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# Perspective is everything: An irreverent discussion of CNS–immune system interactions as viewed from different scientific traditions

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## Abstract

The immune system is a host defense system comprised of both innate mechanisms able to rapidly recognize and respond to conserved pathogen associated molecular patterns (PAMPs) as well as adaptive mechanisms able to respond to a wide variety of non-conserved and conserved pathogen associated molecules. In vitro and in vivo studies have demonstrated that the kinetics and type of immune response triggered by pathogenic insults is a function of both the nature of the insult and the subsequent cross-regulatory interactions between the responding immune cells. In this context, the potential immunomodulatory influences of the nervous system have been often viewed as exerting minimal modulatory effects and thus of being largely irrelevant in the development of immune responses. Here, using a Saturday Night Live (SNL)-styled point:counterpoint format, we discuss whether and to what extent the nervous system can shape the responses of the immune system. Finally, we examine whether primary degenerative disorders of the CNS are likely to lead to alterations in immune function.

### Keywords

Immune privilege; TREM; CD200; VIP; PACAP; Microglia; CNS

## 1. Introduction

The immune system and the nervous system are two organ systems in which the final function is determined as much by stochastic environmental cues as well as by hard wired or inherent mechanisms (Medzhitov and Janeway, 1998). In addition, cells of both organ systems express many receptors (including neurotransmitter, chemokine and cytokine receptors) that potentially allow for direct interactions and counter-regulation between the CNS and the immune systems (Madden et al., 1995; Cabot, 2001; Frohman et al., 2001; Straub, 2004; Wrona, 2006). However, the ability to study the development and function of either system in isolation in vitro without interactions with the other system has contributed to an unstated but frequent misconception. Specifically, CNS:immune system interactions are presumed to be at best of only minor regulatory importance for the in vivo function of either immune or CNS cells. One consequence of this viewpoint is the failure to understand how primary defects in the nervous system may lead to serious alterations in immune function. To highlight these issues, we present here a Saturday Night Live (SNL) ‘70's styled debate that presents polarized viewpoints of the traditional T cell immunologist versus the neuroimmunologist (Fig. 1). For

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those unfamiliar with SNL and the infamous point:counterpoint discussions between Dan Ackroyd and Jane Curtin, the following weblinks are provided for reference (http://en.wikipedia.org/wiki/Weekend_Update and http://snltranscripts.jt.org/78/78iupdate.phtml). Table 1 defines the acronyms used throughout this paper.

## 2. Excerpted from SNL's collection of unaired point–counterpoint discussion between Dan AyCroyd and Jane Kurton

### Dan “the immunologist” Aycroyd

Neuroimmunology is neither neurobiology nor immunology. At best, this discipline has often been referred to as the third rail of immunology for those with insufficient drive to focus on the serious primary issues of immunology such as thymic selection and self/nonself recognition.

Today, we will debate a major topic for Neuroimmunologists: Does the CNS really play any real role in directing immune system functions? Jane will take the pro-neuroimmunologist point that CNS:immune system interactions actually are biologically relevant. I will take the traditional T cell immunologist counterpoint that T cell responses are driven and shaped by pathogen encounters and cross-regulatory interactions between immune cells. Jane?

### Jane “the neuroimmunologist” Kurton

Before I present the case for CNS driven regulation of immune responses, let me review the case for immune system regulation by the peripheral nervous system.

First, nervous system regulation of immune responses is strongly suggested by the high degree of sympathetic innervation of the lymph nodes and spleen (Frohman et al., 2001; Straub, 2004). Nerve terminals branch into all regions of secondary lymphoid tissue terminating in close apposition with lymphocytes. Second, mechanical or chemical denervation of the spleen leads to increased production of IgG2a over IgG1, suggesting that sympathetic innervation normally suppresses the development of Th1 T cell responses (Bakhiet et al., 2006; del Rey et al., 2006). However, denervation of lymphoid tissue also leads to decreased ability of T cells within these lymph nodes to produce proinflammatory cytokines such as IFN$\gamma$. Alterations in the sympathetic innervation of the thymus (associated with seizure activity) leads to altered CD4:CD8 ratios within the thymus and decreased T cell proliferative capacity (Bhatt et al., 2006).

