

The immunology of vitiligo

Mary Jo Turk   & Yina H. Huang 

Abstract

Vitiligo is an autoimmune disease of melanocyte destruction, which manifests as progressive, patchy loss of pigmentation in the skin. As one of most common autoimmune diseases, vitiligo inflicts a significant psychosocial burden. Research over the past two decades has revealed the underlying immune mechanisms of vitiligo, with key studies combining detailed analyses of patient tissue samples with mechanistic experiments in mouse models. Vitiligo has emerged as a prototypical CD8⁺ T cell-mediated autoimmune disease, with cooperation between innate immune cells, dendritic cells, T cells, keratinocytes and fibroblasts driving autoimmune pathology against the uniquely susceptible melanocyte target. The study of vitiligo has also revealed aspects of CD8⁺ T cell memory and resident memory against self-antigens. This work has drawn from, and contributed to, the study of melanoma immunology. Whereas drugs used for other autoimmune conditions have been largely ineffective in treating vitiligo, a growing base of knowledge recently led to the first successful FDA-approved immune-modulating drugs for vitiligo. This review focuses on the immunology of vitiligo: the mechanisms that drive melanocyte destruction, the biology of aberrant T cell responses against melanocytes and therapeutic means for counteracting this autoimmune condition.

Sections

[Introduction](#)[Susceptibility factors in the prelude to disease](#)[Autoimmune pathogenesis](#)[Loss of T cell tolerance to melanocytes](#)[Cytokines and chemokines in vitiligo](#)[CD8⁺ T cell memory in disease persistence and recurrence](#)[Therapeutic approaches](#)[Conclusions](#)

Introduction

Vitiligo is an autoimmune disease of melanocyte destruction that manifests as increasing, patchy loss of pigmentation in the skin. This progressive condition impairs quality of life¹, and inflicts a substantial psychosocial burden². With a worldwide prevalence of 0.5–2% in adults and adolescents, vitiligo is one of most common autoimmune diseases³. In addition to conditions of depression and anxiety^{1,2}, vitiligo is associated with multiple autoimmune comorbidities including thyroid disease, psoriasis, pernicious anaemia, Addison's disease, systemic lupus erythematosus, inflammatory bowel disease and type 1 diabetes^{4–6}. Non-segmental vitiligo, which is characterized by skin lesions that show bilateral symmetry, is the most common form of vitiligo, with 80–90% of patients having this form of the disease⁷.

Vitiligo is exquisitely melanocyte targeted and CD8⁺ T cell mediated. In patients and mouse models, interferon- γ (IFN γ)-producing CD8⁺ T cells that are specific for melanocyte antigens destroy melanocytes and persist as functional memory T cells. However, vitiligo is less strongly associated with the types of inflammation that typically characterize CD4⁺ T cell-mediated autoimmune diseases. Decades of research have provided insight into the triggers of vitiligo, the basis for the loss of immune tolerance to melanocytes, and the mechanisms by which autoimmunity is sustained. As such, the field has assembled an expansive and comprehensive understanding of the immunology of vitiligo, which will be the focus of this review.

Susceptibility factors in the prelude to disease

Genetic and environmental factors

Genome-wide association studies revealed associations of non-segmental vitiligo with many immune-related loci, including genes encoding the MHC molecules HLA-A2 (ref. 8), HLA-DRB1 and HLA-DQB1 (ref. 9); genes associated with innate immunity (*NLRP*, *IL1B*, *IRF4* and *HSP70*); genes encoding immunomodulatory molecules (*CTLA4*, *IL2RA*, *CD80*, *TNFSF11* and *PTPN22*); and genes linked to CD8⁺ T cell cytotoxicity (*GZMB* and *FASLG*)^{10–12}. The melanocyte-intrinsic component of the disease is also represented by polymorphisms in melanocyte-associated genes, most notably in *TYR*, which encodes tyrosinase^{10,13}. However, the concordance of vitiligo in monozygotic twins is only 23%, indicating a major role for non-genetic risk factors^{5,12}.

Strong evidence supports environmental stressors as disease-precipitating factors based on the theory that UV radiation, pollutants and exposure to phenolic compounds triggers oxidative stress in melanocytes. UV-induced melanin production results in reactive oxygen species as a by-product^{14,15}, and melanocytes from individuals with vitiligo appear more susceptible to this stress¹⁶. Accordingly, increased levels of superoxide dismutase and lower catalase levels are apparent in the skin of individuals with vitiligo relative to healthy controls^{17–20}. Heightened oxidative stress and vitiligo can also be observed following exposure to monobenzene²¹, a prototypic phenolic pro-hapten that is metabolized by tyrosinase in melanocytes²². These studies provide support for free radical-mediated damage of melanocytes as an initial pathogenic event. Interestingly, the finding that vitiligo presents in older individuals today as compared with five decades ago²³ suggests a potential delay in environmental exposures and/or changes in behaviours that affect exposures.

Role of the microbiome and viral infections

Skin and gut dysbiosis have been noted in individuals with vitiligo. In a small study, lesional skin showed increased dominance of *Firmicutes* species compared with non-lesional skin²⁴. Compared with healthy

individuals, those with vitiligo showed reduced diversity and richness of the gut microbiome^{25,26} and a reduction of commensal species on lesional skin sites²⁵. Studies using antibiotics in mouse models have also linked the microbiome with vitiligo, although with unclear interpretations. Whereas orally administered ampicillin accelerated vitiligo²⁷, topical application of Neosporin reduced disease²⁸, and oral neomycin and topical Bacitracin had no effect^{27,28}. Thus it remains unclear if microbial changes precede or contribute to disease.

Recent studies have indicated an association between vitiligo and viral exposure. Herpes simplex virus (HSV) infection is an independent risk factor for vitiligo, with HSV-diagnosed individuals having a 1.7 times greater risk of developing the disease²⁹. Animal models support this, with the Smyth line chicken vitiligo model also associated with HSV infection³⁰. Cytomegalovirus exposure is also of interest as anti-cytomegalovirus IgM levels are higher in vitiligo affected versus control individuals³¹. Interestingly, imiquimod (an agonist of Toll-like receptor 7 (TLR7), which is an innate sensor for viral RNA) can directly promote melanocyte apoptosis³² and has been associated with vitiligo cases³³. However, considering the high prevalence of HSV infection in the general population, infection with HSV is likely to be only one of multiple triggering factors.

Melanoma association with vitiligo

One of the earliest reports to associate vitiligo and melanoma involved a patient treated with vaccinia virus in 1960³⁴. Repeated injection of cowpox virus into dermal metastatic melanoma lesions resulted in tumour regression and skin depigmentation, which was termed 'an expression of induced autoimmunity'³⁴. Before the broad use of immunotherapy drugs, vitiligo incidence in individuals with melanoma was reported at 2.8%, which is similar to what is seen in the general population, but a majority of patients (79%) developed vitiligo after melanoma excision³⁵. In individuals with melanoma who are treated with anti-PD1 immune checkpoint inhibitor drugs, vitiligo incidence is as high as 25%³⁶. Of note, development of vitiligo is associated with remission and improved overall survival in metastatic melanoma^{36–40}. Moreover, individuals with idiopathic vitiligo exhibit a statistically reduced incidence of melanoma and other skin cancers^{41–43}, consistent with an increased overall state of skin immunity. Later age of onset for melanoma-associated vitiligo (MAV) versus idiopathic vitiligo underscores melanoma as a precipitating factor⁴⁴, through mechanisms that will be addressed below.

Innate immune factors

In the case of idiopathic (non-melanoma-associated) vitiligo, there is strong evidence that stress responses in melanocytes and keratinocytes trigger innate immune pathways (reviewed in ref. 45). In human melanocytes, the *in vitro* induction of oxidative stress induces mitochondrial DNA release and activation of the cGAS–STING pathway, as well as IL-1 β and IL-18 production⁴⁶. Oxidative stress can induce melanocyte death through multiple mechanisms⁴⁶ (reviewed in ref. 47). Chemical stressors such as monobenzene and related phenols activate the unfolded protein response in melanocytes and induce melanocyte production of IL-6 and IL-8 (ref. 48). Oxidative stress can additionally act directly on keratinocytes, increasing activation of the NLRP3 inflammasome and downstream IL-1 β production in lesional skin⁴⁹. Activation of the intracellular virus sensor melanoma differentiation-associated gene 5 (MDA5) in keratinocytes induces their secretion of CXC-chemokine ligand 10 (CXCL10) and CXCL16 (ref. 31). In individuals with vitiligo, studies have identified increased levels of IL-1 β in lesional skin⁵⁰, increased CXCL16 levels in skin and blood⁴⁹, and increased IL-8 levels in serum⁵¹.

These studies together underscore a role for oxidative stress-induced innate immune activation in triggering vitiligo. However, the limited therapeutic benefit of oral antioxidants⁵² suggests that oxidative stress does not perpetuate disease.

Cell death itself can be immunogenic, particularly when associated with damage-associated molecular patterns (DAMPs)⁵³. Heat shock protein 70 (HSP70) is a DAMP with strong evidence of involvement in vitiligo. Although its normal function is to manage protein misfolding, HSP70 also promotes the maturation of dendritic cells (DCs)⁵⁴. Melanocytes under stress from exposure to the depigmenting chemical *tert*-butyl phenol were shown to produce HSP70 (ref. 55), linking environmental stress to DAMP production. Importantly, studies in a mouse model showed that genetic knockout of intracellular HSP70 inhibits vitiligo⁵⁶, and that exogenous supplementation of HSP70 in the dermis accelerates disease^{56,57}. Accordingly, a dominant-negative mutant form of HSP70, which could not promote DC maturation, reversed depigmentation in a mouse model of vitiligo⁵⁸. Oxidative stress also induces production of high mobility group box 1 (HMGB1) from human melanocytes, which can mature DCs derived from individuals with vitiligo⁵⁹, suggesting the contribution of multiple DAMPs.

Natural killer (NK) cells and innate lymphoid cells (ILCs) also probably contribute to early innate immune triggering in vitiligo. Stress signals received by NK cells and group 1 ILCs (ILC1s) can induce their production of IFN γ , which in turn upregulates melanocyte expression of CXC-chemokine receptor 3 isoform B (CXCR3B) and increases their susceptibility to CXCL10-mediated apoptosis⁶⁰. Individuals with vitiligo have increased numbers of NK cells and ILC1s in their skin and blood⁶⁰, although NK cell numbers are increased in both lesional and non-lesional skin, suggesting heightened innate immunity throughout the skin⁶¹. NK cells have also been implicated in mouse models, where dermal monobenzone application induces hapten-dependent killing of melanocytes by NK cells⁶². Adoptive transfer of hapten-specific NK cells induced mild coat depigmentation⁶², although progressive disease was not noted.

Together, the studies highlighted in the above sections suggest that environmental stressors can lead to melanocyte death, the release of DAMPs, activation of innate immune cells and the initiation of vitiligo disease (Fig. 1).

Autoimmune pathogenesis

Requirement for CD8⁺ T cells

Although stress can be considered an innate immune trigger of vitiligo, overwhelming data underscore a requirement for melanocyte-specific CD8⁺ T cells for disease development. MHC class I tetramer staining of patient-derived blood and skin has revealed high frequencies of CD8⁺ T cells specific for melanocyte differentiation antigens (MDAs), including melan-A (also known as MART1), tyrosinase and gp100 (refs. 63–68). These proteins localize to the melanosomal membrane and are critical for the biosynthetic production of melanin. MDA-specific CD8⁺ T cell numbers are also increased in human vitiligo-affected skin, most strikingly at the lesional border where active melanocyte destruction takes place^{64,65} (reviewed in ref. 69). CD8⁺ T cells from human lesional skin express the cytotoxic molecules perforin and granzymes^{70,71} as well as NKG2D⁶⁸, which promotes autoreactivity⁷² (reviewed in ref. 73). Importantly, melanocyte loss correlates directly with the number of infiltrating CD8⁺ T cells in patient skin, and adoptive transfer of perilesional CD8⁺ T cells from individuals with vitiligo into mice bearing human skin explants results in melanocyte-specific cytotoxicity⁶⁵. These studies establish a causative role for CD8⁺ T cells in melanocyte destruction⁶⁵.

