ABOUT THIS ISSUE

<1> This issue of “Focus on Complement” includes: Flash news demonstrating involvement of the complement system in age-related macular degeneration (AMD) and in pneumococcal infections in the CNS, an article by Peter Ward on the harmful effects of complement activation in sepsis, a historical perspective by Maurice Colomb and Kenneth Reid on Rodney Porter (1972 Nobel Laureate in Physiology or Medicine) in the Witness Corner, and the second (and last) coverage of the oral sessions from the 21st International Complement Workshop that took place last October in Beijing.

<2> “Focus on Complement” is now one year old and the Editorial Board is eager to increase contribution of the readers to content of future bulletin issues. You are all invited to submit to us: short articles, letters, comments, info on new reagents or techniques and queries, for inclusion in the bulletin. We would welcome your suggestions for debates on unresolved issues that matter. Remember, it is your bulletin and you can help us shape it.

<3> The 11th European Meeting on Complement in Human Disease will be held in 8-11 September 2007 in Cardiff, Wales. Paul Morgan and the organizing committee invite you to submit abstracts and attend this meeting – see invitation on page 12.

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Harmful Effects of Complement Activation in Sepsis*

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Sepsis affecting humans in North America has been estimated to include at least 600,000 cases per year, with a morality rate approaching 30-50%. By currently accepted criteria for the clinical definition of sepsis, its diagnosis in humans is associated with cultural confirmation in only about 50% of cases. Currently, the organisms most commonly associated with sepsis are: Staphylococcus aureus (~50%), gram negative bacteria (~35%), and fungi (Candida sp., Aspergillus sp.) (~12%). For the past 20 years, the incidence of sepsis has been rising each year. Whether the same pathophysiological pathways are common to all types of sepsis remains to be determined. Current care for septic humans is largely supportive and extremely costly (~$18 billion per year). The only FDA approved drug for treatment of sepsis is activated protein C (APC), which has anti-thrombotic properties and cannot be used in patients with severe coagulopathy or thrombocytopenia. There is still a desperate need for more effective therapy for these patients. There have been more than 30 failed clinical trials in humans, perhaps because the animal models are not reflective of events occurring in human sepsis. Such models, which are usually done in rodents, include endotoxemia, infusion of live E. coli, cecal ligation and puncture (CLP) and other approaches.

It has long been known that in human sepsis there are several common features: consumptive coagulopathy, an out-of-control proinflammatory response (referred to as “systemic inflammatory response syndrome” or “cytokine storm”), and evidence of extensive activation of the complement system. These features of sepsis suggest that the ability to regulate inflammatory pathways has been lost.

Our own studies of CLP-induced sepsis in rodents demonstrate the role of C5a and C5aR-dependent outcomes that are highly harmful: paralysis of signaling pathways in blood neutrophils resulting in loss of innate immune functions (chemotaxis, phagocytosis and the respiratory burst); lymphoid apoptosis resulting in immunosuppression; defective cardiomyocyte contractibility, which may explain the “cardiomyopathy of sepsis”; consumptive coagulopathy; and a lethal outcome. During experimental sepsis, there is diffuse vascular upregulation of C5aR, which is IL-6 dependent and occurs in several organs (lungs, heart, liver, kidneys). The result of this may cause these organs to be at risk of damage due to neutrophil accumulation.

How can the information obtained from animal models of sepsis be translated into the clinical setting of septic humans? In CLP rats and mice, interception of C5a is highly protective and greatly enhances survival. This intervention also greatly reduces the consumptive coagulopathy of sepsis, suppresses the loss of innate immune functions of blood neutrophils (described above), greatly reduces sepsis-induced apoptosis of lymphoid tissues, and profoundly attenuates the loss of cardiomyocyte contractility during sepsis. It is not altogether clear how long one can delay infusion of anti-C5a after CLP and still have efficacy. Blockade of C5aR has also been shown to be markedly protective in CLP-induced sepsis, whether the intervention involves the use of anti-C5aR or a cyclic synthetic peptide that blocks the ability of C5a to interact with C5aR.

