

# INTERVENTIONS TO REDUCE FIREFIGHTER CANCER AND CARDIOVASCULAR RISKS IN RESPONSE TO ARIZONA FIRE CHIEFS OPPORTUNITY STATEMENT #1 ON FIREFIGHTER AND GENERAL PUBLIC HEALTH

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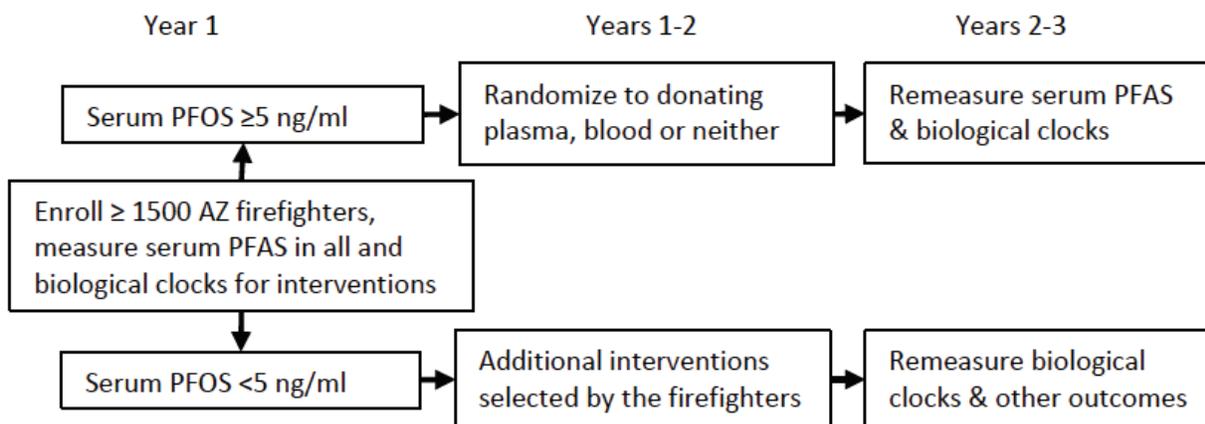
## PROJECT SUMMARY

**Background:** Firefighters have increased cancer rates compared to the general population, as recently determined by the International Agency for Research on Cancer of the World Health Organization. Cardiovascular disease is also a leading cause of firefighter deaths. A major concern of the Arizona fire service is exposure to per- and polyfluoroalkyl substances (PFAS), the so-called forever chemicals based on their persistence in the human body and environment. PFAS exposures have been linked to cancer, cardiovascular disease and other diseases. We have previously shown that Arizona firefighters have higher PFAS levels in their blood than the general population.

Arizona firefighters are requesting a study to test the effectiveness of blood or plasma donation to lower their PFAS levels, based on a single previous study in Australia demonstrating these interventions were effective in lowering PFAS levels over 12 months of time. However, the study did not determine if these interventions also reduced the risks of cancer and cardiovascular disease. Having a cellular biological clock greater than one's chronological age (years since birth), measured through blood DNA methylation markers, is a risk factor for multiple diseases including cancer, cardiovascular, and neurological diseases, as well as death from all causes combined. We have previously shown that firefighters with increased serum PFAS levels also have biological clocks greater than their chronological age. Arizona firefighters are also interested in reducing their cancer and cardiovascular disease risks even if they do not have elevated PFAS levels and have expressed interest in testing a variety of interventions with these outcomes in mind.

**Goal:** The goal of this research is to reduce firefighter cancer and cardiovascular disease risks, including but not limited to risks associated with PFAS exposure.

**Objectives:** We propose to test interventions to reduce firefighter cancer and cardiovascular disease risks, employing a community-based participatory research approach with the fire service. The proposed research will build on our existing national Fire Fighter Cancer Cohort Study (FFCCS) to enroll at least 1,500 Arizona firefighters from multiple fire departments in a three-year study as outlined in Figure 1. Perfluorooctane sulfonate (PFOS) is the PFAS



**Figure 1. Proposal outline: Evaluation of PFAS reduction and other interventions.**

chemical generally found at the highest concentration in blood. As carried out in the Australian study, only firefighters with high serum PFAS ( $\geq 5$  ng/ml PFOS) will be offered participation in a randomized controlled trial comparing plasma donation, blood donation and no treatment (a control group) over a 12-month period, as the blood or plasma donation interventions are likely to be less effective for individuals with lower serum PFAS levels. Firefighters with lower serum PFAS (PFOS  $< 5$  ng/ml) will be offered a variety of interventions (including but not limited to exercise, dietary, nutritional supplement, or nutraceutical interventions) selected by the fire service and shown to reduce cancer or cardiovascular risks in previous peer-reviewed studies in the general population. Biological clocks will be measured in all firefighters participating in the selected interventions. Study participants will receive their personal serum PFAS and biological clock results.