Direct regulation of lymphocyte function by the nervous system is not only plausible but has been demonstrated both in vitro and in vivo. Lymphocytes express a wide variety of neurotransmitter receptors ranging from β-adrenergic, serotonergic, dopaminergic and even cannabinoid receptors (Shepherd et al., 2005). However, these receptors are not equally expressed across all subsets of immune cells and thus provide for neurotransmitter-specific regulation of specific immune cell populations. For example, the β2-adrenergic receptor, (the receptor for the sympathetic neurotransmitter norepinephrine) is expressed at much higher levels in Th1 CD4+ T cells as compared to Th2 CD4 T cells (Sanders et al., 1997). As a consequence, β2-adrenergic agonists induce intracellular increases of cAMP only in Th1 cells and not Th2 cells (Sanders et al., 1997). Lastly, let me present an example of stage-specific serotonin (5-HT) receptor expression with potential relevance to CNS:immune system interactions. Dendritic cells are the most effective antigen-presenting cell (APC) in the immune system (Lo et al., 1999; Harizi and Gualde, 2005). As these cells progress from an immature to mature stage, their phenotype converts from a highly phagocytic cell with lower expression of MHC and co-stimulatory molecules to a non-phagocytic cell with very high expression of

MHC and costimulatory molecules. Correlating with this maturation step, dendritic cells progress from expressing primarily 5-$HT_{1B}$, 5-$HT_{1E}$ and 5-$HT_{2B}$ receptors to expressing primarily 5-$HT_4$ and 5-$HT_7$ receptors (Idzko et al., 2004).

Pharmacological studies have further illustrated the physiological consequences of this differential expression of serotonin receptors. Increases in intracellular $Ca^{2+}$ are induced by 5-$HT_1$- and 5-$HT_2$-specific ligands only in immature and not mature dendritic cells (Idzko et al., 2004). Conversely, 5-$HT_4$- and 5-$HT_7$-specific ligands trigger increases in intracellular cAMP levels in mature dendritic cells. Previous reports have indicated that cAMP elevation in dendritic cells correlates with promotion of Th2 responses and decreased priming of Th1 T cell responses. Consistent with observations, pharmacological studies have also demonstrated that 5-$HT_4$- and 5-$HT_7$-specific ligands trigger the release of interleukin-1beta (IL-1β) and IL-8 while suppressing the secretion of IL-12 and TNFα: cytokines that play critical roles in directing T cell phenotype. An important control for these studies, was the observation that 5-$HT_3$-receptor expression did not change as a function of dendritic cell maturation and that 5-$HT_3$-specific ligands triggered $Ca^{2+}$ influx in both immature and mature dendritic cells.

Taken together, these data are irrefutable examples of the prominent immunoregulatory potential of the nervous system.

## Dan “the immunologist” Aycroyd

Jane, you ignorant neuroimmunologist! You speak about neurotransmitters and even cannabinoids. You really must be on drugs and you are now making mountains out of molehills. You have no appreciation of the small regulatory scale (SRS) of the responses that you're describing versus the robust regulatory responses (RRRs) of the natural triggers of the immune system (Fujita et al., 2004; Beadling and Slifka, 2006)! You have not thought about the response times of our individual homeland defense systems (IHDSs)! I do not doubt that many dedicated and well-intentioned neuroimmunologists (NIs) could and did record the data you mention. However, in case you have forgotten, the immune system defends the body against pathogenic insults (PIs). Our immune cells have evolved a pattern recognition system (PRS) to detect pathogen associated molecular patterns (PAMPS) (Fujita et al., 2004). This system is comprised of pattern recognition receptors (PRRs) such as the Toll-like receptors (TLRs), c-type lectins, and mannose binding proteins (MBP) that elicit responses from macrophages and granulocytes in the initial hours following the pathogenic encounter (PE).

Jane, in your zeal, you have also forgotten the scale and power of the cross-regulatory interactions between immune cells. These same PAMP signals induce and shape the maturation of dendritic cells and thus shape the final effector functions of the recruited and activated lymphocyte populations (Lo et al., 1999; Fujita et al., 2004; Beadling and Slifka, 2006). These adaptive lymphocyte responses take most of a week to develop. Let's compare this to the time frame of neurotransmitter release: much less than days, much less than hours—a time frame of minutes at the maximum. Based on this time frame, are experiments using permanent loss of neurotransmitter exposure (i.e. denervation) really relevant? Are they really specific to the point at hand (PAH)? Doesn't denervation have primary effects on the vasculature and the health of the organ that must confound any subsequent conclusions (ASCs)? Conversely, is the long-term in vivo/in vitro exposure to neurotransmitter agonists over hours or days, as a consequence of long-term infusion intravenously (IV) or as a consequence of addition to culture media a relevant probe of immune cell function? Are all immune cells highly migratory (HIM)? A neurological synapse (NS) is not the same as an immunological synapse (IS)! An immune cell is not tied down to the neurotransmitter source! Chemokines, cytokines and products of the innate immune system are demonstrated to be highly effective at very low concentrations to alter not only the migration but the activation phenotype of immune cells (Beadling and Slifka, 2006; Charo and Ransohoff, 2006)!

