



## ABOUT THIS ISSUE & MORE

### What's inside?

<1> Two flash news items, are presented by Dr. F. Tedesco: (a) the therapeutic potential of rCD59 in AMD, and (b) the role of C3 in muscle wasting diseases or dysferlinopathies.

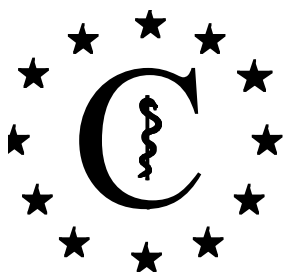
<2> Dr. Tedesco also presents two complement teams: one from Denver, Colorado, and another from Innsbruck, Austria. The Editorial Board of Focus on Complement (FoC) would like to thank Dr. Tedesco for these timely contributions.

<3> Under the "ICS Projects" section, a "mission statement" letter from the new President of ICS, Dr Paul Morgan is presented.

<4> Two, important meetings are also brought to your attention: (a) The "13<sup>th</sup> European Meeting on Complement and Human Disease", will be held in Leiden, The Netherlands (Aug. 21-24, 2011) and (b) The "Interlec24", on lectin biology will be held in Brisbane, Australia (July 27-30, 2011).

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## FLASH NEWS

### Recombinant Membrane-targeted Form of CD59 Inhibits the Growth of Choroidal Neovascular Complex in Mice

Bora NS, Jha P, Lyzogubov VV, Kaliappan S, Liu J, Tytarenko RG, Fraser DA, Morgan BP, and Bora PS *J. Biol. Chem.* 285: 33826-33833, 2010

Evidence has been collected in recent years involving dysregulation of the complement system in the pathogenesis of age-related macular degeneration (AMD). Deposits of complement components and activation products have been detected in drusen, the hallmark clinical finding of early AMD. Human genetic studies have shown that polymorphic variants of complement components and regulators are associated with an increased or decreased risk for AMD. Using a mouse model of CNV obtained by Laser-induced photocoagulation of Bruch's membrane, Bora and colleagues report a therapeutic approach to control choroidal neovascularization (CNV), a characteristic feature of AMD responsible for the loss of central vision. The mice received an intravitreal injection of the recombinant membrane targeted CD59 (rCD59-APT542) and was found to be incorporated in the retinal pigment epithelium. This complement regulator localized in the mouse eye, and proved effective in controlling the growth of the CNV complex and the size of fully developed CNV lesions. Treatment of mice with rCD59-APT542 resulted in decreased cell proliferation and an increased number of apoptotic cells, which is attributed to levels of MAC formation. Several compounds controlling the complement system at different steps of the activation sequence are currently being investigated to prevent progression of AMD and to treat late AMD. Based on these findings, rCD59-APT542 appears to be a promising drug to be included among the emerging pharmacological strategies to treat AMD.

CD59 attenuates severity of AMD - Reporter: F. Tedesco

### Genetic ablation of complement C3 attenuates muscle pathology in *dysferlin*-deficient mice

Han R, Frett E M, Levy JR., Rader EP., Lueck JD, Bansa D, Moore SA., Ng R, Beltrán-Valero de Bernabé D, Faulkner JA, and Campbell KP. *J. Clin. Invest.* 120: 4366-74, 2010

Tissue damage caused by complement activation products is usually observed in immune-mediated disorders and in acute conditions such as sepsis and ischemia-reperfusion. In this study Han and colleagues provide convincing data suggesting the involvement of complement in a group of muscle wasting diseases caused by the deficiency of dysferlin, a protein expressed in striated muscle and immune cells. These diseases known as dysferlinopathies are characterized by contraction-induced injury of muscles associated with a strong inflammatory response. The study was conducted on dysferlin-null mice that exhibit features observed in dysferlin-deficient patients such as reduced muscle force, increased susceptibility to LC-induced damage, and signs of muscle inflammation. RT-PCR of RNA extracted from the skeletal muscle of these mice showed increased expression of C1qa, factor B and C4, and downregulation of CD59 raising the possibility that complement may be involved. The role of complement in muscle injury was further supported by immuno-fluorescence analysis that revealed C3 and MAC deposits on the surface of muscle fibers. Double null mice deficient in C3 and dysferlin rescued muscle pathology, while ablation of C5 in dysferlin-null background mice did not result in improvement in dystrophic features. The finding that the complement system affects the progression of muscle pathology in dysferlinopathy provides important insights into the design of novel therapeutic strategies for these patients.

