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Editorial

Targeting interleukin-5 with benralizumab: a novel treatment for drug rash with eosinophilia and systemic symptoms (DRESS)

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Drug rash with eosinophilia and systemic symptoms (DRESS) is a potentially fatal systemic adverse drug hypersensitivity reaction that presents with fever, lymphadenopathy, rash, and multiple organ involvement.¹ Despite carrying a mortality rate of 10% and a complication rate of 30%, there is a lack of effective, evidence-based therapies for DRESS.¹ Although systemic corticosteroids are the current mainstay of treatment, their use is based on case reports and series, with no evidence from clinical trials.¹ Furthermore, both corticosteroids and current second-line therapies (e.g. immunosuppressants such as cyclosporine) frequently result in high failure rates, relapses upon discontinuation, and high rates of adverse events, such as severe infections.¹ Thus, there is a pressing need to better define the most appropriate therapeutic targets in DRESS, so that targeted therapies can be evaluated in clinical trials. Here, we argue that the interleukin-5 (IL-5) axis plays a critical role in DRESS pathophysiology, and that disruption

of this pathway can lead to rapid downregulation of eosinophilic inflammation and clinical remission in DRESS.

Cutaneous infiltration and tissue damage by eosinophils play a key pathogenic role in DRESS.² Eosinophilia is found in 80% of patients, and is included in both the RegiSCAR and Japanese DRESS diagnostic criteria.^{1, 2} Eosinophil infiltration into skin and other tissues is more pronounced in DRESS compared to other systemic drug reactions, highlighting their salient role in the pathophysiology of DRESS.² Eosinophil proliferation and differentiation is mainly mediated by IL-5, which is secreted by both eosinophils (in an autocrine fashion) as well as CD4+ and CD8+ T cells.² IL-5 then acts in synergy with the chemoattractants eotaxin-1 (CCL11) and thymus and activation-regulated chemokine (TARC/CCL17) to promote migration of eosinophils into tissue.² Compellingly, selective increases in eosinophil, IL-5, eotaxin-1, and TARC levels are seen in the acute phase of DRESS, when compared to patients with maculopapular drug eruption and Stevens-Johnson syndrome/toxic epidermal necrolysis.^{2, 3} IL-5 inhibition results in potent downregulation of eosinophilic inflammation, and has been posited as a major mechanism by which corticosteroids can alleviate symptoms in DRESS.^{2, 3} Thus, targeting IL-5 is a promising approach to achieve target specificity, while minimizing the undesirable adverse events associated with the broad immunosuppressants currently used to treat DRESS.

Binding of IL-5 to the IL-5 receptor (IL-5R) activates downstream intracellular signalling pathways including JAK/STAT, Ras/MAPK and PI3K, which in turn drive eosinophil activation.⁴ The rationale to target the IL-5/IL-5R pathway as a therapeutic target in DRESS is particularly compelling for several reasons. Firstly, it is readily accessible, as IL-5 is found in plasma and IL-5R is a heterodimer with high ligand specificity and an extracellular domain.⁴ Secondly, early animal studies showed that neutralizing antibodies against IL-5 and IL-5R have high efficacy in downregulating eosinophilic tissue damage, comparable to that of IL-5 and IL-5R gene knockouts.⁴ Finally, several monoclonal antibodies (mAbs) targeting IL-5 and IL-5R display favorable safety profiles in humans and are already FDA-approved for other eosinophil-mediated diseases.⁴

Two monoclonal antibodies that bind soluble IL-5 are currently available in the U.S. market: mepolizumab and reslizumab. Studies have shown that a single dose of these agents results in remarkable and dose-dependent reductions in blood and tissue eosinophils and soluble IL-5, which can occur as soon as 24 hours post-administration.⁴

Mepolizumab is a humanized IgG1 κ antibody that is FDA-approved for the treatment of severe eosinophilic asthma, hypereosinophilic syndrome, and eosinophilic granulomatosis with polyangiitis (EGPA).⁴ The recommended dosage is 100-300 mg once monthly by subcutaneous (SC) injection.⁴ The use of mepolizumab in DRESS has been described in one patient with a stem cell transplant for acute myeloid leukemia.⁵ This patient suffered from relapsing DRESS refractory to prednisolone 60-110 mg and multiple intravenous immunoglobulins (IVIG) infusions, yet she showed marked decrease in eosinophilia and clinical improvement within 1 week of a single dose of mepolizumab 100 mg SC. The decision to administer mepolizumab was made due to the unacceptable risk of immunosuppression with long-term high-dose prednisolone, given her recent stem cell transplant.