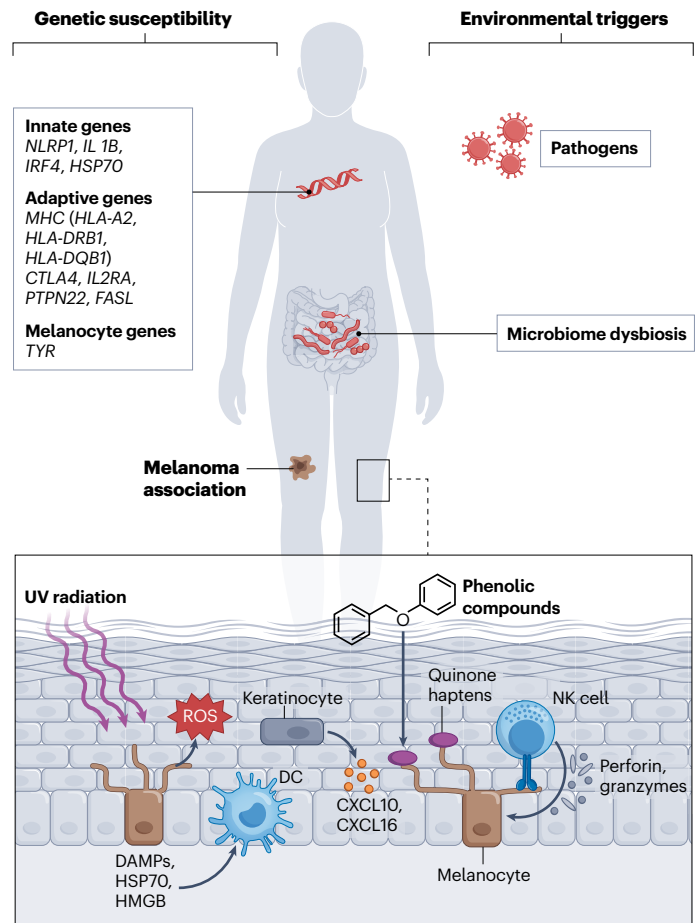


Fig. 1 | Vitiligo susceptibility factors and innate immune activation.

Single-nucleotide polymorphisms in genes encoding components of innate and adaptive immunity and in melanocyte-associated genes can increase vitiligo susceptibility. Environmental triggers, such as herpes simplex virus and cytomegalovirus infections and altered skin and gut microbiome compositions, are also associated with vitiligo. UV radiation-induced melanin production by melanocytes results in the generation of reactive oxygen species (ROS), which activate melanoma differentiation-associated gene 5 (MDA5) in keratinocytes to produce CXC-chemokine ligand 10 (CXCL10) and CXCL16. Oxidative stress also induces the release of damage-associated molecular patterns (DAMPs), which activate dendritic cells (DCs) and promote T cell activation. Phenolic pollutants lead to the generation of haptens that activate natural killer (NK) cells to release perforin and granzymes, resulting in melanocyte killing. Individuals with melanoma can also develop vitiligo, either spontaneously or following immunotherapy (not shown in the figure). HMGB, high mobility group box; HSP70, heat shock protein 70.

Human data and mouse mechanistic studies have greatly informed our understanding of how T cell tolerance to melanocyte antigens can be broken, which we discuss further below.

DCs and T cell priming

Cross-presenting DCs are critical for generating CD8⁺ T cell responses to melanocytes. In patients, significantly more CD11c⁺ cells (taken to be DCs) were found in lesional versus non-lesional skin⁷⁴, and active skin had higher proportions of DCs than control skin or stable lesions⁷⁵.

Virally induced vitiligo did not develop in *Batf3*^{-/-} mice, which lack cross-presenting conventional type 1 DCs (cDCs), although *Batf3*^{-/-} mice were still susceptible to disease in a DC vaccine-induced vitiligo model⁷⁶. Similarly, BATF3-dependent DCs were required for the priming of gp100-specific CD8⁺ T cells in the setting of MAV⁷⁷. Together, these data support a model in which cDC1s mature in response to stress-induced DAMP release, effectively cross-present antigens from dying melanocytes and prime CD8⁺ T cells to attack melanocytes.

Loss of T cell tolerance to melanocytes

Incomplete central tolerance

Incomplete central tolerance of T cells, which may be evident from a higher than normal frequency of naive MDA-reactive CD8⁺ T cells, may predispose to vitiligo development. Indeed, tetramer staining has revealed high frequencies (≥ 1 in 2,500) of naive melan-A-specific CD8⁺ T cells, even in healthy individuals⁷⁸. In mouse models (Fig. 2), central tolerance is variable across MDAs. Vaccination against tyrosinase in HLA-A2.1 transgenic mice induced high-avidity CD8⁺ T cell responses even in tyrosinase-expressing mice⁷⁹. Tolerance to tyrosinase was shown to be incomplete and induced by endothelial cells in lymph nodes, rather than in the thymus⁸⁰. For tyrosinase-related protein 2 (TRP2, also known as TYRP2 and daupochrome tautomerase (DCT)), tetramer enrichment revealed that wild-type mice have high numbers of TRP2-specific T cells that are only slightly increased in *Dct*^{-/-} mice⁸¹. Tolerance of TRP2-specific T cells was cell intrinsic and evidenced by their decreased proliferative and cytotoxic capacity in antigen-sufficient hosts⁸¹. On the other hand, the frequency of gp100-reactive naive CD8⁺ T cells was estimated to be quite low, at <0.0001%⁸². Accordingly, the thymic expression of gp100, but not TRP2, is controlled by autoimmune regulator (AIRE)⁸³. Thus incomplete induction of T cell tolerance in the thymus is likely to contribute to the loss of CD8⁺ T cell tolerance to some, but not all, MDAs.

Overcoming immune privilege

In addition to the dermis, melanocytes are also present in the leptomeninges, retinal pigment epithelium, uveal tract and inner ear⁸⁴. Vogt–Koyanagi–Harada syndrome is a rare melanocyte-directed autoimmune manifestation that results in uveitis, hearing loss and neurological pathologies⁸⁴. However, immune privilege at these sites is thought to limit T cell responses in the vast majority of individuals with vitiligo⁸⁵. Hair follicles are also a site of immune privilege with white hair outgrowth – known as poliosis or leukotrichia – only observed in ~30% of individuals with non-segmental vitiligo⁸⁶. Poliosis indicates destruction of the hair follicle melanocyte stem cell niche from which epidermal melanocytes can repopulate⁸⁷, and is thus non-reversible except in rare cases^{88,89}. Interestingly, poliosis is a defining feature of many vitiligo models in wild-type C57BL/6 mice, wherein melanocytes reside predominantly in hair follicles^{90–93}. However, requirements to overcome this immune privilege are not well understood.

Pathogenicity of altered self

Studies have shown that altered peptide ligands with enhanced binding capacity to MHC class I molecules can overcome immune tolerance to MDAs⁹⁴. Polymorphisms in tyrosinase can affect protein glycosylation and lead to misfolding, thereby increasing the rate of proteosomal processing and MHC presentation^{95,96}. In an HLA-A2.1 transgenic mouse model that expresses human tyrosinase, immunization with a viral vector encoding a xenogeneic isoform of tyrosinase induced a stronger CD8⁺ T cell response against the mutated epitope than the

native antigen, and these tyrosinase-specific CD8⁺ T cells were capable of mediating vitiligo upon adoptive transfer⁷⁹. This study established the principle that altered forms of tyrosinase can trigger vitiligo, which is underscored by the fact that polymorphisms in tyrosinase predispose to vitiligo¹³.

Several mouse models of vitiligo are based on the principle of vaccination with altered MDAs as a means to overcome tolerance, and this work has been informed by decades of research on melanoma vaccines (reviewed in ref. 97). Melanomas result from the oncogenic transformation of melanocytes and typically continue to express melanocyte differentiation antigens. Early melanoma vaccine studies in mice showed that human epitopes from gp100 and TRP2 anchor with higher affinity to MHC class I molecules and can overcome tolerance and induce vitiligo in mice^{98–100}. Moreover, selectively mutated *TYRP1* (also known as *TRP1* and *GP75*) encoding multiple MHC class I-binding epitopes breaks CD8⁺ T cell tolerance to wild-type TRP1 and induces robust vitiligo when administered as a DNA vaccine⁹³.

It is unclear whether the creation of altered peptide ligands underlies the normal pathogenesis of vitiligo in humans, for example, whether environmental factors can induce mutations in melanocyte proteins that serve as targets for CD8⁺ T cells. However, these experimental models have been instructive for understanding the requirements for breaking tolerance. Moreover, the sequencing of melanocyte antigen-specific T cell receptors (TCRs) has led to the development of TCR-transgenic mice as valuable tools for the field. A tyrosinase-specific TCR¹⁰¹ was used as the basis for the ‘Vitesse’ vitiligo model⁹². This is a triple transgenic mouse expressing a tyrosinase-specific TCR, HLA-A2.1 and K14-SCF, which develops a highly symmetrical form of vitiligo that mimics human disease⁹². Interestingly, the tyrosinase-specific T cells in this mouse do not express CD8 (refs. 92,101), presumably owing to a lack of engagement between mouse CD8 and human MHC.

Human gp100 (encoded by *PMEL*) vaccination was the basis for generating gp100-specific TCR-transgenic CD8⁺ T cells. This TCR was raised against human gp100 vaccination in wild-type mice⁹⁰, thus its affinity is considered lower than that of most foreign antigen-specific TCRs. Mice expressing the gp100-specific transgenic TCR develop spontaneous vitiligo with 100% penetrance, and adoptive transfer of the transgenic T cells in the setting of melanoma immunotherapy results in accelerated vitiligo⁹⁰. The gp100-specific T cells are also used to model vitiligo in C57BL/6 KRT14-Kit⁺ mice (expressing mouse *Kitl* under control of the human *KRT14* promoter; known as ‘Kit-L’ mice), which overexpress membrane-bound Kit-L in the epidermis¹⁰². Unlike wild-type mice, Kit-L mice develop epidermal melanocytes, which better models melanocyte distribution in humans¹⁰². Vitiligo (but not poliosis) develops in Kit-L mice that are treated by sublethal irradiation, the transfer of 1 million gp100-specific transgenic T cells and infection with vaccinia virus expressing human gp100 (ref. 102). This clinically relevant model has been valuable for studying the homing, trafficking and persistence of antigen-specific CD8⁺ T cells in the dermis and epidermis. Together, the mouse models described above have provided a useful range of tools to study CD8⁺ T cell involvement in vitiligo (Fig. 2).

Dysfunction of T_{reg} cells

CD4⁺FOXP3⁺ regulatory T (T_{reg}) cells are dominant mediators of peripheral tolerance to self-antigens, and the analysis of vitiligo patient specimens has broadly revealed T_{reg} cell dysregulation. T_{reg} cell proportions are significantly reduced in peripheral blood of individuals with vitiligo relative to healthy controls^{103–105}. T_{reg} cell numbers may fluctuate with disease progression, as FOXP3⁺ T cell proportions and counts in blood

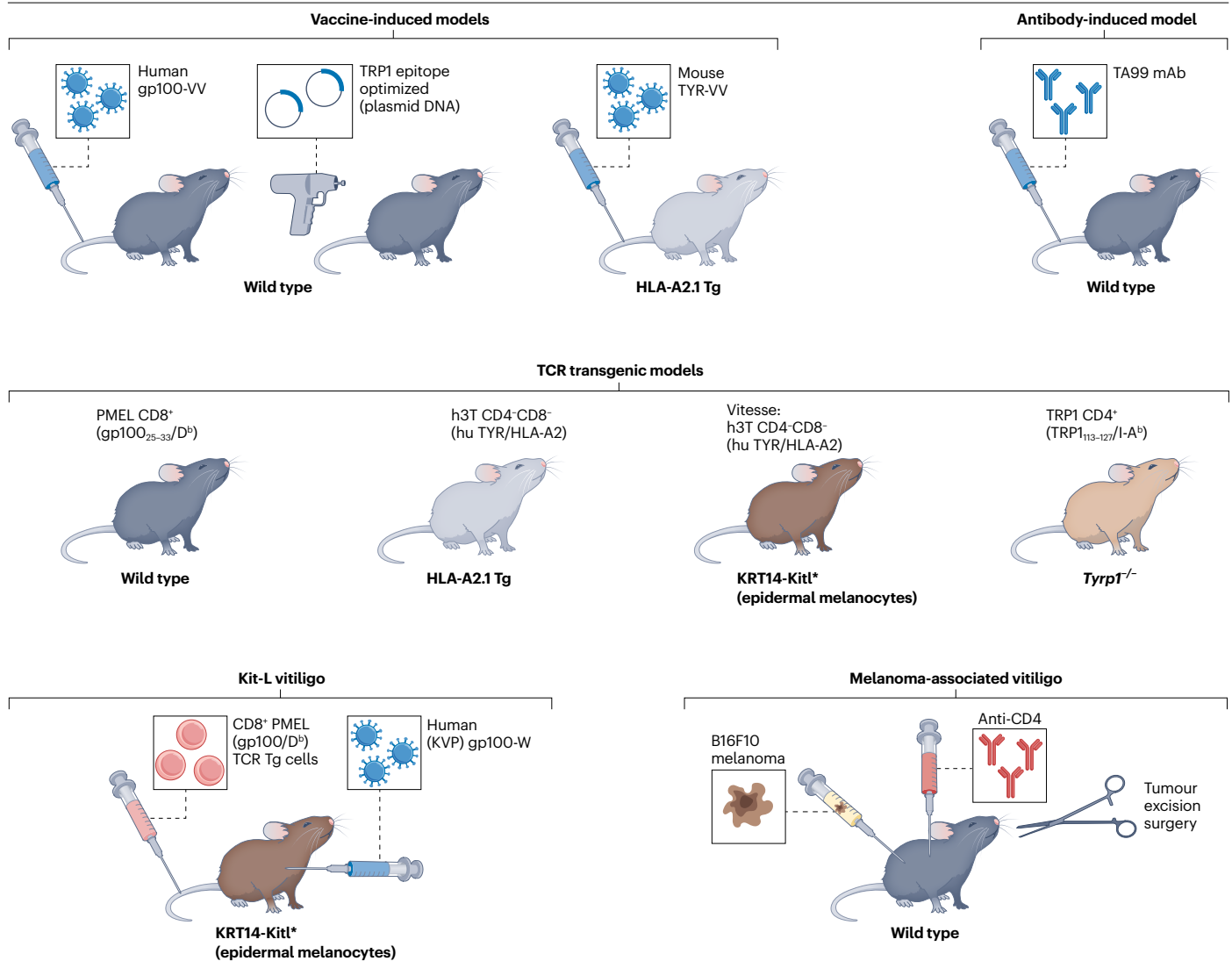


Fig. 2 | Mouse models of vitiligo. Vitiligo has been induced in C57BL/6 mice by vaccination protocols involving high-affinity or xenogeneic variants of gp100, TRP1 (encoded by *Typr1*) or tyrosinase (TYR) introduced in the context of vaccinia virus (VV) injection or plasmid DNA delivered by gene gun into wild-type or HLA-A2 transgenic (Tg) mice. Vitiligo can be induced by injection of high-affinity TRP1-specific TA99 monoclonal antibody (mAb). Spontaneous T cell receptor (TCR)-Tg vitiligo models include gp100/D^b-specific PMEL CD8⁺ T cells and human (hu) TYR/HLA-A2-specific h3T CD4⁺ CD8⁻ T cells on the HLA-A2 Tg background

