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Dear Readers,

Welcome to the 55th Issue of *Focus on Complement* – the official newsletter of the International Complement Society (ICS).

In this issue we highlight the research group of Ashley Frazer-Abel from Colorado, USA, and the group of Mihály Józsi in Budapest, Hungary. Issue contributor Zoltán Prohászka reviews two research articles on complement in dementia and autoimmunity, and we provide an overview of three recent meetings featuring complement researchers. Prof. John Atkinson also provides a memorium to Michael M. Frank.

We also congratulate Dennis Pedersen, who is the winner of the FoC Young Investigator Cover Image Award. A description of Dennis’ research and cover image can be found in the following pages.

I hope you all enjoy the latest issue of *Focus on Complement*.

Trent Woodruff, PhD.
Editor, FoC
Secretary, ICS

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**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](mailto:t.woodruff@uq.edu.au)) or Peter Garred ([Peter.Garred@regionh.dk](mailto: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](http://www.complement.org)  [@complementsoc](https://twitter.com/complementsoc)
Dennis Pedersen: Winner of the Focus on Complement Young Investigator Cover Image Award

Dennis V. Pedersen is a post-doctoral researcher currently working in the group of Professor Gregers Rom Andersen at the Department of Molecular Biology and Genetics, Aarhus University, Denmark. Here, he also did his PhD from 2013-2016 studying the structure and functions of properdin (FP) in the human complement system. FP circulates in the blood as dimers, trimers and tetramers and primarily serves to stabilize the labile alternative pathway C3 convertase, C3bBb. By protein engineering, Dennis generated a functional monomeric unit of FP and in 2019 he determined the crystal structure of this FP monomer and its complex with the C3 convertase, C3bBbP.

The cover image shows a surface representation of C3bBbP illustrating how a structural eye-shaped core of FP (cyan) formed by the FP fragments TB-TSR1 and TSR4-5-6, binds to the C-terminal domain of C3b (grey) in a way that allows FP to form additional contacts to the vWA domain of Bb (violet). The structure rationalizes the effects of FP mutations associated with disease, provides an improved understanding of FP induced convertase stimulation and offers a foundation for the development of novel inhibitors targeting FP, C3b or FB.

The Young Investigator Cover Image Award. Each Issue the ICS board will select a scientific image to highlight on the front cover of FoC. The winning image will include a brief description of the image, and a profile of the winner within the newsletter.

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

Interested applicants should email the FoC Editor (t.woodruff@uq.edu.au) at least 2 weeks prior to each issue release date (release dates: 1st March, 1st June, 1st September, 1st December), with one suggested image of their research. Images could include immunohistochemistry (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.
Exsera is part of a growing movement in the US of having laboratories within academic institutions with different kinds of scientific models that don’t depend on federal research grants. For our group that means we have the privilege of working at the cross-roads of diagnostics for patient care, while supporting basic and translational research but also support the drug development industry. We use our well characterized complement and autoimmunity test across these areas and find surprisingly often the different needs cross pollinate and benefit each other.

Being part of the University of Colorado, we have the opportunity to support research in areas as diverse as diabetic retinopathy and AMD, to Downs Syndrome and Type 1 Diabetes; from rheumatoid arthritis to the role adverse drug reactions and loss of efficacy. This research work in turn helps us keep informed what new testing in complement is needed. This in turn informs what tests we should develop and validate next to help our physicians properly treat patients, particularly those on complement therapeutics. We currently support both our adult and pediatric hospitals on the campus, and for a growing number of outlying hospitals and practices. Our work to help gauge complement inhibition for acutely ill pediatric patients requiring complement inhibition has proven particularly rewarding for the team.

This work with physicians using complement therapeutics and biologics in turn adds a useful perspective and knowledge base when we work in the pharmaceutical and biotech companies working to bring new drugs to the market. While working in the area bring with it quite a bit of regulations and paper work, it can still be quite interesting and rewarding.

Exsera was started in 2016 when Ashley came to the CU campus. Adding Exsera only built on the complement presence on the campus, which continues to grow. Since that time, we have built out our menu of complement testing validated to the US FDA requirements to a list of over 3 dozen. While we have focused on human tests, we also have an extensive list for non-human primates and a few test for canines and a smattering for mice. In addition to multiple species, we have also been successful in measuring a number sample types beyond the standard EDTA-plasma and serum. Specifically we have successfully measured (and validated) vitreous and aqueous humor, and are also working with cerebral spinal fluid, urine and sputum.

Exsera is enjoying having the honor of answering the call for complement testing during this renaissance of interest in this important part of the innate immune and inflammatory systems.
Complement Research in Budapest, Hungary

The group of Dr. Mihály Józsi

Complement research in Hungary has a long tradition, and researchers at Eötvös Loránd University (ELTE) in Budapest have been working on various complement-related projects since the foundation of the Department of Immunology in 1973. Mihály Józsi joined the group of Prof. Anna Erdei and made his PhD research here. His complement research group was founded in 2012, after returning from Germany, with the support of the Hungarian Academy of Sciences (MTA). In 2017, he became associate professor at the Department of Immunology and is head of the MTA-ELTE Complement Research group since July 2019.

