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Targeting the FcRn: A Novel Approach to the Treatment of Pemphigus

Caroline A. Nelson[1] and Mary M. Tomayko[1,2]

Pemphigus is a debilitating autoimmune blistering disorder mediated by IgG autoantibodies to desmosomal cadherins that requires novel steroid-sparing therapies. In this phase 1b/2 trial reported by Werth et al. (2021), the FcRn inhibitor ALXN1840 induced rapid and sustained clinical improvement in patients with chronic, active, refractory pemphigus. FcRn inhibition is a promising new approach to the treatment of pemphigus and other autoantibody-mediated autoimmune disorders.

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Pemphigus is a group of autoimmune blistering disorders mediated by directly pathogenic IgG antibodies that bind desmosomal components critical to keratinocyte cell–cell adhesion in the skin and mucous membranes, leading to acantholysis. Resulting blisters of the skin and mucous membranes are painful and cause significant morbidity and mortality (Figure 1). The primary autoantigens are the cadherins desmoglein (DSG) 1 and 3, and circulating levels of autoantibodies correlate with disease activity (Kasperkiewicz et al., 2017). Mainstays of pemphigus therapy include systemic corticosteroids, B-cell depletion with rituximab, the immunosuppressants mycophenolate mofetil and azathioprine, and intravenous Ig (IVIg). Mortality is approximately two- to three-fold higher in patients with pemphigus than in the general population, principally because of the risk of infection (Huang et al., 2012; Langan et al., 2008), highlighting the need for novel therapeutic strategies that act rapidly and are minimally immunosuppressive.

The FcRn is a major histocompatibility complex (MHC) class I–related receptor consisting of a heavy α-chain and β2-microglobulin. Initially named for its critical role transporting IgG from maternal to fetal circulation across the placenta, FcRn is expressed by multiple cell types, including vascular endothelial cells and antigen-presenting cells (APCs). On vascular endothelial cells, FcRn binds IgG but not other antibody isotypes, protecting it from intracellular degradation. Endocytosed FcRn–IgG complexes are sorted into recycling endosomes and transported back to the cell membrane, where IgG is released. In contrast, unbound Ig is sorted into lysosomes and degraded. Thus, FcRn is the reason why the serum half-life of IgG is significantly longer than that of other isotypes (approximately 21 days) and why Fc engineering is part of the innovation of second-generation therapeutic mAbs, increasing in vivo half-lives. On APCs, FcRn plays a role in antigen uptake and presentation on MHC molecules, required for T-cell activation, thus bridging humoral and cellular adaptive immune responses. Finally, FcRn regulates serum albumin homeostasis by binding albumin at a distinct noncooperative site (Patel and Bussel, 2020; Qiao et al., 2008). FcRn inhibitors, which function as competitive inhibitors of IgG for FcRn binding, are a promising new therapeutic approach for decreasing pathogenic IgG in autoantibody-mediated autoimmune disorders. In pemphigus, the anticipated effect is reduction of circulating IgG, IgG immune complexes (ICs), and anti-DSG1 and anti-DSG3 IgGs, leading to reduced disease activity (Figure 2).

ALXN1840 (SYNT001) is a humanized IgG4 antibody that blocks binding of IgG and IgG ICs to the FcRn. Its efficacy in reducing circulating IgG and IgG ICs in humans was previously demonstrated (Blumberg et al., 2019). In a new article of the *Journal of Investigative Dermatology*, Werth et al. (2021) describe a multicenter, open-label safety and tolerability phase 1b/2 trial demonstrating the efficacy and safety of ALXN1840 in patients with chronic, active pemphigus who did not respond satisfactorily to conventional treatments with high-dose corticosteroids, immunosuppressants, or anti-CD20–mediated B-cell depletion. Eight patients with pemphigus (one foliaceous and seven vulgaris) completed five weekly intravenous doses of ALXN1830 (10 mg/kg). Four of eight completed the 112-day follow-up period and four were withdrawn owing

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Clinical Implications

- FcRn blockade is a promising new approach for the treatment of pemphigus and other autoantibody-mediated autoimmune disorders.
- FcRn inhibitors decrease levels of circulating IgG and IgG immune complexes by preventing their endosomal recycling and thus indirectly promoting their lysosomal degradation in vascular endothelial cells.
- In a phase 1b/2 trial of chronic, active, refractory pemphigus, the FcRn inhibitor ALXN1840, a humanized IgG4 mAb, induced rapid and sustained clinical improvement in some individuals.

to worsening (three) or need for increased immunosuppressant dosing (one). Clinical improvement, as evidenced by reduced pemphigus disease area index, was apparent by day 14 in four patients, by day 28 in a fifth, and by day 84 in a sixth. Four responders maintained improvement through the end of follow-up (up to 84 days after the last FcRn inhibitor infusion). As expected, ALXN1830 reduced circulating IgG and IgG ICs in all patients. In four of six patients with clinical improvement, serum titers of anti-DSG1 and anti-DSG3 IgG were also reduced. All levels returned to baseline during the follow-up period.

