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24 – 28 June 2006, High Tatra Mountains, Slovakia

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Expert Opinion

7th EFIS Tatra Immunology Conference: molecular determinants of T-cell immunity

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This meeting was hosted by the European Federation of Immunological Societies celebrating its 7th meeting in the High Tatra Mountains of Slovakia on 24 – 28 June 2006. Entitled molecular determinants of T-cell immunity, the meeting covered a wide range of novel methods to regulate an unwanted immune response in autoimmunity and boost the immune system to combat viral infection and cancer.

Keywords: ACE2, arthritis, autoimmunity, diabetes, FTY720, HIV-1, HPMA, KRN7000, LYP, MCT1, NKT, SARS, SHP-1, Tec, Treg

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1. Introduction

The European Federation of Immunological Societies (EFIS) Tatra Immunology Conferences are held every other year in a similar style to the Gordon Conferences to cultivate discussions and interactions among scientists with participation limited to ~ 120 people [101,102]. The focus of this meeting was on understanding the molecular determinants of T-cell immunity. This paper highlights some of the key presentations from the conference, with a particular emphasis on those that exemplified the translation of novel therapies from basic research to the clinic and mentions emerging targets in autoimmunity, cancer and viral infection.

2. Autoimmunity

T Baumruker (Novartis Institutes for BioMedical Research, Austria) described FTY720 (2-amino-2[2-(4-octylphenyl)ethyl]-1,3-propane diol), which is a prototype of a new generation of immunomodulators. It is the result of an extensive chemical derivatisation programme of the natural product ISP-I (myriocin), isolated from the culture broth of *Isaria sinclairii* and, as such, is devoid of the initial inhibition of serine palmitoyl transferase (which may induce toxicity but still retains a strong immunomodulatory activity). FTY720 becomes phosphorylated by sphingosine kinase type II *in vivo* that generates a potent sphingosine-1-phosphate (S1P) mimetic [1]. This mimetic is a partial agonist for 4 of the 5 S1Px receptors (S1P1, -3, -4 and -5) where its major mode of action is via the S1P1 receptor [2]. Exposure to FTY720 phosphate internalises the S1P1 receptor on lymphocytes and inhibits their proper egress out of secondary lymphoid organs along a natural existing S1P gradient [3]. This results in a pronounced decrease in peripheral blood T and B cells that translates into an immunosuppressive or immunomodulatory status *in vivo*. FTY720 has been shown to be highly effective in experimental allotransplantation models and autoimmune disease models (e.g., acute experimental autoimmune encephalomyelitis [EAE] in Wistar rats and chronic relapsing EAE in Lewis rats) [4]. Recently, FTY720 has successfully completed a Phase II clinical trial in 281 patients with relapsing multiple sclerosis, the most common form of the disease. The study

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evaluated the effect of FTY720 on disease activity as measured by MRI and clinical relapses as well as its tolerability and safety. Relapse rates were reduced by 55% with FTY720 1.25 mg and 53% with FTY720 5 mg compared with placebo. Efficacy was observed in number and volume of lesions; however, no dose–response relationship was found in this study but this will be addressed in the Phase III studies [4]. There were some adverse events related to non-serious infections and gastrointestinal disorders and a mild and transient reduction in heart rate was noted in a transplantation trial; however, FTY720 appears to be well tolerated. Inhibition of angiogenesis has also been noticed with FTY720, suggesting that this therapeutic approach may have utility in pathological conditions with deregulated angiogenesis. Compounds that are more selective than FTY720 have been discovered and other targets of the sphingomyelin pathway are also being explored.

