初診時視力右（1.2）、左（1.2）。両眼前眼部炎症と硝子体混濁がみられた。蛍光眼底造影では両眼網膜血管からシダ状の蛍光漏出がみられた。その後も眼炎症発作を繰り返し、口腔内アフタ性潰瘍とあわせてベーチェット病と診断された。著明な視力低下を伴う眼炎症発作を繰り返すためコルヒチン内服を開始したが、その後も頻発する眼炎症発作とともに腸管ベーチェット病を発症。インフリキシマブ治療を開始した。その後は大きな眼炎症発作はなく経過し、眼外症状も落ちついている。

D.E.　考察と結論

小児ベーチェット病２症例における眼炎症所見は成人発症例とほぼ同じであり、視力低下をきたす重篤なものであった。陰部潰瘍はみられなかった。インフリキシマブ治療が発作抑制に有効であった。今後、副作用の発現や効果の減弱など長期的な有用性についてはさらに経過観察が必要である。

F. 健康危険情報

特記事項なし。

G.　研究発表

1．論文発表　なし

,2. 学会発表　なし

H. 知的財産権の出願、登録状況

なし

図１．症例１経過

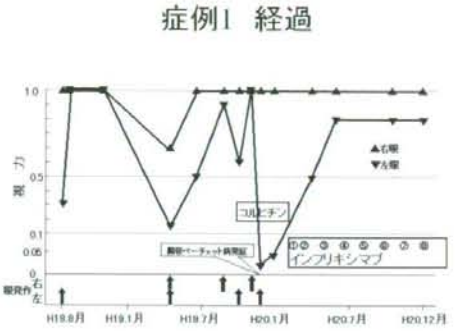
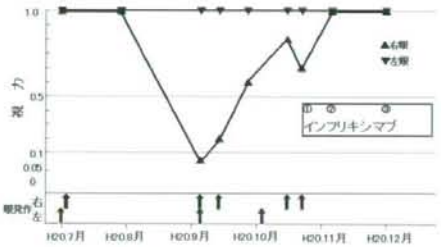


図２．症例２経過



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Fumio KANEKO[1]
Noritaka OYAMA[1]
Hirokatsu YANAGIHORI[2]
Emiko ISOGAI[3]
Kenji YOKOTA[4]
Keiji OGUMA[4]

[1] Institute of Dermato-Immunology and -Allergy, Southern TOHOKU Research Institute for Neuroscience, 7-115 Yatsuyamada, Koriyama, Fukushima, 963-8563
[2] Department of Dermatology, Fukushima Medical University School of Medicine, Fukushima
[3] Department of Disease Control and Molecular Epidemiology (Preventive Dentistry), Health Sciences University of Hokkaido, Ishikari-Tobetsu, Hokkaido
[4] Department of Bacteriology, Okayama University Graduate School of Medicine and Dentistry, Medical School, Okayama, Japan

Reprints: F. Kaneko
<f.kaneko@mt.strins.or.jp>

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The role of streptococcal hypersensitivity in the pathogenesis of Behçet's Disease

Behçet's disease (BD) is still considered as a mysterious multisystemic disorder characterized by recurrent involvement of muco-cutaneous, ocular, intestinal, vascular and/or nervous system organs. In this review, we would like to highlight and discuss several important advances in our understanding of the pathogenesis of BD based on the intrinsic genetic factors including HLA-B51 and MICA expression and extrinsic triggering factors. As one of the extrinsic triggering factors, we focused on the hypersensitivity against oral *streptococci* which might be acquired through the innate immune mechanism. It was found that HLA-B51 restricted CD8 T cell response was clearly correlated with the target tissues expressing MICA*009 by stress in active BD patients with HLA-B51 as the intrinsic factors. *Bes-1* gene and HSP-65 derived from oral *S. sanguinis*, which is the uncommon serotype (KTH-1, strain BD113-20), are supposed to play important roles as an extrinsic factor in BD pathogenesis. The peptides of the *Bes-1* gene are highly homologous with the retinal protein *Brn3b* and moreover, the *Bes-1* peptides were homologous with HSP-65 derived from microorganisms in association with the counterpart human HSP-60, which appeared reactively in the patients. HSP-65/60 also has high homologies with the respective T cell epitope of BD patients. Although HSP-65/60 and the peptides of *Bes-1* gene were found to stimulate PBMCs from BD patients in the production of pro-inflammatory Th1 type cytokines, some homologous peptides of HSP-65 with T cell epitopes were found to reduce IL-8, IL-12 and TNF-α produced from PBMCs of active BD patients. The findings might be correlated with the clinically therapeutic effects for BD patients with severe uveitis, who were led to immunotolerance by the peptide of human HSP-60 (336-351), as previously reported. Then, the pathogenesis of BD was discussed referring to intrinsic genetic factors and extrinsic triggering factors in aspects of streptococcal hypersensitivity, which might be acquired through the innate immune mechanisms. The BD symptoms were thought to be due to vascular reactions as immune responses in correlation with monocyte expressed streptococcal agents.

Key words: Behçet's disease, *Streptococcus sanguinis*, heat shock protein, *Bes-1* gene, vascular reaction

Behçet's disease (BD) [1] or Adamantiades-Behçet's disease [2] is a chronic multisystemic inflammatory disorder characterized by the recurrent involvement of muco-cutaneous (oral and genital ulceration, erythema nodosum (EN)-like eruption, acne-like eruption, etc.), ocular, vascular, digestive and/or nervous system organs. Although the actual etiology of BD is still unclear, the pathogenesis has become generally clearer by investigation of the epidemiology, clinical manifestations and basic etiological research based on the intrinsic genetic and extrinsic triggering factors and the immunological findings [3-13]. The genetic predisposition is included as one of the intrinsic factors, because more than 60% of BD patients are associated with HLA-B51 [3-6]. As one of the extrinsic triggering factors, an unhygienic oral condition may be suspected, because periodontitis, decayed teeth, chronic tonsillitis, etc. are frequently noted in the oral cavity of BD patients [9, 10]. The proportion of *Streptococcus sanguinis (S. sanguinis)*, which was previously recognized as a *species* of the *genus* Streptococcus named "*S. sanguis*" [11-13], was significantly higher in the oral bacterial flora of BD patients than those of healthy and disease controls *(table 1)*. The *S. sanguis* isolated from BD patients was different from reference ATCC strains in DNA homology and sugar constituents. Here, we call these clinical isolates *S. sanguinis*, although they may include not only *S. sanguinis* but also *S. oralis*, because the chemiluminescence of neutrophils obtained from BD patients was in-

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creased in correlation with the proportion of *S. sanguinis* in the oral flora. The strains isolated as *S. sanguinis* were serologically different from various strain types from healthy controls, but the DNA-DNA homology was shown as *S. oralis* and *S. sanguinis*-like species [12, 13]. Then, *S. sanguinis* was identified as an uncommon serotype KTH-1 (so-called BD113-20 strain) by its bacterial and enzymatic properties [12, 13] Most patients tend to acquire delayed type hypersensitivity against *streptococci* in their oral flora, and as previously demonstrated, much stronger cutaneous reactions than the general pathergy test when intracutaneous injections and/or prickle tests were carried out using various killed bacteria and/or their cell wall antigens, including *streptococci, enterococci, staphylococci*, etc. (*table 2*) [9, 10, 14-16]. *In vitro* experiments, IL-6 and INF-γ were significantly produced from PBMCs of BD patients in stimulation by KTH-1 antigens [17]. The serum-antibody titers against *streptococci* were also elevated in BD patients [18]. The 65kDa of a heat shock protein (HSP-65) derived from oral bacteria, including *S. sanguinis*, can be detected along with counterpart human HSP-60 which appears reactively in the sera and lesions of BD patients. The peptides of HSP-65 derived from the bacteria show considerable homology with those of the human HSP-60 [19-21].

Although Sakane *et al.* [22] have reviewed the general clinical manifestations and pathogenesis of BD, based on data since 1972 from the Research Committee for Behçet's Disease organized by Japanese Ministry of Health, Labour and Welfare, our Research Committee, newly organized in 2001, revised the diagnostic criteria established in 1987. In the new criteria, in 2003, we included hypersensitivity skin reactions against *streptococci* in the diagnosis as one of the references and the levels of disease severity of BD patients, as introduced by Suzuki *et al.* [23]. Hence, we would mainly like to discuss the role of abnormally hypersensitive immune reactions against oral *streptococci* as one of the extrinsic triggering factors in connection with the intrinsic factors in the pathogenesis of BD.

HLA genotyping of BD and streptococcal infection

HLA-B51 is supposed to be a highly associated genetic marker of BD patients from many different ethnic groups, including European, Mediterranean and Asian people [3, 5, 24, 25] and BD has several unique epidemiological features which seem to go from Southern Europe to Japan along "the old Silk Route" [3, 5, 6, 25]. Although the HLA-B51 phenotype is important as an intrinsic factor for BD patients, and HLA-B51-transgenic mice show enhanced neutrophil function, because the HLA-B51 gene presents endogenous peptides to CD8 T cells (cytotoxic T lymphocytes; CTLs), these mice do not express BD symptoms [24]. The appearance of BD lesions is not considered to be directly correlated with HLA-B51 in the immunological background of patients, but it was recently found that HLA-B51-restricted CTLs played some roles in BD pathogenesis in correlation with the stressed target tissues expressing major histocompatibility complex class I-related gene A (MICA) [26, 27]. When the transmembrane-MICA located nearly at the HLA-B51 gene is preferentially expressed on epithelial and endothelial cells by stress, they seem to be candidates for the HLA-B51-restricted CTLs response [27]. These findings are based on the following; in HLA-B51 positive BD patients in the acute phase, MICA-transmembrane peptides derived from the amino acid sequence of MICA*009, which is in strong linkage disequilibrium with HLA-B51 [28], were significantly detected as targets of T cell responses. MICA expression was lost after the BD-related symptoms disappeared and the MICA-induced T cell response was also inhibited by anti-HLA class I antibodies and by CD8 T cell depletion. MICA expressed on the stressed epithelium and endothelium are considered to be the ligand for activating natural killer (NK) cells with the NKG2D molecule and CD8 T cells as CTLs [27]. BD lesional reactions might be accelerated by inflammatory cytokines and chemokines secreted from CTLs and NK cells [29, 30]. Regarding NK cell activation, inhibitory CD34/NKG2A and activating CD94/NKG2C molecules are alternatively expressed on NK, $CD4^{+}CD8^{+}$T cells, indicating an imbalance in cytotoxic activity in BD patients [31], although the function of NK cells is supposed to be down-regulated in the active stage and to be up-regulated in the remission stage of BD patients [32].

It is considered that the HSP-65/60 derived from microorganisms including *S. sanguinis* and from human tissues, which is detected in the oral mucosal and skin lesions of BD patients [19, 20], also becomes a stress-inducible factor in connection with MICA*009 expression. Generally, antigen presenting cells (APCs), which produce IL-12 in correlation with Th1 type immune-reactions, are thought to be activated in BD patients with HLA-B51 in the active stage, as indicated by Yasuoka *et al.* [27]. However, we have recently obtained interesting results that PBMCs from BD patients without the HLA-B51 gene can be significantly stimulated by *S. sanguinis* antigen in the expression of IL-12p40 mRNA and in the increasing of protein levels in connection with IL-12p70 (70 kDa composed of p35 and p40 subunits), compared to those of patients with HLA-B51 [33]. It has been suggested that the antibacterial host response in T type immunity mediated by IL-12 is much stronger in HLA-B51-negative BD patients, though the precise findings will be discussed later again.

