

# What is IgG4? A review of the biology of a unique immunoglobulin subtype

Ajay Nirula<sup>a</sup>, Scott M. Glaser<sup>a</sup>, Susan L. Kalled<sup>b</sup> and Frederick R. Taylora<sup>b</sup>

<sup>a</sup>Biogen Idec, 5200 Research Place, San Diego, California and <sup>b</sup>Biogen Idec, 14 Cambridge Center, Cambridge, Massachusetts, USA

Correspondence to Ajay Nirula, Biogen Idec, 5200 Research Place, San Diego, CA 92130, USA  
Tel: +1 858 436 4906; fax: +1 858 795 9640;  
e-mail: [ajay.nirula@biogenidec.com](mailto:ajay.nirula@biogenidec.com)

**Current Opinion in Rheumatology** 2011,  
23:119–124

## Purpose of review

Recent descriptions of the group of clinical disorders collectively defined as IgG4-related systemic disease (IgG4-RSD) have prompted this review of the unique biology of the IgG4 antibody. This article will discuss IgG4 structure and function, the unique phenomenon of half-antibody exchange, and the implications of IgG4 biology for its proposed role in immunologic diseases.

## Recent findings

IgG4 antibodies have unique structural and functional properties and undergo 'half-antibody exchange' *in vivo*, resulting in recombined antibodies composed of two different binding specificities. The production of IgG4 antibodies appears to be driven in part by T helper 2 (Th2) cytokines that mediate allergic responses and IgE production. Although serum IgG4 levels in healthy individuals vary significantly, data from multiple sclerosis (MS) patients suggest tight regulation of individual IgG4 levels over time. IgG4-RSD represents a diverse group of clinical disorders unified by elevated IgG4 levels and specific histopathologic findings. A key unanswered question is whether IgG4, a relatively weak activator of effector cells, is pathogenic in these disorders.

## Summary

IgG4 is a unique antibody biologically and structurally. Increased understanding of its precise role in the clinical syndromes that comprise IgG4-RSD may ultimately elucidate the underlying pathogenesis.

## Keywords

effector function, half-antibody exchange, IgG4, IgG4-related systemic disease, interleukin-21

Curr Opin Rheumatol 23:119–124  
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1040-8711

## Introduction

The various classes and subclasses of immunoglobulin that make up the humoral immune repertoire are primarily defined by their heavy chain constant domain sequences. Immunoglobulin subtypes differ in their underlying biologic regulation, distribution in the body, and in their interaction with receptors on the various effector cells of the immune system [1]. Class-switch gene rearrangement of the constant regions determines which immunoglobulin subtypes are produced in response to a particular immune challenge. Class-switching is regulated in part by the particular cytokines produced in response to the type and location of the immune challenge. A relatively simple example is the production of immunoglobulin E, an antibody without subclasses produced in response to various T helper 2 (Th2) cytokines, which ultimately interacts with IgE receptors on mast cells, basophils, and eosinophils to initiate release of inflammatory mediators associated with an allergic response [2].

In contrast, the IgG class is more complex in structure and biology. There are four subclasses of IgG antibodies, numbered 1 through 4 in the order of their discovery and serum concentration. Properties of individual subtypes are summarized in Table 1 [3–5]. The most abundant subclass, IgG1, is present in serum in the range of 5–11 mg/ml [3], whereas the least abundant subclass, IgG4, is present at mean concentrations of 0.35–0.51 mg/ml [6]. Unlike the other IgG subclasses, the concentration of IgG4 varies greatly among healthy people. IgG4 levels generally range from less than 10 µg/ml to 1.4 mg/ml, with levels over 2 mg/ml noted in a few individuals and levels generally higher in men and older individuals [3,6,7]. Although it is not known what governs this variation in abundance of serum IgG4 between individuals, we have noted little fluctuation in levels over time in a cohort of multiple sclerosis (MS) patients, suggesting tight regulation of IgG4 production and turnover (Biogen Idec, unpublished data). We speculate for now that this tight regulation of IgG4 levels over time is not specific to MS and likely occurs in disease-free individuals, although

this hypothesis warrants verification. As will be discussed elsewhere, tight regulation of IgG4 levels is lost in IgG4-RSD, with elevated antibody levels paralleling disease activity.