If the effects that you mention are so robust, wouldn't immune deficiencies be more apparent in individuals with neurological disorders (either in PNS or CNS disorders)? Even if human models are lacking, what about generating appropriate animal models? The absolute dominant importance of MHC, co-stimulatory molecules and cytokine expression in initiating and driving T cell function has been confirmed past any doubt by using knock-out, knock-in and conditional expression transgenic animals.

If immunologists are to believe in the functional importance of each of the nervous systems you mention, similar targeted and/or conditional expression studies must also be performed for these neurological regulators of immune function. Would exposure to these neurotransmitters in the physiologically relevant timeframes detectably modify the ability or propensity:

- **a.** of IL-23 to promote T cell acquisition of an IL-17 phenotype (Th17 phenotype)?
- **b.** of T regulatory cells (Tregs) to suppress autoimmune responses?
- **c.** of B7 family members and PD-L1 to drive T cell functions toward Th1, Th2 or to tolerant phenotypes
- **d.** of adjuvants (mimics of PAMPs and PRR agonists) to promote autoimmunity or effective vaccinations?

And by the way, the issues about serotonin aren't really relevant to the nervous system. Serotonin is much more plentiful in the immune system than in the CNS. It was first isolated from the gut (Meredith et al., 2005). It is abundantly expressed in the gut's enterochromaffin cells and in platelets. In the absence of inflammation, T and B cells are found in close apposition with the enterochromaffin cells and could be exposed to serotonin. At sites of active inflammation, several immune components such platelet-activating factor, thrombin, anaphylatoxins (complement C3a and C5a) and even immunoglobulin E-containing immune complexes can trigger platelet release of serotonin (Meredith et al., 2005). Thus, I would consider serotonin as more of an interleukin than a neurotransmitter!

All of this leads me to the important issue of whether the site of inflammation really matters. I concede that the CNS is immune privileged and that it's hard to get adaptive immune responses going in the CNS. However, this is less of an issue of the CNS:immune system interactions and more of an issue of not having a really competent immature dendritic cell population residing at all times in the tissue. Thus, the absence of immunity in the CNS is more a matter of an absence of immune recognition. Indeed, I find it singularly ironic that the brain should be a center of immunological ignorance! Once an adaptive immune response has been started outside of the CNS, lymphocytes can readily invade and attack their targets in the CNS (reviewed in Melchior et al., 2006). I also note that several prominent scientists (classical immunologist [CIs] AND NIs) have reported that activation of PRRs by PAMPs (i.e. amplification of adaptive immune responses by co-administering adjuvants such as CFA, PT or even LPS) is one method to “break” immune tolerance (Melchior et al., 2006). Do similar reports exist for neurotransmitters as adjuvants?

Jane, forget your neuro-speak! Immune cell effector function is driven primarily by pathogen encounter and tissue damage (not the type of tissue nor the type of nervous system encountered)!

### Jane “the neuroimmunologist” Kurton

Dan, let me try to address your comments calmly and rationally.

Let us consider your issue about serotonin. Who gets to call a molecule an interleukin, a chemokine or even an anaphylactotoxin is a manner of who placed their flag on that site first! Serotonin clearly is a major product of activated platelets and a classical mediator of inflammation. As you suggest, it is quite plausible that much of the evolutionary selective pressure on immune cell expression of serotonin receptors has been driven by the cross-regulation of the adaptive immune response by the nature of the early innate immune response. However, this just heightens the consequences of immune cell entry into a serotonin-rich environment such as the CNS. As yet classical immunologists have not defined whether or to what extent serotonin (as an interleukin or an innate inflammatory mediator) could play a role in preventing the immune system from reacting to every foreign antigen (i.e. food) that flows through the gut. Although the presence of the blood–brain barrier was long regarded as an impermeable barrier for leukocyte entry into the CNS, numerous studies have now refuted this view (reviewed in Bechmann, 2005; Carson et al., 2006). Several types of T cells can and do enter the healthy CNS: T cells activated outside the CNS by many triggers including antigen, homeostatic and chemokine signals (Bechmann, 2005; Carson et al., 2006). Thus, despite any potential evolutionary pressure provided by optimizing peripheral innate:adaptive immune system interactions, lymphocytes are being continually exposed to CNS expressed serotonin as part of their normal patterns of tissue trafficking.