Reslizumab is a humanized IgG4 κ antibody with FDA approval for severe eosinophilic asthma.⁴ Although mechanistically similar to mepolizumab, reslizumab is given intravenously (3 mg/kg once monthly), and could potentially exhibit differences in Fc biologic activity due to its different isotype.⁴ There are no published reports of reslizumab use in DRESS.

However, of the biologics blocking the IL-5 axis, benralizumab has been the most well-characterized in DRESS. Benralizumab is a humanized afucosylated IgG1 κ anti-IL-5R α antibody approved by the FDA for severe eosinophilic asthma.⁴ Its recommended initial dose is 30 mg SC once monthly. Its administration results in a more potent and rapid drop in eosinophils and IL-5 in comparison to IL-5 binding antibodies, and thus might be the more favorable option in acute DRESS. Binding of benralizumab to IL-5R on eosinophils blocks IL-5 binding, thereby preventing eosinophil activation (Figure). However, benralizumab can also mediate eosinophil killing, either by complement-dependent cytotoxicity (CDC) or by antibody-dependent cellular cytotoxicity (ADCC).⁴ ADCC occurs when IgG Fc receptor-bearing effector cells recognize benralizumab-coated

eosinophils and release granzymes, perforins, and other cytotoxic molecules.⁴ One case report and two case series (n=6) have demonstrated the effectiveness of benralizumab, even in patients refractory to high-dose corticosteroids.^{6, 7} Marked clinical improvement, resolution of blood eosinophilia, and normalization of liver function tests has been noted within 2 days after benralizumab 30 mg SC.^{6, 7} Mechanistic studies have demonstrated that these improvements are associated with marked reductions in serum IL-5, IL-4, TNF, CCL3, CXCL6 and CD8, which play critical roles in eosinophil-mediated and cytotoxic T cell-mediated responses.^{6, 7}

Overall, IL-5/IL-5R-targeting mAbs show extreme promise in DRESS management, especially in severe corticosteroid-refractory cases. Potential advantages of these mAbs over current therapies include rapid onset, once-monthly dosing due to their long half-lives (15-24 days), and avoidance of the immunosuppressive and metabolic adverse events of prolonged high-dose systemic corticosteroids. These agents have been well-tolerated in clinical trials for other indications, with the most common adverse events being headache, injection site pain, back pain, and fatigue.⁴ It is critical that large-scale clinical trials of these agents in DRESS are conducted to verify their safety and efficacy.

Figure Legend

Figure. Structure and mechanisms of action of benralizumab.

A. IgG4 κ structure of benralizumab. The afucosylated glycan at the CH2 84.4 amino acid residue increases Fc receptor binding. B. Binding of benralizumab to the IL-5 receptor and binding of reslizumab and mepolizumab to IL-5 block IL-5-mediated eosinophil activation, differentiation,

