Model-Based Assessment of the Contribution of Fc Proteins and Serum Proteins to the Elevated Clearance of Monoclonal Antibodies

Kyeongmin Kim[1], Bryan Remaily[1], Hannah Lathrop[2], Samuel K. Kulp[1], Latha P. Ganesan[3], Dwight H. Owen[4,5], Xiaokui Mo[6], Thomas A. Mace [2,5], Christopher C. Coss[1,5], and Mitch A. Phelps[1,5]

[1] Division of Pharmaceutics and Pharmacology, College of Pharmacy, The Ohio State University, [2] Division of Gastroenterology, Hepatology & Nutrition, Department of Medicine, The Ohio State University, [3] Division of Rheumatology and Immunology, Department of Internal Medicine, The Ohio State University, [4] Division of Medical Oncology, Department of Internal Medicine, The Ohio State University, [5] The James Comprehensive Cancer Center, The Ohio State University, [6] Center for Biostatistics, Ohio State University

THE OHIO STATE UNIVERSITY
COLLEGE OF PHARMACY

BACKGROUNDS - 1

- Shorter overall survival from immune checkpoint inhibitor (ICI) therapies is associated with high drug catabolic clearance (CL), but not drug exposure, indicating **high CL is a biomarker for, but not a cause of the poor response** [1-3].
- Patient population with rapid ICI CL exhibit phenotypes of cancer cachexia [1]. Essentially, there is a cancer cachexia-associated factor that causes both high CL and poor drug response.

BACKGROUNDS - 2

- **FcRn** (Neonatal Fc receptor) rescues albumin and IgG from lysosomal degradation. It is also important for antigen presentation and is associated with prognosis of various cancers [4].
- **FcγRIIb** (Fc gamma receptor IIb) downregulates immune-cell responses. It also plays a role in the clearance of IgGs within immune complexes and possibly monomeric IgGs by internalizing them into endosomal space [5,6]. In mice, up to 75% of its total expression occurs on liver sinusoidal endothelial cells (LSECs), which are a major site of therapeutic antibody catabolism.
- **Our research revealed the following:**

1) Mouse models of cancer cachexia (C26, LLC) demonstrated increased CL of IgG mAbs compared to tumor-free (TF) mice, replicating the elevated ICI CL observed in humans [7,8].

2) The elevation in CL was lower for IgG mAbs with no binding to FcRn or FcγRs.

Fig 1a. PK of WT and FcRn binding-null IgGs

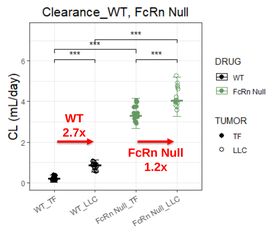
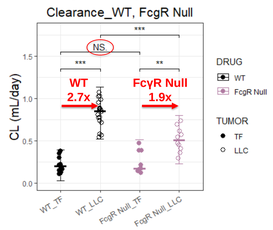


Fig 1b. PK of WT and FcγR binding-null IgGs



3) LLC mice exhibited similar FcRn protein expression and but a 2.3-fold increase in FcγRIIb protein expression in the liver compared to TF mice.

4) Albumin levels were lower in C26 and LLC mice [8].

5) Endogenous IgG levels was positively associated with IgG CL in C26 mice.

- **HYPOTHESIS: Simultaneous alterations in FcRn- and FcγRIIb-mediated pathways are responsible for the rapid CL of IgG antibodies, resulting from their combined effects.**

OBJECTIVES

Aim 1. To explore potential mechanisms and test hypotheses for linking elevated CL to disease-dependent modulation of FcRn, FcγRIIb, endogenous IgG, and albumin through the development of a novel, mechanistic PBPK model.

Aim 2. To investigate the association between Fc proteins, serum proteins, and ICI CL in a clinical trial.

METHODS

Aim 1. A PBPK model was developed by incorporating FcγRIIb-mediated internalization of mAb and endogenous IgG as a competitor for FcRn and FcγR from an initial model adapted from literature [9]. Albumin was included as a surrogate for general catabolic rate and FcRn salvage. Model parameters were obtained from literature, in vitro data, and estimated by simultaneously fitting to observed PK data (using 3 different hIgG1 mAbs in TF and LLC mice), as well as endogenous IgG and albumin levels.

Aim 2. Plasma samples collected prior to the initiation of pembrolizumab or nivolumab treatment from cancer patients were used to determine drug CL, endogenous IgG, and albumin. Expression of FcRn and FcγRs was measured in peripheral blood mononuclear cells by mass cytometry.

RESULTS - 1

PBPK model structure

- Structure of the whole body and the tissue level PBPK model is in Fig 2a and 2b. Total 261 differential equations were used to describe concentration-time profiles of mAb (77 equations), endogenous IgG (77 equations), albumin (77 equations), unbound FcRn (15 equations), and unbound FcγRIIb (15 equations).