The IgG4 subclass was distinguished early on from the other IgG subclasses, as it exhibits negligible binding to the C1q protein complex and is unable to activate the classical complement pathway. It was also found that IgG4 has much reduced binding to the low-affinity Fc-gamma receptors (FcγRIIa and FcγRIIIa) and a 10-fold reduction in binding to the high-affinity FcγRI, compared with IgG1 [3]. This reduction in effector binding has led to the selection of the IgG4 constant domain for use in recombinant antibodies for clinical development wherein effector function is either unnecessary or is potentially undesirable. At least eight IgG4 monoclonal antibodies (mAbs) have been reported to be in various stages of clinical development or are marketed therapeutics (Table 2) (ClinicalTrials.gov (<http://clinicaltrials.gov>) [8–14]. Therapeutics that have shown clinical efficacy include anti-α4 integrin (natalizumab), anti-TNFα (CDP571), and anti-C5 (eculizumab), with the latter antibody containing both IgG2 and IgG4 sequences [9–11].

### IgG4 is a structurally dynamic antibody

Significant insights into the structural properties of IgG4 have been furnished by analysis and modification of specific residues in the constant region. IgG4 shares more than 95% sequence homology in the constant domain regions with the remaining three IgG isotype heavy chains. The differences between IgG1 and IgG4 for binding to C1q and Fc receptors have been localized to a few amino acid differences in the CH2 domain, notably P331S for C1q binding [15,16] and L234F and P331S for Fc receptor binding [17]. The most conspicuous differences in sequences among the four IgG isotypes are in the hinge regions with varying lengths of proline-rich amino acid sequences containing a core

### Key points

- IgG4 antibodies undergo ‘half-antibody exchange’ *in vivo*, resulting in recombined antibodies comprising two different binding specificities.
- IgG4 does not activate complement pathways and has reduced effector function relative to other IgG subtypes.
- IgG4 production is driven in part by Th2 cytokines.
- The role of IgG4 antibodies in the pathogenesis of IgG4-RSD remains unclear at this time.

hinge CXXC element (P, proline; S, serine; L, leucine; F, phenylalanine; C, cysteine; X, any amino acid) that can participate in the formation of covalent disulfide bridges between the two heavy chains. A distinctive feature of IgG4 antibodies is the increased susceptibility of the two core hinge interheavy chain disulfide bonds to chemical reduction [18]. The amino acid sequence of the core IgG4 hinge is CPSC, with the cysteine pair occupying positions 226 and 229 under the EU numbering system [19]. In contrast, the core IgG1 hinge, CPPC, which is less susceptible to reduction, has a proline present at position 228 rather than serine. The S228 in IgG4 results in a more flexible hinge enabling the formation of an intrachain cyclized disulfide [20] and leads to the appearance of ‘half-antibodies’, which contain noncovalently linked heavy chains as determined by analysis of IgG4 antibodies under denaturing conditions [21,22,23<sup>•</sup>]. Angal *et al.* [23<sup>•</sup>] made the observation that the appearance of half-antibodies could be greatly reduced by changing the S228 of the IgG4 to proline as in IgG1. A number of therapeutic IgG4 antibodies have a hinge-engineered region including the S228P alteration (see Table 2).

Over the last decade, ground-breaking work from Aalberse *et al.* [24<sup>••</sup>] has elucidated the basis of the half-antibody exchange reaction, also referred to as Fab arm exchange, unique to IgG4 antibodies. This work

