

厚生労働科学研究費補助金
難病・がん等の疾患分野の医療の実用化研究事業
分担研究報告書

タイトル 免疫難病に対する先駆的治療薬開発 生物製剤を中心とした早期臨床試験拠点の医・薬集学的整備によるFIMの実施とPOCの確立

研究代表者 竹内 勤 慶應義塾大学医学部リウマチ内科 教授

研究要旨：成人スティル病(ASD) は発熱、皮疹、関節炎、リンパ節腫脹、肝脾腫などを認める炎症性疾患である。原因はいまだ不明であるが、血中サイトカインの異常上昇が病態に関係していると考えられ、治療薬として抗インターロイキン(IL)-6 受容体抗体であるトシリズマブ (TCZ) の有用性が期待されている。平成 25 年度は、医師主導型治験として TCZ を対象とした ASD に対する治験遂行体制を整備し試験を開始したのと同時に、類縁疾患である関節リウマチ患者を対象として TCZ 投与下での血中サイトカイン動態を追究し、TCZ がサイトカインネットワークに及ぼす影響と、今後の ASD に対する研究の疾患コントロールとしてのデータを収集し解析した。

A. 研究目的

成人スティル病(ASD)は、小児の若年性特発性関節炎(sJIA)に類似した病態が成人で発症した疾患である。発熱、関節炎、皮疹を主徴とし、全身性炎症をきたす疾患である。sJIAにおいては、インターロイキン(IL)-6 が病態に重要であり、抗 IL-6 受容体抗体製剤であるトシリズマブ(TCZ)が既に治療薬として承認され、現在では中心的治療薬として位置づけられているが、ASD においても TCZ の有用性に関する症例報告が散見されている。

しかし、ASD は本邦における患者数が約 2000 人と希少疾患であり、企業治験の実現性が低いため、エビデンスが欠如している。

そこで我々は本事業の取り組みのひとつとして、ASD に対する TCZ を対象とした医師主導型治験を施行し、Proof of concept を確立するとともに、治療薬としての承認を目指すこととした。

平成 25 年度は、(1) 臨床試験のプロトコルを検討、固定し治験を開始すること、および(2)ASD の類縁疾患である関節リウマチ(RA)を対象として、TCZ 投与前後で血中サイトカイン動態を測定し、ASD と対比可能な疾患コントロールデータを収集すること、の 2 点を目的とした。

B. 研究方法

(1) 医薬品医療機器総合機構との対面助言を経て、治験プロトコルを固定し、治験届け提出、治験開始のスケジュールを計画した。

(2) 2010 年 3 月から 2012 年 3 月までに、TCZ 治療を 1 剤目生物学的製剤として開始された RA 患者 70

例を対象とした。十分な説明の後文書同意を得て、TCZ 投与前から経時的に 1 年間、研究目的でも血液採取を行った。採血検体から血漿を分離し、検出限界 1pg/ml の感度で測定可能な SECTOR Imager 2400 (Meso Scale Discovery, MSD)を使用した電気化学発光 ELISA 法により、サイトカインを含めた種々のバイオマーカー濃度を測定した。臨床情報は匿名化のうえで診療録から収集し、バイオマーカーとの関連を統計解析した。

(倫理面への配慮)

患者の権利、個人情報に十分な配慮を行い、ヘルシンキ宣言に沿った同意説明文書を作成し、施設の倫理委員会の承認を得て、研究を遂行した。

C. 研究結果

(1)2013 年 9 月に医薬品総合機構との対面助言を行った。その後、治験遂行体制を整備すると同時に治験プロトコル作成を進め、2014 年 1 月に治験届けを提出、2 月より治験開始、患者組み入れが可能となった。

