



PMI RESEARCH & DEVELOPMENT

Systems Toxicology-Based Comparisons of Smoking Cessation and Switching to a Non-Combustible Tobacco Product in a Murine Model of COPD

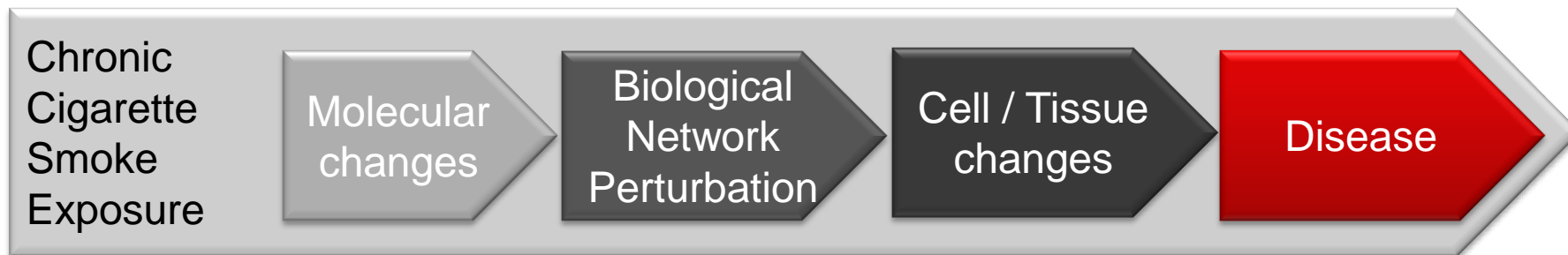
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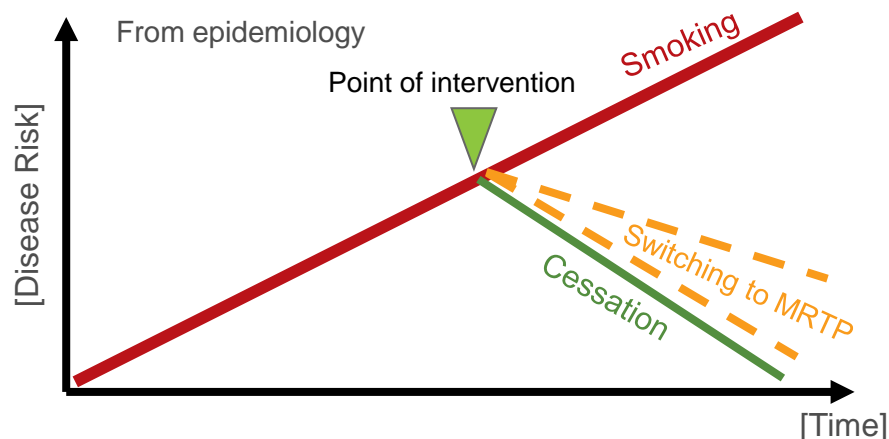
July 2, 2013

International Congress of Toxicology, Seoul, 2013

How Does Biology Respond to pMRTP Aerosols?



What is the biological impact of a pMRTP aerosol compared to cigarette smoke?



- Compare switching to MRTP with continued smoking and benchmark against smoking cessation.
- Assess how close switching to pMRTP is to smoking cessation

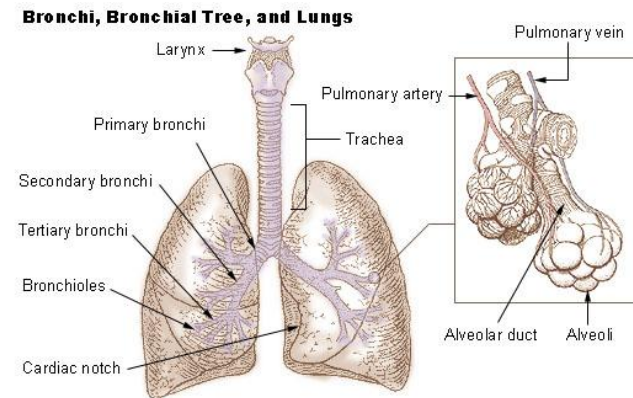


COPD – Chronic Obstructive Pulmonary Disease

COPD is the co-occurrence of chronic bronchitis and emphysema – characterized by airflow limitations which are not fully reversible

Chronic bronchitis:

- Chronic inflammation of the bronchi
- Increased number and size of goblet cells
- Persistent cough
- Increased sputum and mucus
- Narrowing of airways



Emphysema:

- Progressive destruction of lung tissue (notably around the alveoli)
- Pockets of air and airspace collapse during forced expiration.
- Loss of lung elasticity.

* Cigarette smoke is the main etiological factor in the pathogenesis of COPD.

Cigarette Smoke-Induced COPD as an *In Vivo* Model to Assess Smoking Cessation Versus a Switch-to-pMRTP

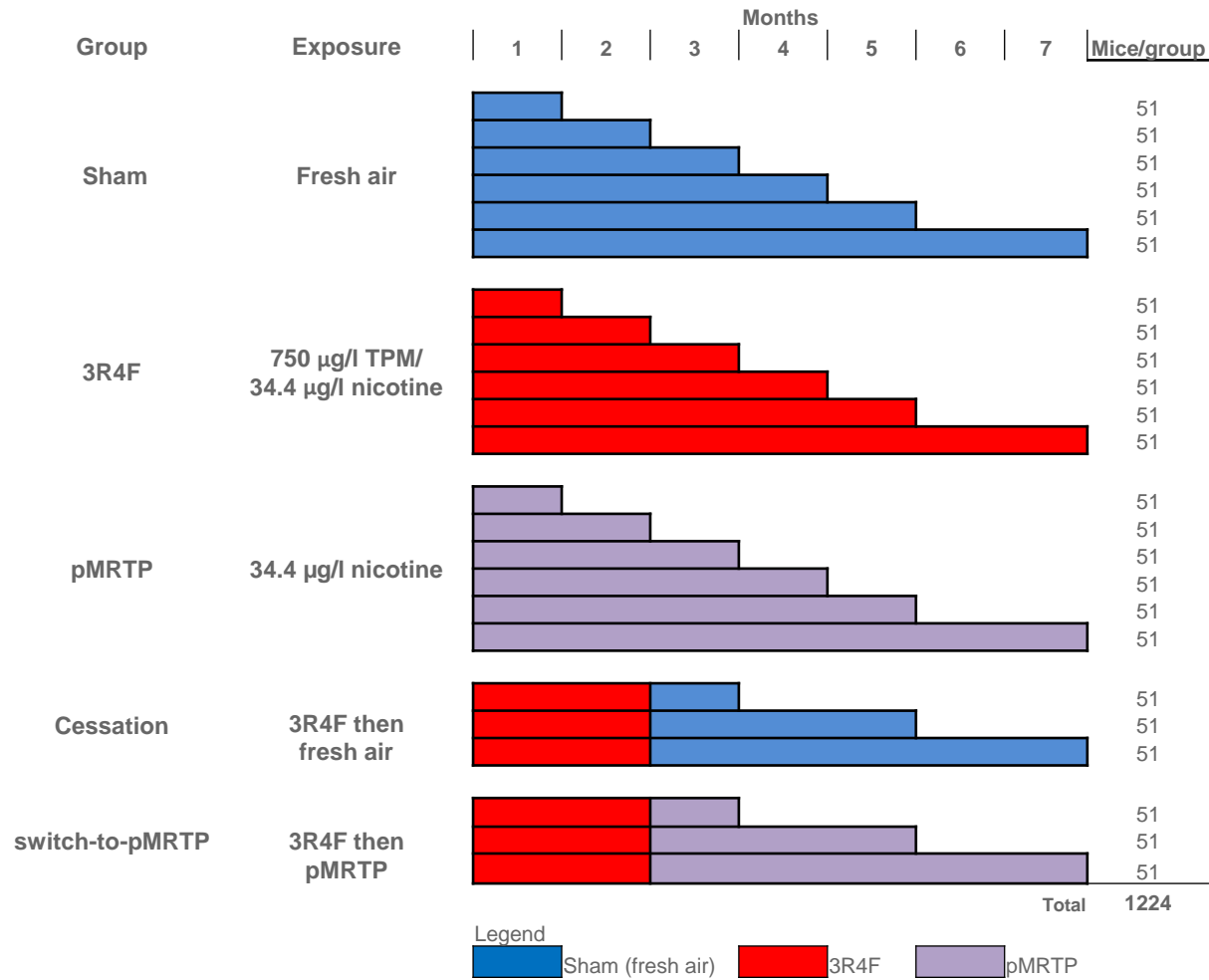
- **Animals:** 1224 female C57Bl/6 mice

Exposure groups:

