International Complement Society

"Complement...we are the Experts!™"

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

ics@complement.org
www.complement.org

President
Peter Garred

Past President
Michael Holers

President-Elect
Claudia Kemper

Treasurer
Daniel Ricklin

Secretary
Trent Woodruff

Councillors
Viviana Ferreira
Claire Harris
Michael Kirschfink
Zoltán Prohászka
Joshua Thurman
Leendert Trouw
Nobutaka Wakamiya
Peter F. Zipfel

Executive Director
Sheilah Jewart

Focus on Complement

Issue #63

Editor
Trent Woodruff

Issue Contributor
Zoltán Prohászka

Focus on Complement

ISSUE #63 SEPTEMBER 2021

Contents

In this 63rd Issue of Focus on Complement:

Hycult Biotech
QUIDEL
ALEXION
CompTech
SVAR Answers in Life Science

From the Editor

Dear Readers,

I welcome you all to the 63rd edition of *Focus on Complement* – the official newsletter of the International Complement Society (ICS).

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

We feature several research groups from Vienna, Austria, and Gdańsk, Poland. Issue contributor Dr. Zoltán Prohászka reviews two articles that summarise the outcomes of two major clinical trials of complement inhibitors for cold agglutinin disease and paroxysmal nocturnal hemoglobinuria.

Finally, we highlight a number of upcoming complement focussed conferences.

I hope you all enjoy this third issue of *Focus on Complement* for 2021.

Professor Trent Woodruff
Editor, FoC
Secretary, ICS

Connect with the ICS

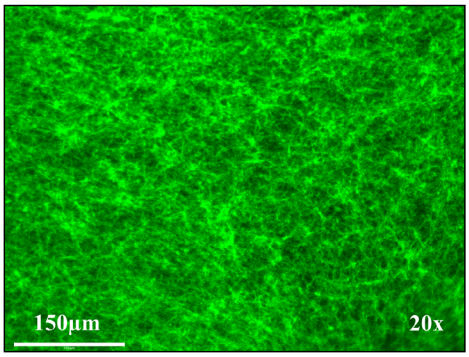
If you would like to contribute with an article to a future issue or have suggestions for a subject theme, please contact Trent Woodruff (t.woodruff@uq.edu.au) or Peter Garred (Peter.Garred@regionh.dk).

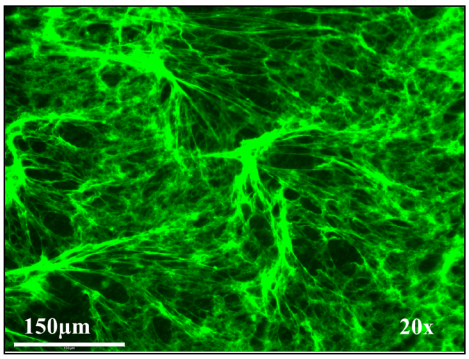
Plus visit our website and follow us on Twitter to keep updated with the latest ICS and complement news.

www.complement.org @complementsoc

Geneviève McCluskey: Winner Focus on Complement Early Career Cover Image Award

Geneviève McCluskey is a final year PhD student in the lab of Dr. Meike Heurich at the School of Pharmacy and Pharmaceutical Sciences at Cardiff University, United Kingdom. Of Irish and English origin, she grew up in Grenoble, France. She attended the Grenoble Alpes University (UGA) as an undergraduate in biology, spending one semester on international exchange at Boston University, USA. She completed a Master's degree in physiology, Epigenetics, Development and Differentiation at UGA in 2017, before moving to the School of Pharmacy in Cardiff. Her research focusses on the molecular crosstalk between the complement and coagulation systems, in particular the role of factor H on thrombin procoagulant and anticoagulant activity.





The images highlight the effect of complement regulator factor H on the coagulation system.

Figure 1. Factor H alters fibrin clot structure. Fibrin clot structure was visualized in the presence of factor H. Fibrin clots were formed in a pure protein system by combining 11.8μM fibrinogen (or 4mg/ml) containing 10% fibrinogen-AF488 with 2.5nM thrombin in the absence (top) or presence (bottom) of 100nM factor H. The clot was left to mature for 2 hours. Images were acquired by fluorescence microscopy (EVOS™ M7000 Imaging System) at 20X magnification.

This work is currently available as preprint while under consideration.

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.

