## Specific Aims

Combination therapy holds considerable promise for overcoming intrinsic and acquired resistance to targeted therapies but relies on our ability to precisely identify the best drug combination for particular tumors. While immense focus exists on using genomic information to direct therapeutic approach, many resistance mechanisms can also arise from entirely tumor-extrinsic factors within the microenvironment. The receptor tyrosine kinase (RTK) AXL is widely implicated in resistance to targeted therapies such as those directed against EGFR. Regulation of AXL by phosphatidylserine (PS), as opposed to mutation, amplification or autocrine ligand, make identifying the tumors that will respond to AXL-targeted therapy especially challenging[Meyer:CellSys].

**Aim 1: Start off strong with a major foray into safe work** *Hypothesis: That Aim 1 is usually work with a greater chance of success.*

- A task that comes with convincing preliminary data
- Another task that is essential to the later efforts
- One more task that needs to be accomplished early on in the project
- Validate model predictions of the relationship between signaling network state and resistance

**Aim 2: That middle area where you will probably end up spending most of your time** *Hypothesis: Middle Aims are where much of the real discovery occurs.*

- One of those tasks that just could not be skipped
- A task I am really looking forward to
- Something pulling this whole aim together

**Aim 3: A third major area that is quite risky** *Hypothesis: Third aims are less likely to be accomplished.*

- Since we are just warming up this task is more likely to be feasible
- Getting this to happen will really be quite pricey
- This task really pulls everything together but will require everything working perfectly

This work will considerably improve our ability to identify efficacious drug combinations by: (a) developing a mechanism-based assay for identifying which RTKs are driving bypass resistance, (b) improving our basic understanding of exactly how network-level bypass resistance arises due to activation of non-targeted RTKs both at the receptor-proximal and downstream signaling layer, and (c) expanding our understanding of the RTK AXL with links to resistance, tumor spread, and immune avoidance.

# Research Strategy

## Significance

**Lung Cancer and Environmental Exposures** Lung cancer remains the leading cause of cancer-related mortality worldwide, with non-small cell lung cancer (NSCLC) accounting for 85% of lung cancer cases in the US.[1] Akin to tobacco smoking, exposure to the complex mixture of air pollution, particularly fine particulate matter ($PM_{2.5}$) and nitric oxide (NO), poses a major risk factor for developing lung cancer. In heavily polluted cities like Los Angeles, exposure to these pollutants significantly increases the risk of developing lung cancer.[x] In 2014, the Nurse's Health Study found that living within 200 meters of a highway and a $10\ \mu g/m^3$ increase in $PM_{2.5}$ levels were associated with an increased risk of lung cancer (HR = 1.57; 95% CI: 1.26, 1.77).[2] Furthermore, a 2019 meta-analysis estimated that a $10\ \mu g/m^3$ increase in $PM_{2.5}$ exposure in Europe and North America increased lung cancer risk by 25%.[3]

Despite the clear evidence linking air pollution exposure to elevated lung cancer risk, the precise molecular mechanisms by which these complex pollutant mixtures initiate and promote NSCLC remain poorly understood,[x] representing a critical knowledge gap. This study will investigate lung cancer in Blacks, an understudied group that exhibits a high prevalence of aggressive, early-onset tumors that are often driven by distinct molecular profiles like EGFR mutations.[x] Elucidating the environmental drivers and biological pathways of lung carcinogenesis in this subgroup could reveal novel diagnostic approaches.

**Addressing Lung Cancer Inequities in Blacks** Although African Americans/Blacks (Blacks) have lower smoking rates compared to non-Hispanic Whites, they experience significantly higher lung cancer incidence and mortality rates, especially among men.[x] This disparity is striking, as Blacks tend to initiate smoking later in life and consume fewer cigarettes compared to their White counterparts.[x] Black women, despite smoking fewer cigarettes, have the same or higher incidence of lung cancer as White women.[x]

Current lung cancer screening guidelines based on pack-years and age fail to adequately identify Blacks at risk.[x] Blacks are diagnosed with lung cancer at a significantly younger age than Whites, often before reaching the screening threshold of 30 pack-years or age 55.[x] The molecular drivers underlying these aggressive, early-onset lung cancers in the Black population remain unclear.[x] However, disparities in environmental exposures, particularly air pollution, are suspected to play a role.[x] Evidence shows that Blacks are consistently exposed to significantly higher levels of $PM_{2.5}$ and NO compared to non-Hispanic Whites.[x] This study will utilize a multi-regional cohort of non-smokers, former smokers, and smokers, to identify the specific molecular connections between air pollutants and lung cancer in Blacks.