Abbreviations: APCs: antigen presenting cells; BD: Behçet's disease; CTLs: cytotoxic T lymphocytes; DNA: deoxyribonucleic acid; EN: erythema nodosum; HHV: human herpes virus; HIs: healthy individuals; HLA: human leukocyte antigen; HSP-65: 65 kDa of heat shock protein; HSV: herpes simplex virus; IL: interleukin; IFN-γ: interferon-γ; MBL: mannose-binding lectin; MICA: major histocompatibility complex class I chain-related gene A; mRNA: messenger ribonucleic acid; NK cell: natural killer cell; PBMCs: peripheral blood mononuclear cells; PCR: polymerase chain reaction; rCTB: recombinant cholera toxin B subunit; sIL-2R: soluble IL-2 receptor; S. sanguinis: Streptococcus sanguinis; Th1 cell: T helper 1 cell; TNF-α: tumor necrosis factor-α

Hypersensitivity against *S. sanguinis*

Generally, oral health is impaired in BD patients [9, 10, 12, 13], which seems to be associated with disease severity

Table 1. Oral bacterial flora in BD patients, disease controls and healthy controls. Subjects: 22 BD patients with oral aphthous ulcerations (age-mean: 35.8) and 10 healthy controls and 8 disease controls including Vogt-Harada disease, sarcoidosis, herpes simplex infection, etc. who were similarly aged to the BD patients. Sampling: Supragingival plaque was taken from the lower first and second premolars or first molar after clinical examinations. Cotton swab specimens were obtained from the surface of the tongue dorsum and buccal mucosa. Each sample was incubated on TYC agar with 5% sucrose and Mitis-Salivarius agar for Streptococcus species at 37 °C for 2 days. For identification of streptococcus species, API-STREP system and confirming tests were used and the total viable count was calculated as percentage, as described by Isogai *et al.* [13]. The proportion of *S. sanguinis (S. sanguis)* was significantly higher in the oral bacterial flora of BD patients than controls

Bacteria	% prominent flora (mean ± SE) of plaque from		
	Patients with BD (n = 22)	Healthy controls (n = 10)	Disease controls (n = 8)
Gram-positive bacteria	66.7 ± 3.6	69.0 ± 6.2	56.0 ± 6.2
Streptococcus	53.3±4.1****	48.1 ± 4.6	39.0 ± 5.7
S. sanguis	26.7±3.7*,***	9.4 ± 0.6	7.5 ± 2.3
S. salivarius	7.4 ± 1.4	6.6 ± 2.4	6.0 ± 1.9
S. mitis	14.9 ± 2.1 (**), (****)	25.9 ± 4.5	24.0 ± 3.6
S. mutans	4.1 ± 1.1*,***	0.2 ± 0.1	1.5 ± 0.6
Other streptococci	0.2 ± 0.1(*)	6.0 ± 2.5	< 0.1
Enterococcus	0.25 ± 0.11	0.01 ± 0.01	0.02 ± 0.01
Staphylococcus	0.26 ± 0.19	0.02 ± 0.01	< 0.001
Lactobacillus	1.6 ± 0.6	0.38 ± 0.02	0.19 ± 0.11
Eubacterium	0.36 ± 0.17	0.23 ± 0.28	0.17 ± 0.08
Gram-positive bacteria	33.2 ± 3.5	29.2 ± 7.1	44.0 ± 6.2
Bacteroides	16.5 ± 2.2*	6.4 ± 1.9	24.1 ± 5.1
Black pigmented *Bacteroides*	3.1 ± 0.7**	0.9 ± 0.2	2.9 ± 1.4
Fusobacterium	2.6 ± 0.6(****)	1.9 ± 0.7	9.3 ± 3.8
Veillonella	3.3 ± 1.1	7.8 ± 3.1	3.1 ± 1.2
Enterobacteriaceae	< 0.001	ND	ND
Others	7.5 ± 1.1	6.8 ± 2.8	4.6 ± 1.3
Molds	0.15 ± 0.08	ND	< 0.01

**Higher %, P < 0.01 vs. healthy controls. ** Higher %, P < 0.05 vs. healthy controls. ***Higher %, P < 0.01 vs. disease controls. ****Higher %, P < 0.05 vs. disease controls.*
(*)Lower %, P < 0.01 vs. healthy controls. (**) lower %, P < 0.05 vs. healthy controls, (***) lower %, P < 0.01 vs. disease controls. (****)Lower %, P < 0.05 vs. disease controls. ND: not detected.

Table 2. The skin tests by bacterial antigens and saline for BD patients and healthy controls. Each 0.01 mL of the bacterial antigens (bacteria vaccines: 1×10^9 org./mL. Hollister-Stier Lab., USA) was intracutaneously injected in 84 BD patients and 10 healthy controls. The reaction was observed at 15 min. and 48 hours after injection. The erythematous skin reactions by streptococcal antigens were significantly stronger than those by other antigens in BD patients [9, 10]

Bacterial vaccines	Behçet's syndrome		Normal controls	
	15 min	48 h	15 min	48 h
S. pyogenes	7 ± 8	41 ± 15	11 ± 11	8 ± 6
S. viridans	8 ± 7	46 ± 11	4 ± 4	2 ± 3
S. non-hemolyticus	7 ± 7	35 ± 14	5 ± 5	3 ± 4
S. faecalis	10 ± 8	40 ± 19	12 ± 11	0
Pneumococcus	16 ± 10	32 ± 14	8 ± 9	3 ± 4
E. coli	6 ± 7	16 ± 11	2 ± 1	1 ± 2
H. influenzae	11 ± 10	15 ± 15	9 ± 13	11 ± 12
Sta. aureus	8 ± 7	12 ± 13	3 ± 7	0 ± 1
Sta. epidemidis	5 ± 7	6 ± 7	2 ± 7	1 ± 2
Prot. vulgaris	10 ± 16	28 ± 13	6 ± 6	17 ± 4
Pseud. aeruginosa	1 ± 1	22 ± 11	2 ± 3	5 ± 0
SK-SD (50 U/mL)		9 ± 12		20 ± 9
Saline		2 ± 4		0 ± 1

The numbers denote mean ± SD(mm) of Length + width/2 erythemas.

[34]. It is not clear that the predisposition of the patients is correlated with streptococcal infection, but the uncommon oral *S. sanguinis* serotypes are significantly increased in BD patients compared with healthy and disease controls, as previously described [12, 13]. The antibodies against *S. sanguinis* in sera from BD patients showed cross reactivity with some synthetic peptides of HSP-65 derived from *S. sanguinis* [35, 36]. The patients show strong delayed type cutaneous hypersensitivity reactions against streptococcal antigens in skin tests and sometimes BD symptoms were provoked by skin injection of the antigens [9, 10, 14-16]. Because aphthous ulceration can be also induced by a prick with streptococcal antigens on the oral mucous membrane of a BD patient [10], the appearance of aphthous ulceration is considered to be based on a hypersensitive reaction against *S. sanguinis*, which may penetrate traumatically into the oral membrane of BD patients. Isogai *et al.* [36] demonstrated that symptoms mimicking BD appeared in germ-free mice when *S. sanguinis* from BD patients was inoculated into their oral tissue which was damaged by heat shock and/or mechanical stress. This report suggests that immunization with *S. sanguinis* through the oral membrane route elicits BD-like symptoms in the animal model, as is seen in BD patients who carry *S. sanguinis* as the pathogenic microorganism in their oral cavity. We tried to find PCR targeting *Bes-1* gene in BD lesions using 2 distinct primer sets (peptides, 229-243 and 373-385) encoding *S. sanguinis* (serotype KTH-1), which was prepared by Yoshikawa *et al.* [37]. *Bes-1* DNA was present in various muco-cutaneous lesions including oral and genital ulcerations and EN-like lesions and the PCR-*in situ* hybridization revealed that *Bes-1* DNA was expressed in the cytoplasm of inflammatory infiltrated monocytes adhering the vascular walls in muco-cutaneous lesions (*figure 1* A and B) [38]. These infiltrated monocytes may express streptococcal antigens on the cell membrane because they were detected by immunofluorescence with anti-streptococcal antibodies, as previously reported (*figure 2* A-C) [10, 15]. In contrast, we failed to detect the DNA of HSV-1, HSV-2, cytomegalovirus, HHV-6 and HHV-7 in the lesions by PCR [39], although HSV infection has been speculated as etiologically important since the report of H. Behçet [1]. However, animal models infected by HSV have been also demonstrated to mimic BD like symptoms [40]. Interestingly, the amino acid sequence of the peptides of *Bes-1* (229-243 and 373-385) shows more than 60% similarity to the human intraocular ganglion peptide, *Brn-3b* which is a subfamily of POU (pit-Oct Unc) domain factors containing *Brn-3a* and *Brn-3c* [41]. The peptide of *Bes-1* (229-243) was also found to be correlated with the peptide of HSP-60 (336-351) [35]. Recently it has been found that the peptide of *Bes-1* (337-385) stimulated the production of IFN-γ and IL-12 from PBMCs of BD patients, although cellular proliferation was not observed [42]. These results suggest that *Bes-1* derived from oral *S. sanguinis* might be an inducer for the retinal and neural involvement possible in BD patients.

HSP-65 derived from microorganisms and human HSP-60

HSPs, which scavenge denatured intracellular proteins, are supposed to be induced by microorganisms and mammalian tissues under a variety of stressful conditions [43] and they may be involved in the pathogenesis of some autoimmune diseases [44]. In BD patients, the serum levels of IgA antibodies to mycobacterial HSP-65, which cross-reacts with selected strains of *S. sanguinis*, are increased significantly [45, 46]. HSPs taken up by APCs are thought to stimulate T cells directly, the monocytes expressing HSP-60 led T cells to undergo apoptosis after IFN-γ production [47] and the presence of HSP-60 was also detected in various lesions of BD patients [46, 48, 49]. On the other hand, 4 peptides of HSP-65 (111-125, 154-172, 219-233 and 311-326) derived from *S. sanguinis* were recognized as immuno-dominant agents for T cell and B cell responses and they showed 50-80% homology to the counterpart human HSP-60, as shown in *figure 3* [20, 48-50]. The 4 peptides of HSP-65 were shown to significantly stimulate and undergo CD4 and CD8 T cell apoptosis in PBMCs from BD patients and HSP-60 also seemed to stimulate them [46, 47]. On the contrary, the other two peptides of HSP-65 (21-35 and 401-415) corresponding to the peptide of human HSP-60 (425-441), are reported not to stimulate PBMCs from BD patients and healthy individuals (HIs) [43]. The peptide of HSP-60 (336-351) was also identified to be highly homologous to the T cell epitope [43, 45-52]. Whole

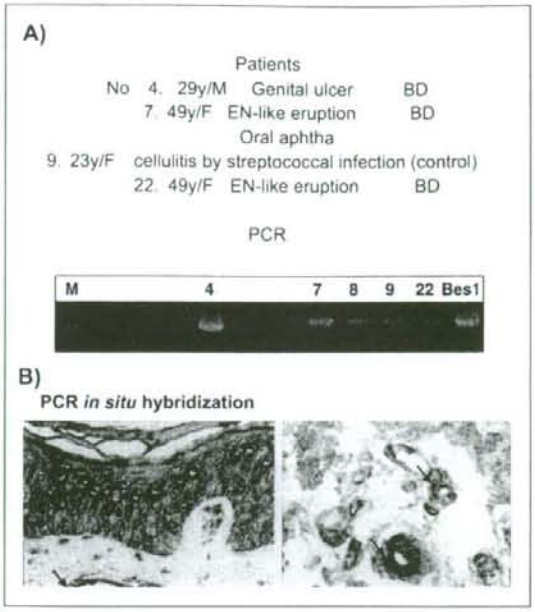

Figure 1. *Bes-1* gene expression in the muco-cutaneous lesions of patients with Behçet's disease (BD) [38]. **A)** Three of 11 BD patients were positive for *Bes-1* DNA in the lesions including aphthous and genital ulcerations and erythema nodosum (EN)-like eruption by amplified polymerase chain reaction (PCR) using the primers: *Bes-1-1* (5'-TAATAACCCTGACCAAGCCTA-3') and *Bes-1-2* (5'-CCCTTTCAAAAGTCATAAATC-3') encoding *S. sanguinis*. **B)** In these positive lesions, *Bes-1* DNA was also detected in the cytoplasm of monocytes adhering to the vascular walls and infiltrated around the vessels by PCR *in situ* hybridization.

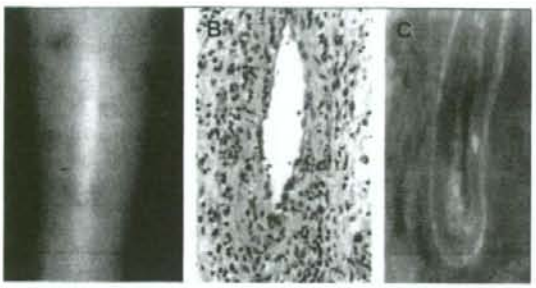

Figure 2. The vascular findings of EN-like eruption of a BD patient. **A)** A clinical finding of EN-like eruptions of a BD patient. **B)** A magnified histological view of the vascular reaction with inflammatory cells including monocytes and a few neutrophils in the EN-like eruption (Hematoxylin-eosin stain, × 400). **C)** An immunofluorescent finding of monocytes adhering to the vascular wall by anti-streptococcal group D antibody (Difco Co., USA). The finding suggests monocytes expressed streptococcal antigen at the vascular wall [10, 15]. Photos: Fukushima Medical University School of Medicine, Department of Dermatology.

HSP-60 is, however, suspected to increase vascular endothelial growth factor (VEGF) which activates, impairs and proliferates vascular endothelial cells [53] and which may lead to thrombophebitis and vasculitis, by damaging endothelial cells in BD patients. Although the term of "vasculitis" has been frequently used in BD lesions, Jorrizo *et al.* [54] previously reported that the real vasculitis, exhibiting "necrotizing vasculitis", was rarely seen in the EN-like eruptions of BD patients, and in most cases, the vascular reaction is surrounded by monocytes and a few neutrophils, as we demonstrated in *figure* 2B. This is so-called "lymphocytic vasculitis" seen histologically, as recently described by other authors [55, 56]. It is observed, however, that the serum levels of soluble(s) adhesion molecules, such as s-selectins and s-intercellular adhesion molecule-1, are elevated [57, 58] and also the expression of VEGF is increased in the presence of HSP in the lesions of BD [59].

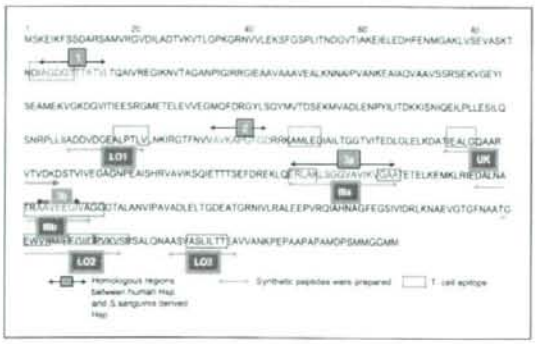

Figure 3. Newly synthesized peptides of HSP-65 derived from *Streptococcus. sanguinis* (*S. sanguinis*) (KTH-1, BD113-20 strain). There are 10 peptides homologous with T cell epitopes including 1, UK, LO1, 3a(IIIa), 3b(IIIb), LO2 and LO3 and they are also highly homologous with human HSP-60 peptides. The peptide of UK(311-326) corresponds to the peptide of human HSP-60 (336-351). (Lin and Oguma, 2003).

