研究成果の刊行に関する一覧表(平成17年度)

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Ⅴ　平成17年度班会議プログラム

平成17年度班会議プログラム

13：00～13：05　　開会の辞

13：05～13：15　　厚生労働省　挨拶

13：15～　　研究発表

1．　13：15～13：35

アナログペプチドによる抗原特異的免疫分子制御法の開発に関する研究

筑波大学大学院人間総合科学研究科先端応用医学専攻臨床免疫学

住田　孝之

2．　13：35～13：55

遺伝子導入ES-DCによる制御性T細胞を介したEAEの発症予防

熊本大学大学院医学薬学研究部免疫識別学分野

西村　泰治

3．　13：55～14：15

関節炎局所に集積しているT細胞レセプターを用いた治療モデルの開発

東京大学大学院医学系研究科アレルギーリウマチ学

山本　一彦

4．　14：15～14：35

免疫制御性分子発現多機能ウイルスベクターを用いた疾患特異的免疫制御法の開発

京都大学大学院医学研究科臨床免疫学

三森　経世

5．　14：35～14：55

MR1拘束性NKT細胞を標的とした免疫療法の開発

国立精神・神経センター神経研究所免疫研究部

山村　隆

… … …　　コーヒーブレイク　14：55～15：10　　… … …

6．　15：10～15：30

制御性T細胞のマスター遺伝子Foxp3を用いたコラーゲン誘導関節炎の制御

東京医科歯科大学大学院医歯学総合研究科膠原病・リウマチ内科学

上阪　等

7．　15：30～15：50

全身性エリテマトーデスにおけるRas-guanyl releasing protein 1発現異常に関する研究

北海道大学大学院医学研究科病態内科学講座・第二内科

小池　隆夫

8．　15：50～16：10

自己抗原および関節炎誘導分子修飾による自己抗体産生制御

筑波大学大学院人間総合科学研究科先端応用医学専攻臨床免疫学

松本　功

9．　16：10～16：30

天疱瘡モデルマウスを用いた自己反応性T細胞株のin vivo病原性のスクリーニング法に関する研究

慶應義塾大学先端医科学研究所

桑名　正隆

16：30～16：40　　閉会の辞

VI　研究成果刊行物・別刷

T cell receptor BV gene repertoire of lymphocytes in bronchoalveolar lavage fluid of polymyositis/dermatomyositis patients with interstitial pneumonitis

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Abstract. We analyzed the T cell receptor (TCR) repertoire of bronchoalveolar lavage fluid (BALF) lymphocytes from polymyositis (PM) and dermatomyositis (DM) patients with interstitial pneumonitis (IP) to elucidate the pathogenic mechanisms of IP in these disorders. Samples from 2 PM patients, 1 DM patient and 3 healthy controls were used. RNA was isolated from BALF, cDNAs were synthesized, and family PCR and Southern blot analysis were performed by primers specific for TCR BV1-25 and TCR BC to determine TCR repertoire. We examined single-strand conformation polymorphism (SSCP) to evaluate T cell clonality. The CDR3 region of TCR BV genes in BALF T cells were determined by DNA sequencer. Our examination showed that TCR repertoire of T cells in BALF was heterogeneous both in patients with PM/DM and control subjects. SSCP analysis demonstrated an increased number of accumulated T cell clones in BALF of three PM/DM patients, but not in the healthy subjects and the junctional sequence analysis showed the presence of conserved amino acid motifs (RGS, GLA, LQG, SGG, DRG, GTS, TSGR, GGS, GQA, GAG, GTG) in the TCR-CDR3 region of BALF lymphocytes from PM/DM patients, which were not detected in the control. Our findings suggest that T cells in BALF may recognize the restricted antigen and accumulate via antigen-driven stimulation, suggesting that T cells may play a crucial role in the development of IP in patients with PM/DM.

