BLOOD

The Journal of
The American Society of Hematology

VOL 77, NO 9 MAY 1, 1991

REVIEW ARTICLE

Interleukin-4: A Prototypic Immunoregulatory Lymphokine

By William E. Paul

THE IMMUNE RESPONSE involves the participation of a large number of distinct cell types whose functions must be coordinated to insure a response that is appropriate in quality and in magnitude to the eliciting antigenic stimulus. This coordination of function is generally believed to be regulated by the action of T lymphocytes, whose receptors are specific for peptides derived from the eliciting antigen, bound to a groove in a class I or a class II major histocompatibility complex (MHC) molecule. Much of the regulatory function of such T cells is mediated by the secretion of a set of potent polypeptides often designated as lymphokines or interleukins (ILs).[1] Those that appear to be principally secreted by immunocompetent cells in response to the interaction of antigen with a specific receptor are listed in Table 1. I will refer to these molecules as "immune recognition-induced lymphokines."

IL-4 IS A PROTOTYPIC IMMUNE RECOGNITION-INDUCED LYMPHOKINE

IL-4 has properties that exemplify many of the characteristics of the set of immune recognition-induced lymphokines. It is made in response to immunologic recognition, principally, although not exclusively, by $CD4^+$ T lymphocytes.[2] It mediates much of its action in short range interactions between target cells and IL-4–producing T cells,[3] and it has a wide range of functions.[4] As with all molecules whose biologic functions are initially detected by in vitro assays, a question remains as to the major physiologic action of IL-4. It is still too early in the study of IL-4 to reach a definitive conclusion on this important point. However, it is clear that it does express at least one critical in vivo function. IL-4 is principally responsible for the production of IgE in mice in response to a variety of stimuli that elicit Ig class switching to the expression of this Ig class.[5] Mice treated with monoclonal anti–IL-4 antibodies fail to develop the striking increases in serum IgE that are normally observed in response to nematode infections and related stimuli.[6] Recently, transgenic mice overexpressing the IL-4 gene have been shown to have elevated levels of serum IgE and serum IgG1.[7]

In vitro analysis has demonstrated a wide range of functions of IL-4 on B cells, on T cells, on macrophages, on hematopoietic precursor cells, and on stromal cells. To what extent these in vitro functions also represent biologically important in vivo functions remains to be determined.

IL-4 was initially described based on its ability to enhance DNA synthesis by purified resting mouse B lymphocytes stimulated with anti-IgM antibodies.[8] For this reason, it was first designated B-cell growth factor (BCGF). When it was shown to act on resting B cells to induce expression of class II MHC molecules[9] and to enhance their subsequent responsiveness to anti-IgM antibodies,[10,11] it was recognized that BCGF was not an entirely appropriate name; in its place, the designation B-cell stimulatory factor-1 was proposed.[12] This was superseded by the name IL-4, which was proposed at the time of the derivation of cDNA clones for the molecule,[13,14] and of the recognition that the molecule was very pleiotropic in its action with non-B cells being important targets of its regulatory function.

IL-4 AND A RELATED SET OF MOLECULES COMPRISE THE "IL-4 FAMILY OF LYMPHOKINES"

IL-4 can be regarded as a prototypic member of a subset of the immune recognition-induced lymphokines that I would propose be designated the IL-4 family of lymphokines. This family consists of IL-4, IL-5, IL-3, and granulocyte-macrophage colony-stimulating factor (GM-CSF). The properties which lead to the grouping of this set of molecules as distinct from the other immune recognition-induced lymphokines (ie, IL-2, interferon γ [IFNγ], and lymphotoxin [tumor necrosis factor β; TNFβ]) are: (1) the linkage of the genes for the members of the IL-4 family[15-19]; (2) the action of each member of the family as a hematopoietic growth factor in addition to any functions it may also exert on lymphoid cells, whereas the other immune recognition-induced lymphokines fail to express such activity; (3) the observation that the receptors for these factors are all members of the newly defined hematopoietin family of receptors, whereas receptors for the other factors (except for the β chain of the IL-2 receptor) are not members of this family[20]; and (4) coexpression of these factors by a subpopu-

From the Laboratory of Immunology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD.
Submitted December 6, 1990; accepted January 22, 1991.
Address reprint requests to William E. Paul, MD, Bldg 10, Room 11N311, National Institutes of Health, Bethesda, MD 20892.

0006-4971/91/7709-0030$0.00/0

Table 1. Immune Recognition-Induced Lymphokines

IL-2
IL-3
IL-4
IL-5
IL-10
GM-CSF
IFNγ
Lymphotoxin (LT; TNFβ)

IL-4, IL-5, IL-3, and GM-CSF may be grouped together as a family (the IL-4 family of lymphokines) based on (1) their genetic linkage; (2) their receptors are each members of the hematopoietin family; (3) they are all hematopoietic growth factors; and (4) they are often coexpressed.

lation of cloned CD4+ mouse T cells (T_{H2} cells)[21] and by mast cells.[22]

MOLECULAR CHARACTERIZATION OF IL-4 AND ITS GENE

IL-4 protein structure and cDNA clones. Murine IL-4 is a glycoprotein with an approximate molecular weight of 19,000 daltons when purified from a T-cell source.[23,24] Recombinant IL-4 (rIL-4) produced in a baculovirus expression system has an approximate molecular weight of 14,000 to 15,000 daltons, whereas rIL-4 produced in yeast is quite heterogenous in molecular weight with some forms having sizes of ~50,000 daltons. These differences represent variable glycosylation. As with many of other glycoprotein growth factors, IL-4 that has been deglycosylated by digestion with endoglycosidase F has full biologic activity in vitro,[25] as does rIL-4 produced in *Escherichia coli.* Human IL-4 has very similar characteristics.[26,27] It exists in molecular weight forms between 15,000 and 19,000 daltons.

cDNAs encoding both mouse and human IL-4 have been obtained.[13,14,26] The mouse IL-4 gene codes for a protein of 140 amino acids, of which the first 20 amino acids are a leader sequence. The mature protein has a calculated molecular weight of ~13,200. N terminal amino acid sequencing of T-cell–derived IL-4[24,25] yields a sequence identical to that inferred from the nucleotide sequence of the cDNA and confirms the inferred N-terminus of the mature protein. Murine IL-4 contains three potential N-linked glycosylation sites and six cysteines. None of the cysteines is available for labeling with ^{125}I-iodoacetamide,[25] suggesting that all participate in disulfide bonds. The apparent molecular weight of unreduced IL-4 on sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) is, as noted above, consistent with the molecular weight anticipated for a glycosylated monomer. Furthermore, the mobility on SDS-PAGE of reduced IL-4 is slightly slower than that of the unreduced molecule. These results indicate that there are no interchain disulfide bonds and suggest that all the cysteines are participants in intrachain bonds. Reduction and alkylation of IL-4 completely destroys its biologic activity. The human IL-4 gene has many features in common with mouse IL-4.

Monoclonal anti–IL-4 antibodies. Monoclonal antibodies (MoAbs) to murine IL-4 have been prepared. One, 11B11, has been widely used because of its capacity to neutralize IL-4 function both in vitro and in vivo.[28] It appears to react with IL-4 near the site at which IL-4 binds to its receptor because it blocks binding to the receptor.[25] Recently, a second monoclonal antimurine IL-4 antibody has been prepared (13E1) that binds principally to denatured forms of IL-4 and is far superior to 11B11 for use in immunoblotting (Atasoy U, Paul WE: manuscript in preparation). On the other hand, 13E1 fails to block IL-4 biologic activity and does not appear to react with native forms of IL-4.

The IL-4 gene is found in the cytokine complex on mouse chromosome 11 and human chromosome 5. The IL-4 gene is found on mouse chromosome 11[15] and on the long arm of human chromosome 5 at 5q23.3-31.2.[16] The IL-4 gene is linked to the IL-5 gene.[17] In the mouse, the distance between the two genes has been estimated by pulsed field electrophoresis to be ~160 kb.[18] The genes for IL-3 and GM-CSF are found at similar locations[16] and are very closely linked.[19] Although the "IL-4/IL-5 pair" and the "IL-3/GM-CSF pair" have not been physically linked, they have been shown by analysis of restriction fragment length polymorphisms in recombinant inbred lines to be within 1 centimorgan of one another.[15] Similarly, in situ hybridization localization of these genes in instances of translocations involving human chromosome 5 also indicate close association of IL-3 and GM-CSF with IL-4 and IL-5.[16] This region also contains other genes believed to be important in regulating the growth of hematopoietic and nonhematopoietic cells including the genes for PDGF-receptor, CSF-1, and the CSF-1 receptor.[29] See Fig 1 for a diagram of this "cytokine" genetic region.

Structure of the IL-4 gene. The IL-4 gene itself consists of 4 exons spanning 6 kb in the mouse[30] and 10 kb in the human.[31] The promoter region of the gene has not yet been analyzed in detail. It does contain a κB-like sequence found in the promoter regions of many cytokine genes,[31] suggesting that it may be regulated by NF-κB or an NF-κB–like DNA-binding protein.

The 3′ untranslated region of the IL-4 mRNA contains an AU-rich region that has been shown to convey instability for other transcripts.[32] Although no direct measurements of IL-4 mRNA half-life have been reported, indirect experiments showing that IL-4 mRNA disappears rapidly after the cessation of receptor-mediated signalling indicate that IL-4 mRNA is rapidly degraded.