- i) Sham (fresh air)
 - ii) 3R4F reference cigarettes (University of Kentucky)
 - iii) pMRTP
 - iv) 2 months 3R4F, then fresh air up to 5 months (cessation)
 - v) 2 months 3R4F, then pMRTP up to 5 months (switch-to-pMRTP)
- **Dose:**
 - 34.4 µg/l nicotine in both 3R4F and pMRTP groups
 - 4 hours per day, 5 days per week
 - 7 months maximum exposure
 - **Switching/cessation point:** after 2 months (when histopathological signs of emphysema begin to emerge)



Experimental Design



Aerosol Generation: Smoke Exposure



**Whole-body exposure chamber
(set-up)**

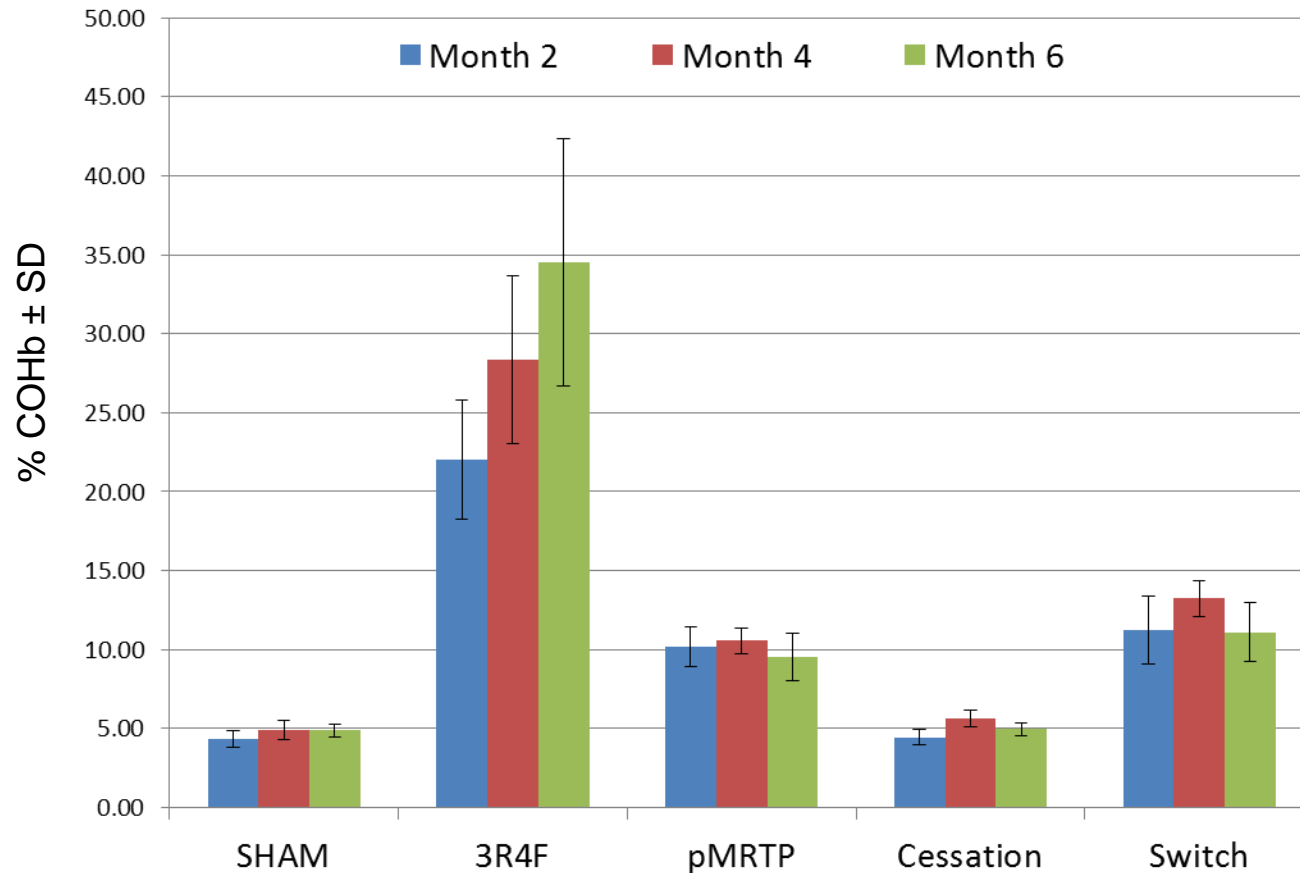


**Conventional cigarette smoking
machines**

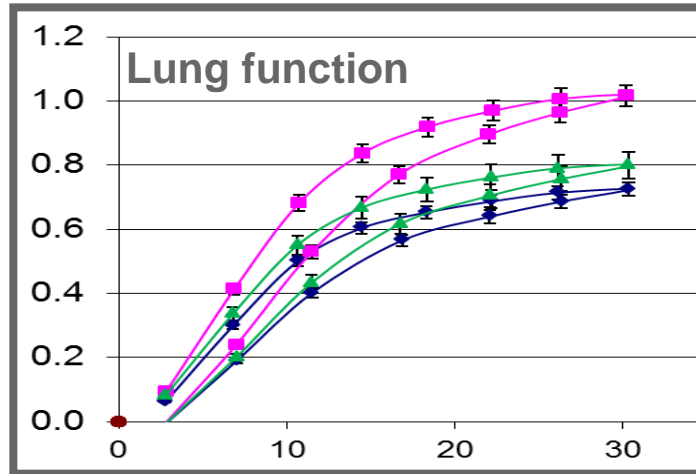


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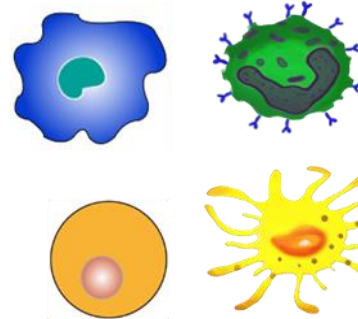
Exposure: Carboxyhemoglobin (COHb) Levels in Blood



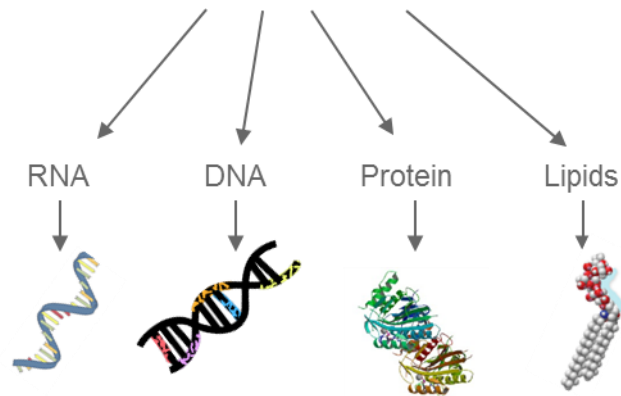
Endpoint analysis: Multi-Parameter Assessment of Emphysema Progression