**Table 1 Properties of immunoglobulin G subtypes**

|                                 | IgG1                | IgG2                             | IgG3                | IgG4                                             |
|---------------------------------|---------------------|----------------------------------|---------------------|--------------------------------------------------|
| Biological target               | Protein antigen     | Carbohydrate antigen             | Protein antigen     | Protein antigen (allergic or anti-inflammatory?) |
| Functional form                 | Monomeric, bivalent | Dimeric, bivalent or tetravalent | Monomeric, bivalent | Bispecific, monovalent for each antigen          |
| Adult serum level range (mg/ml) | 5–11                | 1.5–6                            | 0.2–1               | 0.08–1.4                                         |
| Proportion of total IgG (%)     | 43–75               | 16–48                            | 1.7–7               | 0.8–11.7                                         |
| Half-life (days)                | 21                  | 21                               | 7                   | 21                                               |
| Complement activation           |                     |                                  |                     |                                                  |
| C1q binding                     | ++                  | +                                | +++                 | –                                                |
| Binding to Fcγ receptors        |                     |                                  |                     |                                                  |
| FcγRI (CD64)                    | ++                  | –                                | +++                 | +                                                |
| FcγRII (CD32)                   | ++                  | (a)                              | +++                 | –                                                |
| FcγRIII (CD16)                  | ++                  | –                                | ++                  | –                                                |

(a), FcγRII allotype dependent. IgG, immunoglobulin.

**Table 2 Selected IgG4 therapeutic antibodies in clinical use and/or development**

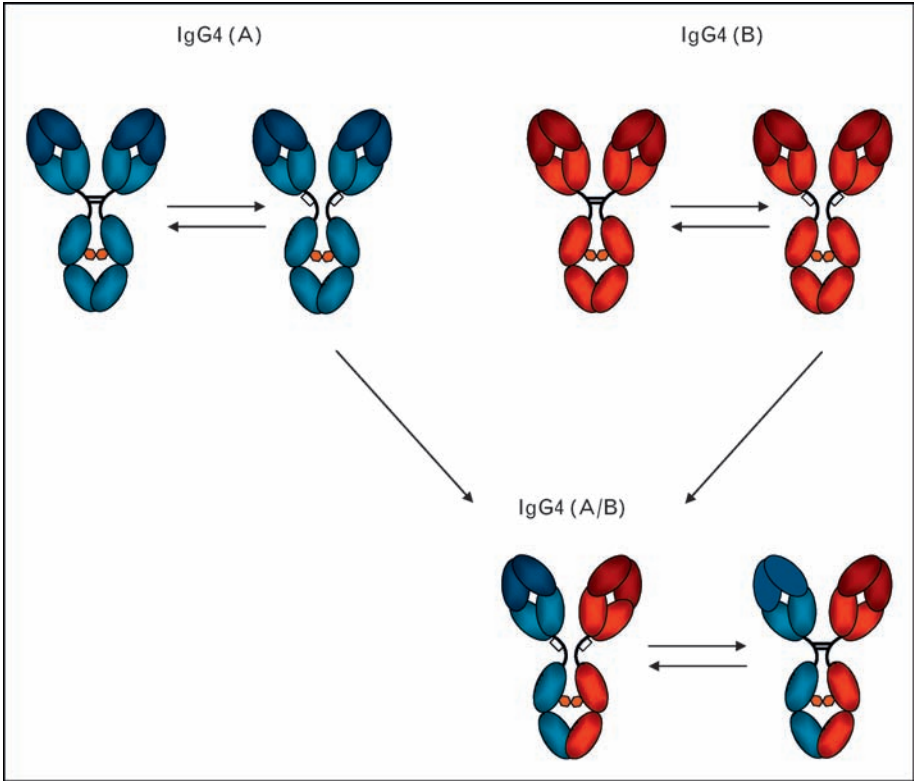
| Therapeutic molecule                                                 | Subtype                                                         | Target                    | Clinical indication(s) and stage                    |
|----------------------------------------------------------------------|-----------------------------------------------------------------|---------------------------|-----------------------------------------------------|
| Natalizumab (Biogen Idec, Weston, Massachusetts, USA)                | IgG4 (humanized)                                                | Anti- $\alpha$ 4 integrin | Approved for multiple sclerosis and Crohn's disease |
| CDP-571 (Celltech/UCB, Brussels, Belgium)                            | IgG4 (humanized)                                                | TNF- $\alpha$             | Phase 2 for rheumatoid arthritis, Crohn's disease   |
| Eculizumab (Alexion, Cheshire, Connecticut, USA)                     | IgG2/IgG4 (humanized)                                           | C5 complement             | Approved for paroxysmal nocturnal hemoglobinuria    |
| BLIB022 (Biogen Idec, Weston, Massachusetts, USA)                    | IgG4 (aglycosylated human hinge-engineered)                     | IGF-1R                    | Phase 1, nonsmall cell lung cancer                  |
| Clenoliximab (Glaxo Smith Kline, King of Prussia, Pennsylvania, USA) | IgG4 (Primatized hinge-engineered)                              | CD4                       | Phase 2, rheumatoid arthritis                       |
| Lebrikizumab (Genentech, South San Francisco, California, USA)       | IgG4 (humanized hinge-engineered)                               | IL-13                     | Phase 2, asthma                                     |
| Ibalizumab (Taimed Biologics, Irvine, California, USA)               | IgG4 (humanized)                                                | CD4                       | Phase 2, HIV-1 infection                            |
| Gemtuzumab ozogamicin (Pfizer, New York, New York, USA)              | IgG4 (humanized hinge-engineered conjugated with calicheamicin) | CD33                      | Previously marketed for AML (withdrawn)             |

