



International Complement Society



European Complement Network

Editorial Board

Claudia Kemper (Editor)
Zvi Fishelson
Peter Garred
Michael Holers
Michael Kirschfink
Bo Nilsson
Matthew Pickering
S. Rodriguez de Cordoba
Wenchao Song
Denise Tambourgi
Andrea Tenner
Trent Woodruff
Peter F. Zipfel

Dear Readers,

Welcome to the June 2016 issue of 'Focus on Complement'.
This 42nd issue of FoC contains:

- **Flash News** reporting on a new role for collectin-11 in renal injury and how complement-mediated enhanced synaptic pruning by microglia may contribute to obsessive-compulsive disorders.
- **The Complement research teams around the world** series featuring the teams of Diana Karpman in Sweden, and of Marciej Cedzyński in Poland.
- **XXVIth International Complement Workshop** announcement

If you would like to contribute with an article to a future issue or have suggestions for a subject theme, please contact Claudia Kemper or Andrea Tenner; Claudia.kemper@kcl.ac.uk; atenner@uci.edu

Thank you for your continuous sponsorship:



Specialty Diagnostics
quidel.com



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



Complement
Technology, Inc.

4801 Troup Hwy, Suite 701
Tyler, Texas 75703

1-903-581-8284 (Phone)

1-903-581-0491 (Fax)

E-mail: contactCTI@aol.com

Website: www.ComplementTech.com

NEWS FLASH (reported by Prof. Peter Garred, Denmark)

Collectin-11 detects stress-induced L-fucose pattern to trigger renal epithelial injury.

Farrar CA, Tran D, Li K, Wu W, Peng Q, Schwaebler W, Zhou W, Sacks SH.

J Clin Invest. 2016 May 2;126(5):1911-25. doi: 10.1172/JCI83000. Epub 2016 Apr 18

Physiochemical stress induces tissue injury as a result of the detection of abnormal molecular patterns by sensory molecules of the innate immune system. Here, the authors described how the recently discovered C-type lectin collectin-11 (CL-11, also known as CL-K1 and encoded by COLEC11) recognizes an abnormal pattern of L-fucose on postischemic renal tubule cells and activates a destructive inflammatory response. They found that intrarenal expression of CL-11 rapidly increases in the postischemic period and colocalizes with complement deposited along the basolateral surface of the proximal renal tubule in association with L-fucose, the potential binding ligand for CL-11. Mice with either generalized or kidney-specific deficiency of CL-11 were strongly protected against loss of renal function and tubule injury due to reduced complement deposition. *Ex vivo* renal tubule cells showed a marked capacity for CL-11 binding that was induced by cell stress under hypoxic or hypothermic conditions and prevented by specific removal of L-fucose. Further analysis revealed that cell-bound CL-11 required the lectin complement pathway-associated protease MASP-2 to trigger complement deposition. Given these results, the authors conclude that lectin complement pathway activation triggered by ligand-CL-11 interaction in postischemic tissue is a potent source of acute kidney injury and is amenable to sugar-specific blockade.

Progranulin Deficiency Promotes Circuit-Specific Synaptic Pruning by Microglia via Complement Activation.

Lui H, Zhang J, Makinson SR, Cahill MK, Kelley KW, Huang HY, Shang Y, Oldham MC, Martens LH, Gao F, Coppola G, Sloan SA, Hsieh CL, Kim CC, Bigio EH, Weintraub S, Mesulam MM, Rademakers R, Mackenzie IR, Seeley WW, Karydas A, Miller BL, Borroni B, Ghidoni R, Farese RV Jr, Paz JT, Barres BA, Huang EJ. *Cell.* 2016 May 5;165(4):921-35. doi: 10.1016/j.cell.2016.04.001. Epub 2016 Apr 21.