**State-of-the-art and current limitations:** Treatment to reduce serum PFAS levels has only been described in a single study to date, and there have been no studies to determine if this reduction is associated with clinical benefits. Measurement of epigenetic clocks using DNA methylation patterns to determine biological age is a state-of-the-art approach to evaluating both the effects of environmental exposures as well as the benefits of interventions to reduce a wide variety of diseases. More advanced biological as compared with chronological age is called epigenetic age acceleration. Multiple epigenetic clocks have been developed, and epigenetic age acceleration for each clock is associated with a range of diseases, particularly cancer, cardiovascular disease and neurodegenerative disease (Figure 2). Furthermore, in preliminary studies we have found that incumbent firefighters have significantly greater epigenetic age

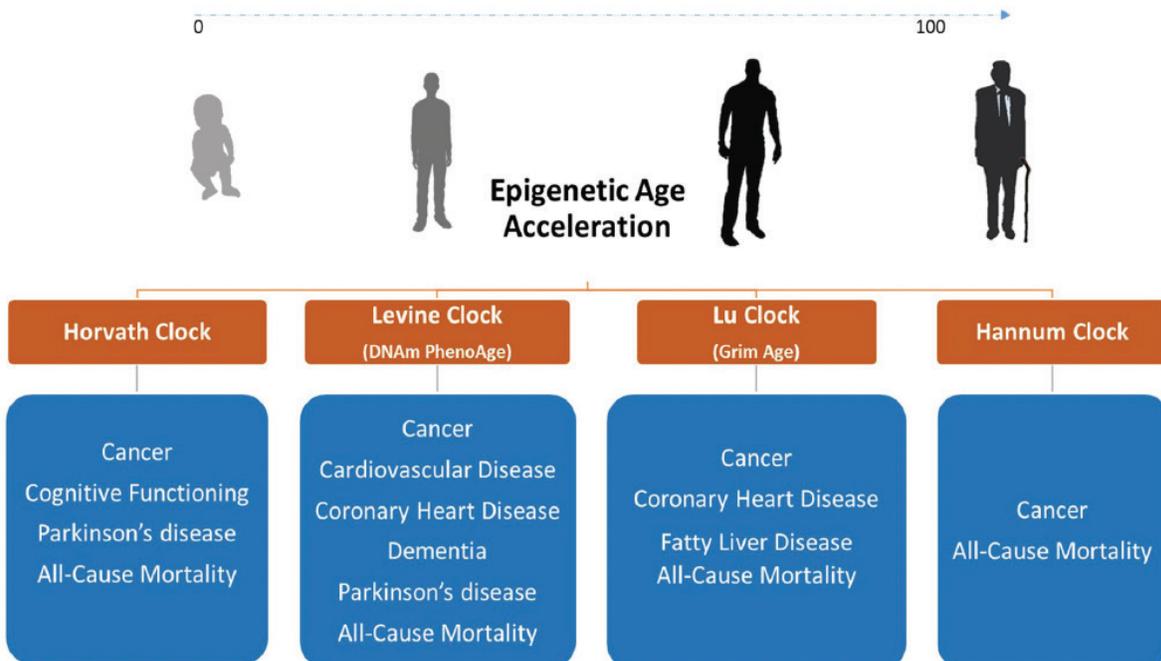


Figure 2. Diseases associated with epigenetic age acceleration using different epigenetic clocks (from Salameh et al., *Frontiers in Genetics*, 2020).

acceleration than recruit firefighters in at least one epigenetic clock, with recruit firefighters generally having very little to no previous occupational exposure as a firefighter. However, while these clocks are predictive of multiple diseases, there are very few interventions that have been tested to reduce epigenetic age acceleration, and none that have been tested in firefighters.

**Innovations:** Innovative aspects of the proposed approach include evaluating for the first time if donating plasma or blood can both reduce serum PFAS levels and improve a person's biological age, thereby potentially lowering their risk of cancer and cardiovascular disease. As PFAS can be measured in the blood of almost every American, not just firefighters, the results of this research will also apply to millions of other people. The other potential interventions to be evaluated (exercise, dietary, nutritional supplements, or nutraceuticals), based on the promise of published studies in the general population and ranking of interest to Arizona firefighters, also have the potential to reduce biological age, increase longevity and reduce cancer and cardiovascular risks in firefighters, and will also apply to the general population. Importantly, this research will be done in collaboration with the firefighters, ensuring that the interventions can be implemented in the most effective way possible, garnering optimal compliance, and ensuring rapid dissemination of the study results to firefighters across the country and internationally.