Complement Research in Vienna, Austria

The Vienna Transplant and Complement Lab (VIETAC)

Complement research at the VIETAC lab is led by Georg Böhmig, transplant nephrologist, and Markus Wahrmann, biochemist at the Medical University of Vienna. Our multidisciplinary team is embedded in the Vienna research cluster for transplant medicine, and our activities are tightly linked to our clinical program. In our lab, postdocs, PhD and diploma students with both life science and medical background, including transplant medicine and surgery, closely collaborate to enable translation from bench to bedside. During all these years, we also had the privilege to collaborate with several leading experts in the field, among them Philip Halloran, Zoltan Prohaszka, Klemens Budde and Caner Süsal. Our projects span from basic and translational science to systematic clinical trials, with a continuous focus on B cell immunity, alloantibodies and associated effector mechanisms in solid organ transplantation.

From the beginning of our research in the late 1990's, complement has been a primary interest. Research from the VIETAC lab contributed to the establishment of C4d staining as an in vivo and in vitro marker of rejection, and the development of clinical protocols for the prevention and treatment of antibody-mediated rejection. Our group has developed a reagent for C4d staining applicable on paraffin-embedded biopsy specimens. This provided the community with a valuable tool for systematic analyses of routine biopsies. In an effort to establish tailored approaches of treatment allocation, a major focus over several years has been to evaluate transplant outcomes in relation to a subtle risk assessment based on solid phase assay-based characterization of HLA antibodies. An early important advance in this area was thereby the first description of a microbead assay to quantify alloantibody-triggered complement binding. In this context, our studies also contributed to a better understanding of the in vitro artefact of complement interference. Our interest also encompasses monitoring of complement activity and split products in blood and urine for non-invasive transplant surveillance, as well as the role of classical and alternative pathway complement genetics in renal transplantation, including C4 gene copy number polymorphism and high-activity C3/fB/fH complotypes.

A major clinical interest has been the development and refinement of desensitization strategies in HLA antibody-incompatible transplantation, in particular peri-transplant immunoadsorption to counteract the deleterious effects of preformed complement-activating DSA. More recently, we have been investigating new therapeutic concepts for the treatment of active antibody-mediated rejection, including the design of clinical transplant trials evaluating classical complement depletion and antagonism, proteasome inhibition, Interleukin-6 antagonism and targeting CD38. We could demonstrate that targeting C1s using a novel monoclonal antibody was able to shutdown classical complement in vivo, including blockade of DSA-triggered C4d deposition in the transplant microcirculation. Another complement-specific project aimed at developing apheresis strategies to enhance complement component depletion, and thus counteract severe manifestations of rejection.

Backrow left to right: Florentina Dermuth, Florian Bauernfeind, Frederik Haupenthal, Anita Borski, Konstantin Doberer, Johannes Kläger, Nicolas Kozakowski, Gregor Bond, Susanne Haindl

Front row left to right: Markus Wahrmann, Farsad Eskandary, Heinz Regele, Georg Böhmig, Jakob Mühlbacher

Contact:

Dr. Georg Böhmig, VIETAC lab, Medical University of Vienna. Email: georg.boehmig@meduniwien.ac.at

Dr. Markus Wahrmann, VIETAC lab, Medical University of Vienna. Email: markus.wahrmann@meduniwien.ac.at

Complement research in Gdańsk, Poland

The group of Dr Marcin Okrój

Complement research was brought to Gdańsk, Poland in 2016 by Marcin Okrój, a former post-doc in the laboratory of Prof. Anna Blom at Lund University, Sweden. Marcin has built his team at the Intercollegiate Faculty of Biotechnology of the University of Gdańsk and the Medical University of Gdańsk. At the moment, the group consists of seven people including an Assistant Professor Grzegorz Stasiłojć and five PhD students: Anna Felberg, Aleksandra Urban, Daria Kowalska, Alicja Kuźniewska, Alan Majeranowski. Anna and Aleksandra will defend their Ph.D. theses in Autumn 2021.

