28th INTERNATIONAL COMPLEMENT VIRTUAL WORKSHOP
December 06-10, 2021
Dear Colleagues,

On behalf of the International Complement Society, we would like to welcome you to the ICW 2021 Virtual Workshop. Having to cancel the ICW 2020 in Berlin due to the impact of the SARS-CoV-2 was a difficult decision for Council and to transition to a fully virtual experience was necessary allowing us to replicate the program for ICW 2021.

We are certain that the virtual experience will serve the purpose of presenting the latest research and provide opportunities for scientific exchange with each other. The poster sessions will be available to visit anytime during the meeting and will be presented live on an interactive platform during the formal poster sessions.

On behalf of the Council and Local Organizing Committee, we thank you for your support and for standing by ICS through the changes, disruptions, and difficulties of the past year. We hope to see each of you in person in New Castle, UK in Sept 2023 for the ICW 2023.

Peter Garred, MD, PhD, President of ICS
Peter Zipfel, PhD, ICW organizer
Christine Skerka, PhD, ICW co-organizer
MAIN VIRTUAL PLATFORM

ICW program (December 07 - 10) will take place on Pheedloop platform. Only pre-registered delegates will have the access to platform for ICW program, as well as the contents saved in the platform. The recorded videos saved in ICW virtual platform for play on demand after the conference and until May 31, 2022.

Pheedloop platform for the delegates: https://pheedloop.com/icw2021/virtual/

POSTER SESSION

Live poster presentations will be held in SpatialChat. All pre-registered delegates are welcome to visit SpatialChat to view all the posters during December 06 - 10.

Poster Session A, Wednesday, December 8, 2021, 18:15 - 20:15 (CET)  
Poster Session B, Thursday, December 9, 2021, 17:45 - 19:45 (CET)

SpatialChat platform for the delegates: please find the link in Pheedloop “POSTER HALL” room.

PLATFORM LOG-IN

Log-in information will be sent to all the pre-registered delegates on December 03, 2021.

TEACHING DAY ON DECEMBER 06

Teaching Day will be held in Zoom platform. All pre-registered delegates will receive the access link and information on December 03, 2021.
TEACHING DAY  MONDAY DECEMBER 06

CET
14:00 - 14:15  Introduction to Teaching Day and Modern Aspects of Complement  
Peter Zipfel (Hans Knöll Institute, Germany)

Moderator: Cláudia Vilhena

14:15 - 14:35  Complement Activation, Anna Bloom (Lund University, Sweden)
14:35 - 14:55  Complement Regulation, Viviana Ferreira (University of Toledo, USA)
14:55 - 15:15  Complement and Inflammation, Trent Woodruff (University of Queensland, Australia)
15:15 - 15:30  Part 1 - Live Q&A

15:30 - 15:50  Complement Disease, Diana Karpman (Lund University, Sweden)
15:50 - 16:10  Complement Therapy, Joshua Thurman (University of Colorado, USA)
16:10 - 16:20  Part 2 - Live Q&A
16:20 - 17:00  Break

Group Exercises I (17:00 - 18:15)

Infections diseases and Inflammation  
Gabriele Pradel (Aachen University, Germany)
Elena G. de Jorge (Complutense University School of Medicine, Spain)

Modern Complement Techniques  
Claire Harris (Newcastle University, UK)
Christian Karsten (University of Lübeck, Germany)

Cancer  
Ruben Pio (University of Navarra, Spain)
Lubka Roumenina (Sorbonne Universités, France)

Neurodegenerative diseases  
Simon Clark (University of Manchester, UK)
Bärbel Rohrer (Medical University of South Carolina, USA)

Group Exercises II (18:30 - 19:45)

Infections diseases and Inflammation  
Gabriele Pradel (Aachen University, Germany)
Elena G. de Jorge (Complutense University School of Medicine, Spain)

Modern Complement Techniques  
Claire Harris (Newcastle University, UK)
Christian Karsten (University of Lübeck, Germany)

Cancer  
Ruben Pio (University of Navarra, Spain)
Lubka Roumenina (Sorbonne Universités, France)

Neurodegenerative diseases  
Simon Clark (University of Manchester, UK)
Bärbel Rohrer (Medical University of South Carolina, USA)
About BioCryst

BioCryst is a global, commercial-stage biotech company that is committed to delivering extraordinary medicines that help patients live ordinary lives. Founded in 1986, we are passionate about advancing novel oral therapies for patients with rare and serious diseases.

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REDEEM-1
Transforming PNH Treatment

Evaluating oral monotherapy in patients with PNH who have an inadequate response to C5 inhibitor therapy

REDEEM-2
Transforming PNH Treatment

Evaluating oral monotherapy in patients with PNH not currently receiving C5 inhibitor therapy

For more information, visit www.biocryst.com/PNH
13:50 - 14:15       WELCOME NOTES
                  Peter Zipfel, Peter Garred, Thomas Kamradt, Christine Skerka

14:15 - 15:25      SESSION I – COMPLEMENT STRUCTURE AND FUNCTION
                  Moderators: Nicole Thielens and Peter Garred

(92)               The significance of complex formation of MASP-3 with pattern recognition molecules of the
                  lectin complement pathway in the long-term retention of MASP-3 in the circulation
                  Machida, Takeshi; Kusakari, Kohei; Ishida, Yumi; Omori, Tomoko; Suzuki, Toshiyuki; Sekimata,
                  Masayuk; Fujita, Teizo; Sekine, Hideharu

(18)               Complexes between C1q and MASPs are present in the circulation and may mediate
                  complement activation
                  Rosbjerg, Anne; Bayarri-Olmos, Rafael; Skjoedt, Mikkel-Ole; Garred, Peter

(24)               Structure-Function Studies of Complement Receptor 3 Specific Nanobodies
                  Lorentzen, Josefine Jensen; Rasmus K. Andersen; Gregers Rom; Vorup-Jensen, Thomas

(176)              Biochemical and X-ray diffraction analysis of the interaction between iC3b and the CR3 αl
                  domain
                  Fernández, Francisco José Santos-López; Jorge Martinez-Barricarte; Rubén Querol-García, Javier;
                  Martín-Merino, Héctor; Navas-Yuste, Sergio; Savko, Martin; Shepard, William E.; Rodríguez de Cór-
                  doba, Santiago; Vega, M. Cristina