Inflammatory cells and cytokines



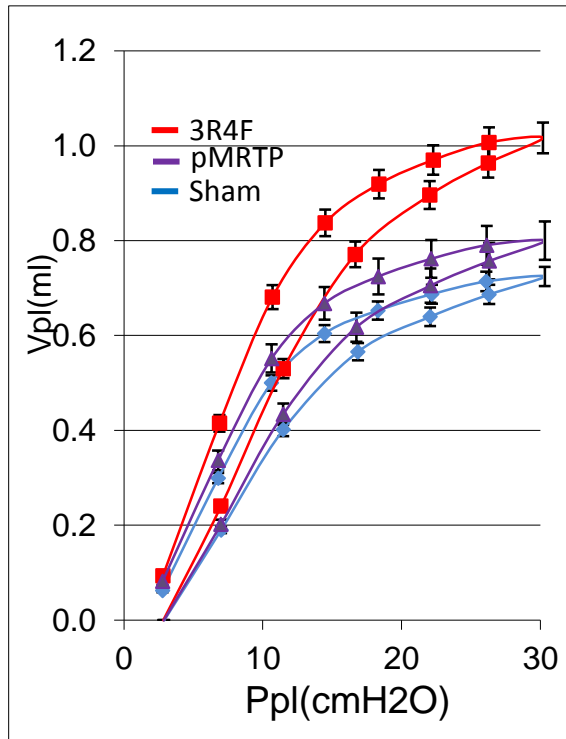
Molecular Biology



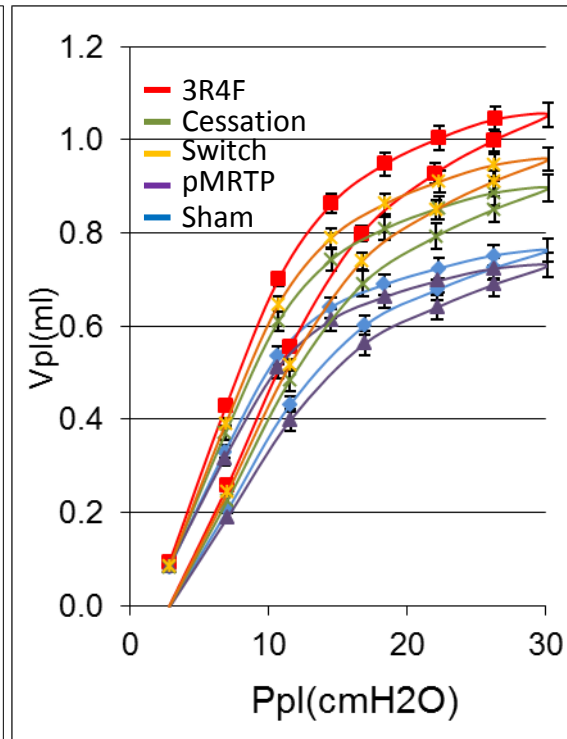
Histopathology and Immunohistochemistry



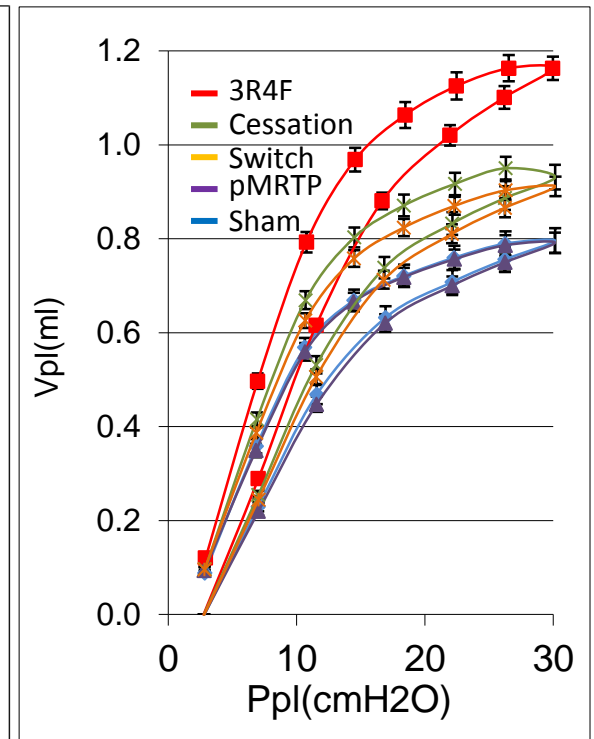
Pulmonary Function: A Physiological Measure of Lung Tissue Compliance and Airflow Resistance



Month 2



Month 3
(1 month switch)

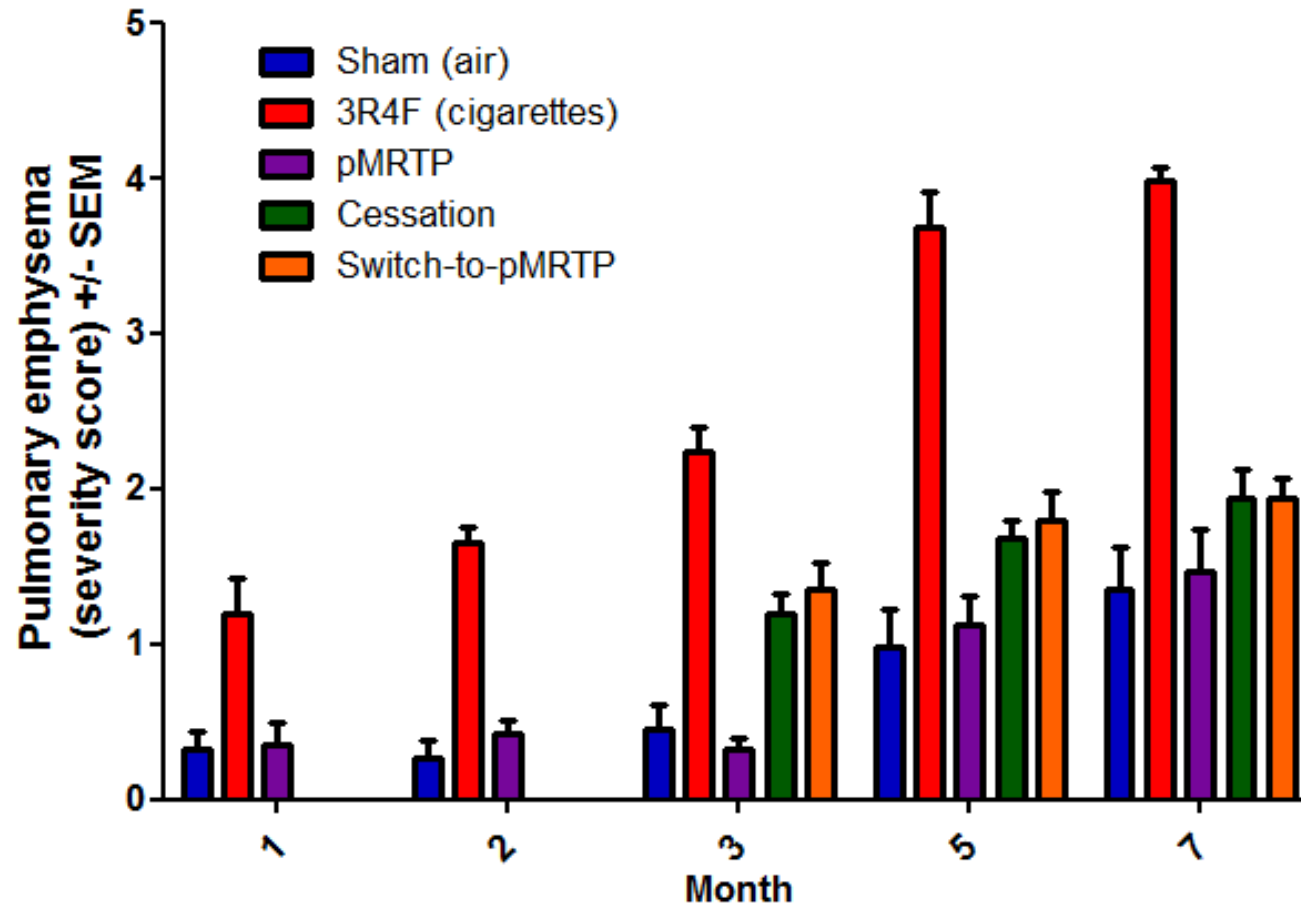


Month 7
(5 month switch)



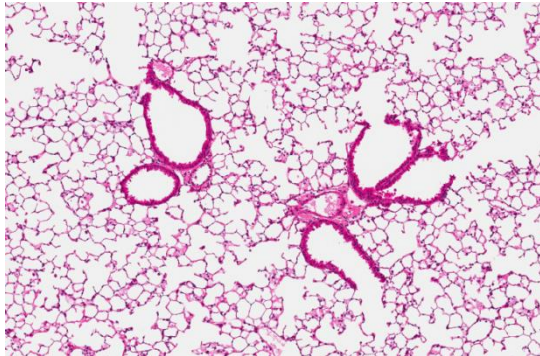
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Histopathology: Pulmonary Emphysema Progression

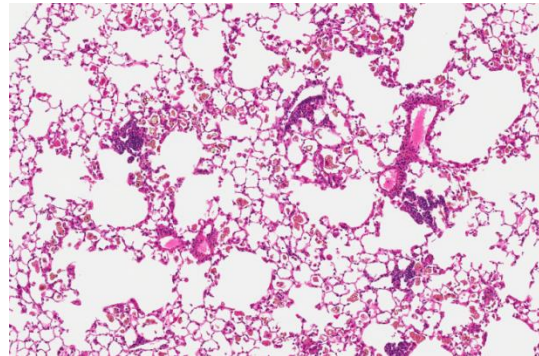


Histopathology: Lung Morphology

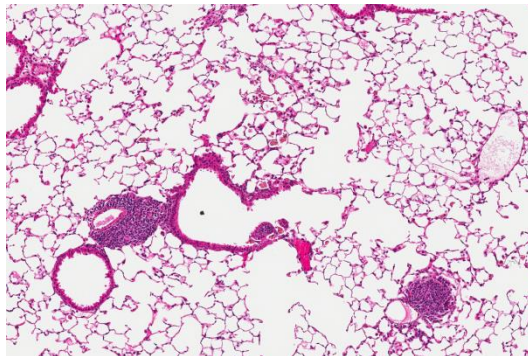
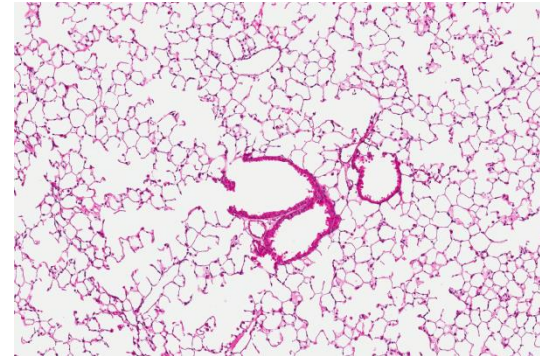
Sham, 7 month



