

# Glyco-Forum section

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## Letter to the Glyco-Forum

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### Biological properties of sulfated fucans: the potent inhibiting activity of algal fucoidan against the human complement system

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In this letter we want to point out that the recently published review by Berteau and Mulloy (2003) about the biological properties of fucoidan, although well documented, omits any mention of the potent inhibiting activity of this polysaccharide against the human complement system. This activity gives rise to an increasing interest, given the involvement of the complement in numerous pathological processes and the strong demand for efficient anticomplementary molecules.

The complement system is a major component of the immunity and is mainly involved in the innate and humoral response. It also allows the link between the innate immunity and the adaptive defense. An uncontrolled activation is harmful for the host organism as observed in ischemic and anaphylactic shocks or xenograft rejection (Mollnes and Fosse, 1994; Sahu and Lambris, 2000).

The algal fucoidan from the fucale *Ascophyllum nodosum* has been first described as an anticomplementary molecule by Blondin *et al.* (1994). Since this first report, other fucoidans from fucales (*Fucus evanescens*) and from other brown algae of Laminariales order have been also described as inhibitors of the complement (Zvyagintseva *et al.*, 2000).

In an attempt to delineate the structural features of fucoidan fractions active on the complement system, a relationship between the anticomplementary activity and the molecular weight ranging from 13,500 to 40,000 g/mol was reported (Blondin *et al.*, 1996). The sulfate groups are also essential although not a sufficient requirement to a high anticomplementary activity, as the decrease of the sulfate content from 36% to 9% did not affect the inhibition level (Blondin *et al.*, 1996; Zvyagintseva *et al.*, 2000). Compared to heparin, the fucoidan was shown to be a much more potent (up to 40-fold) inhibitor of the classical pathway,

whereas both sulfated polysaccharides inhibits the alternative pathway in the same extent.

The first studies on the anticomplementary activity of fucoidan indicated that the formation of the C3 alternative and classical convertases was decreased in presence of fucoidan, but the mechanisms of this inhibitor effect remained to be established (Blondin *et al.*, 1994). It has been recently demonstrated that *A. nodosum* fucoidan blocks the consumption of proteins C2 and C4, and in a less extent of protein C3 (Tissot *et al.*, 2002), indicating that fucoidan interferes with the first steps of the classical pathway activation. This effect is not due to the inhibition of the proteolytic activity of C1s, the protease responsible of the activation of C2 and C4, but results from the interactions between fucoidan and the proteins C1q and C4 as demonstrated by gel coaffinity electrophoresis and affinity capillary electrophoresis, respectively. Fucoidan binding interferes with the association of the catalytic tetramer C1r<sub>2</sub>-C1s<sub>2</sub> and C1q, responsible for the proteolytic activation of the C2 and C4 proteins, and yielding a functionally altered C1 as underscored with the observed decrease of the consumption of the proteins C2 and C4. Finally, it has been proposed that fucoidan inhibits C1 activation by binding to the collagen-like domain of C1q, likely through ionic interactions between positive residues of this domain and sulfate groups of the polysaccharide (Tissot *et al.*, 2003). In addition to C1q, the protein C4 and its cleavage product, C4b, are also a target for fucoidan and the affinity capillary electrophoresis used to monitor the binding of fucoidan to C4 indicated an affinity in the micromolecular range. C4b is directly involved in the formation of the classical C3 convertase, therefore its interaction with fucoidan should lead to the inhibition of the formation of the C3 convertase, thus blocking a central step in the propagation of the complement.

The capacity of fucoidan to block the formation of the classical C3 convertase may be of a great interest because it may prevent the production of the proinflammatory anaphylatoxins and of the C3b fragment. Inhibition by fucoidan at the C1q level could be also valuable to interfere with the binding to C1q receptors present on endothelial cells. Indeed the activation of the endothelial cells induced by complement is involved in graft rejection. It is worthwhile to note that fucoidan from *A. nodosum* has been showing promising properties in the protection of porcine endothelial cells against the complement-mediated lysis, in view of therapeutic applications for xenografts (Charreau *et al.*, 1997).