C3 in muscle pathology- Reporter: F. Tedesco

## SPOTLIGHT ON TEAMS - I

### *COMPLEMENT IN DENVER, COLORADO—USA*

The Diagnostic Complement Laboratory, in Denver Colorado, was formed in 1990 in response to requests from physicians who were looking for a reliable way to diagnose their patients with suspected complement abnormalities, be it a complement deficiency, in vivo activation, primary immunodeficiency, a recurrent infectious disease or problems related to autoimmune disease. We have grown from a research lab that did occasional diagnostic tests to a diagnostic lab that does occasional research projects making us a lab that is not like most of those featured in **Focus on Complement**. We don't rely on grant money, nor do we publish lots of papers with break-through discoveries on new proteins, structures, and the like. Instead, we are work for a non-profit medical and research organization, National Jewish Health, founded over 110 years ago as a TB hospital. Patients still come to our institution from all over the United States and elsewhere for diagnosis and treatment of lung, heart and immune diseases. Among the latter are a growing number of patients with complement deficiencies, autoimmune diseases and complement regulatory problems. In order to offer tests that will become part of the patient's medical record, a clinical laboratory like ours must meet certain regulatory requirements

defined by the U.S. Department of Health and Human Services. We are accredited by the College of American Pathologists (CAP) under the conditions required by the Clinical Laboratories Information Act of 1988 (CLIA) to perform tests of high complexity.



The first few years the lab grew slowly, relying on local requests for testing. From two employees in 1990, the lab has grown to 18 in 2011, and the number of tests per year has increased from approximately 1200 in the first year to over 60,000 per year this past year. Part of that growth has come from the fact that we are recognized as the complement referral lab for physicians, hospital and major reference laboratories throughout the United States. That has been possible because of the breadth of the complement testing we offer and the continued focus on quality and individual service.

The other part of our growth came from our involvement in working with pharmaceutical industry. In 1993 we were asked to investigate the cause of death of a monkey in a pre-clinical trial that involved an antisense oligonucleotide, and we showed that systemic complement activation induced fatal shock. Publication of this incident led to further interest in complement testing among the pharmaceutical

companies and we received additional studies for complement analysis.

This is a niche we have been happy to fill, but one that has brought us into contact with 21, CFR, Part 58 regulations from the FDA (yet another set of regulations that do not usually impact a research lab). We also perform studies to test complement activation in vitro. This can be done in the laboratory using a variety of species and specimen types including whole blood, plasma or serum.

At the present time, these studies account for about half of our business, while the other half is the diagnostic testing. This mix means we get to have an immediate impact on the lives of patient and their families through our diagnostic contributions, while we also are part of bringing new treatments to market. Developing a laboratory devoted to studies of the complement system over the years has been a rewarding experience. We now have the ability to define almost any complement problem that is encountered in the clinic as well as help in the design of new drugs and other compounds that may be employed in treatments of multiple diseases in the coming years. For more information, please see the website for all of the Advanced Diagnostic Laboratories (ADx) at National Jewish Health: [www.NJLabs.org](http://www.NJLabs.org)

Patricia (Patsy) Giclas PhD

Ashley Frazer-Abel, PhD

Complement Laboratory Director

Assistant Director

## SPOTLIGHT ON TEAMS - II

### **COMPLEMENT IN INNSBRUCK—AUSTRIA**

*Manfred Dierich's legacy: three teams carry the complement torch on ...*

**Cornelia Speth – Heribert Stoiber – Reinhard Würzner**

Innsbruck Medical University, Austria

Manfred Dierich, a former member of the famous “Klein School” from Mainz, established a complement lab in Innsbruck in 1982 – thus putting Innsbruck on the “complement map”. Early workers comprise Wilhelm Schwaeble (now at Leicester), Thomas Schulz (Hannover), Clara Larcher (Bozen), and Wolfgang Prodinger— the latter now dedicates his research expertise to tuberculosis and has become the head of the Medical University teaching commission. Heribert Stoiber stayed on after successful completion of his Ph.D. in 1995. Reinhard Würzner originally came from Otto Götze's lab in Göttingen in 1993. He also trained with Bob Sim in Oxford and a PhD studentship with Peter Lachmann in Cambridge. Cornelia Speth joined the Institute in 1996 from the GSF research centre near Munich. Thus, three faculty members now supervise complement research teams in the two newly created Divisions—Div. of Hygiene & Med. Microbiology and Div. of Virology, studying the interplay between complement and microorganisms with a strong focus on complement evasion mechanisms.



Cornelia's group investigates the interaction of viral and fungal pathogens with the cerebral complement system. Since the brain unlike the periphery lacks efficient immune weapons, the complement plays a central role in the antimicrobial defense of the CNS. Her group focuses on HIV as this virus efficiently infects the brain in most patients exploiting monocytes as Trojan horses. In addition, the medically important fungus, *Aspergillus*, is investigated with regards to its ability to activate local complement system in the CNS as well as its evasion strategies.



Heribert's main focus is the complement evasion of viruses, in particular HIV and related mouse viruses. Following his early finding that factor H attaches to HIV resulting in a decrease in lysis, his lab—in close collaboration with Doris

Wilflingseder—now pursues to examine the influence of opsonization on

HIV entry into immune cells, in particular dendritic cells (DCs). The findings published in *PlosPathogen* show that complement opsonization of retroviruses enhances the induction of DCs to mount a robust CTL responses both in vitro and in vivo. Thus, beside its role in the innate immune response, complement is a natural adjuvant for DC-induced differentiation induction of retrovirus-specific CTLs. Reinhard's group is working on one of Manfred's long-standing interests—the CR3 analogue on *Candida*. Studies of his group showed that this molecule functions as HIV binding site and upon binding, fungal virulence is increased. Presently, his group is characterising HGT1, the recently discovered fH-binding molecule on *Candida*. The fact that *Aspergillus* was also found to bind fH (and C4bBp) corroborates the importance of this evasion mechanism. As former head of the Austrian EHEC Reference Centre Reinhard is presently also investigating – together with Dorothea Orth — the role of complement in typical HUS.