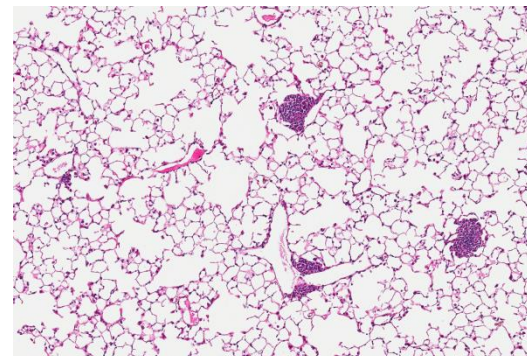
3R4F, 7 month



pMRTP, 7 month

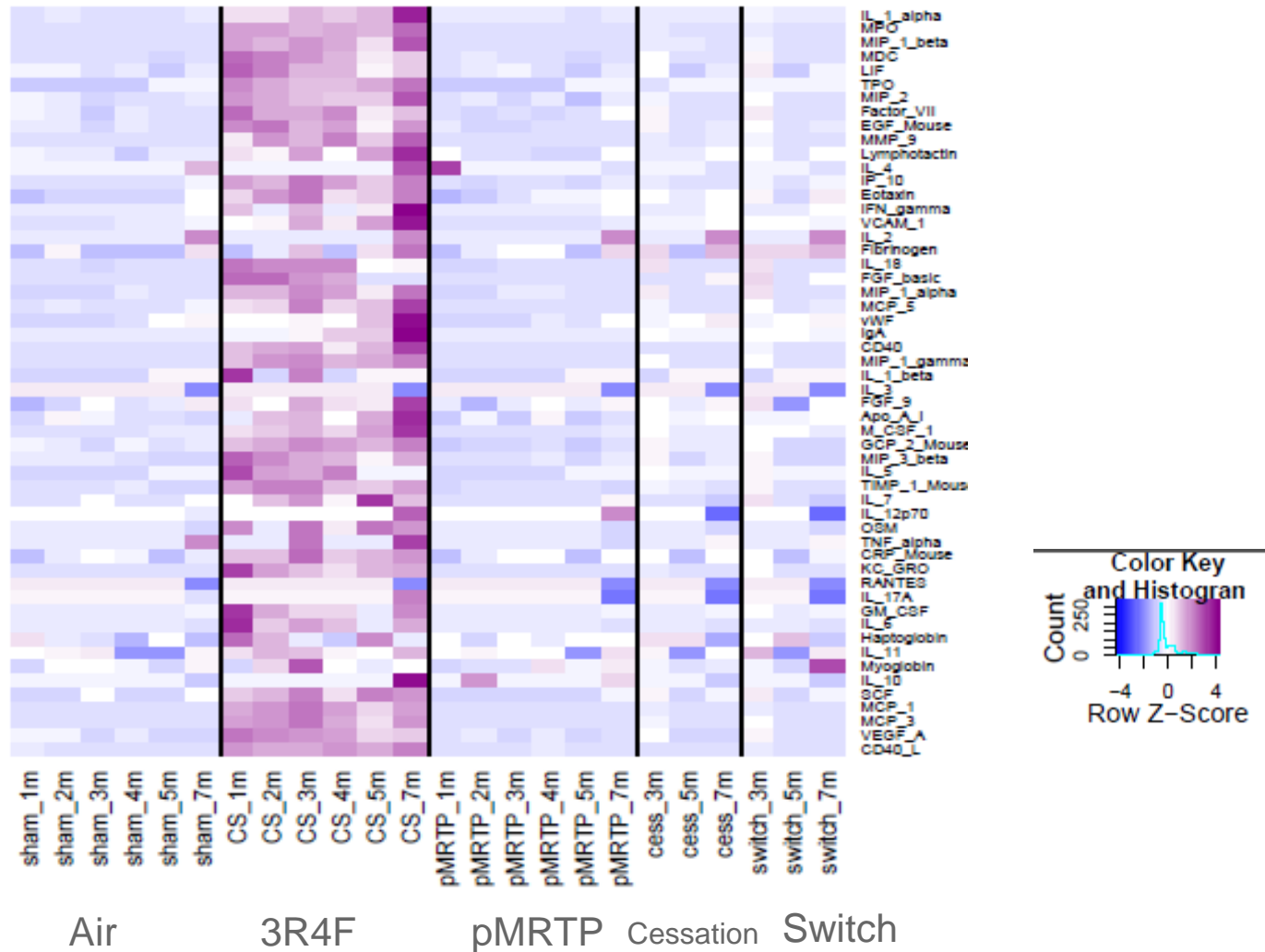


Cessation, 7 month

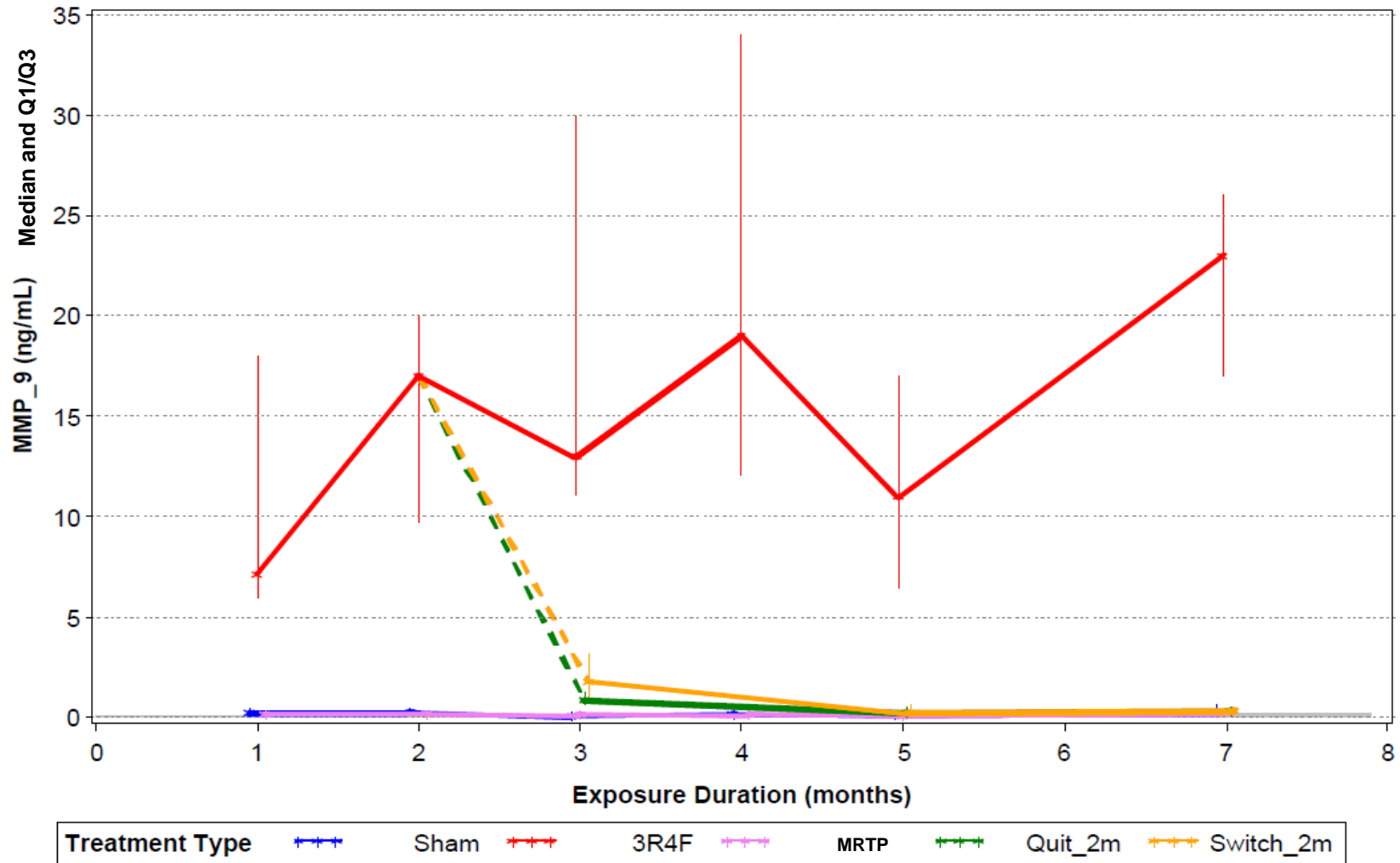


Switch, 7 month