* Summary of the Muller-Eberhard Lecture given by Prof. Peter Ward at the XXI International Complement Workshop, Beijing, October 2006
The harmful effects of complement activation products during experimental sepsis are shown in the figure. Sepsis is associated with complement activation and generation of C5a. In addition, IL-6 is produced and has the ability to increase mRNA and protein for C5aR in a variety of organs (lungs, liver, heart, kidneys) during sepsis. Interaction of C5a with upregulated C5aR on cell membranes of cardiomyocytes is associated with depressed contractility of these cells, often leading to cardiovascular collapse. C5a also interacts with C5aR on thymocytes (and perhaps lymphocytes) causing caspase activation and apoptosis via the intrinsic (mitochondrial) pathway. The end result is immunosuppression. Finally, interaction of C5a with C5aR on neutrophils results in the loss of innate signaling, which compromises the ability of neutrophils to contain bacteria. Collectively, these events depress innate immunity and organ function, resulting in a lethal outcome. These findings suggest that in septic humans, therapeutic strategies that block complement activation, generation of C5a, or interaction of C5a with C5aR should be protective. The role of the second C5a receptor, C5L2, is totally unknown at present.
**Flash News**

**Complement activation by photooxidation products of A2E, a lipofuscin constituent of the retinal pigment epithelium.**
Zhou J, Jang YP, Kim SR, Sparrow JR

Recent discovery identifying factor H as a risk factor for age-related macular degeneration (AMD) implicated local inflammation and activation of complement amongst the processes involved in the pathogenesis of AMD. Bis-retinoid pigments, such as A2E, that accumulate as lipofuscin in retinal pigment epithelial (RPE) cells, also contribute to the disease process. The current paper shows that C3b and C3a are elevated in serum overlying RPE cells that accumulated A2E after irradiation to induce A2E photooxidation. Furthermore, oxidized A2E activates directly complement. Therefore, products of the photooxidation of bis-retinoid lipofuscin pigments in RPE cells could serve as a trigger for complement and that, over time, could contribute to chronic inflammation. These findings link several factors associated with AMD: inflammation, oxidative damage, drusen, and RPE lipofuscin.

**Complement C1q and C3 are critical for the innate immune response to Streptococcus pneumoniae in the central nervous system.**

This study demonstrates that complement plays an integral role in mounting the host immune response to Streptococcus pneumoniae infection of the CNS using a murine model of pneumococcal meningitis. The authors showed that bacterial titers in the CNS were much higher in C1q- and C3-deficient-mice than in wild-type mice. Mean leukocyte counts were reduced as well in both knock-out mice paralleled by a strong reduction of the brain expression of cytokines and chemokines. Intrathecal reconstitution with wild-type serum in C3-deficient mice restored the ability of mice to combat pneumococcal infection. The dampened immune response in C3-deficient mice was accompanied by a reduction of meningitis-induced intracranial complications and with a worsening of short-term outcome (due to more severe bacteremia and, consecutively, more severe systemic complications).
Witness corner

Maurice Colomb and Kenneth Reid on Rodney Porter

Maurice Colomb – On the way (via Oxford)...

Sixteen years after a linguistic stay of one year in London, I found myself in the oxonian Lewis Carroll’s atmosphere of the old building of the Biochemistry Department of Oxford University. Dim corridors, smells of wax...tobacco, an open door...a pipe and behind volutes of dense dancing smoke ... Rodney Porter, my host, head of the Department and director of the Immunochemistry Unit of the MRC.

Porter was awarded the 1972 Nobel Prize in Physiology or Medicine, jointly with Gerald Edelmann, for his work on the structure of immunoglobulins; he was terribly busy at that time but he was a superb mentor for me, sharing time with me everyday when he was in Oxford, and this was of prime importance for my future scientific orientation in Grenoble.

Porter’s humanity was fascinating and contacts with him lasted until his fatal accident in 1985, but this is outside the scope of the present text.

My first steps in immunology in Oxford were on the purification and control of a fragment of rabbit anti-ovalbumin IgG obtained by limited proteolysis of the IgG by plasmin. This fragment that lacked the C-terminal domain of the heavy chain was called Facb (Fragment Antigen and Complement Binding), following results obtained by George Connell, a preceding visitor in the Unit.

