**Potential Role of Fc-gamma Receptors in Elevated Clearance of Immune Checkpoint Inhibitors**

*Bryan Remaily1, Alyssa Marie M. Castillo1, Trang T. Vu1, Sophia G. Liva1, Min Chen1, Zhiliang Xie1, Justin Thomas1, Bryan Remaily1, Yizhen Guo1, Travis Costa2, Timothy H. Helms3, Kyeongmin Kim1, Samuel K. Kulp1, Thomas A. Mace4,5, Mitch A. Phelps1,5\* & Christopher C. Coss1,5\**

*1Division of Pharmaceutics and Pharmacology, College of Pharmacy, The Ohio State University, Columbus, OH, USA, 2Department of Biomedical Engineering, College of Engineering, The Ohio State University, Columbus, OH, USA, 3Department of Veterinary Biosciences, College of Veterinary Medicine, The Ohio State University, Columbus, OH, USA, 4Division of Gastroenterology, Hepatology & Nutrition, Department of Medicine, The Ohio State University, Columbus, OH, USA, 5The Comprehensive Cancer Center, The Ohio State University, Columbus, OH 43210, USA*

1st Year Graduate Student

Division of Pharmaceutics and Pharmacology

Immune Checkpoint Inhibitor (ICI) therapy has revolutionized the field of anti-neoplastic medicine by showing promising anti-tumor outcomes. However, patients experiencing cancer associated muscle wasting, cachexia, have a reduced probability of achieving disease control and shorter overall survival as compared to non-cachectic patients in a retrospective analysis of ICI therapy in patients with non-small cell lung cancer (NSCLC)1. Similarly, a second study observed in NSCLC and melanoma patients receiving pembrolizumab that patients with the highest pembrolizumab clearance had significantly worse overall survival. This effect was not mediated by an increase in dose, indicating elevated clearance was a marker for, but not the cause of, poor overall survival. Lastly the patients displaying elevated clearance and poor survival displayed clinical features of cancer cachexia, and when accounting for other baseline factors found a strong association between cachexia and increased ICI clearance2. The association between cachexia, increased ICI clearance, and poor overall survival prompted the need for an understanding of the causal mechanisms linking them. An important factor in therapeutic outcome of immune checkpoint inhibitor therapy is interaction between the Fc domain of the therapeutic IgG and its endogenous Fc-gamma receptor. Currently, there are 4 different subclasses of Immunoglobulin Gs which are IgG1, IgG2, IgG3, and IgG4. The subclasses of IgG have differential binding affinities to the various FcγR isoforms, of which there are 6 known human FcγRs. These differences upon FcγR binding affinities can have a significant effect upon the efficacy of therapeutic mAbs, as well as play a role in the modulation of the pharmacokinetic parameters of the IgG3. Therapeutic IgG clearance happens mainly through catabolic processes. This is usually initiated by the internalization of the Ab into the cell by pinocytosis or phagocytosis after binding to their target antigen (target mediated elimination), or from Fc- FcγR binding. Internalization and subsequent degradation of IgG by phagocytic cells of the immune system occurs predominantly after Fc- FcγR binding and is a mechanism that is still not fully understood4. Considering all of these factors in tandem creates a demand to better understand how cachexia can affect differences in the expression of FcγRs, how cachectic signaling could modulate Fc- FcγR interaction, and the contribution of both to the elevated clearance of ICIs in patients undergoing therapy. Specifically, we aim to study how cachexia can modulate expression of various FcγR isoforms by utilizing both cachectic and non-cachectic animal models of colon cancer. Quantification of the relative amounts of FcγR expression in cachectic vs non cachectic mice would prove to be imperative to understanding the effects of cachexia upon the immune system and would be completed via immunohistochemistry and flow cytometry. Additionally, we will utilize similar animal modeling methods with engineered chimeric mAbs with differential binding affinities for the FcγRs in order to quantify changes in efficacy as well as pharmacokinetic parameters. This will serve as a way to empirically understand the relationship between binding affinity and increased ICI clearance via FcγRs. A complete knowledge of this information together could lead to potentially lifesaving changes in the clinical approach to Immune Checkpoint Inhibitor therapy in cancer patients.

1. Roch, B., Coffy, A., Jean-Baptiste, S., Palaysi, E., Daures, J., Pujol, J., & Bommart, S. (2020). Cachexia - sarcopenia as a determinant of disease control rate and survival in non-small lung cancer patients receiving immune-checkpoint inhibitors. *Lung Cancer,143*, 19-26. doi:10.1016/j.lungcan.2020.03.003
2. Turner, D. C., Kondic, A. G., Anderson, K. M., Robinson, A. G., Garon, E. B., Riess, J. W., . . . Stone, J. A. (2018). Pembrolizumab Exposure–Response Assessments Challenged by Association of Cancer Cachexia and Catabolic Clearance. *Clinical Cancer Research,24*(23), 5841-5849. doi:10.1158/1078-0432.ccr-18-0415
3. Dahan, R., Sega, E., Engelhardt, J., Selby, M., Korman, A., & Ravetch, J. (2015). FcγRs Modulate the Anti-tumor Activity of Antibodies Targeting the PD-1/PD-L1 Axis. *Cancer Cell,28*(3), 285-295. doi:10.1016/j.ccell.2015.08.004
4. Keizer, R.J., Huitema, A.D.R., Schellens, J.H.M. *et al.* Clinical Pharmacokinetics of Therapeutic Monoclonal Antibodies. *Clin Pharmacokinet* **49,**493–507 (2010). https://doi.org/10.2165/11531280-000000000-00000

The authors would like to gratefully acknowledge Dr. Chris Coss, Dr. Mitch Phelps, Dr. Tom Mace, and others who have helped from the Coss/Phelps lab