THE IL-4 RECEPTOR

Receptor affinity and distribution. IL-4 mediates its functions by binding to receptors expressed on target cells. In

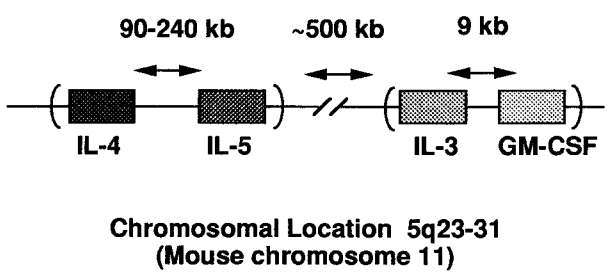

Fig 1. Map of the IL-4 family gene cluster.

both mouse and human cells, responsive cell types express relatively small numbers (~400) of receptors per cell.[33-36] The receptors have an affinity of $\sim 10^{10}$ M^{-1} and appear homogeneous in binding properties by Scatchard analysis. Receptors have been reported to exist on freshly prepared B and T lymphocytes and macrophages, as well as on various cell lines including lymphoid cells, mast cell lines, a variety of other hematopoietic cell lines and fibroblast and stromal cell lines.[33-35] Some but not all Ab-MuLV transformed pre-B cell lines and some plasmacytoma lines lack detectable IL-4 receptors.

Activation of B cells with anti-Ig antibodies or lipopolysaccharide (LPS) and activation of T cells with mitogens increases receptor expression, often to ~2,000/cell.[37] IL-4 itself increases receptor expression on resting T and B lymphocytes. A derivative of the growth-factor–dependent mouse T-cell line CTL.L has been obtained that can grow in IL-4.[38] This line, designated CT.4R, expresses 10,000 to 20,000 receptors/cell. A variant of this line, CT.4S, that expresses little if any α chain of the IL-2 receptor has been obtained by mutagenesis and cell sorting. This line fails to respond to low concentrations of IL-2 (<100 U/mL) and is thus, functionally, an IL-4–specific indicator cell line. It has been used as a sensitive and specific bioassay for IL-4, allowing the detection of less than 3 U/mL (<1.5 pg/mL). Efforts to adapt CT.4S cells to responsiveness to human IL-4, by expressing the human IL-4 receptor gene in them, are underway. Such a line would provide a sensitive and selective bioassay for human IL-4.

Chemical cross-linking of the IL-4 receptor. The mouse IL-4 receptor has been analyzed by chemical cross-linking of cells that have specifically bound ^{125}I-IL-4. On subsequent analysis by SDS-PAGE, in the presence of β-mercaptoethanol, two major species of bands are observed. One, migrating at ~90,000 daltons, is generally the dominant band,[33,34] indicating a 70,000-dalton IL-4 binding molecule. However, when human IL-4 was cross-linked to human B-lymphoblastoid cells and to human gingival fibroblasts, the inferred molecular weight of the IL-4 receptor was ~140,000 daltons.[36] Others reported that a 70,000- to 80,000-dalton IL-4–binding chain also existed on human cells.[39] Subsequently, a 120,000-dalton chain was also observed on mouse cells. These results suggest that IL-4–binding chains with molecular weights of ~120,000 and ~70,000 daltons exist. The relationship of the two IL-4–binding chains (p120 and p70) to one another has not been completely established. Isolation of cross-linked complexes of mouse ^{125}I-IL-4 and the mouse IL-4 receptor, digestion with either chymotrypsin or with V8 protease, and subsequent analysis of ^{125}I-bearing peptides by SDS-PAGE has shown that the pattern of IL-4 cross-linked peptides derived from the two molecular species to be identical.[40] This strongly suggests that the p70 is a degradation product derived from p120. However, p70 has not been observed in any case other than those in which the receptor had been cross-linked with ^{125}I-IL-4, raising the possibility that its derivation is not a simple instance of proteolytic sensitivity of the receptor. It is possible that ligand binding and subsequent cross-linkage increases the susceptibility of p120 to proteolysis. Whether this reflects an increase in a ligand-dependent proteolysis that involves only a small fraction of the receptors and whether such proteolysis may be important in signalling have not yet been determined. The possibility that p70 is an independent chain structurally related to p120 has not been completely excluded, but seems unlikely.

IL-4 receptor cDNA clones. cDNA clones for both the mouse[41,42] and human[43,44] IL-4 receptors have been obtained. The IL-4 receptor of the mouse is a type I membrane protein with a putative extracellular domain consisting of 208 amino acids with five potential N-linked combining sites. It contains two motifs that are characteristic of a set of receptors for growth factors, including the IL-3 receptor, the GM-CSF receptor, the β chain of the IL-2 receptor, the IL-6 receptor, the IL-7 receptor, the G-CSF receptor, the erythropoietin receptor, the growth hormone receptor, and the prolactin receptor. These motifs are a particular spacing of four cysteines with tryptophan located two residues after the second cysteine and, in a membrane proximal location, a WSXWS motif. The family of receptors defined by these motifs is often referred to as the hematopoietin receptor family of molecules.[20,45,46]

The putative cytosolic portion of the murine IL-4 receptor consists of 553 amino acids. It has regions rich in proline and serine and an acidic region that is well conserved between the mouse and human receptors. On the other hand, it has no recognized consensus sequences for kinase activity or for nucleotide binding regions.

Two forms of the IL-4 receptor. In addition to a cDNA clone for the 120,000-dalton form of the IL-4 receptor, a cDNA has also been isolated that appears to represent an alternatively spliced form of the receptor.[41] This cDNA encodes the extracellular domain of the IL-4 receptor followed by a 114-nucleotide insert that codes for the addition of six amino acids followed by a stop codon not found in the 120,000-dalton form. It does not encode the transmembrane or cytosolic regions of the IL-4 receptor. The inferred amino acid sequence of this molecule suggests that it represents a soluble form of the IL-4 receptor.

When expressed in COS-7 cells, the cDNA for the 120,000-dalton chain results in the expression of membrane receptors for IL-4 that bind IL-4 similarly to its binding by the naturally occurring receptor on mouse cells. Furthermore, expression of the cDNA for the putative soluble form of the receptor in COS-7 cells does result in the production of a soluble IL-4–binding molecule with a molecular weight of 40,000 daltons.[41] This soluble molecule has an affinity for IL-4 that is similar to that of the natural receptor, strongly arguing that no additional chain is required for high-affinity binding of IL-4 to its receptor.

The functional evidence in favor of the cDNA for the 120,000-dalton form encoding the actual IL-4 receptor is that expression of the cDNA for the homologous human IL-4 receptor in the mouse CTL.L cell line conveys to these cells the capacity to respond to human IL-4 with DNA synthesis.[43] Human IL-4 does not bind to mouse IL-4 receptors and does not have any detectable biologic action

on CTL.L cells that have not been transfected with cDNA for the human IL-4 receptor.

The existence of a cDNA clone that codes for a potentially soluble form of the IL-4 receptor raises the question of whether such a soluble molecule is normally made and, if so, what its physiologic significance might be. Fernandez-Botran and Vitetta[47] have reported the existence of a molecule found in supernatants of various tissue culture cell lines and in ascitic fluids that inhibits the binding of IL-4 to its receptor and that binds to IL-4 with an affinity similar to that of the IL-4 receptor. The molecular weight of this IL-4–binding protein is ~30,000, compared with the 40,000-dalton molecular weight for the product of the truncated cDNA clone transfected into COS-7 cells. Recently, it has been shown that cells of both a T-cell line and a mast cell line express mRNAs for both the p120 (full-length) receptor and for the truncated receptor.[40] This work made use of polymerase chain reaction amplification of IL-4 receptor mRNA using primers that would allow independent detection of the full-length and the truncated receptor. Furthermore, metabolic labeling with ^{35}S-methionine and precipitation with either Affigel-bound IL-4 or Affigel-bound antibody to the IL-4 receptor shows the existence of a species of ~100,000 and one of ~42,000. During a chase period, both species change in mobility on SDS-PAGE; in particular, the 42,000-dalton product appears to be processed to a 40,000-dalton species, while the 100,000-dalton form is processed to 120,000. This strongly suggests that the p40 chain is derived independently of p120 and is consistent with p40 being a soluble receptor rather than a proteolytic cleavage product. However, no evidence for the secretion of the p40 form of the IL-4 receptor has yet been obtained from normal cells, so that the physiologic significance of the soluble receptor and its relationship to the soluble IL-4–binding molecule described by Fernandez-Botran and Vitetta[47] is not yet certain. However, administration of a purified preparation of soluble recombinant receptor inhibits heart allograft rejection and graft-versus-host responses,[48] implying a potentially important therapeutic role for the soluble receptor.

Mechanism of IL-4–mediated signalling. The biochemical nature of signals induced by the binding of IL-4 to its receptor have not been elucidated. It does appear that the cytosolic domain of the receptor is essential for its signalling function. This conclusion is mainly based on observations made in the course of the derivation of the initial cDNA clones of the mouse IL-4 receptor.[41] In that work, a cell line was derived from CTLL-2 by repetitive sorting and selection of variants that expressed large numbers of IL-4 receptor. The cells selected after 19 rounds of sorting, designated CTLL-19.4, had ~10^6 IL-4 receptors per cell. However, the majority of cDNA clones obtained contained a gene derived as a result of a genetic event in which the coding sequence for the extracellular and transmembrane domains of the IL-4 receptor were expressed without the cytosolic region. The cells expressing this mRNA, although having a very large number of IL-4–binding molecules, failed to respond to IL-4.