with or without epidermal expression of stem cell factor (KRT14-Kitl). TRP1/I-Ab-specific CD4⁺ T cells can develop in TRP1-deficient mice and can induce vitiligo following adoptive transfer into wild-type mice. The adoptive transfer of PMEL TCR Tg CD8⁺ T cells into KRT14-Kitl recipients mediate vitiligo following human (KVP) gp100-VV vaccination in the Kit-L model. Melanoma-associated vitiligo develops in B16F10 melanoma-bearing mice treated with anti-CD4-depleting antibodies followed by tumour excision surgery.

were significantly decreased in individuals with active versus stable disease¹⁰⁶. Analyses of lesional skin also revealed lower frequencies of FOXP3⁺ T_{reg} cells relative to healthy control skin^{105,107}. In one study where T_{reg} cell frequencies were normal, T_{reg} cells from vitiligo-affected skin and blood had stronger T helper 1 (T_H1)-like characteristics (that is, higher expression of T-bet and CXCR3)¹⁰⁸ and higher CCR5 expression⁷¹, relative to healthy controls. T_{reg} cells from individuals with vitiligo also show an impaired capacity to suppress the proliferation and cytotoxic functions of CD8⁺ T cells^{108,109}. Although T_{reg} cells in patient blood have normal levels of CCR4, reduced expression of the CCR4 ligand CCL22 in lesional skin has been associated with impaired T_{reg} cell recruitment¹¹⁰.

An abundance of data from mouse models also indicate that T_{reg} cell dysregulation is a critical factor in vitiligo development and progression. Transient depletion of CD4⁺ T cells, including T_{reg} cells, by treatment with anti-CD4 monoclonal antibody is sufficient to induce vitiligo in wild-type mice bearing B16 melanoma⁹¹. Vitiligo develops ~3 weeks following surgical excision of the melanoma, with 70% penetrance and with Koebner phenomenon seen at the surgical wound site^{91,97} (Fig. 2). Comparison of this MAV model with human vitiligo skin has revealed similar populations of innate and adaptive immune cells and a similar CD8⁺ T cell transcriptional signature¹¹¹. In contrast to models involving altered peptide ligands, this model established that

tolerance to wild-type melanocyte antigens can be overcome by T_{reg} cell depletion. Interestingly, melanocytic nevus formation in mice does not induce gp100-specific $CD8^+$ T cell priming even in the absence of T_{reg} cells¹¹², suggesting that some aspect of malignancy (that is, other than increased antigen expression) is required to break tolerance to melanocytes.

Targeted T_{reg} cell depletion also accelerates vaccine-induced vitiligo in Kit-L mice¹¹³. CCR6 expression was required for T_{reg} cell trafficking to skin¹¹³ whereas CCR5 was needed for optimal suppression of $CD8^+$ T cells⁷¹. In another study, CCL22 was sufficient for T_{reg} cell recruitment to the skin, as administration of the *Ccl22* gene via a gene gun increased FOXP3⁺ T cell infiltration and reversed depigmentation¹¹⁴. Together, the above studies suggest that optimal T_{reg} cell differentiation, trafficking and function are paramount to opposing vitiligo onset and progression.

Roles for helper T cells and antibodies

The existence of MHC class II alleles that are linked to a high risk for developing vitiligo⁹ suggests there is a role for helper T cells in disease. Indeed $CD4^+$ T cells are major mediators of other autoimmune diseases including multiple sclerosis, rheumatoid arthritis and psoriasis, and $CD4^+$ T cell-mediated vitiligo can be recapitulated in mice. A high-affinity tyrosinase-related protein 1 (TRP1, also known as TYRP1)-specific $CD4$ -restricted TCR-transgenic mouse line was raised by vaccinating TRP1-deficient mice with human TRP1 (ref. 115). Adoptive transfer of these transgenic T cells induces pronounced and aggressive depigmentation, indicating that high-affinity $CD4^+$ T cells can mediate vitiligo. It was shown that $CD4^+$ T cells can kill melanocytes through Fas–FasL interactions¹¹⁶ or through recognition of antigen–MHC class II complexes expressed on melanocytes¹¹⁷. Despite this, it remains difficult to implicate $CD4^+$ T cells as major mediators of human vitiligo pathogenesis. $CD8^+$ T cells significantly outnumber conventional $CD4^+$ T cells in human lesional skin^{107,118}. Moreover, in mice with melanoma, conventional $CD4^+$ T cells were shown to suppress cDC1 activation and MDA-specific $CD8^+$ T cell priming, such that the depletion of $CD4^+$ helper T cells was required for vitiligo induction⁷⁷.

$CD4^+$ T cells are also needed for the generation of high-affinity antibodies, and a majority of individuals with active vitiligo generate antibodies against MDAs, including tyrosinase, TRP1, TRP2, gp100 and MART1 (refs. 119–123). Mouse models have borne this out, as vaccination with vaccinia virus expressing human TRP1 induces a $CD4^+$ T cell- and antibody-dependent vitiligo¹²⁴. Separate studies showed that the monoclonal antibody clone TA99 – raised against human TRP1 (ref. 125) – can cross-react with mouse TRP1 and thereby induce vitiligo upon passive transfer into C57BL/6 mice¹²⁶. TA99 antibody-dependent melanocyte killing requires complement and/or macrophages expressing Fc receptors¹²⁷, although the extent of depigmentation is weak compared with that observed for the T cell-dependent models described above. Thus although $CD4^+$ T cells and antibodies can target melanocytes, more limited evidence supports their necessity, and vitiligo has thus become regarded as a prototypical $CD8^+$ T cell-mediated autoimmune disease.

Cytokines and chemokines in vitiligo

A major role for IFN γ

In contrast to other autoimmune conditions, vitiligo is clearly a type-II IFN γ -dependent disease. Individuals with rapidly progressive vitiligo have evidence of type-1 IFN signalling in skin¹²⁸. However, single-cell RNA sequencing of lesions identified a stronger IFN γ -specific signature⁶³, and individuals with progressive vitiligo exhibit higher normalized

IFN γ expression than those with quiescent disease¹¹¹. $CD8^+$ T cells are implicated as the main IFN γ producers with by far the highest levels of *IFNG* transcript levels among cells in lesional skin^{71,111}. IFN γ itself can kill melanocytes by inducing their migration and destabilization from the basal layer of the epidermis, a process known as melanocytorrhagy¹²⁹. IFN γ can also induce melanocyte apoptosis through the action of the alternatively spliced variant CXCR3B⁶⁰.

IFN γ dependency of vitiligo has also been established in mouse models. *Ifngr1*^{-/-} mice do not develop MAV, and MDA-specific TCR-transgenic $CD8^+$ T cells cannot induce vitiligo in *Ifngr1*^{-/-} mice^{111,130}. Neutralization of IFN γ similarly prevents disease in the Kit-L model of vitiligo¹⁰². Accordingly, preclinical studies involving Janus kinase 1 (JAK1) inhibitors, which block IFN γ receptor signalling, were shown to inhibit $CD8^+$ T cell infiltration into the skin and prevent depigmentation¹³¹. A bispecific antibody targeting soluble IFN γ and keratinocyte-expressed desmoglein further restricted IFN γ neutralization to the epidermis and induced localized repigmentation in a mouse model¹³². Together these studies draw a contrast between vitiligo and type-1 IFN-mediated autoimmune diseases (for example, dermatomyositis, systemic sclerosis and SLE), underscoring the requirement of IFN γ and avenues for clinical therapy that will be discussed more below.

The CXCR3 and CXCL9, CXCL10 and CXCL11 axis

Neutralization of IFN γ was shown to specifically impair epidermal $CD8^+$ T cell accumulation in the Kit-L model¹⁰². Cellular sensing of IFN γ is known to induce production of the chemokines CXCL9, CXCL10 and CXCL11, which can recruit CXCR3-expressing $CD8^+$ T cells. Indeed *Cxcr3*^{-/-} gp100-specific transgenic T cells do not induce vitiligo⁶³, and an anti-CXCR3-depleting antibody reverses disease and induces perifollicular repigmentation¹³³. Roles for CXCL9 and CXCL10 are complex, however, as carefully dissected in the Kit-L model⁶³. Although CXCL9 promoted skin recruitment of $CD8^+$ T cells, CXCL9-independent recruitment was still sufficient for vitiligo⁶³. On the other hand, CXCL10 was required for positioning T cells within the epidermis, the acquisition of a more activated T cell phenotype and vitiligo pathogenesis⁶³. Similar mechanisms may function in humans, as CXCR3⁺ T cells are increased in patient skin biopsies^{63,128,134}, as are transcript levels of *CXCL9*, *CXCL10*, and *CXCL11* (ref. 63).

Role of keratinocytes and fibroblasts

Studies have shown that T cells respond minimally to IFN γ in lesional skin¹¹¹, and that paracrine responsiveness to IFN γ – that is, by non-T cells – is required for vitiligo. Indeed, keratinocytes have been identified for their role in this process. In Kit-L mice that specifically lack STAT1 expression (and thus IFN γ responsiveness) in keratinocytes, $CD8^+$ T cell recruitment and vitiligo were significantly reduced¹³⁵. Accordingly, within mouse epidermis, keratinocytes made more than tenfold higher levels of CXCL9 and CXCL10 compared with T cells¹³⁵. Keratinocytes in human lesional skin blister fluid also produced CXCL9, CXCL10 and CXCL11 (ref. 135).

The above study did not evaluate fibroblasts, which are deeper in the dermal layer and not captured in blister fluid⁷¹. However, a study using single-cell RNA sequencing of cells from full-thickness skin of individuals with vitiligo identified fibroblasts as scoring highest for IFN γ signalling pathways, with a majority found to produce CXCL9 and CXCL10 (ref. 111). Using the MAV model and a variety of cell-type specific IFNGR1 knockout mice, only those that exclusively lacked IFN γ responsiveness in fibroblasts failed to develop vitiligo¹¹¹. Similar results were confirmed in the Kit-L vitiligo model¹¹¹ that, in conjunction with

the above study, suggests a potentially duplicative role for fibroblasts and keratinocytes. Interestingly, fibroblasts from different regions of mouse and human skin have different inherent capacities to produce CXCL9 and CXCL10 (ref. 111). Fibroblast differences across dermatomes could potentially explain bilateral symmetry in non-segmental vitiligo¹¹¹. It is also intriguing to speculate that fibroblast activation during wound healing might trigger Koebner phenomenon of new vitiligo lesions, which tend to occur at sites of mechanical friction or trauma¹³⁶. Figure 3 illustrates how the IFN γ signalling axis, and coordination between keratinocytes, fibroblasts and CD8⁺ effector T cells, promotes vitiligo.

Roles for IL-17 and TNF

CD8⁺ T cells isolated from vitiligo patient skin produce IFN γ but distinctly lack IL-17 production, which is in contrast to the IL-17-producing CD8⁺ T cells found in psoriatic lesions⁷⁰. Regardless, several studies have reported increased levels of IL-17 and associated cytokines in individuals with vitiligo. In a large study, serum and skin levels of IL-17 and IL-22 were higher in individuals with vitiligo than in controls, and serum IL-17 levels correlated with disease severity¹⁰⁵. In individuals with active vitiligo, significantly increased T_H17 cell frequencies were present in the circulation, with increased levels of IL-17A, transforming growth factor- β 1 (TGF β 1) and IL-21 in serum¹³⁷. Serum levels of IL-17 were also increased in individuals with MAV¹³⁸. In a separate study, IL-17-producing CD8⁺ T cells were found in only one patient, who also had alopecia⁶⁵. Indeed in mouse models, gp100-specific T cells that are differentiated into an IL-17-producing 'Tc17' state in vitro, induce profound vitiligo following adoptive transfer into mice, although these Tc17 cells revert to producing IFN γ in vivo¹³⁹. Perhaps most telling are the failed therapeutic studies of the anti-IL-17 neutralizing antibody secukinumab, which did not demonstrate measurable efficacy against active vitiligo⁵². Additionally, in individuals with both psoriasis and vitiligo, secukinumab treatment mediated psoriasis clearance despite vitiligo progression¹⁴⁰. Together, these studies do not rule out potential Tc17 cell involvement in a minor subset of individuals with vitiligo, but suggest that IL-17 production does not meaningfully drive disease pathogenesis.