Mihály Józsi’s group is mainly interested in the regulation of the alternative complement pathway and its role in health and disease. Factor H being the major soluble regulator of this pathway, the focus of their research is to understand the physiological roles of factor H and the factor H-related proteins, and the reason for their association with certain diseases, such as age-related macular degeneration, atypical hemolytic uremic syndrome and dense deposit disease. In contrast to factor H, the function of the factor H-related proteins is less characterized and controversial. The group identifies interaction partners and investigates the binding of the factor H family proteins to certain host and non-host ligands, as well as their role in complement activation and regulation. Particularly the interaction of factor H-related proteins with extracellular matrix components, pentraxins and dead cells are investigated. The group described the complement activating capacity for some of the factor H-related proteins via C3b binding and C3 convertase formation, thus an opposite role in complement compared to factor H. In addition, sequence variations and anti-factor H autoantibodies are studied for their effect on the function of the proteins.

In addition to autoantibodies to factor H, autoantibodies to C3 convertase and its components factor B and C3b are being investigated, in collaboration with other groups in Hungary and abroad. Such autoantibodies are prevalent in renal diseases like atypical hemolytic uremic syndrome and C3 glomerulopathy, but the group studies autoantibodies also in other diseases, such as neuromyelitis optica spectrum disorders and rheumatoid arthritis. The aim is to understand functional differences and disease relevance of the autoantibodies.

The non-canonical roles of factor H beyond complement regulation are also poorly explored. In addition to being a major regulator of the alternative complement pathway, factor H binds to receptors and influences cellular functions. Therefore, the group investigates the interaction of factor H and factor H-related proteins with human innate immune cells, such as neutrophil granulocytes, macrophages and dendritic cells, and studies how factor H family proteins modulate the activation and function of these cells.
In collaboration with others, the group strives to build on the knowledge and tools accumulated over the years and explore the possibility of modifying complement activation, and to translate these into improved and novel diagnostic and treatment possibilities, which is one of the main aims of the MTA-supported research.

The group acknowledges support from many complementologists and colleagues around the world, as well as funding from the Hungarian Academy of Sciences (MTA), the National Research, Development and Innovation Office (NKFIH), the Ministry of Human Capacities of Hungary, and the Kidneeds Foundation (Iowa, US).

C1q restrains autoimmunity and viral infection by regulating CD8+ T-cell metabolism


*Science* 2018 May; 360(6388):558-563

In their 2018 Science paper, the group led by Marina Botto from Imperial College, London, UK, using a mouse model of SLE, shows that C1q, but not C3, restrains the response to self-antigens by modulating the mitochondrial metabolism of CD8+ T cells. Systemic lupus erythematosus (SLE) is an autoimmune condition that develops as a result of complex genetic and environmental interactions, and a strong association between SLE and complement C1q deficiency is well known. Chronic graft-versus-host-disease is a well established inducible model of SLE. The authors used this model with combination of C1q and C3 deficiency. In addition, lymphocytic choriomeningitis virus infection was also studied as a trigger, to explore whether C1q also modulates CD8+ T-cell immunity. The observations indicate that C1q plays a pivotal role in regulating effector CD8+ T-cell responses in both autoimmunity and viral infection and suggest that C1q controls the programming and survival of memory precursor effector T cells through its globular domain. The internalization of surface-bound C1q occurred via an endocytic pathway and C1q co-localised with p32/gC1qR in the mitochondria. Altogether these data link C1q to the metabolic reprogramming and regulation of activated CD8+ T cells and lead authors to propose a new paradigm for the protective role of C1q in SLE: C1q limits tissue damage and autoimmunity by acting as a “metabolic rheostat” for effector CD8+ T cells that are capable of propagating autoimmunity via the generation of unique autoantigen fragments by granzyme B. By uncovering the role of effector CD8+ T cells in a lupus-like disease associated with C1q deficiency, these data demonstrate that an aberrant effector CD8+ T-cell response to viral infection may auto-amplify the breakdown of self-tolerance.
Complement C3aR Inactivation Attenuates Tau Pathology and Reverses an Immune Network Deregulated in Tauopathy Models and Alzheimer’s Disease


*Neuron* 2018 Dec; 100(6):1267-1269.

