Characterization of the trafficking and motility of T cells in the joints and joint-draining lymph nodes in an autoimmune murine model or rheumatoid arthritis

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The Examination takes place at the Department of Ophthalmology (Library), Faculty of Medicine, University of Debrecen, on Tuesday Jun 17, 2014, at 11 a.m.

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The PhD Defense takes place at the Lecture Hall of Bldg. A, Department of Internal Medicine, Faculty of Medicine, University of Debrecen, on Tuesday Jun 17, 2014, at 1 p.m.
Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease that affects 1% of the world’s population. It is characterized by symmetrical deforming peripheral polyarthritis at early stages that progresses to a systemic illness with extraarticular organ involvement and chronic inflammation that causes joint destruction. By providing help to B cells, the involvement of autoreactive T cells in the pathogenesis of RA as well as in autoimmune animal models of RA has been well established, however, unanswered questions, such as the role of joint-homing T cells, remain. Animal models of RA are superb experimental tools in demonstrating how T cells trigger joint inflammation, and thus can help to further our knowledge of disease mechanism and potential therapies. One of the murine models, the proteoglycan induced arthritis (PGIA) can be induced in wild type (WT) BALB/c mice by repeated intraperitoneal immunization with human articular cartilage proteoglycan (PG) in adjuvant. PGIA can also be adoptively transferred from arthritic donors to syngenic severe combined immunodeficient (SCID) mice by co-injection of T and B cells from arthritic donors and human PG without adjuvant.

The presence of large populations of innate immune cells such as granulocytes and macrophages in the rheumatoid joint indicates that T cell independent processes and non T cells also have important role in the joint pathology of RA. A minor T cell population was also found in the synovial fluid of patients with rheumatic diseases, however, most of these cells were identified as Tregs. The presence of these cells indicated a secondary recruitment of T cells to the site of inflammation. However, the prevailing view is that upon entry into the joints from the bloodstream, effector T cells can provide cytokine/chemokine stimuli to surrounding cells, and thus they actively trigger and maintain local inflammatory processes.
In recent years, two-photon microscopy imaging in vivo has greatly contributed to our understanding of the motility of T cells, and interactions between T cells and APCs in the lymph nodes. However, most of the two-photon imaging studies use genetically manipulated mice, as the TCR epitope repertoire is diverse and cognate T cells recognizing any single epitope are thought to be rare. These genetically engineered mice express a TCR in a large population of their T cells, which is specific for a single epitope of a model Ag. Studies focusing on T cell motility using TCR mice have controversial results however what they have in common is that T cell interaction with APCs carrying Ag leads to the arrest of the cognate T cells ensuring its activation via long-lived interactions with relevant APC, and that T cells exhibit high motility when they are ready to divide or leave the lymph node. In this study we were investigating T cell – T cell and T cell – DC interactions for the first time in case of a complex autoimmune arthritis model.

**Aims of the study**

In the studies included in the present thesis I have tried to find the answers for the following questions:

- Are T cells necessary for the development of PGIA at target sites (i.e., in the joints)?

To address this question, we employed two-photon microscopy to monitor the migration of T cells labeled with fluorescent dyes into the ankle joints and the joint-draining lymph nodes (JDLN) of syngeneic severe combined immunodeficient (SCID) mice during the course of the adoptive transfer of PGIA. We were unable to find T cells within the synovial tissue of the joints of SCID mice in a consistent manner
in any stage of the arthritis development. On the other hand, depletion of T cells from the spleen cell populations of arthritic donor mice prior to injection into SCID mice eliminated autoAb production and completely prevented the development of adoptively transferred arthritis in the SCID recipients. This suggested that the presence of T cells in the lymphoid organs (such as the lymph nodes), rather than in the peripheral joints, was required for disease induction.

- Is the availability of T cells critical for the development other animal models of arthritis? If so, how effective are T cell targeting therapies in suppressing experimental arthritis in animals or joint involvement in patients with RA?

Using the available literature I found that T cell depletion or T cell targeting approaches proved to be effective in preventing arthritis or reducing inflammation in other animal models like CIA and K/BxN arthritis. However, T cell targeting therapies failed in RA. This difference might be explained by the dissimilarities between animal models and RA with regard to T cell involvement and the clinical course of the disease.