The studies conducted by the team are focused on three main areas. The first topic is complement in immunotherapy of hematological disorders and solid tumors. The group published a proof of concept article on gain-of-function variants of Factor B that can augment the cytocidal activity of anti-CD20 mAbs when added to human serum (Felberg et al., Cancer Immunol Immunother, 2019). Currently, the efforts aim at translating these mutations into the analogous component of the classical complement pathway, C2, and proving the compatibility of such supplementation with a wide panel of therapeutic antibodies. Irrespective of the ongoing studies on the potentiation of immunotherapeutic efficacy, there was another article from the group published in 2020 (Felberg et al., Front Immunol.) showing that monitoring of serum CDC potential, as well as the appearance of complement activation markers, enabled the selection of patients with B cell malignancies who may benefit more from type II than type I anti-CD20 mAbs. In collaboration with other complement teams, Dr. Okroj analyzed the suitability of plasma C4d in the early diagnosis of lung cancer (Ajona et al. 2017, Oncotarget), and now his group works on elucidating the role of FI in the progression of lung cancer.

Another area of the group's scientific interest is the development and validation of complement diagnostic methods. Previously Dr. Okrój designed assays that measure complement convertase activity in human serum (PLoS One 2012; Clin ExpImmunol. 2014; J Clin Immunol. 2016), which are constantly improved by, for example, designing appropriate standards that can mimic C3NeF autoantibodies found in patients with complement-related kidney diseases (Urban et al., 2018, Autoimmunity). Methods for the precise assessment of complement cytotoxic potential in patients receiving anti-CD20 mAbs were recently published in J Immunol Meth. (Stasiłojć et al., 2020).

Last but not least, the group of Dr. Okrój reported the first-ever gain-of-function mutation in the classical convertase component C2 identified in human diseases (Urban et al., 2020, J Allergy Clin Immunol.). Hyperactive C2 was the only rare genetic variant found in a patient with aHUS. Two other cases with the same mutation and similar, adjacent mutations were recently identified in two patients with C3G, suggesting that the genes of the classical complement pathway should be included in routine diagnostics of patients with rare kidney diseases.

Photograph (from the left): Grzegorz Stasiłojć, Anna Felberg, Alicja Kuźniewska, Daria Kowalska, Aleksandra Urban, Marcin Okrój

Sutimlimab in Cold Agglutinin Disease

Röth A, Barcellini W, D'Sa S, Miyakawa Y, Broome CM, Michel M, Kuter DJ, Jilma B, Tvedt THA, Fruebis J, Jiang X, Lin S, Reuter C, Morales-Arias J, Hobbs W, Berentsen S

N Engl J Med; 2021 Apr 8;384(14):1323-1334.

Primary or idiopathic cold agglutinin disease (CAD) is a clonal, low-grade B-cell lymphoproliferative disorder that can be detected in blood or marrow in patients with no clinical or radiologic evidence of malignant conditions and accounts for 15–25% of autoimmune hemolytic anemias. Cold agglutinins, with specificity for the erythrocyte surface carbohydrate antigen termed I, are usually of the immunoglobulin M class and are able to agglutinate red blood cells at an optimum temperature of 3–4°C with subsequent complement-mediated hemolysis. The IgM-antigen complex binds to the C1 complement complex, resulting in the potent activation of C1s with initiation of the classical pathway leading to opsonization and extravascular hemolysis in the liver. In patients with CAD intravascular hemolysis mediated by terminal pathway occurs minimally because of intact CD55 and CD59 mediated regulation. CAD is a rare disease that mainly affects elderly or middle-aged people, and is characterized by agglutination mediated acrocyanosis, higher risk of thromboembolism, and early death.

Sutimlimab is a first-in-class humanized monoclonal antibody that is designed to selectively target and inhibit C1s with the goal of halting C1 mediated agglutination and hemolysis in CAD to prevent the abnormal destruction of healthy red blood cells. The drug entered FDA's priority review process recently for the treatment of CAD, based on the results of the CARDINAL trial.

The CARDINAL study was a 26 week multicenter, open-label, single-group study to assess the efficacy and safety of intravenous sutimlimab. Fifty-four percent of the CAD patients reached the composite primary end point, which was a normalization of the hemoglobin level to 12 g/dL or more, or an increase in the hemoglobin level of 2 g/dL or more from baseline, without red cell transfusion. Activity of the classical complement pathway was rapidly inhibited, as assessed by a functional assay. Serious adverse events occurred in approximately one-third of patients, none of which were determined by the investigators to be related to sutimlimab. No meningococcal infections occurred. The CARDINAL study provided the first evidence that inhibition of classic complement pathway activity rapidly halted hemolysis, increased hemoglobin levels, and reduced fatigue. Sutimlimab, directed to a currently non-targeted part of complement, the recognition complex of classical pathway, is a promising therapeutics for the treatment of - among others - antibody and immune complex mediated diseases.

