T-Cell Recognition and Cytokine Profile Induced by Melanocyte Epitopes in Patients with HLA-DRB1*0405-Positive and -Negative Vogt-Koyanagi-Harada Uveitis

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PURPOSE. Vogt-Koyanagi-Harada disease (VKH), an autoimmune disease targeted against melanocytes, is associated with HLA-DRB1*0405. This study was undertaken to analyze T-cell recognition and the cytokine expression profile induced by melanocyte epitopes in HLA-DRB1*0405-positive and -negative patients with VKH uveitis.

METHODS. Peripheral blood mononuclear cells (PBMC) proliferation and Th1 (IFN-γ) and Th2 (IL-4 and IL-5) cytokine production were analyzed in HLA-DRB1*0405-positive (n = 12) and -negative (n = 22) patients with VKH and HLA-DRB1*0405-positive (n = 9) and -negative (n = 8) control subjects in response to human melanoma cell line lysate (HMCLL) and 28 synthetic peptides derived from the human melanocyte differentiation proteins TYR, TRP1, TRP2, and Pmel17. The peptides were selected using the TEPITOPE algorithm, based on their predicted binding to HLA-DRB1*0405 and to the non-disease-related HLA-DRB1*15.

RESULTS. HMCLL was recognized exclusively by the patients' PBMC (44%) but not by those of the control subjects (P < 0.01). PBMC from patients with VKH recognized an increased breadth of melanocyte-derived peptides at lower peptide concentrations than in the control subjects (68% vs. 25%; P < 0.01, at 1 μM) and did not produce the Th2 cytokine IL-4 in response to disease-specific peptides (0% vs. 50%, P < 0.001). Five peptides were exclusively recognized in patients bearing HLA-DRB1*0405. Furthermore, HLA-DRB1*0405-bearing patients, but not those with HLA-DRB1*15, recognized an increased breadth of melanocyte epitopes in comparison to HLA-matched control subjects (60% vs. 28%; P < 0.05).

CONCLUSIONS. These data indicate that patients with VKH are sensitized to melanocyte epitopes and display a peptide-specific Th1 cytokine response. In addition, the data indicate that patients bearing HLA-DRB1*0405 recognize a broader melanocyte-derived peptide repertoire, reinforcing the importance of this allele in susceptibility to the development of VKH disease.

Vogt-Koyanagi-Harada disease (VKH) is a major cause of endogenous uveitis in Japan1 and Brazil.2,5 It is a tissue-specific, cell-mediated autoimmune disorder against melanocytes that occurs in genetically susceptible individuals. Pigmented tissues of the eye, but also of the central nervous system, internal ear, and skin are affected. It is characterized by an acute bilateral intraocular inflammation preceded by mild meningitis-like symptoms.3 Histopathologic studies of VKH eye globes have demonstrated inflammatory infiltration followed by depigmentation (depletion of pigmented cells in the retina and choroid), mainly in the convalescent phase of the disease.5,6

Findings in several studies have revealed the autoimmune nature of the disease.5,6 It has been shown that uveal pigment inhibits leukocyte migration of peripheral blood mononuclear cells (PBMC) from patients with VKH,4 and that both CD4+ and CD8+ T lymphocytes are cytotoxic against melanocytes in vitro.6 Immunohistochemical studies in eye globes of patients with VKH have also demonstrated the aberrant expression of major histocompatibility complex (MHC) class II molecules on the surface of choroidal melanocytes, pointing out the local production of inflammatory cytokines.9 As suggested by these studies, the immune response is aimed at melanocytes, and thus it is important to pursue its autoantigenic target protein and peptides. Melanocyte-specific proteins, shown to have a major role in differentiation, such as tyrosinase (TYR), tyrosinase-related protein 1 (TRP1) and -2, MART-1/Melan A and Pmel17/gp100,10–12 are also expressed in human melanoma cell lines and are recognized by T lymphocytes of patients with melanoma.13 PBMCs from patients with VKH recognize peptides derived from the tyrosinase family of proteins involved in melanin synthesis,14,15 and peptides derived from TYR, TRP1, and TRP2 induce an autoimmune disease in rats that resembles VKH,16 making these melanocyte proteins candidate autoantigens for VKH.