Furthermore, existing studies do not account for how social determinants of health may modulate susceptibility to environmentally induced cancers.[x] Addressing this gap is crucial for accurately assessing risk and developing prevention strategies in diverse populations.

**Characterization of Environmental Exposure** Outdoor air pollution, including $PM_{2.5}$, is classified as a Group 1 carcinogen by the International Agency for Research on Cancer (IARC).[x] Past studies demonstrate a clear link between residing near major roadways and an elevated risk of developing lung cancer.[x] Exhaust from combustion engines releases a cocktail of carcinogenic compounds into the atmosphere near major roadways. These pollutants include polycyclic aromatic hydrocarbons (PAHs), nitrogen oxides, and toxic heavy metals such as arsenic, nickel, and lead.[x] Previous studies have attempted to map air pollution levels using census tract data.[x] However, these methods only detect a limited subset of pollutants, failing to capture the full complexity of environmental pollutants.[x] Moreover, existing research does not account for how rising global temperatures associated with climate change may alter the chemical composition and carcinogenic potency of air pollution over time. Another major shortcoming is the lack of integration of social determinants of health, such as obesity, diabetes, and chronic inflammatory conditions, which may exacerbate susceptibility to cancer.

**Potential for Transformative Impact** This study will employ advanced geospatial methods to precisely quantify individual exposures to air pollutants in Black communities in LA, Chicago, New Orleans, Charlestown SC, Richmond VA, and Rochester NY. Crucially, it will integrate this environmental exposure data with social determinants of health and biological factors that modulate disease susceptibility in these communities. Black populations in LA have historically faced disproportionately higher exposure to air pollution due to factors like redlining, the placing of industrial facilities near their neighborhoods, and a lack of green spaces. Despite having some of the lowest rates of smoking in the US, LA suffers from some of the worst highway-generated air pollution. By precisely characterizing these elevated exposures and combining them with data on obesity, diabetes, chronic inflammation, and other risk factors prevalent in Black communities, the goal is to develop a comprehensive model elucidating how environmental drivers interact synergistically with social and biological parameters to initiate and promote aggressive, early-onset NSCLC in this population.

This multidisciplinary approach, combining external exposure assessments with internal susceptibility factors, will provide novel mechanistic insights into the environmental carcinogenesis pathways driving the excess lung cancer burden observed in Black communities. By integrating precise air pollution exposure data with epidemiological cohorts and molecular tumor profiling from Black NSCLC patients, this study will generate a comprehensive model of how environmental insults precipitate lung carcinogenesis in the context of social and biological vulnerabilities in this underserved population. Insights from this

innovative approach have the potential to transform our understanding of air pollution's role in NSCLC etiology in Blacks and identify new opportunities for targeted prevention, early detection, and treatment strategies. This is particularly important as while the rates of most lung cancers are declining, the incidence of NSCLC in non-smoking women of color is rapidly rising in LA and other cities.[x]

## Innovation

**Precise Exposure Assessment** While numerous studies have linked air pollution to lung cancer, this proposal introduces several innovative elements. Previous research has relied on census tract-level pollution maps that fail to capture individual exposures and pollutant complexity. This study pioneers advanced geospatial monitoring and modeling to precisely quantify personal exposures to particulate matter, polycyclic aromatic hydrocarbons, nitrogen oxides, and metals - critical for defining exposure-response relationships.

**Integration of Exposures and Social Determinants** Existing studies have not accounted for how social factors like obesity, diabetes, and inflammation modulate environmental cancer risk. This proposal innovatively integrates high-resolution exposure data with comprehensive individual health parameters to model the complex interplay between external exposures and internal susceptibility.

**Multidisciplinary Carcinogenesis Model** By combining cutting-edge exposure science with epidemiology and molecular biology, this study will develop the first comprehensive model elucidating the environmental drivers and biological mechanisms underlying NSCLC initiation and progression from air pollutants.

**Focus on Never-Smokers and Subtypes** While lung cancer in smokers is well-studied, far less is known about environmental contributors in never-smokers who often exhibit distinct molecular profiles. Investigating subtype-specific mechanisms could reveal novel vulnerabilities for targeted therapies.

**Transformative Potential** In summary, this innovative proposal leverages advanced exposure monitoring integrated with epidemiological and molecular approaches to generate an unprecedented multidisciplinary model of environmental lung carcinogenesis. This novel framework has the potential to transform our mechanistic understanding of air pollution's role in NSCLC and identify new avenues for prevention and treatment, especially in high-risk never-smoker populations.

## Approach

### Aim 1: Start off strong with a major foray into safe work

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**Figure 1:** An example figure with caption to explain.

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**Aim 2: That middle area where you will probably end up spending most of your time**

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# Glossary

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