Finally Berteau and Mulloy (2003) underlined the value of specific enzymes to obtain tailored oligosaccharides for structural and biological studies. Regarding fucoidan, the availability of sulfatases is of prime importance, and among the cited references about the fucoidan sulfatase, the authors should add the first report of a fucoidan sulfatase

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activity from the scallop *P. maximus* (Saillard *et al.*, 1999). This activity has been fruitfully coupled to the nonaqueous capillary electrophoresis separation of the sulfated fucose building blocks of fucoidan to identify the positional isomers (Descroix *et al.*, 2003).

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## Meeting Announcements

### The San Diego Glycobiology Symposium

San Diego, California  
February 20–21, 2004

The 7th Annual San Diego Glycobiology Symposium will take place at the Shelter Pointe Hotel and Marina in San Diego, California. The symposium is jointly organized by the UCSD Glycobiology Research and Training Center and the Glycobiology Program of the Burnham Institute.

This annual symposium brings together laboratories in San Diego that have a primary or major interest in the field

of glycobiology. A few laboratories from other University of California campuses will also be represented. The objectives are to exchange information on the latest advances in the field and to promote interactions between members of these laboratories and other attendees from academia, biotechnology, and the pharmaceutical industry. To maximize interactions, the setting will be informal.

Confirmed speakers to date include:

Wayne Akeson, University of California, San Diego  
Raffi Aroian, University of California, San Diego  
Linda G. Baum, University of California, Los Angeles  
Michael Demetriou, University of California, Irvine  
Wolfgang H. Dillmann, University of California, San Diego  
Jeff Esko, University of California, San Diego  
Marilynn Etzler, University of California, Davis  
Hudson Freeze, The Burnham Institute  
Michiko Fukuda, The Burnham Institute  
Minoru Fukuda, The Burnham Institute  
Jacquelyn Gervay-Hague, University of California, Davis  
Bradley K. Hayes, University of California, San Diego  
Brad Gibson, Buck Institute of Age Research  
Jerry L. Hedrick, University of California, Davis  
Julie A. Leary, University of California, Berkeley  
Carlito Lebrilla, University of California, Davis  
Fu-Tong Liu, University of California, Davis  
Jamey D. Marth, University of California, San Diego  
Paul Martin, University of California, San Diego  
Victor Nizet, University of California, San Diego  
James Paulson, The Scripps Research Institute  
Steven Rosen, University of California, San Francisco  
Geert Schmid-Schoenbein, University of California, San Diego  
Ajit Varki, University of California, San Diego  
Yu Yamaguchi, The Burnham Institute

Each speaker will provide an overview of the ongoing research in his or her laboratory. In addition to the oral presentations, there will be a poster session that is open to anyone who wishes to make a presentation.

For further information, contact:

Barbara Thompson  
Tel.: 858-822-1101  
E-mail: b1thomps@ucsd.edu

### 7th Jenner Glycobiology & Medicine Symposium

Exeter College, Oxford, UK  
September 5–8, 2004

The conference will bring together specialists exploring the biological roles of glycoconjugates in health and disease using different approaches. Its goal is to present the state of the art in the field to young and established investigators. The following aspects will be highlighted: glycosylation-dependent bacterial and viral infections, lectin- and proteoglycan-dependent interactions in leukocyte homing processes to lymphoid tissues and inflamed tissues, congenital defects in glycosylation of glycoproteins and

glycolipids, and role of carbohydrates in tumour development and neuropathology, including Creutzfeldt-Jakob disease. Each of eight sessions will be introduced by a keynote speaker.

Topics: Glycosylation dependent bacterial infections, Inflammation, Glycopathology, Glycosylation-dependent viral infections, Congenital defects in glycosylation and glycoimmunology

Organizing committee: John Axford, UK; Pauline Rudd, UK; Ghislain Opdenakker, UK; Jim Van Dijk, The Netherlands; and Claudine Kieda, France.

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