Narrative description of progress towards the goals of the project

Mouse model. We purchased from The Jackson laboratories the transgenic mut-Stat3 mouse strain (JAX 027952), which carries two copies of Stat3V463del, one of the common STAT3 mutations found in Job's syndrome patients. The strain needed to be revived from frozen stocks at the Jackson Laboratories. A colony of the mut-Stat3 mice was established at Mount Sinai animal facility by breeding mut-Stat3 mice with wild type (WT) C57Bl/6 mice. Breeding pairs were established this way so that transgenic mut-Stat3 and non-transgenic wild type (WT) mice will be generated as littermates. Mice were genotyped at 3 weeks of age by PCR on genomic DNA extracted from a small tissue biopsy.

LPS induced lung injury. As a model of lung injury, we proposed to use sterile injury induced by intratracheal administration of LPS. In preliminary experiments, eight weeks old mice were administered 75 μg of LPS (*E. coli* 0111:B4, L2630, Sigma-Aldrich) intra-tracheally in 75 μl of PBS. Typically, mice lose weight in the days after after LPS administration but recover by the end of the first week.
Interestingly, in our experiment, LPS treated WT mice lost about 20% of weight by days 5-6 but underwent full weight recovery by day 9 post-treatment. In contrast, mut-Stat3 mouse lost on average 30% weight by day 6 and only recover only 10% of weight up to day 16 post-treatment (**Fig. 1**).

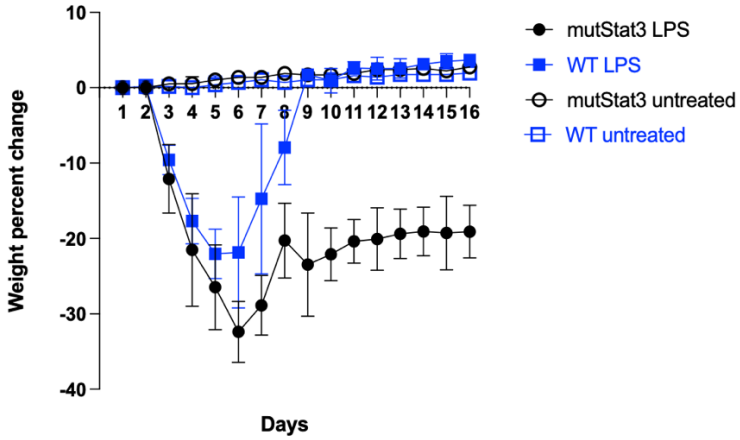

Fig.1. Mut-Stat3 mice fail to recover full weight after intratracheal LPS administration. Groups of mut-Stat3 or WT mice were administered LPS by intra-tracheal route. The mice were weighted every day beginning on the treatment day. The figure shows mean and standard deviation of the weight change per group. n=3 mice per group.

Future studies

We will next profile the cellular composition of structural and inflammatory cells in the lung of mice during the acute phase (days 2-8) and the resolution (WT) chronic phase (mut-Stat3) days 9 and onwards using flow cytometry. Lung structural changes will be monitored by immunohistochemistry. We will also evaluate the expression of pStats in the lung, as well as the production of inflammatory and regulatory cytokines in BAL, lung and serum of mice on these time points. It is possible that the failure in weight recovery in mut-Stat3 is caused by continued inflammation and inflammatory cytokine production (TNF, IL6), and/or by impaired lung tissue repair. Activation of Stat1/2 or Stat6 in mut-Stat3 mice, and deficiency of signaling of regulatory cytokines such as IL-10 or IL-27, both of which signal through Stat3, could also be involved.
We will also analyze changes in the lungs of untreated mut-Stat3 and WT mice in homeostatic conditions as they age.