(2)RA において、TCZ 投与前の血漿 IL-6、IL-17、sICAM-1 濃度が CRP や疾患活動性と相関していた。TCZ 投与開始後 IL-6 濃度は 1 年間経時的に上昇し、同時に IL-1、IL-2、IL-10、IL-17、vascular endothelial growth factor(VEGF)、soluble intercellular adhesion molecule (sICAM)-1 が低下することが示された。特に 54 週では、IL-6 は 366% 上昇し(P=0.00)、IL-1 が-21.7%(P=0.03)、sICAM-1 が-7.2%(P=0.01)、VEGF が-47.7%(P=0.00)低下し、有意であった。

D . 考察

RAにおけるTCZ投与後54週間のサイトカインを含むバイオマーカー動態が明らかとなった。可溶性IL-6Rを阻害するTCZは投与後にIL-6濃度が上昇することは知られていたが、VEGFやIL-2、IL-1が低下することが示された。これらは、他の生物学的製剤であるTNF阻害薬やT細胞副刺激因子阻害薬では異なる動態を示すことが我々の研究から明らかとなっており、TCZがサイトカインネットワークに及ぼす影響を考える上で重要な知見である。また、今後ASD治験遂行の過程で、これらサイトカイン濃度を測定する予定であるが、本研究により関節リウマチを疾患コントロールとした比較が可能となり、ASDの病態解明への道筋となる可能性も示唆された。

E . 結論

生物学的製剤による分子標的療法は、RAにおいては目覚ましい治療効果をあげているが、今後は他疾患への適用を視野に、薬効の解明と科学的な有用性を立証していくことが重要である。本研究により得られたサイトカイン動態をさらに発展させ、病態解明と最適な治療実現へ向けて研究を推進する。

F . 健康危険情報

特になし

G . 研究発表

1 . 論文発表

- 1) Kaneko Y, Kondo H, Takeuchi T. American college of rheumatology/european league against rheumatism remission criteria for rheumatoid arthritis maintain reliable performance when evaluated in 44 joints. *J Rheumatol*. 2013;40(8):1254-8.
- 2) Mitsunaga S, Hosomichi K, Okudaira Y, Nakaoka H, Kunii N, Suzuki Y, Kuwana M, Sato S, Kaneko Y, Homma Y, Kashiwase K, Azuma F, Kulski JK, Inoue I, Inoko H. Exome sequencing identifies novel rheumatoid arthritis-susceptible variants in the BTNL2. *J Hum Genet*. 2013;58(4):210-5.
- 3) Kaneko Y, Kuwana M, Takeuchi T, Oddis CV. Osteolytic change of distal interphalangeal joints and sacroiliac joints in subluxing arthropathy associated with anti-Jo-1 antibody. *Joint Bone Spine*.

2013;80(5):544-5.

- 4) Nishina N, Kaneko Y, Kameda H, Kuwana M, Takeuchi T. Reduction of plasma IL-6 but not TNF- by methotrexate in patients with early rheumatoid arthritis: a potential biomarker for radiographic progression. *Clin Rheumatol*. 2013;32(11):1661-6.
- 5) Nishimoto T, Seta N, Anan R, Yamamoto T, Kaneko Y, Takeuchi T, Kuwana M. A single nucleotide polymorphism of TRAF1 predicts the clinical response to anti-TNF treatment in Japanese patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2013;32(2):211-7.
- 6) Tanaka Y, Takeuchi T, Amano K, Saito K, Hanami K, Nawata M, Fukuyo K, Kameda H, Kaneko Y, Kurasawa T, Nagasawa H, Hoshi D, Sato E, Yamanaka H. Effect of interleukin-6 receptor inhibitor, tocilizumab, in preventing joint destruction in patients with rheumatoid arthritis showing inadequate response to TNF inhibitors. *Mod Rheumatol*. 2013 [in press]
- 7) Kaneko Y, Hanaoka H, Hirakata M, Takeuchi T, Kuwana M. Distinct arthropathies of the hands in patients with anti-aminoacyl tRNA synthetase antibodies: usefulness of autoantibody profiles in classifying patients. *Rheumatology (Oxford)*. 2014 [in press]
- 8) Izumi K, Kaneko Y, Yasuoka H, Seta N, Kameda H, Kuwana M, Takeuchi T. Tocilizumab is clinically, functionally, and radiographically effective and safe either with or without low-dose methotrexate in active rheumatoid arthritis patients with inadequate responses to DMARDs and/or TNF inhibitors: A single-center retrospective cohort study (KEIO-TCZ study) at week 52. *Mod Rheumatol*. 2014. [in press]
- 9) Sugano K, Kinoshita Y, Miwa H, Takeuchi T, and the esomeprazole NSDAID preventive study group. Randomised clinical trial: esomeprazole for the prevention of nonsteroidal anti-inflammatory drug-related peptic ulcers in Japanese patients. *Alimentary Pharmacology and Therapeutics* [in press]
- 10) Nakajima A, Saitoh K, Kojima T, Amano K, Yoshio T, Fukuda W, Inoue E, Taniguchi A,

