

The Guillain–Barré syndrome: a true case of molecular mimicry

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Molecular mimicry between microbial antigens and host tissue forms an attractive hypothetical mechanism for the triggering of autoimmune disease by preceding infections. Recent crucial reviews state that molecular mimicry, as the causative mechanism, remains unproven for any human autoimmune disease. However, the peripheral neuropathy Guillain–Barré syndrome (GBS) is largely overseen in this debate. Based on recent evidence, we argue that GBS should be considered as an excellent paradigm and an attractive model for elucidation of both host and microbial aspects of molecular mimicry.

Molecular mimicry between microbial antigens and host tissue is a popular and appealing hypothetical mechanism for the triggering of autoimmune disease by preceding infections. According to the mimicry hypothesis, autoantibodies and/or autoreactive T cells that are induced by the infection are initially directed against microbial antigens. Owing to the structural resemblance between microbial and particular host antigens, the antibodies and T cells not only destroy the invading pathogen but also attack host tissue. In addition, infections can also lead to activation of autoreactive immune cells by antigenic non-specific mechanisms, called bystander activation (reviewed in Ref. [1]).

The term molecular mimicry was coined by Damian in 1964 [2] but the idea that infections might lead to autoimmune disease as a result of cross-reactive antibodies or T cells had emerged earlier in the literature [3]. In fact, Damian dismissed the idea that molecular mimicry could cause autoimmune disease. Rather, he proposed that from an evolutionary perspective, the sharing of antigens between microbes and host tissue can be regarded as a mechanism for evasion of the immune response. Invading pathogens attempt to go unnoticed by innate and adaptive components of the immune system by making themselves look like their hosts. This phenomenon is also defined as ‘crypsis’, being camouflaged to resemble part of the environment [4]. Hence, the triggering of an immune response towards antigens that ought to function as camouflage could, from the perspective of the microbe,

be considered undesirable. Therefore, in the context of triggering autoimmune disease, it would perhaps even be appropriate to use the term ‘failure of molecular mimicry’.

The claims for mimicry as a causative mechanism of autoimmune disease are numerous (reviewed in Refs [5,6]; Table 1) and parts of the molecular mimicry hypothesis are supported by abundant evidence from experiments with genetically engineered microorganisms and animals [7,8]. However, in contrast to these experimental model systems, some recent crucial reviews stated that in a no clinical disease entity in humans the evidence for a pathogenic role of cross-reactive T cells or antibodies is fully conclusive [5,6,9]. In these discussions, the peripheral neuropathy Guillain–Barré syndrome (GBS) is largely overseen. We argue here that the evidence for a crucial contribution of molecular mimicry at the B-cell level to GBS immunopathogenesis is overwhelming. Hence, GBS is an excellent paradigm for how post-infectious immune-mediated disease in humans can be triggered by molecular mimicry.

The Guillain–Barré syndrome

GBS is an immune-mediated disease of the peripheral nerves, involving both the myelin sheath and the axons, and is named after G. Guillain and J.A. Barré, two French neurologists who described the syndrome in 1916, together with A. Strohl [10]. The immunological attack consists of deposits of immunoglobulins and complement on the axon and Schwann cell surface accompanied by macrophage and T-cell infiltration of the nerve [11]. Patients suffer from generalised weakness, areflexia and a varying degree of sensory disturbances and involvement of cranial nerves. The weakness frequently involves respiratory muscles, rendering patients respirator-dependent [12,13]. GBS is a monophasic disease with an acute course. The weakness is most severe within two to four weeks. Patients recover spontaneously and their recovery is accelerated by immunomodulating therapies, such as plasma exchange and intravenous immunoglobulins [13]. Even when patients are treated in well-equipped intensive care units, mortality rates still range from 3–7% [12]. GBS occurs worldwide and is the most frequent cause of acute paralysis in the western world. The incidence ranges from 1–2 per 100 000 per year [12].

