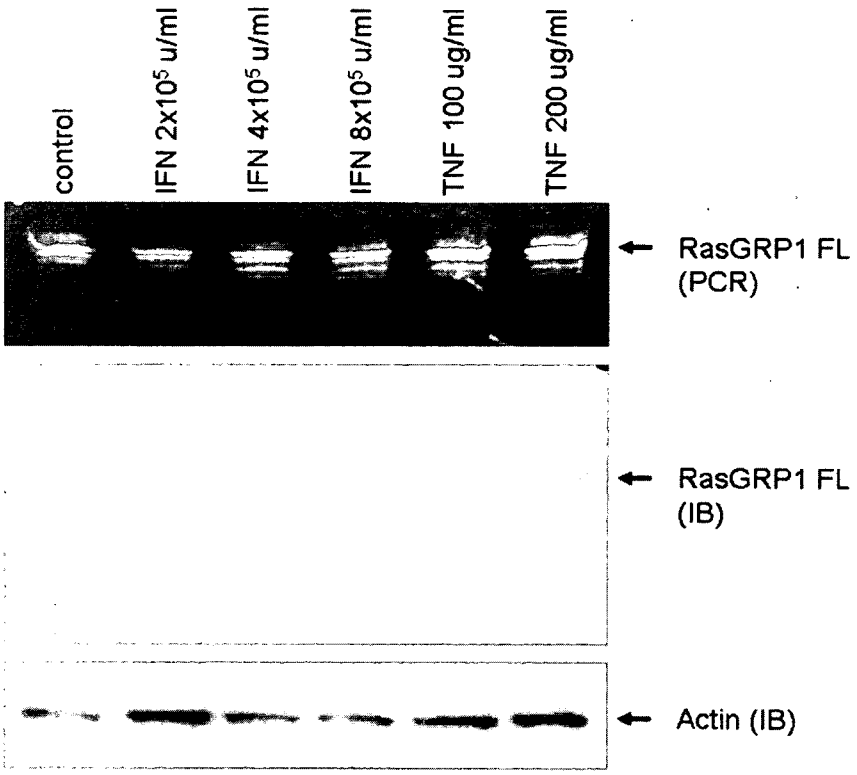
図. 3;Jurkat 細胞を用いたサイトカイン刺激後のRasGRP1 発現検討



IV　研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表(平成19年度)

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三森経世	1.膠原病	山本 一彦:編集 ステロイド薬の選び方・使い方ハンドブック	羊土社 東京	2007 54-82
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桑名正隆	全身性硬化症(強皮症)(内科)	山口徹、北原光夫、福井次矢 今日の治療指針 2009年版ー私はこう治療している	医学書院 東京	印刷中
桑名正隆	全身性強皮症と呼吸器症状・心症状	竹原和彦、尹浩信、佐藤伸一、五十嵐敦之、桑名正隆、遠藤平仁、川口鎮司、相馬良直、久保正英、藤本学、長谷川稔 強皮症のすべて	保健同人社 東京	印刷中
桑名正隆	全身性強皮症	池田宇一、大越教夫、横田千津子 病気と薬パーフェクトガイド2008	南山堂 東京	印刷中
桑名正隆	成人スティル病	池田宇一、大越教夫、横田千津子 病気と薬パーフェクトガイド2008	南山堂 東京	印刷中