- If the recruitment and Ag-induced activation of T cells within the lymphoid organs were necessary for the development of PGIA, we wanted to determine whether there was a difference in the motility behavior between Ag experienced and naïve T cells in the JDLN and whether Ag-experienced T cells from immunized WT mice could mimic the motile behavior of T cells isolated from naïve TCR-Tg mice upon exposure to cognate antigen in a similar fashion, as reported by other studies.
This is also the first study to describe the motile behavior of T cells in PGIA, an autoimmune inflammatory disease model of human RA with two-photon microscopy. When using T cells from genetically manipulated TCR-Tg mice, the response of each of these T cells is an isolated immunological event. In contrast, the response of Ag experienced T cells from arthritic animals to in vivo Ag challenge is linked to the initiation of autoimmune arthritis. That is why understanding Ag induced changes in the motile behavior of these Ag-experienced T cells in the JDLNs may provide some information about the in vivo conditions of T cell activation and disease progression. First we wanted to find out whether there were differences between the motile behavior of naïve and Ag experienced T cells in JDLNs of naive recipients and whether these differences were Ag specific. Then we wanted to see whether Ag experienced wild type T cells recapitulate the behavior or naïve TCR-Tg T cells after in vivo exposure to a relevant Ag.

- Is there a competition for access to antigen presenting cells between naïve and antigen experienced T cells?
- Does joint inflammation influence the motile behavior of T cells in the JDLN?

Finally, we sought to determine whether naïve and Ag experienced T cells compete for access to APCs carrying the relevant Ag and whether inflammation of the joint influences the motile behavior of T cells in the JDLN.

Materials and Methods

Antigen, mice, immunization, and assessment of arthritis

We immunized BALB/c and EGFP-LysM (back-crossed into BALB/c background) mice with proteoglycan isolated from cartilage collected from patients
who underwent knee replacement surgeries. For the first set of experiments we used adult female WT and SCID BALB/c mice and enhanced green fluorescent protein-lysozyme M ‘knockin’ mice (EGFP-LysM KI) which were back-crossed into BALB/c for 10 generations. In the second set of experiments we used adult female WT BALB/c mice as activated and naïve T cell donors as recipients, and also for age matched controls. Human cartilage specific TCR Tg mice were also used for in vitro T cell competition experiments. The severity of developing arthritis was scored on a scale of 0-16.

**Separation, labeling and transfer of immune cells for in vivo imaging studies**

Cells were isolated from the spleens and several JDLNs of naïve or arthritic donor mice and separated by T and non T cell enrichment kits. Depending on the experiment, T cells (arthritic and naïve) and APCs were labeled with fluorescent cell tracked dyes. DCs (as APCs) were generated from bone marrow cells by a 10-day culture in the presence of granulocyte-macrophage colony stimulating factor. In case of EGFP-LysM KI mice, no labeling was necessary, as these mice express green fluorescence in granulocytes. Depending on the aim of the experiment, we conducted various cell transfers:

1) Red T cells and unstained or green APCs into SCID mice to monitor the migration of the injected cells into the inflamed joints or into the popliteal lymph node and we conducted TPM imaging at 2, 4 hours and then 1, 2, 3, 4, 7, 12 and 18 days post transfer. EGFP LysM KI BALB/c mice were imaged to visualize granulocyte recruitment in their joints.
2) Naïve green T cells and Ag-experienced red cells into naïve hosts and 2-3 hours later these mice were given PG injected directly into the ankle joint. Control mice received either PBS or the irrelevant Ag ovalbumin (OVA). TPM imaging was conducted at various time points between 2 and 48 hours to monitor the motility of T cells in the JDLNs. Each mouse received L-selectin blocker MEL-14 prior to the imaging session to prevent new lymphocytes entering the LN.

3) Green naïve T cells and red Ag-experienced T cells were injected into arthritic recipients to study their motility in the JDLNs. Imaging sessions were done at 4, 24, 48 and 72 hours after cell transfer. These mice also received MEL-14 Ag 2 hours prior to imaging.

4) Green naïve T cells were transferred into arthritic recipients to see whether there was competition between naïve and antigen-experienced T cells in the previous experiments. Imaging was performed 4, 24, 48 and 72 hours after T cell transfer. MEL-14 2 hours before imaging session was given in these experiments as well.

5) In the fourth set of experiments, we injected bone-marrow-derived DCs along with PG into the ankle joints of arthritic donors. We did this to visualize the interactions between the DCs and the naïve or Ag-experienced T cells in the JDLNs.

