

## Lung Transplant/Artificial Lung

**Rob Reed** ([rreed@som.umaryland.edu](mailto:rreed@som.umaryland.edu)): Dr. Reed's clinical and translational research focusses on COPD, including potential mechanisms of overlap with atherosclerosis, and lung transplantation including optimization of donor-recipient matching. Dr. Reed participates in several national and multinational networks involving COPD research, including the COPD clinical research network (CCRN), the Pulmonary Trials Collaborative (PTC), and the Trans-Omics for Precision Medicine (TOPMed) network. Dr. Reed is part of a multidisciplinary personalized medicine group that studies gene linkages in the Amish of Lancaster County. As part of this work Dr. Reed established a mobile pulmonary function laboratory which has been used to phenotype ~5000 participants, and he serves as the pulmonary liaison to the Trans-Omics for Precision Medicine (TOPMED) pulmonary working groups.

### Highlighted Publications:

1. Reed RM, Cabral H, Dransfield M, Eberlein M, Merlo C, Mulligan MJ, Netzer G, Sanchez PG, Scharf SM, Sin DD, Celli BR. Survival of Lung Transplant Candidates with COPD: BODE Reconsidered. *Chest*, In press
2. Nugent, K. L., A. Million-Mrkva, J. Backman, S. H. Stephens, Reed, RM, P. Kochunov, T. I. Pollin, A. R. Shuldiner, B. D. Mitchell, and L. E. Hong. Familial Aggregation of Tobacco Use Behaviors in Amish Men. *Nicotine.Tob.Res.* 2014; 16(7):923-930. PMID 24583363
3. Reed RM, A. Amoroso, S. Hashmi, S. Kligerman, A. R. Shuldiner, B. D. Mitchell, and G. Netzer. 2014. Calcified Granulomatous Disease: Occupational Associations and Lack of Familial Aggregation. *Lung*. PMID 25038755
4. Reed RM, Reed AW, McArdle PF, Miller M, Pollin TI, Shuldiner AR, Steinle NI, Mitchell, BD. Vitamin and Supplement Use in the Old Order Amish: Gender-specific prevalence and associations with use. *JAND*. 2014; DOI 10.1016/j.jand.2014.08.020. PMID 25316108
5. Reed RM, Dransfield MT, Eberlein M, Miller M, Netzer G, Pavlovich M, Pollin TI, Scharf SM, Shuldiner AR, Sin D, Mitchell BD. Gender differences in first and secondhand smoke exposure, spirometric lung function and cardiometabolic health in the old order Amish: A novel population without female smoking. *PLoS One* 2017;12(3):e0174354. PMID 28362870

### Links:

Med School faculty page: <http://www.medschool.umaryland.edu/profiles/Reed-Robert/>

### PubMed publications:

<https://www.ncbi.nlm.nih.gov/myncbi/browse/collection/44068698/?sort=date&direction=descending>

**Alexander (Sasha) Krupnick:** Dr. Krupnick is a thoracic surgeon with an academic and clinical focus on the treatment of end-stage lung failure and oncologic disease and Surgical Director of the Lung Transplant Program. His laboratory is focused on lung transplant immunology, including the development of the world's first model of vascularized orthotopic lung transplantation in the mouse (PMC3848695). He has identified numerous mechanistic aspects of lung allograft tolerance and rejection including the role of CD8+ T cells and eosinophils in mediating lung allograft tolerance (PMC3938255, PMC6629120). His work on mechanism and treatment for chronic lung allograft dysfunction have included the role of the recipient microbiome-mediated alteration of the immune response can (PMC7919421) and the role of Thy-1/integrin signaling in controlling chronic lung allograft rejection, which is the topic of this application. In addition to his work on transplantation Dr. Krupnick has also studied methods to reverse the immunological dysfunction associated with cancer. His contributions include describing the role of natural killer

cells in controlling lung cancer development and progression (PMID: 22751136), as well as advancing the understanding of immunological factors that limit natural killer cell function in malignancies (PMID: 30381460, 28123874). Based on this understanding we have developed a rationally designed retargeted cytokine to activate natural killer cells and CD8+ cytotoxic lymphocytes (PMID: 27650575), which are now being advanced toward human applications with an FDA IND application in progress, GMP drug production initiated, and clinical trials planned for summer of 2022.