Studies of inositol phospholipid metabolism and of intracellular calcium concentrations have shown no changes in response to IL-4 in cells that express IL-4 receptors and that respond, biologically, to IL-4.[49] Furthermore, treatment of B cells with IL-4 leads to a striking enhancement of the expression of class II MHC molecule, even in medium in which the calcium concentration has been markedly reduced. Studies of tyrosine phosphorylation in a cell line responsive to both IL-2 and IL-4 (CT.4R) have shown that treatment of these cells with IL-4 causes a striking increase in tyrosine phosphorylation of a series of substrates (Hornbeck P, Paul WE: unpublished observations, 1990). Whether this increase reflects an immediate effect of the binding of IL-4 to its receptor or is an indirect effect resulting from a yet undefined signal process is not known.

FUNCTIONS OF IL-4

Effects of IL-4 on B lymphocytes: Regulation of B-cell growth and expression of membrane antigens. IL-4 was first recognized for its effect on B-cell growth.[8] Mouse B cells, when cultured at low cell density, synthesize DNA poorly or not at all in response to anti-IgM antibody at relatively low concentrations (≤ 5 μg/mL). Although IL-4 by itself does not stimulate resting B cells to undergo DNA synthesis, it markedly enhances their responses to anti-IgM used at the conditions described above. IL-4 does have some capacity to cause B cells blasts to enter S phase,[50] but it does not appear that its major role as a costimulant of B-cell DNA synthesis is as a late-G1 active growth factor. To exert its major effects in promoting B-cell DNA synthesis, IL-4 must be added at the outset of the culture.[10,11] Indeed, preculture of resting B cells with IL-4 will strikingly enhance their subsequent response to anti-IgM or to the B-cell mitogen LPS.[50] IL-4 has other striking effects on resting B cells. It increases or induces their expression of class II MHC molecules[9] and of the "low affinity" receptor for IgE ([FcεRII] [CD23]),[51] as well as increasing the number of IL-4 receptors found on the surface of the cell.[37] It appears likely that these responses of resting B cells play an important role in their function. Indeed, increased expression of class II MHC molecules could be of particular importance because the quantity of antigen that antigen-presenting cells (APC) can display is a direct function of their density of class II MHC molecules.[52]

When mouse B cells are stimulated with LPS and IL-4, a series of striking changes are observed. FcεRII is superinduced, reaching levels 100 times that on resting B cells.[53] By contrast, FcγRII levels increase transiently but then decrease and stabilize at much lower levels in B cells treated with LPS and IL-4 than in B cells treated with LPS only.[54] Thus, LPS blasts express relatively large amounts of FcγRII and relatively small amounts of FcεRII, whereas blasts stimulated with LPS and IL-4 have the opposite phenotype. Although the significance of this difference is not clear, it has been shown that FcεRII can act quite efficiently in the capture and presentation of antigens associated with IgE (ie, antigen-IgE antibody complexes),[55] suggesting that these cells may act to preferentially present, to T cells, antigens for which IgE responses have already been made. This may be significant in view of the action of IL-4 as a

switch factor for IgE (see next section). A final and somewhat enigmatic effect of IL-4 and LPS on resting B cells is that they cause the great majority of these cells to express Thy-1,[56] a membrane molecule generally regarded to be uniquely expressed, among lymphocytes, on T cells.

The effects of IL-4 on human B cells are often somewhat less striking than the effects on mouse B cells. Its action as a costimulant of B-cell proliferation has been shown but is usually less impressive than this activity on mouse cells.[57]

Effects of IL-4 on B lymphocytes: IL-4 is a switch factor for IgE and IgG1. Mouse B cells treated with LPS and IL-4 produce substantial amounts of IgE[58] and IgG1,[59] whereas treatment with LPS only gives rise to virtually no IgE and to modest amounts of IgG1. This effect of IL-4 in directing B cells to produce IgE and IgG1 can also be observed when the B cell "costimulant" is an activated T cell rather than LPS.[60] Indeed, human cells stimulated, in the presence of T cells, with IL-4 will secrete much more IgE than cells treated without IL-4.[61,62]

The effect of IL-4 in the regulation of IgE production pertains in vivo as well as in vitro because neutralization of IL-4 by treatment with a monoclonal anti–IL-4 antibody[6] or a monoclonal antibody to the IL-4 receptor[5] will block the IgE response to helminthic infection or to in vivo polyclonal B-cell activation achieved through the injection of anti-IgD antibodies. Anti–IL-4 also inhibits secondary polyclonal and antigen-specific IgE responses.[63] Recently, it has been shown that mice expressing an IL-4 transgene have strikingly elevated levels of IgE and IgG1,[7] re-affirming the importance of this lymphokine in the production of IgE and IgG1.

The effect of IL-4 in controlling IgE and IgG1 expression appears to be mediated, at least initially, on resting B cells. Preculture of resting B cells with IL-4 alone will prepare them to secrete IgG1 on subsequent culture with LPS and, although IL-4 alone does not have a similar preparative effect for IgE, IL-4 must be added very early in culture if treatment with LPS plus IL-4 is to enhance IgE responses.[64,65]

Resting B cells and certain B-cell lines treated with IL-4 only show expression of an RNA transcribed from a region 5′ to the Cγ1 switch region spliced to Cγ1.[66,67] This transcript has been termed the sterile γ1 transcript because it does not appear to code for a product, or the germ line γ1 transcript, and is observed as early as 6 to 12 hours after the addition of IL-4 to resting B cells. IL-4 also suppresses the expression of a comparable germ line γ2b transcript in transformed pre-B cell lines,[68] which is in keeping with its capacity to suppress the production of IgG2b by B cells treated with LPS.[69] A germ line ϵ transcript is also induced but it requires the presence of both IL-4 and LPS.[66,70]

These germ line transcripts appear before the DNA deletion events involved in traditional Ig class switching in which the VDJ gene is translocated from its initial position 5′ to the Cμ gene to a new position 5′ to the expressed C gene (ie, Cγ1 or Cϵ). This implies that IL-4 acts to regulate the production of new classes of Ig before the actual switch and allows one to classify IL-4 as a "switch factor" regulating switching to IgE and IgG1 in the mouse and to IgE in the human. Additional work suggests that other cytokines regulate switching to other isotypes (ie, IFNγ for IgG2a[71] and TGFβ for IgA[72]).

The mechanisms through which induction of germ line transcripts prepares cells to undergo switching to the "new" isotype has not been demonstrated, but one possibility is that such transcription specifically "opens" the chromatin and makes those regions of the Ig gene complex more favorable targets for translocation events. Although the means through which IL-4 regulates transcription of the germ line ϵ gene has not been directly demonstrated, it has been shown that 5′ of the start site for the germ line ϵ transcript is a sequence[73] quite similar to one implicated as an IL-4 responsive element in the class II MHC gene.[74]

Mutual regulation of Ig class expression by IL-4 and IFNγ. Not only do IL-4 and IFNγ induce the expression of different classes of Igs in vitro and in vivo, they also inhibit one another's switch-promoting function. Thus, IFNγ is a striking inhibitor of IgE and IgG1 production in vitro in response to LPS and IL-4.[69,75] Furthermore, treatment of mice injected with anti-IgD antibodies with anti-IFNγ antibody will enhance IgE responses in those mice, strongly implying that natural production of IFNγ has limited the IL-4–dependent IgE response.[5] Similarly, IL-4 inhibits the production of IgG2a by B cells treated with LPS and IFNγ.[69] These results thus imply that a critical determinant in the production of IgE in a given immune response is the balance of IL-4 and IFNγ produced. Thus, it suggests that the control of production of these two lymphokines is a key element in the qualitative nature of immune responses. Evidence does exist in both mice and humans that immune responses in which large amounts of IgE are produced are associated with the preferential production of IL-4 by antigen-specific T cells.[76-78]

Does IL-4 have a role in B-cell development? The possibility that IL-4 may play a role in B-cell development has been raised by two sets of observations. Culture of bone marrow cells on stromal cell monolayers in the presence of fetal calf serum and 2-mercaptoethanol at 37°C, in the absence of glucocorticoids, has been shown to give rise to B-lineage cell lines dominated by pre-B cells expressing the B220 form of the common leukocyte antigen.[79] Addition of IL-4 to these cultures after they have been established rapidly leads to the disappearance of pre-B cells, but initiating cultures in the presence of IL-4 leads to the appearance of cells with characteristics strongly indicating that they represent more primitive members of the B lineage.[80] This has suggested that IL-4 might act preferentially at a very early step in B-cell development.

Studies of an IL-3–dependent cell line developed from bone marrow of nude mice (LyD9) have shown that these cells can be stimulated to develop into B-lineage cells expressing membrane IgM if cultured on stromal cells in the presence of IL-4.[81] By contrast, culturing such cells in GM-CSF causes them to develop into myeloid lineage cells.

Both of these observations suggest that IL-4 may have potent effects in B-cell development, but they do not determine whether IL-4 plays such a role physiologically.

Much work remains to be done to clarify the role of IL-4 in this process.

IL-4 is a T-cell growth factor. IL-4 has potent effects on T lymphocytes as well as B cells. Resting T cells treated with IL-4 survive in culture without dividing.[82] Treatment of these cells with phorbol esters and IL-4 causes ~50% of the cells to enter S phase and to divide. IL-4 acts as an autocrine growth factor for a set of murine long-term T-cell lines often designated T_{H2} cells.[83-85] T_{H2} cells produce a limited set of lymphokines including IL-4, IL-5, IL-3, GM-CSF, and IL-10 (cytokine synthesis inhibitory factor).[86,87] They fail to produce IL-2, the prototypic T-cell growth factor, and their growth in response to mitogens and IL-1 or to antigen and APC can be inhibited by monoclonal anti–IL-4 antibody.[83] In general, T_{H2} cell lines do not grow well for extended periods in response to antigen and APC alone; they often require supplementation with IL-2 so that the role of IL-4 as a long-term T-cell growth regulator is still uncertain. It is striking that IL-4 producing long-term T-cell lines of the T_{H2} type require IL-1 as a cofactor for growth in response to mitogens or in response to exogenous IL-4.[83]

Long-term murine T-cell lines that produce IL-2 and IFNγ but not IL-4 (T_{H1} cells) fail to proliferate in response to IL-4, with or without IL-1. In general, these cells respond to IL-2 without a requirement for IL-1. T_{H1} cells, if exposed to antigen associated with fixed APC or to anti-CD3 antibodies without APC, will enter a state of clonal anergy, defined by their inability to produce IL-2 in response to subsequent stimulation with antigen and live APC or to anti-CD3 plus APC.[88] By contrast, T_{H2} cells have not been shown to enter such an anergic state.

