



International Complement Society



European Complement Network

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Dear members of the complement community,

Welcome to the June 2014 issue of the 'Focus on Complement'

This 34th issue of FoC contains:

- An announcement on the **XXV ICW in Rio de Janeiro** September 14-18, 2014.
- The **Flash News** in this issue further solidifies our growing understanding that C1q serves an impressive range of key biological functions aside from classical pathway activation. Andrea Tenner's group reports on two studies showing that C1q regulates synaptic refinement and also contributes to angiogenesis and wound healing.
- **Dr. Gudmundur Johann Arason obituary**
- The **Complement research teams around the world 'series'** introduces in this issue a laboratory from The Netherlands (**Dr. Seelen's group**) and Switzerland (**Dr. Rieben's group**).
- An advertisement for three **PhD Studentships in complement research**

If you would like to contribute with an article to a future issue or have suggestions for a subject theme, please contact Claudia Kemper or Zvi Fishelson;
Claudia.kemper@kcl.ac.uk, lifish@post.tau.ac.il

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The 25th International Complement Workshop

Dear Colleagues,

The XXV International Complement Workshop will take place in September 14-18, 2014, for the first time in a South American country. The venue of the Workshop is “Angra dos Reis Auditorium”, Windsor Atlantica Hotel, a five-star hotel located on the renowned Copacabana beach, Rio de Janeiro, Brazil.

The abstract submission deadline is now over and based on the submissions received the organizing committee is currently preparing the final program and the list of travel awardees.

Please visit the Workshop's webpage for regular updates (<http://icwrio2014.com/>).

We look forward to welcoming you in Rio de Janeiro in a few weeks for a scientifically stimulating and socially enjoyable meeting. Warmest regards,

Local Organizing Committee

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FLASH NEWS

FLASH NEWS 1:

TGF- β signaling regulates neuronal C1q expression and developmental synaptic refinement.

Bialas AR, Stevens B. Nat Neurosci. 2013; 16:1773-1782.

Novel roles for the early components of the classical complement pathway continue to be identified, and Bialas and Stevens continue to delve systematically into the pathways and mechanisms of these proteins in the developmentally critical synaptic pruning. Earlier, Stevens and colleagues demonstrated that C1 appears to identify 'inappropriate synapses', initiate C3 cleavage and C3b/iC3b deposition on the synapses which then binds CR3 on microglia leading to ingestion of the targeted synapse. Using appropriate genetic and pharmacological tools, in this current study, they demonstrate that it is the regulated secretion of TGF- β by immature astrocytes engaging TGF β RII on retinal neurons that rapidly induces C1q, C1r and C1s synthesis by the RGC neurons. This pathway does not regulate microglial or astrocyte C1q synthesis in this system and interestingly, the synthesis of C1q by these glial cells does not compensate completely for genetic ablation of the RGC C1q production and RGC axonal segregation, the result of synapse pruning, demonstrating a physiologic significance of this activity. It will be important to determine if and what compensatory mechanisms are in place in the human visual system, and if this neuronal pruning is turned on in CNS diseases. Furthermore, it is currently unclear whether it would be beneficial or detrimental - likely both depending on the level of regulation and the presence of other downstream complement components. This study supports the emerging realization that induction of synthesis of the various complement proteins can be discoordinately regulated in a temporal and cell-specific manner, which could provide a basis for translational intervention in human disease.

Reported by Andrea J. Tenner, University of California, Irvine.

FLASH NEWS 2:

C1q as a unique player in angiogenesis with therapeutic implication in wound healing.

Bossi F, Tripodo C, Rizzi L, Bulla R, Agostinis C, Guarnotta C, Munaut C, Baldassarre G, Papa G, Zorzet S, Ghebrehiwet B, Ling GS, Botto M, Tedesco F. Proc Natl Acad Sci USA. 2014; 111:4209-4214.

