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ABOUT THIS ISSUE & MORE

We are pleased to send to you the second issue of "Focus on Complement". After several enthusiastic responses and receiving new contributions to this and the following issues of the Bulletin, we feel that "Focus on Complement" is ready for take-off. This Bulletin is mailed electronically to members of the ICS and ECN community. If you know of individuals who are interested in joining our mailing list, please refer them to me. We encourage you to regard this Bulletin as your forum in which you can express thoughts, ideas and concerns, supportive and critical, on scientific matters related to complement research and to the complement community. Letters and short articles may be sent directly to me or to any Editorial Board member. The electronic addresses of the Editors and their assignments are given below.

This issue of the Bulletin contains: Flash news on two complement-related novel findings, Spotlight on two complement teams and the first historical personal perspective in our Witness Corner, written by Chester Alper. Sadly, it also contains an Obituary on a dear friend and colleague whom we have just lost, Anders Sjöholm. We send our condolences to his family.

FLASH NEWS

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SPOTLIGHT ON TEAMS

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Paul Morgan
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NEW REAGENTS

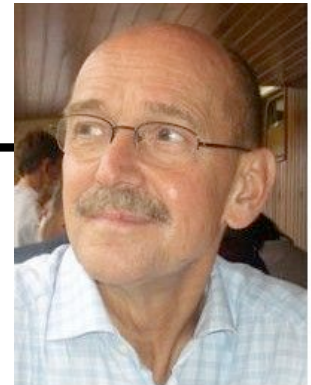
Anna Blom*
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JOB OPPORTUNITIES

Sakari Jokiranta*
Zvi Fishelson
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*, Section coordinator

Anders G. Sjöholm 1942-2006



Anders G. Sjöholm died on June 1, 2006, two days before his sixty-fourth birthday. He died after a period of increasing ill health, a result of the cancer he had struggled bravely against during about ten years.

Anders Sjöholm had a strong commitment to complement and was a former president of the ECN board. He was a clinical immunologist but from the start of his scientific career, which lasted more than 35 years, he was devoted to complement research. This devotion began with work under the guidance of Professor Anna-Brita Laurell in Lund, and he stayed in this laboratory throughout his career, except for short periods as a visiting scientist in the US. His early work dealt primarily with the initiation of activation of the classical complement pathway, C1-INH complexes and methods to accurately measure complement components in serum. He presented his thesis entitled "Studies on complement components and on complement activation" in 1979. A major contribution to the complement field was his discovery and description of properdin deficiency, with publication of the first case in 1982. This was some years later followed by work defining the genetic background to this deficiency. Several papers were also published during these years describing the roles of complement in various clinical situations, particularly in rheumatologic disease and in infections. Studies on various complement deficiency states were continuously utilized by Anders as a source for retrieving new insights about the biology of the complement system. Several papers about C4 and C2 deficiency were published, adding new information. Indeed, recent studies on C2 deficiency were very successful. The use of C2 and MBL deficient serum provided possibilities for studying the role of MBL in generating C3 fragment deposition and just a few weeks before the end of his life these results, demonstrating a novel C3 activation mechanism were published.

With the death of Anders Sjöholm, the complement research community has lost one of our leading clinical complementologists, an individual with long experience and unrivalled knowledge in the field. We will miss his intelligent, analytical mind as well as his humble and warm personality.

Lennart Truedsson
Department of Laboratory Medicine
Lund University
Lund, Sweden



FLASH NEWS

news flash...
The latest in complement research

Reporter: Anna Blom

Helmy et al.

CRlg: a macrophage complement receptor required for phagocytosis of circulating pathogens.

Cell 2006 March 10, email: menno@gene.com

Fragments of C3 deposited on pathogens serve as targets for complement receptors present on phagocytic cells. Kupffer cells, the liver resident macrophages, play a dominant role in clearing particles in circulation. Helmy and colleagues from Genetech identified and characterized a novel complement receptor that belongs to the Immunoglobulin superfamily: CRlg. CRlg on Kupfer cells binds C3b and iC3b and is required for efficient binding and phagocytosis of complement C3-opsonized particles. Kupffer cells from CRlg-deficient mice are unable to efficiently clear C3-opsonized pathogens in the circulation, resulting in increased infection and mortality of the host.

