at South Carolina, USA

The group of Dr. Carl Atkinson

Our complement research encompasses two main areas, organ/tissue transplantation, and respiratory disease. With regard to transplantation, the laboratory is investigating how the complement system impacts overall graft survival through its effects at different stages pre- and post-transplantation. An early important advance in this area was the first description of a mouse model of brain death, and the demonstration that complement activation in the brain dead donor primes immune activation in the donor heart and lung. We have since built on these observations and shown that complement plays a pivotal role in the pathogenesis of ischemia reperfusion injury, acute and chronic graft rejection. Our studies have explored how this early donor graft activation of the complement system drives alloimmune responses and subsequent graft rejection. Given this, a focus of our studies has been the development of strategies to inhibit complement using clinically relevant model systems. To this end, in collaboration with Dr. Stephen Tomlinson (also at MUSC), we have together characterized a number of targeted complement inhibitors. Targeting allows effective delivery of complement inhibition while minimizing unwanted systemic effects, a benefit that is particularly relevant in transplantation in which patients will already be substantially immunosuppressed.

Another key interest is the role of complement in chronic respiratory diseases. Using rodent cigarette smoke exposure models, the laboratory has demonstrated a key role for complement activation in smoking-related diseases of the upper and lower airways, such as chronic rhinosinusitis and emphysema. Recently, using proteomic pathway enrichment analysis of differentially increased proteins, we found an enrichment of the complement cascade pathways in the nasal mucus of individuals with chronic rhinosinusitis as compared to control subjects. Further analysis revealed local sinus mucus levels of C3 correlated with worse subjective disease severity, whereas no significant association could be demonstrated when systemic C3 levels were analyzed. These studies suggested a local dysregulation of complement activation and lead to the discovery of increased intracellular C3 in sinonasal epithelial cells from human chronic rhinosinusitis patients. In collaboration with Dr. Jennifer Mulligan (MUSC), we have begun dissecting the role that respiratory epithelial cell intracellular complement may have on inflammation and sinus disease.

The Medical University of South Carolina is a rich environment for complement research with Drs. Atkinson, Tomlinson, Rohrer and Mulligan, performing research into complement therapeutics, transplantation, autoimmunity, age related macular degeneration, and respiratory disease thus providing a strong collaborative program of complement centered research.

Contact: Dr. Carl Atkinson,
Lee Patterson Allen Transplant Immunobiology Laboratory, Medical University of South Carolina
Email: atkinsoc@musc.edu

Top Row: Zhenxiao Tu, Herman Connor, Changhai Li, Mark Kouame, Dorian Frazier, Logan Langerude. **Bottom Row:** Dianna Nord, Caroline Wallace, Domonique Rivers, Carl Atkinson, Satish Nadig, Jessica Lin, Jerec Ricci, Leah Plumblee.

Targeted Complement Inhibition at Synapses Prevents Microglial Synaptic Engulfment and Synapse Loss in Demyelinating Disease

Werneburg S, Jung J, Kunjamma RB, Ha SK, Luciano NJ, Willis CM, Gao G, Biscola NP, Havton LA, Crocker SJ, Popko B, Reich DS, Schafer DP