Pegcetacoplan versus Eculizumab in Paroxysmal Nocturnal Hemoglobinuria (PNH)

Hillmen P, Szer J, Weitz I, Röth A, Höchsmann B, Panse J, Usuki K, Griffin M, Kiladjian JJ, de Castro C, Nishimori H, Tan L, Hamdani M, Deschatelets P, Francois C, Grossi F, Ajayi T, Risitano A, de la Tour RP

N Engl J Med; 2021, Mar 18;384(11):1028-1037

Eculizumab, the first approved anti-C5 complement inhibitory drug revolutionized the treatment of PNH, a diseases characterized by complement-mediated intravascular hemolysis, severe thrombophilia and bone marrow failure. Despite that anti-C5 treatment leaves proximal (C3-level) inhibition of complement unaffected, it results in control of intravascular hemolysis and lowers thromboembolic risk with improved long-term survival. A novel compstatin based pegylated peptide therapeutic, pegcetacoplan, was developed to target proximal complement activation on the level of C3 with the potential to inhibit both intravascular and extravascular hemolysis in PNH.

Results of the PEGASUS trial provided convincing evidence about the effectiveness and safety of pegcetacoplan for the treatment of adults with PNH having hemoglobin levels lower than 10.5 g/dL despite ongoing eculizumab therapy. The study was a phase 3 open-label, controlled trial with the primary end point of the mean change in hemoglobin level from baseline to week 16. Pegcetacoplan was superior to eculizumab with respect to the change in hemoglobin level, with a mean hemoglobin difference of 3.84 g/dL. A total of 35 patients (85%) receiving pegcetacoplan as compared with 6 patients (15%) receiving eculizumab no longer required transfusions. The most common adverse events that occurred during treatment in the pegcetacoplan and eculizumab groups were injection site reactions (37% vs. 3%), diarrhea (22% vs. 3%), breakthrough hemolysis (10% vs. 23%), headache (7% vs. 23%), and fatigue (5% vs. 15%). There were no cases of meningitis in either group. Pegcetacoplan was superior to eculizumab in improving hemoglobin and clinical and hematologic outcomes in patients with PNH.

The FDA approval of pegcetacoplan, as a new treatment for PNH, opens a completely new and broad area on the landscape of complement inhibitors. Almost 15 years after the approval of the first complement-specific drug for PNH, a novel class of complement inhibitors with a distinct mechanism of action enters the clinic. By the potential of broad hemolysis control, including control of intravascular and extravascular hemolysis, pegcetacoplan may finally offer PNH patients with unmet clinical needs or insufficient responses to anti-C5 therapy an alternative treatment option.

28th International Complement Workshop ICW 2021 Virtual Meeting

December 6 – 10, 2021

Virtual meeting: December 6-10, 2021
Abstract submission closed
Late breaking abstract deadline: TBC
Registration open
Notification of abstract acceptance: End of September, 2021