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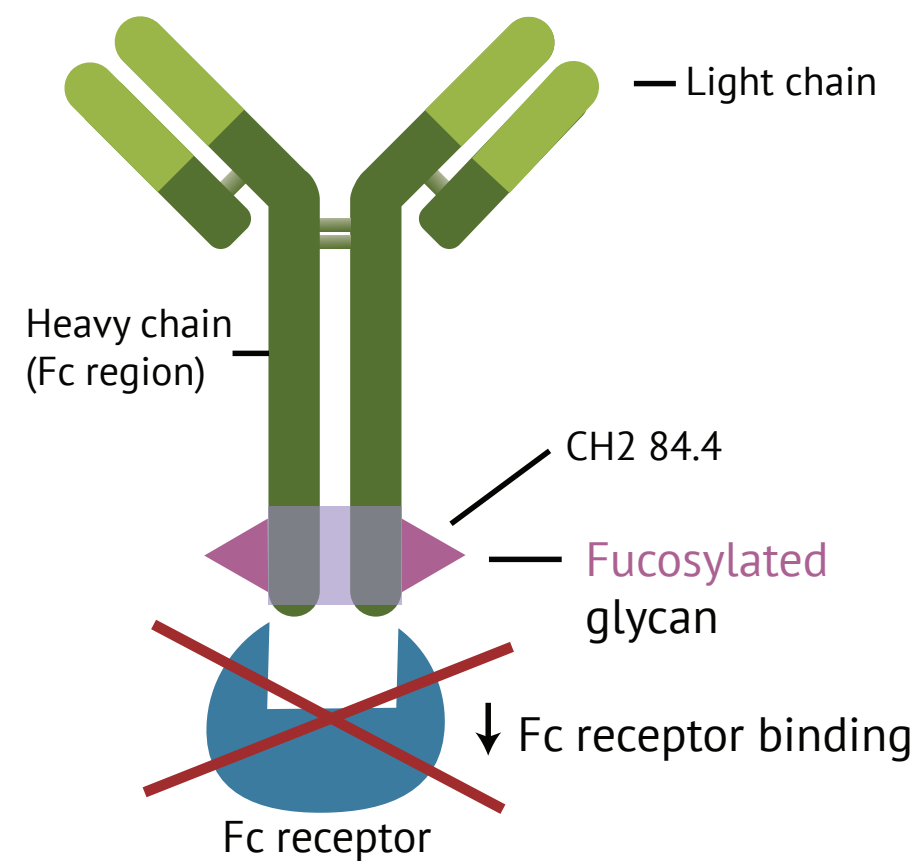
migration, and recruitment to tissues. C-D. Binding can also induce eosinophil cell death by other mechanisms, including complement-dependent cytotoxicity (C) or antibody-dependent cellular cytotoxicity (D). In antibody-dependent cellular cytotoxicity, benralizumab binds to the Fc receptor on effector cells (e.g. NK cells), allowing effector cell-mediated eosinophil killing by various mechanisms, including release of granzymes and perforins. Abbreviations: IL-5R, interleukin-5 receptor; FcR, Fc receptor; IL-5, interleukin-5; C1q, complement component C1q; CDC, complement-dependent cytotoxicity; ADCC, antibody-dependent cellular cytotoxicity.