AML, acute myeloid leukemia; Ig, immunoglobulin; IGF1-R, Insulin-like growth factor-1 receptor; IL, interleukin; TNF- $\alpha$ , tumor necrosis factor-alpha; UCB, union chimique belge.

has shown that the increased susceptibility of the native IgG4 hinge disulfide bonds to reduction allows the heavy chains to separate and randomly re-associate to produce a mixed population of IgG4 molecules with randomized

heavy-chain and light-chain pairs (Fig. 1). One pivotal study demonstrated that the separation of the IgG4 heavy chains is also facilitated by the weaker interaction between the CH3 domains of the IgG4 subclass, as

**Figure 1 Schematic representation of IgG4 half-antibody exchange**



IgG4 antibodies recognizing different antigens, IgG4 (A) depicted in blue with darker blue variable domains and IgG4 (B) in red with darker red variable domains, are shown as interheavy chain and intraheavy chain disulfide bonded structural isoforms in equilibrium. The red hexagon represents the conserved carbohydrate at position Asn297. The intrachain disulfide bonded structural isoforms can participate in the half-antibody exchange reaction resulting in the formation of the bispecific antibody IgG4 (A/B).

substituting the IgG1 CH3 domain into an IgG4 prevents the exchange process [25<sup>••</sup>]. Our pharmacokinetic results in animal models and in human patients with Natalizumab, a commercially approved anti- $\alpha$ 4 integrin IgG4 antibody, shows that this exchange reaction takes several days to reach equilibrium and that the kinetics of the exchange is dependent on the individual's endogenous IgG4 levels (Biogen Idec and Elan, unpublished data).

The result of half-antibody exchange is that most IgG4 molecules in circulation will consist of two different Fab arms rendering them 'bi-specific' and functionally monovalent for a given antigen. Consequently, IgG4 antibodies in the circulation cannot form immune complexes with antigen, as would occur with the other IgG subclasses. The formation of immune complexes activates the complement pathway and immune effector cell function and given their already low affinity for C1q and Fc receptors, IgG4 antibodies have low theoretical potential for immune activation. Moreover, to the degree IgG4 antibodies can displace the binding of those IgG1 or IgE antibodies with related specificities, they could counteract the inflammatory properties of these other subclasses. This counter-inflammatory property may provide an explanation for another observation made by Aalberse *et al.* [24<sup>••</sup>] that IgG4 antibodies commonly arise after long-term exposure to an antigen, such as an allergen, thereby reducing the degree of chronic inflammation to environmental stimuli.