The subcutaneous administration of HSP peptides to mice has been shown to induce uveitis with vascular impairment [60].

On the other hand, it is of interest that the HSP-60 peptide (336-351), linked to the recombinant cholera toxin B subunit (rCTB), reduced the uveitis induced by whole HSP-60, although the peptide without adjuvant is reported to induce uveitis in Lewis strain rats [60, 61]. Recently, a therapeutic trial with the peptide conjugated with rCTB was given orally to BD patients with recurrent uveitis and successful results were obtained, as 5 of 8 patients had no relapse of the uveitis, no side-effects were present and 2 of the remaining 3 patients had improved recurrent oral ulceration, folliculitis, EN-like eruptions, and genital ulcers [62]. In those patients with control of uveitis and extra-articular manifestations, a lack of the peptide-specific CD4 T cell population, a decrease in expression of Th1 type cells (CCR5, CXCR3) and a reduction of IFN-γ, TNF-α, CCR7 T cells and co-stimulatory molecules (CD40 and CD28) were described in comparison to BD patients with relapse of disease [62]. These findings may suggest immunotoleration in active BD patients. It is hypothesized that CTLs play a role in BD pathogenesis by targeting a self antigen selectively expressed in the affected tissues. In BD patients with active disease, the endogenously generated MICA transmembrane-peptide by autoreactive CTLs is present [27] and the excessive inflammatory responses might be induced by extrinsic factors correlated with *S. sanguinis* and other organisms, including *Helicobactor pylori*, *mycoplasma fermentas*, etc. [63-65]. Neutrophilic hyperfunction and a cross-reactive autoimmune response between microbial and human HSPs are proposed to be correlated with the hyperreactivity against microorganisms, including *S. sanguinis*, seen in BD patients [9, 10, 14-17]. These HSPs presented by APCs can directly stimulate αβT and γδ T cells, which play important roles in oral mucosal immunity as the first defense against microorganisms. It is thought that $V\gamma9\delta2^+$ T cells, a major subset of γδ T cells in PBMCs, recognize antigens produced by bacteria and that innate and adaptive immune responses are influenced by secreting IFN-γ, towards a Th1 profile [20, 66, 67]. These γδ T cells seemed to be elevated in PBMCs and in the muco-cutaneous lesions of BD patients [47, 66]. The second major subset, $\gamma\delta1^+$ T cell, is enriched in the mucosa and the antigens are presented by APCs with stress-inducible MICA and MICB. The γδ T cells, which highly express CD29 and CD69, produce IFN-γ and TNF-α from stimulation by HSP-65/60 in the peripheral blood and in the lesions of BD patients with active disease [20, 47, 66]. These activated APCs and γδ T cells might activate αβ T cells by their secretion of sIL-2R, IFN-γ, TNF-α and also high levels of other cytokines, IL-1α, IL-6, IL-8, IL-15, etc., which are detected in the sera of BD patients [67-69]. In the active stage of BD patients, IL-12 is also produced as a sign of an advanced Th1 type reaction. The gene polymorphism in the promoter region regarding a 4 bp insertion within IL-12p40 was significantly higher in HLA-B51 negative BD patients than HLA-B51 positive patients and HIs. The expression of IL-12p40 mRNA and protein levels in conjugation with IL-12p70 induction were also significantly increased in PBMCs from BD patients without HLA-B51 by stimulation with *S. sanguinis* antigen, as previously described [33]. It has been recently found that expression of IL-23, which is composed of a shared p40

subunit of IL-12 and p19 subunit of IL-23, was also increased with IL-12 in EN-like lesions of BD patients [70].

HSPs and BD pathogenesis

Although antibodies against the HSP peptides derived from bacteria including *S. sanguinis* are found in sera of BD patients [35, 36], HSP specific antibodies and T cells are considered to play a complicated role in the pathogenesis of human autoimmune diseases [71]. HSPs might trigger both innate and adaptive immune mechanisms in BD. On the other hand, the therapeutic approaches involving HSP immunomodulation may be available as "oral toleration" using the peptide of HSP (336-351) linked to rCTB for BD patients with advanced uveitis, as demonstrated by Stanford *et al.* [62]. Then, we tried to analyze HSP-65 derived from *S. sanguinis* to find homologous peptides to T cell epitopes of BD patients, and some peptides were found to be highly homologous with T cell epitopes in the correlation with human HSP-60, as indicated in *figure 3*. Attempts have been made to find out how the newly synthesized homologous peptides influence proinflammatory cytokine production from PBMCs of active BD patients. The peptides, LO1 (249-264), IIIa (365-384), IIIb (395-413), LO2 (480-499), LO3 (504-518) and UK (311-326), corresponding to the peptide of human HSP-60 (336-351), were applied to lead immuno-toleration for activated CTLs of BD patients *in vitro*. PBMCs from 7 active BD patients and 5 HIs were incubated with and without these peptides and 7 days after incubation IL-8, IL-12, IFN-γ and TNF-α were measured and compared with those from PBMCs of active BD patients incubated without the peptides as controls. Although IL-12 and IL-8 were actively produced from PBMCs in active BD patients, even though they were not stimulated, a significant reduction of inflammatory cytokines was found by some kinds of the peptides. The 5 peptides, LO1, LO2, LO3, IIIb and UK significantly reduced IL-12 production and also LO1, IIIa and IIIb significantly inhibited IL-8 production, except for LO2 and LO3 (*figure 4*A and B). On the other hand, the cytokines from PBMCs of HIs were significantly increased on stimulation by the peptides. In order to understand the suppressive mechanisms of the cytokine production in PBMCs from active BD patients, we tried to find the binding sites of the peptides on monocytes by cDNA chips (Gene Chip; Human Genome) using NOMO-1 cells (human macrophage cell line) activated by *S. sanguinis* antigen and they were incubated with the peptides. It was found that although the expression of IL-8, IL-16, IL-13R and IL-17R was decreased after incubation with LO1 and UK, respectively, LO2 did not decrease IL-8 production. CD58 (lymphocyte function-associated antigen-3) molecule and/or FK506 binding protein were highly expressed on the cell membrane by LO1 and UK [72]. It is considered that activated CTLs of BD patients might lead to apoptosis and/or dysfunction of lymphoid cells by the binding of LO1 and UK on the cell-receptors.

Toll-like receptor (TLR) expression in innate immunity

Regarding the recognition system for microorganism antigens in humans, 10 members of the TLR family are supposed to act as innate immune receptors by binding particular structures present on bacteria, viruses, fungi, etc. [73]. Although, generally, TLRs are weakly detectable in various human tissues with varying levels, the TLR expression of the organs involved in immune responses and exposed to the environment, is found to be significantly stronger [74]. Our BD Research Group have already found the expressions of TLR-2 (recognize: bacterial lipoprotein, zymosan, lipopolysaccharide (LPS), lipoteicholic acid of microbial antigen, etc.) and TLR-4 (LPS, HSP-65/60, etc.) on PBMCs and their presence has also been recognized in intestinal lesions by immunohistology (not yet published in the English literature) [75]. TLR-3 [ds RNA] and TLR-6 (mycoplasma, staphylococci, etc.) are also reported to have enhanced expression on the neutrophils and monocytes of BD patients, when stimulated by HSP-60 and *S. sanguinis* antigens [76]. In oral ulcer lesions, expression of TLR-9 (unmethylated CpG DNA, bacteria and virus) has recently been found [77]. These findings suggest that the innate immune system contributes to the acquisition of hypersensitivity against oral *S. sanguinis* as the extrinsic factor in the pathogenesis of BD.

Complement system in innate immunity

It is generally accepted that the compliment system is accelerated in relation to chemokine and neutrophilic activation [78, 79]. In BD lesions, deposits of complement C3 with immunoglobulins are frequently detectable by immunofluorescent techniques [15, 56]. With respect to the complement system of BD patients, the titer of serum complement is generally high in the inactive stage but decreases in the active stage, although levels of the mannose-binding lectin (MBL) pathway of complement is reported to be decreased [80]. The MBL pathway is considered to play an important role in innate immunity. It is thought to be a C-type serum lectin secreted by the liver, which binds to mannose and N-acetyl-glucosamine oligosaccharides on the surfaces of yeast, bacteria and viruses [81]. The reaction serves as the initiator of the third pathway of the complement system, independently from antibodies. Ficolin (FCN) is a soluble protein that binds to carbohydrate on the microbial cells and 3 different types of FCN are detected. FCN 1 and 2 genes are located in chromosome 9q34 and the FCN 3 gene is assigned to chromosome 1. FCN 2 binds to lipoteicholic acid on the cell wall constituent in all Gram-positive bacteria and activate immune cells, to produce proinflammatory cytokines [78, 82]. Recently, we have found that novel FCN 2 gene single nucleotide polymorphisms (SNPs) were identified in the promoter regions as well as in the exon regions. The MBL genetic polymorphisms might be involved in immune responses to streptococcus infections in BD patients, because a relationship between MBL gene mutations and microbiological factors is suspected in the lesional immune reaction of BD patients [83]. Although a significant difference was not present in the genotype allele frequencies of MBL gene SNPs between BD patients and HIs, the allele frequencies of FCN2 gene SNPs were significantly recognized in the promoter regions (-557 and -64 sites) among HLA-B51 positive BD patients [84]. The findings suggest the possibility that the FCN gene of the MBL pathway in the complement system contributes to innate immununity in BD patients with the HLA-B51 haplotype.

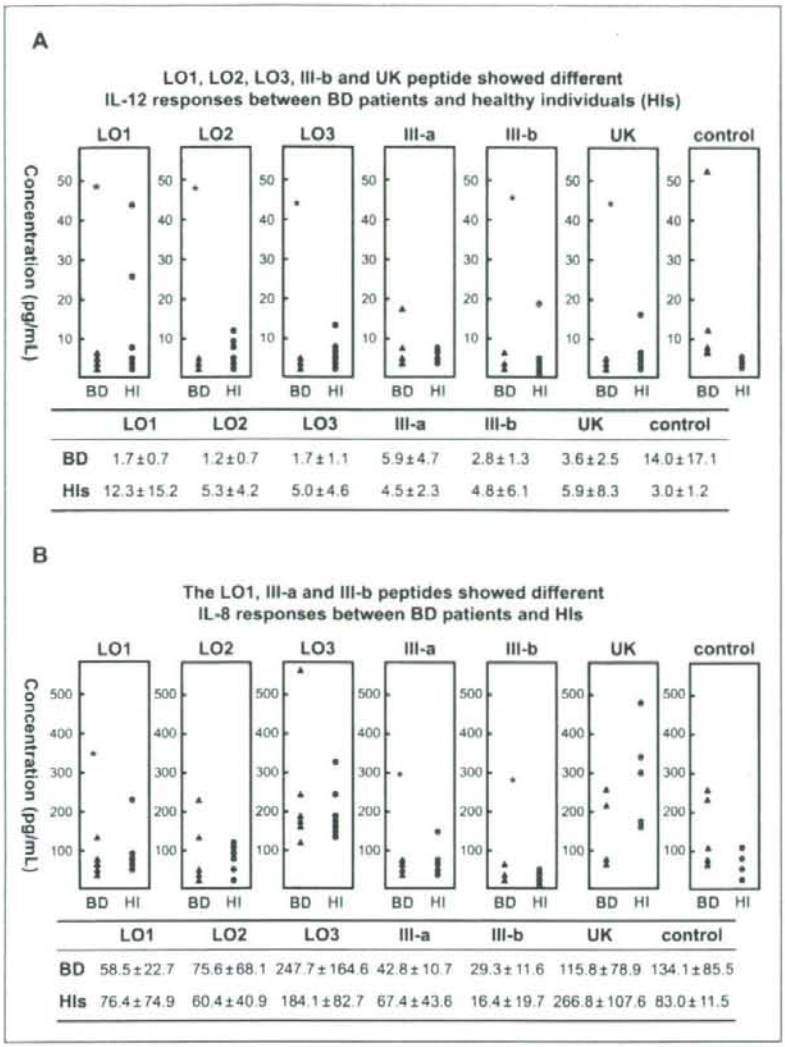

Figure 4. Effects of the peptides of T cell epitope as shown in *figure* 3. **A)** IL-12 was highly produced by PBMCs from active BD patients without stimulation (Control). IL-12 production from BD patients was significantly reduced by incubation with LO1, LO2, LO3, III-b and UK (*). On the other hand, IL-12 production from PBMCs of HIs was elevated by these peptides. **B)** LO1, III-a and III-b significantly reduced IL-8 production from PBMCs of BD patients (*). On the other hand, IL-8 production was accelerated from PBMCs of HIs by these peptides.

How do the muco-cutaneous symptoms appear in BD patients?