**In vivo two-photon microscopy**

To reduce movement artifacts caused by breathing, mice were first anesthetized using a combination of intramuscular ketamine and xylazine for anesthesia induction, and isoflurane through a nose cone in the presence of 100% oxygen for anesthesia maintenance.
The skin covering the lateral side of the ankle and the popliteal area was removed using microsurgical equipment, and then the popliteal lymph node was brought to the surface employing microsurgical techniques. Mice were then fixed in the imaging chamber using veterinary-grade super glue and adhesive strips. The temperature of the imaging chamber and the objective was maintained at 37°C. Images were captured using PrairieView image acquisition software, then image stacks were used to produce 3 dimensional reconstructions of the tissue in case of serial images along the z plane (z-series) or to capture time lapse series (T-series).

**Image processing and analysis**

Cell movements in T-series were analysed with Imaris Track after elimination of breathing movement artifacts. We were interested in the following parameters: displacement, average velocity, motility coefficient – which was calculated as the slope of the mean displacement plotted against the square root of time (\( \frac{D}{T^{1/2}} \); in \( \mu \text{m}/\text{min}^{1/2} \)), and proportion of immotile cells as the percentage of all cells tracked. The data was analyzed with Microsoft Excel.

**Immunohistochemistry**

Hindpaws and JDLNs of SCID mice following transfer of red CMTPX T cells and unstained non-T cells were dissected, embedded in OCT compound and snap-frozen. 8 micrometers thick frozen sections were cut using cryostat and stored in -20°C. Before immunostaining, cryosections were fixed in cold acetone and blocked using 5% normal goat serum and 5 micrograms/milliliter of anti-CD16/32 monoclonal antibody (mAb) (Fc Block) in phosphate-buffered saline. For immune staining, Alexa Fluor 488-conjugated mAb (B220) against B cells, and Pacific Blue-conjugated mAb to
CD35 (a follicular DC-specific marker were used. Fluorescent cells were visualized with two-photon microscopy following post-fixation with 10% buffered formaldehyde.

**MHC II-peptide tetramer binding assay**

We used an allophycocyanin (Apc)-labeled human PG (aggrecan)-specific tetramer (PG tetramer) and an irrelevant control Apc-labeled tetramer. T cells purified from naïve heterozygous PG-TCR-Tg BALB/c mice served as a positive control for PG tetramer binding. Following purification, the three populations of T cells (naïve WT, antigen PG-experienced WT, and naïve PG-TCR-Tg) were cultured separately for 24 hours with 5 ng/ml murine interleukin (IL)-2. Before addition of tetramers, the antigen-experienced WT T cell population was labeled with red fluorescence as described earlier, while the other two were left unlabeled. The T cell samples for the tetramer binding/competition assay were set up as follows: (i) naïve T cells alone, (ii) antigen-experienced WT T cells alone, (iii) PG-TCR-Tg T cells alone, or antigen experienced (red fluorescent) WT T cells mixed with unlabeled T cells from either (iv) naïve WT or (v) naïve PG-TCR-Tg mice. The cells samples were incubated for 16 hours in the presence of 0, 0.3, 0.6, 1.2 and 2.4 μg Apc-labeled PG tetramer or Apc-labeled CLIP tetramer in 100 μl DMEM medium containing 10% FBS under standard tissue culture conditions. The cells were then washed and surface-labeled with Fitc-conjugated anti-mouse CD4 antibody or Fitc-rat IgG2b (isotype control) antibody. The percent of tetramer-binding (Apc+) CD4+ T cells in each sample was determined by flow cytometry.
Statistical analysis

Statistical analysis was performed with Microsoft Excel’s Analysis ToolPak and SPSS software. Depending on the homogeneity of variance, data was analyzed directly or transformed prior to analysis. Two groups were compared using Student’s t test, or Mann-Whitney u test for non-parametric data. P values of less than 0.05 were accepted as statistically significant.