Microglia maintain homeostasis in the brain, but whether aberrant microglial activation can cause neurodegeneration remains controversial. Here, the authors use transcriptome profiling to demonstrate that deficiency in frontotemporal dementia (FTD) gene progranulin (*Grn*) leads to an age-dependent, progressive upregulation of lysosomal and innate immunity genes, increased complement production, and enhanced synaptic pruning by microglia. During aging, *Grn*^{-/-} mice show profound microglia infiltration and preferential elimination of inhibitory synapses in the ventral thalamus, which lead to hyperexcitability in the thalamocortical circuits and obsessive-compulsive disorder (OCD)-like grooming behaviors. Remarkably, deleting C1qa gene significantly reduces synaptic pruning by *Grn*^{-/-} microglia and mitigates neurodegeneration, behavioral phenotypes, and premature mortality in *Grn*^{-/-} mice. Together, their results uncover a previously unrecognized role of progranulin in suppressing aberrant microglia activation during aging. These results represent an important conceptual advance in such that complement activation and microglia-mediated synaptic pruning are major drivers, rather than consequences, of neurodegeneration caused by progranulin deficiency.

COMPLEMENT TEAMS AROUND THE WORLD

Complement in Lund, Sweden:

The Team of Prof. Diana Karpman

The pediatric nephrology team at Lund University and Skåne University Hospital in Lund focuses on comprehensive understanding of renal diseases in children combining advanced clinical care with translational research.

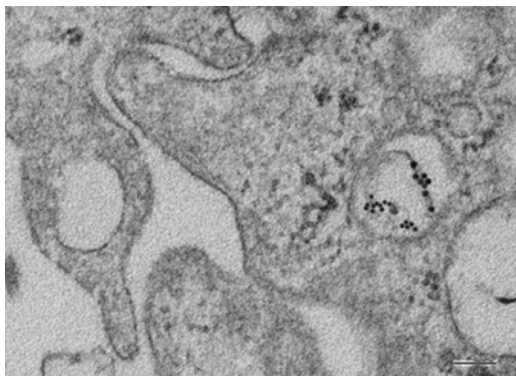
The research projects have mainly concentrated on specific renal diseases such as hemolytic uremic syndrome (HUS), associated with enterohemorrhagic *E. coli* (EHEC) infection or complement-dysfunction, other thrombotic microangiopathies including thrombotic thrombocytopenic purpura (TTP), C3 glomerulopathy, vasculitis and IgA nephropathy.

The importance of complement activation, and the mechanism by which this occurs, has been addressed in all the subprojects regardless of whether complement activation is the primary inducer of disease or secondary to infection or auto-immune disease. Based on clinical observations in patients the molecular pathogenesis of these diseases has been studied using *in vivo* and *in vitro* models and, whenever possible, attempts have been made to benefit patient care by implementing results in the clinic. The team is composed of clinicians and researchers facilitating a continuous constructive interaction.

The team has also defined novel mechanisms of renal cell injury, thrombosis, endothelial damage, blood cell activation and inflammation.

Currently the group, under the lead of Prof. Karpman, who is a member of the Royal Swedish Academy of Sciences, is investigating novel mechanisms of vascular injury whereby host cell-derived microvesicles transfer bacterial toxins and inflammatory mediators to target cells and thus promote inflammation.

The importance of microvesicles in infectious and inflammatory disease is investigated by identifying inflammatory substances that are transported by microvesicles, including complement, and attempts to inhibit their release.



Transmission electron microscopy showing a microvesicle derived from a leukocyte bearing Shiga toxin after uptake within early endosomes of glomerular endothelial cells. Cells were stained with rabbit anti-Stx2 (5 nm gold particles) and mouse anti-human CD45 to identify leukocyte-derived microvesicles (10 nm gold particles). For details see Ståhl AL et al, PLoS Pathogens 2015;11(2):e1004619. Figure taken by Matthias Mörgelin.

The unit of pediatric nephrology has established itself as a regional center for investigation, diagnostics and treatment of all children with complement-mediated renal diseases. In addition, the research unit is also a Nordic diagnostic laboratory for complement gene mutations in renal disease (aHUS and C3 glomerulopathies) and receives samples from national and international cases.

Novel complement mutations in C3, factor H, factor B, factor I and clusterin have been described in aHUS patients. For the combined clinical, diagnostic, research and teaching efforts the pediatric nephrology unit was appointed Center of Excellence in Health for the term 2015-2019.