- Momohara S, Minota S, Takeuchi T, Ishiguro N, Tanaka Y, and Yamanaka H. No increased mortality in patients with rheumatoid arthritis treated with biologics: results from the biologics register of six rheumatology institutes in Japan. *Mod Rheum* [in press]
- 11) Koike T, Harigai M, Inokuma S, Ishiguro N, Ryu J, Takeuchi T, Tanaka Y, Yamanaka H, Hirose T, Yoshinaga T, and Suzukawa M. Safety and effectiveness of 6 months etanercept monotherapy and combination therapy in Japanese patients with Rheumatoid Arthritis: Effect of concomitant disease-modifying anti-rheumatic drugs. *J Rheumatology* [in press]
- 12) Nishimoto N, Koichi Amano, Yasuhiko Hirabayashi, Takahiko Horiuchi, Tomonori Ishii, Mitsuhiro Iwahashi, Masahiro Iwamoto, Hitoshi Kohsaka, Masakazu Kondo, Tsukasa Matsubara, Toshihide Mimura, Hisaaki Miyahara, Shuji Ohta, Yukihiko Saeki, Kazuyoshi Saito, Hajime Sano, Kiyoshi Takasugi, Tsutomu Takeuchi, Shigeto Tohma, Tomomi Tsuru, Yuki-taka Ueki, Jiro Yamana, Jun Hashimoto, Takaji Matsutani, Miho Murakami, Nobuhiro Takagi. Retreatment efficacy and safety of tocilizumab in patients with rheumatoid arthritis in recurrence (RESTORE) study. *Mod Rheum* [in press]
- 13) Koike T, Harigai M, Inokuma S, Ishiguro N, Ryu J, Takeuchi T, Takei S, Tanaka Y, Sano Y, Yamaguchi H, Yamanaka H. Characteristics related to good effectiveness and safety with tocilizumab: Post-marketing surveillance of 7901 rheumatoid arthritis patients in Japan. *J Rheum* [in press]
- 14) Sugano K, Kinoshita Y, Miwa H, Takeuchi T, and Esomeprazole NSAID Prevention study group. Safety and efficacy of long-term esomeprazole 20mg in Japanese patients with a history of peptic ulcer receiving daily non-steroidal anti-inflammatory drugs. *BMC Gastroenterology* [in press]
- 15) Yamamoto K, Takeuchi T, Yamanaka H, Ishiguro N, Tanaka Y, Eguchi K, Watanabe A, Origasa H, Shoji T, Sakamaki Y, van der Heijde D, Miyasaka N, and Koike T. Efficacy and safety of certolizumab pegol plus methotrexate in Japanese rheumatoid arthritis patients with inadequate response to methotrexate: the J-RAPID randomized, placebo-controlled trial. *Mod Rheum* in press.
- 16) Yamamoto K, Takeuchi T, Yamanaka H, Ishiguro N, Tanaka Y, Eguchi K, Watanabe A, Origasa H, Iwai K, Sakamaki Y, van der Heijde D, Miyasaka N, and Koike T. Efficacy and safety of certolizumab pegol without methotrexate co-administration in Japanese patients with active rheumatoid arthritis: the HIKARI randomized, placebo-controlled trial. *Mod Rheum* in press.
- 17) Tanaka Y, Yamamoto K, Takeuchi T, Yamanaka H, Ishiguro N, Eguchi K, Watanabe A, Origasa H, Shoji T, Miyasaka N, and Koike T. Long-term efficacy and safety of certolizumab pegol in Japanese rheumatoid arthritis patients who could not receive methotrexate: 52-week results from an open-label extension of the HIKARI study. *Mod Rheum* in press.
- 18) Tanaka Y, Kubo S, Yamanaka H, Amano K, Hirata S, Tanaka E, Nagasawa H, Yasuoka H, Takeuchi T. Efficacy and safety of abatacept in routine care of patients with rheumatoid arthritis: Oencia as Biological Intensive Treatment for RA (ORBIT) study. *Mod Rheum* in press.
- 19) Takeuchi T, Kawai S, Yamamoto K, Harigai M, Ishida K, Miyasaka M. Post-marketing surveillance of the safety and effectiveness of tacrolimus in 3267 Japanese patients with rheumatoid arthritis. *Mod Rheum* 24:8-16, 2014.
- 20) Tsuboi H, Hagiwara S, Asashima H, Umehara H, Kawakami A, Nakamura H, Sano H, Tsubota K, Ogawa Y, Takamura E, Saito I, Inoue H, Nakamura S, Moriyama M, Takeuchi T, Tanaka Y, Hirata S, Mimori T, Matsumoto I, and Sumida T. Validation of different sets of criteria for the diagnosis of Sjogren's syndrome in Japanese patients. *Mod Rheum* 23:219-225, 2013.
- 21) Takeuchi T, Suzuki K. CD247 variants single nucleotide polymorphisms observed in systemic lupus erythematosus. *Rheumatology* online March 23, 2013.
- 22) Nishina N, Kaneko Y, Kameda H, Kuwana M,

