LIIA

SPECIFIC AIMS.
Dysregulation of immune cascades is considered to be a core component of aging and has been linked with negative cognitive outcomes, including Alzheimer's disease (AD). Epidemiological studies indicate that elevated levels of peripheral immune markers are evident years prior to clinical manifestation of AD. Although peripheral immune dysfunction is a risk factor for cognitive decline, many key unanswered questions remain, including: 1) how to effectively measure peripheral and central nervous system (CNS) immune changes; 2) how to disentangle the mechanistic role of peripheral and CNS immune dysregulation on aging outcomes, and 3) how to evaluate the effect of immune-related health events on cognitive decline1-3. Given that age is the strongest risk factor for AD, studying asymptomatic older adults (AOAs) over time offers a critical window into the early peripheral and CNS immune changes that may steer the aging process along an AD trajectory.
Our central hypothesis is that peripheral immune dysregulation – over and above CNS immune dysregulation – is a critical driver of cognitive decline, and that this relationship is exacerbated by higher AD-related pathology and by recent immune health events. To address gaps in the field, we propose to use longitudinal, multimodal measurements of peripheral and CNS immune markers. We will employ both a targeted and an exploratory immune marker panel, and will record recent immune health events to determine their potential impact on the relationship between immune dysregulation and cognitive decline. Our primary Aims are:

Aim 1: To determine how peripheral immune markers relate to CNS immune Aim 1: To determine how peripheral immune markers relate to CNS immune markers over time.
1a. Higher baseline peripheral (blood) immune marker levels will be associated with higher baseline CNS (CSF) immune marker levels.
~~We will further test whether baseline immune marker levels in periphery-derived EVs show stronger associations with CNS immune markers (i.e., CNS-derived EVs and CSF) compared to circulating blood immune marker levels.~~
1b. Longitudinal increases in peripheral immune markers will be associated with longitudinal increases in CNS immune markers.
~~We will further test whether immune markers in EVs (i.e., periphery- and CNS-derived) show greater increases over time compared to circulating blood and CSF~~.

a) Do a WCGNA analysis
    a. Age- associated blood network, Age- associated CSF network, and then look to see if there are overlapping markers between blood and CSF?
    b. Include Ab42/40 as an interaction? The idea would be to determine whether the presence of an Alzheimer's disease marker changes how well the periphery reflects the central nervous system (meaning, is there a dysregulation in peripheral-CNS cross-talk when Ab42/40 is on board?)

-Look to see if Ab42/40 levels or Ab42/40 cut point impacts association between peripheral and central inflammation?
-Look to see if albumin ratio, which is a proxy for blood brain barrier integrity, impacts association between peripheral and central inflammation? Bri will send Redcap variable.
Covariates: Age, sex
Plan: Siyang will check with Katerina's group about implementing a WCGNA. Initially work on data cleaning
Bri will send website details on NPX signal, send Keenan Walker paper on OLINK

NPX: https://olink.com/faq/what-is-npx/
Keenan Paper w/ OLINK: https://www.nature.com/articles/s41380-023-01975-7

Aim 2: To determine whether peripheral and CNS immune markers show independent associations with cognitive outcomes, and to delineate how AD-related pathology influences these associations.
2a. Higher baseline levels of peripheral immune markers and greater increases in peripheral immune markers will be associated with cognitive decline, even after controlling for CNS immune markers.
2b. AD-related pathology will modify the relationship between peripheral immune markers and cognitive decline, such that subjects with higher levels of peripheral immune markers and higher CSF p-tau levels will

show greater cognitive declines than subjects with higher levels of peripheral immune markers but lower CSF p-tau levels.
We will also test the moderating effect of higher Ab42/40 on the relationship between peripheral immune markers and cognitive decline; however, based on preliminary data, we predict that CSF p-tau levels may have a greater modifying effect than amyloid signal on peripheral immune markers and clinical outcomes.

Aim 3: To evaluate the role of immune health history on the relationship between peripheral and CNS immune markers and cognitive decline. 3a. Recent (i.e. past 12 months) immune health events (i.e., infections and surgical procedures) will show strong associations with peripheral immune markers and CNS immune markers. 3b. AOAs who have higher numbers of recent immune health events will show stronger associations between peripheral immune markers and cognitive decline, even after accounting for CNS immune markers, compared to AOAs who have lower numbers of recent immune health events.
Impact: By determining the contributions of peripheral versus CNS immune signals to cognitive decline, we will be poised to better predict and ultimately treat early immune dysregulation that may drive AD pathogenesis.