Pediatric nephrology team at Lund University and Lund University Hospital

From left: Johan Rebetz, Ida Arvidsson, Sunna Aradottir, Anne-lie Ståhl, Ann-Charlotte Kristoffersson, Zivile Békássy, Karl Johansson, Diana Karpman, Sebastian Loos, Therese Rosenblad, Marika Kanthe, Milan Chromek, Birgitta Bjäre, Katarina Lindahl, Ingrid Ekelund, Sebastian Stroh, Anita Bergelin, Yvonne Franzén, Kristina Persson, Annika Franzén, Lisa Sartz

Picture taken by Max Määttä, Region Skåne

CONTACT INFORMATION:

Prof. Diana Karpman

Department of Pediatrics, Clinical Sciences Lund, Lund University, Sweden

E-mail: Diana.karpman@med.lu.se

http://www.research.med.lu.se/en_projektdetaljer.php?Proj=17

Complement in Łódź, Poland:

The Team of Prof. Maciej Cedzyński

Our team has been investigating complement for approximately 15 years. Currently it includes two associate professors: Maciej Cedzyński and Anna S. Świerzko and four young researchers: Agnieszka Szala-Poździej, Mateusz Michalski, Anna Sokołowska and Łukasz Eppa. Research activity is focused on pattern-recognition molecules and associated serine proteases specific for the lectin pathway (LP).

We began studying a model of anaphylactoid shock, depending on interaction of the MBL-MASP complex (Ra-reactive factor) with bacterial lipopolysaccharide (LPS). Later, investigation of clinical associations of human MBL and MASP-2 was started which was successively extended to ficolins, MASP-1/3, and most recently other complement-activating collectins.

We reported associations of low serum MBL and ficolin-2 concentrations (and/or corresponding genotypes) with recurrence of paediatric respiratory infections (Cedzyński et al., 2004; 2009; Atkinson et al., 2004). Low MBL and ficolin-2 were also associated with neonatal/paediatric sepsis (Świerzko et al., 2016) and neonatal infections in general (Świerzko et al., 2009). A complex study of a large, ethnically homogenous cohort of neonates revealed furthermore that low cord serum levels of ficolin-2, -3 and MASP-2 were associated with premature births (Świerzko et al. 2009; Michalski et al., 2012). Our cohort allowed us to report the biggest series of *MBL2*/serum MBL and *FCN2*/serum ficolin-2 genotype/phenotype relationships in the literature (Świerzko et al., 2009; Kilpatrick et al., 2013). Over the years, several cases of rare MASP-2 and ficolin-3 primary deficiencies were presented and discussed.

Conversely, some adverse effects of high concentrations of lectin pathway factors under certain conditions were found. High levels of MBL, ficolin-2 and ficolin-3 were associated with ovarian cancer. MBL deficiency-associated genotypes predicted prolonged survival in patients. Furthermore, altered local (ovarian) expression of *MBL2*, *FCN2*, *FCN3* and *MASP2* genes was found (Świerzko et al., 2007, 2014; Szala et al., 2013). We have also demonstrated that high preoperative MBL may contribute to the development of sterile SIRS in children undergoing cardiac surgery (although MBL deficiency is a risk factor for postoperative infections) (Pągowska-Klimek et al., 2016).

Another branch of our research is interaction of LP-associated molecules with bacterial cells, its molecular basis and biological consequences. Perhaps the most interesting data concern reactivity of ficolin-3 with *Hafnia alvei*, ficolins-1, -2, and -3 with mycobacteria, and MBL with variety of *Yersinia enterocolitica* mutants. *H. alvei* LPS was proposed to be useful for purification of ficolin-3 from plasma and determination of its concentration in body fluids (Świerzko et al., 2012; Michalski et al., 2012). Later, ficolin-3-LPS interaction was shown to promote phagocytosis of bacteria (Michalski et al., 2015). The mycobacterial Ag85 complex was identified as a target for human ficolins (Świerzko et al., 2016) while mannoheptose residues located in the inner core part of atypical *Yersinia* LPS was a target for MBL (Kasperkiewicz et al., 2015).

