EXPOSURE TO ULTRAFINE PARTICULATE MATTER AND PATHOGENESIS OF NEURODEGENERATIVE DISEASE

I. OBJECTIVE

Emerging evidence suggests that environmental factors, including exposure to air pollutants such as particulate matter (PM), may play a role in neurodegenerative diseases (ND) such as Alzheimer's and Parkinson's disease. These conditions primarily affect the elderly. The cause of these disorders is not understood, and genetic factors alone seem insufficient to explain their prevalence. The objectives of this study are to determine: 1) whether long-term exposure to ultrafine particulate matter (UFPM) is associated with the development of neurodegenerative processes in an animal model of ND; 2) whether UFPM exposure accelerates progression of innate immune responses in the brain; 3) whether cognitive or behavioral deficits develop as a result of UFPM exposures; and 4) how responses to UFPM exposure vary with a subject's age and/or duration of exposure. UFPM is an important size fraction to examine because several reports in the literature have shown that these small particles are transported directly into the brain. The proposed study will help clarify the role of UFPM exposure in the progression of neurodegenerative disease, and will assist ARB in its mission of protecting public health, particularly in the elderly.

II. BACKGROUND

Neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD), are disorders that primarily affect the elderly, and are becoming an increasing public health concern as California's population ages. Alzheimer's disease, the most common ND, was the fifth leading cause of death in California in 2010; moreover, about 1 in 3 seniors who dies each year has AD or dementia (Alzheimer's Association, 2013). Despite the fact that NDs are a serious health issue, little is known about their causes. Although genetic factors have been shown to be partly responsible, environmental factors are suspected to contribute to ND prevalence. Recent evidence suggests that exposure to ambient PM may be associated with the neurodegenerative processes associated with these diseases, as discussed below.

Research findings from human epidemiology, animal exposure, and *in vitro* studies have shown adverse effects of air pollutant exposures on the central nervous system. A series of studies of children and young adults exposed to Mexico City's high levels of ambient air pollution has shown AD- and PD-like pathology, such as evidence of diffuse amyloid plaques (a sign of cortical neurodegeneration resembling early-stage AD development), as well as markers of inflammation and cognitive deficits (reviewed in Calderón-Garcidueñas et al., 2013). From animal studies, we know that inhaled UFPM can travel directly to the brain via the olfactory nerve (Oberdörster et al., 2004; Elder et al., 2006). Consistent with this direct pathway, UFPM was detected in the olfactory bulbs of Mexico City youths (Calderón-Garcidueñas et al., 2007, 2008). Studies of elderly adults have demonstrated declines in cognitive performance with traffic proximity or increases in PM concentration (Ranft et al., 2009; Power et al., 2011; Wellenius et al., 2012; Weuve et al., 2012). Studies in rodent brain cell cultures (e.g. Gillespie et al., 2011; Morgan et al., 2011) and brain tissue of PM-exposed rodents (e.g. Campbell et al., 2005; Kleinman et al., 2008; Guerra et al., 2013) showed pro-inflammatory effects of exposure to PM. Recent studies have shown adverse cognitive and

behavioral effects in exposed rodents as well (e.g. Fonken et al., 2011; Win-Shwe et al., 2012; Davis et al., 2013).

Numerous animal models of neurodegenerative disease have been developed to demonstrate various facets of the disease and associated cognitive deficits, such as declines in spatial learning and memory. A number of rodent studies have recently been published that demonstrated changes in learning, memory, and behavior in response to air pollutant exposures, with some showing symptoms parallel to those observed in human patients. However, little is known about the effects of ultrafine PM exposure on central nervous system pathology and cognition in ND animal models. The proposed research will address this gap.

III. SCOPE OF WORK

This study will investigate the role of long-term UFPM exposure in the onset and/or progression of neurodegenerative disease. More specifically, the project will address whether UFPM exposure activates the central nervous system's innate immune responses. Concurrently, the research will investigate whether UFPM exposure leads to adverse cognitive and or behavioral outcomes. In order to achieve these research objectives, the investigators will work in consultation with ARB staff to develop a detailed work plan. This plan should include the following:

- Selection of an appropriate animal model of neurodegenerative disease, in which both innate immune responses and cognitive/behavioral endpoints can be observed and quantified. The number of animals proposed for this project should allow sufficient power to detect significant differences between experimental treatments. The work plan will need to provide justification for the number of animals proposed. Sufficient background literature and/or preliminary findings should be included to justify model selection and choice of endpoints.

- Chronic UFPM exposure, with relevance to California's ambient environment, in addition to appropriate controls. Because there is little known about how the timing of exposure affects ND onset or progression, different UFPM exposure onset times are desirable.

- Investigation of changes in the central nervous system's innate immune system, in response to the UFPM exposures. This may involve quantification of changes in markers of oxidative stress or inflammation, such as levels of relevant cytokines.

- Examination of pathological changes in CNS tissue. These can include histological assessments of neuronal loss, beta-amyloid plaques, neurofibrillary tangles, etc.

- Examination of relative changes in cognition and/or behavior associated with the UFPM exposures. Assays can include objective measures of differences in learning, memory, and effect. These may consist of standard laboratory tests of spatial memory and learning (e.g. the Morris water maze), but also may involve ecologically relevant behavioral tests such as assays of nest building behavior in mice.

- Copies of signed approval from the investigator's institutional review board, confirming approval of research protocol will be required after the project has been awarded.

- Data analysis and preparation of draft and final reports.

IV. DELIVERABLES

- Quarterly Progress Reports
- Draft and Final Reports
- Peer-reviewed journal article(s), as appropriate
- All data and analyses generated through the course of this project

V. TIMELINE

It is anticipated that this project will be completed 36 months from the start date. This allows 30 months for completion of all work through delivery of a draft final report. The last 6 months are for review of the draft final report by ARB staff and the Research Screening Committee (RSC), modification of the report by the contractor in response to ARB staff and RSC comments, and delivery of a revised final report and data files to the ARB.

VI. BUDGET: $500,000

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