Keeping in the theme of “a rose by any other name is still a rose”, let us also consider CNS expression of several molecules with classical immune regulatory functions. CD22 has been characterized as a B cell marker and as a ligand of the inhibitory receptor, CD45 (also known as leukocyte common antigen) (Mott et al., 2004). Somewhat unexpectedly CNS neurons like B cells constitutively express CD22, and even increase expression upon injury. Thus, like B cells, CNS neurons have the potential to inhibit via the CD45 pathway the function of any leukocyte that they might encounter (Mott et al., 2004).

CNS neurons also express a variety of classic chemokines. For example, upon injury cortical neurons express CCL21, a chemoattractant for dendritic cells, and unactivated and memory CD4+ T cells (Columba-Cabezas et al., 2003). Similarly, a subset of GABAnergic interneurons in the cortex and hippocampus express high levels of CXCL14, a potent macrophage chemoattractant (Melchior et al., 2006). In neither situation has the in vivo consequence of expressing these chemokines been definitively demonstrated. However, the effects on leukocytes that do enter the CNS is unlikely to be completely neutral based on potent effects that these chemokines have on the macrophages, dendritic cells and lymphocytes.

Let us now consider the reverse: the potential interactions of immune cells on neurons. By and large the literature in this field is consistent with your theme that regulation of ongoing immune response is primarily the purview of immune cell cross-regulation and is largely tissue independent (Bechmann, 2005; Carson et al., 2006). Typically these studies characterize the in vivo effects of:

- **a.** Transfer of anti-CNS lymphocytes robustly activated in vitro or
- **b.** Active immunization against CNS antigens using robust adjuvants and activators of pattern recognition receptors.

These types of studies detail the destructive impact of the activated immune system on what appears to be a defenseless CNS.

However, several recent studies from a wide variety of groups and subdisciplines are now defining whether and to what extent immune cells interact with the CNS to promote “wound-healing” responses (Penkowa et al., 2003; Boos et al., 2005; Carson et al., 2006; Ziv et al., 2006). For example, studies using complement inhibitors and KO mice lacking specific components of the complement pathway have clearly demonstrated that in the presence of a

strong pro-inflammatory anti-CNS T cell response, complement production can contribute to neuronal cytotoxicity (Nataf et al., 2000). Complement components are likely to have many sites of actions in the CNS. Surprisingly, CNS neurons express complement receptors including the receptors for the anaphylatoxins: C3a and C5a. Even more surprising is that mice lacking these receptors are deficient in neurogenesis following ischemic injury (Rahpeymai et al., 2006)! The likely cause for the difference in outcomes between ischemic injury and anti-CNS T cell responses: the use of amplifying adjuvant signals activating the pattern recognition system.

In the same vein, several groups have even indicated that the immune function of microglia, the resident macrophage of the CNS swings from neuroprotective/neurogenic to neurodestructive/cytotoxic based on the presence of adjuvant and peripheral infections (reviewed in Carson et al., 2006)!

Dan, don't speak! I already know what you're going to say! Jane, You ignorant neuroimmunologist! Don't you know that you've simply proved my point! Immune responses are primarily driven by pathogenic triggers!

### Dan “the immunologist” Aycroyd

Jane, this is too good to pass up! Not only do you agree with me, I now have to jump on your point about microglia. Even you should know that following the immune responses of the microglia is rather minor under conditions in which peripheral immune cells are involved. These microglial cells are merely incomplete macrophages, the body's best balance for maintaining some local host defense within the CNS without triggering too much neuronal death and dysfunction.

Both CIs and NIs have used irradiation bone marrow chimeric (BMC) methodologies to selectively paralyze, ablate or genetically manipulate either the peripheral immune cell population or the CNS resident microglia population (RMPs) (Hickey and Kimura, 1998). Using these tricks, microglia have been demonstrated to be unnecessary for the initiation of EAE (experimentally induced autoimmune encephalomyelitis) and unlikely to play dominant role in shaping strong pro-inflammatory anti-CNS T cell responses following active immunization or transfer of highly activated T cells (Hickey and Kimura, 1998). The recruited bone marrow derived APC are clearly more important here. At best, microglia appear to play a minor immunomodulatory role in tweaking but not substantially altering destructive T cell responses.

