REVIEW

Recent advances in understanding eosinophil biology [version 1; peer review: 2 approved]

Amy Klion

Human Eosinophil Section, Laboratory of Parasitic Diseases, National Institutes of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA

V1 First published: 07 Jul 2017, 6(F1000 Faculty Rev):1084
<https://doi.org/10.12688/f1000research.11133.1>

Latest published: 07 Jul 2017, 6(F1000 Faculty Rev):1084
<https://doi.org/10.12688/f1000research.11133.1>

Abstract

With the advent of novel therapies targeting eosinophils, there has been renewed interest in understanding the basic biology of this unique cell. In this context, murine models and human studies have continued to highlight the role of the eosinophil in homeostatic functions and immunoregulation. This review will focus on recent advances in our understanding of eosinophil biology that are likely to have important consequences on the development and consequences of eosinophil-targeted therapies. Given the breadth of the topic, the discussion will be limited to three areas of interest: the eosinophil life cycle, eosinophil heterogeneity, and mechanisms of cell-cell communication.

Keywords

eosinophils, life cycle, heterogeneity, cell-cell communication

Open Peer Review

Approval Status

	1	2
version 1 07 Jul 2017		

Faculty Reviews are review articles written by the prestigious Members of **Faculty Opinions**. The articles are commissioned and peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

1. **Ariel Munitz**, Tel-Aviv University, Tel-Aviv, Israel

2. **Andrew Wardlaw**, University of Leicester, Leicester, UK

Any comments on the article can be found at the end of the article.

Corresponding author: Amy Klion (aklion@niaid.nih.gov)

Competing interests: The author declares that she has no competing interests.

Grant information: This work was funded by the Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Copyright: © 2017 Klion A. This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. The author(s) is/are employees of the US Government and therefore domestic copyright protection in USA does not apply to this work. The work may be protected under the copyright laws of other jurisdictions when used in those jurisdictions.

How to cite this article: Klion A. **Recent advances in understanding eosinophil biology [version 1; peer review: 2 approved]**

F1000Research 2017, 6(F1000 Faculty Rev):1084 <https://doi.org/10.12688/f1000research.11133.1>

First published: 07 Jul 2017, 6(F1000 Faculty Rev):1084 <https://doi.org/10.12688/f1000research.11133.1>

Introduction

Eosinophils are primitive myeloid cells found in all vertebrate species, including zebrafish¹. Historically, eosinophils have been viewed as effector cells involved primarily in the defense against parasites and in allergic inflammation, but the role of these cells in homeostasis and immunoregulation has become increasingly clear over the past decade^{2,3}. This is due in large part to the development of several strains of eosinophil-deficient mice^{4–6}, which have been instrumental in demonstrating a role for murine eosinophils in a wide variety of fundamental processes, including antibody production^{7,8}, glucose homeostasis⁹, and muscle and liver regeneration^{10,11}. Although preliminary findings corroborate a role for eosinophils in many of these processes in humans^{7,8,12,13}, definitive data have been elusive. In this regard, the recent explosion in the development of novel therapies that deplete eosinophils or affect eosinophil function^{14,15} provides a unique opportunity to increase our understanding of the role of this multifunctional and complex cell in human health and disease.

A comprehensive list of all of the important recent findings in eosinophil biology is beyond the scope of this review. Consequently, this article will focus on three aspects of eosinophil biology in which there have been major advances in the past several years: (1) the eosinophil life cycle, (2) eosinophil heterogeneity, and (3) mechanisms of cell-cell communication. Each of these has important implications for eosinophil-targeted therapies, especially since the long-term consequences of eosinophil depletion will depend not only on the efficacy of depletion of eosinophils but also on the processes that are perturbed in their absence.

The eosinophil life cycle

Eosinophilopoiesis

As is true of other circulating leukocytes, eosinophils differentiate from CD34⁺ progenitor cells in the bone marrow under the influence of a variety of lineage-specific and common transcription factors and cytokines (reviewed in 16). Beginning in the late 1980s with the discovery of the critical roles of the cytokine, interleukin-5 (IL-5), and the GATA transcription factors^{17–19}, the delineation of the sequential steps involved in eosinophilopoiesis has been instrumental in the development of a number of innovative mouse models to study eosinophilic disorders. These include the *AdblGATA-1* and *PHIL* eosinophil-less mice^{4,5} and the recently described *MBP-1/EPX* double-knockout eosinophil-less mouse⁶ and *Cre* recombinase eosinophil transgenic mouse²⁰. A new addition to this cohort is the recently described *Xbp1*-null mouse, in which deletion of the transcription factor, *Xbp1*, in multi-lineage hematopoietic progenitor cells causes a lineage-restricted late maturational arrest in eosinophil development (due at least in part to dysregulated production and assembly of granule proteins) and a total absence of circulating eosinophils²¹. Since early eosinophilopoiesis is unaffected in the *Xbp1*-null mouse and eosinophil precursors (EoPs) appear to be normal, this model is likely to provide a unique window into the role of eosinophil granule protein packaging in the terminal differentiation of eosinophils. *Xbp1* may also prove to be a novel lineage-specific therapeutic target for the treatment of eosinophilic disorders.

New transcription factors involved in the negative regulation of eosinophil development have also been recently identified. These include RhoH—a negative regulator of eosinophilopoiesis that is upregulated by IL-5, IL-3, and granulocyte-macrophage colony-stimulating factor (GM-CSF) and likely functions through GATA2²²—and Olig2, which is expressed late in eosinophil development and regulates expression of Siglec-8, an inhibitory receptor restricted to eosinophils, basophils, and mast cells²³. Finally, a more global approach using genome-wide transcriptome and epigenome analysis has both confirmed prior findings and led to the identification of previously unreported transcriptional regulators of eosinophil development, including *Helios* and *Aiolos*²⁴.