Growth of normal T-cell populations in the presence of mitogens plus IL-4 alone or IL-2 plus IL-4 generally favors the preferential proliferation of $CD8^+$ T cells, so that such cells come to dominate the growing cell population.[82] In addition, IL-4 appears to enhance the proliferation of precursors of cytotoxic T cells (CTL) and their differentiation into active CTL.[89,90]

The role of IL-4 in T-cell development within the thymus. IL-4 may have an important role to play in intrathymic T-cell differentiation. The most graphic demonstration comes from observations on thymic development in IL-4 transgenic mice. Tepper et al[7] prepared a series of transgenic mice that varied in their degree of expression of the IL-4 transgene. In mice with the highest degree of expression of IL-4, animals died within 2 weeks of birth of severe runting. Animals expressing somewhat less IL-4 survived but showed severe thymic atrophy. Their major cellular deficit lay in the frequency of $CD4^+$, $CD8^+$ cells, while there was an absolute increase in the frequency of $CD4^-$, $CD8^+$ cells in the thymus. In the periphery, these mice showed a striking diminution in the number of T cells but, despite the over-representation of $CD8^+$ cells in the thymus, they had a normal ratio of $CD4^+$ to $CD8^+$ T cells.

Analysis of in vitro thymocyte development has indicated that treatment of cultures with IL-4 markedly inhibits the frequency of $CD4^+$, $CD8^+$ cells that emerge.[91] These studies suggest that IL-4 produced in the thymus may play a critical role in the development of the T-cell population, but its precise physiologic role in this process has not yet been clarified.

Actions of IL-4 on other hematopoietic cells. IL-4 acts on nonlymphoid hematopoietic cells in a variety of ways. It has been shown to inhibit the growth of macrophages[92,93] and to increase their cytotoxic activity for certain tumor cells.[94] On the other hand, it fails, by itself, to induce the capacity of macrophages to destroy amastigotes of *Leishmania major.* It has been reported to synergize with IFNγ in this respect.[95]

IL-4 also has activity as a stimulant of mast cell growth. In vitro, mast cells can be made to grow from bone marrow under the influence of IL-3.[96] IL-4, by itself, will not replace this activity of IL-3 but IL-4 appears to enhance IL-3–mediated mast cell growth.[97] Recently, it has been shown that further synergy can be obtained through the use of IL-3, IL-4, and IL-10 (Mosmann T: personal communication, 1990). Mast cell lines also display responsiveness to IL-4 and some long-term mast cell lines can be adapted to grow in IL-4 only.[97,98]

IL-4 has been shown to enhance formation of hematopoietic colonies in soft agar.[99] In the presence of G-CSF, it augments granulocyte colony formation. It also enhances formation of erythroid colonies in the presence of erythropoietin, and in the presence of IL-1 it enhances the production of mixed colonies that contain erythroid, megakaryocytic, and myeloid elements.

IL-4 treatment of stroma induces inhibitory activity for hematopoietic colony formation. It has also been shown that IL-4 can have a profound indirect effect on formation of GM colonies. The growth of such colonies can be supported by monolayers of stromal cells over which agar, containing bone marrow cells, is placed. Pretreatment of the stromal cells with IL-4 causes a profound inhibition in the capacity of these cells to support the formation of GM colonies.[100] Furthermore, IL-4–treated stroma block the capacity of IL-3 to induce GM colonies in soft agar. This effect is not mediated by the direct action of IL-4 on the hematopoietic precursor cells because addition of IL-4 directly to colony-forming assays in which IL-3 is used as the stimulant without stromal cells causes no inhibition. Moreover, stromal cells can be pretreated with IL-4, washed, and anti–IL-4 antibody added to neutralize any residual IL-4; such stromal cells are profoundly inhibitory to colony formation. This inhibition is not reversed by indomethacin, strongly suggesting that it is not mediated by prostaglandin formation. IL-4 does not induce or enhance the expression of mRNA for IFNγ, IL-1, TNF, or TGFβ, strongly suggesting that it does not mediate its inhibitory activity through the production of these factors. Although no soluble factor mediating the inhibitory activity of IL-4–treated stromal cells has been found, IL-4–treated stromal cells can block colony formation even if they are separated from hematopoietic progenitor cells by an intervening layer of agar. This fact suggests that the effect is mediated by a diffusible product.

Stromal cell layers used in these experiments are mixed cell populations. The target of the action of IL-4 has not been directly identified. However, it has been shown that

fibroblast cell lines do express IL-4 receptors[35] so that it is possible that nonhematopoietic cells can respond to IL-4 and thus the action of the IL-4 could either be on such components of the stroma or on macrophages found in stroma.

Antitumor effects of IL-4. IL-4 has been demonstrated to have a potent antitumor activity by experiments in which a cDNA for IL-4 has been introduced into the murine myeloma J558.[101] IL-4–producing J558 cells fail to form tumors in mice and block tumor formation by a variety of other transplantable tumor lines when these cells are coinjected with IL-4–producing J558 cells. The effects of the transfected J558 cells can be inhibited by treating the recipient mice with anti–IL-4 antibody. The antitumor effect of expression of IL-4 in transplantable cell lines has been confirmed by at least two other groups (Pardoll D: personal communication, 1990; Seder R, Watson C, Chu C: unpublished observations, 1990), and Forni et al[102] have reported that repeated injections of small amounts of IL-4 into draining lymph nodes can limit the growth of cells of several transplantable tumors.

The means through which IL-4 limits tumor cell growth has not been completely established. Tepper et al[101] reported that IL-4 failed to block the in vitro growth of transfected J558 cells indicating that IL-4 was not directly toxic to the tumor cells. They showed that the IL-4–producing J558 cells failed to grow in *nu/nu* mice, suggesting that T-cell immunity was not essential to the elimination of the transplanted cells. On the other hand, Pardoll et al (personal communication, 1990) have shown that treatment of mice with IL-4 transfected into a colon cancer cell line not only prevents those cells from establishing tumors in recipients but that injection of transfected cells induces a state of immunity against nontransfected tumor cells of the same type and that this immunity is associated with the development of specific cytotoxic T cells.

The importance of IL-4 as an antitumor agent, particularly against spontaneous tumors, remains to be more fully investigated. Nonetheless, these studies suggest that IL-4 may marshal endogenous host responses in a particularly potent way to limit growth of certain types of tumors.

PRODUCTION OF IL-4

Production of IL-4 by TH2 T-cell clones. IL-4 was initially recognized as a T-cell product made by long-term lines of factor-dependent[83-85] and transformed[8] T cells. Among long-term cloned murine T-cell lines, IL-4 production appears to be mainly found in cells designated T_{H2} cells.[87] These cells tend to make a specific set of lymphokines including IL-4, IL-5, IL-6, IL-10, IL-3, and GM-CSF. They fail to produce IL-2, IFNγ, and lymphotoxin, and their production of IL-4 depends on a receptor-mediated event. Antigen and antigen-presenting cells or antibodies capable of cross-linking the T-cell receptor induce IL-4 production by such cells. They are also stimulated to produce IL-4 by treatment with phorbol esters and calcium ionophore. Their production of IL-4 is inhibited by cyclosporine A. Thus far, the molecular regulation of IL-4 production in such cells has not been studied in detail.

Although the limitation of expression of IL-4 to the T_{H2} type T-cell clones has been widely confirmed, it is clear that there are T-cell clones that produce both IL-4, IL-2, and IFNγ.[103,104] It has been proposed that such production may be characteristic of relatively "early" T-cell clones that have not yet fully specialized and that the capacity to produce IL-4, IL-2, or IFNγ may represent a differentiative step that occurs after T-cell activation. Specialization to a specific lymphokine-producing pattern may not be complete until quite long into the developmental history of a T-cell clone.[105] Among human T-cell lines, the production of a "mixed" pattern of lymphokines is the rule rather than the exception.[78,106] However, instances have been reported in which human T-cell clones produce IL-4 without IFNγ; among these are cases in which the clones are derived from allergic individuals and are specific for allergens.[107,108]

IL-4 production by freshly isolated T cells. In general, resting T cells isolated from lymph nodes or spleens of normal mice produce very small amounts of IL-4 in response to stimulation with mitogenic lectins or anti-CD3 antibody.[109,110] Estimates of the frequency of cells that do produce IL-4 in such situations are, in general, quite low. Studies using in situ hybridization have yielded a frequency of cells producing IL-4 of under 1%,[111,112] although one group has reported a considerably higher frequency.[113] A bioassay capable of detecting IL-4 production by a single cell has also been used to estimate the frequency of T cells that produce IL-4 in response to stimulation with anti-CD3 antibody bound to the surface of a culture dish. This method yielded a frequency of ~0.1%.[114]

IL-4 production by normal murine T cells stimulated with anti-CD3 coated to the surface of culture wells is substantially enhanced by the addition of IL-2 to culture and is markedly inhibited by the presence of MoAb to IL-2.[115] This strongly suggests that endogenously produced IL-2 is critical to IL-4 production by such cells. This effect is not simply explained by preferential proliferation or survival of IL-4–producing cells but rather can be demonstrated within 2 hours of stimulation with anti-CD3 by strikingly greater levels of IL-4 mRNA in cells treated with IL-2 than in cells treated with anti–IL-2 (Boulay J-L, Seder R, Paul WE: manuscript in preparation).