Treatment with ALXN1830 was generally well tolerated. Circulating albumin levels were unaffected. Headache was the most common adverse event in six patients, and an infusion-related reaction developed in one patient. One patient developed cutaneous herpes simplex and methicillin-resistant *Staphylococcus aureus* infection and subsequent kidney injury secondary to systemic antibiotics; however, these events were deemed unrelated to ALXN1830 (Werth et al., 2021).

The results of this study suggest that FcRn inhibitors may be exciting new tools in our armamentarium for pemphigus, but several important questions remain. First, in terms of efficacy, how can we predict which patients will improve with FcRn inhibitors and which patients will maintain that response? Larger cohorts will be required to answer this question. A surprising finding in this study was the maintenance of clinical improvement observed in four of six patients beyond the treatment period, despite the return of circulating IgG, IgG ICs, anti-DSG1, and anti-DSG3 to baseline levels. The clinical improvement was maintained until the end of follow-up (up to 84 days) in four patients. The authors suggest that this finding may be due to durable effects of ALXN1830 on intracellular FcRn function (Werth et al., 2021). Given the potential role that FcRn-facilitated antigen uptake by APCs plays in antigen presentation, it is also possible that decreased T-cell activation may be a contributing factor (Qiao et al., 2008). These hypotheses bear further analysis.

Second, in terms of safety, what adverse events beyond headache and infusion-related reaction may be associated with FcRn inhibitors? The decrease in serum IgG of all subclasses is likely to increase the risk of infection, so administration of FcRn inhibitors beyond short-term courses may require additional supplemental immunoglobulin therapy. In addition, FcRn inhibition may attenuate vaccination responses, as is noted for IVIg (Tacke et al., 2013). Furthermore, FcRn inhibitors are expected to block IgG transport from maternal to fetal circulation across the placenta, so use in pregnant women may be contraindicated (Patel and Bussel, 2020).

Third, where will FcRn inhibitors fit on the existing therapeutic ladder for pemphigus? Systemic corticosteroids are utilized to achieve rapid disease control before B-cell depletion or other immunosuppressive agents take effect, but high doses and prolonged courses are often associated with serious short- and long-term morbidity. FcRn inhibition, with its rapid onset, may be a useful steroid-sparing therapy at disease presentation, possibly acting as a bridge to B-cell depletion. Investigation will be necessary, however, to ensure that inhibition of IgG recycling does not compromise the efficacy of rituximab, a chimeric mAb with a human IgG constant region. FcRn inhibition may also be effective for pemphigus flares, to hasten remission while other long-term medications are adjusted. FcRn inhibition may also be helpful in refractory pemphigus. In summary, FcRn inhibition is likely to occupy a distinct but overlapping space with existing therapies that lower IgG and IgG ICs, including IVIg, plasma exchange, and immunoadsorption. Similar to FcRn inhibition, IVIg is thought to shorten the half-life of pathogenic autoantibodies through competitive FcRn binding (Patel and Bussel, 2020). FcRn inhibition may be preferable to IVIg, potentially with a lower risk of thrombosis and aseptic meningitis (Kasperkiewicz et al., 2017). Multiple clinical trials are ongoing, testing novel agents from Bruton's tyrosine kinase (BTK) inhibitors to DSG3 chimeric autoantibody receptor T-cell therapy (Kasperkiewicz et al., 2017). As new rungs are added to the therapeutic ladder, the role of FcRn inhibitors in pemphigus will be continually re-evaluated.

FcRn inhibitors will also likely prove relevant for the treatment of other

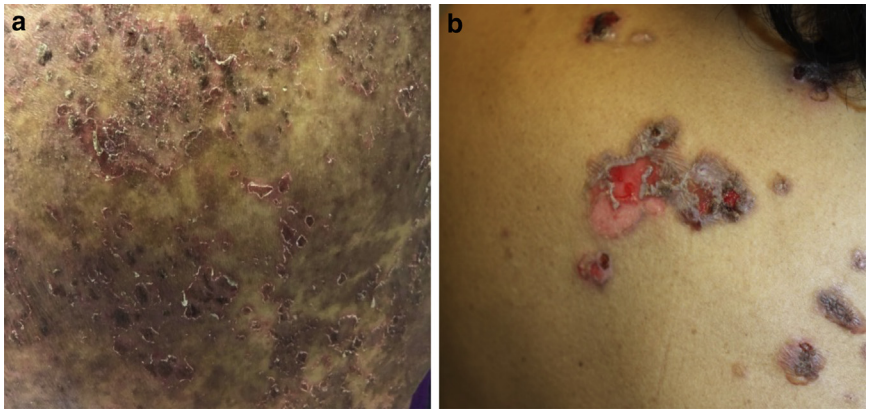

Figure 1. Clinical presentation of pemphigus. (**a**) Pemphigus foliaceous. Scaly crusted erosions on the back. (**b**) Pemphigus vulgaris. Flaccid blisters and hemorrhagic crusted erosions on the back.