Takeuchi T. Reduction of plasma IL-6, but not TNF- by methotrexate in patients with early rheumatoid arthritis: a potential biomarker for radiographic progression. *Clinical Rheumatology* 32:1661-6, 2013.

- 23) **Takeuchi T**, Matsubara T, Nitobe T, Suematsu E, Ohta S, Honjyo S, Abe T, Yamamoto A, Miyasaka N, and The Japan Abatacept Study Group. Phase II dose-response study of abatacept in Japanese patients with active rheumatoid arthritis with inadequate response to methotrexate. *Mod Rheum* 23:226-235, 2013.
- 24) Sakai R, Nagasawa H, Nishi E, Okuyama A, Takei H, Kurasawa T, Kondo T, Nishimura K, Shirai Y, Ito T, Kameda H, **Takeuchi T**, Amano K. Successful treatment of adult-onset Still's disease with tocilizumab monotherapy: two case reports with literature review. *Clin Rheum* 31:569-74, 2012.
- 25) **Takeuchi T**, Harigaya M, Tanaka Y, Yamanaka H, Ishiguro N, Yamamoto K, Miyasaka N, Koike T, Kanazawa M, Ohba T, Yoshinari T, Baker D, and the GO-MONO study group. Golimumab monotherapy in Japanese patients with active rheumatoid arthritis despite prior treatment with disease-modifying anti-rheumatic drugs: results of the Phase 2/3, multicenter, randomized, double-blind, placebo-controlled GO-MONO study through 24 weeks. *Ann Rheum Dis* 72:1488-95, 2013.
- 26) **Takeuchi T**, Miyasaka N, Zang C, Alvarez D, Fletcher T, Wajdula J, Yuasa H, and Vlahos B. A phase 3 randomized, double-blind, multicenter comparative study evaluating the effect of etanercept versus methotrexate on radiographic outcomes, disease activity and safety in Japanese subjects with rheumatoid arthritis. *Mod Rheum* 23:623-33, 2013.

