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PHARMACOTHERAPY



## Dupilumab as an adjunct treatment for a patient with steroid-dependent immunoglobulin G4-related disease complicated by asthma: a case report

Toshihito Otani, MD<sup>a</sup>, Hiroshi Iwamoto, MD, PhD<sup>a</sup> , Yusuke Yoshida, MD, PhD<sup>b</sup> , Kakuhiro Yamaguchi, MD, PhD<sup>a</sup>, Shinjiro Sakamoto, MD, PhD<sup>a</sup>, Yasushi Horimasu, MD, PhD<sup>a</sup>, Takeshi Masuda, MD, PhD<sup>a</sup>, Shintaro Miyamoto, MD, PhD<sup>a</sup>, Taku Nakashima, MD, PhD<sup>a</sup>, Kazunori Fujitaka, MD, PhD<sup>a</sup>, Hironobu Hamada, MD, PhD<sup>c</sup>, Shintaro Hirata, MD, PhD<sup>b</sup> , Eiji Sugiyama, MD, PhD<sup>d</sup>  and Noboru Hattori, MD, PhD<sup>a</sup>

<sup>a</sup>Department of Molecular and Internal Medicine, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan; <sup>b</sup>Department of Clinical Immunology and Rheumatology, Hiroshima University Hospital, Hiroshima, Japan; <sup>c</sup>Department of Physical Analysis and Therapeutic Sciences, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan; <sup>d</sup>Department of Internal Medicine, Yoshida General Hospital, Akitakata, Japan

### ABSTRACT

**Introduction:** Immunoglobulin G4-related disease (IgG4-RD) responds well to glucocorticoids but is often associated with relapses. Interleukin (IL)-4 and IL-13 are involved in the pathogenesis of IgG4-RD. We present the first case in which dupilumab was an effective adjunct treatment for a patient with steroid-dependent IgG4-RD complicated by asthma.

**Case study:** A 57-year-old man was referred to our hospital for further investigation and treatment of proptosis with neck swelling in 2019. He developed a cough and swelling of the neck in 2016. He was diagnosed with asthma in 2017 and started receiving inhaled glucocorticoids and a long-acting beta-agonist. The patient started receiving oral prednisolone at a dose of 20 mg/day. Oral prednisolone reduced his symptoms, but he relapsed when treatment was tapered to less than 10 mg/day. He was diagnosed with IgG4-RD through a parotid gland biopsy.

**Results:** Azathioprine was given to reduce systemic glucocorticoids. The prednisolone dose was gradually tapered to 10 mg/day, resulting in the relapse of proptosis and an asthma attack. We added dupilumab, and his asthma symptoms and proptosis improved. Serum IgG4 levels continued to decrease, and the prednisolone dose was tapered to 2 mg.

**Conclusion:** Dupilumab might be useful as an adjunctive treatment for patients with steroid-dependent IgG4-RD complicated by asthma. Serum IgG4 levels can be used as a marker to monitor dupilumab treatment in IgG4-RD.

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Dupilumab; serum IgG4; prednisolone; steroid-dependent IgG4-RD; asthma

## Introduction

Immunoglobulin G4-related disease (IgG4-RD) is an immune-mediated fibroinflammatory condition characterized by lymphoplasmacytic infiltrations with a predominance of IgG4-positive plasma cells in the affected tissue (1). The response to initial glucocorticoid therapy is generally good, but some patients relapse when they receive a tapered dose. The relapse rate has been reported to be 15–57% (2–11). In addition, higher serum IgG4 concentrations, a history of allergy, and eosinophil elevations are associated with disease relapse (3). Furthermore, 19–31% of patients

with IgG4-RD have histories of allergic disorders, and 11–12% of patients with IgG4-RD have asthma (12,13).

Dupilumab is a fully human monoclonal antibody that binds to the alpha subunit of the IL-4 receptor and inhibits the activities of both interleukin (IL)-4 and IL-13. In IgG4-RD, IL-4 is involved in shifting the IgG subclass to IgG4 and promotes IgG4 production (14). Moreover, IL-13 is involved in fibrosis via fibroblasts, and its expression is increased in IgG4-related diseases (15–18). Therefore, dupilumab might be used to treat IgG4-RD, but its effects in patients with IgG4-RD have not been clearly described (19–22). We present the first case of the steroid-sparing

effect of dupilumab for a patient with steroid-dependent IgG4-RD complicated by asthma.