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Abbreviations: PM/DM, polymyositis/dermatomyositis; IP, interstitial pneumonitis; SSCP, single-strand conformation polymorphism; TCR, T cell receptor; BALF, bronchoalveolar lavage fluid

Key words: interstitial pneumonitis, polymyositis, dermatomyositis, T cell receptor, bronchoalveolar lavage fluid lymphocytes, T cell clones, amino acid motifs

Introduction

Polymyositis (PM) and dermatomyositis (DM) are systemic inflammatory disorders that affect skeletal muscles and various other organ systems including the lungs. Pulmonary interstitial lung disease (ILD) is the most frequent pulmonary pathological finding recognized to be associated with PM/DM. Recent advances in biotechnology in the field of bronchoalveolar lavage (BAL) have provided considerable information on the alveolar cellular components in PM/DM with IP (1). Pulmonary damage and fibrosis represent the consequences of immune response and inflammatory process. Previous studies showed that lymphocytes, especially T cells, and alveolar macrophages play a central role in the pathogenesis of PM/DM with IP, although the mechanism that triggers these cells has not been elucidated (2).

T cells recognize antigens in the context of major histocompatibility complex (MHC) on antigen-presenting cells (APC) through an antigen receptor, the T cell receptor (TCR). Several groups investigating TCR genes in autoimmune diseases such as rheumatoid arthritis (3), Sjögren's syndrome (4,5), and multiple sclerosis (6,7) among other diseases, have demonstrated that T cells accumulate oligoclonally in the inflammatory lesions. Furthermore, conserved amino acid motifs have been observed in the CDR3 region of TCR gene, but no skewed usage of TCR genes (6,7).

Several studies have examined TCR genes of BAL fluid (BALF) T cells in patients with various lung diseases such as sarcoidosis, bronchial asthma, and idiopathic pulmonary fibrosis (IPF). Moller and colleagues (8) demonstrated an increased number of TCR BV8 T cells in BALF of patients with sarcoidosis. Zissel *et al* (9) showed the predominant usage of TCR BV5, BV8, BV12, BV13S3, and BV19 genes in BALF. Bellocq and coworkers (10) found a number of TCR BV19-positive T cells in BALF of patients with sarcoidosis. In asthmatic patients, Hodges *et al* (11) reported expansion of TCR BV5S2/3-positive T cells in BALF. In contrast, there

Table I. Characteristics of study population.

	Patients			Healthy subjects		
	DM-I	PM-1	PM-2	HS-1	HS-2	HS-3
Age (years)	57	57	50	52	32	28
Sex	F	F	F	M	M	M
Smoking	-	-	-	+	+	-
% vital capacity (% predicted value)	102.7	81.4	66.8	ND	118.0	133.4
FEV1 %	93.5	73.1	100.0	ND	80.5	97.4
% DLco	58.1	42.3	45.2	ND	91.7	90.9
PaO_2 (mmHg)	68.0	75.4	100.5	ND	ND	ND
Chest radiograph						
Diffuse reticular infiltrate pattern	±	+	+	-	-	-
BAL analysis						
Total cell count ($x10^5$/ml)	350	3.8	6.1	1	2.6	0.8
Differential count (%)						
Macrophages	57.7	43.1	77.5	90.5	93.0	90.0
Lymphocytes	41.0	14.7	18.1	3.2	3.5	8.0
Neutrophils	1.3	43.1	4.2	4.9	3.0	2.0
Eosinophils	0.0	7.3	0.2	1.4	0.5	0
CD4/CD8 ratio	0.6	0.3	0.4	2.2	0.6	4.7
Absolute number of lymphocytes[a]	1435.0	5.6	11.0	0.3	0.9	0.6

The diagnosis of PM/DM was based on clinical criteria for PM/DM of Bohan and Peter (22). [a]In $x10^4$/ml.

was no dominant usage of TCR BV genes in BALF T cells in patients with non-atopic asthma (12). We also reported conserved amino acid motifs in the CDR3 region of the TCR BV genes in clonally expanded BALF T cells of patients with IPF (13). These findings support the hypothesis that BALF T cells of patients with sarcoidosis, atopic bronchial asthma, and IPF may be induced by antigens on antigen-presenting cells. To our knowledge, there are no reports on the TCR gene of BALF T cells, or possible triggering factors, in patients with IP associated with PM/DM.

The present study was conducted to investigate the pathogenesis of IP in PM/DM and analyze the TCR BV repertoire and clonality of T cells infiltrating the lungs. The results showed oligoclonal expansion of T cells in BALF of patients with IP in PM/DM, suggesting antigen-driven stimulation. Furthermore, highly conserved amino acid sequence motifs were identified in the TCR BV CDR3 region of accumulated BALF T cells. The results indicate that BALF T cells in PM/DM patients with IP recognize a limited epitope on antigens. Based on these findings, we discuss possible pathogenic mechanisms of IP associated with PM/DM.

