Focus on Complement
A newsletter of the International Complement Society

September 1, 2012
Issue 27

About this issue & More

What’s inside?

<1> Two independent but complimentary flash news, are presented by Dr. Sakari Jokiranta on: (a) the role of serine protease MASP-1 as the exclusive activator of MASP-2; (b) the crucial role of MASP-1 in the lectin pathway activation in human serum.

<2> Dr. Sakari Jokiranta also presents one “Complement Team” from the University of Heidelberg.

<3> A final announcement of the fast approaching XXIV International Complement Workshop (ICW) in Crete is included.

www.complement2012.org

<4> This issue also highlights a recent recognition of an ICS member: Dr. Michael Pangburn.

Editorial Board
B. Ghebrehiwet, Editor
John Atkinson
Anna Blom
Teizo Fujita
Sakari Jokiranta
Joerg Koehl
Paul Morgan
Michael Pangburn
Francesco Tedesco
Andrea Tenner

Editorial Board

European Complement Network

Thanks to our sponsors:

Quidel Corp.
Specialty Products
2981 Copper Road
Santa Clara, CA 95051, U.S.A.
Tel.: 408-616-4301
Fax: 408-616-4310
E-mail: custsvc.spg@quidel.com
Website: www.quidel.com

CompTech
Complement Technology, Inc.
4801 Truop Hvy, Suite 701
Tyler, Texas 75703
1-903-581-8284 (Phone)
1-903-581-0491 (Fax)
E-mail: contactCTI@aol.com
Website: www.ComplementTech.com

Hycult biotech
P.O. Box 30
5400 AA UDEN
The Netherlands
T +31 (0)413 251 335
F +31 (0)413 248 353
E info@Hycultbiotech.com
W www.hycultbiotech.com
Crucial role of MASP - Reporter: S. Jokrantz


The Hungarian group used monospecific synthetic inhibitors for MASP-1 and MASP-2 to demonstrate that in human serum specific inhibition of MASP-1 precludes lectin pathway activation, as measured by C4 deposition on mannan surfaces. Using CCP1-CCP2-SP fragments of MASP-1 and MASP-2 expressed in bacterial cells, they furthermore find that MASP-1 is able to cleave MASP-2 at its activation site, and they conclude that MASP-1 plays an important role in activating MASP-2. They also attempt to determine the relative roles of MASP-1 and MASP-2 in cleaving C2, by first binding MBL/MAst complexes from serum on a mannan surface then incubating with purified C4 to make a C4b-saturated plate. Due to the C4b saturation of the plate, the limiting step for C3-convertase formation is the subsequent C2 cleavage. In the second step they add human serum again as a C2 and C3 source, with or without inhibitors, and then measure the C3 deposition. Using this approach, they estimate that 60% of C2 is cleaved by MASP-1. Some points of criticism are that the main conclusion is based on loss-of-function data only, and that cleavage of the recombinant CCP-CCP-SP fragment is non-physiological (it lacks the ability to associate with MBL), and the estimation of C2 cleavage by MASP-1 is confounded by active MASP-1 and MASP-2 added in the last step when human serum is used as a source of C2 and C3. Yet, the study is elegant, and the conclusions are convincing.

Flash News


The Hungarian group used monospecific synthetic inhibitors for MASP-1 and MASP-2 to demonstrate that in human serum specific inhibition of MASP-1 precludes lectin pathway activation, as measured by C4 deposition on mannan surfaces. Using CCP1-CCP2-SP fragments of MASP-1 and MASP-2 expressed in bacterial cells, they furthermore find that MASP-1 is able to cleave MASP-2 at its activation site, and they conclude that MASP-1 plays an important role in activating MASP-2. They also attempt to determine the relative roles of MASP-1 and MASP-2 in cleaving C2, by first binding MBL/MAst complexes from serum on a mannan surface then incubating with purified C4 to make a C4b-saturated plate. Due to the C4b saturation of the plate, the limiting step for C3-convertase formation is the subsequent C2 cleavage. In the second step they add human serum again as a C2 and C3 source, with or without inhibitors, and then measure the C3 deposition. Using this approach, they estimate that 60% of C2 is cleaved by MASP-1. Some points of criticism are that the main conclusion is based on loss-of-function data only, and that cleavage of the recombinant CCP-CCP-SP fragment is non-physiological (it lacks the ability to associate with MBL), and the estimation of C2 cleavage by MASP-1 is confounded by active MASP-1 and MASP-2 added in the last step when human serum is used as a source of C2 and C3. Yet, the study is elegant, and the conclusions are convincing.