Reporter: John Atkinson

Gold B et al.

Variation in factor B (BF) and complement component 2 (C2) genes is associated with age-related macular degeneration.

Nature Genetics 38:458, 2006

Much evidence has accumulated in the past year to implicate the complement system, particularly the regulator protein factor H, in age-related macular degeneration (AMD), the most common cause of irreversible blindness in developed countries. While changes in the factor H are unlikely to be the primary cause of AMD, they appear to accelerate its development, both in regard to age of onset and severity of the retinal process. In this report, two related components required for activation of the classical and lectin pathways (C2) and the alternative pathway (Factor B) are also associated with risk of developing AMD. The underlying concept being that either more efficient activation or less efficient control of the complement system predisposes to AMD. This concept will likely play out relative to innate immune handling of many types of debris including crystals, amyloid lipids and, in AMD, the drusen.

WITNESS CORNER

Chester Alper*: The Alternative Pathway's (Re) Birth

The complement field in the late 1960's was incredibly exciting. It was the time during which physicochemical separation methods were introduced, allowing for the purification and characterization of the complement components, their interactions and the generation of complement-mediated functions. My second Complement Workshop (1971) was the one I remember best. It was 60 years earlier (before even my time) that Sachs and Omorokow discovered a third component of complement because serum depleted of complement activity by cobra venom, (or yeast or gram-negative bacteria) could have its antibody-mediated hemolytic activity restored quantitatively by either normal first component (euglobulin) or second component (pseudoglobulin). Shortly thereafter, it was insightfully observed that serum depleted of complement activity by antigen-antibody still had cobra venom-induced hemolytic activity. Browning and Mackie (1913) pointed out that "It is doubtful --- if [a] third component can explain all the phenomena ---."



In 1954, Louis Pillemer and coworkers described properdin and its participation in C3 activation by zymosan via a pathway that did not involve C1, C4 or C2. Within a few years, the properdin pathway was discredited as an artifact reflecting natural antibody. Nevertheless, the Pillemer group described hydrazine-sensitive properdin Factor A and heat-labile factor B. Irwin Lepow complained bitterly in those days that all of his Factor A preps were contaminated with C3! We stumbled on the scene by identifying a serum protein that we horribly named glycine-rich beta glycoprotein (GBG). Serendipitously, we discovered the first patient with what turned out to be factor I deficiency. He had very low C3, all in the form of C3b, low levels of cleaved GBG and normal C1, C4 and C2. When we added GBG to his serum, it immediately cleaved. In our first publication of studies of this patient, we presciently suggested "--- an alternative physiological mechanism that bypasses the first three complement components."

Walther Vogt and co-workers and Hans Müller-Eberhard and Otto Götze had revisited the cobra venom-complement interaction. The latter had identified a serum protein, C3 proactivator or (C3PA), that formed a complex with purified CoF that inactivated C3.

It was at the 1971 Complement Workshop that the alternative (properdin) pathway (including factor B, also known as GBG and C3PA) was reborn. Lepow put it all into perspective, but we all participated in an exciting vindication of the science of complementology.

* Chester Alper is a Professor at The CBR Institute for Biomedical Research and the Department of Pediatrics, Harvard Medical School, Boston, Massachusetts, USA

Complement and Collectin research: New Human MASP-2 Elisa

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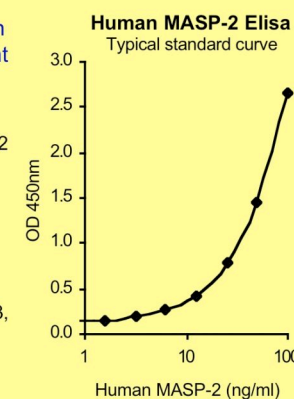
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SPOTLIGHT ON TEAMS

How do we choose the teams to be presented? Simply, we have been issuing a call, to all team leaders interested to be presented in the Bulletin, to complete the online "Update info" form at the [ICS website](#) and to inform one of the "Spotlight on Teams" section editors (see page 1) that their info is ready to be excerpted for inclusion in the Bulletin. The first two volunteers are presented here. We hope to present eventually ALL complement teams around the globe.