Similarly, tumour necrosis factor (TNF) is increased in the lesional skin of individuals with vitiligo⁵⁰ but does not drive pathogenesis. The effects of an anti-TNF therapy (etanercept) on vitiligo in multiple small trials were modest¹⁴¹, but in thousands of patients treated with anti-TNF for other autoimmune indications, the risk of vitiligo was, surprisingly, found to be significantly increased¹⁴². This concurs with other reports of patients developing vitiligo de novo following treatment with anti-TNF for other conditions (reviewed in ref. 143). On the basis of this, it has been suggested that long-term inhibition of TNF may disrupt cytokine equilibrium in unexpected ways that favour vitiligo¹⁴², although this remains speculative.

CD8⁺ T cell memory in disease persistence and recurrence

The concept of autoimmune memory against persisting self antigen is contradictory at face value, as memory is defined by T cell longevity in the absence of antigen. Regardless, persistence of CD8⁺ T cells occurs in vitiligo and without apparent functional exhaustion. In individuals with MAV, clonotypes that co-occupied blood and skin persisted for up to 9 years as evidence of true memory¹⁴⁴. Mouse models underscore the development of melanocyte-specific memory. In mice with MAV, CD8⁺ T cell responses to MDAs persist for months to years after

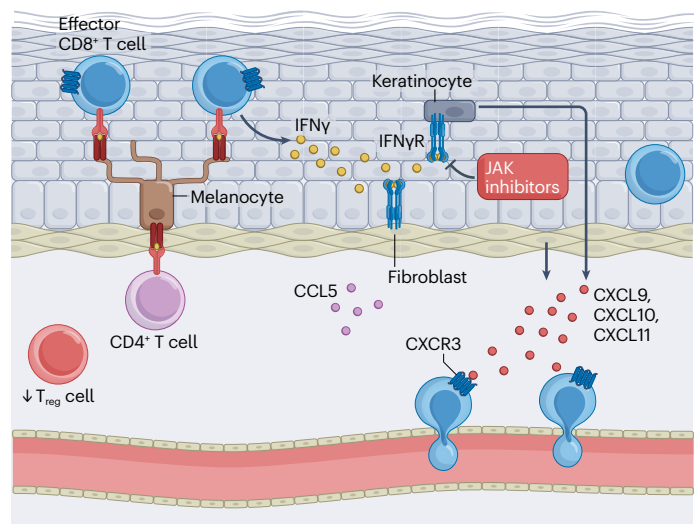


Fig. 3 | Essential roles for IFN γ , keratinocytes, fibroblasts and CD8⁺ T cells in vitiligo. Interferon- γ (IFN γ) is central for the recruitment to the skin of the CD8⁺ T cells that drive vitiligo pathogenesis. The release of IFN γ from melanocyte differentiation antigen (MDA)-specific CD8⁺ T cells in the skin promotes keratinocyte and fibroblast production of chemokines (CXC-chemokine ligand 9 (CXCL9), CXCL10 and CXCL11) to recruit pathogenic CXC-chemokine receptor 3 (CXCR3⁺) effector CD8⁺ T cells. Disrupting CXCR3 with depleting antibodies or blocking IFN γ receptor (IFN γ R) signalling with FDA-approved Janus kinase 1 (JAK1) or JAK2 inhibitors can promote repigmentation in the skin. Vitiligo is also associated with decreased regulatory T (T_{reg}) cell proportions and the activation of CD4⁺ helper T cells.

their initial priming without evidence of T cell exhaustion^{91,145}. In Kit-L mice, gp100-specific CD8⁺ T cells remain functional in producing IFN γ for months¹⁴⁶.

Mechanisms driving the establishment of T cell memory in vitiligo are only partially understood. In melanoma-induced vitiligo, the generation of long-lived CD8⁺ T cell responses to MDAs requires the presence of melanocytes in skin, suggesting the importance of melanocyte antigen engagement (and possibly killing) for memory T cell programming¹⁴⁵. Interestingly, melanocyte destruction itself is not immunogenic and does not appear to induce de novo T cell priming during ongoing disease¹⁴⁷. Accordingly, thymectomy does not impair vitiligo progression, suggesting that the priming of new T cells is not needed for disease progression¹⁴⁷. These studies, and work described below, support a model whereby CD8⁺ T cell memory sustains disease.

Resident memory

In contrast to circulating memory T cells, resident memory T (T_{RM}) cells stably reside in tissue. In fact, skin samples from individuals with vitiligo and mouse models provided some of the earliest evidence that T_{RM} cell responses develop in the context of autoimmune disease (reviewed in ref. 148). MDA-specific CD8⁺ T cell frequencies in patient skin are higher than in blood, and exhibit a CD103⁺CD69⁺CD49a⁺CD122⁺T_{RM} cell phenotype^{67,68,70}. Human vitiligo skin contains MART1-specific T_{RM} cells in both lesional and non-lesional regions, indicating skin-wide colonization of memory⁶⁷. Heterogeneity may exist within T_{RM} cell populations, as individuals with MAV had distinct skin T_{RM} cell subsets that expressed either high *IFNG* or high *TOX*¹⁴⁴. In mice with MAV, T_{RM} cell populations

develop throughout the skin¹⁴⁹ and T_{RM} cells are also unexpectedly found in skin draining lymph nodes¹⁵⁰ where they mediate long-term resistance to melanoma.

T_{RM} cell maintenance in the skin requires specific interactions in tissue microenvironments. In mice with MAV, T_{RM} cells localize to lymphoid aggregates near hair follicles¹⁴⁹, although depletion of CD11c⁺ DCs resulted in rapid disaggregation of these lymphoid structures and T_{RM} cell loss¹⁵¹. This was attributed to disruption of adhesion between CXCR6-expressing T_{RM} cells and CXCL16-expressing DCs¹⁵¹. Indeed, the presence of CXCR6⁺CD8⁺ T cells and CXCL16⁺ DCs was confirmed in lesional skin of individuals with MAV¹⁵¹. Interestingly, melanocyte-specific T_{RM} cells accumulate in greater numbers in follicles containing white hairs than black hairs¹⁴⁹, which could suggest that T_{RM} cell differentiation is supported by antigen elimination. Additionally, keratinocytes in hair follicles produce IL-15 and IL-7; cytokines that support T_{RM} cell maintenance¹⁵².

Roles for circulating versus resident memory T cells

The clearest evidence for the role of memory CD8⁺ T cell cells in vitiligo pathogenesis is the effectiveness of neutralizing IL-15, which is a cytokine required for memory T cell maintenance. In the Kit-L vitiligo model, 2 weeks of high-dose IL-15-neutralizing antibody-depleted T_{RM} cells reduced the function of T_{RM} cells and induced repigmentation⁶⁷.

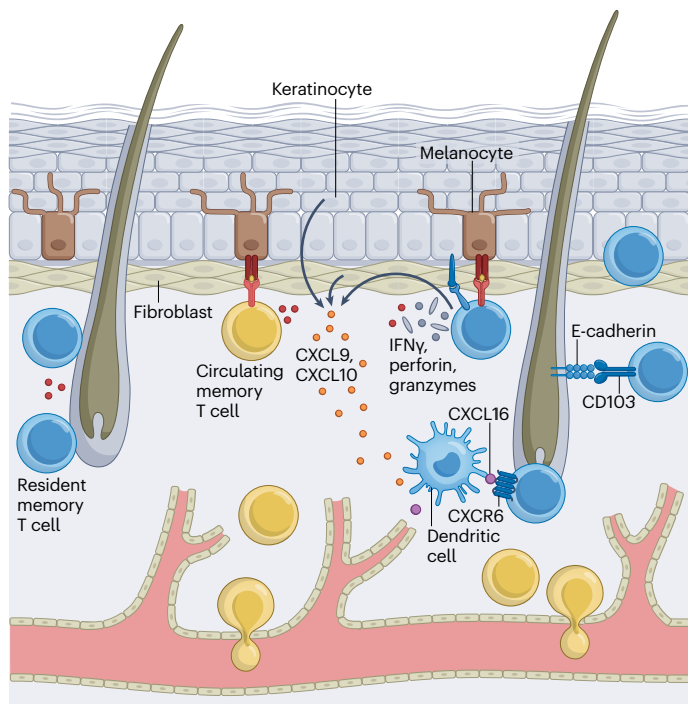


Fig. 4 | The role of memory CD8⁺ T cells in vitiligo. Both circulating CD8⁺ T cells and CD8⁺ resident memory T (T_{RM}) cells in the skin contribute to vitiligo pathogenesis. Melanocyte differentiation antigen-specific T_{RM} cells constitutively express high levels of interferon-γ (IFN_γ), perforin and granzyme B, and can mediate direct melanocyte killing. Vitiligo progression is dependent on T_{RM} cell-expressed CD103, presumably interacting with E-cadherin on the epithelium, and is also dependent on T_{RM} cell-expressed CXC-chemokine receptor 6 (CXCR6) interacting with CXC-chemokine ligand 16 (CXCL16) on the surface of dendritic cells. T_{RM} cells form aggregates with dendritic cells in hair follicles, and are more numerous in follicles growing white versus black hairs.

This is consistent with the finding that IL-15 activates T_{RM} cells isolated from human vitiligo lesions⁷⁰. More prolonged anti-IL-15 treatment (for 8 weeks) depleted both T_{RM} cell and circulating memory T cell populations and resulted in durable disease reversal⁶⁷. These studies reveal a crucial role for IL-15-dependent memory in vitiligo persistence and recurrence⁶⁷, and indicate a therapeutic avenue to durably overcoming disease.

Dissecting this further, circulating memory T cell and T_{RM} cell compartments appear to serve different roles (Fig. 4). In Kit-L mice, treatment with either the sphingosine-1-phosphate receptor (S1PR) inhibitor FTY720 (to block T cell recirculation) or anti-Thy1.1 monoclonal antibody (to specifically deplete circulating memory T cells) reversed vitiligo, indicating that circulating memory T cells are required for disease persistence¹⁴⁶. The role of T_{RM} cell appears to be more nuanced, however. Although not all skin T_{RM} cell populations are CD103 dependent⁶⁷, essentially all T_{RM} cell express CD103 in mice with MAV, and CD103 loss selectively reduced skin T_{RM} cell proportions and prevented vitiligo dissemination beyond the original lesion. Similarly, in CXCR6-deficient mice, skin T_{RM} cell populations were reduced and vitiligo did not spread beyond the original site¹⁵¹. Interestingly, different vitiligo lesions in a single patient were found to have largely discrete clonality, suggesting that T_{RM} cell populations are confined within individual lesions¹⁴⁶. Together, these studies might suggest that the activation of regional T_{RM} cell subpopulations induces new lesions.

In mice and patients treated with JAK inhibitors, vitiligo recurs at the same location. As JAK inhibitors did not appear to eliminate T_{RM} cell populations in a mouse study¹⁵³, it was speculated that T_{RM} cells may promote disease recurrence. In addition to their cytotoxic capacity, T_{RM} cells are known to orchestrate 'sensing and alarm function', whereby they produce chemokines to attract circulating memory T cells¹⁵⁴. In Kit-L mice, gp100-reactive T_{RM} cells themselves express CXCL9 and CXCL10, and were shown to support optimal CD8⁺ T cell recruitment to the epidermis¹⁴⁶.

Therapeutic approaches

Therapies for vitiligo include topical, systemic and surgical treatment options. These can be broadly categorized into treatments that stimulate residual melanocytes to induce skin repigmentation, and those that block autoimmune melanocyte destruction by CD8⁺ T cells, and/or shift the inflammatory state to an immunosuppressive state. Although treatments for vitiligo were first documented several millennia ago¹⁵⁵, much progress has been made over the past several years.