A Leishman (AstraZeneca R&D Charnwood, UK) discussed a recently described novel mechanism whereby T-cell proliferation can be suppressed using small molecular weight inhibitors of the monocarboxylate transporter 1 (MCT1) that, unlike FK506 and ciclosporin, do not exert their activity through effects on IL-2 regulation [5,6]. Following T-cell activation, MCT1 expression is rapidly upregulated to meet the demand for lactate efflux resulting from an increased glycolytic rate. These MCT1 inhibitors block lactate efflux by potent blockade of lactate transport, which results in the accumulation of lactate within the cell and feedback inhibition of glycolysis. Without being cytotoxic, this suppression of cellular metabolism results in the inability of T cells to sustain the rapid rate of cell division occurring during the early immune response. These MCT1 inhibitors have been shown to inhibit: proliferation of human peripheral blood mononuclear cells induced by phorbol 12-myristate 13-acetate (PMA)/ionomycin; recall antigen and mixed lymphocyte reaction; lymph node expansion in the rat graft-versus-host model; and disease progression in the rat collagen-induced arthritis model. In addition, these compounds appear to generate antigen-specific immunological tolerance in a rat heart allograft model. It has been shown that MCT1 activity is not required for many stages of lymphocyte activation, such as cytokine production, or for most normal physiological functions; therefore, blockade of MCT1 is a novel mechanism of immunosuppression distinct from current therapies.

F Brennan (Kennedy Institute of Rheumatology Division, Imperial College, UK) presented TNF-α regulation in chronic inflammation and the involvement of a newly defined population of T cells. An overview of the development and success of current TNF-α-blocking therapies (infliximab [chimaeric antibody], etanercept (soluble TNF-α receptor–Fc fusion protein) and adalimumab [fully human antibody]) was presented [7]. It has been shown that TNF-α-blocking therapies can result in reduced angiogenesis and sustained prevention of structural damage. A total of 60 – 70% of patients respond but this could be even higher if patients were treated earlier. The advantages of administering these TNF-α-blocking therapies in combination with methotrexate were also described (e.g., reduced antibodies to Infliximab resulting in increased duration of action and prevention of rebound phenomenon) [8]. Currently, there are trials ongoing that target other cytokines involved in rheumatoid arthritis (RA; e.g., IL-1Rα, anti-IL-6R and anti-IL-15), which may help the 30 – 40% of patients who do not respond to current TNF-α-blocking therapies [9]. The mechanism(s) responsible for inducing cytokine production in inflammatory sites were investigated to determine if these differ from that required as part of an immune response [10]. It was found that cytokine production in synovial tissue macrophages from RA but not osteoarthritis patients was T-cell dependent. The RA synovial joint T cells resembled bystander-activated T cells generated from normal blood over 8 days using a cocktail of cytokines (TNF-α and IL-2 and -6). These bystander-activated lymphocytes and RA synovial T cells both induced TNF-α production in resting monocytes in a cell contact-dependent manner, which was abrogated by blockage of the transcription factor NF-κB but augmented if PI3K was inhibited. Furthermore, the signalling 'fingerprint' activated in the responding monocyte or macrophage on activation with bystander-activated T cells was found to be identical to that induced with RA synovial T cells. In addition, this signalling fingerprint was different from that induced by conventional T cells. Analysis of the cytokine-activated T cells over the 8-day culture period indicated that these bystander-activated lymphocytes consist of both $CD3^+$ memory T cells and also an expanded population of $CD3^-CD56^+$ NK cells. These data provide strong evidence for the importance of bystander-activated lymphocytes in inducing TNF-α in chronic inflammatory rheumatoid tissue and raises the exciting possibility that selective inhibitors of TNF-α for chronic inflammatory diseases may be developed. The following molecules were also mentioned as useful targets to inhibit these cytokine-activated T cells: CD18 (β_2 integrin), receptor for advanced gylcosylation end products, CD69, lymphocyte function-associated antigen-1, early T-lymphocyte activation protein 1 and p38 MAPK.

H Jonuleit (University of Mainz, Germany) described a new marker for regulatory T cells (Tregs). $CD4^+CD25^+$ regulatory T cells direct the maintenance of immunological self tolerance by actively suppressing autoaggressive T-cell populations. Using differential proteomics, a novel marker (galectin-10) was identified that is predominantly expressed in human $CD4^+CD25^+$ Tregs but almost undetectable in conventional $CD4^+CD25^-$ T cells. Specific siRNA to galectin-10 abolishes anergy and the suppressive activity of human $CD4^+CD25^+$ Tregs; however, it still needs to be determined if galectin-10 expression is regulated by Foxp3, the transcription factor involved in Treg function. In addition, a new method to purify Tregs was described, by first positively selecting $CD25^+$ cells and subsequently depleting $CD8^+$, $CD14^+$ and $CD19^+$ cells to get $CD4^+CD25^+$ Tregs that are also $Foxp3^+$ [11]. The $\alpha_4\beta_1$ and $\alpha_4\beta_7$ Tregs were defined, which produce large

amounts of TGF-β (T_H3-like) and IL-10 (T-regulatory [Tr]-1 like), respectively [12]. The method of action of Tr1 cells appears to be via cell contact and cytokine-dependent mechanisms, whereas T_H3 cells are only dependent on TGF-β and not cell contact. Interestingly, functional analysis of an anti-CD4 antibody has shown that it can also activate functional Tregs, just like anti-CD3 antibody therapy.