IL-4 production by T cells from normal mice is found mainly in cells of low density whereas small, dense T cells are very poor producers of IL-4.[115] The latter cells are usually regarded as resting T cells and the former as activated cells. The concept that IL-4–producing capacity is mainly found in the activated T-cell population is in keeping with the work of Swain et al,[110] who showed that IL-4–producing capacity was very meager in normal T-cell populations but could be markedly enhanced by in vitro culture of these cells. Indeed, examination of the conditions required to increase the frequency of T cells capable of producing IL-4 have shown that stimulation with anti-CD3 in the presence of IL-2 and IL-4 for 2 to 5 days is strikingly effective.[116] Such culture increases the frequency of cells capable of producing IL-4 from ~1/1,000 to ~1/25. Interestingly, although only $CD4^+$ T cells in naive donors produce IL-4, among T-cell populations primed as de-

scribed above, both $CD4^+$ and $CD8^+$ T cells produce IL-4 and the frequency of IL-4–producing cells in the two populations is approximately the same (Seder RA, Boulay J-L, Ben-Sasson SZ, LeGros G, Paul WE: submitted for publication).

Swain et al[117] have recently studied the characteristics of precursors of IL-4–producing T cells by deleting T cells sensitive to antithymocyte serum or by adult thymectomy. The former procedure principally eliminates recirculating T cells whereas the latter procedure removes a source of new thymic emigrants. They observed that the capacity of T cells to be primed in vitro to develop into IL-4–producing cells decayed rapidly after adult thymectomy while it was not affected by antithymocyte serum. They concluded that the bulk of long-term activated T cells in normal mice had not been committed to the production of IL-4 and, thus, their elimination did not diminish the IL-4–producing potential of the animal. By contrast, shutting off the supply of new T cells removed cells that had the capacity to develop into IL-4 producers.

Although these studies indicate the potential of T cells to develop into IL-4 producers and outline some conditions under which they may do so, they leave open the question of the physiologic control of development of cells into an IL-4–producing phenotype. It is known that certain types of infection predispose to the development of responses dominated by IL-4–producing T cells. For example, mice infected with *Schistosoma mansoni* began to produce large amounts of IL-4 and IL-5 when the adult worms began egg laying.[77] There is indirect evidence that indicates that infection with the nematodes *Nippostrongylus brasiliensis*[116] or *Heligmosomoides polygirus* (Urban JF Jr, Katona IM, Paul WE, Finkelman FD: Interleukin-4 is important in protective immunity to a gastrointestinal nematode infection in mice. Proc Natl Acad Sci USA, in press) also preferentially causes IL-4–producing T cells to emerge. A critical issue is to ascertain the cellular and molecular basis for the induction of this pattern of lymphokine production. Although considerable attention has been given to distinctive populations of APC in regulating this event, no definitive information is yet available on this subject.

IL-4 production by mast cells. A second major set of cells capable of producing cytokines in response to cross-linkage of "immune recognition receptors" are mast cells. This was initially appreciated from the finding that many Abelson murine leukemia virus (Ab-MuLV)-transformed mast cells constitutively produce IL-4, and some produce IL-3 and GM-CSF.[98] Factor-dependent mast cell lines can be stimulated by cross-linkage of high-affinity Fcε receptors to secrete IL-4, as well as a series of other lymphokines including IL-3, GM-CSF, IL-5, IL-6, IL-1, TNF, and several of the macrophage inflammatory peptides.[22,118,119] The production of IL-4 by such cells in response to cross-linkage of FcεRI has antigen dose/response characteristics similar to the release of histamine by such cells. High concentrations of antigen cause high degrees of cross-linkage that inhibit both histamine release and lymphokine production. In general, the inhibitory phase of the lymphokine production response is observed at lower concentrations of antigen than is true for histamine release.[22]

In normal spleen and bone marrow cell suspensions, a population of cells exist that lack both B- and T-cell markers and that expresses a high-affinity receptor for IgE. These cells produce IL-4 in response to cross-linkage of their FcεR as well as to cross-linkage of FcγRII or to elevation of intracellular calcium concentrations by calcium ionophores.[120] Although these cells are relatively rare (in the spleen they constitute 1% to 2% of the cells that lack B- or T-cell markers; in the bone marrow ~1% of all cells), when appropriately activated they produce very large amounts of IL-4. The nature of these cells has not been completely resolved. They have been extensively enriched by fluorescence-activated cell sorting; as many as ⅕ of these cells produce IL-4 in response to FcεR cross-linkage. The fact that they express a high-affinity FcεR, presumably FcεRI, suggests that they are either in the mast cell or basophil lineage. Efforts to clarify this issue are now underway. It has been estimated that on a per-cell basis they may produce greater than 100 times more IL-4 than long-term, factor-dependent mast cell lines (Seder RA, Plaut M, Paul WE: submitted for publication). Production of IL-4 by these cells is markedly enhanced if they are pretreated with IL-3.[121] This pretreatment can be performed in vitro or in vivo. Furthermore, infection with the nematode parasite *Nippostrongylus brasiliensis* or injection of anti-IgD antibodies, treatments known to markedly enhance serum IgE levels, cause striking increases in the number and in the IL-4–producing capacity of $Fc\epsilon R^+$ spleen cells.[122] The potential physiologic role of lymphokine production by these cells and the issue of whether human cells of mast cell and/or basophil lineage produce lymphokines in response to cross-linkage of FcεR are issues that require extensive study.

PATHOPHYSIOLOGIC SIGNIFICANCE OF PRODUCTION OF SPECIFIC PATTERNS OF LYMPHOKINES

As already alluded to, the pattern of lymphokines produced can vary considerably in response to different types of immunization. This distinction appears to have considerable pathophysiologic significance. For example, most strains of mice infected with *Leishmania major* organisms develop a transient infection; T-cell clones from such mice specific for Leishmanial antigens generally produce IL-2 and IFNγ but not IL-4.[76] However, in one strain the infection is progressive and is eventually lethal. In these animals, T-cell clones that are obtained produce IL-4 rather than IL-2 and IFNγ. In such animals, the progressive disease can be reversed by treatment with anti–IL-4 antibody,[123] indicating that IL-4, either directly or indirectly, causes an immune response that fails to protect the animal and, indeed, masks or prevents a response that would be protective.

Infection with *S mansoni* leads to a response that is initially dominated by the T-cell production of IFNγ. However, after mature parasites begin to lay eggs, a striking induction of a response in which IL-4 and IL-5 are prominent is observed.[77] Pretreatment of mice by immuniza-

tion with irradiated schistosomes or egg antigens can prevent the appearance of the IL-4/IL-5 dominant response and is also protective against the development of prolonged infection.

Thus, these results indicate that the pattern of lymphokines produced in a T-cell response have a profound effect on the protective nature of that response. They suggest that in both natural immunization and in immunization with vaccines, the use of agents that will influence the type of response that will emerge can be of central significance to the overall effectiveness of the immunization. A detailed understanding of the processes that control the pattern of lymphokines expressed under any specific set of conditions could be of immense value in designing appropriate immunization strategies for optimal protective value.

CONCLUSION

The growing understanding of the biologic and pathophysiologic roles of IL-4 and the other members of the set of immune recognition-induced lymphokines indicate that these molecules are key to the regulation of protective immune responses. The wide range of functions of IL-4 and its congeners mandate that their in vivo regulation must be complex. Understanding these functions in detail will provide many opportunities for intervention in pathophysiologic processes. Among the most promising possibilities is the control of IL-4 function to prevent or ameliorate IgE-mediated allergic conditions. Strategies to neutralize IL-4, to block its production, or to inhibit its action all need to be explored to determine whether real clinical opportunities exist. Although the understanding of IL-4 function in vivo in promoting IgE production is more advanced than our understanding of other physiologic functions of IL-4, that is by no means a guarantee that other equally dramatic and important physiologic functions may not exist. More detailed understanding of these phenomena may provide additional therapeutic opportunities. Furthermore, IL-4 itself may prove to be effective as a pharmacologic agent. The observations that IL-4 has striking antitumor activities raise the possibility that IL-4 or potential small molecule agonists may be potent biologic agents to enhance immune elimination of certain tumor cells.

ACKNOWLEDGMENT

I thank the many colleagues, both in the Laboratory of Immunology and elsewhere, who have worked on the IL-4 problem with me in the decade since the discovery of this lymphokine. In particular, I recognize the superb assistance of three remarkable technicians, Jane Hu-Li, Carol Kinzer, and Cynthia Watson, who have played a major role in much of the work described here. The expert editorial assistance of Shirley Starnes is gratefully acknowledged.