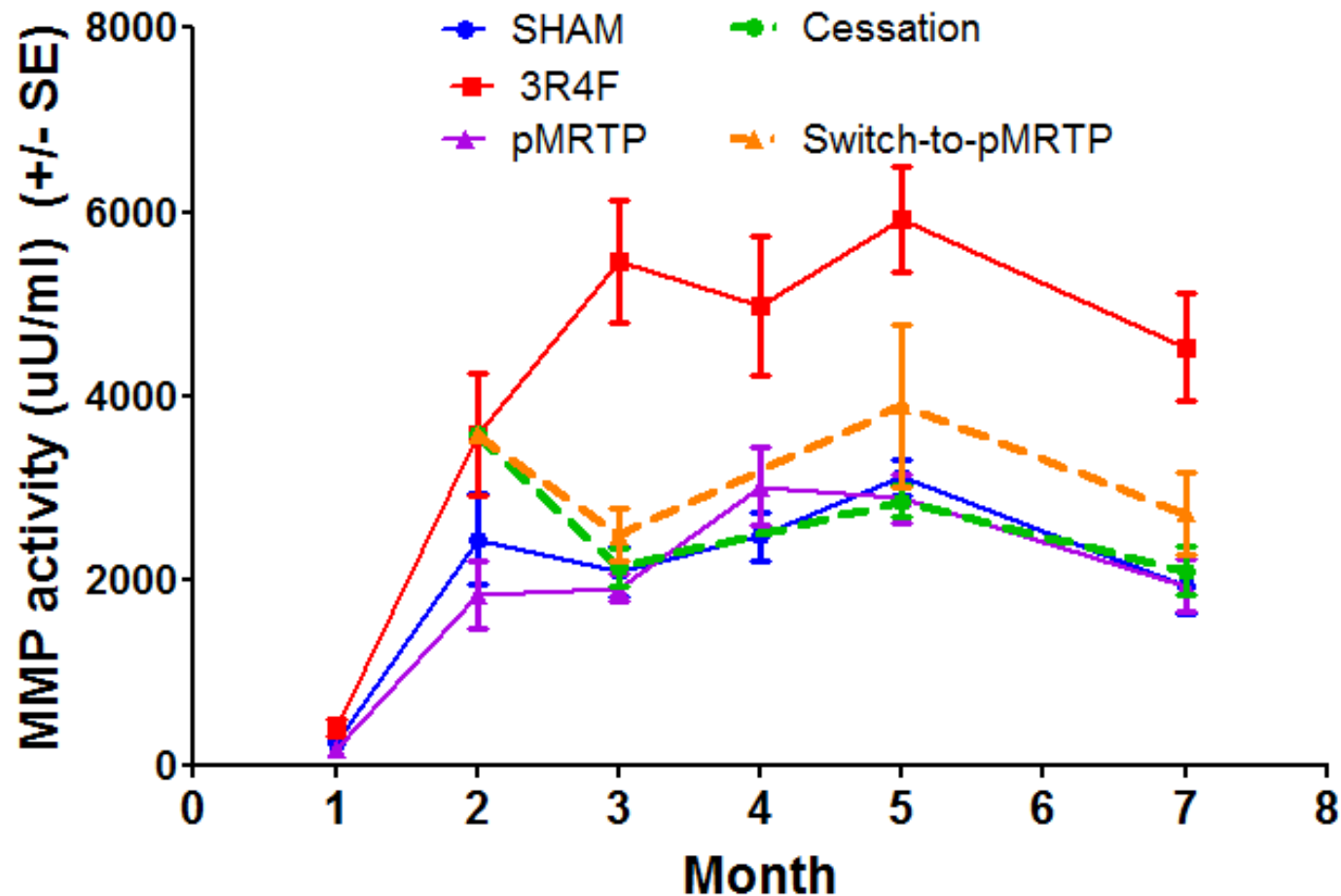
Pulmonary Inflammation: Inflammatory Mediators in the BALF



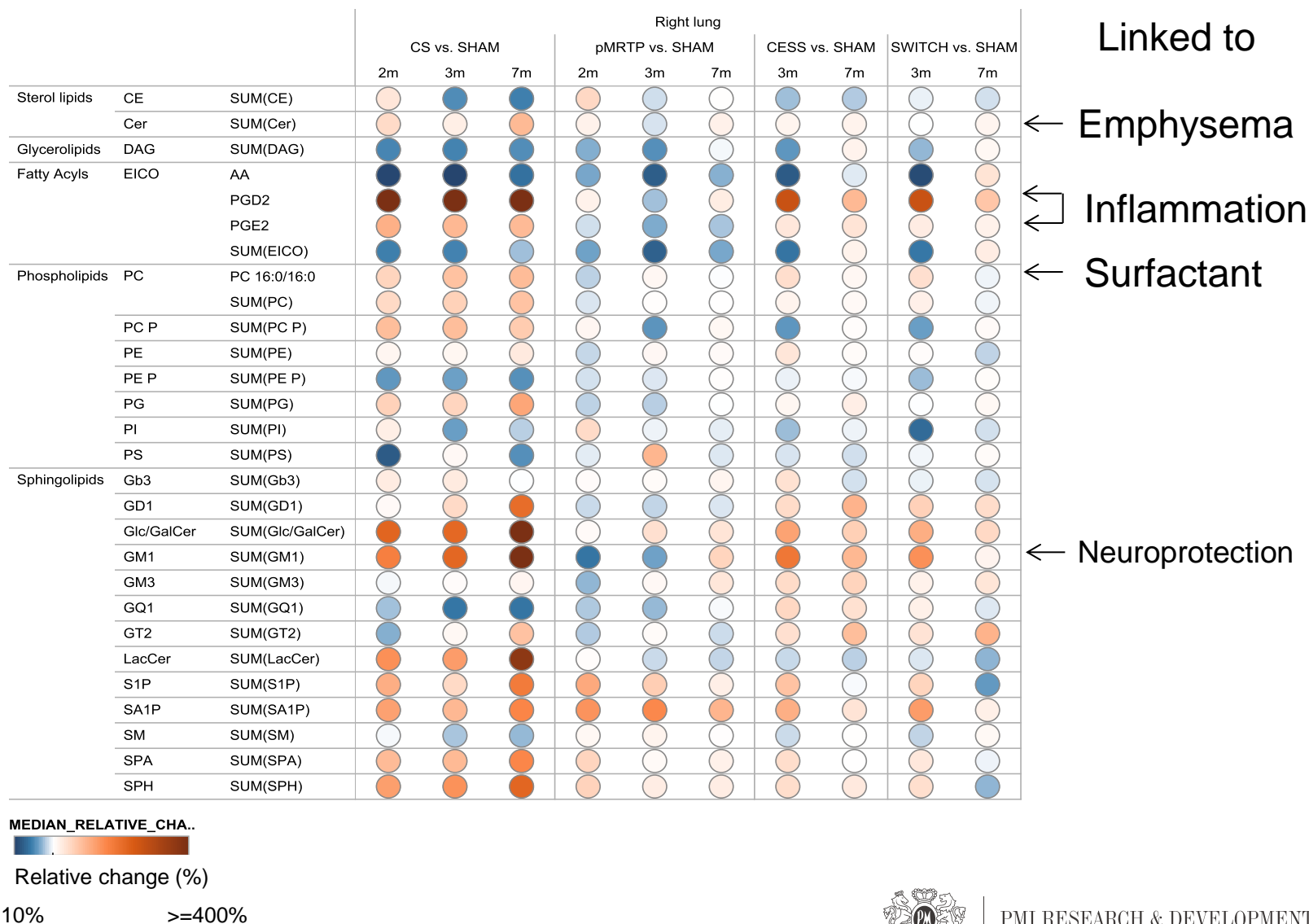
Pulmonary Inflammation: Expression of MMP-9 in the BALF