Microtubule-associated protein tau appears to be critical to normal neuronal activity in the mammalian brain. Strong evidence implicates the complement pathway as an important contributor to amyloid (mainly Aβ-associated effects) pathology in Alzheimer’s disease (AD); however, the role of complement in tau modulation remains unclear. In their 2018 *Neuron* paper Litvinchuk and colleagues from the Baylor College of Medicine, Houston, TX, USA show that the expression of C3 and C3a receptor (C3aR1) are positively correlated with cognitive decline and Braak staging in human AD brains. Deletion of C3ar1 in PS19 mice results in the rescue of tau pathology and attenuation of neuroinflammation, synaptic deficits, and neurodegeneration. Through RNA sequencing and cell-type-specific transcriptomic analysis, authors identify a C3aR-dependent transcription factor network that regulates a reactive glial switch whose inactivation ameliorates disease-associated microglia and neurotoxic astrocyte signatures. Strikingly, this C3aR network includes multiple genes linked to late-onset AD. Mechanistically, the team identifies STAT3 as a direct target of C3-C3aR signaling that functionally mediates tau pathogenesis. Altogether these findings demonstrate a crucial role for activation of the C3-C3aR network in mediating neuroinflammation and tau pathology, and unveil a mechanistic and functional interaction between the C3-C3aR pathway and STAT3 signaling and provide novel insights for interrogating this pathway for therapeutic intervention.
A complement session was convened for the first time at the American Society for Neurochemistry (ASN) meeting Newport Beach, CA in May 2003, chaired by Jessy Alexander and Tony Wyss-Coray. Subsequently, sessions were conducted in 2004, 2008, 2014 and 2017 continuing to sustain the interest in complement at the ASN. This year, the session chaired by Jessy Alexander and Marcela Pekna peeked the interest of the participants attracting a room full of attendees at the International Society for Neurochemistry (ISN) /ASN biennial meeting at Montreal, Canada on August 5th, 2019. The complement system traditionally known to function as an important arm of the innate immune system is now recognized as a multifaceted system participating in a wide range of functions in the central nervous system.

During the session, the speakers discussed the widening complement landscape: Jessy Alexander, Buffalo, USA spoke of the effects of complement on the blood-brain barrier (BBB) that acts as the ‘security system’ by regulating the influx and efflux into and from the brain. C5a/C5aR signaling that is increased upon complement activation renders the BBB dysfunctional with loss of junctional proteins and endothelial cell alterations in neuroinflammatory settings such as experimental systemic lupus erythematosus. Marcela Pekna, Gothenburg, Sweden presented results showing the stimulatory effects of C3a-C3aR signaling on brain plasticity and functional recovery after ischemic stroke and the protective role of C3a in ameliorating cognitive impairment induced by neonatal hypoxic-ischemic brain injury. Their studies also demonstrated the potentially clinically relevant efficacy of intranasally administered C3a in experimental models of ischemic brain injury. Trent Woodruff, Brisbane, Australia moved the session to development and neurogenesis. He presented results that revealed the role of C3aR and C5aR1 signaling in regulation of embryonic neurogenesis, namely polarization and proliferation of neural progenitor cells. Acute inhibition of C3aR or C5aR1 in mouse embryos resulted in altered brain structure and functional deficits in adult mice.
Complement: Sculpting the Developing and Diseased Brain (continued)

Cynthia Lemere, Boston brought the session to a close presenting results showing that genetic inhibition of C3 protected hippocampal synapses and prevented memory deficits in aged wildtype and Alzheimer’s-like mice. The engaged audience participated in lively discussions after the talks. The discussions included the burgeoning of complement therapeutics and clinical applications from the use of antagonists, agonists and inhibitors to mode of delivery.

In summary, the session demonstrated that the multifaceted functions of complement in the central nervous system are highly context dependent, on one hand contributing to tissue damage and degeneration, and on the other hand being necessary for normal brain development as well as promoting cell survival and stimulating neural plasticity after injury. The resurgence of interest in complement with the identification of new functions and targets in both healthy and diseased brain was evident at the recent ISN/ASN meeting that enabled the generation of new ideas, strengthening of old collaborations and development of new ones. We hope to see more brain-centered sessions on complement in the future, as we see the complement tentacles stretch into new areas of (neuro)biology.

(L-R)
Jessy Alexander
Marcela Pekna
Trent Woodruff
Cynthia Lemere
Meeting Report 2

Complement at the 103rd Annual Meeting of the American Association of Immunologists (AAI)
San Diego, USA (9th-13th May 2019)

Viviana Ferreira, D.V.M., Ph.D. Organizer 6th ICS Guest AAI Symposium

The 103rd Annual meeting of the American Association of Immunologists was held in San Diego California, May 9-13, 2019, with over 4,000 participants. This year was a wonderful year for complement at the meeting because there were multiple exciting complement-related talks (at least 20 minutes each) encompassing various areas of interest, including: (a) a highly prestigious Distinguished lecture given by Dr. Andrea Tenner on new discoveries in complement and the nervous system; (b) the 5th ICS Guest Symposium at AAI2019, which was organized by Dr. Viviana Ferreira and co-chaired by Dr. Ron Taylor and Dr. Sanjay Ram and covered topics on complement and cancer, therapeutics, autophagy and dysregulation in disease; (c) The AAI invited Dr. Michael Carroll and Dr. Claudia Kemper to organize a Major Symposium on “Acute and Chronic Inflammation” and three of the six scheduled presentations centered around recent exciting developments in the complement field; (d) a talk on developing fields in complement in the yearly standing-room-only “Back to School” session; and (e) and an additional complement talk in a meeting Block symposia. What follows is a summary of each talk. We look forward to seeing our colleagues at the AAI ICS Guest Symposium 2020 in Honolulu, Hawaii.