Promoting repigmentation

Sun exposure naturally induces melanogenesis or melanin production by melanocytes. Ancient Greeks combined sunlight with topical application or ingestion of plant extracts to treat vitiligo. In the twentieth century, this approach was refined through the isolation of psoralen phytochemicals and the development of lamps capable of emitting high-intensity UVA light, known as psoralen and UVA therapy. More recently, numerous clinical trials have led to the replacement of UVA with narrow-band UVB phototherapy owing to its ability to terminate within the epidermal layer¹⁵⁶. UVB-induced oxidative stress triggers the release of α-melanocyte-stimulating hormone (α-MSH), which in turn binds to melanocortin 1 receptor (MC1R) to stimulate melanocytes to produce UV-absorbing melanin^{157,158}. Promising findings from a phase I clinical trial examining the skin implanted α-MSH afamelanotide with UVB phototherapy showed that combination therapy not only arrested progression of vitiligo disease but also promoted repigmentation in

an increased percentage of patients and at earlier time points than either therapy alone¹⁵⁹. The ability of the Wnt β -catenin pathway to promote melanogenesis in mice and the ability of a Wnt agonist to induce repigmentation in human skin explants support Wnt as a promising therapeutic target for possible evaluation in future clinical trials^{160,161}.

Efforts to stimulate repigmentation, however, are most productive when melanocytes remain within the hair follicles of affected skin¹⁶². In circumstances where hair and surrounding skin are fully depigmented, melanocyte or pigmented skin transplantation resulted in durable repigmentation for most patients¹⁶³. A less invasive method of re-introducing melanocytes, that is currently undergoing clinical trial, uses a spray to distribute skin cells on laser-ablated skin followed by UVB phototherapy (NCT04547998).

Inhibiting CD8⁺ T cell activity, recruitment and survival

On the basis of their dominant role in mediating disease pathogenesis, MDA-specific CD8⁺ T cells, are major targets for immunosuppressive drugs in vitiligo. As with many autoimmune or inflammatory diseases, orally available small molecules that poison rapidly proliferating cells such as fluorouracil and methotrexate, can successfully halt vitiligo progression, and in some cases promote repigmentation¹⁶⁴. However, these broadly immunosuppressive compounds also increase host susceptibility to opportunistic infections. Efficacy has been observed with calcineurin inhibitors that more specifically prevent T cell activation and effector function, particularly when these are applied topically to active vitiligo lesions where they can restrict T cell-dependent melanocyte destruction¹⁶⁵.

Mouse studies identifying IFN γ -mediated mechanisms of vitiligo pathogenesis led to successful therapeutic trials that showed JAK1/JAK3 or JAK1/JAK2 inhibitors could induce repigmentation in the face and/or extremities of patients^{166,167}. These promising findings were followed by large phase II/III clinical trials that demonstrated significant and durable improvements in vitiligo area scoring index scores following topical treatment with the JAK1/JAK2 inhibitor ruxolitinib, resulting in its FDA approval^{168,169}. Although ruxolitinib targets multiple cytokine receptors, it acts in part by targeting the IFN γ -CXCL9/CXCL10/CXCL11 axis, which perpetuates CD8⁺ T cell recruitment and effector activity in the skin¹³¹. Clinical evaluation continues for other JAK family inhibitors, used alone or in combination with phototherapy, to inhibit additional vitiligo-associated pathways and also promote repigmentation. Candidates being tested include JAK1/JAK3 inhibitors capable of targeting both IFN γ receptor and IL-15R signalling, as well as orally administered JAK3/TEC tyrosine kinase inhibitors, which broadly inhibit lymphocyte activation and inflammation¹⁷⁰⁻¹⁷³. Although these ongoing trials seek to expand treatment options for patients, it will be important to determine whether systemic JAK and/or TEC kinase inhibition results in broader immunosuppression and opportunistic infections¹⁷⁴.

Damaged melanocytes expressing stress ligands can be targeted by NKG2D expressing CD8⁺ effector T cells⁷³. Enriched proportions of NKG2D⁺ T cells in individuals with vitiligo and higher levels of NKG2D expression on MDA-specific T_{RM} cells in mouse vitiligo models have motivated an ongoing clinical trial with antibodies specific for the NKG2D binding partner CD94 (refs. 72,175; NCT06602232). Ongoing and recent vitiligo clinical trials are summarized in Table 1 and reviewed in ref. 176.

Enhancing T_{reg} cell function

An anti-inflammatory approach that remains promising aims to increase immunosuppression by T_{reg} cells. T_{reg} cells use many mechanisms to

Glossary

Altered peptide ligands

Peptides differing in one or more amino acids from an original peptide, which bind to MHC proteins and promote TCR signalling.

Autoimmune regulator

(AIRE). A transcription factor that promotes the expression of tissue-specific antigens in the thymus, enabling the elimination of self-reactive T cells.

Central tolerance

The process by which self-reactive T cells are eliminated during their development in the thymus.

Cross-presenting

A term used for DCs that present phagocytosed antigens on cell-surface MHC class I molecules.

Dermatome

An area of skin innervated by a single spinal nerve root.

Desmoglein

A cadherin protein involved in cell-cell adhesion and tissue integrity.

K14-SCF

A transgene in which SCF expression is driven by the keratin-14 promoter, allowing for epidermal homing of melanocytes.

Koebner phenomenon

The appearance of new skin lesions on previously unaffected skin following trauma or injury.

Nevus

A benign skin growth caused by proliferation of melanocytes.

Phenolic compounds

A group of chemical substances found in plants and some industrial products that contain one or more hydroxyl groups attached to an aromatic ring.

Psoralen

A naturally occurring chemical compound found in some plants that makes skin more sensitive to UV light.

Smyth line chicken vitiligo

A naturally occurring autoimmune depigmentation condition seen in a highly inbred strain of chickens.

Tyrosinase

A key enzyme involved in the production of melanin.

Unfolded protein response

A cellular stress response triggered when misfolded or unfolded proteins accumulate in the endoplasmic reticulum.

suppress immune activity, including competition for nutrients and cytokines and direct suppression of T cell priming or effector activity. Rapamycin is a small-molecule inhibitor of the mammalian target of rapamycin (mTOR) pathway that is FDA approved for preventing T cell-mediated kidney transplant rejection. In contrast to its inhibitory effects on cytotoxic T cells, repeated rapamycin treatment expanded T_{reg} cell populations in the Vitesse mouse model and promoted long-lasting vitiligo remission¹⁷⁷. The dual capacity of rapamycin to inhibit effector T cells while promoting inhibitory T_{reg} cell responses has prompted its evaluation in multiple clinical trials for autoimmune diseases, including an open study for topical rapamycin treatment for vitiligo (NCT05342519).

T_{reg} cells can also be selectively expanded with IL-2 owing to their high expression levels of CD25 (also known as IL-2Ra), which is required to form the high-affinity IL-2 receptor complex. T_{reg} cell differentiation and activity is highly dependent on IL-2 signalling¹⁷⁸. A CD25-targeting IL-2 variant fused to the Fc domain of IgG (IL-2-Fc mutein), which is biased for binding to IL-2 receptors on T_{reg} cells over conventional naive T cells and NK cells, demonstrated a dose-dependent increase

Table 1 | Ongoing and recent clinical trials in individuals with vitiligo

Intervention	Type	Mechanism of action	Trial number	Start date	Trial phase	Participants (n)	Results available?
Methotrexate (topical)	AICAR transformylase and dihydrofolate reductase inhibitor	Inhibit cell proliferation and promote immunosuppression	NCT04942860	01 October 2019	III	25	No
5-Fluorouracil (topical)	Thymidylate synthase inhibitor	Disrupt metabolites and DNA/RNA function	NCT06209138	23 January 2024	–	40	No
Afamelanotide (subcutaneous implant)	MC1R agonist	Promote melanogenesis	NCT05210582	11 October 2022	II	6	No
Afamelanotide (subcutaneous implant)	MC1R agonist+UVB therapy	Promote melanogenesis	NCT06109649	11 October 2023	III	200	No
Hair follicle sheath cell suspension and mini-punch graft	Transplantation	Melanocyte transplantation	NCT06619184	01 December 2022	–	21	No
Ablative laser resurfacing plus RECELL and UVB therapy	Spray on skin cells	Melanocyte transplantation	NCT04547998	10 September 2020	–	25	Yes
Povorcitinib (oral)	JAK1 inhibitor	Inhibit cytokine signalling	NCT04818346	06 May 2021	II	171	Yes
Povorcitinib (oral)	JAK1 inhibitor	Inhibit cytokine signalling	NCT06113445	29 November 2023	III	467	No
Povorcitinib (oral)	JAK1 inhibitor	Inhibit cytokine signalling	NCT06113471	27 November 2023	III	450	No
Upadacitinib (Rinvoq; oral)	JAK1 inhibitor	Inhibit cytokine signalling	NCT04927975, PMID: 39475960	30 June 2021	II	185	Yes
Upadacitinib (oral) and NB-UVB therapy	JAK1 inhibitor	Inhibit cytokine signalling	NCT06118411	19 December 2023	III	614	No
Ifidancitinib (topical)	JAK1 and JAK3 inhibitor	Inhibit cytokine signalling	NCT03468855	19 March 2018	II	34	Yes
Baricitinib (oral) plus UVB	JAK1 and JAK2 inhibitor plus UVB therapy	Inhibit cytokine signalling	NCT04822584	16 July 2021	II	49	No
Deucravacitinib (oral)	TYK2 inhibitor	Inhibit cytokine signalling	NCT06327321	05 May 2024	III	128	No
Cerdulatinib (topical)	SYK and JAK inhibitor	Inhibit cytokine and lymphocyte activity	NCT04103060	27 September 2019	II	33	No
Ritlecitinib (oral) and NB-UVB	JAK3 and TEC inhibitor	Inhibit cytokine signalling	NCT0371582, PMID: 36370907	26 November 2018	IIb	366	Yes
Anifrolumab (intravenous)	anti-IFNAR1* UVB	Block type-1 IFN signalling	NCT05917561	15 December 2023	II	48	No
DR-01 (intravenous)	anti-CD94	Block NKG2A, NKG2B, NKG2C, NKG2E, NKG2H receptor signalling	NCT06602232	30 October 2024	I	80	No
Rapamycin (topical)	mTOR inhibitor	T _{reg} cell expansion and effector T cell inhibition	NCT05342519	28 July 2022	II	20	No
MK-6194 (subcutaneous)	Fc-IL-2 mutein	T _{reg} cell expansion	NCT06113328	27 November 2023	IIa	169	No
AMG 714 and NB-UVB (subcutaneous)	anti-IL-15	Inhibit T _{RM} cell survival	NCT04338581	11 December 2020	II	57	No
TEV-53408 (subcutaneous)	anti-IL-15	Inhibit T _{RM} cell survival	NCT06625177	11 November 2024	Ib	28	No
FB102 (intravenous)	anti-CD122	Inhibit T cell survival	NCT06905873	25 March 2025	I	16	No

AICAR, 5-aminoimidazole-4-carboxamide ribonucleotide; IFNAR1, interferon α/β receptor 1; JAK, Janus kinase; NB-UVB, narrow-band ultraviolet B; MC1R, melanocortin 1 receptor; T_{reg} cell, regulatory T cell; T_{RM} cell, resident memory T cell; UVB, ultraviolet B.

in T_{reg} cell numbers in blood of healthy participants¹⁷⁹. A phase II trial is currently underway to evaluate IL-2–Fc mutein in individuals with vitiligo (NCT06113328).

Conclusions

With effective FDA-approved drugs now available and promising clinical trials underway, the field of vitiligo research appears to have entered a new phase. Future efforts are needed towards blocking T cells that destroy melanocytes, without impairing immune function more

broadly. However, one must acknowledge that four decades of work have revealed the underlying mechanisms of vitiligo in impressive detail. An ongoing partnership with the field of melanoma immunotherapy will undoubtedly remain useful in this pursuit. Success in understanding vitiligo disease pathogenesis will, in turn, inform our fundamental understanding of CD8⁺ T cell tolerance and memory against self-antigens.