EoPs were first identified in the peripheral blood and nasal mucosa of atopic subjects in the late 1980s by using colony-forming assays^{25,26}. These results were confirmed by many different groups using flow cytometry, immunohistochemical staining, or *in situ* hybridization (or a combination of these) to identify CD34⁺, and more recently CD34⁺IL-5R α ⁺, cells in the blood and tissues of patients with allergic disorders^{27–30}. Increased circulating levels of EoPs have also been described in patients with active eosinophilic esophagitis (EoE), a food antigen-driven eosinophilic disorder³¹. The clinical relevance of these findings is supported by the correlation of EoPs in blood and sputum with disease activity^{27,31,32}.

Whereas the acquisition of IL-5R α on the surface of CD34⁺ cells has long been recognized as a critical event in the expansion and maturation of EoPs^{33,34}, the factors driving eosinophil lineage commitment are less well understood. Recent data suggest that IL-33 may play a significant role in this process. IL-33 and its receptor, ST2, were first described in 2005³⁵. Although a role for IL-33 in the induction of IL-5 and eosinophilia was first proposed at that time, these effects were attributed to the production of IL-5 by Th2 cells. Eosinophil expression of ST2 was subsequently demonstrated, suggesting that IL-33 might also interact directly with eosinophils³⁶. In their recent report, Johnston *et al.* have taken this one step further, demonstrating in a mouse model that ST2 is expressed on EoPs and that IL-33 both expands the EoP compartment and upregulates IL-5R α expression on EoPs³⁷. The authors conclude that IL-33 precedes IL-5 in regulating lineage commitment in eosinophils and that this is important in maintaining eosinophil homeostasis. In a separate study, Anderson *et al.* showed that IL-5 and IL-33 produced in the lung (but not bone marrow) in a murine model of *Alternaria* exposure lead to increased numbers of eosinophils and EoPs in bone marrow³⁸, suggesting that IL-33 also plays an important role in allergen-induced eosinophilia. The capacity of IL-33 to directly induce murine EoP production of Th2 and inflammatory cytokines associated with allergic inflammation has also been reported³⁹. These data provide a potential explanation for the observation that anti-IL-5 treatment with mepolizumab depletes blood eosinophils but not their precursors in the bone marrow of patients with asthma⁴⁰. Of note, mepolizumab treatment did lead to a decrease in CD34⁺IL-5R α ⁺ cells in bronchial mucosal biopsies from the same patients, suggesting potential differences in IL-5 dependence between lung and bone marrow EoPs.

Whereas the IL-33/ST2 axis clearly plays an important role in the regulation of bone marrow eosinophilia, recent data describing the opposing roles of paired immunoglobulin-like receptor A (PIR-A) and PIR-B on IL-5-induced eosinophil development illustrate the complexities of this process and the implications for eosinophil-associated pathogenesis⁴¹. Using a murine model, the authors demonstrated that PIR-B, in the context of self-recognition through major histocompatibility complex (MHC) class I, allowed IL-5-induced eosinophilopoiesis by blocking the pro-apoptotic activity of PIR-A. Importantly, mice lacking PIR-B had decreased lung eosinophilia in response to aeroallergen challenge. Eosinophil expression of the human homologues of PIR-A and PIR-B, leukocyte immunoglobulin-like receptors B1 and B2 (LILRB1 and LILRB2), has been described⁴², although their function has not been studied to date.

Many of the transcription factors and cytokines involved in eosinophilopoiesis have also been shown to play a role in the development of other lineages, most notably basophils and mast cells. This has important implications for eosinophil-targeted therapies, which may or may not deplete multiple cell types. In an elegant study using reporter mice expressing enhanced fluorescent green protein from GATA-1 and single-cell sequencing, Drissen *et al.* demonstrated that eosinophils, mast cells, and likely basophils (although this was not examined directly) are generated from a dedicated progenitor that arises prior to the segregation of the erythroid-megakaryocytic and lymphoid lineages, rather than from a common myeloid precursor⁴³. The applicability of these data to the human system awaits confirmation.

Eosinophil trafficking

Since tissue eosinophilia is integral to the pathogenesis of a wide variety of eosinophilic disorders, the mediators involved in eosinophil trafficking to the tissue during inflammation provide ideal therapeutic targets. Most early interest focused on eotaxins (CCL11, CCL24, and CCL26) and their receptor CCR3 because of their role in promoting tissue eosinophilia in a wide variety of eosinophilic disorders, including asthma, eosinophilic gastrointestinal (GI) disease, eosinophilic skin diseases, and most recently eosinophil trafficking to the heart in a murine model of myocarditis⁴⁴. Despite promising pre-clinical data, however, a clinical trial with an oral CCR3 antagonist was ineffective in reducing sputum eosinophilia in patients with asthma⁴⁵.

IL-13 is known to promote eotaxin production by a variety of cell types. Consequently, therapies targeting IL-13 would be expected to block migration of eosinophils from the bloodstream to the tissue. Consistent with this hypothesis, clinical trials of monoclonal antibodies to IL-13 or its receptor in patients with asthma have consistently shown increases in peripheral blood eosinophil counts^{46–48}, and tissue eosinophilia was decreased in a recent phase 2 study of anti-IL-13 antibody in EoE⁴⁹. Unfortunately, the effects on eosinophil numbers were mild to moderate in most of these studies, suggesting that the IL-13/eotaxin/eosinophil connection may be more complex than previously thought.

