September 1, 2009
Issue 15

Focus on Complement

A newsletter of the International Complement Society

EUROPEAN COMPLEMENT NETWORK

About this issue & More

What's inside?

<1> Many thanks to Anna Blom, who was extremely prompt in sending in the very interesting flash news despite a short notice. Anna presents two Flash News on: (a) Thrombomodulin mutations in atypical hemolytic-uremic syndrome, and (b) Structure of complement fragment C3b-factor H and implications for host protection by complement regulators.

<2> As the XXIII ICW is only a year away, it felt appropriate to introduce representative complement teams from the New York area. Three complement teams: two from NYC, and one from Stony Brook are presented by Berhane in Spotlights on Teams.

<3> Since the organizing committee of the XXII ICW has received several inquiries about the exact dates (August 1-5, 2010) of the meeting, we have included a short, but detailed description of the venue (Grand Hyatt, New York City), and events. For details also visit the meeting website at: http://www.hsc.stonybrook.edu/ics2010/

FLASH NEWS

Thrombomodulin & aHUS: Reporter: A.Blom

Thrombomodulin Mutations in Atypical Hemolytic-Uremic Syndrome
(M Delvaeye, M Noris, A De Vriese, CT Esmon, NL Esmon, G Ferrell, J Del-Favero, S Plaisance, B Claes, D Lambrechts, C Zoja, G Remuzzi, EM Conway.N Engl J Med 2009 361:345-57).
The atypical hemolytic-uremic syndrome (aHUS) is characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and renal failure in the absence of infection with Shiga toxin-producing bacteria. Approximately half of the patients with aHUS have mutations in genes coding for complement proteins and inhibitors. This study shows that mutations in thrombomodulin are also found in aHUS patients. Thrombomodulin is expressed on endothelial cells and it has anticoagulant, antiinflammatory, and cytoprotective properties due to its ability to accelerate activation of protein C by thrombin. Thrombomodulin gene was sequenced in 152 patients with aHUS and in 380 controls. Seven unrelated patients (5% of the cohort) were found to have six different heterozygous missense mutations in the thrombomodulin gene. The authors found that in vitro, thrombomodulin bound to C3b and factor H and that it enhanced factor I-mediated inactivation of C3b in the presence of cofactors factor H and C4b-binding protein. By promoting activation of the plasma procarboxypeptidase B, thrombomodulin also accelerated the inactivation of anaphylatoxins C3a and C5a. Cultured cells expressing thrombomodulin variants associated with aHUS had diminished capacity to inactivate C3b and to activate procarboxypeptidase B and were thus less protected from activated complement. This study is very important for our understanding of aHUS but also provides evidence for a novel link between the coagulation and complement systems.

Structure of c3b-factor H: Repoorter: A..Blom

Structure of complement fragment C3b-factor H and implications for host protection by complement regulators.
J Wu, Y Wu, D Ricklin, BJC Janssen, JD Lambris, P Gros. Nature Immunol 2009 10(7):728-33.
This is a long awaited publication describing structure of a complex between C3b and the main soluble inhibitor of the alternative pathway, Factor H (FH). The presented structure contains C3b and the first four complement control protein (CCP) domains of FH that has been known for many years to harbor the binding site for C3b crucial of the factor I-cofactor and C3-converatse decay accelerating activities of FH. The authors found that FH interacted with multiple domains of C3b in the crystal structure, covering a large, extended surface area. The structure indicated that FH destabilizes the C3 convertase by competition and electrostatic repulsion and that FH enables proteolytic degradation of C3b by providing a binding platform for protease factor I while stabilizing the overall domain arrangement of C3b.

These results not only provide a general model for complement inhibition by CCP-containing complement inhibitors (decay acceleration of convertases and factor I cofactors) but they also provide structural explanations for disease-related mutations (aHUS, age-related macular degeneration and membranoproliferative glomerulonephritis) in the genes encoding both FH and C3b.