Distinguished Lecture at AAI 2019: Complement: primitive yet powerful – new discoveries in immunity and the nervous system. Andrea J. Tenner, Ph.D., Univ. of California, Irvine

The Distinguished lecture showcased the emerging understanding of a stepwise engagement of complement components in directing an appropriate immune response. The induced expression of C1q in tissue as a response to injury, leads to C1q binding to and clearance of injured/apoptotic cells, suppression of macrophage/dendritic cell proinflammatory cytokine production and prevention of T cell activation and autoimmune responses. When additional pathogenic signals are received, inducing downstream complement activation, C3/C5 fragments appropriately promote the killing of pathogens and the engagement of the adaptive system in host protection. Intriguing new studies have uncovered a neuroprotective activity of C1q and a role for the early classical complement components (C1 through C3) in the fine tuning of neural circuits via complement dependent synaptic pruning. While critical for normal development, aberrant or excessive synapse pruning is implicated in numerous neurological disorders. In addition, there is a clear demonstration in mouse models of Alzheimer’s disease, that C5a engagement of C5aR1 polarizes microglia toward a detrimental inflammatory state ultimately leading to loss of neuronal complexity and behavioral performance. Genetic ablation or pharmacologic inhibition of C5aR1 rescued neuronal branching and behavior in multiple AD models, supporting the therapeutic potential of suppression of C5aR1 signaling for AD and other neurological diseases in humans.
**ICS Guest Symposium at AAI 2019: Newly Defined Essential Roles of Complement**

*Chairs: Dr. Ron Taylor, Univ. of Virginia and Dr. Sanjay Ram, Univ. of Massachusetts Medical School*

**Dr. Maciej Markiewski, Texas Tech University Health Science Center, Complement as an emerging target for cancer immunotherapy:** Complement was thought to contribute to cancer immune surveillance through complement-mediated tumor cell lysis. In contrast to this notion, in this talk, Dr. Markiewski presented data demonstrating that complement promotes tumor growth by inhibiting antitumor immunity. This was mediated by C5a generated through the classical pathway and interacting with C5aR1 expressed on myeloid-derived suppressor cells (MDSC). Follow-up studies confirmed their observations in mice and humans. Currently complement appears to be upstream regulator of several immunosuppressive cells including MDSC, T regulatory cells, and tumor associated macrophages, and C5aR1 and C3aR signaling directly inhibit cytolytic activity of tumor infiltrating CD8+T cells by suppressing IL-10 expression in these cells. C5aR1 contributes cancer metastasis by regulating MDSC recruitment to the lung premetastatic niche and enhancing self-renewal of alveolar macrophages in this niche. These diverse functions of complement in cancer make this system uniquely suited to be a target for novel anticancer therapies.

**Dr. Claire Harris, Newcastle University, United Kingdom, Complement and disease: the changing landscape of treatment and therapy:** Complement plays a role in a large number of diseases affecting diverse tissues including the vasculature, kidneys, brain and eyes. The increasing body of evidence that complement drives disease and the success of eculizumab in treating a number of life-threatening conditions has driven development of a multitude of drugs against different targets. There are challenges to successful drug development, including target concentration and turnover (often very high), side-effects that may be encountered by switching off a crucial arm of immunity and delivery of the drug to the site of pathology. In this session, Dr. Harris discussed pioneering ways that are emerging to clear these hurdles. Next generation drugs are progressing through clinical trial; these include orally-bioavailable molecules, ‘recycling’ antibodies, gene therapies and agents which seek to modulate complement, rather than block completely. There is intense activity, many new Pharma entrants to the area, a broadening of disease focus and a growing enthusiasm to move beyond C5 with some innovative approaches that may reduce costs and address safety issues.

**Dr. Anna Blom, Lund University, Sweden, Regulation of autophagy by complement component C3:** C3 is central component of the complement system. When activated, plasma C3 marks target particles such as bacteria for clearance by phagocytosis. Dr. Blom presented how C3 also exists within the cytosol where it interacts with ATG16L1, and is therefore involved in the intracellular recycling of autophagy in pancreatic beta cells. Knockout of C3 in beta cell line leads to dysfunctional autophagy with deficient fusion of autophagosome with lysosomes, and increased cell death after challenge with diabetogenic stresses, which are usually alleviated by increased autophagic turnover. Accordingly, expression of C3 is increased in pancreatic islets in diabetes type 2. Further, she proposes that C3 may enter cytoplasm via
several mechanisms such as translation directly in cytoplasm from alternative start site located after the signal sequence and retrotranslocation of C3 from endoplasmatic reticulum to cytoplasm.

Dr. Viviana Ferreira, University of Toledo College of Medicine, Properdin and Factor H: Mechanisms of complement dysregulation in disease: The alternative pathway of complement is activated excessively in several inflammatory diseases, particularly when there is a regulatory defect. This talk focused on the role of properdin in pro-thrombotic disorders, atypical hemolytic uremic syndrome (aHUS) and paroxysmal nocturnal hemoglobinuria (PNH). It was determined that inhibition of properdin protects red blood cells and endothelial cells from complement-mediated damage, and is more effective than other clinically relevant complement inhibitors tested in in vitro assays for human aHUS, PNH, and heme-induced endothelial cell complement-mediated damage. In addition, she presented the development of a novel ELISA-based assay that allows to measure the function of properdin in biological samples and how the detected function is directly related to the level of oligomerization of properdin in the sample. This assay may lead to understanding the contribution of the oligomeric distribution of properdin in health and disease.