The recent demonstration that the inhibitory receptor, PIR-B, is involved in preventing IL-13-induced esophageal eosinophilia in

a murine model of EoE provides an important example in support of this conclusion⁵⁰.

Eosinophil senescence

Although the role of cytokines and other mediators in eosinophil survival has been recognized for more than 30 years, very little is known about the mechanisms by which these pro-survival cues determine the eosinophil life span. The recent description of a long non-coding RNA, *Morrbid*, which enables allele-specific control of pro-apoptotic gene transcription in response to extracellular cytokine signals, begins to provide an answer to this very basic question⁵¹. Initially described in mice, *Morrbid* expression was increased in eosinophils from patients with hypereosinophilic syndromes and correlated with serum IL-5 levels, suggesting that *Morrbid* plays a similar regulatory role in human eosinophils and may be a novel target for therapeutic intervention. As mentioned in the Eosinophilopoiesis section, our understanding of the regulation and function of inhibitory receptors, including Siglec-8^{23,36,52,53}, which are important in eosinophil apoptosis, has also advanced significantly in recent years. This has led to the development of novel therapeutic agents for eosinophilic disorders, including two monoclonal antibodies to Siglec-8 that are currently in clinical trials for nasal polyposis and systemic mastocytosis in Europe.

Eosinophil heterogeneity

Eosinophil heterogeneity was first proposed in the early 1980s with the description of hypodense eosinophils in the blood of patients with eosinophilia of varied etiologies, including allergic disease, helminth infection, and idiopathic hypereosinophilic syndrome^{54–56}. The reproduction of this phenomenon *in vitro* and its association with enhanced eosinophil cytotoxic activity and degranulation were described shortly thereafter^{57,58}. Since that time, numerous studies have confirmed the ability of a wide variety of activating stimuli to induce degranulation and a “hypodense” phenotype. Whether all hypodense eosinophils are functionally equivalent despite differences in the activating stimulus remains unclear.

The first evidence that tissue eosinophils might be different from blood eosinophils came from studies in the 1980s comparing density and respiratory burst in blood and bronchoalveolar lavage eosinophils from individuals with pulmonary eosinophilia⁵⁹. Subsequent studies have demonstrated changes in expression of surface receptors, including IL-5R α and integrins, on eosinophils recruited to the lung following segmental allergen challenge^{60–62}. More recently, several groups have demonstrated associations between specific surface phenotypes and eosinophil function in murine models of allergic inflammation in the lung. In one such study, Mesnil *et al.* characterized two distinct eosinophil subsets in the lungs of mice following allergen challenge⁶³. These subsets, resident (rEos) and inflammatory (iEos) eosinophil, differed not only in location (parenchymal versus peribronchial), nuclear morphology (ring-shaped versus segmented), surface phenotype (Siglec-F^{int}CD62L⁺CD101^{lo} versus Siglec-F^{hi}CD62L⁺CD101^{hi}), and dependence on IL-5 (independent versus dependent) but also in their ability to down-modulate the inflammatory response⁶³. Although similar populations have not been functionally characterized in humans, parenchymal rEos in non-asthmatic lungs displayed

a different surface phenotype than iEos in the sputa of patients with eosinophilic asthma⁶³. Whether the presence of IL-5-independent rEos might explain the clinical efficacy of anti-IL-5 antibody therapy in asthma, despite the persistence of tissue eosinophilia⁶⁴, remains to be seen. Using a different set of surface markers (Siglec F and Gr1), Percopo *et al.* identified two morphologically similar eosinophil populations with different cytokine profiles in mouse lung following allergen challenge⁶⁵.

The GI tract provides another example of the potential differences between tissue and blood eosinophils. Eosinophils are normal residents of the lamina propria of the GI tract and, unlike the situation in other tissues, appear to undergo degranulation under homeostatic conditions^{66,67}. The relevance of this finding has become increasingly clear with the demonstration that eosinophils in the GI tract play important roles in mucosal immunity, including the promotion of IgA class switching and the maintenance of IgA plasma cells^{8,68,69}. Although eosinophils increase in the intestine in a number of pathological settings—including intestinal nematode infection, inflammatory bowel disease, and eosinophilic GI disorders—and clearly can contribute to tissue inflammation and damage, recent data from several groups suggest that they may help limit tissue destruction and preserve the intestinal barrier in some settings. Examples include the requirement for eosinophils in the suppression of Th2 responses in Peyer's patches during an intestinal nematode infection in mice⁷⁰ and for IL-25-mediated maintenance of the intestinal barrier during murine infection with *Clostridium difficile* infection⁷¹. Of note, similarities between IL-25 expression in intestinal biopsies in mice and humans with *C. difficile* infection suggest that eosinophils may also be important in the maintenance of tissue integrity in human infection⁷². These protective functions of eosinophils in GI disease seem to be more pronounced in the tissue. In support of this, recent studies have demonstrated that murine lamina propria eosinophils, but not blood eosinophils, are able to induce differentiation of naïve T cells into regulatory T cells *in vitro*⁷² and suppress differentiation of Th17 cells through production of IL-1Ra⁷³. Although abnormal responses to infection have not been reported in patients receiving eosinophil-depleting therapies, vigilance is needed as these therapies reach a wider population with exposure to helminths and other infectious agents.