In the past we had hosted congresses such as the 1997 European Complement Meeting and enjoyed seeing our colleagues in Innsbruck. We hope to welcome the complement community to Innsbruck sometime in the future again. However, fellow complementologists are more than welcome to visit us anytime. Just bring both your scientific “slides” and your skis or mountain boots along with you.

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## ICS PROJECTS

### *LETTER FROM THE NEW ICS PRESIDENT*

I know it all seems like a long time ago, but back in September 2008 at the International Complement Workshop in Basle you ICS members, to my great surprise, kindly voted for me and I became President Elect of the ICS. Being President Elect of the ICS is a bit like being Vice-President of the USA, but with even less to do and a lower media profile. Thankfully, the President remained in rude health and I had a quiet couple of years (at least as far as ICS work was concerned!).

According to the complex rules of the ICS, from 1<sup>st</sup> January 2011 I became President and am ready to put some work in at last! My predecessor, Mike Pangburn, has done a great job and there are a number of important projects underway that I look forward to taking the credit for!

- The 2012 meeting in Crete – in the very capable hands of John Lambris, a great meeting is guaranteed, though I hope to be of some help.
- Complement assay standardisation committee – a much-needed initiative started by George Fust and now being led by Michael Kirschfink, Tom Mollnes, Patsy Giclas and other colleagues – will develop and distribute standards for the common assays, establish protocols for standardisation in all clinical complement labs, and expand the assay range to include less common complement analytes.
- Complement Nomenclature working group – grasping the very prickly nettle of terminology, a long-running problem in our subject and one that needs to be solved. If I achieve nothing else during my presidency, I would leave happy if I succeeded in getting final agreement on the C2a/C2b debate and (perhaps optimistically) lectin pathway nomenclature!
- Increased role in teaching and training – I think that the teaching days have been a great addition to the ICS meetings and are much appreciated by students and others new to the field. I would like to develop other teaching and learning initiatives and would welcome any suggestions in this area.
- Future ICS meetings – the pipeline is a bit thin and this may be in part because potential organisers have not had enough time to develop proposals. We are already canvassing for proposals to host the 2014 meeting and hope to be able to make a decision at the ECN meeting in September this year, giving a full three years for the organisers to make their plans.

This is a really exciting time to be working in complement biology. Almost every month a new disease association with a complement gene pops up and as a result, clinicians from diverse specialties are discovering that complement is an important and fascinating system. As a result, complement expertise is much sought after. I never thought I would get to say it but complement is sexy! Hopefully, the journals and funders will realize this too and our papers and grants will get the result they deserve instead of being dismissed as “boring complement”!

My one exposure to Leadership Training taught me that in the first months in a new job a leader should be in “receive mode”, open to ideas, suggestions and criticism..... I am receptive and look forward to hearing your ideas. Contact me at [morganbp@cardiff.ac.uk](mailto:morganbp@cardiff.ac.uk).

Paul Morgan.



## 13th European Meeting on Complement in Human Disease

Leiden, The Netherlands, August 21-24, 2011

[www.EMCHD2011.com](http://www.EMCHD2011.com)

It is a great pleasure to invite you to the 13th European Meeting on Complement in Human Disease that will be held in Leiden, The Netherlands in August 2011. In line with the good tradition we aim to organize a high quality scientific meeting that will serve as a platform to exchange information in a time-effective and pleasant way. The city of Leiden was selected because of its long academic tradition, a strong history in complement research and excellent travel connections via Amsterdam Schiphol airport (just 20 minutes by train).

Abstracts can be submitted via our website starting February 11, 2011.

The deadline for receipt of abstracts: April 1, 2011 and early registration: June 15, 2011.

Confirmed speakers:

Anna Blom, Marina Botto, Peter Garred, Piet Gros, Michael Holers, Matthew Pickering and Christopher Tang.

Please check our website for our scientific program: [www.EMCHD2011.com](http://www.EMCHD2011.com) or email us: [emchd2011@lumc.nl](mailto:emchd2011@lumc.nl)

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## **MEETING ANNOUNCEMENT:**

Interlec24 will be held in Brisbane, Australia between 27 and 30 July 2011. This is a multidisciplinary meeting that considers all aspects of lectin biology. The major focus of the meeting is the contribution to innate immune defences via the lectin complement pathway. Field leading international speakers will introduce sessions on the following themes; Clinical aspects of lectin biology, Structure – function aspects of novel lectins, Lectin cross talk with the adaptive immune system, Lectin - microbial interactions and Non-mammalian lectin biology. The majority of the meeting will consist of proffered papers. Brisbane is a great location for an international meeting and will be ready for business after its recent floods. On behalf of the Australian lectin-scientific community and the people of Brisbane I encourage you to consider submitting your work to Interlec24 and joining us for a convivial meeting in July of this year. Please see <http://www.interlec24.com/> for more details.

Kind regards

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