AAI2019 Major Symposium: Acute and Chronic Inflammation

Chairs: Dr. Claudia Kemper, NHLBI, NIH and Dr. Michael C. Carroll, Boston Children’s Hospital

Dr. Claudia Kemper, NIH, Non-canonical roles for intracellular complement in normal cell physiology and in inflammatory disease: This major symposium began with an overview about the expanding roles of the intracellular complement system, the complosome, in basic cell metabolism including the control of nutrient influx, glycolysis, oxidative phosphorylation and oxygen metabolism in human T cells, and how these events shape protective T-cell immunity. She then extended the ‘metabolic role’ of the complosome to epithelial cells and presented novel data showing that intracellular C3aR stimulation maintains normal prostate epithelial cell (pEC) proliferation via the regulation of mitochondrial ‘fitness’. Thus, loss of intracellular C3a levels within pECs induced malignant transformation, whilst reconstitution of intracellular C3a reduced prostate cancer growth in vitro and in vivo. She closed with the suggestion that complement may have its evolutionary roots intracellularly and that bi-forked compartmentalization of complement activity occurred over time: liver-secreted and ‘classically -folded’ C3 functions as opsonin and gives rise to convertases and MAC, while intracellular C3 exists mostly in unfolded form and is processed by specific proteases to release C3-domains for distinct metabolic activities.
Dr. Michael C. Carroll, Boston Children’s Hosp., Functional importance of allelic differences in human complement C4A and C4B and inflammatory disease: Although relatively rare, individuals bearing a deficiency in C4 almost always develop lupus. The human C4 locus is characterized by two highly conserved isoforms, i.e. C4A and C4B, which differ by only 4 amino acids. GWAS studies show that deficiency in the C4A isotype which is relatively common, results in an elevated risk for lupus. To test if C4A was more protective against autoimmunity relative to C4B, the authors used gene editing to generate mC4A and mC4B strains. The two strains were bred with a lupus mouse model (564Igi) and characterized over a period of 2-6 months. Remarkably, mC4A lupus mice were protected relative to mC4B based on a reduction in number and size of autoreactive germinal centers, loss of B cell tolerance and reduced ANA. The authors concluded that the isotypic resides of C4A promote more efficient clearance of apoptotic debris and maintenance of B cell tolerance relative to C4B. These findings suggest a therapeutic approach for lupus patients bearing a deficiency in the C4A isoform.

Dr. Jörg Köhl, Univ. of Lübeck, Germany, Non-canonical functions of complement in inflammatory diseases: In his talk, Jörg Köhl presented non-canonical functions of complement in several inflammatory disease. The main focus was on the anaphylatoxin C5a and its interaction with its cognate receptors, C5aR1 and C5aR2. As a first example, he outlined novel functions of C5a as a regulator of B-1 cell homeostasis. Secondly, he showed data that identified C5a/C5aR1 axis activation as a new pathway driving the development of food allergy. The third example focused on an unexpected new role of the C5a/C5aR1 axis as a regulator of glucosphingolipid metabolism in Gaucher disease, suggesting that this pathway controls the generation of autoantibodies against glucosylceramide as a driver of disease pathology. Finally, he presented a novel function of C5aR2 as shuttle receptor that mediates endothelial transcytosis of C5a thereby igniting the flame in experimental arthritis. As an important methodical advancement, he presented floxed anaphylatoxin receptor reporter mice that allow reliable receptor tracking and cell-specific deletion.

Back to School session: A Review of Four Fast-Moving Fields

Dr. Joshua Thurman, Univ. of Colorado, The complement system – new tricks for an old dog: This was one out of four talks in this session and began with a brief overview of the history of complement research and the traditional paradigm of complement as simply a downstream mediator of antibody-induced cell lysis. Recent advances in our understanding of complement biology were then reviewed, with a focus on four areas: alternative pathway mediated diseases, the interaction of complement with the adaptive immune system, the role of the complement cascade in cancer, and the development of anti-complement therapeutics. Work over the past 20 years has revealed that the complement cascade can be engaged by a variety of mechanisms, not just by antibodies and immune-complexes. Rather than functioning solely as a downstream effector of antibodies, it is now clear that all three activation pathways can be activated in an antibody-independent manner. Uncontrolled activation of these pathways is now known to play a critical role in several diseases, including C3 glomerulopathy and atypical hemolytic uremic syndrome.
Furthermore, in addition to functioning downstream of immunoglobulin, complement activation fragments can also function upstream of the adaptive immune system, directly and indirectly shaping the B cell and T cell response to antigens. This broader view of complement biology helps to explain some surprising observations, including the important role of the complement system in promoting the growth of many different types of cancer. Although complement was long believed to help the body eliminate cancers, elegant experimental work has now shown that complement activation can also block anti-tumor immunity, allowing cancers to grow. This broader view of the role of complement in health and disease has revealed many potential indications for anti-complement therapeutics. Several new complement inhibitory drugs are currently in development, and it is likely that some of these will enter clinical use in the near future.

Additional complement-related talk at AAI2019.

