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PhD Candidate

“Restoring Innate NK-cell Immunity with Antibody Therapeutics in CLL B-Cell Malignancy”

November 3rd, 2016
Starling Loving M008
9:00am
VITA

July 25th, 1989              Born – Elgin, IL

2010.              Undergraduate Research Fellow, Loyola University Health Sciences, Chicago, IL

May, 2011              B.S. Chemistry, North Park University, Chicago, IL

July 2011 - present              Graduate Research Associate, Biomedical Sciences Graduate Program, The Ohio State University, Columbus, OH

COMMITTEE MEMBERS

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ABSTRACT

Chronic Lymphocytic Leukemia (CLL) is the most prevalent adult leukemia with estimations in the United States of over 18,900 newly diagnosed cases and 4,600 deaths for 2016. Patients suffer from profound immune system defects. Secondary infection is a leading cause of morbidity and mortality, which is further exacerbated by frontline therapy. A deeper understanding of the immune suppression that is intrinsic to CLL disease is needed. Enhancing Natural Killer (NK) effector functions has emerged as a promising immunotherapy. NK cells are innate immune effectors that survey and kill pathogen-infected or malignant cells, and are a major component of anti-tumor response especially with monoclonal antibody therapeutics (mAbs) that engage NKs and mediate tumor killing. Activating NK anti-tumor functions depends on a tightly regulated network of inhibitory and activating receptors that detect “self” antigens, which are severely deregulated in CLL leading to tumor escape. MAbs that activate NK anti-tumor immunity represent a promising chemotherapy-free therapeutic option that would not only spare patients’ immune system but even enhance the anti-tumor response.

Antibodies generated by glyco-engineering have improved capacity to recruit and activate NK anti-tumor response. Defucosylation is a form of glyco-engineering that removes a fucose moiety at the CH2 locus within the antibody constant region (Fc) and raises the affinity between antibody and NK resulting in more effective NK-mediated killing of targeted cancer cells. B-cell activation factor (BAFF) ligating to BAFF receptor (BAFF-R) triggers critical pro-survival signals in B cells, and blocking this interaction represents a novel target for immunotherapy. We show that glyco-engineered anti-BAFF-R, B-1239, activated superior NK antibody-dependent cellular cytotoxicity (ADCC) over CD20 antibodies like glyco-engineered obinutuzumab. Anti-BAFF-R activated additional innate immune response as demonstrated by TNFα release from monocytes and macrophages and induced
antibody cellular phagocytosis (ADCP). Anti-BAFF-R antagonizes BAFF-mediated protection of CLL cells from apoptosis and blocks NF-κB signaling as shown both in bulk protein analysis and at the single-cell level. Similarly, BAFF signaling was observed in CLL B-cells treated with ibrutinib, which blocks Bruton’s tyrosine kinase (Btk) and mediates B-cell receptor (BCR) signaling cascades and could be antagonized with anti-BAFF-R pretreatment. In vivo, anti-BAFF-R treatment rapidly cleared peripheral blood and effectively combined with ibrutinib to provide survival advantage in a murine CLL model.

CLL patient NK-cell counts correlates with stage of disease and time to treatment, and are severely dysfunctional. CLL B-cells overexpress HLA-E, a MHC class I molecule that differentiates “self” from “non-self,” and leads to NK cell inhibition by binding NKG2A. NKG2A, the primary inhibitory receptor on NKs, has garnered much attention as a promising target of antibody therapy to alleviate NK cell suppression. Specifically anti-NKG2A, monalizumab, is entering phase II clinical trials in various cancers. In CLL, NKG2A is expressed on CD56+ CD16+ NK cells, and blocking NKG2A with monalizumab is sufficient to restore NK-killing capacity thus indicating the significance of HLA-E/NKG2A to drive tumor escape.

These findings demonstrate the impact of NK-cell dysfunction in CLL, and the novel therapeutic approaches of glyco-engineering and antigen selection to generate effective antibody-therapy. Together, these studies deepen our understanding of NK-cell immunosuppression in CLL and contributes to the development of rational combination therapies to eradicate tumor and enhance anti-tumor response.
RECENT ABSTRACTS AND PRESENTATION

E.M. McWilliams, C.R. Lucas, B.K. Harrington, N. Muthusamy, J.C. Byrd. “Anti-BAFF-R Glyco-Engineered Antibody, B-1239, Blocks BAFF Survival and Enhances the in vivo Activity of Ibrutinib in a Pre-clinical Mouse Model of CLL.” OSU Comprehensive Cancer Center – James Annual Scientific Meeting (Columbus, OH, April 2016)


ORAL PRESENTATIONS

“Exploiting Pro-Survival BAFF-Receptor Signaling in Chronic Lymphocytic Leukemia.” Biomedical Sciences Graduate Program Retreat. The Ohio State University, (Columbus, OH), (December, 2013), Invited Presentation.
RECENT PUBLICATIONS


* denotes co-first authorship
** denotes co-senior authorship
FUTURE PLANS

Emily McWilliams is currently looking for post-doctoral opportunities in Boston, MA. She plans to further her training in an industry setting focusing on immuno-therapy based translational oncology research. Her long-term research goals are to integrate basic cancer biology and immune-therapies to push for curative therapies in cancer. As a PhD candidate that is heavily invested in translational research, she strives to comprehensively understand the key regulatory pathways that drive tumorigenesis, how alterations in signaling pathways are involved in cancer biology, and how to apply this knowledge for novel drug development.
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