J Bluestone (University of California, USA) discussed intrinsic and extrinsic regulation of autoimmune diabetes. A number of pathways including Tregs and negative co-stimulatory pathways have been implicated in this process. There is strong evidence that the negative costimulatory pathways, cytotoxic T-lymphocyte-associated antigen 4 and programmed death (PD)-1, as well as Tregs, suppress pathogenic T cells in diabetes [13]. Research using animal models of diabetes suggests that antigen-coupled cell tolerance is PD-L1 dependent and this is due to the activities of PD-1 on effector T cells (not Tregs), further suggesting that this is a good therapeutic target. Data were presented using imaging technologies to directly analyse both the steady-state and inflammatory responses of autoimmunity *in vivo.* Evidence was provided that help to explain the biological basis of dominant tolerance, namely that Tregs function to limit autoreactive T-cell activation by interacting with antigen-presenting dendritic cells, thus preventing their differentiation and acquisition of effector functions. Thus autoimmunity can be prevented or slowed down by limiting the supply of activated pathogenic cells either through direct T-cell ablation or Tregs function. Recent data have shown that CD127 (IL-7Rα) can be used as a reliable surface marker for Tregs as $CD127^{low/-}CD4^+CD25^+$ T cells are nearly all $Foxp3^+$, anergic and suppressive, and can even maintain their suppressor function when expanded [14,15]. Indeed, Foxp3 expression correlates with CD127 expression. The two *ex vivo* approaches to expand Tregs for therapeutic use were described using anti-CD3 or -CD28 beads plus IL-2 (polyclonal expansion) or MHC–peptide dimers plus anti-CD28 beads (antigen-specific expansion); however, they cannot be applied in a clinical setting yet due to variability in expansion of Tregs using these methods.

T Mustelin (Burnham Institute for Medical Research, USA) presented the general autoimmunity gene *PTPN22*. It was recently discovered that a functional variant of the human lymphoid tyrosine phosphatase (LYP [*PTPN22*] is associated with Type 1 diabetes in two different populations [16,17]. This finding has now been expanded to nearly all of the common autoimmune diseases. As LYP is only expressed in leukocytes and acts as a critical gatekeeper of T-cell antigen receptor signalling, it seems likely that the *PTPN22* variant alters T-cell development and/or activation in a manner that predisposes to the autoimmune destruction of insulin-producing β-cells that characterises Type 1 diabetes. Biochemical studies on primary human T cells and Jurkat T-leukaemia cells now show that the disease-predisposing LYP variant (*PTPN22*W620*) is a 'gain of function' mutant. Selective small-molecule inhibitors of LYP are being developed at the Burnham Institute by high-throughput screening of chemical libraries and so on for creating proof-of-principle evidence that LYP is a good drug target for the treatment of autoimmune disease. Indeed, it is proposed that other protein tyrosine phosphatase (PTP) members could provide a rich source of drug targets.

W Ellmeier (Medical University of Vienna, Austria) described genetic analysis of Tec family kinase function in immune cells. Members of the Tec kinase family (Bmx, Btk, Itk, Rlk and Tec) constitute the second largest family of non-receptor tyrosine kinases and are preferentially expressed in the haematopoietic system [18]. Tec was found not to be essential for either T-cell development or T-cell receptor (TCR)-mediated activation of naive T cells; however, Tec expression levels were increased in $CD4^+$ T cells after activation and T_H2 polarisation and Tec was essential for optimal cytokine production of *in vitro* polarised T_H1 or T_H2 T cells and for optimal T-cell responses *in vivo*. Data indicates that there is differential utilisation of Tec family kinases during T-cell development and in naive and (re)-activated T cells and suggests that Tec function is required for finetuning T-cell responses of previously activated T cells. Tec family kinases are also expressed in myeloid cells. The analysis of Btk/Tec- and Btk/Bmx/Tec-deficient mice revealed no defects in myeloid cell development as observed by flow cytometric analysis; however, the recruitment of peritoneal macrophages and neutrophils following thioglycollate injection was severely impaired in mutant mice. Although the combined activities of Tec, Btk and Bmx are dispensible for the development of the myeloid lineage, their activities are required for B-cell development. It is planned to extend the studies in these knockout mice to look at osteoclast development and autoimmunity models to investigate if members of the Tec family could be useful targets for the treatment of autoimmunity.