## PROPOSAL ADVANTAGES

**Public health impact:** A major advantage of this proposal is providing Arizona firefighters the opportunity to measure their serum PFAS levels, as this testing is not part of their annual medical evaluation. If their PFAS levels are elevated, there are specific recently published clinical guidelines to guide additional evaluation. If serum PFAS and their adverse health effects can be reduced through blood or plasma donation, then the results of this study will provide the evidence necessary to recommend these treatments to all firefighters and individuals in the general public with elevated serum PFAS levels. The lack of other known treatments for elevated serum PFAS increases the importance of this study proposal. The other interventions (exercise, dietary, nutritional supplements, or nutraceuticals) prioritized by the firefighters and demonstrating cancer and cardiovascular risk reduction benefits in this study will also be broadly disseminated to the fire service, helping to keep them healthy. The results of research with firefighters will also inform treatments to improve advanced biological age in the general population.

**Risks and risk mitigation:** The health risks of the proposed studies are minimal, given the low risks of adverse effects from phlebotomy and plasma or blood donation for the high PFAS level intervention. The study will also identify firefighters with high serum PFAS levels, providing risk mitigation for them through PFAS level-specific screening for associated adverse health effects. The treatments given in the other interventions chosen by the firefighters will similarly be low risk, having been safely administered in previous studies in the general population. Data privacy will be maintained at all times, with individual results only shared with the participant, and only summary data shared more broadly.

## SCOPE OF WORK

### PHASES

**Phase 1:** Study participants will be enrolled in the Fire Fighter Cancer Cohort Study (FFCCS) and have their serum PFAS at study entry measured and reported back to them.

**Phase 2:** Firefighters with high serum PFAS (PFOS  $\geq 5$  ng/ml) will be offered participation in a 12-month study comparing plasma donation, blood donation or no treatment in a randomized controlled trial. Their change in PFAS levels and epigenetic clocks will be reported back to them.

**Phase 3:** Firefighters will rank other treatments that have been found to increase longevity in animal or human models and which also show promise in reducing cancer and cardiovascular disease risk.

**Phase 4:** Firefighters with lower PFAS levels (PFOS  $< 5$  ng/ml) will be offered interventions rating highest in their prioritization survey. Their change in epigenetic clocks will be reported back to them.

### TASKS

**Phase 1:** Information on the study will be offered to Arizona fire departments. Those departments interested in assisting with the study through provision of a firefighter research liaison for coordination with the FFCCS research team will be eligible for study participation. The study liaisons will share human subjects/Institutional Review Board (IRB)- approved information on the study with their departments' firefighters. At least 1,500 firefighters interested in participation after being provided information about the study will be enrolled in the FFCCS by providing signed informed consent, completing survey information on their firefighting and medical history, diet and exercise, and providing blood and urine samples. The blood samples will be used for serum PFAS and biological clock measurements, and the urine will be stored for potential future analyses associated with the interventions and cancer and cardiovascular disease risks. At least 12 serum PFAS chemicals will be measured and reported back to the firefighter participants with recommendations for clinical follow-up based on their levels.

**Phase 2:** Firefighters with serum PFOS  $\geq 5$  ng/ml and not already regularly donating plasma or blood will be offered participation in a randomized controlled trial comparing plasma donation every six weeks for 12 months, blood donation every 12 weeks for 12 months, and a control group not participating in plasma or blood donation during the same 12-month period, following the protocols of the previous Australian study. The research team will provide the study participants a list of plasma and blood banks near their home and work that are willing to provide services for the study. At the end of 12 months, participating firefighters will have their blood drawn again and at least nine serum PFAS measured. These follow-up levels will also be reported back to the participating firefighters. Changes in serum PFOS levels over the 12-month period will be compared across the three (plasma donation, blood donation, and control/no treatment) groups. Changes in other serum PFAS beyond PFOS

will also be evaluated and reported back to the firefighters. Epigenetic age acceleration will be measured in all firefighters using blood collected at study entry and follow-up and also compared across the three treatment groups, with individual results reported back to each participating firefighter. De-identified (with all personal identifying information removed) summary study results will be published in peer-reviewed journals and shared with the study participants and firefighters throughout Arizona and beyond.