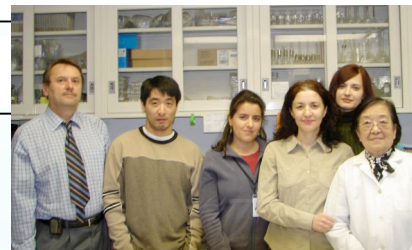
Horea Rus, MD, PhD - Baltimore, Maryland

My laboratory is interested in understanding the role of the complement membrane attack complex (MAC) in oligodendrocyte (OLG) survival. Activation of the terminal pathway has a major role in inflammatory responses of the brain. Sublytic MAC increases survival and protection of OLG from apoptosis through inhibition of a mitochondrial pathway. We hypothesized that complement activation and MAC assembly might have a protective role *in vivo*. We tested this hypothesis using C5 deficient mice and an experimental autoimmune encephalomyelitis (EAE) model. Our data indicate that complement C5, which is essential for the formation of MAC, is necessary for the efficient recovery in EAE by promoting remyelination, axonal survival and preventing OLG apoptosis.

Collaborators include: Florin Niculescu MD, PhD, Moon L. Shin, MD, Violeta Rus, MD, Cornelia Cudrici MD, fellow, Matthew Fosbrink, PhD student, Ekatherina Zafranskaia MD, and fellow, Chun Min Chi MD.

Refs: (1) Cudrici et al.. C5b-9 Terminal Complex Protects Oligodendrocytes from Apoptotic Cell Death by Inhibiting Caspase-8 Processing and Up-Regulating FLIP. *J. Immun.* 2006; 176:3173. (2) Niculescu et al. Effect of complement C5 on apoptosis in experimental autoimmune encephalomyelitis. *J. Immunol.* 2004, 172: 5702-7.

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Arvind Sahu, Ph.D. - Pune, India

I am a research scientist at the National Centre for Cell Science, Pune. I did my post-doctoral training with Drs. Mike Pangburn (University of Texas, Tyler) and John Lambris (University of Pennsylvania, Philadelphia) and I came back to India in May 2000 after receiving The Wellcome Trust Overseas Senior Fellowship. Now I have a small group of seven people and we are working on viral complement control proteins (vCCPs) of vaccinia, KSHV and HVS.

My group has shown that like vaccinia CCP (VCP), the CCP of KSHV (ORF 4) also inhibits complement (Mullick et al., 2003, *J. Virol.* 77(6): 3878-3881). We have named this protein as Kaposica (the Kaposi,s sarcoma-associated herpesvirus inhibitor of complement activation). We are also probing into the molecular mechanisms involved in the interaction of these proteins with human complement proteins, a part of which has been published (Bernet et al., 2004, *J. Virol.* 78(17): 9446-9457). My group has also contributed on the structure-function analysis of these viral proteins (Mullick et al., *J. Virol.* 79(9):5850-5856 and Mullick et al., *J. Virol.* 79(19):12382-12393). We believe that these vCCPs play an essential role in immune evasion (Mullick et al., 2003, *Trends Immunol.* 24(9):500-507).

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ADVANCED NOTICE – DATES FOR YOUR DIARY

XIth European meeting on Complement in Human Disease.

Dear Colleagues,

On behalf of the Board of the European Complement Network and the local organising committee, it is a great pleasure to invite you to participate in the XIth European Meeting on Complement in Human Disease to be held September 8th – 11th 2007 in Cardiff, the capital city of Wales. The meeting will be held in City Hall, a historic building in the heart of this vibrant city. On September 8th, we will hold a teaching day where an international faculty will lead reviews and debates on key topics in complement for students and junior fellows. Main sessions will take place on September 9th – 11th. The science will be complemented by a great social programme and opportunities to visit historic sites in Cardiff and around South Wales.

Cardiff is easily accessible, just two hours from London by train or car and with direct air connections from many European cities.

We can promise you a warm welcome and a great scientific and social experience so mark the dates in you Diaries now. The meeting Website will go live in the next few weeks. In the meanwhile any enquiries can be addressed to me at (morganbp@cardiff.ac.uk). I look forward to welcoming you in 2007.

Paul Morgan.



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