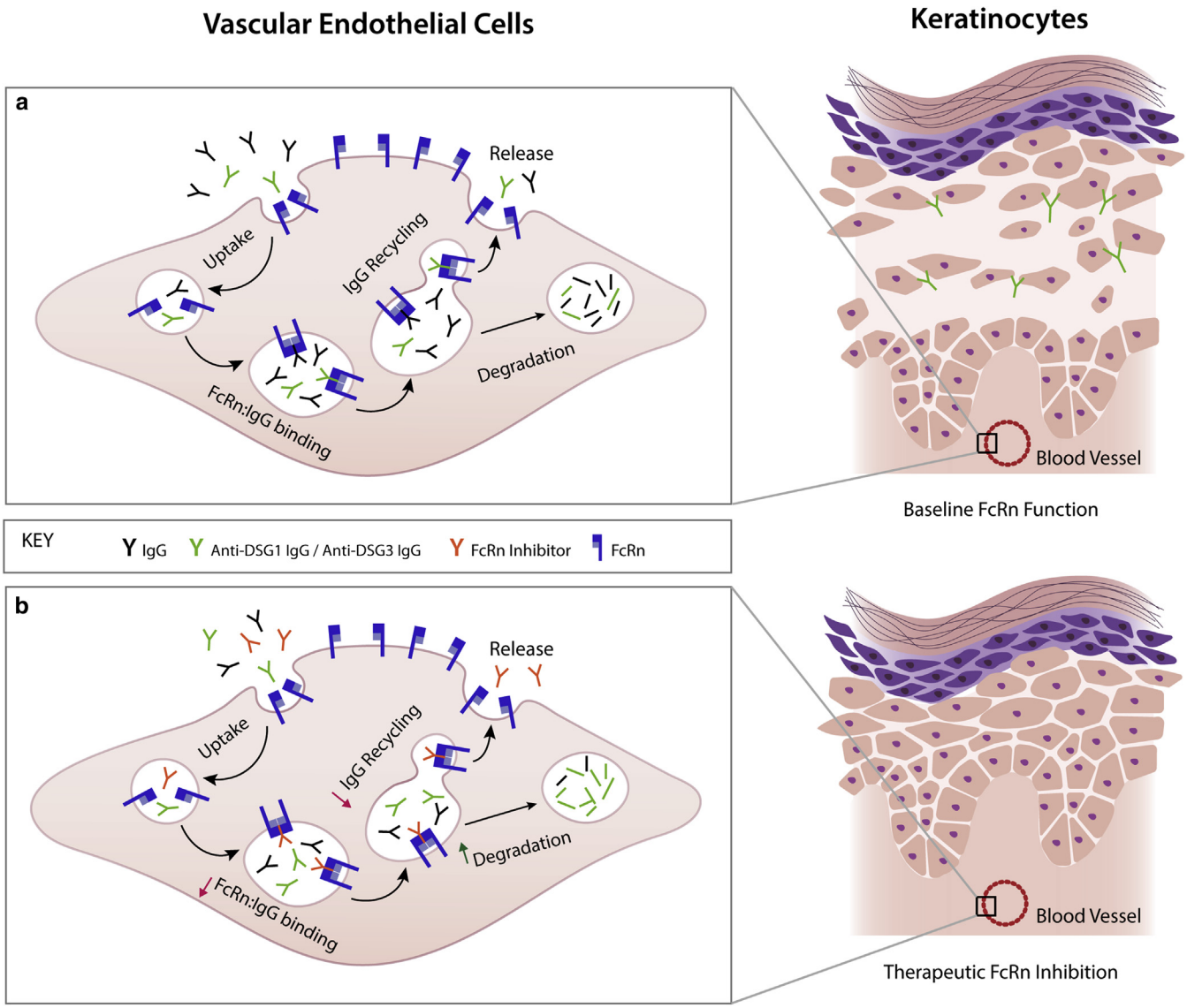

Figure 2. Schematic representation of the effect of FcRn inhibition on pemphigus disease activity. (**a**) Baseline FcRn function. FcRn–IgG complexes are efficiently recycled, and IgG is released. Circulating anti-DSG1 and anti-DSG3 IgG autoantibodies (green) disrupt keratinocyte cell–cell adhesion in the skin and mucous membranes, resulting in pemphigus. In addition (not shown), FcRn within APCs mediates the presentation of antigens bound to IgG ICs, possibly resulting in T-cell activation. (**b**) Therapeutic FcRn inhibition. Competitive inhibition of FcRn-IgG binding by the FcRn inhibitor (red) leads to decreased IgG recycling, increased IgG degradation in lysosomes, decreased circulating anti-DSG1 and anti-DSG3 IgG autoantibodies, and decreased pemphigus disease activity. In addition (not shown), inhibition of FcRn within APCs may lead to decreased antigen presentation and T-cell activation. APC, antigen-presenting cell; DSG, desmoglein; IC, immune complex.