(181)              Visualizing DNA mediated complement activation using cryo-electron tomography
                  Abendstein, Leoni

15:25 - 15:45      SESSION I – LIVE Q&A

15:45 - 16:15      Break

16:15 - 16:45      KEYNOTE LECTURE I
                  Complement: A key regulator of neural circuit degeneration
                  Introduction: Cláudia Vilhena

Professor Dorothy Schafer
Associate Professor, Department of Neurobiology, University of Massachusetts Chan Medical
School, Worcester, USA
SESSION II – COMPLEMENT ACTIVATION
Moderators: Christoph Schmidt and Elena Goicoechea de Jorge

(48)
Complement Gene Expression and Biodistribution of Complement Proteins in the Synovium from Early Rheumatoid Arthritis Patients
Banda Nirmal; Deane, Kevin; Seifert, Jennifer; Strickland, Colin; Bemis, Elizabeth; Jordan, Kimberly; Goldman, Katria; RA/SLE Network, Accelerating Medicines Partnership (AMP); Morgan, B. Paul; Lewis, Myles J.; Pitzalis, Costantino; Moreland, Larry W.R.; Holers, Michael

(222)
Complement downregulation promotes an inflammatory signature that renders colorectal cancer susceptible to immunotherapy
Guglietta, Silvia; Weber, Lukas; Fosso, Bruno; Marzano, Marinella; Hardiman, Gary; Robinson, Mark; Krieg, Carsten

(140)
Inhibition of neuro-inflammation induced gliomagenesis by CSMD1
Tuysuz, Emre Can; Gialeli, Chrysostomi; Blom, Anna M.

(6)
IgA-Complement immune complexes: A novel mechanism for the delivery of complement proteins to the glomerulus in IgA nephropathy
Hamed, Mohamed

(128)
Novel gain-of-function mutations R249C and S250C in complement C2 protein in patients suffering from rare kidney diseases
Kowalska, Daria; Urban, Aleksandra; Kuźniewska, Alicja; Skrobińska, Anna; de Córdoba, Santiago Rodriguez; Arjona, Emilia; Okrój, Marcin

SESSION II – LIVE Q&A

17:55 - 18:15

18:15 - 18:45
Break

18:45 - 19:15
HANS MÜLLER EBERHARDT LECTURE
Complement in human disease
Introduction: Michael Holers

Professor Mohammed R. Daha
Emeritus Professor, Leiden University Medical Center, Leiden, The Netherlands
SESSION III – COMPLEMENT GENETICS; CROSSTALK; AUTOREACTIVITY AND INFLAMMATION
Moderators: Marina Noris and Kevin Marchbank

(82)
Upregulation of check-point ligand PD-L1 in patients with PNH explained by proximal complement activation
Hafner, Susanne; Anliker, Markus; Drees, Daniela; Loacker, Lorin; Griesmacher, Andrea; Hoermann, Gregor; Fux, Vilmox; Schennach, Harald; Hörtnagl, Paul; Dopler, Arthur; Schmidt, Stefan; Bellmann-Weiler, Rosa; Weiss, Günter, Marx-Hofmann, Astrid; Körper, Sixten; Höchsmann, Britta; Schrezenmeier, Hubert; Schmidt, Christoph Q.

Activation of MASP-3 by PCSK6 links the complement and the proprotein convertase systems in the blood
Dobó, József; Oroszlán, Gábor; Dani, Ráhel; Végh, Barbara M.; Varga, Dóra; Ács, Andrea V.; Pál, Gábor; Závodszky, Péter; Farkas, Henriette; Gál, Péter

(109)
The lectin pathway is associated with platelet activation during clot formation in a microfluidic bleeding model
Golomingi, Murielle; Dobó, József; Gál, Péter; Pál, Gábor Lam, Wilbur; Schroeder, Verena

(227)
Regulatory architecture of the RCA gene cluster captures an intragenic TAD boundary at the CR1 segmental duplication and long-range enhancer
Cheng, Jessica; Clayton, Joshua; Acemel, Rafael; Zheng, Ye; Taylor, Rhonda; Keleș, Sündüz; Franke, Martin; Harley, John; Quail, Elizabeth; Gómez-Skarmeta, José Luis; Ulgiati, Daniela

(218)
Bulk and single-cell RNA-seq analysis of complement and coagulation cascades in severe inflammation; The whole blood model versus patient data
Emblem, Åse; Slåtsve, Arne Martin; Knutsen, Erik; Mjelle, Robin; Lau, Corinna; Landsem, Anne; Nilsson, Per; Brekke, Ole-Lars; Mollnes, Tom Eirik; Karlsen, Bård

SESSION III – LIVE Q&A
Improving the lives of patients—it’s at the heart of everything we do

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CET
14:00 - 15:10  SESSION IV – COMPLEMENT RECEPTORS AND INTRACELLULAR COMPLEMENT
Moderators: Bärbel Rohrer and Santiago Rodriguez de Cordoba

(146) Investigation of complement C3 activation and expression in human skeleton muscle myotubes under pro-inflammatory cytokine stress
Licht, Christoph; Jat, Harpreet; Gilbert, Penney

(27) Intracellular cytosolic C3 protects pancreatic β-cells from IL-1β-driven cytotoxicity
Kulak, Klaudia; Mckay, Marina; Blom, Anna; King, Ben

(22) The Systemic Absence of C5a Receptor 2 Contributes to an Impaired Establishment of Lung Metastases and a Better Disease Outcome in Mice
Hennig, Caroline; Karsten, Christian M.