This paper importantly extends the appreciation of a role for C1q in the response to injury beyond that reported by the authors' earlier paper on decidual endothelial cells as well as reports in the recent past of effects of classical pathway-independent C1q functions on injured endothelial cells and neurons. The authors provide evidence that C1q binds directly to activated endothelial cells via the C1q globular head resulting in increased endothelial cell proliferation and migration, as well as new vessel formation and vessel sprouting in vitro. These data strongly support a direct role for C1q in angiogenesis and consistent with this notion, C1q^{-/-} mice exhibit defective wound healing. The exciting observation that topical application of C1q rescues angiogenesis deficits in C1q^{-/-} skin wounds provides direct clinical implications for at least some disorders of angiogenesis. It will be of interest to see if these concepts can be applied to internal tissues and for regulating angiogenesis in solid tumors. Outstanding questions include the regulation of C1q expression in endothelial cells: what turns on C1q production in injured skin? Interestingly, the effect of C1q on migration was maximal at 12 hours. Although the authors provide evidence that ERK1/2 becomes phosphorylated 30 min after C1q application, the persistent pro-angiogenic effect of C1q suggests that there may be a transcriptional component as well.

Reported by Sarah Lutz and Andrea J. Tenner, University of California, Irvine.

OBITUARY

Tribute to Dr. Gudmundur Johann Arason (1954 - 2014)



*It is with deep regret that The International Complement Society shares the news of the loss of Gudmundur Johann Arason on April 09, 2014. Gudmundur received his B.Sc. in Biology from the University of Iceland in 1984 and his Ph.D. in 1988, from Bedford College, University of London. From 1986 to 2002 he was a Lecturer in Immunology and Histology at the Landspítali University Hospital in Reykjavik, Iceland, where he was promoted to Senior Lecturer in 2005 and then appointed as Clinical Associate Professor in 2008. His Ph.D. thesis research was on the internal defense reactions of plants, specifically the common periwinkle. From 1984 on, Gudmundur developed an interest in the complement system and until the year 2000, his research centered around developing enzyme immunoassays to measure autoantibodies against C1q, the measurement of complement-mediated binding of immune complexes to red blood cells in systemic lupus erythematosus (SLE) and to refine methods for reconstitution of opsonizing activity by infusion of mannose-binding lectin (MBL) to MBL-deficient humans. Furthermore, from 2000 on, Gudmundur expanded his research profile and added additional focus on the relationship between smoking-induced disease states and specific allelic expression of gene alleles coding for complement proteins. In a collaboration with Hungarian scientists (George Füst group), he found that the C4B*Q0 allele increases the risk for angina pectoris and myocardial infarction (MI) in smokers and also leads to increased one-year mortalities after MI. Furthermore, in studies using the vaccinia virus complement control protein (VCP), he contributed to novel insights demonstrating that complement played a critical role in the pathogenesis of atherosclerosis (Ann NY Acad Sci 2005). Gudmundur was a very meticulous scientist whose love for the complement field spanned across half of his life. He received Icelandic and European grant support including most recently the Eurostars Grant Award. Gudmundur was also keen on applying his basic research findings to potential therapeutic usage and in 2008, he founded the company Icelandic Cardiopharma (IceCP) to explore the development of complement inhibitors as therapeutics in cardiac diseases. He was listed as co-inventor in several patents awarded in the USA and in Canada.*

He was married to Anna Yates and is survived by his children Vala, Ari and Rognvaldur and three brothers. Gudmundur's passion for life and enthusiasm for research will be missed. May his soul rest in peace.

Dr. Girish J. Kotwal

COMPLEMENT TEAMS AROUND THE WORLD

Complement in The Netherlands: Marc Seelen's Team

My complement research group at the University Medical Center Groningen is part of the experimental nephrology laboratory of the nephrology department. After clinical training in Nephrology and my PhD program at the Leiden University Medical Center I started my own complement research group in Groningen inspired by Prof Moh Daha.

Focused on complement activation analysis and autoimmune diseases during my years in Leiden, I converged my interest to the role of complement in renal transplantation. Working as a renal transplant physician this brought me into a position to translate basic science to clinical practice. In close collaboration with the group of Dr Henri Leuvenink at the surgical laboratory in Groningen we started to investigate the role of complement activation during donor brain death.