Results

Only a small number of T cells can be found locally in the joints during the development of PGIA following adoptive transfer of the disease to SCID mice

We were unable to lymphocytes from donor mice in the ankle joints in a consistent manner using two-photon microscopy. At early time points sometimes we found dyed leukocytes (which were stained along with T cells) from donor mice and occasionally we were able to find T cells in the synovial vessels but not in the synovium, several days after transfer. However, both red (T cells) and green (APCs) cells migrated readily to the JDLNs and occupied their separate territories. We were able to visualize them consequently at each time point up to 18 days after transfer. Extended studies using immunohistochemistry and flow cytometry confirmed the above findings.
Naïve and Ag experienced T cells exhibit different motility characteristics in the JDLN of naïve hosts after encountering a single dose of intraarticularly injected PG

We injected green labeled naïve T cells isolated from naïve mice, and activated T cells extracted from arthritic mice to a naïve host and monitored their motile behavior with two-photon microscopy in the JDLN in response to in vivo antigen challenge. This setting ensured the priming of the rarer naïve cognate T cells and the re-stimulation of the antigen experienced T cells by the mice’s own antigen presenting cells. Similarly to other antigen models investigated with two-photon microscopy, both cell groups exhibited high motility during the first two hours following the administration of antigen. By 4 hours following antigen exposure, each cell group exhibited reduced cell motility. The percentage of immotile cells was also significantly higher in the antigen-experienced population than in the naïve. This indicates that antigen presentation is most efficient in the joint-draining lymph node 4 hours after intraarticular antigen administration leading to the arrest of T cells dominantly in the antigen experienced population. Two hours later, T cells regained some of their mobility but they stayed below their baseline motility level. However, antigen experienced T cells showed significantly reduced motility as compared with naïve T cells. The difference in the motility parameters of the two T cell group was clearly the result of the preferential recognition of PG by the antigen experienced T cell group. The same experiments using irrelevant ovalbumin antigen or phosphate buffer saline did not lead to the above differences.

8 hours post antigen injection however; both T cell groups regained their original motility. These results suggest that a single encounter with PG in the recipient mouse leads to a short-term presentation of the antigen and to short term
interactions between the T cells and the antigen presenting cells. Although the antigen presenting cells are not visible in this study, we theorize that the differences in the motility parameters of the antigen-experience and naïve T cell groups were due to the higher number of cognate cells and their higher affinity to MHC-PG

**Ag-experienced T cells engage in long-lasting interactions with APCs in the JDLN when transferred into arthritic recipients. Naïve T cells do not show similar behavior.**

Following the previous experiment, we wanted to determine whether a transfer of the same number of antigen-experienced and naïve T cells into an arthritic host would lead to a more profound arrest in the joint-draining lymph node following PG injection into the ankle joint - than in the naïve host. Imaging sessions were done 4, 8, 24, 48 and 72 hours after transfer.

The arrest of naïve T cells was also more profound at 4 hours compared to their arrest in the naïve host and nearly equal proportions of the two T cell groups were arrested at this early time point. The naïve cells however disengaged from the antigen presenting cells by 24 hours and became very motile by 72 hours after PG injection. Their behavior suggested that either they were only transiently engaged with antigen presenting cells in the arthritic lymph node or they had limited access to these cells because of out competition by their antigen experienced counterparts.

**Competition for Ag is proportional with the frequency of Ag specific T cells among the competing populations and can be demonstrated in vitro**

Antigen-experienced T cells clearly have the advantage in competing for antigen over their naïve counterparts because of their higher numbers and higher
affinity to the relevant antigen. In the above experiments, the concentration of the intraarticularly injected PG was probably very low in the joint-draining lymph node thus making ideal circumstances for T cell competition. In this experiment we sought to determine whether this competition can be demonstrated in vitro with tetramer assay using flow cytometry. The binding of the PG tetramer could be clearly demonstrated even at suboptimal (non-saturating) dose of the tetramer. The number of binding naïve T cells was higher in the absence of the PG experienced T cells which indicated that they were outcompeted by them for tetramer binding. The specificity of PG tetramer binding could be confirmed by demonstration of further competition between antigen-experienced T cells and naïve PG-TCR-Tg T cells. No competition was demonstrated at higher (saturating) doses of the PG tetramer and it was also not observed when T cells were incubated with the control CLIP tetramer at any dose. This experiment shows that the differences in T cell motility between the antigen-experienced and naïve T cell populations are likely due to competition for access to antigen presenting cells presenting PG epitopes.