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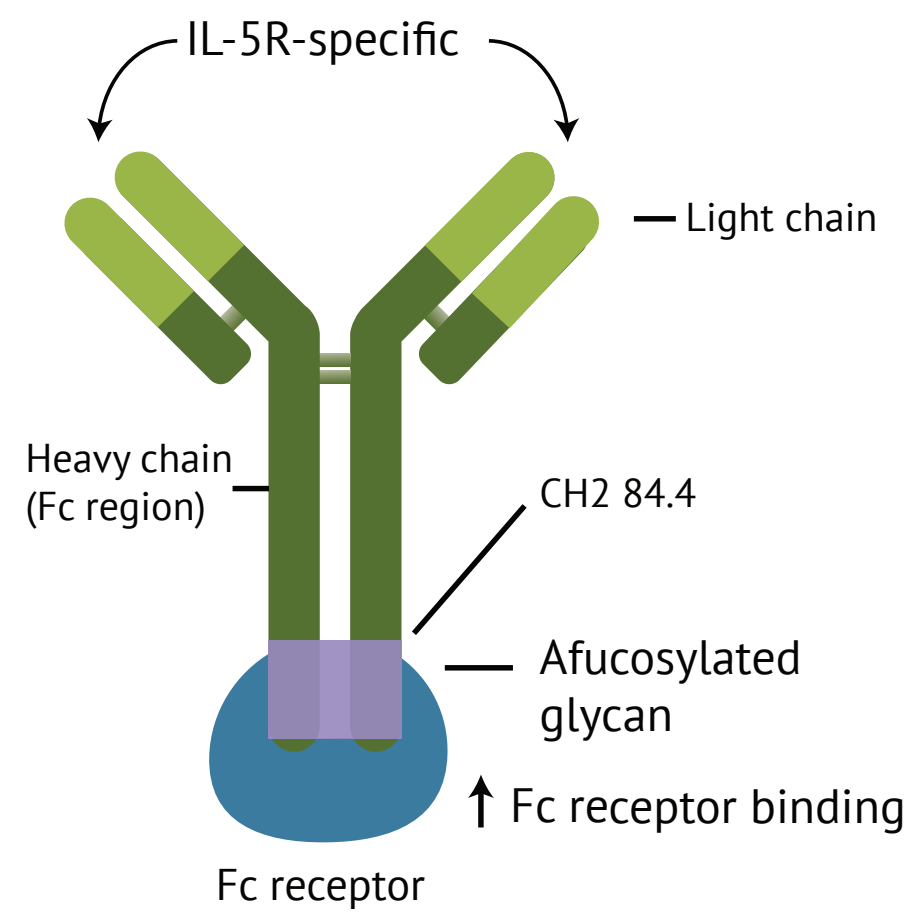
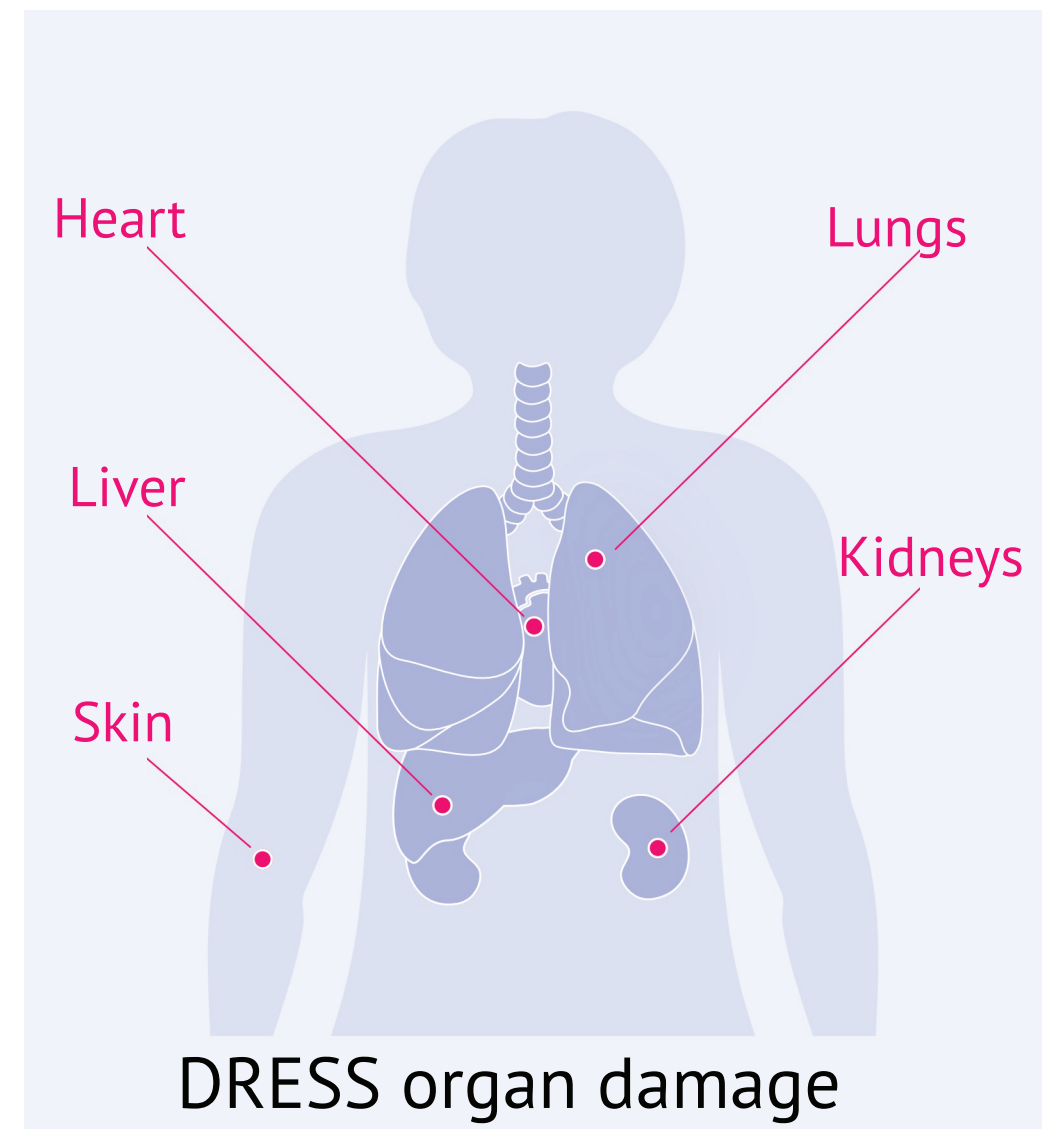