Currently, our investigations are focused mainly on involvement of the LP in haematological malignancies.

These achievements were made possible by invaluable collaborations with outstanding groups of scientists and medical doctors from elsewhere in Poland, Scotland, Denmark, Japan and Finland; the team is therefore a part of a multinational network.



Photo description (from left to right):

Anna S. Świerzko, Agnieszka Szala-Poździej; Mateusz Michalski, Maciej Cedzyński, Łukasz Eppa. **Additional photo:** Anna Sokołowska

CONTACT INFORMATION:

Prof. Maciej Cedzyński

Laboratory of Immunobiology of Infections, Institute of Medical Biology, Polish Academy of Sciences, Lodowa 106, 93-232 Łódź, Poland. E-mail: mcedzynski@cbm.pan.pl; OR

Prof. Anna S. Świerzko: E-mail: aswierzko@cbm.pan.pl

ANNOUNCEMENTS



On behalf of the organizing committee, Dr. Teizo Fujita (Chair) and Dr. Nobutaka Wakamiya (President of the Japanese Association for Complement Research, JACR) invite members of the complement community and beyond to the 26th International Complement Workshop in Japan. The meeting will take place in the historical city of Kanazawa from September 4th to 8th 2016.

Please visit www.icwkanazawa2016.com for abstract submission updates as well as program and travel information.

ALEXION PHARMACEUTICALS



Title: Research Scientist III, Protein Sciences
Location: Cheshire, CT, USA

Position Summary:

Provides leadership in identifying and prosecuting discovery research programs, specifically in the field of complement biology, and also in other disease pathways as needed; participates in proposing, identifying, evaluating new targets/programs for the research portfolio; provides leadership in designing screening cascades in aid of lead identification, in developing cellular and PK/PD assays in support of the discovery projects; participates in performing diligence activities in support of Business Development initiatives and in performing competitive intelligence analyses; establishes and manages external collaborations as needed.

Qualifications:

- Ph.D. in biochemistry/cell biology /molecular biology /pharmacology/structural-biology with 5-6 years of relevant industrial/academic research experience
- Extensive knowledge in complement biology, structure-function relationships, disease areas related to complement dysregulation
- A sound understanding of the theory governing macromolecular behavior
- Experience in research programs towards identifying therapeutic lead molecules is a plus
- Experience in collaborating/managing/directing within a matrix research organization desirable
- Ability to effectively allocate efforts amongst multiple projects and drive to aggressive timelines
- Good oral and written communications skills

COMPLEMENT REAGENT RESOURCES



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



What's in the Q?

Conducting research in any of these areas?

Alternative Pathway Studies | Kidney Disease | Ocular Disease
 Schizophrenia | Bacterial Resistance | Tumor Cells | Asthma

Consider Complement Factor H

Welcome the newest member to the Quidel queue,
 MicroVue™ Factor H EIA.

Ask your Quidel representative or your local distributor about the MicroVue Factor H EIA
 Cat #A039 | Cat #A040 (CE)
quidel.com/spg



For **Research Use Only** in the United States. Not for use in diagnostic procedures.

ADA397200EN00 (03/16)

CEDARLANE®

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/iC3b, 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

You can also download a copy of the **Complement Antibodies and Proteins Brochure**.

Canada: 1-800-268-5058

4410 Paletta Court,
Burlington, ON L7L 5R2
general@cedarlanelabs.com

USA: 1-800-721-1644

1210 Turrentine Street,
Burlington, NC 27215
service@cedarlanelabs.com

www.cedarlanelabs.com

ISO 9001:2008 and ISO 13485:2003 registered.

The Complement Company

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



- Broad portfolio for your Complement research.
- Also specialized in other fields of Innate Immunity: TLR, Tissue damage, Antimicrobial Peptides and more!
- New! C3c ELISA (HK368): a stable complement biomarker without any interference of other C3 based products.
- New ELISA's: gC1qR, MAP44 and Rat TCC.
- Highlighted: Coagulation factor XII (HM2322) and Complement factor I (HM2319).
- Contact us for special Bulk Antibody prices!

For more information or to sign up for our newsletter visit: www.hycultbiotech.com