Immunity, Volume 52, Issue 1, 2020, Pages 167-182.e7

In demyelinating diseases, such as multiple sclerosis (MS), microglia, the resident macrophage of the central nervous system, engulf and eliminate neuronal synapses, contributing to disease. Given previous work demonstrating the role of the classical pathway in synaptic changes in neurodevelopment and Alzheimer's disease, and data showing increased C3 levels in plasma and cerebral spinal fluid correlate to disease severity in MS patients, the authors sought to determine if complement drives synaptic loss in MS. These data show that C3 is important in facilitating microglia synapse engulfment and loss. The authors assessed synaptic changes in the retinogeniculate system, a nerve tract relaying visual information from the retina to the thalamus that is often compromised in MS. Using two MS mouse models, the authors demonstrated C3, but not C1q, enrichment at synapses. To determine if synapse-localized, activated C3 was responsible for microglial-mediated synapse engulfment and elimination, authors employed a gene therapy strategy using adeno-associated virus to overexpress complement inhibitor Crry (murine homolog of MCP), at sites of C3 activation. Crry was fused to a domain of complement receptor 2 (receptor for activated C3). Attenuation of C3 resulted in reduced microglial synaptic engulfment and loss, and visual acuity loss. The authors propose the alternative pathway modulates this phenomenon; however, more work is warranted to support this claim. Overall, this work contributes to understanding the role of complement in neurodegenerative diseases and provides an example of targeted gene therapy treatment. Finally, this study encourages further work to explain what initiates complement-mediated synaptic loss.

Microglia mediate forgetting via complement-dependent synaptic elimination

Wang C, Yue H, Hu Z, Shen Y, Ma J, Li J, Wang X, Wang L, Sun B, Shi P, Wang L, Gu Y.

Science, **Volume 367, 2020, Pages 688–694.**

Engram cells are neurons involved in storing memory. Engram cell reactivation results in recalling memory and failure to reactivate leads to forgetting memories. Synapses between engram cells may be substrates for memory storage. Previous work showed that the resident macrophages, microglia, play crucial roles in monitoring synapses and determining wiring of the brain. The goal of this work is to assess the role of microglia in affecting synaptic connections within the engram neuron circuit where memories are allocated. Using mouse models, the study showed that microglia eliminate synaptic components and that depleting or inhibiting phagocytic activity of microglia prevented forgetting. The authors showed that C1q-dependent classical pathway is actively involved in synapse elimination by microglia. Overexpressing CD55/DAF using a Cre-dependent adeno-associated virus vector expressing CD55 in the engram cells prevented forgetting. Because lack of reactivation of engram cells leads to forgetting, the authors examined whether the process of forgetting mediated by microglia is influenced by engram neuron activity. Using tamoxifen to induce expression of inhibitory DREADD receptor in tagged engram cells, followed by administration of DREADD ligand clozapine-N-oxide (CNO) that suppresses engram cell activity, they showed that CNO-treated mice exhibited significant memory loss and that depleting microglia prevented forgetting in CNO-treated mice. Additionally, CD55 expression prevented accelerated forgetting and decreased reactivation rate of CNO-treated engram cells. Using memantine (a pro-neurogenic drug) and a glial fibrillary acidic protein-thymidine kinase mouse model, the authors also showed that microglia contribute to both neurogenesis-mediated and non–neurogenesis-mediated forgetting. Overall, this study revealed complement-dependent synapse elimination by microglia as a mechanism underlying the forgetting of remote memories.

ECCO at ICW 2020

ECCO, the Early-Career Complementologists, is a network for the junior scientists in the Complement field. We strive to assist scientists in the development of their careers, so make sure you keep up to date via our online platforms (complement.org/ECCO, Facebook: @earlycomplement, and LinkedIn, search: early-career complementologists). Here we communicate about science, grant opportunities, as well as the "early-career scientist of the month". Finally, we arrange networking events – and we have a great one coming up!!

In conjunction with the 2020 ICW meeting in Berlin, ECCO is arranging a satellite meeting for early-career scientists **12th of September 2020**. So, join us to boost your network and learn from the exciting programme, including:

- A workshop on science-communication.
- Teaching-sessions on novel techniques from both academic and industry experts.
- A careers-guidance talk.

The ECCO meeting is FREE OF CHARGE, and takes place the day before the teaching day of the main conference. Registration for this meeting is through the official ICW2020 website: www.icw2020.de. So, if you're coming to Berlin, and you're looking for a great way to start off the conference, come and join us!