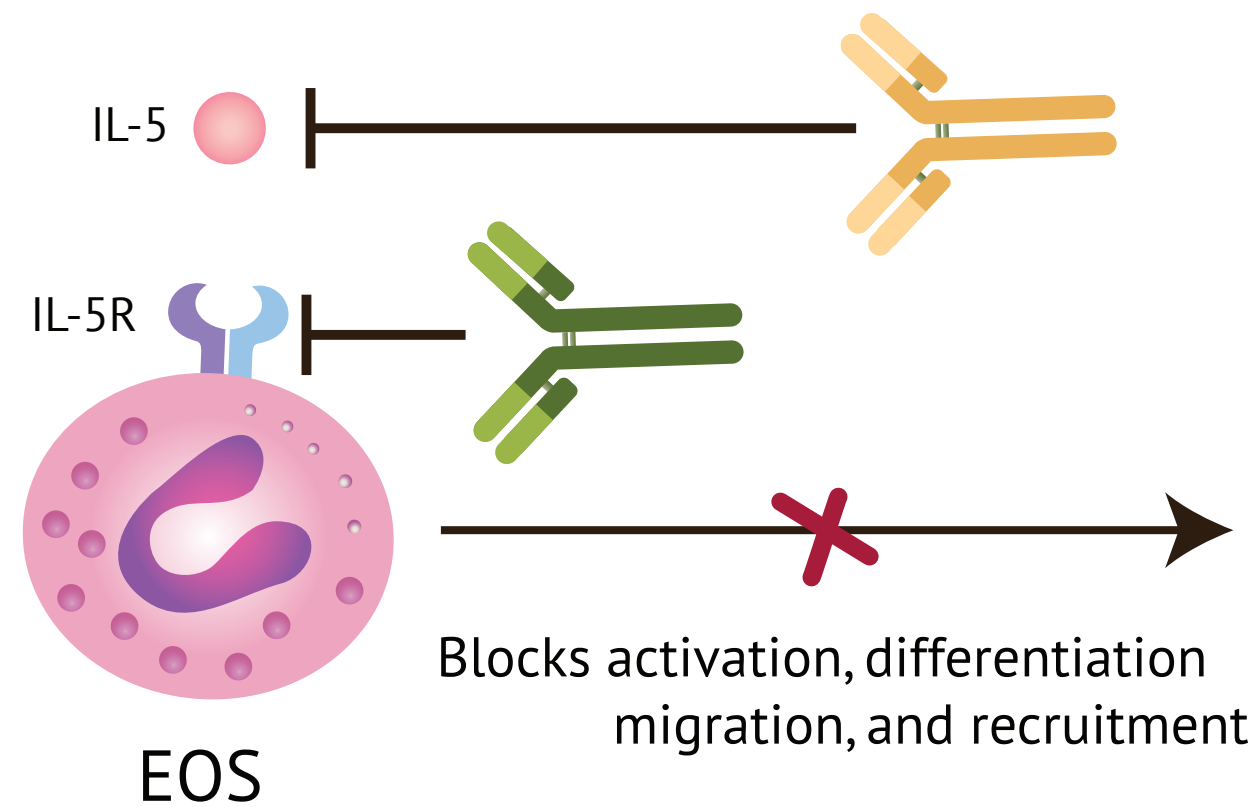
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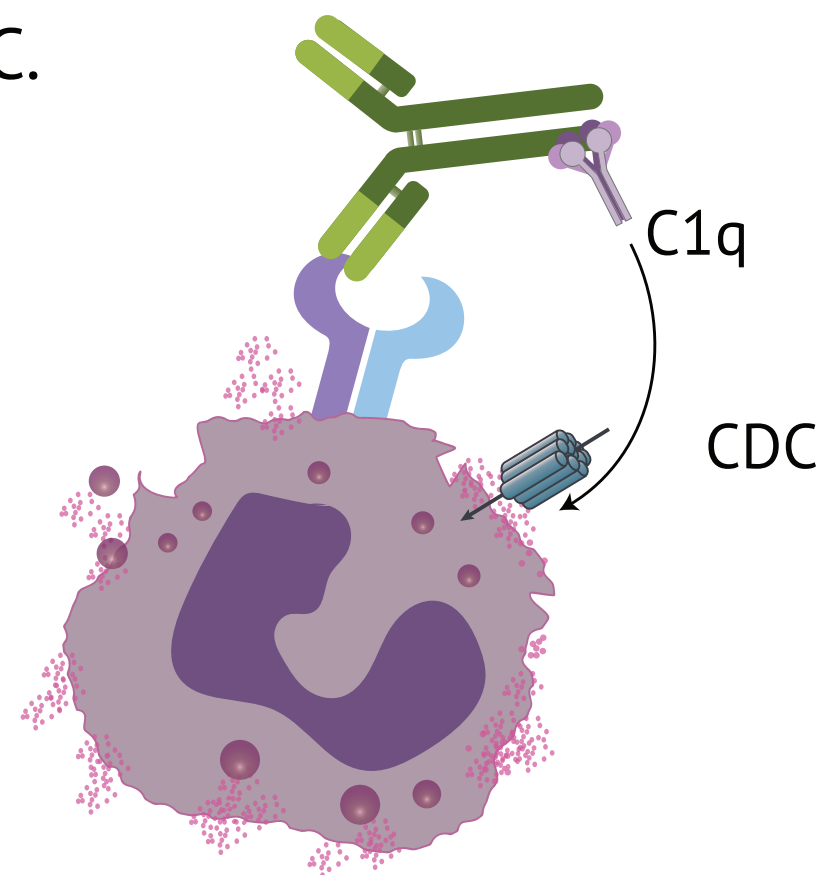