During this year I learned all the fundamentals of protein biochemistry centered on sequencing, proteolytic cleavage sites, location of sugar residues, domains... all major bases of modern molecular and structural biology. I also took my first contact with complement haemolytic assays to assess activation of the classical pathway by Facb-ovalbumin aggregates. I became also familiar with C1 proteins through discussions with Ken Reid and Bob Sim, in an already impressive lab.

Back to Grenoble I rapidly realized that my previous experience in enzymes' mechanisms joined to the recent expertise gained in Oxford could well contribute to studies on proteases and related proteins of the complement system. This way I started then a lab in Grenoble centered first on the study of C1 proteases and the initial activation of the complement cascade. Later on, Gérard Arlaud, after a PhD in the lab and a post-doctoral stay in Oxford, took the lead of a new lab on this line of research.
Further responsibilities in Immunology at the Faculty of Medicine led me to invest on another aspect of complement dealing with C3 proteolysis and the chaperone role of C3 fragments beyond complement receptor-mediated uptake by antigen-presenting cells (APC). The idea was to analyse the role of complement in the generation of antigenic diversity due to modifications of the intracellular routing and processing of antigens inside APC by associated C3 fragments. In fact, when tetanus toxin covalently linked to C3b was incubated with APC, its kinetics of transcytosis inside antigen presenting cells was modified, as well as its presentation to specific T cells.

Finally the hypothesis that complement and/or complement-related proteins could play a role in their native intracellular state was pushed forward. Preliminary results on MBL produced inside hepatocytes showed a binding capacity of precursor forms of the lectin; this chaperoning is reminiscent of the role played by calreticulin in autoimmunity.

This trip in complement has been favoured by many exchanges within the complement community with special milestones such as the organization in 1987 of the 12th International Complement Workshop in Chamonix and the friendly Michael Loos’ Mainz Meetings on C1 and C1-related proteins.

After thirty years I still think that there are many ways in complement or in its vicinity. Porter’s pipe was magic with its veil of smoke inviting to imagination ... now, fortunately in non smoking labs, the knowledge and the tools of nanotechnologies are available for complementologists to feed their research work with imagination. This was my way, it is up to everyone to choose his/her own way, with hopefully a light, even without smoke!

* Maurice Colomb was Professor of Biochemistry, then Professor of Immunology at the Faculty of Medicine / University J Fourier in Grenoble, France. He is presently an Honorary Professor. Contacts: Maurice Colomb 532, chemin des Arriots F 38330 Montbonnot Tel 33(0)4 76 90 60 16 maurice.colomb@wanadoo.fr

Kenneth Reid* - more on Rod Porter, the Prof

Professor Rodney Porter was appointed to the Whitley Chair of Biochemistry at Oxford University in 1967, and also as the Director of the newly formed MRC Immunochemistry Unit. The initial major remit of the Unit was to study immunoglobulin structure and function, however by the early 1970s the characterisation of the structures of the early acting components and control proteins of the complement system became a major focus of much of the research in the Unit.

I joined the Immunochemistry Unit, as a post-doctoral research fellow, in 1969, to carry out studies on the structural features of the IgG molecule, that were
important in activating the classical pathway of complement. Coming from Aberdeen, Scotland, and a lab that overlooked the North Sea, I had thought that I probably would stay no longer than the two years of my ICI Fellowship in Oxford (which is about as far from the sea as any other point in Britain).

However, I was soon completely won over by the relaxed, but very effective, manner in which Rod Porter, always known as “Prof”, ran the Unit – and consequently, almost 40 years later, I am still in Oxford. I first experienced his straight forward, down-to earth, approach, in 1968, when I went for an interview to discuss making fellowship applications – and met Prof sitting taking optical density measurements of column samples – then had to follow him down to his office, located in Old Biochemistry, and got left behind at the “Paternoster” – a continuing revolving lift system –which was a nightmare for first time visitors to the Department. However, I did get to the office and successfully have my interview. Research went slowly to begin with and I recall many meetings with Prof in the lab – when he would often sit, cross-legged, on a desk – start to light a pipe, which never seemed to get fully going – and he would patiently listen and advise on even the smallest practical details – and reassure that eventually the problems would be solved. However, once you did complete any substantial piece of work – and you waited for the praise – he would sort of give a very characteristic, throat-clearing, “harumph” and say “well Ken that’s nice – what are you going to do next?” I think this sympathetic but direct and forward-looking approach marked all the research carried out under Prof’s direction – and resulted in the Unit making considerable contributions to the understanding of the structures and functions of the components of the complement system. The Unit unfortunately is scheduled to close in September 2008 – and a short survey of its contributions to complement research will be given, in “Focus on Complement”, early in 2008.