桑名正隆	リウマチ性多発筋痛症	池田宇一、大越教夫、横田千津子	南山堂	印刷中
		病気と薬パーフェクトガイド2008	東京	
桑名正隆	アレルギー性肉芽腫性血管炎	池田宇一、大越教夫、横田千津子	南山堂	印刷中
		病気と薬パーフェクトガイド2008	東京	
桑名正隆	ウェゲナー肉芽腫症	池田宇一、大越教夫、横田千津子	南山堂	印刷中
		病気と薬パーフェクトガイド2008	東京	
桑名正隆	大動脈炎症候群	池田宇一、大越教夫、横田千津子	南山堂	印刷中
		病気と薬パーフェクトガイド2008	東京	
桑名正隆	レイノー症候群	池田宇一、大越教夫、横田千津子	南山堂	印刷中
		病気と薬パーフェクトガイド2008	東京	
桑名正隆	リウマチ性多発性筋痛症；全身のこわばりと筋痛で受診した82歳女性	鈴木則宏	日本医事新報社	印刷中
		New専門医を目指すCASE METHOD APPROACH 神経疾患第1版	東京	
桑名正隆	ベーチェット病(Behçet's Disease)(内科)	山口徹、北原光夫、福井次矢	医学書院	2008
		今日の治療指針 2008年版-私はこう治療している	東京	632-633
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		EBM血液疾患の治療2008-2009	東京	492-495
松本 功	解糖系酵素と自己免疫疾患	奥村 康、平野俊夫、佐藤昇志	中外医学社	in press
		Annual review 免疫	東京	
Sumida T, Wakamatsu E, Nakamura Y, Matsumoto I.	Autoantibodies against muscarinic acetylcholine receptor in patients with Sjogren's syndrome.(review)	Y.Shoenfeld, M.E.Gershwin, P.L.Meroni	ELSEVIER	2007
		In Textbook of autoantibodies Second edition		681-686

Ⅴ　平成19年度班会議プログラム

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

免疫応答の人為的制御をめざしたヒト ES 細胞からの樹状細胞の分化誘導法の開発

熊本大学大学院医学薬学研究部免疫識別学分野

千住　覚

3．　13：55～14：15

自己抗原に関連するＴ細胞応答のシングルセル解析を用いた研究

東京大学医学部アレルギーリウマチ内科

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

実験的自己免疫性脳脊髄炎における腸内フローラの役割に関する研究

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

コラーゲン誘導関節炎におけるTREM-1の役割に関する研究

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

免疫性血小板減少性紫斑病におけるHelicobacter pylori除菌効果発現機序に関する研究

慶應義塾大学内科

桑名　正隆

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

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

16：30～16：40　　閉会の辞

VI　研究成果刊行物・別刷

ARTHRITIS & RHEUMATISM
Vol. 58, No. •, Month 2008, pp 000–000
DOI 10.1002/art.•

Crucial Role of the Interleukin-6/Interleukin-17 Cytokine Axis in the Induction of Arthritis by Glucose-6-Phosphate Isomerase

Keiichi Iwanami,[1] Isao Matsumoto,[2] Yoko Tanaka-Watanabe,[1] Asuka Inoue,[1] Masahiko Mihara,[3] Yoshiyuki Ohsugi,[4] Mizuko Mamura,[1] Daisuke Goto,[1] Satoshi Ito,[1] Akito Tsutsumi,[1] Tadamitsu Kishimoto,[5] and Takayuki Sumida[1]

Objective. **To clarify the glucose-6-phosphate isomerase (GPI)–specific CD4+ T cell lineage involved in GPI-induced arthritis and to investigate their pathologic and regulatory roles in the induction of the disease.**

Methods. **DBA/1 mice were immunized with GPI to induce arthritis. CD4+ T cells and antigen-presenting cells were cocultured with GPI, and cytokines in the supernatant were analyzed by enzyme-linked immunosorbent assay. Anti–interferon-γ (anti-IFNγ) monoclonal antibody (mAb), anti–interleukin-17 (anti–IL-17) mAb, or the murine IL-6 receptor (IL-6R) mAb MR16-1 was injected at different time points, and arthritis development was monitored visually. After mAb MR16-1 was injected, percentages of Th1, Th2, Th17, and Treg cells were analyzed by flow cytometry and CD4+ T cell proliferation was analyzed using carboxyfluorescein diacetate succinimidyl ester.**