I Stefanova (National Institutes of Health, USA) discussed the role of viruses in the development of autoimmunity. T cells respond to peptides derived from self proteins presented by self MHC by eliciting a partial phosphorylation of the TCR-ζ-chain. This signal is not sufficient to trigger the T-cell effector response but it facilitates the T-cell signalling to the pathogen-derived agonist ligands [19]. Detailed analysis of T-cell clones isolated from a patient with multiple sclerosis during disease exacerbation revealed a decreased amount of the TCR-negative regulator, PTP Src-homology phosphatase (SHP)-1. Expression of SHP-1 inversely correlates with the responsiveness of the individual T-cell clones and it may account for the loss of the ligand-discriminatory potential that led to overt autoreactivity. The screening for potential pathogens that might have induced expansion of these clones using the combinatorial peptide libraries suggested several viral peptides as candidates (e.g., Teno virus and human herpesvirus-5 and -6); therefore, it is possible that these clones were originally triggered during the response to a viral infection. Temporary downregulation of the TCR-negative feedback may represent a physiologically relevant adjustment

of T-cell response to a pathogen with a high mutation rate because it would allow T cells to recognise viral escape mutants that may be generated in the course of infection. Isolation of the T-cell clones locked in the stage with poor ligand discrimination suggests that such cells may occasionally persist *in vivo* and contribute to the development of autoimmune disease. TLR engagement can convert T-cell autoreactivity into overt autoimmunity; this is because infection results in the release of TNF-α, which increases calpain levels that (in turn) downregulates SHP-1 in T cells. In contrast, low concentrations of ionomycin (which provides a very weak signal) stabilises the expression of the calpain inhibitor calpastatin. In addition, naive T cells can increase levels of the transcriptional repressor Foxp3 when stimulated with low concentrations of antigen. Weak signalling stabilises Foxp3 expression in T cells and induces the upregulation of tolerance-inducing genes; however, Foxp3 is not stable and needs to be actively maintained. TNF-α inhibits Foxp3 and thus strong TCR signalling plus TNF-α (which is needed for the preservation of the synaptic strength) provides T cells with an agonist signal that prevents tolerance induction. This was an excellent talk revealing some of the mechanisms whereby viral infection can trigger autoimmunity.

G Wick (Innsbruck Medical University, Austria) presented post-inflammatory fibrosis. The increased proliferation of fibroblasts and excessive deposition of collagenous and non-collagenous extracellular matrix proteins is called fibrosis and develops as a consequence of large groups of pathological conditions (such as inflammation during autoimmune disease). In all of these cases, profibrotic mediators produced by inflammatory cells (notably mononuclear cells involved in innate and adaptive immunity) stimulate fibroblast proliferation and extracellular matrix production or impaired turnover, respectively. Irrespective of the underlying primary disease, fibrosis is following rather stereotypic rules, such as an overproduction of collagen type III in early stages followed by increased deposition of collagen type I later on; therefore, inhibition of the α1 subunit of collagen has been patented as a therapy for early fibrosis. In addition, although TGF-β_1 induces fibrosis, TGF-β_2 and -β_3 are both antifibrotic and it is understood that Renovo plans to initiate a Phase II trial to investigate the effects of locally delivered TGF-β_3 (Justiva™) [103].

