Get to know members of the RSF Assembly

Is your research clinical, basic science or translational?
Basic Science

Tell us about your research?
My research focuses on the mechanisms regulating epithelial cell injury and regeneration. Our current focus is on defining pathways associated with normal repair, and how disrupting these leads to fibrotic remodelling and loss of functional alveoli. These days our main focus is on the role of alveolar Yap and Taz, and how these effectors of the Hippo pathway appear to be playing distinct roles in directing cell fate decisions associated with AT2 to AT1 cell differentiation and maintenance. The other focus of the group is how LncRNAs regulate cell plasticity during injury repair—hopefully more on that in the near future. To accomplish these studies we use complex genetic mouse models in combination with human and mouse in-vitro and ex-vivo models.

Where do you see yourself in 5 years?
I want to be right where I am, hopefully with my first R01 funded, maybe a second one on our other project, and a slightly larger research group continuing our studies. I really enjoy working with the group of people our Division has put together, and the strong mentoring environment built there that I hope to contribute to in the next few years.

What do you find is the major benefit of RSF Assembly Membership?
Collaboration, networking, and friends.

Jason J Gokey, PhD
Research Assistant Professor
Department of Medicine
Vanderbilt University Medical Center

Please follow us on X @ATS_RSF and like our Facebook page!
If you or someone you know would like to be featured as an ATS RSF ECP please email Katrina Tonga (katrina.tonga@sydney.edu.au)
## Abstract Title:
Sustained activation of Yap/Taz after injury leads to aberrant alveolar differentiation and failure of alveolar repair.

### Introduction:
Recurrent injury to and dysregulated repair of the alveolar epithelium is believed to play a central role in the development of interstitial lung diseases. Our recent work identified dynamic Yap/Taz activity in AT2 cells following alveolar injury, in which, Yap was by activated 7-days, Taz activated by 14-days, and both were down-regulated by 21-days after bleomycin induced injury. Our previous work identified aberrant sustained Yap activation in AT2 cells of patients with idiopathic pulmonary fibrosis. Herein, we sought to determine whether sustained AT2 cell Yap/Taz activity prevents functional alveolar repair and promotes the pathogenesis of pulmonary fibrosis.

### Methods:
Lineage labeled transgenic mice with AT2-cell specific, conditional activation of Yap/Taz (SftpcCreERT2 Stk3f/f Stk4f/f) (referred to as YTAT2 hereafter) 2-weeks after a single dose (0.08IU) of bleomycin injury and assessed 2 and 6 weeks later (4-8 weeks post-injury). Lung fibrosis was quantified by automated image analysis of Masson’s Trichrome staining and Sircol collagen assays and immunofluorescence analysis of epithelial cell type markers was used to assess alveolar epithelial cell differentiation. Single-Cell RNA and ATAC sequencing was used to define the transcriptional networks regulated by Yap/Taz activity.

### Results:
YTAT2 mice had increased fibrotic remodeling at 28 days compared to wild-type mice, and this increased collagen persisted out to 56-days post-injury. Immunofluorescence analysis of lineage labeled Yap/Taz active AT2 cells showed a subset of AT2 cells expressing both AT2 and AT1 cell markers suggesting persistence of transitional cells that normally resolve after regeneration. Analysis of single-cell ATAC sequencing showed bleomycin injured Yap/Taz active AT2 cells had open chromatin associated with promoters of genes normally restricted to AT1 (Ager) and proximal airways (Scgb1a1, Muc5b) consistent with abnormal alveolar epithelial cell differentiation.

### Conclusion:
These studies find that sustained Yap/Taz activity in AT2 cells results in the abnormal differentiation of AT2 cells. This failure of normal adaptive repair leads to increased fibrotic remodeling that fails to resolve out to 56-days.

---

**Jason J. Gokey, PhD**  
Research Assistant Professor  
Department of Medicine  
Vanderbilt University Medical Center  

---

**Please follow us on X @ATS_RSF and like our Facebook page!**

*If you or someone you know would like to be featured as an ATS RSF ECP please email Katrina Tonga (katrina.tonga@sydney.edu.au)*