(200) The C5a / C5a receptor 1 axis in platelets controls tissue revascularization through preferential release of CXCL4
Nording, Henry; Baron, Lasse; Emschermann, Frederic; Haberthür, David; Borst, Oliver; Chavakis, Emmanouil; von Hundelshausen, Philipp; Karsten, Christian; Köhl, Jörg; Langer, Harald

(79) Canonical and non-canonical functions of C1s in cancer
Revel, Margot; Daugan, Marie; Gaboriaud, Christine; Sautes-Fridman, Catherine; Fridman, Wolf Hermann; Roumenina, Lubka

15:10 - 15:30  SESSION I – LIVE Q&A

15:30 - 15:45  Break

15:45 - 16:15  SPECIAL LECTURE
How Complement Wires and Unwires Brain Circuits in Development & Disease
Introduction: Markus Huber-Lang

Beth Stevens, Ph.D
F.M. Kirby Neurobiology Center, Children's Hospital Boston, USA
SESSION V – COMPLEMENT REGULATION AND DISEASE
Moderators: Veronique Fremeaux Bacchi and Leendert Trouw

(76) Atypical hemolytic uremic syndrome-associated FHR1 isoform FHR1*B accelerates complement activation and inflammation
Kang, Yuqi Xu, Boyang; Du, Yujing; Guo, Weiyi; Zhu, Li; Zhang, Hong

(193) Implications for properdin, a complement regulatory protein, in disease
Moore, Sara R.; Nigrovic, Peter A.; Sparks, Jeffrey A.; Lee, Janet; Bain, William; Khuder, Sadik; Ferreira, Viviana P.

(175) MASP3 deficiency in mice reduces but does not abrogate alternative pathway complement activity due to pro-factor D activity
Gullipalli, Damodara; Miwa, Takashi; Golla, Madhu; Sato, Sayaka; Angampalli, Sree; Song, Wenchao

(221) Modeling the complement system for therapeutics development
Alfonso-González, Lucía; Fernández, Francisco José; Vega, M. Cristina; Abvance Biotech, Centro de Investigaciones Biológicas Margarita Salas (CIB-CSIC)

(25) Properdin is essential for alternative pathway C5 convertase activity and C5b-9 formation
Michels, Marloes; Maas, Rianne; van der Velden, Thea; van de Kar, Nicole; Volokhina, Elena van den Heuvel, Bert

SESSION V – LIVE Q&A

17:25 - 17:45

Break

17:45 - 18:15
12:15 - 20:15

VIRTUAL POSTER SESSION
Run in SpatialChat platform

20:15 - 20:45

PIioneerinG WOMEn in COMPlEment
Moderators:
Andrea Tenner
University of California, Irvine
&
Claudia Kemper
NIH, National Heart, Lung and Blood Institute, Bethesda, MD, USA

20:45 - 21:54

SESSION VI – COMPlEment INFECTIOUS DISEASES
Moderator: Robert Rieben and Anna Blom

(70)
Activation of human complement and release of complement-dependent cytokines by synthetic oligodeoxynucleotides cpg motifs
De Boer, Eline; Sokolova, Marina; Quang, Huy; McAdam, Karin; Woodruff, Trent; Götz, Maximilian; Garred, Peter; Nilsson; Mollnes, Tom Eirik; Pischke, Søren

(124)
C4b binding protein protects Group A streptococci from killing by phagocytosis and is internalised in human macrophages together with bacteria
Bettoni, Serena; Dziedzic, Mateusz; Blom, Anna M

(67)
Super-resolution microscopy to decipher the subcellular localization of complement regulatory proteins at the surface of Streptococcus pneumoniae
Vilhena, Cláudia; Du, Shanshan; Cseresnyes, Zoltán; Zimmermann, Lioba; Battista, Miriana; Jost, Aurélie; Eggeling, Christian; Kohler, Thomas; Skerka, Christine; Hammerschmidt, Sven; Figge, Marc Thilo; Zipfel, Peter

(65)
The alternative pathway of complement and long pentraxin ptx3 form a functional axis in the immune response to aspergillus fumigatus
Parente, Raffaellae; Possetti, Valentina; Stravalaci, Matteo; Sironi, Marina; Valentino, Sonia; Day, Anthony; Bottazzi, Barbara -; Cunha, Cristina -; Carvalho, Agostinho ; Mantovani, Alberto; Inforzato, Antonio

(154)
FHR1 increases the risk of severe malaria anemia in a cohort study
González Delgado, Andrés; Reiss, Timo; Zipfel, Peter; Fendel, Rolf; Pradel, Gabriele; Skerka, Christine

21:54 - 22:15

SESSION VI – LIVe Q&A
Rare Inspiration. Changing Lives.

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Panel 1
- Ba
- C2 Intact
- C3 Intact
- C4d
- sC5b-9
- Factor H
- Factor I

Panel 2
- C1q
- C3 Intact
- C4 Intact
- CS Intact
- Factor D
- Factor P

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CET
11:00 - 11:30  KEYNOTE LECTURE II (LIVE PRESENTATION)
Cell-based Medicine
Introduction: Olaf Strauss
Prof. Nikolaus Rajewsky
Berlin Institute for Medical Systems Biology, Berlin, Germany

14:00 - 15:10  SESSION VII – COMPLEMENT AND COVID-19
Moderators: Reinhard Würzner and Nicole van der Kar

(46)
Associations between complement activation and the von Willebrand factor – ADAMTS13 axis in hospitalized COVID-19 patients
Sinkovits, György; Mező, Blanka; Réti, Marienn; Prohászka, Zoltán

(130)
Classical complement pathway responses in vitro differ between SARS-CoV-2 antigens and according to disease severity
Lamerton, Rachel; Marcial Juarez, Edith; Faustini, Sian; Perez-Toledo, Marisol; Goodall, Margaret; Jossi, Sian; Shields, Adrian; Henderson, Ian; Rayes, Julie; Watson, Steve; Crispin, Max; Richter, Alex; Cunningham, Adam

(83)
Development of Immunoassays for Specific Classical and Lectin Pathway Activation Markers and Investigation of Complement Activation in COVID-19
Hurler, Lisa; Toonen, Erik J M; Kajdácsi, Erika; van Bree, Bregje; Sinkovits, György; Cervenak, László; Prohászka, Zoltán

(34)
Local NETosis and Systemic Inflammation and Complement Activation predicts Clinical Outcome of Severe SARS-CoV-2 Infections
Huber, Silke; Massri, Mariam; Grasse, Marco; Fleischer, Verena; Knabl, Ludwig; Knabl Sr., Ludwig; Heinzer, Tatjana; Rambach, Günter; Neurauter, Magdalena; Speth, Cornelia; Würzner, Reinhard