### Jane “the neuroimmunologist” Kurton

Dan, I've tried to stay calm and rational, but I have to stop you there! I think that neuroimmunology as a field has served to bring a new and necessary viewpoint to the issue of anti-CNS T cell responses. Most of us are not strongly immunized with our CNS antigens presented in the context of an oil emulsion of heat-killed mycobacterium and pertussis toxin. Nor do we receive anti-CNS T cells strongly polarized toward a robust pro-inflammatory Th1 phenotype by in vitro culture methods. I am unsure what type of survivable peripheral infection that such treatments are meant to represent. However, even while these methods demonstrate the cytodestructive potential of activated T cells, such models do not accurately represent the insults that most of us are likely to receive to our CNS.

Therefore, it was perhaps not surprising to learn that CD4+ T cells have demonstrated neuroprotective functions in a model of Wallerian degeneration (Byram et al., 2004). Wait! I know you believe that T cell responses are usually protective, but only when the immune responses leads to destruction and elimination of pathogens and infected cells. However, here

I describe neuroprotective effects of an *autoimmune* CD4+ T cells response in the absence of destructive cytotoxicity! Indeed, in the absence of strong adjuvants, CD4+ T cells decrease the rate of motoneuron cell death following facial axotomy (Byram et al., 2004). Using knock-out and irradiation bone marrow chimeric methodologies, a very different antigen-presenting cell function has been revealed for microglia. These chimeric types of studies have manipulated whether the peripheral immune system or the CNS resident cells could express MHC class II and thus whether peripheral immune cells versus CNS cells could present antigen to CD4+ T cells. Consistent with the EAE studies you describe, antigen-presentation by peripheral immune cells was required to initiate CD4+ T cell responses. However, antigen-presentation by CNS resident cells was absolutely required to either evoke or sustain the neuroprotective CD4+ T cell phenotype.

Even though CNS-infiltrating peripheral macrophages could be detected within axotomized CNS, these peripheral cells could not substitute for microglia as protective antigen-presenting cells. Thus, rather than just proving you right about activation of the immune system by PAMPs, these data indicate that PAMP-induce activation may not only way to model physiologically relevant anti-CNS T cell responses. You may argue that axotomy is a lab-induced injury, however it does model the normal wear and tear of mechanical injuries one is likely to encounter as part of living. Thus, these and similar types of studies by a wide variety of labs prove both of us right! The immune system can be strongly regulated by both external pathogen associated cues and internal homeostatic cues.

And to bring this all back to neurotransmitters and neuropeptides, kinetics and relevance, I bring up the cross-regulatory role of neurotransmitter, PACAP in a model of neuroprotective T cell responses (Armstrong et al., 2003; Armstrong et al., 2004; Boeshore et al., 2004; Suarez et al., 2006). Following axotomy, PACAP expression is robustly increased in the facial motoneuron nucleus for several days, but only in wild-type and not T cell deficient mice. Knock-out models indicate that the presence of CD4+ T cells are required to induce the expression of PACAP following axotomy. In vitro and in vivo studies illustrate that PACAP then acts to inhibit Th1 T cell responses, while promoting Th2 responses (Delgado et al., 2003; Ganea and Delgado, 2003). These data provide a concrete example that peripheral immune cells and CNS resident cells can cross-regulate each other similar to the cross-regulatory interactions between antigen-presenting cells and T cells!

We now also know that chronic progressive neurological disorders of the CNS are associated with changes in the antigen-presenting cell phenotype of the microglia. In murine models of Alzheimer's disease, and epilepsy and stroke, microglia not only express higher levels of MHC, they express increased levels of molecules such as TREM-2 that trigger an increase in both phagocytic and antigen-presenting cell activity (reviewed in Melchior et al., 2006). Furthermore, in the interest of developing minimally invasive screens for neurological dysfunction, large scale screens of peripheral blood are being conducted in many patient populations with classic CNS disorders (ranging from Alzheimer's disease to autism and schizophrenia) (Casal et al., 2003). Strikingly, these studies are beginning to detect neurologically-associated changes in the phenotype of leukocytes in peripheral circulation! So to bring this full-circle from our conversations starting point: I suggest that these two phenomena are linked and may be direct results of chronic and prolonged exposure of immune cells to dysfunctional neurons! And just to prove that that improper neurotransmitter control of immune cells can have systemic immunological consequences, I refer you to some elegant studies about VIP receptors (VPAC2R) using both transgenic overexpression and knock-out approaches (Goetzl et al., 2001; Voice et al., 2001; Goetzl, 2006). Just as you stated at the beginning of our conversation, if molecules such as VIP are significant regulators of immune responses, these transgenic and KO approaches should lead to overt changes in immunological responses. And indeed they do! VPAC2R overexpressors develop allergies and exhibited