SPOTLIGHT ON TEAMS - I

COMPLEMENT IN NEW YORK CITY-1

Research in complement at Hospital for Special Surgery (HSS) began 11 years ago, when Jane Salmon, in response to a suggestion by Michael Holers (University Colorado, Denver), embarked on a series of experiments that drew her laboratory firmly into the field. Dr. Salmon's laboratory, in the Program in Autoimmunity and Inflammation and the Kirkland Center for Lupus Research at HSS, is focused on complement and Fc receptors as critical for effector mechanisms of tissue injury in systemic lupus erythematosus (SLE),

SLE is a prototypic autoimmune disease characterized by inflammation in skin, joints, kidneys, brain, and blood vessels, much of which is related to immune complex deposition and complement activation. It is a disease that predominantly affects women in their reproductive years.

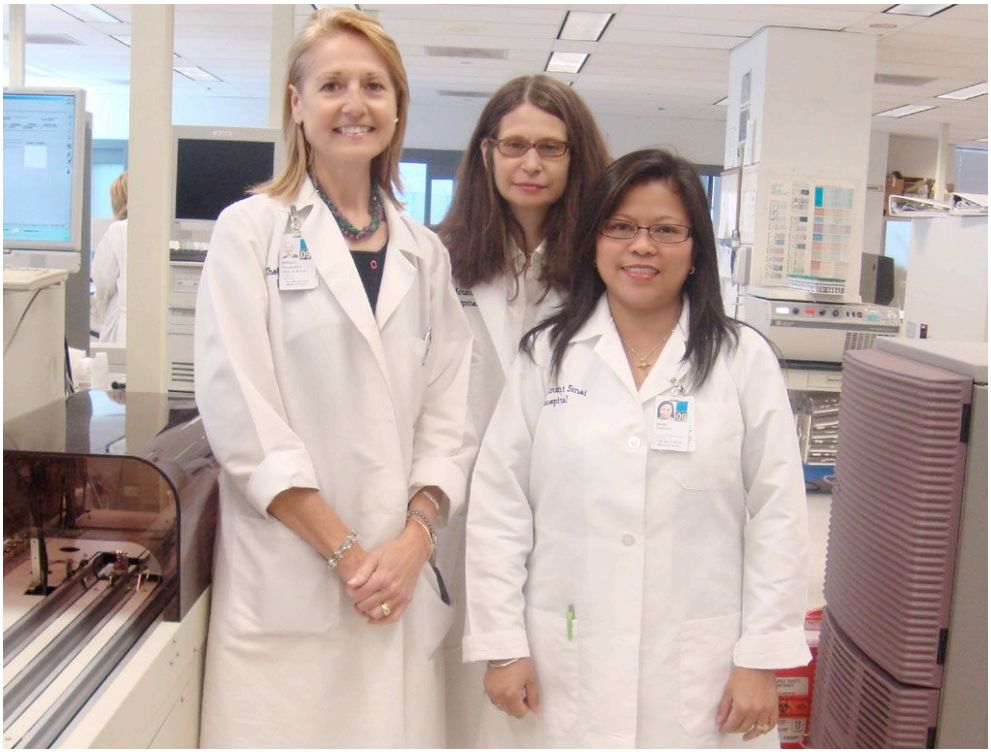
The Salmon laboratory was the first to describe the role of complement in pregnancy complications associated with lupus, and specifically those mediated by antiphospholipid (APL) antibodies. APL antibodies, typically associated with thrombosis and pregnancy loss, were thought to mediate damage by initiating coagulation. Through the remarkable generosity of the complement community, which donated many critical reagents including KO mice deficient in complement components or receptors, we were able to examine the role of complement activation in pregnancy complications, the question Michael Holers had originally posed. Our studies in a mouse model of pregnancy loss induced by passive transfer of human APL antibodies showed that complement activation plays an essential and causative role in fetal loss and growth restriction, specifically in C5a-C5a receptor interactions, and that heparins, the standard treatment for these patients, prevent obstetrical complications because they block activation of complement induced by aPL antibodies targeted to decidual tissues, rather than by preventing placental thrombosis. We have extended our work to antibody-independent models of pregnancy complications and identified a key role for complement in the angiogenic imbalance associated with placental dysfunction and preeclampsia.