(134)
C1 esterase inhibitor and the kinin-kallikrein system in COVID-19
Caccia, Sonia; Berra, Silvia; Parolin, Debora; Suffritti, Chiara; Polcia, Andrea; Zanichelli, Andrea; Cogliati, Chiara; Riva, Agostino; Gidaro, Antonio

15:10 - 15:30  SESSION VII – LIVE Q&A

15:30 - 15:45  Break

15:45 - 16:15  KEYNOTE LECTURE III
The Genetic History of Plague: What we learn from past pandemics
Introduction: Christine Skerka
Prof. Johannes Krause
Department of Archaeogenetics, Max Planck Institute for Evolutionary Anthropology, Leipzig, Germany
**VIRTUAL SATELLITE SYMPOSIUM - sponsored by Vifor Pharma:**

Pathophysiology of ANCA associated vasculitis and clinical results of the C5-Receptor Antagonist AVACOPAN

Introduction: Peter F. Zipfel

Pathophysiology of ANCA associated vasculitis and the link to the Complement System

Prof. Dr. Ralph Kettritz
Charité and Max-Delbrueck-Center for Molecular Medicine in the Helmholtz Association (MDC), Berlin, Germany

C5-Antagonist AVACOPAN: Results from clinical studies (CLEAR/Ph2 and ADVOCATE/Ph3)

Prof. Dr. Bernhard Hellmich
Medius Klinik Kirchheim, Kirchheim unter Teck, Germany

**LIVE Q&A**

17:15 - 17:45 Break

17:45 - 19:45 **VIRTUAL POSTER SESSION**
Run in SpatialChat platform

19:45 - 20:25 **LAMBRIS COMPLEMENT TRAINING AWARD**
Introduction: Paul Morgan
Presentation by Wioleta Zelek

20:25 - 20:55 **KEYNOTE LECTURE II (REPLAY - NO LIVE Q&A)**
Cell-based Medicine
Introduction: Olaf Strauss

Prof. Nikolaus Rajewsky
Berlin Institute for Medical Systems Biology, Berlin, Germany

20:55 - 21:25 **SOCIAL EVENT - COMPLEMENT BY ART**
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CET
14:00 - 14:42  **SESSION VIII – COMPLEMENT DIAGNOSTICS; STANDARDIZATION AND ANIMAL MODELS**
Moderators: Zoltan Prohaska and Lubka Roumenina

(30) **Immunosuppressive effect of C5a receptor antagonist via macrophage regulation on intestinal transplant in a rat model**
Toyama, Chiyoshi; Maeda, Akira; Kogata, Shuhei; Yoneyama, Tomohisa; Ueno, Takehisa; Tazuke, Yuko; Okuyama, Hiroomi; Miyagawa, Shuji

(219) **Normothermic machine perfusion reconstitutes porcine kidney tissue metabolism but stimulates inflammation which is partly complement dependent**
De Boer, Eline; Sokolova, Marina; Jager, Neeltina; Weiss, Marc; Schjalm, Camilla; Liavåg, Olav; Thorgersen, Ebbe; Nilsson, Per; Jespersen, Bente; Leuvenink, Henri; Mollnes, Tom Eirik; Pischke, Søren

(161) **Development of an ELISA for characterization of mannose-binding lectin-associated serine protease 2 (MASP-2) in human serum and plasma**
Götz, Maximilian; Skjoedt, Mikkel-Ole; Garred, Peter; Bayarri Olmos, Rafael; Rosbjerg, Anne

14:43 - 15:00  **SESSION VII – LIVE Q&A**

15:00 - 15:45  **EARLY CAREER AWARD FOR RESEARCH IN COMPLEMENT**
Introduction: John Atkinson
Presentation by: Hrishikesh Kulkarni

Introduction: Trent Woodruff
Presentation by: John Lee

15:45 - 16:00  **ECCO PhD JOURNAL ARTICLE AWARD**
Introduction: Nicole Schaefer

16:00 - 16:15 Break
SESSION IX – COMPLEMENT THERAPEUTICS ON THE WAY TO THE CLINIC
Moderators: Daniel Ricklin and Claire Harris

(136)
Insight into mode-of-action and structural determinants of the compstatin family of clinical complement inhibitors
Lamers, Christina; Smiesko, Martin; Xue, Xiaoguang; van Son, H; Wagner, Bea; Sfyroera, G; Berger, Nadja; Gros, Piet; Lambris, John D.; Ricklin, Daniel

(100)
Gain-of-function variants of complement C2 support cytocidal activity of anticancer monoclonal antibodies
Urban, Aleksandra; Majeranowski, Alan; Stasiłoć, Grzegorz; Koszałka, Patrycja; Felberg, Anna; Taszner, Michał; Zaucha, Jan M; Okrój, Marcin

(151)
Optimization of Factor H-Binding Peptides for the Protection of Biosurface
Umnyakova, Ekaterina; Bechtler, Clément; Pouw, Richard; Lambris, John; Ricklin, Daniel

(10)
Development of Pharmacodynamic Assays to Assess Ex Vivo MASP-2 Inhibition and Their Use to Characterize the Pharmacodynamics of Narsoplimab (OMS721) in Humans and Monkeys
Freeman, Jeremy; Cummings, Jason; Dudler, Thomas

(168)
Syndrome induced by Shiga-like toxin producing E.coli (STEC-HUS) activation of the complement alternative pathway favors thrombus formation on microvascular endothelial cells
Santarsiero, Donata; Gubser, Miriam; Gastoldi, Sara; Schubart, Anna; Vivarelli, Marina; Bresin, Elena; Benigni, Ariela; Noris, Marina; Remuzzi, Giuseppe

17:25 - 17:45  
SESSION IX – LIVE Q&A

17:45 - 18:10  
Break

18:10 - 18:15  
ORAL / POSTER PRESENTATION AWARDS
SESSION X – TRANSLATIONAL COMPLEMENT
Moderators: Andrea Tenner and Wenchao Song