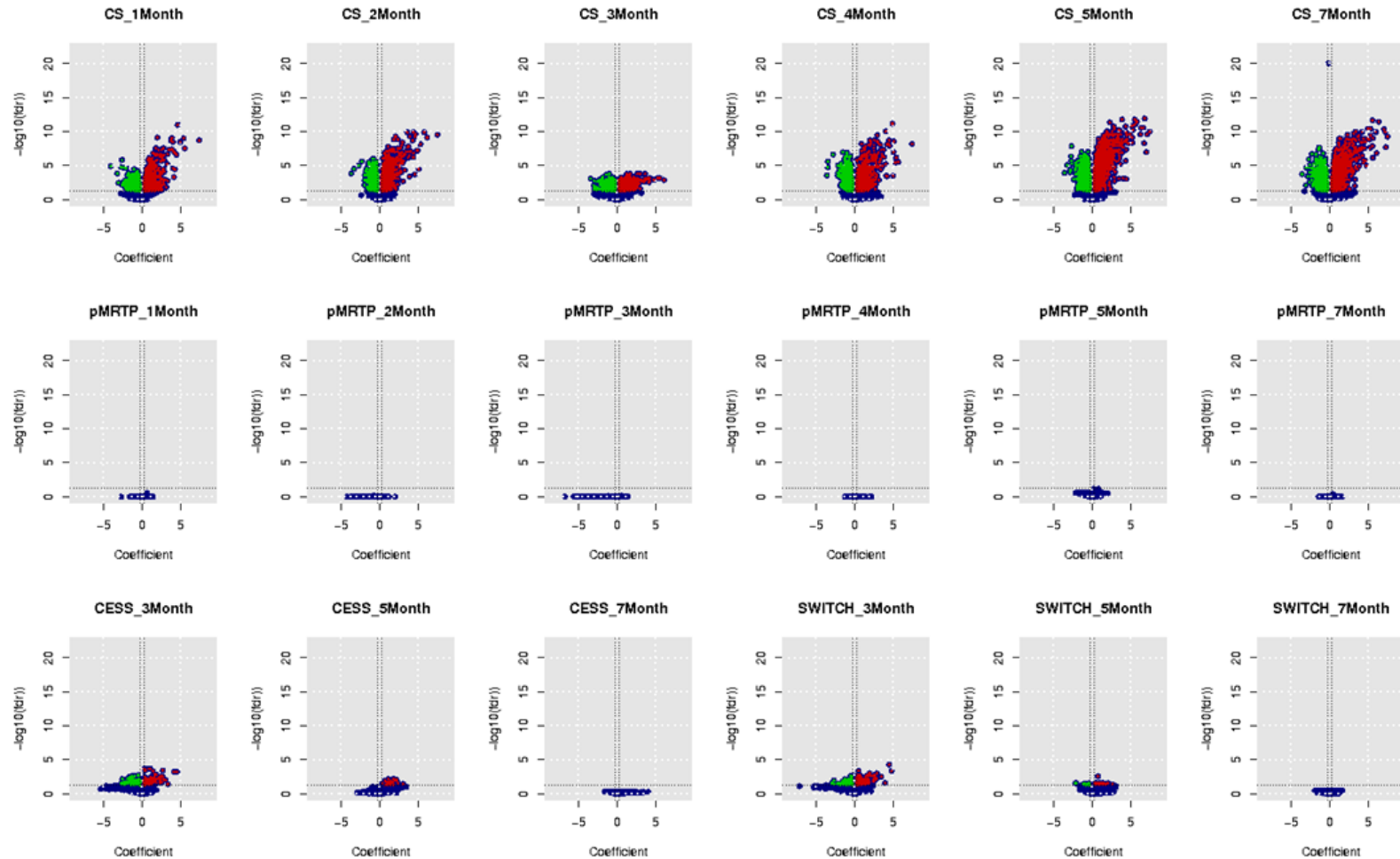
Pulmonary Inflammation: MMP (Gelatinolytic) Activity in the BALF



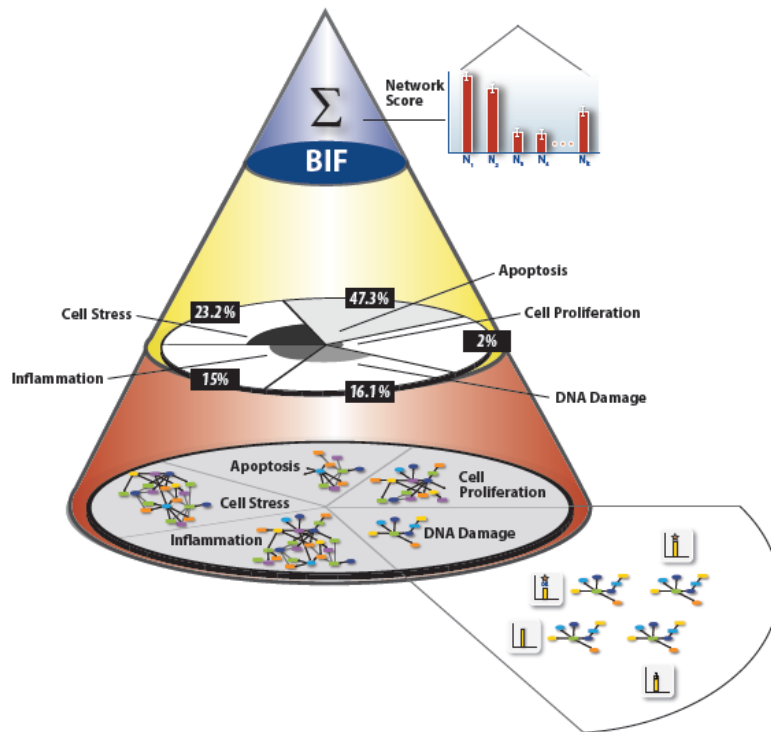
Lung Lipidomics: Differential Lipid Levels in the Lungs of Smoke or pMRTTP-Exposed Mice



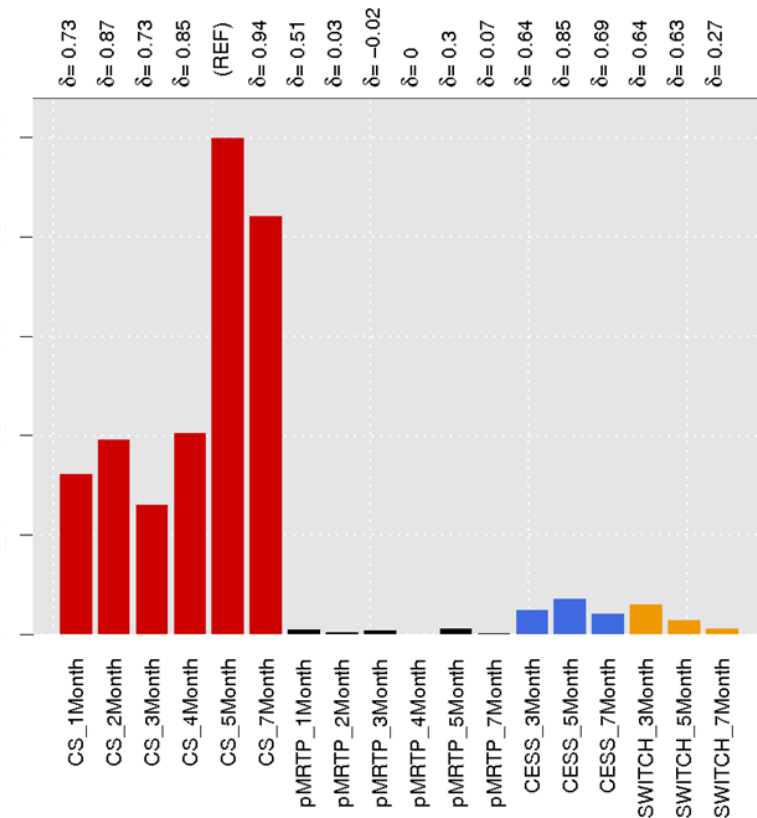
Transcriptomics: Differential Gene Expression in the Lungs of Smoke or pMRTP-Exposed Mice



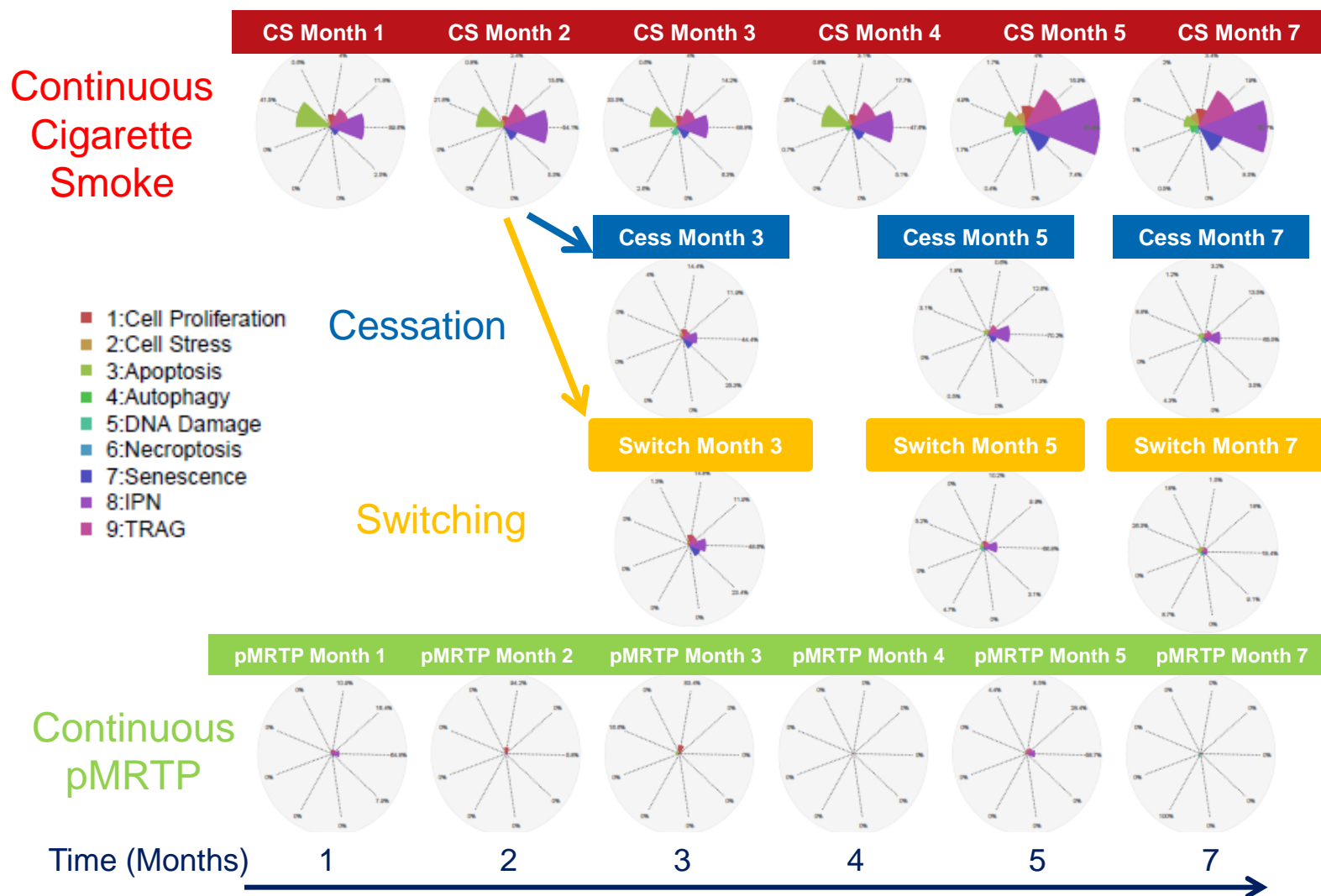
The Biological Impact Factor (BIF)