Materials and methods

Patients and histopathological examination. Two patients with PM and 1 patient with DM were referred to Tsukuba University Hospital. Each patient met the criteria for PM or DM diagnosis, including clinical features, laboratory findings, chest X-ray and chest CT findings, and endoscopic biopsies. We also recruited three healthy subjects who had no respiratory-related complaints and negative chest X-ray films. The clinical characteristics of the 3 patients with PM/DM and healthy subjects are summarized in Table I. Written informed consent was obtained from all patients. A transbronchial lung biopsy was performed, and the tissue was stained with hematoxylin and eosin. No open lung biopsy was performed.

Bronchoalveolar lavage and peripheral blood lymphocytes. BAL was performed on the involved lung segment (right lower lobe and posterior segment) of the 3 patients with IPF and three healthy control subjects. After topical anesthesia, the fiberoptic bronchoscope (Olympus type BF20, Olympus Co., Tokyo, Japan) was advanced into the described segment and wedged, and 50 ml sterile 0.9% saline at 37°C was injected through the bronchoscope. The latter process was performed three times. The volume of BALF recovered from the involved segment was approximately 100 ml. Cells in BALF were passed through sterile gauze to remove debris. BALF from patients was centrifuged at 20 x g and 4°C for 10 min, and washed twice with phosphate-buffered saline (PBS). Following cell count, part of the cell mass was subjected to flow cytometric analysis. A number of cells

($2x10^5$) were stained with monoclonal antibodies (mAbs) against Leu 4 (anti-CD3), Leu 3a (anti-CD4), and Leu 2a (anti-CD8) (Becton Dickinson, Mountain View, CA). After flow cytometry, peripheral blood lymphocytes (PBLs) from patients with IP associated with PM/DM were obtained by Ficoll-Hypaque density gradient centrifugation, and immediately analyzed.

Polymerase chain reaction, Southern blot analysis and single-strand conformation polymorphism. Total RNA from BALF cells was prepared with Isogen (Nippon Gene Co., Tokyo). PCR and cDNA synthesis were performed as described previously by Sumida *et al* (4). Briefly, first-strand cDNA was synthesized from 1 μg total RNA in a 20-μl reaction mixture containing an oligo(dT) primer by avian myeloblastosis virus reverse transcriptase. Amplification was performed with *Taq* polymerase in 50 μl standard buffer, using 0.2 μl cDNA (corresponding to 10 ng total RNA), with primers specific for 25 different TCR BV genes and BC gene. The sequences of the primers were obtained from previously published data (5). Denaturing was performed at 95°C for 1.5 min, annealing at 60°C for 1.0 min, and extension at 72°C for 1.0 min, for 30 cycles in a DNA Thermal Cycler (Perkin-Elmer Corp., Norwork, CT). One-tenth of each amplified PCR product was subjected to 2% agarose gel electrophoresis and transferred to a nylon membrane. Membranes were further hybridized with digoxygenin-labeled TCR BC probe, and visualized using the DIG luminescent detection kit (Boehringer Mannheim, Mannheim, Germany). The digoxygenin-labeled TCR BC probe was synthesized employing the PCR DIG probe synthesis kit (Boehringer Mannheim), with 5'-TCR BC (5'-GAGGATCTGAGAAATGTGACT-3') and 3'-TCR BC (5'-CAAGCACACACGAGGGTAGCCT-3') primers. For individual single-strand conformation polymorphism (SSCP) assays, amplified DNA was diluted (1:20) in a denaturing solution [95% formamide, 10 mM ethylenediaminetetraacetic acid (EDTA), 0.1% bromophenol blue, 0.1% xylene cyanol] at 90°C for 2 min. Diluted samples (2:1) were subjected to electrophoresis in non-denaturing 5% polyacrylamide gels containing 10% glycerol (14). Gels were run at 35 W constant power for 2 h. Following electrophoresis, DNA was transferred to Immobilon-S (Millipore Intertech, Bedford, MA), and hybridized with biotinylated TCR BC probe [5'-A (AC) AA (GC) GTGTTCCCACCCGAGGTCGCTGTGTT-3'], streptavidin, biotinylated alkaline phosphatase, and a chemiluminescent substrate system (Plex™ Luminescence kit, Millipore).

