Asthma

Sergei Atamas (satamas@som.umaryland.edu):

Dr. Atamas's research focuses on the molecular and cellular mechanisms of pulmonary fibrosis and asthma, specifically the interplay between immune inflammation and fibrosis. The Atamas lab utilizes advanced methods of gene delivery in experimental animals in vivo (adenovirus- and lentivirus-mediated delivery of mouse and human genes), various genetically altered mouse models, cell culture-based molecular research that focuses on intracellular signaling pathways that regulate fibroblast differentiation, proliferation and production of extracellular matrix, and advanced methods of gene and protein expression. Prior work has focused on the cytokines an alternatively spliced variant of IL-4, CCL18/PARC, oncostatin M, CCL2/MCP-1, and IL-33, and the cell surface molecules CD40–CD40L and T cell-associated integrins. More recently, the focus of the Atamas lab has expanded to include intracellular/intranuclear regulators of inflammation and fibrosis, including IL-33 precursor, NEU1 sialidase, and sirtuins.

Highlighted Publications:

1. Luzina IG, Todd NW, Nacu N, Lockatell V, Choi J, Hummers LK, Atamas SP. Regulation of pulmonary inflammation and fibrosis through expression of integrins αVβ3 and αVβ5 on pulmonary T lymphocytes. Arthritis Rheum 2009, 60:1530-9

2. Luzina IG, Salcedo MV, Rojas-Peña ML, Wyman AE, Galvin JR, Sachdeva A, Clerman A, Kim J, Franks TJ, Britt EJ, Hasday JD, Pham SM, Burke AP, Todd NW, Atamas SP. Transcriptomic evidence of immune activation in macroscopically normal-appearing and scarred lung tissues in idiopathic pulmonary fibrosis. Cell Immunol. 2018, 325:1-13.

3. Luzina IG, Pickering EM, Kopach P, Kang PH, Lockatell V, Todd NW, Papadimitriou JC, McKenzie AN, Atamas SP*. Full-length IL-33 promotes inflammation but not Th2 response in vivo in an ST2-independent fashion. J Immunol. 2012, 189:403-10. **Faculty of 1000 Prime Recommended (Article Recommendation 717959565)*

4. Luzina IG, Kopach P, Lockatell V, Kang PH, Nagarsekar A, Burke AP, Hasday JD, Todd NW, Atamas SP. Interleukin-33 potentiates bleomycin-induced lung injury. Am J Respir Cell Mol Biol. 2013, 49:999-1008

5. Kopach P, Lockatell V, Pickering EM, Haskell RE, Anderson RD, Hasday JD, Todd NW, Luzina IG, Atamas SP. IFN-γ directly controls IL-33 protein level through a STAT1- and LMP2-dependent mechanism. J Biol Chem. 2014, 289:11829-43

6. Clerman A, Noor Z, Fishelevich R, Lockatell V, Hampton BS, Shah NG, Salcedo MV, Todd NW, Atamas SP*, Luzina IG. The full-length interleukin-33 (FLIL33)-importin-5 interaction does not regulate nuclear localization of FLIL33 but controls its intracellular degradation. J Biol Chem. 2017, 292:21653-61. *Senior co-author and corresponding author

Links:
Med School faculty page: http://www.medschool.umaryland.edu/profiles/Atamas-Sergei/
PubMed publications:
https://www.ncbi.nlm.nih.gov/myncbi/browse/collection/41582342/?sort=date&direction=descending
Google Scholar https://scholar.google.com/citations?user=C2LOTocAAAAJ

Gregg Duncan (gaduncan@umd.edu):

Research in the Duncan Lab is focused on using nanotechnology and bioengineering as tools to broaden understanding of the lung airway microenvironment with ultimate goal of developing new and/or improved treatments and diagnostics. Current areas of interest in my laboratory include airway mucus clearance, virus-induced pulmonary exacerbations, and viral & nanoparticle-based therapeutics. Our work in these areas is currently supported by the American Lung Association, Burroughs Wellcome Fund, the Cystic Fibrosis Foundation, and the NIH.

Highlighted Publications:

1. Joyner K, Song D, Hawkins R, Silcott R, **Duncan GA**. “A rational approach to form disulfide-linked mucin hydrogels”. Soft Matter. 15, 9632-9639, 2019.
2. **Duncan GA**, Kim N, Colon-Cortes Y, Rodriguez J, Mazur M, Birket SE, Rowe SM, West NE, Livraghi-Butrico A, Boucher RC, Hanes J, Aslanidi G, Suk JS. “An adeno-associated viral vector capable of penetrating the mucus barrier to inhaled gene therapy”. Molecular Therapy: Methods & Clinical Development. 9, 296-304, 2018.
3. **Duncan GA**, Jung J, Joseph A, Thaxton AL, West NE, Boyle MP, Hanes J, Suk JS. “Microstructural Alterations of Sputum in Cystic Fibrosis Lung Disease”. JCI Insight, 1(18), e88198, 2016.
4. **Duncan GA**, Jung J, Hanes J, Suk JS. “The Mucus Barrier to Inhaled Gene Therapy”. Molecular Therapy. 24(12), 2043-53, 2016.