strong Th2-type immune responses while KO mice are hypoallergenic and exhibited strong delayed type hypersensitivity (Th1-type) responses (Goetzl et al., 2001; Voice et al., 2001; Goetzl, 2006)!

### Dan “the immunologist” Aycroyd

Alright, so you want me to admit that the immune system is sensitive to regulation by elements of the CNS. Okay, I can be a sensitive guy. In fact, let me turn it around and suggest that the immune system is simply a superior sensory organ (Blalock, 2005). It's so good that it can respond to stimuli in ranges beyond the dog's hearing, detecting even the least amount of endotoxin or dust mite allergen!

### Jane “the neuroimmunologist” Kurton

on that note, I thank you and say good night.

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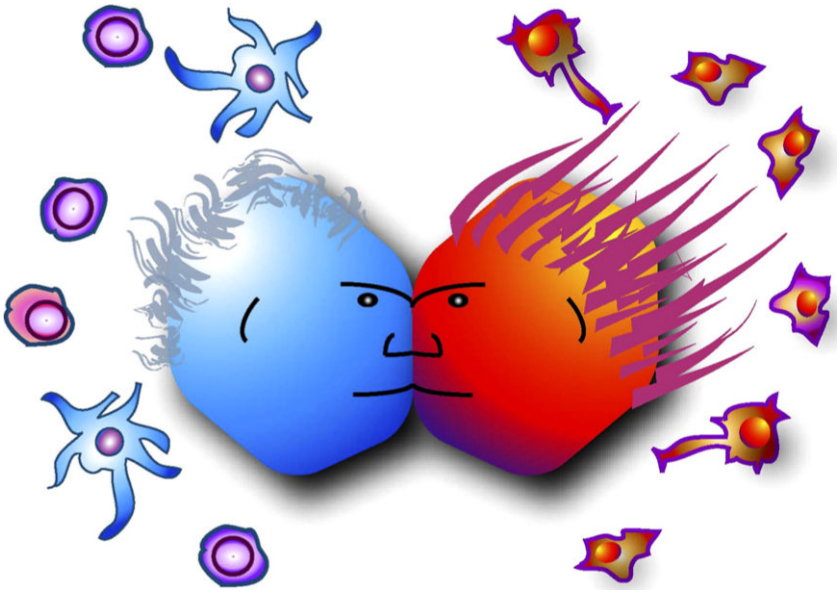

**Fig. 1.**
Point–counterpoint of the neuro-immune divide.

**Table 1**

You shall recognize the true immunologist by the number of abbreviations and acronyms used!

| Acronym/abbreviation | Definition |
|---|---|
| 5-HT | Serotonin |
| ASC | Any subsequent conclusion |
| CFA | Complete Freund's adjuvant |
| CI | Classical immunologist |
| CNS | Central nervous system |
| HIM | Highly migratory |
| IHDS | Individual homeland defense systems |
| IS | Immunological synapse |
| IV | Intravenous |
| KO | Knock-out |
| LPS | lipopolysaccharide |
| MBP | Mannose binding proteins |
| MHC | Major histocompatibility complex |
| NI | Neuroimmunologist |
| NS | Neurological synapse |
| PACAP | Pituitary adenylyl cyclase-activating peptide |
| PAH | Point at hand |
| PAMP | Pathogen associated molecular patterns |
| PE | Pathogenic encounter |
| PI | Pathogenic insults |
| PNS | Peripheral nervous system |
| PRR | Pathogen recognition receptor |
| PRS | Pathogen recognition system |
| PT | Pertussis toxin |
| RRR | Robust regulatory responses |
| SNL | Saturday Night Live |
| SRS | Small regulatory scale |
| Th | T helper |
| TLR | Toll-like receptor |
| Treg | Regulatory T cell |
| TREM | Triggering receptor expressed on myeloid cells |
| VIP | Vasoactive intestinal protein |
| VPAC2R | G protein coupled receptor 2 for VIP |