Published online: 02 January 2026

References

- Bohm, M. et al. Vitiligo — a disease: a position paper on stigmatization, life quality impairment and psychosocial comorbidity. *J. Dtsch Dermatol. Ges.* **22**, 1327–1335 (2024).
- Ezzedine, K. et al. Psychosocial effects of vitiligo: a systematic literature review. *Am. J. Clin. Dermatol.* **22**, 757–774 (2021).
- Akl, J. et al. Estimating the burden of vitiligo: a systematic review and modelling study. *Lancet Public Health* **9**, e386–e396 (2024).
- Sheth, V. M., Guo, Y. & Qureshi, A. A. Comorbidities associated with vitiligo: a ten-year retrospective study. *Dermatology* **227**, 311–315 (2013).
- Alkhateeb, A., Fain, P. R., Thody, A., Bennett, D. C. & Spritz, R. A. Epidemiology of vitiligo and associated autoimmune diseases in caucasian probands and their families. *Pigment Cell Res.* **16**, 208–214 (2003).
- Lee, J. H. et al. Comorbidities in patients with vitiligo: a systematic review and meta-analysis. *J. Invest. Dermatol.* **143**, 777–789.e776 (2023).
- van Geel, N. & Speeckaert, R. Segmental vitiligo. *Dermatol. Clin.* **35**, 145–150 (2017).
- Liu, J. B. et al. Association of vitiligo with HLA-A2: a meta-analysis. *J. Eur. Acad. Dermatol. Venereol.* **21**, 205–213 (2007).
- Fain, P. R., Babu, S. R., Bennett, D. C. & Spritz, R. A. HLA class II haplotype DRB1*04-DQB1*0301 contributes to risk of familial generalized vitiligo and early disease onset. *Pigment Cell Res.* **19**, 51–57 (2006).
- Jin, Y. et al. Genome-wide association analyses identify 13 new susceptibility loci for generalized vitiligo. *Nat. Genet.* **44**, 676–680 (2012).
- Jin, Y. et al. Genome-wide association studies of autoimmune vitiligo identify 23 new risk loci and highlight key pathways and regulatory variants. *Nat. Genet.* **48**, 1418–1424 (2016).
- Okamura, K. & Suzuki, T. Genetics and epigenetics in vitiligo. *J. Dermatol. Sci.* **117**, 45–51 (2025).
- Jin, Y. et al. Variant of TYR and autoimmunity susceptibility loci in generalized vitiligo. *N. Engl. J. Med.* **362**, 1686–1697 (2010).
- This genome-wide association study shows that human polymorphisms in tyrosinase and MHC class I genes are associated with predisposition to vitiligo, underscoring a link between genetic determinants and melanocyte-targeted autoimmunity.**
- Puri, N., Mojamdar, M. & Ramaiah, A. In vitro growth characteristics of melanocytes obtained from adult normal and vitiligo subjects. *J. Invest. Dermatol.* **88**, 434–438 (1987).
- Schallreuter, K. U. et al. In vivo and in vitro evidence for hydrogen peroxide (H₂O₂) accumulation in the epidermis of patients with vitiligo and its successful removal by a UVB-activated pseudocatalase. *J. Invest. Dermatol. Symp. Proc.* **4**, 91–96 (1999).
- Maresca, V. et al. Increased sensitivity to peroxidative agents as a possible pathogenic factor of melanocyte damage in vitiligo. *J. Invest. Dermatol.* **109**, 310–313 (1997).
- Passi, S., Grandinetti, M., Maggio, F., Stancato, A. & De Luca, C. Epidermal oxidative stress in vitiligo. *Pigment Cell Res.* **11**, 81–85 (1998).
- Sravani, P. V. et al. Determination of oxidative stress in vitiligo by measuring superoxide dismutase and catalase levels in vitiliginous and non-vitiliginous skin. *Indian J. Dermatol. Venereol. Leprol.* **75**, 268–271 (2009).
- Ozel Turcku, U., Solak Tekin, N., Gokdogan Edgunlu, T., Karakas Celik, S. & Oner, S. The association of FOXO3A gene polymorphisms with serum FOXO3A levels and oxidative stress markers in vitiligo patients. *Gene* **536**, 129–134 (2014).
- Yildirim, M., Baysal, V., Inaloz, H. S. & Can, M. The role of oxidants and antioxidants in generalized vitiligo at tissue level. *J. Eur. Acad. Dermatol. Venereol.* **18**, 683–686 (2004).
- Khalid-Meften, A. et al. The effect of monobenzone cream on oxidative stress and its relationship with serum levels of IL-1β and IL-18 in vitiligo patients. *J. Cosmet. Dermatol.* **23**, 4085–4093 (2024).
- Manini, P., Napolitano, A., Westerhof, W., Riley, P. A. & d'Ischia, M. A reactive orthoquinone generated by tyrosinase-catalyzed oxidation of the skin depigmenting agent monobenzone: self-coupling and thiol-conjugation reactions and possible implications for melanocyte toxicity. *Chem. Res. Toxicol.* **22**, 1398–1405 (2009).
- Jin, Y., Santorico, S. A. & Spritz, R. A. Pediatric to adult shift in vitiligo onset suggests altered environmental triggering. *J. Invest. Dermatol.* **140**, 241–243.e244 (2020).
- Ganju, P. et al. Microbial community profiling shows dysbiosis in the lesional skin of vitiligo subjects. *Sci. Rep.* **6**, 18761 (2016).
- Bziouche, H. et al. Analysis of matched skin and gut microbiome of patients with vitiligo reveals deep skin dysbiosis: link with mitochondrial and immune changes. *J. Invest. Dermatol.* **141**, 2280–2290 (2021).
- Luan, M. et al. Metagenomic sequencing reveals altered gut microbial compositions and gene functions in patients with non-segmental vitiligo. *BMC Microbiol.* **23**, 265 (2023).
- Dellacecca, E. R. et al. Antibiotics drive microbial imbalance and vitiligo development in mice. *J. Invest. Dermatol.* **140**, 676–687.e676 (2020).
- Touni, A. A. et al. Topical antibiotics limit depigmentation in a mouse model of vitiligo. *Pigment Cell Melanoma Res.* **37**, 583–596 (2024).
- Li, J. X., Yu, T. S., Hsu, S. B., Lin, H. J. & Tsai, F. J. Association of herpes simplex virus infection and vitiligo: a nationwide retrospective cohort study. *Arch. Dermatol. Res.* **317**, 90 (2024).
- Erf, G. F., Bersi, T. K., Wang, X., Sreekumar, G. P. & Smyth, J. R. Jr. Herpesvirus connection in the expression of autoimmune vitiligo in Smyth line chickens. *Pigment Cell Res.* **14**, 40–46 (2001).
- Zhuang, T. et al. Intracellular virus sensor MDA5 exacerbates vitiligo by inducing the secretion of chemokines in keratinocytes under virus invasion. *Cell Death Dis.* **11**, 453 (2020).
- Yu, H., Cen, J., Lin, X., Cheng, H. & Seifert, O. Imiquimod induced vitiligo-like lesions — a consequence of modified melanocyte function. *Immun. Inflamm. Dis.* **10**, 70–77 (2022).
- Alatabani, M., Ghobara, Y. & Alissa, A. Vitiligo-like depigmentation following treatment with imiquimod 5% cream for condylomata acuminata. *Case Rep. Dermatol.* **13**, 36–41 (2021).
- Burdick, K. H. & Hawk, W. A. Vitiligo in a case of vaccinia virus-treated melanoma. *Cancer* **17**, 708–712 (1964).
- Quaglino, P. et al. Vitiligo is an independent favourable prognostic factor in stage III and IV metastatic melanoma patients: results from a single-institution hospital-based observational cohort study. *Ann. Oncol.* **21**, 409–414 (2010).
- Hua, C. et al. Association of vitiligo with tumor response in patients with metastatic melanoma treated with pembrolizumab. *JAMA Dermatol.* **152**, 45–51 (2016).
- Nishitani, N., Bito, T., Ikeda, T., Tokura, Y. & Nishigori, C. Complete remission of metastatic malignant melanoma after surgery in association with development of systemic vitiligo. *J. Dermatol.* **37**, 770–772 (2010).
- Teulings, H. E. et al. Vitiligo-like depigmentation in patients with stage III–IV melanoma receiving immunotherapy and its association with survival: a systematic review and meta-analysis. *J. Clin. Oncol.* **33**, 773–781 (2015).
- Nardin, C. et al. Vitiligo under anti-programmed cell death-1 therapy is associated with increased survival in melanoma patients. *J. Am. Acad. Dermatol.* **82**, 770–772 (2020).
- Freeman-Keller, M. et al. Nivolumab in resected and unresectable metastatic melanoma: characteristics of immune-related adverse events and association with outcomes. *Clin. Cancer Res.* **22**, 886–894 (2016).
- Wu, W. et al. Inverse relationship between vitiligo-related genes and skin cancer risk. *J. Invest. Dermatol.* **138**, 2072–2075 (2018).
- Lindelf, B., Hedblad, M. A. & Sigurgeirsson, B. On the association between vitiligo and malignant melanoma. *Acta Derm. Venereol.* **78**, 483–484 (1998).
- Teulings, H. E. et al. Decreased risk of melanoma and nonmelanoma skin cancer in patients with vitiligo: a survey among 1307 patients and their partners. *Br. J. Dermatol.* **168**, 162–171 (2013).
- This retrospective cohort study showed that individuals with vitiligo have a threefold decreased probability of developing melanoma, underscoring a strong link between autoimmunity and antitumour immunity.**
- Lommerts, J. E. et al. Melanoma-associated leukoderma and vitiligo cannot be differentiated based on blinded assessment by experts in the field. *J. Am. Acad. Dermatol.* **75**, 1198–1204 (2016).
- Marchioro, H. Z. et al. Update on the pathogenesis of vitiligo. *Bras. Dermatol.* **97**, 478–490 (2022).
- Xu, X., Lu, X., Zheng, Y., Xie, Y. & Lai, W. Cytosolic mtDNA-cGAS-STING axis mediates melanocytes pyroptosis to promote CD8⁺ T-cell activation in vitiligo. *J. Dermatol. Sci.* **117**, 61–70 (2025).
- Wu, X., Yang, Y., Xiang, L. & Zhang, C. The fate of melanocyte: mechanisms of cell death in vitiligo. *Pigment Cell Melanoma Res.* **34**, 256–267 (2021).
- Toosi, S., Orlow, S. J. & Manga, P. Vitiligo-inducing phenols activate the unfolded protein response in melanocytes resulting in upregulation of IL6 and IL8. *J. Invest. Dermatol.* **132**, 2601–2609 (2012).
- Li, S. et al. Oxidative stress drives CD8⁺ T-cell skin trafficking in patients with vitiligo through CXCL16 upregulation by activating the unfolded protein response in keratinocytes. *J. Allergy Clin. Immunol.* **140**, 177–189.e179 (2017).
- Biról, A. et al. Increased tumor necrosis factor alpha (TNF-α) and interleukin 1 alpha (IL1-α) levels in the lesional skin of patients with nonsegmental vitiligo. *Int. J. Dermatol.* **45**, 992–993 (2006).
- Yang, L. et al. Role of chemokines and the corresponding receptors in vitiligo: a pilot study. *J. Dermatol.* **45**, 31–38 (2018).
- Speeckaert, R. et al. Critical appraisal of the oxidative stress pathway in vitiligo: a systematic review and meta-analysis. *J. Eur. Acad. Dermatol. Venereol.* **32**, 1089–1098 (2018).
- Green, D. R., Ferguson, T., Zitvogel, L. & Kroemer, G. Immunogenic and tolerogenic cell death. *Nat. Rev. Immunol.* **9**, 353–363 (2009).
- Kuppner, M. C. et al. The role of heat shock protein (hsp70) in dendritic cell maturation: hsp70 induces the maturation of immature dendritic cells but reduces DC differentiation from monocyte precursors. *Eur. J. Immunol.* **31**, 1602–1609 (2001).
- Kroll, T. M. et al. 4-Tertiary butyl phenol exposure sensitizes human melanocytes to dendritic cell-mediated killing: relevance to vitiligo. *J. Invest. Dermatol.* **124**, 798–806 (2005).
- Mosenson, J. A. et al. HSP70i is a critical component of the immune response leading to vitiligo. *Pigment Cell Melanoma Res.* **25**, 88–98 (2012).
- Denman, C. J. et al. HSP70i accelerates depigmentation in a mouse model of autoimmune vitiligo. *J. Invest. Dermatol.* **128**, 2041–2048 (2008).
- Mosenson, J. A. et al. Mutant HSP70 reverses autoimmune depigmentation in vitiligo. *Sci. Transl. Med.* **5**, 174ra128 (2013).
- This study revealed the DAMP molecule HSP70 as a link between stress and vitiligo pathogenesis, and demonstrated that mutant HSP70 effectively promotes repigmentation in a mouse model.**