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Table 1. Selected immune-mediated diseases with a proposed role of molecular mimicry

Immune-mediated disease	Host-antigen	Microbe and antigen	Comment	Refs
Acute rheumatic fever	Multiple cardiac glycoproteins	Group A streptococci, M-protein	Relative role of T cells and antibodies is unclear	[23]
Chagas' disease	Cardiac myosin heavy chain	<i>Trypanosoma cruzi</i> , B13 protein	Parasitic antigen demonstrated in heart tissue; disease could be caused by immune response against persistent microbial antigen	[9,52]
Guillain-Barré syndrome	Peripheral nerve gangliosides	<i>Campylobacter jejuni</i> , lipooligosaccharides	Also associated with cytomegalovirus, Epstein-Barr virus and <i>Mycoplasma pneumoniae</i>	
Herpetic keratitis	Corneal antigen, not identified	Herpes simplex virus type 1, UL6 protein	Host antigen not identified	[6]
Insulin-dependent diabetes mellitus	Multiple, GAD65, insulin, other islet cell antigens	Coxsackie virus B4, protein P2-c; Cytomegalovirus, major DNA-binding protein	Direct infection of pancreas with Coxsackie virus leads to local tissue damage and release of auto-antigens	[9,53]
Lyme arthritis	LFA-1	<i>Borrelia burgdorferi</i> , OSP-A	No animal model	[6]
Multiple sclerosis	MBP, PLP, MOG	Multiple viruses, <i>Chlamydia</i>	Epidemiological relation with infectious agents is weak	[9]

Abbreviations: GAD, glutamic acid decarboxylase 65; LFA-1, leucocyte function-associated antigen-1; MBP, myelin basic protein; MOG, myelin oligodendrocyte glycoprotein; OSP A, outer surface protein A; PLP, proteolipid protein.

Definition of molecular mimicry

The discussion as to whether molecular mimicry is a mechanism for the induction of autoimmune disease is hampered by loose definitions of molecular mimicry and the inconsistent use of previously defined criteria for a disease to be deemed due to this mechanism. The term molecular mimicry is both used to simply indicate the sharing of antigens between hosts and microorganisms and to cover the immunological process of cross-reactivity. We operationally define molecular mimicry as dual recognition of structures of a microbe and host by a single B- or T-cell receptor (TCR). Thus, molecular mimicry is the mechanism by which infections trigger cross-reactive antibodies or T cells that cause the symptoms of autoimmune disease.

Five levels of immunological cross-reactivity can be distinguished. Examples are given for all these levels to emphasise that searching in protein databases for amino acid homology between human and microbial peptides is clearly not sufficient to identify all possible levels of cross-reactivity.

First, and most obvious, is the well known sharing of identical amino acid sequences and homologous but non-identical amino acid sequences [14]. Database searches have identified many examples of this level of cross-reactivity (e.g. the PEVKEK sequence in the pancreatic islet-cell antigen GAD65 and Coxsackie B virus P2-C protein, implicated in the development of insulin-dependent diabetes mellitus) [15] (Table 1). Second, because B-cell receptors (BCRs) and TCRs show a high level of degeneracy, a second level of cross-reactivity is the recognition of non-homologous peptide sequences by a single BCR or TCR [16]. Estimates on the number of peptides that can be recognised by a single TCR range from thousands to billions [16]. Third, it has recently been demonstrated that a single T cell can recognise different peptides in the context of different human leukocyte antigen (HLA) molecules [17]. Fourth, it is often neglected that immunological receptors recognise structural similarity in complex molecular structures and their binding preferences are not necessarily based on biochemical

classification. To restrict oneself to proteins will therefore erroneously exclude many biological molecules. Examples are antibodies directed against double-stranded DNA in systemic lupus erythematosus, anti-carbohydrate antibodies in autoimmune hemolytic anaemia [18] and CD1-restricted natural killer T cells directed against glycolipids [19,20]. Finally, to complicate matters even further, so called mimotopes have been described. These are peptides that are bound by either antibodies or T cells directed against unrelated antigens, for example, carbohydrates, suggesting that cross-reactivity can be induced by biochemically distinct molecules [21].