At that time our PhD student Jeffrey Damman showed local and systemic complement activation after induction of brain dead in a rat model. We were able to show improved early graft function of transplanted rat kidneys with inhibition of donor complement activation.

The results obtained in our rat model were confirmed with analyses of human bio-materials obtained from the donor. We demonstrated complement C3 deposition in renal allografts of brain dead donors. The intensity of complement C3 deposition was associated with graft survival after transplantation. Currently, we are working on a project to intervene in complement activation in human organ donors with Felix Poppelaars as MD/PhD-student. Systemic and local complement activation in organ donors suggested a possible interplay between systemic complement activation products, like C5a, and complement receptors in the kidney. MD/PhD student Maaïke van Werkhoven investigated in detail the localization and expression of the C5a receptors, C5aR (C5R1) and C5L2 (C5aR2), in renal allografts comparing tissue from living and post-mortal donors. These results showed local complement regulation during the renal transplant procedure and suggested a possible interaction between systemic derived complement components and local expression of complement receptors.

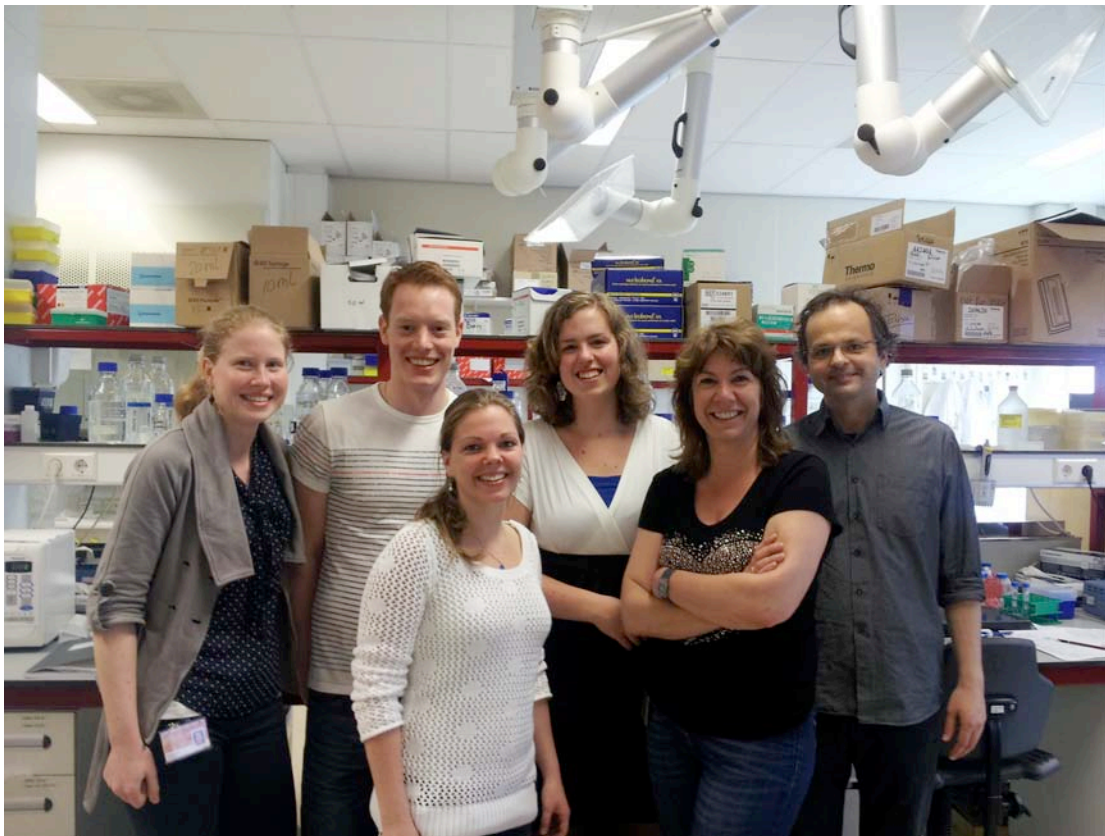
To study the effect of complement receptor ligands in renal tissue we have developed a precision-cut method for kidney slices in collaboration with Dr Peter Ollinga from the Department of Pharmaceutical Technology and Biopharmacy. PhD student Isabel Stribos studies the effect of complement activation products and TLR-ligands known to be released during brain death using this model. Finally, the effect of circulating activation products released by donor brain death is studied in an *ex vivo* organ perfusion model by PhD student Aukje Brat in collaboration with Dr Henri Leuvenink. With this model we investigate different drugs inhibiting complement activation on renal graft protection.