Cell-cell communication

Eosinophils have a complex subcellular structure that includes primary and secondary granules, lipid bodies, and a dynamic intracellular vesicular system⁷⁴. Moreover, contained within their secondary granules are cationic granule proteins and a host of preformed cytokines and other soluble mediators that can be rapidly mobilized for secretion in response to a wide variety of stimuli⁷⁵. Although a variety of secretory processes have been described (piecemeal degranulation, exocytosis, and cytolysis), the mechanisms by which eosinophils selectively secrete mediators are incompletely understood and remain an active area of research. Some of the more exciting recent advances in this field are described below.

Surface receptors

CD63 is a member of the transmembrane-4 glycoprotein superfamily (tetraspanins) that is found on the surface of secretory granules in multiple cell types, including eosinophils. Translocation

of CD63 to the eosinophil cell surface during piecemeal degranulation was first demonstrated in 2002⁷⁶. Recent studies using CD63 labeling provide evidence for distinct CD63-dependent secretory processes in eosinophils depending on the stimulus provided (piecemeal degranulation in response to CCL11 versus compound exocytosis in response to tumor necrosis factor alpha, or TNFα)⁷⁷.

Eosinophil-derived extracellular DNA traps

Eosinophil-derived extracellular DNA traps (EETs) containing eosinophil granules were first described in 2008 in the GI tract, where they were believed to play a primary role in antibacterial defense⁷⁸. Although these initial EETs contained mitochondrial DNA that was catapulted from an intact cell, subsequent studies have demonstrated that eosinophils can also release nuclear DNA into the extracellular space during cytolysis (ETosis)⁷⁹. EETs have been described in a variety of tissues, including skin, lung, and the GI tract, where their presence has been correlated with disease activity⁸⁰. More recently, EETs have been identified in eosinophil-rich secretions from patients with eosinophilic rhinosinusitis and otitis media⁸¹. Ultrastructural analysis of ultrathin sections using transmission electron microscopy demonstrated globular chromatin fibers containing intact eosinophil granules, providing a potential explanation for persistent effects of eosinophilic inflammation once the eosinophil itself is no longer present.

Exosomes

Secreted microvesicles that are believed to function in extracellular communication, exosomes have recently been demonstrated in the culture supernatants of human eosinophils^{82,83}. As expected, eosinophil exosomes express CD63 and CD9 on their surface and contain a variety of eosinophil proteins, including eosinophil cationic protein and eosinophil peroxidase⁸⁴. Eosinophil production of exosomes was increased in patients with asthma and in response to *in vitro* stimulation with CCL11, TNFα, or interferon gamma^{82,83}. Moreover, eosinophil-derived exosomes induced an increase in reactive oxygen intermediates by eosinophils and could induce eosinophil adhesion and chemotaxis *in vitro*⁸⁴. Since the composition of eosinophil exosomes appears to be similar between asthmatic patients and normal controls, these data suggest that selective packaging of mediators into exosomes may play an important role in modulating the outcomes of eosinophil activation in different settings.

Conclusions and therapeutic implications

The past several years have seen the publication of the eosinophil transcriptome, proteome, and epigenome^{85–88}. These tools, coupled with the availability of innovative mouse models and increasing numbers of targeted therapies in humans, are likely to dramatically increase our understanding of the basic biology of eosinophils and their role in a wide variety of disorders associated with blood and tissue eosinophilia. Conversely, unraveling the complexity of the eosinophil and its role in homeostasis and pathogenesis will certainly lead to the identification of novel therapeutic agents, as evidenced by the development of monoclonal antibodies to IL-5 and IL-5 receptor for the treatment of eosinophilic asthma and other eosinophilic disorders. Despite these advances, a number of questions remain, including the morphological and functional features that define eosinophil activation, the relationship of these

features to disease pathogenesis, and the long-term safety of therapies that target eosinophils, particularly those that deplete eosinophils more completely in the tissues than currently approved agents and those that concomitantly target additional lineages, including mast cells and basophils. The interactions between eosinophils and other cells in the bone marrow, blood, and tissues are key factors in this regard. Negotiating the balance between eosinophil-driven pathogenesis and maintenance of homeostasis will be the next major challenge.

Abbreviations

EET, eosinophil-derived extracellular DNA trap; EoE, eosinophilic esophagitis; EoP, eosinophil precursor; GI, gastrointestinal; iEos, inflammatory eosinophil; IL, interleukin; PIR, paired

immunoglobulin-like receptor; rEos, resident eosinophil; TNF α , tumor necrosis factor alpha.

Competing interests

The author declares that she has no competing interests.