#### Highlighted Publications:

1. Kreisel D, Richardson SB, Li W, Lin X, Kornfeld CG, Sugimoto S, Hsieh CS, Gelman AE, **Krupnick AS**. Cutting edge: MHC class II expression by pulmonary nonhematopoietic cells plays a critical role in controlling local inflammatory responses. *J Immunol*. 2010 Oct 1;185(7):3809-13. PMC3897247 \***Nominated to Faculty of 1000**.
2. Christopher B. Medina, Parul Mehrotra, Sanja Arandjelovic, Justin S. A. Perry, Yizhan Guo, Sho Morioka, Brady Barron, Scott F. Walk, Bart Ghesquière, **Alexander S. Krupnick**, Ulrike Lorenz & Kodi S. Ravichandran. Metabolites released from apoptotic cells act as tissue messengers. *Nature* 2020 Mar 18; 580, pp130–135.
3. Onyema OO, Guo Y, Wang Q, Stoler MH, Lau C, Li K, Nazarov CD, Wang X, Li W, Kreisel D, Gelman AE, Lee JJ, Jacobsen EA, **Krupnick AS**. Eosinophils promote inducible NOS-mediated lung allograft acceptance. *JCI Insight*. 2017 Dec 21;2(24). pii: 96455. doi: 10.1172/jci.insight.96455. PMID:29263310.
4. Onyema OO, Guo Y, Mahgoub B, Wang Q, Manafi A, Mei Z, Banerjee A, Li D, Stoler MH, Zaidi MT, Schrum AG, Kreisel D, Gelman AE, Jacobsen EA, **Krupnick AS**. Eosinophils Downregulate Lung Alloimmunity by Decreasing TCR Signal Transduction. *JCI Insight*. 2019 Jun 6;4(11). pii: 128241. doi: 10.1172/jci.insight.128241. eCollection 2019 Jun 6. PMID: 31167966.
5. Arefanian S, Schäll D, Chang S, Ghasemi R, Higashikubo R, Zheleznyak A, Guo Y, Yu Asgharian H, Li W, Gelman AE, Kreisel D, French AR, Zaher H, Plougastel-Douglas B, Maggi L, Yokoyama W, Beer-Hammer S, **Krupnick AS**. Deficiency of the Adaptor Protein SLy1 Results in a Natural Killer Cell Ribosomopathy Affecting Tumor Clearance. *Oncoimmunology*, Sep 27;5(12):e1238543. doi: 10.1080/2162402X.2016.1238543. (2016) PMID:28123874
6. Shi L, Li K, Guo Y, Banerjee A, Wang Q, Lorenz U, Parlak M, Sullivan LC, Onyema OO, Arefanian S, Stelow EB, Brautigam DL, Bullock TN, Brown MG, **Krupnick AS**. Modulation of NKG2D, NKp46 and Ly49C/I Facilitates Natural Killer Cell-Mediated Control of Lung Cancer. *Proceedings of the National Academy of Science* 2018 Nov 13;115(46):11808-11813. doi: 10.1073/pnas.1804931115. Epub 2018 Oct 31. PMID:303814604.
7. Guo Y, Wang Q, Li D, Onyema OO, Mei Z, Manafi A, Banerjee A, Mahgoub B, Stoler MH, Barker TH, Wilkes DS, Gelman AE, Kreisel D, Krupnick AS. Vendor-Specific Microbiome Controls both Acute and Chronic Murine Lung Allograft Rejection by Altering CD4+Foxp3+ Regulatory T Cell Levels *American Journal of Transplantation*. 2019 Jul 6. doi: 10.1111/ajt.15523. PMID: 31278849, PMC7919421.