Links:
Faculty webpage: https://bioe.umd.edu/clark/faculty/797/Gregg-Duncan
Lab webpage: http://duncan.umd.edu
PubMed publications: https://www.ncbi.nlm.nih.gov/myncbi/gregg.duncan.1/bibliography/public/

Stella Hines (Shines@som.umaryland.edu):

Dr. Hines studies occupational & environmental lung disease with a particular focus on pulmonary physiology. She has a distinct interest in characterizing unique exposures in military populations, ranging from inhalational and systemic metal exposures, blast impact and other airborne hazards in relation to measures of pulmonary physiology, including respiratory impedance. She also studies the use of different forms of respiratory protection among healthcare workers as protection from occupational hazards, with goals of improving preparedness for emerging infectious disease threats and strengthening the healthcare workforce infrastructure

Highlighted Publications:

1. Hines SE, Gucer P, Kligerman S, Breyer R, Centeno J, Gaitens J, Oliver M, Engelhardt S, Squibb K, McDiarmid M. Pulmonary Health Effects in Gulf War I Service Members Exposed to Depleted Uranium. Journal of Occupational and Environmental Medicine. 2013:55;937-944.
2. Hines SE, Barker EA, Robinson M, Knight V, Gaitens J, Sills M, Duvall K, Rose CS. Cross-Sectional Study of Respiratory Symptoms, Spirometry, and Immunologic Sensitivity in Epoxy Resin Workers. Clinical and Translational Science. 2015:8;722-28.
3. Hines SE, Mueller N, Oliver M, Gucer P, McDiarmid M. Qualitative Analysis of Origins and Evolution of an Elastomeric Respirator-based Hospital Respiratory Protection Program. Journal of the International Society for Respiratory Protection. 2017:34:95-111.
4. Hines et al. Impulse Oscillometry Measurement of Distal Airways Obstruction in Depleted Uranium Exposed Gulf War Veterans. American Journal of Industrial Medicine. Am J Ind Med. 2018 Feb 9. doi: 10.1002/ajim.22816. PMID: 29424024 DOI: 10.1002/ajim.22816
5. Kalchiem-Dekel, O. Hines SE. Forty years of reference values for respiratory system impedance in adults: 1977-2017. Respiratory Medicine. 2018;136:37-47.

Links:
Med School faculty page: http://www.medschool.umaryland.edu/occupational/
PubMed publications:

Achsah Keegan (akeegan@som.umaryland.edu)**:**

Dr. Keegan's laboratory focuses on IL-4 and IL-13 signaling in the context of Th2 type inflammation and asthma with a recent focus on macrophage reprogramming. The laboratory has utilized advanced flow cytometry and cell sorting, genetically engineered mice, and mouse models of allergic asthma to make several key findings including (i) characterization of the role of the IRS2 and STAT6 pathways in protecting cells from apoptosis, (ii) identification of residues

within the IL-4Rα required for signal transduction, (iii) elucidation of the effect of allergy-associated polymorphisms in the IL-4Rα on IL-4-induced signaling, (iv) characterization of the complex roles of IL-4Rα, STAT6, and IRS2 in allergic inflammation *in vivo*; (v) how IL-4 promotes the alternative activation of macrophages (M2) and the formation of multinucleated giant cells (MNG) by a STAT6-dependent mechanism; and (vi) how semaphorin 4A and Plexin B1 downregulates allergic airway inflammation.

Highlighted Publications:

1. Nkyimbeng-Takwi, E.H., Shanks, K., Smith, E.P., Iyer, A., Lipsky, M.M., DeTolla, L.J., Kikutani, H., Keegan, A.D., Chapoval, S.P. (2012). Neuroimmune semaphorin 4A downregulates the severity of allergic response. *Mucosal Immunology*. 5:409-419. PMID: 22472774

2. Dorsey, N.J., Chapoval, S.P., Smith E. P., Skupsky, J., Scott, D.W., and Keegan, A.D. 2013. STAT6 controls the number of regulatory T cells in vivo thereby regulating allergic lung inflammation. *J. Immunol*. 191(4):1517-28. NIHMS490589

3. Shanks, K., Nkyimbeng-Takwi, E.H., Smith, E.P., Lipsky, M.M., DeTolla, L.J., Keegan, A.D., Chapoval, S.P. (2013). Neuroimmune semaphorin 4D is necessary for optimal lung allergic inflammation. *Molecular Immunology*. 56:480-487. PMID: 23911404