2.学会発表

- 1) Yuko Kaneko, Hironari Hanaoka, et al. Distinct arthropathies in patients with anti-aminoacyl tRNA synthetase antibodies: utility of autoantibody profiles in discrimination. American College of Rheumatology 77th Annual Meeting, San Diego, October 26-30, 2013
- 2) **T. Takeuchi**, Y. Kaneko, T. Atsumi, Y. Tanaka, M. Inoh, H. Kobayashi, K. Amano, M. Miyata, Y. Murakawa, T. Fujii, A. Kawakami, H. Yamanaka, K. Yamamoto, N. Miyasaka, T. Mimori: Adding tocilizumab or switching to tocilizumab monotherapy in patients with inadequate response to methotrexate: 24-week results from a randomized controlled study (surprise study). Madrid, Spain. 2013.6.13
- 3) H. Yamanaka, K. Yamamoto, **T. Takeuchi**, N. Ishiguro, Y. Tanaka, K. Eguchi, A. Watanabe, H. Origasa, T. Shoji, S. Onodera, N. Miyasaka, T. Koike: Week 12 clinical response to certolizumab pegol predicts long-term outcomes regardless of concomitant medications and baseline disease characteristics in Japanese patients with active rheumatoid arthritis. Madrid, Spain. 2013.6.13
- 4) **T. Takeuchi**, N. Wakasugi, H. Makino. Keio University, Astellas Pharma Inc., Tokyo, Okayama University, Okayama, Japan: Long-term safety and efficacy of tacrolimus for lupus nephritis patients -interim analysis of post marketing surveillance in 1375 patients in Japan (TRUST study). Madrid, Spain. 2013.6.13
- 5) N. Nishina, J. Kikuchi, M. Hashizume, K. Yoshimoto, H. Kameda, **T. Takeuchi**: baseline soluble interleukin-6 receptor levels predict the clinical effectiveness of tocilizumab in patients with rheumatoid arthritis. Madrid, Spain. 2013.6.14
- 6) J. Kikuchi, H. Kameda, K. Yoshimoto, **T. Takeuchi**: Low serum interleukin-6 level at baseline, rather than at follow-up, is associated with favorable radiographic outcome in rheumatoid arthritis patients treated with abatacept. Madrid, Spain. 2013.6.14
- 7) **T. Takeuchi**, M. Harigai, Y. Tanaka, H. Yamanaka, N. Ishiguro, K. Yamamoto, Y. Murakami, T. Yoshinari, D. Baker, N. Miyasaka, T. Koike: golimumab monotherapy in patients with active rheumatoid arthritis despite dmard therapy: week 104 results of clinical, radiographic and safety assessments

including evaluation of remission using the new acr/eular criteria. Madrid, Spain. 2013.6.14