### Case study

A 57-year-old man was referred to our hospital for further investigation and treatment of proptosis with neck swelling in 2019. He developed a cough and swelling of the neck in 2016. He was diagnosed with asthma in 2017 and started receiving inhaled glucocorticoids and a long-acting beta-agonist. In January 2018, the parotid and lacrimal glands became more swollen. Proptosis and diplopia were noted in the enlarged upper eyelid, and the serum IgG4 level was elevated. The patient started receiving oral prednisolone at a dose of 20 mg/day. Oral prednisolone reduced his symptoms, but they relapsed when it was tapered to less than 10 mg/day.

His upper eyelid was enlarged ([Figure 1A](#)). Wheezing was noted upon chest auscultation. Laboratory tests revealed high serum IgG4 and IgE levels (270 mg/dL and 715 IU/mL, respectively) and eosinophilia. Spirometry showed that the pre-bronchodilator forced expiratory volume in 1 s (FEV1) was 2.60 L, 67.2% of the predicted value. His fractional exhaled nitric oxide level was elevated at 132 ppb. Magnetic resonance imaging showed swelling of the parotid glands on T2-weighted imaging ([Figure](#)

[2A](#)). Computed tomography and  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography showed airway wall and pleural thickness (maximum standard uptake value, 2.2). ([Figure 3A](#) and B). The biopsy specimen of the parotid gland showed chronic inflammation and fibrosis with increased plasma cell infiltration and IgG4+ plasma cell infiltration. The IgG4+/IgG+ cell ratio was approximately 66%, and there were 103 IgG4+ plasma cells per high-power field ([Figure 4](#)). Based on the comprehensive diagnostic criteria for IgG4-RD, the patient was definitively diagnosed with IgG4-RD ([Table 1](#)) (23).

### Results

After confirming the IgG4-RD diagnosis, azathioprine (50 mg/day) was administered to reduce systemic glucocorticoids. However, azathioprine induced liver injury, and thus, its dosage was reduced to 25 mg/day. The prednisolone dose was gradually tapered to 10 mg/day; however, this resulted in proptosis relapse and an asthma attack. At this time, dupilumab was initiated to treat severe asthma with a loading dose of 600 mg, followed by subcutaneous injection of 300 mg every 2 weeks. As a result, asthma symptoms, proptosis, and swelling of the eyelid and parotid glands improved ([Figures 1B](#) and [2B](#)). The serum IgG4 levels continued to decrease, and the

(A)



(B)



