ABSTRACT
Atopic dermatitis (AD) is caused by complex interactions between a variety of genetic and environmental factors that contribute to the maintenance of the chronic inflammatory skin condition. Most conventional treatments have been designed for the so-called ‘average patient’. In recent years however, many previously unknown details pertaining to the mechanisms of the pathogenesis of AD have been elucidated, and novel treatments based on these pathological mechanisms or on subgroup classifications have been developed. Herein, how future treatment strategies for AD can be developed is described.

1. Introduction
The Japanese Dermatological Association defines atopic dermatitis (AD) as a ‘disease in which a patient presents with a primary lesion of eczema with repeated exacerbation and remission’ [1]. The current consensus is that the onset of the condition is caused by complex interactions between a variety of genetic and environmental factors (acquired aggravating factors), as is the ongoing maintenance of the chronic inflammatory skin condition.

AD usually develops in early childhood, and, in most cases, spontaneous remission occurs with age. In some cases, however, symptoms repeatedly disappear and reappear, there is a shift to adult-type AD, or AD develops in older childhood and the symptoms remain into adulthood. Moreover, AD first develops in adulthood in some cases. Thus, there is considerable variation in AD types, and in aspects of the onset of the disease.

It is possible to control skin symptoms in the majority of AD cases via the three pillars of treatment advocated by the Japanese Dermatological Association: appropriate pharmacotherapy, removal of aggravating factors, and skin care [1]. However, some patients’ symptoms are difficult to control using the currently available therapies. In recent years, many previously unknown details pertaining to pathophysiological mechanisms involved in AD have been elucidated, and novel treatments based on these mechanisms have been developed.

2. Approaches from ‘barrier disorder’ perspectives
2.1. Physical barrier
One of the three pillars of AD treatment advocated by the Japanese Dermatological Association is ‘skin care’ [1]. Skin barrier dysfunction has been widely recognised as an important element of the pathogenesis of AD, and various studies have been conducted based on this premise [2,3]. Since the relationship between filaggrin gene mutations and AD was first reported in 2016, investigation of the pathology of AD from a ‘barrier dysfunction’ perspective has gained further attention.

Filaggrin is one of the important elements in skin barrier formation, and when mutation is present there is an increased possibility that skin barrier function will be compromised, facilitating exogenous invasion and sustained intrusion of an allergen which may contribute to the onset or exacerbation of AD. This speculation is supported by data from many studies [4–7]. Notably, however, cumulative evidence from multiple studies suggests that filaggrin gene mutations are only present in approximately 30% of patients with AD [8], and, conversely, there are many individuals with filaggrin gene mutations who have a normal phenotype [8]. Thus, it may be safer to say that reduced filaggrin expression in the skin is one of many factors that can lead to the onset or exacerbation of AD.

Mutation in the filaggrin gene results in a degree of loss of skin barrier function and is a
risk factor for subsequent skin problems. Accordingly, if filaggrin gene mutations can be detected via screening, it will be possible to better characterise one of the multiple risk factors for AD. Moreover, in 2014 it was reported that the onset of AD can be prevented by aggressive use of moisturising agents from infancy [9,10]. With regard to skin barrier dysfunction, these are important observations concerning the onset or exacerbation of AD.

2.2. Functional barrier

Human skin constitutes both a so-called physical barrier, composed of filaggrin and other proteins, and a functional barrier that inhibits infection by pathogenic microorganisms. Peptides that exhibit antibacterial or antiviral activities, which are collectively referred to as antimicrobial peptides (AMPs), are produced from epidermal keratinocytes, and contribute to the primary biological defence of the skin’s surface [11–13]. Reduced localised expression of the AMPs LL-37, human beta-defensin (hBD)-2, and hBD-3 has been reported in the skin of patients with AD [14–16]. These findings suggest that deficiency of these factors is associated with bacterial infection of the skin surface in patients with AD. It is often observed in clinical practice that microbial infection of the skin exacerbates AD symptoms. Even when infection is not present but fixation of pathogenic microorganisms has occurred, the exotoxin produced may act as a superantigen and contribute to exacerbation of AD symptoms by promoting the activation of non-specific T cells [17].

2.3. Others

Some in vitro data suggest there is reduced expression of proteins involved in the physical skin barrier (e.g., filaggrin) and AMPs (i.e., LL-37, hBDs) involved in the functional skin barrier when Th2 cytokines are present, even when there are no genetic mutations [14,18]. There are many patients with AD in which abnormal increases in Th2-type immune responses are thought to be involved in the pathogenesis of the condition. Treatments designed to address abnormal enhancement of Th2-type immune responses in patients with AD may not only suppress the inflammatory reactions involved in these immune responses but also promote the recovery of skin barrier function.