* Kenneth Reid is a Professor of Biochemistry and Head of the MRC Immunochemistry Unit at the Department of Biochemistry, Oxford University, Oxford, UK.
Cutting Edge Session I  
Chairs: Andrea Tenner & John Atkinson

A major advance in disease predisposition has occurred over the past decade with the realization that haploinsufficiency of FH, MCP (CD46) and FI accounts for 50% of cases of atypical (no-preceding E. coli mediated or enteropathic diarrhea) hemolytic uremic syndrome (aHUS). There is no model of this disease in animals. M.C. Pickering and colleagues (London) solved this problem by knocking into the FH/-/- mouse a form of mouse FH lacking CCPs 16-20. Remarkably, such mice developed a spontaneous form of aHUS between 6 and 12 weeks. It seems to be a quite remarkable replica of the human disease. A key point here was that both an active complement system plus reduced inhibitory capacity were required for disease development.

Dennis Hourcade (St. Louis) described a role for properdin (P) in the initiation of the alternative complement pathway. The straightforward paradigm outlined was that AP activation occurred upon properdin binding to chip (Biacore system), a yeast (zymosan), a cell, or a bacteria (Neisseria) and then exposure to a C3 source and other components of the alternative cascade. He also reported on targeting properdin to an erythrocyte surface via a single chain Fv to trigger pathway activation. These data suggest a “positive” P initiated model as a means to initiate and facilitate AP activation. These data imply that local synthesis of P or release of P from neutrophil granules would be a means to activate the alternative pathway at sites of injury and infection.

The next two papers provided beautiful structures of FB and of CR1g bound to C3b. These papers are also commented on by Piet Gros and Paul Barlow in their review of oral session I entitled, “Structure and Function of Complement Proteins.” The large shifts in C3 going to C3b have now been clearly shown by 3 groups. In addition, the Genentech group, Christian Wiesmann et al. (San Francisco) provided the crystal structure of C3c (C3b is the same) attached via its β-chain to CR1g at 1Å resolution (wow!). CR1g is newly identified macrophage complement receptor and participates in the removal of pathogens that are coated with C3b and iC3b.

Piet Gros and colleagues (Utrecht) presented a crystallographic structure of factor B that had several remarkable features. The factor D cleavage site is protected from the exterior by salt bridges to the linker region and the VWA domain, an arrangement that constrains the VWA domain into a unique inactive conformation. The N-terminal CCPs that constitute most of the Ba region adopt a triad structure that provides a binding site for C3b. Links between the CCPs, the VWA domain and the linker region likely coordinate the exposure of the scissile bond and the activation of the VWA C3b-binding site during the association of factor B with C3b.
Focus on Complement

Oral Session II: Animal Models of Human Disease
Chairs: Marina Botto & Richard Quigg

This was a very exciting session that highlighted the importance of using animal models to investigate disease pathogenetic mechanisms. The group of Guillermina Girardi and Jane Salmon (New York) has shown in a series of insightful studies that fetal loss in anti-phospholipid antibody syndrome is attributable to complement activation through the alternative pathway with resultant C5a-mediated inflammation. In the exciting work presented at the ICW, they described their work in the CBAxDBA mouse model of spontaneous fetal loss. This could be reduced by global C3 convertase inhibition, as well as with inhibitory antibodies to C5 and factor B, and a peptide blocking C5a receptor activation. They further showed C5aR activation led to release of sVEGFR-1 by monocytes. Given the inhibitory activities of sVEGFR-1 on native VEGF, this provides a compelling paradigm for spontaneously abortions occurring clinically. Rick Wetsel et al. (Houston) presented the phenotypic effects in mice with targeted disruption of the mouse carboxypeptidase N 1 gene (CPN1) generated by his laboratory. Given the role of CPN to inactivate the C3a and C5a anaphylatoxins, as well as its association with angioedema in humans, their data showing these mice had no spontaneous abnormalities was a surprise. Yet, in a model of infection with the highly pathogenic Pseudomonas bacteria, CPN1-deficient mice had enhanced inflammation, as might be expected from persistence of the anaphylatoxins. In spite of this, there was also an increased bacterial burden. Thus, alterations in the normal metabolic effects of CPN1 profoundly affect normal immunity and inflammation.