**Figure 1.** Upper eyelid before (A) and after (B) dupilumab treatment. Proptosis and eyelid swelling was improved.

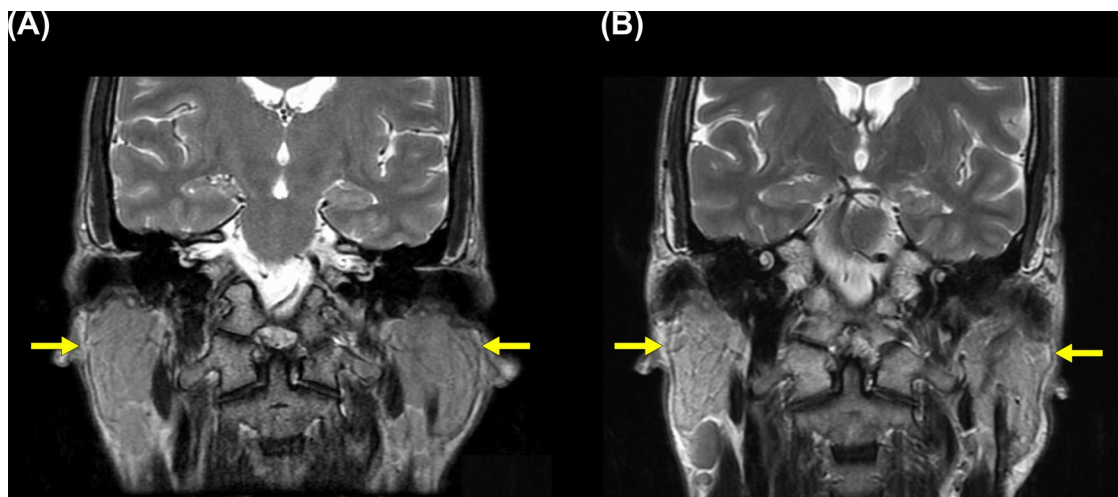


**Figure 2.** Magnetic resonance imaging on T2-weighted imaging before (A) and after (B) dupilumab treatment. Swelling of the parotid glands (arrow) was improved.

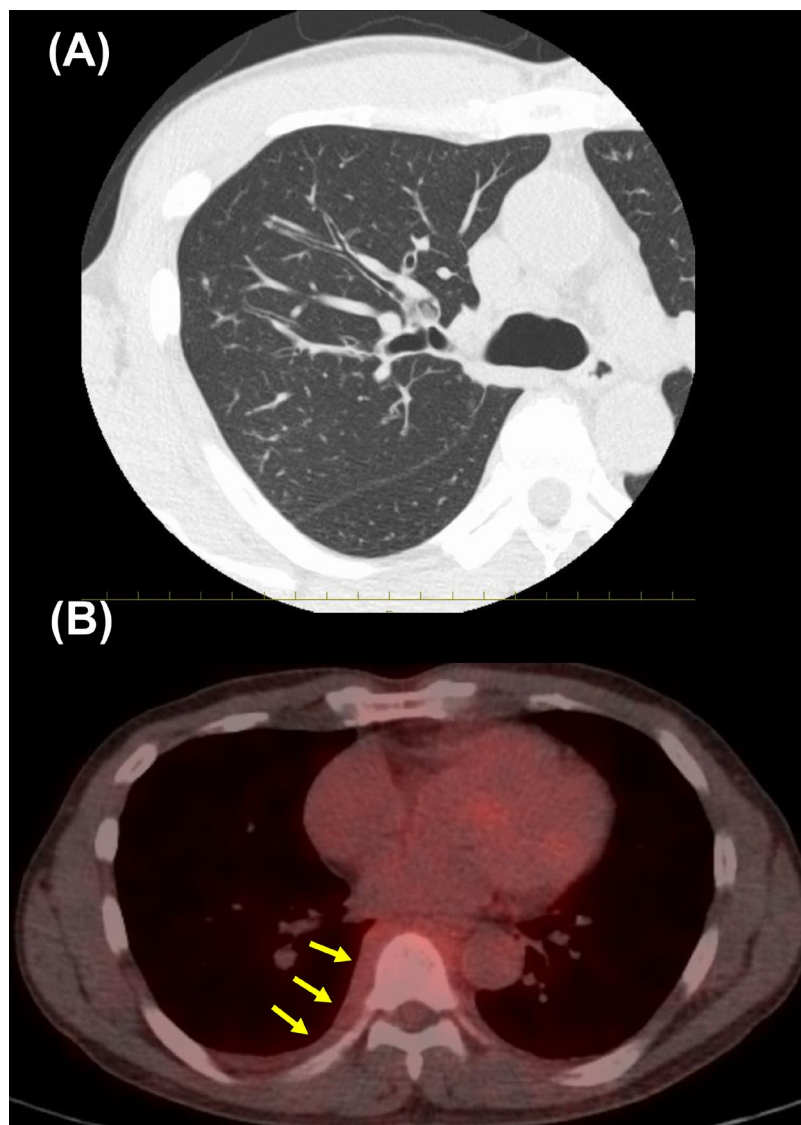


**Figure 3.** Computed tomography (A) and <sup>18</sup>F-fluorodeoxyglucose positron emission tomography (B) before dupilumab treatment showing airway wall and pleural thickness [maximum standard uptake value, 2.2] (arrow).