59. Cui, T. et al. Oxidative stress-induced HMGB1 release from melanocytes: a paracrine mechanism underlying the cutaneous inflammation in vitiligo. *J. Invest. Dermatol.* **139**, 2174–2184.e2174 (2019).
60. Tulic, M. K. et al. Innate lymphocyte-induced CXCR3B-mediated melanocyte apoptosis is a potential initiator of T-cell autoreactivity in vitiligo. *Nat. Commun.* **10**, 2178 (2019).
61. Yu, R. et al. Transcriptome analysis reveals markers of aberrantly activated innate immunity in vitiligo lesional and non-lesional skin. *PLoS ONE* **7**, e51040 (2012).
62. van den Boorn, J. G. et al. Inflammation-dependent induction of adaptive NK cell memory. *Immunity* **44**, 1406–1421 (2016).
- Demonstrating a link between innate immunity and melanocyte killing, this study shows that memory-like NK cells recognize haptens produced by the depigmenting agent monobenzone, leading to NK cell recognition and killing of melanocytes.**
63. Rashighi, M. et al. CXCL10 is critical for the progression and maintenance of depigmentation in a mouse model of vitiligo. *Sci. Transl. Med.* **6**, 223ra223 (2014).
64. Palermo, B. et al. Specific cytotoxic T lymphocyte responses against Melan-A/MART1, tyrosinase and gp100 in vitiligo by the use of major histocompatibility complex/peptide tetramers: the role of cellular immunity in the etiopathogenesis of vitiligo. *J. Invest. Dermatol.* **117**, 326–332 (2001).
65. van den Boorn, J. G. et al. Autoimmune destruction of skin melanocytes by perilesional T cells from vitiligo patients. *J. Invest. Dermatol.* **129**, 2220–2232 (2009).
- This human study provided compelling mechanistic evidence that CD8⁺ T cells mediate vitiligo disease pathogenesis.**
66. Ogg, G. S., Rod Dunbar, P., Romero, P., Chen, J. L. & Cerundolo, V. High frequency of skin-homing melanocyte-specific cytotoxic T lymphocytes in autoimmune vitiligo. *J. Exp. Med.* **188**, 1203–1208 (1998).
67. Richmond, J. M. et al. Antibody blockade of IL-15 signaling has the potential to durably reverse vitiligo. *Sci. Transl. Med.* **10**, eaam7710 (2018).
- Studies here showed a critical role for IL-15 and memory T cells in sustaining vitiligo pathogenesis, and further established IL-15 blocking antibodies as a promising therapeutic tool.**
68. Boniface, K. et al. Vitiligo skin is imprinted with resident memory CD8 T cells expressing CXCR3. *J. Invest. Dermatol.* **138**, 355–364 (2018).
69. Richmond, J. M., Frisoli, M. L. & Harris, J. E. Innate immune mechanisms in vitiligo: danger from within. *Curr. Opin. Immunol.* **25**, 676–682 (2013).
70. Cheuk, S. et al. CD49a expression defines tissue-resident CD8⁺ T cells poised for cytotoxic function in human skin. *Immunity* **46**, 287–300 (2017).
- This was the first study to implicate skin CD8⁺ T_{RM} cells in human vitiligo by revealing T_{RM} cell presence in patient skin and the propensity to produce IFN γ .**
71. Gellatly, K. J. et al. scRNA-seq of human vitiligo reveals complex networks of subclinical immune activation and a role for CCR5 in T_{reg} function. *Sci. Transl. Med.* **13**, eabd8995 (2021).
- These studies show the importance of T_{reg} cells in suppressing vitiligo through the CCR5–CCL5 axis.**
72. Zloza, A. et al. Engagement of NK receptor NKG2D, but not 2B4, results in self-reactive CD8⁺ T cells and autoimmune vitiligo. *Autoimmunity* **44**, 599–606 (2011).
73. Plaza-Rojas, L. & Guevara-Patino, J. A. The role of the NKG2D in vitiligo. *Front. Immunol.* **12**, 624131 (2021).
74. Wang, C. Q. et al. Th17 cells and activated dendritic cells are increased in vitiligo lesions. *PLoS ONE* **6**, e18907 (2011).
75. Srivastava, N. et al. Dendritic cells sub-sets are associated with inflammatory cytokine production in progressive vitiligo disease. *Arch. Dermatol. Res.* **313**, 759–767 (2021).
76. Frisoli, M. L., Richmond, J. M. & Harris, J. E. IL-12/IL-23-independent function of BATF3-dependent dendritic cells is required for initiation of disease in a mouse model of vitiligo. *J. Invest. Dermatol.* **144**, 2574–2577.e2572 (2024).
77. Ramirez, D. E. et al. Depletion of conventional CD4⁺ T cells is required for robust priming and dissemination of tumor antigen-specific CD8⁺ T cells in the setting of anti-CD4 therapy. *J. Immunother. Cancer* **12**, e010170 (2024).
78. Pittet, M. J. et al. High frequencies of naive melan-A/MART-1-specific CD8⁺ T cells in a large proportion of human histocompatibility leukocyte antigen (HLA)-A2 individuals. *J. Exp. Med.* **190**, 705–715 (1999).
79. Colella, T. A. et al. Self-tolerance to the murine homologue of a tyrosinase-derived melanoma antigen: implications for tumor immunotherapy. *J. Exp. Med.* **191**, 1221–1232 (2000).
- This study showed how an altered peptide ligand from tyrosinase can overcome self tolerance, leading to the destruction of melanocytes in a mouse model.**
80. Nichols, L. A. et al. Deletional self-tolerance to a melanocyte/melanoma antigen derived from tyrosinase is mediated by a radio-resistant cell in peripheral and mesenteric lymph nodes. *J. Immunol.* **179**, 993–1003 (2007).
81. Truckenbrod, E. N. et al. CD8⁺ T cell self-tolerance permits responsiveness but limits tissue damage. *eLife* **10**, e65615 (2021).
82. Rizzuto, G. A. et al. Self-antigen-specific CD8⁺ T cell precursor frequency determines the quality of the antitumor immune response. *J. Exp. Med.* **206**, 849–866 (2009).
83. Trager, U. et al. The immune response to melanoma is limited by thymic selection of self-antigens. *PLoS ONE* **7**, e35005 (2012).
84. Barnes, L. Vitiligo and the Vogt-Koyanagi-Harada syndrome. *Dermatol. Clin.* **6**, 229–239 (1988).
85. Frisoli, M. L., Essien, K. & Harris, J. E. Vitiligo: mechanisms of pathogenesis and treatment. *Annu. Rev. Immunol.* **38**, 621–648 (2020).
86. Agarwal, S., Ojha, A. & Gupta, S. Profile of vitiligo in Kumaun region of Uttarakhand, India. *Indian J. Dermatol.* **59**, 209 (2014).
87. Nishimura, E. K. et al. Dominant role of the niche in melanocyte stem-cell fate determination. *Nature* **416**, 854–860 (2002).
88. Bae, J. M., Kwon, H. S., Lee, J. H. & Kim, G. M. Repigmentation of poliosis in a patient with segmental vitiligo. *J. Am. Acad. Dermatol.* **75**, e23–e24 (2016).
89. Tabbara, K. F. Reversal of poliosis and vitiligo following Vogt-Koyanagi-Harada disease. *Arch. Ophthalmol.* **130**, 394–396 (2012).
90. Overwijk, W. W. et al. Tumor regression and autoimmunity after reversal of a functionally tolerant state of self-reactive CD8⁺ T cells. *J. Exp. Med.* **198**, 569–580 (2003).
- This study introduced the gp100-specific TCR transgenic mouse which has been widely used as a model of vitiligo.**
91. Zhang, P., Cote, A. L., de Vries, V. C., Usherwood, E. J. & Turk, M. J. Induction of postsurgical tumor immunity and T-cell memory by a poorly immunogenic tumor. *Cancer Res.* **67**, 6468–6476 (2007).
92. Eby, J. M. et al. Immune responses in a mouse model of vitiligo with spontaneous epidermal de- and repigmentation. *Pigment Cell Melanoma Res.* **27**, 1075–1085 (2014).
93. Guevara-Patino, J. A. et al. Optimization of a self antigen for presentation of multiple epitopes in cancer immunity. *J. Clin. Invest.* **116**, 1382–1390 (2006).
94. Bakker, A. B. et al. Analogues of CTL epitopes with improved MHC class-I binding capacity elicit anti-melanoma CTL recognizing the wild-type epitope. *Int. J. Cancer* **70**, 302–309 (1997).
95. Ostankovitch, M., Altrich-Vanlith, M., Robila, V. & Engelhard, V. H. N-glycosylation enhances presentation of a MHC class I-restricted epitope from tyrosinase. *J. Immunol.* **182**, 4830–4835 (2009).
96. Ostankovitch, M., Robila, V. & Engelhard, V. H. Regulated folding of tyrosinase in the endoplasmic reticulum demonstrates that misfolded full-length proteins are efficient substrates for class I processing and presentation. *J. Immunol.* **174**, 2544–2551 (2005).
97. Byrne, K. T. & Turk, M. J. New perspectives on the role of vitiligo in immune responses to melanoma. *Oncotarget* **2**, 684–694 (2011).
98. Overwijk, W. W. et al. gp100/pm17 is a murine tumor rejection antigen: induction of “self”-reactive, tumoricidal T cells using high-affinity, altered peptide ligand. *J. Exp. Med.* **188**, 277–286 (1998).
99. Weber, L. W. et al. Tumor immunity and autoimmunity induced by immunization with homologous DNA. *J. Clin. Invest.* **102**, 1258–1264 (1998).
100. Bowne, W. B. et al. Coupling and uncoupling of tumor immunity and autoimmunity. *J. Exp. Med.* **190**, 1717–1722 (1999).
101. Mehrotra, S. et al. A coreceptor-independent transgenic human TCR mediates anti-tumor and anti-self immunity in mice. *J. Immunol.* **189**, 1627–1638 (2012).
102. Harris, J. E. et al. A mouse model of vitiligo with focused epidermal depigmentation requires IFN- γ for autoreactive CD8⁺ T-cell accumulation in the skin. *J. Invest. Dermatol.* **132**, 1869–1876 (2012).
- This study established CD8⁺ T cells and IFN γ as dominant mediators of vitiligo pathogenesis in a mouse model.**
103. Tembhere, M. K. et al. Alteration in regulatory T cells and programmed cell death 1-expressing regulatory T cells in active generalized vitiligo and their clinical correlation. *Br. J. Dermatol.* **172**, 940–950 (2015).
104. Willemsen, M. et al. Immunophenotypic analysis reveals differences in circulating immune cells in the peripheral blood of patients with segmental and nonsegmental vitiligo. *J. Invest. Dermatol.* **142**, 876–883.e873 (2022).
105. Elela, M. A., Hegazy, R. A., Fawzy, M. M., Rashed, L. A. & Rasheed, H. Interleukin 17, interleukin 22 and FoxP3 expression in tissue and serum of non-segmental vitiligo: a case-controlled study on eighty-four patients. *Eur. J. Dermatol.* **23**, 350–355 (2013).
106. Dwivedi, M., Laddha, N. C., Arora, P., Marfatia, Y. S. & Begum, R. Decreased regulatory T-cells and CD4⁺/CD8⁺ ratio correlate with disease onset and progression in patients with generalized vitiligo. *Pigment Cell Melanoma Res.* **26**, 586–591 (2013).
107. Abdallah, M., Lotfi, R., Othman, W. & Galal, R. Assessment of tissue FoxP3⁺, CD4⁺ and CD8⁺ T-cells in active and stable nonsegmental vitiligo. *Int. J. Dermatol.* **53**, 940–946 (2014).
108. Chen, J. et al. Th1-like Treg in vitiligo: an incompetent regulator in immune tolerance. *J. Autoimmun.* **131**, 102859 (2022).
109. Lili, Y. et al. Global activation of CD8⁺ cytotoxic T lymphocytes correlates with an impairment in regulatory T cells in patients with generalized vitiligo. *PLoS ONE* **7**, e37513 (2012).
110. Klarquist, J. et al. Reduced skin homing by functional treg in vitiligo. *Pigment Cell Melanoma Res.* **23**, 276–286 (2010).
111. Xu, Z. et al. Anatomically distinct fibroblast subsets determine skin autoimmune patterns. *Nature* **601**, 118–124 (2022).
- These studies implicate fibroblasts for their role in IFN γ response and CD8 T cell recruitment to the skin, and illustrate a model whereby regional fibroblast populations govern patterns of autoimmune skin depigmentation.**
112. Shabaneh, T. B. et al. Oncogenic BRAF(V600E) governs regulatory T-cell recruitment during melanoma tumorigenesis. *Cancer Res.* **78**, 5038–5049 (2018).
113. Essien, K. I., Katz, E. L., Strassner, J. P. & Harris, J. E. Regulatory T cells require CCR6 for skin migration and local suppression of vitiligo. *J. Invest. Dermatol.* **142**, 3158–3166.e3157 (2022).
114. Eby, J. M. et al. CCL22 to activate Treg migration and suppress depigmentation in vitiligo. *J. Invest. Dermatol.* **135**, 1574–1580 (2015).