Grant information

This work was funded by the Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

References

1. Balla KM, Lugo-Villarino G, Spitsbergen JM, *et al.*: Eosinophils in the zebrafish: prospective isolation, characterization, and eosinophilia induction by helminth determinants. *Blood*. 2010; 116(19): 3944–54.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | **F1000 Recommendation**
2. Wen T, Rothenberg ME: The Regulatory Function of Eosinophils. *Microbiol Spectr*. 2016; 4(5).
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
3. Rosenberg HF, Dyer KD, Foster PS: Eosinophils: changing perspectives in health and disease. *Nat Rev Immunol*. 2013; 13(1): 9–22.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
4. Yu C, Cantor AB, Yang H, *et al.*: 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*. 2002; 195(11): 1387–95.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
5. Lee JJ, Dimina D, Macias MP, *et al.*: Defining a link with asthma in mice congenitally deficient in eosinophils. *Science*. 2004; 305(5691): 1773–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | **F1000 Recommendation**
6. Doyle AD, Jacobsen EA, Ochkur SI, *et al.*: Expression of the secondary granule proteins major basic protein 1 (MBP-1) and eosinophil peroxidase (EPX) is required for eosinophilopoiesis in mice. *Blood*. 2013; 122(5): 781–90.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
7. Chu VT, Fröhlich A, Steinhauser G, *et al.*: Eosinophils are required for the maintenance of plasma cells in the bone marrow. *Nat Immunol*. 2011; 12(2): 151–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | **F1000 Recommendation**
8. Chu VT, Beller A, Rausch S, *et al.*: Eosinophils promote generation and maintenance of immunoglobulin-A-expressing plasma cells and contribute to gut immune homeostasis. *Immunity*. 2014; 40(4): 582–93.
[PubMed Abstract](#) | [Publisher Full Text](#) | **F1000 Recommendation**
9. Wu D, Molofsky AB, Liang HE, *et al.*: Eosinophils sustain adipose alternatively activated macrophages associated with glucose homeostasis. *Science*. 2011; 332(6026): 243–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | **F1000 Recommendation**
10. Heredia JE, Mukundan L, Chen FM, *et al.*: Type 2 innate signals stimulate fibro/adipogenic progenitors to facilitate muscle regeneration. *Cell*. 2013; 153(2): 376–88.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | **F1000 Recommendation**
11. Goh YP, Henderson NC, Heredia JE, *et al.*: Eosinophils secrete IL-4 to facilitate liver regeneration. *Proc Natl Acad Sci U S A*. 2013; 110(24): 9914–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | **F1000 Recommendation**
12. Brestoff JR, Kim BS, Saenz SA, *et al.*: Group 2 innate lymphoid cells promote beiging of white adipose tissue and limit obesity. *Nature*. 2015; 519(7542): 242–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | **F1000 Recommendation**
13. Amini M, Bashirova D, Prins BP, *et al.*: Eosinophil Count Is a Common Factor for Complex Metabolic and Pulmonary Traits and Diseases: The LifeLines Cohort Study. *PLoS One*. 2016; 11(12): e0168480.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
14. Legrand F, Klion AD: Biologic therapies targeting eosinophils: current status and future prospects. *J Allergy Clin Immunol Pract*. 2015; 3(2): 167–74.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
15. Bochner BS: Novel Therapies for Eosinophilic Disorders. *Immunol Allergy Clin North Am*. 2015; 35(3): 577–98.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
16. Anon: Eosinophilopoiesis. In: *Eosinophils in health and disease*. Elsevier, 2013; 73–119.
[Publisher Full Text](#)
17. Lopez AF, Begley CG, Williamson DJ, *et al.*: Murine eosinophil differentiation factor. An eosinophil-specific colony-stimulating factor with activity for human cells. *J Exp Med*. 1986; 163(5): 1085–99.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
18. Yamaguchi Y, Suda T, Suda J, *et al.*: Purified interleukin 5 supports the terminal differentiation and proliferation of murine eosinophilic precursors. *J Exp Med*. 1988; 167(1): 43–56.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
19. Zon LI, Yamaguchi Y, Yee K, *et al.*: Expression of mRNA for the GATA-binding proteins in human eosinophils and basophils: potential role in gene transcription. *Blood*. 1993; 81(12): 3234–41.
[PubMed Abstract](#)
20. Doyle AD, Jacobsen EA, Ochkur SI, *et al.*: Homologous recombination into the eosinophil peroxidase locus generates a strain of mice expressing Cre recombinase exclusively in eosinophils. *J Leukoc Biol*. 2013; 94(1): 17–24.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
21. Bettigole SE, Lis R, Adoro S, *et al.*: The transcription factor XBP1 is selectively required for eosinophil differentiation. *Nat Immunol*. 2015; 16(8): 829–37.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | **F1000 Recommendation**
22. Stoeckle C, Geering B, Yousefi S, *et al.*: RhoH is a negative regulator of eosinophilopoiesis. *Cell Death Differ*. 2016; 23(12): 1961–72.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | **F1000 Recommendation**
23. Hwang SM, Uhm TG, Lee SK, *et al.*: Olig2 is expressed late in human eosinophil development and controls Siglec-8 expression. *J Leukoc Biol*. 2016; 100(4): 711–23.
[PubMed Abstract](#) | [Publisher Full Text](#)
24. Bouffi C, Kartashov AV, Schollaert KL, *et al.*: Transcription Factor Repertoire of Homeostatic Eosinophilopoiesis. *J Immunol*. 2015; 195(6): 2683–95.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | **F1000 Recommendation**
25. Otsuka H, Dolovich J, Richardson M, *et al.*: Metachromatic cell progenitors and specific growth and differentiation factors in human nasal mucosa and polyps. *Am Rev Respir Dis*. 1987; 136(3): 710–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
26. Gibson PG, Dolovich J, Girgis-Gabardo A, *et al.*: The inflammatory response in asthma exacerbation: changes in circulating eosinophils, basophils and their progenitors. *Clin Exp Allergy*. 1990; 20(6): 661–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
27. Robinson DS, Damia R, Zeibecoglou K, *et al.*: CD34(+)/interleukin-5Ralpha messenger RNA+ cells in the bronchial mucosa in asthma: potential airway eosinophil progenitors. *Am J Respir Cell Mol Biol*. 1999; 20(1): 9–13.
[PubMed Abstract](#) | [Publisher Full Text](#)
28. Sergejeva S, Johansson AK, Malmhäll C, *et al.*: Allergen exposure-induced differences in CD34+ cell phenotype: relationship to eosinophilopoietic responses in different compartments. *Blood*. 2004; 103(4): 1270–7.
[PubMed Abstract](#) | [Publisher Full Text](#)