The PROMISSE Study (***P**redictors of p**R**egnancy **O**utcome: bio**M**arkers **I**n antiphospholipid antibody **S**yndrome and **S**ystemic lupus **E**rythematosus)*, a multicenter effort coordinated from HSS, represents a first-time attempt to translate these novel research findings in mice to humans and to determine whether elevations of complement split products predict pregnancy complications in patients with aPL antibodies and/or SLE. To date, over 500 pregnant patients have been enrolled in this multicenter, prospective observational study. The analyses of biomarkers that predict poor pregnancy outcomes in PROMISSE are not limited to complement, but the mouse studies engendered sufficient confidence to design such a large study. PROMISSE has also served as a platform to examine complement regulatory proteins as inherited risk factors for preeclampsia in study patients, and in collaboration with Veronique Fremeaux-Bacchi (Hôpital Européen Georges Pompidou, Paris, France) and John P. Atkinson (Washington University School of Medicine, St. Louis, MO) we have identified mutations, similar to those described in aHUS, in a number of lupus patients who develop preeclampsia. The work of a collaborator, Anne Lynch (University of Colorado, Denver), who identified the association of elevated Bb early in pregnancy with the later development of preeclampsia, underscores the importance of complement regulation in pregnancy. Contact information: salmonj@hss.edu

SPOTLIGHT ON TEAMS - II

COMPLEMENT IN NEW YORK CITY-2

Dr. Peerschke's laboratory at Mount Sinai School of Medicine in New York, NY, studies the interactions between complement and coagulation systems at a cellular level. The laboratory's interest in complement began in the mid 1980's through collaboration with Dr. Berhane Ghebrehiwet at Stony Brook University in New York and Kenneth B.M. Reid at Oxford University, Oxford, UK. Dr. Peerschke characterized two distinct C1q binding sites, cC1qR/calreticulin and gC1qR/p33, on platelets and endothelial cells, and demonstrated their role in cellular activation and generation of procoagulant activity.



Currently, Dr. Peerschke's laboratory is building on the growing recognition that the complement system is involved in the pathogenesis of acute and chronic vascular diseases, and plays a major role in infection and inflammation. Her laboratory provided the first evidence for the intrinsic capacity of activated platelets, platelet micro particles, and endothelial cells to initiate the classical complement pathway, in the absence of immune complex formation, and demonstrated a role for the gC1qR in *Staphylococcus aureus* pathogenesis. Collaborating with Dr. Arnold Bayer at University of California Los Angeles, the group demonstrated prophylactic effects of gC1qR blockade by specific antibodies in a rat model of infective endocarditis.

Further collaborations with Dr. Jane Salmon and Dr. Deborah Alpert at The Hospital for Special Surgery in New York have allowed Dr. Peerschke to extend her investigation of complement activation by platelets to include immune mediated complement activation on platelets in patients with systemic lupus erythematosus and the anti phospholipid syndrome. This collaboration revealed an association between complement activation on platelets and arterial thrombosis.

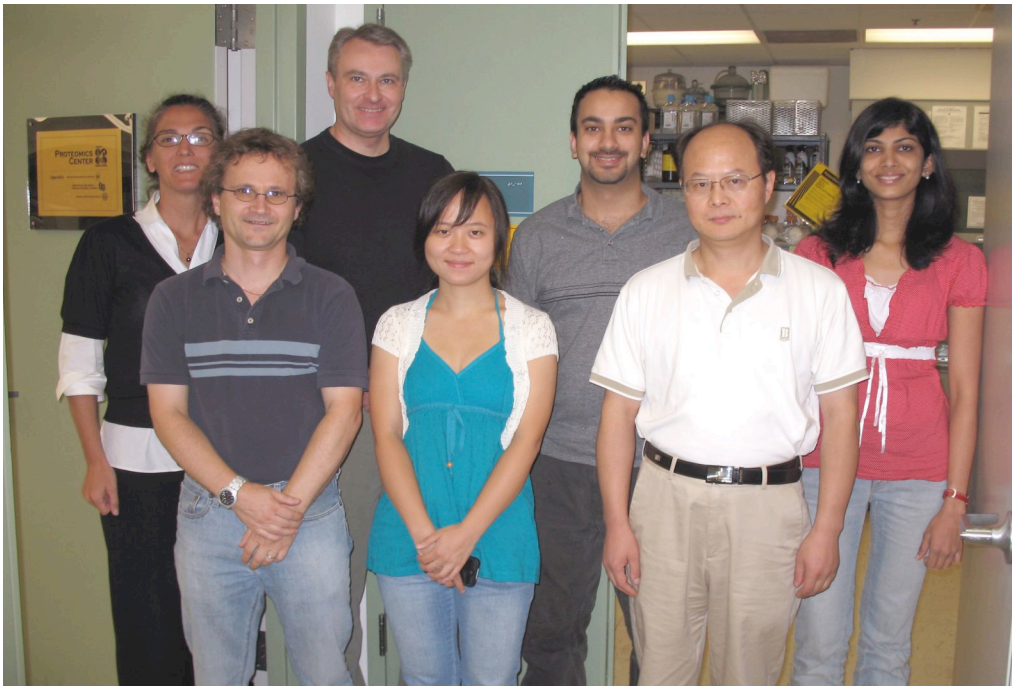
Dr. Peerschke's laboratory is currently focusing on the hypothesis that platelets and endothelial cells direct complement activation to sites of vascular injury. Understanding the biochemical and molecular mechanisms involved, and their regulation, will have a significant impact on identifying novel therapeutic targets for treating patients suffering from thrombotic complications associated with atherosclerosis, ischemia/reperfusion injury, and APS.

