ABSTRACT FACE PAGE

1. Presenting Author's name: __Catherine Weathered_____
2. Presenting Author's affiliation: __Purdue University_____
3. Presenting Author's title: __*Mycobacterium avium* Infection in the Lungs: Effects of Bacterial Phenotypes and Biofilm_____
4. Presenting Author's email: _weathered@purdue.edu_____
5. Presenting Author's gender (optional): ___female_____
6. Presenting Author's race (optional): _____
7. Presenting Author's ethnicity (optional): _____
8. Presenting Author's affiliation sector: (check one or more)

   ✓ **Academia**
   o Industry
   o FederalEmployee/Contractor
   o PrivateFoundation
   o Other:_____

9. Presenting Author's Career stage: (check one)

   o K-12student
   o Undergraduate student
   ✓ **Graduate Student**
   o Post-doctoral Trainee
   o Young employee (within first 3 year of post-training position)
   o Mid-level employee (3-10 years of post-training position)
   o Senior-level employee (10+ years of post-training position)
   o Other:_____

10. Website / twitter handle / other public links (optional): _____
11. Is this the research presented in this abstract supported by IMAG MSM-related U01 funding?
    No

12. If the Presenting Author is a trainee, who is the trainee's primary research advisor?
    _Dr. Elsje Pienaar_____

13. If the Presenting author is a trainee, would the Presenting Author like to enter his/her abstract in the Trainee Poster Competition*?
    Yes

14. If the Presenting author is a trainee, would the Presenting Author like to enter his/her abstract in the Trainee Oral Presentation Competition**?
    Yes

MYCOBACTERIUM AVIUM INFECTION IN THE LUNGS: EFFECTS OF BACTERIAL PHENOTYPES AND BIOFILM

[1]Catherine Weathered* and [1]Elsje Pienaar
[1]Purdue University, West Lafayette, IN, USA
Email: weathered@purdue.edu

INTRODUCTION: Mycobacterium avium complex (MAC), a member of the nontuberculous mycobacteria family, are environmental microbes, capable of colonizing and infecting humans following inhalation of the bacteria. MAC-pulmonary disease is notoriously difficult to treat and prone to recurrence, and both incidence and prevalence have been increasing [1]. MAC are well known to form biofilms and diverse colonies in the environment. These biofilms have been shown to aid in epithelial cell invasion [2], cause premature apoptosis in macrophages [3], and inhibit antibiotic efficacy [4]. We hypothesize that both phenotypic diversity and biofilm formation are key to establishing and prolonging infections in the lung. To address these hypotheses, we developed a model that shows the interactions between bacteria, biofilm and immune cells as an agent-based model (ABM). This model allows us to explore both the intracellular scale (bacterial phenotypes and macrophage killing), and tissue scale (biofilm formation and epithelial invasion).

METHODS: We used Repast Simphony to develop a three-dimensional ABM of an *in vivo* MAC infection. The grid represents a length of lung airway with a layer of mucus/epithelial lining fluid (ELF). Bacteria agents are divided into either sessile (slow-growing, within biofilm and less susceptible to antibiotics), or planktonic (more quickly growing but not protected by biofilm) phenotypes. Biofilm is represented by continuous variables in each grid compartment, with values corresponding to the amount of extracellular matrix produced by bacteria in that grid compartment. To represent the protective properties of biofilm, the amount of biofilm is inversely related to the likelihood of a macrophage phagocytosing bacteria from that biofilm. All bacterial agents also release a chemoattractant that is represented by continuous variables in each grid compartment, and that diffuses throughout the grid. Macrophages probabilistically follow this chemoattractant gradient. Macrophages can phagocytose bacteria, prioritizing planktonic bacteria (not within biofilms), which are either killed immediately or infect the macrophage. Macrophages also accumulate "apoptotic signal" through exposure to biofilm and internal bacteria.

RESULTS: The model was parameterized through a literature search, test cases based on *in vitro* experiments and a Latin Hypercube Sampling for unknown parameter values. Though analysis is ongoing, we see an early relationship between the initial number of macrophages and the ratio of planktonic to sessile bacteria. Larger initial macrophage numbers result in a stronger and more sustained reduction in planktonic bacteria early after exposure. However, as the infection progresses, the bacterial population is sustained by the sessile bacteria that are protected in biofilms or inside infected macrophages, allowing the planktonic population to recover (Fig. 1).

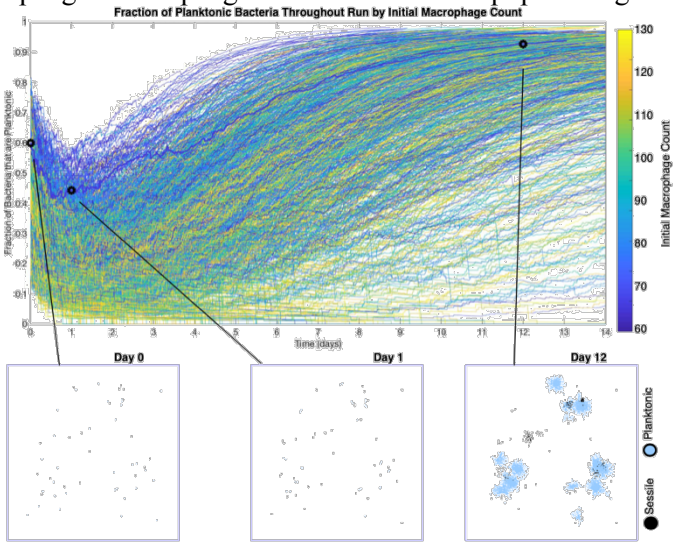

Figure 1. Fraction of planktonic bacteria over time, colored by initial macrophage counts. Gradients are shown in the outcomes. Below is a representative bacteria distribution.

CONCLUSIONS: We have developed a multiscale agent-based model that allows us to study the initial colonization and infection in MAC-pulmonary disease on both the cellular- and tissue level. Early results show distinct contributions of bacterial phenotypes to bacterial persistence. Future directions of this work include further exploring the role of phenotypes and adding drug pharmacokinetics and cell-level pharmacodynamics to better understand the role of biofilm in treatment efficacy.

REFERENCES:

1. Lee, et al. *Antimicrob Agents Chemother*, **59**(6): 2972-2977, 2015.
2. Yamazaki, et al. *Cell Microbiol* **8**(5): 806-814, 2006.
3. Rose and Bermudez. *Infect Immun* **82**(1): 405-412, 2014.
4. Falkinham. *J Med Microbiol* **56**(Pt 2): 250-254, 2007.