BD symptoms are characterized by vascular involvements, histologically showing swollen endothelial cells of the micro-arteries, infiltrated by inflammatory monocytes and a few neutrophils, a so-called "vascular reaction" seen in EN-like eruptions *(figure 2B)* and other lesions [15, 54-56]. The strong hypersensitivity reaction against *S. sanguinis* agents [9, 10, 14-17] which might be caused by APCs through the innate immune mechanism, can be suspected as the extrinsic triggering factor in the pathogenesis of BD. In the treatment by antibiotics for the involvement of oral *S. sanguinis*, minocycline, which reduces not only the growth of streptococci but also suppresses IL-1β and IL-6 production from inflamed T cells, was especially clinically effective for aphthous ulceration, acne-like eruption and EN-like lesions in BD patients [10]. Other studies also showed that combination therapy, colchicine and benzathine penicillin, were effective to suppress BD symptoms, compared to colchicine monotherapy [85, 86]. Muncu *et al.* [86] and others [6-8] have already reviewed the role of infectious agents in the pathogenesis of BD, but we also dare to propose the hypothesis that after the *Bes-1* gene is taken into the cytoplasm of APCs *(figure 1A and B)* through the TLRs in the oral cavity, the APCs, which are expressing

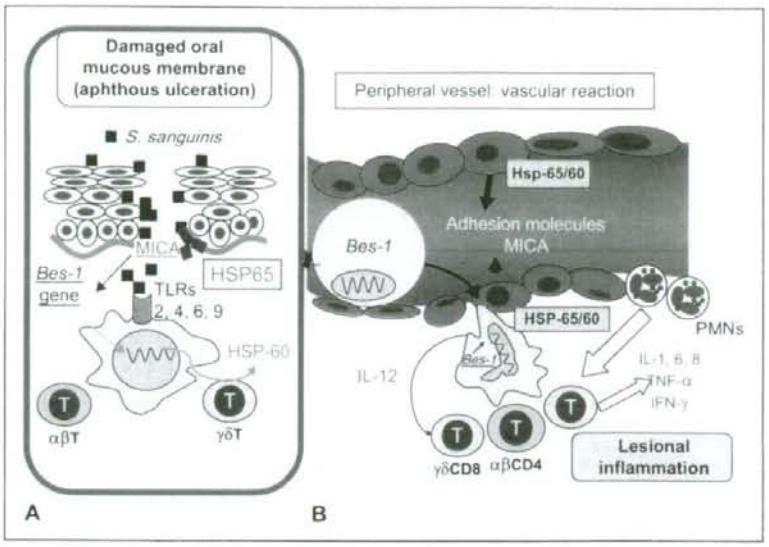

Figure 5. Hypothesis of the mechanisms in the appearance of various lesions of BD patients. **A)** The antigen presenting cells (APCs) (macrophages and/or dendritic cells) immunized by *S. sanguinis* agents through TLRs in the oral cavity might be carried to the peripheral regions. **B)** If the APCs in the blood flow adhered to the impaired and/or MICA and adhesion molecules expressed endotherial cells of vascular walls, the immunological reaction might appear as a BD lesion.

the streptococcal antigen as seen in *figure* 2C, produce HSP-65. If these APCs are carried in the blood flow to the impaired and/or MICA expressed endothelium of the vessels in correlation with HSP-65/60, VEGF, adhesion molecules, etc., BD lesions might be induced with "vascular reaction" and/or "lymphocytic vasculitis" as the immunological reaction by the APCs expressing the *S. sanguinis* antigen *(figure 5)*.

Conclusion

The pathogenesis of BD was discussed, including aspects of the intrinsic genetic factors and with oral bacteria antigens as one of the extrinsic triggering factors. HLA-B51 restricted CTL was found to target the MICA expressed organs by stress in correlation with HSP-65/60 derived from oral bacteria, including *S. sanguinis*. The immune responses which are based on a Th1 type reaction with chemotaxis to the bacterial agents are considered to correlate with various BD symptoms, histologically exhibiting "vascular reaction" and/or "lymphocytic vasculitis". ■

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References

1. Behcet H. Uber rezidivierende, aphthous durch ein Virus verursachte Geschwuere am Mund, am Auge und an den Genitalien. *Dermatol Wochenschri* 1937; 105: 1152-7.
2. Adamantiades B. Sur un cas d'iritis a hypopion recidivant. *Ann Ocul (Paris)* 1931; 168: 271-8.
3. Altenburg A, Papoutsis N, Orawa H, Martus P, Krause L, Zouboulis CC. Epidemiology and clinical manifestations of Adamantiades-Behcet's disease in Germany- Current pathogenic concepts and therapeutic possibilities. *J Dtsch Dermatol Ges* 2006; 4: 49-64.
4. Alpsoy E, Zouboulis CC, Ehrlich GE. Mucocutaneous lesions of Behcet's disease. *Yonsei Med J* 2007; 48: 573-85.
5. Ohno S, Ohguchi M, Hirose S, Matsuda H, Wakisaka A, Aizawa M. Close association of HLA-Bw51 with Behcet's disease. *Arch Ophthalmol* 1982; 100: 1455-8.
6. Zouboulis CC, May T. Pathogenesis of Adamantiades-Behcet's disease. *Med Microbiol Immunol (Berl)* 2003; 192: 149-55.
7. Karaycian A, Zouboulis CC. An update on Behcet's disease. *J Eur Acad Dermat-Venereol* 2007; 21: 1-10.

8. Krause I, Weinberger A. Behcet's disease. *Current Opin Rheum* 2008; 20: 82-7.
9. Kaneko F, Kaneda T, Ohnishi O, Kishiyama K, Takashima I, Fukuda H, Kado Y. Infection allergy in Behcet's disease (1). *Jpn J Allergol* 1978; 27: 440-50.
10. Kaneko F, Oyama N, Nishibu A. Streptococcal infection in the pathogenesis of Behcet's disese and clinical effects of minocycline on the disease symptoms. *Yonsei Med J* 1997; 38: 444-54.
11. Yokota K, Hayashi S, Araki Y, Isogai E, Kotake S, Yoshikawa K, Fujii N, Hirai Y, Oguma K. Characterization of *Streptococcus sanguis* isolated from patients with Behcet's disease. *Microbiol Immunol* 1995; 39: 729-32.
12. Isogai E, Ohno S, Takashi K, Yoshikawa K, Turumizu T, Isogai H, Yokota Y, Hashimoto T, Shimizu H, Matsuda H, Fujii N, Yamaguchi M, Oguma K. Close association of *Streptococcus sanguis* uncommon serotypes with Behcet's disease. *Bifidobacteria Microflora* 1990; 9: 27-41.
13. Isogai E, Ohno S, Kotake S, Isogai E, Tsurumizu T, Fujii N, Syuto B, Yamaguchi M, Matsuda H, Oguma K. Chemiluminescence of neutrophils from patients with Behcet's disease and its correlation with an increased proportion of uncommon selotypes of *Streptococcus sanguis* in the oral flora. *Arch Oral Biol* 1990; 35: 43-8.
14. Graykowski EA, Baril MF, Boyd LM, Stanley HR. Recurrent aphthous stomatitis: Clinical therapeutic and histopathologic and hypersensitivity aspects. *JAMA* 1966; 196: 637-44.
15. Kaneko F, Takahashi Y, Muramatsu Y, Miura Y. Immunological studies on aphthous ulcer and erythema nodosum-like eruptions in Behcet's disease. *Br J Dermatol* 1985; 113: 303-12.
16. Mizushima Y, Matsuda T, Hoshi K, Ohno S. Induction of Behcet's disease symptoms after dental and streptococcal antigen skin test. *J Rheum* 1988; 15: 1029-30.
17. Hirohata S, Oka H, Mizushima Y. Streptococcal antigens stimulate production of IL-6 and interferon-γ by cells from patients with Behcet's disease. *Cell Immunol* 1992; 140: 410-9.
18. Yokota K, Hayashi S, Fujii N, Yoshikawa K, Kotake S, Isogai E, Ohono S, Araki Y, Oguma K. Antibody response to oral streptococci in Behcet's disease. *Microbiol Immunol* 1992; 36: 815-22.
19. Lehner T. The role of heat shock protein, microbial and autoimmune agents in the etiology of Behcet's disease. *Intern Rev Immunol* 1997; 14: 21-32.
20. Kaneko S, Suzuki N, Yamashita N, Nagafuchi H, Nakajima T, Wakisaka S, Yamamoto S, Sakane T. Characterization of T cells specific for an epitope of human 60-kD heat shock protein (hsp) in patients with Behcet's disease (BD) in Japan. *Clin Exp Immunol* 1997; 108: 204-12.
21. Kibaroglu A, Eksioglu-Demiralp E, Akoglu T, Direskeneli H. T and NK cell subset changes with microbial extracts and human HSP60-derived peptides in Behcet's disease. *Clin Exp Rheumatol* 2004; 22(Suppl. 34): S59-S63.
22. Sakane T, Takeno M, Suzuki N, Inaba G. Current concepts: Behcet's disease. *N Engl J Med* 1999; 341: 1284-91.
23. Suzuki-Krokawa M, Suzuki N. Behcet's disease. *Clin Exp Med* 2004; 3: 10-20.
24. Takeno M, Kariyone A, Yamashita N, Takiguchi M, Mizushima Y, Kaneoka H, Sakane T. Excessive function of peripheral blood neutrophils from patients with Behcet's disease and from HLA-B51 transgenic mice. *Arthritis Rheum* 1995; 38: 426-33.
25. Mizuki N, Inoko H, Ohno S. In: Lee S, Bang D, Lee E-S, Sohn S, eds. *Molecular genetics (HLA) of Behcet's disease. Behcet''s Disease A guide to its Clinical Understanding*. Springer, 2001: 87-100.
26. Liblau RS, Wong FS, Mars LT, Santamaria P. Autoreactive CD8 T cells in organ-specific autoimmunity: emerging targets for therapeutic intervention. *Immunity* 2002; 17: 1-6.
27. Yasuoka H, Okazaki Y, Kawakami Y, Hirakata M, Inoko H, Kuwana M. Autoreactive CD8+ cytotoxic T lymphocytes to major histocompatibility complex class I chain-related gene A in patients with Behcet's disease. *Arthritis Rheum* 2004; 50: 3658-62.
28. Mizuki N, Ota M, Kimura M, Ohno S, Ando H, Katsuyama Y, Yamazaki M, Watanabe K, Goto K, Nakamura S, Bahram S, Inoko H. Triplet repeat polymorphism in the transmembrane region of the MICA gene: a strong association of six GCT repetitions with Behcet's disease. *Proc Natl Acad Sci USA* 1997; 94: 1298-303.
29. Zierhut M, Mizuki N, Ohno S, *et al*. Immunology and functional genomics of Behcet's disease. *Cell Mol Life Sci* 2003; 60: 1903-22.
30. Pay S, Simsek I, Erden H, Dinc A. Immunopathogenesis of Behcet's disease with special emphasize on the possible role of antigen presenting cells. *Rheumatol Int* 2006; 14: 1-14.
31. Seo J, Park JS, Nam JH, Bang D, Shon S, Lee ES, Park KS. Association of CD94/NKG2A, CD94/NKG2C and its ligand HLA-E polymorphisms with Behcet's disease. *Tissue Antigens* 2007; 70: 307-13.
32. Kaneko F, Takahashi Y, Muramatsu R, Minagawa T. Natural killer cell numbers and function in peripheral lymphoid cells in Behcet's disease. *Br J Dermatol* 1985; 113: 313-8.
33. Yanagihori H, Oyama N, Nakamura K, Mizuki N, Oguma K, Kaneko F. Role of IL-12B promoter polymorphisum in Adamantiades-Behcet's disease susceptibility: An involvement of Th1 immmunoreactivity against Streptococcus sanguinis antigen. *J Invest Dermatol* 2006; 126: 1534-40.
34. Mumcu G, Inanc N, Ergan T, Ikiz K, Gunes M, islek U, Yavuz S, Sur H, Atalay T, Direskeneli H. Oral health is impaired in Behcet's disease and is associated with disease activity. *Rheumatol* 2004; 43: 1028-33; (Oxford)
35. Isogai E, Isogai H, Kotake S, Ohno Ishihara M, Aeki K, Tojo M, Kaneko F, Yokota K, Oguma K. Antibody cross reactivity from sera of patients with Behcet's disease with synthetic peptides that have homologies with protein from Streptococcus sanguis. *J Appl Res* 2002; 2: 1-7.
36. Isogai E, Isogai H, Kotake S, Ohno S, IKimura K, Oguma K. Role of *Streptococcus sanguis* and traumatic factors in Behcet's disease. *J Appl Res* 2003; 3: 64-75.
37. Yoshikawa K, Kotake S, Kubota T, Kimura K, Isogai E, Fujii N. Cloning and sequencing of BES-1 gene encoding the immunogenic antigen of Streptococcus sanguis KTH-1 isolated from patients with Behcet's disease. *Zent bl Bakteriol* 1998; 287: 449-60.
38. Tojo M, Yanagihori H, Zheng X, Oyama N, Isogai E, Kimura K, Nakamura K, Kaneko F. Bes-1 DNA fragment encoding Streptococcal antigen in skin lesions from patients with Behcet's disease. *J Apl Res* 2003; 3: 232-8.
39. Tojo M, Zheng X, Yanagihori H, Oyama N, Takahashi K, Nakamura K, Kaneko F. Detection of herpes virus genomes in skin lesions from patients with Behcet's disease and other related inflammatory disease. *Acta Derm Venereol* 2003; 83: 1-4.
40. Sohn S, Lee ES, Bang D, Lee S. Behcet's disease-like symptoms induced by the herpes simplex virus in ICR mice. *Eur J Dermatol* 1998; 8: 21-3.
41. Xiang M, Zhou L, Peng Y, Eddy RI, Shows TB, Nathans J. Brn 3b: POU domain gene expressed in a subset of retinal ganglion cells. *Neuron* 1993; 11: 689-701.
42. Kulaber A, Tugal-Turkan I, Yentur SP, Akman-Demir G, Kaneko F, Gul A, Saruhan-Direskeneli G. Proinflammatory cellular immune response in Behcet's disease. *Rheumatol Int* 2007; 27: 1113-8.
43. Jindal S, Dudani AK, Singh B, Harley CB, Gupta RS. Primary structure of a human mitochondrial protein homologous to the bacterial and plant chaperonins and to the 65-kilodalton mycobacterial antigen. *Mol Cell Biol* 1989; 9: 2279-83.
44. Lamb JR, Young DB. T cell recognition of stress proteins: a link between infections and autoimmune disease. *Mol Biol Med* 1990; 7: 311-21.
45. Lehner T, Lavery E, Smith R, van der Zee R, Mizushima Y, Shinnick T. Association between the 65-kilodalton heat shock protein, *Streptococcus sanguis*, and the corresponding antibodies in Behcet's syndrome. *Infect Immun* 1991; 59: 1434-41.
46. Pervin K, Childerstone A, Shinnick T, Mizushima Y, van der Zee R, Hasan A, Vaughan R, Lehner T. T cell epitope expression of mycobacterial and homologous human 65-kilodalton heat shock protein peptides in short term cell lines from patients with Behcet's disease. *J Immunol* 1993; 151: 2273-82.
47. Poccia F, Pielli P, Vendetti S, Back S, Amendola A, Placido R, Celizzi V. Heat shock protein expression on the membrane of T cells undergoing apoptosis. *Immunol* 1996; 88: 6-12.
48. Ergun T, Ince U, Eksioglu-Demiralp E, Direskeneli H, Gurbuz O, Gurses L, Aker F, Akoglu T. HSP60 expression in mucocutaneous lesions of Behcet's disease. *J Am Acad Dermatol* 2001; 45: 904-9.
49. Direskeneli H, Ekisiogu-Demiralp E, Yavuz S, Ergan T, Shinnick T, Lehner T, Akogl T. T cell responses to 60/65 kDa heat shock protein derived peptides in Turkish patients with Behcet's disease. *J Rheumato* 2000; 27: 708-13.
50. Imamura Y, Kurokawa MS, Yoshikawa H, Nara K, Takada E, Masuda C, Tsukikawa S, Ozaki S, Matsuda T, Suzuki N. Involvement of Th1 cells and heat shock protein 60 in the pathogenesis of internal Behcet's disease. *Clin Exp Immunol* 2005; 139: 371-8.
51. Suzuki N, Sakane T. Characterisation of heat shock protein specific T cells in patients with Behcet's disease. *Rev Rheum* 1996; 63: 531-63.
52. Direskeneli H, Saruhan-Direskeneli G. The role of heat shock proteins in Behcet's disease. *Clin Exp Rheumatol* 2003; 21(Suppl. 30): S44-S48.
53. Shaker O, Ay El-Deen MA, El Hadid H, Grace BD, ElSherif H, Adbel Haim A. The role of heat shock protein 60, vascular endothelial factor and antiphospholipid antibodies in Behcet's disease. *Br J Dermatol* 2007; 156: 32-7.
54. Jorrizzo JL, Abernathy JL, White WL, Mongelsdorf HC, Zouboulis CC, Sarica R, Gaffney K, Mat C, Yazici H, Al Lalaan A, Assad-Kahalil SH, Kaneko F, Jorizzo EAF. Mucocutaneous criteria