Dr. Peerschke has also begun developing a Division of Translational and Applied Laboratory Medicine within the Department of Pathology at Mount Sinai Medical Center. The goal of this new Division is to advance research leading to new diagnostic laboratory tests by bringing together basic scientists, clinicians, and industry in the advancement patient care. Dr. Peerschke is currently working on translating and extending an *in vitro* test, measuring complement activation on immobilized platelets, to patients with autoimmune diseases involving platelets, such as anti phospholipid syndromes and immune thrombocytopenia. Contact information: Ellinor.Peerschke@mountsinai.org

SPOTLIGHT ON TEAMS - III

COMPLEMENT AT STONY BROOK, LONG ISLAND, NY

There are two complement research laboratories at Stony Brook University School of Medicine, Stony Brook, New York. Berhane Ghebrehiwet's lab in the Department of Medicine and Richard Kew's lab in the Department of Pathology. Berhane's lab has been focused on the structure and function of C1q receptors, particularly the receptor for the globular heads of C1q, the gC1qR. He presented a detailed history of this research entitled "*C1q receptors: we have come a long way; but we are not at the end"* in issue #9 of *Focus on Complement*.



Dr. Kew's lab has been interested in complement and leukocyte chemotaxis for several years and has been working to uncover the mechanism of how the vitamin D binding protein, also known as Gc-globulin, functions as a chemotactic cofactor for C5a and C5a des Arg. While a graduate student at Stony Brook, Richard worked under the direction of both Berhane Ghebrehiwet and the late Aaron Janoff to demonstrate that cigarette smoke activates the alternative pathway, both in vitro and in vivo, leading to C5a generation and subsequent recruitment of inflammatory cells into the airspaces. This is thought to be one of the initial pathogenic mechanisms in the lung triggered by cigarette smoke exposure. While a postdoctoral fellow with Bob Webster in St. Louis, Richard showed unequivocally that the serum C5a co-chemotaxin was the vitamin D binding protein. The C5a co-chemotaxin was previously described as an "activity" in serum by three different prominent complement researchers. However, defining precisely how this protein enhances the chemotactic activity of C5a is still a work-in-progress. Nevertheless, the lab has made great strides recently and will present exciting new results to the complement research community at the next ICW in New York City. Richard Kew and Ellinor Peerschke from the Mount Sinai School of Medicine in New York are assisting Berhane as part of the Local Organizing Committee for the XXIII ICW.

Stony Brook University is located on the north shore of Long Island about 100 km (62 miles) east of New York City and about 80 km (50 miles) west of the Hamptons (the summer playground of the rich and famous). Both Stony Brook complement research labs collaborate extensively and are eager to interact with others to advance our understanding of complement. Numerous investigators from around the globe have been guests at Stony Brook and both new and old friends are *always* welcome. Visitors will be treated to a breathtaking panoramic view of Long Island Sound and the Connecticut coastline from Berhane's office! Contact Information: Berhane Ghebrehiwet: bghebrehiwet@notes.cc.sunysb.edu, 631-444-2352; Richard Kew: rkew@notes.cc.sunysb.edu, 631-444-3941