29. Cameron L, Christodoulopoulos P, Lavigne F, *et al.*: Evidence for local eosinophil differentiation within allergic nasal mucosa: inhibition with soluble IL-5 receptor. *J Immunol.* 2000; 164(3): 1538–45.
[PubMed Abstract](#) | [Publisher Full Text](#)
30. Sehmi R, Howie K, Sutherland DR, *et al.*: Increased levels of CD34+ hemopoietic progenitor cells in atopic subjects. *Am J Respir Cell Mol Biol.* 1996; 15(5): 645–55.
[PubMed Abstract](#) | [Publisher Full Text](#)
31. Morris DW, Stucke EM, Martin LJ, *et al.*: Eosinophil progenitor levels are increased in patients with active pediatric eosinophilic esophagitis. *J Allergy Clin Immunol.* 2016; 138(3): 915–918.e5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
32. Sehmi R, Smith SG, Kjarsgaard M, *et al.*: Role of local eosinophilopoietic processes in the development of airway eosinophilia in prednisone-dependent severe asthma. *Clin Exp Allergy.* 2016; 46(6): 793–802.
[PubMed Abstract](#) | [Publisher Full Text](#)
33. Sehmi R, Wood LJ, Watson R, *et al.*: Allergen-induced increases in IL-5 receptor alpha-subunit expression on bone marrow-derived CD34+ cells from asthmatic subjects. A novel marker of progenitor cell commitment towards eosinophilic differentiation. *J Clin Invest.* 1997; 100(10): 2466–75.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
34. Tomaki M, Zhao LL, Lundahl J, *et al.*: Eosinophilopoiesis in a murine model of allergic airway eosinophilia: involvement of bone marrow IL-5 and IL-5 receptor alpha. *J Immunol.* 2000; 165(7): 4040–50.
[PubMed Abstract](#) | [Publisher Full Text](#)
35. **F** Schmitz J, Owyang A, Oldham E, *et al.*: IL-33, an interleukin-1-like cytokine that signals via the IL-1 receptor-related protein ST2 and induces T helper type 2-associated cytokines. *Immunity.* 2005; 23(5): 479–90.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
36. Cherry WB, Yoon J, Bartemes KR, *et al.*: A novel IL-1 family cytokine, IL-33, potentially activates human eosinophils. *J Allergy Clin Immunol.* 2008; 121(6): 1484–90.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
37. **F** Johnston LK, Hsu CL, Krier-Burris RA, *et al.*: IL-33 Precedes IL-5 in Regulating Eosinophil Commitment and Is Required for Eosinophil Homeostasis. *J Immunol.* 2016; 197(9): 3445–53.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
38. Anderson EL, Kobayashi T, Iijima K, *et al.*: IL-33 mediates reactive eosinophilopoiesis in response to airborne allergen exposure. *Allergy.* 2016; 71(7): 977–88.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
39. Tsuzuki H, Arinobu Y, Miyawaki K, *et al.*: Functional interleukin-33 receptors are expressed in early progenitor stages of allergy-related granulocytes. *Immunology.* 2017; 150(1): 64–73.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
40. Menzies-Gow A, Flood-Page P, Sehmi R, *et al.*: Anti-IL-5 (mepolizumab) therapy induces bone marrow eosinophil maturational arrest and decreases eosinophil progenitors in the bronchial mucosa of atopic asthmatics. *J Allergy Clin Immunol.* 2003; 111(4): 714–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
41. Ben Baruch-Morgenstern N, Shik D, Moshkovits I, *et al.*: Paired immunoglobulin-like receptor A is an intrinsic, self-limiting suppressor of IL-5-induced eosinophil development. *Nat Immunol.* 2014; 15(1): 36–44.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
42. Tedla N, Bandeira-Melo C, Tassinari P, *et al.*: Activation of human eosinophils through leukocyte immunoglobulin-like receptor 7. *Proc Natl Acad Sci U S A.* 2003; 100(3): 1174–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
43. **F** Drissen R, Buza-Vidas N, Woll P, *et al.*: Distinct myeloid progenitor-differentiation pathways identified through single-cell RNA sequencing. *Nat Immunol.* 2016; 17(6): 666–76.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
44. **F** Diny NL, Hou X, Barin JG, *et al.*: Macrophages and cardiac fibroblasts are the main producers of eotaxins and regulate eosinophil trafficking to the heart. *Eur J Immunol.* 2016; 46(12): 2749–60.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
45. Neighbour H, Boulet LP, Lemiere C, *et al.*: Safety and efficacy of an oral CCR3 antagonist in patients with asthma and eosinophilic bronchitis: a randomized, placebo-controlled clinical trial. *Clin Exp Allergy.* 2014; 44(4): 508–516.
[PubMed Abstract](#) | [Publisher Full Text](#)
46. **F** Wenzel S, Castro M, Corren J, *et al.*: Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β_2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *Lancet.* 2016; 388(10039): 31–44.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
47. Hanania NA, Korenblat P, Chapman KR, *et al.*: Efficacy and safety of lebrikizumab in patients with uncontrolled asthma (LAVOLTA I and LAVOLTA II): replicate, phase 3, randomised, double-blind, placebo-controlled trials. *Lancet Respir Med.* 2016; 4(10): 781–96.
[PubMed Abstract](#) | [Publisher Full Text](#)