for the diagnosis of Behcet's disease: an analysis of clinicopathologic data from multiple international centers. *J Am Acad Dermatol* 1995; 32: 968-76.
55. Yi SW, Kim EH, Kang HY, Kim YC, Lee ES. Erythema nodosum: clinicopathologic correlations and their use in differential diagnosis. *Yonsei Med J* 2007; 48: 601-8.
56. Iikunur T, Pabuccuoglu U, Akin C, Lebe B, Gunes AT. Histopathologic and direct immunofluorescence findings of the papulopustular lesions in Behcet's disesase. *Eur J Dermatol* 2006; 16: 146-50.
57. Ates A, Tiryaki OA, Olmez U, Tukkak H. Serum-soluble selectin levels in patients with Behcet's disease. *Clin Rheumatol* 2007; 26: 411-7.
58. Lee MT, Hooper LC, Kump L, Hayashi K, Nussenblatt R, Hooks JJ, Detrick B. Interferon-beta and adhesion molecules (E-selectin and s-intercellular adhesion molecule-1) and detected in sera from patients with retinal vasculitis and are induced in retinal vascular endothelial cells by Toll-like receptor 3 signalling. *Clin Exp Immunol* 2007; 147: 71-80.
59. Yalcin B, Arda N, Tezel GG, *et al*. Expression of vascular endothelial growth factor and CD34 in oral aphthous lesions of Behcet's disease. *Anal Quant Cytol Histol* 2006; 28: 303-6.
60. Hu W, Hasan A, Wilson A, Stanford MR, Li-Yang Y, Todryk S, Whiston R, Shinneck T, van der Zee, Lehner T. Experimental mucosal induction of uveitis with the 60-kDa heat shock protein-derived peptide 336-351. *Eur J Immunol* 1998; 28: 2444-55.
61. Phipps PA, Stanford MR, Sun JB, Xiao BG, Holmgren J, Shinnick T, Hasan A, Mizushima Y, Lehner T. Prevention of mucosally induced uveitis with a HSP60-derived peptide linked to cholera toxin B subunit. *Eur J Immunol* 2003; 33: 224-32.
62. Stanford M, Whittal T, Bergemeier LA, Lindbald M, Lundin S, Shinnick T, Mizushima Y, Holmgren J, Lehner T. Oral tolerization with peptide 336-351 linked to cholera toxin B subunit in preventing relapses of uveitis in Behcet's disease. *Cln Exp Immunol* 2004; 137: 201-8.
63. Ersoy O, Ersoy R, Yayar O, Demirci H, Tatlican SH. pylori infection in patients with Behcet's disease. *World J Gastroentrol* 2007; 7: 2985.
64. Apan TZ, Gursel R, Dolgun A. Increased eropositivity of Helicobactor pylori cytotoxi-associated gene A in Behcet's disease. *Clin Rheumatol* 2007; 26: 88-9.
65. Zouboulis CC, Turnbull JR, Muhlradt F. High seroprevarence of anti-mycoplasma fermentans antibodies in patients with malignant aphthosis. *J Invest Dermatol* 2003; 121: 211-2.
66. Chen ZW, Letvin NL. Adaptive immune response f Vγ2Vδ2 cells: A new paradign. *Trends Immunol* 2003; 24: 213-9.
67. Bank I, Duvelevani M, Livneh A. Expansion of γδ T-cells in Behcet's disease: Role of disease activity and microbial flora in oral ulcers. *J Lab Clin Med* 2003; 141: 33-41.
68. Radiuddin S, Al-Dalaan A, Bahabri S, Siraj AK, Al-Sedairy S. Divergent cytokine production profile in Behcet's disease. Altered Th1/Th2 cell cytokine pattern. *J Rheumatol* 1998; 25: 329-33.
69. Hamzaoui K, Hamzaoui A, Ghorbel I, Khanfir M, Houman H. Levels of IL-15 in serum and cerebrospinal fluid of patients with Behcet's disease. *Scand J Immunol* 2006; 64: 655-60.
70. Lew W, Chang JY, Jung TY, Bang D. Increased expression of interleukin-23 p19mRNA in erythema nodosum-like lesion of Behcet's disease. *Br J Dermatol* 2008; 158: 505-11.
71. Zugel U, Kaufman HE. Role of heat shock proteins in protection from and pathogenesis of infectious diseases. *Clin Microbiol Rev* 1999; 12: 19-39.
72. Oguma K, Shin R, Yokota K. Studies on immunological responses by bacterial antigens in Behcet's disease. Report of the Research Group for Behcet's Disesae organized by the Japanese Ministry of Health. *Labour and Welfare* 2008; 2006-2007: 31-3; (in Japanese).
73. Zarember KA, Godowski PJ. Tissue expression of human Toll-like receptors and differential regulation of Toll-like receptor mRNAs in leukocytes in response to microbes, their products, and cytokines. *J Immunol* 2002; 168: 554-61.
74. Hornung V, Rothenfusser S, Britsch S, Krug A, Jahrsdörfer B, Giese T, Endres S, Hartmann G. Quantitative expression of Toll-like receptor 1-10 mRNA in cellular subsets of human peripheral blood mononuclear cells and sensitivity to CpG oligodeoxynucleotides. *J Immunol* 2002; 168: 4531-7.
75. Suzuki N, Kurokawa M, Nara K, Yoshikawa H, Nonaka N, Matsuda T, Ikeshima H, Kaneko S, Morita S. A study for abnormal immunity and inflammation in lesions of Behcet's disesase. Report of the Research Group for Behcet's Disease organized by Japanese Ministry of Health, Labour and Welfare, 2007, 35-9 (in Japanese).
76. Yavus S, Elbir Y, Tulunay A, Eksioglu-Demirap E, Direskeneli H. Differential expression of toll-like receptor 6 on granulocytes and monocytes implicates the role of microorganisms in Behcet's disease etiopathogenesis. *Rheumatol Int* 2007; (DOI 10.1007/s00296-007-0470-y).
77. Durranni O, Wallace GR, Hamburger J, *et al*. Toll-like receptors (TLRs) expression in oral ulcer biopsies from Behcet's disease (BD) patients: a role for the innate immune syste in BD. *Clin Exp Rheumatol* 2004; 22(Suppl. 34): S-93.
78. Medzhitov R, Janeway CA. Innate immunity. *N Engl J Med* 2000; 343: 338-44.
79. Kilpatrick DC, Mannose-binding lectin: clinical significance and applications. *Biochin Biophys Acta* 2002; 1572: 401-13.
80. Inanc N, Mumcu G, Birtas E, Blsir Y, Yavuz S, Fresko I, Direskeneli H. Serum mannose-binding lectin levels are decreased in Behcet's disease and associated with disease severity. *J Rheumatol* 2005; 32: 287-91.
81. Matsushita M, Fujita T. The role of ficolins in innate immunity. *Immunobiology* 2002; 205: 490-7.
82. Lynch NJ, Roscher S, Hartung T, Morath S, Matsushita M, Maennel DN, Kuraya M, Fujita T, Schwaeble WJ. L-ficolin specifically binds to lipoteic acid, a cell wall constituent of Gram-positive bacteria and activates the lectin pathway of complement. *J Immunol* 2004; 172: 1198-202.
83. Wang H, Nakamura K, Inoue T, Yanagihori H, Kawakami Y, Hashimoto S, Oyama N, Kaneko F, Fujita T, Nishida T, Mizuki N. Mannose-binding lectin polymorphisms in patients with Behcet's disease. *J Dermatol Sci* 2004; 36: 115-7.
84. Chen X, Katoh Y, Nakamura K, Oyama N, Kaneko F, Endo Y, Fujita T, Nishida T, Mizuki N. Single nucleotide polymorphisms of Ficolin 2 gene in Behcet's disease. *J Dermatol Sci* 2006; 43: 201-5.
85. Calguneri M, Ertenli I, Kiraz S, Ertenli I, Benek-Li M, Karaorslan Y, Celik I. Effect of prophylacticbenzathine penicilline on mucocutaneous symptoms of Behcet's. *Dermatology* 1996; 192: 125-8.
86. Mumcu G, Inac N, Yavuz S, Direskeneli H. The role of infectious agents in the pathogenesis, clinical manifestations and treatment strategies in Behcet's disease. *Clin Exp Rheumatol* 2007; 25: S27-S33.