#### Links:

Med School faculty page: <https://www.medschool.umaryland.edu/surgery/Research-Research-Divisions/Thoracic-Surgery-Research/Dr-Alexander-Krupnicks-Lab/>

PubMed publications:

<https://pubmed.ncbi.nlm.nih.gov/?term=krupnick+as&sort=date>

**Christine Lau**: Dr. Lau is Professor and Chair of the Department of Surgery at the University of Maryland, a thoracic surgeon specializing in lung transplantation, and a surgeon-scientist. Her research focuses on the pathogenesis and prevention of lung transplant rejection. Specifically, she has studied (1) biomarkers of bronchiolitis obliterans focusing on the CXCR4/CXCL12 axis, NKT cells, and loss of epithelial cells; and (2) the therapeutic potential of adenosine analogs in mitigating lung transplant injury utilizing a porcine ex vivo lung perfusion and preclinical models.

Highlighted Publications:

1. Harris DA, Zhao Y, Lapar DL, Emaminia A, Steidle J, Kron IL, Lau, CL. Inhibiting Fibrocyte Attenuates Bronchiolitis Obliterans in a Murine Tracheal Transplant Model, JTCVS, 2013 Mar;145(3):854-61.
2. LaPar DJ, Burdick M, Emaminia A, Harris D, Liu L, Strieter BA, Robbins M, Kron IL, Strieter RM, Lau CL. Circulating Fibrocytes Correlate with Bronchiolitis Obliterans Syndrome Development Following Lung Transplantation: A Novel Clinical Biomarker. Ann Thorac Surg 2011;92(2):470-7.
3. Gillen JR, Zhao Y, Harris DA, Lapar DJ, Stone ML, Fernandez LG, Kron IL, Lau CL. Rapamycin blocks fibrocyte migration and attenuates bronchiolitis obliterans in a murine model. Ann Thorac Surg. 2013 May;95(5):1768-75.
4. Lau CL, Zhao Y, Kron IL, Stoler MH, Laubach VE, Ailawadi G, Linden J. (2009) The role of adenosine A2A receptor signaling in bronchiolitis obliterans. Ann Thorac Surg. 88(4):1071-8.
5. Zhao Y, LaPar DJ, Steidle J, Emaminia A, Kron IL, Ailawadi G, Linden J, Lau CL. (2010) Adenosine signaling via the adenosine 2B receptor is involved in bronchiolitis obliterans development. J Heart Lung Transplant. 29:1405-14.
6. Emaminia A, Lapar DJ, Zhao Y, Steidle JF, Harris DA, Laubach VE, Linden J, Kron IL, Lau CL. Adenosine A(2A) Agonist Improves Lung Function During Ex Vivo Lung Perfusion. Ann Thorac Surg. 2011 Nov;92(5):1840-6.
7. Zhao Y, Steidle JF, Upchurch GR, Kron IL, Lau CL. Prevention of the second stage of epithelial loss is a potential novel treatment for bronchiolitis obliterans. J Thorac Cardiovasc Surg. 2013 Apr;145(4):940-947.
8. Gillen JR, Zhao Y, Harris DA, Lapar DJ, Kron IL, Lau CL. Short-course rapamycin treatment preserves airway epithelium and protects against bronchiolitis obliterans. Ann Thorac Surg. 2013 Aug;96(2):464-72.
9. Zhao Y, Gillen JR, Harris DA, Kron IL, Murphy MP, Lau CL. Treatment with placenta-derived mesenchymal stem cells mitigates development of bronchiolitis obliterans in a murine model. J Thorac Cardiovasc Surg. 2014 May;147(5):1668-1677
10. Stone ML; Sharma AK; Mas VR; Gehrau RC; Mulloy DP; Zhao Y; Lau CL; Kron IL; Huerter ME; Laubach VE. Ex Vivo Perfusion With Adenosine A2A Receptor Agonist Enhances Rehabilitation of Murine Donor Lungs After Circulatory Death.. Transplantation. 99(12):2494-503, 2015.

Links:

Med School faculty page: <https://www.medschool.umaryland.edu/profiles/Lau-Christine/>