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

EMCHD 2022

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

QUIDEL®

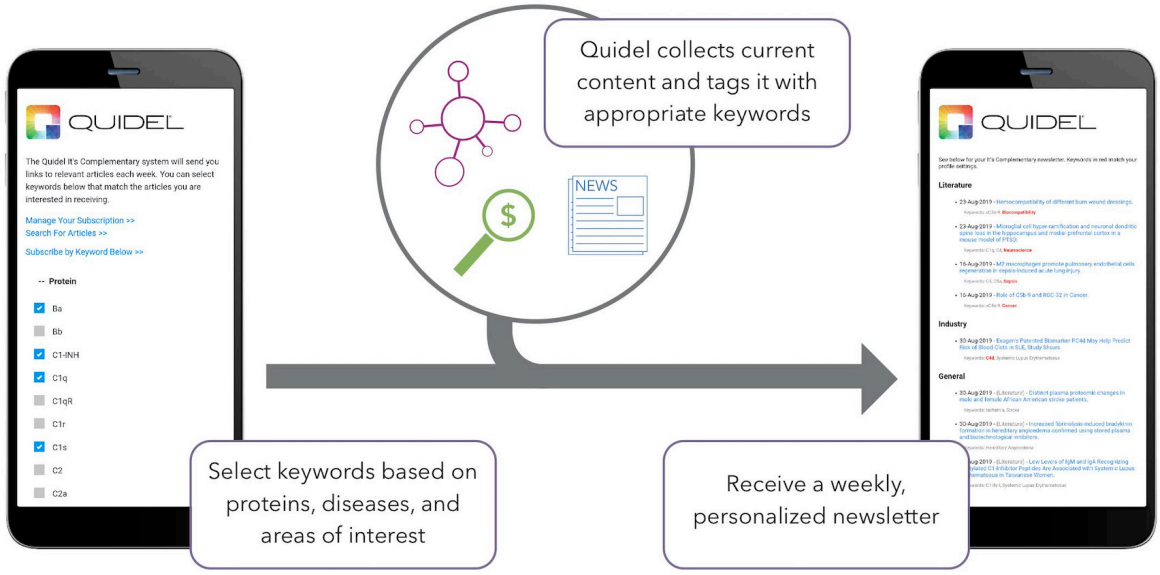
It's Complementary

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.

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

From Our Sponsors

CompTech

Your primary source of complement proteins and reagents.

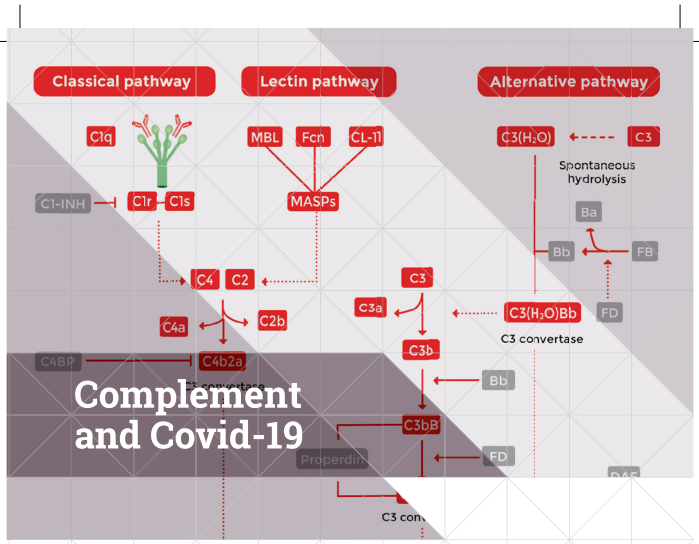
- Purified Complement Proteins
- Complement Cells (EA, Er) & Buffers
- Antisera to complement proteins
- Sera depleted of complement components
- Human Anaphylatoxins – C3a, C4a and desArg forms of C3a, C4a and C5a
- Now available: Human C5a (real C5a, not recombinant protein)

Complement Technology, Inc.
www.ComplementTech.com
Email: contactCTI@aol.com
Phone: 1-903-581-8284
Fax: 1-903-581-0491

Let us guide you on the Complement Path

Register to receive your free poster showing the complement system cascade

Svar Life Science AB I www.svarlifescience.com



Working on Covid-19 and Complement?

Let's share knowledge and contact us!

HycultBiotech bringing innate immunity to the next level

CEDARLANE®

CEDARLANE® offers a wide range of complement related antibodies to mouse, rat and human specificities in various formats *(purified, biotin, FITC, PE, enzyme conjugates).*

Proteins	C1q, C3/C3b/iC3b, C3a, C3d,C4, C5, C6, MBL.
Regulators	C1 Inhibitor, Factor H, Factor I, Crry, DAF, CD59.
Receptors	C3aR, C5aR (CD88), CR3 (CD11b/CD18), CR1 (CD35), CR2 (CD21), gC1q-R.

Browse for targets, species and formats at
www.cedarlanelabs.com/complement
You can also download a copy of the **Complement Antibodies and Proteins Brochure.**

Canada: 1-800-268-5058
4410 Paletta Court,
Burlington, ON L7L 5R2
general@cedarlanelabs.com

USA: 1-800-721-1644
1210 Turrentine Street,
Burlington, NC 27215
service@cedarlanelabs.com

www.cedarlanelabs.com
ISO 9001:2008 and ISO 13485:2003 registered.

Advertise in FoC

If you would like to advertise your complement products or services in the FoC, please contact Trent Woodruff (t.woodruff@uq.edu.au) or the ICS President Peter Garred (Peter.Garred@regionh.dk).