Work on complement was also presented during the Block Symposium ‘T cell Regulation and Function’ by Dr. Erin E. West from the Kemper laboratory. Her presentation detailed that CD46 stimulation on T-cells upregulates both the arginine transporter CAT-1 and, unexpectedly, Arginase-1 expression. While Arginase-1 is well characterized in macrophages where it is associated with the immunoregulative M2-type, its function in T cells has not been described. Surprisingly, CD4+ T cells isolated from four patients with rare Arginase-1-deficiency initially mount normal Th1-responses, but display a hastened transition into the Th1-contraction phase. Furthermore, metabolic profiling of the patients’ cells demonstrates that they shunt into a compensatory ‘amino-acid-pathway’ for their critical ornithine and polyamine generation driving Th1-induction. Overall, these data demonstrate a complosome-driven intrinsic role for Arginase-1 and unveil an important compensatory mechanism for maintenance of protective Th1-function in the absence of normal arginine-catabolism, thus, explaining why patients with Arginase-1-deficiency do not suffer from recurrent infections.
Workshop report: 2nd YCI Meeting

The second meeting of the “Young Complement Investigators” was held from June 7th – 9th, 2019 at the Luxembourg Institute of Health (LIH), “The House of BioHealth (HoBH)” in Esch-sur-Alzette, Luxembourg. The workshop was designed to be an opportunity for early career scientists to share and discuss their projects within different areas of the complement field. Here, we review the course and the highlights of this cozy and informal meeting.

Luxembourg, with its incredible variety of fascinating cultural places and “The House of BioHealth (HoBH) – where the next generation begins”, provided an exceptional opportunity for a group of ten scientists from six different European countries. A perfect place to discuss the various complement research projects, methodological problems, and future directions within the complement field (e.g. job opportunities, grant applications).

Impressions of the second YCI-Meeting 2019 in Luxembourg

After arrival in Luxembourg, we started our workshop on Thursday evening with a welcome dinner at an Italian restaurant. The following day, Professor Markus Ollert, director of the Department of Infection and Immunity at the LIH, commenced our first YCI Science Day with a total of six talks at the HoBH. Professor Ollert leads basic and translational research with a focus on immune-related disorders including asthma, allergic rhinitis and anaphylaxis and he is highly interested in the complement system. He presented an overview of the research units and companies at the HoBH and informed about possible research grants and applications.
Nikolaj Kirketerp-Møller (University Hospital Copenhagen, Denmark) began with the first scientific topic “C1q/TNF-related protein 6 is a new pattern recognition molecule of the Lectin Pathway”, discussing the biological role of CTRP6 within the complement system.

The second talk was given by Martin P. Reichhardt (University of Oxford, UK) presenting “From ticks to human biology – a structural insight into the inhibition of complement C5”. His amazing work consider a novel complement C5 inhibitor from tick saliva, CirpT1 (Complement Inhibitor from Rhipicephalus pulchellus of the Terminal pathway). He presented among others the crystal structure of CirpT1 bound to C5 macroglobulin domain 4.

After a delicious lunch break at “The cloud” in HoBH, Loek Willems from Hycult (Uden, Netherlands) shed light on to various aspects of collaborations between academia and industry. He gave great advices for grant applications, building training networks and answered all of our numerous questions. Especially for young scientists, this seminar opened up new future perspectives for working in the complement field.

Mariana Gaya da Costa and Felix Poppelaars (both University of Groningen, Netherlands) gave the talks of the afternoon session, discussing the role of the complement system during hemodialysis and renal transplantation. Mariana highlighted in her talk “Administration of intravenous iron formulations induces complement activation in-vivo”, that iron sucrose resulted in complement activation in non-dialysis chronic kidney disease patients and even more in hemodialysis patients. Felix finished the session with “The influence of a new complement gene polymorphism on kidney transplant outcome”. His work suggests that the CFHR3/1 polymorphism might impact the development of acute rejection and provides a new role for these complement regulators in acute renal rejection.

The first YCI Science Day was completed by a visit of the LIH HoBH facilities and spacious labs filled with high-tech equipment – a perfect place to study the complement system. We finished the day with an amazing dinner at the beef Restaurant “Beeftro” close to the historical blast furnaces at Belval, Luxembourg.

The second YCI Science Day, started with the role of the complement system in the eye and retinal diseases given by Yassin Jabri and Nicole Schäfer (both University Hospital Regensburg, Germany). Yassin described the “Age-dependent complement expression in a mouse model for Stargardt macular degeneration”, proving on one the hand age-related changes in complement expression in different retinal cell types while on the other hand showing local changes of complement activity in the diseased eye. Afterwards, Nicole presented her work on “Properdin-dependent local complement activity of stressed primary human retinal pigment epithelium (RPE) cells” providing evidence at both RNA and protein level that primary human RPE cells express complement components independently from the systemic complement system. Furthermore, oxidative stress and properdin were able to change this local RPE complement activity.

After a coffee break, Jack Reddaway (Cardiff University, UK) presented “Differential complement gene expression underlies synaptic plasticity in associative learning”. He showed a so far novel interface between the immune system and normal plasticity, discussing the influence of the complement system on schizophrenia and synaptic pruning respectively to strong genetic associations.