Immunogenetic studies have revealed that HLA-DRB1*0405 and DRB1*0410 are strongly associated with VKH in the Japanese population (relative risk [RR] = 100).17 Recently, our group has shown that HLA-DRB1*0405 is the predominant allele associated with VKH, with a RR of 12 in Brazilian patients.18 This cohort of patients was an ethnically heterogeneous population, with Japanese descent in only three patients. The coincident finding of disease association with HLA-DRB1*0405 in ethnically different populations suggests that this HLA class II allele, and not another closely linked HLA-encoded factor, is the major susceptibility determinant. Given the role of the HLA molecule in antigen presentation to T cells, it has been hypothesized that HLA-DRB1*0405 plays a selective role in presenting the target epitopes.18 However, the actual mechanism of this association is unknown.

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In contrast to Japanese patients with VKH, the fact that a significant number of individuals do not carry the susceptibility allele in the Brazilian VKH population\(^\text{18}\) provides a unique opportunity to search for differences in the cellular immune responses against melanocyte peptides between patients carrying the HLA susceptibility allele and those carrying other alleles, consistent with a selective presentation of target epitopes. In the present study, we sought to analyze the role of HLA-DRB1*0405 in melanocyte-derived peptide presentation, by measuring PBMC proliferation and cytokine secretion by DRB1*0405-positive and -negative patients with VKH and HLA-matched normal control subjects, in response to a human melanoma cell line lysate and 28 synthetic peptides selected from human melanocyte differentiation proteins.

**METHODS**

**Patients and Normal Subjects**

Thirty-four patients with VKH (7–64 years old; 6 men and 28 women), attending the Uveitis Service (Department of Ophthalmology, University of São Paulo School of Medicine), were included in the present study. As declared by the patients, ethnic distribution was as follows: white, 25 (67%); black, 4 (12%); Asian, 3 (9%); and mixed black and white, 4 (12%). The mean duration of the disease at the time of the blood sampling was 9 ± 6 years (range, from a few days to 26 years). Five patients had disease in the initial, untreated stage, 12 in the chronic or recurrent phase, and 17 in the inactive convalescent phase. Eleven patients were taking systemic immunosuppressant drugs: cyclosporine (n = 7), chlorambucil (n = 2), cyclophosphamide (n = 1), and methotrexate (n = 1). Diagnosis was based on the revised guidelines of the American Uveitis Society.\(^\text{19}\)

Seventeen healthy individuals were included in a control group (28–52 years old; 8 men and 9 women). Ethnic distribution was 82% white, 6% black, and 12% Asian.

All 34 patients and 17 control subjects were typed for HLA-DRB with low-resolution polymerase chain reaction–sequence specific primer (PCR-SSP).\(^\text{20}\) In HLA-DR4-positive samples, PCR was followed by hybridization with sequence-specific oligonucleotide probes with DR4-specific primers for exon-2 amplification, according to 12th International Histocompatibility Workshop protocols.\(^\text{21}\) Patients and control subjects were divided into different groups according to their HLA-DRB1 types: carriers of disease-associated HLA-DRB1*0405 (7 patients and 9 control subjects), carriers of non–disease-related HLA-DRB1*1501 (8 patients and 8 control subjects), carriers of both alleles HLA-DRB1*0405 and DRB1*1501 (5 patients), and carriers of other HLA alleles (14 patients).

Written, informed consent has been given by every participant of the study, which was approved by the Institutional Review Board of the University of São Paulo School of Medicine. The research followed the tenets of the Declaration of Helsinki.

**Peptide Selection**

The amino acid sequences of TYR (M27160), TRP1 (AF001295), TRP2 (D17547), Pmel17 (M77348), and MART1 (U06654), all human melanocyte-derivied proteins was: TYR, 5 peptides; TRP1, 7 peptides; TRP2, 6 peptides, and Pmel17, 10 peptides.

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A given HLA-DR molecule (e.g., a 5% threshold selects sequences with HLA-binding scores equal to or higher than those 5% of the sequences with highest binding scores to a given HLA-DR molecule in the TEPITOPE database) are selected by the software. The algorithm also allows the selection of sequences predicted to bind simultaneously—thus, promiscuously—to several HLA-DR molecules. Peptides were selected based on their chance of binding to the disease susceptibility HLA allele HLA-DRB1*0405 and/or to the non–disease-related HLA allele HLA-DRB1*15, with a threshold of 5%, with the exception of two peptides predicted to bind to HLA-DRB1*0405 above the 8% threshold.