REFERENCES

1. Paul WE: Pleiotropy and redundancy: T cell-derived lymphokines in the immune response. Cell 57:521, 1989

2. Ben-Sasson SZ, Le Gros G, Conrad DH, Finkelman FD, Paul WE: IL-4 production by T cells from naive donors. IL-2 is required for IL-4 production. J Immunol 145:1127, 1990

3. Poo WJ, Conrad L, Janeway CAJ: Receptor-directed focusing of lymphokine release by helper T cells. Nature 332:378, 1988

4. Paul WE: Interleukin 4/B cell stimulatory factor 1: One lymphokine, many functions. FASEB J 1:456, 1988

5. Finkelman FD, Holmes J, Katona IM, Urban JF Jr, Beckmann MP, Park LS, Schooley KA, Coffman RL, Mosmann TR, Paul WE: Lymphokine control of *in vivo* immunoglobulin isotype selection. Annu Rev Immunol 8:303, 1990

6. Finkelman FD, Katona I, Urban J, Snapper C, Ohara J, Paul WE: Suppression of *in vivo* polyclonal IgE responses by monoclonal antibody to the lymphokine BSF-1. Proc Natl Acad Sci USA 83:9765, 1986

7. Tepper RI, Levinson DA, Stanger BZ, Campos-Torres J, Abbas AK, Leder P: IL-4 induces allergic-like inflammatory disease and alters T cell development in transgenic mice. Cell 62:457, 1990

8. Howard M, Farrar J, Hilfiker M, Johnson B, Takatsu K, Hamaoka T, Paul WE: Identification of a T-cell derived B-cell growth factor distinct from interleukin 2. J Exp Med 155:914, 1982

9. Noelle R, Krammer PH, Ohara J, Uhr JW, Vitetta ES: Increased expression of Ia antigens on resting B cells: A new role for B cell growth factor. Proc Natl Acad Sci USA 81:6149, 1984

10. Rabin E, Ohara J, Paul WE: B cell stimulatory factor (BSF)-1 activates resting B cells. Proc Natl Acad Sci USA 82:2935, 1985

11. Oliver K, Noelle RJ, Uhr JW, Krammer PH, Vitetta ES: B-cell growth factor (B-cell growth factor 1 or B-cell stimulating factor, provisional 1) is a differentiation factor for resting B cells and may not induce growth. Proc Natl Acad Sci USA 82:2465, 1985

12. Paul WE: Nomenclature of lymphokines which regulate B-lymphocytes. Mol Immunol 21:343, 1984

13. Lee F, Yokota T, Otsuka T, Meyerson P, Villaret D, Coffman R, Mosmann T, Rennick D, Roehm N, Smith C, Zlotnick A, Arai K: Isolation and characterization of a mouse interleukin cDNA clone that expresses B-cell stimulatory factor 1 activities and T-cell– and mast-cell–stimulating activities. Proc Natl Acad Sci USA 83:2061, 1986

14. Noma Y, Sideras T, Naito T, Bergstedt-Lindqvist S, Azuma C, Severinson E, Tanabe T, Kinashi T, Matsuda F, Yaoita T, Honjo T: Cloning of cDNA encoding the murine IgG1 induction factor by a novel strategy using SP6 promoter. Nature 319:640, 1986

15. D'Eustachio P, Brown M, Watson C, Paul WE: The IL-4 gene maps to chromosome 11, near the gene encoding IL-3. J Immunol 141:3067, 1988

16. Le Beau MM, Lemons ERS, Espinosa R III, Larson RA, Arai N, Rowley JD: IL-4 and IL-5 map to human chromosome 5 in a region encoding growth factors and receptors and are deleted in myeloid leukemias with a del(5q). Blood 73:647, 1988

17. Takahashi M, Yoshida MC, Satoh H, Hilgers J, Yaoita Y, Honjo T: Chromosomal mapping of the mouse IL-4 and human IL-5 genes. Genomics 4:47, 1989

18. Lee JS, Campbell HD, Kozak CA, Young IG: The IL-4 and IL-5 genes are closely linked and are part of a cytokine gene cluster on mouse chromosome 11. Somat Cell Mol Genet 15:143, 1989

19. van Leeuwen BH, Martinson ME, Webb GC, Young IG: Molecular organization of the cytokine gene cluster, involving the human IL-3, IL-4, IL-5, and GM-CSF genes, on human chromosome 5. Blood 73:1142, 1989

20. Bazan JF: Haemopoietic receptors and helical cytokines. Immunol Today 11:350, 1990

21. Mosmann TR, Coffman RL: TH1 and TH2 cells: Different patterns of lymphokine secretion lead to different functional properties. Annu Rev Immunol 7:145, 1989

22. Plaut M, Pierce JH, Watson CJ, Hanley-Hyde J, Nordan RP, Paul WE: Mast cell lines produce lymphokines in response to cross linkage of FcεRI or to calcium ionophores. Nature 339:64, 1989

23. Ohara J, Lahet S, Inman J, Paul WE: Partial purification of murine B-cell stimulatory factor (BSF)-1. J Immunol 135:2518, 1985

24. Grabstein K, Eisenman J, Mochizuki D, Shanebeck K, Conlon P, Hopp T, March C, Gillis S: Purification to homogeneity of B cell stimulating factor. J Exp Med 163:1405, 1986

25. Ohara J, Coligan J, Zoon K, Maloy WL, Paul WE: High efficiency purification and chemical characterization of B cell stimulatory factor-1/interleukin-4. J Immunol 139:1127, 1987

26. Yokota T, Otsuka T, Mosmann T, Banchereau J, Defrance T, Blanchard D, de Vries JE, Lee F, Arai K: Isolation and characterization of a human interleukin cDNA clone homologous to mouse B-cell stimulatory factor 1 that expresses B-cell– and T-cell–stimulatory activities. Proc Natl Acad Sci USA 83:5894, 1986

27. Le HV, Ramanathan L, Labdon JE, Mays-Ichinco CA, Syto R, Arai N, Hoy P, Takebe Y, Nagabhushan TL, Trotta PP: Isolation and characterization of multiple variants of recombinant human interleukin 4 expressed in mammalian cells. J Biol Chem 263:10817, 1988

28. Ohara J, Paul WE: B cell stimulatory factor (BSF)-1: Production of a monoclonal antibody and molecular characterization. Nature 315:333, 1985

29. Le Beau MM, Pettenati MJ, Lemons RS, Diaz MO, Westbrook CA, Larson RA, Sherr CJ, Rowley JD: Assignment of the GM-CSF CSF-1 and FMS genes to human chromosome 5 provides evidence for linkage of a family of genes regulating hematopoiesis and for their involvement in the deletion (5q) in myeloid disorders. Cold Spring Harbor Symp Quant Biol 51:899, 1986

30. Otsuka T, Villaret D, Yokota T, Takebe Y, Lee F, Arai N, Arai K: Structural analysis of the mouse chromosomal gene encoding interleukin 4 which expresses B cell, T cell and mast cell stimulating activities. Nucleic Acids Res 15:333, 1987

31. Arai N, Nomura D, Villaret D, De Waal Malefijt R, Seiki M, Yoshida M, Minoshima S, Fukuyama R, Maekawa M, Kudoh J, Shimizu N, Yokota K, Abe E, Yokota T, Takebe Y, Arai K: Complete nucleotide sequence of the chromosomal gene for human interleukin 4 and its expression. J Immunol 142:274, 1989

32. Shaw G, Kamen R: A conserved AU sequence from the 3′ untranslated region of GM-CSF mRNA mediates selective mRNA degradation. Cell 46:659, 1986

33. Ohara J, Paul WE: Receptors for B cell stimulatory factor-1 expressed on cells of hematopoietic lineage. Nature 325:537, 1987

34. Park L, Friend D, Grabstein K, Urdal D: Characterization of the high-affinity cell-surface receptor for murine B cell stimulating factor. Proc Natl Acad Sci USA 84:1669, 1987

35. Lowenthal J, Castle B, Schreurs J, Rennick D, Arai N, Hoy P, Takebe Y, Howard M: Expression of high affinity receptors for interleukin 4 on hemopoietic and non-hemopoietic cells. J Immunol 140:456, 1988

36. Park L, Friend D, Sassenfeld H, Urdal D: Characterization of the human B cell stimulatory factor 1 receptor. J Exp Med 166:476, 1987

37. Ohara J, Paul WE: Up-regulation of interleukin 4/B-cell stimulatory factor 1 receptor expression. Proc Natl Acad Sci USA 85:8221, 1988

38. Hu-Li J, Ohara J, Watson C, Tsang W, Paul WE: Derivation of a T cell line that is highly responsive to IL-4 and IL-2 (CT.4R) and of an IL-2 hyporesponsive mutant of that line (CT.4S). J Immunol 142:800, 1989

39. Galizzi JP, Zuber CE, Cabrillat H, Djossou O, Banchereau J: Internalization of human interleukin 4 and transient down-regulation of its receptor in the CD23-inducible Jijoye cells. J Biol Chem 264:6984, 1989

40. Keegan AD, Beckmann MP, Park LS, Paul WE: The interleukin-4 receptor: Biochemical characterization of IL-4–binding molecules in a T cell line expressing large numbers of receptors. J Immunol 1990 (in press)

41. Mosely B, Beckmann MP, March CJ, Idzerda RL, Gimpel SD, VandenBos T, Friend D, Alpert A, Anderson D, Jackson J, Wignall J, Smith C, Gallis B, Sims JE, Urdal DL, Widmer MB, Cosman D, Park LS: The murine interleukin-4 receptor: Molecular cloning and characterization of secreted and membrane forms. Cell 59:335, 1989

42. Harada N, Castle BE, Gorman DM, Itoh N, Schreurs J, Barrett RL, Howard M, Miyajima A: Expression cloning of a cDNA encoding the murine interleukin 4 receptor based on ligand binding. Proc Natl Acad Sci USA 87:857, 1990

43. Idzerda RL, March CJ, Mosely B, Lyman SD, VandenBos T, Gimpel SD, Din WS, Grabstein KH, Widmer MB, Park LS, Cosman D, Beckmann MP: Human interleukin 4 receptor confers biological responsiveness and defines a novel receptor superfamily. J Exp Med 171:861, 1990

44. Galizzi J-P, Zuber CE, Harada N, Gorman DM, Djossou O, Kastelein R, Banchereau J, Howard M, Miyajima A: Molecular cloning of a cDNA encoding the human interleukin 4 receptor. Int Immunol 2:669, 1990

45. Bazan JF: A novel family of growth factor receptors: A common binding domain in the growth hormone, prolactin erythropoietin and IL-6 receptors, and the p75 IL-2 receptor β-chain. Biochem Biophys Res Commun 164:788, 1989

46. D'Andrea AD, Fasman GD, Lodish HF: Erythropoietin receptor and interleukin-2 receptor β chain: A new receptor family. Cell 58:1023, 1989

47. Fernandez-Botran R, Vitetta ES: A soluble, high affinity, interleukin-4–binding protein is present in the biological fluids of mice. Proc Natl Acad Sci USA 87:4202, 1990

48. Fanslow WP, Clifford K, VandenBos T, Teal A, Armitage RJ, Beckmann MP: A soluble form of the IL-4 receptor in biological fluids (submitted)

49. Mizuguchi J, Beaven MA, Ohara J, Paul WE: BSF-1 action on resting B cells does not require elevation of inositol phospholipid metabolism or increased $[Ca^+]_i$. J Immunol 137:2215, 1986

50. Rabin EM, Mond JJ, Ohara J, Paul WE: B cell stimulatory factor (BSF)-1 prepares resting B cells to enter S phase in response to anti-IgM and to lipopolysaccharide. J Exp Med 164:517, 1986

51. Kikutani H, Inui S, Sato R, Barsumian E, Owaki H, Yamasaki K, Kalaho T, Uchibayashi N, Hardy R, Hirano T, Taunasawa S, Sakiyama S, Suemura M, Kishimoto T: Molecular structure of human lymphocyte receptor for immunoglobulin. Cell 47:657, 1986

52. Matis LA, Glimcher LH, Paul WE, Schwartz RH: The magnitude of response of histocompatibility-restricted T cell clones is a function of the product of the concentrations of antigen and Ia molecules. Proc Natl Acad Sci 80:6019, 1983

53. Keegan AD, Snapper CM, Van Dusen R, Paul WE, Conrad DH: Superinduction of the murine B cell FcεRII by T helper cell clones. J Immunol 142:3868, 1989

54. Snapper CM, Hooley JJ, Atasoy U, Finkelman FD, Paul WE: Differential regulation of murine B cell FcγRII expression by $CD4^+$ T helper subsets. J Immunol 143:2133, 1989

55. Kehry MR, Yamashita LC: Low-affinity IgE receptor (CD23)

function on mouse B cells: Role in IgE-dependent antigen focusing. Proc Natl Acad Sci USA 86:7556, 1989

56. Snapper CM, Hornbeck P, Atasoy U, Pereira G, Paul WE: Interleukin 4 induces membrane Thy-1 expression on normal murine B cells. Proc Natl Acad Sci USA 85:6107, 1988

57. Defrance T, Vandervliet B, Aubry J-P, Takebe Y, Arai N, Miyajima A, Yokota T, Lee F, Arai K, de Vries JE, Banchereau J: B cell growth-promoting activity of recombinant human interleukin-4. J Immunol 139:1135, 1987

58. Coffman RL, Ohara J, Bond MW, Carty J, Zlotnick A, Paul WE: B cell stimulatory factor-1 enhances the IgE response of lipopolysaccharide-activated B cells. J Immunol 136:4538, 1986

59. Vitetta ES, Ohara J, Myers C, Layton J, Krammer PH, Paul WE: Serologic, biochemical and functional identity of B cell stimulatory factor-1 and B cell differentiation factor for IgG_1. J Exp Med 162:1726, 1985

60. Lebman DA, Coffman RL: Interleukin 4 causes isotype switching to IgE in T cell-stimulated clonal B cell cultures. J Exp Med 168:853, 1988

61. Del Prete G, Maggi E, Parronchi P, Chetrien I, Tiri A, Macchia D, Ricci M, Banchereau J, de Vries J, Romagnani S: IL-4 is an essential factor in the IgE synthesis induced in vitro by human T cell clones and their supernatants. J Immunol 140:4193, 1988

62. Pene J, Rousset F, Briere F, Chretien I, Bonnefoy JY, Spits H, Yokota T, Arai N, Arai K, Banchereau J, de Vries JE: IgE production by normal human lymphocytes is induced by interleukin 4 and suppressed by interferon γ and α and prostaglandin E_2. Proc Natl Acad Sci USA 85:6880, 1988

63. Finkelman FD, Katona IM, Urban JF Jr, Holmes J, Ohara J, Tung AS, Sample JvG, Paul WE: IL-4 is required to generate and sustain *in vivo* IgE responses. J Immunol 141:2335, 1988

64. Snapper CM, Paul WE: B cell stimulatory factor-1 (interleukin 4) prepares resting murine B cells to secrete IgG1 upon subsequent stimulation with bacterial lipopolysaccharide. J Immunol 139:10, 1987

65. Snapper CM, Finkelman FD, Paul WE: Differential regulation of IgG1 and IgE synthesis by interleukin 4. J Exp Med 167:183, 1988

66. Stavnezer J, Radcliffe G, Lin YC, Nietupski J, Berggreu L, Sitia R, Severinson E: Immunoglobulin heavy-chain switching may be directed by prior induction of transcripts from constant-region genes. Proc Natl Acad Sci USA 85:7704, 1988

67. Berton MT, Uhr JW, Vitetta ES: Synthesis of germ-line gamma 1 immunoglobulin heavy-chain transcripts in resting B cells: Induction by interleukin 4 and inhibition by interferon gamma. Proc Natl Acad Sci USA 86:2829, 1989

68. Lutzker S, Rothman P, Pollock R, Coffman R, Alt FW: Mitogen- and IL-4–regulated expression of germ-line Ig gamma 2b transcripts: Evidence for directed heavy chain class switching. Cell 53:177, 1988

69. Snapper CM, Paul WE: Interferon gamma and B cell stimulatory factor-1 reciprocally regulate Ig isotype production. Science 236:944, 1987

70. Rothman P, Lutzker S, Cook W, Coffman R, Alt FW: Mitogen plus interleukin 4 induction of epsilon transcripts in B lymphoid cells. J Exp Med 168:2385, 1988

71. Snapper CM, Peschel C, Paul WE: IFN-γ stimulates IgG2a secretion by murine B cells stimulated with bacterial lipopolysaccharide. J Immunol 140:2121, 1988

72. Coffman RL, Lebman DA, Shrader B: Transforming growth factor beta specifically enhances IgA production by lipopolysaccharide-stimulated murine B lymphocytes. J Exp Med 170:1039, 1989

73. Gerondakis S: Structure and expression of murine germ-line immunoglobulin epsilon heavy chain transcripts induced by interleukin 4. Proc Natl Acad Sci USA 87:1581, 1990

74. Boothby M, Liou HC, Glimcher LH: Differences in DNA sequence specificity among MHC class II X box binding proteins. J Immunol 142:1005, 1989

75. Coffman RL, Carty J: A T-cell activity that enhances polyclonal IgE production and its inhibition by interferon-γ. J Immunol 136:949, 1986

76. Heinzel FP, Sadick MD, Holaday BJ, Coffman RL, Locksley RM: Reciprocal expression of interferon gamma or interleukin 4 during the resolution or progression of murine leishmaniasis. Evidence for expansion of distinct helper T cell subsets. J Exp Med 169:59, 1989

77. Scott P, Natovitz P, Coffman RL, Pearce E, Sher A: Immunoregulation of cutaneous leishmaniasis. T cell lines that transfer protective immunity or exacerbation belong to different T helper subsets and respond to distinct parasite antigens. J Exp Med 168:1675, 1988

78. Romagnani S, Maggi E, Del Prete GF, Parronchi P, Macchia D, Tiri A, Ricci M: Role of interleukin 4 and gamma interferon in the regulation of human IgE synthesis: Possible alterations in atopic patients. Int Arch Allergy Appl Immunol 88:111, 1989

79. Whitlock CA, Witte ON: Long-term culture of murine bone marrow precursors of B lymphocytes. Methods Enzymol 150:275, 1987

80. Peschel C, Green I, Paul WE: Preferential proliferation of immature B lineage cells in long-term stromal cell-dependent cultures with IL-4. J Immunol 142:1558, 1989

81. Kinashi T, Inaba K, Tsubata T, Tashiro K, Palacios R, Honjo T: Differentiation of an interleukin 3-dependent precursor B-cell clone into immunoglobulin-producing cells in vitro. Proc Natl Acad Sci USA 85:4473, 1988

82. Hu-Li J, Shevach EM, Mizuguchi J, Ohara J, Mosmann T, Paul WE: B cell stimulatory factor-1 (interleukin 4) is a potent costimulant for normal resting T lymphocytes. J Exp Med 165:157, 1987

83. Kurt-Jones EA, Hamberg S, Ohara J, Paul WE, Abbas AK: Heterogeneity of helper/inducer T lymphocytes. I. Lymphokine production and lymphokine responsiveness. J Exp Med 166:1774, 1987

84. Greenbaum LA, Horowitz JB, Woods A, Pasqualini T, Reich EP, Bottomly K: Autocrine growth of CD4+ T cells. Differential effects of IL-1 on helper and inflammatory T cells. J Immunol 140:1555, 1988

85. Fernandez-Botran R, Sanders VM, Mosmann TR, Vitetta ES: Lymphokine-mediated regulation of the proliferative response of clones of T helper 1 and T helper 2 cells. J Exp Med 168:543, 1988

86. Fiorentino DF, Bond MW, Mosmann TR: Two types of mouse T helper cell. IV. Th2 clones secrete a factor that inhibits cytokine production by Th1 clones. J Exp Med 170:2081, 1989

87. Mosmann TR, Cherwinski H, Bond MW, Giedlin MA, Coffman RL: Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. J Immunol 136:2348, 1986

88. Mueller DL, Jenkins MK, Schwartz RH: Clonal expansion versus functional clonal inactivation: A costimulatory signalling pathway determines the outcome of T cell antigen receptor occupancy. Annu Rev Immunol 7:445, 1989

89. Widmer MB, Grabstein KH: Regulation of cytolytic T-lymphocyte generation by B-cell stimulatory factor. Nature 326:795, 1987

90. Trenn G, Takayama H, Hu-Li J, Paul WE, Sitkovsky MV: B cell stimulatory factor 1 (IL-4) enhances the development of

cytotoxic T cells from Lyt-2+ resting murine T lymphocytes. J Immunol 140:1101, 1988

91. Plum J, De Smedt M, Leclercq G, Tison B: Inhibitory effect of murine recombinant IL-4 on thymocyte development in fetal thymus organ cultures. J Immunol 145:1066, 1990

92. McInnes A, Rennick DM: Interleukin 4 induces cultured monocytes/macrophages to form giant multinucleated cells. J Exp Med 167:598, 1988

93. Jansen JH, Wientjens GJ, Fibbe WE, Willemze R, Kluin-Nelemans HC: Inhibition of human macrophage colony formation by interleukin 4. J Exp Med 170:577, 1989

94. Crawford RM, Finbloom DS, Ohara J, Paul WE, Meltzer MS: BSF-1: A new macrophage activation factor: B cell stimulatory factor-1 (interleukin-4) activates macrophages for increased tumoricidal activity and expression of Ia antigens. J Immunol 139:135, 1987

95. Belosevic M, Davis CE, Meltzer MS, Nacy CA: Regulation of activated macrophage antimicrobial activities. Identification of lymphokines that cooperate with IFN-gamma for induction of resistance to infection. J Immunol 141:890, 1988

96. Schrader JW: The panspecific hemopoietin of activated T lymphocytes (interleukin-3). Annu Rev Immunol 4:205, 1986

97. Mosmann TR, Bond MW, Coffman RL, Ohara J, Paul WE: T cell and mast cell lines respond to B cell stimulatory factor-1. Proc Natl Acad Sci USA 83:5654, 1986

98. Brown MA, Pierce JH, Watson CJ, Falco J, Ihle JN, Paul WE: B cell stimulatory factor-1/interleukin-4 mRNA is expressed by normal and transformed mast cells. Cell 50:809, 1987

99. Peschel C, Paul WE, Ohara J, Green I: Effects of B-cell stimulatory factor-1/interleukin-4 on hematopoietic progenitor cells. Blood 70:254, 1987

100. Peschel C, Green I, Paul WE: Interleukin-4 induces a substance in bone marrow stromal cells which reversibly inhibits factor-dependent and factor-independent cell proliferation. Blood 73:1130, 1989

101. Tepper RI, Pattengale PK, Leder P: Murine interleukin-4 displays potent anti-tumor activity in vivo. Cell 57:503, 1989

102. Forni G, Giovarelli M, Bosco MC, Caretto P, Modesti A, Boraschi D: Lymphokine-activated tumor inhibition: Combinatory activity of a synthetic nonapeptide from interleukin-1, interleukin-2, interleukin-4, and interferon-gamma injected around tumor-draining lymph nodes. Int J Cancer Suppl 4:62, 1989

103. Kelso A, Gough NM: Coexpression of granulocyte-macrophage colony-stimulating factor, gamma interferon, and interleukins 3 and 4 is random in murine alloreactive T-lymphocyte clones. Proc Natl Acad Sci USA 85:9189, 1988

104. Firestein GS, Roeder WD, Laxer JA, Townsend KS, Weaver CT, Hom JT, Linton J, Torbett BE, Glasebrook AL: A new murine CD4+ T cell subset with an unrestricted cytokine profile. J Immunol 143:518, 1989

105. Street NE, Schumacher JH, Fong TA, Bass H, Fiorentino DF, Leverah JA, Mosmann TR: Heterogeneity of mouse helper T cells. Evidence from bulk cultures and limiting dilution cloning for precursors of Th1 and Th2 cells. J Immunol 144:1629, 1990

106. Del Prete G, Maggi E, Parronchi P, Chretien I, Tiri A, Macchia D, Ricci M, Banchereau J, De Vries J, Romagnani S: IL-4 is an essential factor for the IgE synthesis induced in vitro by human T cell clones and their supernatants. J Immunol 140:4193, 1988

107. O'Hehir RE, Bal V, Quint D, Moqbel R, Kay AB, Zanders ED, Lamb JR: An in vitro model of allergen-dependent IgE synthesis by human B lymphocytes: Comparison of the response of an atopic and a non-atopic individual to *Dermatophagoides* spp. (house dust mite). Immunology 66:499, 1989

108. Wierenga EA, Snoek M, de Groot C, Chretien I, Bos JD, Jansen HM, Kapsenberg ML: Evidence for compartmentalization of functional subsets of CD2+ T lymphocytes in atopic patients. J Immunol 144:4651, 1990

109. Powers GD, Abbas AK, Miller RA: Frequencies of IL-2– and IL-4–secreting T cells in naive and antigen-stimulated lymphocyte populations. J Immunol 140:3352, 1988

110. Swain SL, McKenzie DT, Weinberg AD, Hancock W: Characterization of T helper 1 and 2 cell subsets in normal mice. Helper T cells responsible for IL-4 and IL-5 production are present as precursors that require priming before they develop into lymphokine-secreting cells. J Immunol 141:3445, 1988

111. Sideras P, Funa K, Zalcberg-Quintana I, Xanthopoulos KG, Kisielow P, Palacios R: Analysis by in situ hybridization of cells expressing mRNA for interleukin 4 in the developing thymus and in peripheral lymphocytes from mice. Proc Natl Acad Sci USA 85:218, 1988

112. Sander B, Cardell S, Heremans H, Andersson U, Moller G: Detection of individual interleukin 4- and gamma interferon-producing murine spleen cells after activation with T-cell mitogens. Scand J Immunol 30:315, 1989

113. Carding SR, West J, Woods A, Bottomly K: Differential activation of cytokine genes in normal CD4-bearing T cells is stimulus dependent. Eur J Immunol 19:231, 1989

114. Seder RA, Le Gros G, Ben-Sasson SZ, Urban J Jr, Finkelman FD, Paul WE: Increased frequency of IL-4 producing T cells as a result of polyclonal priming. Use of a single cell assay to detect IL-4 producing cells. Eur J Immunol 1991 (in press)

115. Ben-Sasson SZ, Le Gros G, Conrad DH, Finkelman FD, Paul WE: IL-4 production by T cells from naive donors. IL-2 is required for IL-4 production. J Immunol 145:1990 (in press)

116. Le Gros G, Ben-Sasson SZ, Seder R, Finkelman FD, Paul WE: Generation of IL-4–producing cells in vivo and in vitro. IL-2 and IL-4 are required for in vitro generation of IL-4–producing cells. J Exp Med 172:921, 1990

117. Swain SL, Weinberg AD, English M: CD4+ T cell subsets. Lymphokine secretion of memory cells and of effector cells that develop from precursors in vitro. J Immunol 144:1788, 1990

118. Wodnar-Filipowicz A, Heusser CH, Moroni C: Production of the haemopoietic growth factors GM-CSF and interleukin-3 by mast cells in response to IgE receptor-mediated activation. Nature 339:150, 1989

119. Burd PR, Rogers HW, Gordon JR, Martin CA, Jayaraman S, Wilson SD, Dvorak AM, Galli SJ, Dorf ME: Interleukin 3-dependent and -independent mast cells stimulated with IgE and antigen express multiple cytokines. J Exp Med 170:245, 1989

120. Ben-Sasson S, Le Gros G, Conrad DH, Finkelman FD, Paul WE: Cross-linking Fc receptors stimulate splenic non-B, non-T cells to secrete interleukin 4 and other lymphokines. Proc Natl Acad Sci USA 87:1421, 1990

121. Le Gros G, Ben-Sasson SZ, Conrad DH, Clark-Lewis I, Finkelman FD, Plaut M, Paul WE: Interleukin-3 promotes production of IL-4 by splenic non-B, non-T cells in response to Fc receptor cross-linkage. J Immunol 145:2500, 1990

122. Conrad DH, Ben-Sasson SZ, Le Gros G, Finkelman FD, Paul WE: Infection with *Nippostrongylus Brasiliensis* or injection of anti-IgD antibodies markedly enhances Fc-receptor-mediated interleukin 4 production by non-B, non-T cells. J Exp Med 171:1497, 1990

123. Sadick MD, Heinzel FP, Holaday BJ, Pu RT, Dawkins RS, Locksley RM: Cure of murine leishmaniasis with anti-interleukin 4 monoclonal antibody. Evidence for a T cell-dependent, interferon gamma-independent mechanism. J Exp Med 171:115, 1990

blood 1991 77: 1859-1870

Interleukin-4: a prototypic immunoregulatory lymphokine

WE Paul

Blood (print ISSN 0006-4971, online ISSN 1528-0020), is published weekly by the American Society of Hematology, 2021 L St, NW, Suite 900, Washington DC 20036.