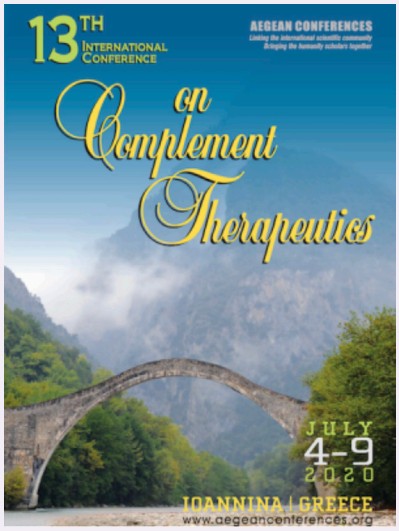
The ECCO committee is recruiting: Application Deadline 31.03.2020

If you are interested in ECCO's work, and want to have an influence on shaping this global scientific early-career network – join us! Learn more about our work through the online channels listed above, or reach out to any of the current committee members.

To apply for the current open position, please submit a cover letter (max 500 words), a CV, as well as a letter of recommendation. Send your application to ecco@complement.org

On behalf of the ECCO committee,
Martin Parnov Reichhardt, PhD, Chair

13th 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 concepts and drug leads 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:
John Lambris, PhD
Dimitrios Mastellos, PhD
Daniel Ricklin, PhD
Antonio Risitano, MD
Lubka Roumenina, MD

4th - 9th July 2020
Ioannina, Greece

Link: https://www.immunology2020.org/scientific-program/

Please plan to attend the

International Complement Society Guest Symposium

at the 2020 Meeting of the American Association of Immunologists (May 8-12, 2020)

Complement: Alive and Kicking!

Chairs:

- **Claudia Kemper**, NHLBI, National Institutes of Health
- **Trent Woodruff**, The University of Queensland, Australia

Speakers:

- **Trent Woodruff**, The University of Queensland, Australia, *From the Beginning to the End: The Complement System in Neural Development and Degeneration*
- **Lubka Roumenina**, Cordeliers Research Center, INSERM, France, *Context-Dependent Roles of Complement in Cancer*
- **Michael Holers**, The University of Colorado, *Complement in Human Rheumatoid Arthritis: From Mucosal Initiation of Autoimmunity to Eventual Joint Destruction*
- **Diana Karpman**, Lund University, Sweden, *Complement-Mediated Kidney Diseases*

Date and time: **Saturday, May 9, 12:30-2:30**

We would like to thank our generous sponsors:

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National Jewish Health
Quidel
Pangburn Charitable Fund

Early registration closes March 26: https://www.immunology2020.org/registration/

Contact: Viviana Ferreira, D.V.M., Ph.D. Viviana.Ferreira@utoledo.edu

28th International Complement Workshop

Dear Colleagues,

You are invited to the 28th International Complement Workshop which will take place from September 13-17 in Berlin the vibrant capital of Germany in the heart of Europe.
Berlin is recognized as a lively modern world city of culture and medicine. Berlin is also a historical city and the birthplace and home of complement. The term complement was coined in 1890 by the German Physician and Nobel Laureate Paul Ehrlich. In Berlin you can follow in his footsteps and those of Rudolf Virchow by visiting the collection of anatomical specimens collected by this famous pathologist. You can also visit the Robert Koch Institute, the place where Robert Koch, who discovered the tubercle bacillus worked.
This international meeting will cover state of the art lectures on complement in health and disease and emphasizes will be given on the translational aspects. Renowned international speakers will cover exciting and recent newest developments of complement in diseases and the role of complement therapeutics.
The local organising committee together with the President and the advisory board of the International Complement Society will put together an attractive programme which will cover timely topics of basic complement research, on the translational character of the field and the input in the clinics and in therapy.
The meeting will also include a Teaching Day and - for the first time - a Modern Complement Day 2020 (MCD). The MCD 2020 is a very new format with presentations and discussion on complement essentials, on complement activation and biomarkers, aspects of central disease mechanisms and therapy of complement associated diseases. In this new forum state of the art information will be presented and discussed by speakers from academia and industry.

We look forward to seeing you in Berlin, in September 2020.