Among peptides selected by the TEPITOPE algorithm, 28 peptides with different chances of binding to the respective HLA allele were synthesized: 11 predicted to bind to the HLA-DRB1*0405 molecule and not to HLA-DRB1*15, 13 predicted to bind to HLA-DRB1*15 and not to HLA-DRB1*0405, and 4 predicted to bind to both HLA molecules, as shown in Table 1. The peptide distribution among the melanocyte-derived proteins was: TYR, 5 peptides; TRP1, 7 peptides; TRP2, 6 peptides, and Pmel17, 10 peptides.

To increase the efficiency of T-cell recognition of the TEPITOPE-selected nonamers, N- and C-terminal flanking amino acids were added. The resultant 15-mer peptides were synthesized by solid-phase technology, with a 9-fluorenlymethoxycarbonyl (Fmoc) strategy\(^\text{23}\) on an automated bench-top simultaneous multiple solid-phase peptide synthesizer (PSSM8; Shimadzu, Tokyo, Japan) with Fmoc protected amino acid residues and TGR resin (Novabiochem, San Diego, CA). The resultant peptides were analyzed by reversed-phase high performance liquid chromatography (RP-HPLC; Shimadzu) on a C18 column eluted at 1 mL/min with a 5% to 95% gradient of 90% acetonitrile in 0.1% TFA over 30 minutes. Peptide quality was assessed by matrix-assisted desorption ionization mass spectrometry (MALDI-TOF-MS; ToFSpec-E; Micromass, Manchester, UK) using a-cyano-4 hydroxy cinnamic acid as the matrix with >80% purity. Synthetic peptides were lyophilized and reconstituted in dimethyl sulfoxide (DMSO) at 25 mM for storage at −20°C before use in cell culture.

**Melanoma Cell Line Lysate**

Human melanoma cell line lysate was prepared from MMAc, a human melanoma cell line whose donor carried the HLA-DRB1*0405 and HLA-DRB1*1502 alleles (kindly donated by Manabu Mochizuki, Kurume University, Japan). Melanoma cells were lysed through 10 sessions of freezing and thawing on liquid nitrogen and a water bath at 37°C.\(^\text{24}\) Melanoma cell lysate concentration was adjusted to 1 mg/mL and was tested in PBMC proliferation assays at five concentrations (10, 20, 50, 100, and 200 μg/mL).

**PBMC Proliferation Assay**

PBMC were separated by density gradient centrifugation (d = 1.077 g/mL). Cells were incubated in RPMI 1640 medium (Invitrogen-Gibco, Grand Island, NY) supplemented with 10% heat-inactivated normal human serum, 2 mM l-glutamine, 1 mM sodium pyruvate, 50 μg/mL gentamicin, and 10 mM HEPES buffer (complete medium), in triplicate on 96-well U-bottomed culture plates (10 cells/well; final volume, 0.2 mL) in the presence of melanocyte-derived peptide (1, 10, and 50 μM), phytohemagglutinin (PHA, 2.5 μg/mL; Difco Laboratories, Detroit, MI), purified protein derivative (PPD, 5 μg/mL; kindly donated by Yuijio Fujino, University of Tokyo, Japan) or complete medium alone. Plates were incubated in 5% CO\(_2\) at 37°C for 5 days and cultures were pulsed with \(^{3}H\) thymidine at 0.5 μCi/well for the last 18 hours before the end of culturing. Cells were harvested, and the uptake of the \(^{3}H\) thymidine (Amersham Pharmacia Biotech, Piscataway, NJ) was measured by a β-counter (1205 BS Betaplate; Wallac, Turku, Finland). Data are presented as the stimulation index (SI), calculated by dividing mean counts per minute in cultures with antigen by mean counts per minute in cultures without antigen. A stimulation index ≥2.0 was considered positive.\(^\text{25,26}\)
**Cytokine Detection in Culture Supernatants**

PBMC were isolated and cultured with or without antigen (10 μM peptide, 2.5 μg/mL PHA, or 5 μg/mL PPD) as just described, and supernatants were collected 48 hours after stimulation. Cytokine quantitation was performed with anti-human cytokine antibody pairs for IFN-γ (Pierce-Endogen; Rockford, IL) and IL-4 (BD-Pharmingen, San Diego, CA). IL-5 detection was performed by human IL-5 colorimetric ELISA kit (Pierce-Endogen). Specific cytokine production was expressed as: (mean values from duplicate experiments in stimulated wells) – (mean values from duplicate control wells). The detection limit of each assay was as follows: IFN-γ, 4 to 30 pg/mL; IL-4, 10 to 40 pg/mL; and IL-5, 4 to 10 pg/mL.

