1. No.
   2023G002

2. Title
   Analyzing Molecular Mechanisms of Tobacco Smoke Condensate-Mediated Activation of Androgen Receptor

3. Period
   2023-2025

4. Summary
   In this study, we investigated the molecular mechanism by which tobacco smoke condensate (TSC) activates androgen receptor (AR) signaling. In the first year, pharmacological screening using a standard inhibitor library identified 83 compounds that suppressed TSC-induced AR activation, among which 5-alpha reductase inhibitors were of particular interest. In the second year, we analyzed AR-associated transcriptional coregulator complexes formed under TSC stimulation using the RIME method and confirmed that these complexes were largely similar to those formed under dihydrotestosterone (DHT) stimulation. In the final year, we found that the water-based extract CSE did not induce significant AR activation, whereas HPLC fractionation of TSC enabled enrichment of the AR-activating factor(s) in lipophilic fractions. Taken together, these findings suggest that lipophilic component(s) in tobacco smoke may promote AR activation through endogenous androgen metabolism, particularly via 5-alpha reductase. Identification of the AR-activating factor(s) may not only help clarify the mechanism underlying the increased prostate cancer-specific mortality associated with smoking, but may also provide a basis for developing risk-reduction strategies targeting these compounds.