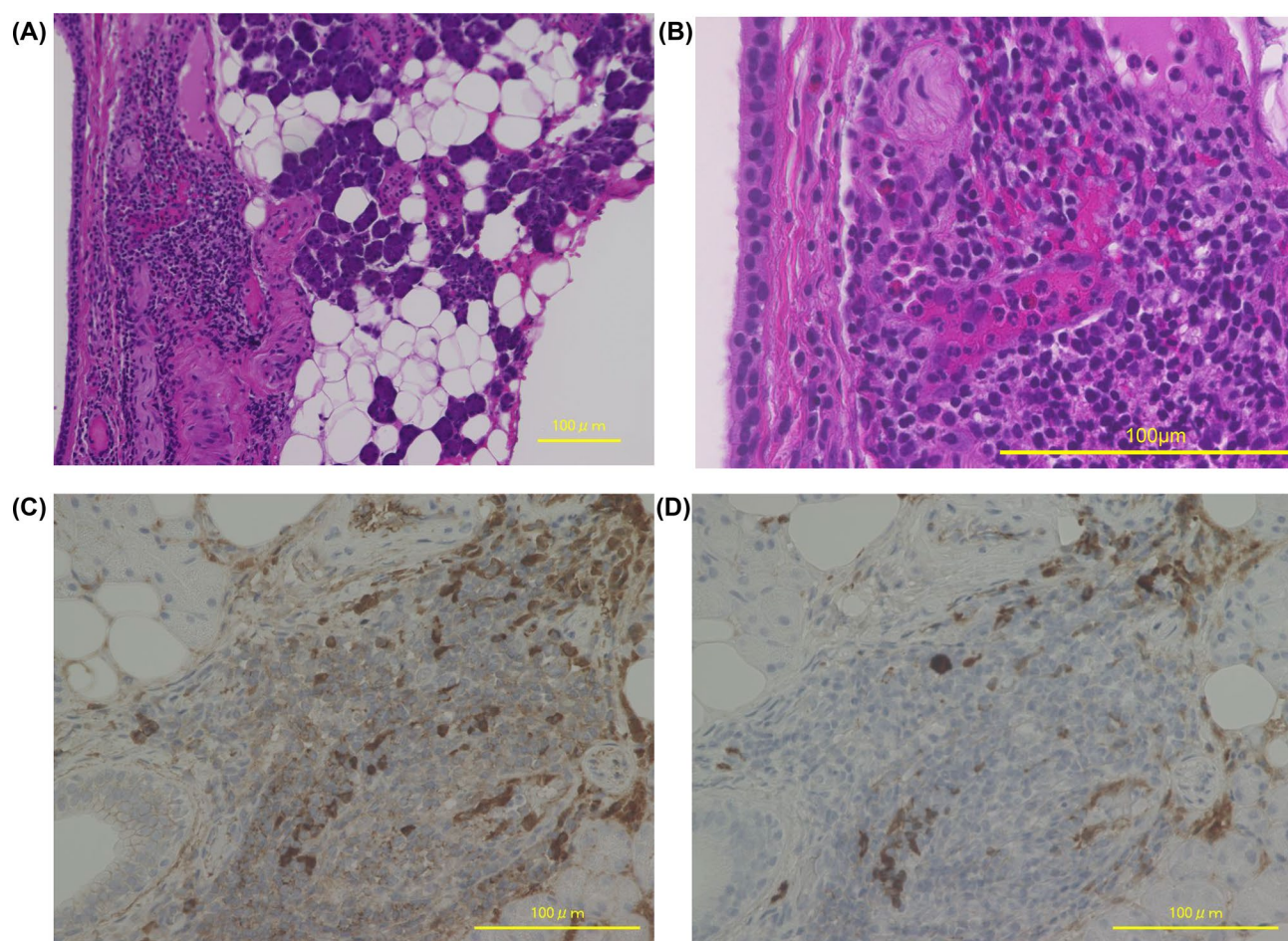


**Figure 4.** Hematoxylin and eosin staining of the biopsy specimen from the parotid gland showing lymphoid infiltration (A, B). Immunohistochemical staining of IgG+ plasma cells (C) and IgG4+ plasma cells (D).