**Statistical Analysis**

The nonparametric Mann-Whitney rank sum test was used to compare SIs and cytokine production for each antigen among clinical groups. The χ² or Fisher exact test was used to compare frequencies of responding and nonresponding individuals.

**RESULTS**

**Proliferative Response against Melanoma Cell Line Lysate in PBMCs**

PBMC from 44% of the 16 patients with VKH tested recognized a melanoma cell line lysate in proliferation assays, in at least one of the tested concentrations, compared with none of the PBMC of the 14 control subjects tested (P = 0.007). Among the four HLA-DRB1*0405-positive patients, three were responders, whereas among the five HLA-DRB1*15-positive patients, one was responder.

**PBMC Recognition Profile of the Melanocyte-Derived Peptides**

Taking into account responses to all three peptide concentrations tested, the overall frequency of responders and the number of peptides recognized were similarly high in both patients and control subjects, targeting several peptides from several proteins. In contrast, the analysis of the lymphoproliferative responses to peptides at different concentrations showed that, at the lowest concentration (1 μM), PBMC from the patients as a group recognized a more diverse array of peptides (68%, 19/28 peptides) than those from the control group (25%, 7/28 peptides; P = 0.003; Fig. 1). Concerning cytokine secretion, the overall frequency of peptide-induced IFN-γ producers and the number of peptides able to induce IFN-γ secretion were similarly high in patients and control subjects, targeting several peptides from several proteins (Fig. 2, Table 2). In contrast, it was striking that, whereas PBMC from 50% of the control subjects secreted IL-4 in response to any peptide (43 ± 20 pg/mL), none of the PBMC from patients secreted peptide-induced IL-4 (P < 0.001; Fig. 2, Table 2). Peptide-induced IL-5 secretion was obtained from PBMC of only one patient (Table 2).
Some peptides elicited more frequent responses by both lymphoproliferation and IFN-γ production: TYR496-510 (35% and 40%, respectively), TRP1167-181 (21% and 43%), and TRP1308-322 (32% and 45%).

In our sample, we did not find any correlation between disease stage, systemic therapy, and immune responses against melanocyte-derived peptides in patients with VKH (data not shown).

Recognition Profile of Patients with VKH Bearing the Major Susceptibility Allele HLA-DRB1*0405

The peptide-specific lymphoproliferative and cytokine responses were similar between HLA-DRB1*0405-positive and -negative patients and control subjects, except for peptide-induced IL-4, as previously mentioned (Table 2). Peptide-induced IL-4 was not detected in any patient with VKH irrespective of HLA typing, whereas it was detected in 50% (DRB1*0405) and in 50% (DRB1*15) of control subjects (Table 2).

Data were also analyzed based on the number of peptides recognized in lymphoproliferative assays. As a group and at any concentration, DRB1*0405-positive PMBC of patients recognized a higher number of peptides (including peptides predicted to bind to HLA-DRB*15 but not to HLA-DRB1*0405) than those of HLA-matched control subjects (17/28 vs. 8/28; P = 0.031), whereas DRB1*15 patients’ PMBC recognized a lower number of peptides than those of the HLA-matched control subjects, including peptides predicted to bind to HLA-DRB*0405 but not to HLA-DRB1*15 (16/28 vs. 25/28; P = 0.014; Figs. 3, 4). The average number of melanocyte-derived peptides individually recognized by each subject in the four groups were: DRB1*0405 VKH, 3.4 (range, 0–17); DRB1*0405 control, 1.4 (range, 0–4); DRB1*15 VKH, 3.6 (range, 1–10); and DRB1*15 control, 6.5 (range, 1–18).

Among patients, five peptides were exclusively recognized by cells of HLA-DRB1*0405-positive patients, either in lymphoproliferative (TYR348-362, TRP1296-310, and TRP1263-277) (data not shown).