Recently we have developed a mouse brain dead model in close collaboration with Dr Henri Leuvenink and Prof Carl Atkinson's lab. With this model we will look in more detail at the different complement components involved in brain dead induced complement activation and subsequently tissue injury.

Using our brain dead animal models and *ex vivo* organ perfusion and tissue culture model, the consequences of brain death on renal allograft outcome is being pursued to improve allograft survival and patient wellbeing.

Contact:

Marc AJ Seelen, University Medical Center Groningen, Dept. of Nephrology, The Netherlands.
m.seelen@umcg.nl



From left: Isabel Stribos (MD/PhD-student), Felix Poppelaars (MD/PhD-student), Maaïke van Werkhoven (MD/PhD-student), Aukje Brat (PhD-student), Anita Meter (MSc), Marc Seelen (MD, PhD).

Complement in Switzerland: Robert Rieben's team

Our "Cardiovascular Research Group" is part of the Department of Clinical Research at the University of Bern. As such, our main goal is to link basic, biomedical research to clinical application. We have been working on ischemia/reperfusion (I/R) injury, both of the myocardium and skeletal muscle, as well as allo- and xenotransplantation. Activation of the complement system is an important common denominator in all these situations and indeed, in many of our projects we could show that blocking of complement activation can prevent or attenuate the related tissue injury.

We could for example show that endothelial cell protection by low molecular weight dextran sulfate (DXS) leads to accommodation in hamster-to-rat cardiac xenotransplantation as well as to re-establishment of tolerance induction in allotransplantation after prolonged cold graft ischemia. DXS is a known inhibitor of all three pathways of the complement system. Indeed, also the CR1-based, membrane targeted construct APT070 of Richard Smith prevented I/R injury in a pig myocardial infarction model, just as did DXS in the same model.

As we recently found that peripheral muscle I/R injury in a rat hindlimb model is attenuated by C1-inhibitor, but not by DXS or APT070, we started to investigate into contribution of the kinin pathway, because in contrast to the latter two inhibitors, C1-INH also blocks bradykinin formation. Currently, therefore, the interconnections between complement, coagulation, fibrinolysis and the kinin system are in the focus of our investigations.

In the field of xenotransplantation we have recently been investigating the effects of transgenic expression of human CD46, together with HLA-E to block NK cells, and also human thrombomodulin on activation of human complement and coagulation. The transgenic pigs we get via a collaboration with the German Transregio Xenotransplantation Project from Eckhard Wolf's group in Munich and we use an ex vivo perfusion system of pig legs which we developed originally to keep human, traumatically amputated limbs alive for a prolonged period of time. For this and other projects with pigs we established multiplex assays for the detection of porcine complement activation markers, cytokines, chemokines and growth factors. – Contact us if you would like to do such analyses!

Most of these studies, in particular the work with pigs, was done in close collaboration with clinics of the Bern University Hospital, such as Plastic and Hand Surgery, Cardiology, Cardiovascular Surgery, and Orthopedic Surgery.