Results. **GPI-specific CD4+ T cells were differentiated to Th1 and Th17 cells, but not Th2 cells. Administration of anti–IL-17 mAb on day 7 significantly ameliorated arthritis ($P < 0.01$), whereas administration of anti-IFNγ mAb exacerbated arthritis. Neither anti–IL-17 mAb nor anti-IFNγ mAb administration on day 14 ameliorated arthritis. MR16-1 administration on day 0 or day 3 protected against arthritis induction, and MR16-1 administration on day 8 significantly ameliorated existing arthritis ($P < 0.05$). After administration of MR16-1, there was marked suppression of Th17 differentiation, without an increase in Th1, Th2, or Treg cells, and CD4+ T cell proliferation was also suppressed.**

Conclusion. **IL-6 and Th17 play an essential role in GPI-induced arthritis. Since it has previously been shown that treatment with a humanized anti–IL-6R mAb has excellent effects in patients with rheumatoid arthritis (RA), we propose that the IL-6/IL-17 axis might also be involved in the generation of RA, especially in the early effector phase.**

Rheumatoid arthritis (RA) is characterized by symmetric polyarthritis and joint destruction. Although the etiology of RA is considered to be an autoimmune reactivity to antigens that are specifically expressed in joints, this remains a controversial hypothesis. It has been reported that autoimmune reactivity to a ubiquitous cytoplasmic enzyme, glucose-6-phosphate isomerase (GPI), provokes joint-specific inflammation in K/BxN mice (1,2). This finding highlights the potential role of systemic autoreactivity to certain ubiquitous autoantigens in the pathogenesis of RA.

More recently, it was reported that arthritis can also be induced in DBA/1 mice by immunization with GPI (3). GPI-induced arthritis is different from collagen-induced arthritis (CIA) with regard to the priority of T cells and B cells. In CIA, treatment with anti-CD4 monoclonal antibodies (mAb) is ineffective after the mice have produced antibodies to type II collagen (4,5), and CD4-deficient mice can develop CIA

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at the same incidence and severity as untreated mice (6). Adoptive transfer of IgG antibodies purified from mice with CIA can induce arthritis even in strains that are not susceptible to CIA induction by conventional immunization. In GPI-induced arthritis, administration of anti-CD4 mAb rapidly ameliorates arthritis after its onset, despite the absence of changes in the anti-GPI antibody titers. Fcγ receptor–deficient mice are resistant to GPI-induced arthritis, and adoptive transfer of purified IgG antibodies alone is not able to induce arthritis in these mice (3). These findings indicate that although autoantibodies are necessary for GPI-induced arthritis, CD4+ T cells are indispensable even after antibody production.

The present study was designed to further characterize the importance of CD4+ T cells in GPI-induced arthritis. Specifically, we investigated the CD4+ T cell lineage involved in GPI-induced arthritis and the regulatory mechanisms of pathogenic T cells. The results demonstrated that GPI-specific CD4+ T cells shifted to Th1 and Th17 cells and that Th17 played a crucial role in the development of GPI-induced arthritis. We also found that blockade of interleukin-6 receptor (IL-6R) significantly suppressed the arthritis and inhibited Th17 differentiation. The main message of this study is that the IL-6/IL-17 axis may be essential for the development of T cell–dependent autoimmune arthritis.

MATERIALS AND METHODS

Mice. Male DBA/1 mice were purchased from Charles River Laboratories (Yokohama, Japan). All mice were maintained under specific pathogen–free conditions, and all experiments were conducted in accordance with the institutional ethics guidelines.

GPI-induced arthritis. Recombinant human GPI was prepared as described previously (7). Briefly, human GPI complementary DNA was inserted into plasmid pGEX-4T3 (Pharmacia, Uppsala, Sweden) for expression of glutathione S-transferase–tagged proteins. The *Escherichia coli*–harboring pGEX-hGPI plasmid was allowed to proliferate at 37°C before the addition of 0.1 m*M* IPTG to the medium, which was followed by a further culture overnight at 30°C. The bacteria were lysed with a sonicator, and the supernatant was purified with a glutathione–Sepharose column (Pharmacia). The purity was estimated by sodium dodecyl sulfate–polyacrylamide gel electrophoresis.