115. Muranski, P. et al. Tumor-specific Th17-polarized cells eradicate large established melanoma. *Blood* **112**, 362–373 (2008).
 116. Lambe, T. et al. CD4 T cell-dependent autoimmunity against a melanocyte neoantigen induces spontaneous vitiligo and depends upon Fas–Fas ligand interactions. *J. Immunol.* **177**, 3055–3062 (2006).
 117. Le Poole, I. C. et al. A novel, antigen-presenting function of melanocytes and its possible relationship to hypopigmentary disorders. *J. Immunol.* **151**, 7284–7292 (1993).
 118. van den Wijngaard, R. et al. Local immune response in skin of generalized vitiligo patients. Destruction of melanocytes is associated with the prominent presence of CLA⁺ T cells at the perilesional site. *Lab. Invest.* **80**, 1299–1309 (2000).
 119. Naughton, G. K., Eisinger, M. & Bystryjn, J. C. Antibodies to normal human melanocytes in vitiligo. *J. Exp. Med.* **158**, 246–251 (1983).
 120. Kemp, E. H., Gawkrödger, D. J., MacNeil, S., Watson, P. F. & Weetman, A. P. Detection of tyrosinase autoantibodies in patients with vitiligo using 35S-labeled recombinant human tyrosinase in a radioimmunoassay. *J. Invest. Dermatol.* **109**, 69–73 (1997).
 121. Kemp, E. H., Waterman, E. A., Gawkrödger, D. J., Watson, P. F. & Weetman, A. P. Autoantibodies to tyrosinase-related protein-1 detected in the sera of vitiligo patients using a quantitative radiobinding assay. *Br. J. Dermatol.* **139**, 798–805 (1998).
 122. Kemp, E. H., Gawkrödger, D. J., Watson, P. F. & Weetman, A. P. Autoantibodies to human melanocyte-specific protein pmel17 in the sera of vitiligo patients: a sensitive and quantitative radioimmunoassay (RIA). *Clin. Exp. Immunol.* **114**, 333–338 (1998).
 123. Teulings, H. E. et al. The antibody response against MART-1 differs in patients with melanoma-associated leucoderma and vitiligo. *Pigment Cell Melanoma Res.* **27**, 1086–1096 (2014).
 124. Overwijk, W. W. et al. Vaccination with a recombinant vaccinia virus encoding a “self” antigen induces autoimmune vitiligo and tumor cell destruction in mice: requirement for CD4⁺ T lymphocytes. *Proc. Natl Acad. Sci. USA* **96**, 2982–2987 (1999).
 125. Thomson, T. M., Mattes, M. J., Roux, L., Old, L. J. & Lloyd, K. O. Pigmentation-associated glycoprotein of human melanomas and melanocytes: definition with a mouse monoclonal antibody. *J. Invest. Dermatol.* **85**, 169–174 (1985).
 126. Hara, I., Takechi, Y. & Houghton, A. N. Implicating a role for immune recognition of self in tumor rejection: passive immunization against the brown locus protein. *J. Exp. Med.* **182**, 1609–1614 (1995).
 127. Trcka, J. et al. Redundant and alternative roles for activating Fc receptors and complement in an antibody-dependent model of autoimmune vitiligo. *Immunity* **16**, 861–868 (2002).
 128. Bertolotti, A. et al. Type I interferon signature in the initiation of the immune response in vitiligo. *Pigment Cell Melanoma Res.* **27**, 398–407 (2014).
 129. Boukhedouni, N. et al. Type-1 cytokines regulate MMP-9 production and E-cadherin disruption to promote melanocyte loss in vitiligo. *JCI Insight* **5**, e133772 (2020).
 130. Gregg, R. K., Nichols, L., Chen, Y., Lu, B. & Engelhard, V. H. Mechanisms of spatial and temporal development of autoimmune vitiligo in tyrosinase-specific TCR transgenic mice. *J. Immunol.* **184**, 1909–1917 (2010).
 131. Tang, Q. et al. Rational design of a JAK1-selective siRNA inhibitor for the modulation of autoimmunity in the skin. *Nat. Commun.* **14**, 7099 (2023).
 132. Hsueh, Y. C. et al. A keratinocyte-tethered biologic enables location-precise treatment in mouse vitiligo. *J. Invest. Dermatol.* **142**, 3294–3303 (2022).
 133. Richmond, J. M. et al. CXCR3 depleting antibodies prevent and reverse vitiligo in mice. *J. Invest. Dermatol.* **137**, 982–985 (2017).
 134. Wang, X. X. et al. Increased expression of CXCR3 and its ligands in patients with vitiligo and CXCL10 as a potential clinical marker for vitiligo. *Br. J. Dermatol.* **174**, 1318–1326 (2016).
 135. Richmond, J. M. et al. Keratinocyte-derived chemokines orchestrate T-cell positioning in the epidermis during vitiligo and may serve as biomarkers of disease. *J. Invest. Dermatol.* **137**, 350–358 (2017).
 136. Zhang, X. et al. Characteristics and pathogenesis of koebner phenomenon. *Exp. Dermatol.* **32**, 310–323 (2023).
 137. Zhou, L. et al. Increased circulating T_H17 cells and elevated serum levels of TGF-β and IL-21 are correlated with human non-segmental vitiligo development. *Pigment Cell Melanoma Res.* **28**, 324–329 (2015).
 138. Carbone, M. L. et al. Insight into immune profile associated with vitiligo onset and anti-tumoral response in melanoma patients receiving anti-PD-1 immunotherapy. *Front. Immunol.* **14**, 1197630 (2023).
 139. Nelson, M. H. et al. The inducible costimulator augments Tc17 cell responses to self and tumor tissue. *J. Immunol.* **194**, 1737–1747 (2015).
 140. Kim, J. C. & Lee, E. S. Progression of pre-existing vitiligo during secukinumab treatment for psoriasis. *Ann. Dermatol.* **35**, S117–S121 (2023).
 141. Kim, N. H., Torchia, D., Rouhani, P., Roberts, B. & Romanelli, P. Tumor necrosis factor-alpha in vitiligo: direct correlation between tissue levels and clinical parameters. *Cutan. Ocul. Toxicol.* **30**, 225–227 (2011).
 142. Bae, J. M. et al. Increased risk of vitiligo following anti-tumor necrosis factor therapy: a 10-year population-based cohort study. *J. Invest. Dermatol.* **138**, 768–774 (2018).
 143. Webb, K. C. et al. Tumour necrosis factor-α inhibition can stabilize disease in progressive vitiligo. *Br. J. Dermatol.* **173**, 641–650 (2015).
 144. Han, J. et al. Resident and circulating memory T cells persist for years in melanoma patients with durable responses to immunotherapy. *Nat. Cancer* **2**, 300–311 (2021).
 145. Byrne, K. T. et al. Autoimmune melanocyte destruction is required for robust CD8⁺ memory T cell responses to mouse melanoma. *J. Clin. Invest.* **121**, 1797–1809 (2011).
 146. Richmond, J. M. et al. Resident memory and recirculating memory T cells cooperate to maintain disease in a mouse model of vitiligo. *J. Invest. Dermatol.* **139**, 769–778 (2019).
 147. Byrne, K. T., Zhang, P., Steinberg, S. M. & Turk, M. J. Autoimmune vitiligo does not require the ongoing priming of naive CD8 T cells for disease progression or associated protection against melanoma. *J. Immunol.* **192**, 1433–1439 (2014).
 148. Molodtsov, A. & Turk, M. J. Tissue resident CD8 memory T cell responses in cancer and autoimmunity. *Front. Immunol.* **9**, 2810 (2018).
 149. Malik, B. T. et al. Resident memory T cells in the skin mediate durable immunity to melanoma. *Sci. Immunol.* **2**, eaam6346 (2017).
 150. Molodtsov, A. K. et al. Resident memory CD8⁺ T cells in regional lymph nodes mediate immunity to metastatic melanoma. *Immunity* **54**, 2117–2132.e2117 (2021).
 151. Vella, J. L. et al. Dendritic cells maintain anti-tumor immunity by positioning CD8 skin-resident memory T cells. *Life Sci. Alliance* **4**, e202101056 (2021).
 152. Kruger, C. & Schallreuter, K. U. A review of the worldwide prevalence of vitiligo in children/adolescents and adults. *Int. J. Dermatol.* **51**, 1206–1212 (2012).
 153. Azzolino, V. et al. Jak inhibitors reverse vitiligo in mice but do not deplete skin resident memory T cells. *J. Invest. Dermatol.* **141**, 182–184.e181 (2021).
 154. Schenkel, J. M., Fraser, K. A., Vezys, V. & Masopust, D. Sensing and alarm function of resident memory CD8⁺ T cells. *Nat. Immunol.* **14**, 509–513 (2013).
 155. Millington, G. W. & Levell, N. J. Vitiligo: the historical course of depigmentation. *Int. J. Dermatol.* **46**, 990–995 (2007).
 156. Bae, J. M. et al. Phototherapy for vitiligo: a systematic review and meta-analysis. *JAMA Dermatol.* **153**, 666–674 (2017).
 157. Bohm, M. et al. α-Melanocyte-stimulating hormone protects from ultraviolet radiation-induced apoptosis and DNA damage. *J. Biol. Chem.* **280**, 5795–5802 (2005).
 158. Chakraborty, A., Slominski, A., Ermak, G., Hwang, J. & Pawelek, J. Ultraviolet B and melanocyte-stimulating hormone (MSH) stimulate mRNA production for αMSH receptors and proopiomelanocortin-derived peptides in mouse melanoma cells and transformed keratinocytes. *J. Invest. Dermatol.* **105**, 655–659 (1995).
 159. Lim, H. W. et al. Afamelanotide and narrowband UV-B phototherapy for the treatment of vitiligo: a randomized multicenter trial. *JAMA Dermatol.* **151**, 42–50 (2015).
 160. Regazzetti, C. et al. Transcriptional analysis of vitiligo skin reveals the alteration of wrnt pathway: a promising target for repigmenting vitiligo patients. *J. Invest. Dermatol.* **135**, 3105–3114 (2015).
 161. Yamada, T. et al. Wnt/β-catenin and kit signaling sequentially regulate melanocyte stem cell differentiation in UVB-induced epidermal pigmentation. *J. Invest. Dermatol.* **133**, 2753–2762 (2013).
 162. Goldstein, N. B. et al. Narrow band ultraviolet b treatment for human vitiligo is associated with proliferation, migration, and differentiation of melanocyte precursors. *J. Invest. Dermatol.* **135**, 2068–2076 (2015).
 163. Mulekar, S. V. Long-term follow-up study of 142 patients with vitiligo vulgaris treated by autologous, non-cultured melanocyte-keratinocyte cell transplantation. *Int. J. Dermatol.* **44**, 841–845 (2005).
 164. Jafarzadeh, A. et al. A systematic review of case series and clinical trials investigating systemic oral or injectable therapies for the treatment of vitiligo. *Skin Res. Technol.* **30**, e13642 (2024).
 165. Lee, J. H. et al. Treatment outcomes of topical calcineurin inhibitor therapy for patients with vitiligo: a systematic review and meta-analysis. *JAMA Dermatol.* **155**, 929–938 (2019).
 166. Craiglow, B. G. & King, B. A. Tofacitinib citrate for the treatment of vitiligo: a pathogenesis-directed therapy. *JAMA Dermatol.* **151**, 1110–1112 (2015).
 167. Harris, J. E. et al. Rapid skin repigmentation on oral ruxolitinib in a patient with coexistent vitiligo and alopecia areata (AA). *J. Am. Acad. Dermatol.* **74**, 370–371 (2016).
 168. Harris, J. E. et al. Safety and efficacy of ruxolitinib cream for the treatment of vitiligo: a randomised controlled trial secondary analysis at 3 years. *Skin Health Dis.* **4**, e404 (2024).
 169. Rosmarin, D. et al. Two phase 3, randomized, controlled trials of ruxolitinib cream for vitiligo. *N. Engl. J. Med.* **387**, 1445–1455 (2022).
- Two phase II clinical trials demonstrated the efficacy of a topical JAK1/2 inhibitor for repigmentation of vitiligo lesions, leading to the first FDA approval of a drug for the treatment of vitiligo.**
170. Ezzedine, K. et al. Efficacy and safety of oral ritlicitinib for the treatment of active nonsegmental vitiligo: a randomized phase 2b clinical trial. *J. Am. Acad. Dermatol.* **88**, 395–403 (2023).
 171. Guttman-Yassky, E. et al. Improvements in immune/melanocyte biomarkers with JAK3/TEC family kinase inhibitor ritlicitinib in vitiligo. *J. Allergy Clin. Immunol.* **153**, 161–172.e168 (2024).
 172. Phan, K., Phan, S., Shumack, S. & Gupta, M. Repigmentation in vitiligo using janus kinase (JAK) inhibitors with phototherapy: systematic review and meta-analysis. *J. Dermatol. Treat.* **33**, 173–177 (2022).
 173. Seneschal, J. et al. Combination of baricitinib and phototherapy in adults with active vitiligo: a randomized clinical trial. *JAMA Dermatol.* **161**, 375–382 (2025).
 174. Hu, X., Li, J., Fu, M., Zhao, X. & Wang, W. The JAK/STAT signaling pathway: from bench to clinic. *Signal Transduct. Target. Ther.* **6**, 402 (2021).
 175. Jacquemin, C., Taieb, A., Boniface, K., Seneschal, J. & Fhu, A. Imbalance of peripheral follicular helper T lymphocyte subsets in active vitiligo. *Pigment Cell Melanoma Res.* **32**, 588–592 (2019).

176. Picone, V. et al. Potential future biologic therapies for the treatment of vitiligo: focus on phase 2 and 3. *Expert Rev. Clin. Immunol.* **21**, 711–721 (2025).
177. Chatterjee, S. et al. A quantitative increase in regulatory T cells controls development of vitiligo. *J. Invest. Dermatol.* **134**, 1285–1294 (2014).
178. Chinen, T. et al. An essential role for the IL-2 receptor in T_{reg} cell function. *Nat. Immunol.* **17**, 1322–1333 (2016).
179. Scheid, J. F. et al. Safety, pharmacokinetics, and pharmacodynamics of MK-6194, an IL-2 mutein designed to selectively activate regulatory T cells: single ascending dose and multiple ascending dose trial data. *Immunohorizons* **9**, vlaf005 (2025).

Author contributions

The authors contributed equally to all aspects of the article.

Competing interests

The authors declare no competing interests.

Additional information

Peer review information *Nature Reviews Immunology* thanks Katia Boniface, Ziqi Liu, Elena Peeva and Chenfeng Zhang for their contribution to the peer review of this work.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.

© Springer Nature Limited 2026