- 8) **T. Takeuchi**, T. Yano, T. Inui, T. Yoshinari, N. Miyasaka, T. Abe, T. Koike: Achievement of low disease activity (lda) at 3 months predicts clinical remission (rem) at 1 year of infliximab (ifx) therapy in ra: post-hoc analysis of a randomized double-blind clinical study (rising study). Madrid, Spain. 2013.6.14
- 9) **T. Takeuchi**, K. Yamamoto, H. Yamanaka, N. Ishiguro, Y. Tanaka, K. Eguchi, A. Watanabe, H. Origasa, Y. Wada, T. Shoji, N. Miyasaka, T. Koike: Immunogenicity of certolizumab pegol without concomitant methotrexate and clinical response in rheumatoid arthritis patients: post-hoc analysis of the hikari study. Madrid, Spain. 2013.6.14
- 10) Y. Tanaka, M. Harigai, **T. Takeuchi**, H. Yamanaka, N. Ishiguro, K. Yamamoto, Y. Murakami, T. Yoshinari, D. Baker, N. Miyasaka, T. Koike: Golimumab administered subcutaneously every four weeks in patients with active rheumatoid arthritis despite methotrexate therapy: long-term clinical, radiographic and safety results, including evaluation of remission using the new acr/eular criteria. Madrid, Spain. 2013.6.14
- 11) Y. Tanaka, **T. Takeuchi**, T. Mimori, N. Miyasaka, T. Koike and RRR Study Investigators: The possibility and predictive factors of maintaining low disease activity and joint structure after discontinuation of infliximab in ra patients: results from 3-year experience of rrr study. Madrid, Spain. 2013.6.14
- 12) G. Burmester, **T. Takeuchi**, O. Barbarash, G. Ranganna, D. Close, A. Godwood, D. Saurigny and EARTH Study Group.: Consistent efficacy and safety outcomes between european and japanese subjects with rheumatoid arthritis following treatment with mavrilimumab in the phase 2 earth study. Madrid, Spain. 2013.6.14
- 13) K. Amano, T. Matsubara, H. Inoue, M. Iwahashi, A. Yamazaki, C. S. Karyekar, **T. Takeuchi** and Department of RheuJapan Abatacept Study Group: Long-term safety and efficacy of treatment with subcutaneous abatacept in japanese patients with ra who were mtx inadequate responders - 76-week results. Madrid, Spain. 2013.6.14
- 14) **T. Takeuchi** on behalf of ORION study group, T. Matsubara, S. Ohta, M. Mukai, K. Amano, S. Tohma, Y. Tanaka, H. Yamanaka, N. Miyasaka and ORION study group: Abatacept biologic-free remission study in established rheumatoid arthritis patients orion study. Madrid, Spain. 2013.6.15
- 15) M. Harigai, S. Inokuma, N. Ishiguro, J. Ryu, **T. Takeuchi**, S. Takei, Y. Tanaka, H. Yamanaka, Y. Sano, H. Yagurumaki, T. Koike: Characteristics associated with better effectiveness and safety in rheumatoid arthritis patients treated with intravenous tocilizumab: results from full analysis of all-patient postmarketing surveillance in japan. Madrid, Spain. 2013.6.15
- 16) **T. Takeuchi**, Y. Tanaka, K. Amano, J. Kikuchi, E. Tanaka, S. Hirata, H. Nagasawa, H. Yasuoka, H. Yamanaka: Effectiveness of abatacept against rheumatoid arthritis in daily clinical practice - ORBIT STUDY. Madrid, Spain. 2013.6.15
- 17) Yoshiya Tanaka, Kazuhiko Yamamoto, **Tsutomu Takeuchi**, Nobuyuki Miyasaka, Takayuki Sumida, Tsuneyo Mimori, Takao Koike, Kazuhiro Endo: Efficacy Of Rituximab In Patients With Refractory Lupus Nephritis, a Post-Hoc Analysis From Phase II Trial In Japan. San Diego, USA. 2013.10.27
- 18) Hidekata Yasuoka, Yuichiro Shirai, Yuichi Tamura, Toru Satoh, **Tsutomu Takeuchi**, Masataka Kuwana: Baseline Characteristics That Predict a Short-Term Response To Immunosuppressive Treatment In Patients With Pulmonary Arterial Hyper- tension Associated With Connective Tissue Disease. San Diego, USA. 2013.10.27
- 19) Hidekata Yasuoka, Ken Stern, Yuka Okazaki, Tetsuya Nishimoto, **Tsutomu Takeuchi**, Masataka Kuwana: Up-Regulated Expression Of CXCL5 In Circulating Platelets From Patients With Systemic Sclerosis: A Role In Fibrosis. San Diego, USA. 2013.10.27
- 20) Misato Hashi- zume, Keiko Esaki, Keiko