4. Zhang ZQ, Wang J, Hoy Z, Keegan A, Bhagwat S, Gigliotti F, Wright TW. Neither classical nor alternative macrophage activation is required for Pneumocystis clearance during immune reconstitution inflammatory syndrome. Infection and immunity. 2015; 83(12):4594-603. PMID: 26371121

5. Dasgupta P, Dorsey NJ, Li J, Qi X, Smith EP, Yamaji-Kegan K, Keegan AD. The adaptor protein insulin receptor substrate 2 inhibits alternative macrophage activation and allergic lung inflammation. Science signaling. 2016; 9(433):ra63. PMID: 27330190

6. Keegan AD, Shirey KA, Bagdure D, Blanco J, Viscardi RM, Vogel SN. Enhanced allergic responsiveness after early childhood infection with respiratory viruses: Are long-lived alternatively activated macrophages the missing link? Pathogens and disease. 2016; 74(5). PMID: 27178560

Links:

Med School faculty page: http://www.medschool.umaryland.edu/profiles/Keegan-Achsah/

PubMed publications:

http://www.ncbi.nlm.nih.gov/sites/myncbi/achsah.keegan.1/bibliography/41138906/public/?sort=date&direction=ascending

Erik Lillehoj (elillehoj@peds.umaryland.edu)**:**

The Lillehoj laboratory focuses on the host response to lung infections caused by Pseudomonas aeruginosa, an opportunistic pathogen that impacts the morbidity and mortality of patients with a variety of respiratory diseases, including cystic fibrosis, ventilator-associated pneumonia, and chronic obstructive pulmonary disease. We have established that P. aeruginosa binds to airway epithelial cells through interaction of its flagellin with MUC1, a membrane-tethered mucin. More recently, using in vitro and in vivo model systems, we demonstrated that the P. aeruginosa flagellin-MUC1 interaction is regulated by neuraminidase-1 (NEU1), a host cell enzyme that desialylates MUC1. NEU1-mediated MUC1 desialylation not only renders it hyperadhesive for flagellin, but also increases its proteolytic shedding as a soluble decoy receptor that competitively inhibits P. aeruginosa adhesion to cell-associated MUC1. Our future goal is to develop the MUC1 decoy receptor as a novel therapeutic intervention for P. aeruginosa, and potentially other flagellated microbial pathogens, infecting the lungs.

Highlighted Publications:

1. Lillehoj EP, Hyun SW, Feng C, Zhang L, Liu A, Guang W, Nguyen C, Luzina IG, Atamas SP, Passaniti A, Twaddell WS, Puché AC, Wang LX, Cross AS, Goldblum SE. NEU1 sialidase expressed in human airway epithelia regulates epidermal growth factor receptor (EGFR) and MUC1 protein signaling. J Biol Chem. 2012 Mar 9;287(11):8214-31. doi: 10.1074/jbc.M111.292888. Epub 2012 Jan 13. PMID: 22247545.

2. Lillehoj EP, Hyun SW, Feng C, Zhang L, Liu A, Guang W, Nguyen C, Sun W, Luzina IG, Webb TJ, Atamas SP, Passaniti A, Twaddell WS, Puché AC, Wang LX, Cross AS, Goldblum SE. Human airway epithelia express catalytically active NEU3 sialidase. Am J Physiol Lung Cell Mol Physiol. 2014 May 1;306(9):L876-86. doi: 10.1152/ajplung.00322.2013. Epub 2014 Mar 21. PMID: 24658138.

3. Lillehoj EP, Hyun SW, Liu A, Guang W, Verceles AC, Luzina IG, Atamas SP, Kim KC, Goldblum SE. NEU1 sialidase regulates membrane-tethered mucin (MUC1) ectodomain adhesiveness for Pseudomonas aeruginosa and decoy receptor release. J Biol Chem. 2015 Jul 24;290(30):18316-31. doi: 10.1074/jbc.M115.657114. Epub 2015 May 11. PMID: 25963144.

4. Hyun SW, Liu A, Liu Z, Cross AS, Verceles AC, Magesh S, Kommagalla Y, Kona C, Ando H, Luzina IG, Atamas SP, Piepenbrink KH, Sundberg EJ, Guang W, Ishida H, Lillehoj EP, Goldblum SE. The NEU1-selective sialidase inhibitor, C9-butyl-amide-DANA, blocks sialidase activity and NEU1-mediated bioactivities in human lung in vitro and murine lung in vivo. Glycobiology. 2016 Aug;26(8):834-49. doi: 10.1093/glycob/cww060. Epub 2016 May 25. PMID: 27226251.

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