Against this background on cross-reactivity, four criteria need to be satisfied to allow the conclusion that a disease is triggered by molecular mimicry [6,22].

Criterion #1: establishment of an epidemiological association between an infectious agent and the immune-mediated disease

Defining the infectious agent(s) associated with the autoimmune disease is crucial in directing the search for the target antigen in the triggering microbe(s). This can be achieved with case-control studies using culture, serological and nucleic acid amplification techniques. In chronic autoimmune diseases it can be difficult to define the precipitating pathogen owing to the time lag between the precipitating infection and the occurrence of immune-mediated pathology. It is important to note that there is no one-to-one relationship between infectious agent and autoimmune disease. A particular disease can be precipitated by multiple infectious agents (e.g. the GBS; Table 1) and a single microbe can trigger more than one disease pattern (e.g. group A streptococcal infections have cardiac, nephrological and neurological sequelae [23]).

GBS is preceded by acute infections

The majority of GBS patients report the occurrence of an infectious disease in the weeks preceding the neurological symptoms [24]. This short interval between the acute infection and the development of symptoms enables identification of the triggering infectious agents and

even their culture *in vitro* for further microbial investigations. Case control studies using culture and serological techniques have consistently documented a relation of GBS with the enteric pathogen *Campylobacter jejuni* [25,26]. Infections with herpes viruses, such as cytomegalovirus and Epstein–Barr virus, and the airway pathogen *Mycoplasma pneumoniae* also precede GBS [24,25]. Thus, there is strong epidemiological evidence for the association between acute infectious disease and GBS.

Criterion #2: identification of T cells or antibodies directed against host target antigens in patients

This is the demonstration of autoreactive T cells or antibodies in patients. The T cells or antibodies must have a pathogenic effect, demonstrated *in vivo* or *in vitro*. Ideally, the observed effect in the experimental situation directly reflects the symptoms observed in the human disease. It is a challenge to satisfy this criterion because in many instances the experimental limitations do not enable sufficient matching with the clinical situation.

Autoantibodies against self-gangliosides are present in patients with GBS

In serum taken from GBS patients in the acute phase of the disease, antibodies against gangliosides, major constituents of the nerve cell membrane, are present [27] (Figure 1). Gangliosides are sialic acid-containing glycolipids, expressed abundantly in the nervous system [27]. They are composed of a ceramide tail inserted in the lipid bilayer and a highly variable oligosaccharide moiety protruding externally. More than 100 different types of gangliosides have been identified. Gangliosides are implicated in cell growth and differentiation but they also serve as receptors for bacterial toxins and have a function in signal transduction [28].

The specificity of these ganglioside autoantibodies is closely related to the nature of the preceding infections in GBS. Infections with *Campylobacter jejuni* are associated with antibodies against gangliosides GM1, GM1b, GD1a and GalNAc-GD1a (reviewed in Ref. [27]). Furthermore, cytomegalovirus infections are related to antibodies against GM2, whereas preceding infections with *M. pneumoniae* are related to antibody reactivity against galactocerebroside [27]. There is also a relationship between the specificity of the autoantibodies and the pattern of clinical features of GBS patients. GM1, GM1b GD1a and GalNAc-GD1a antibodies are related to a subform of GBS affecting only motor nerves, whereas antibodies against ganglioside GQ1b are associated with the Miller Fisher syndrome [27]. The Miller Fisher syndrome is a subform of GBS affecting predominantly the nerves that innervate muscles governing eye movements [29]. In other words, the structure of the infectious agent apparently determines, to a reasonable extent, the clinical features of the patient, mediated by the ganglioside specificity of the autoantibodies.

Contrary to what is expected from an antibody response against carbohydrate antigens, the isotype of the ganglioside antibodies in GBS patients is not only IgM but also IgA and IgG [27]. Furthermore, the IgG antibodies have a high titer and are of the IgG1 and IgG3 subclass [27], pointing to an isotype switch involving T-cell help.