**When there is no competition, arrest of naïve T cells can be demonstrated in the JDLNs of arthritic hosts.**

To investigate the effect of the lack of competition on the in vivo motility of the naïve T cells in similar setting, we injected only naïve T cells into arthritic hosts. The total number if injected naïve T cells equaled the combined number of injected T cells in the in vivo experiments described above. We conducted imaging at 4, 8, 24, 48 and 72 hours post transfer and PG injection. Naïve T cells arrested and remained immotile for the first 24 hours. Their motility coefficient increased and the percentage of immotile cells dropped in an almost linear fashion between 24 and 72
hours. This suggested that when naïve T cells had to compete only with the endogenous antigen experienced T cells in this setting, they indeed had better access to antigen then in the presence of transferred antigen-experienced competitors.

The motile behavior of naïve T cells in the JDLN is modulated by joint inflammation

In this experiment we repeated the experiment described in the previous topic but we imaged the joint-draining lymph node that drained a not visibly inflamed ankle joint. We found that although the initial velocity of the T cells in the non-arthritic JDLN was slightly higher, T cells in arthritic JDLN regained their motility sooner. These findings suggest that inflammation (in this case, arthritis) has a modulating effect on the dynamics of antigen presentation in lymph nodes draining inflammatory sites.

Ag-experienced T cells make contacts with transferred, recently migrated DCs but they engage in long lasting interactions with endogenous (LN-resident) APCs

In a limited number of experiments, we co-transferred fluorescence labeled dendritic cells with antigen into the ankle joints and naïve or antigen experienced T cells intravenously into arthritic mice to visualize their interaction with two-photon microscopy. By 24 hours a number of dendritic cells migrated into the joint-draining lymph node and they were visible in the T cells zones of the lymph nodes. Both naïve and antigen-experienced T cells made contacts with these dendritic cells, however these contacts were mainly temporary (i.e. were lasting for less than 10 minutes.) The same T cells however were noticed to engage in long term interactions with
autofluorescent spots we thought to be endocytic vesicles of mice’s own resident antigen presenting cells.

**Discussion**

We monitored the migration of fluorescence-labeled antigen experienced T cells into the ankles and LNs of mice during the adoptive transfer of PGIA with TPM for the first time in an autoimmune model of RA. Interestingly we were unable to find T cells in the joint at any stage of the disease in a consistent manner with two-photon microscopy. Similarly to our findings, Holmdahl and colleagues and other studies on murine CIA in DBA/1 mice, and PGIA in BALB/c mice, described low proportion of joint-homing T cells, suggesting that the paucity of these cells in the arthritic joints is characteristic for both CIA and PGIA.

When T cells were depleted prior to transfer from arthritic donor to SCID recipients, arthritis did not develop in the SCID mice, indicating that the presence of T cells in the recipient was necessary for disease development by helping B cells to produce auto antibodies.

On the other hand, in RA, despite the availability of T cell targeting therapies since the 1990s, clinical trials using anti-CD4, anti-CD5, anti-CD7 and anti-CD52 mAbs have not been able to demonstrate a definite clinical efficacy or connection between antibody-induced T-cell depletion and disease status. The reason for this might be that RA is characterized by ‘waxing and waning’ of disease symptoms and a persistence of polyclonally or oligoclonally expanded T cells including self-reactive populations. In most rodent models however, joint inflammation is preceded by a robust and single-Ag focused T cell response, hence they can be described as monophasic. Only a part of this response is directed against self. By deleting T cells or
knocking out molecules essential for the effector function of T cells, the development of arthritis is easily preventable. Also in animal models, T cells show an early involvement in arthritis thus anti-CD4 therapies are most effective if used as a prophylaxis and administered before the appearance of clinical symptoms. Administration of anti-CD4 treatment in the CIA model after the disease onset did not suppress the disease or eliminate the CII-reactive pathogenic population of T cells. This might in part explain the why this treatment proved inefficient when used in established RA. Also, in the majority of animal models, counter-regulatory mechanisms mainly involving innate immune cells such as joint-infiltrating myeloid-derived suppressor cells kick in early during the course of inflammation. By effectively reducing T cell responses and inflammation in a reasonably short period of time, these innate immune cells mask the potentially beneficial effects of T cell targeting therapeutics administered after disease onset.