autoantibody-mediated autoimmune disorders. Early candidates include chronic inflammatory demyelinating polyradiculoneuropathy, idiopathic thrombocytopenic purpura, myasthenia gravis, Grave's ophthalmopathy, hemolytic disease of the fetus and newborn, neuromyelitis optica, and warm autoimmune hemolytic anemia. Multiple FcRn inhibitors with distinct structures and biophysical properties are currently in development. In addition to pemphigus, for example, the FcRn-binding IgG1 Fc fragment efgartigimod is in clinical trials for immune thrombocytopenic purpura and myasthenia gravis (Howard et al., 2019; Newland et al., 2020). Expansion to systemic autoimmune disorders, such as cryoglobulinemic vasculitis, rheumatoid arthritis, and systemic lupus erythematosus, may be on the horizon (Patel and Bussel, 2020). In the end, delivery on the promise of this new therapy will depend not only on demonstrated efficacy and safety but also on availability and affordability across national, racial, ethnic, and socioeconomic groups.

In conclusion, the results of this carefully designed study suggest that targeting FcRn may be an effective and safe therapeutic strategy for pemphigus. With rapid onset and a targeted mechanism of action, FcRn inhibitors are well positioned to function as steroid-sparing therapy at diagnosis, when rapid disease control is needed, and for control of flares during maintenance therapy with B-cell depletion therapy or other immunosuppressants. Grounded in a strong scientific rationale, the mechanism of action of this emerging drug class exemplifies the promise of bench-to-bedside translational research and has far-reaching implications for

other autoantibody-mediated autoimmune disorders. Although further research is required, FcRn inhibition represents a significant step forward in the management of pemphigus.

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CONFLICT OF INTEREST
The authors state no conflict of interest.

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Cathelicidin LL-37 Ignites Primed NLRP3 Inflammasomes in Rosacea

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Microbes and commensal mites contribute to the development of inflammation and neurovascular dysregulation in rosacea. Cathelicidin family proteins are epithelial antimicrobial peptides expressed in higher-order mammals. In humans, mature LL-37 is cleaved from its precursor in response to microbial infection, UV light, and injury. In their new article in the *Journal of Investigative Dermatology,* Yoon et al. expand on existing evidence supporting LL-37 proinflammatory activity in lipopolysaccharide (LPS)- and UV-primed models of rosacea. They show in vitro that LL-37 promotes NLRP3-mediated inflammasome activation through lysosomal destabilization in the presence of LPS and that the injection of LL-37 in vivo leads to skin inflammation that is abrogated by direct NLRP3 inhibition and homozygous knockout in a murine model.

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The role of LL-37 in cutaneous immune regulation

The pleiotropic role of LL-37 in the cutaneous response to pathogen-associated molecular patterns (PAMPs) is rapidly emerging. LL-37 is the C-terminal domain of the sole human cathelicidin precursor, hCAP18, which is cleaved by kallikrein 5 in response to UV, tissue injury, and microbial infection (Moreno-Angarita et al., 2020). The effector cathelicidin, LL-37, has been shown to directly impair microbial function as a pore-forming toxin (Xhindoli et al., 2016). In addition to its bactericidal activity, LL-37 both inhibits IL-1B and amplifies proinflammatory signaling through lipopolysaccharide (LPS) binding in vitro and in vivo (Dombrowski et al., 2011; Hu et al., 2014). LL-37 has also been shown to be upregulated in the skin of patients with psoriasis, suggesting an overarching relevant role in the mediation of cutaneous inflammatory disease (Lande et al., 2007).

LL-37 promotes inflammasome activation with LPS costimulation

On the basis of the previous conflicting reports of LL-37 action on IL-1 signaling and inhibition as well as the synergistic amplification of LPS and other PAMPs, Yoon et al., 2021 treated bone marrow–derived macrophages with LL-37 in the presence and absence of LPS. They found that LPS priming followed by treatment of LL-37 induced caspase-1 cleavage and IL-1B production, whereas treatment with LL-37 and LPS alone as well as with LL-37 primed by TNF-α and IFN-γ was insufficient in activating inflammasomes. This was also seen in dendritic cells (DCs) and

> "Repeated exposure to LL-37 can activate the NLRP3-mediated inflammasome pathway, which in turn promotes the recruitment of inflammatory cells and skin inflammation, triggering rosacea-like phenotypes."