(170) Complement C5aR2 contributes to the proliferation of neural progenitor cells during murine neurogenesis
Read, Austin; Lee, John; Woodruff, Trent

(29) Investigating the role of the complement system in the radioresistance of rectal cancer
O’Brien, Rebecca; Buckley, Croí; Cannon, Aoife; Meltzer, Sebastian; Røe Redalen, Kathrine; Lysaght, Joanne; Lynam-Lennon, Niamh

(144) Acquisition of complement-dependent cytotoxicity by type II anti-CD20 therapeutic antibody Obinutuzumab
Kuźniewska, Alicja; Majeranowski, Alan; Kowalska, Daria; Urban, Aleksandra; Henry, Sara; Okroj, Marcin

(135) Liver targeted gene therapy is far superior to protein infusions of HDM-FH in long term dosing studies
Kamala, Ola; Smith Jackson, Kate; Hallam, Thomas; Gibson, Beth; Pappworth, Isabel; Cox, Tom; Alexander, Ian; Logan, Grant; Pickering, Mathew; Marchbank, Kevin

(85) Complement Activation Contributes to Hydrocephalus Development following Germinal Matrix Hemorrhage
Mallah, Khalil; Alshareef, Mohammed; Vasas, Tyler; Alawieh, Ali; Borucki, Davis; Couch, Christine; Cutrone, Jonathan; Shope, Chelsea; Eskandari, Ramin; Tomlinson, Stephen

SESSION X – LIVE Q&A

Break

CLOSING SESSION

Closing Remarks - Christine Skerka
ICS Election Results - Claudia Kemper
Farewell by the ICS President - Peter Garred
European Complement Network 2022 – Bern, Switzerland, Robert Rieben
ICW 2023 – Newcastle, UK, Claire Harris & Kevin Marchbank
Farewell by the LOC - Peter Zipfel
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LATE BREAKING ABSTRACTS
A panel of monoclonal antibodies against complement proteins for potential research, diagnostic and therapeutic applications

Józsi, Mihály1,2; Uzonyi, Barbara2; Papp, Alexandra2; Matola, Alexandra2; Nagy, Mátka2; Kovács, Boglárka2; Rabb, Márton1; Szabó, Zsóka2; Cserhalmi, Marcell2; Csincai, Ádám I.2; Lázár, József3; Takács, László3

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Monoclonal antibodies (mAbs) represent a powerful tool for research, diagnostics and as therapeutics. Given the multifaceted role that complement plays in health and disease, there is increasing need for complement specific reagents to reliably detect components and diagnose diseases, as well as to manipulate this complex protein network. Novel anti-complement mAbs with well-characterized specificity, epitopes and functional effects could thus be valuable tools.

To this end, we tested mAbs from Biosystems’ QuantiplasmaTM library produced against natural protein epitopes by a protected technology1,2. A total of 156 mAbs reacting with either C1q, C3, C4, C5, C6, C7, C8, C9, C4b-binding protein (C4BP) or factor H (FH) were further analyzed in ELISA, complement activation and hemolysis assays.

From these mAbs, we identified altogether 42, among them 5 C3, 4 C4, 3 C5, 7 C6, 4 C7 and 8 C9 specific mAbs that could inhibit hemolysis of rabbit and/or hemolysin-sensitized sheep erythrocytes to various extent. In a solid-phase assay, the 5 anti-C3 mAbs inhibited the activity of the C3bBbP convertase. In addition, one anti-C4 mAb rather enhanced hemolysis. From the antibodies that recognized the classical/lectin pathway regulator C4BP, one mAb enhanced and three mAbs inhibited complement activation. Among the 69 mAbs that recognized FH, 22 cross-reacted with factor H (FH). 19 anti-FH mAbs bound to the N-terminal complement regulatory domains and 17 to C-terminal domains 19-20; 5 and 12 mAbs, respectively, induced alternative pathway-mediated hemolysis of sheep erythrocytes. However, 8 anti-FH mAbs inhibited complement activation.

In summary, we generated and characterized a panel of novel mAbs that could be useful as research and diagnostic tools, to develop specific ELISAs, and as potential therapeutics to inhibit complement activation at various levels of the cascade.

Reference 1:

Reference 2:
Laszlo Takacs, Andras Guttmann, William S. Hancock, Barry L. Karger, Manuel Duval,Patrick Berna: Monoclonal antibody based biomarker discovery and development platform US 20070172887 A1

Cholesterol Crystals, Complement C1q and von Willebrand Factor are Present in Atherosclerotic Human Carotid Arteries

Tuncer, Eylul

Atherosclerosis is an inflammatory disease characterized by the formation of cholesterol crystals (CC) within atherosclerotic plaques. CC can trigger complement activation and hemostasis with growing evidence on the cross-talk between both systems, including the interaction between complement C1q and von Willebrand factor (vWF). We have previously shown that the interaction of C1q and vWF occurs on CC surfaces in vitro forming CC-C1q-vWF complexes, and leading to downstream anti-inflammatory effects on human macrophages. However, the role of C1q and vWF in human atherosclerosis is not well established. Therefore, we examined the presence and localization of C1q and vWF in human carotid artery tissues of individuals with or without atherosclerotic manifestations by immunohistochemistry on paraffin-embedded sections and by immunofluorescence on frozen sections. We observed by immunohistochemistry that C1q and vWF localize around CC clefts of atherosclerotic carotid artery tissue. C1q and as well as vWF signal intensities were stronger in tissues from individuals with or without atherosclerotic manifestations by immunohistochemistry on paraffin-embedded sections and by immunofluorescence on frozen sections. We observed by immunohistochemistry that C1q and vWF localize around CC clefts of atherosclerotic carotid artery tissue. C1q and as well as vWF signal intensities were stronger in tissues from individuals with or without atherosclerotic compared to individuals with normal arteries. The signal intensity between C1q and vWF correlated strongly and in specimens with atherosclerotic manifestations by immunohistochemistry on paraffin-embedded sections and by immunofluorescence on frozen sections. We observed by immunohistochemistry that C1q and vWF localize around CC clefts of atherosclerotic carotid artery tissue. C1q and as well as vWF signal intensities were stronger in tissues from individuals with or without atherosclerotic compared to individuals with normal arteries. The signal intensity between C1q and vWF correlated strongly and in specimens with atherosclerotic manifestations by immunohistochemistry on paraffin-embedded sections and by immunofluorescence on frozen sections. We observed by immunohistochemistry that C1q and vWF localize around CC clefts of atherosclerotic carotid artery tissue. C1q and as well as vWF signal intensities were stronger in tissues from individuals with or without atherosclerotic compared to individuals with normal arteries. The signal intensity between C1q and vWF correlated strongly and in specimens with atherosclerotic manifestations by immunohistochemistry on paraffin-embedded sections and by immunofluorescence on frozen sections. We observed by immunohistochemistry that C1q and vWF localize around CC clefts of atherosclerotic carotid artery tissue. C1q and as well as vWF signal intensities were stronger in tissues from individuals with or without atherosclerotic compared to individuals with normal arteries. The signal intensity between C1q and vWF correlated strongly and in specimens with atherosclerotic manifestations by immunohistochemistry on paraffin-embedded sections and by immunofluorescence on frozen sections.
present in human atherosclerotic plaques. This observation suggests that C1q-vWF and also CC-C1q-vWF complex formation can occur in vivo and thus might play a role in the pathogenesis of atherosclerosis.