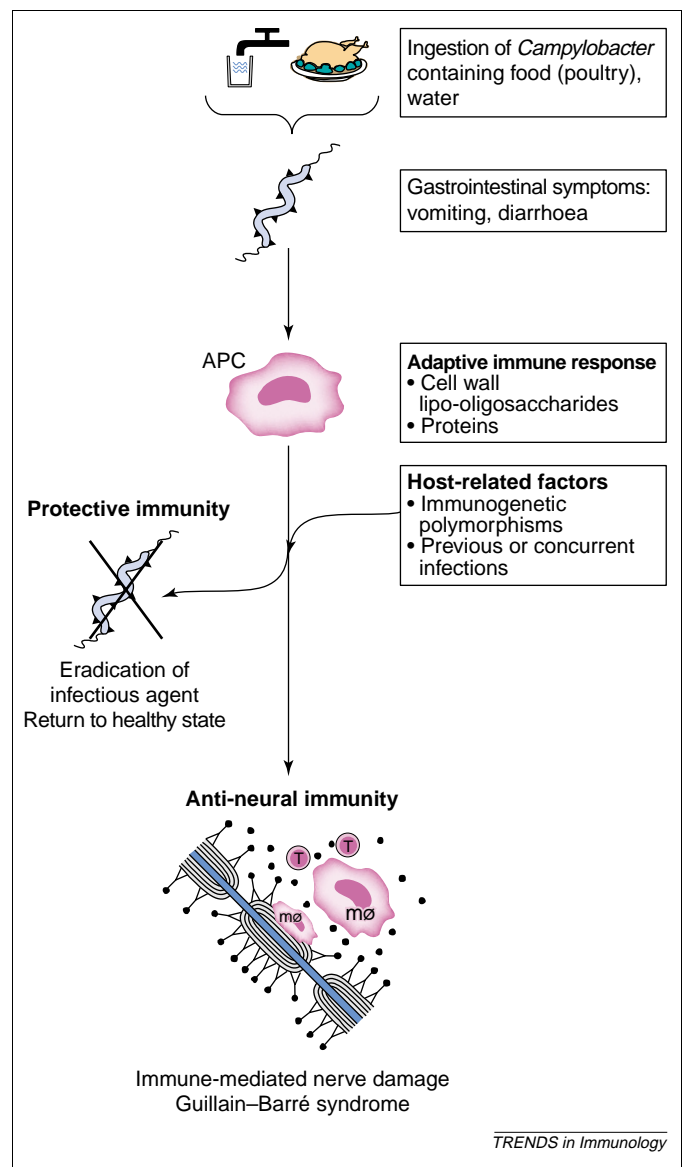


Figure 1. Presumed role of molecular mimicry in the Guillain–Barré syndrome. Food-borne infection with *Campylobacter* leads to diarrhoea and/or vomiting. The host mounts an adaptive immune response towards *Campylobacter* antigens, including cell wall lipo-oligosaccharides. The type of APC and the molecules involved in recognition and presentation of lipo-oligosaccharides are currently unknown. Under the influence of host-related factors, such as polymorphisms in immune response genes and priming of the immune system by previous or concomitant infections, the immune response is diverted and high titer cross-reactive anti-ganglioside antibodies are produced. Guided by antibodies bound to the outer surface of the Schwann cell and axon, which cause complement activation, macrophages attack the Schwann cell and axon. $\alpha\beta$ and $\gamma\delta$ T cells probably produce cytokines and might be involved in the breakdown of the blood–nerve barrier. Abbreviations: APC, antigen presenting cell; m ϕ , macrophage; T, T cell.