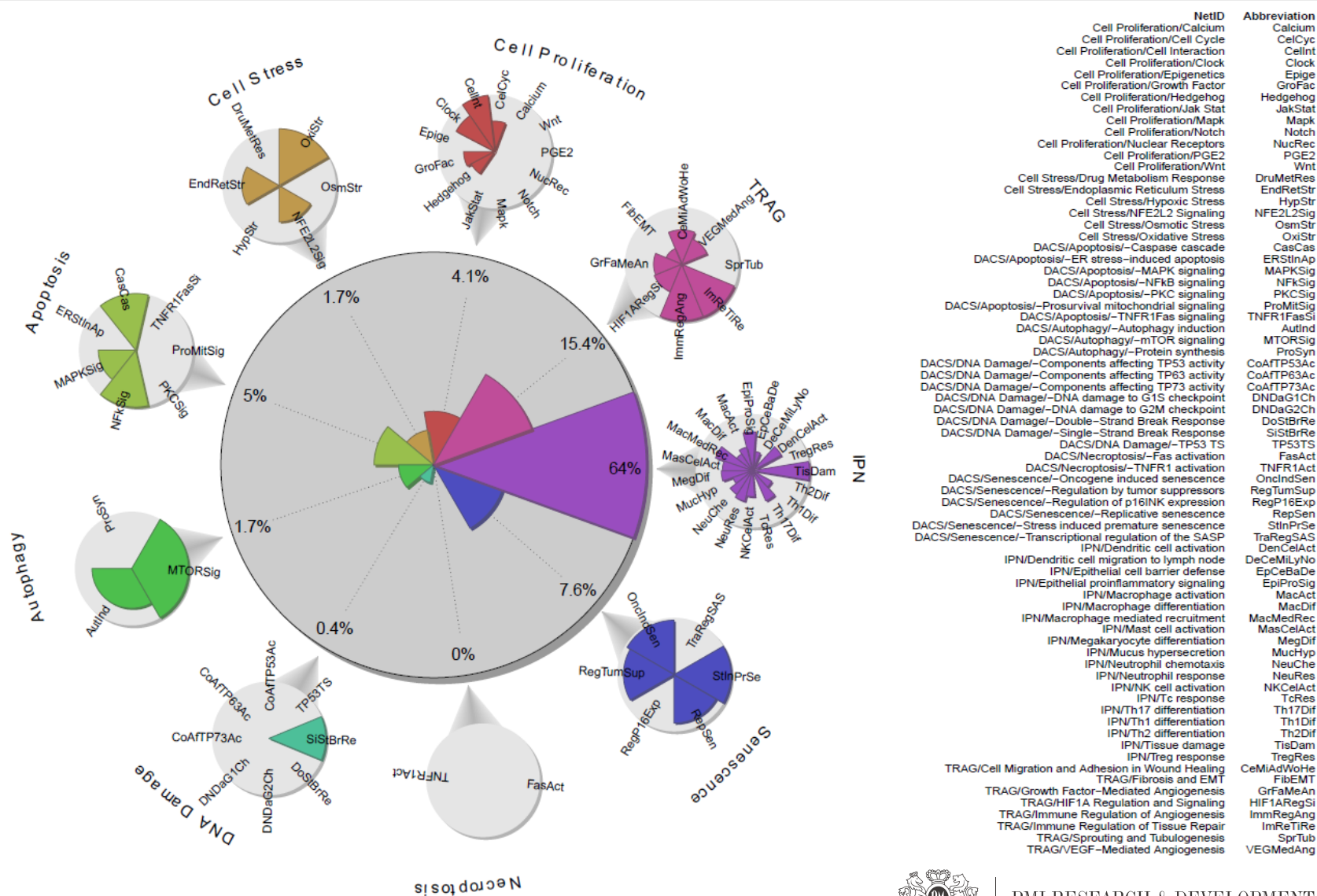
Relative BIF on lung tissue



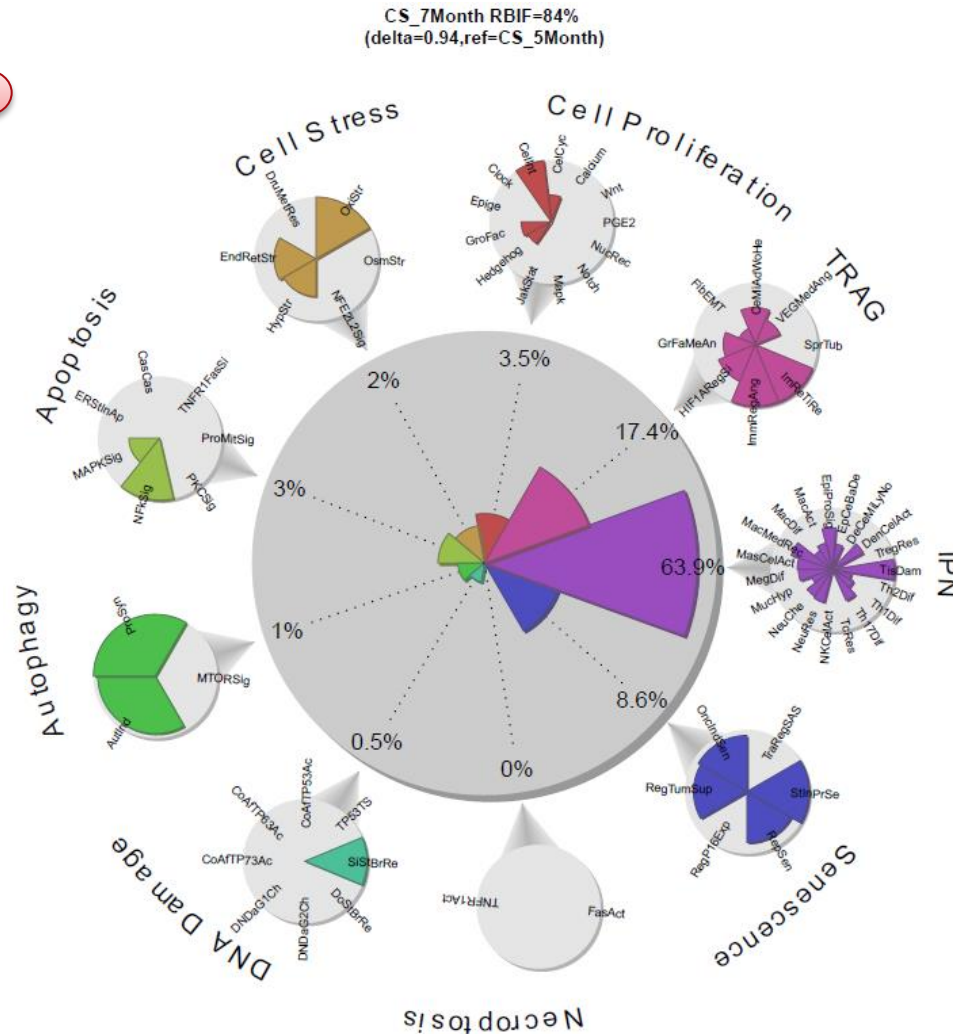
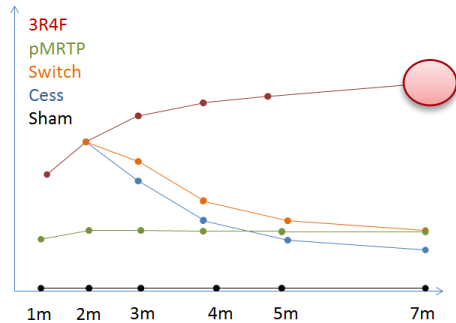
Network Perturbations and Biological Impact in the Lung (Gene Expression)