Xavier Dervillez (Luxembourg Institute of Health, Luxembourg) introduced “FHR4-based Complement-activating Multimeric immunotherapeutic compleXes (CoMiX) inhibit tumors growth of HER2-expressing xenografts in NUDE mice”, an innovative complement-mediated destructive tumor cell targeting strategy. Immunoconjugates
consisting of small antibody fragments, a multimerisation domain and FHR-4 (CoMiX) promote the activation of the complement alternative and/or classical pathways on tumor cells. Xavier was honored for his excellent presentation with the YCI-presentation award, sponsored by Hycult - a full travel award to EMCHD2019 in Madrid. After the lunch break, Shinjini Chakraborty (University Hospital Ulm, Germany) gave her talk on “Generation of Complement fragments in intestinal mucus could be a putative effect of enhanced protease activity during experimental sepsis”. She presented her preliminary data on complement activation (C3a and C5a) during sepsis and trauma.

The second YCI Science Day was completed by Inkeri Lokki giving a review on “Aberrant complement regulation, apoptosis, and inflammation in pre-eclamptic pregnancy”. She gave an overview of preeclampsia and the underlying failure in regulating vascular and hemodynamic changes in pregnancy, which may be due to dysregulation of immunological processes. During the evening we visited the beautiful historic places in Luxembourg-City and afterwards we enjoyed dinner and dancing at the famous nightlife district Clausen.

Our second YCI meeting was completed on Sunday morning with a boat trip and farewell lunch at the river Mosel. There, we summarized the workshop: With the 2nd YCI meeting, we provided an opportunity for highly motivated young complementologists to discuss their science. We were able to explore the methodological pitfalls, discuss lab protocols and set up new collaborations. All attendees expressed their motivation for the complement work, and voted to continue with an annual event for young complementologists. The YCI will be active again in Madrid in September 2019, and we are all looking forward to having many more events for young scientists in the complement field in the future!

We thank all participants and our supporters for this fantastic YCI workshop.

The organizers
Xavier Dervillez (local organizer) and Nicole Schäfer (YCI organizer events/meetings)
In Memoriam

Michael M. Frank, MD
02/28/37 – 08/01/19

Michael M. Frank, M.D., the Emeritus Samuel L. Katz Professor and Chairman of Pediatrics at Duke University School of Medicine, died a few days after a large intracerebral bleed which was a complication of a low platelet count secondary to underlying myelofibrosis. Mike was a wonderful family friend, long-standing scientific colleague and a remarkable mentor for many of us in the complement field.

Dr. Frank was a Ford Foundation scholar at the University of Wisconsin (1952-1956) which he entered at age 15. He then attended Harvard Medical School (1956-1960). After a year of internship in Internal Medicine on the Harvard Medical Service at the Boston City Hospital, he served 1 year as a Junior Asst. Resident in Pediatrics at the Johns Hopkins Hospital in Baltimore. From 1962-64 he was a Clinical Associate at the National Institute of Mental Health of the National Institutes of Health in Bethesda, MD working by special arrangement in the Immunology Section of Cancer Institute with Herb Rapp & Tibor Borsos. He then completed a Pediatric Residency at Johns Hopkins Hospital. From 1965-66 Mike was a Visiting Scientist at the National Institute of Medical Research in Mill Hill, London, England with Dr. J.H. Humphrey. He then joined the Senior Staff at the NIH working in the Immunology Section of the Biology Branch, National Cancer Institute. He next was recruited to the Laboratory of Clinical Investigation of the National Institute of Allergy and Infectious Diseases where he became Chief of the Clinical Immunology Section. He served as Chief of the Laboratory and Clinical Director of NIAID for 13 years. In 1990, Dr. Frank left the NIH and began a second career in academic medicine as the Samuel L. Katz Professor and Chairman of Pediatrics at Duke University Medical School. In embracing his new role, he combined his love of clinical medicine and child health with his skills as a bench researcher.

Under his leadership, the Department of Pediatrics grew, doubling the number of faculty. Feeling strongly that the Department of Pediatrics needed its own space, Dr. Frank was instrumental in the construction of the Duke Children’s Hospital and Health Care System in 2000. The hospital is widely regarded as one of the top children’s hospitals in the country and remains as a legacy to his perseverance and drive. After 14 years as Chair of Department of Pediatrics he returned to the laboratory and continued his research career.

On the Complement System
With fellows from the US Public Health Service who had joined his laboratory, Mike published the initial description of a clinical cohort of patients with Hereditary Angioedema (HAE), a disease at that time with an approximate 20% mortality. Frank’s group was the first to report the highly successful use of the attenuated androgen (danazol) in the treatment of HAE and this became the standard of therapy (life-saving) for decades. Mike’s group also did the initial controlled studies on the use of C1 inhibitor in treatment of acute attacks of HAE and its prophylaxis. It also became used worldwide for prophylaxis of HAE and for treatment of acute HAE attacks. As a result of these studies, Dr. Frank received the first lifetime achievement award of the HAE patient’s association. He was still working on HAE in his “retirement” and gave a presentation on his work at the World Allergy Meeting in Jerusalem in December 2016. Further, Mike, at the age of 82, gave a wonderful talk at a symposium entitled, “Hereditary angioedema with normal C1-INH inhibitor: Back to a learner’s permit.” His goal was to develop a simple test (biomarker) for HAE with normal C1 inhibitor. As he pointed out, he also had plans for accomplishing the more
In Memoriam

interesting question about whether he could explain the pathophysiology of the disease. He did not know the answer and hoped to find out. He was a highlight of the symposium and widely congratulated by young and old immunologists. The FAAAAI Foundation “honored the life and work” of Dr. Michael Frank by creating Michael M. Frank M.D. FAAAAI Lectureship. US Hereditary Angioedema Foundation provided a substantial gift for launching this lectureship.