Allyson Wood and colleagues (Denver) discussed their work dissecting the complement dependence of the mouse model of arthritis induced by passive transfer of anti-collagen II antibodies (collagen-induced arthritis). Their previous data indicated independence from C4, and by inference, the classical or lectin pathways. This left the alternative pathway as the likely culprit, for which their data showing factor B dependence was fully consistent. However, in the work presented at the ICW, mice deficient in mannose-binding lectins A and C (MBL) either had delayed or absent disease. They further showed that the MBL pathway could directly activate C3, bypassing the need for C4, which is consistent with their previous findings. This is a fascinating example of an antibody-induced activation of the MBL pathway in which there is direct C3 activation and amplification pathway-mediated disease, in this case, one that models human rheumatoid arthritis.

Lihua Bao and colleagues (Chicago) evaluated the effect of local kidney Crry deficiency in the setting of an intact complement system by transplanting Crry/C3-deficient mouse kidneys into syngeneic wild-type mice. These Crry-deficient kidneys developed marked inflammatory cell infiltration, tubular damage, and interstitial fibrosis, whereas similar changes were absent in control transplanted kidneys. Deficiency of Crry in the entire kidney led to spontaneous complement activation primarily in the tubulointerstitium associated with upregulation of several chemokines and extracellular matrix proteins. The data collectively provided compelling evidence that Crry is an essential complement regulator in the kidney. This presentation was followed by another very stimulating talk by Michael Braun (Houston). He showed very nicely that C3aR and C5aR may play a different role in the pathogenesis of the membranoproliferative glomerulonephritis associated with Factor H deficiency. By analyzing double deficient animals he demonstrated that C3aR is likely to have a dominant role in regulating extracellular matrix and that TGF-beta is the key cytokine involved in this process. The session finished with a presentation by Hongwei Gao (Michigan) describing the role IL-17 in sepsis. This cytokine was found to be elevated during experimental sepsis in mice and intravenous therapy with an anti-IL17 antibody significantly improved the inflammatory response. Very intriguingly he showed that the in this model the production of IL-17 depended on the engagement of C5a with C5aR. These presentations taken together provided important novel insight into the role of complement in the pathogenesis of a wide range of human conditions.
Focus on Complement

Oral Session VI: Complement and Infection
Chairs: Robert Finberg & Berhane Ghebrehiwet

This session featured several presentations defining mechanisms by which microorganisms resist attack by complement. Suzan Rooijakkers et al. (Utrecht) presented new information on Staphylococcal Complement Inhibitors (SCIN). SCIN binds to surface C3 convertases and inhibits C3b deposition, phagocytosis, and C5a production. They demonstrated that, in addition, *S. aureus* produces three distinct but homologous proteins that inhibit the alternative pathway (with no effect on the classical or lectin pathway). Biologically active sequences in the SCIN protein were also defined. Two presentations focused on microbial CRASPs (Complement Regulator-Acquiring Surface Proteins). Sohia Poltermann et al (Jena), defined a new yeast surface protein (CaCRASP-1) that binds factor H and FHL-1 (Factor H-like protein) as well as human plasminogen, and is important in the ability of *Candida albicans* to escape complement. Peter Zipfel and colleagues (Jena) defined the Factor H and FHL-1 binding protein BbCRASP-2, one of five different complement regulator proteins of *Borrelia burgdorferi*. Complementation of a serum sensitive strain of *B. burgdorferi* with BbCRASP-2 led to serum resistance, demonstrating the importance of the protein to bacterial survival.