48. Brightling CE, Chaney P, Leigh R, *et al.*: Efficacy and safety of tralokinumab in patients with severe uncontrolled asthma: a randomised, double-blind, placebo-controlled, phase 2b trial. *Lancet Respir Med.* 2015; 3(9): 692–701.
[PubMed Abstract](#) | [Publisher Full Text](#)
49. Rothenberg ME, Wen T, Greenberg A, *et al.*: Intravenous anti-IL-13 mAb QAX576 for the treatment of eosinophilic esophagitis. *J Allergy Clin Immunol.* 2015; 135(2): 500–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
50. **F** Ben Baruch-Morgenstern N, Mingler MK, Stucke E, *et al.*: Paired Ig-like Receptor B Inhibits IL-13-Driven Eosinophil Accumulation and Activation in the Esophagus. *J Immunol.* 2016; 197(3): 707–14.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
51. Kotzin JJ, Spencer SP, McCright SJ, *et al.*: The long non-coding RNA *Morrbid* regulates *Bim* and short-lived myeloid cell lifespan. *Nature.* 2016; 537(7619): 239–43.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
52. Schleimer RP, Schnaar RL, Bochner BS: Regulation of airway inflammation by Siglec-8 and Siglec-9 sialoglycan ligand expression. *Curr Opin Allergy Clin Immunol.* 2016; 16(1): 24–30.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
53. Kano G, Bochner BS, Zimmermann N: Regulation of Siglec-8-induced intracellular reactive oxygen species production and eosinophil cell death by Src family kinases. *Immunobiology.* 2017; 222(2): 343–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
54. Fukuda T, Dunnette SL, Reed CE, *et al.*: Increased numbers of hypodense eosinophils in the blood of patients with bronchial asthma. *Am Rev Respir Dis.* 1985; 132(5): 981–5.
[PubMed Abstract](#)
55. Prin L, Capron M, Tonnel AB, *et al.*: Heterogeneity of human peripheral blood eosinophils: variability in cell density and cytotoxic ability in relation to the level and the origin of hypereosinophilia. *Int Arch Allergy Appl Immunol.* 1983; 72(4): 336–46.
[PubMed Abstract](#) | [Publisher Full Text](#)
56. White CJ, Maxwell CJ, Gallin JI: Changes in the structural and functional properties of human eosinophils during experimental hookworm infection. *J Infect Dis.* 1986; 154(5): 778–83.
[PubMed Abstract](#) | [Publisher Full Text](#)
57. Rothenberg ME, Owen WF Jr, Silberstein DS, *et al.*: Eosinophils cocultured with endothelial cells have increased survival and functional properties. *Science.* 1987; 237(4815): 645–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
58. Peters MS, Gleich GJ, Dunnette SL, *et al.*: Ultrastructural study of eosinophils from patients with the hypereosinophilic syndrome: a morphological basis of hypodense eosinophils. *Blood.* 1988; 71(3): 780–5.
[PubMed Abstract](#)
59. Prin L, Charon J, Capron M, *et al.*: Heterogeneity of human eosinophils. II. Variability of respiratory burst activity related to cell density. *Clin Exp Immunol.* 1984; 57(3): 735–42.
[PubMed Abstract](#) | [Free Full Text](#)
60. Johansson MW, Kelly EA, Busse WW, *et al.*: Up-regulation and activation of eosinophil integrins in blood and airway after segmental lung antigen challenge. *J Immunol.* 2008; 180(11): 7622–35.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
61. Sedgwick JB, Calhoun WJ, Vrtis RF, *et al.*: Comparison of airway and blood eosinophil function after *in vivo* antigen challenge. *J Immunol.* 1992; 149(11): 3710–8.
[PubMed Abstract](#)
62. Kroegel C, Liu MC, Hubbard WC, *et al.*: Blood and bronchoalveolar eosinophils in allergic subjects after segmental antigen challenge: surface phenotype, density heterogeneity, and prostanoid production. *J Allergy Clin Immunol.* 1994; 93(4): 725–34.
[PubMed Abstract](#) | [Publisher Full Text](#)
63. **F** Mesnil C, Raulier S, Paulissen G, *et al.*: Lung-resident eosinophils represent a distinct regulatory eosinophil subset. *J Clin Invest.* 2016; 126(9): 3279–95.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
64. Flood-Page P, Menzies-Gow A, Phipps S, *et al.*: Anti-IL-5 treatment reduces deposition of ECM proteins in the bronchial subepithelial basement membrane of mild atopic asthmatics. *J Clin Invest.* 2003; 112(7): 1029–36.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
65. Percopo CM, Brenner TA, Ma M, *et al.*: SiglecF^{hi}Gr1^{hi} eosinophils are a distinct subpopulation within the lungs of allergen-challenged mice. *J Leukoc Biol.* 2017; 101(1): 321–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
66. Kato M, Kephart GM, Morikawa A, *et al.*: Eosinophil infiltration and degranulation in normal human tissues: evidence for eosinophil degranulation in normal gastrointestinal tract. *Int Arch Allergy Immunol.* 2001; 125(Suppl 1): 55–58.
[PubMed Abstract](#)
67. DeBrosse CW, Case JW, Putnam PE, *et al.*: Quantity and distribution of eosinophils in the gastrointestinal tract of children. *Pediatr Dev Pathol.* 2006; 9(3): 210–218.
[PubMed Abstract](#) | [Publisher Full Text](#)
68. **F** Travers J, Rothenberg ME: Eosinophils in mucosal immune responses. *Mucosal Immunol.* 2015; 8(3): 464–75.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)