Working with Baruch Benacerraf, Ira Green and Lenny Ellman, Mike’s laboratory identified C4 deficiency in the guinea pig. These animals had no detectable classical complement pathway function. He followed up this study with a definitive demonstration of the existence of an alternative pathway of complement activation. This observation was followed by a series of studies on the role of the classical vs alternative complement pathway in immunopathologic states. An important finding in another set of studies of these animals was that C4 deficiency is associated with a profound antibody synthetic defect. Also, the availability of C4 deficient guinea pigs and cobra venom factor to deplete C3 led to seminal studies on the role of antibody and complement in the clearance of erythrocytes from the circulation. This in turn led key functional studies of complement and Fc receptors in man. He showed first in animal studies and then in human beings that an IgG-sensitized red blood cell is removed by IgG Fc receptors primarily in the spleen and that the rate of removal of the red cell was a function of both magnitude of the antibody coating and state of splenic Fc receptor activation. Similar informative studies were performed employing C3b coated erythrocytes in guinea pigs and man.

Working with Keith Joiner, Mike’s group defined a clear-cut mechanism by which pathogenic organisms resist attack by antibody and complement. He showed that, with non-pathogenic gram-negative bacteria, complement inserts in the lipid outer membrane of the bacteria leading to pore formation and bacterial death. With pathogenic gram-negative bacteria, the entire membrane attack complex is bound to the outer membrane but, instead of the hydrophobic membrane attack complex inserting into the outer membrane to destroy the bacteria, the complex is shed. The serum resistant gram-negative organisms consumed all of the complement available without being damaged, while the serum sensitive organisms utilized only a limited amount of complement in being lysed.

In retirement, Mike, along with his ongoing work on HAE, focused on the role of complement in HIV infections that was supported by the Gates Foundation. In this work, he first studied survival of the envelope on injection and found that, after it entered the circulation, it was removed by asialoglycoprotein receptors. Further, it was basically destroyed within minutes of injection, something the people who worked on vaccine development had never appreciated.

Mike was a true Physician-Scientist. He contributed much both to our understanding of human disease (especially HAE) and to our basic understanding of the biology of the complement system. He was a seasoned and accomplished investigator and clinician.
In Memoriam

A leader in the field of complement, Dr. Frank mentored some of the most prominent allergists and immunologists in the world today and was immensely proud of the success enjoyed by his trainees.

Dr. Frank was author of over 450 peer reviewed scientific papers, an invited lecturer all over the world and co-authored the fifth edition of Samter’s Immunological Diseases.

We especially want to bring to your attention an article Mike wrote with Eric Wagner which is a wonderful comprehensive review entitled “Therapeutic Potential of Complement Modulation” that was published in Nature Reviews in 2010. It is worth a careful read. He concluded the Review noted above with the following statement “As we further understand the role of the complement proteins in normal physiology and host defense, we may have a better understanding of the proteins that can be safely inhibited and those that cannot”.

With great thanks and respect – John P Atkinson and Jeffrey Gelfand

Michael M. Frank, MD

February 28, 1937 – August 1, 2019
We are pleased to announce and to invite you to the “17th European Meeting on Complement in Human Disease” (EMCHD 2019), to be held in Madrid, Spain, from September 14th to 17th, 2019.

This EMCHD 2019 meeting represents a new edition of a very successful series of congresses in which the expanding role of complement in human disease and the excitement of novel diagnostic and therapeutic developments will be updated. It will be a fruitful and stimulating encounter for professionals in the complement field from all over the world and an opportunity to share and discuss cutting-edge topics in this continuously evolving area. Our scientific program will include several top-notch keynote speakers, selected presentations from the best abstracts submitted, and poster viewing sessions. A satellite meeting will address specific questions on complement-related kidney diseases. Commercial stands, placed in a large hall shared with refreshment break meeting points, and industry-fostered luncheon seminars will round up the program.

We very much hope you will join us and enjoy Madrid, a modern, cosmopolitan and fun city, along with the warmth of its people and the taste of its food and wines.

We look forward to welcoming you in Madrid!

Prof. Santiago Rodríguez de Córdoba
Chairman of EMCHD 2019

Local Organizing Committee:
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Meeting Topics:
Complement structure and function
Complement crosstalk
Complement genetics
Infection and autoimmunity
Complement-related diseases
Animal models
Complement therapies

Our website is already available at: http://emchd2019.com

If you would like to be automatically updated on news and other useful information regarding EMCHD-2019, then please CLICK HERE
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.

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