Mice were immunized intradermally with 300 μg of recombinant human GPI in Freund's complete adjuvant (Difco, Detroit, MI). Recombinant human GPI and Freund's complete adjuvant were emulsified at a 1:1 ratio (volume/volume). For induction of arthritis, 150 μl of the emulsion was injected intradermally into the base of the tail. For intracellular staining and cell proliferation assay, 50 μl was injected into each footpad of the hind paw. Arthritis was evaluated visually, and changes in each paw were scored on a scale of 0–3, where 0 = no evidence of inflammation, 1 = subtle inflammation or localized edema, 2 = easily identified swelling that was localized to either the dorsal or ventral surface of the paw, and 3 = swelling of all aspects of the paw.

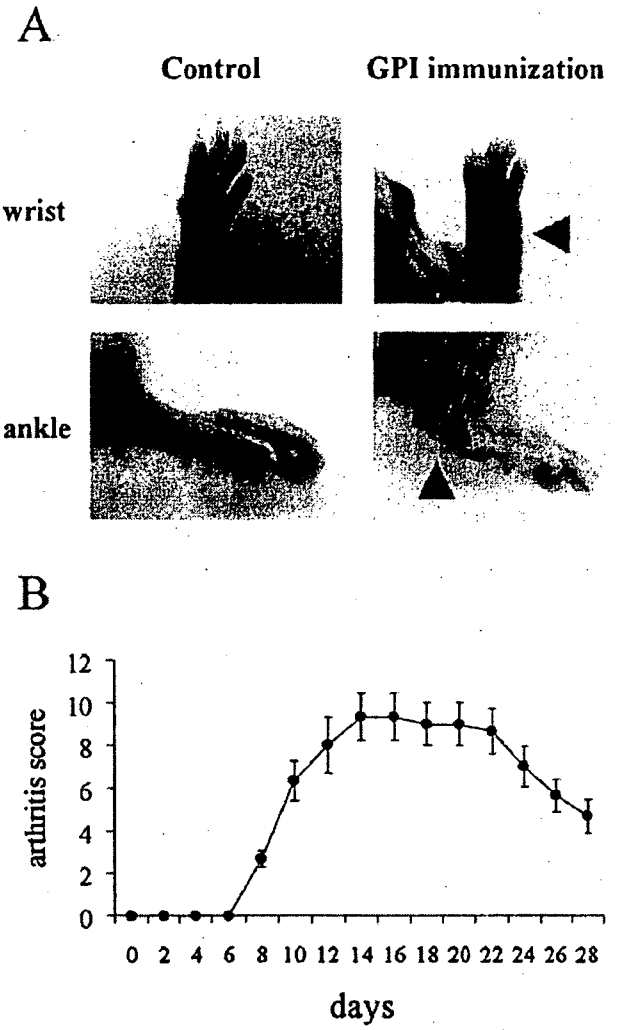

Figure 1. Induction of severe polyarthritis by immunization with recombinant human glucose-6-phosphate isomerase (GPI). DBA/1 mice were immunized with 300 μg of recombinant human GPI, and the development of arthritis was monitored visually and scored on a scale of 0–3 (see Materials and Methods for details). Arthritis was clinically apparent beginning on days 7–8, peaked in severity on day 14, and then gradually subsided. A, Severe swelling of the wrist and ankle joints (**arrowheads**) in mice immunized with GPI as compared with control mice. B, Mean ± SEM arthritis scores on days 0–28 in 10 mice from a representative experiment.