Loss of intracellular Complement Factor H (CFH) in Retinal Pigment Epithelium (RPE) cells causes retinal degeneration in a novel human RPE-porcine retinal explant co-culture system

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Background: The Y402H polymorphism in the Complement Factor H gene (CFH/FH) represents one of the major genetic risk loci for Age related macular degeneration (AMD), a progressive and degenerative disease of the macula, leading cause of blindness in the elderly population. In our previous work, we show that FH holds additional functions beside regulating complement system in the extracellular space. We showed that intracellular FH is important for RPE cells homeostasis and FH loss impairs metabolic capacity and oxidative balance of RPE cells. In this study we investigated the impact of RPE cells damaged by FH loss on the neuroretina.

Methods: We established a co-culture model comprising hTERT-RPE1 cells and porcine retinal explants, obtained from the visual streak of the porcine retina and rich in cone photoreceptors (PR). We silenced CFH in hTERT-RPE1 cells (siCFH) prior to co-culture initiation. Additionally, cultures were supplemented with exogenous complement sources (FH and C3). Cultures were maintained for 3 days, then fixed and sectioned for imaging and Raman microspectroscopy analyses.

Results: RPE cells deprived of FH causes retinal degeneration in the co-cultured retinal explants compared to retinae cultured with RPE controls. In detail, we observed a reduction in retinal thickness, outer nuclear layer (ONL) thickness and number of PR cells in the ONL. Raman analyses revealed that CFH-silenced RPE cells leads to reduced mitochondrial activity and increased levels of oxidized lipids in the ONL. Moreover, no beneficial or detrimental effects were observed in response of additional complement sources and the damage was not directly mediated by the activation of either microglia or Müller glia cells.

Conclusions: Our data support the hypothesis that RPE-derived FH plays a wider role in retinal homeostasis out with its known complement-regulatory function. As a result of CFH silencing, RPE cells are unable to properly metabolically support the neuroretina and protect it from oxidative stress, ultimately leading to photoreceptor loss, primarily rods. These findings may help elucidate the function of FH in the retina and our co-culture system may provide a suitable model to test medical interventions.

MAP-2:CD55 chimeric construct effectively modulates complement activation

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1. Copenhagen University Hospital

Background: The complement system is a complex tightly regulated protein cascade involved not only in the defence against pathogens but also in the pathogenesis of several diseases. Thus, development of complement modulators has risen as potential treatment for complement-driven inflammatory pathologies. Mannose-binding lectin (MBL)/ficolin/collectin-associated protein-2 (sMAP or MAP-2) has been reported as an inhibitor of the lectin pathway (LP) by competing with its homologous MASP-2. On the other hand, CD55 is a membrane-bound complement regulator that acts on the C3/C5 convertase level, thus modulating the activation of the three pathways of the complement system. In this study, we produced a recombinant chimera inhibitor to modulate complement activation at two different levels of the complement cascade.

Methods: The recombinant inhibitor was designed using the full-length sequence of MAP-2 followed by the CCP domains 1 to 4 of CD55 (CD551-4). MAP-2:CD551-4, and also MAP-2 and CD551-4 alone, were produced in ExpiCHO cells and purified by affinity chromatography using a C-terminal FLAG-tag. The structural properties of the recombinant proteins were assessed by size exclusion chromatography (SEC). Binding and complement deposition assays were performed on ELISA-based assays.

Results: Proteins were successfully expressed and purified. Size exclusion chromatography (SEC) results suggest that MAP-2:CD551-4 forms dimers in the presence of calcium, and that dimers are resistant to 24 hours incubation with EDTA and EGTA. MAP-2:CD551-4 bound to the LP pattern recognition molecules MBL,
ficolin-3, and collectin-11 in a calcium-dependent manner. Using the WIELISA total complement screen, we demonstrate an efficient inhibition of the LP (IC50 0.14 nM) as well as the classical and the alternative pathways (IC50 8.908 nM and 14.05 nM, respectively).

Conclusion: Here we showed that MAP-2:CD551-4, a protein-based chimeric inhibitor, is effective in vitro at modulating all three pathways of the complement system, probably due to the unique combination of a targeting (MAP-2) and a potent regulatory moiety (CD55).

Novel single cell proteotranscriptomics reveals new insights into C5a receptor functions during pneumococcal pneumonia

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Background
Bacterial pneumonia is a life-threatening infection with a high risk of acute respiratory distress syndrome (ARDS) and subsequent death. The complement system is pivotal for the clearance of encapsulated bacteria such as Streptococcus pneumoniae (Spn), a major pathogen of pneumonia. Complement activation liberates C5a which activates its two homologous receptors, C5aR1 and C5aR2. While many experimental studies have suggested that C5a aggravates the severity of ARDS, it is not entirely clear whether C5a has beneficial or detrimental effects on the outcome of Spn infection. Moreover, the extent of functional overlap and role distribution between C5aR1 and C5aR2 remains enigmatic.

