Rebekah L. Browning
PhD Candidate

“Combination Therapies with Interleukin-21 in Chronic Lymphocytic Leukemia”

April 1, 2015
DHLRI 165
2:00 p.m.
VITA

1980 ............................... Born – Columbus, Ohio

2002 ............................... B.A., Davidson College

2002-2005 ......................... Post-baccalaureate premedical studies, The Ohio State University

2005-2006 ........................ Research Assistant, The Ohio State University

2006-2008 ........................ Medical student, The Ohio State University

2008-2010 ........................ HHMI Medical Research Training Fellow

2010-present ........................ Graduate Research Associate/Graduate Fellow, The Ohio State University

COMMITTEE MEMBERS

Dr. John C. Byrd

Dr. Natarajan Muthusamy

Dr. William H. Carson, III

Dr. Shusheela Tridandapani
ABSTRACT

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia, with over 15,000 new cases diagnosed in the United States each year. CLL is characterized by an accumulation of malignant B cells and is associated with severe immune compromise, making infection a leading cause of morbidity and mortality in this population. Unfortunately, most frontline therapies for CLL exacerbate immune compromise. Therefore it is of great interest to develop treatment options that target the malignancy while sparing or even enhancing immune function. Interleukin-21 (IL-21) has emerged as one such candidate. IL-21 is a pleiotropic immune-modulating cytokine that is produced by activated T cells. Its many effects include plasma cell differentiation and antibody production in normal B cells, enhanced activity of cytotoxic T cells and natural killer cells, and suppression of regulatory T cell development. IL-21 is of particular interest for therapy of CLL because it is directly cytotoxic to CLL B cells. However, effective cytotoxicity correlates with level of expression of the IL-21 receptor (IL-21R) on the tumor cells, and this expression is highly heterogeneous between patients. Thus, combining IL-21 with other treatments that increase IL-21R expression could result in a more effective therapeutic profile.

CpG oligodeoxynucleotides (CpG ODNs) are synthetic oligodeoxynucleotides with unmethylated CG regions that mimic bacterial DNA and are recognized as pathogen-associated molecular patterns by the human immune system. CpG ODNs have been demonstrated to increase IL-21R expression and enhance IL-21-mediated cytotoxicity in CLL cells. However, the mechanism by which CpG ODNs upregulate IL-21R has not been elucidated. In T cells, T cell receptor-induced upregulation of IL-21R is mediated through binding of the transcription factor Sp1 to the IL-21R promoter. However, we demonstrated that while luciferase promoter constructs containing the Sp1 binding site did show more baseline luciferase activity in CLL B cells as compared to constructs not containing the Sp1 binding site, these constructs did
not show enhanced luciferase activity with CpG ODN treatment. This suggests that Sp1 may be involved in constitutive expression of IL-21R but is not responsible for CpG ODN-mediated upregulation of IL-21R. As CpG ODNs signal through toll-like receptor 9 (TLR9), and NF-κB is involved in downstream TLR9 signaling, we hypothesized that upregulation of IL-21R by CpG ODN is mediated through NF-κB. Treatment of CLL cells with NF-κB inhibitor Bay 11 abrogated CpG ODN-mediated upregulation of IL-21R, indicating that CpG ODN activation of NF-κB is responsible for the enhanced expression of IL-21R.

Given that CD40 stimulation also upregulates IL-21R on CLL cells, and lenalidomide induces both CD40 and CD154 (CD40 ligand) on CLL cells, we hypothesized that this clinically relevant compound may also induce IL-21R on CLL cells. Lenalidomide is an immunomodulatory drug that, although not directly cytotoxic to CLL cells, has demonstrated efficacy against CLL in clinical trials, most likely through enhanced immune function and alteration of microenvironment interactions. We found that lenalidomide induces IL-21R in CLL B cells. In addition, we demonstrated that lenalidomide induces production of IL-21 in T cells, whether from healthy volunteers or CLL patients. Treatment of CLL cells with the combination of lenalidomide and IL-21 enhanced IL-21-mediated cytotoxicity. This combination is associated with induction of p21 and the pro-apoptotic protein Bid. In addition, we found that combined lenalidomide and IL-21 leads to a decrease in Lck, which is involved in pro-survival B cell receptor (BCR) signaling in CLL cells. We found that lenalidomide combined with IL-21 leads to reduced phosphorylation of SYK and PLCγ2, indicating that the combination reduces BCR signaling. These findings demonstrate a new potential combination therapy for CLL.

Taken together, these studies enhance our understanding of the regulation of IL-21R and can contribute to development of rational combination therapies with both direct anti-tumor effects and enhanced immune function.

Browning, RL; Jones, J; Muthusamy, N; Byrd, JC. “Lenalidomide and Interleukin-21 Show Synergistic Cytotoxicity in Chronic Lymphocytic Leukemia B Cells.” Poster presentation. OSUCCC-James Annual Scientific Meeting. Columbus, OH, 2013.

Browning, RL; Johnson, AJ; Muthusamy, N; Byrd, JC. “Synergistic Activity of Lenalidomide and Interleukin-21 in Chronic Lymphocytic Leukemia.” Poster presentation. OSUWMC Trainee Research Day. Columbus, OH, 2013.

RECENT PUBLICATIONS


Maddocks, K; Ruppert, AS; Browning, R; Jones, J; Flynn, J; Kefauver, C; Gao, Y; Jiang, Y; Rozewski, DM; Poi, M; Phelps, MA; Harper, E; Johnson, AJ; Byrd, JC; Andritsos, LA. “A dose escalation feasibility study of lenalidomide for treatment of symptomatic, relapsed chronic lymphocytic leukemia.” Leukemia Research. 38 (9):1025-1029. 2014.

Lapalombella, R; Andritsos, L; Liu, Q; Browning, RL; Pham, LV; Blum, KA; Blum, W; Ramanunni, A; Raymond, CA; Smith, LL; Lehman, A; Mo, X; Jarjoura, D; Chen, CS; Ford, R Jr; Rader, C; Muthusamy, N; Johnson, AJ; Byrd, JC. “Lenalidomide treatment promotes CD154 expression on CLL cells and enhances production of antibodies by normal B cells through a PI3-kinase-dependent pathway.” Blood. 115(13):2619-29. 2010.

In preparation:
Browning, RL; Byrd, WH; Gupta, N; Mo, X; Bo, L; Muthusamy, N; Byrd, JC. “Lenalidomide induces interleukin-21 production by T cells and enhances IL-21-mediated cytotoxicity in chronic lymphocytic leukemia B cells.”
AWARDS AND HONORS

NCI F30 Ruth L. Kirschstein Individual Predoctoral NRSA for MD/PhD Fellowship 1F30CA174232-01, 2013-2016.

The Ohio State University Board of Trustees Student Recognition Award, 2010

American Society of Hematology Trainee Research Award, 2010

Ohio State University Comprehensive Cancer Center Annual Scientific Meeting, Second Place Innate Immunity Poster, 2010

FUTURE PLANS

I will be returning to medical school with plans to pursue a career as a physician-scientist.