Yunfeng Ma and colleagues (Wuhan and Fukushima) showed that administration of L-ficolin protected the host against lethal infection with Salmonella. In this study, human L-ficolin cDNA was cloned to the eukaryotic expression plasmid pcDNA3.1. It was then administered into BALB/C mice via intramuscular electroporation before challenge with a lethal dose of virulent *Salmonella typhimurium*. There was a dramatic reduction in the number of bacteria in the target organs (spleen and liver) of the Ficolin-L treated animals as compared to the vehicle plasmid treated animals. This protection was accompanied by a 3-fold increase (over control) in IFN-γ levels in the splenocytes. In another interesting presentation, Jo Anne Welsch et al (Oakland, CA & Worcester, MA) described the potential for the factor H-binding protein (FHBP) of encapsulated *N. meningitides* (Genome-derived Neisserial antigen 1870) in vaccine generation. This possibility is based on the identification of two mAbs recognizing distinct epitopes on the FH binding protein including one that inhibits FH binding that individually are not bactericidal but together are. Finally, using genetically deficient mice for either the classical (C1q), alternative (factor B) or all pathways (C3) of complement activation, Paul Giacomin and colleagues (Adelaide and London) revealed that the alternative pathway is important for the early (<2.5 h) innate recognition and leukocyte-mediated killing of the helminth, *Nippostrongylus brasiliensis*. Subsequently (>2.5 hrs), the parasite evades complement-mediated killing by an unknown mechanism.

Oral Session VII: Animal Models of Human Disease and Therapeutics
Chairs: Jane Salmon & Rick Wetsel

In this session six abstracts related to complement as target for therapy in different animal models were discussed. First, Dirk Spitzer and colleagues (St Louis) showed that in vivo gene transfer of a targeted form of the mouse complement component regulator Cryn to Cryn/C3 double KO mice provides a long-term and sustained protein supply. The increased expression of Cryn on RBCs protected them from complement attack in vitro, they survived to the same extent as wild type RBCs. This novel approach can provide long-term, stable host-derived synthesis of complement inhibitors for site-specific blockade of pathogenic complement activation. The second abstract by Natalie Hepburn and colleagues (Cardiff) focused on a C5-binding protein (OmCI) recently identified in the salivary gland of the soft tick Ornithodoros moubat. OmCI inhibits the terminal pathway without inhibiting the opsonic roles of complement. OmCI was shown to be effective in preventing experimental autoimmune myasthenia gravis induced by passive transfer in normal Lewis rats. This molecule presents a broad cross-species activity, a much slower clearance than other small, biological agents, and it offers exciting prospects for targeted treatment of complement-mediated diseases.
Francesco Tedesco and his group (Trieste) reported the beneficial effects of neutralizing mniantibodies to CD55 and CD59 (MB55-MB59) in Rituximab-dependent complement-mediated killing on CD20+ lymphoma cells. These antibodies, recently isolated from a human phage display library, enhance the therapeutic effects of Rituximab on lymphoma cells resulting in an increase in mice survival. Jessy Alexander and colleagues (Chicago) described that complement factor H (CfH) is present in rodent podocytes, and behaves functionally like human CR1. These authors performed renal transplants between wildtype and CfH-/- mice and induced serum sickness through immunization with apoferritin. CfH-/- kidneys in a wild type host had marked accumulation of IgG adjacent to the lacking CfH podocytes, while wildtype kidneys in a CfH-/- host had podocyte-associated CfH with absent IgG deposits. These studies showed that locally produced podocyte CfH is important to process ICs in the subepithelial space and limits complement activation.

Yi Wang and his group at Alexion Pharmaceuticals demonstrated that aerosol delivery of anti-mouse C5 mAb via nebulization achieved intrapulmonary C5 inhibition and significantly blocked methacoline-induced airway hyperresponsiveness (AHR) in a mouse model of asthma induced by sensitizations with OVA. Combined therapy with corticosteroid and anti-C5 mAb enhanced efficacy. Blocking intrapulmonary activation of C5 inhibits the generation of both C5a and C5b-9 and provides a potential clinical approach for treating patients with asthma. The session finished with a presentation by Xun Zhang and collaborators (Cincinnati) describing how C5a regulates B7 costimulatory molecule expression on distinct pulmonary dendritic cells (DCs) to protect from type-2 immunity in asthma. They studied the impact of C5aR signaling on the expression of B7 molecules in immunogenic myeloid DCs dendritic cells (mDCs) and tolerogenic plamacytoid DCs (pDCs) . mDCs function as the main APCs that drive Th2-immune responses whereas pDCs counteract the mDC-driven activation and differentiation of naïve Th cells. Using a mouse model of asthma, they found that C5a prevents the generation and activation of Th2 effector cells by different regulatory effects on pulmonary pDCs and mDCs These findings suggest a novel pathway of complement-mediated regulation of type 2 immunity in asthma. This interesting and stimulating session revealed the important advances in therapies targeted to the complement system that hold promise for application to several human diseases.