Materials and Methods
We generated homozygous C5aR1/2-/- double-knockout mice using CRISPR/Cas9 guided gene editing for phenotyping and functional studies using BALF cells after Spn TIGR4 infection. To further profile alveolar cell populations at the single cell level, we performed TOTAL-seq on FACSorted live CD45+ BALF cells. This novel and innovative single cell proteotranscriptomics workflow utilizes ~200 oligonucleotide-conjugated antibodies (ADT) to enable simultaneous detection of surface protein markers and RNA (Figure 1a).

Results
The C5a-induced influx of neutrophils to the airways was abrogated in C5aR1/2-/- mice. Surprisingly, the dual genetic absence of C5a receptors was associated with a stronger inflammatory response in alveolar spaces after Spn TIGR4 infection, as suggested by higher numbers of neutrophils, increased amount of inflammatory cytokines and chemokines such as IL-6, TNFα, CXCL1, CXCL10 and exacerbated lung vascular permeability. Single cell data analysis revealed 26 distinct cell clusters including 8 subclusters of alveolar macrophages and 8 subclusters of neutrophils after Spn infection (Figure 1b). C5aR1/2-/- mice showed higher neutrophils but lower macrophage counts than C57BL/6J wildtype (WT) mice. WT alveolar cells exhibited heterogeneous levels of C5aR1 ADT and C5aR2 RNA expression among macrophage and neutrophil clusters (Figure 1c). We also observed a small subset within the alveolar macrophage cluster in the WT mice that was barely detectable in the C5aR1/2-/- mice. Further studies are needed to fully decipher its nature and functions.

Conclusion
TOTAL-seq is a powerful method for characterization of immune cell phenotypes in C5aR1/2-/- mice after bacterial pneumonia and will help to elucidate potential synergisms and redundancies of C5aR1 and C5aR2.
Potential involvement of terminal complement pathway overactivation in the pathogenesis of ANCA-associated vasculitis

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Background: Clinical, in vitro, and animal model-derived evidence has demonstrated a critical involvement of the alternative complement pathway in the pathogenesis of ANCA-associated vasculitis (AAV). However, the role of the terminal complement pathway (TCP) is less well studied (1). The current study aimed to explore new experimental approaches to assess the potential role of TCP in this condition.

Methods: A prospective, observational, multicenter study analyzing first episodes and relapses of patients with AAV, with a minimum follow-up of 6 months, was performed. Blood samples were collected at diagnosis (AAV-t1) and at remission (AAV-t2). Control population consisted of age and sex-matched individuals. Complement activation was assessed by analyzing the complement membrane attack complex (C5b-9) deposition on cultured endothelial cells (HMEC-1), by indirect immunofluorescence, after exposing them to activated plasma (patient’s citrated plasma mixed with healthy subjects’ sera pool, 1:1). C5b-9 deposits induced by patient’s activated plasma were calculated as percentage of labeled area with respect to the total area analyzed. Results from patient and control samples were expressed as fold increase (mean±SEM) vs. those obtained with the pool of activated plasma from healthy subjects. TCP soluble factors in plasma, such as sFBb and sC5b-9, were also measured (mean±SEM).

Results: The present results are those obtained with samples from 13 AAV-MPO patients who achieved complete remission (38% men, age 63±14 years) and 10 controls (45% men, age 66±6 years). At AAV-t1, there was a significant increase (p<0.05) of C5b-9 deposition on endothelial cells in response to patients’ plasma (fold increase of 5.3±1.3) compared to controls (fold increase of 1.2±0.2). Samples obtained at AAV-t2 induced less C5b-9 deposition than at AAV-t1 (fold increase of 0.9±0.2; p<0.05), with values similar to controls. Regarding TCP soluble factors, levels were significantly increased in AAV-t1 (1882±418 for sC5b-9, and 3.2±0.4 for sFBb; p<0.05) vs. AAV-t2 (852±104 for sC5b-9, and 1.9±0.2 for sFBb; p<0.05). Levels at AAV-t2 were similar to controls (708±42 for sC5b-9, and 2.4±0.2 for sFBb).

Conclusion: Our results suggest that TCP may be dysregulated in AAV. Further characterization of this dysregulation may lead to new diagnostic or disease activity biomarkers, as well as new therapeutic options for the management of patients with AAV.

Reference 1:

Strong complement activation in Fabry Disease patients at the level of C3

Laffer, Björn¹; Hoffmann, Inken¹; Muschol, Nicole²; Köhn, Anja Friederike²; vom Dahl, Stephan³; Miglinas, Marius⁴; Degulys, Andrius⁴; Suvajdzic, Nada⁵; Fekete, György⁶; Kovac, Arpat⁶; Canaan-Kühl, Sima⁷; Tylki-Szymańska, Anna⁸; Dostálová, Gabriela⁹; Germain, Dominique¹⁰; Lenders, Malte¹¹; Heidenreich, Karin¹²; Brand, Eva¹¹; Köhl, Jörg¹

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11. Department of Internal Medicine D, and Interdisciplinary Fabry Center (IFAZ), University Hospital Münster, Germany
12. Eleva GmbH, Freiburg, Germany

Background
Lysosomal storage disorders (LSD) are characterized by accumulation of specific substrates in lysosomes resulting from mutations encoding lysosomal enzymes or the receptors for their delivery to this organelle. Recently, we found strong complement activation in Gaucher disease, driving the inflammation in this LSD (Pandey et al. Nature 2017). Here, we determined complement activation in Fabry disease (FD), an X-linked LSD caused by mutations in the α-galactosidase A gene. Such mutations lead to the cellular accumulation of globotriaosylceramide (Gb3) associated with several clinical manifestations including cardiac disease, renal failure and cerebrovascular disease.

Material and Methods
We analyzed blood samples from “classic” FD patients (18-55 years). Patient were either treatment-naïve or received enzyme replacement therapy (ERT). Lyso-Gb3 serum concentrations in both groups were >0.5 nmol/l. Samples were collected from 9 European hospitals. Further, blood from healthy controls was collected at the University Medical Center Schleswig-Holstein. The concentrations of C3a and C5a from healthy controls (n=28), treatment-naïve FD patients (n=25) and FD patients treated with ERT (n=13) were determined by ELISA (Hycult Biotech). The study was approved by the Ethics Committee of the University of Lübeck (Ref No: 20-151).