**Table 1.** Comprehensive diagnostic criteria for IgG4-related disease, 2011.

1. Clinical examination shows characteristic diffuse/localized swelling or masses in single or multiple organs
2. Hematological examination shows elevated serum IgG4 concentrations (135 mg/dL)
3. Histopathologic examination shows:
  - (1) Marked lymphocyte and plasmacyte infiltration and fibrosis.
  - (2) Infiltration of IgG4+ plasma cells: ratio of IgG4+/IgG+ cells > 40% and >10 IgG4+ plasma cells/HPF

Definite: 1) + 2) + 3)

Probable: 1) + 3)

Possible: 1) + 2)

Adapted from Umehara et al. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. *Mod Rheumatol.* 2012;22:21–30. (23)

prednisolone dose was tapered to 2 mg. Relapse was not observed (Figure 5).

## Discussion

Herein, we present the first case of effective adjunct treatment with dupilumab for a patient with IgG4-RD complicated by asthma. In the present case, the patient was treated with systemic glucocorticoids for more than 2 years but tapering the prednisolone dose resulted in a relapse of the symptoms. Moreover, the addition of azathioprine, administered at a dose of 25 mg/day to avoid liver injury, could not reduce the

concentration of systemic glucocorticoids. The symptoms associated with asthma and IgG4-RD recurred when prednisolone was tapered to 10 mg/day. Adjunct treatment with dupilumab effectively reduced these symptoms, indicating that dupilumab has additive therapeutic effects on intractable IgG4-RD.

There have been two case reports of IgG4-RD treated with dupilumab. First, Simpson et al. (19) reported that dupilumab was effective against retroperitoneal fibrosis. Initially, the patient reported taking prednisolone, but in a subsequent correspondence response, it was revealed that the patient was not actually taking prednisone (20). This correspondence

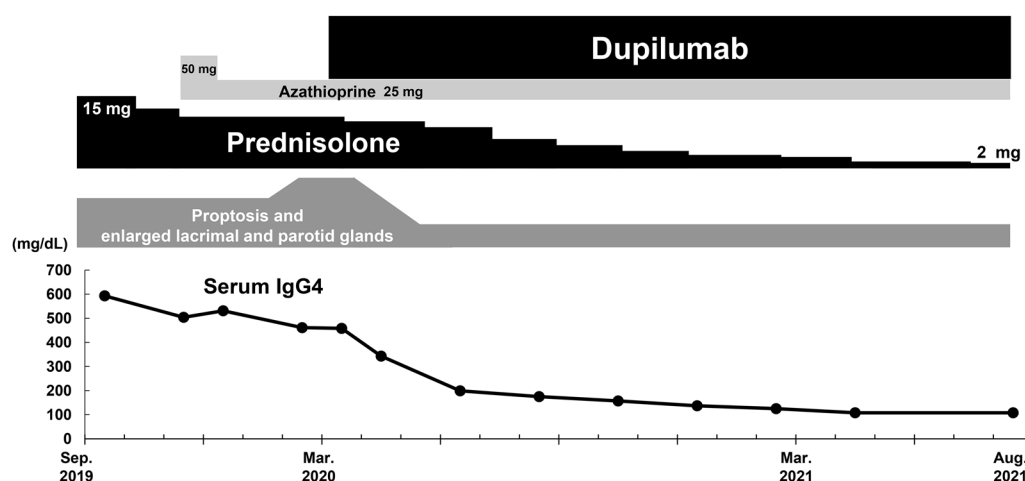


Figure 5. Clinical time course.