Interestingly, activated T cells have been identified in the affected nerves and acute phase blood samples from GBS patients. These activated cells are CD4⁺ and CD8⁺ and express $\alpha\beta$ or $\gamma\delta$ TCRs (reviewed in Ref. [24]). Until now, there have been no reports describing glycolipid reactive T cells in GBS patients, although $\gamma\delta$ T cells reacting with non-peptidic *Campylobacter* antigens have been recovered from nerves and peripheral blood of GBS patients [30]. Their exact specificity and function in the development of GBS is unknown (Box 1).

Box 1. Outstanding questions

- Why is myelin and axonal damage restricted to the peripheral nervous system? Gangliosides are not only present in the peripheral part of the nervous system but also abundantly expressed in the brain and spinal cord. However, the relative expression and amount of gangliosides varies considerably between parts of the nervous system. Do differences in the ganglioside composition influence binding of ganglioside antibodies and thereby the site of damage? Are differences between the blood–nerve and blood–brain barriers responsible for sparing of the central nervous system (CNS)?
- What is the specificity and function of T cells in Guillain–Barré syndrome (GBS) patients? It is not known whether glycolipid antigens are the targets for activated $\alpha\beta$ and $\gamma\delta$ T cells in GBS patients. Techniques for answering these questions are available and glycolipid reactive T cells have been identified in other clinical situations, including autoimmune disease of the CNS (e.g. multiple sclerosis) [50]. An impaired $\gamma\delta$ T-cell response towards non-peptidic antigens has been described in GBS patients with an antecedent *Campylobacter jejuni* infection, perhaps underlying the deviant antibody response [51].
- Which antigen *in vivo* routing, recognition and presenting pathways are involved in the immune response against *Campylobacter* lipo-oligosaccharides? Are *Campylobacter* lipo-oligosaccharides recognised by Toll-like receptors, and presented by CD1? Which factors (T-cell derived cytokines, co-stimulatory pathways) are involved in the isotype switch of ganglioside antibodies?
- Which genetic factors mediate the divergence of the immune response towards self-antigens following infection and (co-) determine disease severity, response to therapy and outcome? These questions can be answered using large cohorts of well-defined GBS patients and careful analysis of GBS cases following outbreaks of *Campylobacter* infections [45].
- Is it possible to develop an animal model using *Campylobacter* infection? Until now, clinical symptoms in animals are induced by immunisation with gangliosides or with purified *Campylobacter* lipo-oligosaccharides. The experiment providing ultimate proof for the molecular mimicry hypothesis in GBS would consist of the induction of cross-reactive antibodies and clinical symptoms following experimental oral infection with a *Campylobacter* strain bearing a ganglioside mimic, whereas infection with a mutant strain lacking only the ganglioside mimic leaves the animals unaffected.

Ganglioside auto-antibodies are neuropathogenic

Polyclonal and monoclonal anti-ganglioside antibodies bind to the Schwann cell surface, nodes of Ranvier and axons in peripheral nerves, depending on the specificity of the anti-ganglioside antibodies [31,32]. The isotype and subclass of the anti-ganglioside antibodies indicate that they are able to bind complement and this has indeed been demonstrated [33]. In the mouse phrenic nerve–diaphragm model, monoclonal and polyclonal anti-GQ1b and anti-GD3 antibodies disturb function and integrity of the motor nerve terminal, in a complement-dependent fashion [33,34]. This effect can be blocked by administration of intravenous immunoglobulins [35], an effective therapy for GBS [13]. However, it remains uncertain whether the pathogenic action of anti-ganglioside antibodies is also responsible for the symptoms observed in humans [27]. Other possible pathways of anti-ganglioside mediated pathology are blocking of ion channel function and impairment of the blood–nerve barrier [36,37]. In addition to damage to the nervous system, ganglioside

antibodies might modulate the immune system using ganglioside enriched lipid rafts and Fc receptors [38,39].

Taken together, the presence of ganglioside autoantibodies with neuropathogenic potential in GBS patients satisfies the criterion of identification of T cells or antibodies against host target antigens.