In conclusion, these two original and independent studies provide a novel understanding of the function of the lectin pathway in man.


Using serum from a 3MC patient with a non-sense mutation in the common part of the MASP1 gene, and hence deficient in MASP-1, MASP-3 and MAP44, the group in Aarhus found that this patient did not have a functional lectin pathway, despite normal levels of MASP-2 and after reconstitution with MBL to boost low-level endogenous MBL. This group had previously reported on a MASP-2 deficient individual with a defective lectin pathway, and questioned whether MASP-1 and MASP-2 co-operated. Subsequently, they found that mixing the two sera reconstituted activity thus restoring C4 deposition. They next demonstrated that the functionality of the lectin pathway in a MASP1 deficient individual could be reconstituted with rMASP-1 in a dose-dependent manner, while a catalytically inactive variant of rMASP-1 could not, thus pinpointing MASP-1 as the central molecule. Furthermore, the full-length, mammalian expressed, human rMASP-1 and complexed with MBL on a mannan surface could activate similarly expressed MASP-2. In vitro, experiments using only recombinant components demonstrated that the rate of C4 cleavage by MASP-2 was entirely dictated by the catalytic activity of MASP-1. Finally, these investigators showed that MASP-1 and MASP-2 could be found in the same MBL complexes in human serum, providing evidence for trans-activation and highlighting the essential role of MASP-1 in the both the loss-of-function and gain-of-function data in intact human serum as well as in a simplified system. Using the same 3MC serum, another important observation was that, neither MASP-1 nor MASP-3 are required for alternative pathway activity, as has been suggested to be the case in the mouse.

In conclusion, these two original and independent studies provide a novel understanding of the function of the lectin pathway in man.
Spotlight on teams-I
Complement Research in Heidelberg, Germany

Complement research at the University of Heidelberg started in the early 1970ies with Klaus and Ursula Rother at the Institute of Immunology and remained in focus since then. From the beginning, the introduction of a comprehensive complement analysis by Ursula Rother was considered indispensable to understand the importance of complement in physiology and disease development.

After having returned from a postdoctoral fellowship at Tibor Borsos’ lab at the National Cancer Institute, NIH, USA, in Frederick MD; Michael Kirschfink took over in the late 1980s. Since then the group tried to keep up with the Heidelberg tradition to conduct research at the interface between basic and clinical complement science. Over the last 20 years the role of complement in SIRS and multiple organ failure after polytrauma, burn, sepsis, in allergy, in various forms of nephropathy and after renal transplantation were investigated in clinical as well as experimental studies.

With the increasing acceptance of the importance of complement in severe inflammatory disorders during the 1990s, we became more and more interested in the development of drugs targeting complement. After many years trying to promote therapeutic strategies to interfere with complement-mediated tissue destruction in various animal experiments the group is now involved in the first successful treatment of severe nephropathies like aHUS/HUS and MPGN with Eculizumab.

Almost 15 years ago we also became interested in molecular mechanisms employed by tumors to escape the immune system. These studies, from the beginning performed in a successful and wonderful collaboration with Zvi Fishelson, Tel Aviv, helped to identify overexpression of membrane complement regulators as key mechanisms of cancer cell complement resistance. Since then, the Heidelberg complement lab has been at the forefront in the development of targeted knock down of membrane complement regulators on cancer cells to improve antibody-based cancer immunotherapy.

In a still continuing fruitful collaboration with Peter Zipfel (Jena), Peter Kraiczzy (Frankfurt), and Reiner Wallich (Heidelberg), we were able to characterize immune evasion molecules on Borrelia spp., which are responsible for their serum (i.e complement) resistance.

As an accredited diagnostic lab we are currently serving many national and international clinics as well as pharmaceutical institutions (preclinical, clinical studies) with a broad panel of modern complement tests. Collaboration with many clinicians in Germany and abroad (esp. with Anete Grumach, (Sao Paulo, Brasil) and Christoph Licht, (Toronto, Canada) has led over the years to the identification and characterization of several complement-deficiencies. Following George Füst’s initiative, Michael Kirschfink is currently coordinating the IUIS standardization program on complement analysis. The combination of basic and translational research is what has made the Heidelberg complement lab a well-respected training and research center.