### Control of IgG4 production

Exposure of appropriately activated B cells to a particular cytokine milieu will direct B cells to differentiate into antibody-producing plasma cells that secrete antibody of a specific isotype. All B cells express IgM until signals are provided to initiate isotype switching to produce an IgA, IgE or an IgG subtype [1]. The driving force behind IgG4 production is not fully understood, especially in light of the fact that most cytokines found to be involved in promoting or enhancing IgG4 production have similar effects on IgE production. What shifts the balance between IgG4 and IgE is not clear, although there are some hints emerging. Based on data from a variety of in-vitro assays and analyses of individuals with specific allergies and parasitic infections, the drive to IgG4 production appears to be dependent upon the stimulating antigen and the immediate micro-environment.

In the context of an allergic response, generation of IgE-producing plasma cells is largely dependent on interleukin-4 (IL-4), a Th2 cytokine. Other cytokines such as IL-5, IL-6, IL-7, IL-9, and IL-13 have also been described to be involved in triggering IgE production [26]. These

same cytokines, as well as IL-10 and IL-12 [27,28], promote and enhance IgG4 production. It is hypothesized that initial low-level exposure to an allergen results in an IgE immune response that produces long-lived plasma cells, but without a germinal center reaction and development of B cell memory. In one model, it is proposed that chronic exposure to an allergen provides a strong stimulus to generate a germinal center reaction wherein exposure to IL-4 and other cytokines stimulate a switch to IgG4, and wherein IgE-expressing B cells do not survive [29].

In-vitro data in which human peripheral blood mononuclear cells were stimulated with IL-4 or IL-13 showed that addition of IL-10 into the culture media resulted in a preferential production of IgG4 over IgE [27]. Data also suggest that IL-10-producing T-regulatory cells may suppress IgE production, thus leading to a 'modified Th2' response, which results in allergen-specific IgG4-producing plasma cells [30]. More recently, it was described that IL-21, a pleiotropic cytokine produced by activated T cells, can either activate or inhibit IgE and IgG4 production depending on the B cell activating conditions. Interestingly, IL-21 appears to stimulate the secretion of IgG4 protein without causing IgG4 switch, suggesting that IL-21 promotes activation or expansion of B cells already committed to IgG4 production [31<sup>•</sup>].

Little has been done to determine whether B cells with a particular phenotype are biased toward IgG4 production. A single report examined IgG4 production *in vitro* from two distinct B cell subsets [32]. The expression of CD148, a receptor-type protein tyrosine phosphatase, was examined on human splenic B cells with CD148<sup>+</sup> B cells exhibiting characteristics of memory B cells. In in-vitro cultures of CD148<sup>+</sup> and CD148<sup>-</sup> human B cells with various stimuli, IgG4 was produced predominantly from CD148<sup>-</sup> naive B cells.

### Implications of IgG4 structure, function, and biology for a specific role in IgG4-related systemic disease

As discussed in detail elsewhere in this issue, a seemingly disparate group of inflammatory diseases (including sclerosing forms of sialadenitis, pancreatitis, and cholangitis, as well as aortitis, thyroiditis, and retroperitoneal fibrosis) appear to be unified by similar histopathologic findings and elevated IgG4 levels, and have been described collectively as IgG4-RSD [24<sup>••</sup>,33–35]. It is unclear whether IgG4 directly mediates the disease process or reflects a protective response induced by anti-inflammatory cytokines, and could regardless represent an important biomarker. These are critical questions being raised in ongoing research on IgG4-associated diseases.

One disease entity where the pathologic role of IgG4 antibodies is well understood is the blistering skin disease pemphigus [36]. Here, an IgG4 antibody to the epithelial antigen desmoglein causes direct disruption of the epithelial layer and blister formation without antibody-mediated effector function or complement activation. Given the properties of IgG4 described herein, proposal of a direct pathologic role for IgG4 would not generally encompass a significant role for effector cells or any role for complement. It must be noted that in some settings, the residual binding of IgG4 mAbs to Fc receptors can lead to effector cell activation [37], and Fc variants with further ablation of effector function have actually been engineered into IgG therapeutic antibodies [38,39]. The timing of half-antibody exchange of IgG4 molecules *in vivo* is relevant to proposed pathophysiology. If antibody-mediated cross-linking and activation of effector function are required for disease, these events would likely occur prior to exchange of IgG4 arms and conversion of the antibody from its original bivalent form.