Criterion #3: identification of microbial mimic of target antigen

This comprises demonstration of cross-reactivity of auto-reactive T cells or antibodies with a microbial antigen, derived from an organism that has been epidemiologically linked to the disease. Subsequently, the microbial mimic must be purified and chemically characterised. This is essential for the design of further experiments, such as establishing the extent of cross-reactivity of antibodies or T cells and determining the influence of microbial strain differences on the development of post-infectious sequelae.

C. jejuni lipo-oligosaccharides (LOS) mimic gangliosides

The relationship between GBS, infections and anti-ganglioside antibodies has been investigated most extensively in *C. jejuni* induced GBS. *C. jejuni* is a Gram-negative spiral shaped rod and is the most frequently identified bacterial pathogen in infectious gastro-enteritis [40]. Less than 1 out of 1000 *C. jejuni* enteritis patients proceeds to GBS and the determinants controlling this include host genetic factors as well as bacterial strain differences [40]. The complete genome of *C. jejuni* has recently become available, enabling the identification of neuropathogenic virulence factors [41]. Serological and biochemical studies have demonstrated that the LOS fraction of the outer cell wall of *C. jejuni* contains structures that mimic gangliosides [42] (Figure 2). IgG, IgM and IgA anti-ganglioside antibodies from GBS patients do indeed recognise *C. jejuni* LOS and this forms strong evidence that these anti-ganglioside antibodies have been induced by an infection with *C. jejuni* [27]. Some strains appear to have a higher potential for inducing neurological complications and this is related to the presence of specific genes in the LOS biosynthesis locus [43]. Remarkably, high titer cross-reactive anti-ganglioside and LOS antibodies are absent in serum from patients with an uncomplicated *Campylobacter* enteritis [44,45]. The identification and biochemical characterisation of *Campylobacter* LOS as the microbial mimic for gangliosides satisfies the third criterion for molecular mimicry.

Criterion #4: reproduction of the disease in an animal model

Reproduction of the disease can be achieved either by infection or by immunisation with the precipitating microbe or purified antigens. On infection or immunisation, the animal develops a cross-reactive immune response, with similar specificity as seen in patients. In addition, the clinical symptoms and pathological features must closely resemble the human disease. When available, the animal model can also be used to investigate other aspects of mimicry, using genetically engineered microbes and animals.