3. Cancer

B Rihova (Institute of Microbiology, Czech Republic) described water-soluble *N*-(2-hydroxypropyl)methacrylamide (HPMA) conjugates that are polymer therapeutics designed for drug delivery to improve the therapeutic index of classical cytostatics. HPMA co-polymer is a biocompatible, non-immunogenic, nontoxic and targetable polymeric carrier to which drugs are bound covalently via a peptidyl spacer. The drug becomes biologically inactive once it is bound to the polymeric carrier and is reactivated only intracellularly depending on the proteolytic or hydrolytic cleavable bond between the drug and spacer. Numerous cancer cell lines and experimental cancer models were used to prove *in vitro* and *in vivo* activity of HPMA-based macromolecular therapeutics [20]. New data provide evidence that an impressive antitumour effect is partly due to the cytotoxic and immunomobilising activity of the co-polymer-bound drugs and establishment of significant antitumour resistance is regularly observed following treatment. Therefore, although these free drugs normally damage the immune system, they appear to preserve the immune system when bound to a co-polymer. Indeed, no polymer-related toxicity has been observed with several copolymer-based drugs tested in > 200 patients. Proteolytically cleavable conjugates containing doxorubicin were allowed to enter clinical trials in the UK. A total of eight female patients suffering from progressive disease and were refractory to conventional therapy were treated in experimental palliative therapy in the Czech Republic with doxorubicin–HPMA–human Ig. Experimental and clinical data demonstrate the following: increased efficacy compared with free drugs; decreased immunogenicity of conjugated proteins; long-term circulation in the bloodstream (half-life of 24 – 72 h with significant levels found even 1 week after administration); increased maximum-tolerated dose; activity toward multi-drug-resistant cells; reduced myelotoxicity, hepatotoxicity, cardiotoxiciy, nephrotoxicity and toxicity against thymus; and an enhanced accumulation in solid tumours due to the enhanced permeability and retention effect. Generally, monoclonal antibodies are better than polysaccharides for active targeting of the drug to the cancerous cells; however, passive targeting using a pH-sensitive prodrug gave an enhanced therapeutic effect due to decreased clearance of the drug and Winn's assay has shown that $CD8^+$ T cells could transfer the antitumour immunity to naive mice. The compelling evidence of the therapeutic potential of a HPMA-based conjugate with pH-sensitive release of doxorubicin has attracted interest from the pharmaceutical company Zentiva that is currently completing preclinical studies [104]. A Phase I clinical trial is in preparation. However, because cathepsins are required to release the drug, preclinical studies will need to address if the immune system is affected. In addition, it is necessary to investigate the effect of these therapeutics on an immune response to antigen in immunised mice as most of the data are generated in immunologically naive mice.

M Dhodapkar (Rockefeller University, USA) discussed harnessing the host immune response to preneoplasia. Preneoplastic growths of transformed cells are common and identify a population at risk for clinical cancer. Recent studies have shown that tumour cells in preneoplastic monoclonal gammopathy of undetermined significance (MGUS) carry several of the cytogenetic changes initially observed in the malignant counterpart, multiple myeloma. It was recently shown that T cells in the tumour bed in preneoplastic gammopathy are enriched for preneoplasia-specific effector T cells (IFN-γ producers), which includes both CD4 and $CD8^+$ T cells [21]. Freshly isolated T cells from the myeloma tumour bed lack this

effector function. Progressive myeloma is also associated with a loss of effector function of innate glycolipid reactive NK T cells (NKT) [22]. Together, these data suggest that changes in the immune microenvironment may contribute to malignant transformation in myeloma. Current studies have focused on identifying and characterising the nature of antigenic targets of both T as well as NKT cells in these patients. Serum antibody detection array revealed different patterns of antigenic reactivity in patients. The presence of anti-SRY-related HMG-box gene 2 (SOX2) IgG antibodies is exclusively restricted to MGUS patients, whereas anti-DNA methyltransferase-3 antibodies were detected in patients with multiple myeloma. Furthermore, SOX2-reactive T cells with a T_H1 phenotype were restricted to MGUS and not myeloma or normal patients. Further studies confirmed that intranuclear SOX2 marks the preplasma cell ($CD138^-$) compartment in multiple myeloma. Primary myeloma cells express CD1d and are sensitive to NKT cell killing and lipids (e.g., lyso-PC) isolated from myeloma sera binds to CD1d-restricted NKT cells. Increased levels of lyso-PC have also been found in other severe chronic inflammatory states in humans (e.g., cancer, allergic inflammation and atherosclerotic plaques). Harnessing the naturally occurring host innate and adaptive immune response in preneoplastic states may be a powerful approach for targeted immune prevention of cancer. It has been suggested that NKT cells are more effective than TLR ligands at activating dendritic cells. α-GalCer (KRN7000) is presented by CD1d to Vα24Vβ11 NKT cells in humans. A Phase I trial of α-GalCer pulsed mature dendritic cells in patients with advanced cancer resulted in a sustained expansion of NKT cells for several months in both the blood and bone marrow compartments [23]. New better versions of KRN7000 are also being investigated; however, it was proposed that boosting NKT cell function in combination with T-cell-based approaches would be most efficacious. Another useful target could be IL-17 because it has a role in driving NKT cell-mediated inflammation.