Sequencing of cDNA encoding TCR BV genes. Complementary DNA, encoding TCR BV genes from BALF and PBLs, was purified from polyacrylamide gels for SSCP, and amplified by PCR using the primers described above. PCR products were ligated to plasmids using the TA cloning kit (Invitrogen, San Diego, CA, USA), transformed into competent INVαF' *Escherichia coli* cells, and grown under appropriate conditions. After selection of TCR BC-positive colonies, plasmid DNA was purified by alkaline lysis for DNA sequencing. Sequencing reactions were performed using an automated DNA sequencer (model 377A, Applied Biosystems, Foster City, CA).

Results

Heterogeneous TCR BV repertoire of BALF T cells in patients with IP associated with PM/DM. The mean number of lymphocytes was significantly higher in BALF of PM/DM with IP patients (5,300,000/ml) compared with the control (6,200/ml). The majority of expanded lymphocytes were $CD8^+$ T cells, because CD4/CD8 ratio was decreased in PM/DM + IP to 0.43 from 2.5 in the control. To analyze the pathogenesis of IP associated with PM/DM, we examined the TCR repertoire of BALF T cells from the three patients (DM-1, PM-1, and PM-2) using the family PCR method. PBLs from identical patients were used as a control. Table I lists the clinical profiles of PM/DM patients with IP. Chest CT revealed diffuse reticulonodular opacities, honey combing and ground-glass attenuation. Histopathological examination of lung biopsies from these patients showed a large number of mononuclear cells in the inflamed alveolar septa. The pathological changes in the interstitial septa, alveolar spaces, bronchial mucosa, and pleura were similar to those in the lungs of usual interstitial pneumonia (UIP). No infectious agents or parasites were observed, and there was no evidence of vasculitis. TCR analysis showed expression of the majority of TCR BV family genes in both BALF T cells and PBL in all patients (data not shown). These results suggest that the TCR BV repertoire of T cells in the lung is heterogeneous and that there is no restricted predominant usage of TCR BV genes.

Lung-specific T cell clones in patients with IP associated with PM/DM. TCR BV genes in BALF and peripheral T cells were examined by PCR-SSCP in order to investigate the clonality of pulmonary T cells in patients with IP associated with PM/DM. Fig. 1 depicts lung-specific bands that were found in several TCR BV genes of the three IP patients with PM/DM. These bands were detected in TCR BV2, 3, 4, 5, 6, 8, 9, 10, 11, 12, 13, 16, 17, 19, 20, 23, 24, and 25 genes. The number of bands encoding TCR BV genes in the lung is summarized in Table II. We observed a significant increase in the number of expanded clones in BALF of three IP patients (27, 23 and 21 clones), compared with three healthy subjects (6, 9 and 8 clones) ($p<0.05$). These results indicate accumulation of some T cells in the lungs of PM/DM patients with IP, suggesting that these cells proliferate by antigen stimulation.

Conserved amino acid sequence motifs in the CDR3 region of TCR BV genes from BALF-specific T cells of IP associated with PM/DM. To examine the amino acid sequences of the CDR3 region in the TCR BV gene, we focused on the lung-specific T cell clones by SSCP analysis. DNAs encoding the TCR BV genes from BALF-specific bands were eluted from gels, followed by sequencing the corresponding CDR3 regions. As shown in Table III, the CDR3 region of the lung-specific accumulated T cell clones contained conserved amino acid motifs. In DM-1 patient, RGS, GLA, LQG, SGG, DRG, and GTS motifs were found in BV2-1, BV19-2 and BV20-3, BV5-1 and BV10-1, BV9-2 and BV13-3, BV10-2 and BV24-2, BV13-2 and BV20-3, and BV9-3 and BV24-2 clones, respectively. In PM-1 patient, TSGR, GGS, GQA, GAG motifs were found in BV4-2 and BV12-1, BV8-2 and