![Figure 1](https://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/933438/)  
**Figure 1.** Breadth of recognition and magnitude of proliferative responses against melanocyte-derived peptides in patients with VKH and control subjects in different peptide concentrations. (A) Frequency of human melanocyte-derived peptides (n = 28) recognized by PMBC of patients with VKH (n = 34) and control subjects (n = 17) in lymphoproliferative assays at each peptide concentration. (B) Mean stimulation index ± SD of all melanocyte-derived peptides recognized (SI ≥ 2.0) at each peptide concentration among patients with VKH (n = 34) and control subjects (n = 17). (■) Patients with VKH; (□) normal control subjects.

![Figure 2](https://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/933438/)  
**Figure 2.** IFN-γ (■) and IL-4 (○) production induced by melanocyte-derived peptides in PBMCs from patients with VKH and control subjects. (A) Patients with VKH, mean ± SD (n = 21); (B) Normal control subjects, mean ± SD (n = 14). The values represented on the graphs are: (level of peptide-induced cytokine) – (level of cytokine produced by PBMC only). *Not tested.
not shown) or IFN-γ (TRP2277-291 and TRP2139-153) detection assays (data not shown). In contrast, we found two peptides exclusively recognized by cells of DRB1*15-bearing patients: TRP2277-291 and TRP2139-153 (data not shown).

Furthermore, cells of DRB1*0405-bearing patients as a group, but not those of DRB1*15 patients, had a tendency to recognize a more diverse array of peptides at 1 μM than did cells of HLA-matched control subjects (11/28 vs. 4/28 peptides; P = 0.068; data not shown); this tendency disappeared at 10 and 50 μM.

**DISCUSSION**

We have studied T-cell recognition of melanocyte-derived peptides in DRB1*0405-positive or -negative patients with VKH and in control subjects. PBMC from patients with VKH recognized a more diverse array of melanocyte-derived peptides at lower peptide concentrations than did those of control subjects, and exhibited a Th1 type cytokine response against these peptides. Moreover, PBMC from HLA-DRB1*0405-positive patients, but not from HLA-DRB1*15-positive patients, recognized an increased breadth of peptides compared with cells of HLA-matched control subjects.

The clear cut difference in response against the human melanoma cell line lysate observed among patients with VKH and control subjects is in line with previous observations of T-cell cytotoxicity against melanocyte and melanoma cell lines in patients with VKH.29,30 Furthermore, it reinforces the importance of the melanocyte as the target of autoimmunity in this disease.5,6,9 and the validity of pursuing the responses against peptides derived from melanocyte-derived proteins. The finding that cells from patients with VKH recognize a broader range of peptides at low concentration (1 μM) than do those from control subjects in proliferative responses (Fig. 1) is consistent with epitope spreading secondary to a sensitization by a still undefined self-antigen.31 The increased breadth of peptide recognition at the lower concentration in patients compared with control subjects indicates that, for most peptides, patients show a lower threshold for T-cell activation, in line with previous in vivo sensitization with the tested melanocyte-derived peptides. This suggests that T cells from patients with VKH recognize melanocyte-derived peptides with high affinity.32 Conversely, T cells from control subjects show low-affinity responses to epitopes from proteins without prior exposure, in line with the expected behavior of a cross-reactive T-cell response.33 The property of cross-reactivity seems to be inherent in T-cell recognition.34

In addition, our data have demonstrated for the first time that PBMC from patients with VKH do not produce an anti-Th1 cytokine, such as IL-4, against disease-specific peptides (Fig. 2, Table 2). A similar Th1 cytokine profile has been described in PBMC from patients with VKH after an unspecified anti-CD3 stimulation.35,36 It is noteworthy that most human organ-specific autoimmune diseases,37 as well as murine models,38 are reported to be mediated by autoreactive T1-type T cells, and rodent strains that are prone to the induction of T-cell-dependent autoimmune disease often have a genetic predisposition to a predominantly T1-type cytokine response.39,40 Significantly, there is clinical and laboratory evidence of viral infection preceding the acute ocular VKH symptoms (Usui M, et al. IOVS 1991;32:ARVO Abstract 807).41,42 which suggest the participation of infection that could activate Toll-like receptors and induce a T1 response.42