In Th2 immune responses elevated levels of IgG4 can be associated with increases in IgE and IgG1 antibodies, which have more potent inflammatory properties. Increased IgE levels have indeed been noted in some reports of IgG4-RSD [40], although levels of IgE reportedly show poorer correlation with these diseases than IgG4 (Arezou Khosroshahi & John Stone, personal communication). The characteristic biopsy finding of the diseases is a lymphoplasmacytic infiltrate with IgG4-staining plasma cells and/or CD20 positive cells [40]. Given case reports of good therapeutic responses to the anti-CD20 B-cell depleting antibody Rituximab (Genentech, South San Francisco, California, USA) in IgG4-RSD [41] further work is required to characterize the relative importance of CD20 positive cells and/or plasma cells in production of IgG4, as well as the specificities of IgG4 antibodies produced.

## Conclusion

IgG4 is a unique antibody from the standpoint of structure, function, and immunologic regulation. The role of Th2 cytokines in IgG4 biology provides functional linkage to allergic responses. IgG4-RSD represents a newly described category of diseases with a potential role for IgG4 antibodies. The lack of effector function of IgG4 and the phenomenon of half-antibody exchange raise complex questions as to whether antibodies of this subtype are pathogenic or alternatively, mediate a counter-regulatory response to ongoing immunologic disease. Increased understanding of the precise role of IgG4 in these clinical syndromes will likely be pivotal for elucidation of the underlying pathophysiology.

## Acknowledgement

We thank Larisa Miller, Michaela Lerner, Paula Hochman, and Tatiana Plaviana from Biogen Idec for allowing us to reference their data on stable IgG4 levels in MS patients. We also thank these individuals as well as Nancy Wehner and Ted Yednock from Elan Pharmaceuticals, for allowing us to reference their unpublished data on timing of half-antibody exchange. We thank Susan Goelz from Biogen Idec for helpful input and review of the manuscript.

A.N., S.M.G., S.L.K., and F.R.T. are all employees of Biogen Idec and may hold stock and/or stock options in the company.