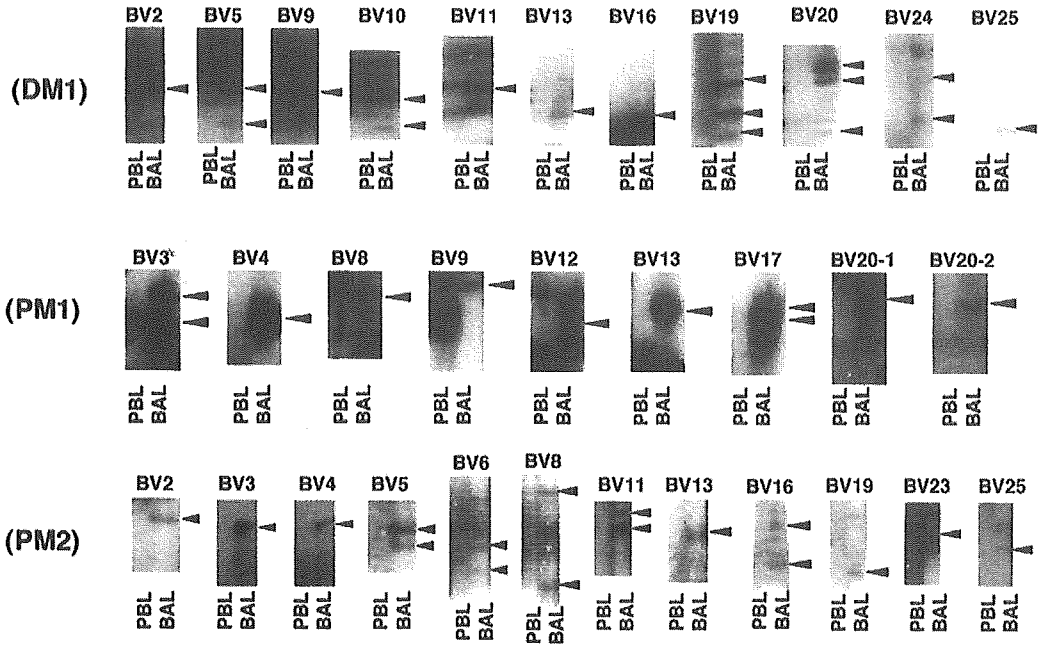

Figure 1. BALF-specific T cell clones. SSCP on TCR BV1-25 genes were carried out using cDNA from BALF and PBL of PM/DM patients and healthy subjects. Arrowheads show BALF-specific T cell clones.

Table II. Accumulated T cell clones in BALF of patients with PM/DM + IP.

TCR BV gene	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	Total
DM-1	0	1	0	0	2	0	0	0	3	5	1	0	3	0	0	3	0	0	3	3	0	0	0	2	1	27
PM-1	0	0	4	2	0	0	0	2	2	0	0	3	2	0	0	0	4	0	0	4	0	0	0	0	0	23
PM-2	0	1	1	1	2	2	0	3	0	0	2	0	3	0	0	2	0	0	1	0	0	0	2	0	1	21
HS-1	1	2	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	2	-	-	-	-	-	6
HS-2	0	0	0	0	0	1	0	1	0	0	1	0	0	1	1	0	0	1	0	0	0	0	0	1	2	9
HS-3	0	0	1	0	0	0	1	0	0	1	0	0	0	1	0	0	0	1	0	1	1	0	0	1	0	8

Numbers represent T cell clones accumulated in BAL of patients with PM/DM + IP. The distinct bands encoding TCR BV genes on SSCP were described as the number of BAL-specific T cell clones. -, not done.

BV20-1, BV9-2 and BV20-3, and BV12-3 and BV17-1 clones, respectively. In PM-2 patient, GTG motif was found in BV8-2 and BV16-2 clones, respectively (Table III). In contrast, BALF-specific bands of the healthy subjects did not reveal any conserved amino acid motifs in the CDR3 region (Table IV). The conserved amino acid motifs in the CDR3 region of TCR are summarized in Table V. These findings suggest that accumulated T cells in the lungs of patients with IP associated with PM/DM recognize a limited epitope on antigens.

Discussion

Recent studies on TCR of PBL and T cells infiltrating into muscles showed clonal expansion of $CD8^+$ T cells in peripheral blood and muscles, although the TCR repertoire was heterogeneous (15-21). In contrast, there are no studies on TCR of BALF T cells of PM/DM patients with IP. In the present study, we analyzed the TCR repertoire and sequences of TCR CDR3 regions and determined that the TCR BV repertoire was not skewed, but there were conserved amino acids in the CDR3 region in BALF T cells of PM and DM patients. We speculate that some T cells recognize the antigen in the context of HLA molecule and trigger autoimmune reaction. These results are similar to those reported in patients with IPF (13) but not those with sarcoidosis and atopic asthma (9-11).