- Yoshimoto, Hideto Kameda, **Tsutomu Takeuchi**, Yoshihiro Matsumoto: Novel Function Of Soluble Interleukin-6 Receptor As An Antagonist Of Interleukin-27-Mediated Anti-Inflammatory Responses. San Diego, USA. 2013.10.28
- 21) Yoshiya Tanaka, **Tsutomu Takeuchi**, Naoki Ishiguro, Hisashi Yamanaka, Toshiyuki Yoneda, Harry K. Genant and Désirée van der Heijde: Estimation Of The Effect Of Denosumab On Bone Loss From The Results Of The 12-Month Phase II Study In Patients With Rheumatoid Arthritis (RA) On Background Methotrexate (MTX). San Diego, USA. 2013.10.28
- 22) Takao Koike, Masayoshi Harigai, Naoki Ishiguro, Shigeko Inokuma, Junnosuke Ryu, Syuji Takei, **Tsutomu Takeuchi**, Y. Tanaka, Masahiko Watanabe, Hisashi Yamanaka: Safety and Effectiveness Of Abatacept In 3985 Japanese Patients With Rheumatoid Arthritis; Japan All-Cases Post-Marketing Surveillance. San Diego, USA. 2013.10.28
- 23) Gerd-Rüdiger Burmester, **Tsutomu Takeuchi**, Olga Barbarash, Duncan Porter, Didier Saurigny, David Close, Alex Godwood, Yoojung Yang and Ancilla W. Fernandes: Early and Sustained Improvement In Pain and Physical Function As Measured By Visual Analog Scale and Short Form-36 Physical Component Summary Score In Rheumatoid Arthritis Patients Treated With Mavrilimumab, An Investigational Anti-GM-CSFR-Alpha Monoclonal Antibody, In a Phase 2a Study. San Diego, USA. 2013.10.28
- 24) M Weinblatt, P Mease, E Mysler, **T Takeuchi**, E Drescher, A Berman, M Zilberstein, J Xing and P Emery: A Phase IIb Study Of The Efficacy and Safety Of Subcutaneous Clazakizumab (anti-IL-6 monoclonal antibody) With Or Without Methotrexate In Adults With Moderate-To-Severe Active Rheumatoid Arthritis and An Inadequate Response To Methotrexate. San Diego, USA. 2013.10.28
- 25) Keiko Yoshimoto, Maiko Tanaka, Masako Kojima, Hideko Ogata, Eriko Ishioka, Ayumi Nishikawa, Katsuya Suzuki, Hideto Kameda, Tohru Abe and **Tsutomu Takeuchi**: Increased Expression of BAFF Receptor On Monocytes Is a Contributory Factor of Hypergammaglobulinemia in Patients With Primary Sjögren's Syndrome. San Diego, USA. 2013.10.29
- 26) Keiko Yoshimoto, Maiko Tanaka, Masako Kojima, Hideko Ogata, Eriko Ishioka, Ayumi Nishikawa, Katsuya Suzuki, Hideto Kameda, Tohru Abe, **Tsutomu Takeuchi**: BAFF Induces Production of Matrix Metalloproteinase-9 By Peripheral Monocytes in Patients With Primary Sjögren's Syndrome Through a Signaling Pathway That Involves NF-Kb and PI3 Kinase. San Diego, USA. 2013.10.29
- 27) Yuko Kaneko, Hironari Hanaoka, Michito Hirakata, **Tsutomu Takeuchi**, Masataka Kuwana: Distinct Arthropathies In Patients With Anti-Aminoacyl tRNA Synthetase Antibodies: Utility Of Autoantibody Profiles In Discrimination. San Diego, USA. 2013.10.29
- 28) **Tsutomu Takeuchi**, Kazuhiko Yamamoto, Hisashi Yamanaka, Naoki Ishiguro, Yoshiya Tanaka, Katsumi Eguchi, Akira Watanabe, Hideki Origasa, Mariko Kobayashi, Toshiharu Shoji, Nobuyuki Miyasaka and Takao Koike: Post-Hoc Analysis Showing Better Clinical Response With The Loading Dose Of Certolizumab Pegol In Japanese Patients With Active Rheumatoid Arthritis. San Diego, USA. 2013.10.29
- 29) Yoshiya Tanaka, Kazuhiko Yamamoto, **Tsutomu Takeuchi**, Hisashi Yamanaka, Naoki Ishiguro, Katsumi Eguchi, Akira Watanabe, Hideki Origasa, Tadao Okamoto, Yumiko Wada, Toshiharu Shoji, Nobuyuki Miyasaka and Takao Koike: Comprehensive Disease Remission Achieved By Certolizumab Pegol Treatment, and Factors Associated With Certolizumab Pegol Comprehensive Disease Remission, In Rheumatoid Arthritis Patients With Predominantly High Disease Activity. San Diego, USA. 2013.10.29
- 30) Yoshiya Tanaka, Yasuhiko Shinmura, Ryo Nakajima, Takahiro Muramatsu, Shuichi Komatsu, Tadamichi Kubo, Aki Kuroki, Ataru Igarashi, Toshiro Tango, **Tsutomu Takeuchi**: Economic Impact Of Adalimumab Treatment In Japanese Patients With Rheumatoid Arthritis: Analysis Of 24 Weeks Data From The Anouveau Study. San Diego, USA. 2013.10.29

