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## Maternal exposure to environmental particles leads to transgenerational epigenetic transmission of asthma risk

**Statement of the Problem:** Allergic asthma has origins early in life and results from a complex interaction of genome, epigenome and environment. Maternal asthma history and especially gestational environmental exposures increase the risk of asthma in humans and animal models. Exposure of pregnant mice to diesel exhaust particles (DEP) or concentrated urban air particles (CAP) results in an increase in asthma susceptibility in F1 pups in our model. Here, we sought to test the hypothesis that this transmission continues trans-generationally and occurs via epigenetic mechanisms.

**Methodology & Theoretical Orientation:** After the pregnant dams received intranasal instillations of particle suspensions or control, their F1, F2 and F3 offspring were tested for ovalbumin allergy predisposition. We treated a subset of mice at F1 with a DNMT inhibitor to test if this would abrogate the transmission of the phenotype. Moreover, we have previously shown that dendritic cells (DCs) in the F1 progeny are key to the phenotype because they convey the disease predisposition upon isogenic transplant and harbor DNA methylation aberrations; we therefore analyzed the DCs' methylome (eRRBS) in this transgenerational study in all three generations.

**Findings:** We found that the elevated asthmatic susceptibility after maternal exposure to particles during pregnancy persists into F2 and with more variability, into F3 generations: low dose ovalbumin increased levels of eosinophils, IL-5 and IL-13 in broncho-alveolar lavage and histopathologic changes of allergic airway disease, not seen/minimal in controls. The DCs in these generations continued to display DNA methylation changes in several thousand loci, the number was diminishing towards F3. Lineages treated with DNMT inhibitor at F1 no longer showed asthma susceptibility at F2 or F3.

**Conclusion & Significance:** The data indicate that pregnancy airway exposure to particles triggers transgenerationally transmitted asthma susceptibility and suggests a mechanistic role for epigenetic alterations in DCs in this process.

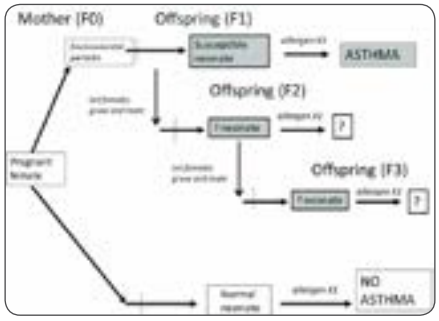


**Figure 1:** Schematic of the transgenerational protocol.

## Recent Publications

1. Shang et al. (2016) Peptide substituted oligonucleotide synthesis & non-toxic passive cell delivery. Signal Transduction & Targeted Therapy 1:e16019.
2. Paul et al. (2015) Oxidative substitution of borane-phosphonate di-esters as a route to post-synthetic modified DNA. Journal of the American Chemical Society 137(9):3253-3264.
3. Caruthers M (2013) The chemical synthesis of DNA/RNA: our gift to science. Journal of Biological Chemistry 288(2):1420-1427.
4. Dellinger et al. (2011) Streamlined process for the chemical synthesis of RNA using 2'-O-thionocarbamate protected nucleoside phosphoramidites in the solid phase. Journal of the American Chemical Society 133:11540-11556.
5. Le Proust E et al. (2010) Synthesis of high quality libraries of long (150mer) oligonucleotides by a novel depurination controlled process. Nucleic Acids Research 38(8):2522-2540.

## Biography

Alexey V Fedulov has his expertise in Epigenetic Engineering and Transgenerational Epigenetic Studies. His lab has built a model of targeted reactivation of epigenetically silenced genes by fusion complexes comprised of DNA demethylase enzymes and sequence-specific DNA binding domains. His laboratory studies are in immune and epigenetic mechanisms of lung disease including early life asthma origins. The ultimate goal of the studies is to find novel therapeutic approaches by modulating epigenetic control of gene expression.