Our homepage:

http://www.cvrc.dkf.unibe.ch/content/research_groups/ischemia_reperfusion/index_eng.html

Contact:

Robert Rieben: Department of Clinical Research and Graduate School for Cellular and Biomedical Sciences, University of Bern, Bern, Switzerland.

robert.rieben@dkf.unibe.ch



Front row, from the left: Yvonne Roschi (house staff), Mai Abdelhafez (PhD-student), Shengye Zhang (PhD-student), Anjan Bongoni (postdoc), Robert Rieben (Prof Dr). **Middle row**, from the left: Jane Shaw (technician), Julie Denoyelle (technician/Master student), Maria Arnold (master student), Jonas Schnider (MD, staff surgeon), Manuel Krüsi (student technician). **Back row**, from the left: Alain Despont (MSc, technician), Bernadeta Bac (Erasmus student), Pavan Garimella (student), Bettina Trüeb (master student), Hyrije Ademi (master student).

PhD STUDENTSHIPS IN COMPLEMENT RESEARCH

STUDENTSHIP 1:

PhD studentship in Complement Research at Oslo University

A 3-year PhD Studentship is available at Prof. Tom Mollnes laboratory in Oslo on a project entitled ***“Double-blockade of complement and CD14 as a therapeutic regimen for inflammatory diseases”***. The position will be announced shortly on the ECN website: <http://www.ecomplement.org>
Please contact postdoc Per H. Nilsson (per.nilsson@rr-research.no) or Tom Mollnes (t.e.mollnes@medisin.uio.no) for further details.

STUDENTSHIP 2:

International PhD studentship in Complement Research at Cardiff University.

An opportunity has arisen for an International (non-EC) student to apply for a funded PhD Studentship in Prof. Paul Morgan's laboratory in Cardiff. The project will fit one of the current themes in the laboratory that broadly encompass roles of complement in disease. Applicants will be expected to have or anticipate having a 1st Class Honours degree (or the equivalent in country of origin) in a relevant field of biological or physical sciences; exceptionally, individuals with an upper 2nd class (or equivalent) degree will be considered if they have additional relevant experience or qualifications.

Expressions of interest and informal enquiries can be addressed to Professor Paul Morgan (morganbp@cardiff.ac.uk) until 14th June 2014. A successful applicant would be expected to start 1st October 2014.

STUDENTSHIP 3:

PhD studentship in Complement Research at Cardiff University.

A fully funded PhD Studentship is available to work in Prof. Paul Morgan's laboratory in Cardiff. The project, entitled ***Inflammatory effects of the complement terminal pathway: exploring the molecular mechanisms***, is a four-year BBSRC CASE Award in partnership with Glaxo Smith Kline (GSK). The appointee will be primarily based in Cardiff but will be expected to spend up to 25% of the time at GSK's Stevenage facility, supervised by Prof. Claire Harris, Head of Complement Research at GSK. Both are exceptional environments in which to learn and develop skills in complement biology.

The overall goal of the project is to test the hypothesis that, in metabolically active nucleated cells, products of the terminal pathway link directly or indirectly with conserved signalling pathways that mediate inflammation. The student will seek to gain a comprehensive understanding of the signalling pathways recruited by the terminal pathway of complement to trigger inflammation programmes in nucleated cells. An understanding of these processes is essential for comprehension of the roles that complement plays in inflammatory diseases and for the development of therapies for diseases in which this important innate immune effector system is implicated. The work will inform the development of new therapies that target complement activation.

Applications should be submitted to Professor Paul Morgan (morganbp@cardiff.ac.uk) and/or Professor Claire Harris (Claire.I.harris@GSK.com). Informal enquiries can be addressed to Prof Morgan. Applicants will be expected to have or anticipate having a 1st Class Honours degree (or equivalent) in a relevant field of biological or physical sciences; exceptionally, individuals with an upper 2nd class (or equivalent) degree will be considered if they have additional relevant experience or qualifications. BBSRC Eligibility criteria state that only individuals "Settled in and ordinarily resident in the UK" can apply; if in doubt please consult the BBSRC website for clarification (<http://www.bbsrc.ac.uk/>). The closing date for applications is 1st July 2014; the successful applicant will be expected to start 1st October 2014.

Professor B. Paul Morgan, Institute of Infection and Immunity, School of Medicine, Cardiff University, Henry Wellcome Building, Heath Park, Cardiff CF14 4XN, UK, Tel. (+44) 2920687096

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