AD more than 11-fold.[1] From a clinical point of view, this is highly important: AD is not just a skin disease but has been shown to be a systemic disease associating with several comorbidities besides other atopic diseases already in children and adolescents.[5,6] As the risk for comorbidities increases with disease severity, it is important to recognize the individuals at highest risk as early as possible.[7] Perhaps in the next decade we will even have the possibility to prevent these comorbidities by treating moderate-to-severe AD with new treatment modalities or by focusing on factors that increase the risk of AD. Nakamura and coworkers found that polysensitization and lack of breastfeeding were specific risk factors for persistent AD. A previous birth cohort study has also shown that early childhood factors can have a protective effect against allergic sensitization that persists into adulthood.[8] Nevertheless, more longitudinal studies are needed to find the factors that are most useful in AD prevention.

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## Targeting CD56 with an antibody–drug conjugate in Merkel cell carcinoma

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Merkel cell carcinoma (MCC) is a rare but aggressive skin cancer with 5-year survival rates of 50%. The pathogenesis of MCC is associated with either the clonal integration of the Merkel cell polyomavirus (MCV) or ultraviolet radiation-induced genomic alterations. MCV-associated MCCs exhibit a low mutational burden and no recurring oncogenic alterations besides the viral integration in the tumour genome, whereas MCV-negative, ultraviolet radiation-associated MCCs show ~100-fold higher mutational load with recurrent inactivating mutations in *RB1* and *TP53*.[1] However, the mechanisms driving these two independent oncogenic processes are unknown, hindering mechanism-based therapeutic strategies.

Conventional treatments such as radio- or chemotherapy have limited and short-lived clinical efficacy.[2] Immunotherapy with checkpoint inhibitors, such as anti-programmed death 1 (pembrolizumab) or anti-programmed death ligand 1 (avelumab), has been shown to be effective for MCC treatment, with objective responses rates of 46–56%.[3,4] However, new therapeutic targets are needed for patients who do not respond to, who progress under, or who are not eligible for immunotherapy.

In this issue of the *BJD*, Esnault and colleagues[5] investigated a new antibody–drug conjugate (ADC) targeting CD56, named Adcitmer®, in preclinical MCC models. ADCs enable the delivery of antineoplastic agents to cancer cells by exploiting the expression of cell-surface antigens specific to cancer cells.[6] Nine ADCs are currently approved as cancer treatments, including trastuzumab deruxtecan, which reduced the risk of disease progression or death by 72% in patients with HER2-positive breast cancer, demonstrating the great potential of this class of therapies.[7]

ADCs consist of three main components – an antibody, a linker and a payload – all three influencing the clinical properties.[6] Esnault *et al.* synthesized a novel ADC by linking an already established CD56-specific antibody with a monomethyl auristatin E (MMAE) payload through an innovative bioconjugation process. MMAE is a potent antineoplastic agent that binds to tubulin dimers, thereby inhibiting tubulin polymerization and disrupting mitosis.[6] CD56, also known as neural cell adhesion molecule 1 (NCAM1), encodes a cell-surface adhesion protein, expressed primarily in neuronal and haematopoietic lineages.[8] Esnault and colleagues report that 66% of their MCC tumours express CD56, independently of MCV integration. They found that cytotoxicity is mediated via cell cycle arrest and cell death in their *in vitro* models, and

observed strongly reduced tumour outgrowth in an *in vivo* MCC xenograft mouse model.

Taking the results together, Adcitmer® is an interesting addition to the growing list of targeted therapies, including inhibitors of mammalian target of rapamycin,[9] phosphoinositide 3-kinase[9] and lysine-specific demethylase 1,[10] that are effective in preclinical MCC models. Given these encouraging results, further studies are needed to evaluate the drug-safety profile of Adcitmer®, particularly its effects on normal, CD56-expressing cell populations, especially natural killer cells and neuronal cell types. Reduced natural killer cell function might influence antitumour and antiviral responses,[8] and peripheral neuropathy is a common side-effect in patients treated with MMAE.[6] With a favourable drug-safety profile, Adcitmer® should also be considered as a treatment option for other CD56-expressing tumours, such as blastic plasmacytoid dendritic cell neoplasms. As combination therapies are likely to be more effective, it is of interest whether Adcitmer® can stimulate the immune system (e.g. by releasing tumour antigens) to enhance the efficacy of immune checkpoint inhibitors.

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## Genome-wide scan for structural variation underlying psoriasis

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Every human genome contains many structural variants (SVs): insertions, deletions, inversions and copy number variations of DNA segments, ranging from 50 base pairs up to several megabases in length.[1] In many ways, it is a wonder that any of us function at all. Unlike single-nucleotide polymorphisms (SNPs) and short insertions and deletions, SVs are not captured directly by the genotyping arrays or imputation reference panels that have been used in genome-wide association studies (GWAS) to successfully map out genomic regions contributing to psoriasis risk.[2,3]

In this issue of the BJD, Zhen *et al.* report a thorough evaluation of the contribution of SVs to psoriasis susceptibility, using five Han Chinese case–control studies.[4] First, they performed extensive validation analysis to show that, with appropriate SV reference data, SVs can be imputed into targeted sequencing data or microarray genotype data with reasonable confidence. Next, their genome-wide meta-analysis highlighted significant SV associations with psoriasis at known susceptibility loci harbouring the *HLA-C*, *IL12B* and *LCE3B/C* genes.

A key challenge in GWAS interpretation remains the identification of causal biological mechanisms at susceptibility loci, because linkage disequilibrium causes correlation among nearby genetic variants. SVs could play a causal role in psoriasis if, for example, they overlap coding or regulatory regions of relevant genes. Zhen *et al.* have not found convincing evidence that the Alu element insertion identified at *IL12B* is causal, its association signal being ameliorated