Oral Session VIII: Structure Function / Evolution / Genetic Deficiency
Chairs: Susan Lea & Masaru Nonaka

The first two presentations gave structural information. Kirstin Leath (Oxford) reported high resolution crystal structures for CD59 which reveal structural rearrangements following binding of a small molecule ligand in the putative C8/C9 binding face. Whilst Xiaojiang Chen (Los Angeles) revealed the structure of the massively glycosylated Epstein Barr virus major envelope glycoprotein. Yoshiko Murakami (Osaka) then went on to reveal a meticulous study of a single point mutation in the mannosyltransferase-encoding PIG-M gene promoter region demonstrating links between the mutation and an inherited glycosylphosphatidylinositol deficiency. The last three presentations focused on evolution of the complement system. Georgia Sfyroera (Philadelphia) reported molecular cloning of C3a receptor from a urochordate Ciona intestinalis, indicating that the complement-mediated proinflammatory system was established before the emergence of vertebrates. Ayuko Kimura (Tokyo) reported liver EST analysis of lamprey, a jawless vertebrate, concluding that most complement gene duplications which played important roles in establishing the classical pathway occurred in the jawed vertebrate lineage. Oriol Sunyer (Philadelphia) reported that in rainbow trout, a bony fish, large subsets of B cells show phagocytic activity, and trout complement has an opsonizing activity to enhance it. The trout system may represent an evolutionary transitional state of the B cell and complement cooperation.
Dear Colleagues,

On behalf of the European Complement Network, we are delighted to invite you to the 11th European Meeting on Complement in Human Disease. The Meeting will be held in Cardiff from 8th to 11th September 2007.

On Saturday, 8th September we will host a Teaching Day for students, junior post-docs and others new to the field, staffed by an International Expert Faculty. This Day has been generously supported by the International Complement Society and commercial sponsors, and is free to eligible Meeting attendees.

The Meeting will begin with Registration followed by a Welcome Reception in the historic setting of Cardiff City Hall on the evening of 8th September. Scientific Sessions will start bright and early on Sunday 9th September and run through to Lunch on Tuesday 11th September. Topics for Sessions will, as usual, be decided based upon submitted abstracts.

We have three outstanding Invited Speakers, chosen to give a broader perspective to disease areas of current relevance to complement research. Martin Glennie will review how therapeutic antibodies recruit complement and other effector mechanisms. Mark Pepys will discuss the controversies surrounding the roles of C-reactive protein in disease. Greg Hageman will discuss the tsunami triggered by the association of factor H polymorphism with age-related macular degeneration. There will also be Industry Sessions where the state of progress towards complement therapeutics will be expertly reviewed by experts at the sharp end.

The Gala Dinner will be held on Monday evening in the beautiful surroundings of Cardiff Museum and will include tours of the outstanding impressionist art collection. There will be a variety of Organised Excursions to local attractions on Tuesday afternoon.

The Meeting Venue is in the heart of the city, convenient for hotels of all standards and the many shopping and entertainment opportunities of a Capital City. Budget accommodation is available in University Halls close to the venue.

More information is available on the Meeting Website, now live for registration, hotel booking and abstract submission at www.complementcardiff.org.uk

Abstracts will be published in a special meeting issue of Molecular Immunology.

The Deadline for Abstract Submission and Early Registration is 4th May 2007.

We look forward to welcoming you to Cardiff.
Rhyd ni’n edrych ymaen at croesawí chi i Caerdydd.

The Local Organising Committee
Claire Harris, Tim Hughes, Eamon McGreal, Paul Morgan, Brad Spiller, Carmen van den Berg, Anwen Williams