Sincerely,
Peter F. Zipfel Christine Skerka

Invited Speakers and Abstracts

Invited Speakers
Prof. Dr. Johannes Krause
Director Max Planck Institute for the Science of Human History
Jena/Germany

Prof. Dr. Beth Stevens
Harvard Medical School,
Center for Life Sciences
Boston, MA/USA

Abstracts
We cordially invite you to submit your abstract to one of the following abstract topics online at **www.icw2020.de**.

Abstracts must be submitted in English **by 15 March 2020**.

Abstract Topics

- Animal Models in Complement Research
- Autoreactive and inflammatory Complement
- Complement and Complement Activation Products in Diseases
- Complement Crosstalk
- Complement Diagnostics and Standardization
- Complement Genetics
- Complement in Infectious Diseases
- Complement Receptors and Intracellular Complement
- Complement Regulation
- Complement Structure and Function
- Complement Therapeutics on the Way to the Clinics
- New Developments in Complement in Health and Diseases
- Translational Complement

Venue
Langenbeck-Virchow-Haus
Luisenstr. 58/59
10117 Berlin/Germany

Date
September 13–17, 2020

Conference Website
www.icw2020.de

Hosting Society
International Complement Society

ICS INTERNATIONAL COMPLEMENT SOCIETY
Complement... we are the experts!™

ICS Council Nomination

Nominations for new positions to serve on the ICS council from 2021 will open soon. Positions for Councilors (2), Secretary, Treasurer, and President Elect are due to for election. Information on how to nominate someone will be sent out to all active ICS members by email, with nomination links provided on the ICS website. Voting will occur by ballot at the 28th ICW in September 2020.

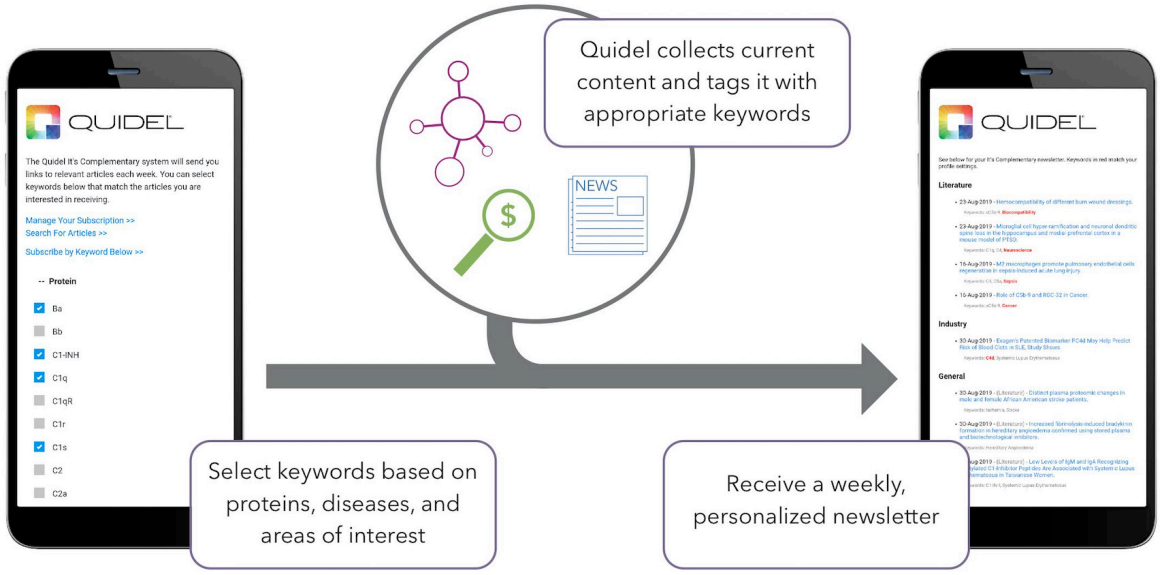
It's Complementary

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.

Visit https://www.itscomplementary.com/ to learn more and subscribe.

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