3. Approaches from ‘immunological disorder’ perspectives

3.1. Type 2 immunity and anti-interleukin-4Rα antibody for AD

Overproduction of IgE antibodies is often detected in patients with AD, and it has been previously suggested that increased Th2-type immune responses may be an important factor in AD onset or exacerbation [19]. Although classifications can be determined on the basis of intrinsic AD or non-Th2-type immune response AD (normal IgE antibody levels) and extrinsic AD or Th2-type immune response AD (elevated IgE antibody levels) [20], the dominance of Th2-type immunity has also been observed in locally inflamed skin in cases of intrinsic AD [21] regardless of IgE antibody status. Thus, increased Th2-type immune responses may be involved to varying degrees in all patients with AD.

As alluded to above, it has been reported that in the presence of the Th2-type cytokine interleukin (IL)-4 the production of many proteins responsible for the barrier function of human skin is suppressed. It has also been reported that Th2-type immune responses are causally involved in skin inflammatory responses. These observations have prompted speculation that enhancement of Th2-type immune response is an important factor in the onset or exacerbation of AD, both in terms of inflammatory response and skin barrier function. Moreover, some evidence suggests that Th2-type cytokines such as IL-4 and thymic stromal lymphopoietin are able to activate sensory neurons and elicit itching sensations [22,23]. In 2017, Oetjen et al. [23] reported functional expression of the IL receptors IL-4Ra, IL-13Ra1, and IL-31Ra on both human and mouse dorsal root ganglion neurons. They concluded that IL-4 and IL-13 may act to sensitize neurons, and lower the threshold for itching [23].

The concept of treating AD by addressing an errant Th2-type immune response is concordant with consideration of AD as a pathological condition, as compared with more conventional AD treatments such as suppressing inflammatory responses. Moreover, it is speculated that suppression of cell-mediated immunity will not occur mechanically, and it is difficult to make short-term predictions about the possibility that serious side effects will occur. Trials investigating AD therapy using the fully humanised anti-IL-4 receptor α monoclonal antibody dupilumab have been conducted in Europe, and the results of phase I/IIa [24] and IIb trials [25] were, respectively, reported in 2014 and 2015. Those results suggest that it causes no serious side effects and has favourable therapeutic effects in cases of moderate to severe AD. Phase 3 results
were reportedly good [26], and based on those results dupilumab was approved for AD treatment in Europe, the USA and Japan during 2017 and 2018. Notably, however, many details remain to be determined including those pertaining to dosage parameters, indications, the safety of long-term use, and how to address associated high medical expenses, among others. As well as suppression of skin inflammation, dupilumab also has a significant effect on itching. It exhibits good therapeutic effects overall.

3.2. Novel biological agents

A wide range of factors are responsible for the pathogenesis of AD, and each patient exhibits a different clinical presentation. The elements that comprise the pathogenesis of AD are gradually being elucidated, and development of treatment methods targeting the well characterised elements that are shared by a comparatively large number of patients is progressing.

Clinical trials targeting cytokines other than IL-4 are being conducted. Two IL-13-targeting antibodies, tralokinumab and lebrikizumab, are the most advanced IL-13-specific biologics for the treatment of AD. They have been evaluated in monotherapy and combination therapy (with topical therapy) studies in cases of moderate-to-severe AD, and they are evidently associated with clinical improvement of AD [27,28].

AD treatment with dupilumab revealed that Th2 cytokine-targeted therapy had good therapeutic effects in most patients, though notably the immune status of AD patients varies between individuals. However, in patients with intrinsic AD, paediatric AD, and Asian AD, activation of the Th17/IL-17/IL-23 axis reportedly cannot be overlooked [29], and in these sub-groups of patients IL-17-targeted therapy may be beneficial [30,31].

Nemolizumab is a monoclonal antibody directed against IL-31 receptor A [32]. In two recent phase II trials, in adult patients with refractory moderate to severe AD there were reportedly dramatic reductions in pruritus in conjunction with improvement of clinical signs of AD, as compared with the placebo group [33,34].

3.3. Small molecule inhibitors

As well as biologics, several small molecule inhibitors are in various stages of development. For example, the Food and Drug Administration in the USA specified upadacitinib as a breakthrough therapy for AD in January 2018. It is likely that several oral and/or topical Janus kinase inhibitors will emerge in the clinical field of AD treatment in the near future.