- 31) Masako Tsukamoto, Katsuya Suzuki, Keiko Yoshimoto, Hideto Kameda, **Tsutomu Takeuchi**: Pleiotropic Roles Of Fc Receptors Upregulated On Circulating Monocytes In Rheumatoid Arthritis Patients. San Diego, USA. 2013.10.29
- 32) Masataka Kuwana, Yuichiro Shirai, Hidekata Yasuoka, **Tsutomu Takeuchi**, Kenichi Masui: Utility Of Autoantibody Testing For Predicting Risk Of Pulmonary Arterial Hypertension: A Retrospective Analysis In Routine Autoantibody Laboratory. San Diego, USA. 2013.10.29
- 33) Yoshiya Tanaka, Hisashi Yamanaka, Naoki Ishiguro, Nobuyuki Miyasaka, Katsuyoshi Kawana, Tadamichi Kubo, Aki Kuroki, **Tsutomu Takeuchi**: Clinical Remission After 52 Weeks Of Treatment Is a Predictor Of Adalimumab-Free Disease Control In Patients With Early Rheumatoid Arthritis: HOPEFUL 2 Study. San Diego, USA. 2013.10.29
- 34) **Tsutomu Takeuchi**, Yoshiya Tanaka, Naoki Ishiguro, Hisashi Yamanaka, Toshiyuki Yoneda, Harry K. Genant and Désirée van der Heijde: Dose-Response Effects Of Denosumab, a Novel Subcutaneous RANKL Inhibitor, On The Progression Of Bone Erosion In Japanese Patients With Rheumatoid Arthritis Treated With Methotrexate: Results Of Phase II DRIVE Study—A Twelve Month Placebo Controlled, Randomized, Double Blind Study. San Diego, USA. 2013.10.30

出願番号：特願 2013-132852

特許出願日：2013 年 6 月 25 日

発明者：竹内 勤、亀田秀人、吉本桂子

2. 実用新案登録

特になし

3. その他

特になし

H. 知的財産権の出願・登録状況

(予定を含む)

1. 特許取得

・抗BAFF抗体

国際出願番号：PCT/JP2005/013496

国際出願日：2005 年 8 月 30 日

欧州登録通知：2013 年 8 月 20 日

発明者：竹内 勤、吉本桂子

登録番号および登録日については後日通知

・炎症性疾患の予防および/又は治療剤

出願番号：特願 2013-210440

特許出願日：2013 年 10 月 7 日

発明者：竹内 勤、吉本桂子

・炎症性疾患を治療又は予防するための医薬組成物