Analysis of cytokine profiles. Mice were killed on day 7 or day 14. Spleens were harvested and hemolyzed with a solution of 0.83% NH_4Cl, 0.12% $NaHCO_3$, and 0.004% disodium EDTA in phosphate buffered saline (PBS). Single-cell suspensions were prepared in RPMI 1640 medium (Sigma-Aldrich, St. Louis, MO) containing 10% fetal bovine serum

(FBS), 100 units/ml of penicillin, 100 μg/ml of streptomycin, and 50 μ*M* 2-mercaptoethanol. CD4+ T cells were isolated by magnetic-activated cell sorting (Miltenyi Biotec, Bergisch Gladbach, Germany). The purity (>97%) was confirmed by flow cytometry. Splenic feeder cells treated with 50 μg/ml of mitomycin C were used as antigen-presenting cells (APCs). Purified CD4+ T cells and APCs were cocultured with 5 μg/ml of GPI at a ratio of 5:1 for 24 hours at 37°C in an atmosphere containing 5% CO_2. The supernatants were assayed for interferon-γ (IFNγ), IL-4, and IL-17 by enzyme-linked immunosorbent assay (ELISA) using a Quantikine ELISA kit (R&D Systems, Minneapolis, MN).

Treatment of arthritis with antibodies. To neutralize IL-17 and IFNγ, mice were injected intraperitoneally with 100 μg of neutralizing antibody or isotype control on day 7 or day 14. Anti–IL-17 mAb MAB421 (IgG2a) and anti-IFNγ mAb MAB485 (IgG2a) were purchased from R&D Systems. IgG2a isotype control was purchased from eBioscience (San Diego, CA). For IL-6 neutralization, mice were injected intraperitoneally with 2 mg or 4 mg of MR16-1 (an IgG1-specific mAb against murine IL-6R) or control IgG (purified from the serum of nonimmunized rats) on day 0, 3, 8, or 14. MR16-1 was a gift from Chugai Pharmaceutical (Tokyo, Japan), and control IgG was purchased from Jackson ImmunoResearch (West Grove, PA).

Anti-GPI antibody analysis. Sera were obtained on day 28 or day 35 and diluted 1:500 in blocking solution (25% Block-Ace [Dainippon Sumitomo Pharma, Osaka, Japan] in PBS) for analysis of antibody. Then, 96-well plates (Sumitomo Bakelite, Tokyo, Japan) were coated with 5 μg/ml of recombinant human GPI for 12 hours at 4°C. After washing twice with washing buffer (0.05% Tween 20 in PBS), the blocking solution was applied for 2 hours at room temperature to block nonspecific binding. After 2 washes, 150 μl of diluted sera was added, and the plates were incubated for 2 hours at room temperature. After 3 washes, alkaline phosphatase (AP)–conjugated anti-mouse IgG was added at a final dilution of 1:5,000 for 1 hour at room temperature. After 3 washes, color was developed with substrate solution, consisting of 1 tablet of AP tablet (Sigma-Aldrich) per 5 ml of AP reaction solution (9.6% diethanolamine and 0.25 m*M* $MgCl_2$, pH 9.8). Plates were incubated for 20 minutes at room temperature, and the optical density was read at 405 nm using a microplate reader.

Intracellular cytokine staining and flow cytometric analysis. Mice were killed on day 7. Popliteal lymph nodes were harvested, and single-cell suspensions were prepared as described above. Cells (1×10^6/ml) were stimulated with 100 μg/ml of recombinant human GPI in 96-well round-bottomed plates (Nunc, Roskilde, Denmark) for 24 hours. GoldiStop (BD PharMingen, San Diego, CA) was added during the last 2 hours of each culture. Cells were stained extracellularly, fixed, and permeabilized with Cytofix/Cytoperm solution (BD PharMingen), then the cells were stained intracellularly. A mouse regulatory T cell staining kit (eBioscience) was used to stain Treg cells according to the protocol supplied by the manufacturer. Samples were analyzed with a FACSCalibur flow cytometer (Becton Dickinson, Mountain View, CA), and data were analyzed with FlowJo software (Tree Star, Ashland, OR). AQ: 6

Cell proliferation assay. Mice were killed on day 10. Popliteal lymph nodes were harvested, and single-cell suspensions were prepared as described above. Cells (2×10^7/ml) in PBS were stained with 1.25 μ*M* carboxyfluorescein diacetate succinimidyl ester (CFSE-DA; Molecular Probes, Eugene, OR) for 8 minutes. Stained cells were cultured with 25 μg/ml of recombinant human GPI at 1×10^6/ml in 96-well round-bottomed plates (Nunc) for 60 hours and then analyzed by flow cytometry.