4. Nucleic acid drugs for the treatment of AD

Drugs containing molecules that utilise nucleic acids with a variety of functions are referred to as ‘nucleic acid drugs’ [35]. They are currently being investigated in various fields. For example, antisense DNA, microRNA, and decoy oligodeoxynucleotides (decoy ODNs) have been developed to inhibit gene expression and are used for various purposes [35]. Below we explain the decoy ODNs and small interfering RNAs (siRNAs) that we have examined.

A DNA sequence that a specific transcription factor binds to in the transcriptional regulatory region that controls the gene expression of DNA is artificially synthesised and double-stranded DNA fragments are obtained. These are decoy ODNs. When administered intracellularly, the transcriptional regulatory factors are competitively trapped by the decoy ODNs, thereby exerting inhibitory effects on gene expression (Figure 1).

RNA interference (RNAi) is a phenomenon that was originally discovered in nematodes, and a similar phenomenon was subsequently found to exist in various species including humans. In short, when double-stranded RNA is inserted into cells the decomposition of mRNA with a complementary base sequence occurs [36]. The phenomenon has been used to inhibit the expression of specific genes.

Figure 1. Gene suppression mechanisms of decoy ODNs. The DNA sequence of a binding site of a transcription factor is artificially synthesised and used as decoy ODN. When decoy ODNs are administered intracellularly, the corresponding transcription factors are competitively trapped by them, thereby inhibiting gene expression.
4.1. Nucleic acid drugs that target signal transducer and activator of transcription 6 for the treatment of AD

We have previously focused on the Th2-type immune shifted pathophysiological mechanisms of AD. Signal transducer and activator of transcription 6 (Stat6) is a transcriptional regulatory factor of intracellular signal transduction of IL-4 and IL-13, and in 2000 Yokozeki et al. [37] reported the interesting observation that hapten-induced contact hypersensitivity reaction was inhibited in Stat6 knockout mice [37]. These results suggest that Th2-type immune responses are involved in the induction of skin allergy inflammatory reactions. It has subsequently been confirmed that the Stat6-mediated response pathway is also involved in the pathogenesis of various skin allergic inflammatory reactions. It has also been reported that Stat6 siRNA [43]. Thus, it may be possible to treat allergic inflammatory reactions via inhibition of Stat6 function, that is, inhibition of Th2-type immune responses. Furthermore, as described above, it has recently been reported that excessive Th2-type immune response can inhibit the production of molecules responsible for skin barrier function [18,44]. Therefore, we postulated that the treatment of AD by inhibiting Th2-type immunity may be effective, and this was unexpectedly confirmed by results observed after dupilumab therapy.

When developing nucleic acid drugs that target STAT6 for clinical use, the most critical problem was the high molecular weight of the nucleic acid drugs (10,000–20,000 Da). The skin has stringent physical barrier properties, and the size of substance

Figure 2. Trial of Stat6 decoy ODN ointment as an AD therapy. Clinical changes (a) and changes in visual analogue scale (VAS) scores (b) for pruritus of facial lesions. Data are expressed as means. (A) Clinical features of facial erythema in a representative case at baseline and (B) at week 2. (C) Clinical changes and (D) changes in VAS scores for pruritus of facial lesions. Data are expressed as mean percentages of baseline scores ± standard error of the mean. *p < .05.
constituents that can penetrate the skin relatively freely is no greater than 500 Da [45]. Notably, in clinical studies using the aforementioned ointment containing STAT6 decoy ODNs, efficacy was not observed in all cases. One of the reasons for this appeared to be associated with a lack of permeability with regard to nucleic acid penetration into the skin. If the problem of permeability can be solved, the utility of the strategy may be greatly improved in terms of therapeutic effects and economic aspects associated with the commercialisation of products (i.e., if efficacy with a small amount of nucleic acid can be achieved, costs can be reduced). Using novel technologies to enhance efficacy in terms of skin permeability, highly polymerised compounds such as STAT6 decoy ODNs have been introduced into skin cells, and an improved version of STAT6 decoy ODN ointment has been developed [46]. It was recently confirmed that this new technology facilitates the introduction of STAT6 decoy ODNs into the skin with significantly higher efficiency than was previously achieved [46].

Although many relevant details remain to be determined, the effects of STAT6 decoy ODNs that inhibit similar pathways as dupilumab, which has been shown to be effective in AD treatment, render it a viable treatment strategy for AD. Furthermore, because of the superiority of the external preparation, it is likely to yield favourable outcomes.

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Disclosure statement

The author reports that there are no conflicts of interest.

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