Contact: M. Kirschfink, DVM PhD; Inst. Immunol; University of Heidelberg; e-mail: kirschfink@uni-hd.de
ANNOUNCEMENT

Dear Colleagues,

The **XXIV International Complement Workshop** will be held on **October 10-15, 2012**, on the scenic island of **Crete, Greece**. It will serve as a timely and lively scientific platform to share the latest research updates, discuss emerging trends and concepts in the field, meet current and future collaborators, and get inspired by new ideas. Submitted abstracts will be peer-reviewed and selected for either an oral presentation in the top-modern conference center, or for the poster sessions. In addition to the scientific highlights, the Greek sun, cuisine, and cultural attractions will certainly contribute to a relaxed and unforgettable workshop experience. The regular registration package will include wonderful room accommodations in a 5-star hotel—located directly on the banks of the Mediterranean Sea—, breakfast, lunch, dinner, and coffee breaks, as well as a social program including trips to Cretan highlights and, of course, some dancing.

Rarely before has the field of complement research seen such dramatic changes and exciting developments than during the past decade. Driven by seminal discoveries ranging from molecular to clinical aspects, and fueled by recent progress in the therapeutic intervention in complement-mediated diseases, novel insights into the function of complement appear at an increasingly rapid pace. New players in the network have been discovered, and several functional aspects have been redefined or extended, recently. At the same time, we are coming to realize that the physiological spectrum of complement by far exceeds host antimicrobial defense and that the complement network is highly intertwined with a variety of bodily systems. Open and vivid scientific discussions, the integration of new research ideas and talents, and the interaction with peripheral fields can further drive complement research to new horizons.

**The keynote speakers of the meeting are:**

**Alberto Mantovani, M.D.** Professor, University of Milan Scientific Director, Istituto Clinico Humanitas.

**Hans J. Müller-Eberhard Memorial Lecture:** *The humoral arm of innate immunity: recurrent themes and regulatory pathways*

**Shankar Subramaniam, Ph.D.** Professor and Chair Department of Bioengineering, University of California, San Diego.

*Systems Biology and Innate Immunity*

**Joe Nadeau, Ph.D.** Director of Research and Academic Affairs of the Systems Biology Institute, Seattle.

*Tipping complex systems from disease to health: genetic and dietary influences on metabolic disease, cancer and inflammation*

**Additional speakers will be selected from the submitted abstracts**

The deadline for receipt of abstracts, early registration, and hotel reservations is **July 10, 2012**. Please
note that the cost of the registration fee is **575 Euro** and hotel accommodations from **85-110 Euro/night**.

Additional information will be sent only to people who respond to this announcement and pre-register on-line. For your convenience and to expedite the communication process, registration materials, including abstract and hotel reservation forms, are available on the web site. Information on Crete, travel to Greece, hotel accommodations, etc. is also available on the web site. Updated information will be available through this site.

http://www.complement2012.org or http://www.aegeanconferences.org

To pre-register to the conference please visit:

https://www.aegeanconferences.org/registOpen.do?method=open

To encourage the participation of young scientists, the following **Trainee Travel Awards** will be available to offset a portion of the travel expenses to the Conference:

- **Trainee Travel Awards**
- The Lambris Complement Training Award (LCTA)
- **Young Investigator Awards for Research in Complement**

For more information please visit the workshop’s website.

We look forward to welcoming you in Crete for a scientifically stimulating and socially enjoyable meeting.