XXIII International Complement Workshop
August 1-5, 2010
New York, NY, USA

The XXIII International Complement Workshop (ICW) will be held at the Grand Hyatt in New York City (August 1-5, 2010). In order to make it convenient for *all* the participants, this will be a unique ***all-in-one-site*** meeting, where the Teaching Day, scientific sessions, and other functions including Welcome Reception and Gala Dinner will be held in the Hotel premises. The Grand Hyatt, which gets its name from the fact that it is connected to Grand Central Station, is conveniently located in the heart of Manhattan on 42nd Street between Park and Lexington Avenues only steps away from Times Square, Broadway Theaters, the UN, Central Park and Fifth Avenue shopping. In addition to being the home to some of the best Museums in the world (Metropolitan, Museum of Modern Art, Guggenheim, etc.), the scientific culture of New York is also unparalleled; with some of the most renowned Biomedical Research Centers and Institutions located in Manhattan and its boroughs. These include: Columbia University, Weill Cornell Medical Center including the Hospital for Special Surgery, The Rockefeller University Memorial Sloan Kettering Cancer Center, New York University, Mount Sinai Medical Center and Albert Einstein Medical College. Three International airports—JFK, LGA and Newark—connect New York to the rest of the world; and each is accessible by Taxi or Train. We look forward to welcoming you to the *"City that Never Sleeps"*

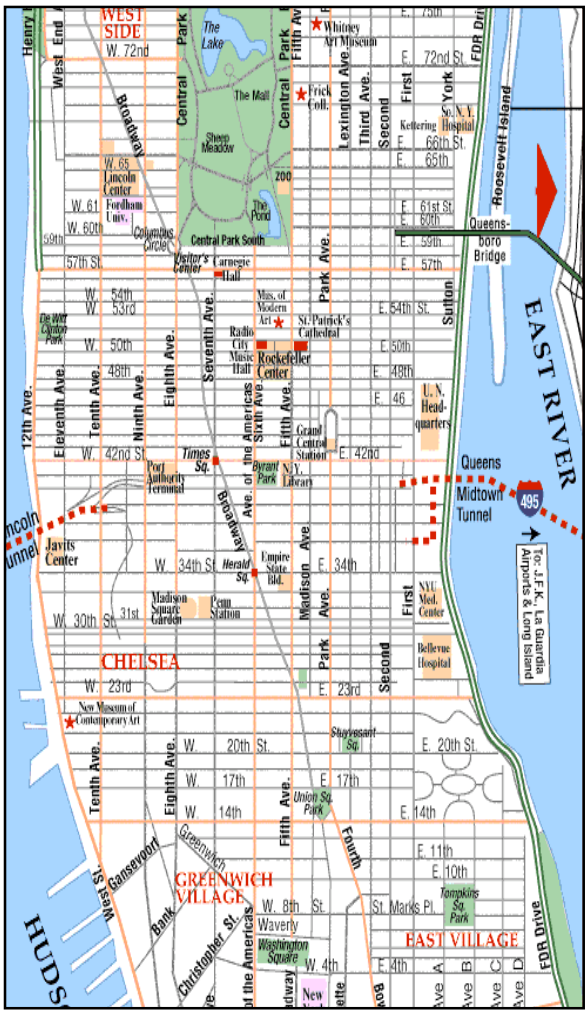
The Local Organizing Committee:
B.Ghebrehiwet, R.R. Kew, E.I. Peerschke

SCIENTIFIC PROGRAM

Aug 1: Teaching Day/Welcome Reception
Aug. 2-5: Scientific Meetings
Aug 5: Gala Dinner

CONFERENCE VENUE

The meetings will be held at the Grand Hyatt in New York. ***250 rooms at $209/room*** have been Reserved; a steal by NYC standard. This ***rate*** will be honored should guests wish to stay an additional week. Participants *should* consider staying at this hotel where the scientific meetings and functions will be held. For details, call (800) 2331234, and to view facilities click: (www.grandnewyork.hyatt.com)



REGISTRATION

Registration fee is $1200/person and includes, breakfast, lunch, reception and gala dinner: **ICW Website:** http://www.hsc.stonybrook.edu/ics2010/

LOCAL ORGANIZING CONTACT

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