## References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 130).

- 1 Abbas A, Lichtman AH, Pober JS. Cellular and molecular immunology. 4th ed. New York, USA: WB Saunders; 2000.
- 2 Stone KD, Prussin C, Metcalfe DD. IgE, mast cells, basophils, and eosinophils. *J Allergy Clin Immunol* 2006; 125:S73–S80.
- 3 Meulenbroek AJ, Zeijlemaker WP. Human IgG Subclasses: useful diagnostic markers for immunocompetence [online]. Sanquin, Laboratory for Experimental and Clinical Immunology University of Amsterdam, the Netherlands; 1996 (<http://www.xs4all.nl/~ednieuw/IgGsubclasses/subkl.htm>).
- 4 Salfeld JG. Isotype selection in antibody engineering. *Nat Biotechnol* 2007; 25:1369–1372.
- 5 Morrell A, Terry WD, Waldmann TA. Metabolic properties of IgG subclasses in man. *J Clin Invest* 1970; 49:673–680.
- 6 Aucouturier A, Danon F, Daveau M, *et al.* Measurement of serum IgG4 levels by a competitive immunoenzymatic assay with monoclonal antibodies. *J Immunol Methods* 1984; 74:151–162.
- Useful overview of normal IgG4 levels in adults stratified by age group and sex.
- 7 French MA. Serum IgG subclasses in normal adults. *Monogr Allergy* 1986; 19:100–107.
- 8 Lefranc M-P, Giudicelli V, Ginestoux C, *et al.* IMGT<sup>®</sup>, the international ImMunoGeneTics information system<sup>®</sup>. *Nucleic Acids Res* 2009; 37(Suppl 1):D1006–D1012.
- 9 Feldmann M, Charles P, Taylor P, *et al.* Biological insights from clinical trials with anti-TNF therapy. *Springer Semin Immunopathol* 1998; 20:211–228.
- 10 Miller DH, Khan OA, Sheremata WA, *et al.* A controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2003; 348:15–23.
- 11 Chan AC, Carter PJ. Therapeutic antibodies for autoimmunity and inflammation. *Nat Rev Immunol* 2010; 10:301–316.
- 12 Von Mehren M, Britten C, Lear K, *et al.* Phase I, dose-escalation study of BLI022 (anti-IGF-1R antibody) in advanced solid tumors. *J Clin Oncol* 2010; 28 (Suppl):15s; abstract 2612.
- 13 Newman R, Hariharan K, Reff M, *et al.* Modification of the Fc region of a primate IgG antibody to human CD4 retains its ability to modulate CD4 receptors but does not deplete CD4<sup>+</sup> T cells in chimpanzees. *Clin Immunol* 2001; 98:164–174.
- 14 Labrijn AF, Buijsse AO, van den Bremer ET, *et al.* Therapeutic IgG4 antibodies engage in Fab-arm exchange with endogenous human IgG4 *in vivo*. *Nat Biotechnol* 2009; 27:767–771.
- 15 Tao MH, Smith RIF, Morrison SL. Structural features of human immunoglobulin G that determine isotype-specific differences in complement activation. *J Exp Med* 1993; 178:661–667.
- 16 Brekke OH, Michaelsen TE, Aase A, *et al.* Human IgG isotype-specific amino acid residues affecting complement-mediated cell lysis and phagocytosis. *Eur J Immunol* 1994; 24:2542–2547.
- 17 Canfield SM, Morrison SL. The binding affinity of human IgG for its high affinity Fc receptor is determined by multiple amino acids in the CH2 domain and is modulated by the hinge region. *J Exp Med* 1991; 173:1483–1491.
- 18 Petersen JG, Dorrington KJ. An *in vitro* system for studying the kinetics of interchain disulfide bond formation in immunoglobulin G. *J Biol Chem* 1974; 249:5633–5641.
- 19 Kabat EA, Wu TT, Perry HM, *et al.* Sequences of proteins of immunological interest. Bethesda: US Department of Health and Human Services, NIH; 1991.