Ⅳ 研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書籍名	出版社名	出版地	出版年	ページ
Mizuki N, Inoko H, Ohno S	Recent advance in the pathogenesis of Behçet's disease. Proceedings of the 9th International Conference on Behçet's Disease					In Press	
小野江和則			医科免疫学	南江堂		2008	470
小野江和則			分子細胞生物学辞典（第2版）	東京化学同人		2008	
小野武紀, 柳川芳毅, 岩渕和也, 野々村克也, 小野江和則	Th2細胞誘導樹状細胞の分化とglycogen synthase		臨床免疫・アレルギー科			2008	50, 17-24
柳川芳毅, 小野江和則	樹状細胞からのIL-10産生とTLR		臨床免疫・アレルギー科			2008	49, 259-264
岩渕和也	NKT細胞とTh1/Th2バランス制		医学のあゆみ			2008	225(2), 139-144
小野江和則	秋山財団賞 受賞研究「自己と非自己を識別するT系列リンパ球の生成メカニズムと生体内役割」		秋山財団年報			2008	20, 25-45
小野江和則	T系列リンパ球の生成メカニズムと機能		生化学			印刷中	
磯貝恵美子	ライム病		動物病理学各論	文永堂出版		印刷中	
磯貝恵美子, 磯貝 浩	ライム病	清水実嗣監修	人獣共通感染症	養賢堂		2007	218-226
磯貝恵美子, 磯貝 浩	茶抽出エキスの歯周病予防効果	本好茂一監修	ペットフードの開発	シーエムシー出版		2006	115-127
磯貝恵美子	犬のライム病		動物の感染症（第2班、ハイブリッドCD付）	近代出版		2006	243
桑名正隆	ベーチェット病(Behçet's Disease)(内	山口徹、北原光夫、福井次矢監修	「今日の治療指針 2008年版-私はこう治療している」	医学書院	東京	2008	632-633
桑名正隆	Behçet病	池田康夫、鈴木則宏監修	「内科研修マニュアル（改訂第2版）」	南江堂	東京	2006	561
伊藤亜紀子、水木信久	ベーチェット病の眼発作時の対応	眼科診療のコツと落とし穴				印刷中	
冨山隆一、水木信久	眼内炎の鑑別	樋田哲夫、江口秀一郎編集	眼科診療のコツと落とし穴3. 検査・診断	中山書店		2008	136-137
林孝彦、水木信久	炎症性眼疾患とHLA分子の相関		眼科プラクティス			2007	16,41-43
水木信久	視力	大野重昭、木下茂編	標準眼科学	医学書院		2007	291-300
大野重昭、北市伸義、南場研一、猪子英俊、水木信久、太田正穂	ベーチェット病に対するシクロスポリン治療	シクロスポリン学術国際シンポジウム編集	免疫の進化、IV Autoimmune Disease -Contribution of Ciclosporin	医薬ジャーナル社		2006	196-203
水木信久	新入医局員集め奮闘記		日本の眼科			2006	77(9): 1127-1129
佐々木亘、水木信久	HLA検査	水木信久編集	基礎からわかるぶどう膜炎	金原出版		2006	100-104
伊藤亜紀子、水木信久	髄液検査	水木信久編集	基礎からわかるぶどう膜炎	金原出版		2006	108-110
上石智子、水木信久	皮内反応	水木信久編集	基礎からわかるぶどう膜炎	金原出版		2006	111-113
西田朋美、水木信久	ベーチェット病	水木信久編集	基礎からわかるぶどう膜炎	金原出版		2006	147-155
蓮見由紀子、水木信久	乾癬に伴うぶどう膜炎	水木信久編集	基礎からわかるぶどう膜炎	金原出版		2006	178-180
林孝彦、水木信久	ヘルペス性虹彩毛様体炎	水木信久編集	基礎からわかるぶどう膜炎	金原出版		2006	247-252
蓮見由紀子、水木信久	全身病 ライム病、眼科診療プラクティス 12	田野保雄編集	眼底アトラス	文光堂		2006	358
廣畑俊成	14.膠原病及び類縁疾患 全身性エリテマトーデス	山口徹、北原光夫、福井次矢 総編集	「今日の治療指針 2008」	医学書院	東京	2008	616-619
廣畑俊成	4.自己免疫疾患・アレルギー疾患・免疫不全 VIII. ベーチェット病	井村裕夫 編集主幹	「わかりやすい内科学」第3版	文光堂	東京	2008	420-423
廣畑俊成	IX.大動脈疾患 血管Behçet病 新領域別症候群No.6「循環器症候群(第2		別冊 日本臨床	日本臨床社	東京	2008	312-315
蕪城 俊克	ぶどう膜炎 1)原因不明の虹彩炎	根木 昭 編集	眼科診療プラクティス23「眼科薬物治療」	文光堂	東京	2008	126-127
川島秀俊、蕪城 俊克	ぶどう膜疾患	水流 忠彦 編集	「看護のための最新医学講座」	中山書店	東京	2008	153-161
蕪城 俊克	ぶどう膜および眼悪性腫瘍の手術	水流 忠彦 編集	「看護のための最新医学講座」	中山書店	東京	2008	286-292

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Motohashi K, Ito S, Hagihara M, Maruta A, Ishigatsubo Y, Kanamori H.	Cutaneous zygomycosis caused by Cunninghamella bertholletiae in a patient with chronic myelogenous leukemia in blast crisis.	Am J Hematol.	in press		2008
Koharazawa H, Kanamori H, Sakai R, Hashimoto C, Takemura S, Hattori M, Taguchi J, Fujimaki K, Tomita N, Fujita H, Fujisawa S, Harano H, Ogawa K, Motomura S, Maruta A, Ishigatsubo Y.	Long-term outcome of L86 and L97 protocols for adult acute lymphoblastic leukemia.	Leuk Lymphoma.	49(11)	2133-40.	2008
Kobayashi M, Miyazawa N, Takeno M, Murakami S, Kirino Y, Okouchi A, Kaneko T, Ishigatsubo Y.	Circulating carbon monoxide level is elevated after sleep in patients with obstructive sleep apnea.	Chest.	134(5)	904-10.	2008
Naganawa S, Yokoyama M, Shiino T, Suzuki T, Ishigatsubo Y, Ueda A, Shirai A, Takeno M, Hayakawa S, Sato S, Tochikubo O, Kiyoura S, Sawada K, Ikegami T, Kanda T, Kitamura K, Sato H.	Net positive charge of HIV-1 CRF01_AE V3 sequence regulates viral sensitivity to humoral immunity.	PLoS ONE.	12;3(9)	e3206	2008
Suda A, Nagaoka S, Ohono S, Ideguchi H, Soga T, Ishigatsubo Y.	The efficacy and safety of bucillamine as a second-line DMARD in the treatment of rheumatoid arthritis: a retrospective cohort study.	Mod Rheumatol.			2008
Kirino M, Kirino Y, Takeno M, Nagashima Y, Takahashi K, Kobayashi M, Murakami S, Hirasawa T, Ueda A, Aihara M, Ikezawa Z, Ishigatsubo Y.	Heme oxygenase 1 attenuates the development of atopic dermatitis-like lesions in mice: implications for human disease.	J Allergy Clin Immunol.	122(2)	290-7, 297.e1-8.	
Fujita A, Tomita N, Fujita H, Motohashi K, Hyo R, Yamazaki E, Hattori M, Fujisawa S, Kanamori H, Ogawa K, Motomura S, Kodama F, Ishigatsubo Y.	Features of primary extranodal lymphoma in Kanagawa, a human T-cell leukemia virus type 1 nonendemic area in Japan.	Med Oncol.			2008
Ideguchi H, Ohno S, Takase K, Ueda A, Ishigatsubo Y.	Outcomes after switching from one bisphosphonate to another in 146 patients at a single university hospital.	Osteoporos Int.	19(12)	1777-83.	2008
Murakami S, Takeno M, Oka H, Ueda A, Kurokawa T, Kuroiwa Y, Ishigatsubo Y.	Diagnosis of tuberculous meningitis due to detection of ESAT-6-specific gamma interferon production in cerebrospinal fluid enzyme-linked immunospot assay.	Clin Vaccine Immunol.	15(5)	897-9.	2008
Fujimaki K, Tanaka M, Takasaki H, Hyo R, Kawano T, Sakai R, Fujita H, Fujisawa S, Kanamori H, Maruta A, Ishigatsubo Y.	Thiotepa/cyclophosphamide/TBI as a conditioning regimen for allogeneic hematopoietic stem cell transplantation in patients aged 50 years and over.	Intern Med.	47(5)	379-83.	2008
Kirino Y, Takeno M, Watanabe R, Murakami S, Kobayashi M, Ideguchi H, Ihata A, Ohno S, Ueda A, Mizuki N, Ishigatsubo Y.	Association of reduced heme oxygenase-1 with excessive Toll-like receptor 4 expression in peripheral blood mononuclear cells in Behçet's disease.	Arthritis Res Ther.	10(1)	R16.	2008
Suzuki T, Ueda A, Kobayashi N, Yang J, Tomaru K, Yamamoto M, Takeno M, Ishigatsubo Y.	Proteasome-dependent degradation of alpha-catenin is regulated by interaction with ARMc8alpha.	Biochem J.	411(3)	581-91.	2008
omita N, Kodama F, Motomura S, Itoh S, Ohshima R, Hyo R, Kawano T, Hashimoto C, Takemura S, Yamazaki E, Fujita H, Fujisawa S, Ogawa K, Kanamori H, Ishigatsubo	Adjuvant radiotherapy to an initial bulky mass in diffuse large B-cell lymphoma: lack of survival benefit.	Int J Lab Hematol.	30(1)	53-7.	2008
Miyazaki T, Fujimaki K, Shirasugi Y, Yoshiba F, Ohsaka M, Miyazaki K, Yamazaki E, Sakai R, Tamaru J, Kishi K, Kanamori H, Higashihara M, Hotta T, Ishigatsubo Y.	Remission of lymphoma after withdrawal of methotrexate in rheumatoid arthritis: relationship with type of latent Epstein-Barr virus infection.	Am J Hematol.	82(12)	1106-9.	2007

Ideguchi H, Ohno S, Takase K, Hattori H, Kirino Y, Takeno M, Ishigatsubo Y.	Successful treatment of refractory lupus-associated haemophagocytic lymphohistiocytosis with infliximab.	Rheumatology (Oxford).	46(10)	1621-2.	2007
Inoue S, Oshiro H, Watanuki Y, Miyazawa N, Kudo M, Goto H, Tsukiji J, Kaneko T, Ishigatsubo Y.	Metastatic brain mass caused by slow-growing small-cell lung cancer: differential vascular endothelial growth factor expression in primary and metastatic tumor.	Clin Lung Cancer.	8(7)	436-8.	2007
Ideguchi H, Ohno S, Hattori H, Ishigatsubo Y.	Persistence with bisphosphonate therapy including treatment courses with multiple sequential bisphosphonates in the real world.	Osteoporos Int.	18(10)	1421-7.	2007
Ishizawa J, Fujita H, Iguchi M, Tachibana T, Taguchi J, Ishigatsubo Y.	Quantification of circulating varicella-zoster virus DNA for follow-up in a case of visceral varicella-zoster infection ameliorated with intravenous acyclovir.	Int J Hematol.	85(3)	242-5.	2007
Kobayashi N, Yang J, Ueda A, Suzuki T, Tomaru K, Takeno M, Okuda K, Ishigatsubo Y.	RanBPM, Muskelin, p48EMLP, p44CTLH, and the armadillo-repeat proteins ARMC8alpha and ARMC8beta are components of the CTLH complex.	Gene.	396(2)	236-47.	2007
Okamura M, Yamaji S, Nagashima Y, Nishikawa M, Yoshimoto N, Kido Y, Iemoto Y, Aoki I, Ishigatsubo Y.	Prognostic value of integrin beta1-ILK-pAkt signaling pathway in non-small cell lung cancer.	Hum Pathol.	38(7)	1081-91	2007
Ideguchi H, Ohno S, Ishigatsubo Y.	Risk factors associated with the cumulative survival of low-dose methotrexate in 273 Japanese patients with rheumatoid arthritis.	J Clin Rheumatol.	13(2)	73-8.	2007
Tomita N, Motomura S, Hyo R, Takasaki H, Takemura S, Taguchi J, Fujisawa S, Ogawa K.	Takeuchi K. Comparison of peripheral T-cell lymphomas and diffuse large B-cell lymphoma.	Cancer.	109(6)	1146-51.	2007
Ideguchi H, Ohno S, Ueda A, Ishigatsubo Y.	Catastrophic antiphospholipid syndrome associated with malignancies (case report and review of the literature).	Lupus.	16(1)	59-64.	2007
Kirino Y, Takeno M, Murakami S, Kobayashi M, Kobayashi H, Miura K, Ideguchi H, Ohno S, Ueda A, Ishigatsubo Y.	Tumor necrosis factor alpha acceleration of inflammatory responses by down-regulating heme oxygenase 1 in human peripheral monocytes.	Arthritis Rheum.	56(2)	464-75.	2007
Ideguchi H, Ohno S, Ishigatsubo Y.	A case of pure red cell aplasia and systemic lupus erythematosus caused by human parvovirus B19 infection.	Rheumatol Int.	27(4)	411-4.	2007
Sakai R, Fujimaki K, Yamazaki E, Sakamoto H, Kanamori H, Miura I, Ishigatsubo Y.	Acute myelomonocytic leukemia with dysplastic bone marrow eosinophils showing t(5;17)(q13;q11) and a secondary chromosomal aberration, inv(16)(p13q22).	Int J Hematol.	84(5)	417-20.	2006
Sato T, Takeno M, Honma K, Yamauchi H, Saito Y, Sasaki T, Morikubo H, Nagashima Y, Takagi S, Yamanaka K, Kaneko T, Ishigatsubo Y.	Heme oxygenase-1, a potential biomarker of chronic silicosis, attenuates silica-induced lung injury.	Am J Respir Crit Care Med.	174(8)	906-14.	2006
Tomita N, Kodama F, Kanamori H, Motomura S, Ishigatsubo Y.	Secondary central nervous system lymphoma.	Int J Hematol.	84(2)	128-35.	2006
Takeno M, Ishigatsubo Y.	Behcet's disease and familial Mediterranean fever.	Intern Med.	45(13)	805-6.	2006
Ohno S, Ishigatsubo Y.	The incidence of Lofgren's syndrome in Japanese: the number of patients affected, number of patients diagnosed and number of cases reported.	Intern Med.	45(12)	745-6.	2006
Tomita N, Kodama F, Oshima R, Hashimoto C, Koharazawa H, Takemura S, Yamazaki E, Fujimaki K, Sakai R, Fujita H, Fujisawa S, Kanamori H, Motomura S, Ishigatsubo Y.	Phase II study of CHOP-GR therapy for advanced-stage follicular lymphoma.	Leuk Lymphoma.	47(6)	1041-7.	2006