Focusing our attention to T cell-T cell and T cell-DC interactions and to the motile behavior of T cells we found, that Ag experienced T cells from genetically unmanipulated mice immunized with PG, exhibited similar behavior to naïve TCR-Tg cells in response to encountering Ag presenting cells that carry cognate Ag in the lymph nodes. The differences in motility between the Ag experienced and naïve T cells were clearly detectable in both arthritic and naïve recipients following co-transfer of these cells. These findings are consistent with our theory that repeated immunization with PG in the presence of adjuvant considerably increases the number of Ag-experienced T cells expressing specific TCRs. The high number of these cells in PGIA allowed proper analysis of motility in the context of presentation of PG in the lymph nodes of naïve and arthritic recipient mice. The higher affinity of the TCRs of PG-experienced memory cells to MHC-PG peptide complexes and the higher
expression of co-stimulatory and adhesion molecules as compared to naïve T cells facilitate the establishment of long-lived contacts between APCs and Ag-experienced T cells. These long-lived contacts limit the exposure of the naïve T cells to the same APCs when co-transferred as proved by our in vivo and in vitro experiments. However the arrest of these naïve cells is much more robust when transferred into the arthritic lymph node. This can be explained by the increased frequency and higher Ag presenting potency of the APCs presenting cells in the arthritic lymph node. However other factors for example new peptide epitopes (including autoepitopes) generated in the host mice upon repeated immunization and/or inflammatory joint destruction might contribute to the more robust arrest. When these Ags presented to naïve T cells, self-tolerance can be broken in BALB/c mice during the induction of PGIA, as the arthritic mice show reactivity with self PG and other Ags like citrullinated proteins and self IgGs which are not related to PG. These reactivities are known to arise due to intra- and intermolecular epitope spreading in both BALB/c mice with PGIA of humans with RA.

APCs in the lymph nodes of mice with PGIA are likely able to present a large repertoire of antigenic peptides with diverse specificities. Cognate T cells for these peptides may exist in the transferred naïve and Ag experienced populations. The fact that Ag experienced T cells preferentially engage in long-lasting interactions with endogenous APCs and that they only transiently contact recently emigrated exogenous dendritic cells in the lymph nodes after the transfer of these dendritic cells into arthritic recipient mice supports this theory.

Last, we found that T cells initiate long term contacts less frequently in the absence of inflammation (arthritis) at the site of Ag injection.
Summary

In my PhD study I characterized the trafficking and motility of T cells in the joint and JDLN in PGIA. My new findings are as follows:

- Development of PGIA does not involve significant influx of T cells into the joints.
- I monitored activation-related T cell motility in vivo in genetically unaltered mice for the first time in a complex autoimmune inflammatory disease.
- The motility of Ag-experienced T cells is similar to the motility of TCR transgenic T cells described by other research groups using model antigens.
- T cells are preferentially arrest in JDLN of mice with PGIA.
- The motility of naïve T cells is influenced by cellular competition and inflammation.
- The effectiveness of T cell depletion therapies in murine models of RA can be explained by the elimination of T cells before disease onset (which is possible in experimental arthritis but not in RA), and by the different course of the disease in animal models and RA.

Animal models of RA are essential for in vivo investigation and analysis of T cell recruitment, T cell-APC interactions and competition between Ag experienced and naïve T cells for Ag-bearing APCs in the lymphoid organs. These investigations are not accessible for in vivo studies in humans. The poor availability of these cells in the distal joints and the relatively limited amount of synovial fluid makes these models less ideal to study function of these cells at target sites. Additional studies are needed to refine our understanding of T-cell pathology in autoimmune arthritis and
to further enhance the value of preclinical animal studies in predicting the outcome of T-cell-focused therapeutic interventions in RA.
List of publications related to the dissertation

   DOI: http://dx.doi.org/10.1038/nrrheum.2013.205

   DOI: http://dx.doi.org/10.1016/j.cellimm.2012.08.003
   IF:1.743

   DOI: http://dx.doi.org/10.1186/ar2954
   IF:4.357
List of other publications

   DOI: http://dx.doi.org/10.1016/j.joca.2011.01.012
   IF: 3.904

5. Hamel, K.M., Cao, Y., Wang, Y., Rodeghero, R., Kobezda, T., Chen, L., Finnegan, A.: B7-H1 expression on non-B and non-T cells promotes distinct effects on T- and B-cell responses in autoimmune arthritis.
   DOI: http://dx.doi.org/10.1002/eji.201040690
   IF: 4.942

   DOI: http://dx.doi.org/10.1002/art.24842
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Total IF of journals (all publications): 28.843
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The Candidate's publication data submitted to the Publication Database of the University of Debrecen have been validated by Kenezy Life Sciences Library on the basis of Web of Science, Scopus and Journal Citation Report (Impact Factor) databases.

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