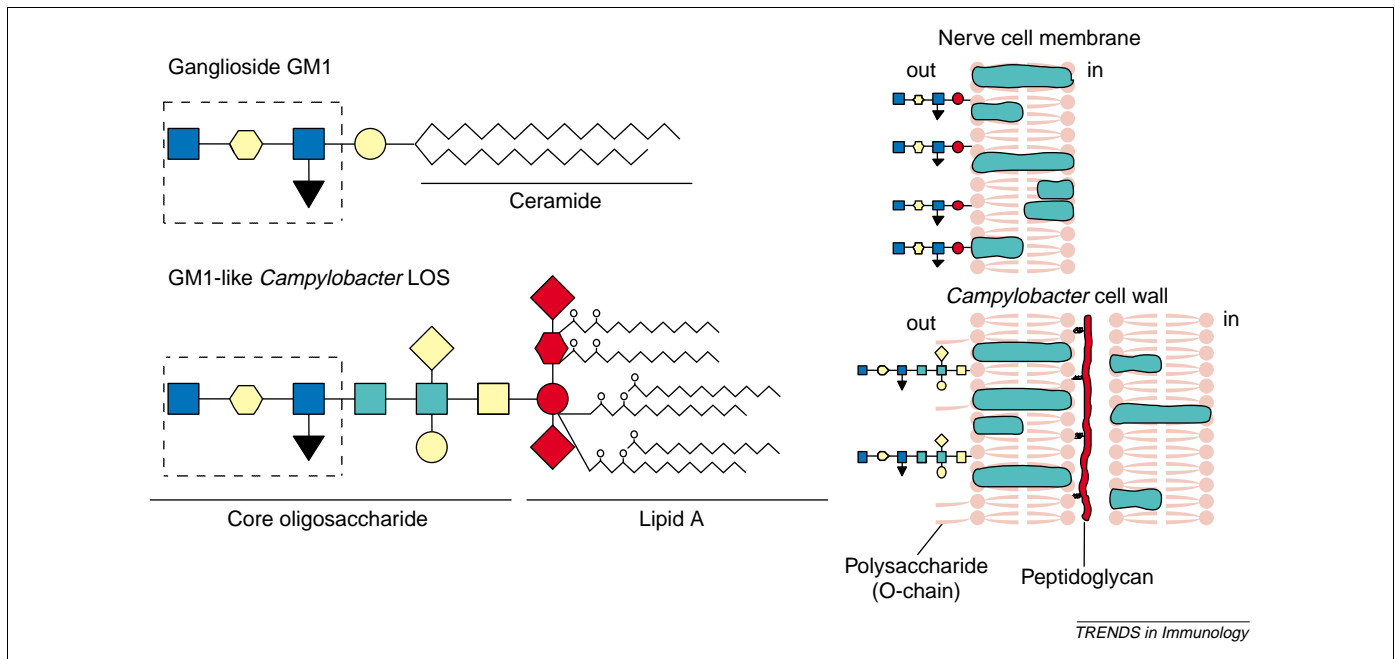


Figure 2. Molecular mimicry of gangliosides and *Campylobacter* lipo-oligosaccharides (LOS). Overview of the biochemical structure of molecular mimics involved in the Guillain–Barré syndrome. Gangliosides are located in the nerve cell membrane and consist of a ceramide tail and a polar headgroup, containing galactose, glucose, N-acetyl-galactosamine and sialic acid molecules. LOS-containing ganglioside mimics are located in the outer part of the cell wall of *Campylobacter jejuni*.

New animal models for GBS

Animal studies have shown that immunisation and infection with *C. jejuni* or purified LOS result in a cross-reactive anti-ganglioside and LOS response [46,47]. As expected, the specificity of the anti-ganglioside antibodies in the animals was similar to the specificity in GBS patients from whom these *Campylobacter* strains were derived [46]. This forms strong evidence that the ganglioside autoantibodies in humans can be induced by molecular mimicry between *Campylobacter* LOS and gangliosides. The immunised and infected animals did not develop neuropathy but the anti-ganglioside antibodies generated in animals share pathogenic properties with human GBS sera [47].

Furthermore, immunisation of rabbits with purified gangliosides induces neurological disorders, some of which resemble GBS. In the model recently described by Yuki and colleagues, not only gangliosides (the self-antigen) but also purified *C. jejuni* LOS (the microbial mimic) are used to immunise Japanese white rabbits, resulting in a neuropathy with clinical, electrophysiological and histopathological features closely resembling GBS [48,49]. With these recent findings, also the last criterion for molecular mimicry, reproduction of the disease in an animal model, has been satisfied.

Concluding remarks

The reasons for the relative obscurity of GBS among immunologists are unknown although the evidence discussed here convincingly implicates molecular mimicry as the causative mechanism in the development of GBS. We argue that GBS is a model disease with an enormous potential for studying many aspects of post-infectious immune-mediated disease.

GBS occurs worldwide and is the most frequent cause of flaccid paralysis in the Western world, making it relatively easy to obtain samples from human subjects. Large collections of GBS-related and unrelated *Campylobacter* strains are available for study. The complete *C. jejuni* sequence now enables the identification of virulence factors determining the neuropathogenic potential of *Campylobacter* strains and the generation of mutant bacterial strains to investigate other aspects of molecular mimicry. Using large cohorts of GBS patients with detailed information on antecedent infections and clinical features, it should be feasible to determine genetic susceptibility and disease modifying factors for autoimmune disease. Finally, the immune response against gangliosides and *Campylobacter* LOS touches on several other hot topics in immunology, such as lipopolysaccharide recognition by Toll-like receptors, $\gamma\delta$ T cells and glycolipid reactive T cells.

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