**Phase 3:** Interventions of interest beyond the serum PFAS reduction study will be discussed with the firefighter research liaisons from each participating fire department and the University of Arizona and Arizona State University researchers. Interventions of potential interest to be discussed include exercise programs, dietary interventions, and the use of supplements or nutraceuticals that have been shown to have beneficial effects on cancer, cardiovascular or aging outcomes. A partial list of potential supplements and nutraceuticals includes NAD<sup>+</sup> precursor supplements (nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN)), broccoli sprout extract (Avmacol), or omega-3 fatty acids. These supplements and/or nutraceuticals are readily available to the public without a prescription, and for the selected interventions will be provided for the study participants. There are limited published peer-reviewed studies on the effectiveness of these treatments to reduce cancer and/or cardiovascular risk as well as advanced epigenetic age or other DNA methylation markers, but they have not been tested in firefighters or more broadly in the public. Additional interventions of interest to the fire service and with peer-reviewed study results supporting their effectiveness will also be discussed with the fire service research liaisons and added to a potential intervention list. The list of potential interventions will be provided through an on-line survey to all  $\geq 1,000$  Arizona firefighters in the overall study for them to collectively rank which interventions most interest them.

**Phase 4:** The top-ranking interventions from Aim 3 will be selected for randomized controlled trial testing in firefighters with serum PFOS  $<5$  ng/ml. The number of interventions chosen will depend on the number of study participants needed to achieve adequate statistical power based on previously published studies and the cost of each intervention. The duration of the interventions will also vary depending on previously published successful studies. Study entry and post-treatment epigenetic age acceleration will be measured in treatment and control (no treatment groups) for each intervention. Additional study outcomes will be evaluated based on individual interventions. For example, peak oxygen uptake may be added as an outcome for an exercise intervention. The results of their individual change in epigenetic clocks will be reported back to each participating firefighter. The overall study results will also be reported back to the study participants and the de-identified summary results published in peer-reviewed journals.

**Deliverables & Metrics of Success**

Performance Period	Anticipated Deliverables	Metrics (if applicable)
Year 1 (Complete Phases 1 &3 and start Phases 2 & 4)	<ul style="list-style-type: none"> <li>Participant Enrollment</li> <li>Serum PFAS measurement and report back</li> <li>Start PFAS blood/plasma/no treatment control intervention</li> <li>Prioritize other study interventions and start the highest-ranking interventions</li> </ul>	<ul style="list-style-type: none"> <li>&gt;1500 firefighters</li> <li>&gt;1500 firefighters</li> <li>~300 firefighters</li> <li>≥400 firefighters</li> </ul>
Year 2 (Complete Phase 4)	<ul style="list-style-type: none"> <li>Continue study interventions</li> <li>Evaluate intervention effectiveness</li> </ul>	<ul style="list-style-type: none"> <li>Compliance with intervention protocols</li> </ul>
Year 3 (Complete Phase 2 and report back on all study phases)	<ul style="list-style-type: none"> <li>Evaluate intervention effectiveness (if additional time needed for Phase 2)</li> <li>Report back all study outcomes to study participants and fire departments</li> </ul>	<ul style="list-style-type: none"> <li>Compliance with intervention protocols</li> </ul>
Final Product(s) / Deliverable(s)	<ul style="list-style-type: none"> <li>Study outcome dissemination to the fire service in Arizona and beyond</li> <li>Peer-reviewed and firefighter trade journal publications</li> </ul>	<ul style="list-style-type: none"> <li>Number of presentations</li> <li>Number of articles</li> </ul>

The team plans to meet regularly (at least once per quarter) with the appropriate agency designee to discuss progress on the project. In addition, the team will coordinate with the UArizona Research, Innovation & Impact office, Arizona State University, and ABOR on tri-university coordination at a cadence to be determined.

**Team Members (partial list)**

Name	Department	Institution
Jeff Burgess, MD, MS, MPH (PI)	Community, Environment and Policy	University of Arizona Mel and Enid Zuckerman College of Public Health
Floris Wardenaar, PhD (Co-PI)	College of Health Solutions	Arizona State University
Melissa Furlong, PhD (Co-Investigator)	Community, Environment and Policy	University of Arizona Mel and Enid Zuckerman College of Public Health
Shawn Beitel, MS (Study Coordinator)	Community, Environment and Policy	University of Arizona Mel and Enid Zuckerman College of Public Health

PI=Principal Investigator

**Total 3-year Budget:** \$4,000,000