Fig 2a.

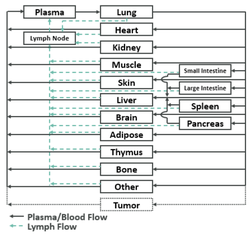
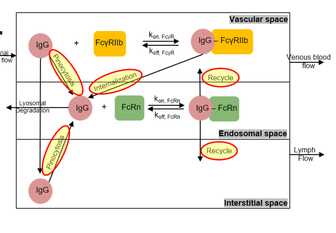


Fig 2b.



Model prediction vs. Observation

Fig 3. Model predicted vs. observed PK

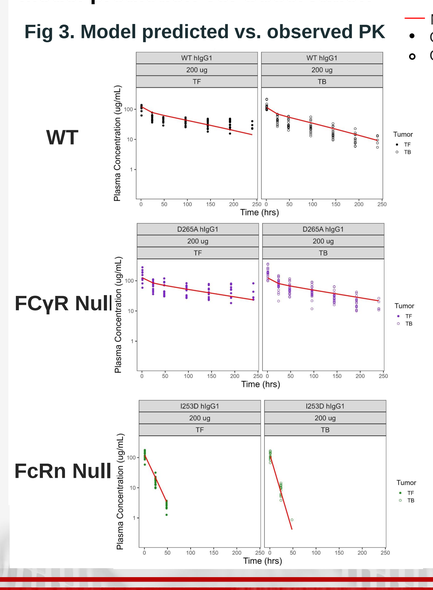


Fig 4. Model predicted vs. observed CL and serum protein levels

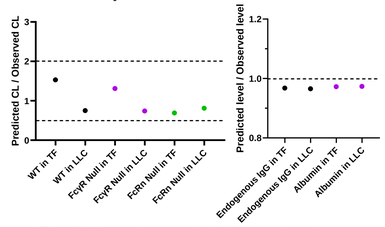
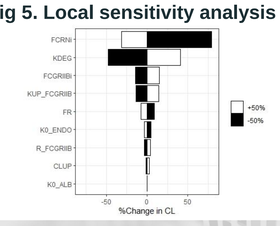


Fig 5. Local sensitivity analysis



RESULTS - 2

Associations between Fc receptors, serum proteins, and CL of ICI from clinical study OSU20001 (PI: Dwight H. Owen, MD)

- Observational study in patients with non-small cell lung cancer (NSCLC) and renal cell carcinoma (RCC)

Fig 6. ICI baseline CL vs. Serum protein levels

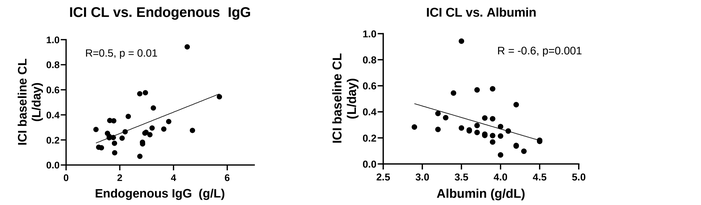
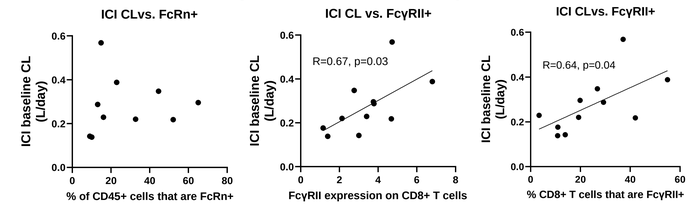


Fig 7. ICI baseline CL vs. Expression of FcRn / FcγRII



CONCLUSION & FUTURE DIRECTIONS

- The model appropriately described the observed plasma PK of three hIgG1 antibodies with varying binding affinities to FcRn and FcγRs, as well as endogenous IgG and albumin in TF and LLC mice.
- CL in LLC mice tended to be underpredicted. The model will be further refined using PK data from hIgG1 mAb lacking binding to both FcRn and FcγRs, which will provide additional insights into non-FcRn- and non-FcγRIIb-mediated catabolic pathways.
- This model was used to predict the CL of IgG mAbs through dynamic simulation of key factors associated with the clearance pathways, which enhanced our ability to explore the complex mechanisms linking ICI CL, Fc proteins, and serum proteins and to test our hypotheses utilizing clinical samples and data.

ACKNOWLEDGEMENTS: Study was supported by The Ohio State University Comprehensive Cancer Center (OSUCCC) and the National Cancer Institute, grants P30CA016058, R01CA273924 and R01CA201382.

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