4. Viral infection

J Penninger (Institute of Molecular Biotechnology, Vienna, Austria) presented their learning from severe acute respiratory syndrome (SARS) infections. A second angiotensin-converting enzyme (i.e., ACE2) regulates the renin–angiotensin system by counterbalancing ACE activity [24]. Accumulating evidence in recent years has demonstrated a physiological and pathological role of ACE2 in the cardiovascular systems. Recent data has shown that the SARS coronavirus (the cause of SARS) utilises ACE2 as an essential receptor for *in vivo* infections in mice. SARS spike binds to human and mouse ACE2 and downregulates ACE2 expression worsening acute lung failure [25]. ACE2 acts as a protective factor in various experimental models of acute lung failure as well as being a key determinant for SARS virus entry into cells and thus contributing to SARS pathogenesis; therefore, a new company to make recombinant human ACE2 as a therapy for lethal adult respiratory distress syndrome is being set up. Meantime, it has been noted that people taking ACE inhibitors have a reduced susceptibility to SARS; however, recombinant human ACE2 should be a cleaner therapeutic than ACE blockers. Collectin is a novel homologue of ACE2 and studies with $collectin^{-/-}$ mice are underway.

J Mestecky (University of Alabama, USA) described mucosal immune responses in HIV-1-infected individuals. In striking contrast to other mucosally encountered microbial infections, HIV-1 induces neither vigorous specific IgA immune responses in any body fluid nor in peripheral blood antibody-secreting cells. The dominant isotype induced is IgG. A significant proportion of IgG in genital tract secretions is derived from the circulation and systemic immunisation with several microbial vaccines induces antigen-specific IgG antibodies in these fluids. Therefore, combined systemic and mucosal immunisations may induce long-lasting humoral responses in the systemic and mucosal (both genital and intestinal) compartments required for protective immunity at these sites [26].

5. Expert opinion

This EFIS Tatra Immunology Conference on molecular determinants of immunity highlighted a wide range of therapeutic approaches for autoimmunity, cancer and viral infection.

The mechanism of action of new approaches to suppress T-cell function via FTY720 and MCT1 inhibitors were described for which there is much exciting preclinical data for these compounds in models of autoimmunity and transplantation. Indeed, the clinical trial data with FTY720 looks promising for this new immunomodulator. In addition, progress is being made towards understanding the key cells involved in driving the pathogenesis of autoimmune disease with respect to synovial T cells in RA, triggering of autoimmunity by viral antigens and molecules involved in T-cell signalling (e.g., LYP, Tec and SHP-1). Research into the mode of action of Tregs is progressing, which will be aided by recently identified Treg markers (galectin-10 and CD127).

Very different promising therapies for the treatment of cancer were described. HPMA-based macromolecular therapeutics to deliver cytostatics appear to have good properties in terms of half-life and safety, as well as leading to the development of an effective antitumour $CD8^+$ T-cell response. The ability of KRN7000 to boost NKT cell function is clear but it will likely need to be used in combination with other therapeutic approaches to realise its full potential.

The speed at which so much understanding around the mode of action of SARS coronavirus has been generated is extremely impressive. This learning has already led to recombinant human ACE2 being investigated as a therapy for lethal adult respiratory distress syndrome. Progress has been made into understanding the requirements of an effective vaccine to HIV-1 and it is likely that combined systemic and mucosal immunisations will be required to generate long-lasting humoral immunity.

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