69. **F** Jung Y, Wen T, Mingler MK, *et al.*: **IL-1 β in eosinophil-mediated small intestinal homeostasis and IgA production.** *Mucosal Immunol.* 2015; 8(4): 930–42.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
70. **F** Strandmark J, Steinfeldt S, Berek C, *et al.*: **Eosinophils are required to suppress Th2 responses in Peyer's patches during intestinal infection by nematodes.** *Mucosal Immunol.* 2017; 10(3): 661–672.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
71. **F** Buonomo EL, Cowardin CA, Wilson MG, *et al.*: **Microbiota-Regulated IL-25 Increases Eosinophil Number to Provide Protection during *Clostridium difficile* Infection.** *Cell Rep.* 2016; 16(2): 432–43.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
72. **F** Chen HH, Sun AH, Ojcius DM, *et al.*: **Eosinophils from Murine Lamina Propria Induce Differentiation of Naïve T Cells into Regulatory T Cells via TGF- β 1 and Retinoic Acid.** *PLoS One.* 2015; 10(11): e0142881.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
73. **F** Sugawara R, Lee EJ, Jang MS, *et al.*: **Small intestinal eosinophils regulate Th17 cells by producing IL-1 receptor antagonist.** *J Exp Med.* 2016; 213(4): 555–67.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
74. Melo RC, Weller PF: **Vesicular trafficking of immune mediators in human eosinophils revealed by immunoelectron microscopy.** *Exp Cell Res.* 2016; 347(2): 385–90.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
75. Spencer LA, Bonjour K, Melo RC, *et al.*: **Eosinophil secretion of granule-derived cytokines.** *Front Immunol.* 2014; 5: 496.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
76. Mahmudi-Azer S, Downey GP, Moqbel R: **Translocation of the tetraspanin CD63 in association with human eosinophil mediator release.** *Blood.* 2002; 99(11): 4039–47.
[PubMed Abstract](#) | [Publisher Full Text](#)
77. Carmo LA, Bonjour K, Ueki S, *et al.*: **CD63 is tightly associated with intracellular, secretory events chaperoning piecemeal degranulation and compound exocytosis in human eosinophils.** *J Leukoc Biol.* 2016; 100(2): 391–401.
[PubMed Abstract](#) | [Publisher Full Text](#)
78. **F** Yousefi S, Gold JA, Andina N, *et al.*: **Catapult-like release of mitochondrial DNA by eosinophils contributes to antibacterial defense.** *Nat Med.* 2008; 14(9): 949–53.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
79. Ueki S, Melo RC, Ghiran I, *et al.*: **Eosinophil extracellular DNA trap cell death mediates lytic release of free secretion-competent eosinophil granules in humans.** *Blood.* 2013; 121(11): 2074–83.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
80. Simon D, Radonjic-Hösl S, Straumann A, *et al.*: **Active eosinophilic esophagitis is characterized by epithelial barrier defects and eosinophil extracellular trap formation.** *Allergy.* 2015; 70(4): 443–52.
[PubMed Abstract](#) | [Publisher Full Text](#)
81. Ueki S, Konno Y, Takeda M, *et al.*: **Eosinophil extracellular trap cell death-derived DNA traps: Their presence in secretions and functional attributes.** *J Allergy Clin Immunol.* 2016; 137(1): 258–67.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
82. Akuthota P, Carmo LA, Bonjour K, *et al.*: **Extracellular Microvesicle Production by Human Eosinophils Activated by “Inflammatory” Stimuli.** *Front Cell Dev Biol.* 2016; 4: 117.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
83. Mazzeo C, Cañas JA, Zafra MP, *et al.*: **Exosome secretion by eosinophils: A possible role in asthma pathogenesis.** *J Allergy Clin Immunol.* 2015; 135(6): 1603–13.
[PubMed Abstract](#) | [Publisher Full Text](#)
84. Cañas JA, Sastre B, Mazzeo C, *et al.*: **Exosomes from eosinophils autoregulate and promote eosinophil functions.** *J Leukoc Biol.* 2017; 101(5): 1191–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
85. Wilkerson EM, Johansson MW, Hebert AS, *et al.*: **The Peripheral Blood Eosinophil Proteome.** *J Proteome Res.* 2016; 15(5): 1524–33.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
86. Barnig C, Alsaleh G, Jung N, *et al.*: **Circulating Human Eosinophils Share a Similar Transcriptional Profile in Asthma and Other Hypereosinophilic Disorders.** *PLoS One.* 2015; 10(11): e0141740.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
87. Straub C, Pazdrak K, Young TW, *et al.*: **Toward the Proteome of the Human Peripheral Blood Eosinophil.** *Proteomics Clin Appl.* 2009; 3(10): 1151–73.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
88. Shen ZJ, Hu J, Esnault S, *et al.*: **RNA Seq profiling reveals a novel expression pattern of TGF- β target genes in human blood eosinophils.** *Immunol Lett.* 2015; 167(1): 1–10.
[PubMed Abstract](#) | [Publisher Full Text](#)

Open Peer Review

Current Peer Review Status:

Editorial Note on the Review Process

Faculty Reviews are review articles written by the prestigious Members of **Faculty Opinions**. The articles are commissioned and peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

The reviewers who approved this article are:

Version 1

1. **Andrew Wardlaw**

University of Leicester, Leicester, UK

Competing Interests: No competing interests were disclosed.

2. **Ariel Munitz**

Department of Clinical Microbiology and Immunology, Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel

Competing Interests: No competing interests were disclosed.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research