Yoshimi R, Takeno M, Yamanaka S, Shiina M, Kirino Y, Takeda Y, Sekiguchi A, Kobayashi H, Ihata A, Motoji K, Ohno S, Ueda A, Soga T, Ishigatsubo Y.	Systemic sclerosis and pseudomesotheliomatous adenocarcinoma of the lung.	Mod Rheumatol.	16(3)	165-8.	2006
Tomita N, Kodama F, Motohashi K, Fujita A, Hyo R, Hashimoto C, Takemura S, Yamazaki E, Taguchi J, Sakai R, Fujisawa S, Kanamori H, Motomura S, Ishigatsubo Y, Takeuchi K.	Outcome of involved-field radiotherapy for stage 1 follicular lymphoma.	Int J Hematol.	83(4)	370-2.	2006
Takasaki H, Kanamori H, Takabayashi M, Yamaji S, Koharazawa H, Taguchi J, Fujimaki K, Ishigatsubo Y.	Non-Hodgkin's lymphoma presenting as multiple bone lesions and hypercalcemia.	Am J Hematol.	81(6)	439-42.	2006
Ideguchi H, Ohno S, Hattori H, Senuma A, Ishigatsubo Y.	Bone erosions in rheumatoid arthritis can be repaired through reduction in disease activity with conventional disease-modifying antirheumatic drugs.	Arthritis Res Ther.	8(3)	R76.	2006
Tomita N, Kodama F, Motomura S, Koharazawa H, Fujita H, Harano H, Kanamori H, Ishigatsubo Y.	Prognostic factors in diffuse large B-cell lymphoma treated by risk-adopted therapy.	Intern Med.	45(5)	247-52.	2006
Kobayashi H, Takeno M, Saito T, Takeda Y, Kirino Y, Noyori K, Hayashi T, Ueda A, Ishigatsubo Y.	Regulatory role of heme oxygenase 1 in inflammation of rheumatoid arthritis.	Arthritis Rheum.	54(4)	1132-42.	2006
Yoshimi R, Yamaji S, Suzuki A, Mishima W, Okamura M, Obana T, Matsuda C, Miwa Y, Ohno S, Ishigatsubo Y.	The gamma-parvin-integrin-linked kinase complex is critically involved in leukocyte-substrate interaction.	J Immunol.	15;176(6)	3611-24.	2006
Takeno M, Ishigatsubo Y.	Intestinal manifestations in systemic lupus erythematosus.	Intern Med.	45(2)	41-2.	2006
Sakai R, Fujisawa S, Fujimaki K, Kanamori H, Ishigatsubo Y.	Long-term remission in a patient with hepatosplenic gammadelta T cell lymphoma after cord blood stem cell transplantation following autologous peripheral blood stem cell transplantation.	Bone Marrow Transplant.	37(5)	537-8.	2006
Miyazaki A, Kitaichi N, Ohgami K, Iwata D, Jin XH, Iwabuchi K, Morohashi T, Ohno S, Onoe K.	Anti-inflammatory effect of angiotensin type 1 receptor antagonist on endotoxin-induced uveitis in rats.	Graefes Arch Clin Exp Ophthalmol.	246	747-57	2008
Horie Y, Namba K, Kitaichi N, Ohno S.	Sister cases of Behcet's disease and Vogt-Koyanagi-Harada disease.	Br J Ophthalmol.	92	433-4,	2008
Kitaichi N, Shimizu T, Yoshida K, Honda A, Yoshihisa Y, Kase S, Ohgami K, Norisugi O, Makino T, Nishihira J, Yamagishi SI, Ohno S	Macrophage migration inhibitory factor ameliorates UV-induced photokeratitis in mice.	Exp Eye Res.	86	929-935	2008
Yoshida K, Tomioka Y, Kase S, Morimatsu M, Shinya K, Ohno S, Transgenic mice gererating group, Ono E	Microphthalmia and lack of vitreous body in transgenic mice expressing the first immunoglobulin-like domain of nectin-1.	Graefes Arch Clin Exp Ophthalmol	246	543-549	2008
Kitaichi N, Ohno S	Behcet disease in children.	Int Ophthalmol Clin	48	87-91	2008
Meguro A, Ota M, Katsuyama Y, Oka A, Ohno S, Inoko H, Mizuki N	Association of the toll-like receptor 4 gene polymorphisms with Behcet's disease.	Ann Rheum Dis	67	725-727	2008
Zhenyu Dong, Namba K, Kitaichi N, Goda C, Kitamura M, Ohno S	Efficacy and complications of intravitreal injection of triamcinolone acetonide for refractory cystoid macular edema associated with intraocular inflammation.	Jpn J Ophthalmol	52	374-379	2008
Izumi-Nagai K, Nagai N, Ohgami K, Satofuka S, Ozawa Y, Tsubota K, Ohno S, Oike Y, Ishida S.	Inhibition of choroidal neovascularization with an anti-inflammatory carotenoid astaxanthin.	Invest Ophthalmol Vis Sci.	49	1679-85	2008
Ito A, Ota M, Katsuyama Y, Inoko H, Ohno S, Mizuki N	Lack of Association of Toll-like receptor 9 gene polymorphism with Behcet's disease in Japanese patients.	Tissue Antigens	70	423-426	2007
Inamori Y, Ota M, Inoko H, Okada E, Nishizaki R, Shiota T, Mok J, Oka A, Ohno S, Mizuki N	The COL1A1 gene and high myopia susceptibility in Japanese.	Hum Genet	122	151-157	2007

Katsuyama Y, Ota M, Mizuki N, Ito A, Okada E, Ohno S, Matsunaga T, Fukushima H, Ohmori S	MDR1 polymorphisms effect cyclosporine AUC0-4 values in Behcet's disease patients.	Clin Ophthalmol	1	297-303	2007
Kase S, Saito W, Ohgami K, Yoshida K, Furudate N, Saito A, Yokoi M, Kase M, Ohno S	Expression of erythropoietin receptor in human epiretinal membrane of proliferative diabetic retinopathy.	Br J Ophthalmol	91	1376-1378	2007
Kase S, Osaki M, Sato I, Takahashi S, Nakanishi K, Yoshida K, Ito H, Ohno S	Immunolocalization of E-cadherin and (beta)-catenin in human pterygium.	Br J Ophthalmol	91	1209-1212	2007
Uchio E, Fuchigami A, Kadonosono K, Hayashi A, Ishiko H, Aoki K, Ohno S	Anti-adenoviral effect of anti-HIV agents in vitro in serotypes inducing keratoconjunctivitis.	Graefes Arch Clin Exp Ophthalmol	245	1319-25	2007
Harada C, Nakamura K, Guo X, Kitaichi N, Mitamura Y, Yoshida K, Ohno S, Yoshida H, Harada T	Neuroprotective effect of geranylgeranylacetone against ischemia-inducedretinal injury.	Mol Vis	7	1601-1607	2007
Yokoi M, Yamagishi S, Saito A, Yoshida Y, Matsui T, Saito W, Hirose S, Ohgami K, Kase M, Ohno S	Positive association of pigment epithelium-derived factor with total antioxidant capacity in the vitreous fluid of patients with proliferative diabetic retinopathy.	Br J Ophthalmol	91	885-7	2007
Yokoi M, Yamagishi S, Takeuchi M, Matsui T, Yoshida Y, Ohgami K, Amano-Okamoto T, Ohno S	Positive correlation between vitreous levels of advanced glycation end products and vascular endothelial growth factor in patients with diabetic retinopathy sufficiently treated with photocoagulation.	Br J Ophthalmol	91	397-8	2007
Jin XH, Ohgami K, Shiratori K, Koyama Y, Yoshida K, Kase S, Ohno S	Inhibition of nuclear factor-kappa B activation attenuates hydrogen peroxide-induced cytotoxicity in human lens epithelial cells.	Br J Ophthalmol	91	369-71	2007
Kase S, Yokoi M, Saito W, Furudate N, Ohgami K, Kitamura M, Kitaichi N, Yoshida K, Kase M, Ohno S, Uede T	Increased osteopontin levels in the vitreous of patients with diabetic retinopathy.	Ophthalmic Res	39	143-7	2007
Nitta T, Kase M, Shinmei Y, Yoshida K, Chin S, Ohno S	Mydriasis with light-near dissociation in Fisher's syndrome.	Jpn J Ophthalmol	51	224-227	2007
Kitamura M, Iwabuchi K, Kitaichi N, Kon S, Kitamei H, Namba K, Yoshida K, Denhardt T. D, Rittling R. Susan, Ohno S, Uede T, Onoe K	Osteopontin aggravates experimental autoimmune uveoretinitis in mice.	J Immunol	178	6567-6572	2007
Kase S, Takahashi S, Sato I, Nakanishi K, Yoshida K, Ohno S	Expression of p27(KIP1) and cyclin D1, and cell proliferation in human pterygium.	Br J Ophthalmol	91	958-961	2007
Shinmei Y, Kase M, Suzuki Y, Nitta T, Chin S, Yoshida K, Goto Y, Nagashima T, Ohno S	Ocular motor disorders in mitochondrial encephalopathy with lactic acid and stroke-like episodes with the 3271 (T-C) point mutation in mitochondrial DNA.	J Neuroophthalmol.	27	22-8	2007
Hayashi T, Inoko H, Nishizaki R, Ohno S, Mizuki N	Exclusion of transforming growth factor-beta1 as a candidate gene for myopia in the Japanese.	Jpn J Ophthalmol	51	96-9	2007
Matsuda A, Ebihara N, Kumagai N, Fukuda K, Ebe K, Hirano K, Sotozono C, Tei M, Hasegawa K, Shimizu M, Tamari M, Namba K, Ohno S, Mizuki N, Ikezawa Z, Shirakawa T, Hamuro J, Kinoshita S	Genetic polymorphisms in the promoter of the interferon gamma receptor 1 gene are associated with atopic cataracts.	Invest Ophthalmol Vis Sci	48	583-9	2007
Yatsu K, Mizuki N, Hirawa N, Oka A, Itoh N, Yamane T, Ogawa M, Shiwa T, Tabara Y, Ohno S, Soma M, Hata A, Nakao K, Ueshima H, Ogihara T, Tomoike H, Miki T, Kimura A, Mano S, Kulski JK,	High-resolution mapping for essential hypertension using microsatellite markers.	Hypertension	49	446-52	2007
Kase S, Yokoi M, Saito W, Furudate N, Ohgami K, Kitamura M, Kitaichi N, Yoshida K, Kase M, Ohno S, Uede T	Increased osteopontin levels in the vitreous of patients with diabetic retinopathy.	Ophthalmic Res	39	143-147	2007
Ochiai M R, Shimada Y, Konno T, Yamazaki S, Aoki K, Ohno S, Suzuki E, Ishiko H	Quantitative detection and rapid identification of human adenoviruses.	J Clin Microbiol	45	958-967	2007