Results
C3a and C5a serum levels in treatment-naïve and ERT-treated FD patients were significantly higher than in healthy controls, whereas they were similar in treatment-naïve and ERT-treated FD patients. Of note, 40% of treatment-naïve and 23% of ERT-treated FD patients had C5a levels in the range of healthy controls. In contrast, C3a serum levels from treatment-naïve and ERT-treated FD patients were consistently higher than those in healthy controls (Figure 1). Regression analysis showed no significant correlation between C3a and C5a serum levels.

Conclusions
Our findings demonstrate strong complement activation in treatment-naïve and ERT-treated FD patients. Surprisingly, C3 cleavage was more pronounced than C5 cleavage suggesting canonical and non-canonical C3 activation. The high C3a and C5a serum levels after ERT treatment suggest sustained complement activation despite enzyme substitution. This ongoing complement activation may explain endothelial dysfunction and the high risk of thrombotic events observed in FD patients. Follow-up studies need to define the mechanisms underlying primary and ongoing C3 cleavage in FD patients.

Reference 1:

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Successful second kidney transplantation after plasmapheresis for suspected anti-endothelial cell antibodies

Lammerts, Rosa 1; van den Born, Jaap; Huberts-Kregel, Magdalena; Gomes-neto, Antonio; Daha, Mohammed; Hepkema, Bouke; Sanders, Jan-Stephan; Pol, Robert; Diepstra, Arjan; Berger, Stefan

1. Univerisity Medical Center Groningen

Successful second kidney transplantation after plasmapheresis for suspected anti-endothelial cell antibodies

Lammerts, Rosa 1; van den Born, Jaap; Huberts-Kregel, Magdalena; Gomes-neto, Antonio; Daha, Mohammed; Hepkema, Bouke; Sanders, Jan-Stephan; Pol, Robert; Diepstra, Arjan; Berger, Stefan

1. Univerisity Medical Center Groningen

Tissue specific non-HLA antigens can play crucial roles in allograft immunity and have been shown to trigger humoral responses leading to rejection of HLA-matched kidney allografts. Interest in the role of endothelial...
TGF-β-induced renal complement expression is associated with fibrosis and depends on the genetic background of mice

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Aims: Renal fibrosis is a hallmark of chronic kidney disease (CKD) and represents a significant health concern due to the increasing number of patients. However, progression rates vary among patients, presumably due to individual genetic differences. We have previously described the strain-dependent progression of renal fibrosis in TGFβ-transgenic mice, with C57BL/6J (B6) mice showing resistance (1). As renal complement expression has been associated with experimental and human kidney diseases, we hypothesize that intrarenal complement expression in TGFβ-transgenic mice depends on the genetic background.

Methods: Kidneys of B6-TGFβ (B6-Tg) and CBAxB6-TGFβ F1 (CBA-Tg) male transgenic mice and their wild-type (WT) controls (B6 and CBAxB6 F1) were investigated at 14 days (n=6/group) for mRNA and protein expressions. Statistical significance was determined via the Kruskal-Wallis test and set at p<0.05.

Results: The survival rate of CBA-Tg transgenic mice was one-tenth of the B6-Tg mice, although plasma TGF-β1 levels were comparably elevated in both transgenic strains. However, only CBA-Tg mice had elevated urinary protein creatinine ratio. In CBA-Tg mice, we observed severe glomerulosclerosis and tubulointerstitial fibrosis, accompanied by a 60-fold increase in complement C3, a 7-fold increase in complement C4, and a 4-fold increase in C3aR mRNA expressions. Immunohistochemistry for C3 protein revealed abundant staining in CBA-Tg kidneys with mostly intra-tubular localization. There was no difference in any of the abovementioned parameters between WT groups.

Conclusion: Genetic background determines the intrarenal complement components expression rates in our murine model of renal fibrosis. The genetically altered renal complement expression might influence the progression of renal fibrosis.

The complement system, a synaptic organizer controlling glutamate transmission in the CNS of healthy and EAE mice.

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Background: The term “synaptic organizers” indicates those molecules which regulate the formation, the development, the functions and the removal of synapses in selected regions of the central nervous system (CNS). These molecules include “presynaptic organizers” that control the specialization of the synaptic boutons (in term of functional efficiency and structural refinement) and therefore their participation to synaptic communications. In recent years we provided evidence that complement selectively releases glutamate from nerve terminals of different CNS regions including the cortex, the hippocampus and the spinal cord (Merega et al., 2014; Olivero et al., 2019).

Methods and Results: Complement (dilution 1:10 to 1:10000) elicited per se the release of glutamate from isolated nerve endings (synaptosomes) isolated from the above-mentioned CNS regions in mouse and rats as well as from the release of glutamate from human cortical nerve, leaving unaltered the release of GABA, noradrenaline or acetylcholine. A comparable releasing activity was also observed in astrocytic processes (gliosomes) isolated from mouse cortex. Interestingly, the complement-evoked releasing activity in both cortical synaptosomes and gliosomes involves a carrier-mediated mechanism, being almost totally prevented by the concomitant presence of the excitatory aminoacid transporters (EAAT) blocker DL-tBOA. In both particles, the complement-evoked releasing activity depended on the C1q and the C3 component of the immune-complex. We extended the study of the releasing activity in the cortex of mice suffering from the experimental autoimmune encephalomyelitis (EAE) an animal model of demyelinating disorder. We found a significant increase of the endogenous levels of both C1q and C3 proteins in both cortical synaptosomes and gliosomes of EAE mice at the acute stage of the disease (21 days post immunization), but a reduced efficiency of the complement-evoked releasing activity in the synaptosomes but not in gliosomes.

Conclusion: These results unveiled that the presynaptic organizer activity of complement on glutamate transmission is altered in a cell-dependent fashion during the course of the disease. The impact of these vents on the onset of the clinical symptoms that typify MS remains to be established.

Reference 1:

Reference 2: