Journal of Allergy and Clinical Immunology
Volume 119, Issue 6, June 2007, Pages 1303-1310

doi:10.1016/j.jaci.2007.03.048 Cite or Link Using DOI

Reviews and feature articles

Eosinophil trafficking in allergy and asthma

Helene F. Rosenberg MD[a], Simon Phipps PhD[b] and Paul S. Foster PhD[b]

[a]From the Laboratory of Allergic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda

[b]Center for Asthma and Respiratory Diseases, School of Biomedical Sciences, University of Newcastle and Hunter Medical Research Institute

Received 14 February 2007; revised 27 March 2007; accepted 28 March 2007. Bethesda, Md, and Newcastle, Australia
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Blood eosinophilia and tissue eosinophilia are characteristic features of allergic inflammation and asthma, conditions associated with prominent production of T_H2 cytokines IL-4, IL-5, and IL-13. In this review, we will consider recent advances in our understanding of the molecular mechanisms that promote expansion and differentiation of eosinophil progenitors in bone marrow, eosinophil recruitment in response to chemokine receptor 3 agonists eosinophil transit mediated by specific ligand-receptor interactions, and prolonged survival of eosinophils in peripheral tissues. Novel rational therapies including antiselectin and antichemokine receptor modalities designed to block eosinophil development and trafficking are

discussed, together with the implications of recent clinical studies that have evaluated the efficacy of humanized anti–IL-5 mAb therapy.

Key words: Inflammation; ILs; cytokines; hematopoiesis

Abbreviations: IL-5R, IL-5 receptor; PSGL, P-selectin glycoprotein ligand; Siglec, Sialic acid–binding Ig-like lectin; VCAM, Vascular cell adhesion molecule; VLA, Very late antigen

Article Outline

Human eosinophils are distinguished phenotypically by their bilobed nuclei and large acidophilic cytoplasmic granules (Fig 1). They are granulocytic leukocytes and share many features with neutrophils, including growth and development in the bone marrow. However, in contrast with neutrophils, which exit the bone marrow and reside in the bloodstream, eosinophils are tissue leukocytes and are found primarily in the gastrointestinal tract under homeostatic conditions. During maturation, release into the bloodstream, and recruitment to tissues, eosinophils respond to signals from cytokines, chemokines, and other proinflammatory mediators via cell-specific receptors. Perhaps most interesting, despite >100 years of research, is that the evolutionary role and biological function of the human eosinophil remain subjects of profound controversy. Although peripheral blood and tissue eosinophilia are hallmarks of parasitic helminth infection, the way in which this benefits the host remains unclear.[1], [2] and [3] Likewise, although many studies have documented a role for eosinophils in the pathogenesis of acute and/or chronic asthma,[4], [5], [6] and [7] it is important to recognize that in this setting, eosinophils are participating in an aberrant response—that is, one that does not benefit the host in any direct fashion. Recent explorations directed at modeling the hygiene hypothesis[8], [9] and [10] may ultimately elucidate mechanisms of inflammatory balance that have evolved to confront endemic parasitism. Ultimately, these studies may provide novel insights into the nature of the eosinophil and its role in host defense.

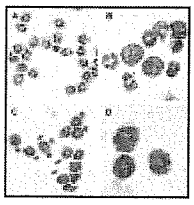
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Fig 1. Microscopic anatomy of mouse and human eosinophils. The mouse eosinophils (**A** and **B;** original magnifications, ×40, from bronchoalveolar lavage fluid, and ×100, from bone marrow, respectively) display typical morphology, including red staining granules and bilobed nucleus. The human eosinophils (**C** and **D;** original magnifications ×20 and ×63, both from peripheral blood) likewise display the prominent and clearly defined, slightly larger cytoplasmic granules. Cells were stained with a modified Giemsa preparation (Dade Behring AG, Dudingen, Switzerland). *B-D,* Courtesy of Drs Kimberly D. Dyer and Jennifer M. Moser, Laboratory of Allergic Diseases, NIAID.

A caveat on human versus mouse eosinophils

It is important to recognize that most of the findings to be discussed result from work performed in mouse models of disease. Although all investigations can suffer from overinterpretation of cross-species findings,[11] and [12] the problems are particularly large when examining results related to the eosinophil. Although mouse eosinophils, like human eosinophils, can be identified by red-staining granules in blood, bone marrow, and tissue preparations stained either with hematoxylin and eosin or Giemsa stains, there are profound differences between these cell types (Fig 1). Structurally, mouse eosinophil granules are smaller and less refractile. Among the granule proteins are the mouse eosinophil–associated ribonucleases, which are remarkably divergent (>50%) orthologs of human eosinophil–derived neurotoxin and eosinophil cationic protein,[13] and Charcot-Leyden crystal protein, a major human eosinophil component, cannot even be identified in the mouse genome. Furthermore, human eosinophils express the high-affinity IgE receptor, FcεRI, whereas mouse eosinophils do not. Likewise, mouse eosinophils express Siglec F, a sialic acid–binding Ig-like lectin that is a functional correlate, but likewise a highly divergent ortholog of human Siglec 8.[14], [15] and [16] Finally, and highly relevant to asthma and allergy models, mouse eosinophils have distinct responses to chemotactic cytokines[17] and have a very limited propensity to degranulate in our current models of disease, a feature that may be an inherent property of this cell type, or a limitation of the stimuli used to model specific disorders.[18] Although these limitations do not preclude studies of eosinophil trafficking in mice, it is crucial to keep in mind that human versus mouse parallels may need to be explored quite carefully, given issues of species

divergence.

Eosinophil expansion in response to allergic provocation

An allergic response is initiated *in situ* as a $CD4^+$ naive T lymphocyte responds to specific stimulation by developing into a T_H2 lymphocyte. T_H2 lymphocytes synthesize and secrete the cytokines IL-4, IL-13, and IL-5. IL-4 promotes eosinophilia indirectly via promoting autocrine development of T_H2 lymphocytes, and murine eosinophils themselves produce IL-4.[19] and [20] Human eosinophils express IL-4 receptor ∗ (IL-4R∗).[21] and [22] IL-4 also activates human vascular endothelial and respiratory epithelial cells to produce eosinophil chemoattractant cytokines[23] and directs IgE synthesis and mast cell growth and activation in both human and murine experimental systems.[24] and [25] IL-13 also promotes eosinophilia indirectly in mouse models, as it induces eotaxin production and has been identified as the major factor activating the respiratory epithelium, promoting the subsequent development of bronchospasm.[26] and [27]

The pivotal role of IL-5

The T_H2 cytokine IL-5 is a central factor mediating eosinophil expansion, priming, recruitment, and prolonged tissue survival in response to allergic stimuli. Originally identified as murine T-cell replacing factor, a B-cell growth factor and eosinophil differentiation factor, IL-5 is synthesized predominantly by T_H2 lymphocytes, but in smaller amounts by mast cells and eosinophils. IL-5 promotes differentiation of terminally committed human and murine eosinophil precursors in bone marrow.[28], [29], [30] and [31] The IL-5 receptor (IL-5R) includes a unique ligand-binding ∗-chain and β-chain shared with receptors for IL-3 and GM-CSF that mediates signaling via the Janus kinase (JAK)/signal transducer and activator of transcription pathway and via activation of phosphoinositol-3-kinase (PI-3Kinase).[32] The IL-5R is expressed on human eosinophils and eosinophil progenitors. In mice, IL-5R can be detected on eosinophils and their progenitors and on $CD5^+$ B1 lymphocytes,[33] which are prominent in both peritoneal and pleural cavities and produce IgM. Although IL-5 has a unique and specific impact on nearly all aspects of eosinophil biology, it works in synergy with IL-4, IL-13, and the family of chemotactic cytokines (or chemokines), termed *eotaxins*, to promote eosinophil-mediated inflammatory responses.

Eosinophil development in the bone marrow

Committed eosinophil progenitors are derived from pluripotent $CD34^+$ stem cells found in normal bone marrow. Of note, committed $CD34^+$IL-$5R^+$ eosinophil progenitor cells have also recently been

identified in murine lung tissue.[34] Studies of *ex vivo* bone marrow cultures have shown that eosinophils develop from these progenitors in response to GM-CSF, IL-3, and IL-5. When they are phenotypically mature, eosinophils are released from the bone marrow into the circulation.

As noted, IL-5 is a strong and specific stimulus for eosinophil differentiation. Allergic stimulation results in elevated levels of serum IL-5, which leads to the expansion (10-fold to 20-fold or even greater) of IL-5R$^+$ eosinophil progenitors in the bone marrow and their differentiation into mature cells for release into the peripheral blood (Fig 2). Despite its pivotal role in allergic eosinophilia, IL-5 is not required for eosinophil growth and differentiation under homeostatic conditions. IL-5 gene-deleted mice have mature eosinophils in bone marrow and peripheral blood, albeit in reduced numbers.[35] Interestingly, no IL-5–dependent, eosinophil-specific transcription factors or transcriptional events have been elucidated, although the transcription factors PU.1, CAAT enhancer binding proteins κ and ε, and GATA-1 have been implicated in eosinophil development.[36] and [37] The recent finding that deletion of a specific enhancer in the proximal promoter of the gene encoding the hematopoietic transcription factor, GATA-1, results in selective eosinophil ablation[38] suggests that there are more subtle GATA-mediated interactions directing eosinophil differentiation that remain to be elucidated.

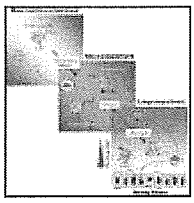

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Fig 2. Pathways of eosinophil trafficking. Committed eosinophil progenitors (CD34$^+$IL-5R$^+$) differentiate and mature in response to cytokines IL-3, IL-5, and GM-CSF. Both forms exit the bone marrow and enter the bloodstream, where they respond to chemotactic signals from allergen-challenged respiratory epithelial cells. Eosinophils exit the bloodstream in response to interactions mediated by cell surface selectins and integrins and chemokine signaling (Fig 3) and enter the lung tissue and airways. The cytokine IL-13 results in augmented expression of P-selectin and integrin VLA-4 eosinophils as well as increased P-selectin/VLA-4 dependent adherence of eosinophils to IL-4/IL-13–treated endothelial cells.[111] Both phenotypically mature and immature eosinophil precursors can enter the lung, where the latter can differentiate into mature effector cells.[34] Eosinophil viability is maintained by cytokines and chemokines present in the allergic lung.

Eosinophil transit into tissues

Mature eosinophils leave the bone marrow and are attracted to sites of allergic inflammation by the actions of proinflammatory chemokines, which are produced in response to allergic stimulation by endothelial and epithelial cells activated by, among other mediators, IL-4 and IL-13. Eosinophils express receptors for the CC group of chemokines (those that contain adjacent cysteines near the amino terminus). Several CC chemokines have been characterized as eosinophil chemoattractants, including RANTES (chemoattractant cytokine ligand 5 [CCL5]) and macrophage inflammatory protein 1* (CCL3), although neither of these is a specific eosinophil chemoattractant. The eotaxins, which interact with CCR3, 1 of the 7 transmembrane receptors common to all chemokines among other cell-signaling mediators, are the only known chemoattractants that interact uniquely with eosinophils. Eotaxin (or eotaxin-1) was first described by Williams and colleagues[39] as a novel component in bronchoalveolar lavage fluid of allergen sensitized guinea pigs that promoted specific recruitment of eosinophils (see review[40]). Eotaxin-1 is produced by epithelial cells in response to IL-4 and IL-13 via signal transducer and activator of transcription 6–dependent pathways[41] and functions synergistically with IL-5 to promote eosinophil recruitment to the allergen-challenged lung.[42] and [43] Several lines of evidence suggest that eotaxin-1 plays a central role in eosinophil recruitment to the lung tissue of patients with asthma.[44] and [45] Eotaxin-1 regulates homeostatic levels of eosinophils in the gastrointestinal tract.[46] Eotaxin also promotes eosinophil hematopoiesis[47] and [48] and is directly responsible for mobilizing eosinophil progenitors in the bone marrow for exit into the peripheral circulation.[48] and [49]

Interestingly, the second member of the eotaxins group, eotaxin-2, discovered by Baggiolini and colleagues,[50] has little specific amino acid sequence homology (~30%) with eotaxin-1, but also serves as a specific eosinophil chemoattractant acting via CCR3. After allergen challenge in mouse models, eotaxin-1 expression is detected at earlier time points (6 hours), followed later by eotaxin-2 (24 hours).[51] Eotaxin-2 also functions together with IL-5 to promote lung eosinophilia and production of IL-13.[52] and [53] Cooperative interactions between eotaxin-2 and IL-13 promote eosinophil recruitment in response to allergen challenge[54] and specific synergy between eotaxins 1 and 2, with a dominant role for eotaxin-2 in the accumulation of eosinophils in the airway lumen.[55] Eotaxin-3, a third homolog, is also expressed at later time points in response to allergen challenge and most likely supports prolonged eosinophil recruitment, and has been implicated as a mediator of eosinophilia in postbypass pleural effusions.[56] Most recently, eotaxin-3 has been identified as a marker for the allergic disorder, eosinophilic esophagitis; a single nucleotide polymorphism (+2496T>G) in the

gene encoding eotaxin-3, with potential to disrupt an AU-rich RNA-stability regulatory element, has been identified in strong association with susceptibility to eosinophilic esophagitis.[57] and [58] Specific polymorphisms in genes encoding eotaxins 2 and 3 have also been associated with elevated peripheral blood eosinophil counts in patients with asthma.[59] and [60]

In addition to eosinophil-selective chemoattractants, there has been significant therapeutic focus on the role of eosinophil-specific adhesion molecules, particularly the β1 integrin very late antigen (VLA)–4, a ligand for the integrin vascular cell adhesion molecule (VCAM)–1, and the P-selectin glycoprotein ligand (PSGL)–1 ligand for P-selectin, both with potential to mediate the specific transit of eosinophils across epithelial and endothelial barriers (Fig 3). Eotaxin-1 modulates expression of VLA-4 on eosinophils,[61] and [62] and studies performed with anti-integrins and VLA-4 blockade on mice subjected to allergen sensitization and challenge suggest that this ligand is a crucial component of the eosinophil inflammatory response.[63] and [64] Because the VLA-4/VCAM-1 interaction promotes specific adhesion of eosinophils (and not neutrophils), several small molecule inhibitors of the VLA-4/VCAM-1 interaction are under exploration as asthma therapeutics.[65] and [66] Among these, IVL745, a specific VLA-4 antagonist, was studied in a placebo-controlled, double-blind, randomized, 2-way crossover study.[67] IVL745 had no statistically significant impact on symptoms but did yield a moderate reduction in sputum eosinophils. Likewise, the role of selectins in promoting eosinophil transit has been explored. PSGL-1 is expressed uniquely on eosinophils; thus, moieties that disrupt interactions between PSGL-1 and P-selectin have the potential to be eosinophil-specific. In contrast, L-selectins are common to all leukocytes, and inhibitory strategies are likely to have an effect on trafficking of both eosinophils and neutrophils. Interestingly, P-selectin gene-deleted mice display reduced pulmonary eosinophilia,[68] and an L-selectin mAb was particularly effective in modulating disease in sheep.[69] Although selectin inhibitors have entered clinical trials, there is currently no successful therapeutic strategy based on this approach.[70], [71] and [72] The most promising at this writing is Bimosiamose (TBC1269; Revotar Pharmaceuticals, Hemmingsdorf, Germany), a small molecule pan-selectin antagonist. In a recent randomized, double-blind, placebo-controlled clinical crossover trial, inhaled Bimosiamose effectively reduced late-phase asthmatic reactions in a series of 12 male subjects with mild allergic asthma, although the specific impact on eosinophil trafficking remains uncertain.[73]

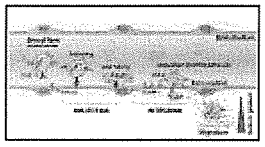
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Fig 3. The role of selectins and integrins in promoting eosinophil transit from the bloodstream. Selectins and their ligands present on eosinophils and the vascular endothelium promote initial tethering and rolling of eosinophils. Integrins mediate eosinophil activation, adhesion, and transit through the endothelium in a direction determined via chemokine gradients. Eosinophil-specific interactions with the endothelium are mediated via the integrin VLA-4 and PSGL-1 binding to P-selectin.

Eosinophil survival and apoptosis

A final aspect of eosinophil trafficking involves its survival and functioning within peripheral tissues. There are several excellent reviews that detail general findings relating to apoptosis signaling pathways described in eosinophils.[74], [75] and [76] Among the findings that relate uniquely to the biology of eosinophils, IL-5 clearly promotes eosinophil survival *in vitro*, and the absence of IL-5 results in spontaneous cellular apoptosis. Simon et al[76] and Simon[77] have shown that IL-5 is also associated with prolonged eosinophil survival in explants of nasal polyps. The cytokines IL-3 and GM-CSF also result in delayed eosinophil apoptosis in *in vitro* studies,[78] and [79] as does the chemokine eotaxin,[80] and biochemical blockade of cysteinyl-leukotriene receptors (CysLT1) partially reversed the antiapoptotic effects promoted by GM-CSF.[81] Interestingly, interactions with extracellular matrix proteins fibronectin and lamnin also resulted in prolonged eosinophil survival, in large part as a result of autocrine production of GM-CSF.[82]

In contrast with spontaneous apoptosis, resulting from withdrawal of cytokines necessary for prolonged cellular survival, cellular apoptosis can also be induced directly via extrinsic (receptor mediated) or intrinsic (direct mitochondrial perturbation) mechanisms.[83] Among the characterized proapoptotic or death receptors on the eosinophil cell surface, activation of CD95 (Fas) with a specific mAb has been shown to promote cellular apoptosis.[84] and [85] In contrast, the cytokines TNF-* and TNF-related apoptosis-inducing ligand, ligands for the extrinsic pathway death receptors TNF receptor 1 and TNF-related apoptosis-inducing ligand receptor 1, appear to prolong eosinophil survival.[86] and [87] Other eosinophil cell surface receptors for proapoptotic signals include CD137,[88] Siglec 8,[89] and CD30,[90] which induces the expression of the eosinophil-specific nuclear receptor, NOR1.[91] Apoptotic signals are transmitted in eosinophils via members of inhibitor of apoptosis protein and Bcl-2 families; eosinophils express the proapoptotic

protein Bax at a particularly high level.[92] The result is the activation of the proteolytic caspase cascade; caspases 3, 8, and 9 have been identified as mediating apoptotic responses in human eosinophils.[93]

Although IL-5 appears to be the primary modulator of eosinophil survival *in vitro*, the results of the clinical studies designed to evaluate the therapeutic potential of humanized mAbs demonstrate that eosinophils are clearly capable of persisting in the tissue despite effective blockade of endogenous IL-5. This result implies that there may be other, as yet to be characterized signals that promote eosinophil survival *in vivo* in response to allergen challenge, a point that is clearly worthy of experimental exploration.

Clinical implications

Given the pivotal role of IL-5, it seemed reasonable to assume that blockade of IL-5 would result in the elimination of eosinophilia and thus the reduction in symptomatology associated with allergic asthma. This hypothesis was tested in clinical trials using 2 humanized monoclonal anti–IL-5 antibodies, SCH55700 (Schering-Plough Research Institute, Kenilworth, NJ) and mepolizumab (GlaxoSmithKline, Middlesex, United Kingdom). In a randomized, double-blind study of mepolizumab, clinical symptoms of patients with asthma were unaffected despite a dramatic decline in peripheral blood eosinophils. Most interesting, despite repeated administration of anti–IL-5 therapy, eosinophils persisted in the lung tissue and in the airway. An independent trial performed with SCH55700 likewise resulted in a depletion of peripheral blood eosinophils without improvement in clinical symptoms.[94], [95] and [96]

Although disappointing, the existence of residual eosinophils in tissues suggests that IL-5 may not act alone in promoting eosinophil survival in lung tissue. There is evidence suggesting that IL-3, GM-CSF, and/or eotaxin may also contribute to eosinophil viability.[78] and [79] Likewise, eosinophil trafficking in other tissues might be more readily altered by these monoclonal reagents.[97], [98] and [99] Similarly, a study by Liu et al[100] indicated that airway eosinophils are relatively unresponsive to IL-5, and that bronchoalveolar lavage fluid from atopic individuals contained elevated concentrations of the soluble IL-5 receptor.

It is important to recognize that the disappointing results may be also be related to complexities of specific disease states. Although anti–IL-5 therapy has likewise been of little benefit in the treatment of atopic dermatitis despite clear reduction in peripheral blood eosinophil counts,[101] and [102] several groups have reported success using anti–IL-5 therapy for hypereosinophilic syndromes[94], [103] and [104] and eosinophilic esophagitis.[105]

Conclusion and future directions

Despite some controversial findings, the balance of data suggests that eosinophils promote 1 or more aspects of respiratory dysfunction characteristic of allergic asthma. As such, the possibility that drugs directed at inhibition of eosinophil migration or activation or even outright eosinophil ablation might prove to be effective therapeutic strategies certainly remains worthy of further exploration. Among the avenues that might be considered is the possibility that coordinate inhibition of IL-5 and CCR3 might result in more effective eosinophil depletion in lung tissue and airways. Several small molecule antagonists of CCR3 are under experimental review,[106], [107], [108] and [109] and an exploration of the therapeutic potential of the newly characterized eosinophil inhibitory receptors certainly warrants further consideration.[110] Furthermore, a directed exploration of the factors permitting prolonged survival of eosinophils in tissue even in the presence of effective IL-5 blockade might uncover additional eosinophil depletion strategies (Table I).

Table I.

Key points

1. Eosinophils are bone marrow–derived granulocytes that are effector
2. The T_H2 cytokine IL-5 is a central modulator of eosinophil differential
3. The eotaxins are chemoattractant cytokines that promote eosinophil
4. Eosinophil transit to the tissues is mediated via cell surface selectins
5. Clinical trials with humanized anti–IL-5 mAbs in patients with allergic
6. Anti-CCR3, anti-integrin, and antiselectin strategies are currently in d

Full-size table

References

1 A.D. Klion and T.B. Nutman, The role of eosinophils in host defense against helminth parasites, *J Allergy Clin Immunol* **113** (2004), pp. 30–37. **Article** | PDF (139 K) | View Record in Scopus | Cited By in Scopus (55)

2 C.A. Behm and K.S. Ovington, The role of eosinophils in parasitic helminth infections: insights from genetically modified mice, *Parasitol Today* **16** (2000), pp. 202–209. Abstract | PDF (152 K) | View Record in Scopus | Cited By in Scopus (58)

3 M.E. Rothenberg and S.P. Hogan, The eosinophil, *Annu Rev Immunol* **24** (2006), pp. 147–174. **Full Text** via CrossRef | View

Record in Scopus | Cited By in Scopus (84)

4 A.J. Wardlaw, Eosinophil trafficking in asthma, *Clin Med* **1** (2001), pp. 214–218. View Record in Scopus | Cited By in Scopus (23)

5 A.P. Watt, B.C. Schock and M. Ennis, Neutrophils and eosinophils: clinical implications of their appearance, presence and disappearance in asthma and COPD, *Curr Drug Targets Inflamm Allergy* **4** (2005), pp. 415–423. **Full Text** via CrossRef | View Record in Scopus | Cited By in Scopus (10)

6 B.S. Bochner and W.W. Busse, Allergy and asthma, *J Allergy Clin Immunol* **15** (2005), pp. 953–959. **Article** | PDF (183 K) | View Record in Scopus | Cited By in Scopus (38)

7 G.M. Walsh, D.W. Sexton and M.G. Blaylock, Corticosteroids, eosinophils and bronchial epithelial cells: new insights into the resolution of inflammation in asthma, *J Endocrinol* **178** (2003), pp. 37–43. **Full Text** via CrossRef | View Record in Scopus | Cited By in Scopus (30)

8 D. Vercelli, Mechanisms of the hygiene hypothesis: molecular and otherwise, *Curr Opin Immunol* **18** (2006), pp. 733–737. **Article** | PDF (130 K) | View Record in Scopus | Cited By in Scopus (15)

9 A.H. Liu and D.Y. Leung, Renaissance of the hygiene hypothesis, *J Allergy Clin Immunol* **117** (2006), pp. 1063–1066. **Article** | PDF (90 K) | View Record in Scopus | Cited By in Scopus (18)

10 C.D. Ramsey and J.C. Celedon, The hygiene hypothesis and asthma, *Curr Opin Pulm Med* **11** (2005), pp. 14–20. **Full Text** via CrossRef | View Record in Scopus | Cited By in Scopus (20)

11 M. Rehli, Of mice and men: species variations of Toll-like receptor expression, *Trends Immunol* **23** (2002), pp. 375–378. **Article** | PDF (43 K) | View Record in Scopus | Cited By in Scopus (80)

12 J. Mestas and C.C. Hughes, Of mice and not men: differences between mouse and human immunology, *J Immunol* **172** (2004), pp. 2731–2738. View Record in Scopus | Cited By in Scopus (179)

13 H.F. Rosenberg, The eosinophil ribonucleases, *Cell Mol Life Sci* **54** (1998), pp. 795–803. **Full Text** via CrossRef | View Record in Scopus | Cited By in Scopus (49)

14 J.Q. Zhang, B. Biedermann, L. Nitschke and P.R. Crocker, The murine inhibitory receptor mSiglec-E is expressed broadly on cells of the innate immune system whereas mSiglec-F is restricted to

eosinophils, *Eur J Immunol* **34** (2004), pp. 1175–1184. **Full Text** via CrossRef | View Record in Scopus | Cited By in Scopus (32)

15 M. Zhang, T. Angata, J.Y. Cho, M. Miller, D.H. Broide and A. Varki, Defining the in vivo function of Siglec-F, a CD33-related Siglec expressed on mouse eosinophils, *Blood* (2007) Feb 1 [Epub ahead of print].

16 T. Angata, Molecular diversity and evolution of the Siglec family of cell-surface lectins, *Mol Divers* **10** (2006), pp. 555–566. **Full Text** via CrossRef | View Record in Scopus | Cited By in Scopus (6)

17 M.T. Borchers, T. Ansay, R. DeSalle, B.L. Daugherty, H. Shen and M. Metzger *et al.*, In vitro assessment of chemokine receptor-ligand interactions mediating mouse eosinophil migration, *J Leukoc Biol* **71** (2002), pp. 1033–1041. View Record in Scopus | Cited By in Scopus (28)

18 J.J. Lee and N.A. Lee, Eosinophil degranulation: an evolutionary vestige or a universally destructive effector function?, *Clin Exp Allergy* **35** (2005), pp. 986–994. **Full Text** via CrossRef | View Record in Scopus | Cited By in Scopus (15)

19 A. Gessner, K. Mohrs and M. Mohrs, Mast cells, basophils, and eosinophils acquire constitutive IL-4 and IL-13 transcripts during lineage differentiation that are sufficient for rapid cytokine production, *J Immunol* **174** (2005), pp. 1063–1072. View Record in Scopus | Cited By in Scopus (35)

20 D. Voehringer, K. Shinkai and R.M. Locksley, Type 2 immunity reflects orchestrated recruitment of cells committed to IL-4 production, *Immunity* **20** (2004), pp. 267–277. **Article** | PDF (697 K) | View Record in Scopus | Cited By in Scopus (76)

21 A.E. Elovic, H. Ohyama, A. Sauty, J. McBride, T. Tsuji and M. Nagai *et al.*, IL-4-dependent regulation of TGF-alpha and TGF-beta1 expression in human eosinophils, *J Immunol* **160** (1998), pp. 6121–6127. View Record in Scopus | Cited By in Scopus (43)

22 G.R. Dubois, R.C. Schweizer, C. Versluis, C.A. Bruijnzeel-Koomen and P.L. Bruijnzeel, Human eosinophils constitutively express a functional interleukin- 4 receptor: interleukin-4 -induced priming of chemotactic responses and induction of PI-3 kinase activity, *Am J Respir Cell Mol Biol* **19** (1998), pp. 691–699. View Record in Scopus | Cited By in Scopus (21)

23 N. Terada, N. Hamano, T. Nomura, T. Numata, K. Hirai and T. Nakajima *et al.*, Interleukin-13 and tumour necrosis factor-alpha synergistically induce eotaxin production in human nasal fibroblasts,

Clin Exp Allergy **30** (2000), pp. 348–355. **Full Text** via CrossRef | View Record in Scopus | Cited By in Scopus (37)

24 J.W. Steinke, Anti-interleukin-4 therapy, *Immunol Allergy Clin North Am* **24** (2004), pp. 599–614. Abstract | View Record in Scopus | Cited By in Scopus (18)

25 A. Kelly-Welch, E.M. Hanson and A.D. Keegan, Interleukin-4 (IL-4) pathway, *Sci STKE* (2005) cm9.

26 M. Wills-Karp, Interleukin-13 in asthma pathogenesis, *Immunol Rev* **202** (2004), pp. 175–190. **Full Text** via CrossRef | View Record in Scopus | Cited By in Scopus (93)

27 A. Kelly-Welch, E.M. Hanson and A.D. Keegan, Interleukin-13 (IL-13) pathway, *Sci STKE* (2005) cm8.

28 P.S. Foster, A.W. Mould, M. Yang, J. Mackenzie, J. Mattes and S.P. Hogan *et al.*, Elemental signals regulating eosinophil accumulation in the lung, *Immunol Rev* **179** (2001), pp. 173–181. View Record in Scopus | Cited By in Scopus (88)

29 J.A. Denburg, R. Sehmi, H. Saito, J. Pil-Seob, M.D. Inman and P.M. O'Byrne, Systemic aspects of allergic disease: bone marrow responses, *J Allergy Clin Immunol* **106** (2000), pp. S242–S246. View Record in Scopus | Cited By in Scopus (66)

30 Y. Yamaguchi, T. Suda, J. Suda, M. Eguchi, Y. Miura and N. Harada *et al.*, Purified interleukin 5 supports the terminal differentiation and proliferation of murine eosinophilic precursors, *J Exp Med* **167** (1988), pp. 43–56. **Full Text** via CrossRef | View Record in Scopus | Cited By in Scopus (209)

31 G.J. Roboz and S. Rafii, Interleukin-5 and the regulation of eosinophil production, *Curr Opin Hematol* **6** (1999), pp. 164–168. **Full Text** via CrossRef | View Record in Scopus | Cited By in Scopus (32)

32 M. Martinez-Moczygemba and D.P. Huston, Biology of common beta receptor-signaling cytokines: IL-3, IL-5, and GM-CSF, *J Allergy Clin Immunol* **112** (2003), pp. 653–665.

33 L. Zabeau, P. Gevaert, C. Bachert and J. Tavernier, Interleukin-5, eosinophilic diseases and therapeutic intervention, *Curr Drug Targets Inflamm Allergy* **2** (2003), pp. 319–328. **Full Text** via CrossRef | View Record in Scopus | Cited By in Scopus (8)

34 B. Sitkauskiene, A.K. Johansson, S. Sergejeva, S. Lundin, S. Sjostrand and J. Lotvall, Regulation of bone marrow and airway CD34+ eosinophils by interleukin-5, *Am J Respir Cell Mol Biol* **30**

(2004), pp. 367–378. View Record in Scopus | Cited By in Scopus (8)

35 M. Kopf, F. Brombacher, P.D. Hodgkin, A.J. Ramsay, E.A. Milbourne and W.J. Dai *et al.*, IL-5-deficient mice have a developmental defect in CD5+ B-1 cells and lack eosinophilia but have normal antibody and cytotoxic T cell responses, *Immunity* **4** (1996), pp. 15–24. **Article** | PDF (361 K) | View Record in Scopus | Cited By in Scopus (307)

36 J. Du, M.J. Stankiewicz, Y. Liu, Q. Xi, J.E. Schmitz and J.A. Lekstrom-Himes *et al.*, Novel combinatorial interactions of GATA-1, PU.1, and C/EBPepsilon isoforms regulate transcription of the gene encoding eosinophil granule major basic protein, *J Biol Chem* **277** (2002), pp. 43481–43494. **Full Text** via CrossRef | View Record in Scopus | Cited By in Scopus (27)

37 A.F. Gombart, S.H. Kwok, K.L. Anderson, Y. Yamaguchi, B.E. Torbett and H.P. Koeffler, Regulation of neutrophil and eosinophil secondary granule gene expression by transcription factors C/EBP epsilon and PU.1, *Blood* **101** (2003), pp. 3265–3273. **Full Text** via CrossRef | View Record in Scopus | Cited By in Scopus (42)

38 C. Yu, A.B. Cantor, H. Yang, C. Browne and R.A. Wells, Targeted deletion of a high-affinity GATA-binding site in the GATA-1 promoter leads to selective loss of the eosinophil lineage in vivo, *J Exp Med* **195** (2002), pp. 1387–1395. **Full Text** via CrossRef | View Record in Scopus | Cited By in Scopus (98)

39 P.J. Jose, D.A. Griffiths-Johnson, P.D. Collins, D.T. Walsh, R. Moqbel and N.F. Totty *et al.*, Eotaxin: a potent eosinophil chemoattractant cytokine detected in a guinea pig model of allergic airways inflammation, *J Exp Med* **179** (1994), pp. 881–887. **Full Text** via CrossRef | View Record in Scopus | Cited By in Scopus (519)

40 M.E. Rothenberg, Eotaxin: an essential mediator of eosinophil trafficking into mucosal tissues, *Am J Respir Cell Mol Biol* **21** (1999), pp. 291–295. View Record in Scopus | Cited By in Scopus (87)

41 C. Blanchard, S. Durual, M. Estienne, S. Emami, S. Vasseur and J.C. Cuber, Eotaxin-3/CCL26 gene expression in intestinal epithelial cells is up-regulated by interleukin-4 and interleukin-13 via the signal transducer and activator of transcription 6, *Int J Biochem Cell Biol* **37** (2005), pp. 2559–2573. **Article** | PDF (586 K) | View Record in Scopus | Cited By in Scopus (7)

42 L. Simson and P.S. Foster, Chemokine and cytokine cooperativity: eosinophil migration in the asthmatic response,

Immunol Cell Biol **78** (2000), pp. 415–422. **Full Text** via CrossRef | View Record in Scopus | Cited By in Scopus (17)

43 S.M. Pope, E.B. Brandt, A. Mishra, S.P. Hogan, N. Zimmermann and K.I. Matthaei *et al.*, IL-13 induces eosinophil recruitment into the lung by an IL-5- and eotaxin-dependent mechanism, *J Allergy Clin Immunol* **108** (2001), pp. 594–601. Abstract | PDF (726 K) | View Record in Scopus | Cited By in Scopus (54)

44 H.S. Park, S.H. Kim and C.S. Park, The role of novel genes in modifying airway responses in asthma, *Curr Allergy Asthma Rep* **6** (2006), pp. 112–116. **Full Text** via CrossRef | View Record in Scopus | Cited By in Scopus (2)

45 J.E. Pease, Asthma, allergy and chemokines, *Curr Drug Targets* **7** (2006), pp. 3–12. **Full Text** via CrossRef | View Record in Scopus | Cited By in Scopus (13)

46 M.E. Rothenberg, Eosinophilic gastrointestinal disorders (EGID), *J Allergy Clin Immunol* **113** (2004), pp. 11–28. **Article** | PDF (278 K)

47 E.J. Quackenbush, B.K. Wershil, V. Aguirre and R.C. Gutierrez-Ramos, Eotaxin modulates myelopoiesis and mast cell development from embryonic hematopoietic progenitors, *Blood* **92** (1998), pp. 1887–1897.

48 R.T. Palframan, P.D. Collins, T.J. Williams and S.M. Rankin, Eotaxin induces a rapid release of eosinophils and their progenitors from the bone marrow, *Blood* **91** (1998), pp. 2240–2248. View Record in Scopus | Cited By in Scopus (153)

49 R. Sehmi, S. Dorman, A. Baatjes, R. Watson, R. Foley and S. Ying *et al.*, Allergen-induced fluctuation in CC chemokine receptor 3 expression on bone marrow CD34+ cells from asthmatic subjects: significance for mobilization of haemopoietic progenitor cells in allergic inflammation, *Immunology* **109** (2003), pp. 536–546. **Full Text** via CrossRef | View Record in Scopus | Cited By in Scopus (28)

50 U. Forssmann, M. Uguccioni, P. Loetscher, C.A. Dahinden, H. Langen and M. Thelen *et al.*, Eotaxin-2, a novel CC chemokine that is selective for the chemokine receptor CCR3, and acts like eotaxin on human eosinophil and basophil leukocytes, *J Exp Med* **185** (1997), pp. 2171–2176. **Full Text** via CrossRef | View Record in Scopus | Cited By in Scopus (222)

51 N. Zimmermann, G.K. Hershey, P.S. Foster and M.E. Rothenberg, Chemokines in asthma: cooperative interaction

between chemokines and IL-13, *J Allergy Clin Immunol* **111** (2003), pp. 227–242. Abstract | PDF (553 K)

52 J. Mattes and P.S. Foster, Regulation of eosinophil migration and Th2 cell function by IL-5 and eotaxin, *Curr Drug Targets Inflamm Allergy* **2** (2003), pp. 169–174. **Full Text** via CrossRef | View Record in Scopus | Cited By in Scopus (15)

53 M. Yang, S.P. Hogan, S. Mahalingam, S.M. Pope, N. Zimmermann and P. Fulkerson *et al.*, Eotaxin-2 and IL-5 cooperate in the lung to regulate IL-13 production and airway eosinophilia and hyperreactivity, *J Allergy Clin Immunol* **112** (2003), pp. 935–943. **Article** | PDF (129 K) | View Record in Scopus | Cited By in Scopus (35)

54 S.M. Pope, P.C. Fulkerson, C. Blanchard, H.S. Akei, N.M. Nikolaidis and N. Zimmermann *et al.*, Identification of a cooperative mechanism involving inerleukin-13 and eotaxin-2 in experimental allergic lung inflammation, *J Biol Chem* **280** (2005), pp. 13952–13961. View Record in Scopus | Cited By in Scopus (16)

55 S.M. Pope, N. Zimmermann, K.F. Stringer, M.L. Karow and M.E. Rothenberg, The eotaxin chemokines and CCR3 are fundamental regulators of allergen-induced pulmonary eosinophilia, *J Immunol* **175** (2005), pp. 5341–5350. View Record in Scopus | Cited By in Scopus (28)

56 I. Kalomenidis, G.T. Stathopoulos, R. Barnette, Y. Guo, R.S. Peebles and T.S. Blackwell *et al.*, Eotaxin-3 and interleukin-5 pleural fluid levels are associated with pleural fluid eosinophilia in post-coronary artery bypass grafting pleural effusions, *Chest* **127** (2005), pp. 2094–2100. **Full Text** via CrossRef | View Record in Scopus | Cited By in Scopus (5)

57 C. Blanchard, N. Wang, K.F. Stringer, A. Mishra, P.C. Fulkerson and J.P. Abonia *et al.*, Eotaxin-3 and a uniquely conserved gene-expression profile in eosinophilic esophagitis, *J Clin Invest* **116** (2006), pp. 536–547. View Record in Scopus | Cited By in Scopus (67)

58 C. Blanchard, N. Wang and M.E. Rothenberg, Eosinophilic esophagitis: pathogenesis, genetics, and therapy, *J Allergy Clin Immunol* **118** (2006), pp. 1054–1059. **Article** | PDF (546 K) | View Record in Scopus | Cited By in Scopus (17)

59 H. Nakamura, A.D. Luster, T. Nakamura, K.H. In, L.A. Sonna and A. Deykin *et al.*, Variant eotaxin: its effects on the asthma phenotype, *J Allergy Clin Immunol* **108** (2001), pp. 946–953. Abstract | PDF (158 K) | View Record in Scopus | Cited By in

Scopus (29)

60 S.C. Chae, Y.C. Lee, Y.R. Park, J.S. Shin, J.H. Song and J.G. Oh *et al.*, Analysis of the polymorphisms in eotaxin gene family and their association with asthma, IgE, and eosinophil, *Biochem Biophys Res Commun* **320** (2004), pp. 131–137. **Article** | PDF (136 K) | View Record in Scopus | Cited By in Scopus (13)

61 G.Q. Jia, J.A. Gonzalo, A. Hidalgo, D. Wagner, M. Cybulsky and J.C. Gutierrez-Ramos, Selective eosinophil transendothelial migration triggered by eotaxin via modulation of Mac-1/ICAM-1 and VLA-4/VCAM-1 interactions, *Int Immunol* **11** (1999), pp. 1–10. **Full Text** via CrossRef | View Record in Scopus | Cited By in Scopus (46)

62 K.P. Sung, L. Yang, J. Kim, D. Ko, G. Stachnick and D. Castaneda *et al.*, Eotaxin induces a sustained reduction in the functional adhesive state of very late antigen 4 for the connecting segment 1 region of fibronectin, *J Allergy Clin Immunol* **106** (2000), pp. 933–940. Abstract | PDF (223 K) | View Record in Scopus | Cited By in Scopus (10)

63 M.H. Gascoigne, K. Holland, C.P. Page, A. Shock, M. Robinson and R. Foulkes *et al.*, The effect of anti-integrin monoclonal antibodies on antigen-induced pulmonary inflammation in allergic rabbits, *Pulm Pharmacol Ther* **16** (2003), pp. 279–285. **Article** | PDF (313 K) | View Record in Scopus | Cited By in Scopus (18)

64 G.C. Koo, K. Shah, G.J. Ding, J. Xiao, R. Wnek and G. Doherty *et al.*, A small molecule very late antigen-4 antagonist can inhibit ovalbumin-induced lung inflammation, *Am J Respir Crit Care Med* **167** (2003), pp. 1400–1409. **Full Text** via CrossRef | View Record in Scopus | Cited By in Scopus (21)

65 H. Okigami, K. Takeshita, M. Tajimi, H. Komura, M. Albers and T.E. Lehmann *et al.*, Inhibition of eosinophilia in vivo by a small molecule inhibitor of very late antigen (VLA)-4, *Eur J Pharmacol* **559** (2007), pp. 202–209. **Article** | PDF (500 K) | View Record in Scopus | Cited By in Scopus (2)

66 W.K. Hagmann, The discovery and potential of N-sulfonylated dipeptide VLA-4 antagonists, *Curr Top Med Chem* **4** (2004), pp. 1461–1471. **Full Text** via CrossRef | View Record in Scopus | Cited By in Scopus (5)

67 V. Norris, L. Choong, D. Tran, Z. Corden, M. Boyce and H. Arshad *et al.*, Effect of IVL745, a VLA-4 antagonist, on allergen-induced bronchoconstriction in patients with asthma, *J Allergy Clin Immunol* **116** (2005), pp. 761–767. **Article** | PDF (221 K) | View

Record in Scopus | Cited By in Scopus (10)

68 D.H. Broide, S. Sullivan, T. Gifford and P. Sriramarao, Inhibition of pulmonary eosinophilia in P-selectin- and ICAM-1-deficient mice, *Am J Respir Cell Mol Biol* **18** (1998), pp. 218–225. View Record in Scopus | Cited By in Scopus (61)

69 W.M. Abraham, A. Ahmed, J.R. Sabater, I.T. Lauredo, Y. Botvinnikova and R.J. Bjercke *et al.*, Selectin blockade prevents antigen-induced late bronchial responses and airway hyperresponsiveness in allergic sheep, *Am J Respir Crit Care Med* **159** (1999), pp. 1205–1214. View Record in Scopus | Cited By in Scopus (63)

70 S.J. Romano and D.H. Slee, Targeting selectins for the treatment of respiratory diseases, *Curr Opin Investig Drugs* **2** (2001), pp. 907–913. View Record in Scopus | Cited By in Scopus (28)

71 G. Constantin, PSGL-1 as a novel therapeutic target, *Drug News Perspect* **17** (2004), pp. 579–586. **Full Text** via CrossRef | View Record in Scopus | Cited By in Scopus (6)

72 K. Uchimura and S.D. Rosen, Sulfated L-selectin ligands as a therapeutic target in chronic inflammation, *Trends Immunol* **27** (2006), pp. 559–565. **Article** | PDF (656 K) | View Record in Scopus | Cited By in Scopus (7)

73 K.M. Beeh, J. Beier, M. Meyer, R. Buhl, R. Zahlten and G. Wolff, Bimosiamose, an inhaled small-molecule pan-selectin antagonist, attenuates late asthmatic reactions following allergen challenge in mild asthmatics: a randomized, double-blind, placebo-controlled clinical cross-over-trial, *Pulm Pharmacol Ther* **19** (2006), pp. 233–241. **Article** | PDF (154 K) | View Record in Scopus | Cited By in Scopus (20)

74 B.R. Chaudhari, R.F. Murphy and D.K. Agrawal, Following the TRAIL to apoptosis, *Immunol Res* **35** (2006), pp. 249–262. **Full Text** via CrossRef | View Record in Scopus | Cited By in Scopus (12)

75 H. Kankaanranta, E. Moilanen and X. Zhang, Pharmacological regulation of human eosinophil apoptosis, *Curr Drug Targets Inflamm Allergy* **4** (2005), pp. 433–445. **Full Text** via CrossRef | View Record in Scopus | Cited By in Scopus (10)

76 H.U. Simon, S. Yousefi, C. Schranz, A. Schapowal, C. Bachert and K. Blaser, Direct demonstration of delayed eosinophil apoptosis as a mechanism causing tissue eosinophilia, *J Immunol* **158** (1997), pp. 3902–3908. View Record in Scopus | Cited By in Scopus (270)

77 H.U. Simon, Molecules involved in the regulation of eosinophil apoptosis, *Chem Immunol Allergy* **92** (2006), pp. 49–58. View Record in Scopus | Cited By in Scopus (7)

78 M. Morita, B. Lamkhioued, A. Soussi Gounni, D. Aldebert, E. Delaporte and A. Capron *et al.*, Induction by interferons of human eosinophil apoptosis and regulation by interleukin-3, granulocyte/macrophage-colony stimulating factor and interleukin-5, *Eur Cytokine Netw* **7** (1996), pp. 725–732. View Record in Scopus | Cited By in Scopus (19)

79 S. Yousefi, D.C. Hoessli, K. Blaser, G.B. Mills and H.U. Simon, Requirement of Lyn and Syk tyrosine kinases for the prevention of apoptosis by cytokines in human eosinophils, *J Exp Med* **183** (1996), pp. 1407–1414. **Full Text** via CrossRef | View Record in Scopus | Cited By in Scopus (158)

80 K. Shinagawa, A. Trifilieff and G.P. Anderson, Involvement of CCR3-reactive chemokines in eosinophil survival, *Int Arch Allergy Immunol* **130** (2003), pp. 150–157. **Full Text** via CrossRef | View Record in Scopus | Cited By in Scopus (10)

81 E. Lee, T. Robertson, J. Smith and S. Kilfeather, Leukotriene receptor antagonists and synthesis inhibitors reverse survival in eosinophils of asthmatic patients, *Am J Respir Crit Care Med* **161** (2000), pp. 1881–1886. View Record in Scopus | Cited By in Scopus (97)

82 G.M. Walsh and A.J. Wardlaw, Dexamethasone inhibits prolonged survival and autocrine granulocyte-macrophage colony-stimulating factor production by human eosinophils cultured on laminin or tissue fibronectin, *J Allergy Clin Immunol* **100** (1997), pp. 208–215. **Article** | PDF (827 K) | View Record in Scopus | Cited By in Scopus (28)

83 S. Fulda and K.-M. Debatin, Extrinsic versus intrinsic apoptosis pathways in anticancer chemotherapy, *Oncogene* **25** (2006), pp. 4798–4811. **Full Text** via CrossRef | View Record in Scopus | Cited By in Scopus (47)

84 A. Druihe, Z. Cai, S. Haile, S. Chouaib and M. Pretolani, Fas-mediated apoptosis in cultured human eosinophils, *Blood* **87** (1996), pp. 2822–2830.

85 H. Hebestreit, S. Yousefi, I. Balatti, M. Weber, R. Crameri and D. Simon *et al.*, Expression and function of the Fas receptor on human blood and tissue eosinophils, *Eur J Immunol* **26** (1996), pp. 1775–1780. **Full Text** via CrossRef | View Record in Scopus | Cited By in Scopus (69)

86 K. Tsukahara, A. Nakao, M. Hiraguri, S. Miike, M. Mamura and Y. Saito *et al.*, Tumor necrosis factor-alpha mediates antiapoptotic signals partially via p38 MAP kinase activation in human eosinophils, *Int Arch Allergy Immunol* **120** (1999), pp. 54–59. **Full Text** via CrossRef | View Record in Scopus | Cited By in Scopus (18)

87 N.M. Robertson, J.G. Zangrilli, A. Steplewski, A. Hastie, R.G. Lindemeyer and M.A. Planeta *et al.*, Differential expression of TRAIL and TRAIL receptors in allergic asthmatics following segmental antigen challenge: evidence for a role of TRAIL in eosinophil survival, *J Immunol* **169** (2002), pp. 5986–5996. View Record in Scopus | Cited By in Scopus (17)

88 H.U. Simon, Evidence for a pro-apoptotic function of CD137 in granulocytes, *Swiss Med Wkly* **131** (2001), pp. 455–458. View Record in Scopus | Cited By in Scopus (3)

89 E. Nutku, H. Aizawa, S.A. Hudson and B.S. Bochner, Ligation of Siglec-8: a selective mechanism for induction of human eosinophil apoptosis, *Blood* **101** (2003), pp. 5014–5020. **Full Text** via CrossRef | View Record in Scopus | Cited By in Scopus (60)

90 A.I. Berro, G.A. Perry and D.K. Agrawal, Increased expression and activation of CD30 induces apoptosis in human blood eosinophils, *J Immunol* **173** (2004), pp. 2174–2183. View Record in Scopus | Cited By in Scopus (8)

91 R. Hashida, N. Ohkura, H. Saito and G. Tsujimoto, The NR4A nuclear receptor family in eosinophils, *J Hum Genet* **52** (2007), pp. 13–20. View Record in Scopus | Cited By in Scopus (1)

92 G. Dewson, G.M. Walsh and A.J. Wardlaw, Expression of Bcl-2 and its homologues in human eosinophils: modulation by interleukin-5, *Am J Respir Cell Mol Biol* **20** (1999), pp. 720–728. View Record in Scopus | Cited By in Scopus (42)

93 E. Nutku, S.A. Hudson and B.S. Bochner, Mechanism of Siglec-8-induced human eosinophil apoptosis: role of caspases and mitochondrial injury, *Biochem Biophys Res Commun* **336** (2005), pp. 918–924. **Article** | PDF (257 K) | View Record in Scopus | Cited By in Scopus (8)

94 A.B. Kay and A.D. Klion, Anti-interleukin-5 therapy for asthma and hypereosinophilic syndrome, *Immunol Allergy Clin North Am* **24** (2004), pp. 645–666. Abstract | View Record in Scopus | Cited By in Scopus (16)

95 M.J. Leckie, Anti-interleukin-5 monoclonal antibodies: preclinical

and clinical evidence in asthma models, *Am J Respir Med* **2** (2003), pp. 245–259. View Record in Scopus | Cited By in Scopus (22)

96 P.M. O'Byrne, M.D. Inman and K. Parameswaran, The trials and tribulations of IL-5, eosinophils, and allergic asthma, *J Allergy Clin Immunol* **108** (2001), pp. 503–508. Abstract | PDF (172 K) | View Record in Scopus | Cited By in Scopus (82)

97 S. Phipps, P. Flood-Page, A. Menzies-Gow, Y.E. Ong and A.B. Kay, Intravenous anti-IL-5 monoclonal antibody reduces eosinophils and tenascin deposition in allergen-challenged human atopic skin, *J Invest Dermatol* **122** (2004), pp. 1406–1412. **Full Text** via CrossRef | View Record in Scopus | Cited By in Scopus (25)

98 A.D. Klion, B.S. Bochner, G.J. Gleich, T.B. Nutman, M.E. Rothenberg and H.U. Simon *et al.*, The Hypereosinophilic Syndromes Working Group. Approaches to the treatment of hypereosinophilic syndromes: a workshop summary report, *J Allergy Clin Immunol* **117** (2006), pp. 1292–1302. **Article** | PDF (201 K) | View Record in Scopus | Cited By in Scopus (42)

99 D. Simon, L.R. Braathen and H.U. Simon, Anti-interleukin-5 antibody therapy in eosinophilic diseases, *Pathobiology* **72** (2005), pp. 287–292. **Full Text** via CrossRef | View Record in Scopus | Cited By in Scopus (16)

100 L.Y. Liu, J.B. Sedgwick, M.E. Bates, R.F. Vrtis, J.E. Gern and H. Kita *et al.*, Decreased expression of membrane IL-5 receptor alpha on human eosinophils, I: loss of membrane IL-5 receptor alpha on airway eosinophils and increased soluble IL-5 receptor alpha in the airway after allergen challenge, *J Immunol* **169** (2002), pp. 6452–6548.

101 J.M. Oldhoff, U. Darsow, T. Werfel, K. Katzer, A. Wulf and J. Laifaoui *et al.*, Anti-IL-5 recombinant humanized monoclonal antibody (mepolizumab) for the treatment of atopic dermatitis, *Allergy* **60** (2005), pp. 693–696. View Record in Scopus | Cited By in Scopus (16)

102 J.M. Oldhoff, U. Darsow, T. Werfel, I.C. Bihari, K. Katzer and J. Laifaoui *et al.*, No effect of anti-interleukin-5 therapy (mepolizumab) on the atopy patch test in atopic dermatitis, *Int Arch Allergy Immunol* **141** (2006), pp. 290–294. **Full Text** via CrossRef | View Record in Scopus | Cited By in Scopus (4)

103 S.G. Plotz, H.U. Simon, U. Darsow, D. Simon, E. Vassina and S. Yousefi *et al.*, Use of an anti-interleukin-5 antibody in the hypereosinophilic syndrome with eosinophilic dermatitis, *N Engl J Med* **349** (2003), pp. 2334–2339. **Full Text** via CrossRef | View

Record in Scopus | Cited By in Scopus (88)

104 J.K. Garrett, S.C. Jameson, B. Thomson, M.H. Collins, L.E. Wagoner and D.K. Freese *et al.*, Anti-interleukin-5 (mepolizumab) therapy for hypereosinophilic syndromes, *J Allergy Clin Immunol* **113** (2004), pp. 115–119. **Article** | PDF (96 K) | View Record in Scopus | Cited By in Scopus (151)

105 M.L. Stein, M.H. Collins, J.M. Villanueva, J.P. Kushner, P.E. Putnam and B.K. Buckmeier *et al.*, Anti-IL-5 (mepolizumab) therapy for eosinophilic esophagitis, *J Allergy Clin Immunol* **118** (2006), pp. 1312–1319. **Article** | PDF (1632 K) | View Record in Scopus | Cited By in Scopus (35)

106 I. Sabroe, M.J. Peck, B.J. Van Keulen, A. Jorritsma, G. Simmons and P.R. Clapham *et al.*, A small molecule antagonist of chemokine receptors CCR1 and CCR3: potent inhibition of eosinophil function and CCR3-mediated HIV-1 entry, *J Biol Chem* **275** (2000), pp. 25985–25992. **Full Text** via CrossRef | View Record in Scopus | Cited By in Scopus (122)

107 M. Wegmann, R. Goggel, S. Sel, S. Sel, K.J. Erb and F. Kalkbrenner *et al.*, Effects of a low-molecular-weight CCR-3 antagonist on chronic experimental asthma, *Am J Respir Cell Mol Biol* **36** (2007), pp. 61–67. View Record in Scopus | Cited By in Scopus (14)

108 T. Nakamura, M. Ohbayashi, M. Toda, D.A. Hall, C.M. Horgan and S.J. Ono, A specific CCR3 chemokine receptor antagonist inhibits both early and late phase allergic inflammation in the conjunctiva, *Immunol Res* **33** (2005), pp. 213–221.

109 C.P. Bertrand and P.D. Ponath, CCR3 blockade as a new therapy for asthma, *Expert Opin Investig Drugs* **9** (2000), pp. 43–52. **Full Text** via CrossRef | View Record in Scopus | Cited By in Scopus (37)

110 Munitz A, Levi-Schaffer F. Inhibitory receptors on eosinophils: a direct hit to a possible Achilles heel? J Allergy Clin Immunol 2007; Mar 1 [Epub ahead of print].

111 G. Woltmann, C.A. McNulty, G. Dewson, F.A. Symon and A.J. Wardlaw, Interleukin-13 induces PSGL-1/P-selectin-dependent adhesion of eosinophils, but not neutrophils, to human umbilical vein endothelial cells under flow, *Blood* **95** (2000), pp. 3146–3152. View Record in Scopus | Cited By in Scopus (45)

(Supported by an unrestricted educational grant from Genentech, Inc. and Novartis Pharmaceuticals Corporation)Series editors:

Joshua A. Boyce, MD, Fred Finkelman, MD, William T. Shearer, MD, PhD, and Donata Vercelli, MDDisclosure of potential conflict of interest: S. Phipps has received grant support from the Australian Lung Foundation. H. F. Rosenberg and P. S. Foster have declared that they have no conflict of interest.

Reprint requests: Helene F. Rosenberg, MD, Laboratory of Allergic Diseases, Building 10, Room 11C215, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 9000 Rockville Pike, Bethesda, MD 20892.

Journal of Allergy and Clinical Immunology
Volume 119, Issue 6, June 2007, Pages 1303-1310