The Ohio State University
Integrated Biomedical Science Graduate Program
Summer 2011

Alan J. Smith
PhD Candidate

“IL-23 Receptor Expression and Effects of Signaling on T Cell Encephalitogenicity”

June 27, 2011
Room 105 Biomedical Research Tower
9:00 AM
VITA

1977 . . . . . . . . . . . . . . . . . . Born – Kalispell, MT

1996 . . . . . . . . . . . . . . . . . . Clarkston High School

2002 . . . . . . . . . . . . . . . . . . B.S. Zoology, Brigham Young University

COMMITTEE MEMBERS

Amy Lovett-Racke PhD, Advisor
Natarajan Muthusamy DVM/PhD
Abhay Satoskar MD/PhD
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AWARDS AND HONORS

2010 TL1 Trainee Award, Center for Clinical and Translational Science, The Ohio State University, Columbus, Ohio

2009 MD/PhD Scientific Achievement Travel Award, The Ohio State University, Columbus, Ohio

FUTURE PLANS

After I earn my PhD, I plan to return to medical school and finish my MD degree. Once I finish my education at OSU, I plan to enter residency training in a field yet to be determined.
ABSTRACT

Multiple Sclerosis (MS) is an immune mediated disease of the central nervous system characterized by the destruction of myelin sheaths surrounding nerve axons, and it is the leading cause of non-traumatic neurologic disability in young adults. The cause of MS remains unknown, but insights behind the mechanisms of this demyelinating disease are provided through use of animal models. Experimental autoimmune encephalomyelitis (EAE) is the most common mouse model used to study MS. The model is similar to MS in that it is also characterized by inflammation and demyelination within the central nervous system. Interleukin-23 (IL-23) has been implicated as a critical factor for the induction of EAE as mice deficient in IL-23 are resistant to EAE, and systemic administration of neutralizing anti-IL-23 antibodies significantly reduces the incidence and severity of EAE. There is limited knowledge of the functions of this cytokine beyond its ability to enhance IL-17 production in CD4^+ T cells. The goal of this study is to determine the role IL-23 plays in enhancing the encephalitogenic capacity of myelin-specific T cells. To address this goal, the expression of IL-23 receptor (IL-23R) was characterized and was found to be positively regulated by IL-6 and IL-23 and negatively regulated by IL-4 and IFN-\(\gamma\). This characterization of IL-23R expression was then translated to the EAE model. Using adoptive transfer of myelin-specific T cells, we found that signaling of IL-23 through the IL-23R significantly enhances T cell encephalitogenicity. Additionally, IL-23 caused an increase in inflammatory eye disease resembling optic neuritis, a condition commonly observed in MS patients. We also sought to determine if replacing the Mycobacterium tuberculosis found within the Complete Freund’s adjuvant (CFA) with a bacterium that induces an IL-23-dependent Th17 cell response during infection would induce EAE with a different phenotype. Citrobacter rodentium, a bacterium that requires IL-23 for protective immunity, was used as the adjuvant in EAE and compared to CFA. Mice immunized with C. rodentium adjuvant
(CRA) developed classical signs of EAE, similar to CFA-immunized mice, but disease was less severe with a later onset and slower progression than CFA. The clinical course of CRA immunizations resembles that of MS patients better than CFA immunizations suggesting that the use of CRA immunizations may serve as a useful alternative model for studying EAE pathogenesis and potential therapeutics for MS. The effect of IL-23R signaling on T cell encephalitogenicity, the development of optic neuritis and the results of using an IL-23-dependent bacterium in the adjuvant suggest that IL-23 and IL-23R signaling are important factors in the pathogenesis of MS, and an understanding of these may give important insights into the development of demyelinating disease.

**RECENT ABSTRACTS AND PRESENTATION**