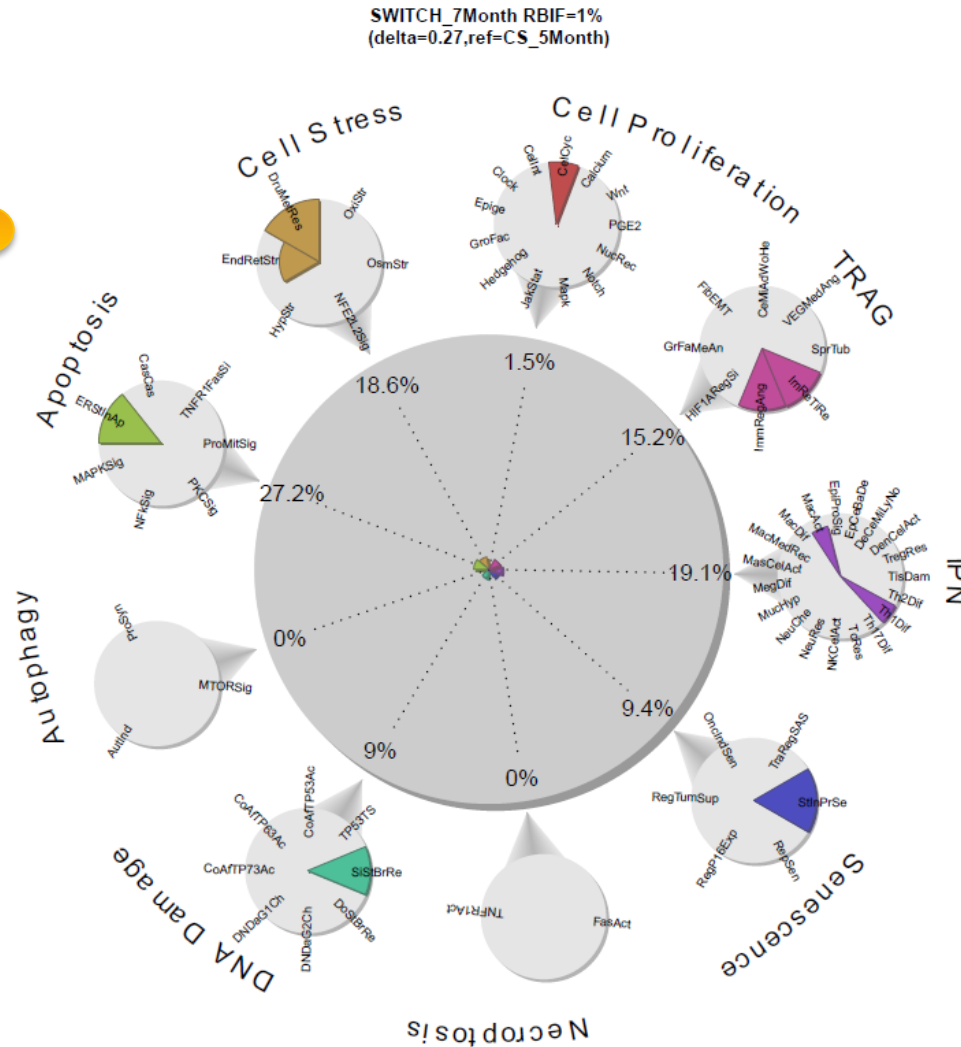
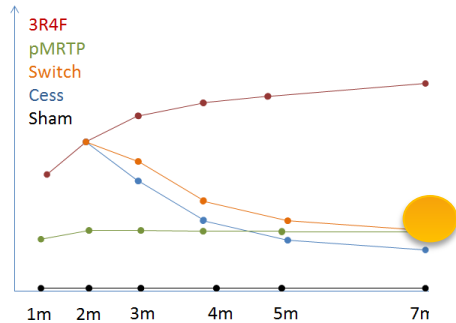
Digging Into the Details: Legend



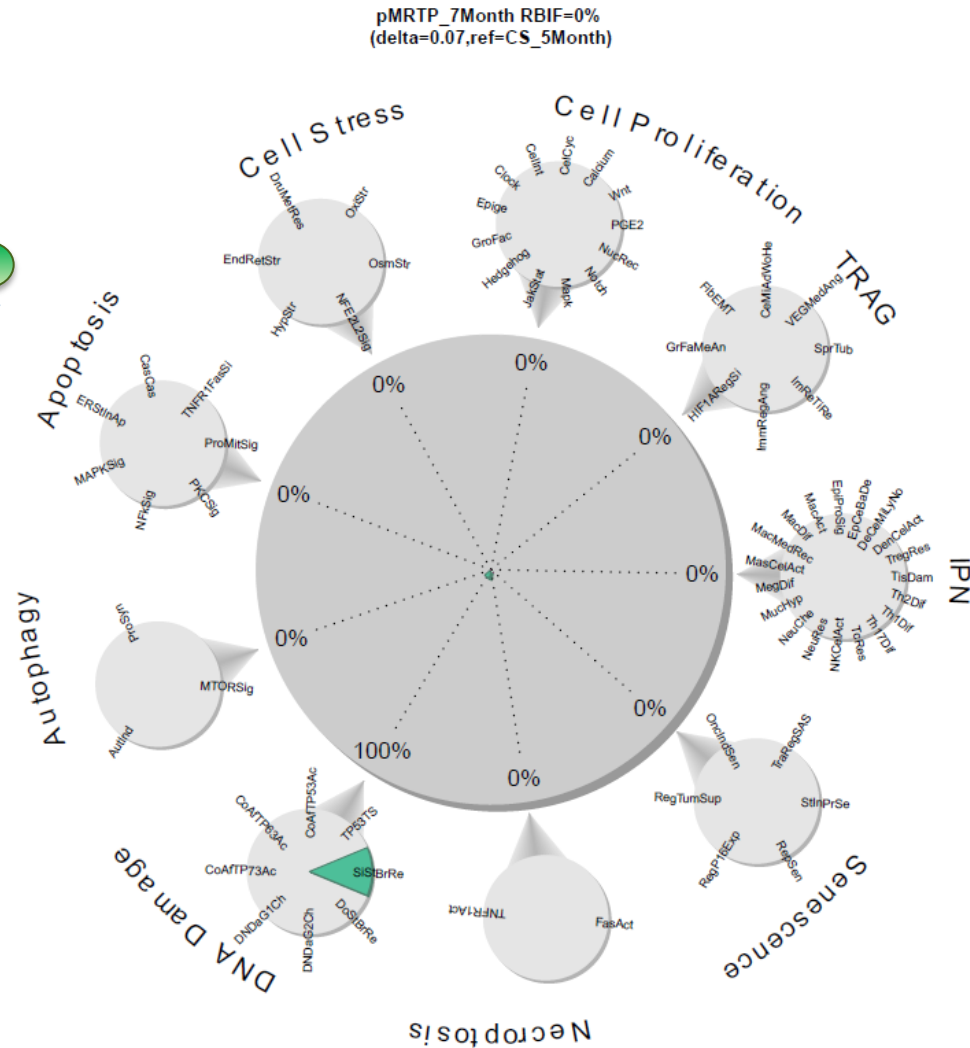
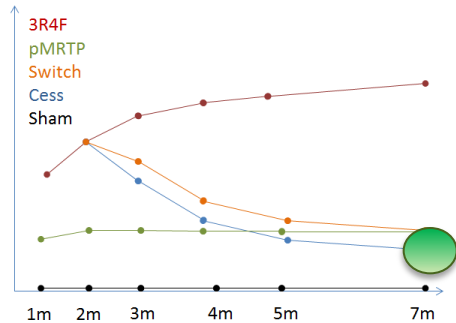
Network Perturbations and Biological Impact in the Lung : Cigarette Smoke, Month 7



Network Perturbations and Biological Impact in the Lung : Switching to pMRTP, Month 7



Network Perturbations and Biological Impact in the Lung : pMRTP, Month 7



Summary of Results

- Establishment of an *in vivo* model of cigarette smoke-induced COPD with the following characteristics:
 - Pulmonary function was decreased
 - Infiltration of inflammatory cells and mediators in the lungs
 - time-dependent progression of pulmonary emphysema (histopathology)
- The above parameters were ameliorated with cessation or switch-to-pMRTP
- The perturbations of major biological networks were markedly reduced following switching-to-pMRTP, very similar to cessation.
 - This led to the conclusion that the Biological Impact Factor (BIF) of switching is very similar to that of cessation and markedly different from ongoing cigarette smoke exposure.
- Seven months of exposure to pMRTP had a minimal Biological Impact.