Statistical analysis. Data are expressed as the mean ± SEM or mean ± SD. Differences between groups were examined for statistical significance using the Mann-Whitney U test. *P* values less than 0.05 were considered significant.

RESULTS

Induction of severe symmetric polyarthritis by immunization with GPI. For the induction of arthritis, we immunized DBA/1 mice with 300 μg of recombinant human GPI emulsified with Freund's complete adjuvant. Of the 177 mice immunized with recombinant human GPI, 167 (94.4%) developed severe swelling of the wrist and ankle joints (Figure 1A). The arthritis appeared on days 7–8, showed peak severity on day 14, then gradually subsided (Figure 1B). AQ: 7 F1

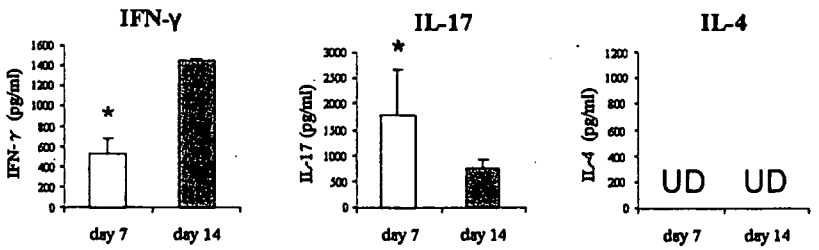

Figure 2. Differentiation of glucose-6-phosphate isomerase (GPI)–specific CD4+ T cells into Th1 and Th17 cells. CD4+ T cells and mitomycin C–treated antigen-presenting cells were stimulated for 24 hours with GPI on either day 7 (induction phase) or day 14 (effector phase) and then assessed for the production of interferon-γ (IFNγ), interleukin-17 (IL-17), and IL-4 by enzyme-linked immunosorbent assay. Values are the mean and SD of 3 independent experiments (n = 3 mice per experiment). * = $P < 0.05$ versus cells stimulated on day 14, by Mann-Whitney U test. UD = undetectable (<2 pg/ml).