- 20 Bloom JW, Madanat MS, Marriott D, *et al.* Intrachain disulfide bond in the core hinge region of human IgG4. *Protein Sci* 1997; 6:407–415.
- 21 Schuurman J, Perdok GJ, Gorter AD, *et al.* The inter-heavy chain disulfide bonds of IgG4 are in equilibrium with intra-chain disulfide bonds. *Mol Immunol* 2001; 38:1–8.
- 22 Taylor FR, Prentice HL, Garber EA, *et al.* Suppression of sodium dodecyl sulfate-polyacrylamide gel electrophoresis sample preparation artifacts for analysis of IgG4 half-antibody. *Anal Biochem* 2006; 353:204–208.
- 23 Angal S, King DJ, Bodmer MW, *et al.* A single amino acid substitution abolishes the heterogeneity of chimeric mouse/human (IgG4) antibody. *Mol Immunol* 1993; 30:105–108.  
Identification of the amino acid residue responsible for differences between IgG subtypes in generation of a 'half-antibody'.
- 24 Aalberse RC, Stapel SO, Schuurman J, *et al.* Immunoglobulin G4: an odd antibody. *Clin Exp Allergy* 2009; 39:469–477.  
A recent review and discussion of IgG4 biology by the leading expert in the field. The review touches on the relationship of IgG4 function to allergic disease and autoimmune syndromes associated with elevated IgG4 levels.
- 25 Van der Neut Kolfschoten M, Schuurman J, Losen M, *et al.* Anti-inflammatory activity of human IgG4 antibodies by dynamic Fab arm exchange. *Science* 2007; 317:1554–1557.  
A detailed characterization of the phenomenon of IgG4 half-antibody exchange in preclinical models.
- 26 Hussain R, Poindexter RW, Ottesen EA. Control of allergic reactivity in human filariasis. Predominant localization of blocking antibody to the IgG4 subclass. *J Immunol* 1992; 148:2731–2737.
- 27 Jeannin P, Lecoanet S, Delneste Y, *et al.* IgE versus IgG4 production can be differentially regulated by IL-10. *J Immunol* 1998; 160:3555–3561.
- 28 Horner AA, Widhopf GF, Burger JA, *et al.* Immunostimulatory DNA inhibits IL-4-dependent IgE synthesis by human B cells. *J Allergy Clin Immunol* 2001; 108:417–423.
- 29 Aalberse RC, Platts-Mills TA. How do we avoid developing allergy: modifications of the TH2 response from a B-cell perspective. *J Allergy Clin Immunol* 2004; 113:983–986.
- 30 Robinson DS, Larche M, Durham SR. Tregs and allergic disease. *J Clin Invest* 2004; 114:1389–1397.
- 31 Wood N, Bourque K, Donaldson DD, *et al.* IL-21 effects on human IgE production in response to IL-4 or IL-13. *Cell Immunol* 2004; 231:133–145.  
Report showing a role for IL-21 in shifting Th2 response away from IgE production toward IgG4 production.
- 32 Tangye SG, Liu YJ, Aversa G, *et al.* Identification of functional human splenic memory B cells by expression of CD148 and CD27. *J Exp Med* 1998; 188:1691–1703.
- 33 Stone JH, Caruso PA, Deshpande V. 2009. Case records of the Massachusetts General Hospital. Case 24-2009: a 26 year old woman with painful swelling of the neck. *N Engl J Med* 2009; 361: 511–518.
- 34 Dahlgren MN, Khosroshahi A, Nielsen GP, *et al.* Riedel's thyroiditis and multifocal fibrosclerosis are part of the IgG4-related systemic disease spectrum. *Arthritis Care Res* 2010; 62:1312–1318.
- 35 Stone JH, Khosroshahi A, Deshpande V, Stone JR. IgG4-related systemic disease accounts for a significant proportion of thoracic lymphoplasmacytic aortitis cases. *Arthritis Rheum* 2010; 62:316–322.
- 36 Rock B, Martins CR, Theofilopoulos AN, *et al.* The pathogenic effect of IgG4 autoantibodies in endemic pemphigus foliaceus (fogo selvagem). *N Engl J Med* 1989; 320:1463–1469.
- 37 Holland M, Hewins P, Goodall M, *et al.* Antineutrophil cytoplasm antibody IgG subclasses in Wegener's granulomatosis: a possible pathogenic role for the IgG4 subclass. *Clin Exp Immunol* 2004; 138:183–192.  
Unexpected finding that IgG4 anti-neutrophil cytoplasmic antibodies (ANCA) can be pathogenic in Wegener's granulomatosis with discussion of potential mechanisms.
- 38 Bolt S, Routledge E, Lloyd I, *et al.* The generation of a humanized, nonmitogenic CD3 monoclonal antibody which retains in vitro immunosuppressive properties. *Eur J Immunol* 1993; 23:403–411.
- 39 Armour KL, van de Winkel JG, Williamson LM, Clark MR. Differential binding to human FcγRIIIa and FcγRIIb receptors by human IgG wildtype and mutant antibodies. *Mol Immunol* 2003; 40:585–593.
- 40 Masaki Y, Dong L, Kurose N, *et al.* Proposal for a new clinical entity, IgG4-positive multiorgan lymphoproliferative syndrome: analysis of 64 cases of IgG4-related disorders. *Ann Rheum Dis* 2009; 68:1310–1315.  
Interesting detailed comparison of clinical findings, laboratory results, and histopathologic data from Sjogren's syndrome and IgG4-positive multiorgan lymphoproliferative syndrome.
- 41 Khosroshahi A, Bloch DB, Deshpande V, *et al.* Rituximab therapy leads to rapid decline of serum IgG4 levels and prompt clinical improvement in IgG4-related systemic disease. *Arthritis Rheum* 2010; 62:1755–1762.  
Report of a study to assess the clinical and serologic response to B lymphocyte depletion therapy with rituximab in patients with IgG4-RSD.