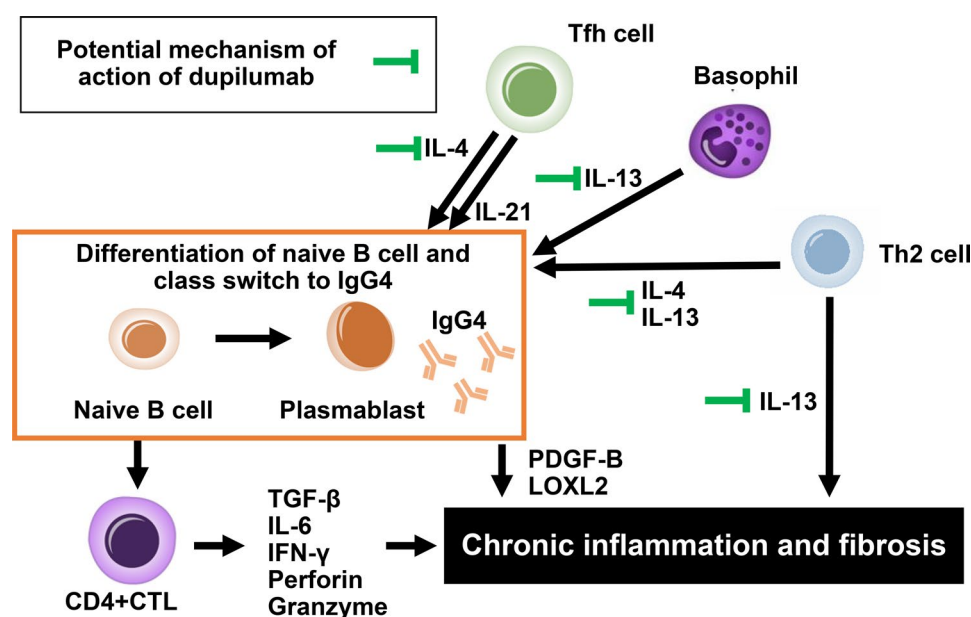


Figure 6. Potential mechanism of action of dupilumab based on current insights in patients with IgG4-related disease complicated by asthma. Abbreviations: Tfh cell, T follicular helper cell; Th2 cell, T helper 2 cell; CD4+CTL, CD4+ cytotoxic T lymphocyte; IL, interleukin; IFN, interferon; TGF, transforming growth factor; LOXL, lysyl oxidase homolog; PDGF, platelet-derived growth factor

is controversial, and the patient was not considered to be on standard therapy for IgG4-RD. Second, Ebbo et al. (21) reported that dupilumab monotherapy was ineffective against IgG4-RD relapse. In contrast to the results of these cases, we are the first to report the efficacy of adjunct treatment with dupilumab for a patient refractory to glucocorticoids and azathioprine, the standard treatment for IgG4-RD.

In the present case, the serum IgG4 level was elevated before dupilumab treatment despite prednisolone and azathioprine treatment. The serum IgG4 levels continued to decrease after dupilumab treatment, and

the prednisolone dose was tapered without relapse. Additionally, the previous case report of ineffective dupilumab monotherapy reported that serum IgG4 levels remained fairly stable (21). These observations suggest that IgG4 can be used as a marker to monitor dupilumab treatment in IgG4-RD. The steroid-sparing effect of dupilumab and the possible role of IgG4 as a biomarker should be confirmed in randomized clinical trials.

IL-4 and IL-13 are reportedly involved in the production of IgG4 and fibrosis. Thus, these cytokines have essential roles in the pathogenesis of IgG4-RD

(14–18). It has been suggested that various inflammatory cells, such as T-follicular helper cells, CD4+ cytotoxic T cells, and activated B cells, are involved in the pathogenesis of IgG4-RD (24–29) (Figure 6). Therefore, blocking the IL-4 and IL-13 pathways with dupilumab might not completely inhibit IgG4-RD pathogenesis. This finding is consistent with previous case reports, which showed that dupilumab monotherapy was ineffective against IgG4-RD (21). In contrast, the present case report indicates that dupilumab is a potential steroid-sparing adjunctive therapy for patients with IgG4-RD. A history of allergies and elevated eosinophils and IgG4 were associated with a high relapse rate after tapering or withdrawing glucocorticoids and/or immunosuppressants (3). These observations suggest that type-2 inflammation participates in recurrent IgG4-RD since dupilumab effectively suppressed the surge in type-2 inflammation during the tapering of systemic glucocorticoids.

## Conclusion

Dupilumab might be useful in tapering systemic glucocorticoids and as an adjunctive treatment for patients with steroid-dependent IgG4-RD complicated by asthma. Furthermore, serum IgG4 levels can be used as a marker to monitor dupilumab treatment in IgG4-RD.

## Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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## ORCID

Hiroshi Iwamoto  <http://orcid.org/0000-0003-4922-5334>  
Yusuke Yoshida  <http://orcid.org/0000-0002-0774-0509>  
Shintaro Hirata  <http://orcid.org/0000-0002-2474-9943>  
Eiji Sugiyama  <http://orcid.org/0000-0001-8534-6729>

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