Best personal regards,

Local Organizing Committee

**John D. Lambris** (www.lambris.com)
University of Pennsylvania, USA
Chair of the Organizing Committee

**George Hajishengalis**
University of Louisville, USA

**Daniel Ricklin**
University of Pennsylvania, USA

Program Committee

The Program Committee will consist primarily of ICS Board members (see www.complement.org), and possibly a few ad hoc members. The committee will select the abstracts for presentation, travel awards, and the keynote speakers. The Chair of the Program Committee is the current President of the ICS, **Dr. Paul B. Morgan**, University of Wales College of Medicine. The other members are as follows:

**Michael Pangburn**, Past President (*University of Texas Health Sci. Ctr.. USA*)
**Berhane Ghebrehiwet**, Secretary (*Stony Brook University, USA*)
**Zvi Fishelson**, President Elect (*Tel Aviv University, Israel*)
**Andrea J. Tenner**, Treasurer (*Univ. of California, Irvine, USA*)
**Anna Blom** (*Lund University, Sweden*)
**Mohamed Daha** (*University Hospital Leiden, Netherlands*)
**Peter Garred** (*University of Copenhagen, Denmark*)
**Claudia Kemper** (*King’s College London, UK*)
**Jörg Kühl** (*University of Lübeck, Germany*)
**Tom E. Mollnes** (*Rikshospitalet University Hospital, Norway*)
**Matthew C. Pickering** (*Imperial College, Hammersmith, UK*)
**Santiago Rodriguez de Cordoba** (*Centro de Investigaciones Biologicas, Spain*)
**Wenchao Song** (*University of Pennsylvania, USA*)
RECENT AWARDS AND RECOGNITION of ICS MEMBERS

Michael Pangburn, Ph.D. – Professor of biochemistry and Director of the Center’s graduate program in biotechnology at The University of Texas Health Science Center at Tyler, has received the Regents Outstanding Teaching Award from The University of Texas System Board of Regents. Dr. Pangburn is one of 40 faculty members from UT system’s six health institutions to receive this 2012 prestigious award. Congratulations!
Focus on Complement
A newsletter of the International Complement Society

Complement Reagents Corner

CompTech
Your primary source of complement proteins and reagents.

- Purified Complement Proteins
- Complement Cells (EA, Er) & Buffers
- Antisera to complement proteins
- Sera depleted of complement components
- Human Anaphylatoxins – C3a, C4a and desArg forms of C3a, C4a and C5a
- Now available: Human C5a (real C5a, not recombinant protein)

Complement Technology, Inc.
www.ComplementTech.com
Email: contactCTI@aol.com
Phone: 1-903-581-8284
Fax: 1-903-581-0491

Outstanding & Unique

Innate Immunity • Acute phase proteins
Antimicrobial peptides • LPS, Microbial toxins • Scavenger receptors • TLR
Inflammation • Cell & Tissue damage
Complement • Lipid binding proteins
Oxidative stress

- Launch of Outstanding New ELISA’s for Human Properdin and Mouse C1q.
- Now available: 1-plate assays, for example for Human MBL and CFH.
- New: Low Endotoxin Antibodies for Functional Studies.
- New: BSA-free Antibodies for Immuno Assays.
- Hycult™ Biotech Inc. Direct Sales & Support in the Americas.
  Tel: 1-610 260 1491. E-mail: orders-us@hycultbiotech.com.
- American Association of Immunology, May 4 – 9.
  Visit us at booth 1328 for our new products and raffle!

For more information or to register for our Newsletter, www.hycultbiotech.com

CEDARLANE® offers a wide range of complement related antibodies to mouse, rat and human specificities in various formats (purified, biotin, FITC, PE, enzyme conjugates).

- Proteins... C1q, C3/C3b/C3c, C3a, C3d, C4, C5, C6, MBL.
- Regulators... C1 Inhibitor, Factor H, Factor I, Crry, DAF, CD59.
- Receptors... C3aR, C5aR (CD88), CR3 (CD11b/CD18), CR1 (CD35), CR2 (CD21), gC1q-R.

Browse for targets, species and formats at... www.cedarlanelabs.com/complement

In CANADA (New Address):
4410 Paletta Court, Burlington, ON L7L 5R2
Toll Free: 1-800-268-5058
ph: (289) 288-0001, fax: (289) 288-0020
General e-mail: general@cedarlanelabs.com

In the USA:
1210 Torrentine Street,
Burlington, NC 27215
Toll Free: 1-800-721-1644
ph: (336) 513-5135, fax: (336) 513-5138
General e-mail: service@cedarlanelabs.com

We are an ISO 9001:2000 and ISO 13485:2003 registered company.
Interested in reading previous bulletin issues?

All previous bulletin issues can be freely downloaded from the ICS Homepage: http://www.complement.org
(Publications → Archive)