The identification of three novel epitopes derived from TYR, TRP1, and TRP2 that are exclusively or preferentially recognized by PMBC of patients bearing HLA-DRB1*0405, further supports the role of HLA-DRB1*0405 in the presentation of melanocyte-derived peptides. Yamaki et al.15 have shown that

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**Table 2. Number of Individuals with a Positive Response in PBMC Proliferation and Cytokine Secretion Assays**

<table>
<thead>
<tr>
<th>Type of Assay</th>
<th>Patients</th>
<th>Control Subjects</th>
</tr>
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<tbody>
<tr>
<td>PBMC proliferation</td>
<td>All (3.0 ± 1.8)</td>
<td>26/34 (3.1 ± 1.6)</td>
</tr>
<tr>
<td>IFN-γ secretion</td>
<td>17/21 (24 ± 31)</td>
<td>3/4 (26 ± 43)</td>
</tr>
<tr>
<td>IL-4 secretion</td>
<td>0/20* (0/4)</td>
<td>0/4 (0/4)</td>
</tr>
<tr>
<td>IL-5 secretion</td>
<td>1/18 (5)</td>
<td>0/5 (0/4)</td>
</tr>
</tbody>
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PBMC proliferation results include individuals who had a stimulation index (SI) ≥2.0 for at least one melanocyte-derived peptide at any peptide concentration. In parentheses: PBMC proliferation (mean SI from positive results only ± SD) and cytokine detection (mean picograms per milliliter peptide-induced cytokine production from positive results only ± SD).

*P < 0.001 (peptide-induced IL-4 secretion in patients and control subjects).

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**Figure 3.** Breadth of recognition of melanocyte-derived peptides by HLA-DRB1*0405- and HLA-DRB1*15-positive individuals in lymphoproliferative assays at any peptide concentration. (A) HLA-DRB1*0405 individuals (patients, n = 7; control subjects, n = 9). (B) HLA-DRB1*15 individuals (patients, n = 8; control subjects, n = 8). ( ) Patients with VKH; ( ) normal control subjects.
the peptides TYR\textsubscript{442-456} (SKDLGYDYSYLQDSD), and TRP\textsubscript{1263-1277} (DDLMGSRSNFDSTLI), also recognized by cells in our study, were preferentially recognized by T-cell clones from patients with acute, nontreated VKH. The finding of melanocyte-derived peptides that are specifically recognized by PMBC of HLA-DRB1*0405-positive patients with VKH may have a bearing on the association of HLA-DRB1*0405/VKH with the pathogenesis of the disease.

The fact that only DRB1*0405-positive patients with VKH showed an increased breadth of recognition of melanocyte epitopes in comparison to HLA-matched control subjects (Fig. 3) is in line with the phenomenon of epitope spreading found in other autoimmune diseases\textsuperscript{43} and supports melanocytes as the target of the autoimmune response in DRB1*0405-bearing patients with VKH. However, the reduced breadth of peptide recognition by DRB1*15-positive patients with VKH in comparison to HLA-matched control subjects (Fig. 3) is puzzling. A possible explanation would be the existence of other target proteins not analyzed in this study, preferentially recognized by patients carrying HLA-DRB1*15 or other non-HLA-DRB1*0405 alleles.

Even though the peptide selection method has been successfully used for depicting immunodominant T-cell epitopes in immune-mediated diseases,\textsuperscript{14, 45} there is still no guarantee that all selected peptides are indeed naturally produced. However, the high peptide concentrations used in the study, similar to other epitope mapping studies,\textsuperscript{14, 15} could be responsible for the increased frequency of positive lymphoproliferative responses against melanocyte-derived peptides in comparison to melanoma lysate. Such synthetic peptide concentrations would be well in excess of the peptide concentration attainable in the melanoma lysate.

In summary, we have shown that patients with VKH are sensitized to melanocyte antigens, displaying a melanocyte peptide-specific Th\textsubscript{1} cytokine response. We also found that HLA-DRB1*0405-positive patients are sensitized to a significant number of melanocyte-differentiation, protein-derived epitopes. Future studies could further elucidate the underlying reasons for the predominant Th\textsubscript{1} cytokine profile and the increased breadth of melanocyte peptide recognition by HLA-DRB1*0405-bearing patients with VKH and the implications in their susceptibility to VKH.

References