The conserved amino acid sequences in the CDR3 region of BALF T cells of patient DM1 are RGS motif in TCR BV2-1, BV19-2 and BV20-3, GLA motif in TCR BV5-1 and BV10-1, LQG motif in TCR 9-2 and BV13-3, SGG motif in TCR BV10-2 and BV24-2, DRG motif in TCR BV13-2 and

Table III. Conserved amino acid motifs in the CDR3 region of BALF-specific T cells of patients with PM/DM.

A, DM-1

	V				N-D-N								J			
clone	92							96							106	
BV2-1	C	S	A			H	P	R	G	S	P	P	G	G	Y	BJ1S2
BV5-1	C	A	S	S			L	G	L	A	F			Q		BJ2S1
BV5-2	C	A	S	S		S	T	V	S					E	Q	BJ2S7
BV9-1	C	A	S	S			Q	P	S	E	V	E		T	Q	BJ2S3
BV9-2	C	A	S	S			R	K	L	Q	G		T	G	E	L	BJ2S2
BV9-3	C	A	S	S			G	T	S	I	S			G	Y	BJ1S2
BV10-1	C	A			C	T	G	L	A	K	G		Y	N	E	Q	BJ2S1
BV10-2	C	A	S			P	R	L	S	G	G			T	Q	BJ2S3
BV10-3	C	A	S			G	D						N	Q	P	Q	BJ1S5
BV10-4	C	A	S	S			K	S	T	G	R	P	T		Q	BJ2S7
BV10-5	C	A	G	S			D	P	G	T	G			E	Q	BJ2S1
BV11-1	C	A	S			V	N	T	R	T	F			E	A	BJ1S1
BV13-1	C	A	S	S		Y	S	Q					N	Q	P	Q	BJ1S5
BV13-2	C	A	S			D	D	R	G					D	T	Q	BJ2S3
BV13-3	C	A	S	S			L	P	L	Q	G			E	K	L	BJ1S4
BV16-1	C	A	S	S			Y	T	D	G	V	E		T	Q	BJ2S3
BV16-2	C	A	S			P	H	I	M	G	A	R	R		Q	BJ2S3
BV16-3	C	A	S	S			R	S	G	S	F		S	Y	E	Q	BJ2S7
BV19-1	C	A	S	S			L	R	R	E				Q	P	Q	BJ1S5
BV19-2	C	A	S			R	N	R	G				S	Y	E	Q	BJ2S7
BV19-3	C	A	S	S			Q	S	R	G	K	R			E	Q	BJ2S1
BV20-1	C	A	W	S			R	G	Q				N	E	K	L	BJ1S4
BV20-2	C	A	W			R	G	H	R	T	R	I			Q		BJ2S1
BV20-3	C	A	W			K	G	D	R	G	S	D			Q		BJ2S3
BV24-1	C	A	T	S			S	F	G	G				E	T	Q	BJ2S5
BV24-2	C	A	T	S			S	D	S	G	G	T	S		T	Q	BJ2S5
BV25-1	C	A	S			S	P	G	Q	P	T			Y	E	Q	BJ2S7

B, PM-1

	V				N-D-N								J			
clone	92							96							106	
BV3-1	C	A	S	S			A	P	R	D	T	E	A	F	F	BJ1S1
BV3-2	C	A	S	S			P	P	G	L	R	E		P	Q	BJ1S5
BV3-3	C	A	S	S		L	G	Y	L				T	G	E	L	BJ2S2
BV3-4	C	A	S	S			P	Q	K	M	G	T	G	Q	P	Q	BJ2S1
BV4-1	C	S	A				A	S	R	G			N	T	E	A	BJ1S1
BV4-2	C	S	V				A	G	T	S	G	R	S	S	Y	E	Q	BJ2S1
BV8-1	C	A	S	S			L	R	G				S	Y	N	E	Q	BJ2S1
BV8-2	C	A			N	P	F	R	G	G	S				E	Q	BJ2S1
BV9-1	C	A	S	S			A	G	L					S	Y	E	Q	BJ2S7