Goto H, Mochizuki M, Yamaki K, Kotake S, Usui M, Ohno S	Epidemiological survey of intraocular inflammation in Japan.	Jpn J Ophthalmol	51	41-44	2007
Kitamei H, Kitaichi N, Yoshida K, Nakai A, Fujimoto M, Kitamura M, Iwabuchi K, Miyazaki A, Namba K, Ohno S, Onoe K	Association of heat shock protein 70 induction and the amelioration of experimental autoimmune uveoretinitis in mice.	Immunobiology	212	11-18	2007
Kitaichi N, Matoba H, Ohno S	The positive role of lumbar puncture in the diagnosis of Vogt-Koyanagi-Harada disease: lymphocyte subsets in the aqueous humor and cerebrospinal fluid.	Int Ophthalmol	27	97-103	2007
Nitta T, Kase M, Shinmei Y, Yoshida K, Chin S, Ohno S	Mydriasis with Light-Near Dissociation in Fisher's Syndrome.	Jpn J Ophthalmol.	51	224-227	2007
Kase S, Yoshida K, Osaki M, Adachi H, Ito H, Ohno S	Expression of erythropoietin receptor in human Merkel cell carcinoma of the eyelid.	Anticancer Res	26(6B)	4535-7	2006
Saito W, Sakaguchi T, Furudate N, Amino Y, Ohno S	Pseudomonas scleral abscess following pars plana vitrectomy.	Jpn J Ophthalmo	50	564-6	2006
Saito W, Saito A, Namba K, Kase S, Shiratori M, Ohno S	Chronic panuveitis and scleritis in a patient with cryptogenic organizing pneumonia.	Jpn J Ophthalmol	50	558-61	2006
Namba K, Sonoda KH, Kitamei H, Shiratori K, Ariyama A, Iwabuchi K, Onoe K, Saniabadi AR, Inaba S, Ishibashi T, Ohno S	Granulocytapheresis in patients with refractory ocular Behcet's disease.	J Clin Apher.	21	121-8	2006
Goda C, Kanaji T, Kanaji S, Tanaka G, Arima K, Ohno S, Izuhara K	Involvement of IL-32 in activation-induced cell death in T cells.	Int Immunol	18	233-40	2006
Kase S, Yoshida K, Sakai M, Ohgami K, Shiratori K, Kitaichi N, Suzuki Y, Harada T, Ohno S	Expression of cyclin D1 in the developing lens of c-maf-/-mice.	Acta Histochemica	107	469-472	2006
Ilieva I, Ohgami K, Jin X H, Suzuki Y, Shiratori K, Yoshdia K, Kase S, Ohno S	Captopril suppresses inflammation in endotoxin-induced uveitis in rats.	Exp Eye Res	83	651-657	2006
Horie Y, Takemoto Y, Miyazaki A, Namba K, Kase S, Yoshida K, Ota M, Hasumi Y, Mizuki N, Ohno S	Tyrosinase gene family and Vogt-Koyanagi-Harada disease in Japanese patients.	Molecular Vision	12	1601-1605	2006
Jin XH, Ishiko H, Thanh Ha N, Ohguchi T, Akanuma M, Aoki K, Ohno S	Molecular epidemiology of adenoviral conjunctivitis in Hanoi, Vietnam.	Am J Ophthalmol	142	1064-1066	2006
Kase S, Kitaichi N, Namaba K, Miyazaki A, Yoshida K, Ishikura K, Ikeda M, Nakashima T, Ohno S	Elevation of serum KL-6 levels in patients with tubulointerstitial nephritis and uveitis (TINU) syndrome.	Am J Kidney Dis	48	935-941	2006
Kase S, Namba K, Kitaichi N, Ohno S	Epstein-Barr virus-infected cells in the aqueous humor originated from nasal NK/T cell lymphoma.	Br J Ophthalmol	90	244-5	2006
Kitamura M, Kitaichi N, Namba K, Kitamei H, Ohno S	Correspondence - Reply to Comparative study of two sets of criteria for the diagnosis of Vogt-Koyanagi-Harada Disease.	Am J Ophthalmol	141	778-779	2006
Kase S, Kitaichi N, Furudate N, Yoshida K, Ohno S	Increased expression of mucinous glycoprotein KL-6 in human pterygium.	Br J Ophthalmol	90	1208-1209	2006
Kitaichi N, Ariga T, Ohno S, Shimizu T	Acute unilateral conjunctivitis after rubella vaccination: the detection of the rubella genome in the inflamed conjunctiva by reverse transcriptase-polymerase-chain reaction.	Br J Ophthalmol	90	1436-1437	2006
Kitaichi N, Shimizu T, Honda A, Abe R, Ohgami K, Shiratori K, Shimizu H, Ohno S	Increase in macrophage migration inhibitory factor levels in lacrimal fluid of patients with severe atopic dermatitis.	Graefe's Arch Clin Exp Ophthalmol	244	825-828	2006
Kitamei M, Iwabuchi K, Namba K, Yoshida K, Yanagawa Y, Kitaichi N, Kitamura M, Ohno S, Onoe K	Amelioration of experimental autoimmune uveoreitinitis (EAU) with an ininhibitor of nuclear factor kappa B (NF-kappaB), pyrrolidine dithiocarbamate.	J Leukocyte Biol	79	1193-1201	2006
Jin X H, Ohgami K, Shiratori K, Suzuki Y, Hirano T, Koyama Y, Yoshida K, Ilieva I, Iseki K, Ohno S	Inhibitory effects of lutein on endotoxin-induced uveitis in lewis rats.	Invest Ophthalmol Vis Sci	47	2562-2568	2006

Kase S, Yoshida K, Ohgami K, Shiratori K, Nakayama K I, Ohno S	Phosphorylation of p27 (KIP1) in the mitotic cells of the corneal epithelium.	Curr Eye Res	31	307-312	2006
Kitaichi N, Ariga T, Kase S, Yoshida K, Namba K, Ohno S	Usefulness of quantiyfying serum KL-6 levels in the follow-up of uveitic patients with sarcoidosis.	Graefe's Arch Clin Exp Ophthalmol	244	433-437	2006
Suzuki Y, Ohgami K, Shiratori K, Jin X H, Ilieva I, Koyama Y, Yazawa K, Yoshida K, Kase S, Ohno S	Suppressive effects of astaxanthin against rat endotoxin-induceduveitis by inhibiting the NF-<kappa>B signaling pathway.	Exp Eye Res	82	275-281	2006
Jin XH, Ohgami K, Shiratori K, Suzuki Y, Koyama Y, Yoshida K, Ilieva I, Tanaka T, Onoe K, Ohno S	Effects of blue honeysuckle (Lonicera caerulea L.) extract on lipopolysaccharide-induced inflammation in vitro and in vivo.	Exp Eye Res	82	860-867	2006
Kase S, Yoshida K, Sakai M, Ohgami K, Shiratori K, Kitaichi N, Suzuki Y, Harada T, Ohno S	Immunolocalization of cyclin D1 in the develoing lens of c-maf-/- mice.	Acta Histochem	107	469-472	2006
Kase S, Yoshida K, Ohgami K, Shiratori K, Suzuki Y, Nakayama K, Ohno S	Expression of cdc2 and p27 (KIP1) phosphorylation in mitotic cells of the human retinoblastoma.	Int J Mol Med	17	465-468	2006
Harada C, Nakamura K, Namekata K, Okumura A, Mitamura Y,Iizuka Y, Kashiwagi K, Yoshida K, Ohno S, Matsuzawa A, Tanaka K, Ichijo H, Harada T	Role of apoptosis signal-regulating kinase 1 in stress-induced neural cell apoptosis in vivo.	Am J Pathol	168	261-269	2006
Kase S, Saito W, Yokoi M, Yoshida K, Furudate N, Muramatsu M, Saito A, Kase M, Ohno S	Expression of glutamine synthetase and cell proliferation in human idiopathic epiretinal membrane.	Br J Ophthalmol	90	96-98	2006
Hasumi Y, Inoko H, Mano S, Ota M, Okada E, Kulski JK, Nishizaki R, Mok J, Oka A, Kumagai N, Nishida T, Ohno S, Mizuki N	Analysis of single nucleotide polymorphisms at 13 loci within the transforming growth factor-induced factor gene shows no association with high myopia in Japanese subjects.	Immunogenetics	58	947-53	2006
Kase S, Yoshida K, Jin X H, Koyama Y, Kitaichi N, Ohgami K, Shiratori K, Ilieva I, Ohno S	Phosphorylation of p27(KIP1) in lens epithelial cells after extraction of fiber cells.	Int J Mol Med	18	1187-1191	2006
Itoh Y, Inoko H, Kulski JK, Sasaki S, Meguro A, Takiyama N, Nishida T, Yuasa T, Ohno S, Mizuki N	Itoh Y, Inoko H, Kulski JK, Sasaki S, Meguro A, Takiyama N, Nishida T, Yuasa T, Ohno S, Mizuki N	Tissue Antigens	67	390-4	2006
Yabe T, Matsuo T, Hirayasu K, Kashiwase K, Kawamura-Ishii S, Tanaka H, Ogawa A, Takanashi M, Satake M, Nakajima K,Tokunaga K, Inoko H, Saji H, Ogawa S, Juji T, Sasazuki T,Kodera Y, Morishima	Donner killer immunoglobulin-like receptor (KIR) genotype-patient cognate KIR ligand combination and antithymocyte globulin preadministration are critical factors in outcome of HLA-C-KIR ligand-mismatched T Cell-replete unrelated bone marrow transplantation.	Biology of Blood and Marrow Transplantation (BBMT)	14	75-87	2008
Hui J, Oka A, James A, Palmer LJ, Musk AW, Beilby J, Inoko H	A genome-wide association scan for asthma in a general Australian population.	Hum Genet	123	297-306	2008
Meguro A, Ota M, Katsuyama Y, Oka A, Ohno S, Inoko H, Mizuki N	Association of the toll-like receptor 4 gene polymorphisms with Behcet's disease.	Ann Rheum Dis	67	725-727	2008
Ohtsuka M, Inoko H, Kulski JK, Yoshimura S	Major histocompatibility complex (Mhc) class Ib gene duplications, organization and expression patterns in mouse strain C57BL/6.	BMC Genomics	9	178-192	2008
Kimura T, Kobayashi T, Munkhbat B, Oyungerel G, Bilegtsaikhan T, Anar D, Jambaldorj J, Munkhsaikhan S, Munkhtuvshin N, Hayashi H, Oka A, Inoue I Inoko H	Genome-wide association analysis with selective genotyping identifies candidate loci for adult height at 8q21.13 and 15q22.33-q23 in Mongolians	Hum Genet	123	655-660	2008
Ando A, Uenishi H, Kawata H, Tanaka-Matsuda M, Shigenari A, Flori L, Chardon P, Lunney JK, Kulski JK, Inoko H	Microsatellite diversity and crossover regions within homozygous and heterozygous SLA haplotypes of different pig breeds	Immunogenetics	60	399-407	2008

Holland LZ, Albalat R, Azumi K, Benito-Gutiérrez E, Blow MJ, Bronner-Fraser M, Brunet F, Butts T, Candiani S, Dishaw LJ, Ferrier DE, Garcia-Fernàndez J, Gibson-Brown JJ, Gissi C, Godzik A, Hallböök F, Hirose D, Hosomichi K, Ikuta T, Inoko H, Kasahara M, Kasamatsu J, Kawashima T, Kimura A, Kobayashi M, Kozmik Z, Kubokawa K, Laudet V, Litman GW, McHardy AC, Meulemans D, Nonaka M, Olinski RP, Pancer Z, Pennacchio LA, Pestarino M, Rast JP, Rigoutsos I, Robinson-Rechavi M, Roch G, Saiga H, Sasakura Y, Satake M, Satou Y, Schubert M, Sherwood N, Shiina T, Takatori N, Tello J, Vopalensky P, Wada S, Xu A, Ye Y, Yoshida K, Yoshizaki F, Yu JK, Zhang Q, Zmasek CM, de Jong PJ, Osoegawa K, Putnam NH, Rokhsar DS, Satoh N, Holland PW	The amphioxus genome illuminates vertebrate origins and cephalochordate biology	Genome Res	18	1100-1111	2008
Shibuya E, Meguro A, Ota M, Kashiwagi K, Mabuchi F, Iijima H, Kawase K, Yamamoto T, Nakamura M, Negi A, Sagara T, Nishida T, Inatani M, Tanihara H, Aihara M, Araie M, Fukuchi T, Abe H, Higashide T, Sugiyama K, Kanamoto T, Kiuchi Y, Iwase A, Ohno S, Inoko H, Mizuki N	Association of toll-like receptor 4 gene polymorphisms with normal tension glaucoma	Invest Ophthalmol Vis Sci	49	4453-4457	2008
Kulski JK, Shigenari A, Shiina S, Ota M, Hosomichi K, James I, Inoko H	Human endogenous retrovirus (HERVK9) structural polymorphism with haplotypic HLA-A allelic associations	Genetics	108	446-457	2008
Takemoto Y, Naruse T, Namba K, Kitaichi N, Ota M, Shindo Y, Mizuki N, Gul A, Madanat W, Chams H, Davatchi F, Inoko H, Ohno S, Kimura A	Re-evaluation of heterogeneity in HLA-B*510101 associated with Behçet's disease	Tissu Antigens	72	347-353	2008
Sumiyama D, Kitamura S, Terasawa F, Hori Y, Murata K, Kulski JK, Inoko H	Paternity determination of captive bottlenose dolphins (Tursiops truncatus) using microsatellite DNA analysis	J Vet Med Sci	70	711-713	2008
Hosomichi K, Miller MM, Goto RM, Wang Y, Suzuki S, Kulski JK, Nishibor20 M, Inoko H, Hanzawa K, Shiina T	Contribution of mutation, recombination, and gene conversion to chicken MHC-B haplotype diversity	J Immunol	181	3393-3399	2008
Akiyama M, Yatsu K, Ota M, Katsuyama Y, Kashiwagi K, Mabuchi F, Iijima H, Kawase K, Yamamoto T, Nakamura M, Negi A, Sagara T, Kumagai N, Nishida T, Inatani M, Tanihara H, Ohno S, Inoko H, Mizuki NAkiyama M, Yatsu K, Ota M, Katsuyama Y, Kashiwagi K, Mabuchi F, Iijima H, Kawase K, Yamamoto T, Nakamura M, Negi A, Sagara T, Kumagai N, Nishida T, Inatani M, Tanihara H, Ohno S, Inoko H, Mizuki N	Microsatellite analysis of the GLC1B locus on chromosome 2 points to NCK2 as a new candidate gene for normal tension glaucoma	Br J Ophthalmol	92	1293-1296	2008
Kulski JK, Shigenari A, Shiina T, Ota M, Hosomichi K, James I, Inoko H	Human endogenous retrovirus (HERVK9) structural polymorphism with haplotypic HLA	A allelic associations Genetics	180	445-457	2008
Bahram S, Inoko H	Microsatellite markers for genome-wide association studies	Nature Reviews Genetics	8	164	2007
Yasuno K, Ando S, Misumi S, Makino S, Kulski JK, Muratake T, Kaneko N, Amagane H, Someya T, Inoko H, Suga H, Kanemoto K,	Synergistic association of mitochondrial uncoupling protein (UCP) genes with schizophrenia	Am J Med Genet B Neuropsychiatr Genet	144	250-253	2007
Ota M, Katsuyama Y, Hamano H, Umemura T, Kimura A, Yoshizawa K, Kiyosawa K, Fukushima H, Bahram S, Inoko H, Kawa S	Two critical genes (HLA-DRB1 and ABCF1)in the HLA region are associated with the susceptibility to autoimmune pancreatitis.	Immunogenetics	59	45-52	2007