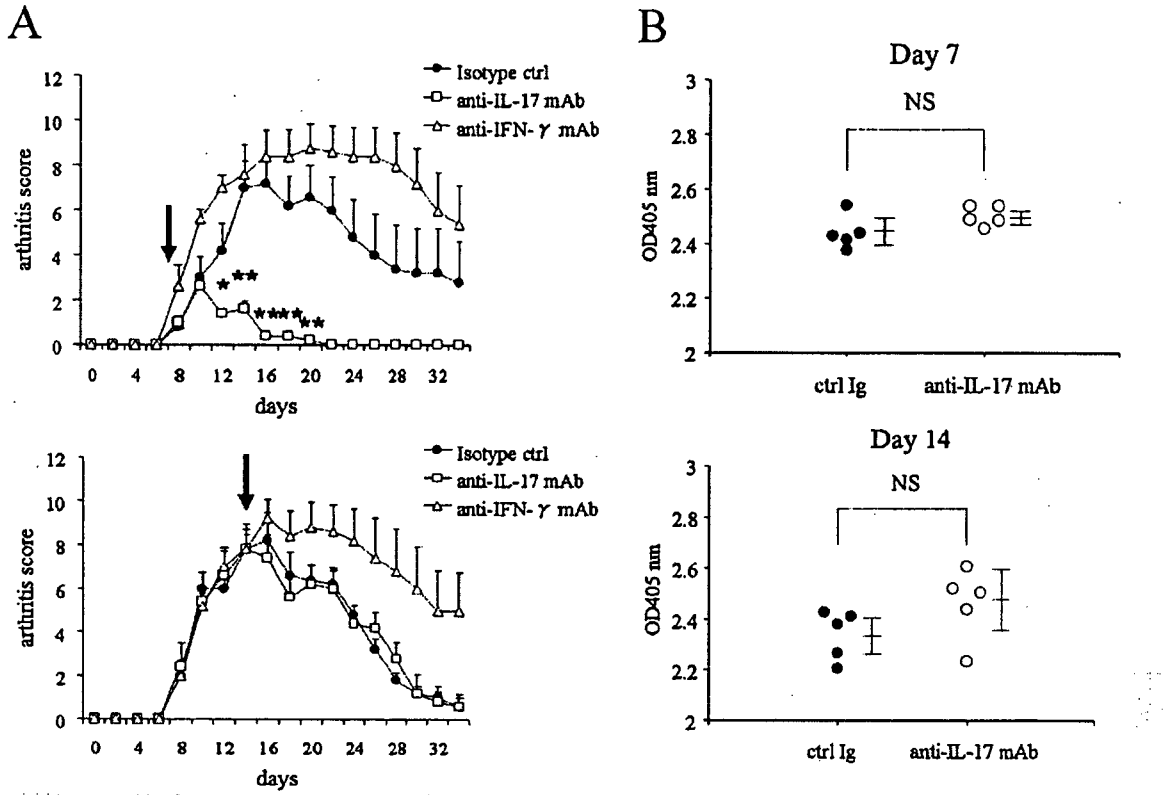

Figure 3. Suppression of the development of glucose-6-phosphate isomerase (GPI)–induced arthritis by treatment with by anti–interleukin-17 (anti–IL-17) monoclonal antibody (mAb). A, Arthritis scores following intraperitoneal injection of 100 μg of anti–IL-17 mAb or anti–interferon-γ (anti-IFNγ) mAb on day 7 or day 14 after GPI immunization (arrow). Values are the mean and SEM of 5 mice per group. Results are representative of 2 independent experiments. * = $P < 0.05$; ** = $P < 0.01$ versus isotype control at the same time point, by Mann-Whitney U test. B, Titers of anti-GPI antibody in sera obtained on day 35 following intraperitoneal injection of 100 μg of anti–IL-17 mAb on day 7 or day 14 after GPI immunization, as determined by enzyme-linked immunosorbent assay. Each symbol represents a single mouse. Bars show the mean ± SD optical density (OD) at 405 nm. NS = not significant (by Mann-Whitney U test).

Differentiation of GPI-specific CD4+ effector T cells to Th1 and Th17 cells, but not Th2 cells. CD4+ T cells are indispensable for both the induction phase and the effector phase of GPI-induced arthritis (3); however, the lineage to which GPI-specific CD4+ effector T cells are differentiated remains to be elucidated. To determine the lineage, we stimulated CD4+ T cells withrecombinant human GPI on day 7 (induction phase) or day 14 (effector phase) in vitro and then assessed cytokine production by ELISA. GPI-specific CD4+ T cells produced IFNγ and IL-17, but not IL-4, on days 7 and 14 (Figure 2). Interestingly, IFNγ production was lower on day 7 than on day 14 ($P < 0.05$), whereas IL-17 production was higher on day 7 than on day 14 ($P < 0.05$). These data demonstrated that GPI-specific CD4+ effector T cells are differentiated to Th1 and Th17 and are regulated differently during the development of arthritis.

Crucial role of Th17 cells in the induction phase. If GPI-specific CD4+ T cells produce both IFNγ and IL-17, then which of these two cytokines affects the development of arthritis? To answer this question, we injected 100 μg of anti-IFNγ mAb or anti–IL-17 mAb intraperitoneally on day 7 or day 14 after immunization with recombinant human GPI. Injection of anti–IL-17 mAb on day 7 resulted in significant improvement in the arthritis scores as compared with injection of isotype control ($P < 0.05$ or $P < 0.01$), but injection of anti–IL-17 mAb on day 14 did not affect the course of the disease (Figure 3A). In contrast, injection of anti-IFNγ mAb on day 7 and day 14 did not ameliorate arthritis, but rather, tended to exacerbate it (Figure 3A).