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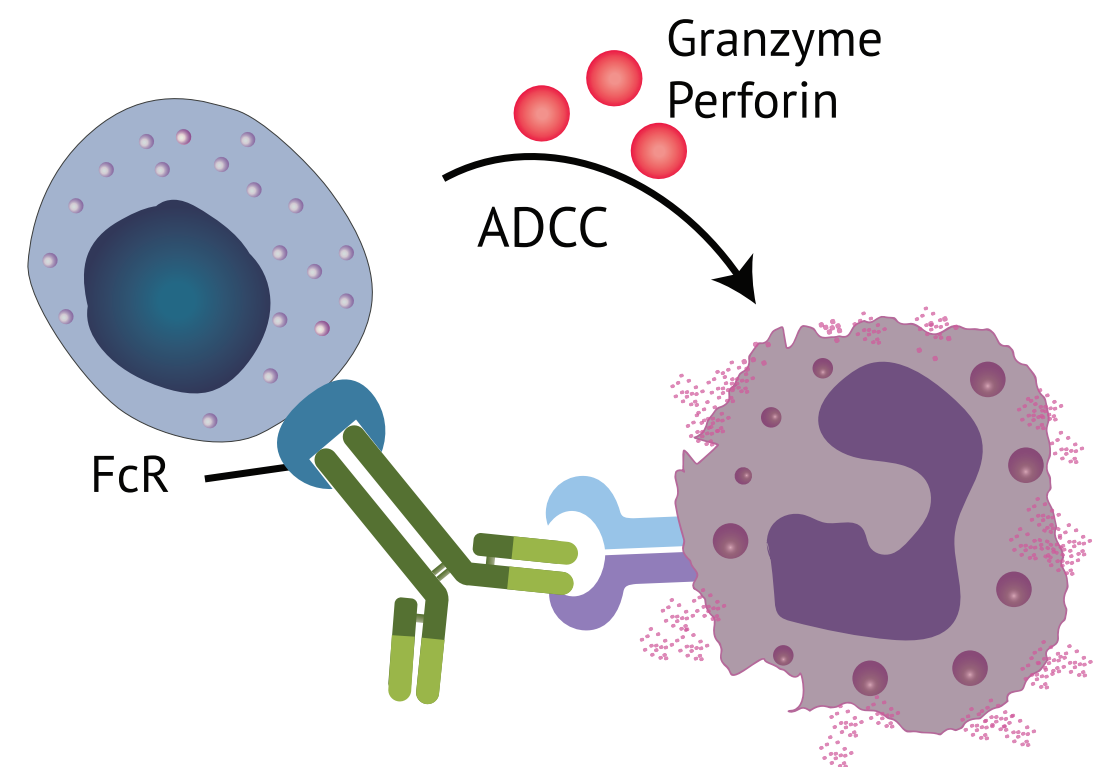
Benralizumab

C.



Induces CDC

D.



Induces ADCC

